High-Field ^{1}H NMR Spectroscopic Studies of Prochiral Protons Attached to Chiral Moieties used in Asymmetric Reactions

Tariq R.A. Abbas B.Sc.

Thesis presented for the degree of
Doctor of Philosophy

The University of Edinburgh

1998

For my mum and dad and my wife and my children

Acknowledgements

I would like to thank both my supervisors Dr. Ian Gosney and Dr. Ian Sadler for their supervision and encouragement during my PhD, and also Dr. Saleh Azmerly and Dr. Mohammed Saleh Tawfeeg for their advice and expertise.

Dr. Keith Grant is to be thanked , particularly for some excellent advice I received regarding the aldol condensation reactions of *N*-propionate derivative of Chirabornox auxiliary.

Also I`d like to thank all of the technical staff within the department especially Mr J.R.Millar and Mr W.Kerr for running NMR spectra, Mr A.Taylor for running mass spectra and also Dr. S.Parsons for crystal structure determinations.

Thanks must also go to Department of Chemistry in King Abdul Aziz University in Jeddah in Saudi Arabia for funding my PhD project.

Finally, I must thank all my colleagues in lab 64 for making my research very enjoyable, namely, "Stuarty-Boy" Gebbie, Laurence Joly, Jamie Mayo, Allan Doyle, Paul Thorburn and Derek Kilgour.

Courses Attended

The following is a statement of courses attended during the period of research:-

1. NMR Spectroscopy, Dr. I.Sadler, Department of Chemistry, The University of Edinburgh, 1994.
2. Mass Spectrometry, Dr. H.McNab, Department of Chemistry, The University of Edinburgh, 1994.
3. Spectroscopy, Prof. D.Rankin, Department of Chemistry, The University of Edinburgh, 1994.
4. Electronic Spectroscopy, Dr. L.Yellowless, Department of Chemistry, The University of Edinburgh, 1994.
5. Organic Research Seminars, Department of Chemistry, The University of Edinburgh, 3 years attendance.
6. Current Topics in Organic Chemistry, various speakers, Department of Chemistry, The University of Edinburgh, 3 years attendance.
7. Royal Society of Chemistry, Perkin Division (Scottish Section), annual meetings, various speakers, 3 years attendance.
8 Industrial Biocatalysts, Smith-Kline Beecham, various speakers, Department of Chemistry, The University of Edinburgh, 1994.
9. Development , Explanation and Applications of NMR Spectroscopy, Dr.I. Sadler and Dr. P.Barlow, Department of Chemistry, The University of Edinburgh, 1995.
10. Industrial Chemistry, Zeneca Grangemouth, various speakers, Department of Chemistry, The University of Edinburgh, 1995.
11. The Discovery of Agrochemicals, Dr. C.Godfrey and Dr. T.Perrior, Department of Chemistry, The University of Edinburgh, 1995.
12. Ames Symposium Combinatorial Libraries, various speakers, Department of Chemistry, The University of Edinburgh, 1996.

Abstract

The synthesis of *N*-substituted propionyl- and phenylacetyl- substituted chiral moieties based on the oxazolidin-2-one or 1,3-oxazin-2-one ring systems has been acheived *via* the use of a variety of different reagents and bases. A ^{1}H NMR spectroscopic study of the prochiral protons H_a and H_b in the methylene group of these systems has been undertaken at 200, 250 and 360 MHz with the aim of determining the extent, if any, to which the diastereotopicity imparted by the chiral auxiliary in a specific asymmetric transformation is reflected in the NMR parameters.

For the *N*-propionyl derivatives the coupling patterns of the prochiral methylene protons H_a and H_b are almost the same, *viz.* a doublet of quartets for each proton. The chemical shifts and the coupling constants are very similar and fall in the range 2.63-3.03 ppm, and 16.5-18.3 Hz for J_{HaHb} and 7.3±0.2 Hz for $J_{Ha\text{-}Hb/Me}$. The coupling patterns for H_a and H_b of the *N*-phenylacetyl derivatives of most of these chiral auxiliaries are pairs of doublets with a coupling constant J_{HaHb} in the range 15.5-16.2 Hz, whilst some of them have the same chemical shift and therefore appear as a singlet.

In these systems no correlation was observed between the diastereotopicity imparted by the chiral auxiliary as measured by the stereochemical outcome for the aldol reactions (and Diels-Alder reactions for the corresponding acrylate derivatives) in terms of diastereomeric excess (*d.e.*%) and the chemical shift separation of the diastereotopic protons.

Attempts to distinguish between the prochiral methylene protons H_a and H_b in the *N*-propionyl derivatives of the different auxiliaries by ^{1}H NMR nOe difference spectra failed apart from that based on the bornyl moiety. For this purpose, its titanium-derived complex was prepared by treatment of the *N*-propionyl derivative with titanium tetrachloride in deuteriated chloroform. Compared to the freely rotating system, both H_a and H_b in the complex had distinct chemical shifts and appeared as a doublet of quartets, which were well separated from each other. In addition, the signals were shifted to higher frequency relative to the free propionate, indicative of electron donation to the titanium.

A comparison of the chiral efficiency of both the carbohydrate- and terpenoid-derived auxiliaries found that the measured levels of asymmetric induction imparted by lithium enolate systems, which are generated *via* lithium diisopropylamide, were markedly different and in favour of the former presumably due to chelation control by ketal and/or pyranose ring oxygens. On the other hand, much higher levels of induction are measured with boron enolates derived from terpenoid-based auxiliaries with di-*n*-butylboron triflate (Bu_2BOTf),

and moreover, can bring about the opposite sense of induction compared to the lithium enolate systems. These aspects of stereocontrol are discussed in terms of different transition states.

In the presence of excess Bu_2BOTf used to promote *anti*-selectivity in asymmetric aldol reactions with benzaldehyde, a homochiral terpenoid-derived 1,3-oxazin-2-one resulted unexpectedly in ring cleavage by an intramolecular process to form a *N*-substituted tetrahydro-1,3-oxazine-2,4-dione in virtually quantitative yield. Mechanistic aspects of this unusual reaction are discussed.

General Contents

Introduction

Contents page

Contents page

Experimental

Contents page

Appendices

Contents page

Glossary of Terms used in Organic Stereochemistry*

Achiral- An entity, such as a molecule, is achiral if it is superposable with its mirror image.

Anisochronism- The resonance frequencies of two geminal nuclei are not equivalent.

Anisochronous protons- Description of two prochiral hydrogen atoms H_a and H_b of a methylene group that do not become equivalent even by (rapid) rotation about the three-dimensional arrangement of atoms. Consequently, H_a and H_b always give rise to separate NMR signals and are termed anisochronous.

Anti- Used to denote the relative configuration of any two stereogenic centres in a chain. If the chain is drawn in a planar zig-zag conformation and the ligands at the stereogenic centre are on opposite sides of the plane, the relative configuration is called *anti*. In a non-linear molecule X-A-B-Y, X and Y are *anti* if the torsion angle about the A-B bond is between +150° and -150°.

Asymmetric induction- A term referring to the extent of excess of one enantiomer over the other achieved in an asymmetric synthesis.

Asymmetric synthesis- *De novo* synthesis of a chiral substance from an achiral precursor such that one enantiomer predominates over the other. Due to a lack of arrangement on how to extend the definition to substances where molecules already contain at least one chiral element and where the synthesis introduces a new chiral centre, it is preferable to replace this term by stereoselective synthesis, enantioselective synthesis or diastereoselective synthesis as the case may be.

---

* For comprehensive details, consult "Stereochemistry of Organic Compounds", E.L.Eliel and S.H.Wilen, Wiley, New York, 1994.

Asymmetric transformation- The transformation of a mixture of stereoisomers into a single stereoisomer, or into a different mixture of stereoisomers.

CIP system- Abbreviation for the "Cahn-Ingold-Prelog" system. A system of rules for the assignment of descriptors (*R*, *S*, *E*, *Z*) for different stereoisomers.

Chiral- Not superposable with its mirror image, and applied to molecules, conformations, as well as macroscopic objects, such as crystals. The term has been extended to samples of substances whose molecules are chiral, even if the macroscopic assembly of such molecules is racemic.

Chiral centre- In a tetrahedral (Xabcd) or trigonal pyramidal(Xabc) structure, the atom X to which four (or three, respectively) different ligands abc(d) are attached and to which a CIP chirality descriptor *R* or S can be assigned. Reflection of the molecule reverses the sense of chirality and changes the descriptor.

***cis-trans* Isomers-** Applied to specify stereochemical (spatial) relationships in cyclanes (and for double bonds), *viz. cis* "on the same side" and *trans* "on opposite sides".

Configuration- The spatial array of atoms that distinguishes stereoisomers (isomers of the same constitution) other than distinctions due to difference in conformation.

Conformation- The spatial array of atoms in a molecule of given constitution and configuration. Conformation of such molecules can be changed by (rapid) rotation around single bonds (and, in the definition of some, by rapid inversion at trigonal pyramidal centres) without, in general, affecting the constitution and configuration.

Conformational analysis- The interpretation of physical and chemical properties and of relative energy content of substances in terms of the conformation or conformations of their molecules.

Diastereomers- Stereoisomers not related as mirror images. They usually differ in physical and chemical properties.

Diastereomeric excess (*d.e.*)- The proportion of the major diasteromer (*A*) produced less that of the minor one (*B*) and is commonly expressed as a percentage % *d.e.* = 100 (A-B) / (A+B).

Diastereoselective synthesis- A chemical reaction in which a new stereogenic unit is introduced in such a way that diastereomers are produced in unequal amounts. The reaction or synthesis is said to display diastereoselectivity and the outcome is expressed in terms of diastereomeric excess (% *d.e.*).

Diastereospecific- A reaction that gives a product of 100% *d.e.*.

Diastereotopic faces- Faces of a double bond that are not symmetry related (*q.v. re*, *si*).

Diastereotopic protons- The protons of a methylene group which is close to a chiral centre in a molecule. They do not have the same chemical shifts unless by accident, since they cannot exchange positions by rotation.

***E* (*entgegen*), *Z* (*zusammen*)-** Stereochemical descriptors for alkenes (or for cumulenes) with an odd number of double bonds (and their heteroanalogues) with at least two non-geminal substituents (other than H) at the two ends of the double bonds. *E* denotes that the substituents of highest CIP priority at each end of the double bond are *trans* to each other, *i.e.* on opposite sides. If the pertinent substituents are on the same side (*cis* to each other) the descriptor is *Z*.

Enantiomer- One of two different forms in which the molecular structures are constitutionally identical but differ in the three-dimensional arrangement of atoms such that they are related as mirror images.

Enantiomeric excess (*e.e.*)- In a mixture of enantiomers (*R* and *S*) the proportion of the major enantiomer less that of the minor enantiomer and is commonly expressed as a percentage (*cf.* diastereomeric excess).

Enantioselective synthesis- A chemical reaction or synthesis that produces the two enantiomers of a chiral product in unequal amounts. The reaction is said to display enantioselectivity and the outcome is expressed in terms of enantiomeric excess (% *e.e.*).

Enantiospecific- A reaction that gives a product of 100% *e.e.*.

Enantiotopic- Two atoms or groups in an achiral molecule differ in that reaction of one, as opposed to the other, leads to enantiomeric products.

endo- Stereochemical descriptor in a bicyclic system of a substituent on a bridge (not bridgehead) that points toward the larger of the two remaining bridges. If the substituent points toward the smaller remaining bridge, its descriptor is ***exo***.

Epimers- Diastereomers differing in configuration at one of two or more stereogenic units.

Heterochiral- Two isometric molecules are heterochiral if their sense of chirality is opposite, *e.g.* if one is *R* and the other *S*.

Heterofacial- On opposite sides of a defined plane or face. Thus, in a trigonal bipyramid the two apices of the bipyramid are heterofacial with respect to the (triangular) basal plane.

Homochiral- Isometric molecules are homochiral if they have the same sense of chirality, *i.e.* if they are all *R* or *S*. The term should not be used to describe enantiomerically pure substances.

Isometric- Species that are either superposable or mirror images of each other are called isometric.

Optical activity- The property in which enantiomers do differ and that is the direction in which they rotate the plan of plan-polarised light. **N.B.** optical antipodes is an obsolete term for enantiomers.

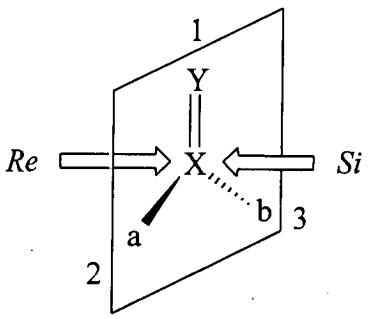
Percentage diastereoselectivity (% *ds.*)- Simply the percentage of the major diastereomer formed, and in general considered to be a most unsatisfactory term since it does not correspond with the normal concept of selectivity.

Prochirality- A term referring to the existence of stereoheterotopic ligands or faces in a molecule, such that appropriate replacement of one such ligand or addition to one such face in an achiral precursor gives rise to chiral products. A more general term is "pro-stereoisomerism" since, in some cases, replacement of one or other of two heterotopic ligands or addition to one or other of two heterotopic faces gives rise to achiral diastereomers that contain stereogenic (but not chiral) units. The descriptors *pro-R* or *pro-S* are used for heterotopic ligands, depending on whether replacement of a given ligand by one identical, but arbitrarily assumed to be of higher priority, gives rise to a chiral element with descriptor *R* or *S*, respectively. The descriptors *Re* and *Si* are used for heterotopic faces.

Pseudo-axial, pseudo-equatorial- Description of a bond or ligand attached to the allylic atoms C(3) or C(6) in a cyclohex-1-ene or heteroanalogue. Because of the similar torsion angle (45° versus 55° in cyclohexane) such bonds (or ligands), while recognisably similar to axial or equatorial bonds (or ligands) are somewhat differently inclined. Therefore, one uses the prefix "pseudo", which is also applied in rings other than six-membered, to substituents and bonds that are not truly axial or equatorial because of deviation of ring torsion angles from 60°.

Racemic mixture or racemate- A 1:1 mixture of enantiomers (*e.e.* = 0%) and it is denoted by prefix (±) - or *rac*- or (*RS*).

Re, Si- Descriptors for heterotopic faces as in abX=Y, indicating their two-dimensional chirality. When additions to X=Y gives rise to a pseudo-asymmetric rather than a chiral centre, the symbols are *Re* and *Si*, *e.g.*



Rotamer- One of a set of conformers arising from restricted rotation about one or several single bonds.

Stereochemistry (adjective stereochemical)- Chemistry in three dimensions, chemistry with consideration of its three-dimensional aspects, but also used in relation to chemical and physical properties of *cis-trans* isomers in alkenes.

Stereogenic unit- A unit within a molecule which gives rise to the existence of stereoisomers. For more complex chiral molecules there are not only two possible stereoisomeric forms (enantiomers), but anywhere up to 2^n where n is the number of stereogenic units.

Stereoisomers- Isomers of identical constitution but differing in the arrangement of their atoms in space. Sub-classes are enantiomers and diastereomers.

Stereoselectivity- The preferential formation of one stereoisomer over another in a chemical reaction. If the stereoisomers are enantiomers, one speaks of

enantioselectivity (% *e.e.*), if they are diastereomers, one speaks of diastereoselectivity (% *d.e.*).

Superposable- Two structures, stereoformulas or models, said to be superposable if, after suitable translation and rigid rotation, they can be brought into coincidence. The terms is often extended to structures that can be brought to coincidence only after internal rotation, or in disregard of internal rotation, about single bonds. Thus, two molecules of (*S*)-2-bromobutane may be said to be superposable regardless of their conformations.

Syn- Antonym of *anti*. In a non-linear molecule X-A-B-Y, X and Y are *syn* if the torsion angle about the A-B bond is between -30° and +30°.

symmetry axis (C_n)- A symmetry axis of order *n* is an axis such that rotation of a molecule, model or object by any angle of 360°/*n* about such an axis produces a superposable entity.

Symmetry plane- A plane such that if a molecule, model or any object is reflected across this plane, the reflected entity is superposable with the original one.

Torsion angle- In a non-linear molecule A-B-C-D, the (dihedral) angle ω between the planes containing A-B-C and B-C-D.

INTRODUCTION

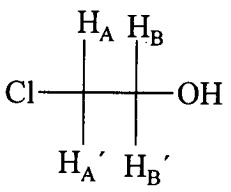
1. ^{1}H NMR spectroscopic assignments of prochiral protons in various compounds

In recent years, increasing attention has focused on the chemical shift non-equivalence and coupling patterns of geminal protons in prochiral methylene groups, *i.e.* "diastereotopic protons", using high-field ^{1}H NMR spectroscopy. The diastereotopic protons H_a and H_b of the methylene group attached to chiral moieties in ^{1}H NMR spectra are frequently anisochronous, giving rise to separate signals with different chemical shifts. Many different groups have studied and reported on such systems of prochiral protons for conformational reasons and for the assignment of the relative configuration in order to determine the exact stereochemistry of such a system of compounds. Selected details of chosen systems are outlined in the following sections to give the necessary background for the reader to understand the purpose behind this thesis.

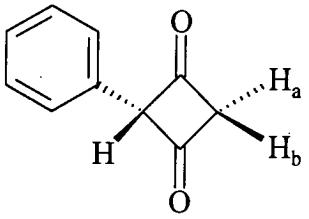
1.1 Prochiral methylene protons attached to chiral moieties

In ^{1}H NMR spectroscopy, the methylene protons at a prochiral centre in a chiral molecule exist in magnetically non-equivalent environments and may exhibit different chemical shifts[1]. Most of the examples cited hitherto are concerned with acyclic moieties on the basis that these are inherently more interesting and this is where possible confusion can most readily arise[2]. This source of confusion in the past has been the use of the term "magnetic non-equivalence" to describe cases where geminal protons have different chemical shifts. Mislow *et al*[3] reported that this term should not be used without further clarification as it has also been employed to describe a completely different phenomenon in NMR spectroscopy. For example, in 2-chloroethanol **1** the geminal protons H_A and H_A' (also H_B and H_B') can be termed magnetically non-equivalent even though they have identical chemical shifts. This type of magnetic non-equivalence arises entirely in the coupled spin system, as H_A

and H_A' both couple differently to a given adjacent proton, *e.g.* H_B (*i.e.* $J_{AB} \neq J_{AB'}$). It is therefore necessary to state whether the magnetic non-equivalence refers to chemical shift or spin coupling or to use of the terms "chemical shift non-equivalence" or "spin coupling non-equivalence". The structure of cyclobutadione **2** may also cause some confusion since the cyclic methylene carbon is not a C_2 centre due to the fact that it does not lie on a C_2 symmetry axis, nor is it strictly a prochiral centre according to the following definition: *viz.* i) pick out the relevant prochiral or C_2 tetrahedral centres in the molecule, ii) if a centre is C_2 the paired ligands will be equivalent, *i.e.* "homotopic" and iii) if the centre is prochiral the paired ligands will be either enantiopic or diastereotopic. Fortunately, the relationship of H_a and H_b can be clearly seen to be diastereotopic since the former is *cis* to the phenyl group and the latter is *trans*. However, for the purist, centres of this type should be treated as if they are prochiral and rule (iii) is applied.

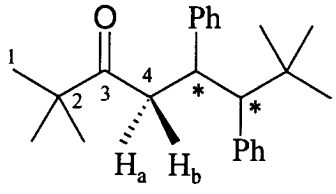


1

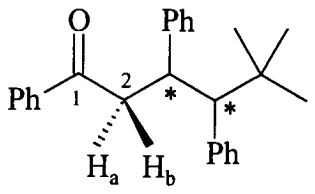


2

A conformational study and the assignment of the relative configurations [(*RR*,*SS*) and (*RS*,*SR*)] to the diastereomeric racemates of two acyclic ketones with two asymmetric carbons has been reported by Alvarez-Ibarra *et al*[4]. This study was achieved by analysis of the ^1H and ^{13}C NMR magnetic parameters taking into account prior selection of the significant conformers in each diastereomer of (±)-2,2,7,7-tetramethyl-5,6-diphenyloctan-3-one **3** and (±)-5,5-dimethyl-1,3,4-triphenylhexan-1-one **4** (* denotes chiral centre).



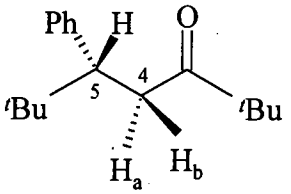
3



4

C-4 in compound **3** corresponds to a methylene group bonded to a carbonyl group and also a chiral centre, and C-2 in compound **4** corresponds to a methylene group bonded to chiral centre on one side and to a carbonyl group on the other side. The prochiral methylene protons H_a and H_b absorb at 2.83 and 2.84 ppm ($^2J_{HaHb}$= 16.0Hz) for C-4 in compound **3** and 3.34 and 3.22 ppm ($^2J_{HaHb}$= 16.0Hz) for C-2 in compound **4**.

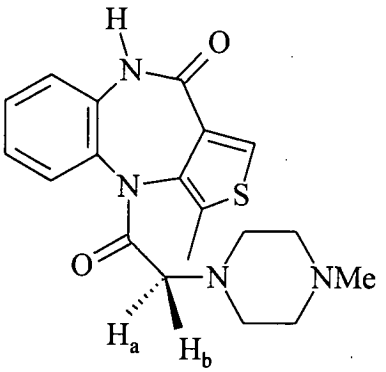
Conformational analysis of the chiral acyclic ketone 2,2,6,6-tetramethyl-5-phenylheptan-3-one **5** with only one asymmetric carbon has been reported also[5]. Thus, analysis of ^{1}H-^{1}H and ^{13}C-^{1}H geminal and vicinal coupling constants and ^{13}C-^{1}H direct coupling constants observed in solution was used for the calculation of the conformational populations. The protons bonded to C-4 and C-5 form an ABC system since no coupling is observed between the aromatic protons and the benzyl hydrogen. In particular, there is a geminal coupling of 17.6Hz between the diastereotopic methylene protons H_a and H_b at 2.53 and 2.96 ppm, respectively.



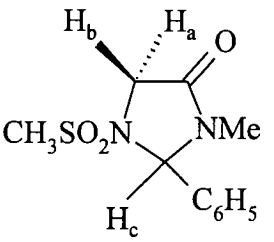
5

Telenzepine (Tz) **6**[6], with an exocyclic amido function, exists as binary mixture of conformers on account of restricted rotation about the CO-NH bond, which is slow on the NMR time-scale. In this case, this is made evident by duplication of resonances in both its ^{1}H and ^{13}C NMR spectra, pointing to a conformer ratio of *ca.* 2:1. Thus, $^2J_{HaHb}$ of the exocyclic prochiral methylene group equals 17Hz and the signals of the diastereotopic protons H_a and H_b for the major conformer of (Tz) appear as a pair of doublets at 4.32 and 3.76 ppm.

Although there is also long-range coupling between H_a and H_c in 4-imidazolidinone **7**[7], there is a geminal coupling of 15.2Hz between the anisochronous diastereotopic methylene protons H_a and H_b at 4.25 and 4.01 ppm, respectively.

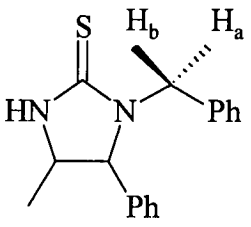


6

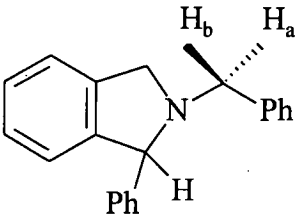


7

Structural effects probably contribute to the remarkably large non-equivalence of the benzyl methylene protons in compounds **8** and **9**, where $\Delta\delta$ = 1.99 and 1.75 ppm, respectively[2] and these effects are a combination of conformational preference and selective anisotropic effects.



8



9

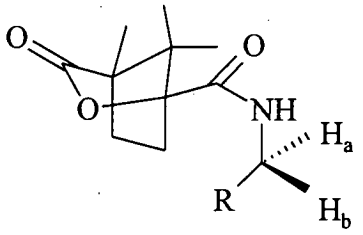
It is proposed by Parker[8] that the observed chemical shift non-equivalence, $\Delta\delta_{obs}$, is made up of an intrinsic diastereotopic shielding term, $\Delta\delta i$ and a conformational term $\Delta\delta c$. In the ^1H NMR spectra of a series of alkyl camphanamides **10a-f**, H_a consistently resonates at a higher frequency to that of H_b. The resonances for diastereotopic protons H_a and H_b are clearly separated at medium field in d_6-benzene solvent, with the chemical shift difference between H_a and H_b varying between 0.12 and 0.21 ppm. Examination of molecular models suggests that the observed non-equivalence of the diastereotopic methylene protons is due to the neighbouring amide carbonyl anisotropy. In order to probe the origins of the anisochronism of the geminal methylene protons in **10a-f**, compound **10f** has been examined in detail.

In the ^1H NMR spectrum of **10f** in d_6-benzene at 298K, two doublet of doublets may be observed at 4.11 and 3.95 ppm, corresponding to H_a and H_b respectively. The

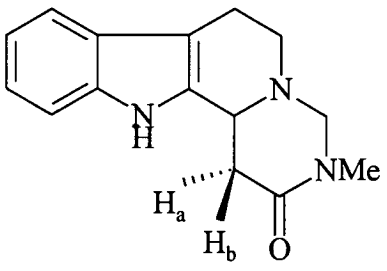
chemical shift difference between H_a and H_b increases linearly with decreasing temperature. Similar behaviour is observed with **10a** and the chemical shift difference is independent of amide concentration. The observed anisochronism is also sensitive to the NMR solvent used. With **10f**, $\Delta\delta(H_aH_b)$ is a maximum in non-polar aromatic solvents and is lower in polar aliphatic solvents. Similar behaviour is observed with **10d**, for which $\Delta\delta(H_aH_b)$ at 308K is 0.03 ppm in $CDCl_3$, 0.05 ppm in CCl_4, 0.06 ppm in d_6-acetone and 0.15 ppm in C_6D_6.

The outcome of the studies related above confirm that the observed chemical shift non-equivalence of the geminal methylene protons in camphanamides **10** is due to differential shielding of the diastereotopic methylene protons by the anisotropic amide carbonyl group.

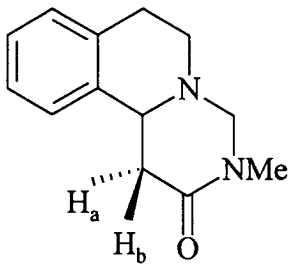
10a) R= Me
10b) R= Et
10c) R= CH_2CH_2Br
10d) R= CH_2Et
10e) R= Ph
10f) R= *p*-BrPh



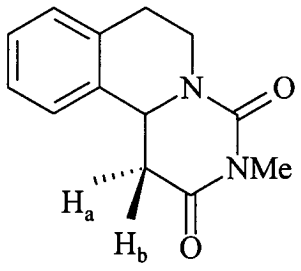
The effect of amide carbonyl anisotropy on an adjacent methylene group has also come under study, *e.g.* 3-methyl-1,2,3,4,6,7,12,12b-octahydropyrimido[1′,6′:1,2] pyrido[3,4-b]indole-2-one **11,** 3-methyl-3,4,6,7,11b-hexahydropyrimido[6,1-a] isoquinolin-2-one **12** and the related system **13**, which were selected for a conformational study by Crabb *et al*[9]. The prochiral methylene protons H_a and H_b absorb at 2.56 and 2.95 ppm ($^2J_{HaHb}$=16.9Hz) for compound **11**, 2.52 and 2.86 ppm ($^2J_{HaHb}$=17.2Hz) for compound **12** and 2.59 and 3.10 ppm ($^2J_{HaHb}$=16.5Hz) for compound **13**.



11

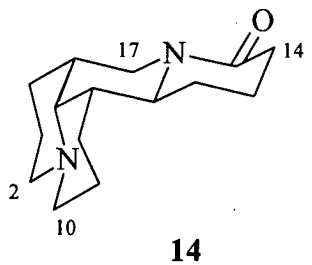


12



13

In a related study following a recent stereoselective synthesis of *d,l*-matrine **14**, J.Chen *et al*[10] have carried out a full ^{1}H and ^{13}C NMR analysis in which complete ^{1}H and ^{13}C chemical shift assignments were made by employing both 1D and 2D NMR experiments. C-14 corresponds to a methylene group bonded to a carbonyl group, which in turn is bonded to a chiral centre. The prochiral methylene protons H_a and H_b for C-14 absorb at 2.06 and 2.37 ppm and their coupling constant $^{2}J_{HaHb}$=17.0Hz. C-2, C-10 and C-17 correspond to methylene groups which are bonded directly to nitrogen atom chiral centres. The prochiral methylene protons appear at 1.62 and 2.49 ppm ($^{2}J_{HaHb}$=11.1Hz) for C-2, 1.64 and 2.55 ppm ($^{2}J_{HaHb}$=11.1Hz) for C-10 and 3.03 and 4.73 ppm ($^{2}J_{HaHb}$=12.5Hz) for C-17.

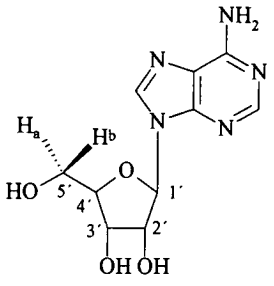


14

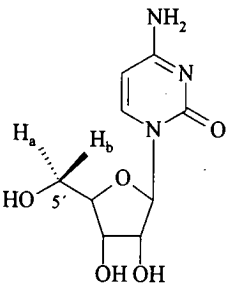
1.2 Prochiral methylene protons at C-5′ of ribonucleosides

An important aspect of ^{1}H NMR studies of ribonucleosides and their derivatives is the stereochemical assignment of the diastereotopic protons on C-5′. Several indirect techniques have been used to make these assignments, which can also be made by evaluating complementary spin couplings between the C-5′ protons H_a and H_b and H-4′ [$^{3}J_{HH}$] and the C-3′ protons [$^{4}J_{CH}$]. However, in a few cases, namely adenosine **15**, cytidine **16**, guanosine **17** and uridine **18** have the prochiral (C-5′) protons been assigned unequivocally by replacing stereoselectively one of the C-5′ protons with deuterium. This method for preparing sugars containing a chiral hydroxymethyl group was reported by Kline *et al*[11]. The ^{1}H NMR spectra of ribonucleosides in D_2O show well resolved quartets for the diastereotopic protons and a comparison of spectra of unenriched and deuteriated compounds permits an unequivocal assignment

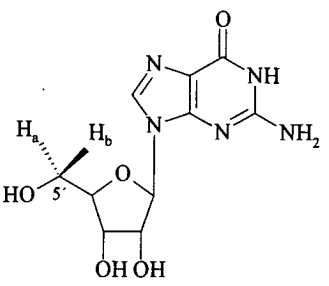
of C-5′ H_a and H_b protons. In deuteriated **15-18**, a significant decrease in the intensity of the high frequency C-5′ proton signal identifies this signal as that of H_a.



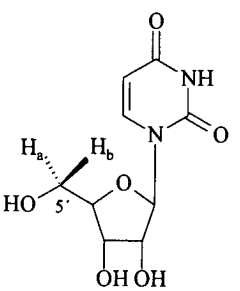
15



16

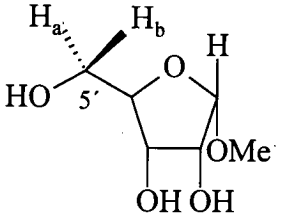


17

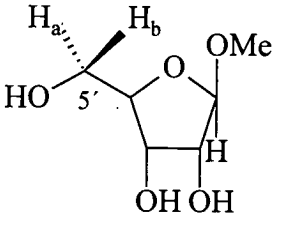


18

The ribonucleosides **15-18** are the building block molecules of ribonucleic acid (RNA) and have been the focus of numerous NMR studies since the original work by Jardetzky[12] and Lemieux[13]. These compounds have been prepared chemically with ^{13}C enrichment (99 atom%) at C-1′ and C-2′ of the ribose ring[14]. High resolution ^{1}H NMR and ^{13}C NMR spectra of the enriched ribonucleosides have been obtained, and ^{13}C-^{13}C and ^{13}C-^{1}H coupling constants have been measured within the β-D-ribofuranose ring and across the *N*-glycoside bond in aqueous solution. Related couplings were determined in methyl α- and β-D-ribofuranosides **19** and **20**. Geminal coupling constants for the diastereotopic protons of C-5′ are 12.8Hz for compounds **15**, **16**, **17** and **18**, 12.4Hz for compound **19** and 12.2Hz for compound **20**.



19

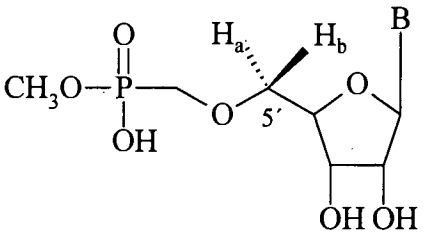


20

Conformational properties of ribonucleoside 5′-*O*-phosphonmethyl derivatives have been determined by ^{1}H NMR spectroscopy and compared with those of natural nucleosides and 5′-nucleotides[15]. ^{1}H NMR spectra of compounds **21-26** were measured firstly in d_6-DMSO. In compounds **22**, **24** and **26** some protons formed

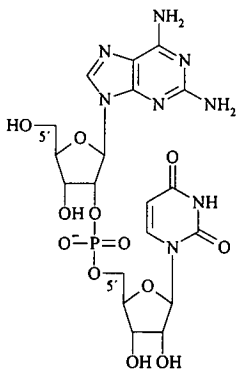
strongly interacting spin systems and it was difficult to determine the NMR parameters. Consequently, these compounds were measured in D_2O, for which the dispersion of chemical shifts was more favourable. In order to obtain the most accurate values of chemical shifts and particularly the coupling constants of the sugar component, simulation analysis of the spectra of **21-26** were performed. Signals of the geminal protons H_a and H_b were assigned at 3.78 and 3.71 ppm ($^2J_{HaHb}$= 10.4Hz) for compound **21**, 3.87 and 3.82 ppm ($^2J_{HaHb}$= 11.2Hz) for compound **22**, 3.80 and 3.74 ppm ($^2J_{HaHb}$= 11.3Hz) for compound **23**, 3.89 and 3.78 ppm ($^2J_{HaHb}$= 11.3Hz) for compound **24**, 3.62 and 3.50 ppm ($^2J_{HaHb}$= 10.0Hz) for compound **25** and 3.95 and 3.79 ppm ($^2J_{HaHb}$= 11.4Hz) for compound **26**. The chemical shift difference $\Delta\delta$ of H_a and H_b is somewhat more marked in the pyrimidine **24-26** ($\Delta\delta$=0.13) than in the purine **21-23** ($\Delta\delta$=0.06) derivatives.

21) B= adenin-9-yl
22) B= guanin-9-yl
23) B= inosin-9-yl
24) B= uracil-1-yl
25) B= 6-azauracil-1-yl
26) B= cytosin-1-yl



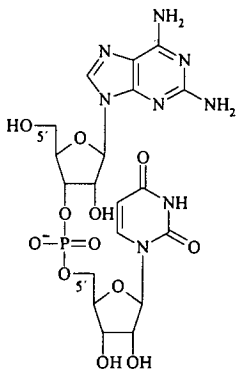
Self-complementary diribonucleoside monophosphates containing 2-aminoadenosine (n^2A) and uridine (U) residues, (2′-5′)n^2ApU **27**, (3′-5′)n^2ApU **28**, (2′-5′)Upn^2A **29** and (3′-5′)Upn^2A **30**, were synthesised by condensation of suitably protected nucleosides and nucleotides units using dicyclohexylcarbodiimide (DCC). The dimers **29** and **30** were also obtained from uridine 2′,3′-cyclic phosphates and unprotected 2-aminoadenosine using 2,4,6-triisopropylbenzenesulfonyl chloride as the condensing agent. The conformational properties of these dimers were examined by UV, CD and NMR spectroscopy[16]. It should be noted that H_b of C-5′ resonance of the phospho uridine (-pU) residue in (2′-5′)-n^2ApU (adenosine phospho uridine) appears at high field in the ^{1}H NMR spectrum, whereas the presence of the phosphate group on C-5′ causes a marked downfield shift of the C-5′ protons resonances. This result indicates that H_b is close to the 2-aminoadenosine residue from which it

receives its shielding effect. A similar upfield shift of the H_b resonance of the 5′-linked residue (-pU or phospho cytidine (-pC) residue) is also observed for (2′-5′)GpU (guanosine phospho uridine) and (2′-5′)ApC (adenosine phospho cytidine). The diastereotopic protons of C-5′ absorb at 3.83 and 3.73 ppm ($^2J_{HaHb}$=12.9Hz) for the adenosine phosphate (Ap) residue of compound **27**, 3.94 and 3.84 ppm ($^2J_{HaHb}$=12.9Hz) for the adenosine phosphate (Ap) residue of compound **28**, 3.97 and 3.70 ppm ($^2J_{HaHb}$=12.7Hz) for the uridine phosphate (Up) residue of compound **29** and 3.77 and 3.69 ppm ($^2J_{HaHb}$=13.1Hz) for the uridine phosphate (Up) residue of compound **30**.



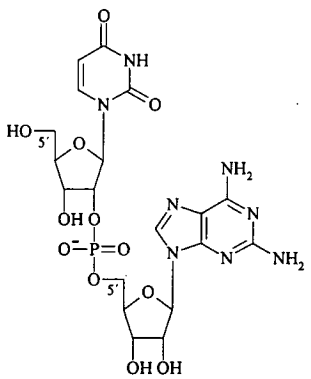
(2′-5′)n²ApU

27



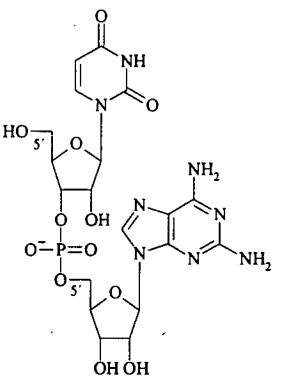
(3′-5′)n²ApU

28



(2′-5′)Upn²A

29

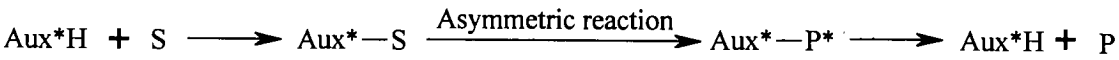


(3′-5′)Upn²A

30

2 Other chiral appendages or chiral auxiliaries

The methylene protons at a prochiral centre in a chiral molecule also play an important role in the stereocontrol of reactions related to attached acyl fragments, especially in asymmetric synthesis which is an area of chemistry that has been expanded rapidly through the study and use of specially designed chiral appendages or auxiliaries. A chiral auxiliary is an optically pure compound (Aux*H) to which a prochiral substrate (S) is attached by a chemical reaction (Scheme 1). A chemical transformation is then performed on this substrate, during which the auxiliary stereochemically directs its course, resulting in the formation of a chiral product (Aux*-P*). After the reaction is complete, the chiral auxiliary can be removed chemically and in many cases it may be recycled.



Scheme 1

Chiral auxiliaries are generally obtained either by modifying a readily available natural product, or artificially by synthesis followed by resolution.

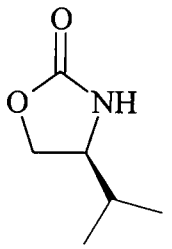
The main requirements of a chiral auxiliary are: (a) it must be available in an enantiomerically pure form, and preferably both enantiomers should be available, (b) it must be easily attached to substrates, (c) it must induce a high level of stereoselective induction in the ensuing chemical transformation and (d) it must be easily removed and preferably recycled.

In the following sections, an account of some of the most commonly used and most efficient chiral auxiliaries will be given, together with details of their use in two of the most common chemical transformations, *viz.* aldol and Diels-Alder reactions.

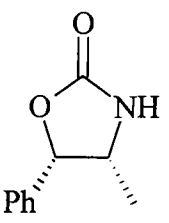
The stereochemical outcome of such reactions for derivatives of these chiral auxiliaries is measured in terms of diastereomeric excess (*d.e.* %) which is determined by analysis of the crude diastereomeric product by high-field ^{1}H NMR spectroscopy.

2.1 Evans` oxazolidin-2-ones

The most widely used and versatile chiral auxiliaries are the two chiral oxazolidin-2-ones **31** and **32**, both of which have been synthesised by Evans[17,18] from the naturally occurring (*S*)-valine and (1*S*,2*R*)-norephedrine, respectively.

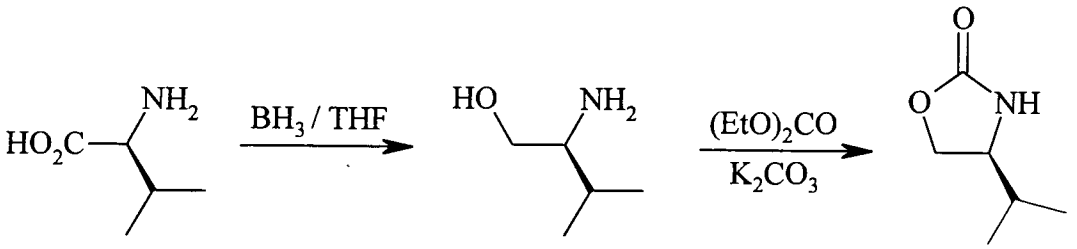


31



32

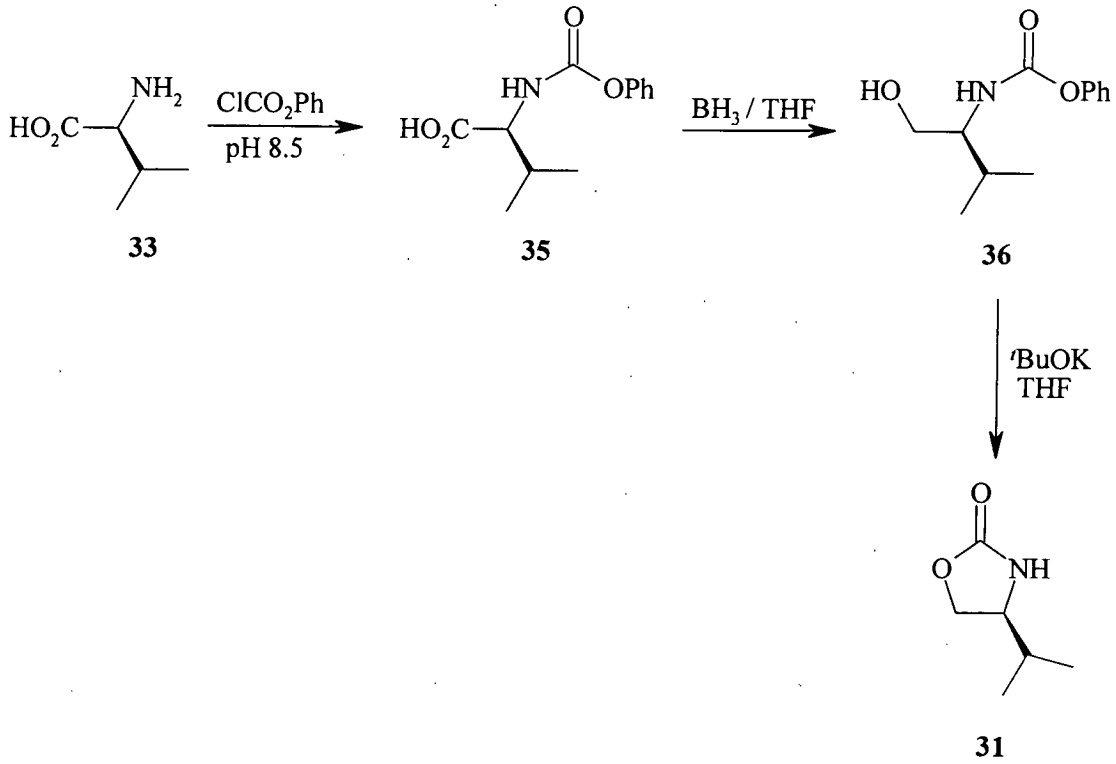
For example, (*S*)-valine **33** is reduced to the β-amino alcohol (*S*)-valinol **34**, followed by cyclocarbamation using diethyl carbonate under basic conditions (Scheme 2).



33 **34** **31**

Scheme 2

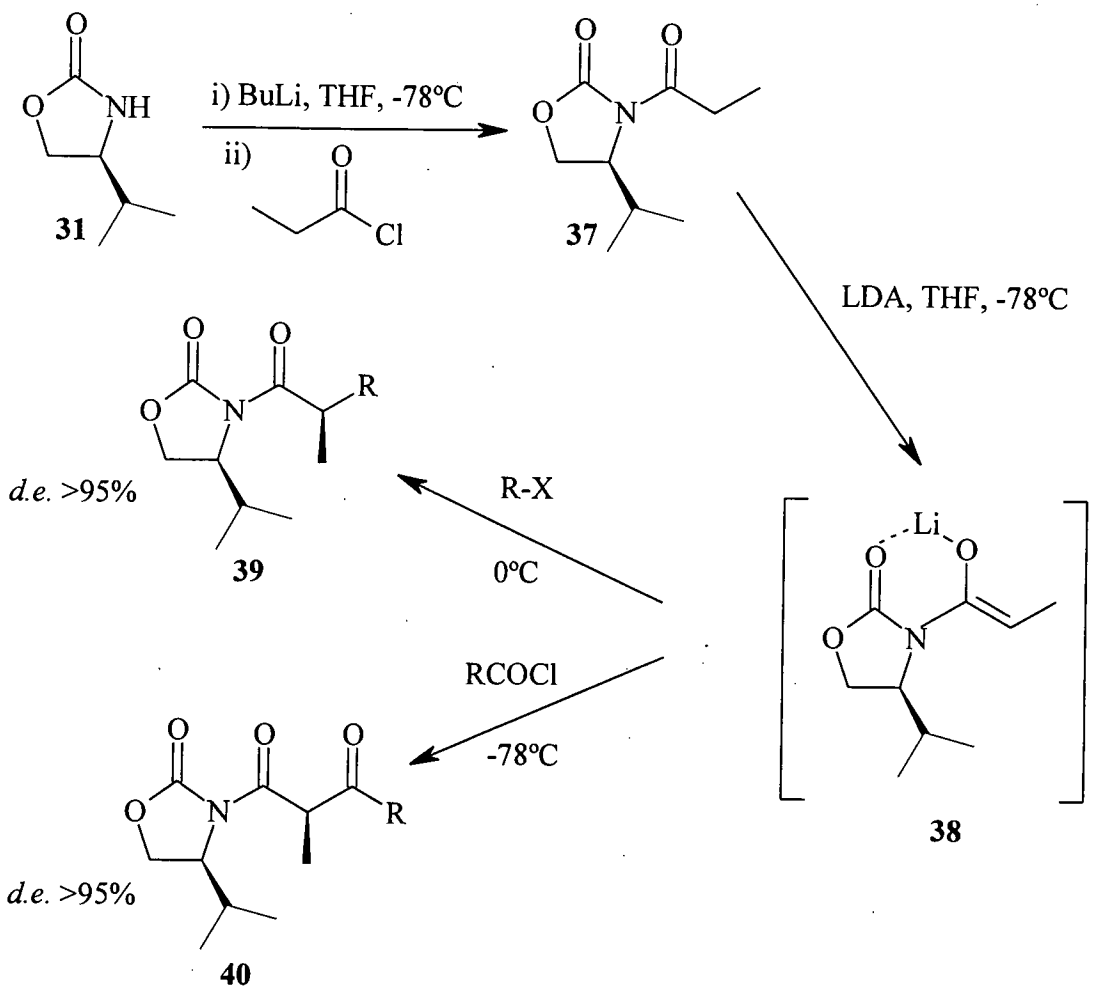
An improved synthesis of this auxiliary is reported by Wust *et al*[19] whereby **33** is first acylated with phenyl chloroformate to yield **35**, which is then reduced with borane to yield alcohol **36**. Subsequent treatment with a catalytic amount of potassium *tert*-butoxide gives the desired auxiliary **31** in 43% overall yield (Scheme 3).



33 **35** **36** **31**

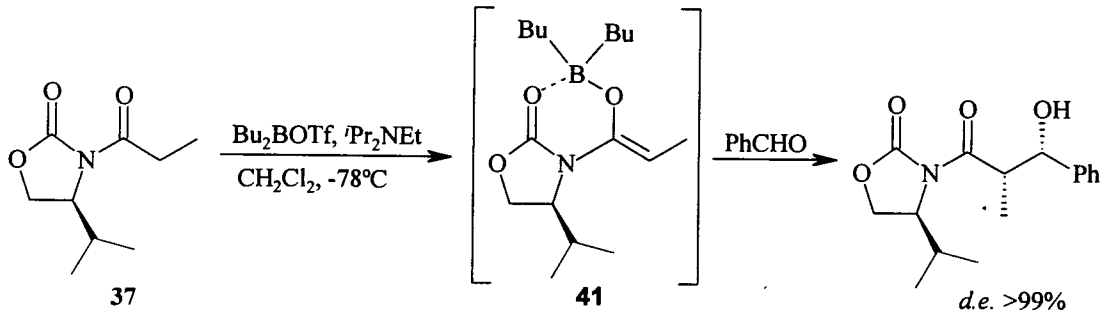
Scheme 3

The (*S*)-valine derived auxiliary **31** can be easily functionalised by treatment with *n*-butyllithium and propionyl chloride to form the imide **37** (Scheme 4). Deprotonation of **37** with lithium di-isopropylamide (LDA) affords the kinetically favoured *Z*-enolate **38**, which can be alkylated[20] to form **39** or acylated[21] to form **40**. Both reactions proceed with very high levels of diastereoselectivity, *i.e.* high diastereomeric excess (*d.e.* > 95%).



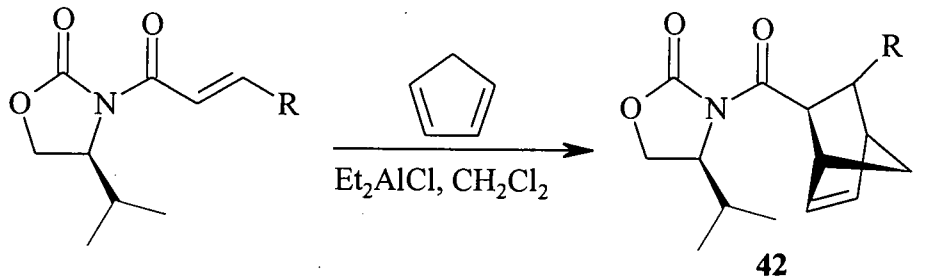
Scheme 4

Excellent levels of asymmetric induction can be achieved also in the aldol reaction when the corresponding boron enolate **41** is used[22] (Scheme 5).



Scheme 5

The chiral oxazolidin-2-one **31** has also been employed in Lewis-acid catalysed asymmetric Diels-Alder reactions by attachment of an acrylate function and reaction with cyclopentadiene[23] (Scheme 6). In such cycloaddition reactions, the *exo/endo* selectivities and the diastereomeric excess (*d.e.*) for the *endo* isomer **42** are reported to be excellent.



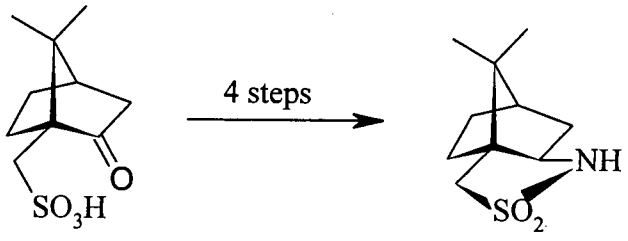
42

d.e. (*endo*)= 86-90%

Scheme 6

2.2 Oppolzer`s chiral sultam

Another widely used and recognised chiral auxiliary is the chiral sultam **43** developed by Oppolzer[24]. This auxiliary is synthesised in four steps from (1*S*)-(+)-10-camphorsulfonic acid **44** in very good yield (63%)[25] (Scheme 7).

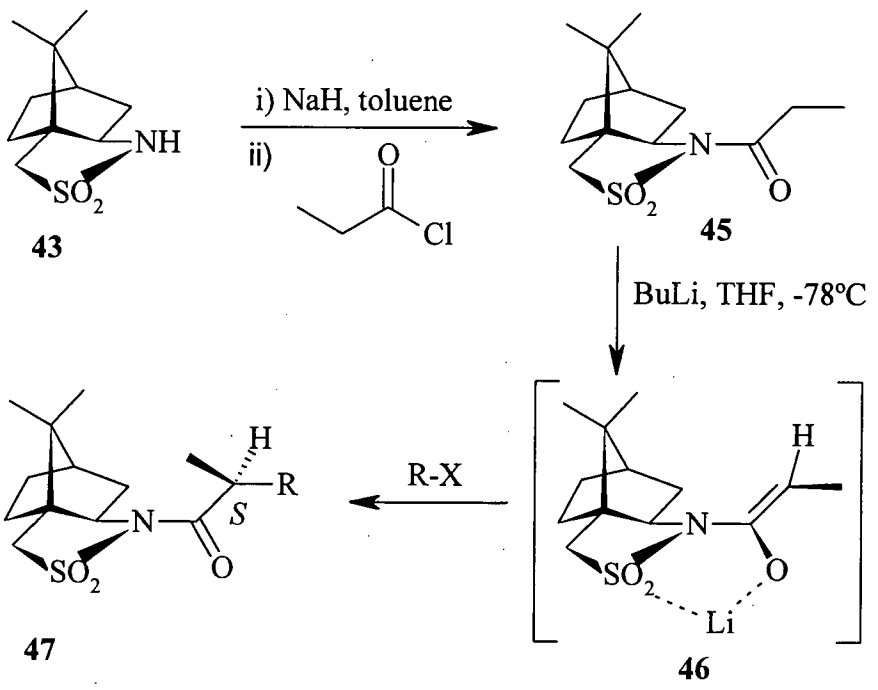


44 **43**

Scheme 7

N-acylation of **43** using sodium hydride and acid chloride yields the corresponding imide **45**, which can be treated with *n*-butyllithium to afford the chelated *Z*-enolate

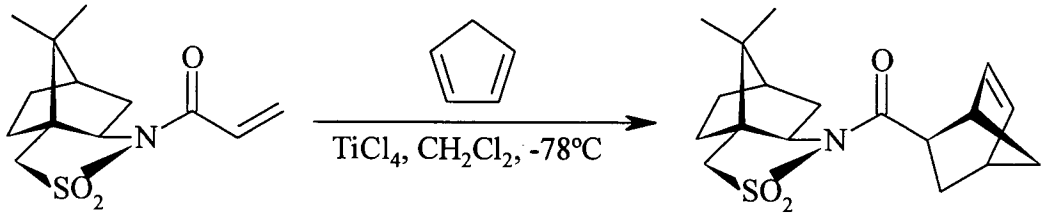
46 (Scheme 8) for use in a variety of asymmetric transformations. For example, reaction of **46** with alkyl halides[26] generates the chiral products **47** with very high levels of selectivity, or alternatively with aldehydes[27] to produce aldol products (*vide infra*).



43 **45** **47** **46**

Scheme 8

Chiral sultam **43** has also been employed successfully in Lewis-acid catalysed Diels-Alder reactions[28] (Scheme 9).

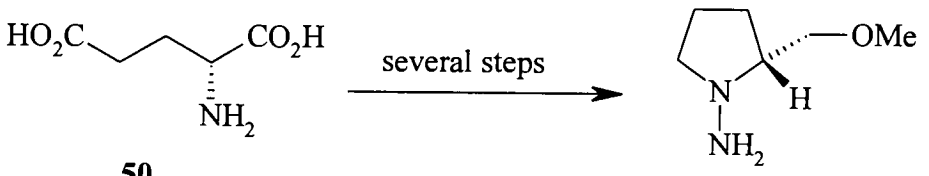


(*endo*) *d.e.* = 94%

Scheme 9

2.3 Enders` SAMP and RAMP

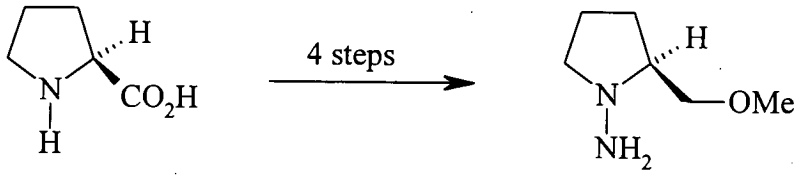
Enders and co-workers have provided the two chiral hydrazines (*R*)- and (*S*)-1-amino-2-methoxymethylpyrrolidine[29,30], which are known simply as RAMP **48** and SAMP **49**. For example, RAMP **48** is derived from (*R*)-glutamic acid **50** in several steps and an overall yield of 39% (Scheme 10).



50 **48**

Scheme 10

The other enantiomer SAMP **49** is prepared from (*S*)-proline **51** in four synthetic steps in an overall yield of 50% (Scheme 11).



51 **49**

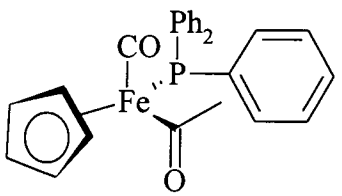
Scheme 11

SAMP and RAMP have been used in a variety of asymmetric reactions including α-alkylation of aldehydes[31] and ketones[32,33], aldol reactions and Michael reactions to α,β unsaturated esters[34].

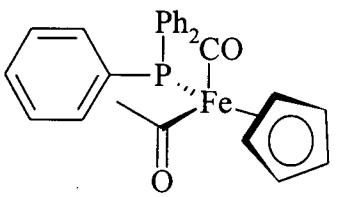
2.4 Davies` auxiliary

Metal complexes may also serve as chiral auxiliaries, *e.g.* Davies` reagent[35,36] $[(C_5H_5)Fe(CO)(PPh_3)]$ (*R*)-**52** and its enantiomer (*S*)-**52** (Fig. 1), for stereochemical control over the reactions of the attached acyl ligands. X-ray analysis shows that the

complex is close to octahedral in geometry in which rotation of the triphenylphosphine leaves one of the phenyl groups under the acetyl ligands, effectively blocking one face. It is worth noting that this chiral auxiliary is designed and not obtained by modification of a naturally-occurring source, *i.e.* it requires resolution during its synthesis.



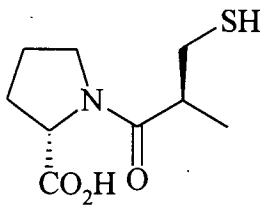
acetyl *R*(-)-**52**



acetyl *S*(+)-**52**

Figure 1

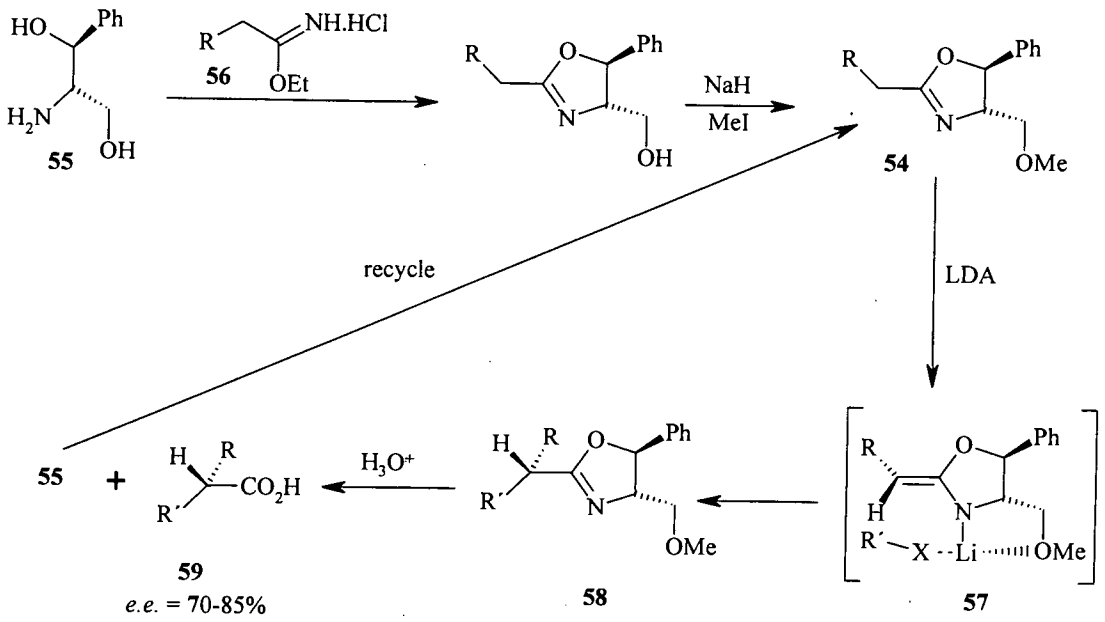
Nonetheless, complex **52** is a good example of an organometallic species that may be exploited in a wide variety of asymmetric transformations, *e.g.* the asymmetric alkylation reaction in the synthesis of the ACE inhibitor Catopril **53**[37]; it also shows high levels of asymmetric induction in the aldol reaction[38].



53

2.5 Meyers` chiral oxazolines

Meyer has developed a versatile chiral auxiliary **54** based on the oxazoline ring system[39,40]; the reagent is formed by reaction of commercially available (1*S*,2*S*)-(+)-2-amino-1-phenyl-1,3-propanediol **55** with the imino ether **56** as shown in Scheme 12.



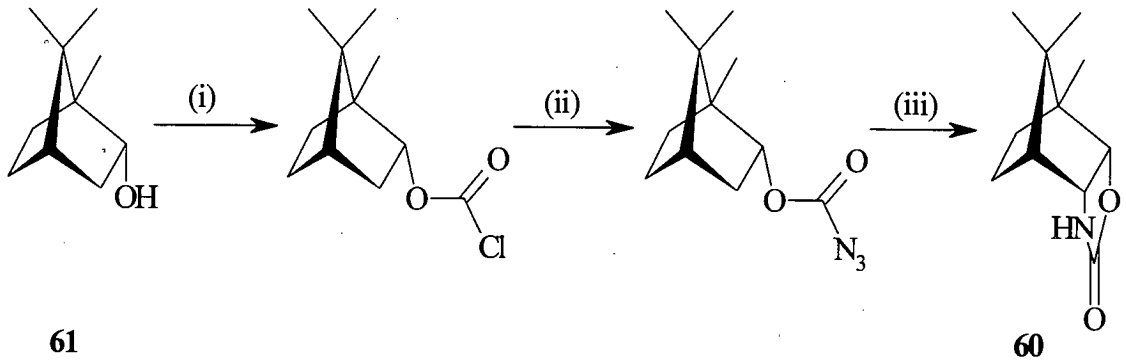
Scheme 12

One of the most common uses of **54** is in the synthesis of C_α-disubstituted carboxylic acids of high optical purity in most cases[41]. Thus, treatment of **54** with LDA generates predominantly the *Z*-lithiooxazole **57** which undergoes reaction with alkyl halides to form adducts **58**. Hydrolysis of the latter by acid affords the desired substituted acid **59** with high *e.e.* and regeneration of the starting amino alcohol **55** for re-use (Scheme 12). In addition to alkylation reactions, the auxiliary has been used for the synthesis of β-hydroxyesters *via* the aldol reaction[42]; it has been exploited as a chiral reducing agent[43] and has been used in kinetic resolution experiments using the chiral recognition phenomenon[44].

2.6 Chiral oxazolidin-2-one auxiliaries from Edinburgh

In recent years, here in Edinburgh a number of novel chiral oxazolidin-2-ones have been synthesised from cheap readily available terpenes and carbohydrates. As discussed previously, the direct cyclocarbamation of expensive, optically-pure β-amino alcohols, or the tedious separation of racemic analogues[45,46], has been

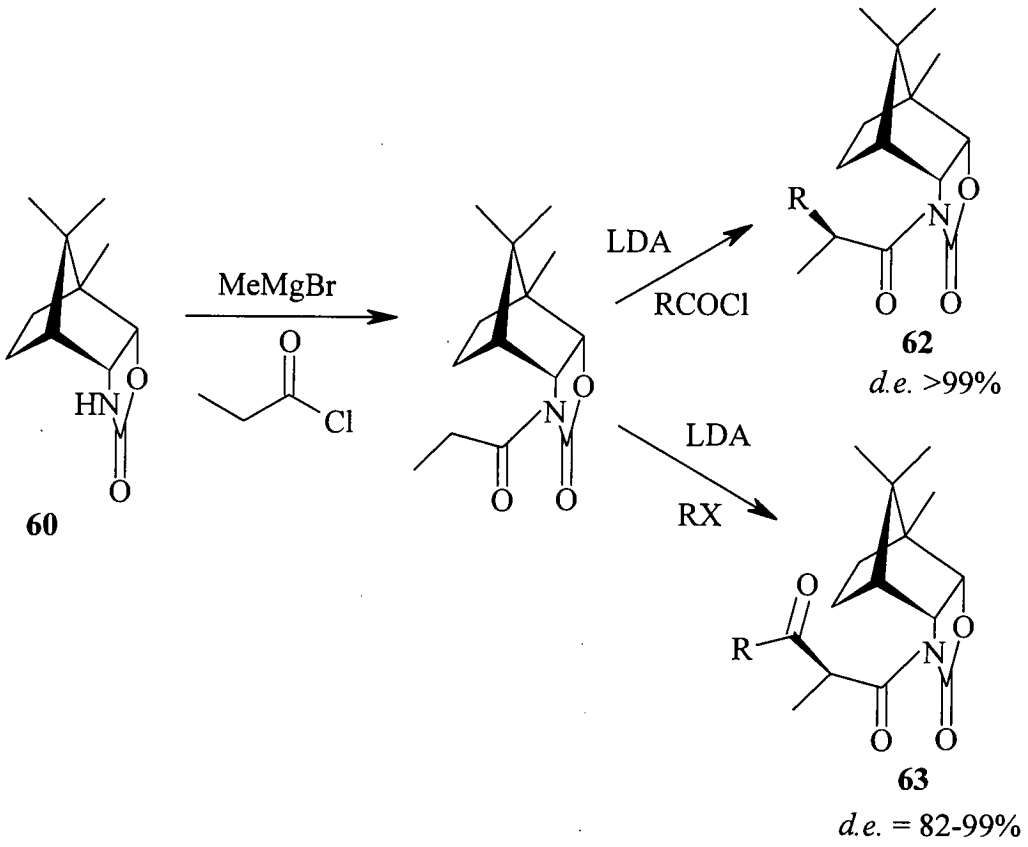
employed as the major route to chiral oxazolidinones. The Edinburgh approach was markedly different and used a nitrene-mediated route to convert a naturally-occurring alcohol into a nitrenoformate (*via* the corresponding chloroformate and azidoformate) which inserts stereospecifically into a C-H bond to form invariably a 5-membered oxazolidinone ring system. For example, Chirabornox **60**[47] is furnished in three steps and 43% overall yield from commercially available (1*S*)-(-)-borneol **61** (Scheme 13). As will be shown later, other minor products may be formed by insertion on the nitrene into other available sites (see chapter 7).



61 **60**

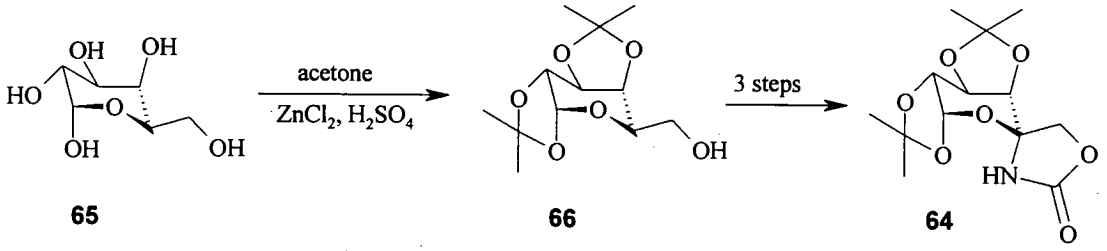
Scheme 13. *Reagents and conditions:* (i), phosgene, triethylamine, toluene-ether, 0°C; (ii), sodium azide, tetrabutylammonium bromide, CH_2Cl_2-water, 25°C; (iii), spray pyrolysis, 300°C, 0.1-0.5 mmHg.

The highly crystalline auxiliary **60** is easily acylated by treatment with methylmagnesium bromide, followed by reaction with propionyl chloride (Scheme 14). Chirabornox afforded excellent levels of diastereoselectivity in alkylation and acylation reactions to give products **62** and **63**, respectively (Scheme 14).



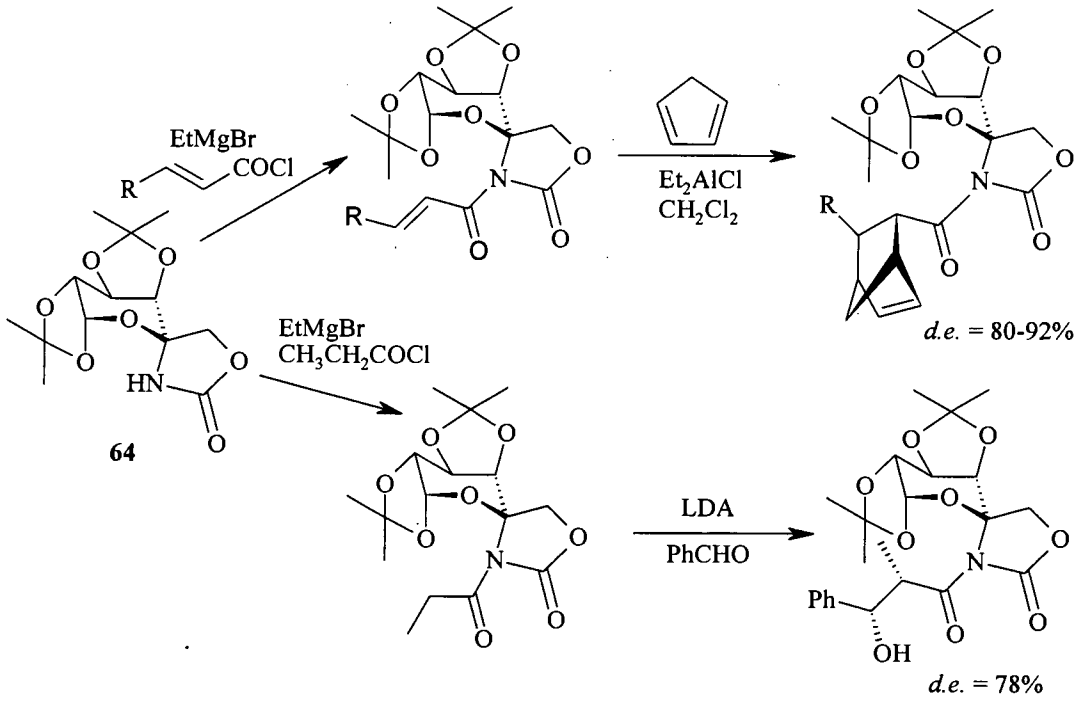
Scheme 14

In further work, the carbohydrate-based spiro-oxazolidin-2-one **64**, called Chiragalox, was obtained in the same way[48] and overall yield of 53% from *D*-(+)-galactose **65** *via* the protected alcohol **66** and subsequent decomposition of the corresponding azide (Scheme 15).



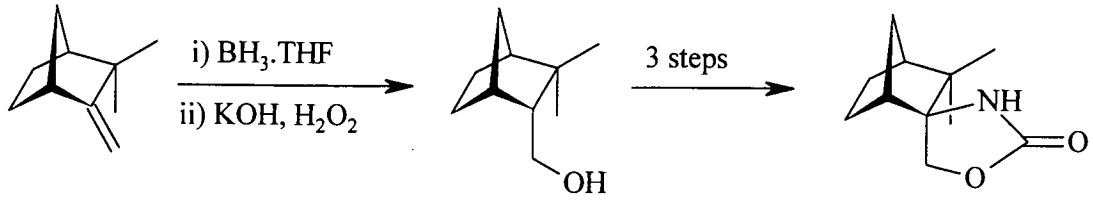
Scheme 15

Unlike Chirabornox **60**, this chiral oxazolidinone afforded excellent levels of diastereoselectivity in both aldol and Diels-Alder reactions. Thus, following acylation of **64** with propionyl chloride as shown in Scheme 16, reaction of the resulting imide with benzaldehyde *via* the lithium enolate (*vide infra*), gave a high diastereomeric excess of product (78%), even though a number of workers[22,27,49] had reported that use of lithium enolates in aldol reactions produced low levels of diastereoselectivity of products; Chiragalox **64** was seen to confound this generalisation and also gave a good *d.e.* in Diels-Alder reactions. Nonetheless, its weakness proved to be *in-situ* racemisation upon recovery after cleavage to obtain the chiral product.



Scheme 16

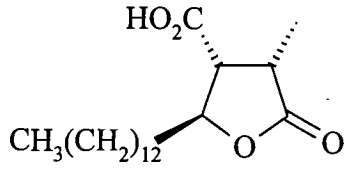
Further research followed in these laboratories to avoid this problem and led to the development in Edinburgh of the camphene-derived reagent **67**, termed Chiracamphox[50], which has turned out to be the most versatile of auxiliaries for use in organic synthesis. Thus, hydroboration of camphene **68** gave rise overwhelmingly to *endo*-camphenol **69**, which by following the nitrene-insertion methodology yielded the spiro-oxazolidin-2-one **67** in good yield (70%) (Scheme 17).



68 **69** **67**

Scheme 17

Chiracamphox could be easily converted into highly crystalline derivatives which afforded excellent levels of diastereoselectivity in both lithium enolate mediated alkylation and acylation reactions, boron enolate aldol reactions, Lewis-acid catalysed Diels-Alder reactions and in 1,4-conjugate additions. These versatile chemical manipulations were amply demonstrated in the synthesis of the tri-substituted γ-lactone referred to as (-)-dihydroprotolichesterinic acid **70**[51] containing three contiguous chiral centres in 5 steps and 57% overall yield. The successful strategy adopted utilised Chiracamphox in consecutive stereocontrolled 1,4-conjugate addition and *syn*-aldol condensation reactions and is a considerable improvement on the previous synthesis of **70** by Mulzer *et al*[52] which involved 14 steps and led to **70** in only 0.4% overall yield.



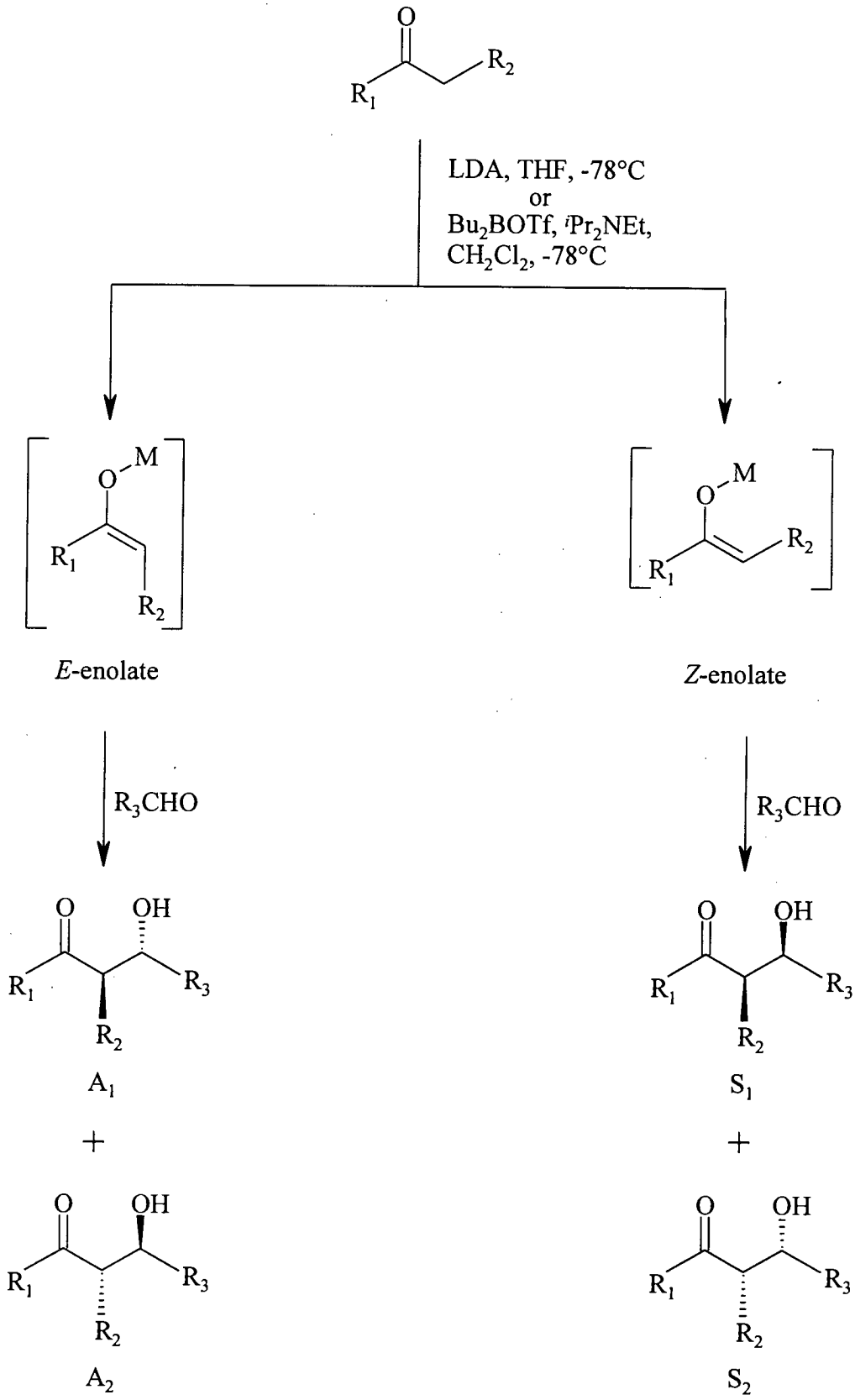
70

In next section, special attention is devoted to the use of chiral auxiliaries in bringing about asymmetric induction in aldol reactions, details of which are necessary in order to understand the main aspect of the thesis.

3 Stereoselective aldol reactions

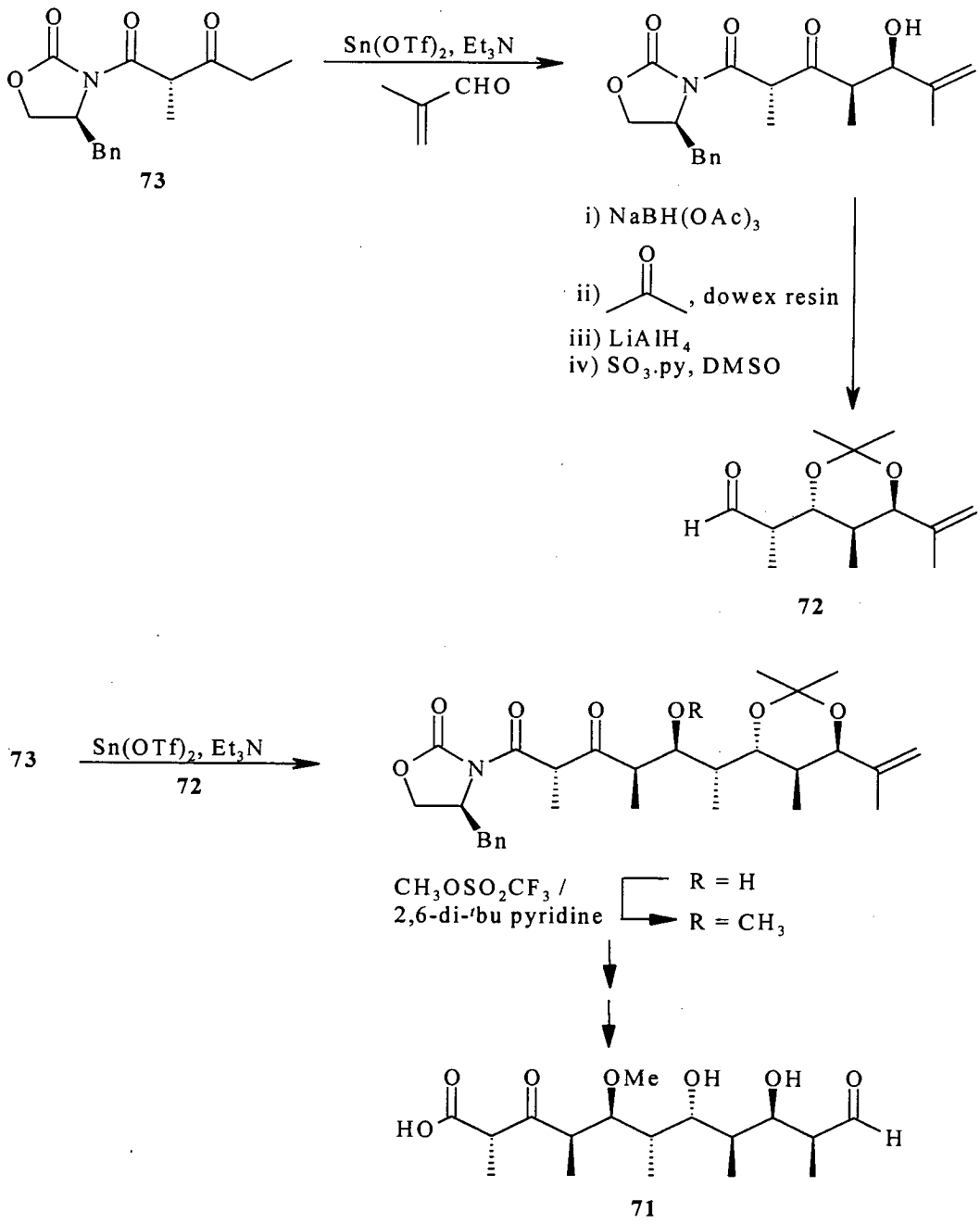
The aldol reaction has been developed into one of the most powerful and selective carbon-carbon bond forming reactions in synthetic organic chemistry[53]. In particular over the last decade, it has become an efficient and versatile method for the control of acyclic stereochemistry, especially in the construction of complex natural products. For the control of the absolute and relative stereochemistry of the aldol addition, a range of different techniques is currently available, but a chiral auxiliary (or reagent) is frequently employed to direct enolisation and bring about π-face selectivity.

The aldol reaction is used to prepare β-hydroxy carbonyl compounds with the simultaneous generation of two new chiral centres; one from the α-carbon of the imide keto function and one from the aldehydic or ketonic electrophile. In essence, the aldol reaction can yield four possible products; two *syn* isomers (S_1 and S_2) and two *anti* isomers (A_1 and A_2) as shown in Scheme 18. Heathcock[54] has shown that the geometry of the enolate undergoing reaction is crucial in determination of the configuration of the aldol product. Thus, *Z*-enolates have been shown to yield *syn*-isomers whilst *E*-enolates produce *anti*-isomers. In order to obtain high stereoselectivity in an asymmetric aldol reaction, both the *Z*/*E* geometry of the enolate and the π-facial selectivity needs to be controlled by use of a chiral auxiliary in place of the grouping R_1 (see Scheme 18). The stereochemical outcome of such reactions will be discussed in detail later in chapter 5 and at this stage it will suffice to touch upon the key aspects, including catalytic developments, that are available for use in organic synthesis.


LDA, THF, -78°C
or
Bu2BOTf, iPr2NEt,
CH2Cl2, -78°C
E-enolate
Z-enolate
R3CHO
R3CHO
A1
+
A2
S1
+
S2

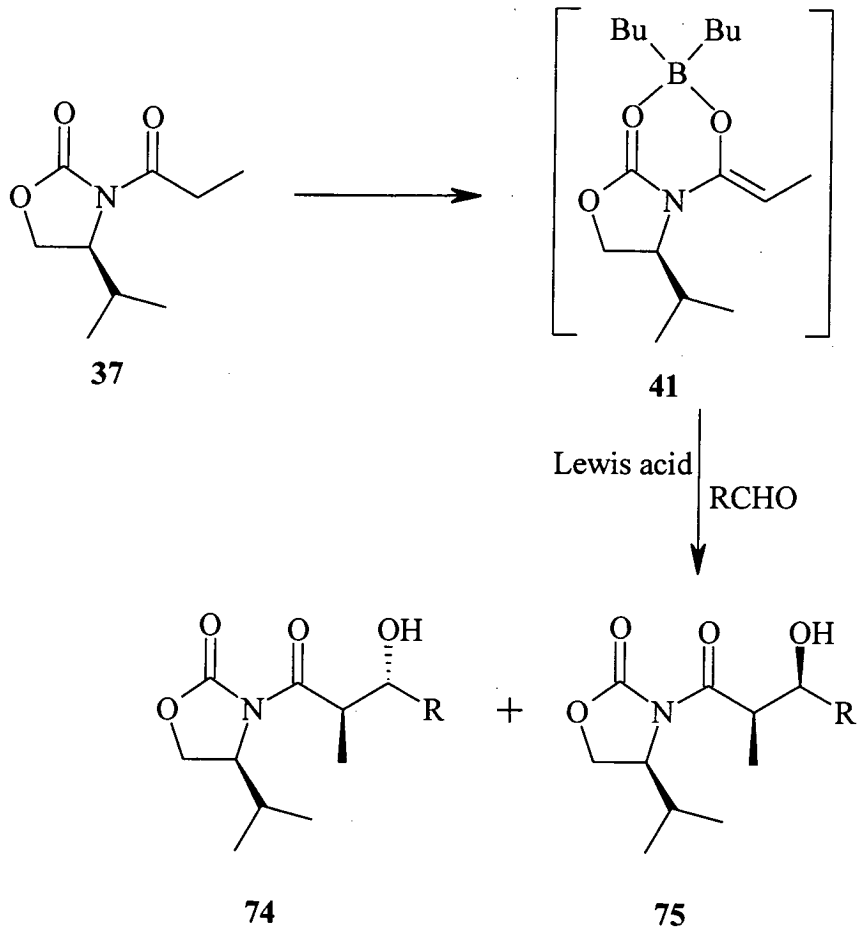
Scheme 18

For example, the aldol reaction is of paramount importance especially in the construction of polyketide systems[17,55]. Thus, with the aid of Evans` auxiliary the C_1-C_{11} synthon **71** of the antibiotic Lonomycin has been synthesised by a convergent route *via* intermediate **72**, which is generated from **73** by two tin enolate-mediated reactions[55] (Scheme 19).



Scheme 19

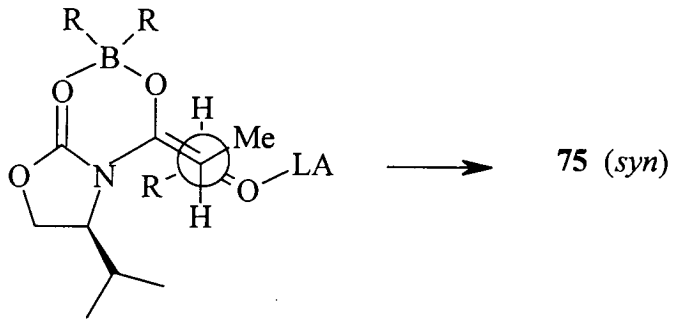
In a significant development, Walker *et al*[56] showed how the boron enolate of the Evans` reagent, imide **37**, reacts with aldehydes that are complexed to Lewis acids to provide the *anti* aldol **74** favourably, or "non-Evans" *syn* aldol **75**, depending upon the reaction conditions (Scheme 20). The boron enolate **41** can under certain circumstances react with aldehydes that are complexed with a Lewis acid, presumably through an open transition state , to give *anti* aldols. This original *anti* aldol method, which consisted simply of using 2 equiv of dibutylboron triflate and ethyldiisopropylamine (Hünig's base) when forming the boron enolate, was discovered in work with β-(arylthio)- and β-(alkylthio)-acrolein derivatives[57].



Scheme 20

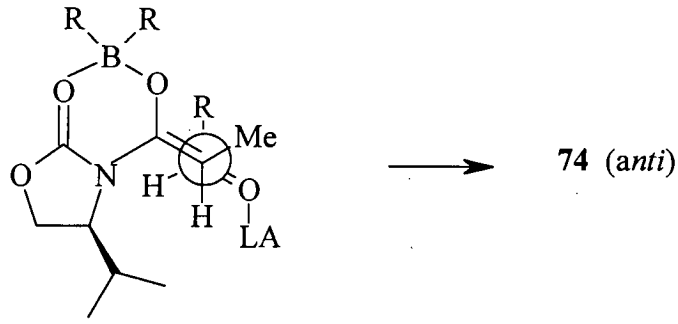
Three different protocols were evaluated. In Method A, the imide was first treated with 1 equiv each of dibutylboron triflate and Hünig's base in dichloromethane at 0°C to form the boron enolate. After the solution was cooled to -78°C, the Lewis acid was added in one portion followed by the aldehyde over a 30 minutes period. In Method B, the boron enolate was prepared at 0°C, cooled to -78°C, and treated with the aldehyde followed by addition of the Lewis acid with a syringe pump over a period of 3-4 h. In method C, the aldehyde was pre-complexed with the Lewis acid in dichloromethane at -78°C, and the boron enolate was added to the cooled solution with a cannula.

The stereoselectivity, both in sense and in magnitude, is dependent on several factors, *viz.* the nature of the Lewis acid, the number of equivalents of Lewis acid (with respect to aldehyde), and the order in which the reactants are combined. The configurational dependence on the Lewis acid to aldehyde ratio is related to the effective steric bulk of the Lewis acid. The working hypothesis of Walker *et al*[56] as illustrated in Scheme 21, is that the aldol products **75** and **74** result from an open transition state **A** and **B**, respectively. If the Lewis acid (LA) used is small, transition state **A** is preferred because it minimises gauche interactions about the forming bond. However, if the Lewis acid is large, transition state **B** becomes competitive because of the methyl-Lewis acid interaction in **A**. The authors argued that Et_2AlCl acts as a bulky Lewis acid and gives *anti* aldol because the O-Al bond is short and the ligands are relatively bulky. On the other hand, $SnCl_4$ and $TiCl_4$ are effectively smaller than Et_2AlCl because of the longer Sn-O and Ti-O bond lengths. However with $SnCl_4$ and $TiCl_4$, slow addition of the Lewis acid to the aldehyde gives a reactive 2:1 complex[58] in which the effective bulk of the Lewis acid is increased because of its octahedral co-ordination; hence this protocol gives rise to *anti*-aldol.



A : favored for small Lewis acids (LA)

75 (*syn*)

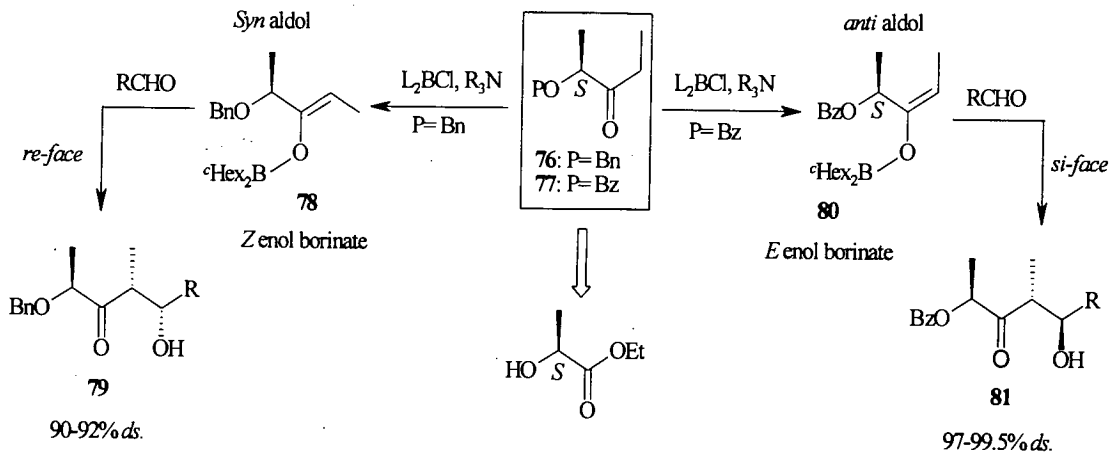


B : favored for large Lewis acids (LA)

74 (*anti*)

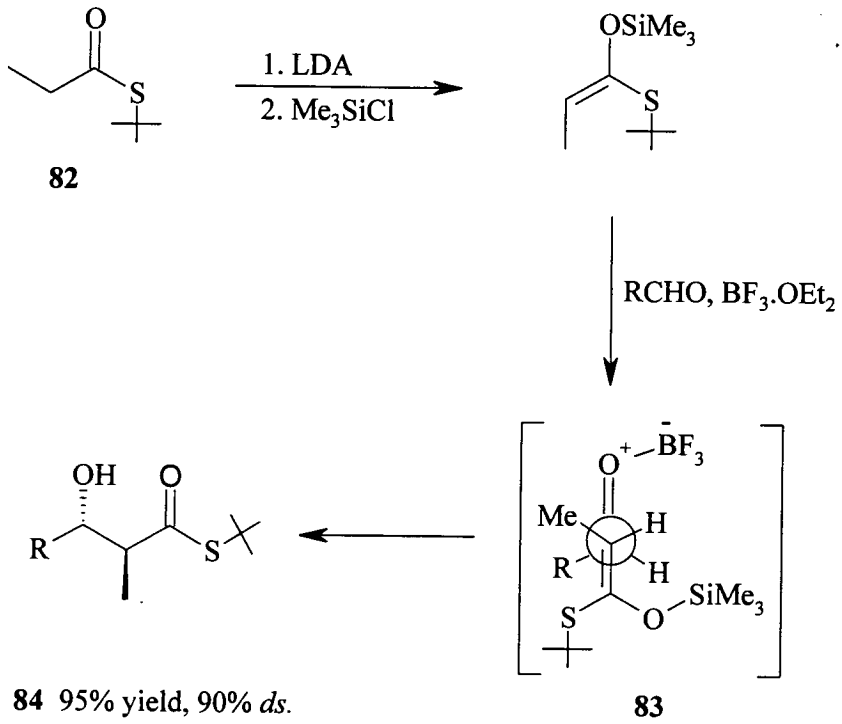
Scheme 21

High π-face selectivity in *syn*- and *anti*-aldol reactions of chiral boron enolates of lactate-derived ketones has been achieved by Paterson *et al*[59,60]. The use of $^{c}Hex_2BCl/Me_2NEt$ in the aldol reaction of the α′-benzoyloxy **77** with aldehydes leads to high stereoselectivity (97-99.5% *ds.*) for the crystalline **81**. Under similar conditions, the corresponding benzyl ether **76** favours formation of the *syn* **79** (Scheme 22). The *Z* and *E* enol dicyclohexylborinates of the related lactate-derived ketones **76** and **77** add to aldehydes to give *syn*- and *anti*-aldol adducts with useful levels of π-face selectivity, as in **78**→**79** and **80**→**81**.



Scheme 22

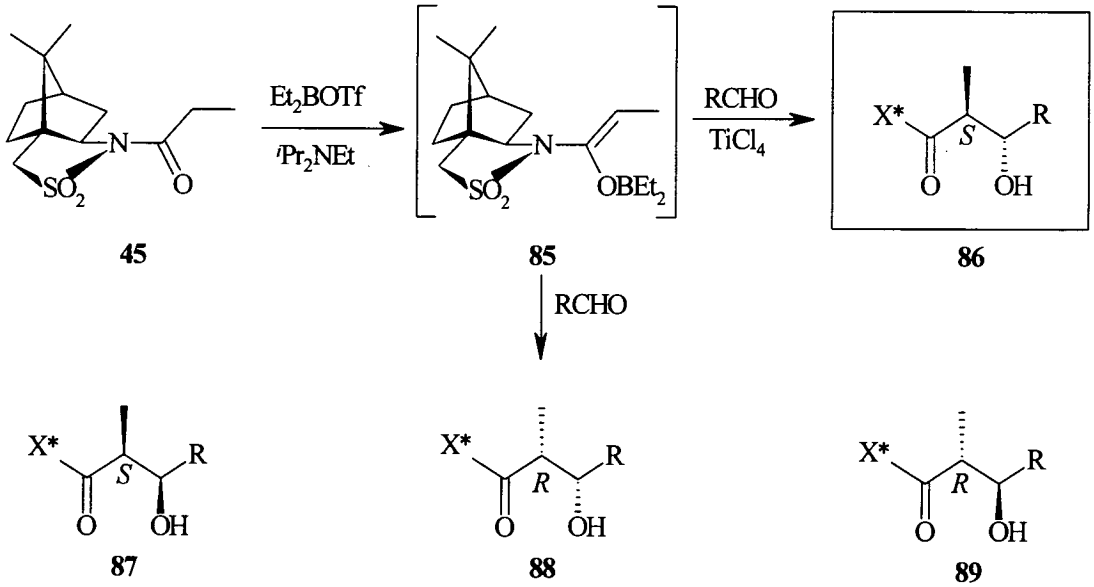
Since its discovery, the Lewis-acid catalysed reaction of enolsilanes with aldehydes (Mukaiyama aldol reaction)[61] has attracted the interest of synthetic organic chemists. Gennari *et al*[62] have developed the reaction for use of *t*butyl thioester **82** with $BF_3.OEt_2$ as Lewis acid to produce the *anti*-aldol product **84** in high diastereoselectivity (90% *ds.*) and *ca.* 95% yield (Scheme 23).



Scheme 23

The observed *anti* preference to the aldol reaction is independent of the silyl ether geometry and an acyclic transition state **83** has been proposed to explain this high diastereoselectivity. Preliminary theoretical (MNDO) calculations suggest that the deviation from planarity of the bulky ^{t}Bu and $SiMe_3$ groups determines an increase of the C=C-Me bond angle (130°). As a consequence the interaction between Me and BF_3 in the transition state leading to the *syn* isomer becomes more important. Moreover, the Me-BF_3 Lewis-acid interaction cannot be released by a rotation of the aldehyde because of the R-$SiMe_3$ (R-^{t}Bu) "pinwheel" steric repulsion. The result is the observed dramatic enhancement of the diastereoselectivity in favour of *anti* product.

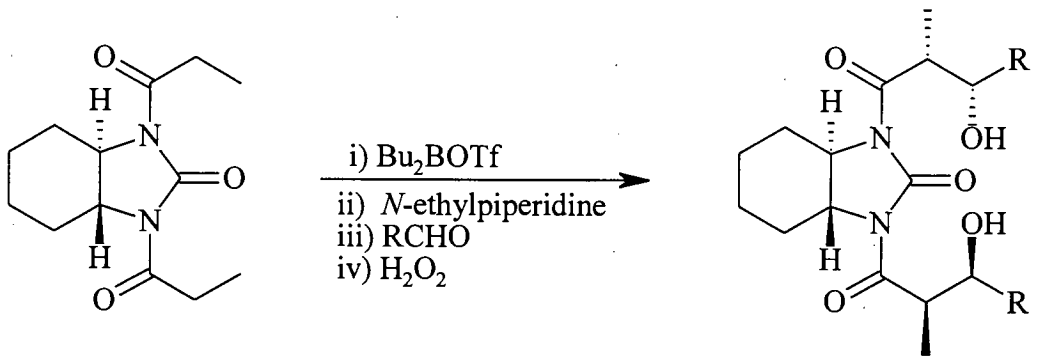
Oppolzer *et al*[63,64] have similarly explored the outcome of the aldol condensation of the sultam-derived boryl enolate **85** in the presence of various Lewis acids. Boryl enolate **85** was obtained by successive treatment of the *N*-propionylsultam **45** with (*in situ* prepared) Et_2BOTf and $^i Pr_2EtN$ and the influence of $TiCl_4$ as a Lewis acid on the condensation of non-isolated enolate **85** with different aldehydes was tested. The outcome of this aldol condensation resulted in formation of *anti*-aldol **86** as the major product, together with the two *syn*-aldols **87** and **88** and the other *anti*-isomer **89** in variable diastereoselectivities, depending upon the reaction conditions (Scheme 24).



Scheme 24

For example, when benzaldehyde was condensed with **85** at -78°C, the stereoselectivity was increased from 92:8 to 99:1 upon changing the $TiCl_4$/aldehyde ratio from 2:1 to 1:1. This lower $TiCl_4$/aldehyde ratio also proved suitable for the *anti* aldolization of other aromatic aldehydes such as furfural and *p*-nitrobenzaldehyde.

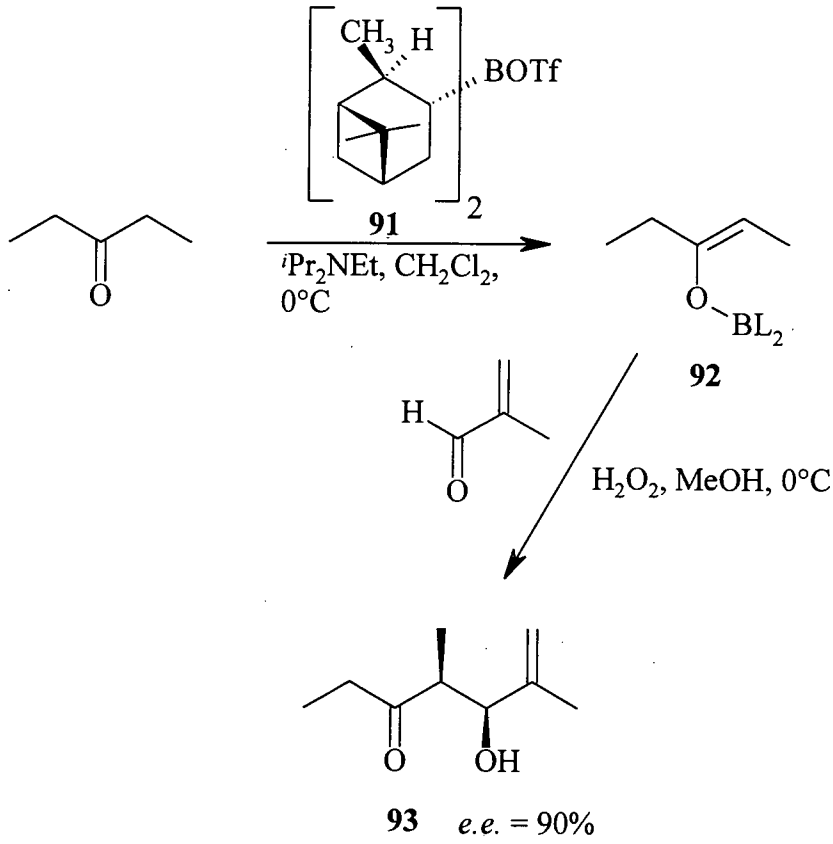
Developments continue apace in the use of chiral appendages in asymmetric aldol reactions. For example, Davies has developed[65] the imidazolidinone auxiliary **90** and this has been employed in asymmetric boron enolate mediated aldol reactions to produce both *syn* isomers in high diastereoselectivity (Scheme 25).



90

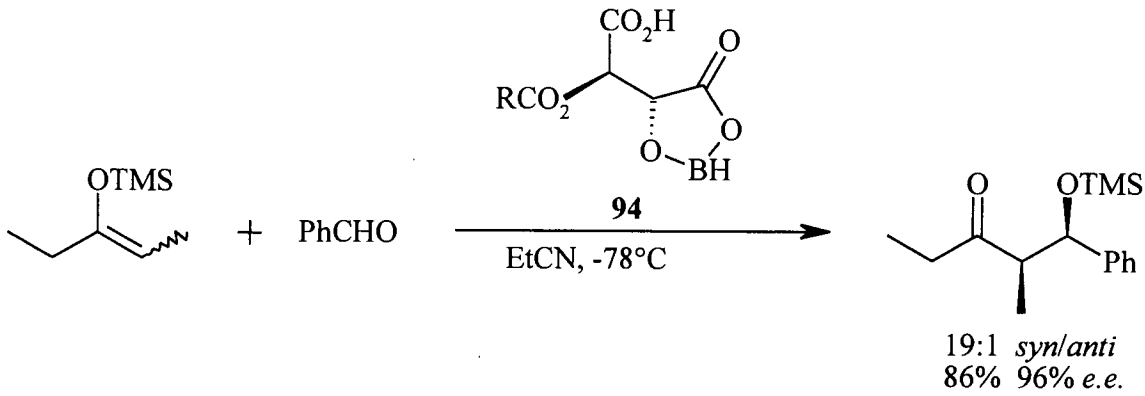
Scheme 25

Inexpensive and readily available (+)- and -(-)-α-pinene can also be utilised as a chiral ligand to prepare the chiral boron reagent **91** for use in asymmetric aldol reactions[66] (Scheme 26). In order to achieve optimum results, this reagent needs to be used in conjunction with a tertiary amine, *e.g.* triethylamine or diisopropylethylamine in dichloromethane as solvent. In the reaction illustrated in Scheme 26, diethyl ketone is enolised by use of the boron triflate **91** to generate the chiral boron enolate **92**, which then adds stereoselectively to methacrolein at 0°C to give the *syn* stereoisomer **93** in 75% yield and 90% enantiomeric excess. Other aldehydes are reported to give similar results.



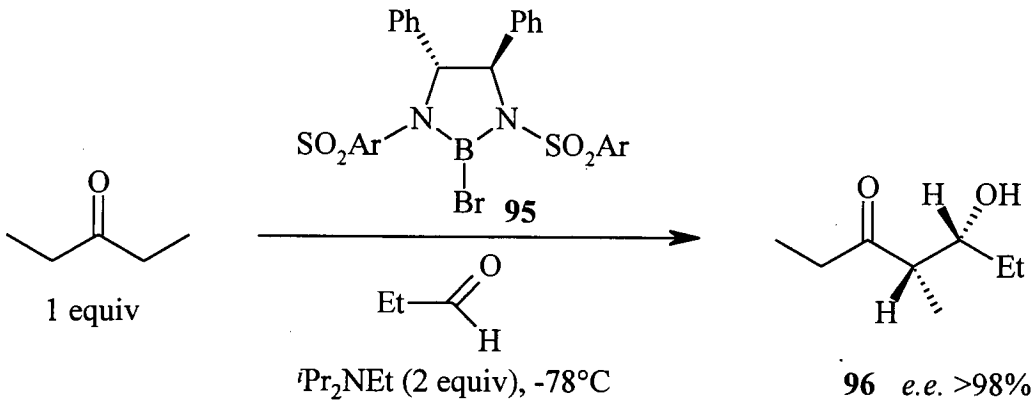
Scheme 26

Although asymmetric aldol condensations have been achieved for many years using methodologies in which the chiral information is covalently bound to one of the reacting species (substrate, auxiliary or reagent control), a catalytic approach to this problem has only recently been successful. Thus, Yamamoto has used the chiral acyloxyborane (CAB) complex **94** in a catalytic asymmetric version of the Lewis-acid mediated Mukaiyama condensation of silyl enol ethers and ketene acetals[67]. As illustrated in Scheme 27, aldol condensations carried out in the presence of 20 mol % of CAB catalyst **94** proceed in good yield and with excellent stereocontrol to produce predominantly *syn* aldol product.



Scheme 27

Corey *et al*[68] have also employed a benzil-derived boron chiral catalyst **95** in the synthesis of the rice and corn weevil aggregation pheromone Sitophilure **96**[69] (Scheme 28).



Scheme 28

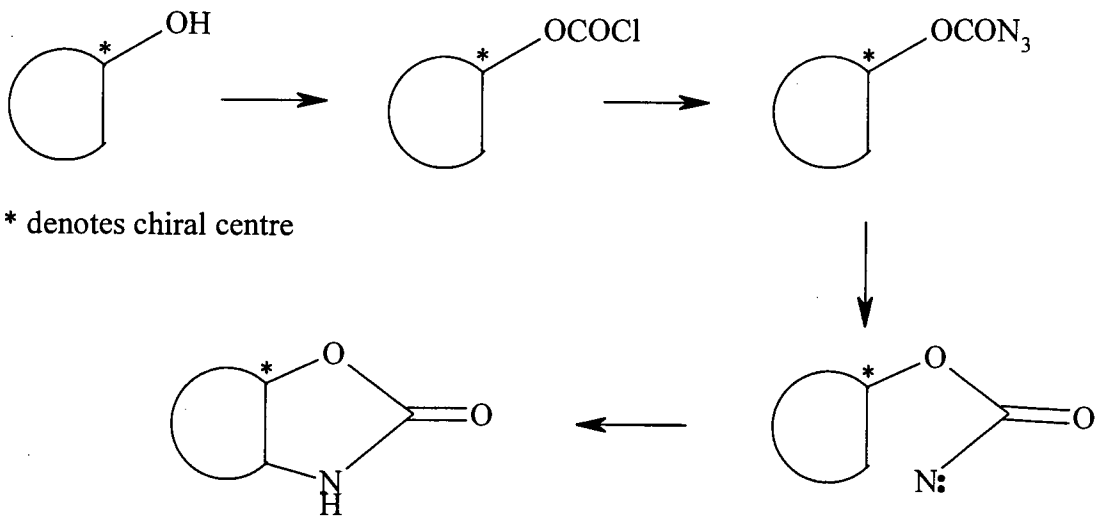
DISCUSSION

4. High-field ^{1}H NMR spectroscopic studies of prochiral protons attached to chiral moieties

The purpose of this research is to consider the chemical shift non-equivalence and NMR spectroscopic coupling patterns of geminal protons in prochiral methylene groups attached to chiral moieties. Such diastereotopic protons are termed anisochronous, giving rise to separate signals or different chemical shifts in high-field ^{1}H NMR spectra.

The initial phase of the work has been mainly concerned with the synthesis of *N*-substituted propionyl and phenylacetyl substituted chiral moieties based on the oxazolidin-2-one or oxazinone ring systems for spectroscopic studies.

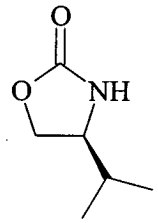
All of these chiral moieties, often referred to as auxiliaries, have been synthesised from cheap, readily available naturally-occurring chiral alcohols by means of the well-known but little used nitrene insertion process.



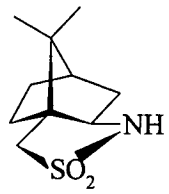
Scheme 29. Stereoselective nitrenoformate route to chiral oxazolidin-2-one

In recent years an increasing demand, especially by the pharmaceutical industry, for chirally pure compounds has raised the study into and use of homochiral oxazolidin-2-one ring systems as stoichiometric chiral auxiliaries[70], especially for the

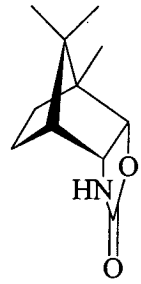
stereocontrol of reactions related to attached acyl fragments. Chemical elaboration of naturally occurring compounds (amino acids, terpenes and carbohydrates) from the chiral pool provides preparative access to the more synthetically useful chiral oxazolidin-2-ones. Of these, Evans' (*S*)-valinol-derived auxiliary **31** is one of the most commonly encountered, whilst this group has reported[47] the enantiospecific synthesis of the tricyclic oxazolidin-2-one **60**' (and its *exo*-analogue) from (-)-camphor. Oppolzer *et al* have also exploited (+)-camphor in the synthesis of a number of different auxiliaries[71], notably Chirasultam **43**, which is easily functionalised using acid chlorides and other different reagents for asymmetric reactions. *D*-galactose is also an example of a carbohydrate which can be converted by the nitrene-based route into Chiragalox **64**[48] to exhibit high levels of stereoselectivity in a variety of asymmetric transformations.



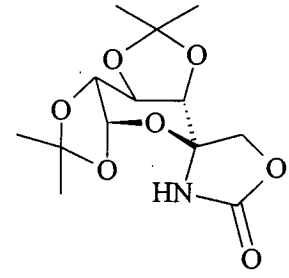
31



43



60



64

Functionalisation of oxazolidin-2-one chiral auxiliaries with acyl-moieties has routinely been achieved *via* deprotonation of the relatively acid N-*H* by organometallics such *n*-butyl lithium, sodium hydride, diethyl zinc or ethylmagnesium bromide. The resulting lithium, sodium, zinc or bromomagnesium salts are subsequently reacted at low temperature with the relevant acid halide. The ability of such reagents to form rigid chelates with metal ions, coupled with the masking of one face of the enolate by the auxiliary moiety, makes these reagents one of the most reliable and versatile tools for the synthesis of homochiral fragments[70].

A high-field ^{1}H NMR spectroscopic study of the prochiral protons in the methylene group of such systems was undertaken with the aim of determining the extent, if any, to which the diastereotopicity imparted by the chiral auxiliary in a specific asymmetric transformation is reflected in the NMR parameters. For the *N*-propionyl derivatives the coupling patterns of the prochiral methylene protons H_a and H_b are almost the same; *viz.* a doublet of quartets for each proton. For the *N*-phenylacetyl derivatives the coupling patterns of H_a and H_b are almost the same; *viz.* a doublet for each proton, but in the some cases only a singlet is observed. In the next section the coupling patterns expected for H_a and H_b of *N*-propionyl and *N*-phenylacetyl derivatives are discussed.

4.1 Analysis of the high-field ^{1}H NMR spectra for prochiral methylene protons of *N*-propionyl derivatives and *N*-phenylacetyl derivatives of chiral auxiliaries

Typically the ^{1}H NMR spectrum of prochiral methylene protons H_a and H_b of *N*-propionyl derivatives and *N*-phenylacetyl derivatives of chiral auxiliaries is expected to show four centres (lines) indicative of an AB spin system. The splitting pattern is shown in Fig.2 with the analyses started by numbering the resonance frequencies of the four lines from left to right as C1, C2, C3 and C4. The coupling constant J_{HaHb} is equal to the frequency interval between lines 1 and 2 or between 3 and 4 or the average between these two values.

C1= Centre 1 [Hz]

C2= Centre 2 [Hz]

J_{HaHb} = C1 - C2 [Hz]

C3= Centre 3 [Hz]

C4= Centre 4 [Hz]

J_{HaHb} = C3 - C4 [Hz]

J_{HaHb} = ((C1 - C2) + (C3 - C4))/2 [Hz]

In an AB spin system the chemical shift difference $\Delta\nu$ is of the same order of magnitude as the coupling constant J_{HaHb}. The chemical shifts are given by the centres of gravity of the line pairs 1 and 2 and of 3 and 4. Although it would be possible from an experimental standpoint to calculate the centres of gravity from the signal intensities, this would be too inaccurate and it is easier to calculate the chemical shift difference from the next equation :

$\Delta\nu = ((C1-C4)(C2-C3))^{-1/2}$ [Hz]

where $\Delta\nu$ is in fact the geometrical mean of the distances between the two outer and the two inner signals.

The centre frequency $\nu_z = (C2+C3) / 2$ [Hz]

For the chemical shift difference $\Delta\nu$ and the centre frequency ν_z, the following expressions hold:

$\nu_a = \nu_z + (\Delta\nu/2)$ [Hz]

$\nu_b = \nu_z - (\Delta\nu/2)$ [Hz]

$\delta_a = \nu_a$ / SF = ppm

$\delta_b = \nu_b$ / SF = ppm

(SF = spectrometer frequency , $\Delta\nu$ = difference in resonance frequencies of spin A and B, ν_z = centre of AB system).

Each centre of the AB system in the *N*-propionyl derivatives is split into a quartet by coupling of the diastereotopic protons H_a and H_b with the vicinal methyl protons. This effect affords the coupling patterns of the prochiral methylene protons H_a and H_b; *viz.* a doublet of quartets for each proton. In the *N*-phenylacetyl derivatives there is no visible effect from coupling of the diastereotopic protons H_a and H_b with the vicinal phenyl protons on the overall coupling patterns of the prochiral methylene protons. In some cases, the chemical shift difference $\Delta\nu$ is zero and only a singlet appears in the spectrum, *i.e.* the resonance frequencies are accidentally equal (isochronous) and the AB spectrum is changed to an A_2 spectrum.

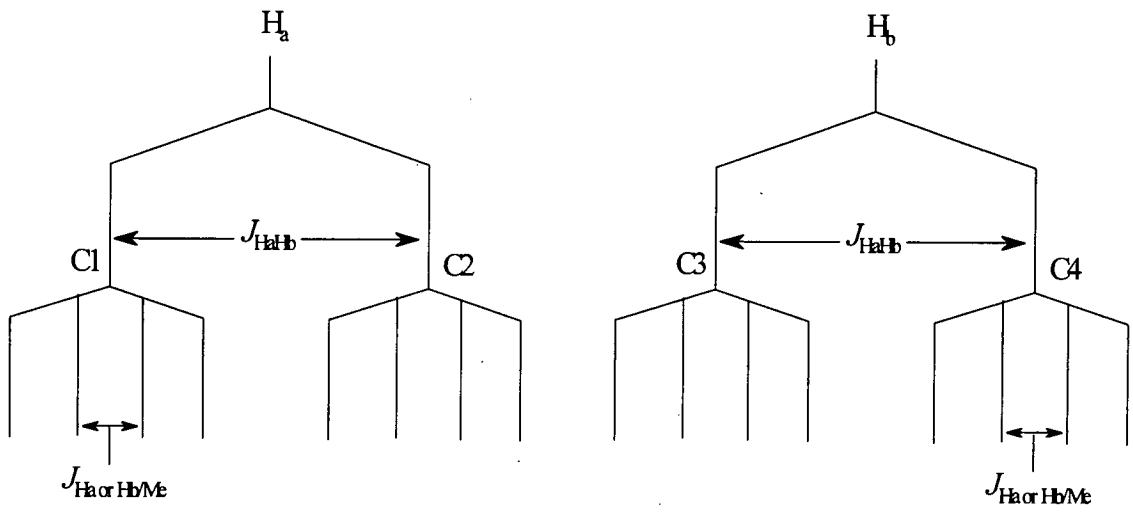
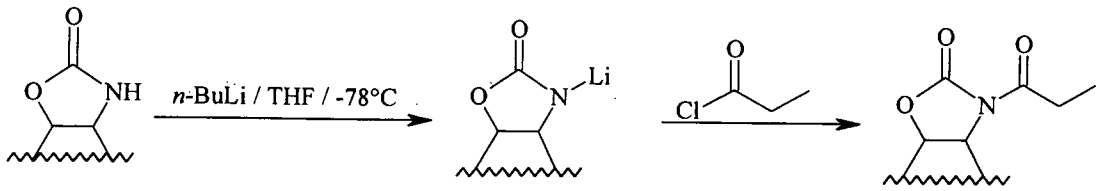


Figure 2. Splitting patterns of prochiral methylene protons H_a and H_b for *N*-propionyl derivatives of chiral moieties

4.2 *N*-Propionyl derivatives of various chiral auxiliaries

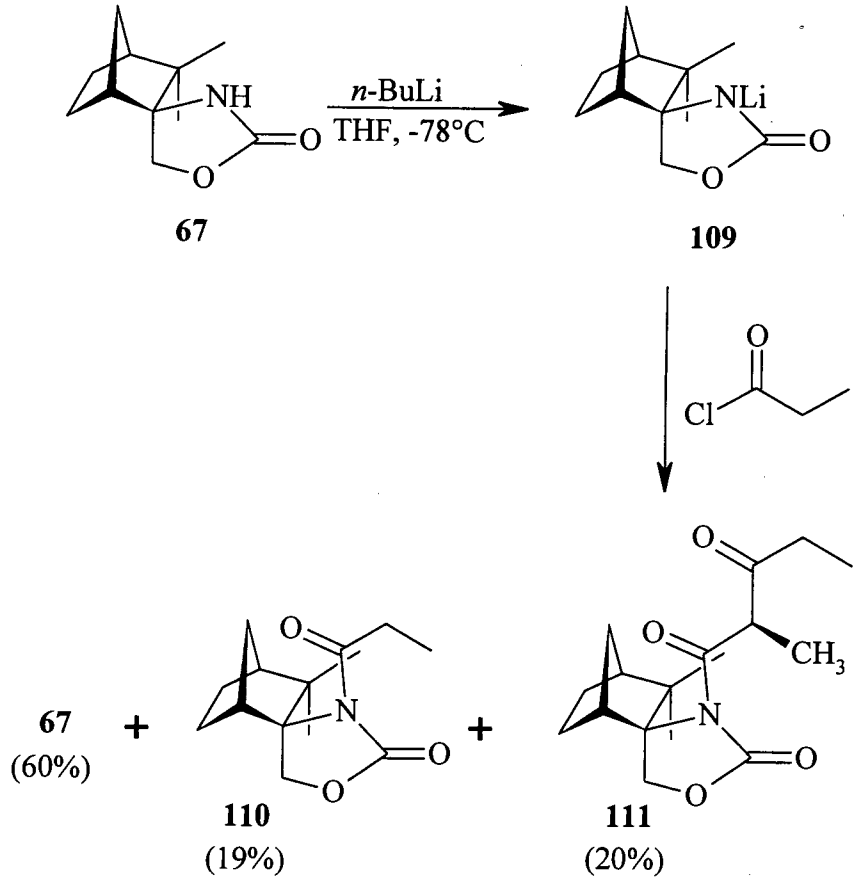
4.2.1 Synthesis of *N*-propionyl derivatives of various chiral auxiliaries

Apart from those that are commercially available such as Evans` or Oppolzer`s reagents, the chiral auxiliaries required for this study were synthesised from naturally-occurring chiral alcohols by the previously mentioned nitrene insertion process[72]. The corresponding *N*-propionyl- derivatives were prepared by different procedures depending upon the nature of the chiral auxiliary. Specifically, *N*-propionyl derivatives of chiral auxiliaries **31**, **43**, **60**, **64**, **97-99**, **101-104**, **106** and **108** (see Table 1) were prepared in excellent yields by the procedure of Evans *et al*[22], which involved treatment of a solution of the auxiliary in anhydrous THF with *n*-butyllithium at -78°C, followed by acylation of the resulting anion with freshly distilled propionyl chloride (Scheme 30).



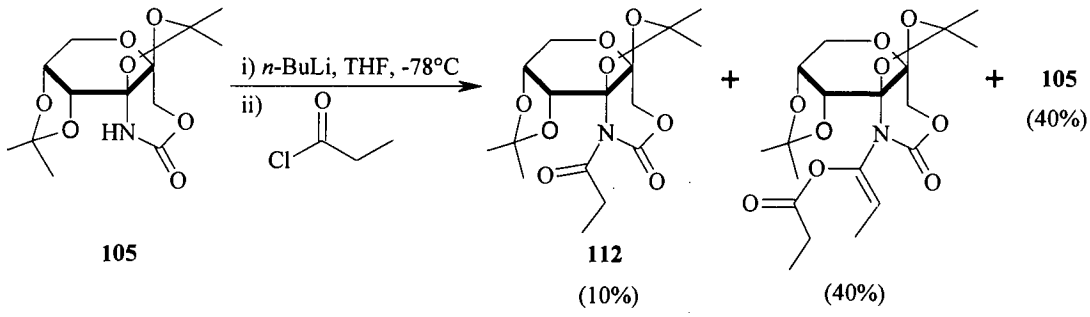
Scheme 30

Attempts to use the same procedure to prepare the *N*-propionyl derivative **110** from Chiracamphox **67** *via* the *N*-lithium salt **109** led to a very low yield (19%) of the desired product, together with the *C*-acylated adduct **111** (20%) and recovered starting material (60%) (Scheme 31).



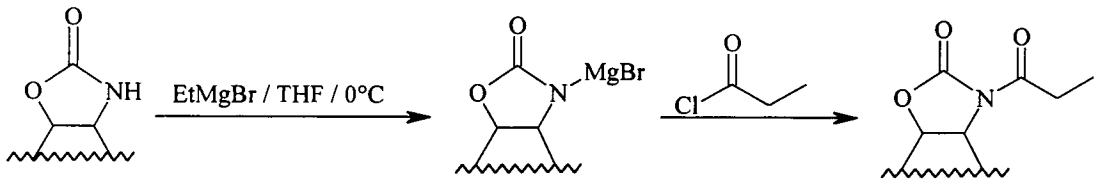
Scheme 31

The formation of such diacylated species had been noted before in this laboratory by McDougal[73], when attempting to functionalise Chirafructox **105** under similar conditions (Scheme 32). The reason for the formation of such products is clear when one compares the steric crowding at the nitrogen in these highly hindered oxazolidin-2-one or oxazinone ring systems with the more open position in oxazolidin-2-ones such as **31** or **60**. In consequence, the *N*-propionyl imide once formed is more likely to react directly with the acid chloride than the hindered system it self.



Scheme 32

In order to overcome the problem, the alternative method used by Evans *et al*[74] was employed for the preparation of the *N*-propionyl derivatives of chiral auxiliaries **67**, **100** and **105**. In essence, the auxiliary was treated with freshly prepared ethylmagnesium bromide at 0°C in anhydrous THF to form an intermediate magnesium species, which was then treated with freshly distilled propionyl chloride (Scheme 33).

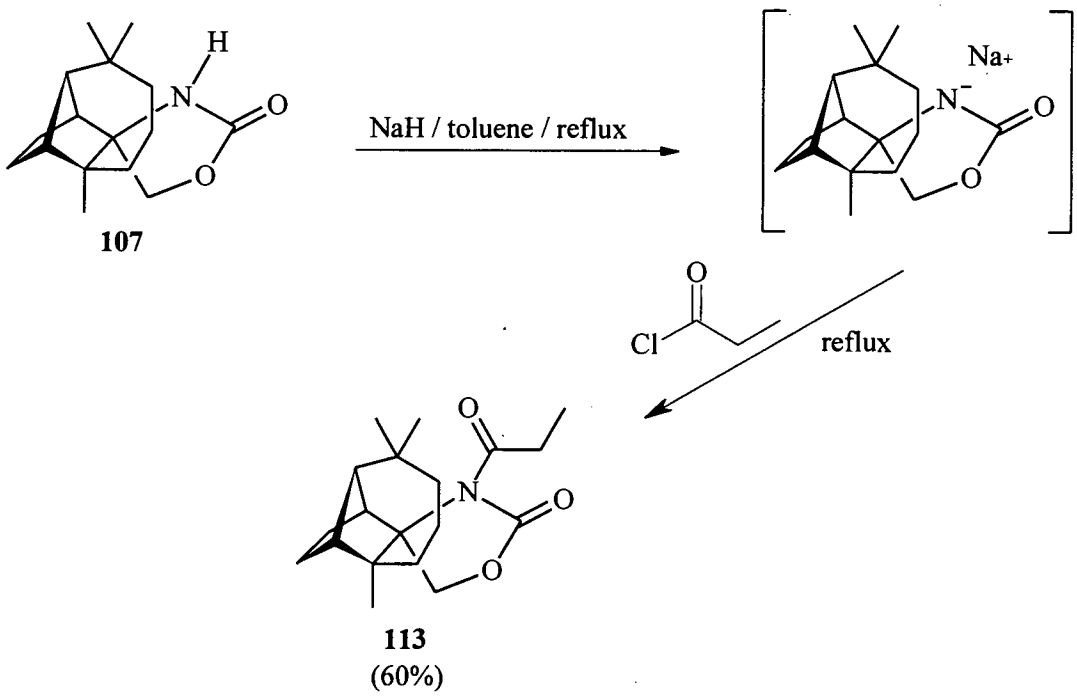


Scheme 33

Thus, use of this procedure with the Chirafructox **105** gave a 92% yield of the desired *N*-propionyl oxazolidin-2-one **112**, whilst the terpenoid-based reagent **100** gave a 99% yield of the required *N*-propionyl derivative. When the same procedure was used with Chiracamphox **67**, the yield of **110** also increased to 78%.

In passing, it is worth noting that this method of functionalisation originally introduced by Evans *et al*[74] was chosen because of the relatively mild nature of the base used. A stronger base such as *n*-butyllithium can be employed but such use leads to more ionic intermediates which are know to induce anionic polymerisation[23,74].

The *N*-propionyl derivative of the spiro-oxazolidinone **107** was prepared in an acceptable yield (60%) by boiling the latter with sodium hydride under reflux in toluene, followed by cooling to room temperature and treatment dropwise with freshly distilled propionyl chloride. After boiling under reflux for a further 24 hours, followed by chromatography, the imide **113** was isolated as a colourless solid (Scheme 34).

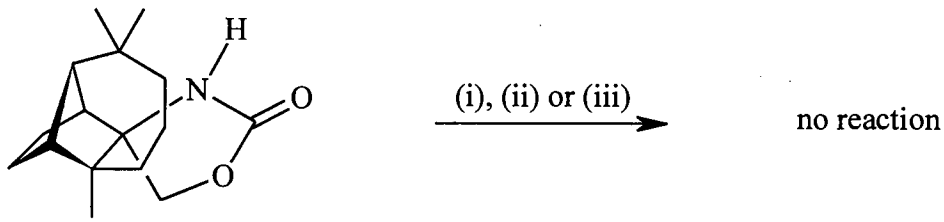


107

113
(60%)

Scheme 34

This method of functionalisation was required after failure of a number of different procedures (Scheme 35). The first set of conditions employed involved (i) the use of *n*-butyllithium as the base, followed by the addition of propionyl chloride. Unfortunately, no reaction occurred and the spiro-oxazolidi-2-one **107** was recovered unchanged. The next method involved (ii) the use of ethylmagnesium bromide as base; this had worked successfully in the preparation of the *N*-propionyl derivatives of chiral auxiliaries **67**, **100** and **105**, but no reaction was found to occur with **107** even after prolonged boiling and the latter was recovered. Finally, the procedure (iii) involving treatment of the auxiliary with diethylzinc in diethylether at room temperature (*vide infra*) and then addition of freshly distilled propionyl chloride at -78°C, followed by boiling under reflux also failed and the starting material was recovered unchanged.



107

Scheme 35. *Reagents and conditions:* (i), *n*-BuLi, THF, -78°C; CH_3CH_2COCl, -78°C; (ii), EtMgBr, THF, 0°C; CH_3CH_2COCl, -78°C; (iii), Et_2Zn, Et_2O, CH_3CH_2COCl, -78°C.

The inability of the spiro-oxazolidin-2-one **107** to be functionalised easily is presumably due to the nitrogen atom of the oxazolidinone ring being too sterically crowded to allow approach of the reagents shown in Scheme 35. An X-ray crystal structure of the spiro-oxazolidin-2-one **107** (Fig. 3) has confirmed[75] that the flexible hydrocarbon chain from the bridging carbon C12 to the carbon atom C10, is the

cause of this steric hinderance, which could be overcome only if a stronger, albeit smaller deprotonation reagent like sodium hydride was employed or if a smaller acid chloride was used.

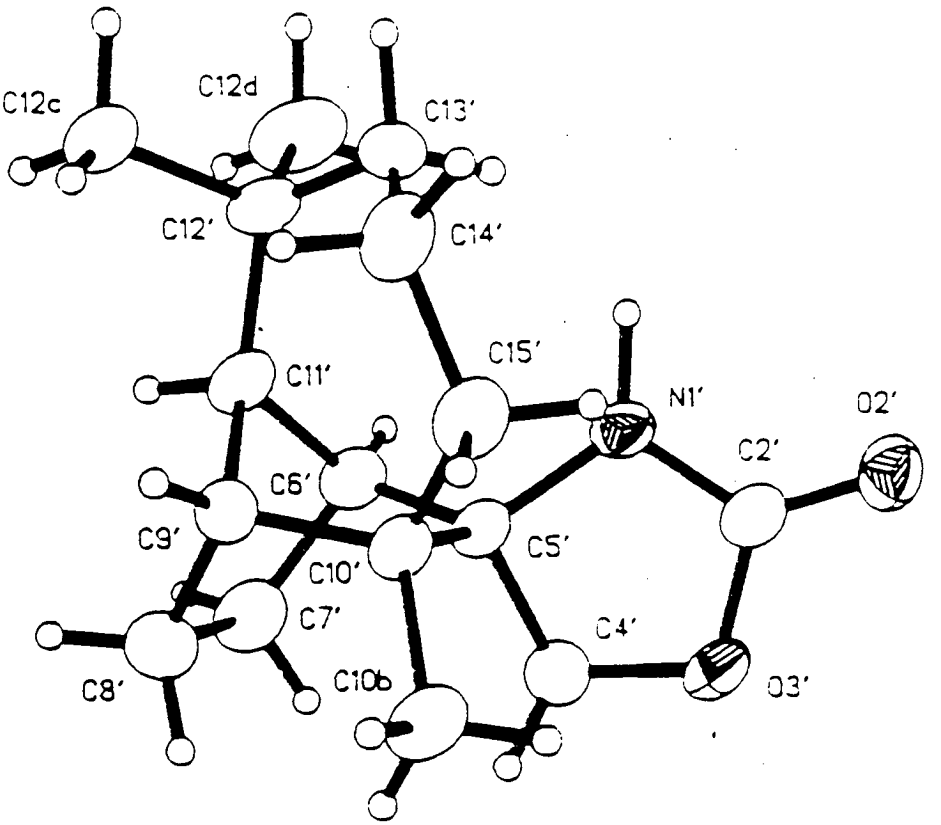
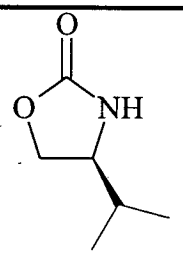


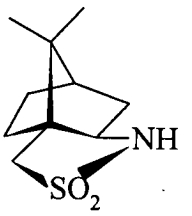
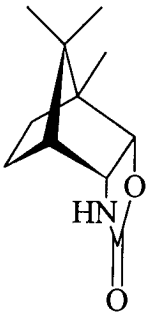
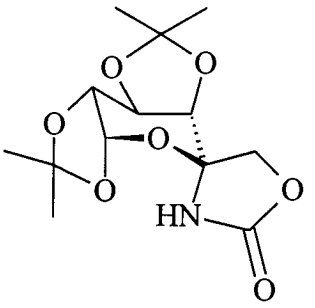
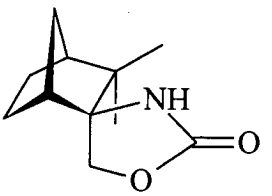
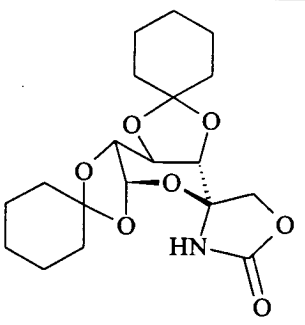
Figure 3. X-ray crystal structure of the spiro-oxazolidin-2-one **107**[75]

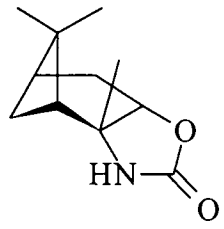
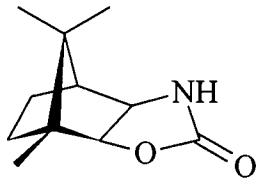
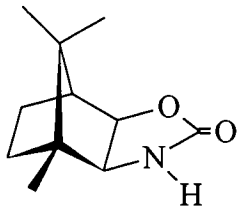
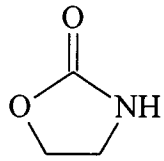
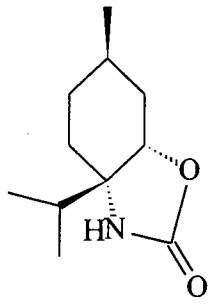
4.2.2 ^{1}H NMR spectroscopic studies of the prochiral protons in the methylene group of *N*-propionyl derivatives of chiral auxiliaries (Aux*H)

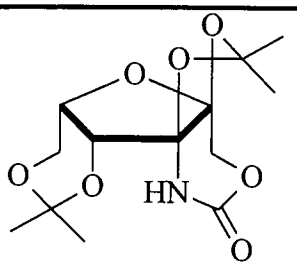
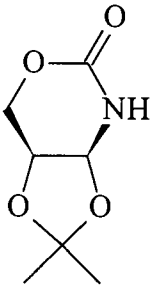
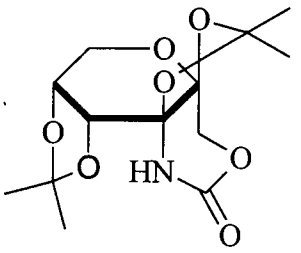
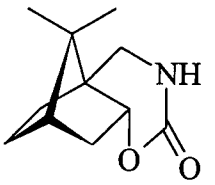
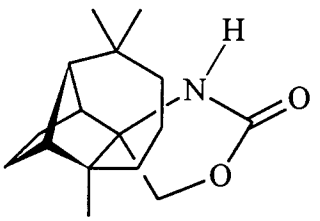
Table 1 depicts the various chiral auxiliaries **31**, **43**, **60**, **64**, **67**, **97-108** studied, together with the splitting patterns for the corresponding *N*-propionyl derivatives, including the chemical shifts of the prochiral methylene protons H_a and H_b , and their coupling constants J_{HaHb} and $J_{Ha\text{-}Hb/Me}$. The coupling patterns of the prochiral methylene protons H_a and H_b in each of these compounds are a doublet of quartets for each proton, except for the *N*-propionyl derivative of Chirasultam **43**, in which there is a doublet of quartets of doublets for each proton indicating the presence of an additional, long-range coupling of unknown origin. In all cases, the chemical shifts of the prochiral protons H_a and H_b absorb in the region 2.63-3.03 ppm and the coupling constants J_{HaHb} fall in the range 16.5 - 18.3 Hz with a further coupling to the methyl protons of between 7.1 and 7.5 Hz.

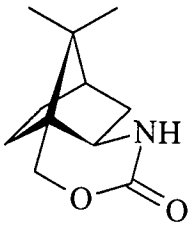
Table 1. Chemical shifts (δ) and couplings constants (*J*) for prochiral methylene protons in *N*-propionyl derivatives of chiral auxiliaries (Aux*H).

Chiral auxiliary Aux*H[a]	Coupling patterns	Chemical shifts (ppm)	Coupling J_{HaHb} (Hz)	Constants $J_{Ha\text{-}Hb/Me}$
 **31**	dq dq	$\delta H_a = 2.93$ $\delta H_b = 2.87$	17.7	7.4

 **43 (128)**	dqd dqd	$\delta H_a = 2.75$ $\delta H_b = 2.71$	17.1	7.3
 **60 (120)**	dq dq	$\delta H_a = 2.97$ $\delta H_b = 2.94$	17.7	7.4
 **64**	dq dq	$\delta H_a = 2.96$ $\delta H_b = 2.88$	18.3	7.4
 **67 (110)**	dq dq	$\delta H_a = 2.99$ $\delta H_b = 2.80$	17.9	7.3
 **97**	dq dq	$\delta H_a = 2.95$ $\delta H_b = 2.88$	18.3	7.3

 **98 (122)**	dq dq	$\delta H_a = 2.93$ $\delta H_b = 2.88$	17.9	7.3
 **99**	dq dq	$\delta H_a = 2.84$ $\delta H_b = 2.82$	10.5[b]	7.4
 **100**	dq dq	$\delta H_a = 2.91$ $\delta H_b = 2.86$	17.5	7.4
 **101**	q	δ of H_a and H_b = 2.91	not measurable[c]	7.4
 **102**	dq dq	$\delta H_a = 2.93$ $\delta H_b = 2.85$	17.7	7.1

 **103 (131)**	dq dq	$\delta H_a = 2.92$ $\delta H_b = 2.73$	16.8	7.4
 **104**	dq dq	$\delta H_a = 3.03$ $\delta H_b = 2.63$	17.7	7.4
 **105 (112)**	dq dq	$\delta H_a = 2.78$ $\delta H_b = 2.74$	16.5	7.4
 **106 (149)**	dq dq	$\delta H_a = 2.99$ $\delta H_b = 2.74$	17.9	7.3
 **107 (113)**	dq dq	$\delta H_a = 2.89$ $\delta H_b = 2.86$	17.4	7.3

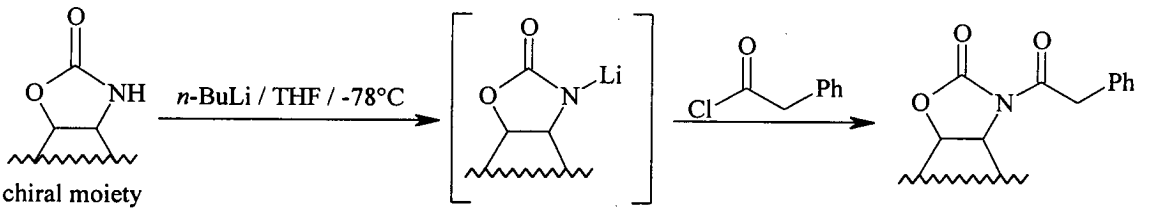
 **108**	dq dq	$\delta H_a = 2.97$ $\delta H_b = 2.78$	18.1	7.5

[a] Figures in brackets refer to *N*-propionyl derivatives, [b] This figure[49] seems very low compared with all the other data, [c] Deuteriation of H_a or H_b is required to calculate J_{HaHb}.

4.3 *N*-Phenylacetyl derivatives of various chiral auxiliaries

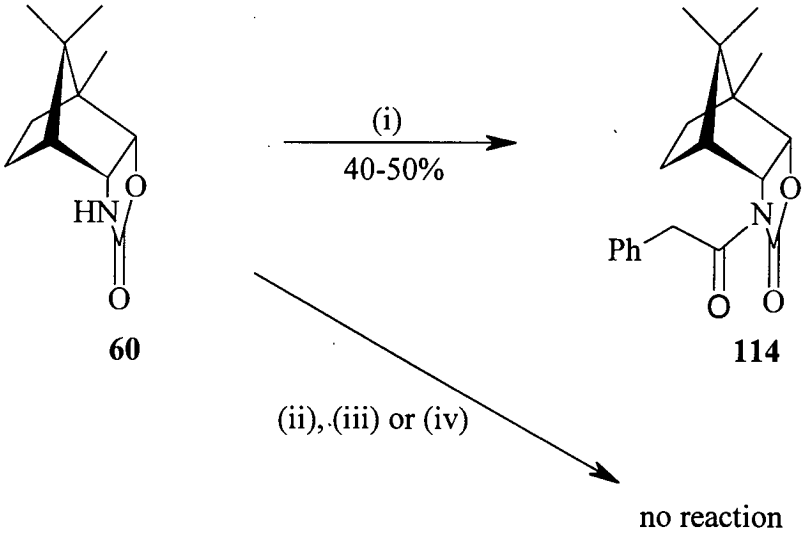
4.3.1 Synthesis of *N*-phenylacetyl derivatives of various chiral auxiliaries

The corresponding *N*-phenylacetyl derivatives of chiral auxiliaries **60**, **64**, **104** and **106** were prepared in excellent yields by treatment of a solution of the auxiliary in tetrahydrofuran with *n*-butyllithium at -78°C, followed by acylation of the resulting anion with freshly distilled phenylacetyl chloride (Scheme 36).



Scheme 36

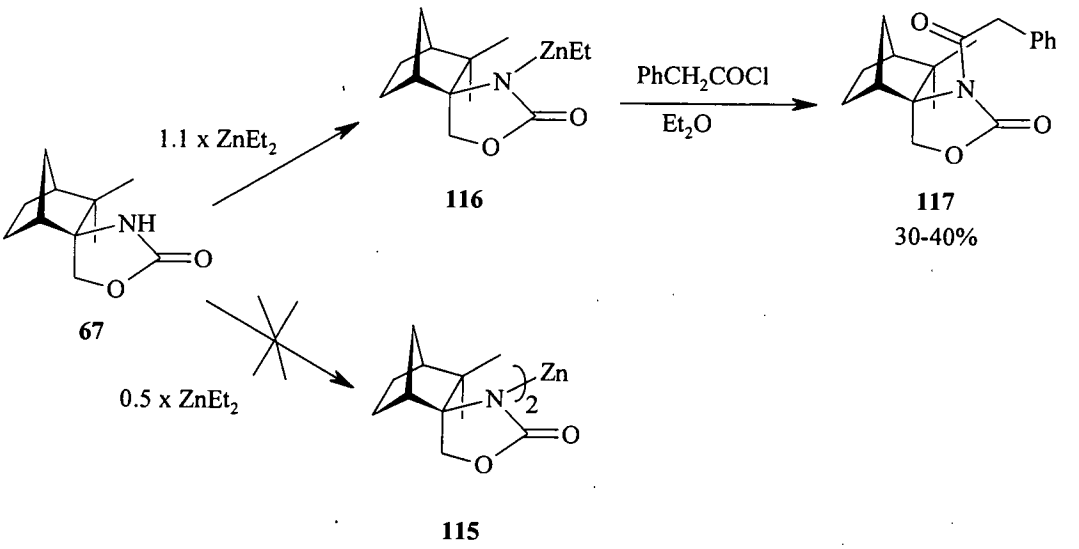
In a variant of this procedure, treatment of **60** in tetrahydrofuran with *n*-butyllithium at -78°C, followed by acylation of the resulting anion with phenylacetic anhydride afforded the desired *N*-phenylacetyl derivative **114** in acceptable yield (50%) (Scheme 37 i). This method of functionalisation was employed after failure occurred with *N*,*N*-dimethylaminopyridine and triethylamine in dichloromethane as base (Scheme 37 ii). Similarly, treatment of the auxiliary with *n*-butyllithium at -78°C, followed by attempted reaction of the resulting anion with freshly distilled phenylacetyl-4-toluenesulfonate (Scheme 37 iii) or phenylacetyl-4-nitrobenzenesulfonate (Scheme 37 iv) as acylating reagent also ended in failure.



Scheme 37. *Reagents and conditions:* (i), *n*-BuLi, THF, -78°C; $(PhCH_2CO)_2O$, -78°C; (ii), DMAP, Et_3N, CH_2Cl_2, 0°C; $(PhCH_2CO)_2O$, 0°C; (iii), *n*-BuLi, THF, -78°C; $PhCH_2COOSO_2C_6H_4CH_3$, -78°C; (iv), *n*-BuLi, THF, -78°C; $PhCH_2COOSO_2C_6H_4NO_2$, -78°C.

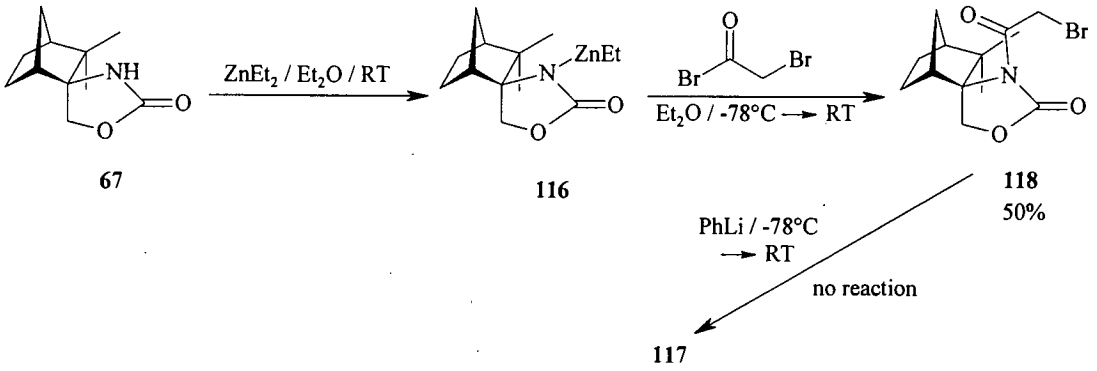
In a different approach, Chiracamphox **67** was treated with diethyl zinc[72] in an attempt to generate the corresponding bis-oxazolidin-2-one zinc salt **115** for subsequent acylation. Thus, a solution of **67** in anhydrous THF was treated with 0.5 equivalents of diethyl zinc at 0°C for one hour before cooling the mixture to -78°C and adding an excess of phenylacetyl chloride. The reaction was warmed to room temperature and after stirring for 72 hours, analysis by TLC showed that no significant reaction had taken place. This outcome indicated that the bis-oxazolidin-2-one zinc salt **115** had not formed and consequently reaction of Chiracamphox **67** was carried out with 1.1 equivalents of diethyl zinc in an attempt to form the *N*-ethylzinc salt **116**. In addition, a large excess of freshly distilled acid chloride was used since it was anticipated that a considerable quantity would be consumed in side reactions. Thus, the reaction mixture was left to stir at room temperature for 72 hours, and after work-up and chromatography, the *N*-phenylacetyl derivative **117** was

isolated in acceptable yield (~30% yield), as a colourless solid (Scheme 38). Presumably, this poor yield is simply a result of the steric bulk of phenylacetyl chloride since the corresponding reaction with propionyl chloride proceeded in 70% yield.



Scheme 38

This method of functionalisation was used after failures were encountered with both *n*-butyllithium and ethylmagnesium bromide as generating base. It is also worth noting that treatment of the auxiliary with butyllithium, coupled with acylation using phosgene, followed by reaction with benzylmagnesium bromide, *i.e. via* Barbier reaction[76], which depends on adding benzyl bromide to the reaction mixture, followed by adding the entire reaction mixture to magnesium turnings also failed. An attempted reaction between the *N*-bromoacetyl derivative **118** and phenyl lithium also failed to produce any trace of the *N*-phenylacetyl derivative **117** (Scheme 39).



Scheme 39

4.3.2 Preparation and 2D ^{1}H NMR studies of (5*S*)-*N*-bromoacetyl-4-aza-2-oxa-6, 6-dimethyl-7,10-methylene-5-spiro[4.5]decan-3-one 118 and (5*S*)-*N* -iodoacetyl-4-aza-2-oxa-6,6-dimethyl-7,10-methylene-5-spiro[4.5]decan-3-one 119

The *N*-bromoacetyl derivative **118** was prepared as mentioned previously in acceptable yield by treatment of Chiracamphox **67** with 1.1 equivalents of diethylzinc, followed by acylation with an excess of freshly distilled bromoacetyl bromide. The reaction mixture was left to stir at room temperature for 24 hours, and after work-up and chromatography, the *N*-bromoacetyl-derivative **118** was isolated in 50% yield as a yellow oil which recrystallised slowly upon standing (Scheme 39). Interestingly, identification of **118** by ^{1}H NMR spectroscopy revealed an unexpected conformational behaviour that warranted further, more detailed spectroscopic analysis.

Fig. 4 shows the two-dimensional (C,H)-correlated 360 MHz NMR spectrum of **118.** The one-dimensional ^{1}H NMR spectrum is shown at the left-hand edge , and the top is the projection of the two-dimensional spectrum onto the F_1 axis , *i.e* the ^{13}C NMR spectrum, both of which show the presence of two, non-isolable rotamers I and II in ratio 2:1.

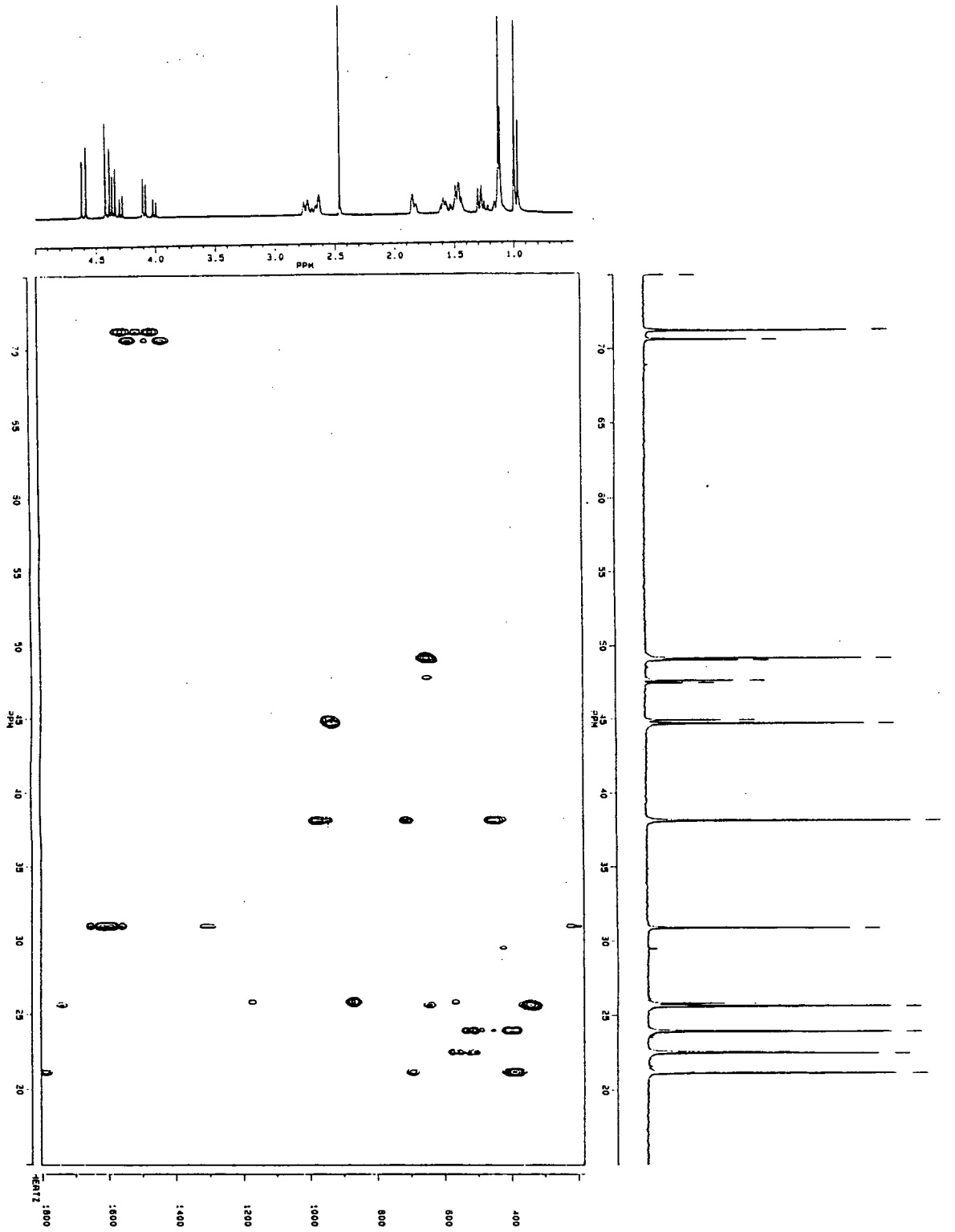
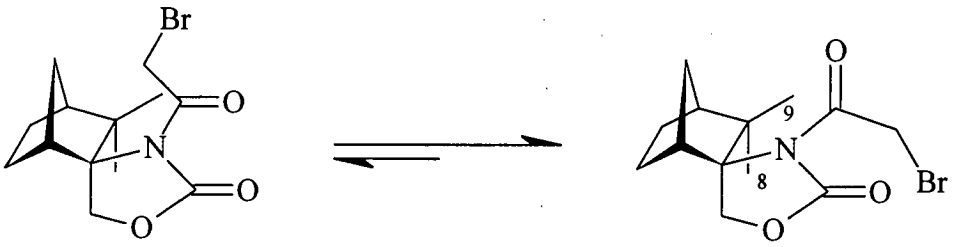


Figure 4 . The reverse two-dimensional (C,H)-correlated 360 MHz NMR spectrum of **118**.

The ^{1}H NMR spectrum at the left-hand edge shows that $\Delta\delta$ for CH_3-8 is likely to be larger than that for CH_3-9 , because it is closer to the slowly rotating moiety (C(O)–N).

The rotation of N–C(O)CH_2Br imide bond is very slow, because the C–N bond has a high proportion of double bond character that leads to rotation being hindered. Hence, we find two forms of signals, whose intensities depend on the proportions of rotamers I and II (*syn* and *anti*) in the equilibrium mixture (Scheme 40). It can be argued that greater steric hindrance to the proximity of the CH_2Br in I to the steric bulk of the camphane unit favours II which is present in the greater proportion (*ca.* 2:1).



(**I**) *syn*-**118** (**II**) *anti*-**118**

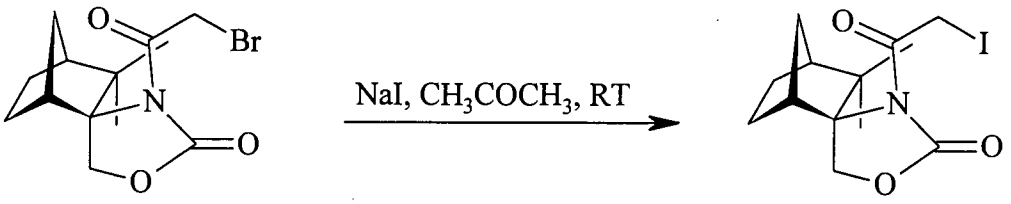
Scheme 40

The corresponding *N*-iodoacetyl derivative **119** was prepared in excellent yield *via* the Finkelstein reaction[77] which is often applied to the preparation of iodides and fluorides. Iodides can be prepared from chlorides or bromides by taking advantage of the fact that sodium iodide is soluble in acetone, whereas the chloride or bromide is insoluble. The reaction is an equilibrium process, and when the alkyl bromide or chloride is treated with a solution of sodium iodide in acetone, the equilibrium is shifted to the right by precipitation of sodium chloride or bromide:

$$RX + Na^+I^- \underset{}{\overset{\text{acetone}}{\rightleftharpoons}} RI + Na^+X^- \downarrow$$

where X = Cl or Br

Thus the *N*-bromoacetyl derivative **118** was treated with an excess of sodium iodide in dry acetone and the reaction mixture was allowed to stir at room temperature for 24 hours. After work-up, the *N*-iodooacetyl-derivative **119** was isolated in 97% yield as a yellow-brown oil which recrystallised on standing to afford a pale yellow solid (Scheme 41).



118 **119** (97 %)

Scheme 41

Fig. 5 shows the two-dimensional (C,H)-correlated 360 MHz NMR spectrum for the iodo-compound **119.** The one-dimensional ^1H NMR spectrum is shown at the left-hand edge , and the top is the projection of the two-dimensional spectrum onto the F_1 axis , *i.e.* the ^{13}C NMR spectrum. Comparison shows that the ^1H- and ^{13}C-NMR spectra of **119** are almost the same as for the bromo-derivative **118** owing to the presence of two rotamers in ratio 2:1.

In the 2D spectrum, all of the peaks of the major isomer are visible, but unfortunately the CH_2I signals for the minor isomer are comparable to the noise levels. Consequently, it is not possible to obtain sufficient resolution in the 2D C-H correlation spectrum to separate the CH_2I signals from the *syn*- and *anti*- isomers.

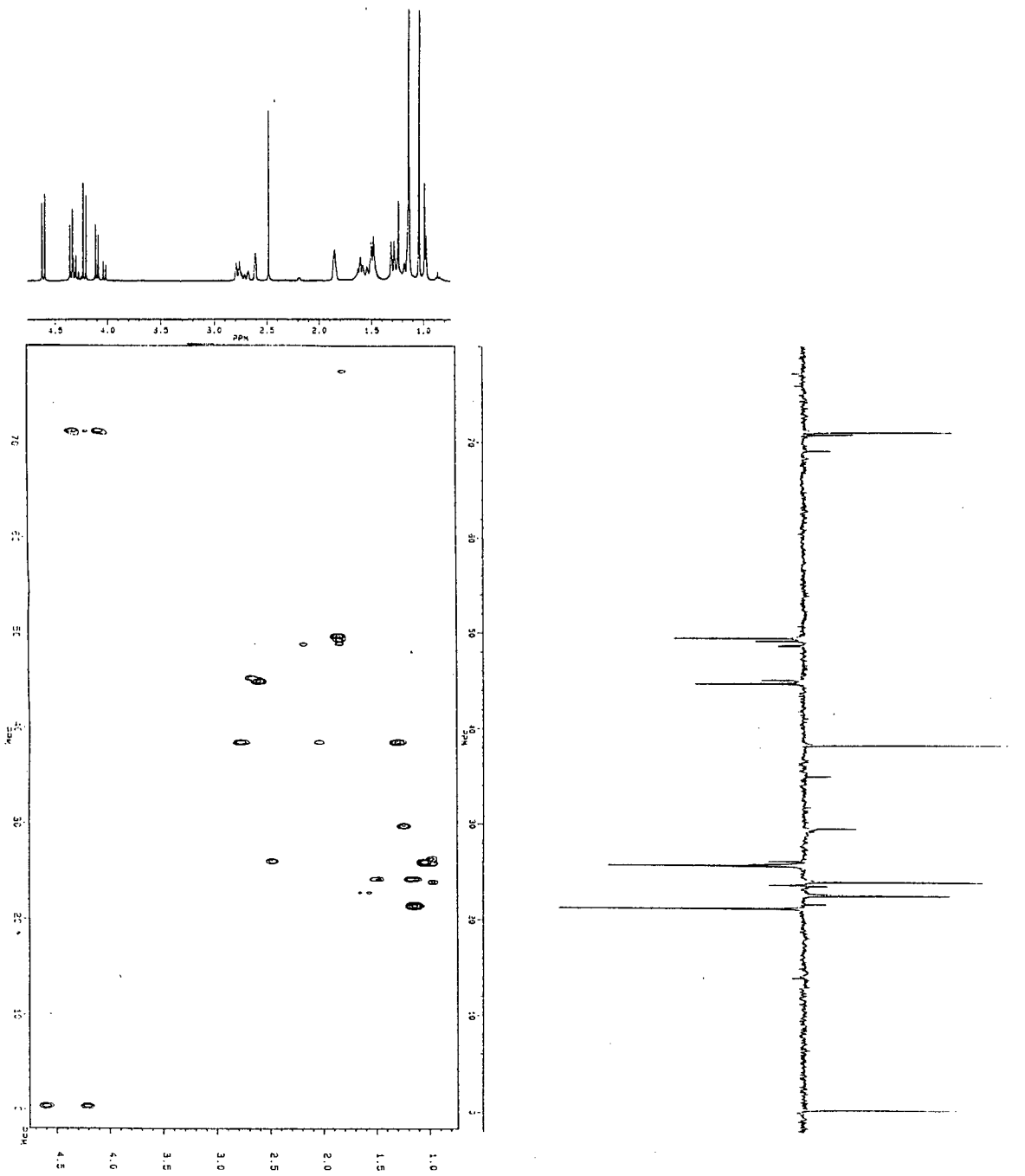
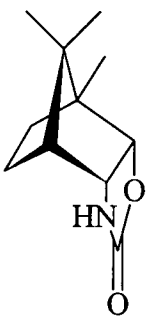


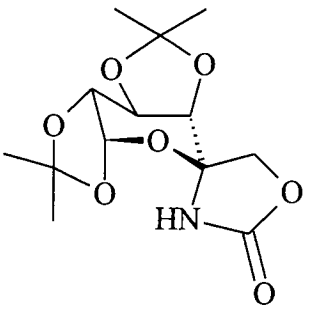
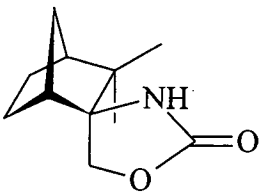
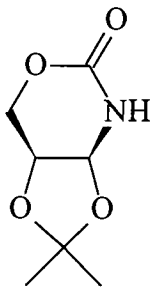
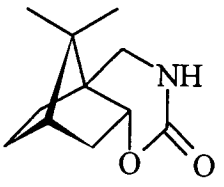
Figure 5 . The reverse two-dimensional (C,H)-correlated 360 MHz NMR spectrum of **119**.

4.3.3 ^{1}H NMR Spectroscopic studies of the prochiral protons in the methylene group in the phenylacetyl derivatives of various chiral auxiliaries

The splitting patterns for the corresponding *N*-phenylacetyl derivatives of chiral auxiliaries **60**, **64**, **67**, **104** and **106** are given in Table 2 together with the chemical shifts of the prochiral methylene protons H_a and H_b and the corresponding coupling constants J_{HaHb}. From an inspection of the data, it can be seen that for the auxiliaries **60**, **67** and **104** the chemical shifts for the simple doublets H_a and H_b range from 4.13 to 4.33 ppm, whilst the coupling constant J_{HaHb} ranges from 15.5 to 16.2 Hz. By contrast, the coupling patterns for the prochiral methylene protons H_a and H_b of the *N*-phenylacetyl derivatives of chiral auxiliaries **64** and **106** are singlets, *i.e* coupling is not observed, and the chemical shifts of H_a and H_b are at 3.81 for **64** and 4.28 ppm for **106**.

Table 2. Chemical shifts (δ) and couplings constants (*J*) for prochiral methylene protons in α-phenylacetyl derivatives of chiral auxiliaries (Aux*H).

Chiral auxiliary Aux*H[a]	Coupling pattern	Chemical shift of H_a and H_b (ppm)	Coupling constants J_{HaHb} (Hz)
 **60 (114)**	d d	$\delta H_a = 4.33$ $\delta H_b = 4.28$ $\Delta\delta$=0.05	15.5

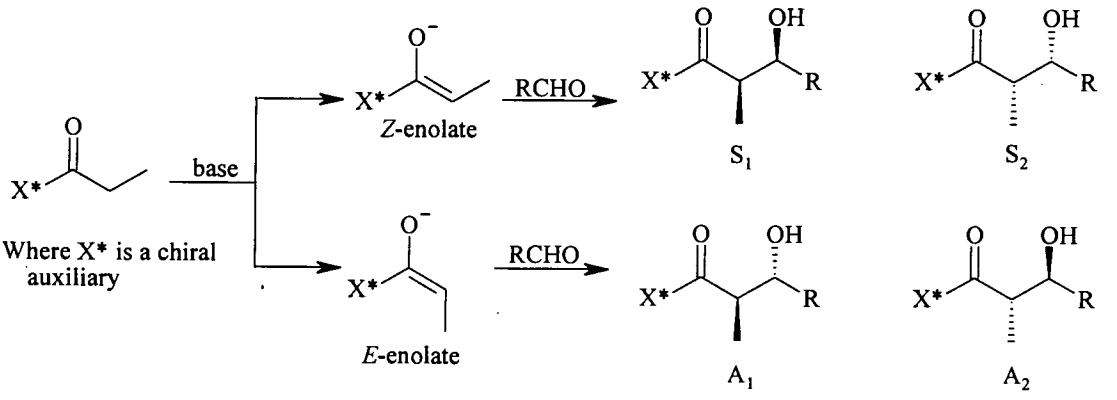
 **64**	s	δH_a and H_b = 3.81	not measurable
 **67 (117)**	d d	δH_a = 4.27 δH_b = 4.23 $\Delta\delta$=0.04	16.2
 **104**	d d	δH_a = 4.24 δH_b = 4.13 $\Delta\delta$=0.11	15.8
 **106**	s	δH_a and H_b = 4.28	not measurable

[a] Figures in brackets refer to *N*-phenylacetyl derivatives.

5 Attempts to correlate the diastereotopicity imparted by chiral auxiliaries in asymmetric aldol reactions and the chemical shift differences of the diastereotopic protons in the attached *N*-propionyl moiety

A ^{1}H NMR spectroscopic study of the prochiral protons H_a and H_b in the methylene group of the *N*-propionyl derivatives of various chiral auxiliaries has been carried out with the aim of determining the extent, if any, to which the diastereotopicity imparted by the chiral auxiliary in a specific asymmetric transformation is reflected in the NMR parameters. The reactions chosen to study here are asymmetric aldol reactions of the prochiral methylene derivatives with benzaldehyde.

The asymmetric aldol reaction is one of the most useful C-C bond construction reactions in organic chemistry, and a number of excellent reviews dealing with this reaction are available [78,79]. In asymmetric aldol reactions there is the possibility obtaining four different products (Scheme 42), *viz.* two *syn* isomers S_1 and S_2 and two *anti* isomers A_1 and A_2. The product range obtained depends on the induction provided by the attached auxiliary (X*) and on the type of enolate that is generated, *viz. Z*- or *E*-enolate which condense with an aldehyde (RCHO) to afford *syn*- or *anti*-products, respectively.



Scheme 42

The stereochemical outcome for the asymmetric aldol reaction of the prochiral methylene derivatives with benzaldehyde is measured in terms of diastereomeric

excess (*d.e.* %) which is determined by analysis of the crude product by high-field ^{1}H NMR spectroscopy, paying particular attention to the resonances arising from the carbinol protons.

Table 3 depicts the relationship between the diastereomeric excess (*d.e.* %) found for the aldol reactions with benzaldehyde and the difference in chemical shift ($\Delta\delta$) of the prochiral methylene protons H_a and H_b in the *N*-propionyl derivatives of various chiral auxiliaries **31**, **43**, **60**, **64**, **67**, **97-100**, **103**, **105**, **106** and **108**.

From an inspection of the data, it can be seen that the difference in chemical shift ($\Delta\delta$) of the prochiral methylene protons H_a and H_b is small in the *N*-propionyl derivatives of chiral auxiliaries **31**, **43**, **60**, **64**, **97-100**, **102** and **105**, and larger for the *N*- propionyl compounds **67**, **103**, **104**, **106** and **108**.

From the spectra obtained, it was found that the most informative region was the chemical shift range 4.80-5.10 ppm which contained the doublet of resonances arising from the carbinol proton (PhC*H*-OH) for each diastereomer. For example, integration of these signals for the sugar-based spiro-oxazolidin-2-one **64** established that for the lithium-enolate two *syn*-isomers and a single *anti*-isomer had been formed in the ratio of 6:89:5 respectively, giving rise to a diastereomeric excess of 78%. These assignments are made by measuring the vicinal coupling constants of the carbinol protons, and using the known fact [54] that for this proton, $^3J_{syn}$ is typically 3-6 Hz and $^3J_{anti}$ is typically 7-9 Hz; the values found in the foregoing reaction were $^3J_{syn}$ = 5.2 Hz and $^3J_{anti}$ =8.6 Hz. By comparison, reaction of the corresponding lithium enolate bearing the *endo*-borneol-derived oxazolidin-2-one **60** gave all four possible diastereomeric products in the ratio 55:29:10:6, giving rise to a diastereomeric excess of only 10%; these were identified as *syn* and *anti* by their respective vicinal coupling constants of 4.2 and 8.0 Hz. The corresponding *exo*-analogue **99** gave an equally low level of diastereoselection (2:52:40:0)[49], and interestingly, transposition of the dormant methyl group from C-1 in **99** to C-7 in **100** failed to induce sufficient topological bias to raise the diastereoselection but led to formation of mostly *anti*-aldol product ($^3J_{anti}$ =7.4 Hz). A low level of asymmetric induction is also imparted by Oppolzer's camphor sultam **43** (*d.e.* 52%) and the spiro-oxazolidin-2-one **67** obtained from (-)-camphene. In this case also, the poor diastereoselection is coupled

with use of a lithium enolate and with the formation of mostly *anti*-aldol product. The ^{1}H NMR spectrum showed the presence of one *anti*- and one *syn*-product (J = 8.2 *vs.* 2.9 Hz) together with traces of the other two diastereomers in the ratio of 32:5:58:5.

The poor levels of stereoregulation found for these lithium enolate-mediated reactions matches those obtained with chiral oxazolidin-2-ones which are prepared from optically pure β-amino alcohols. Thus, in our hands, the (*S*)-valinol-derived oxazolidin-2-one **31** produced three of the four possible diastereomeric aldol products in the ratio 24:10:66, *i.e.* a diastereomeric excess of only 32% which can, of course, be raised to >99% upon changing to the corresponding boron-chelated enolate. Indeed, the boron enolate-mediated aldol reactions with benzaldehyde yielded the highest values of diastereomeric excess (*d.e.* %) of all the reagents, while the corresponding titanium enolate resulted in the lowest, apart from that employing **108**[80] which afforded "chelation-controlled" *syn*-product with excellent stereoselection (*d.e.* 99%).

The exclusive use of a lithium enolate resulted in good values of diastereomeric excess only with the carbohydrate-based auxiliaries **64**, **97**, **103**, and **105**. Indeed, as noted earlier the spiro-oxazolidin-2-one **64** gave a diastereomeric excess of 78%; this increased to over 95% (with 68% recovery) after a single recrystallisation of the crude aldol product. Disappointingly, attempts to raise the stereoselectivity by incorporation of cyclohexylidene protective groups failed. It was envisaged that the greater steric bulk of such groups in auxiliary **97** would lead to more efficient π-face shielding of the enolate system, but reaction with benzaldehyde produced three diastereomers, *viz.* two *syn* (^3J = 5.2 Hz) and one *anti* (^3J = 8.6 Hz), in the ratio of 2:90:7, giving rise to a diastereomeric excess of 81%. It is still unclear whether this performance, *i.e.* without recourse to the use of hazardous and expensive di-*n*-butylboron triflate as the mediating agent, is due to metal chelation to ketal and/or pyranose oxygens or some other significant stereoelectronic factor. Nonetheless, this quality of diastereocontrol is further highlighted by the carbohydrate-based oxazin-2-ones **103** (*d.e.* 82%)[81] and **105** (*d.e.* 78%), especially when compared to the terpenoid-derived reagents **106** and **108**, which proved ineffective for the same aldol

reaction under analogous conditions. On the other hand, both of these structurally isomeric oxazin-2-ones imparted considerable diastereoselectivity (*d.e.* >99%) in boron-mediated aldol reactions to give almost only *syn*-products (S_1 *vs.* S_2), although **108** was not so effective and needed added `chelation-control` by use of a titanium (IV) enolate to bring about complete diastereoselection[80].

The higher level of asymmetric induction that results with boron enolates derived from terpenoid-based reagents can be explained in terms of a shorter boron-oxygen bond (B-O = 1.36-1.47 A°) compared with the lithium-oxygen bond length (Li-O = 1.92-2.00 A°)[79]. This change leads to a much tighter six-membered Zimmerman-Traxler transition state in which the steric interactions, especially between the phenyl group of the aldehyde and the auxiliary, are amplified by the bulky butyl groups on the tetra-cordinate boron atom; in consequence the phenyl group is forced reside in an equatorial position in the chair form as shown in Fig. 6.

It is worth noting that use of the boron-enolate methodology with the terpenoid-based auxiliary **98** was surprisingly poor and afforded both *syn*-products in poor yields. Examination of the 360 MHz ^{1}H NMR spectrum of the aldol product with benzaldehyde showed that both diastereomers (^3J = 3.9 and 4.5 Hz) had been formed in the ratio of 53:47.

On the point of steric shielding, attempts to functionalise the imide nitrogen in the spiro-oxazolidin-2-one **107** proved difficult and preparation of the *N*-propionyl derivative succeeded only under forcing conditions (*vide supra*), albeit in 58% yield with recovery of unreacted starting material. Even so, attempts to carry out an aldol reaction with benzaldehyde failed.

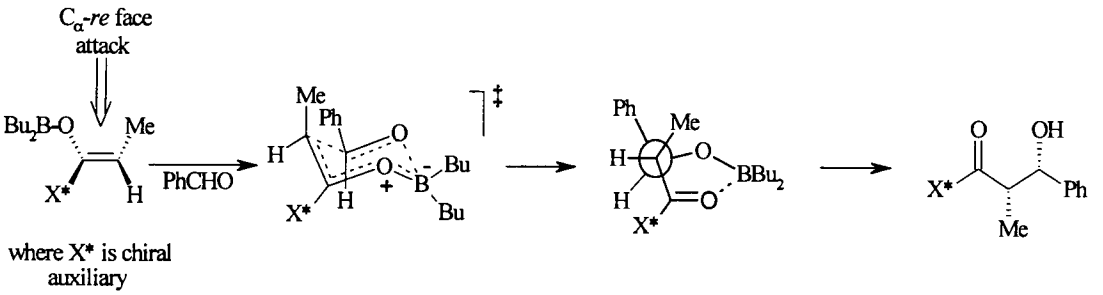
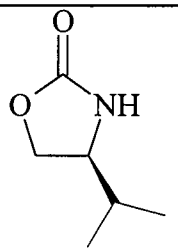
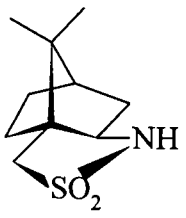
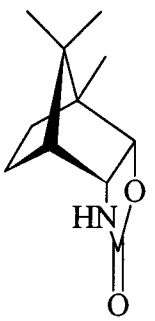
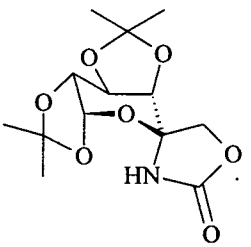
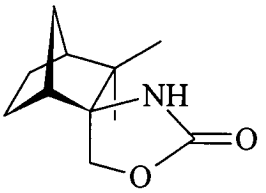
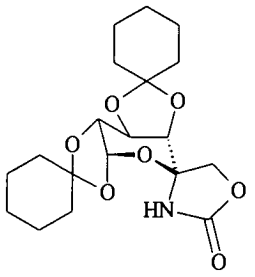
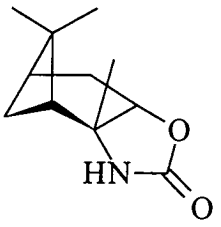
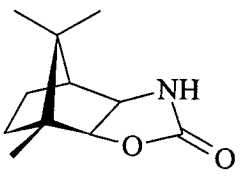
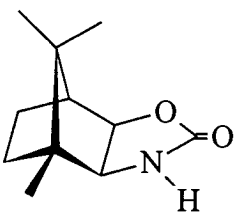
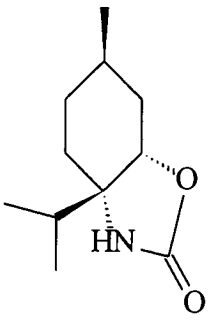
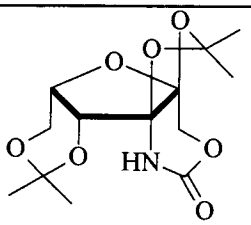
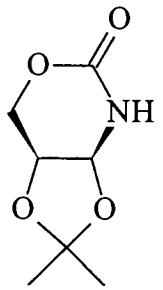
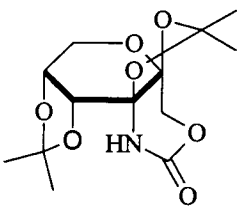
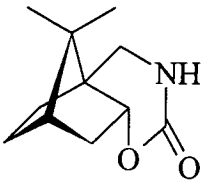


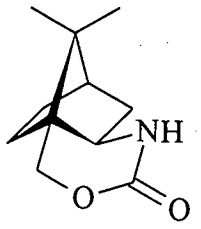
Figure 6. Zimmerman-Traxler transition state for *syn*-aldol reaction *via* boron-chelated *Z*-enolate

Table 3. Diastereomeric excess (*d.e.* %) of aldol reaction with benzaldehyde, and Δδ of H_a and H_b in *N*-propionyl derivative for various chiral auxiliaries[a].

Auxiliary Aux*H	Diastereomeric excess (*d.e.* %) of aldol reaction with PhCHO (S_1:S_2:A_1:A_2)	Δδ of H_a and H_b in *N*-propionyl derivative (ppm)
 **31**	32% (24:10:66:0) LDA / THF / -78°C ------ >99% (<1:>99:0:0) Bu_2BOTf / $^iPr_2NEt$ CH_2Cl_2 / -78°C	δH_a =2.93 δH_b =2.87 Δδ =0.06
 **43**	52% (10:75.7:9.1:5.2) LDA / THF / -78°C ------ 98% (99:1:0:0) Bu_2BOTf / $^iPr_2NEt$ CH_2Cl_2 / -78°C	δH_a =2.75 δH_b =2.71 Δδ =0.04
 **60**	11% (55.4:28.7:10.3:5.7) LDA / THF / -78°C ------ >99% (>99:<1:0:0) Bu_2BOTf / $^iPr_2NEt$ CH_2Cl_2 / -78°C ------ 9% (0:45.5:0:54.5) $TiCl_4$ / Et_3N CH_2Cl_2 / -78°C	δH_a =2.97 δH_b =2.94 Δδ =0.03
 **64**	78% (6:89:5:0) LDA / THF / -78°C	δH_a =2.96 δH_b =2.88 Δδ =0.08

 **67**	16% (32:5:58:5) LDA / THF / -78°C ------ >95% (0:98:2:0) Bu_2BOTf / $^iPr_2NEt$ CH_2Cl_2 / -78°C	δH_a =2.99 δH_b =2.80 $\Delta\delta$ =0.19
 **97**	81% (2:90:7:0) LDA / THF / -78°C	δH_a =2.95 δH_b =2.88 $\Delta\delta$ =0.07
 **98**	6% (53:47:0:0) LDA / THF / -78°C ------ 22% (61:39:0:0) Bu_2BOTf / $^iPr_2NEt$ CH_2Cl_2 / -78°C→RT ------ 2% (51:49:0:0) $TiCl_4$ / $^iPr_2NH$ CH_2Cl_2 / -78°C	δH_a =2.93 δH_b =2.88 $\Delta\delta$ =0.05
 **99**	16% (2:52:40:0) LDA / THF / -78°C ------ 58% (2:79:19:0) LDA / $ClTi(O^iPr)_3$ / Ether / -78°C	δH_a =2.84 δH_b =2.82 $\Delta\delta$ =0.02
 **100**	35% (25:7.5:67.5:0) LDA / THF / -78°C ------ 99% (99.5:0.5:0:0) Bu_2BOTf / $^iPr_2NEt$ CH_2Cl_2 / -78°C	δH_a =2.91 δH_b =2.86 $\Delta\delta$ =0.05

 **102**		δH_a =2.93 δH_b =2.85 $\Delta\delta$ =0.08
 **103**	82% (9:91:0:0) LDA / THF / -78°C	δH_a =2.92 δH_b =2.73 $\Delta\delta$ =0.19
 **104**		δH_a =3.03 δH_b =2.63 $\Delta\delta$ =0.40
 **105**	78% (89:11:0:0) LDA / THF / -78°C	δH_a =2.78 δH_b =2.74 $\Delta\delta$ =0.04
 **106**	<0% (29:0:38:33) LDA / THF / -78°C --- 100% (100:0:0:0) Bu_2BOTf / $^iPr_2NEt$ CH_2Cl_2 / -78°C	δH_a =2.99 δH_b =2.74 $\Delta\delta$ =0.25

 **108**	4% (4:44:0:52) LDA / THF / -78°C ------ 98% (0:99:1:0) LDA / $ClTi(O^iPr)_3$ / Ether / -78°C	δH_a =2.97 δH_b =2.78 $\Delta\delta$ =0.19

[a] The applications of compound **102** were not pursued, because attempts at functionalising these compounds resulted in the formation of thick gums which proved extremely difficult to purify, and applications of **104** have not been investigated in any great detail.

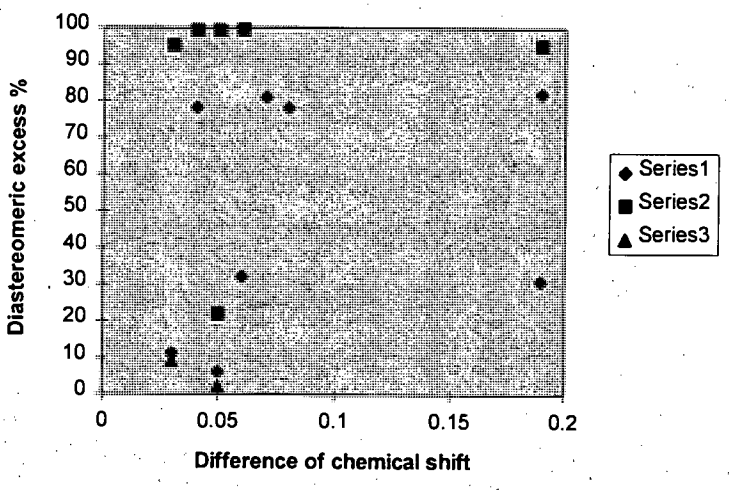


Figure 7. Relationship between diastereomeric excess (*d.e.* %) of aldol reaction with PhCHO and $\Delta\delta$ of H_a and H_b in *N*-propionyl derivatives under 3 different series (Series 1 : LDA, Series 2 : Bu_2BOTf, and Series 3 : $TiCl_4$.

Conclusions

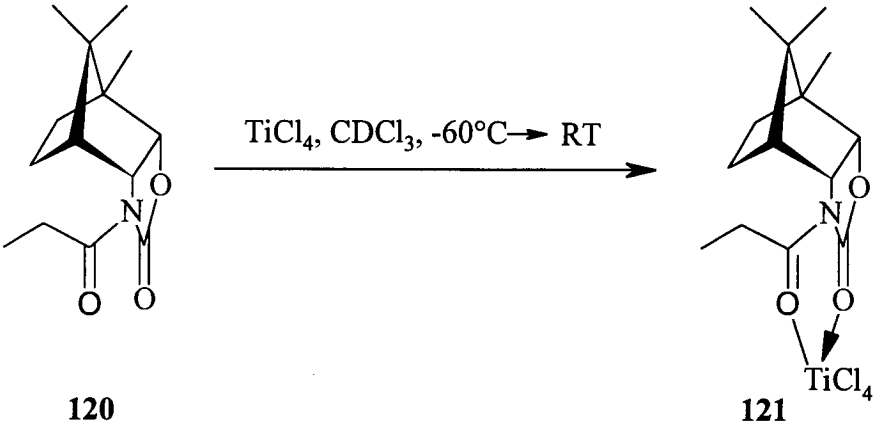
A detailed analysis reveals clearly that there is no correlation between the observed chemical shift non-equivalence ($\Delta\delta$) of the diastereotopic methylene protons H_a and H_b and the differential diastereotopic steric shielding provided by the attached chiral oxazolidin-2-one and 1,3-oxazin-2-one ring systems as measured in terms of the diastereomeric excess (*d.e.* %) achieved in aldol reactions with PhCHO. From Fig. 7, it is evident that for lithium-enolate promoted reactions there is random scatter with poor levels of diastereoselectivity except for the carbohydrate-based auxiliaries **64**, **97**, **103**, and **105**, which provide good values of diastereomeric excess. For example, chirafructox **105** and the chiral auxiliary **103** from di-*O*-isopropylidene-2-keto-L-gulonic acid achieve almost the same levels of diastereoselection (*d.e.* 78% *vs.* 82%, respectively), but notably they have markedly different $\Delta\delta$, *viz.* 0.04 ppm for **105** and 0.19 ppm for **103**. Our observations also show that boron-enolate mediated aldol reactions occur with high chiral efficiency for only the terpenoid-based reagents with the exception of **98**, which suffers from steric hindrance at both faces; the corresponding reactions for carbohydrate-derived auxiliaries failed to proceed for reasons that are not clear. For example, $\Delta\delta$ for Oppolzer's chiral sultam **43** is only 0.04 ppm, and this auxiliary achieves levels of diastereoselection of 99% in aldol reaction. By comparison, chiracamphox **67** gives the same levels of diastereoselection, but $\Delta\delta$ in this case is 0.19 ppm. $\Delta\delta$ for chirabornox **60** is only 0.03 ppm, and this auxiliary achieves levels of diastereoselection of >99% with use of a boron enolate. By comparison, the *exo*-isomer **100** achieves almost the same levels of diastereoselection (99%) with use of a boron enolate, but $\Delta\delta$ in this case is 0.05 ppm.

6 NOE Studies of titanium and tin complexes of *N*-propionyl derivatives of various chiral auxiliaries

As part of the foregoing investigations into enolate chemistry, nuclear Overhauser effect (nOe) studies of titanium and tin complexes of *N*-propionyl derivatives of various auxiliaries were carried out in an attempt to distinguish between the prochiral methylene protons H_a and H_b. Whilst there is observed chemical shift non-equivalence ($\Delta\delta$) of these protons in the freely rotating system, it was thought that an increase might also be observed in the complex, if formed.

6.1 Titanium complex of [(2*S*,6*R*)-*endo*]-*N*-propionyl-5-aza-1,10,10-trimethyl-3-oxatricyclo[5.2.1.$0^{2,6}$]decan-4-one 120

It is worth noting that attempts to distinguish between the prochiral methylene protons H_a and H_b in the *N*-propionyl derivatives of different auxiliaries failed apart from **60**. For this purpose, the titanium complex **121** was prepared by treatment of the *N*-propionyl derivative **120** with titanium tetrachloride in deuteriated chloroform (Scheme 43).

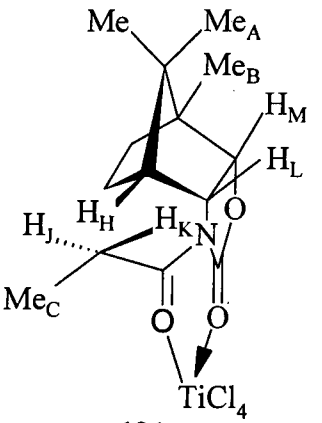


120 **121**

Scheme 43

Compared to the freely rotating system, both H_a and H_b in the complex had distinct chemical shifts and appeared as a doublet of quartets, which are well separated from

each other. In addition, the signals were shifted to higher frequency relative to the free propionate, indicative of electron donation to the titanium as illustrated. An increase in the chemical shift non-equivalence ($\Delta\delta$) of H_a and H_b was also observed from 0.03 ppm in the freely rotating system to 0.31 ppm in the complex. ^{1}H NMR nOe difference spectra of the complex are accumulated in Table 4 and illustrated in Fig. 8 and in particular show that irradiation of the bridgehead proton H_H caused a 2.5% enhancement of the signal due to H_J (H_a), but negligible enhancement of the H_K (H_b) signal, thus confirming the "locked" conformation of the complex. Discrimination between H_a and H_b was achieved by irradiation of H_L which brought about 3% enhancement of the signal for H_K (H_b).



121

Table 4. ^{1}H NMR steady state nOe data for titanium complex **121**.

Irradiation site	Signal enhancement (%)				
	H_H	H_J	H_K	H_L	H_M
H_A	4	-	-	4	5
H_B	-	-	-	2	4
H_H	-	2.5	-	3	-
H_L	3	-	3	-	-
H_M	-	-	-	-	-
H_K	-	10	-	3	-
H_J	2	-	10	-	-

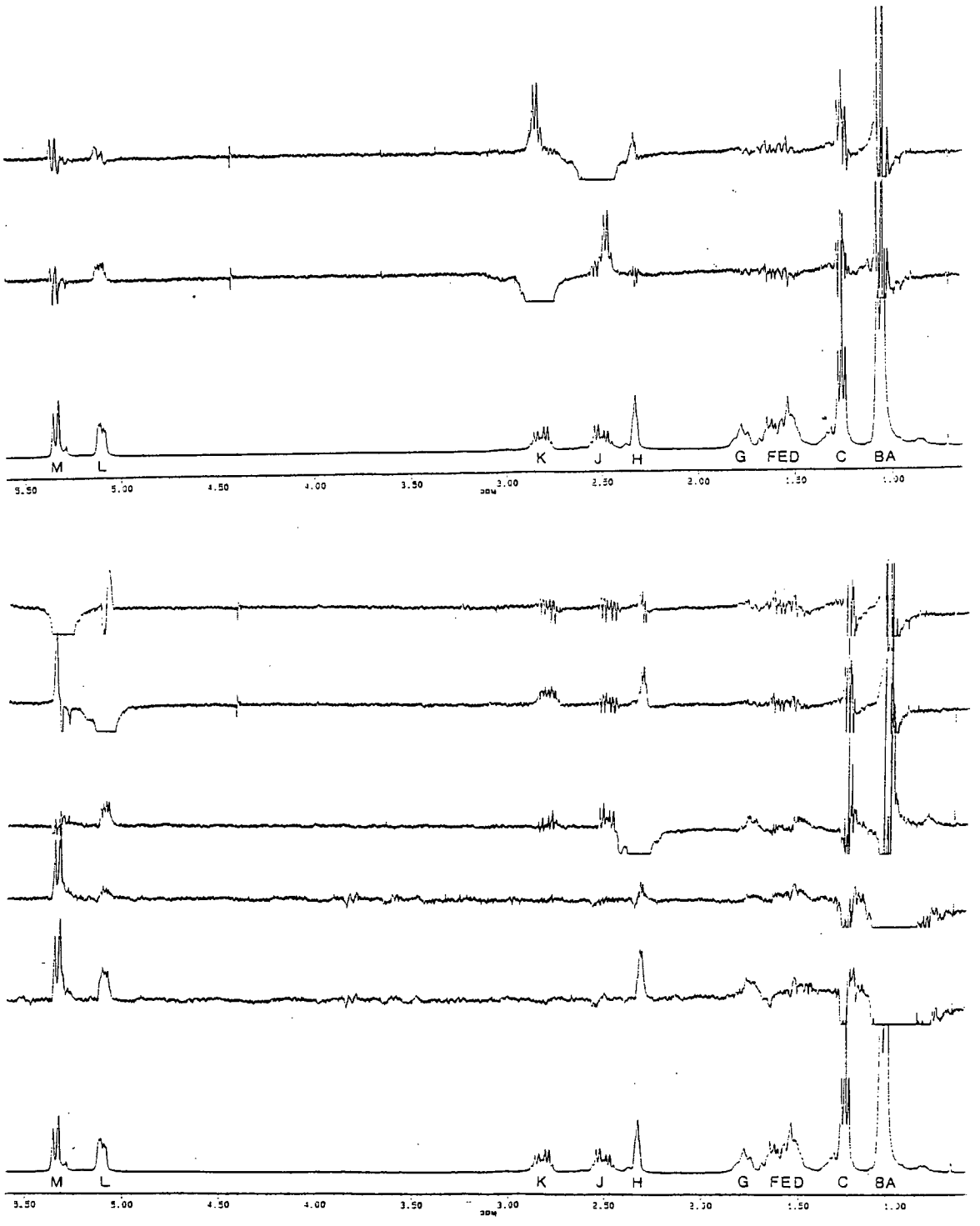
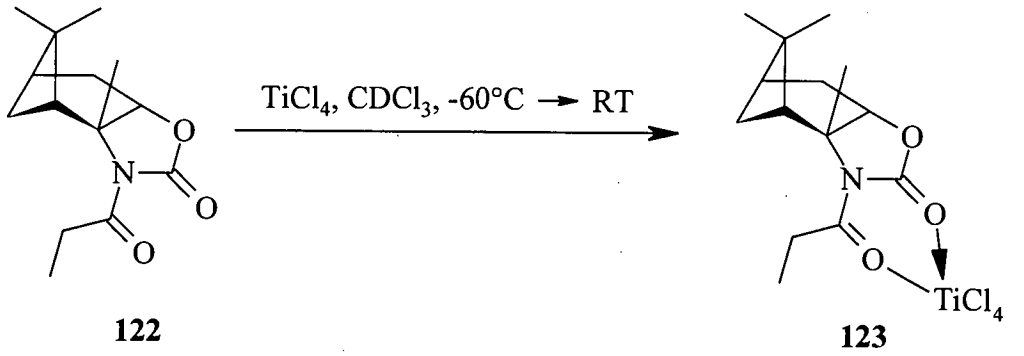


Figure 8. ^{1}H NMR 360 MHz nOe difference spectra for titanium complex **121**.

6.2 Titanium complex of (2*R*,6*S*)-*N*-propionyl-3-aza-2,9,9-trimethyl-5-oxatricyclo[6.1.1.$0^{2,6}$]decan-4-one 122

The titanium complex **123** was easily prepared by the same method used for complex **121**. After treatment of the *N*-propionyl derivative **122** with titanium tetrachloride in deuteriated chloroform (Scheme 44) at -60°C, the solution was allowed to warm to room temperature and the spectra recorded.



122 **123**

Scheme 44

From the ^{13}C- and ^{1}H-NMR spectra of complex **123**, it is evident that the signals of the complex are shifted to higher frequency relative to the spectrum of the free propionate **122** pointing to electron donation to the titanium as found with **121**, and increase in $\Delta\delta$ from 0.05 in the free *N*-propionate **122** to 0.13 ppm in the complex **123**. The complex also proved to be sufficiently stable to allow recording of the ^{1}H NMR 360 MHz nOe difference spectra (Fig. 9), which showed the following points used to assign its proton spectrum :

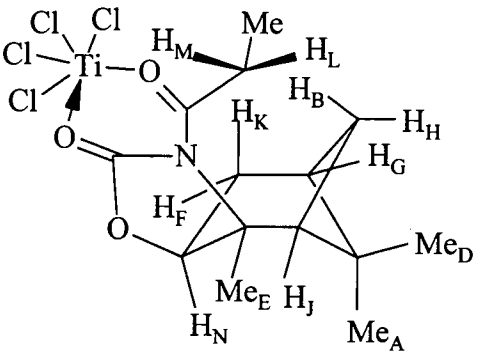
1. Irradiation of A gave 5% enhancement of signal for N, 3% for J, 1% for G, 2% for E, and 2% for D.
2. Irradiation of D gave 2% enhancement of signal for J, 6% for H, 2% for G, and 1% for A.

3. Irradiation of E gave 4% enhancement of signal for N, 3% for M, 1% for L, 1.5% for J, and 1.5% for A.

4. Irradiation of N gave 2% enhancement of signal for J, 1% for E, and 1% for A.

5. Irradiation of H gave 2% enhancement of signal for G, 2% for D, and 10% for B.

Significantly, irradiation of H_E (methyl group) gave 3% enhancement of the signals for prochiral proton H_M and 1% for H_L, confirming that both are close in space to the methyl group with H_M being the closer. Nonetheless, unlike the previous complex it was not possible to distinguish between the prochiral methylene protons in this case, presumably due to free rotation about (C)-(C=O) bond, which is reflected in the poor asymmetric induction imparted by the free propionate in aldol reactions.



123

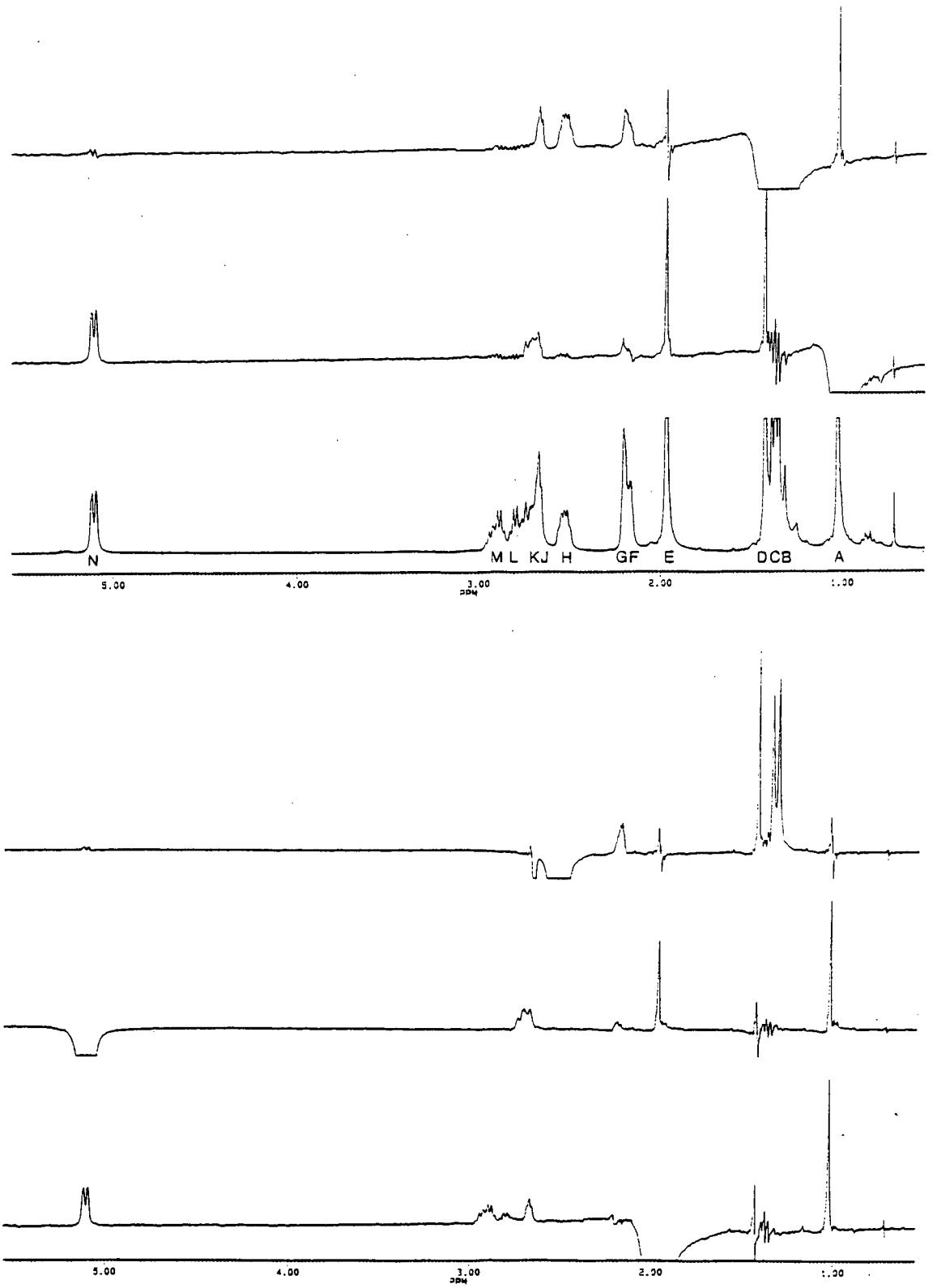
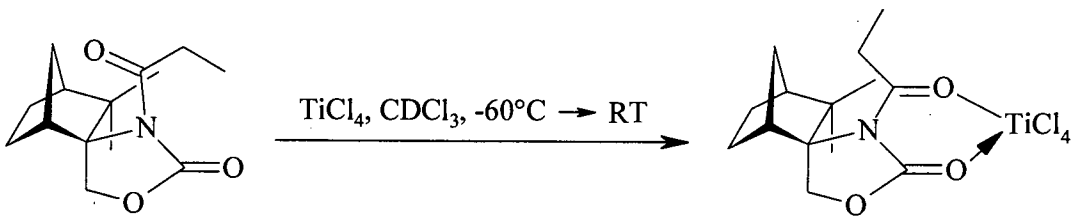


Figure 9. ^{1}H NMR 360 MHz nOe difference spectra for titanium complex **123**.

6.3 Titanium and tin complexes of (5*S*)-*N*-propionyl-4-aza-2-oxa-6,6-dimethyl-7,10-methylene-5-spiro[4.5]decan-3-one 110

As shown earlier in the thesis, the masked *tert*-butyl group in the chiral auxiliary used to prepare the *N*-propionyl derivative **110** proved to be a powerful asymmetric bias in a variety of reactions[72]. Consequently, it was of interest to investigate its influence in preventing free rotation about the (C)-(C=O) bond in the titanium complex **124** which was prepared as before by treating the *N*-propionyl derivative **110** with titanium tetrachloride in deuteriated chloroform (Scheme 45). Interestingly, ^{1}H NMR spectroscopic studies of complex **124** showed that the signals for the prochiral methylene protons H_a and H_b overlapped each other and made it very difficult to determine δH_a and δH_b and consequently $\Delta\delta$. Moreover, complex **124** was found to be too unstable to allow nOe studies and during the experiment degraded the homogeneity of the solution by depositing material within the NMR tube.

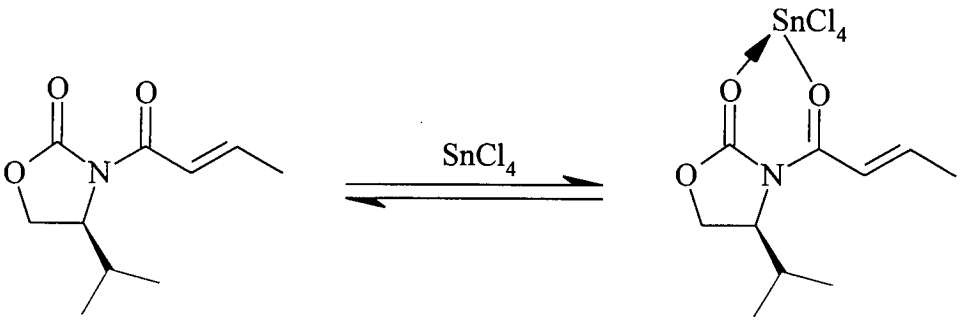


110 **124**

Scheme 45

The reason for this instability are not clear but attention was turned to other more stable complexes. Thus, Castellino[82] had treated the (*S*)-valine derived crotonyl oxazolidinone **125** with various amounts of tin tetrachloride at different temperatures and found that the resulting complexes were sufficiently stable to be studied by ^{119}Sn NMR (Scheme 46). ^{119}Sn is a convenient nucleus to study since it has a spin 1/2 and also possesses an absolute sensitivity of more than twice that of a ^{13}C nucleus, which is studied routinely. In this study, Castellino did not find any evidence for complexes other than the bidentate ("1:1") complex **126**, for which the broadness of the signal

due to the ^{119}Sn nuclei changed by varying the temperature. Presumably, no "2:1" complexes are formed with tin tetrachloride in this particular case due to the steric influence of the chiral appendage.

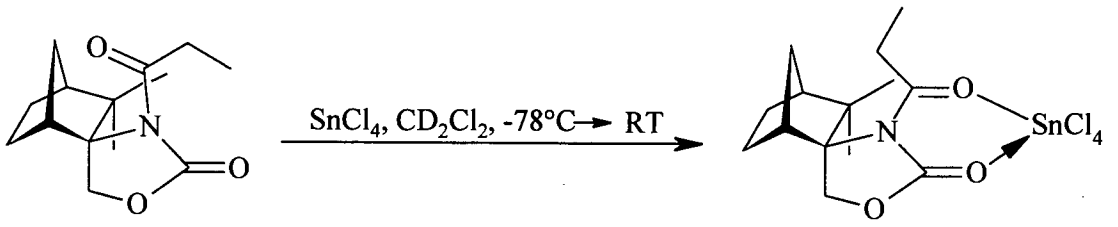


125 **126**

Scheme 46

In light of Castellino's work, the treatment of *N*-propionyl derivatives of various auxiliaries with tin tetrachloride was undertaken in an attempt to establish whether their tin complexes could be prepared and of sufficient stability to be used in studies on the differentiation of the prochiral methylene protons H_a and H_b .

The first case to be studied involved the *N*-propionyl derivative **110** whose tin complex **127** was prepared by treatment with tin tetrachloride in deuteriated dichloromethane, albeit at -78°C (Scheme 47). Evidence for the formation of **127** was given by the change in chemical shift to higher frequency and decrease in $\Delta\delta$ from 0.19 to 0.10 ppm.



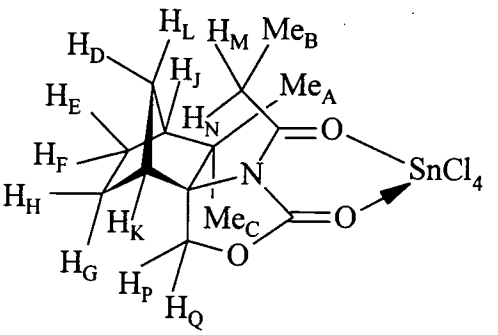
110 **127**

Scheme 47

In sharp contrast to its titanium counterpart, the complex **127** was remarkably stable and allowed accumulation of nOe data. Fig. 10 shows the ^{1}H NMR 360 MHz nOe difference spectra for complex **127**. The following points were used to assign the proton spectrum :

1. Irradiation of Q gave 20% enhancement of signal for P, 1% for H, and 1.5% for C.
2. Irradiation of N gave 1% enhancement of signal for B and C.
3. Irradiation of P gave 20% enhancement of signal for Q, 2.5% for K and <1% for C.
4. Irradiation of M and K gave 1% enhancement of signal for P, and 1% for B.
5. Irradiation of L gave 1.5% enhancement of signal for K, 2.5% for J, 22% for D and 2.5% for A.
6. Irradiation of D gave 3% enhancement of signal for K, 17% for L and 3% for J.
7. Irradiation of K gave 1% enhancement of signal for P.
8. Irradiation of J gave 1% enhancement of signal for D.
9. Irradiation of A gave 7% enhancement of signal for L and 8% for J.

Unfortunately, coincidental irradiation of H_B and H_C (methyl groups) affected both H_M and H_N equally; in other words, there is no differential enhancements of the prochiral protons H_a and H_b (M+N), *i.e.* the protons are not distinguishable.



127

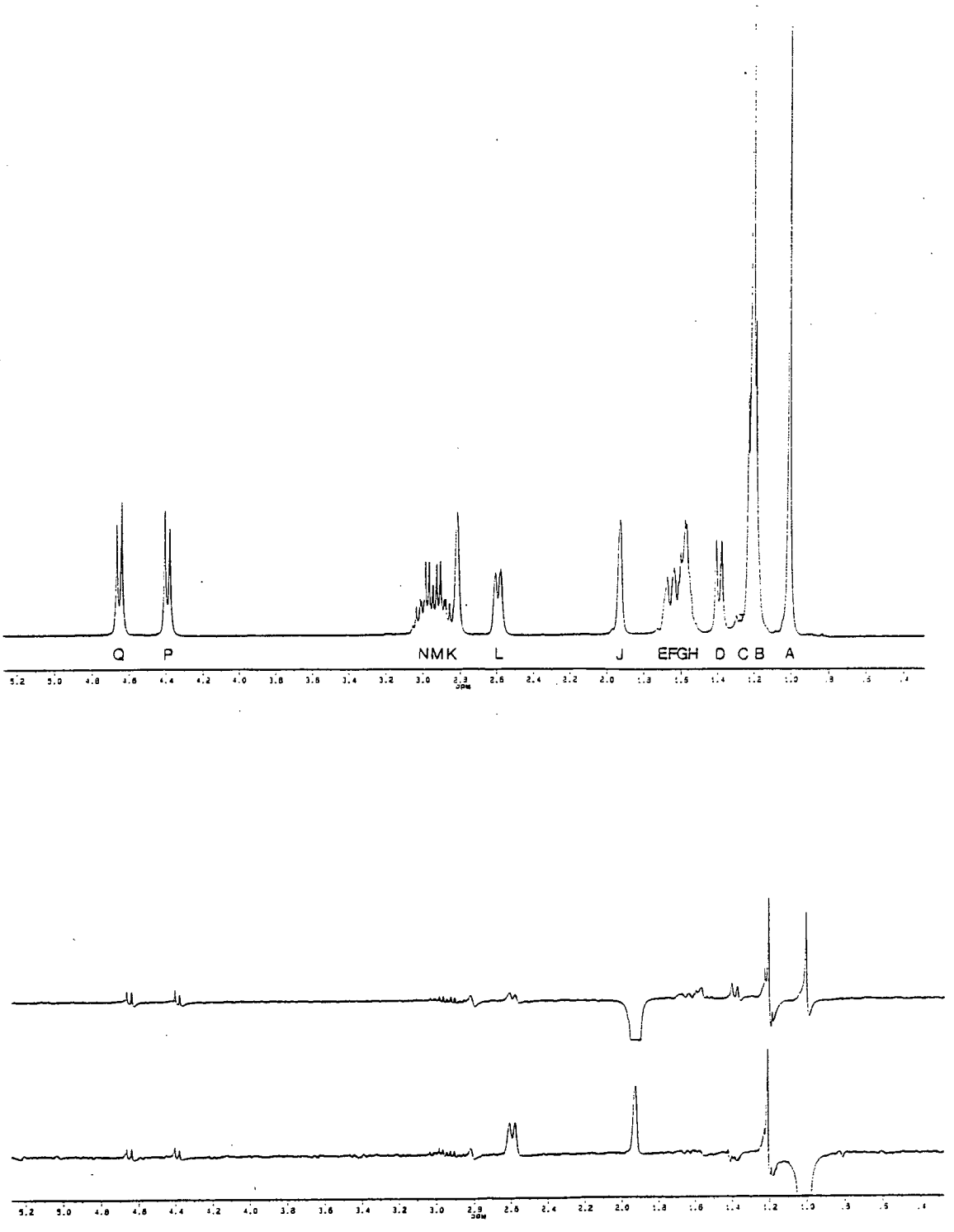


Figure 10. ^{1}H NMR 360 MHz nOe difference spectra for tin complex **127**

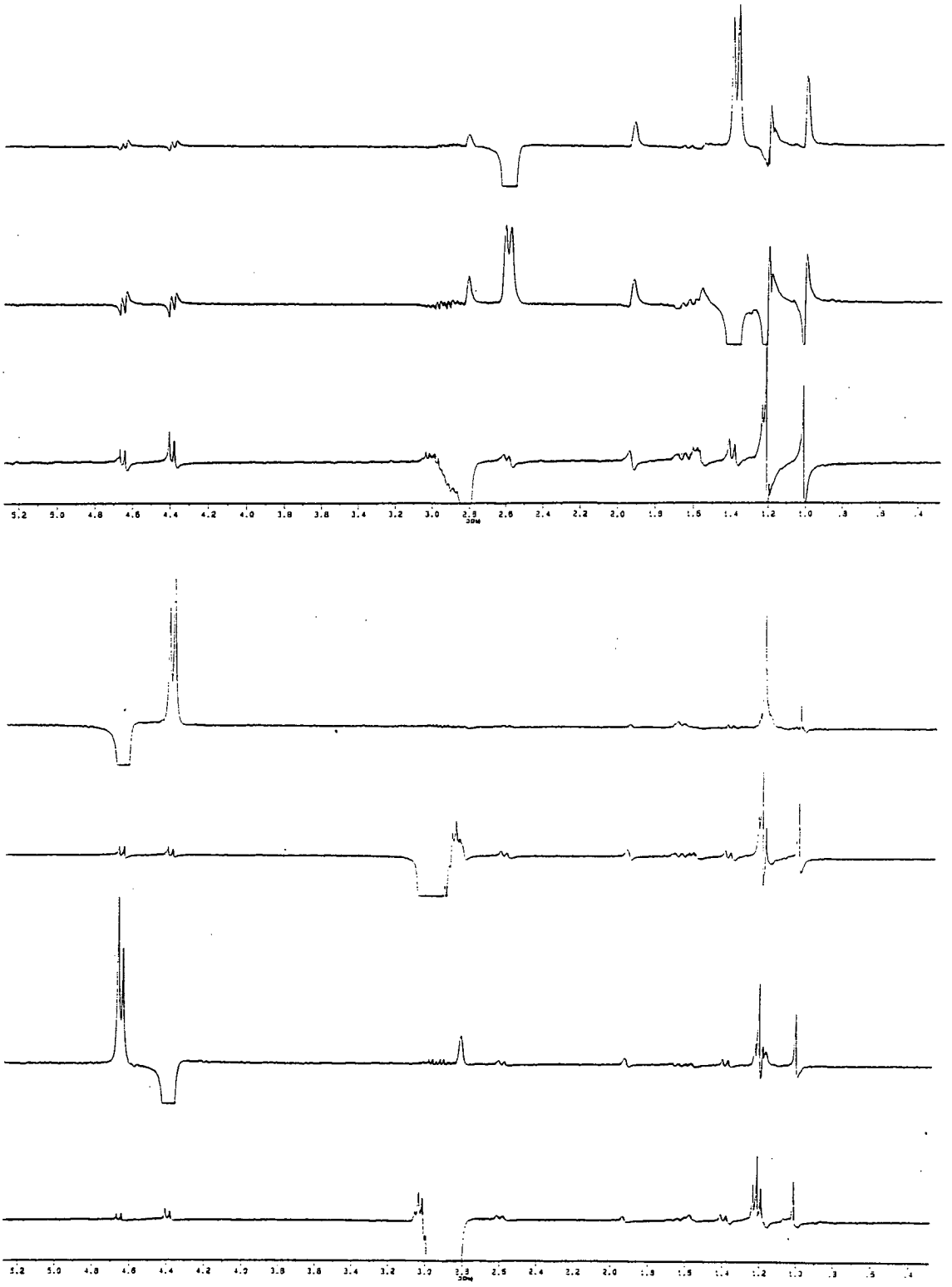
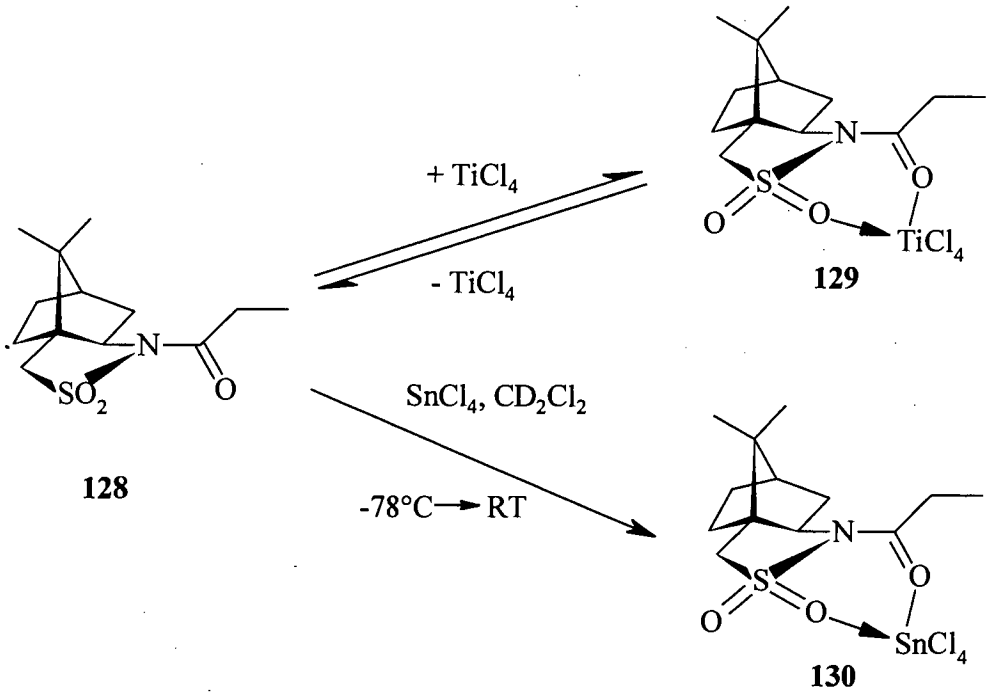


Figure 10. continued

6.4 Titanium and tin complexes of (7*R*)-*N*-propionyl-10,10-dimethyl-5-thia-4 -azatricyclo[5.2.1.$0^{3,7}$]decan-5,5-dioxide 128

Attempts were also made to prepare the corresponding titanium complex by treating the *N*-propionyl derivative **128** with titanium tetrachloride in the usual manner (Scheme 48). ^{1}H NMR 360 MHz spectrum of the solution obtained showed very broad signals, probably due to exchange between the complex **129** and the freely rotating system **128** as illustrated in Scheme 48. By contrast, treatment of **128** with tin tetrachloride in deuteriated dichloromethane at low temperature followed by warming of the solution to room temperature produced the tin complex **130** which was sufficiently stable to allow the gathering of nOe data.



Scheme 48

^{1}H NMR 360 MHz spectrum of complex **130** showed that the signals were shifted to higher frequency relative to the free *N*-propionate **128** and an increase in the chemical shift ($\Delta\delta$) was also observed from 0.04 to 0.07 ppm in the complex.

Fig. 11 shows the ^{1}H NMR 360 MHz nOe difference spectra for complex **130** from which the following points were used to assign the proton spectrum:

1. Irradiation of A gave 4% enhancement of signal for M, 3% for E and F, and 1% for B.

2. Irradiation of B gave 2% enhancement of signal for M, 2.5% for G, 1% for F and 1.5% for A.

3. Irradiation of G gave 3% enhancement of signal for N, 1% for F and 1% for B.

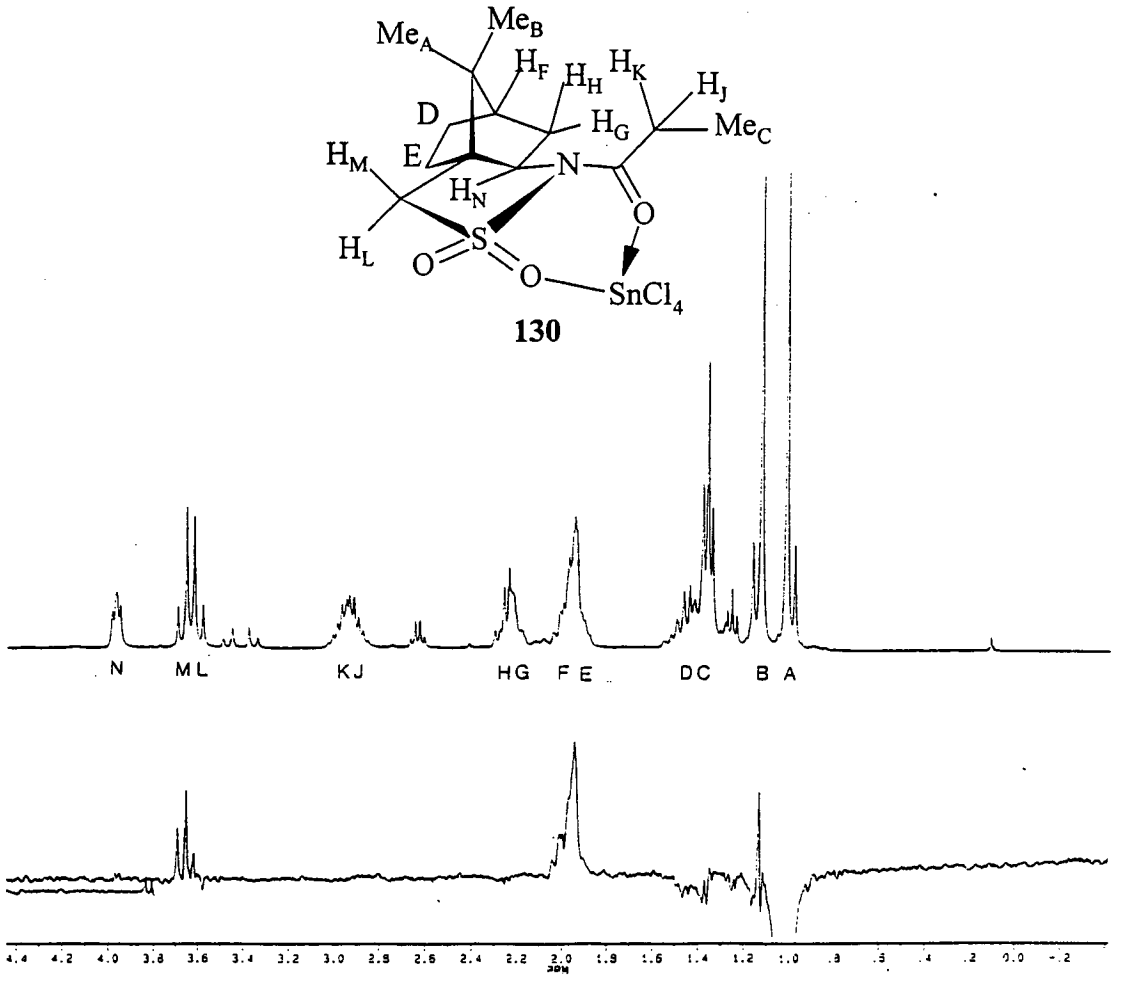
4. Irradiation of H gave 10% enhancement of signal for N, 1.5% for E and 1% for B.

5. Irradiation of L gave 2% enhancement of signal for M.

6. Irradiation of M gave 2% enhancement of signal for L, and <1% for A.

7. Irradiation of N gave 1% enhancement of signal for L, 2.5% for G and H and 5% for D.

Disappointingly, H_a and H_b are not distinguishable, there being no differential enhancements of the prochiral protons (J+K) on irradiation of any other protons.



130

Figure 11. ^{1}H NMR 360 MHz nOe difference spectra for tin complex **130**

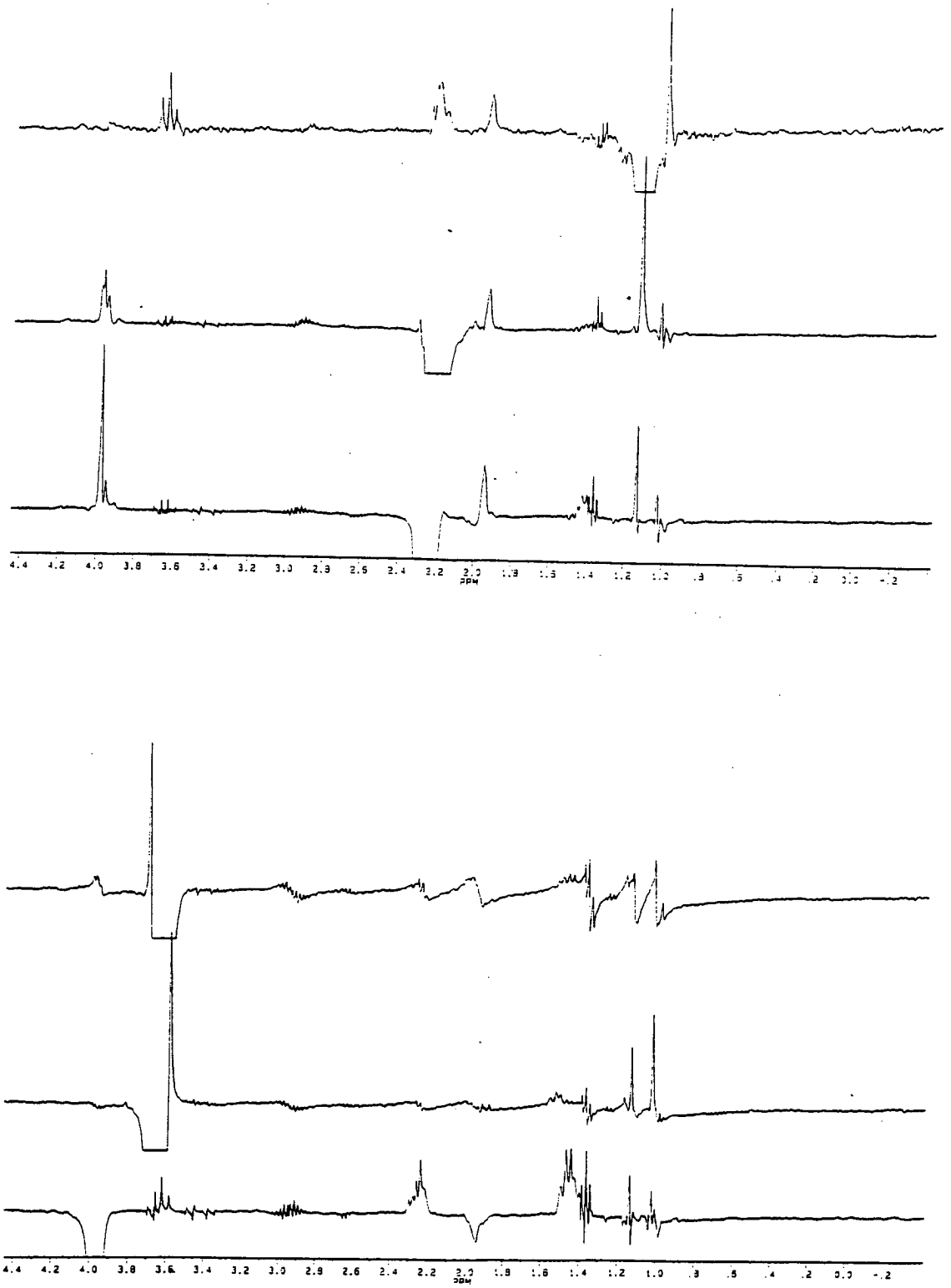
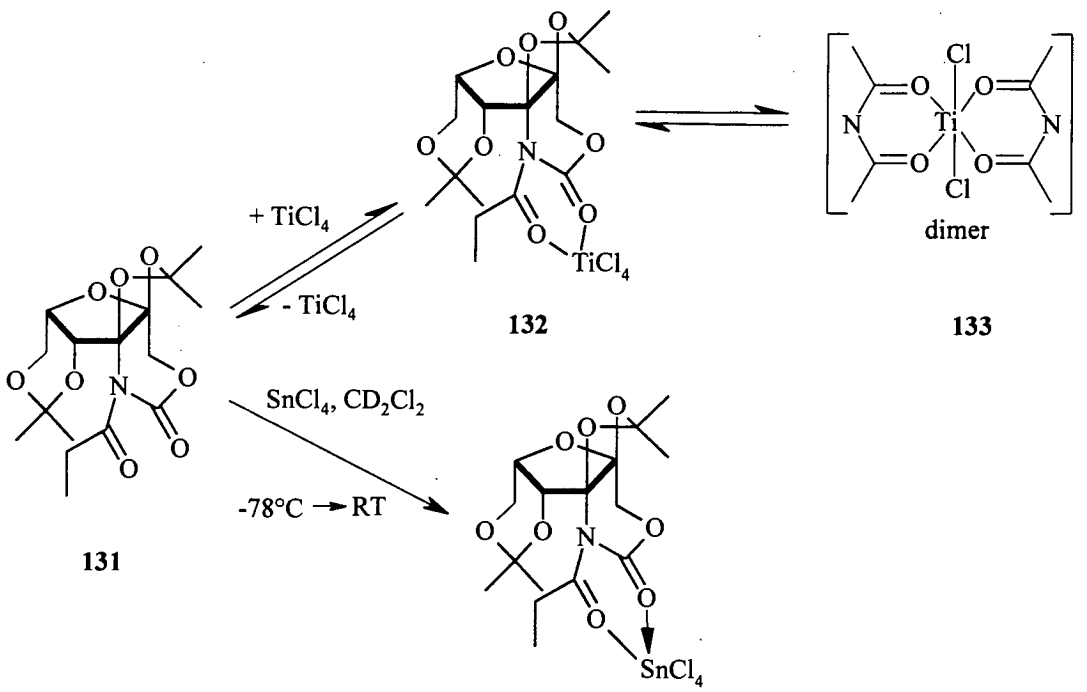


Figure 11. continued

6.5 Titanium and tin complexes of (1*S*,6*S*)-*N*-propionyl-5-aza-1,6:7,10-di-*O*-isopropylidene-8-hydromethyl-3,9-dioxabicyclo[4.3.0]nonan-4-one 131

Attempts to prepare the complex **132** were made by treating the *N*-propionyl derivative **131** with titanium tetrachloride in deuteriated methylene chloride under usual conditions.

From an examination of the ^{1}H NMR 360 MHz spectrum of the solution, it was clear that more than a single compound is present. One compound appeared as slightly broadened resonances, whilst there was also a number of very broad signals suggesting that chemical exchange is occurring at an intermediate rate. With this evidence in hand, it is likely that there is an equilibrium present between the propionyl derivative **131** and the monodentate **132**, which is also in equilibrium with the bidentate complex **133** (Scheme 49). Consequently, it was not possible to make any measurements on the desired $TiCl_4$ complex **132**, which is not surprising bearing in mind that these types of complex are known to be very labile[83,84].



Scheme 49

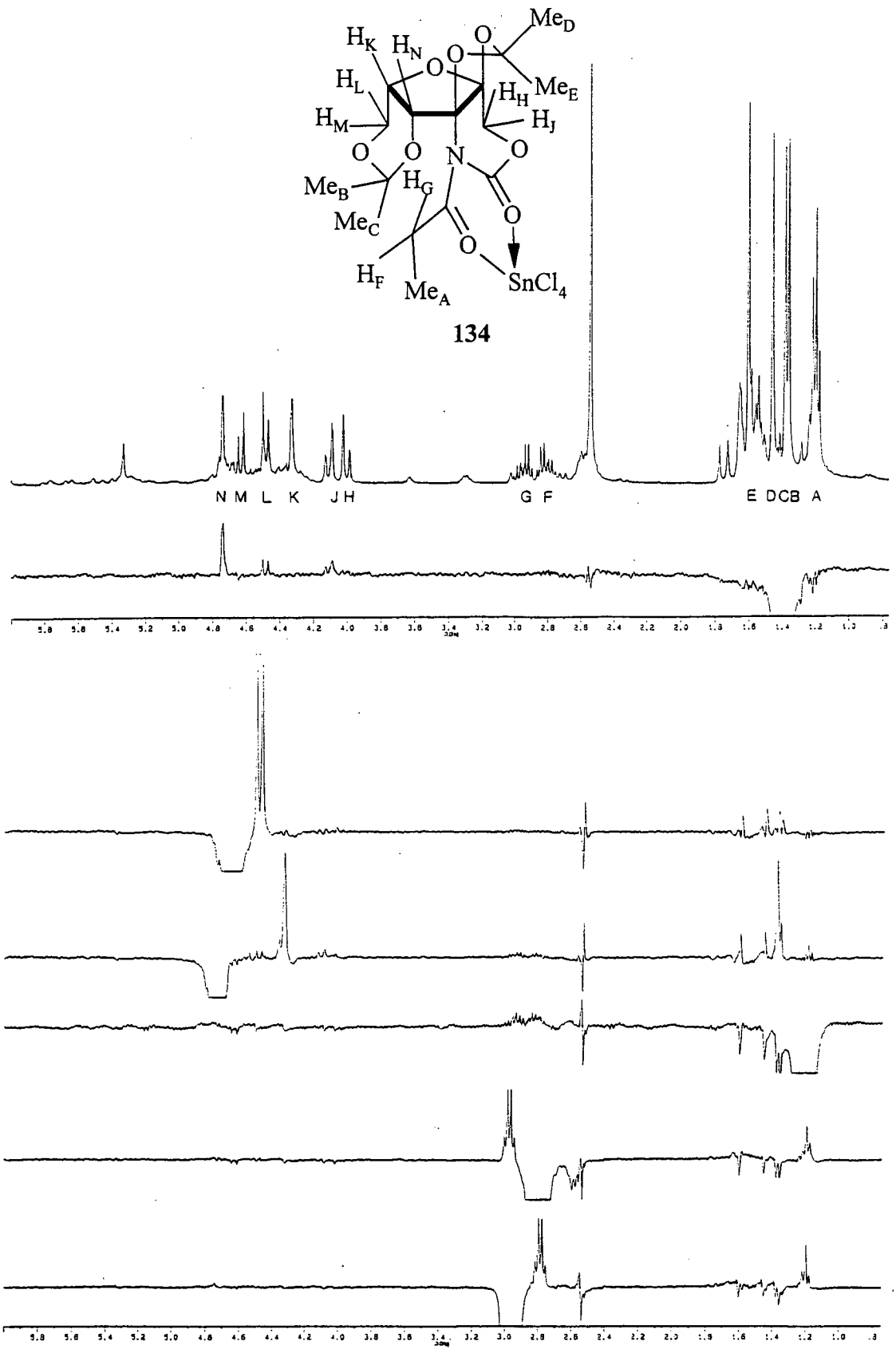
By contrast, the corresponding tin complex **134** was prepared by treatment of **131** with tin tetrachloride in deuteriated dichloromethane at -78°C and allowing the solution to warm to room temperature.

From the ^{13}C- and ^{1}H-NMR spectra of complex **134**, it is evident that the signals of the complex are shifted to higher frequency relative to the spectrum of the free propionate **131**, and decrease in $\Delta\delta$ from 0.19 in the free *N*-propionate **131** to 0.13 ppm in the complex **134**.

In sharp contrast to the titanium complex **132**, its tin counterpart **134** was stable and allowed the accumulation of nOe difference spectra (Fig. 12) from which the following points were used to assign the structure :

1. Irradiation of B gave 4% enhancement of signal for N, 1.5% for L and 1.5% for J.
2. Irradiation of C gave 12% enhancement of signal for N and 6.5% for J.
3. Irradiation of D gave 2% enhancement of signal for M and 1.5% for E.
4. Irradiation of H gave 3% enhancement of signal for K and 15% for J.
5. Irradiation of J gave 3% enhancement of signal for N, 8% for K and 22% for H.
6. Irradiation of K gave 14% enhancement of signal for N and 4.5 % for both J and H.
7. Irradiation of L gave 35% enhancement of signal for M.
8. Irradiation of M gave 28% enhancement of signal for L.
9. Irradiation of N gave 11% enhancement of signal for K and 2% for C.
10. Irradiation of F gave 20% enhancement of signal for G and <1% for A.
11. Irradiation of G gave 15% enhancement of signal for F and <1% for A.

From this data, it is evident that there is no differential enhancements of the prochiral protons H_a and H_b (F+G) upon irradiation of any other protons, *i.e.* H_a and H_b are indistinguishable, indicating free rotation.



134

Figure 12. ^{1}H NMR 360 MHz nOe difference spectra for tin complex **134**

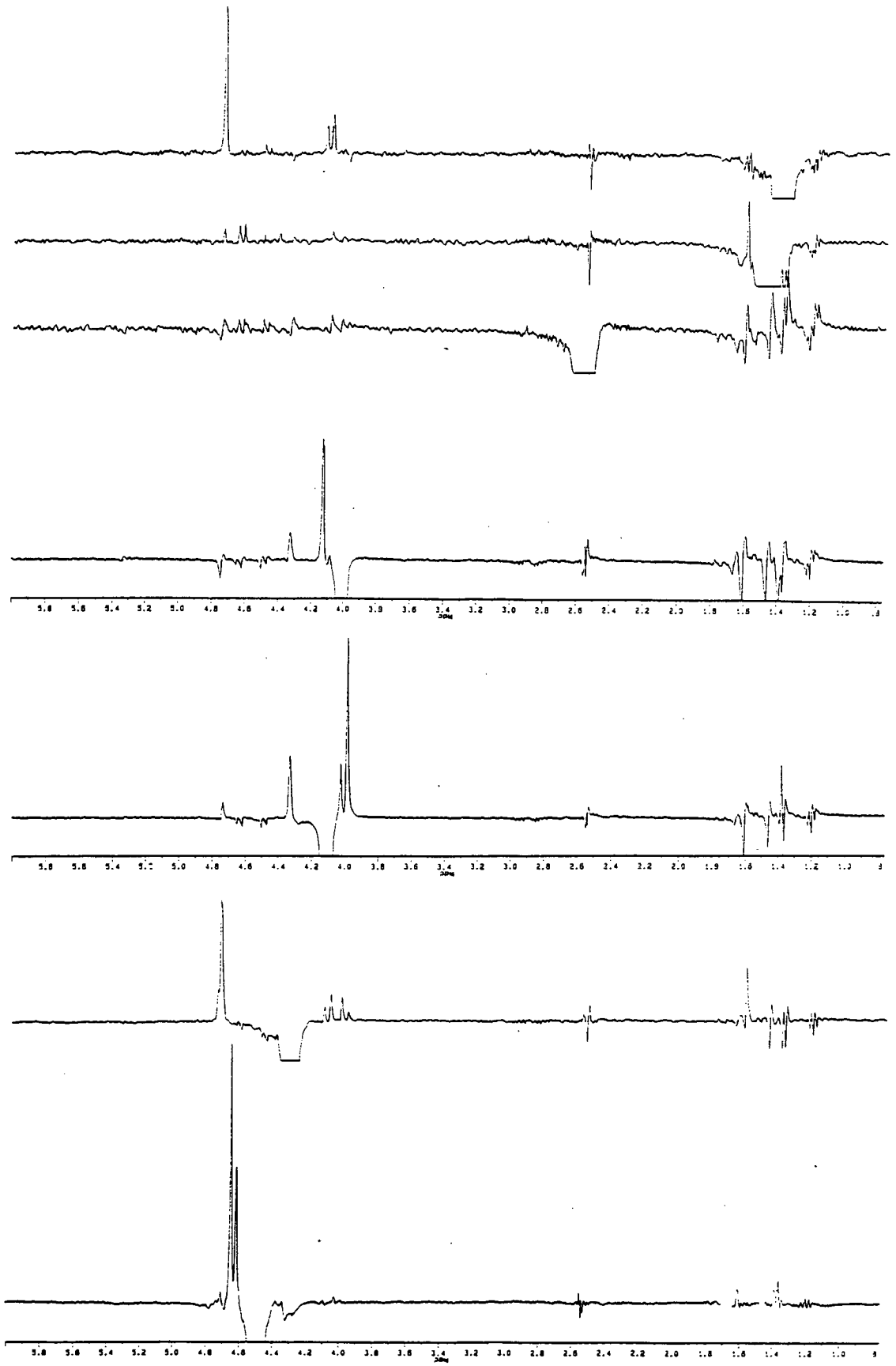
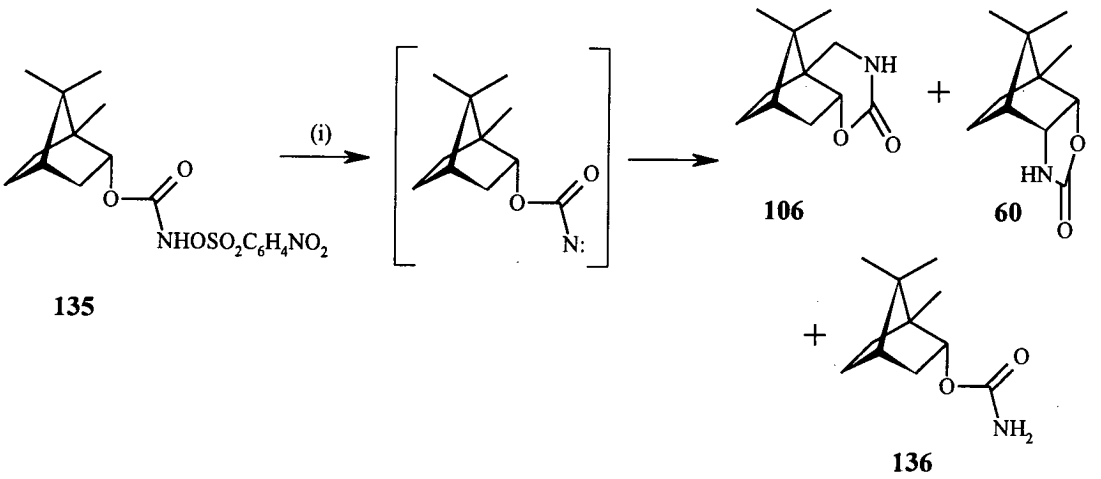


Figure 12. continued

7 Asymmetric aldol reactions with benzaldehyde for *N*-propionyl derivatives of various chiral auxiliaries *via* different types of enolisation

As was noted previously in chapter 2, the six-membered 1,3-oxazin-2-one **106** was synthesised as a *ca.* 1:1 mixture with the tricyclic oxazolidin-2-one **60**[47] by application of the INIR (Intramolecular Nitrene Insertion Reaction) method to the optically-active nitrene which is most conveniently generated from carbamate precursor **135** as shown in Scheme 50 in a two-phase system. Separation of the isomeric products was easily achieved by flash chromatography on silica (cyclohexane:ethylacetate) which furnished well-formed crystals of the chiral oxazinone **106** in an enantiomerically pure form [mp 170-171°C; $[\alpha]_D^{23}$ = +72.1°; c = 5.1 (ethanol)] in 36% yield and well-formed crystals of the chiral oxazolidin-2-one **60** [mp 163-163.5°C; $[\alpha]_D^{21.5}$= -73.4°; c = 5.1(ethanol)] in 43% yield, together with carbamate side-product **136** (14%) formed by hydrogen abstraction.



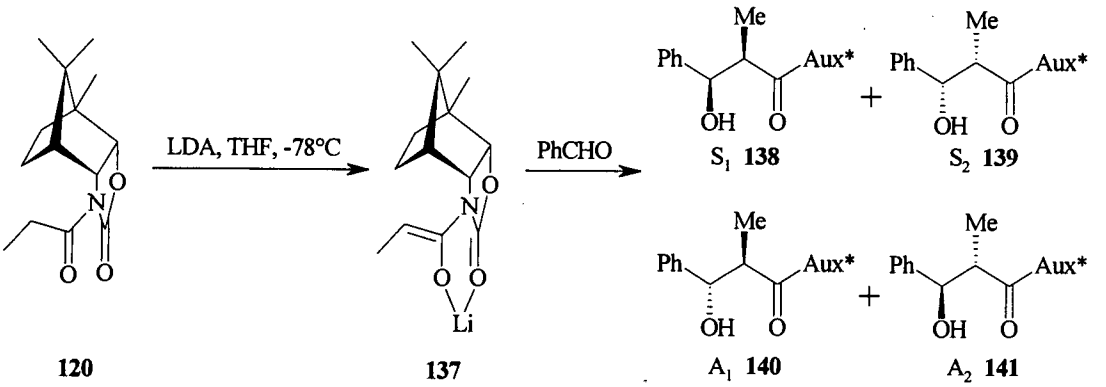
Scheme 50. *Reagents and conditions:* (i), benzyltriethylammonium chloride, sodium hydrogen carbonate, CH_2Cl_2-water, 25°C.

With these two potential chiral auxiliaries in hand in substantial quantity, it was intended to investigate their potential in asymmetric *syn-* and *anti-* aldol reactions here in this chapter by looking at the condensation between different types of enolate,

resulting from the *N*-propionyl derivatives of **60** and **106**, with benzaldehyde under carefully controlled conditions.

7.1 Asymmetric aldol reactions for [(2*S*,6*R*)-*endo*]-*N*-propionyl-5-aza-1,10,10-trimethyl-3 -oxatricyclo[5.2.1.$0^{2,6}$]decan-4-one 120 with benzaldehyde *via* different methods of enolisation

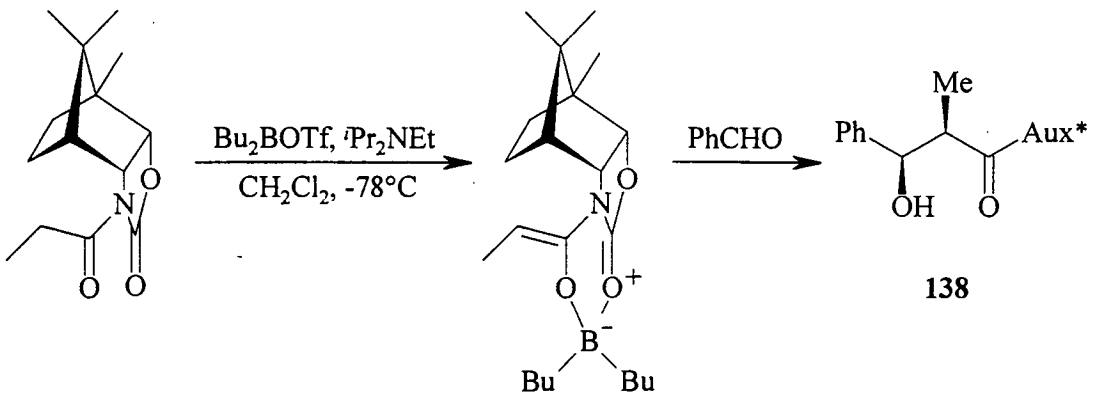
In our laboratory Banks *et al*[47] reported that reaction of the lithium enolate **137**, generated by deprotonating imide **120** with lithium diisopropylamide (LDA), with benzaldehyde, and quenching after thirty seconds, yielded a colourless crystalline solid which was shown by high field ^{1}H NMR spectroscopy to be a mixture of the four possible aldol products (Scheme 51) in a ratio of 55.4:28.7:10.3:5.7 giving diastereomeric excess of 11%; these components were not assigned to the four possible structures.



Scheme 51

To find a solution to the problem of poor selectivity observed with the lithium enolate **137**, Gallagher and Donohoe (quoted in *ref.* 47) employed the boron enolate **142** of the propionate **120**, which was generated using dibutylboron triflate and diisopropylethylamine. Reaction of this enolate with benzaldehyde for thirty minutes at -78°C and one and three quarter hours at room temperature yielded the crude aldol product, which upon purification by flash chromatography, furnished a single isomer as shown by high field ^{1}H NMR spectroscopy. On behalf of the workers at

Edinburgh, Gallagher and Donohoe also obtained an X-ray crystal structure for the principle product (Fig. 13) and confirmed that it possessed the *syn* structure **138** as depicted in Scheme 52.



120 **142** **138**

Scheme 52

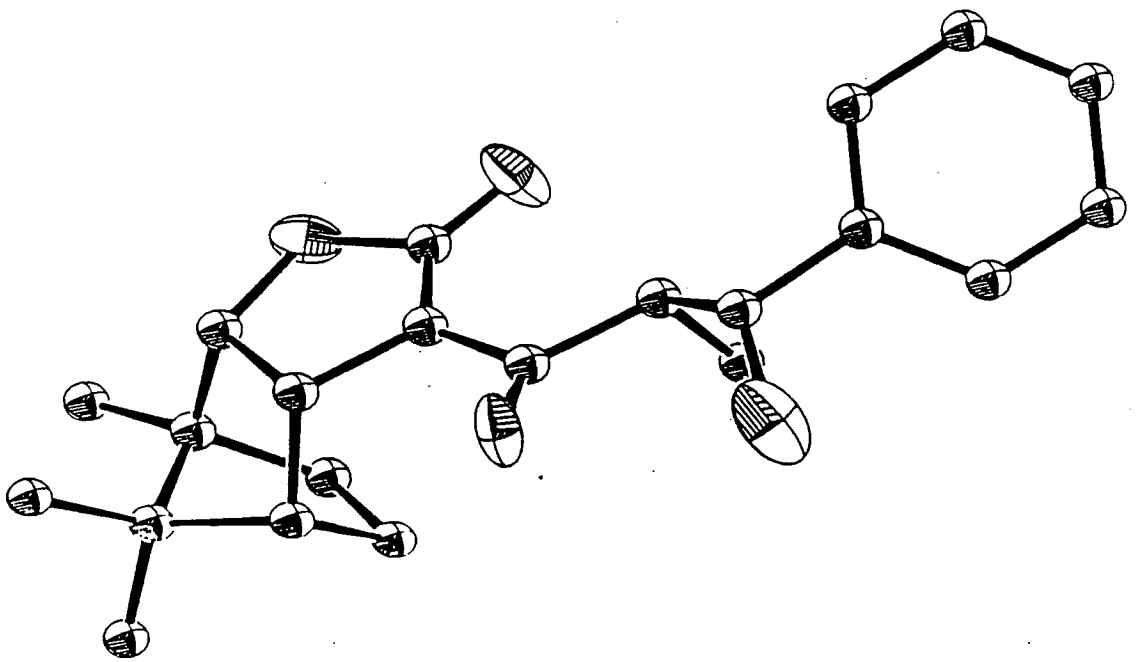
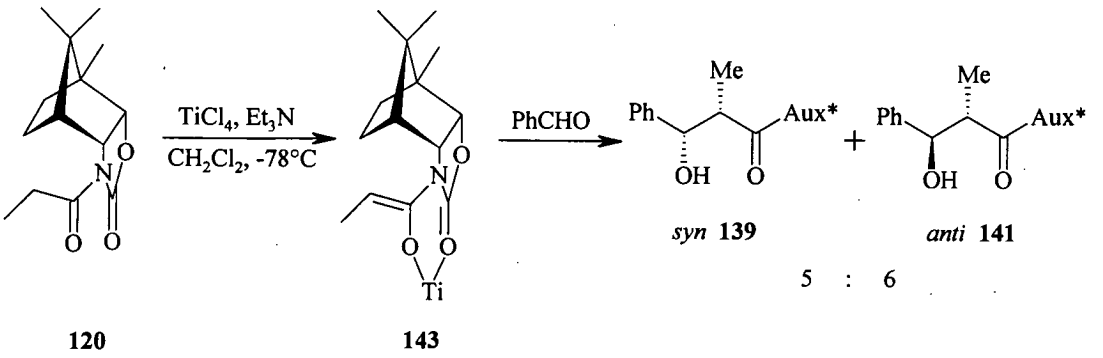


Figure 13. X-ray crystal structure of the *syn*-aldol product **138** obtained by Gallagher *et al*[47]

In an effort to avoid the use of relatively expensive dibutylboron triflate, which furthermore cannot be stored for extensive periods without significant decomposition, Grant[85] employed the titanium enolate **143** of the propionate **120**, which was generated using titanium tetrachloride and triethylamine. Reaction of titanium enolate **143** with benzaldehyde for 4 h. at -78°C yielded the crude product (Scheme 53), which was analysed by high field ^{1}H NMR spectroscopy to give the interesting result that only two of the four possible isomers were present in the reaction mixture. Moreover, these could be identified as *anti* **141** and *syn* **139** in the ratio 6:5 (diastereomeric excess = 9%) by their respective vicinal coupling constants of 8.0 and 4.2 Hz.



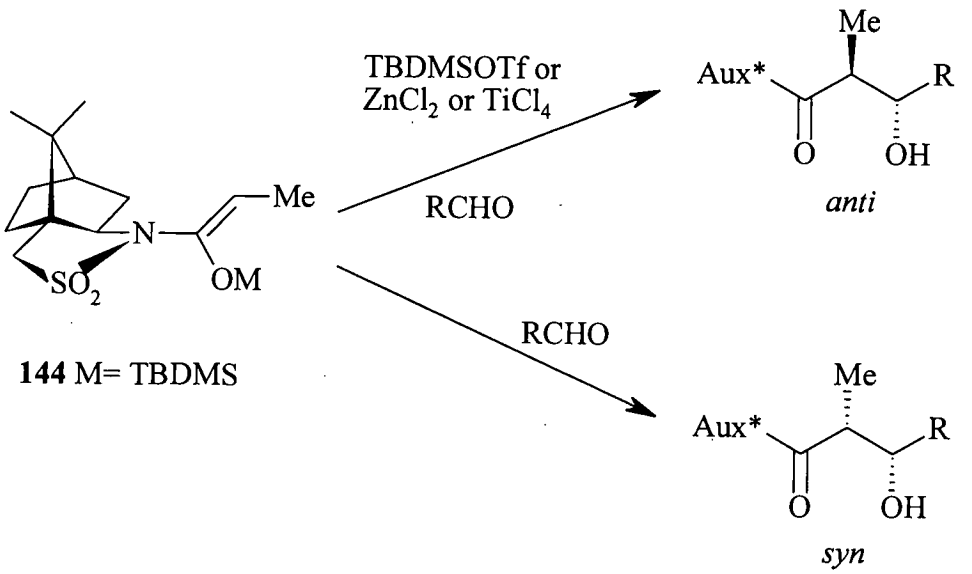
120 **143**

Scheme 53

7.1.1 Aldol reactions for [(2*S*,6*R*)-*endo*]-*N*-propionyl-5-aza-1,10,10-trimethyl-3-oxatricyclo[5.2.1.0^{2,6}]decan-4-one 120 with benzaldehyde *via* excess of boron enolate

Danda *et al*[57] reported that Evans' boron enolate-derived system **41** (Scheme 20, p. 27) gave *syn* adducts in the absence of Lewis acid, but in the presence of excess dibutylboron triflate furnished *anti* aldol products. Similarly, Oppolzer *et al*[64,86]

found that Lewis acid-mediated aldol reactions of the TBDMS enol ether **144** in the presence of $ZnCl_2$ or $TiCl_4$ gave *anti* aldol products (Scheme 54). Analogous observations have been found by Walker and Heathcock[56] and Xiang *et al*[87].

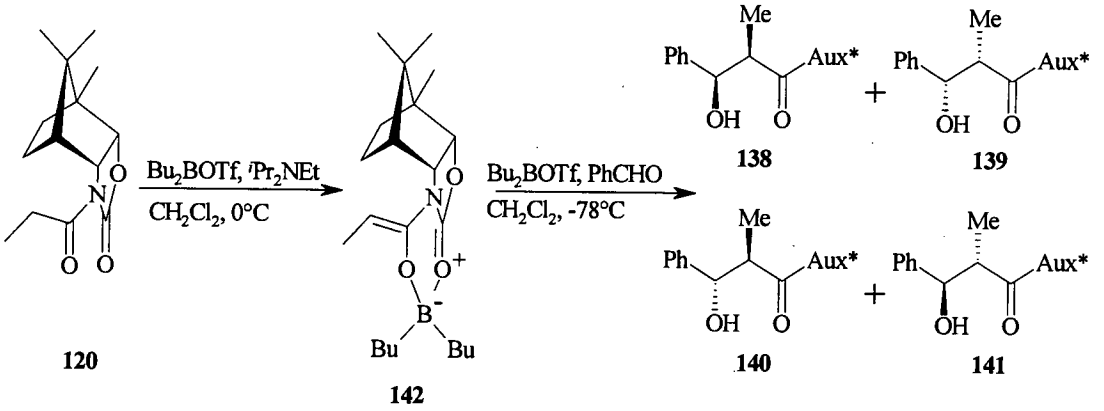


Scheme 54

In further continuation of Banks, Gallagher and Grant's work, and in an effort to raise the proportion of *anti*-isomer, the *N*-propionate **120** was treated with an excess of dibutylboron triflate (2.2 eq) in the presence of diisopropylethylamine to yield the boron enolate **142**. Reaction of the resultant enolate with benzaldehyde in the presence of excess of dibutylboron triflate for thirty minutes at -78°C and one and three quarters hours at room temperature led to the aldol crude product (Scheme 55), which upon purification by flash column chromatography, furnished four aldol products; two isolated *anti*-aldol products and two non-isolated *syn*-aldol products. The diastereomer product ratios resulting from this reaction were determined by analysing the high-field ^1H NMR spectra of the crude aldol product. The most informative region in this spectrum was the chemical shift range 5.15-4.70 ppm, where the doublet resonances arising from the carbinol proton (PhC*H*OH) of diastereomers **138**, **139** and **141** and triplet resonance for **140** appeared. Integration of these signals showed that a mixture of four possible aldol products **138**, **139**, **140** and

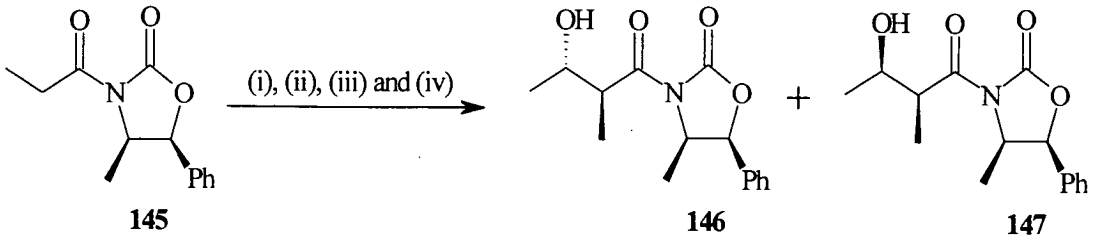
141 had been formed in the ratio 31.5:10.5:44:14, respectively, *i.e.* without diastereomeric excess.

Whilst the diastereomeric excess of this reaction was disappointing, the proportion of both *anti*-isomers was high and each was isolated and characterised. The above *syn/anti* assignments were made by measuring the vicinal coupling constants of the carbinol protons and using the known fact[54] that, for this proton, $^3J_{syn}$ is typically 3-6 Hz, and $^3J_{anti}$ is typically 7-9 Hz; the values found in this reaction were $^3J_{syn}$ =3.5 Hz for **138** and 4.2 Hz for **139**, and $^3J_{anti}$ = 6.8 Hz for **140** and 8.0 Hz for **141**. In this respect, it is worth noting that X-ray crystal structures of the two *anti* aldol products were obtained and confirmed both to exhibit the designated structures **140** and **141** as depicted in Scheme 55, together with bond data in appendices 1 and 2.



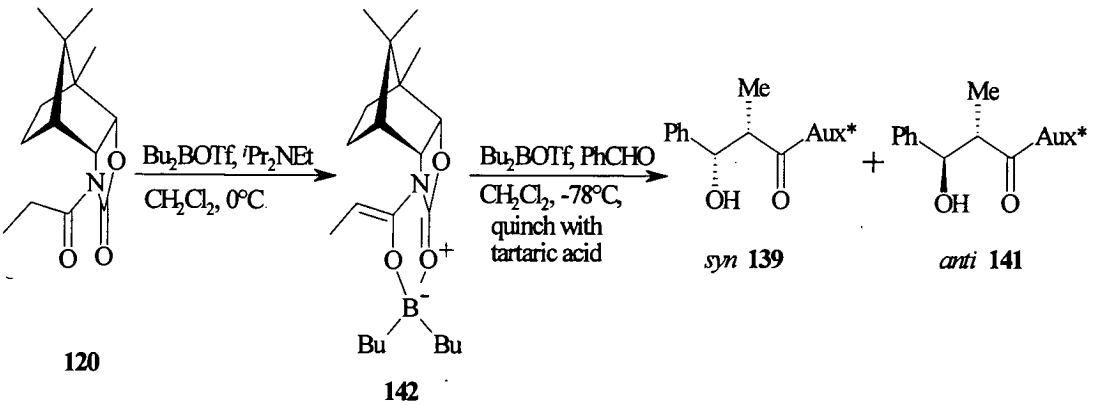
Scheme 55

Heathcock *et al*[88] have reported an efficient procedure for the *anti*-selective aldol reaction of the chiral imide **145** and acetaldehyde, and included within the process, a novel work-up protocol utilising tartaric acid. This protocol raised the diastereomeric excess of *anti*-**146** and *syn*-**147** aldol products and the yield from 7:1 and 50-70%, to 11:1 and 79% yield in favour of the *anti*-aldol product **146** (Scheme 56).



Scheme 56. *Reagents and conditions:* (i), excess of Bu_2BOTf, $^iPr_2NEt$, CH_2Cl_2, 0°C; (ii), CH_3CHO, CH_2Cl_2, -78°C; (iii), tartaric acid, -78°C; (iv), H_2O_2, MeOH.

In an attempt to improve the *anti*-aldol diastereoselectivity, this novel protocol was applied to the reaction of boron enolate **142** with benzaldehyde in the presence of excess of dibutylboron triflate (Scheme 57). The crude aldol product was analysed by 200 MHz ^{1}H NMR, the resonances of interest being the doublets in the chemical shift range 5.15-4.70 ppm arising from the chiral carbinol proton PhC*H*OH. Analysis revealed that one *anti* isomer **141** (^3J = 7.4 Hz) and one *syn* isomer **139** (^3J = 4.4 Hz) had formed in a ratio of 61:39 respectively, giving a diastereomeric excess of 22%. Thus, while the stereoselectivity obtained was slightly better, this protocol led to a poorer product yield (40%).

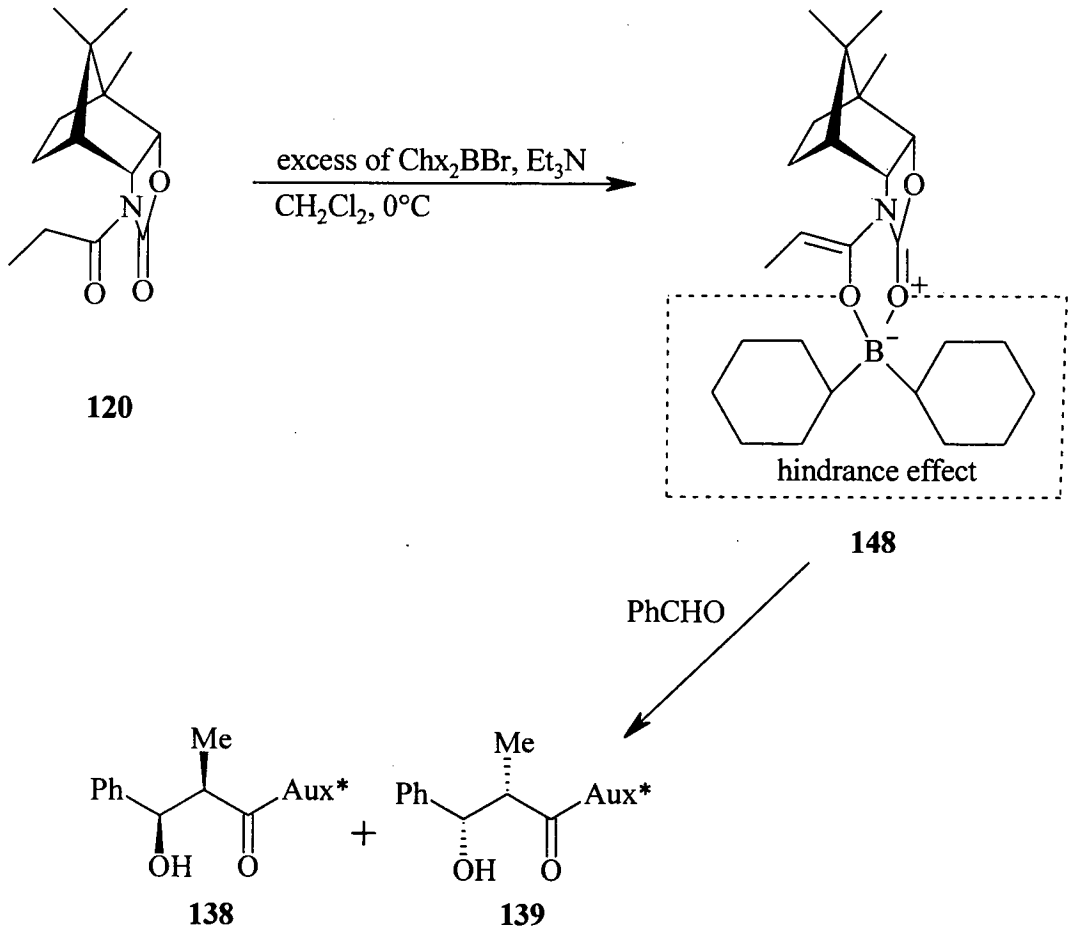


Scheme 57

Brown *et al*[89], Paterson *et al*[59,60,90], Enders *et al*[91] and others[92,93] have carried out asymmetric aldol reactions with boron enolates which have been generated by using

the new reagent, dihexylboron bromide or chloride, in combination with triethylamine. The diastereoselectivities obtained in these reactions were very high. The employment of this type of boron enolate procedure with imide **120** (Scheme 58) furnished a very poor yield of combined aldol products (*ca.* 15%). Presumably, this outcome is simply a result of the steric bulk of cyclohexyl groups in the boron enolate **148**, preventing approach by the benzaldehyde.

The diastereoselectivity was determined by analysis of the 250 MHz ^{1}H NMR spectrum of the crude aldol product, containing only two *syn*-isomers (^3J = 2.6 and 3.3 Hz), which had formed in the ratio of 76:24 respectively (diastereomeric excess = 52%). This ratio was determined by integration of the doublets in the range 5.23-5.02 ppm, arising from the PhC*H*OH protons; the *syn*/*syn* assignments were made on the basis of the vicinal coupling constants, which are quoted.

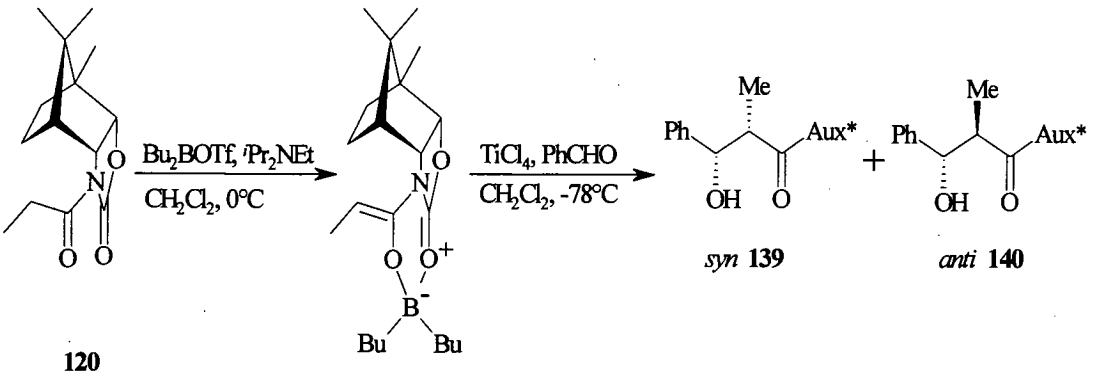


120 **148** **138** **139**

Scheme 58

7.1.2 Influence of $TiCl_4$ on the *anti*-aldolisation of boron enolate of [(2*S*,6*R*)-*endo*]-*N*-propionyl-5-aza-1,10,10-trimethyl-3-oxatricyclo[5.2.1.$0^{2,6}$]decan-4-one 120 with benzaldehyde

In view of Grant's observation (*vide supra*) on the effect of titanium tetrachloride upon the *anti*-selectivity in aldol reactions of **120** with benzaldehyde, it was decided to react the boron enolate **142** with a mixture of benzaldehyde (2 equiv.) and titanium tetrachloride (2 equiv.) at -78°C for thirty minutes. After allowing the reaction to warm to room temperature and a further one and three quarters hours at room temperature, work-up yielded the crude aldol product as a pale yellow oil in low yield 45% (Scheme 59).



Scheme 59

Analysis of the crude product by 200 MHz ^{1}H NMR spectroscopy showed unequivocally that one *syn* diastereomer **139** (^3J= 4.4Hz) and one *anti* diastereomer **140** (^3J= 7.3 Hz) had formed in the ratio of 26:74 respectively, giving a diastereomeric excess of 48%. This ratio was determined by integration of the doublet for **139** and the triplet for **140** in the range 5.15-4.65 ppm, arising from the

PhC*H*OH protons; the *syn*/*anti* assignments were made on the basis of the vicinal coupling constants, which are quoted.

Upon purification of the aldol crude product by flash column chromatography using hexane :ether (4:1) elution, the *anti*-aldol product was isolated first in 25% yield and then the *syn* aldol product, which was obtained in a lower yield of 20%. Whilst the yield of aldol products as low (45%), the stereoselectivity obtained was much better in this reaction than the previous reactions. This may have been due in some part to the use of commercial dibutylboron triflate, which is extremely air and moisture sensitive and will deteriorate rapidly, even when thoroughly sealed and stored under anhydrous conditions. It has been reported by the other workers[94] that similar problems have been encountered with this reagent.

7.2 Asymmetric aldol reactions of [6(*S*)-*endo*]-*N*-propionyl-3-aza-11,11 -dimethyl-5-oxatricyclo[6.2.1.0^{1,6}]undecan-4-one 149 with benzaldehyde *via* different methods of enolisation

In light of the results obtained with chiral oxazolidinone **60**, attention was turned to its isomer **106** bearing the more flexible six-membered oxazin-2-one ring. The following three sections discuss the results obtained in lithium- and boron-mediated aldol reactions with the *N*-propionyl imide **149** derived from **106** in the usual manner.

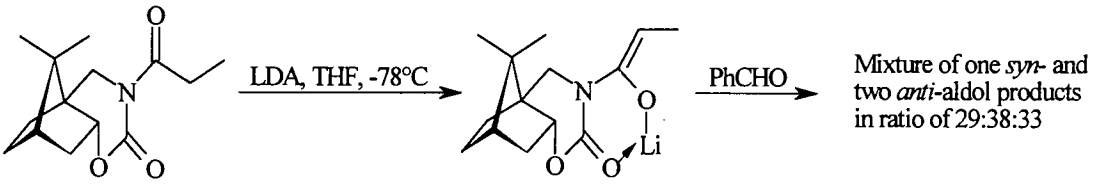
7.2.1 Aldol reaction of [6(*S*)-*endo*]-*N*-propionyl-3-aza-11,11-dimethyl-5-oxatricyclo[6.2.1.0^{1,6}]undecan-4-one 149 with benzaldehyde *via* lithium enolate

It has already been shown in a previous section that the terpenoid-derived auxiliary **60**, like other similar-based reagents, exhibit poor selectivity in lithium-enolate promoted aldol reactions. By contrast, the carbohydrate-based oxazolidin-2-ones **64** and **97** and the oxazin-2-ones **103** and **105** provided high diastereoselection in such reactions[48,73,85]. It was not clear where this diastereoselctivity came from, but its origin might be due to better placing of the steric control groups, chelation of the lithium to one of the many available oxygens, or perhaps the anomeric nature of the oxazolidin-2-one.

For initial experiments the *Z*(O) lithium enolate **150** was formed from imide **149** using *n*-butyllithium and diisopropyl amine and then treated with freshly distilled benzaldehyde. Only short reaction period of `30 seconds` was allowed in order that a kinetic product mixture, rather that an equilibrated thermodynamic product, would be obtained.

After work-up, the crude aldol product was isolated as a colourless gum in excellent yield (90%), and then examined by high-field ^{1}H NMR and ^{13}C NMR spectroscopy, which showed that a mixture of only three aldol products had been formed (Scheme

60). One of these was found to be a *syn* diastereomer (^3J= 2.6 Hz), whilst the other two proved to be *anti* diastereomers (^3J= 11.5 Hz), all of which were formed in approximately equal amounts (29:38:33 respectively). These ratios were determined by integration of the doublets in the range 5.28-4.97 ppm, arising from the PhC*H*OH protons.



149 **150**

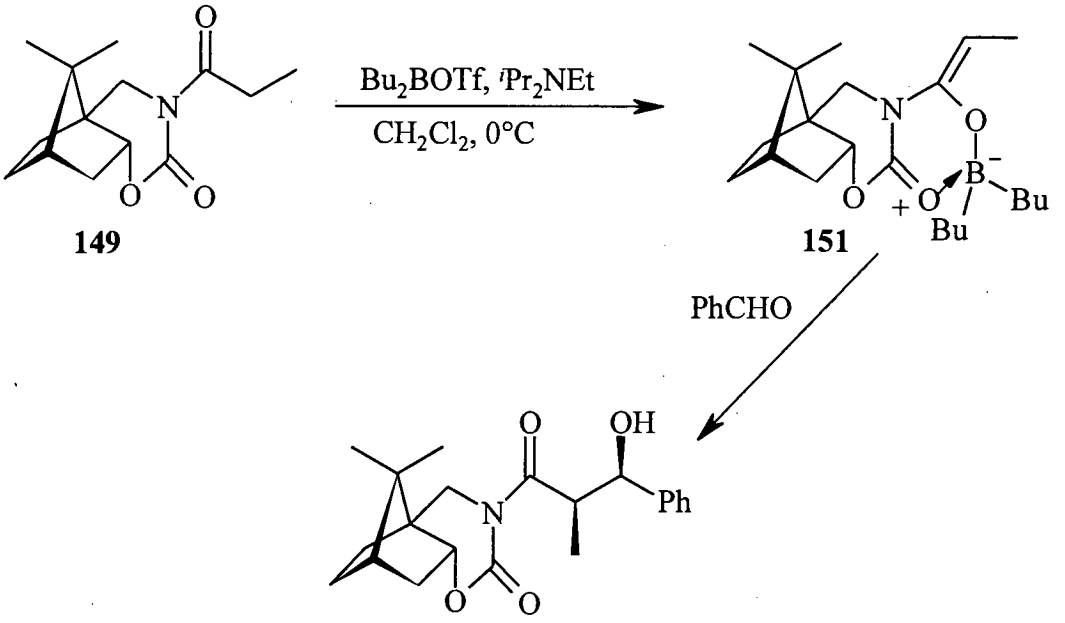
Scheme 60

Complete assignment of individual structures to this crude aldol product was not undertaken because it has been shown by a number of workers[22,27,49] that lithium-mediated aldol reactions exhibit poor levels of diastereoselection and this test reaction just helped to enforce this point. It should be noted that the poor diastereoselection can be attributed to a less "tight" transition state compared to other enolate system, *e.g.* that of boron, due to the relatively long Li-O bond length[95]. Furthermore, lithium does not possess true ligands, other than those of solvent, *e.g.* alkyl groups, which would make steric interactions in the aldol transition state greater.

7.2.2 *Syn*-aldol reaction of [6(*S*)-*endo*]-*N*-propionyl-3-aza-11,11-dimethyl-5-oxatricyclo[6.2.1.0^{1,6}]undecan-4-one 149 with benzaldehyde *via* boron enolate and influence of $TiCl_4$ on the aldolisation of this boron enolate

After this not unexpected poor demonstration of selectivity with the lithium-based-enolate **150**, attention was turned towards boron-mediated aldol reactions in this section. As shown previously in section (7.1), use of the boron-enolate derivative of the *N*-propionyl derivative **120** had brought about a very high level of asymmetric induction in the aldol reaction with benzaldehyde and this also had been reported by Evans[22] and others[27] with other reagents.

Thus, the boron enolate **151** was generated by treatment of the *N*-propionate **149** with 1.1 equiv. of dibutylboron triflate (Bu_2BOTf) and diisopropylethylamine (Hünig's base) and allowed to react with freshly distilled benzaldehyde for thirty minutes at -78°C. Once complete, the solution was warmed to room temperature for one and three quarter hours and worked-up to yield the crude aldol product, which upon purification by flash column chromatography, furnished a crystalline single isomer (*d.e.*= 100%) as shown by high field ^{1}H NMR spectroscopy.



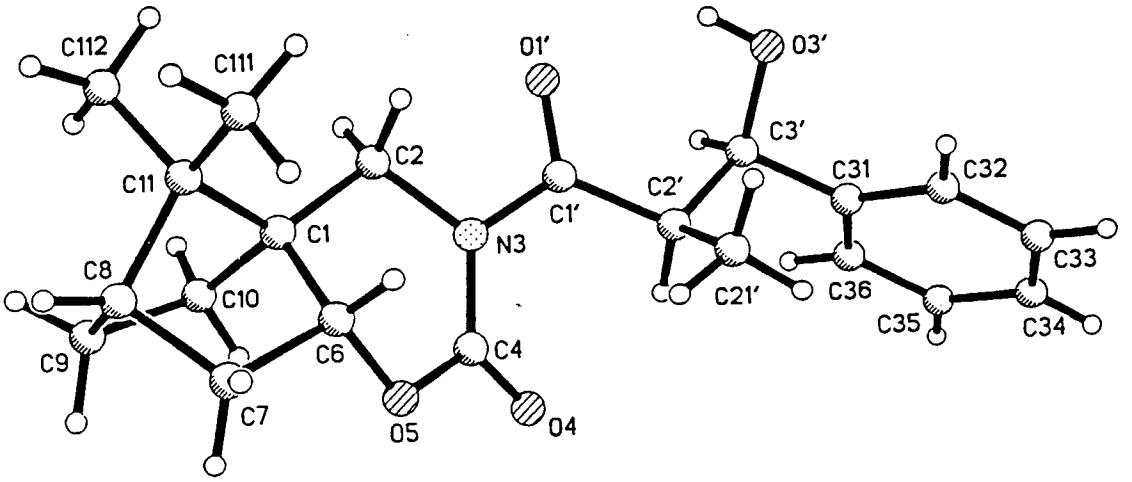
149 **151** **152**

Scheme 61

Despite the poor yield (30%), the level of asymmetric induction imparted by the auxiliary under these specific conditions is excellent and ^{13}C NMR spectroscopy indicated only one aldol product had been formed. Also important was the observation that ^{1}H NMR 250 MHz showed the product to be a *syn* isomer due to the presence of small vicinal coupling constants (J= 2.6 Hz) with one doublet at 5.27 ppm arising from the PhC*H*OH proton.

The X-ray crystal structure of **152** is shown in Fig. 14a (see also appendix 3) and confirms that the absolute stereochemistry of the two newly formed chiral centres is *syn* as depicted.

(a)



(b)

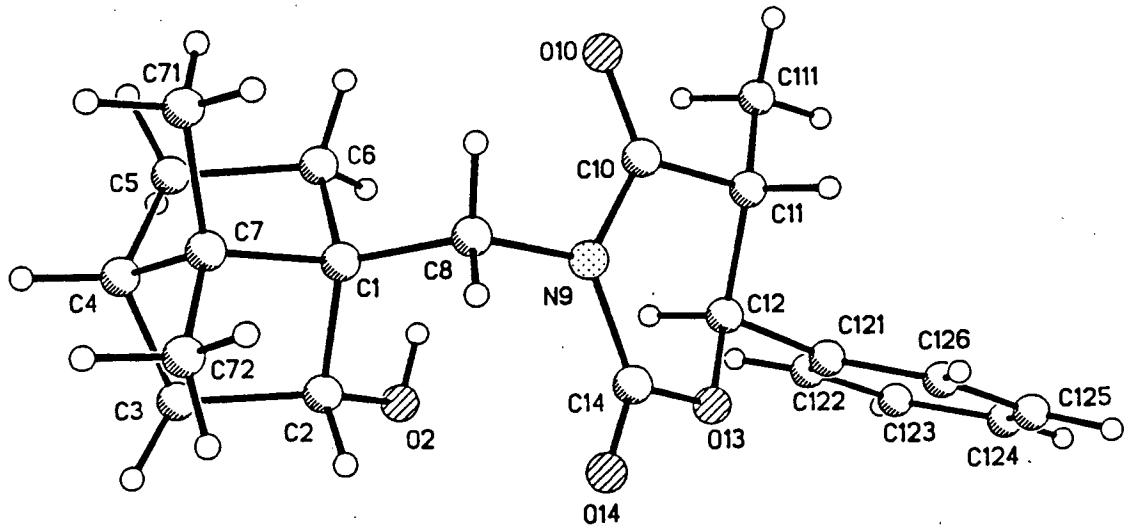
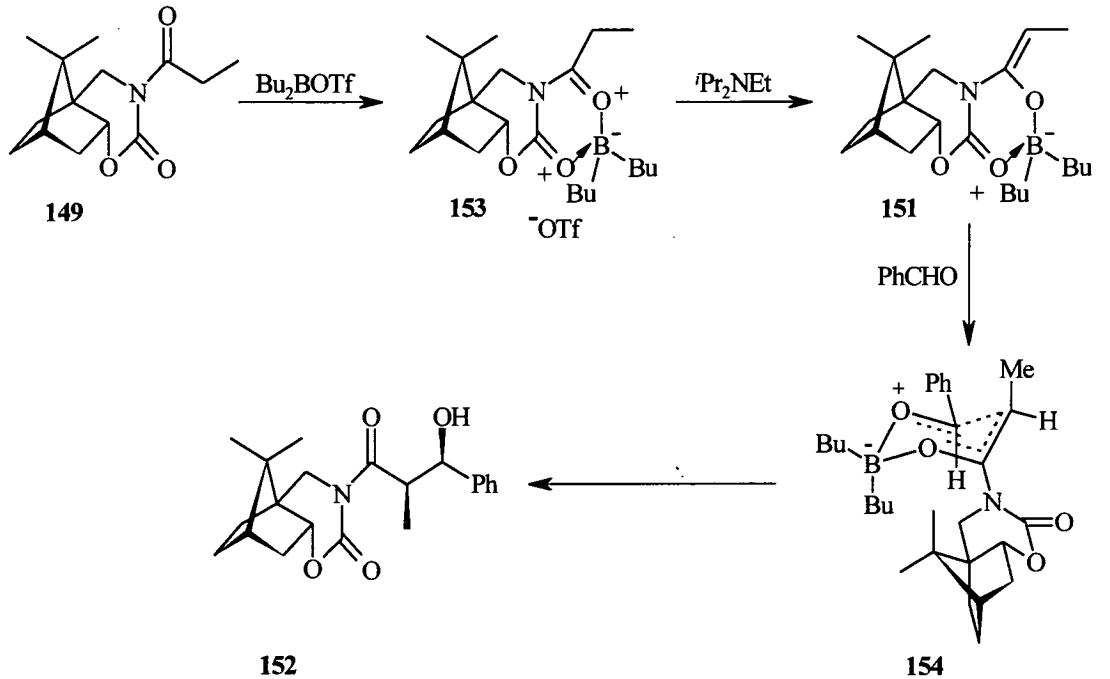


Figure 14. **(a)** Molecular structure of *syn*-aldol **152**, and **(b)** of tetrahydro-1,3-oxazine-2,4-dione **156**

This sense of diastereofacial selectivity is similar to that reported for the corresponding aldol reaction of **108** *via* the boron enolate under the original Evans' conditions[80], but in this case, *anti*-isomers were also formed. The high level of asymmetric induction imparted by oxazinone **106** in this model aldol reaction can be explained by formation of the six-membered Zimmerman-Traxler transition state **154** as shown in Scheme 62.

Essentially from a mechanistic viewpoint, when the dibutylboron triflate is added to **149**, the boron initially co-ordinates to the *N*-acyl carbonyl groups in a tetrahedral fashion to form complex **153**, subsequent treatment of which with diisopropylethylamine then forms the boron enolate **151** (Scheme 62). When benzaldehyde is added to **151**, the B-O bond pertaining to the six-membered ring imide ring is cleaved, and the auxiliary is free to rotate 180° about the N-C bond, thus allowing the boron to co-ordinate to the oxygen of the carbonyl of the incoming aldehyde. The overall outcome is the formation of the six-membered Zimmerman-Traxler transition state **154** as depicted in Scheme 62. It is also worth noting that in the transition state **154**, attack of the benzaldehyde occurs on the C_α-*re* face of the enolate since the bulk of the auxiliary shields the C_α-*si* face.



Scheme 62

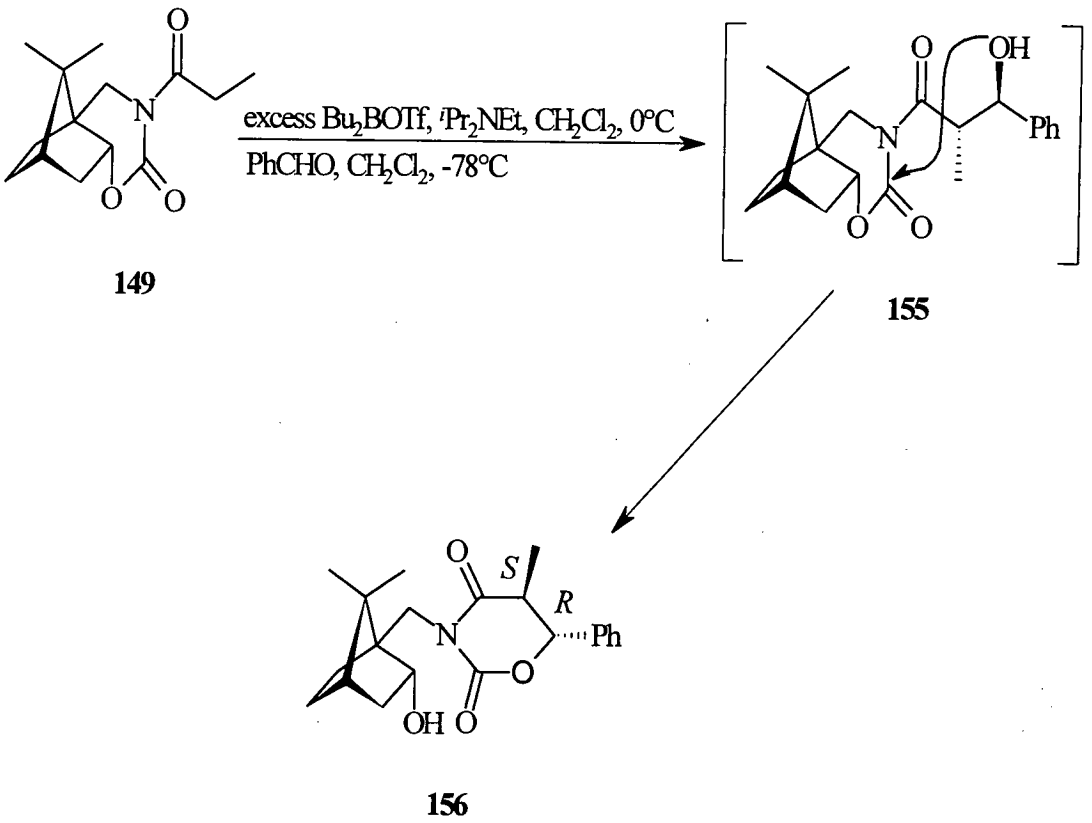
An attempt was made to influence the outcome of the aldol reaction by judicious addition of titanium tetrachloride. Thus, reaction of the boron enolate **151** with a mixture of benzaldehyde (2 equiv.) and titanium tetrachloride (2 equiv.) at -78°C for thirty minutes and then quenching of the reaction with tartaric acid at -78°C yielded a pale yellow oil as a crude aldol product in low yield 40%. Once again, examination of the 250 MHz ^{1}H NMR spectrum of the product established that only one *syn* diastereomer, *viz.* **152** (^3J= 2.6 Hz) had been formed, although, upon purification by flash column chromatography, the starting material **149** was also recovered in 35% yield.

This recovery may have been due in some part to the commercial dibutylboron triflate that was used, but it is also worth noting that an attempted aldol reaction of the *N*-propionate **149** with benzaldehyde in the presence of titanium tetrachloride failed and that the starting material **149** was recovered in 95% yield (*cf.* terpenoid-derived auxiliary **120** in Scheme 53).

7.2.3 Asymmetric *anti*-aldol reaction of [6(*S*)-*endo*]-*N*-propionyl-3-aza-11,11 -dimethyl-5-oxatricyclo[6.2.1.0^{1,6}]undecan-4-one 149 with benzaldehyde *via* excess of boron enolate

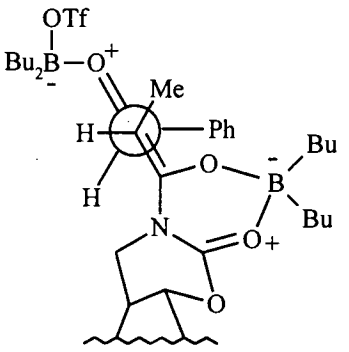
In an attempt to induce *anti*-selectivity with well defined facial bias, we had occasion to investigate the outcome of the same aldol reaction using Heathcock's protocol[57] with an excess of dibutylboron triflate. Thus, treatment of *N*-propionate **149** with 2.2 equiv. of dibutylboron triflate and diisopropylethylamine followed by reaction of the boron enolate with freshly distilled benzaldehyde for thirty minutes at -78°C, and then one and three quarter hours at room temperature, yielded the crude aldol product. However, upon purification by flash chromatography the product isolated in nearly quantitative yield (75%) proved to be the rearranged compound **156** (Scheme 63). Further crystallisation from cyclohexane furnished colourless crystals of the enantiopure tetrahydro-1,3-oxazine-2,4-dione **156** (mp 125-127°C) whose structure

was confirmed by microanalysis, mass spectral and NMR spectroscopy. X-Ray diffraction analysis confirmed the stereochemical integrity of **156** and has shown that the absolute configuration of the chiral centres at C(3) and C(4) is (5*S*,6*R*) (see Fig. 14b and also appendix 4).



Scheme 63

From a mechanistic viewpoint, such a stereochemical outcome provides strong support for the intermediacy of the *anti*-adduct **155** arising from a transition state like **157** where the enolate boron is chelated to the oxazinone carbonyl to give not only the correct sense of diastereofacial selectivity, but also to facilitate ring cleavage of the oxazinone ring. To our knowledge, this seems to be the first example of such a transformation and it is conceivable that the reaction may be extended to related systems under the influence of a Lewis acid.



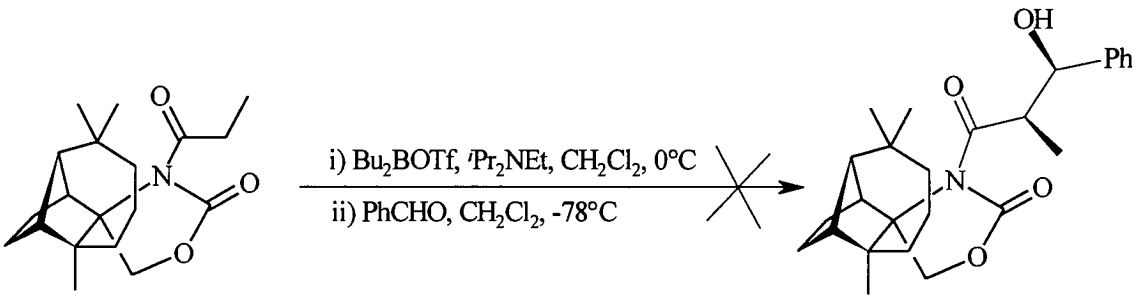
157

Further control experiments also showed that treatment of the *syn*-aldol product **152** with excess boron triflate under Heathcock's conditions gave 1,3-oxazine-2,4-dione **156** in excellent yield (90%) with the required *anti*-stereochemistry exclusively. This outcome pointed to the realisation of a *retro*-aldol reaction and events as before, or else α-epimerisation of **152** before rearrangement. The true pathway is not clear at this stage and will require much more work for a fuller understanding.

7.3 Attempted aldol reaction of (5*R*, 6*S*)-*N*-propionyl-2-oxa-4-aza-8,8,12-trimethyl-5-spiro[4,7]tricyclo[5.3.1.$0^{7,13}$]dodecan-3-one 113 with benzaldehyde *via* boron enolate

It has already been explained that in some instances, steric shielding hindered the functionalisation of certain chiral auxiliaries. For example, the spiro-oxazolidin-2-one **107** was recovered unchanged under usual conditions (see p. 44), and instead required a more forcing method of functionalisation (NaH / toluene / reflux). Even so, treatment of the resulting *N*-propionate **113** with 1.1 equiv. dibutylboron triflate and diisopropylethylamine and then reaction of the resultant enolate with benzaldehyde at -78°C failed to produce an aldol product, and after work-up, gave the recovered starting material **113** (80%), together with a small amount of the cleaved auxiliary **107** (17%). Presumably, this particular reaction did not produce the

desired aldol product **158** due to steric hindrance of the terpenoid structure that prevented approach of the aldehyde (Scheme 64).



113 **158**

Scheme 64

Conclusions

From the diastereotopicity imparted by the terpenoid-derived chiral auxiliaries **60**, **67**, **98**, **99**, **100**, **106** and **108** as measured in terms of diastereomeric excess (*d.e.* %), it is clear that lithium-mediated aldol reactions with benzaldehyde exhibit poor levels of diastereoselectivity, whilst in sharp contrast the corresponding boron enolate reactions with 1.1 equiv. of Bu_2BOTf give rise to only one of the *syn*-aldol products in very high levels of diastereoselectivities.

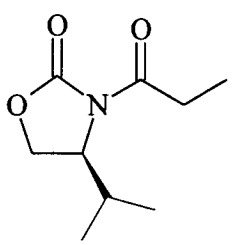
Upon using excess of Bu_2BOTf the boron enolate aldol reaction of **120** produces a mixture of *anti*- and *syn*-aldol products with very poor diastereoselectivity. By quenching the reaction to pH 7, and using a novel work-up protocol utilising tartaric acid, the diastereomeric excess was raised to 22% and moreover, the reaction yielded only one *anti*- and one *syn*-aldol products.

In an attempt to induce further variation in selectivity, the same boron enolate aldol reaction was carried out with 1.1 equiv. of Bu_2BOTf in the presence of titanium tetrachloride. Under these conditions, the reaction yields both *anti*- and *syn*-aldol products in good selectivity (*e.g. anti*:*syn* = 74:26, *d.e* = 48% for propionate **120**).

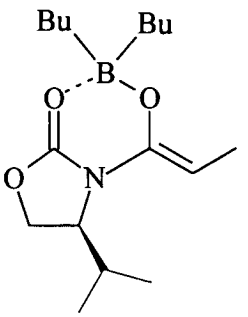
In the presence of excess Bu_2BOTf to promote *anti*-selectivity (Heathcock's conditions), the aldol reaction with the terpenoid-derived 1,3-oxazin-2-one **106** as the chiral control element resulted unexpectedly in ring cleavage by an intramolecular process to form a *N*-substituted tetrahydro-1,3-oxazin-2,4-dione **156**, in virtually quantitative yield, presumably *via* an *anti*-aldol intermediate. Interestingly, when only one equiv. of Bu_2BOTf is used in the same reaction, no ring cleavage is observed and the newly formed chiral centres are found to be *syn* (J = 2.6 Hz). Nonetheless, treatment of this *syn*-aldol product **152** with excess boron triflate under Heathcock's conditions gave the same 1,3-oxazine-2,4-dione **156** with *anti*-stereochemistry exclusively, pointing to realisation of a *retro*-aldol reaction, or else α-epimerisation before rearrangement.

8 Chromium-Reformatsky reaction of α-bromo *N*-propionyl derivatives of certain terpenoid-based auxiliaries

As discussed previously, different aldol stereoisomers can be synthesised from the same carbonyl precursor by simply changing the reaction conditions. Under normal circumstances, when a terpenoid-based *N*-propionyl derivative, *e.g.* **37** is employed in a lithium-enolate mediated asymmetric aldol reaction with benzaldehyde, very low levels of asymmetric induction are observed (*d.e.* = 32%), but access is gained to all four diastereomers with *syn* and *anti*-stereochemistry. By comparison, very high levels of asymmetric induction can be achieved in such reactions if boron enolates are used instead of their lithium counterparts. For example, when the corresponding boron enolate frrom **37** is used, it affords only one *syn*-aldol product upon reaction with benzaldehyde. Indeed, development of such methodology by using different techniques of enolisation of the appropriate *N*-propionyl derivative by employment of various Lewis acids provides access to either *syn* or *anti* aldol products. The stereoselectivity is dependent on several factors, *viz.* the nature of the Lewis acid, the number of equivalents of Lewis acid (with respect to aldehyde), and the order in which the reactants are combined. For example, Walker *et al*[56] showed that the boron enolate derived from **41** can under certain circumstances react with complexed benzaldehyde to give an *anti*-aldol, albeit in conjunction with the *syn*-isomer (74:26). The method consisted simply of using 2 equiv. of dibutylboron triflate in conjunction with diisopropylethylamine (Hünig's base) when forming the boron enolate (see Scheme 20, p. 27).

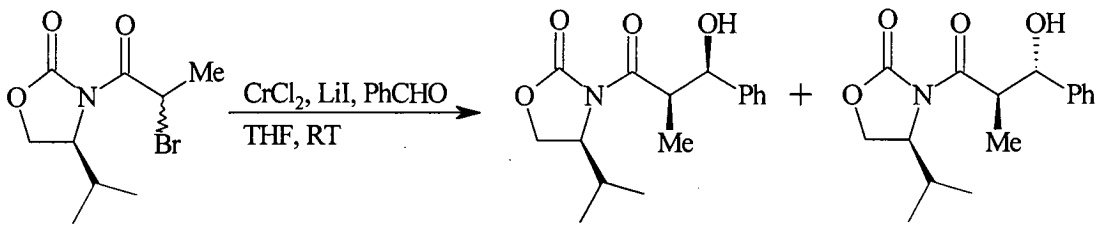


37



41

In an interesting variant of this reaction, Gabriel *et al*[96] employed a chromium-Reformatsky reaction on an α-bromo derivative to achieve an *anti*-selective aldol reaction. Thus, treatment of the 2-bromo propionyl derivative **159** with chromium(II) chloride in presence of lithium iodide, followed by addition of benzaldehyde at room temperature gave a good yield of an aldol product, which was shown by ^{1}H NMR analysis to consist of the *syn*- **160** and *anti*- **161** diastereomers (Scheme 65) in the ratio of 23:77, respectively, *i.e.* the diastereofacial selection (induction) is opposite to that of boron enolates which yields *syn*-preference.

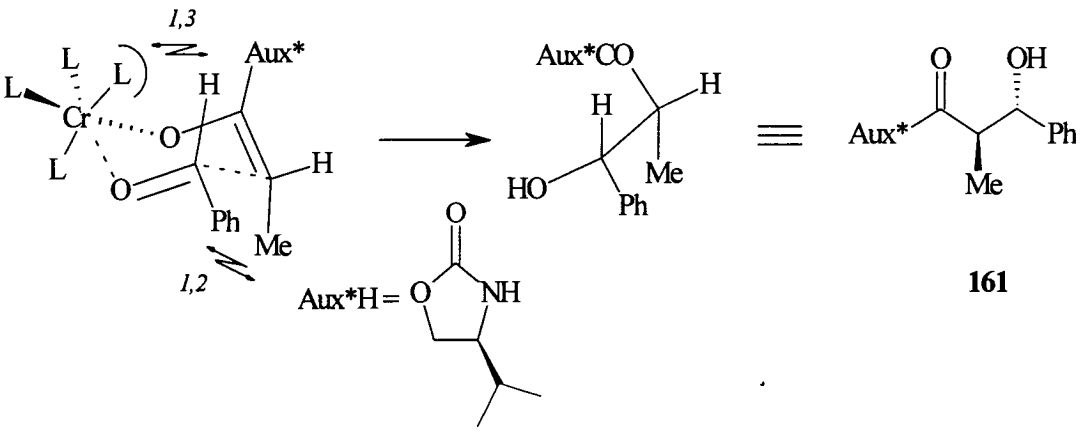


159 **160** **161**

23 : 77

Scheme 65

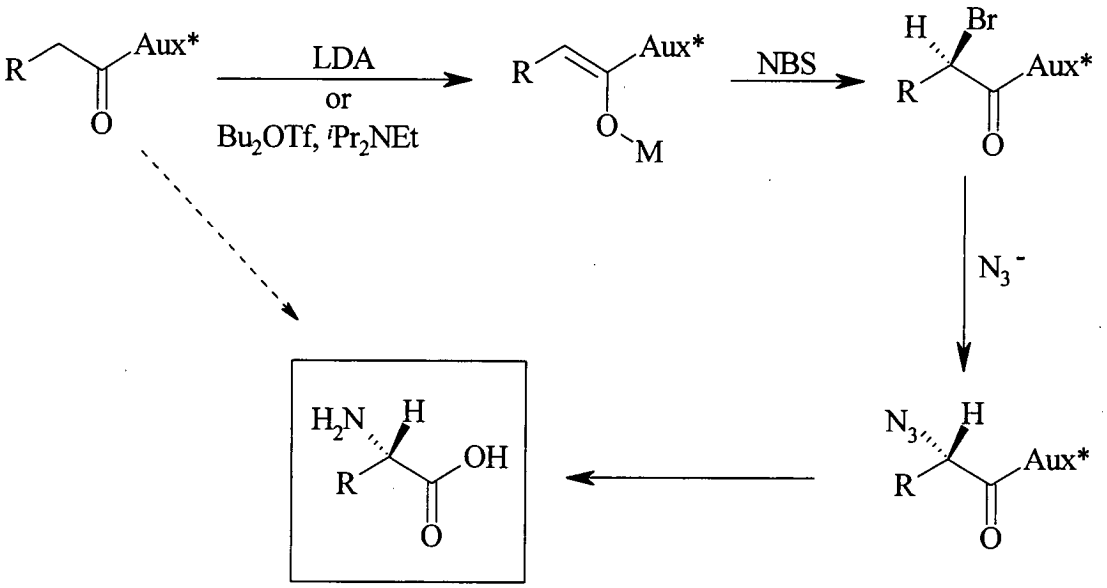
A Zimmerman-Traxler transition state model as depicted in Scheme 66 can be invoked to explain the stereochemical outcome of the reaction[97,98]. In particular, reduced 1,3-interaction of the *endo*-axial chromium ligand with the pseudo-axially oriented aldehydic proton greatly encourages reaction to bring about aldol formation with *anti*-preference, *i.e.* formation of **161**.



161

Scheme 66

It is worth noting that no consideration is given to the stereochemical purity of the α-bromo derivative **159** in its conversion into an aldol product, the outcome being rationalised by complete bond cleavage and the generation of a discrete enolate intermediate as shown in Scheme 66. In this chapter, work was undertaken to explore this aspect in light of access to such α-bromo propionyl derivatives stereoselectively from boron enolates using *N*-bromosuccinimide (NBS). Such methodology has been investigated by Evans[99] and Grant[85] in the Edinburgh laboratories and is of key importance, following displacement of the bromine with azide ion in the synthesis of α-amino acids as depicted in Scheme 67. Grant[85] also examined the selectivity of the reaction of lithium-enolate **137** with NBS and this reaction served as a platform for the attempted synthesis of the model amino acid system, (L)-(+)-alanine (R = Me).

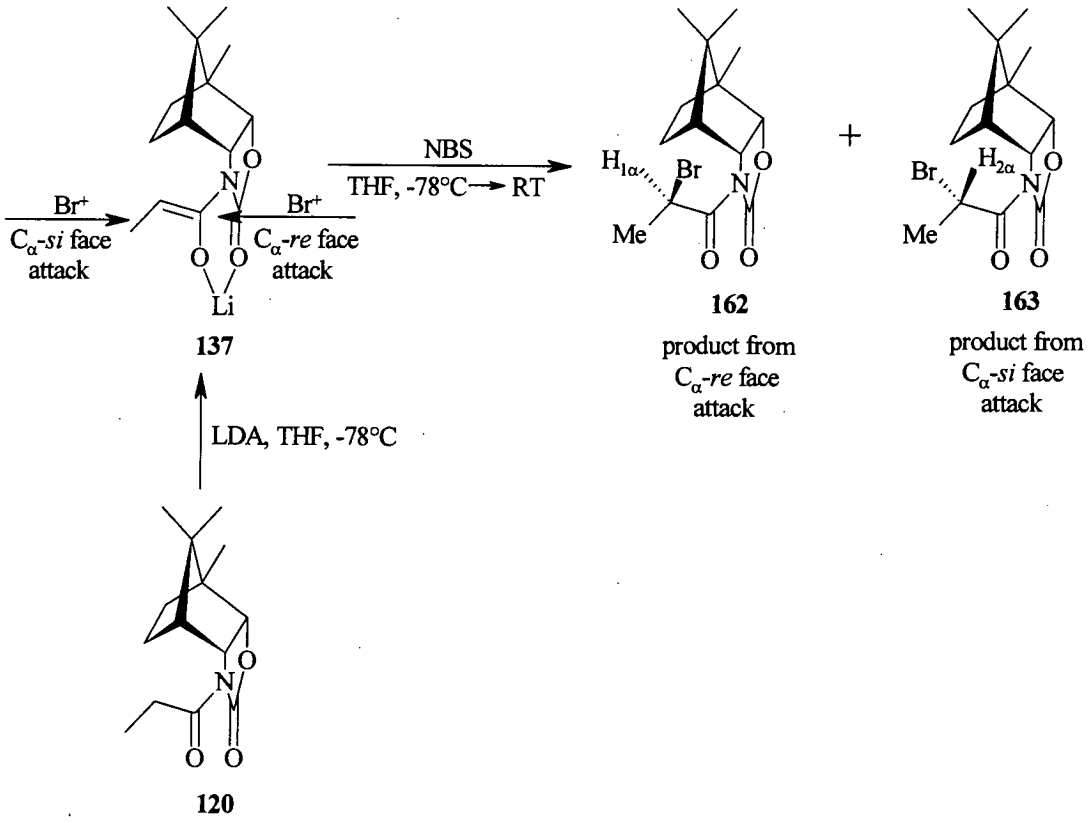


Scheme 67

8.1 α-Bromination reaction of [(2*S*,6*R*)-*endo*]-*N*-propionyl-5-aza-1,10,10-trimethyl-3-oxatricyclo[5.2.1.$0^{2,6}$]decan-4-one 120 with NBS

Following the procedure described by Grant[85], treatment of lithium enolate **137** (see p. 89) with NBS at -78°C for three hours and subsequent analysis by thin-layer chromatography showed that both possible epimers **162** and **163** arising from attack

by bromine at different faces of the enolate had been formed (Scheme 68). The reaction was allowed to warm to room temperature and stirred overnight. After quenching the reaction, the ^{1}H NMR spectrum of the crude product showed that together with the two epimers significant amounts of starting material remained. From thin-layer chromatography, the spot with higher R_f value was the fainter of the two epimers. In fact, this epimer was the minor isomer and was easily separated from the mixture by flash column chromatography on silica in very low yield (9%), followed by the starting material **120** (40%) and then the last fraction, which was the major isomer and isolated in good yield (50%).



Scheme 68

The ratio of the two epimers **162** and **163** could not be determined from analysis of the ^{1}H NMR spectrum of the crude product due to overlap of the signals due to $H_{1\alpha}$ and $H_{2\alpha}$ (Scheme 68). In order to find a solution to this problem, the pair of doublets

due to the vicinal methyl groups at 1.80 ppm were decoupled to make the methine protons collapse to separated singlets. This technique yielded an isomer ratio for the two epimers depicted in Scheme 68 of 6:1.

From consideration of a model of the lithium enolate **137**, it is evident that electrophilic attack can occur from both faces as illustrated, although it is expected that the preferred mode of attack by Br^+ is at the less hindered C_α-*re* face. On this basis, **162** would be predicted to be the configuration of the major epimer, and the product from C_α-*si* face attack, *viz.* **163** being the minor epimer. It is worth noting in this connection that the corresponding α-chloro isomers of **162** and **163** have been synthesised previously in these laboratories by Banks and Dawson[100] and the isomer with the higher R_f value was shown to be the chlorine analogue of **163** by X-ray crystallography (Fig. 15).

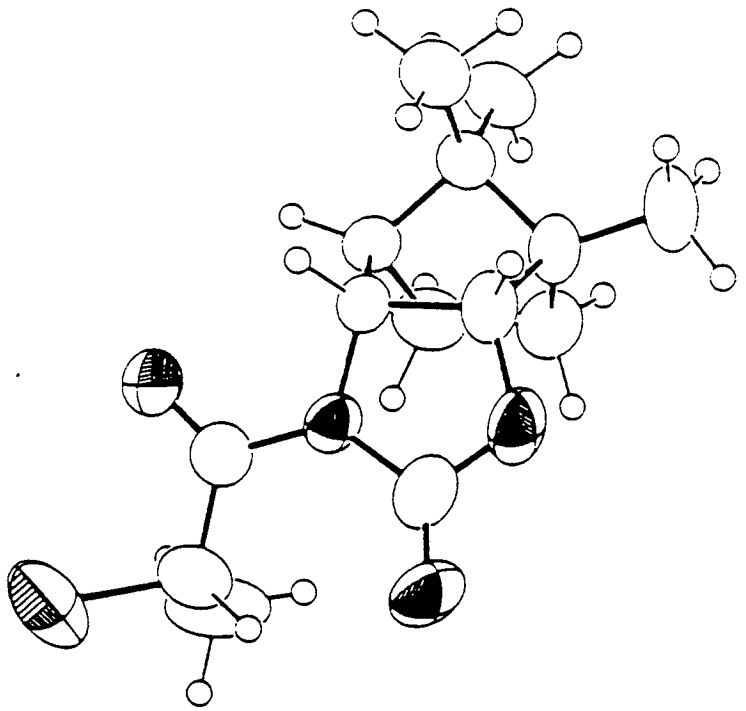
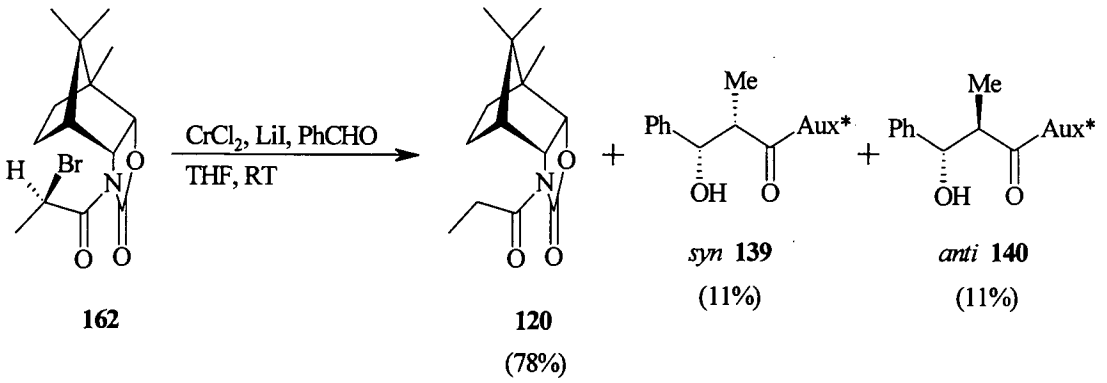


Figure 15. X-ray crystal structure of the α-chloro analogue of **163**.

With the desired α-bromo propionyl compound **162** in hand, application of the chromium-Reformatsky reaction was undertaken. Thus, **162** was treated with chromium chloride (II) in presence of lithium iodide at room temperature, followed by addition of freshly distilled benzaldehyde and stirred at this temperature overnight (Scheme 69). The reaction was quenched with brine to yield the crude product as a pale yellow gum which was analysed by ^{1}H NMR spectroscopy to show large amounts of *N*-propionamide **120** had formed, but also one *syn*-diastereomeric aldol product **139** (^3J = 4.4 Hz) and one *anti*-diastereomer **140** (^3J = 7.0 Hz) in the ratio of 46:58. This ratio was determined by integration of the doublets in the range 5.18-4.80 ppm, arising from the PhC*H*OH protons. The *N*-propionate **120** was isolated in big yield (78%) by flash column chromatography, followed by the *anti*-diastereomer **140** and then the *syn*-diastereomer **139** respectively in equal yield (11%) for each.



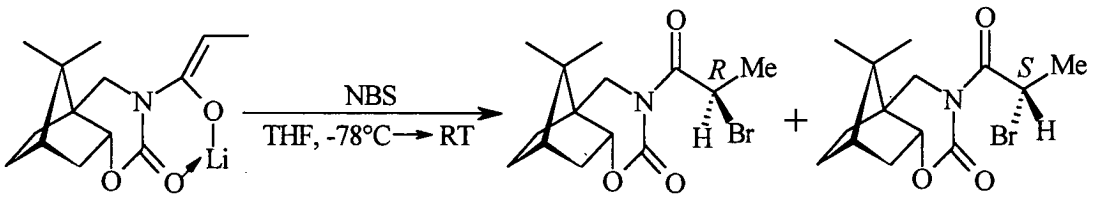
162 → **120** (78%) + *syn* **139** (11%) + *anti* **140** (11%)

Scheme 69

The outcome of the foregoing reaction is stereochemically disappointing, but it is worth comparing the result with that for the lithium-enolate promoted aldol reaction of the parent auxiliary **120** which gave a mixture of all four possible aldol products in a ratio of 55.4:28.7:10.3:5.7, providing a diastereomeric excess of 11%. On the other hand, the boron-enolate afforded virtually only a single isomer (in the ratio >99:<1:0:0) which was confirmed by X-ray crystallography (see chapter 7) to possess the alternative *syn* structure **138**. In essence, all three different approaches allow preparative access to substantial amounts of different aldol products.

8.2 α-Bromination reaction of [6(*S*)-*endo*]-*N*-propionyl-3-aza-11,11-dimethyl-5-oxatricyclo[6.2.1.$0^{1,6}$]undecan-4-one 149 with NBS

Whilst the above studies was carried out with a chiral oxazolidin-2-one, it was decided to extend this work to a six-membered 1,3-oxazin-2-one system. For this purpose, the lithium enolate **150** was generated from imide **149** by means of lithium diisopropylamide as discussed before in section 7.2.1. This was subsequently treated with a solution of NBS, at -78°C in tetrahydrofuran to yield the crude α-bromo derivative as a mixture of diastereomers **164** and **165** in 95% yield (Scheme 70). The diastereoselectivity of this reaction was determined by examination of the 200 MHz ^{1}H NMR spectrum and integration of the quartets at δ 5.87-5.67 ppm, arising from the chiral centre proton C*H*Br. The spectrum revealed that two epimers had been formed in the ratio of 6:1. The major isomer **164** was separated by flash column chromatography in good yield (56%), followed by the starting material **149** (30%), and then the minor isomer **165**, which was obtained in very low yield (9%). The major isomer **164** was recrystallised from cyclohexane (mp = 110.6-111.8°C) and its X-ray crystal structure was obtained and confirmed it to exhibit *R*-stereochemistry as depicted in Scheme 70 (see appendix 5).

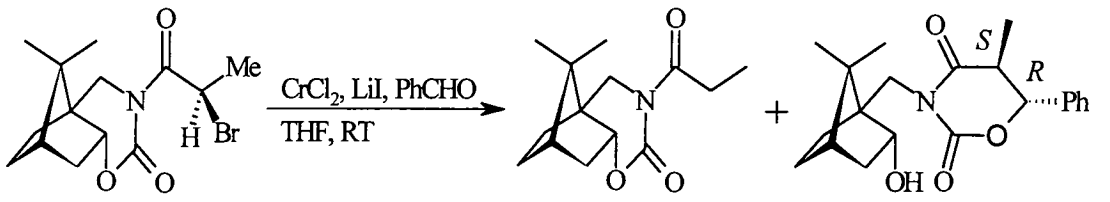


150 **164** **165**

Scheme 70

With the major isomer **164** in hand, the standard procedure used for the chromium-Reformatsky reaction was employed in the hope of obtaining an *anti* aldol product (Scheme 71). Upon work-up in the usual manner, the product was isolated as a pale

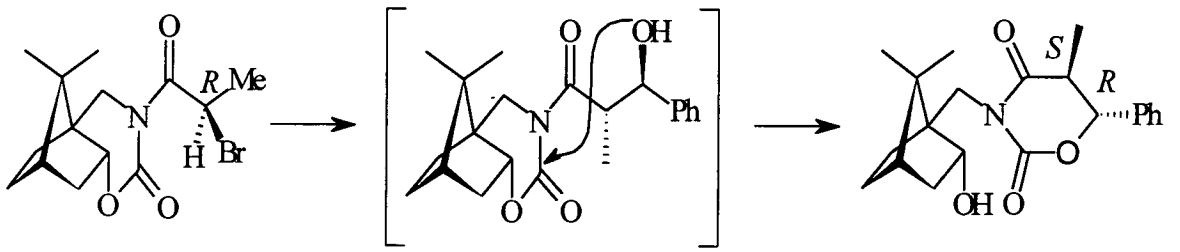
yellow gum, analysis of which by 200 MHz ^{1}H NMR spectroscopy showed large amounts of the *N*-propionate **149** together with the tetrahydro-1,3-oxazin-2,4-dione **156**, which had been previously isolated by an unexpected ring-cleavage of an intermediate *anti*-aldol product (see chapter 7).



164 **149** (75%) **156** (20%)

Scheme 71

The isolation of the ring-cleaved compound **156** (20%) can be taken as strong evidence for the formation of an *anti*-aldol intermediate **155** and its subsequent conversion into **156** as shown in Scheme 72. In passing, it is worth noting that unlike its five-membered ring analogue **162**, the six-membered oxazin-2-one bromo-derivative **164** apparently gave only *anti*-aldol product before rearrangement with no evidence for the *syn*-isomer (*cf.* **139**).



164 **155** **156**

Scheme 72

EXPERIMENTAL

Symbols and Abbreviations

Ar	aromatic
$[\alpha]_D$	specific rotation
b	broad
BP	boiling point
Bu	butyl
cm	complex multiplet
d	doublet
δ	chemical shift
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	*N,N*-dimethylformamide
EI	electron impact
equiv.	equivalents
Et	ethyl
FAB	fast atom bombardment
FT IR	Fourier transform infrared spectroscopy
J	spin-spin coupling constant
Lit.	literature value
M	mol dm^{-3}
M^+	molecular ion
mmol	millimoles
Me	methyl
mp	melting point
m	multiplet
NMR	nuclear magnetic resonance spectroscopy
o,m,p	*ortho, meta, para*
Ph	phenyl
ppm	parts per million
Pr	propyl
s	singlet

TBAB	tetrabutylammonium bromide
TCE	1,1,2,2-tetrachloroethane
THF	tetrahydrofuran
TLC	thin layer chromatography
t	triplet
q	quartet
quat	quaternary
υ_{max}	maximum wave number

1. Instrumentation and General Techniques

1.1 NMR Spectroscopy

Routine ^{1}H NMR spectra were obtained using a Joel PMX-60 spectrometer. Higher field spectra were obtained on a Bruker WP-200 SY operating at 200.13 MHz for ^{1}H and at 50.32 MHz for ^{13}C, or on a Bruker AC-250 spectrometer operating at 250.13 MHz for ^{1}H and at 62.9 MHz for ^{13}C, operated by Mr J.R.A. Millar or Mr W. Kerr. Further high field spectra were obtained on a Bruker WH-360 spectrometer operating at 360.13 MHz for ^{1}H and at 90.56 MHz for ^{13}C, operated by Dr D. Reed.

Chemical shifts (δ) are reported in parts per million using tetramethylsilane (δ 0.0) as a reference.

1.2 Infrared Spectroscopy

Infrared spectra were recorded on a Bio-Rad FTS-7 spectrometer. Liquid samples were recorded as thin films and solid samples as nujol mulls, both on sodium chloride plates.

1.3 Mass Spectrometry

FAB and accurate mass measurements were obtained on a Kratos MS-50 TC spectrometer, operated by Mr A. Taylor. EI spectra were recorded on a AEI MS 902 instrument by Miss E. Stevenson.

1.4 Elemental Analysis

Elemental analysis for carbon, hydrogen and nitrogen were carried out on a Perkin-Elmer 2400 CHN elemental analyser, operated by Mrs L. Eades.

1.5 X-Ray Crystallography

X-Ray crystal structures were determined on a Stoe STADI-4, four circle diffractometer, operated by Dr A. Blake or by Dr S. Parsons.

1.6 Melting Points

Melting points were measured on a digital Gallenkamp capillary tube apparatus and are uncorrected.

1.7 Optical Rotations

Optical rotations were measured on an Optical Activity AA 1000 polarimeter; readings were taken at 589 nm (the sodium D-line) using a 1 dm cell.

1.8 Flash Column Chromatography

Flash column chromatography was routinely carried out using Merck silica gel 60 (mesh size 0.040 - 0.063 mm) as solid support, and a pressure of 10 p.s.i. of compressed air to aid the elution of solvent.

1.9 Thin Layer Chromatography

For analytical purposes, aluminium backed plates, coated with a 0.2 mm layer of silica gel 60, and containing fluorescent indicator were used. Component spots were visualised by ultra-violet light, iodine vapour or by dipping into a 5% sulfuric acid/ethanol solution followed by gentle flaming.

1.10 Drying and Purification of Solvents

Dichloromethane, toluene and TCE were all dried by distilling from finely divided calcium hydride (Fisons) under an argon or nitrogen atmosphere. THF and ether were dried by distilling from sodium and benzophenone, under an argon or nitrogen atmosphere, the solvent was collected when the deep purple colour, due to sodium benzophenone ketyl, had formed.

1.11 Drying of Glassware and Inert Gases

Before conducting moisture sensitive reactions, reaction flasks were dried thoroughly by heating with a strong Bunsen flame whilst flushing with a strong flow of argon.

Argon gas used for reactions was dried by passing the gas through a series of Dreschel vessels containing concentrated sulfuric acid, calcium chloride and self indicating silica gel.

1.12 Moisture Sensitive Reactions

All moisture sensitive reactions were carried out in dry, freshly distilled solvents, under an argon atmosphere using oven or flame-dried glassware.

2 Preparation of *N*-propionyl derivatives of various chiral auxiliaries

2.1 Preparation of (5*S*)-*N*-propionyl-4-aza-2-oxa-6,6-dimethyl-7,10-methylene-5 -spiro[4.5]decan-3-one 110

To dry Mg turnings (0.077g, 3.22mmol, 1.2eq) at room temperature, under argon, was added sufficient ethyl bromide solution in THF (5ml) to just cover the turnings (0.406g, 3.76mmol, 1.4eq). After reaction commenced, more ethyl bromide was added at rate sufficient to sustain the reaction. When all of the Mg turnings had been consumed , the solution was cooled to 0°C and a solution of *auxiliary* **67** (0.427g, 2.69 mmol) in THF (5ml) was added *via* syringe. After stirring at 0°C for 15 minutes, the solution was cooled to -78°C and a solution of freshly distilled propionyl chloride (0.373g, 4.03mmol, 1.5eq) in THF (5ml) was added. The reaction mixture was stirred at -78°C for 1/2 hour , warmed to room temperature, and then left to stir at this temperature under argon for overnight. TLC showed that the reaction was complete. The reaction was quenched with 1M sodium bicarbonate solution, followed by vigorous stirring for 15 minutes. THF was removed *in vacuo*. The mixture was then extracted with dichloromethane (3x50ml), the combined dichloromethane extracts were washed with water (20ml), dried ($MgSO_4$), filtered and evaporated. The resulting residue was subjected to flash column chromatography (100g silica) using hexane:ether (9:1) elution to give **110** as a colourless solid (0.384g , 70%); mp 52-53.5°C (from pentane); $[\alpha]_D^{19}$ = +110.5° (c=6.3,CH_2Cl_2); FTIR (nujol) ν_{max} 1775(oxazolidinone C=O), 1710(C=O) cm^{-1}; ^1H NMR (250MHz , $CDCl_3$) δ 4.32-4.01 (2H, dd, *J*=9.1 Hz, CH_2O), 2.99 (1H, dq, *J*=17.9, 7.3Hz, CH_aH$_b$CH$_3$), 2.80 (1H, dq, *J*=17.9, 7.3Hz, CH$_a$$H_bCH_3$), 2.75 (1H, d, *J*=10.7 Hz, H_L), 2.68 (1H, s, H_K), 1.83 (1H, m), 1.59-1.44 (4H, m), 1.38-1.28 (1H, d, *J*=10.4 Hz, H_D), 1.13 (3H, s, CH_3), 1.12 (3H, t, *J*=7.3 Hz, CH_3CH$_2$), 0.98 (3H, s, CH_3) ppm; ^{13}C NMR (50.3MHz, $CDCl_3$) δ 174.74(C=O), 155.74(C=O), 75.07(C-N), 70.68(CH_2O), 49.04(CH), 47.47($C(CH_3)_2$), 45.00(CH), 38.20(CH_2), 30.54(CH_2), 25.60(CH_3), 23.99,22.54 (2xCH_2), 21.1(CH_3), 8.06(CH_3) ppm; MS (FAB) m/z 135(66%),

196(84), 252(58 M+H); Accurate mass (FAB); Found : 252.15852; $C_{14}H_{22}NO_3$ requires 252.15997.

2.2 Preparation of [(2*S*,6*R*)-*endo*]-*N*-propionyl-5-aza-1,10,10-trimethyl-3 -oxatricyclo[5.2.1.$0^{2,6}$]decan-4-one 120

To a solution of *auxiliary* **60** (0.50 g, 2.56 mmol) in dry THF (20ml), at -78°C under argon, was added *n*-butyllithium (1.76ml of 1.6M solution, 2.82 mmol, 1.1 eq) *via* syringe. After stirring for 30 minutes a solution of freshly distilled propionyl chloride (0.37g, 4.00mmol, 1.56 eq) in THF (5ml) was added dropwise *via* syringe. The resulting solution was stirred at -78°C for 5 minutes before being allowed to warm to room temperature. TLC analysis revealed that the reaction was complete and quenching was effected with sodium carbonate solution. After stirring for 10 minutes at room temperature, the layers were separated and the aqueous layer extracted with dichloromethane (3x20ml). The combined organic extracts were washed successively with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried over ($MgSO_4$), filtered and evaporated to yield a pale yellow oil which was purified by flash chromatography (50g silica) using *n*-hexane:ether (4:1) as elution solvent, followed by Kugelrohr distillation to yield a colourless oil (0.55g, 86%) identified as *the title compound* by comparison to a sample obtained from Grant[85], Bp= 150°C/0.1mmHg; FTIR ν_{max} 1771.5(oxazolidinone C=O), 1697.2 (C=O) cm^{-1}; ^1H NMR (250 MHz , $CDCl_3$) δ 4.56-4.51 (2H, m, C*H*O and C*H*N), 2.97 (1H, dq, *J*=17.7, 7.4 Hz, C$H_a$$H_b$$CH_3$), 2.94 (1H, dq, *J*=17.7, 7.4 Hz, $CH_a$$H_b$$CH_3$), 2.29 (1H, t, *J*=4.3 Hz, bridgehead C*H*), 1.69-1.52 (2H, m), 1.42-1.08 (2H, m) superimposed on 1.12 (3H, t, *J*=7.4 Hz, CH_3CH_2), 0.97 (3H, s, CH_3), 0.96 (3H, s, CH_3), 0.94 (3H, s, CH_3) ppm; ^{13}C NMR (50.3 MHz , $CDCl_3$) δ 170.04(C=O), 154.17(C=O), 82.44(CH), 57.55(CH), 49.23(quatC), 48.26 (quatC), 47.60(CH), 28.79(CH_2), 26.13(CH_2), 19.67(CH_3), 19.61(CH_2), 17.82(CH_3), 13.61(CH_3), 8.16(CH_3) ppm.

2.3 Preparation of (1*S*,4*R*,6*S*)-*N*-propionyl-9-aza-1-isopropyl-4-methyl-7-oxabicyclo[4.3.0]nonane-8-one

A similar procedure to that for the preparation of **120** was adopted for the *N*-propionyl derivative of *auxiliary* **102** although the combined ether extracts were washed with water (20ml), dried ($MgSO_4$), filtered and evaporated to yield a slightly pale yellow viscous oil. The residue was subjected to flash column chromatography (50g silica) using hexane:ether (1:1) elution to give the *title compound* as clear oil which crystallised on standing (0.27g, 42%); mp 51.9-53.2°C; ^{1}H NMR (250 MHz , $CDCl_3$) δ 4.44 (1H, t, C*H*O), 2.93 (1H, dq, *J*=17.7, 7.1 Hz, CH_aH$_b$CH$_3$), 2.85 (1H, dq, *J*=17.7, 7.1 Hz, CH$_a$$H_bCH_3$), 2.68 (1H, septet, CH), 2.25 (1H, m, CH), 1.95-1.08 (6H, m), 0.96-0.91 (9H, m, 3CH_3), 0.86 (3H, t, *J*=7.1 Hz, CH_3CH$_2$) ppm; MS (FAB) m/z 57(22%), 95(17), 137(23), 154(18), 198(32), 254(base M+H); Accurate mass (FAB); Found : 254.17480; $C_{14}H_{24}NO_3$ requires 254.17562.

2.4 Preparation of (1*S*,6*S*)-*N*-propionyl-5-aza-1,6:7,10-di-*O*-isopropylidene-8-hydromethyl-3,9-dioxabicyclo[4.3.0]nonan-4-one 131

A similar procedure to that used for the preparation of **120** was adopted for **131** (from auxiliary **103**), although the combined ether extracts were washed with water (10ml), dried ($MgSO_4$), filtered and evaporated to yield **131** as a colourless syrup, which partially crystallised on standing (0.49g, 83%); $[\alpha]_D^{25}$ = +36.6° (c=2.14,CH_2Cl_2); IR (thin film) ν_{max} 1740(C=O), 1720(C=O) cm^{-1}; ^{1}H NMR (200MHz , $CDCl_3$) δ 4.81 (1H, d, *J*=2.3 Hz, C*H*O), 4.37 (1H, d, *J*=11.3 Hz, CH_2O), 4.30 (1H, d, *J*=11.3 Hz, CH_2O), 4.30-4.27 (1H, m, C*H*) , 4.08 (1H, dd, *J*=13.8, 2.3 Hz, CH_2O-C=O), 4.00 (1H, dd, *J*=13.8, 1.5 Hz, CH_2O-C=O), 2.92 (1H, dq, *J*=16.8, 7.4 Hz, CH_aH$_b$CH$_3$), 2.73 (1H, dq, *J*=16.8, 7.4 Hz, CH$_a$$H_bCH_3$),1.56 (3H, s, C$H_3$), 1.43 (3H, s, C$H_3$),1.35 (3H, s, C$H_3$), 1.34 (3H, s, C$H_3$), 1.14 (3H, t, *J*=7.4 Hz ,CH_3CH$_2$) ppm; ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 173.41(C=O), 153.12(C=O), 116.1(quat C), 108.19(quat C), 100.27(quat C), 97.81(quat C), 73.84(CH), 71.94(CH), 67.01(CH_2), 59.97(CH_2),

30.01(CH_2), 28.53(CH_3), 28.46(CH_3), 27.91(CH_3), 18.31(CH_3), 7.96(CH_3) ppm; Accurate mass (FAB) Found : 358.15015 , $C_{16}H_{24}NO_8$ (M+H) requires 358.15017.

2.5 Preparation of (1*S*,6*S*)-*N*-propionyl-8,8-dimethylbicyclo[4.3.0]-5-aza-3,7,9-trioxanonan-4-one

A similar procedure to that used for the preparation of **120** was adopted for the *N*-propionyl derivative of *auxiliary* **104** although the combined ether extracts were washed with water, dried ($MgSO_4$), filtered and evaporated by high *vacuo* to yield the *title compound* as a pale yellow oil (0.58g, 88%); FTIR ν_{max} 1749(C=O), 1713(C=O) cm^{-1} ; ^1H NMR (250 MHz , $CDCl_3$) δ 6.29 (1H, d, *J*=7.1 Hz, C*H*N), 4.65-4.61 (1H, dt, *J*=7.1, 1.4 Hz, C*H*-CH_2O), 4.38 (1H, dd, *J*=12.5,1.4 Hz, CH_2O) , 4.08 (1H, dd, *J*=12.5,1.4 Hz, CH_2O), 3.03 (1H, dq, *J*=17.7,7.4 Hz, C$H_a$$H_b$$CH_3$), 2.63 (1H, dq, *J*=17.7,7.4 Hz, $CH_aH_bCH_3$) , 1.45 (3H, s, CH_3), 1.39 (3H, s, CH_3), 1.14 (3H, t, *J*=7.4 Hz, C$H_3$$CH_2$) ppm; MS (FAB) m/z 41(61%), 57(25), 98(55), 131(58), 172(85), 214(41), 230(base, M+H); Accurate mass (FAB); Found : 230.10210; $C_{10}H_{16}NO_5$ requires 230.10285.

2.6 Preparation of (7*R*)-*N*-propionyl-10,10-dimethyl-5-thia-4-azatricyclo [5.2.1.0^{3,7}]decan-5,5-dioxide 128

A similar procedure to that used for the preparation of **120** was adopted for **128** (from auxiliary **43**), although the reaction was quenched with saturated ammonium chloride aqueous solution (5ml) and poured onto ether/H_2O (1:1) (20ml). The ether layer was separated and the aqueous layer extracted with ether (3x30ml). The combined ether extracts were washed with water (10ml), dried ($MgSO_4$), filtered and evaporated to yield a colourless solid which recrystallised from hexane/ethylacetate to yield clear colourless needles (0.38g, 60%); mp 149.3-150.7°C (Lit.[86] 134-135°C); ^1H NMR (250 MHz , $CDCl_3$) δ 3.84 (1H, dd, *J*=5.2,2.3 Hz, C*H*N), 3.47 (1H, d, *J*=13.8 Hz,

CH_2-SO_2), 3.41 (1H, d, J=13.8 Hz, CH_2-SO_2), 2.75 (1H, dqd, J =17.1, 7.4, 0.4 Hz, $CH_aH_bCH_3$), 2.71 (1H, dqd, J =17.1, 7.4, 0.4 Hz, $CH_aH_bCH_3$), 2.2-2.03 (1H, m, CH), 1.92-1.84 (4H, m, $2CH_2$), 1.43-1.33 (2H, m, CH_2), 1.14 (3H, t, J =7.4 Hz, CH_3CH_2), 1.14 (3H, s, CH_3), 0.95 (3H, s, CH_3) ppm.

2.7 Preparation of [6(*S*)-*endo*]-*N*-propionyl-3-aza-11,11-dimethyl-5-oxatricyclo [6.2.1.$0^{1,6}$]undecan-4-one 149

A similar procedure to that used for the preparation of **120** was adopted for **149** (from auxiliary **106**), although the combined ether extracts were washed with water (20ml), dried ($MgSO_4$), filtered and evaporated to yield a slightly pale green oil. The residue was subjected to flash column chromatography (50g silica) using hexane:ether (4:1) elution to give **149** which crystallised on standing (0.63g, 98%); mp 79-80°C; FTIR ν_{max} 1739(C=O), 1680(C=O) cm^{-1} ; ^{1}H NMR (250 MHz , $CDCl_3$) δ 4.50-4.42 (1H, ddd, J=4.0,2.5,1.9Hz, C*H*O), 3.53 (1H, d, J=12.2Hz, CH_2N), 3.42 (H, d, J=12.2Hz, CH_2N), 2.99 (1H, dq, J=17.9,7.3Hz, $CH_aH_bCH_3$), 2.74 (1H, dq, J=17.9,7.3Hz, $CH_aH_bCH_3$), 2.26-2.13 (1H, m, C*H* bridgehead), 1.95-1.18(6H, m, $3CH_2$), 1.08 (3H, t, J=7.3Hz, CH_3CH_2), 0.97 (3H, s, CH_3), 0.94 (3H, s, CH_3) ppm; ^{13}C NMR (63MHz, $CDCl_3$) δ 177.83(C=O), 152.64(C=O), 83.58(CH), 47.80(CH_2), 46.75(quat C), 46.25(CH), 45.49(quat C), 32.39(CH_2), 31.20(CH_2), 27.33(CH_2), 24.80(CH_2), 19.63(CH_3), 18.42(CH_3), 9.02(CH_3) ppm; MS (FAB) m/z 57(52%), 135(88), 152(16), 196(22), 251(26 M^+), 252(base M+H); Accurate mass (FAB); Found : 252.15958; $C_{14}H_{22}NO_3$ requires 252.15997.

2.8 Attempted preparation of (5*R*, 6*S*)-*N*-propionyl-2-oxa-4-aza-8,8,12-trimethyl-5-spiro[4,7]tricyclo[5.3.1.$0^{7,13}$]dodecan-3-one 113

(i) *via* Et_2Zn

Diethylzinc (0.63ml of a 1.0M solution, 0.63mmol, 1.1eq) was added to a solution of *auxiliary* **107** (0.15g, 0.57mmol) in dry diethyl ether (30ml) under argon , and the

mixture stirred at room temperature for 1 hour. The reaction mixture was cooled to -78°C and stirred for 10 minutes and then a solution of freshly distilled propionyl chloride (0.159g, 1.71mmol, 3eq) in dry ether (5ml) was added dropwise *via* syringe. The reaction mixture was warmed to room temperature and stirred at this temperature under argon overnight (72 hours). Further analysis by TLC showed that no significant change had taken place and the reaction was quenched with a saturated aqueous solution of sodium bicarbonate (10ml) and stirred vigorously for 15 minutes. The layers were separated and the aqueous layer was extracted into ether (3x20ml). The combined ether extracts were washed with water (2x10ml), dried ($MgSO_4$), filtered and evaporated *in vacuo* to yield a colourless solid which was shown by 200 MHz ^1H NMR spectroscopy to be only starting material.

(ii) *via* EtMgBr

To dry Mg turnings (0.038g, 1.54mmol, 1.2eq) at room temperature under argon, was added sufficient ethyl bromide solution in THF (5ml) to just cover the turnings (0.194g, 1.80mmol, 1.4eq). After reaction commenced, more ethyl bromide was added at rate sufficient to sustain the reaction. When all of the Mg turnings had been consumed, the solution was cooled to 0°C and a solution of *auxiliary* **107** (0.337g, 1.282 mmol) in THF (5ml) was added *via* syringe. After stirring at 0°C for 15 minutes, the solution was cooled to -78°C and a solution of freshly distilled propionyl chloride (0.298g, 1.923mmol, 1.5eq) in THF (5ml) was added. The reaction mixture was stirred at -78°C for 1/2 hour , warmed to room temperature, and then left to stir at this temperature under argon overnight; further analysis by TLC showed that no significant change had taken place. The reaction was quenched with 1M sodium bicarbonate solution, followed by vigorous stirring for 15 minutes. THF was removed *in vacuo* and the residue was then extracted with dichloromethane (3x30ml). The combined dichloromethane extracts were washed with water (20ml), dried ($MgSO_4$), filtered and evaporated *in vacuo* to yield a colourless solid which was shown by 200 MHz ^1H NMR spectroscopy to be only starting material.

2.9 Preparation of (5*R*, 6*S*)-*N*-propionyl-2-oxa-4-aza-8,8,12-trimethyl-5-spiro[4,7]tricyclo[5.3.1.$0^{7,13}$]dodecan-3-one 113

A solution of *auxiliary* **107** (0.150g, 0.57mmol, 1eq) in anhydrous toluene (20 ml) was added to a stirred suspension of oil-free sodium hydride (0.028g, 1.14mmol, 2eq) in toluene (5 ml) under argon. The reaction mixture was heated under reflux for 3 hours, cooled to room temperature and treated dropwise with propionyl chloride (0.11g, 1.14 mmol, 2eq) in toluene (3 ml). The reaction mixture was heated and stirred under reflux for overnight, and then cooled to room temperature and quenched with a saturated aqueous solution of sodium bicarbonate (10 ml) and stirred vigorously for 15 minutes. The layers were separated and the aqueous layer was extracted into dichloromethane (3x20ml). The combined dichloromethane extracts were washed with water (2x10ml), dried ($MgSO_4$), filtered and evaporated *in vacuo* to yield a pale yellow oil. The oil was purified by flash column chromatography (100g silica) using hexane:ether (4:1) elution to give the desired product **113** as a pale yellow oil which crystallised upon standing (0.105g , 58%); mp 84.8 - 86.1°C ; FTIR (nujol) ν_{max} 1791(C=O), 1710(C=O) cm^{-1}; ^1H NMR (250 MHz , $CDCl_3$) δ 4.35 (1H, d, *J*= 8.9 Hz, CH_2O), 4.05 (1H, d, *J*= 8.9 Hz, CH_2O), 3.77 (1H, s, C*H* bridgehead), 2.89 (1H, dq, *J*=17.4, 7.3Hz, CH_aH$_b$CH$_3$), 2.86 (1H, dq, *J*=17.4, 7.3Hz, CH$_a$$H_bCH_3$), 2.07 (1H, s, C*H* bridgehead), 1.92-1.39 (9H, cm, 4 CH_2 and C*H*), 1.25-1.20 (2H, m, CH_2), 1.17 (3H, s, CH_3), 1.13 (3H, t, *J*=7.3Hz, CH_3CH$_2$), 1.12(3H, s, CH_3), 0.97 (3H, s, CH_3) ppm; ^{13}C NMR (63MHz, $CDCl_3$) δ 174.68(C=O), 156.30(C=O), 73.20(CH_2), 69.53(CH), 52.08(quatC), 45.97(CH), 41.90(CH), 38.18(CH_2), 36.12(CH_2), 33.64(quatC), 32.12(CH_3), 31.28(CH_2), 29.57(quatC), 29.05(CH_3), 26.99(CH_2), 25.67(CH_3), 23.49(CH_2), 20.89(CH_2), 8.91(CH_3) ppm; MS (FAB) m/z 29(81%), 41(base),57(44), 69(93), 100(31), 116(18), 204(66), 220(20), 248(43), 263(59), 290(24), 304(59), 320(82 M+H); Accurate mass (FAB); Found : 320.22282; $C_{19}H_{30}NO_3$ requires 320.22257.

3 Preparation of *N*-phenylacetyl derivatives of various chiral auxiliaries

3.1 Preparation of (5*R*)-*N*-phenylacetyl-4-aza-7,8:9,10-di-*O*-isopropylidene-2,6-dioxa-5-spiro[4,5]decan-3-one

To a solution of *auxiliary* **64** (0.1g, 0.33mmol) in dry THF (30ml) at-78°C under argon, was added *n*-butyllithium (0.23ml of 1.6M solution, 0.37mmol, 1.1eq) *via* syringe. After stirring for 30 minutes, a solution of freshly distilled phenylacetyl chloride (0.103g, 0.66mmol, 2eq) in THF (5ml) was added dropwise *via* syringe. The reaction mixture was stirred at -78°C for 5 minutes, and then warmed to room temperature and stirred at this temperature for 2 hours, after which time TLC showed that the reaction was complete. Excess acid chloride was hydrolysed by addition of aqueous saturated sodium carbonate solution (10ml), followed by vigorous stirring for 15 minutes. The solution was poured onto ether/water (1:1) (20ml) and separated. The aqueous layer was extracted with ether (3x20ml) and the combined ether extracts were washed with water (10ml), dried ($MgSO_4$), filtered and silica (3g) added. Evaporation of the solvent gave a free flowing powder which was subjected to flash column chromatography (50g silica) using hexane:ether (1:1) elution to give the *title compound* as a yellow foam. Recrystallisation of the crude product from ethanol gave the desired compound as a colourless solid(0.111g, 80%); mp 155-156°C ; ^{1}H NMR (250 MHz , $CDCl_3$) δ 7.36-7.13 (5H, m, Ph), 5.42 (1H, d, *J*=2.5 Hz, C-1*H*), 4.90 (1H, d, *J*=5.7 Hz, C-4*H*) , 4.57 (1H, d, *J*=5.8 Hz, C-3*H*), 4.53 (1H, d, *J*=10.0 Hz, CH_2O), 4.36 (1H, d, *J*=10.0 Hz, CH_2O), 4.10 (1H, dd, *J*=1.8, 0.7 Hz, C-2*H*), 3.81 (2H, s, CH_2Ph), 1.58 (3H, s, CH_3), 1.45 (3H, s, CH_3), 1.42 (3H, s, CH_3), 1.34 (3H, s, CH_3) ppm. The ^{1}H NMR (250 MHz) spectrum of the prochiral methylene protons H_a and H_b displayed a sharp singlet at 3.81 ppm.

3.2 Preparation of [6(*S*)-*endo*]-*N*-phenylacetyl-3-aza-11,11-dimethyl-5-oxatricyclo[6.2.1.0^{1,6}]undecan-4-one

A similar procedure to that used for the preparation of the *N*-phenylacetyl derivative of *auxiliary* **64** was adopted for *auxiliary* **106** although the reaction was quenched with saturated aqueous solution of sodium bicarbonate (10ml), and then stirred vigorously for 10 minutes. THF was removed *in high vacuo*, and the product was extracted into dichloromethane (3x30ml). The combined extracts were washed with water (10ml), dried ($MgSO_4$), filtered and evaporated to yield a colourless syrup, which was subjected to flash column chromatography (100g silica) using hexane:ether (4:1). Elution gave the *title compound* which crystallised on standing (1.22g, 76%); mp 108.9-110.1°C; FTIR ν_{max} 3062(Ar), 1732(C=O), 1681(C=O) cm^{-1}; ^{1}H NMR (250 MHz , $CDCl_3$) δ 7.40-7.16(5H, m, Ph), 4.51-4.44 (1H, ddd, *J*=4.0,2.4,1.9Hz, C*H*O), 4.28(1H, s, CH_2Ph), 3.60 (1H, d, *J*=12.2Hz, CH_2N), 3.47 (H, d, *J*=12.2Hz, CH_2N), 2.29-2.17 (1H, m, C*H* bridgehead), 2.00-1.25(6H, m, 3CH_2), 1.01(3H, s, CH_3), 0.97(3H, s, CH_3) ppm; ^{13}C NMR (63MHz, $CDCl_3$) δ 175.23(C=O), 152.73(C=O), 134.53(quatC Ar), 129.51(2CH Ar), 128.21(2CH Ar), 126.72(CH Ar), 80.59(CH), 48.22(CH_2), 46.88(quat C), 46.31(CH), 45.66(quat C), 34.90(CH_2), 32.54(CH_2), 27.41(CH_2), 24.91(CH_2), 19.69(CH_3), 18.52(CH_3); ppm; MS (FAB) m/z 41(65%), 93(34), 18(74), 135(60), 152(30), 178(22), 196(46), 237(10), 270(28), 314(base, M+H); Accurate mass (FAB); Found : 314.17563; $C_{19}H_{24}NO_3$ requires 314.17562.

3.3 Preparation of (1*S*,6*S*)-*N*-phenylacetyl-8,8-dimethylbicyclo[4.3.0]-5-aza-3,7,9-trioxanonan-4-one

A similar procedure to that used for the preparation of the *N*-phenylacetyl derivative of *auxiliary* **64** was adopted for *auxiliary* **104** although the reaction was quenched with saturated aqueous solution of sodium bicarbonate (10ml), and then stirred vigorously for 10 minutes. THF was removed *in high vacuo* and the product was

extracted into dichloromethane (3x30ml). The combined extracts were washed with water (10ml), dried ($MgSO_4$), filtered and evaporated to yield a pale yellow oil which was subjected to flash column chromatography (100g silica) using hexane:ether (1:1) elution to give the *title compound* as a sticky colourless gum (0.96g, 57%) that failed to crystallise; FTIR ν_{max} 3063(Ar), 1766(C=O), 1697(C=O) cm^{-1} ; ^1H NMR (250 MHz , $CDCl_3$) δ 7.36-7.16(5H, m, Ph), 6.22 (1H, d, *J*=7.0 Hz, C*H*N), 4.57 (1H, dt, *J*=4.4, 1.5 Hz, C*H*-CH_2O), 4.31 (1H, dd, *J*=11.3,1.1 Hz, CH_2O), 4.24 (1H, d, *J*=15.8 Hz, C$H_a$$H_b$Ph), 4.13 (1H, d, *J*=15.8 Hz, CH_aH_bPh), 3.81 (1H, dd, *J*=11.0,1.5 Hz, CH_2O), 1.47 (3H, s, CH_3), 1.38 (3H, s, CH_3) ppm; ^{13}C NMR (63MHz , $CDCl_3$) δ 173.85(C=O), 151.24(C=O), 133.75(quatC Ar), 129.36(2CH Ar), 128.39(2CH Ar), 127.07(CH Ar), 111.13(quatC), 80.86(CH), 71.77(CH), 66.03(CH_2), 43.18(CH_2), 26.50(CH_3), 25.44(CH_3) ppm; MS (FAB) m/z 41(18%), 116(base), 131(16), 158(7), 174(54), 234(10), 276(8), 292(38, M+H); Accurate mass (FAB); Found : 292.11912; $C_{15}H_{18}NO_5$ requires 292.11850.

3.4 Preparation of phenylacetyl-4-toluenesulfonate

A solution of 4-toluenesulfonyl chloride (12.36g, 64.81mmol, 1eq) in dry DME (20ml) was added to a solution of sodium phenylacetate (10.24g, 64.81mmol, 1eq) in dry DME (40ml). The reaction mixture was heated under reflux overnight (22 hours) and allowed to cool to room temperature, whereupon it was filtered to remove sodium chloride, and the solvent removed *in vacuo*. The crude product obtained was purified by Kugelrohr distillation to yield a pale yellow oil (4.89g, 26%); Bp= 170°C/1.5mmHg; FTIR (nujol) ν_{max} 1712.2 (C=O), 1450, 1175 (OSO_2) cm^{-1}; ^1H NMR (250 MHz , $CDCl_3$) δ 7.93 (2H, d, *J*= 8.5Hz, Ar), 7.41 (2H, d, *J*= 8.7Hz, Ar), 7.35 (5H, m, Ph), 3.66 (2H, s, CH_2), 2.49 (3H, s, CH_3) ppm; ^{13}C NMR (63 MHz , $CDCl_3$) δ 177.94(C=O), 146.72(ArC-SO_2), 141.29(ArC-CH_2), 133.04(ArC-CH_3), 130.04(Ar 2CH), 129.15(Ar 2CH), 128.40(Ar 2CH), 127.09(Ar CH), 126.76(Ar 2CH), 40.80(CH_2), 21.53(CH_3) ppm; MS (EI) m/z 40(26%), 43(7), 51(7), 58(11), 59(27), 63(14), 65(34), 91(base), 92(11), 155(4), no M^+.

3.5 Preparation of phenylacetyl-4-nitrobenzenesulfonate

A solution of 4-nitrobenzenesulfonyl chloride (0.93g, 4.177mmol, 1eq) in dry DME (20ml) was added to a solution of sodium phenylacetate (0.66g, 4.177mmol, 1eq) in dry DME (40ml). The reaction mixture was heated under reflux overnight (22 hours), and allowed to cool to room temperature and then filtered to remove sodium chloride. The solvent was removed *in vacuo* and the crude product was purified by trituration with ether to yield a pale yellow solid (0.23g, 20%); mp 61.5-63.3°C; FTIR (nujol) ν_{max} 3090(Ar CH), 1813(C=O), 1609+1292(NO_2), 1350, 1168 (OSO_2) cm^{-1}; ^1H NMR (250 MHz , $CDCl_3$) δ 8.45 (2H, d, *J*= 9.2Hz, Ar 2 C*H*), 8.24 (2H, d, *J*= 9.2Hz, Ar 2C*H*), 7.32-7.29 (5H, m, Ph), 3.72 (2H, s, CH_2) ppm; ^{13}C NMR (63 MHz, $CDCl_3$) δ 176.94(C=O), 166.78(Ar*C*-NO_2), 148.33(Ar*C*-SO_2), 131.80(Ar*C*-CH_2), 129.21(Ar 2CH), 128.58(Ar 2CH), 128.33(Ar 2CH), 127.41(Ar CH), 124.86(Ar 2CH), 41.82(CH_2), ppm; MS (FAB) m/z 51(56%), 89(50), 91(base), 118(49), 119(55), 156(3), 202(6), 227(32), 256(36), no M^+.

3.6 Preparation of phenylacetic anhydride[101]

A solution of freshly distilled phenylacetyl chloride (5.26g, 34.02mmol, 1eq) in dry ether (20ml) was added to a solution of sodium phenylacetate (5.38g, 34.02mmol, 1eq) in dry ether (20ml) with stirring. The reaction mixture was stirred under argon at room temperature overnight, filtered to remove sodium chloride, and the solvent removed *in vacuo*. The crude product was recrystallised from ether-hexane to yield a colourless solid (8.21g, 95%); mp 71-72.4°C; FTIR (nujol) ν_{max}; 3062(Ar), 1808(C=O), 1740.7(C=O) cm^{-1}; ^1H NMR (60 MHz , $CDCl_3$) δ 7.31 (10H, m, 2Ph), 3.72(4H, s, $2CH_2$) ppm.

3.7 Attempted preparation of [(2*S*,6*R*)-*endo*]-*N*-phenylacetyl-5-aza-1,10,10-trimethyl-3-oxatricyclo[5.2.1.$0^{2,6}$]decan-4-one 114

To a solution of *auxiliary* **60** (0.15g, 0.77mmol) in dry THF (20ml) at -78°C under argon, was added *n*-butyllithium (0.53ml of 1.6M solution, 0.85mmol, 1.1eq) *via* syringe. After stirring for 30 minutes, a solution of phenylacetyl-4-toluenesulfonate (0.45g, 1.54mmol, 2eq) in THF (5ml) was added dropwise *via* syringe. The resulting solution was stirred at -78°C for 5 minutes before being allowed to warm to room temperature. TLC analysis showed that no reaction occurred upon standing overnight or when the reaction was heated under reflux for 22 hours.

A similar reaction in which phenylacetyl-4-nitrobenzenesulfonate was used also failed.

3.8 Preparation of [(2*S*,6*R*)-*endo*]-*N*-phenylacetyl-5-aza-1,10,10-trimethyl -3-oxatricyclo[5.2.1.$0^{2,6}$]decan-4-one 114

(i) *via n*-BuLi and phenylacetyl chloride

To a solution of *auxiliary* **60** (0.15g, 0.77mmol) in dry THF (20ml), at -78°C under argon, was added *n*-butyllithium (0.53ml of 1.6M solution, 0.846mmol, 1.1eq) *via* syringe. After stirring for 30 minutes a solution of phenylacetyl chloride in THF (5ml) was added dropwise *via* syringe. The resulting solution was stirred at -78°C for 5 minutes before being allowed to warm to room temperature. After the reaction mixture reached room temperature it was allowed to stir for overnight at which point the reaction was quenched with saturated aqueous solution of sodium bicarbonate (10ml), and then stirred vigorously for 10 minutes. THF was removed *in high vacuo*, and the product was extracted into dichloromethane (3x30ml). The combined extracts were washed with water (10ml), dried ($MgSO_4$), filtered and evaporated to yield a pale yellow oil, which was subjected to flash column chromatography (100g silica) using hexane:ether (4:1). The *title compound* **114** was eluted as a sticky oil which on

recrystallisation from hexane , followed by washing with pentane gave a colourless solid (0.233g, 97%); mp 75-76.6°C; FTIR (nujol) ν_{max} 3027(Ar), 1771(C=O), 1707(C=O) cm^{-1}; ^1H NMR (250 MHz , $CDCl_3$) δ 7.33-7.22 (5H, m, Ph), 4.60-4.54 (1H, ddd, *J*=9.9, 4.1, 1.3 Hz, C*H*N), 4.52-4.47 (1H, ddd, *J*=9.8, 1.6, 0.8 Hz, C*H*O), 4.33 (1H, d, *J*=15.5 Hz, CH_2Ph), 4.28 (1H, d, *J*=15.5 Hz, CH_2Ph), 2.26 (1H, t, *J*=4.1 Hz, C*H* bridgehead), 1.66-1.24 (4H, m, 2CH_2), 0.97 (3H, s, CH_3), 0.94 (3H, s, CH_3), 0.93 (3H, s, CH_3) ppm; ^{13}C NMR (63 MHz , $CDCl_3$) δ 171.28(C=O), 154.19(C=O), 133.55-126.99 (Ph-), 82.55(CHO), 57.86(CHN), 49.34(quatC), 48.40(quatC), 47.16(CH), 41.29(CH_2), 26.19(CH_2), 19.76(CH_3), 19.53(CH_2), 17.91(CH_3), 13.72(CH_3) ppm; MS (FAB) m/z 41(93%), 69(base), 93(54), 118(68), 135(68), 152(39), 178(64), 196(63), 237(7), 270(24), 314(86, M+H); Accurate mass (FAB); Found : 314.17533 (M+H); $C_{19}H_{24}NO_3$ requires 314.175620.

(ii) *via n*-BuLi and phenylacetic anhydride

To a solution of *auxiliary* **60** (0.172g, 0.88mmol) in dry THF (20ml), at -78°C under argon, was added *n*-butyllithium (0.61ml of 1.6M solution, 0.97mmol, 1.1eq) *via* syringe. After stirring for 30 minutes a solution of phenylacetic anhydride (0.448g, 1.76mmol, 2eq) in THF (5ml) was added dropwise *via* syringe. The resulting solution was stirred at -78°C for 5 minutes before being allowed to warm to room temperature and then stirred at this temperature under argon overnight. The reaction was quenched by saturated aqueous solution of sodium bicarbonate (10ml), and then stirred vigorously for 10 minutes. THF was removed *in vacuo*, and the product was extracted into dichloromethane (3x30ml). The combined extracts were washed with water (10ml), dried ($MgSO_4$), filtered and evaporated to yield a pale yellow oil which was subjected to flash column chromatography (100g silica) using hexane:ether (4:1). Elution afforded the *title compound* **114** as a sticky oil which upon recrystallisation from hexane , followed by washing with pentane was isolated as a colourless solid (0.11g, 40%); mp 74.4-76°C, spectroscopically identical to the compound obtained *via* phenylacetyl chloride (Section 3.8(i))

3.9 Attempted preparation of (5*S*)-*N*-phenylacetyl-4-aza-2-oxa-6,6-dimethyl-7,10-methylene-5-spiro[4.5]decan-3-one 117

(i) *via* EtMgBr and phenylacetyl chloride

To dry Mg turnings (0.074g, 3.08mmol, 1.2eq) at room temperature under argon, was added sufficient ethyl bromide solution in THF (5ml) to just cover the turnings (0.388g, 1.59mmol, 1.4eq). After reaction commenced, more ethyl bromide was added at rate sufficient to sustain the reaction. When all of the Mg turnings had been consumed, the solution was cooled to 0°C and a solution of *auxiliary* **67** (0.5g, 2.56mmol) in THF (5ml) was added *via* syringe. After stirring at 0°C for 15 minutes ,the solution was cooled to -78°C and a solution of freshly distilled phenylacetyl chloride (0.596g, 3.85mmol, 1.5eq) in THF (5ml) was added. The reaction mixture was stirred at -78C for 1/2 hour, warmed to room temperature, and then left to stir at this temperature under argon overnight. Analysis by TLC confirmed that no significant reaction had taken place, and upon work-up, the *auxiliary* **67** was recovered unchanged.

(ii) *via n*-BuLi and phenylacetyl chloride

To a solution of *auxiliary* **67** (0.5g, 2.56mmol) in dry THF (20ml), at -78°C under argon, was added *n*-butyllithium (1.8ml of 1.6M solution, 2.82mmol, 1.1eq) *via* syringe. After stirring for 30 minutes a solution of freshly distilled phenylacetyl chloride (0.793g, 5.13mmol, 2eq) in THF (5ml) was added dropwise *via* syringe. The resulting solution was stirred at -78°C for 5 minutes before being allowed to warm to room temperature. After the reaction mixture reached room temperature it was allowed to stir overnight at which point TLC analysis showed that no reaction had occurred even upon further heating under reflux for 22 hours. Work-up in the usual manner led to the complete recovery of the *auxiliary*.

(iii) *via* NaH and phenylacetic anhydride

A solution of *auxiliary* **67** (0.150g, 0.77mmol, 1eq) in anhydrous toluene (20 ml) was added to a stirred suspension of oil-free sodium hydride (0.037g, 1.54mmol, 2eq) in toluene (5 ml) under argon. The reaction mixture was heated under reflux overnight, cooled to room temperature and treated dropwise with phenylacetic anhydride (0.293g, 1.15 mmol, 1.5eq) in toluene (3 ml). The reaction mixture was heated and stirred under reflux for 24 hours and then cooled to room temperature, but analysis by TLC showed that no significant change had taken place. Work-up in the usual manner resulted in complete recovery of *auxiliary*.

(iv) *via* BzMgBr by using Barbeir reaction method[76]

To a solution of *auxiliary* **67** (0.195g, 1mmol) in dry THF (20ml) at -78°C under argon, was added *n*-butyllithium (0.69ml of 1.6M solution, 1.1mmol, 1.1eq) *via* syringe. After stirring for 30 minutes, the resulting anion solution was added dropwise into an excess of phosgene (pre-treated with calcium hydride to remove traces of HCl) (20ml of 20% solution in toluene). The reaction mixture was stirred at -78°C for 5 minutes, warmed to room temperature and stirred for overnight. Excess of phosgene was evaporated by warming the flask with a water bath whilst maintaining a strong flow of argon. To the carbamyl chloride, which was isolated after evaporation of excess phosgene, was added a solution of benzyl chloride (0.253g, 0.23ml, 2mmol, 2eq) in dry THF (20ml) and the solution added to dry magnesium turnings (0.048g, 2mmol, 2eq) at room temperature under argon *via* syringe pump over 1 hour. TLC analysis showed that no reaction had taken place even when the mixture was heated under reflux overnight. Work-up in the usual manner led to the complete recovery of the *auxiliary*.

(v) *via* α-bromoacetyl derivative 118 and phenyllithium

To a solution of α-bromoacetyl derivative **118** (which was prepared *via* reaction of the *auxiliary* **67** with bromoacetyl bromide, see 3.11) (0.176g, 0.56mmol) in dry THF (20ml) at -78°C under argon, was added phenyllithium (0.43ml of 1.7M solution, 0.73mmol, 1.3eq) *via* syringe. The resulting solution was stirred at -78°C for 3 hours before being allowed to warm to room temperature and stirred at this temperature under argon overnight. TLC analysis of the reaction mixture showed that no significant change had taken place and work-up in the usual manner resulted in complete recovery of starting material.

3.10 Preparation of (5*S*)-*N*-phenylacetyl-4-aza-2-oxa-6,6-dimethyl-7,10-methylene-5-spiro[4.5]decan-3-one 117

Diethylzinc (2.82ml of a 1.0M solution, 2.82mmol, 1.1eq) was added to a solution of *auxiliary* **67** (0.5g, 2.56mmol) in dry diethyl ether (30ml) under argon, and the mixture stirred at room temperature for 1 hour. The reaction mixture was then cooled to -78°C and after 10 minutes, a solution of freshly distilled phenylacetyl chloride (1.19g, 7.69mmol, 3eq) in dry ether (5ml) was added dropwise *via* syringe. The reaction mixture was allowed to warm to room temperature and stirred under argon for 72 hours. The reaction was quenched by addition of a saturated aqueous solution of sodium bicarbonate (10ml) and stirred vigorously for 15 minutes. The layers were separated and the aqueous layer was extracted into ether (3x20ml). The combined ether extracts were washed with water (2x10ml), dried ($MgSO_4$), filtered and evaporated *in vacuo* to yield a pale yellow oil, which was purified by flash column chromatography (100g silica) using hexane:ether (9:1) elution to give the desired product **117** as a colourless solid (0.24g, 30%); mp 83.8-85.4°C; FTIR (nujol) ν_{max} 3030(Ar), 1767(C=O) , 1700(C=O) cm^{-1}; ^1H NMR (250 MHz , $CDCl_3$) δ 7.35-7.23 (5H, m, Ph), 4.27 (1H, d, *J*=16.2 Hz, CH_2Ph), 4.23 (1H, d, *J*=16.2 Hz, CH_2Ph), 4.30 (1H, d, *J*=9.0Hz, CH_2O), 3.99 (1H, d, *J*=9.0 Hz, CH_2O), 2.73 (1H, d, *J*=10.7 Hz, H_L),

2.63 (1H, d, *J*=1.7 Hz, H_K), 1.83 (1H, d, *J*=1.9 Hz, C*H*), 1.59-1.43 (4H, m, 2CH_2), 1.25 (1H, d, *J*=10.7 Hz, C*H*), 1.14 (3H, s, CH_3), 1.00 (3H, s, CH_3) ppm; ^{13}C NMR (63 MHz , $CDCl_3$) δ 171.99(C=O), 155.76(C=O), 134.17-126.79(-Ph), 75.48(quatC), 70.73(CH_2), 49.07(CH), 47.49(quatC), 44.90(CH), 43.27(CH_2), 38.23(CH_2), 25.67(CH_3), 23.99(CH_2), 22.51(CH_2), 21.13(CH_3) ppm; MS (FAB) m/z 133(base), 180(6%), 196(27), 298(6), 314(15, M+H) ; Accurate mass (FAB); Found : 314.176709; $C_{19}H_{24}NO_3$ (M+H) requires 314.17562.

Further elution with ethanol:ether (1:1) resulted in recovery of unreacting *auxiliary* (0.35g , 70%).

3.11 Preparation of (5*S*)-*N*-bromoacetyl-4-aza-2-oxa-6,6-dimethyl-7,10-methylene-5-spiro[4.5]decan-3-one 118

Diethylzinc (2.2ml of a 1.0M solution, 2.2mmol, 1.1eq) was added to a solution of *auxiliary* **67** (0.39g, 2.0mmol) in dry diethylether (20ml) under argon, and the mixture stirred at room temperature for 1 hour. The reaction mixture was then cooled to -78°C and after 10 minutes, a solution of freshly distilled bromoacetyl bromide (1.21g, 0.52ml, 6.0mmol, 3eq) in dry ether (5ml) was added dropwise *via* syringe. The reaction mixture was allowed to warm to room temperature and stirred under argon for 24 hours. The reaction was quenched by addition of a saturated aqueous solution of sodium bicarbonate (10ml) and stirred vigorously for 15 minutes. The layers were separated and the aqueous layer was extracted into ether (3x20ml). The combined ether extracts were washed with water (2x10ml), dried ($MgSO_4$), filtered and evaporated *in vacuo* to yield a yellow oil, which was purified by flash column chromatography (100g silica) using hexane:ether (9:1) elution to give the *title compound* as a colourless solid (0.30g, 48%); mp 108.8 - 110°C; FTIR (nujol) ν_{max} 1769(C=O), 1697(C=O) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.64-4.39 (2H, dd, *J*=13.1Hz, CH_2O), 4.36 (1H, d, *J*=9.1 Hz, CH_2Br I), 4.30 (1H, d, *J*=9.1 Hz, CH_2Br II), 4.10 (1H, d, *J*=9.1 Hz, CH_2Br I), 4.03 (1H, d, *J*=9.1 Hz, CH_2Br II), 2.79-2.70 (1H, dm, C-7 H_L), 2.64-2.27 (1H, m, C-4 *H*), 1.84 (1H, d, *J*=1.9 Hz, C-1 *H*), 1.50-

1.45 (4H, m, C-5H_2 and C-6H_2), 1.30 (1H, d, J=10.6 Hz, C-7H_D), 1.14 (3H, s, CH_3 I), 1.12 (3H, s, CH_3 II), 1.00 (3H, s, CH_3 I), 0.97 (3H, s , CH_3 II) ppm; ^{13}C NMR (63 MHz , $CDCl_3$) δ 171.06(C=O II), 166.37(C=O I), 155.94(C=O II), 155.44(C=O I), 75.95(quat C I), 75.05(quat C II), 71.29(CH_2Br I), 70.68(CH_2Br II), 49.15(CH I), 49.03(CH II), 47.64(quat C I), 47.50(quat C II), 44.96(CH II), 44.73(CH I), 38.16(CH_2), 30.96(CH_2), 25.88(CH_3 II), 25.66(CH_3 I), 23.96(CH_2 II), 23.94(CH_2 I), 22.57(CH_2 II), 22.50(CH_2 I), 21.24(CH_3 I), 21.15(CH_3 II) ppm; MS (FAB) m/z 121(11%), 196(base), 236(20), 238(17), 316(18, M^+ ^{79}Br), 318(10, M^+ ^{81}Br); Accurate mass (FAB); Found : 316.05245; $C_{13}H_{19}{}^{79}BrNO_3$ (M^+ ^{79}Br) and 318.05439; $C_{13}H_{19}{}^{81}BrNO_3$ (M^+ ^{81}Br) requires 316.05483 and 318.05291.

Further elution with ethanol:ether (1:1) resulted in recovery of unreacted *auxiliary* (0.21g, 52%).

3.12 Preparation of (5*S*)-*N*-iodoacetyl-4-aza-2-oxa-6,6-dimethyl-7,10-methylene-5-spiro[4.5]decan-3-one 119

A solution of sodium iodide (0.15g, 1mmol, 2eq) in dry acetone (2ml) was added dropwise to a solution of bromo-derivative **118** (0.158g, 0.5mmol, 1eq) in dry acetone (25ml) at room temperature. The reaction mixture immediately gave a yellow colouration and resulted in formation of a precipitate. After being left to stir at room temperature overnight, the reaction mixture was filtered and the solvent removed *in vacuo*. The isolated product was dissolved in ether, and the solution filtered to remove traces of sodium iodide, and then evaporated *in vacuo* to yield a brown-yellow oil which crystallised slowly upon standing to give **119** as a pale yellow solid (0.175g, 97%); mp 139.8-141.9°C; FTIR (nujol) ν_{max} 1778(C=O), 1689(C=O) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.59 (1H, d, J=10.0Hz, CH_2O), 4.21 (1H, d, J=10.0Hz, CH_2O), 4.34 (1H, d, J=9.1 Hz, CH_2I I), 4.30 (1H, d, J=9.1 Hz, CH_2I II), 4.09 (1H, d, J=9.1 Hz, CH_2I I), 4.02 (1H, d, J=9.1 Hz, CH_2I II), 2.79-2.72 (1H, dm, C-7 H_L), 2.69-2.60 (1H, m, C-4 *H*), 1.85 (1H, s, C-1 *H*), 1.64-1.43 (4H, m, C-5H_2 and C-6H_2), 1.29 (1H, d, J=10.7 Hz, C-7H_D), 1.14 (3H, s, CH_3 I), 1.13 (3H, s,

CH_3 II), 1.03 (3H, s, CH_3 I), 0.98 (3H, s , CH_3 II) ppm; ^{13}C NMR (63 MHz , $CDCl_3$) δ 171.09(C=O II), 168.12(C=O I), 155.89(C=O II), 155.38(C=O I), 75.79(quat C I), 75.00(quat C II), 70.97(CH_2I I), 70.70(CH_2I II), 49.34(CH I), 49.06(CH II), 47.88(quat C I), 47.52(quat C II), 44.99(CH II), 44.63(CH I), 38.26(CH_2), 29.55(CH_2), 25.91(CH_3 II), 25.70(CH_3 I), 23.98(CH_2), 22.59(CH_2 II), 22.53(CH_2 I), 21.21(CH_3 I), 21.18(CH_3 II) ppm; MS (FAB) m/z 43(base), 57(96%), 97(65), 195(60), 196(42), 236(34), 238(50), 364(50, M^+H); Accurate mass (FAB); Found : 364.04047; $C_{13}H_{19}INO_3$ (M^+H) requires 364.04097.

4 Preparation of titanium and tin complexes of *N*-propionyl derivatives of various chiral auxiliaries

4.1 Formation of titanium complex of [(2*S*,6*R*)-*endo*]-*N*-propionyl-5-aza-1,10,10-trimethyl-3-oxatricyclo[5.2.1.$0^{2,6}$]decan-4-one 120

To a solution of *N*-propionamide **120** (0.05g, 0.2mmol, 1eq) in dry chloroform (1ml) at -60°C under argon was added a solution of titanium tetrachloride (0.025ml, 0.23mmol, 1.15eq) *via* syringe. The reaction mixture was warmed to room temperature and then left to stir at this temperature for 2 hours. An attempt to isolate the complex proved impossible due to immediate decomposition upon removal of solvent. A sample of the complex was prepared *in situ* for spectroscopic analysis; ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.34 (1H, d, *J*= 9.8 Hz, C*H*O), 5.12-5.08 (1H, dd, *J*=9.5, 4.1 Hz, C*H*N), 2.82 (1H, dq, *J*= 18.7, 7.0 Hz, $CH_aH_bCH_3$), 2.51 (1H, dq, *J*= 18.7, 7.0 Hz, $CH_aH_bCH_3$), 2.33 (1H, t, *J*= 4.1 Hz, bridgehead C*H*), 1.79-1.48 (4H, m, $2CH_2$), 1.26 (3H, t, *J*= 7.0 Hz, CH_3CH_2), 1.08 (3H, s, CH_3), 1.05 (6H, s, $2CH_3$) ppm; ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 180.41(C=O), 157.44(C=O), 88.71(CH), 61.23(CH), 49.53(quat C), 49.40(quat C), 47.87(CH), 30.36(CH_2), 26.20(CH_2), 19.86(CH_2), 19.73(CH_3), 17.99(CH_3), 13.41(CH_3), 7.12(CH_3) ppm.

4.2 Formation of titanium complex of (2*R* , 6*S*)-*N*-propionyl-3-aza-2,9,9 -trimethyl-5-oxatricyclo[6.1.1.$0^{2,6}$]decan-4-one 122

A procedure similar to that used for **120** was adopted for the formation of the titanium complex of **122**; ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.10 (1H, dd, *J*= 9.0, 2.3 Hz, C*H*O), 2.90 (1H , dq, *J*= 17.4, 7.2 Hz, CH_aH_bC=O), 2.77 (1H, dq, *J*= 17.4, 7.2 Hz, CH_aH_bC=O), 2.70 (1H, d, *J*= 3.8 Hz, H_K), 2.66 (1H, t, *J*= 5.0 Hz, H_J), 2.56-2.49 (1H, m, H_H), 2.21-2.17 (1H, m, H_C), 2.15 (1H, d, *J*= 3.8 Hz, H_F), 1.97 (3H, s, CH_3), 1.43 (3H, s, CH_3), 1.37 (3H, t, *J*= 7.2 Hz, CH_3CH_2), 1.32 (1H, s, H_B), 1.02 (3H, s,

CH_3) ppm; ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 181.39(C=O), 157.37(C=O), 81.02(CH), 72.16(quat C), 49.88(CH), 38.92(quat C), 38.44(CH), 33.52(CH_2), 31.04(CH_2), 27.61(CH_3), 27.21(CH_3), 27.12(CH_2), 24.00(CH_3), 8.53(CH_3) ppm.

4.3 Formation of tin complex of (5*S*)-*N*-propionyl-4-aza-2-oxa-6,6-dimethyl-7,10-methylene-5-spiro[4.5]decan-3-one 110

To a solution of *N*-propionamide **110** (0.05g, 0.20mmol, 1eq) in dry dichloromethane (1ml) at -78°C under argon was added a solution of tin tetrachloride (0.026ml, 0.22mmol, 1.1eq) *via* syringe. The reaction mixture was warmed to room temperature and then left to stir at this temperature for 2 hours. Due to immediate oxidative breakdown, a sample of the complex was prepared *in situ* for spectroscopic analysis; ^1H NMR (360MHz, CD_2Cl_2) δ 4.65 (1H, d, *J*=9.4 Hz, CH_2O), 4.39 (1H, d, *J*=9.4 Hz, CH_2O), 2.99 (1H, dq, *J*=17.5, 7.3Hz, CH_aH$_b$CH$_3$), 2.89 (1H, dq, *J*=17.9, 7.3Hz, CH$_a$$H_bCH_3$), 2.81 (1H, s, H_K), 2.59 (1H, d, *J*=10.9 Hz, H_L), 1.93 (1H, s, H_J), 1.69-1.54 (4H, m, 2CH_2), 1.39 (1H, d, *J*=10.9 Hz, H_D), 1.21 (3H, t, *J*=7.3 Hz, CH_3CH$_2$), 1.20 (3H, s, CH_3), 1.01 (3H, s, CH_3) ppm; ^{13}C NMR (90.6MHz, CD_2Cl_2) δ 175.47(C=O), 160.47(C=O), 79.06(C-N), 74.11(CH_2O), 49.33(CH), 48.38(C(CH_3)$_2$), 45.45(CH), 38.51(CH_2), 31.96(CH_2), 26.03(CH_3), 24.71, 22.71 (2xCH_2), 21.38(CH_3), 9.39(CH_3) ppm.

4.4 Formation of tin complex of (7*R*)-*N*-propionyl-10,10-dimethyl-5-thia-4-azatricyclo[5.2.1.0^{3,7}]decan-5,5-dioxide 128

A procedure similar to that used for **110** was adopted for the formation of the tin complex of **128**; ^1H NMR (360 MHz , CD_2Cl_2) δ 3.96 (1H, dd, *J*=5.6, 1.8 Hz, C*H*N), 3.67 (1H, d, *J*=14.0Hz , CH_2-SO_2), 3.59 (1H, d, *J*=14.0 Hz, CH_2-SO_2), 2.96 (1H, dq, *J* =21.7, 7.6Hz, CH_aH$_b$CH$_3$), 2.89 (1H, dq, *J* =21.7, 7.6 Hz, CH$_a$$H_bCH_3$), 2.29-2.16 (2H, m, C$H_2$), 2.04-1.88 (3H, m, C*H* and CH_2), 1.49-1.39 (2H, m, CH_2), 1.36 (3H, t,

J= 7.6Hz, C*H*$_3$CH$_2$), 1.13 (3H, s, C*H*$_3$), 1.02 (3H, s, C*H*$_3$) ppm; ^{13}C NMR (90.6 MHz, CD_2Cl_2) δ 179.12(C=O), 65.98(CH), 53.22(CH_2), 49.08(quat C), 48.11(quat C), 45.01(CH), 38.78(CH_2), 33.08(CH_2), 29.16(CH_2), 26.31(CH_2), 20.94(CH_3), 19.78(CH_3), 10.76(CH_3) ppm.

4.5 Formation of tin complex of (1*S*,6*S*)-*N*-propionyl-5-aza-1,6:7,10-di-*O*-isopropylidene-8-hydromethyl-3,9-dioxabicyclo[4.3.0]nonan-4-one 131

A procedure similar to that used for **110** was adopted for the formation of the tin complex of **131**; ^{1}H NMR (360MHz, $CDCl_3$) δ 4.74 (1H, d, *J*=2.4 Hz, C*H*O), 4.64 (1H, d, *J*=11.4 Hz, C*H*$_2$O), 4.49 (1H, d, *J*=11.4 Hz, C*H*$_2$O), 4.34-4.32 (1H, m, C*H*), 4.11 (1H, dd, *J*=11.9, 2.3 Hz, C*H*$_2$O-C=O), 4.00 (1H, dd, *J*=11.9, 2.3 Hz, C*H*$_2$O-C=O), 2.95 (1H, dq, *J*=17.4, 7.3 Hz, C*H*$_a$H$_b$CH$_3$), 2.82 (1H, dq, *J*=17.4, 7.3 Hz, CH$_a$*H*$_b$CH$_3$),1.60 (3H, s, C*H*$_3$), 1.46 (3H, s, C*H*$_3$),1.38 (3H, s, C*H*$_3$), 1.36 (3H, s, C*H*$_3$), 1.20 (3H, t, *J*=7.3 Hz ,C*H*$_3$CH$_2$) ppm; ^{13}C NMR (90.5 MHz , CD_2Cl_2) δ 176.35(C=O), 156.88(C=O), 117.32(quat C), 108.33(quat C), 100.73(quat C), 98.70(quat C), 74.12(CH), 72.22(CH), 69.59(CH_2), 60.19(CH_2), 32.45(CH_2), 28.84(CH_3), 28.41(CH_3), 27.88(CH_3), 18.73(CH_3), 9.55(CH_3) ppm.

5 Asymmetric aldol reactions

5.1 Reaction of [(2*S*,6*R*)-*endo*]-*N*-propionyl-5-aza-1,10,10-trimethyl-3-oxatricyclo[5.2.1.$0^{2,6}$]decan-4-one 120

(i) with benzaldehyde in the presence of excess of Bu_2BOTf

To a solution of *N-propionamide* **120** (0.15g, 0.60mmol, 1.0eq) in anhydrous dichloromethane (5ml) at 0°C under argon was added di-*n*-butylboron triflate (1M in dichloromethane, 1.32ml, 1.32mmol, 2.2eq) followed by diisopropylethylamine (0.14g, 1.08mmol, 1.8eq) in dry dichloromethane (*ca.* 5ml). The resulting pale yellow solution was stirred at 0°C for 1 hour before being cooled to -78°C. A solution of freshly distilled benzaldehyde (0.10g, 0.90mmol, 1.5eq) in dichloromethane (2ml) was added dropwise to the boron enolate solution and the reaction mixture was stirred for 30 minutes, whereupon the temperature was allowed to rise to 20°C. The mixture was stirred for a further 1.5 h, quenched with a pH 7 phosphate buffer (50ml) and then extracted into dichloromethane (3x30ml). After evaporation *in vacuo*, the residue was dissolved in methanol (30ml) and the solution cooled to 0°C before being treated with hydrogen peroxide (100 volumes, 3ml) at this temperature. The reaction mixture was then stirred at room temperature overnight, sodium sulfite solution (10ml) was added and the mixture evaporated *in vacuo*. The aqueous residue was extracted with dichloromethane (3x20ml) and the combined organic extracts dried over magnesium sulfate, filtered and evaporated *in vacuo* to yield the crude aldol product as a pale yellow oil (0.195g, 93%). Analysis of this crude aldol product by 200 MHz ^{1}H NMR spectroscopy indicated that two *syn* diastereomers (^3J = 3.5 and 4.2 Hz) and two *anti* diastereomers (^3J = 6.8 and 8.0 Hz) had been formed in the ratio of 31.5:10.5:44:14 respectively (these ratios were determined by integration of the doublets in the range 5.15-4.70 ppm, arising from the PhC*H*OH protons; the *anti*/*syn* assignments were made on the basis of the vicinal coupling constants, which are given). The crude product was subjected to flash

column chromatography using hexane:ether (3:1) for elution. The first fraction to be eluted was unreacted starting material **120** (0.04g, 26%); the second fraction was *anti* diastereomer **140** (0.06g, 30%); mp 114.3-115.5°C; FTIR ν_{max} 3477(OH), 1779(oxazolidinone C=O), 1678(C=O) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.41-7.25 (5H, m, Ph), 4.74 (1H, t, *J*= 6.8 Hz, C*H*OH) 4.59-4.46 (2H, cm, C*H*O and C*H*N), 4.37 (1H, dq, *J*=6.9, 1.1 Hz, C*H*CH_3), 3.13 (1H, d, *J*=6.4 Hz, O*H*), 2.24 (1H, t, *J*=4.0 Hz, bridgehead C*H*), 1.59-1.50 (2H, cm, CH_2), 1.41-1.24 (2H, cm, CH_2), 1.06 (3H, d, *J*=6.9 Hz, CH_3CH), 0.96 (3H, s, CH_3), 0.93 (6H, s, 2CH_3) ppm; ^{13}C NMR (63 MHz, $CDCl_3$) δ 176.79(C=O), 154.21(C=O), 141.96(Ar quatC), 128.35(Ar 2CH), 127.76(Ar CH), 126.46(Ar 2CH), 82.45(CH), 77.03(CH), 58.21(CH), 49.26(quatC), 48.35(quatC), 47.74(CH), 44.09(CH), 26.18(CH_2), 19.76(CH_3), 19.04(CH_2), 17.95(CH_3), 14.84(CH_3), 13.71(CH_3) ppm; MS (FAB) m/z 41(32%), 55(18), 95(7), 117(27), 135(42), 145(62), 178(7), 236(15), 296(11), 340(base), 358(8, M+H); Accurate mass (FAB); Found : 358.20278; $C_{21}H_{28}NO_4$ (M+H) requires 358.20183. The third fraction to be eluted contained two non-separable *syn* diastereomers **138** and **139** (0.07g, 35%); mp 119.9-120.9°C; FTIR ν_{max} 3495(OH), 1777(oxazolidinone C=O), 1688(C=O) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.44-7.21 (5H, m, Ph), 5.13 (1H, d, *J*= 4.2 Hz, C*H*OH I), 5.11 (1H, d, *J*= 3.5 Hz, C*H*OH II) 4.60-4.45 (2H, cm, C*H*O and C*H*N), 4.21 (1H, dq, *J*=7.0, 2.9 Hz, C*H*CH_3 II), 4.12 (1H, dq, *J*=7.0, 2.9 Hz, C*H*CH_3 I), 3.24 (1H, d, *J*=0.3 Hz, O*H* I), 2.92 (1H, d, *J*=0.3 Hz, O*H* II), 2.29 (1H, t, *J*=4.0 Hz, bridgehead C*H* I), 2.23 (1H, t, *J*=4.0 Hz, bridgehead C*H* II), 1.68-1.53 (2H, cm, CH_2), 1.47-1.24 (2H, cm, CH_2), 1.22 (3H, d, *J*=7.0 Hz, CH_3CH II), 1.17 (3H, d, *J*=7.0 Hz, CH_3CH I), 0.97 (3H, s, CH_3), 0.96 (3H, s, CH_3), 0.94 (3H, s, CH_3) ppm; ^{13}C NMR (63 MHz, $CDCl_3$) δ 177.34(C=O I), 176.56(C=O II), 153.84(C=O II) 153.64(C=O I), 141.20(Ar quatC II), 141.09(Ar quatC I), 128.10(Ar 2CH), 127.40(Ar CH II), 127.29(Ar CH I), 126.16(Ar 2CH II), 126.00(Ar 2CH I), 82.52(CH), 77.11(CH), 73.58(CH II), 73.16(CH I), 57.88(CH II), 57.64(CH I), 49.40(quatC I), 49.34(quatC II), 48.48(quatC I), 48.43(quatC II), 47.62(CH), 44.19(CH), 26.18(CH_2), 19.78(CH_3), 19.51(CH_2 I), 19.26(CH_2 II), 17.94(CH_3), 13.71(CH_3), 10.67(CH_3) ppm; MS (FAB) m/z 41(25%), 55(17), 95(10), 117(31), 135(73), 145(98), 178(9), 196(11), 236(18), 296(5), 340(base), 358(11,

M+H); Accurate mass (FAB); Found : 358.20152; $C_{21}H_{28}NO_4$ (M+H) requires 358.20183. The fourth fraction to be eluted contained the other *anti* diastereomer **141** (0.02g, 10%); mp 131.7-132.9°C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.39-7.25 (5H, m, Ph), 4.78 (1H, dd, *J*= 8.0, 4.6 Hz, C*H*OH) 4.60-4.45 (2H, cm, C*H*O and C*H*N), 4.29 (1H, dq, *J*=7.0, 1.2 Hz, C*H*CH_3), 2.96 (1H, d, *J*=5.4 Hz, O*H*), 2.29 (1H, t, *J*=4.2 Hz, bridgehead C*H*), 1.68-1.53 (2H, cm, CH_2), 1.42-1.14 (2H, cm, CH_2), 1.09 (3H, d, *J*=7.0 Hz, CH_3CH), 0.97 (3H, s, CH_3), 0.96 (3H, s, CH_3), 0.94 (3H, s, CH_3) ppm; ^{13}C NMR (63 MHz, $CDCl_3$) δ 176.68(C=O), 154.05(C=O), 141.67(Ar quatC), 128.41(Ar 2CH), 127.88(Ar CH), 126.57(Ar 2CH), 82.51(CH), 76.72(CH), 57.66(CH), 49.39(quatC), 48.45(quatC), 47.68(CH), 44.55(CH), 26.20(CH_2), 19.78(CH_3), 19.54(CH_2), 17.93(CH_3), 15.05(CH_3), 13.72(CH_3) ppm; MS (FAB) m/z 41(36%), 55(23), 95(12), 117(37), 135(45), 145(base), 178(16), 236(16), 296(3), 340(85), 358(21, M+H); Accurate mass (FAB); Found : 358.20119; $C_{21}H_{28}NO_4$ (M+H) requires 358.20183.

(ii) with benzaldehyde in the presence of excess of Bu_2BOTf and quenching with tartaric acid

The foregoing reaction was quenched at -78°C with tartaric acid (4g), and then warmed to room temperature for 2 hours, following which the reaction mixture was partitioned between dichloromethane and water. After separation, the aqueous layer was extracted with dichloromethane (2x15ml) and the combined organic layers washed with a saturated aqueous solution of sodium bicarbonate (2x20ml), cooled to 0°C and mixed with a 3:1 methanol/30% hydrogen peroxide solution (20ml). After stirring overnight at room temperature, the solution was further extracted with dichloromethane (2x20ml), washed with saturated aqueous solution of sodium bicarbonate (20ml) and brine (20ml). The combined organic extracts were dried over magnesium sulfate, filtered and evaporated *in vacuo* to yield the crude aldol product as a colourless solid (0.17g, 81%). Analysis of which by 200 MHz ^{1}H NMR spectroscopy showed that one *syn* diastereomer **139** (^3J = 4.4 Hz) and one *anti*

diastereomer **141** (^3J = 7.4 Hz) had been formed in the ratio of 39:61, respectively as determined by integration of the doublets in the range 5.15-4.70 ppm, arising from the PhC*H*OH protons; the *anti/syn* assignments were made on the basis of the vicinal coupling constants, which are given. The crude aldol product was subjected to flash column chromatography using hexane:ether (3:1) elution. The first fraction to be eluted was unreacted starting material **120** (0.08g, 53%), followed by a second fraction that contained the *anti* diastereomer **141** (0.05g, 25%); the third fraction contained the *syn* diastereomer **139** (0.04g, 20%).H_3), 0.88 (6H, s, 2CH_3) ppm. Both compounds were in complete spectroscopic agreement with those described in part (i).

(iii) with benzaldehyde in the presence of dicyclohexylboron bromide

To a solution of *N-propionamide* **120** (0.15g, 0.60mmol, 1.0eq) in anhydrous dichloromethane (15ml) at 0°C under argon was added dicyclohexylboron bromide[92] (0.262g, 1.02mmol, 1.7eq) followed by freshly distilled triethylamine (0.11g, 1.08mmol, 1.8eq) in dry dichloromethane (*ca.* 2ml). The resulting pale yellow solution was stirred at 0°C for 1.5 hour before being cooled to -78°C. A solution of freshly distilled benzaldehyde (0.1g, 0.9mmol, 1.5eq) in dichloromethane (2ml) was added dropwise *via* syringe to the boron enolate solution and the reaction mixture allowed to stir at -78°C for 4 hours before being warmed to room temperature and stirred overnight. The solution was quenched with a pH 7 phosphate buffer (30ml) and then extracted into dichloromethane (3x20ml). After evaporation *in vacuo*, the residue was dissolved in 3:1 methanol:pH 7 buffer (30ml) and the solution cooled to 0°C before being treated with hydrogen peroxide (100 volumes, 3ml) at this temperature. The reaction mixture was then stirred at room temperature for 30 minutes, diluted with water (10ml) and then the mixture evaporated *in vacuo*. The aqueous residue was extracted with dichloromethane (3x20ml) and the combined organic extracts dried over magnesium sulfate, filtered and evaporated *in vacuo* to yield the crude aldol product as a pale yellow oil. Analysis of this crude aldol product

by 250 MHz ^{1}H NMR spectroscopy showed that only two *syn* diastereomers (^3J = 2.6 and 3.3Hz) had been formed in the ratio of 76:24 respectively (these ratios were determined by integration of the doublets in the range 5.23-5.02 ppm, arising from the PhC*H*OH protons; the *syn/syn* assignments were made on the basis of the vicinal coupling constants, which are given). The crude product was subjected to flash column chromatography using hexane:ether (4:1) for elution. The first fraction to be eluted was unreacted starting material **120** (0.125g, 83%); the second fraction contained two non-separable *syn* diastereomers **138** and **139** (0.03g, 16%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35-7.15 (5H, m, Ph), 5.22 (1H, d, *J*= 2.6 Hz, C*H*OH II), 5.05 (1H, d, *J* = 3.3 Hz, C*H*OH I) 4.51-4.38 (2H, cm, C*H*O and C*H*N), 4.06 (1H, dq, *J* =7.0, 3.7 Hz, C*H*CH_3), 3.18 (1H, bs, O*H*), 2.23 (1H, t, *J* =4.0 Hz, bridgehead C*H*), 1.63-1.49 (2H, cm, CH_2), 1.40-1.18 (2H, cm, CH_2), 1.11 (3H, d, *J* =7.0 Hz, CH_3CH I), 1.10 (3H, d, *J* =7.0 Hz, CH_3CH II), 0.92 (3H, s, CH_3), 0.91 (3H, s, CH_3), 0.88 (3H, s, CH_3) ppm (*vide supra*).

(iv) with benzaldehyde in the presence of Bu_2BOTf and titanium tetrachloride

To a solution of *N-propionamide* **120** (0.15g, 0.60mmol, 1.0eq) in anhydrous dichloromethane (10ml) at 0°C under argon was added di-*n*-butylboron triflate (1M in dichloromethane, 0.66ml, 0.66mmol, 1.1eq) followed by diisopropylethylamine (0.14g, 1.08mmol, 1.8eq) in dry dichloromethane (*ca.* 5ml). The resulting pale yellow solution was stirred at 0°C for 1 hour before being cooled to -78°C. A solution of freshly distilled benzaldehyde (0.13g, 1.20mmol, 2eq) and titanium tetrachloride (1M in dichloromethane, 1.2ml, 1.2mmol, 2eq) in dichloromethane (5ml) was added dropwise *via* syringe to the boron enolate solution and the reaction mixture was stirred for 30 minutes. When warmed to room temperature, the solution was stirred for a further 1.5 hour before being quenched with a pH 7 phosphate buffer (30ml) and then extracted into dichloromethane (3x30ml). After evaporation *in vacuo*, the residue was dissolved in methanol (30ml) and the solution cooled to 0°C before being treated with hydrogen peroxide (100 volumes, 3ml) at this temperature.

The reaction mixture was then stirred at room temperature overnight, sodium sulfite solution (10ml) was added and the solution evaporated *in vacuo*. The aqueous residue was extracted with dichloromethane (3x20ml) and the combined organic extracts dried over magnesium sulfate, filtered and evaporated *in vacuo* to yield the crude aldol product as a pale yellow oil (0.175g, 83%). Analysis of this crude material by 200 MHz ^{1}H NMR spectroscopy showed that one *syn* diastereomer **139** (^3J = 4.4Hz) and one *anti* diastereomer **140** (^3J = 7.3 Hz) had been formed in the ratio of 74:26 respectively (these ratios were determined by integration of the doublets in the range 5.15-4.65 ppm, arising from the PhC*H*OH protons; the *anti/syn* assignments were made on the basis of the vicinal coupling constants, which are given). The crude product was subjected to flash column chromatography using hexane:ether (4:1) elution. The first fraction to be eluted was unreacted starting material **120** (0.08g, 53%); followed by a second fraction that contained the *anti* diastereomer **140** (0.05g, 25%); the third fraction to be eluted was *syn* diastereomer **139** (0.04g, 20%).

5.2 Reaction of [6(*S*)-*endo*]-*N*-propionyl-3-aza-11,11-dimethyl-5-oxatricyclo [6.2.1.0$^{1.6}$]undecan-4-one149

(i) with benzaldehyde in the presence of Bu_2BOTf

To a solution of *N-propionamide* **149** (0.25g, 1mmol, 1.0eq) in anhydrous dichloromethane (10ml) at 0°C under argon was added di-*n*-butylboron triflate (1M in dichloromethane, 1.1ml, 1.1mmol, 1.1eq) followed by diisopropylethylamine (0.23g, 1.8mmol, 1.8eq) in dry dichloromethane (*ca.* 5ml). The resulting pale yellow solution was stirred at 0°C for 1 hour before being cooled to -78°C. A solution of freshly distilled benzaldehyde (0.16g, 1.5mmol, 1.5eq) in dichloromethane (2ml) was added dropwise to the boron enolate solution and the reaction mixture was stirred for 30 minutes, whereupon the temperature was allowed to rise to 20°C. The mixture was stirred for a further 2 hours, quenched with a pH 7 phosphate buffer (30ml) and then extracted into dichloromethane (3x20ml). After evaporation *in vacuo*, the

residue was dissolved in methanol (30ml) and the solution cooled to 0°C before being treated with hydrogen peroxide (100 volumes, 3ml) at this temperature. The reaction mixture was then stirred at room temperature overnight, sodium sulfite solution (10ml) was added and the mixture evaporated *in vacuo*. The residue was extracted with dichloromethane (3x20ml) and the combined organic extracts dried over magnesium sulfate, filtered and evaporated *in vacuo* to yield the crude aldol product as a pale yellow oil (0.20g, 55%). Examination of the 250 MHz ^{1}H NMR spectrum of this crude aldol product confirmed that only one *syn* diastereomer **152** (^3J = 2.6 Hz) had been formed. (diastereomeric excess =100%) (only one doublet at 5.27 ppm arising from the PhC*H*OH proton). The crude product was subjected to flash column chromatography using hexane:ether (4:1) for elution. The first fraction to be eluted was unreacted starting material **149** (0.084g, 33.5%) and the second fraction contained the *syn* diastereomer **152** (0.086g, 25%); mp 120.7-122.2°C; FTIR (nujol) ν_{max} : 3560(OH), 1732(C=O), 1674(C=O) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.44-7.20 (5H, cm, Ph), 5.27 (1H, d, *J* =2.6Hz, C*H*OH), 4.56-4.49 (1H, ddd, *J* =4.0,2.4,2.0Hz, C*H*O), 4.10 (1H, dq, *J* =7.1, 2.6Hz, C*H*CH_3), 3.59 (1H, d, *J* =12.2Hz, CH_2N), 3.48 (1H, d, *J* =12.2Hz, CH_2N), 2.73 (1H, broad s, O*H*), 2.31-2.21 (1H, m, C*H* bridgehead), 1.99-1.24 (6H, cm, 3CH_2), 1.02 (3H, d, *J* =7.1Hz, CH_3CH), 1.02 (3H, s, CH_3), 0.99 (3H, s, CH_3) ppm; ^{13}C NMR (63 MHz, $CDCl_3$) δ 181.16(C=O), 152.67(C=O), 141.26(Ar C), 127.94(Ar 2CH), 127.01(Ar CH), 125.95(Ar 2CH), 80.84(CH), 72.64(CH), 48.34(CH_2), 46.99(quat C), 46.38(CH), 45.85(quat C + CH), 32.48(CH_2), 27.44(CH_2), 25.00(CH_2), 19.75(CH_3), 18.61(CH_3), 10.58(CH_3) ppm; MS(FAB) m/z 55(29%), 95(11), 117(64), 135(80), 145(base), 178(7), 240(3), 296(12), 340(68), 358(11); Accurate mass (FAB); Found : 358.20073; $C_{21}H_{28}NO_4$ (M+H) requires 358.20183.

(ii) with benzaldehyde in the presence of lithium diisopropylamide (LDA)

A solution of LDA (0.66mmol, 1.1eq) was prepared by the dropwise addition of *n*-butyllithium (0.42ml of 1.6M solution, 0.66mmol, 1.1eq) to a solution of anhydrous

diisopropylamine (0.067g, 0.66mmol, 1.1eq) in dry THF (10ml) at 0°C under argon. The solution was stirred at 0°C for 30 minutes, cooled to -78°C and treated with a solution of *N-propionamide* **149** (0.15g, 0.60mmol, 1eq) in THF (10ml). The reaction mixture was stirred at this temperature for a further 30 minutes before addition of a solution of freshly distilled benzaldehyde (0.070g, 0.66mmol, 1.1eq) in dry THF (2ml) with rapid stirring. The reaction mixture was quenched after 2 minutes with saturated ammonium chloride solution (5ml), water (20ml) was added and the products were extracted into ether (3x20ml). The combined ether layers were washed with water (10ml), dried over magnesium sulfate and evaporated to dryness *in vacuo* to yield the crude aldol product as a colourless gum (0.19g, 90%). Analysis of this product by 250 MHz ^{1}H NMR spectroscopy showed that only one *syn* diastereomer (^3J= 2.6 Hz) and two *anti* diastereomers (^3J= 11.5 Hz) had formed in the ratio of 29:38:33 respectively (these ratios were determined by integration of the doublets in the range 5.28-4.97 ppm, arising from the PhC*H*OH protons).

(iii) with benzaldehyde in the presence of Bu_2BOTf and titanium tetrachloride

To a solution of *N-propionamide* **149** (0.15g, 0.60mmol, 1.0eq) in anhydrous dichloromethane (10ml) at 0°C under argon was added di-*n*-butylboron triflate (1M in dichloromethane, 0.66ml, 0.66mmol, 1.1eq) followed by diisopropylethylamine (0.14g, 1.08mmol, 1.8eq) in dry dichloromethane (*ca.* 5ml). The resulting pale yellow solution was stirred at 0°C for 1 hour before being cooled to -78°C. A solution of freshly distilled benzaldehyde (0.13g, 1.20mmol, 2eq) and titanium tetrachloride (1M in dichloromethane, 1.2ml, 1.2mmol, 2eq) in dichloromethane (5ml) was added dropwise *via* syringe to the boron enolate solution and the reaction mixture was stirred for 30 minutes. The reaction was quenched at -78°C with tartaric acid (4g), warmed to room temperature, and then stirred for a further 2 hours before being partitioned between dichloromethane and water. The aqueous layer was extracted with dichloromethane (2x15ml), and the combined organic layers washed with saturated aqueous solution of sodium bicarbonate (2x20ml), separated and

cooled to 0°C before treatment with a 3:1 methanol/30% hydrogen peroxide solution (20ml). After leaving overnight at room temperature, the solution was extracted with dichloromethane (2x20ml), washed with saturated aqueous solution of sodium bicarbonate (20ml), and then brine (20ml). The combined organic extracts were dried over magnesium sulfate, filtered and evaporated *in vacuo* to afford the crude aldol product as a pale yellow oil (0.14g, 67%). Examination of the 250 MHz ^{1}H NMR spectrum of this crude material showed that only one *syn* diastereomer **152** (^3J = 2.6 Hz) had been formed. (diastereomeric excess =100%) owing to the presence of only one doublet arising from the PhC*H*OH proton at 5.27 ppm. The crude product was subjected to flash column chromatography using hexane:ether (4:1) for elution. The first fraction to be eluted was unreacted starting material **149** (0.05g, 35%) and the second fraction contained the *syn* diastereomer **152** (0.077g, 38%) (*vide supra*).

5.3 Preparation of 1-methylene-*N*-tetrahydro-(5`*S*)-methyl-(6`*R*)-phenyl-1`,3`-oxazin-2`,4`-dione-7,7-dimethyl-[(3*S*)-*endo*]-hydroxy-bicyclo[2.2.1]heptane 156

(i) by treatment of [6(*S*)-*endo*]-*N*-propionyl-3-aza-11,11-dimethyl-5-oxatricyclo [6.2.1.0$^{1.6}$]undecan-4-one 149 with benzaldehyde in the presence of excess of Bu_2BOTf

To a solution of *N-propionamide* **149** (0.15g, 0.60mmol, 1.0eq) in anhydrous dichloromethane (10ml) at 0°C under argon was added di-*n*-butylboron triflate (1M in dichloromethane, 1.32ml, 1.32mmol, 2.2eq) followed by diisopropylethylamine (0.14g, 1.08mmol, 1.8eq) in dry dichloromethane (*ca.* 5ml). The resulting pale yellow solution was stirred at 0°C for 1 hour before being cooled to -78°C. A solution of freshly distilled benzaldehyde (0.10g, 0.9mmol, 1.5eq) in dichloromethane (2ml) was added dropwise to the boron enolate solution and the reaction mixture was stirred for 30 minutes, whereupon the temperature was allowed

to rise to 20°C. The mixture was stirred for a further 2 hours, quenched with a pH 7 phosphate buffer (30ml) and then extracted into dichloromethane (3x20ml). After evaporation *in vacuo*, the residue was dissolved in methanol (30ml) and the solution cooled to 0°C before being treated with hydrogen peroxide (100 volumes, 3ml) at this temperature. The reaction mixture was then stirred at room temperature overnight, sodium sulfite solution (10ml) was added and the mixture evaporated *in vacuo*. The residue was extracted with dichloromethane (3x20ml) and the combined organic extracts dried over magnesium sulfate, filtered and evaporated *in vacuo* to yield the crude aldol product as a yellow gum (0.20g, 94%). This crude material was subjected to flash column chromatography using hexane:ether (3:1) for elution. The first fraction to be eluted contained unreacted starting material **149** (0.035g, 24%). The second fraction to be eluted was the *title compound* **156** which was recrystallised from cyclohexane to afford a colourless solid (0.160g, 75%); mp 125.5-127.0°C; FTIR (nujol) ν_{max} : 3485(OH), 1765(C=O), 1677(C=O) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.43-7.25(5H, cm, Ph), 4.99(1H, d, *J*=11.6Hz, PhC*H*O), 4.24(1H, dd, *J* =8.9,2.1Hz, C*H*OH), 3.96(2H, s, CH_2N), 2.88(1H, dq, *J* =11.6,7.0Hz, C*H*CH_3), 2.31-2.13(2H, cm, O*H* and C*H* bridgehead), 2.06-1.70(2H, cm, CH_2), 1.59-1.23(4H, cm, 2CH_2), 1.06(3H, d, *J* =7.0Hz, CH_3CH), 1.02(3H, s, CH_3), 0.90(3H, s, CH_3) ppm; ^{13}C NMR (63 MHz, $CDCl_3$) δ 171.87(C=O), 152.07(C=O), 135.09(Ar C), 129.50(Ar CH), 128.79(Ar CH), 128.62(Ar CH), 126.97(Ar CH), 125.28(Ar CH), 80.84(CH), 73.76(CH), 52.59(quat C), 48.54(quat C), 46.04(CH), 42.18(CH_2), 41.81(CH), 37.82(CH_2), 27.75(CH_2), 23.45(CH_2), 20.08(CH_3), 18.99(CH_3), 11.43(CH_3) ppm; MS(FAB) m/z 41(base), 55(53%), 95(20), 117(50), 135(44), 145(97), 178(27), 240(6), 296(11), 340(68), 358(13); Accurate mass (FAB); Found : 358.20129; $C_{21}H_{28}NO_4$ (M+H) requires 358.20183.

(ii) by treatment of [6(*S*)-*endo*]-*N*-(3`*R*)-hydroxy-(2`*R*)-methyl-3`-phenylpropionyl-3-aza-11,11-dimethyl-5-oxatricyclo[6.2.1.0^{1,6}]undecan-4-one 152 with excess of Bu_2BOTf

To a solution of *syn*-aldol product **152** (0.040g, 0.112mmol, 1.0eq) in anhydrous dichloromethane (10ml) at 0°C under argon was added di-*n*-butylboron triflate (1M in dichloromethane, 0.25ml, 0.25mmol, 2.2eq) followed by diisopropylethylamine (0.026g, 0.202mmol, 1.8eq) in dry dichloromethane (*ca.* 2ml). The reaction mixture was stirred at 0°C for 1 hour before being warmed to room temperature and stirred for a further 2 hours at this temperature. The reaction mixture was quenched with a pH 7 phosphate buffer (25ml) and then extracted into dichloromethane (3x20ml) and the combined organic extracts dried over magnesium sulfate, filtered and evaporated *in vacuo* to yield the crude aldol product as a colourless solid. The crude product was purified by flash column chromatography using hexane:ether (4:1) elution and then recrystallised from cyclohexane to afford **156** (0.035g, 89%). This compound was in complete spectroscopic agreement with that described in part (i).

5.4 Attempted aldol reaction of (5*R*, 6*S*)-*N*-propionyl-2-oxa-4-aza-8,8,12-trimethyl-5-spiro[4,7]tricyclo[5.3.1.0^{7,13}]dodecan-3-one 113 with benzaldehyde *via* boron enolate

To a solution of *N-propionamide* **113** (0.15g, 0.47mmol, 1.0eq) in anhydrous dichloromethane (10ml) at 0°C under argon was added di-*n*-butylboron triflate (1M in dichloromethane, 0.52ml, 0.52mmol, 1.1eq) followed by diisopropylethylamine (0.11g, 0.846mmol, 1.8eq) in dry dichloromethane (*ca.* 5ml). The resulting pale yellow solution was stirred at 0°C for 1 hour before being cooled to -78°C. A solution of freshly distilled benzaldehyde (0.075g, 0.71mmol, 1.5eq) in dichloromethane (1ml) was added dropwise to the boron enolate solution and the reaction mixture was stirred for 30 minutes, whereupon the temperature was allowed to rise to 20°C. The mixture was stirred for a further 1.5 hour, quenched with a pH 7

phosphate buffer (50ml) and then extracted into dichloromethane (3x20ml). After evaporation *in vacuo*, the residue was dissolved in methanol (30ml) and the solution cooled to 0°C before being treated with hydrogen peroxide (100 volumes, 3ml) at this temperature. The reaction mixture was then stirred at room temperature overnight, sodium sulfite solution (10ml) was added and the mixture evaporated *in vacuo*. The aqueous residue was extracted with dichloromethane (3x20ml) and the combined organic extracts dried over magnesium sulfate, filtered and evaporated *in vacuo* to yield the crude product as a pale yellow oil, which was subjected to flash column chromatography using hexane:ether (6:1) elution. The first fraction to be eluted was unreacted starting material **113** (0.120g, 80%) and the second fraction was the cleaved auxiliary **107** (0.020g, 17%), both compounds having identical spectroscopic properties to authentic samples.

6 Asymmetric α-bromination reactions of *N*-propionyl derivatives with *N*-bromosuccinimide (NBS)

6.1 Asymmetric α-bromination reaction of the lithium enolate of [(2*S*,6*R*)-*endo*]-*N*-propionyl-5-aza-1,10,10-trimethyl-3-oxatricyclo[5.2.1.$0^{2,6}$]decan-4-one 120 with NBS

To a solution of dry diisopropylamine (0.24g, 2.4mmol, 1.2eq) in dry THF (4ml) at 0°C under argon, was added *n*-butyllithium (1.44ml of 1.6M solution, 2.3mmol, 1.15eq). The resulting solution was allowed to stir at 0°C for 15 minutes before being cooled to -78°C. A solution of **120** (0.50g, 2mmol, 1eq) in dry THF (10ml) was added dropwise and the resulting solution was then stirred for one hour. A solution of NBS (0.71g, 4mmol, 2eq) in dry THF (15ml) was added to the LDA solution and stirred at -78°C for 3 hours and then warmed to room temperature and stirred overnight. After quenching with saturated aqueous ammonium chloride solution, the mixture was concentrated *in vacuo*. The product was extracted with dichloromethane (3x30ml) and the combined organic extracts were washed with saturated aqueous sodium bicarbonate solution and then saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered and evaporated to yield a brown solid which was analysed by 200 MHz ^{1}H NMR spectroscopy to show that the reaction was *ca.* 60% complete. By decoupling the proton doublet at δ 1.8 ppm, the epimer ratio was found to be 6:1. The crude product was subjected to flash column chromatography using hexane:ether (7:1) for elution. The first fraction to be eluted was the minor isomer **163** (0.06g, 9%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.79 (1H, q, *J*= 7.0Hz, C*H*CH_3), 4.59-4.47 (2H, m, C*H*O and C*H*N), 2.34 (1H, m, bridgehead C*H*), 1.84 (3H, d, *J*=7.0 Hz, CH_3CH), 1.69-1.08 (4H, m, $2CH_2$), 0.97 (3H, s, CH_3), 0.97 (3H, s, CH_3), 0.96 (3H, s, CH_3) ppm; MS (FAB) m/z 41(42%), 43(38), 67(19), 69(23), 77(8), 79(19), 81(14), 91(29), 93(18), 95(21), 133(9), 135(48), 153(base), 250(4), 330(12, M+H ^{79}Br), 332(16, M+H ^{81}Br); Accurate mass (FAB); Found : 330.06931;

$C_{14}H_{21}{}^{79}BrNO_3$ (M+H ^{79}Br) and 332.06999; $C_{14}H_{21}{}^{81}BrNO_3$ (M+H ^{81}Br) requires 330.07048 and 332.06856; the second fraction was unreacted starting material **120** (0.20g, 40%). The third fraction to be eluted contained the major isomer **162** (0.30g, 50%); mp 152-153°C; FTIR (nujol) ν_{max} 1770(C=O), 1704(C=O) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.76 (1H, q, *J*= 7.0Hz, C*H*CH_3), 4.62-4.53 (2H, m, C*H*O and C*H*N), 2.35 (1H, t, *J*=4.0 Hz, bridgehead C*H*), 1.83 (3H, d, *J*=7.0 Hz, CH_3CH), 1.70-1.26 (4H, m, $2CH_2$), 1.0 (3H, s, CH_3), 0.99 (3H, s, CH_3), 0.98 (3H, s, CH_3) ppm; ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 169.48(C=O), 153.10(C=O), 82.72(CH), 57.44(CH), 49.37(quat C), 48.59(quat C), 47.55(CH), 38.19(CH), 26.04(CH_2), 20.18(CH_3), 19.67(CH_3), 19.19(CH_2), 17.87(CH_3), 13.65(CH_3) ppm; MS (FAB) m/z 41(37%), 43(22), 67(16), 69(16), 77(43), 79(19), 81(11), 91(29), 93(19), 95(20), 133(8), 135(49), 153(base), 250(5), 330(25, M+H ^{79}Br), 332(36, M+H ^{81}Br); Accurate mass (FAB); Found : 330.07153; $C_{14}H_{21}{}^{79}BrNO_3$ (M+H ^{79}Br) and 332.06726; $C_{14}H_{21}{}^{81}BrNO_3$ (M+H ^{81}Br) requires 330.07048 and 332.06856.

6.2 Asymmetric α-bromination reaction of the lithium enolate of [6(*S*)-*endo*]-*N*-propionyl-3-aza-11,11-dimethyl-5-oxatricyclo[6.2.1.0^{1,6}]undecan-4-one 149 with NBS

To a solution of dry diisopropylamine (0.15g, 1.43mmol; 1.2eq) in dry THF (4ml) at 0°C under argon, was added *n*-butyllithium (0.86ml of 1.6M solution, 1.38mmol, 1.15eq). The resulting solution was allowed to stir at 0°C for 15 minutes before being cooled to -78°C. A solution of **149** (0.30g, 1.195mmol, 1eq) in dry THF (10ml) was added dropwise and the resulting solution was then stirred for one hour. A solution of NBS (0.426g, 2.39mmol, 2eq) in dry THF (15ml) was added to the LDA solution and stirred at -78°C for 3 hours and then warmed to room temperature and stirred for overnight. After quenching with saturated aqueous ammonium chloride solution, the mixture was concentrated *in vacuo*. The product was extracted with dichloromethane (3x30ml) and the combined organic extracts were washed with saturated aqueous

sodium bicarbonate solution and then saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered and evaporated to yield a colourless solid which was analysed by 200 MHz ^{1}H NMR spectroscopy. This showed that the reaction was *ca.* 60% complete and integration of the quartets at δ 5.87-5.67 ppm, arising from the chiral centre proton C*H*Br, revealed that two epimers had been formed and the ratio was found to be 6:1. The crude product was subjected to flash column chromatography using hexane:ether (8:1) elution. The first fraction to be eluted was the major isomer **164** (0.022g, 56%); mp 110.6-111.8°C; FTIR (nujol) ν_{max} 1732(C=O), 1696(C=O) cm^{-1}; ^{1}H NMR (250 MHz , $CDCl_3$) δ 5.78(1H, d, *J*= 6.7 Hz, C*H*CH_3) 4.61-4.44 (1H, ddd, *J*=4.0, 2.4, 2.0Hz, C*H*O), 3.64 (1H, d, *J*=12.0Hz, CH_2N), 3.45 (H, d, *J*=12.0Hz, CH_2N), 2.33-2.21 (1H, m, C*H* bridgehead), 2.00-1.84 (2H, m, CH_2), 1.84 (3H, d, *J*=6.7Hz, CH_3CH), 1.59-1.23 (4H, m, 2CH_2), 1.03 (3H, s, CH_3), 1.00 (3H, s, CH_3) ppm; ^{13}C NMR (63MHz, $CDCl_3$) δ 173.97(C=O), 152.66(C=O), 80.94(CH), 48.82(CH_2), 47.07(quat C), 46.42(CH), 46.17(quat C), 41.41(CH), 32.43(CH_2), 27.46(CH_2), 25.15(CH_2), 21.12(CH_3), 19.77(CH_3), 18.64(CH_3) ppm; MS (FAB) m/z 41(71%), 43(95), 55(76), 57(78), 79(9), 81(47), 93(45), 95(24), 133(41), 135(79), 152(21), 196(9), 226(base), 250(13), 276(25), 330(30, M+H ^{79}Br), 332(10, M+H ^{81}Br); Accurate mass (FAB); Found : 330.07135; $C_{14}H_{21}{}^{79}BrNO_3$ (M+H ^{79}Br) and 332.06843; $C_{14}H_{21}{}^{81}BrNO_3$ (M+H ^{81}Br) requires 330.07048 and 332.06856. The second fraction to be eluted was unreacted starting material **149** (0.91g, 30%). The third fraction to be eluted was the minor isomer **165** (0.037g, 9%); ^{1}H NMR (250 MHz , $CDCl_3$) δ 5.74(1H, d, *J*= 6.8 Hz, C*H*CH_3) 4.58-4.51 (1H, ddd, *J*=3.8, 2.4, 2.1Hz, C*H*O), 3.58 (2H, s, CH_2N), 2.33-2.20 (1H, m, C*H* bridgehead), 2.04-1.81 (2H, m, CH_2), 1.82 (3H, d, *J*=6.8Hz, CH_3CH), 1.59-1.24 (4H, m, 2CH_2), 1.03 (3H, s, CH_3), 0.99 (3H, s, CH_3) ppm; MS (FAB) m/z 41(67%), 43(base), 55(68), 57(36), 79(41), 81(89), 93(28), 95(35), 135(27), 196(4), 252(6), 330(2, M+H ^{79}Br), 332(3, M+H ^{81}Br); Accurate mass (FAB); Found : 330.07067; $C_{14}H_{21}{}^{79}BrNO_3$ (M+H ^{79}Br) and 332.06955; $C_{14}H_{21}{}^{81}BrNO_3$ (M+H ^{81}Br) requires 330.07048 and 332.06856.

6.3 Chromium-Reformatsky reaction of [(2*S*,6*R*)-*endo*]-*N*-α-bromopropionyl-5-aza-1,10,10-trimethyl-3-oxatricyclo[5.2.1.$0^{2,6}$]decan-4-one 162 with benzaldehyde

Anhydrous chromium chloride (0.14g, 1.14mmol, 2.5eq) and dry lithium iodide (0.006g, 0.046mmol, 0.1eq) were suspended in dry THF (5ml) at room temperature under argon. To the light gray-green suspension were added benzaldehyde (0.12g, 1.14mmol, 2.5eq) in dry THF (2ml) *via* syringe, followed by addition of a solution of *2-bromopropionate* **162** (0.15g, 0.46mmol, 1eq) in dry THF (10ml). The reaction mixture was stirred at room temperature under argon for overnight and then quenched with brine (10ml) and vigorously stirred for 15 minutes. The organic layer was separated, and the aqueous phase was extracted with dichloromethane (3x20ml). The combined organic layers were washed with diionised water to remove traces of Chromium(III) residue, dried over magnesium sulfate, filtered and evaporated to yield the crude aldol product as a pale yellow gum. Analysis of this crude aldol product by 200 MHz ^{1}H NMR spectroscopy indicated that one *syn* diastereomer (^3J= 4.4 Hz) and one *anti* diastereomer (^3J= 7.0Hz) had formed in the ratio of 46:58 respectively (diastereomeric excess = 8%) (these ratios were determined by integration of the doublets in the range 5.18-4.80 ppm, arising from the PhC*H*OH protons; the *anti/syn* assignments were made on the basis of the vicinal coupling constants, which are given). The crude product was subjected to flash column chromatography using hexane:ether (4:1) elution. The first fraction to be eluted was *N*-propionamide **120** (0.09g, 78%). The second fraction to be eluted was *anti* diastereomer **140** (0.018g, 11%). The third fraction to be eluted was *syn* **139** diastereomers (0.018g, 11%), all compounds having identical spectroscopic properties to authentic samples (see sections 2.2 and 5.1 (i)).

6.4 Chromium-Reformatsky reaction of [6(*S*)-*endo*]-*N*--α-bromopropionyl-3-aza-11,11-dimethyl-5-oxatricyclo[6.2.1.$0^{1,6}$]undecan-4-one 164 with benzaldehyde

Anhydrous chromium chloride (0.135g, 1.1mmol, 2.5eq) and dry lithium iodide (0.005g, 0.04mmol, 0.1eq) were suspended in dry THF (5ml) at room temperature under argon. To the light gray-green suspension were added benzaldehyde (0.1g, 0.91mmol, 2.5eq) in dry THF (2ml) *via* syringe, followed by addition of a solution of *2-bromopropionate* **164** (0.12g, 0.37mmol, 1eq) in dry THF (10ml). The reaction mixture was stirred at room temperature under argon for overnight and then quenched with brine (10ml) and vigorously stirred for 15 minutes. The organic layer was separated, and the aqueous phase was extracted with dichloromethane (3x20ml). The combined organic layers were washed with deionised water to remove traces of chromium(III) residue, dried over magnesium sulfate, filtered and evaporated *in vacuo* to yield the crude aldol product as a pale yellow gum. Analysis of this crude aldol product by 200 MHz ^{1}H NMR spectroscopy indicated that large amounts of *N*-propionate **149** and the ring cleaved product **156** (^3J= 11.5Hz) at 5.01 ppm, arising from the PhC*H*OH proton, had formed. The crude product was subjected to flash column chromatography using hexane:ether (5:1) elution. The first fraction to be eluted was *N*-propionamide **149** (0.064g, 75%). The second fraction to be eluted was *1-methylene-N-tetrahydro-(5`S)-methyl-(6`R)-phenyl-1`,3`-oxazin-2`,4`-dione-7,7-dimethyl-[(3S)-endo]-hydroxy-bicyclo[2.2.1]heptane* **156** (0.025g, 20%); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.43-7.25(5H, cm, Ph), 4.99(1H, d, *J*=11.6Hz, PhC*H*O), 4.24(1H, dd, *J* =8.9,2.1Hz, C*H*OH), 3.96(2H, s, CH_2N), 2.88(1H, dq, *J* =11.6,7.0Hz, C*H*CH_3), 2.31-2.13(2H, cm, O*H* and C*H* bridgehead), 2.06-1.70(2H, cm, CH_2), 1.59-1.23(4H, cm, 2CH_2), 1.06(3H, d, *J* =7.0Hz, CH_3CH), 1.02(3H, s, CH_3), 0.90(3H, s, CH_3) ppm. Both compounds were in complete spectroscopic agreement with those described in sections (2.7) and (5.3 (i)).

REFERENCES

1. H.S.Gutowsky, *J. Chem. Phys.*, 1962, **37**, 2196.
2. W.B.Jennings, *Chem. Rev.*, 1975, **75**, 3, 307.
3. K.Mislow and M.Raban, *Top. Stereochem.*, 1967, **1**, 1.
4. C.Alvarez-Ibarra, M.S.Arias-Perez and E.Moya, *Magn. Reson. Chem.*, 1990, **28**, 617.
5. C. Alvarez-Ibarra, M.S.Arias-Perez, A.de Andres and J.L.Balcazar, *Magn. Reson. Chem.*, 1986, **24**, 568.
6. A.F.Casy, *Magn. Reson. Chem.*, 1993, **31**, 416.
7. T.Polonsky, *Org. Magn. Reson.*, 1984, **22**, 177.
8. D.Parker, R.J.Taylor, G.Ferguson and A.Tonge, *Tetrahedron.*, 1986, **42**, 617.
9. T.A.Crabb and A.V.Pattel, *Magn. Reson. Chem.*, 1991, **29**, 1040.
10. N.C.Gonnella and J.Chen, *Magn. Reson. Chem.*, 1988, **26**, 185.
11. P.C.Kline and A.S.Serianni, *Magn. Reson. Chem.*, 1988, **26**, 120.
12. C.D.Jardetzky, *J. Am. Chem. Soc.*, 1960, **82**, 229.
13. R.U.Lemieux, *Can. J. Chem.*, 1961, **39**, 116.
14. P.C.Kline and A.S.Serianni, *J. Am. Chem. Soc.*, 1990, **112**, 7373.
15. M.Masojidkova, J.Zajicek, M.Budesinsky, I.Rosenberg and A.Holy, *Collect. Czech. Chem. Commun.*, 1985, **50**, 1899.
16. M.Muraoka, A.Iida, S.Takahashi, T.Ebata and S.Uesugi, *Nucleosides and Nucleotides*, 1991, **10**, 1317.
17. D.A.Evans, *Aldrichimica Acta.*, 1982, **15**, 23 and references cited therein.
18. G.M.Coppola and H.F.Schuster, *"Asymmetric Synthesis-Construction of Chiral Molecules using Amino Acids"*., John Wiley and Sons, New York, 1987, 95.
19. P.G.M.Wuts and L.E.Pruitt, *Synthesis*, 1989, 622.
20. D.A.Evans, M.D.Ennis and D.J.Mather, *J. Am. Chem. Soc.*, 1982, **104**, 1737.
21. D.A.Evans, M.D.Ennis and T.Le, *J. Am. Chem. Soc.*, 1984, **106**, 1154.
22. D.A.Evans, J.Bartroli and T.L.Shih, *J. Am. Chem. Soc.*, 1981, **103**, 2127.
23. D.A.Evans, K.T.Chapman and J.Bisaha, *J. Am. Chem. Soc.*, 1988, **110**, 1238.
24. W.Oppolzer, *Pure. App. Chem.*, 1988, **60**, 39.
25. W.Oppolzer, C.Vullioud, M.Vandewalle and J.Van der Eycken, *Tetrahedron.*, 1986, **42**, 4035.

26. W.Oppolzer, R.Moretti and S.Thomi, *Tetrahedron Lett.*, 1989, **30**, 5603.
27. W.Oppolzer,J.Blagg, I.Rodriguez and E.Walther, *J. Am. Chem. Soc.*, 1990, **112**, 2767.
28. W.Oppolzer, C.Chapuis and G. Bernardinelli, *Helv. Chim. Acta.*, 1984, **67**, 1397.
29. D.Enders, *Chem. Tech.*, 1981, **11**, 504.
30. D.Enders in *"Asymmetric Synthesis"*, vol.**3**, J.D.Morrison (Ed), Academic press, Orlando, 1984, *p.* 275.
31. K.G.Davenport, H.Eichenauer, D.Enders, M.Newcomp and D.E.Bergbreiter, *J. Am. Chem. Soc.*, 1979, **101**, 5654.
32. D.Enders and H.Eichenauer, *Angew. Chem., Int. Ed. Engl.*, 1976, **15**, 549.
33. D.Enders and H.Eichenauer, *Angew. Chem., Int. Ed. Engl.*, 1979, **18**, 397.
34. D.Enders and K.Papadopoulos, *Tetrahedron Lett.*, 1983, **24**, 4967.
35. S.G.Davies, *Aldrichimica Acta.*, 1990, **23**, 31.
36. S.G.Davies, *Chem. in Brit.*, 1989, **25**, 269.
37. G.Bashiardes and S.G.Davies, *Tetrahedron Lett.*, 1987, **28**, 5563.
38. R.P.Beckett,S.G.Davies and A.A.Mortlocck, *Tetrahedron Asymm.*, 1992, **3**, 123.
39. A.I.Meyers, *Acc. Chem. Res.*, 1978, **11**, 375.
40. K.A.Lutomski and A.I.Meyers in *"Asymmetric Synthesis"*, vol.**3**, J.D.Morrison (Ed), Academic press, Orlando, 1984, *p.* 213.
41. A.I.Meyers, G.Knaus, K.Kamata and M.E.Ford, *J. Am. Chem. Soc.*, 1976, **98**, 567.
42. A.I.Meyers and P.J.Reider, *J. Am. Chem. Soc.*, 1979, **101**, 2501.
43. A.I.Meyers and P.M.Kendall, *Tetrahedron Lett.*, 1974, **15**, 1337.
44. A.I.Meyers and K.Kamanda, *J. Am. Chem. Soc.*, 1976, **98**, 2290.
45. W.H.Pirkle and K.A.Simmons, *J. Org. Chem.*, 1983, **48**, 2520.
46. K.Kimura, K.Murata, K.Otsuka, T.Ishizuka, M.Haratake and T.Kunieda, *Tetrahedron Lett.*, 1992, **33**, 4461.
47. M.R.Banks, A.J.Blake, J.I.G.Cadogan, I.M.Dawson, I.Gosney, K.J.Grant, S.Gaur, P.K.G.Hodgson, K.S.Knight, G.W.Smith and D.E.Stevenson, *Tetrahedron*, 1992, **48**, 7979.

48. M.R.Banks, A.J.Blake, J.I.G.Cadogan, I.M.Dawson, S.Gaur, I.Gosney, K. J. Grant, R.O.Gould and P.K.G.Hodgson, *J. Chem. Soc., Chem. Commun.,* 1993, 1146.
49. M.P.Bonner and E.R.Thornton, *J. Am. Chem. Soc.*, 1991, **113**, 1299.
50. M.R.Banks, J.I.G.Cadogan, I.Gosney, K.Grant, P.K.G.Hodgson and P.Thorburn, *Heterocycles*, 1994, **37**, 199.
51. M.R.Banks, I.M.Dawson, I.Gosney, P.K.G.Hodgson and P.Thorburn, *Tetrahedron Lett.*, 1995, **36**, 3567.
52. J.Mulzer, N.Salimi and H.Hartl, *Tetrahedron Asymm.*, 1993, **4**, 457.
53. C.H.Heathcock, *"Asymmetric Synthesis"*, J.D.Morrison (Ed), Academic Press, 1984, vol.**3,** Chapter 2.
54. C.H.Heathcock, C.T.Buse, W.A.Kleschick, M.C.Pirrung, J.E.Sohn and J.Lampe, *J. Org. Chem.*, 1980, **45**, 1066.
55. D.A.Evans, J.S.Clark, R.Metternich, V.J.Novack and G.S.Sheppard, *J. Am. Chem. Soc.*, 1990, **112**, 866.
56. M.Walker and C.H.Heathcock, *J. Org. Chem.*, 1991, **56**, 5747.
57. H.Danda, M.N.Hansen and C.H.Heathcock, *J. Org. Chem.*, 1990, **55**, 173.
58. S.Shambayati, W.E.Crowe and S.L.Schreiber, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 256.
59. I.Paterson, D.J.Wallace and S.M.Velazquez, *Tetrahedron Lett.*,1994, **35**, 9083.
60. I.Paterson and D.J.Wallace, *Tetrahedron Lett.*,1994, **35**, 9477.
61. T.Mukaiyama, K.Narasaka and K.Banno, *Chem. Lett.*, 1973, 1011.
62. C.Gennari, M.G.Beretta, A.Bernardi, G.Moro, C.Scolastico and R.Todeschini, *Tetrahedron*, 1986, **42**, 893.
63. W.Oppolzer and P.Lienard, *Tetrahedron Lett.*, 1993, **34**, 27, 4321.
64. W.Oppolzer, C.Starkmann, I.Rodriguez and G.Bernardinelli, *Tetrahedron Lett.* 1991, **32**, 61.
65. N.S.Simpkins, *Chem. Ind.*, 1988, 387 and references cited therein.
66. I.Patterson, *Chem. Ind.*, 1988, 390 and references cited therein.
67. K.Furuta, T.Maruyama and H.Yamamoto, *J. Am. Chem. Soc.*, 1991, **113**, 1041.
68. E.J.Corey, R.Imwinkelried, S.Pikul and Y.B.Xiang, *J. Am. Chem. Soc.*, 1989,

111, 5493.

69. N.R.Schmuff, J.K.Phillips, W.E.Burkholder, H.M.Fales, C-W.Chen, P.P.Roller and M.Ma, *Tetrahedron Lett.*, 1984, **25**, 1533.
70. D.G.Ager, I.Prakash and D.R.Schaad, *Aldrichimica Acta.*, 1997, **30**, 3 for an updated review of the utility of chiral oxazolidinones as auxiliaries for asymmetric transformations, see also reference 17.
71. W.Oppolzer, C.Chapius and G.Bernardinelli, *Tetrahedron Lett.*, 1984, **25**, 5885, see also reference 25.
72. J.I.G.Cadogan, A.A.Doyle, I.Gosney, P.K.G.Hodgson and P.Thorburn, *Enantiomer*, 1997, **2**, 81, for a mini-review showing the scope of our nitrene-mediated route used to construct the oxazolidin-2-one ring.
73. D.McDougal, PhD Thesis, 1997, The University of Edinburgh.
74. D.A.Evans, K.T.Chapman and J.Bisaha, *J. Am. Chem. Soc.*, 1984, **106**, 4261.
75. J.S.McGuinn, B.Sc. Honours Report, The University of Edinburgh, 1995.
76. C.Blomberg and F.A.Hartog, *Synthesis*, 1977, 18.
77. J.March, *Advanced Organic Chemistry*, 3rd Ed., 1984, *p.* 381.
78. C.H.Heathcock, *Aldrichimica Acta*, 1990, **23**, 99.
79. C.H.Heathcock, *"The Aldol Addition Reactions" in Asymmetric Synthesis*, vol.**3**, J.D.Morrison (Ed), Academic press, 1984, *p.* 111.
80. K.H.Ahn, S.Lee and A.Lim, *J. Org. Chem.* 1992, **57**, 5065.
81. M.R.Banks, J.I.G.Cadogan, I.Gosney, S.Gaur and P.K.G.Hodgson, *Tetrahedron Asymmetry*, 1994, **5**, 2447.
82. S.Castellino, *J.Org.Chem.*, 1990, **55**, 5197.
83. R.C.Fay and R.N.Lowry, *Inorganic Chemistery*, 1974, **13**, 1309.
84. A.F.Lindmark and R.C.Fay, *Inorganic Chemisrery*, 1975, **14**, 282.
85. K.J.Grant, PhD Thesis, 1993, The University of Edinburgh.
86. W.Oppolzer and C.Starkemann, *Tetrahedron Lett.*, 1992, **33**, 2439.
87. Y.Xiang, E.Olivier and N.Ouimet, *Tetrahedron Lett.*, 1992, **33**, 457.
88. B.C.Raimundo and C.H.Heathcock, *Synlett.*, 1995, **12**, 1213.
89. H.C.Brown, K.Ganesan, and R.K.Dhar, *J. Org. Chem.*,1993, **58**, 147.
90. I.Paterson and D.J.Wallace, *Tetrahedron Lett.*,1994, **35**, 9087.

91. D.Enders, O.F.Prokopenko, G.Raabe and J.Runsink, *Synthesis*. 1996, **9**, 1095.
92. C.Gennari, D.Moresca, S.Vieth and A.Vulpetti, *Angew. Chem. Int. Ed. Engl.*, 1993, **32**, 1618.
93. E.J.Corey and D.H.Lee, *Tetrahedron Lett.*, 1993, **34**, 1737.
94. J.R.Gage and D.A.Evans, *Organic Synthesis*, J.D.White (Ed), 1990, **68**, 83.
95. C.H.Heathcock, *"The Aldol Addition Reactions" in Asymmetric Synthesis*, vol.**3,** J.D.Morrison (Ed), Academic press, 1984, *p.* 157.
96. T.Gabriel and L.Wessjohann, *Tetrahedron Lett.*, 1997, **38**, 4387.
97. L.Wessjohann and H.Wild, *Synlett*, 1997, 731.
98. C.T.Buse and C.H.Heathcock, *Tetrahedron Lett.*, 1978, **19**, 1685.
99. D.A.Evans, J.A.Ellman and R.L.Dorow, *Tetrahedron Lett.*, 1987, **28**, 1123.
100. M.R.Banks, J.I.G.Cadogan, I.M.Dawson, I.Gosney, K.J.Grant, S.Gaur, P.K.G.Hodgson and D.E.Thomson, *Chromatographia*, 1992, **34**, 48.
101. J.March, *Advanced Organic Chemistry*, 3rd Ed., 1984, *p.* 355.
102. O.Diels and K.Alder, *Justus. Lieb. Ann.*, 1928, **460**, 98.
103. W.Oppolzer, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 876.
104. I.Fleming, *Frontier Orbitals and Organic Chemical Reactions*, John Wiley and Sons, Chichester, 1976, *p.* 161.

APPENDICES

Appendix 1. X-ray crystal structure of [(2*S*,6*R*)-*endo*]-*N*-((3`*R*)-hydroxy-(2`*S*)-methyl-3`-phenylpropionyl)-5-aza-1,10,10-trimethyl-3-oxatricyclo[5.2.1.$0^{2,6}$] decan-4-one 140

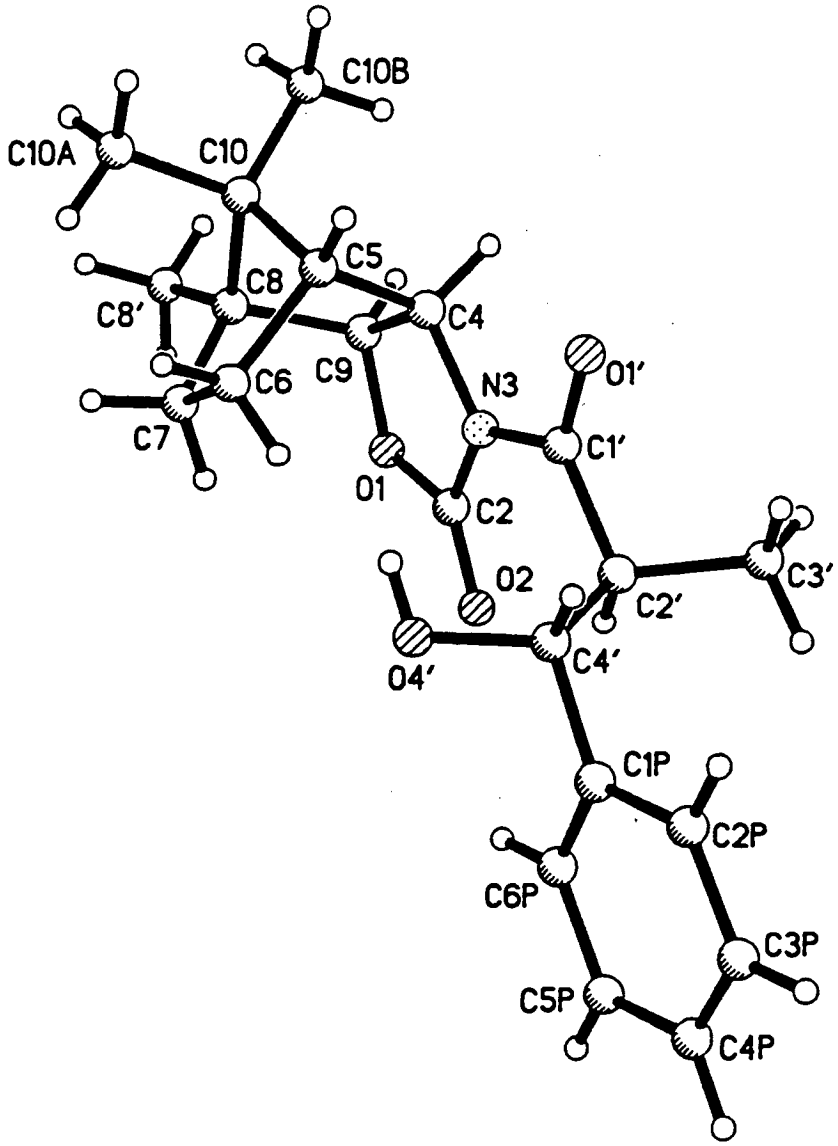


Table 1. Crystal data and structure refinement for exp115 at 293(2) K.

Empirical formula	C21 H27 N O4
Formula weight	357.44
Wavelength	1.54184 A
Crystal system	Orthorhombic
Space group	P 21 21 21
Unit cell dimensions	a = 8.251(2) A alpha = 90 deg. b = 21.547(3) A beta = 90 deg. c = 10.760(2) A gamma = 90 deg.
Volume	1913.0(6) A^3
Z	4
Density (calculated)	1.241 Mg/m^3
Absorption coefficient	0.689 mm^-1
F(000)	768
Crystal description	Colourless plate developed in (010)
Crystal size	0.43 x 0.19 x 0.04 mm
Theta range for data collection	4.10 to 60.14 deg.
Index ranges	-9<=h<=9, -23<=k<=24, -12<=l<=12
Reflections collected	3465
Independent reflections	2676 [R(int) = 0.0473]
Scan type	omega-theta
Data / restraints / parameters	2671/0/235 (Full-matrix least-squares on F^2
Goodness-of-fit on F^2	1.023
Conventional R [F>4sigma(F)]	R1 = 0.0714 [1299 data]
R indices (all data)	R1 = 0.1665, wR2 = 0.1669
Absolute structure parameter	-0.3(7)
Final maximum delta/sigma	0.001
Weighting scheme calc w=1/[\s^2^(Fo^2^)+(0.0570P)^2^+0.0000P] where P=(Fo^2^+2Fc^2^)/3	
Largest diff. peak and hole	0.197 and -0.211 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for 1. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1)	8479(7)	4921(2)	933(6)	100(2)
C(2)	7071(10)	4615(4)	833(8)	85(3)
O(2)	6971(7)	4091(2)	493(7)	128(3)
N(3)	5821(7)	5008(2)	1160(5)	50(1)
C(4)	6420(8)	5629(3)	1470(6)	57(2)
C(5)	6013(9)	6151(3)	566(9)	79(2)
C(6)	6177(14)	5904(4)	-778(9)	115(4)
C(7)	7977(13)	5809(4)	-884(8)	111(3)
C(8)	8709(9)	6029(3)	311(7)	62(2)
C(8')	10514(9)	6181(4)	270(8)	96(3)
C(9)	8241(8)	5553(3)	1301(7)	66(2)
C(10)	7553(8)	6564(3)	682(7)	67(2)
C(10A)	7568(10)	7109(3)	-228(10)	132(4)
C(10B)	7866(11)	6833(4)	1968(9)	117(4)
C(1')	4172(9)	4874(3)	1312(6)	54(2)
O(1')	3323(6)	5284(2)	1714(5)	70(2)
C(2')	3548(8)	4242(3)	958(6)	49(2)
C(3')	2392(9)	4012(3)	1989(6)	85(2)
C(4')	2625(8)	4282(3)	-269(6)	49(2)
O(4')	3675(5)	4576(2)	-1155(4)	61(1)
C(1P)	2147(9)	3652(3)	-710(6)	53(2)
C(2P)	579(11)	3447(4)	-604(8)	87(3)
C(3P)	151(15)	2847(6)	-938(10)	120(4)
C(4P)	1281(19)	2464(5)	-1391(11)	128(5)
C(5P)	2846(16)	2642(4)	-1506(9)	116(4)
C(6P)	3280(11)	3247(3)	-1145(7)	79(2)

Table 3. Bond lengths [A] and angles [deg] for 1.

O(1)-C(2)	1.341(8)
O(1)-C(9)	1.432(7)
C(2)-O(2)	1.189(8)
C(2)-N(3)	1.380(8)
N(3)-C(1')	1.400(8)
N(3)-C(4)	1.466(7)
C(4)-C(9)	1.522(9)
C(4)-C(5)	1.525(9)
C(5)-C(6)	1.547(11)
C(5)-C(10)	1.557(9)
C(6)-C(7)	1.504(12)
C(7)-C(8)	1.498(10)
C(8)-C(8')	1.525(10)
C(8)-C(9)	1.527(9)
C(8)-C(10)	1.550(9)
C(10)-C(10B)	1.522(10)
C(10)-C(10A)	1.529(9)
C(1')-O(1')	1.207(7)
C(1')-C(2')	1.506(8)
C(2')-C(4')	1.527(8)
C(2')-C(3')	1.544(8)
C(4')-O(4')	1.436(6)
C(4')-C(1P)	1.490(8)
C(1P)-C(6P)	1.362(9)
C(1P)-C(2P)	1.372(10)
C(2P)-C(3P)	1.388(12)
C(3P)-C(4P)	1.336(14)
C(4P)-C(5P)	1.352(14)
C(5P)-C(6P)	1.407(10)

C(2)-O(1)-C(9)	111.8(6)
O(2)-C(2)-O(1)	123.5(8)
O(2)-C(2)-N(3)	127.5(8)
O(1)-C(2)-N(3)	109.0(6)
C(2)-N(3)-C(1')	129.0(6)
C(2)-N(3)-C(4)	111.5(6)
C(1')-N(3)-C(4)	119.3(5)
N(3)-C(4)-C(9)	102.0(6)
N(3)-C(4)-C(5)	117.0(6)
C(9)-C(4)-C(5)	102.7(6)
C(4)-C(5)-C(6)	108.9(6)
C(4)-C(5)-C(10)	101.0(6)
C(6)-C(5)-C(10)	101.5(7)
C(7)-C(6)-C(5)	101.8(7)
C(8)-C(7)-C(6)	106.9(7)
C(7)-C(8)-C(8')	115.9(7)
C(7)-C(8)-C(9)	106.5(6)
C(8')-C(8)-C(9)	114.3(6)
C(7)-C(8)-C(10)	102.0(6)
C(8')-C(8)-C(10)	116.7(6)
C(9)-C(8)-C(10)	99.5(6)
O(1)-C(9)-C(4)	105.7(6)
O(1)-C(9)-C(8)	114.2(6)
C(4)-C(9)-C(8)	105.1(6)
C(10B)-C(10)-C(10A)	106.8(6)
C(10B)-C(10)-C(8)	114.3(7)
C(10A)-C(10)-C(8)	113.7(7)
C(10B)-C(10)-C(5)	115.4(7)
C(10A)-C(10)-C(5)	113.3(6)
C(8)-C(10)-C(5)	93.2(5)

O(1')-C(1')-N(3)	117.1(6)
O(1')-C(1')-C(2')	123.7(7)
N(3)-C(1')-C(2')	119.2(6)
C(1')-C(2')-C(4')	109.8(5)
C(1')-C(2')-C(3')	108.6(5)
C(4')-C(2')-C(3')	109.4(5)
O(4')-C(4')-C(1P)	110.5(5)
O(4')-C(4')-C(2')	107.4(5)
C(1P)-C(4')-C(2')	110.8(5)
C(6P)-C(1P)-C(2P)	118.0(7)
C(6P)-C(1P)-C(4')	120.7(7)
C(2P)-C(1P)-C(4')	121.1(7)
C(1P)-C(2P)-C(3P)	121.2(9)
C(4P)-C(3P)-C(2P)	119.4(11)
C(3P)-C(4P)-C(5P)	121.7(12)
C(4P)-C(5P)-C(6P)	118.7(10)
C(1P)-C(6P)-C(5P)	120.9(9)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for 1. The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
O(1)	62(3)	55(3)	182(6)	26(4)	31(4)	15(3)
C(2)	72(6)	53(5)	131(7)	27(6)	24(6)	0(5)
O(2)	88(4)	42(3)	254(8)	3(4)	66(5)	5(3)
N(3)	51(3)	46(3)	53(4)	-1(3)	1(3)	7(3)
C(4)	52(5)	62(5)	57(5)	-12(4)	-7(4)	-4(4)
C(5)	61(5)	46(5)	130(8)	8(5)	-16(5)	10(4)
C(6)	156(10)	94(7)	95(7)	48(6)	-88(8)	-60(7)
C(7)	158(10)	106(7)	69(6)	1(5)	-6(7)	-50(7)
C(8)	62(5)	50(4)	75(5)	-7(4)	1(5)	0(4)
C(8')	74(6)	82(6)	132(8)	18(6)	21(6)	5(5)
C(9)	46(5)	66(5)	85(6)	17(5)	-13(4)	5(4)
C(10)	50(4)	52(4)	99(6)	1(4)	-9(5)	3(4)
C(10A)	97(7)	63(5)	235(12)	44(7)	-58(8)	-19(6)
C(10B)	99(7)	111(7)	141(8)	-67(6)	6(7)	-36(6)
C(1')	69(5)	59(5)	34(4)	6(4)	-6(4)	5(4)
O(1')	62(3)	63(3)	84(4)	-22(3)	16(3)	9(3)
C(2')	54(4)	50(4)	44(4)	6(3)	9(4)	3(3)
C(3')	117(7)	88(5)	49(4)	5(4)	5(5)	-16(6)
C(4')	51(4)	53(4)	42(4)	9(3)	2(4)	-3(4)
O(4')	80(3)	50(2)	53(3)	9(2)	0(3)	-13(3)
C(1P)	62(5)	55(4)	43(4)	6(4)	7(4)	-11(4)
C(2P)	104(7)	75(6)	82(6)	20(5)	-12(6)	-26(5)
C(3P)	123(10)	145(11)	93(8)	29(8)	-7(8)	-60(9)
C(4P)	176(14)	96(9)	114(11)	12(7)	-18(11)	-66(9)
C(5P)	186(12)	72(6)	91(8)	-27(5)	-18(8)	8(8)
C(6P)	99(6)	59(5)	78(6)	-12(5)	0(6)	-5(5)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for 1.

	x	y	z	U(eq)
H(4)	6148(8)	5743(3)	2327(6)	69
H(5)	4991(9)	6366(3)	740(9)	94
H(6A)	5592(14)	5518(4)	-888(9)	138
H(6B)	5791(14)	6205(4)	-1379(9)	138
H(7A)	8220(13)	5374(4)	-1016(8)	133
H(7B)	8406(13)	6045(4)	-1578(8)	133
H(8'1)	10864(9)	6316(4)	1076(8)	144
H(8'2)	10702(9)	6504(4)	-325(8)	144
H(8'3)	11110(9)	5817(4)	34(8)	144
H(9)	8810(8)	5639(3)	2082(7)	79
H(10A)	7374(10)	6959(3)	-1054(10)	197
H(10B)	8604(10)	7311(3)	-197(10)	197
H(10C)	6735(10)	7400(3)	-3(10)	197
H(10D)	7866(11)	6504(4)	2570(9)	175
H(10E)	7030(11)	7126(4)	2170(9)	175
H(10F)	8899(11)	7038(4)	1976(9)	175
H(2')	4458(8)	3952(3)	873(6)	59
H(3'1)	1985(9)	3609(3)	1775(6)	127
H(3'2)	1504(9)	4297(3)	2071(6)	127
H(3'3)	2970(9)	3989(3)	2762(6)	127
H(4')	1651(8)	4536(3)	-154(6)	58
H(4'1)	3927(5)	4922(2)	-901(4)	91
H(2P)	-212(11)	3715(4)	-303(8)	104
H(3P)	-912(15)	2712(6)	-847(10)	144
H(4P)	984(19)	2066(5)	-1633(11)	154
H(5P)	3620(16)	2369(4)	-1817(9)	139
H(6P)	4356(11)	3372(3)	-1205(7)	94

Appendix 2. X-ray crystal structure of [(2*S*,6*R*)-*endo*]-*N*-((3`*S*)-hydroxy-(2`*R*)-methyl-3`-phenylpropionyl)-5-aza-1,10,10-trimethyl-3-oxatricyclo[5.2.1.$0^{2,6}$] decan-4-one 141

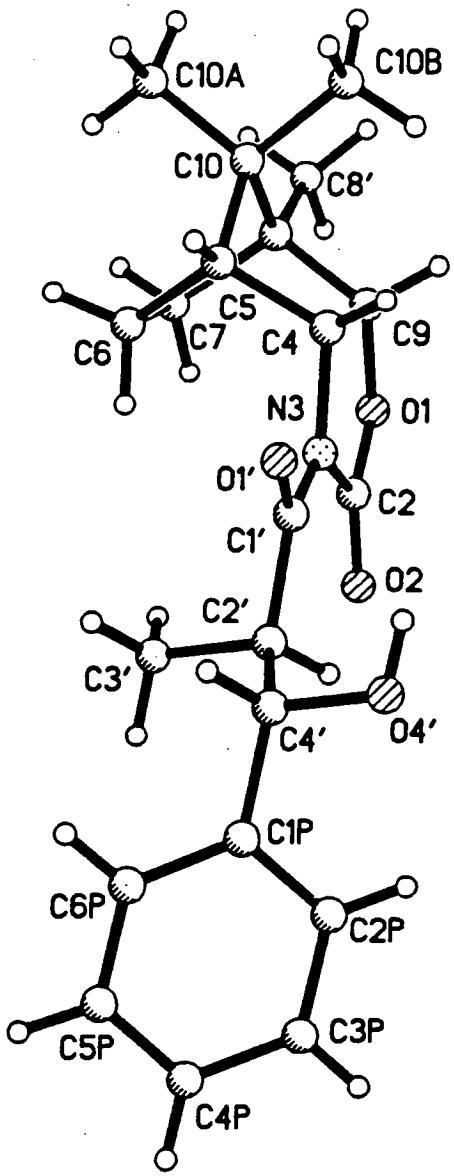


Table 1. Crystal data and structure refinement for exp5p4 at 220(2) K.

Empirical formula	C21 H27 N O4
Formula weight	357.44
Wavelength	1.54184 A
Crystal system	Orthorhombic
Space group	P 21 21 21
Unit cell dimensions	a = 6.634(4) A alpha = 90 deg. b = 11.771(10) A beta = 90 deg. c = 24.046(12) A gamma = 90 deg.
Volume	1878(2) A^3
Z	4
Density (calculated)	1.264 Mg/m^3
Absorption coefficient	0.702 mm^-1
F(000)	768
Crystal description	Colourless needle
Crystal size	0.27 x 0.04 x 0.04 mm
Theta range for data collection	3.68 to 59.98 deg.
Index ranges	0<=h<=7, -11<=k<=13, 0<=l<=27
Reflections collected	2999
Independent reflections	2378 [R(int) = 0.0940]
Scan type	omega-theta with learnt profile
Data / restraints / parameters	2355/0/236 (Full-matrix least-squares on F^2
Goodness-of-fit on F^2	1.059
Conventional R [F>4sigma(F)]	R1 = 0.0818 [1284 data]
R indices (all data)	R1 = 0.1658, wR2 = 0.1983
Absolute structure parameter	-1.1(9)
Extinction coefficient	0.0007(4)
Final maximum delta/sigma	-0.005
Weighting scheme calc w=1/[\s^2^(Fo^2^)+(0.0561P)^2^+0.0000P] where P=(Fo^2^+2Fc^2^)/3	
Largest diff. peak and hole	0.251 and -0.239 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for 1. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1)	-902(9)	7667(4)	8336(2)	34(1)
C(2)	-62(15)	8261(8)	8750(3)	41(2)
O(2)	-669(10)	9178(5)	8893(2)	43(2)
N(3)	1634(11)	7672(6)	8948(2)	32(2)
C(4)	1844(12)	6554(7)	8677(3)	30(2)
C(5)	3679(12)	6347(6)	8310(3)	33(2)
C(6)	4150(14)	7447(6)	7985(3)	37(2)
C(7)	2346(13)	7486(6)	7576(3)	36(2)
C(8)	1100(13)	6407(7)	7701(3)	34(2)
C(8')	-309(15)	6060(8)	7234(3)	48(3)
C(9)	70(13)	6563(7)	8270(3)	28(2)
C(10A)	4223(16)	5281(8)	7384(4)	53(3)
C(10B)	2031(16)	4398(7)	8090(4)	51(3)
C(1')	2931(15)	7968(7)	9377(3)	38(2)
O(1')	4115(11)	7267(5)	9538(2)	54(2)
C(2')	2859(14)	9170(6)	9602(3)	34(2)
C(3')	3882(16)	9939(6)	9163(3)	41(2)
C(4')	3932(16)	9238(7)	10161(3)	44(2)
O(4')	3014(10)	8518(5)	10570(2)	55(2)
C(10)	2800(14)	5556(7)	7867(3)	35(2)
C(2P)	2330(21)	10881(10)	10656(4)	76(4)
C(3P)	2438(32)	12003(14)	10862(5)	116(7)
C(4P)	4154(41)	12669(11)	10783(5)	131(9)
C(5P)	5769(32)	12200(11)	10514(5)	112(7)
C(6P)	5708(20)	11098(8)	10327(4)	66(3)
C(1P)	3992(18)	10430(7)	10383(3)	42(2)

Table 3. Bond lengths [A] and angles [deg] for 1.

O(1)-C(2)	1.338(10)
O(1)-C(9)	1.459(9)
C(2)-O(2)	1.201(10)
C(2)-N(3)	1.404(11)
N(3)-C(1')	1.388(10)
N(3)-C(4)	1.474(10)
C(4)-C(5)	1.523(11)
C(4)-C(9)	1.530(10)
C(5)-C(10)	1.530(10)
C(5)-C(6)	1.543(10)
C(6)-C(7)	1.550(11)
C(7)-C(8)	1.545(11)
C(8)-C(8')	1.517(10)
C(8)-C(9)	1.541(11)
C(8)-C(10)	1.561(11)
C(10A)-C(10)	1.531(11)
C(10B)-C(10)	1.551(11)
C(1')-O(1')	1.203(9)
C(1')-C(2')	1.515(11)
C(2')-C(4')	1.524(10)
C(2')-C(3')	1.548(10)
C(4')-O(4')	1.433(9)
C(4')-C(1P)	1.502(11)
C(2P)-C(1P)	1.389(15)
C(2P)-C(3P)	1.41(2)
C(3P)-C(4P)	1.40(3)
C(4P)-C(5P)	1.37(2)
C(5P)-C(6P)	1.373(15)
C(6P)-C(1P)	1.389(14)

C(2)-O(1)-C(9)	111.3(6)
O(2)-C(2)-O(1)	122.8(9)
O(2)-C(2)-N(3)	128.0(9)
O(1)-C(2)-N(3)	109.1(8)
C(1')-N(3)-C(2)	128.6(7)
C(1')-N(3)-C(4)	119.6(7)
C(2)-N(3)-C(4)	111.5(7)
N(3)-C(4)-C(5)	118.3(7)
N(3)-C(4)-C(9)	101.7(6)
C(5)-C(4)-C(9)	104.2(6)
C(4)-C(5)-C(10)	101.3(7)
C(4)-C(5)-C(6)	108.7(7)
C(10)-C(5)-C(6)	103.6(6)
C(5)-C(6)-C(7)	101.0(6)
C(8)-C(7)-C(6)	105.4(6)
C(8')-C(8)-C(9)	114.6(7)
C(8')-C(8)-C(7)	114.0(7)
C(9)-C(8)-C(7)	108.2(7)
C(8')-C(8)-C(10)	117.5(7)
C(9)-C(8)-C(10)	99.7(6)
C(7)-C(8)-C(10)	101.0(7)
O(1)-C(9)-C(4)	106.0(6)
O(1)-C(9)-C(8)	113.5(6)
C(4)-C(9)-C(8)	103.1(7)
O(1')-C(1')-N(3)	118.2(8)
O(1')-C(1')-C(2')	123.1(8)
N(3)-C(1')-C(2')	118.7(8)
C(1')-C(2')-C(4')	110.5(6)
C(1')-C(2')-C(3')	106.8(6)
C(4')-C(2')-C(3')	111.5(7)

O(4')-C(4')-C(1P)	108.7(7)
O(4')-C(4')-C(2')	112.0(7)
C(1P)-C(4')-C(2')	112.0(7)
C(5)-C(10)-C(10A)	115.0(8)
C(5)-C(10)-C(10B)	114.8(7)
C(10A)-C(10)-C(10B)	106.2(7)
C(5)-C(10)-C(8)	93.6(6)
C(10A)-C(10)-C(8)	112.8(7)
C(10B)-C(10)-C(8)	114.5(7)
C(1P)-C(2P)-C(3P)	118.9(14)
C(4P)-C(3P)-C(2P)	121.2(17)
C(5P)-C(4P)-C(3P)	118.5(14)
C(4P)-C(5P)-C(6P)	120.8(16)
C(5P)-C(6P)-C(1P)	121.8(14)
C(6P)-C(1P)-C(2P)	118.6(9)
C(6P)-C(1P)-C(4')	121.1(10)
C(2P)-C(1P)-C(4')	120.3(10)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for 1. The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
O(1)	28(3)	39(3)	35(3)	-4(3)	-7(3)	2(3)
C(2)	40(6)	51(6)	32(5)	1(5)	4(5)	5(6)
O(2)	48(4)	42(3)	38(3)	-10(3)	-5(3)	15(4)
N(3)	34(4)	39(4)	23(3)	-4(3)	-8(3)	10(4)
C(4)	27(5)	33(5)	29(5)	0(4)	-4(5)	3(5)
C(5)	26(6)	25(4)	49(5)	3(4)	1(5)	1(4)
C(6)	23(5)	35(5)	51(5)	-10(5)	-3(5)	0(5)
C(7)	42(6)	31(5)	34(4)	10(4)	8(5)	-12(5)
C(8)	28(5)	42(5)	33(5)	-4(4)	1(5)	1(5)
C(8')	42(6)	66(6)	37(5)	-19(5)	-1(5)	-8(6)
C(9)	32(5)	23(4)	30(4)	-2(4)	-5(4)	-3(4)
C(10A)	37(6)	61(6)	62(6)	-19(5)	13(6)	12(6)
C(10B)	50(6)	42(5)	60(6)	-3(5)	8(6)	-1(6)
C(1')	43(6)	45(5)	26(5)	9(4)	-11(5)	13(5)
O(1')	58(5)	53(4)	51(4)	1(3)	-26(4)	10(4)
C(2')	31(5)	31(5)	38(5)	10(4)	-3(5)	4(5)
C(3')	53(7)	38(5)	33(5)	-2(4)	-7(5)	-6(5)
C(4')	43(6)	51(6)	37(5)	9(5)	-15(5)	-3(6)
O(4')	67(5)	59(4)	40(3)	18(3)	-17(4)	-20(4)
C(10)	31(6)	34(5)	41(5)	-6(4)	2(5)	-3(5)
C(2P)	126(12)	67(8)	35(6)	4(6)	-7(7)	7(9)
C(3P)	210(22)	94(12)	44(8)	-1(8)	-12(11)	24(13)
C(4P)	296(30)	63(9)	35(8)	-14(7)	-50(13)	16(16)
C(5P)	215(21)	62(9)	58(8)	1(7)	-37(11)	-76(12)
C(6P)	103(10)	55(7)	41(6)	0(5)	-6(7)	-32(8)
C(1P)	62(7)	34(5)	29(5)	-7(4)	-3(6)	-4(6)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for 1.

	x	y	z	U(eq)
H(4)	1689(12)	5935(7)	8952(3)	35
H(5)	4852(12)	6027(6)	8510(3)	40
H(6A)	5439(14)	7393(6)	7788(3)	44
H(6B)	4168(14)	8112(6)	8231(3)	44
H(7A)	1535(13)	8171(6)	7637(3)	43
H(7B)	2821(13)	7483(6)	7190(3)	43
H(8'1)	452(15)	5981(8)	6891(3)	72
H(8'2)	-1339(15)	6637(8)	7186(3)	72
H(8'3)	-941(15)	5341(8)	7325(3)	72
H(9)	-881(13)	5935(7)	8349(3)	34
H(10A)	3548(16)	4778(8)	7125(4)	80
H(10B)	5424(16)	4913(8)	7527(4)	80
H(10C)	4596(16)	5978(8)	7196(4)	80
H(10D)	1502(16)	3952(7)	7784(4)	76
H(10E)	974(16)	4527(7)	8362(4)	76
H(10F)	3137(16)	3992(7)	8264(4)	76
H(2')	1436(14)	9405(6)	9648(3)	40
H(3'1)	3868(16)	10720(6)	9291(3)	62
H(3'2)	3155(16)	9884(6)	8814(3)	62
H(3'3)	5264(16)	9694(6)	9108(3)	62
H(4')	5339(16)	8979(7)	10107(3)	52
H(4'1)	2973(10)	7856(5)	10451(2)	83
H(2P)	1154(21)	10447(10)	10703(4)	91
H(3P)	1332(32)	12307(14)	11056(5)	139
H(4P)	4200(41)	13422(11)	10912(5)	158
H(5P)	6935(32)	12638(11)	10456(5)	134
H(6P)	6858(20)	10787(8)	10157(4)	80

Appendix 3. X-ray crystal structure of [6(*S*)-*endo*]-*N*-((3`*R*)-hydroxy-(2`*R*)-methyl-3`-phenylpropionyl)-3-aza-11,11-dimethyl-5-oxatricyclo[6.2.1.$0^{1,6}$] undecan-4-one 152

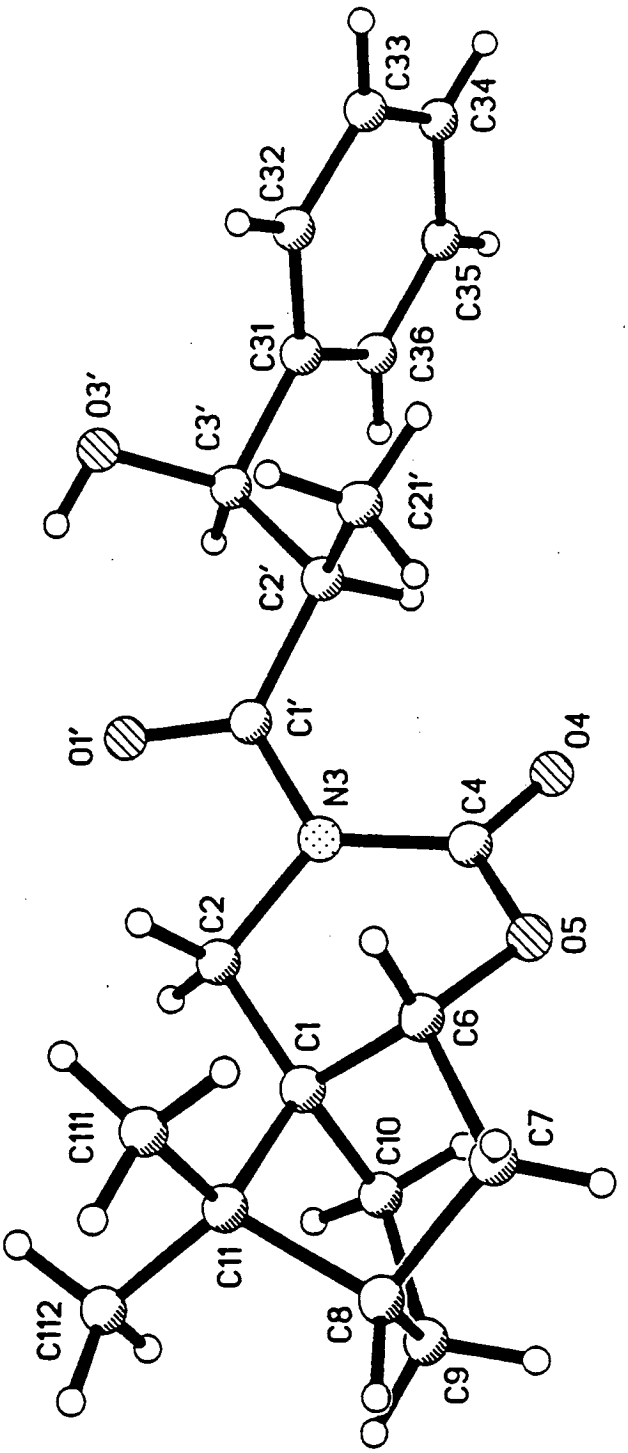


Table 1. Crystal data and structure refinement for xta047 at 220(2) K.

Empirical formula	C21 H27 N O4
Formula weight	357.44
Wavelength	1.54178 A
Crystal system	Monoclinic
Space group	P2(1)
Unit cell dimensions	a = 6.8542(12) A alpha = 90 deg. b = 10.229(4) A beta = 98.25(2) deg. c = 13.353(5) A gamma = 90 deg.
Volume	926.5(5) A^3
Z	2
Density (calculated)	1.281 Mg/m^3
Absorption coefficient	0.711 mm^-1
F(000)	384
Crystal description	Colourless lath
Crystal size	0.47 x 0.23 x 0.12 mm
Theta range for data collection	3.34 to 60.21 deg.
Index ranges	-7<=h<=7, -11<=k<=11, -8<=l<=15
Reflections collected	2802
Independent reflections	2662 [R(int) = 0.0150]
Scan type	omega-theta
Data / restraints / parameters	2662/1/240 (Full-matrix least-squares on F^2
Goodness-of-fit on F^2	1.064
Conventional R [F>4sigma(F)]	R1 = 0.0347 [2443 data]
R indices (all data)	R1 = 0.0392, wR2 = 0.0866
Absolute structure parameter	-0.3(2)
Extinction coefficient	0.0057(7)
Final maximum delta/sigma	-0.001
Weighting scheme calc w=1/[\s^2^(Fo^2^)+(0.0525P)^2^+0.0973P] where P=(Fo^2^+2Fc^2^)/3	
Largest diff. peak and hole	0.140 and -0.123 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for 1. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
C(1)	8665(3)	288(2)	-1248(2)	32(1)
C(2)	8992(3)	623(2)	-149(2)	40(1)
N(3)	7450(2)	-32(2)	375(1)	34(1)
C(4)	6001(3)	-871(2)	-118(2)	36(1)
O(4)	5155(3)	-1684(2)	315(1)	49(1)
O(5)	5549(2)	-761(2)	-1121(1)	38(1)
C(6)	6467(3)	305(2)	-1598(2)	34(1)
C(7)	6268(3)	190(3)	-2749(2)	45(1)
C(8)	8434(3)	332(3)	-2939(2)	42(1)
C(9)	9425(4)	-984(3)	-2681(2)	54(1)
C(10)	9491(4)	-1047(2)	-1520(2)	44(1)
C(11)	9368(3)	1211(2)	-2050(2)	36(1)
C(111)	8535(4)	2594(2)	-2055(2)	49(1)
C(112)	11610(3)	1338(3)	-1958(2)	49(1)
C(1')	7617(3)	262(2)	1405(2)	34(1)
O(1')	9091(2)	847(2)	1782(1)	47(1)
C(2')	5929(3)	5(2)	2001(2)	34(1)
C(21')	4149(3)	820(3)	1553(2)	46(1)
C(3')	6614(3)	281(2)	3128(2)	40(1)
O(3')	7120(3)	1615(2)	3309(2)	58(1)
C(31)	5040(3)	-69(2)	3768(2)	42(1)
C(32)	3590(4)	806(3)	3928(2)	59(1)
C(33)	2107(4)	436(4)	4482(2)	74(1)
C(34)	2079(5)	-788(4)	4876(2)	78(1)
C(35)	3523(6)	-1653(4)	4737(2)	74(1)
C(36)	5009(4)	-1297(3)	4188(2)	54(1)

Table 3. Bond lengths [A], angles and torsions [deg] for 1.

C(1)-C(2)	1.493(3)
C(1)-C(6)	1.512(3)
C(1)-C(10)	1.542(3)
C(1)-C(11)	1.556(3)
C(2)-N(3)	1.505(3)
N(3)-C(1')	1.397(3)
N(3)-C(4)	1.402(3)
C(4)-O(4)	1.208(3)
C(4)-O(5)	1.336(3)
O(5)-C(6)	1.451(3)
C(6)-C(7)	1.529(3)
C(7)-C(8)	1.548(3)
C(8)-C(9)	1.525(4)
C(8)-C(11)	1.552(3)
C(9)-C(10)	1.546(4)
C(11)-C(111)	1.526(3)
C(11)-C(112)	1.530(3)
C(1')-O(1')	1.219(3)
C(1')-C(2')	1.519(3)
C(2')-C(21')	1.527(3)
C(2')-C(3')	1.537(3)
C(3')-O(3')	1.419(3)
C(3')-C(31)	1.512(3)
C(31)-C(36)	1.377(4)
C(31)-C(32)	1.377(4)
C(32)-C(33)	1.393(4)
C(33)-C(34)	1.359(5)
C(34)-C(35)	1.361(5)
C(35)-C(36)	1.386(4)

C(2)-C(1)-C(6)	107.7(2)
C(2)-C(1)-C(10)	115.3(2)
C(6)-C(1)-C(10)	108.7(2)
C(2)-C(1)-C(11)	121.3(2)
C(6)-C(1)-C(11)	100.0(2)
C(10)-C(1)-C(11)	102.4(2)
C(1)-C(2)-N(3)	109.8(2)
C(1')-N(3)-C(4)	123.1(2)
C(1')-N(3)-C(2)	113.4(2)
C(4)-N(3)-C(2)	123.5(2)
O(4)-C(4)-O(5)	118.7(2)
O(4)-C(4)-N(3)	123.6(2)
O(5)-C(4)-N(3)	117.8(2)
C(4)-O(5)-C(6)	116.8(2)
O(5)-C(6)-C(1)	109.4(2)
O(5)-C(6)-C(7)	113.7(2)
C(1)-C(6)-C(7)	104.5(2)
C(6)-C(7)-C(8)	102.0(2)
C(9)-C(8)-C(7)	106.7(2)
C(9)-C(8)-C(11)	102.6(2)
C(7)-C(8)-C(11)	103.2(2)
C(8)-C(9)-C(10)	102.2(2)
C(1)-C(10)-C(9)	103.9(2)
C(111)-C(11)-C(112)	107.0(2)
C(111)-C(11)-C(8)	114.9(2)
C(112)-C(11)-C(8)	114.2(2)
C(111)-C(11)-C(1)	114.4(2)
C(112)-C(11)-C(1)	113.8(2)
C(8)-C(11)-C(1)	92.3(2)

O(1')-C(1')-N(3)	117.3(2)
O(1')-C(1')-C(2')	121.1(2)
N(3)-C(1')-C(2')	121.2(2)
C(1')-C(2')-C(21')	109.0(2)
C(1')-C(2')-C(3')	109.4(2)
C(21')-C(2')-C(3')	113.5(2)
O(3')-C(3')-C(31)	108.0(2)
O(3')-C(3')-C(2')	112.1(2)
C(31)-C(3')-C(2')	111.5(2)
C(36)-C(31)-C(32)	118.4(2)
C(36)-C(31)-C(3')	120.0(2)
C(32)-C(31)-C(3')	121.5(2)
C(31)-C(32)-C(33)	120.3(3)
C(34)-C(33)-C(32)	120.5(3)
C(33)-C(34)-C(35)	119.7(3)
C(34)-C(35)-C(36)	120.3(3)
C(31)-C(36)-C(35)	120.7(3)

C(6)-C(1)-C(2)-N(3)	39.8(2)
C(10)-C(1)-C(2)-N(3)	-81.7(2)
C(11)-C(1)-C(2)-N(3)	153.9(2)
C(1)-C(2)-N(3)-C(1')	-178.3(2)
C(1)-C(2)-N(3)-C(4)	2.5(3)
C(1')-N(3)-C(4)-O(4)	-21.8(3)
C(2)-N(3)-C(4)-O(4)	157.3(2)
C(1')-N(3)-C(4)-O(5)	158.5(2)
C(2)-N(3)-C(4)-O(5)	-22.4(3)
O(4)-C(4)-O(5)-C(6)	174.5(2)
N(3)-C(4)-O(5)-C(6)	-5.8(3)
C(4)-O(5)-C(6)-C(1)	50.3(2)
C(4)-O(5)-C(6)-C(7)	166.7(2)
C(2)-C(1)-C(6)-O(5)	-67.4(2)
C(10)-C(1)-C(6)-O(5)	58.2(2)
C(11)-C(1)-C(6)-O(5)	165.0(2)
C(2)-C(1)-C(6)-C(7)	170.6(2)
C(10)-C(1)-C(6)-C(7)	-63.9(2)
C(11)-C(1)-C(6)-C(7)	42.9(2)
O(5)-C(6)-C(7)-C(8)	-127.5(2)
C(1)-C(6)-C(7)-C(8)	-8.3(2)
C(6)-C(7)-C(8)-C(9)	78.2(2)
C(6)-C(7)-C(8)-C(11)	-29.5(2)
C(7)-C(8)-C(9)-C(10)	-68.8(2)
C(11)-C(8)-C(9)-C(10)	39.3(2)
C(2)-C(1)-C(10)-C(9)	-166.3(2)
C(6)-C(1)-C(10)-C(9)	72.8(2)
C(11)-C(1)-C(10)-C(9)	-32.4(2)
C(8)-C(9)-C(10)-C(1)	-4.0(2)
C(9)-C(8)-C(11)-C(111)	-175.5(2)
C(7)-C(8)-C(11)-C(111)	-64.8(2)
C(9)-C(8)-C(11)-C(112)	60.2(3)
C(7)-C(8)-C(11)-C(112)	171.0(2)
C(9)-C(8)-C(11)-C(1)	-57.2(2)
C(7)-C(8)-C(11)-C(1)	53.5(2)
C(2)-C(1)-C(11)-C(111)	-57.3(3)
C(6)-C(1)-C(11)-C(111)	60.6(2)
C(10)-C(1)-C(11)-C(111)	172.5(2)
C(2)-C(1)-C(11)-C(112)	66.2(3)
C(6)-C(1)-C(11)-C(112)	-175.9(2)
C(10)-C(1)-C(11)-C(112)	-64.0(2)
C(2)-C(1)-C(11)-C(8)	-176.0(2)
C(6)-C(1)-C(11)-C(8)	-58.1(2)
C(10)-C(1)-C(11)-C(8)	53.8(2)
C(4)-N(3)-C(1')-O(1')	169.7(2)
C(2)-N(3)-C(1')-O(1')	-9.5(3)

C(4)-N(3)-C(1')-C(2')	-17.2(3)
C(2)-N(3)-C(1')-C(2')	163.6(2)
O(1')-C(1')-C(2')-C(21')	111.3(2)
N(3)-C(1')-C(2')-C(21')	-61.5(3)
O(1')-C(1')-C(2')-C(3')	-13.4(3)
N(3)-C(1')-C(2')-C(3')	173.8(2)
C(1')-C(2')-C(3')-O(3')	63.6(2)
C(21')-C(2')-C(3')-O(3')	-58.4(2)
C(1')-C(2')-C(3')-C(31)	-175.2(2)
C(21')-C(2')-C(3')-C(31)	62.8(3)
O(3')-C(3')-C(31)-C(36)	-144.5(2)
C(2')-C(3')-C(31)-C(36)	91.9(3)
O(3')-C(3')-C(31)-C(32)	36.9(3)
C(2')-C(3')-C(31)-C(32)	-86.6(3)
C(36)-C(31)-C(32)-C(33)	-1.5(4)
C(3')-C(31)-C(32)-C(33)	177.0(3)
C(31)-C(32)-C(33)-C(34)	0.4(5)
C(32)-C(33)-C(34)-C(35)	0.6(5)
C(33)-C(34)-C(35)-C(36)	-0.6(5)
C(32)-C(31)-C(36)-C(35)	1.6(4)
C(3')-C(31)-C(36)-C(35)	-177.0(2)
C(34)-C(35)-C(36)-C(31)	-0.6(4)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for 1. The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
C(1)	28(1)	31(1)	38(1)	-1(1)	7(1)	-1(1)
C(2)	31(1)	47(1)	43(1)	3(1)	7(1)	-11(1)
N(3)	30(1)	37(1)	37(1)	-2(1)	7(1)	-7(1)
C(4)	31(1)	33(1)	44(1)	-2(1)	10(1)	-2(1)
O(4)	57(1)	44(1)	47(1)	-2(1)	12(1)	-22(1)
O(5)	33(1)	41(1)	39(1)	-1(1)	5(1)	-9(1)
C(6)	29(1)	34(1)	41(1)	1(1)	7(1)	-2(1)
C(7)	37(1)	52(1)	44(1)	0(1)	2(1)	-5(1)
C(8)	43(1)	47(1)	38(1)	-1(1)	13(1)	0(1)
C(9)	55(2)	46(2)	63(2)	-14(1)	21(1)	2(1)
C(10)	39(1)	35(1)	59(2)	3(1)	13(1)	6(1)
C(11)	31(1)	38(1)	42(1)	2(1)	11(1)	3(1)
C(111)	54(2)	38(1)	59(2)	6(1)	18(1)	4(1)
C(112)	34(1)	54(2)	61(2)	3(1)	15(1)	-6(1)
C(1')	30(1)	32(1)	40(1)	1(1)	3(1)	-1(1)
O(1')	36(1)	62(1)	45(1)	-10(1)	8(1)	-14(1)
C(2')	32(1)	30(1)	41(1)	2(1)	6(1)	-2(1)
C(21')	39(1)	51(1)	51(1)	8(1)	11(1)	7(1)
C(3')	39(1)	40(1)	43(1)	-2(1)	10(1)	-2(1)
O(3')	69(1)	52(1)	59(1)	-19(1)	29(1)	-23(1)
C(31)	44(1)	48(1)	34(1)	1(1)	5(1)	-6(1)
C(32)	52(2)	68(2)	61(2)	8(2)	23(1)	7(2)
C(33)	55(2)	109(3)	62(2)	-2(2)	27(1)	4(2)
C(34)	74(2)	124(3)	41(2)	1(2)	22(2)	-37(2)
C(35)	95(3)	85(2)	43(2)	14(2)	12(2)	-33(2)
C(36)	67(2)	57(2)	37(1)	5(1)	6(1)	-6(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for 1.

	x	y	z	U(eq)
H(2A)	8919(3)	1572(2)	-64(2)	48
H(2B)	10306(3)	332(2)	156(2)	48
H(6)	5908(3)	1148(2)	-1412(2)	41
H(7A)	5439(3)	889(3)	-3083(2)	54
H(7B)	5719(3)	-659(3)	-2984(2)	54
H(8)	8587(3)	669(3)	-3618(2)	51
H(9A)	10754(4)	-1008(3)	-2871(2)	64
H(9B)	8646(4)	-1704(3)	-3017(2)	64
H(10A)	8672(4)	-1765(2)	-1328(2)	53
H(10B)	10845(4)	-1168(2)	-1181(2)	53
H(11A)	7107(4)	2559(3)	-2189(14)	74
H(11B)	9026(21)	3104(6)	-2578(9)	74
H(11C)	8941(22)	2999(7)	-1402(5)	74
H(11D)	12203(4)	475(3)	-1901(13)	73
H(11E)	12095(4)	1846(15)	-1361(8)	73
H(11F)	11955(4)	1774(16)	-2554(7)	73
H(2')	5567(3)	-930(2)	1927(2)	41
H(21A)	3014(7)	576(12)	1870(10)	69
H(21B)	3866(16)	661(13)	830(3)	69
H(21C)	4435(10)	1740(3)	1672(11)	69
H(3')	7795(3)	-259(2)	3352(2)	48
H(3'1)	7991(37)	1825(10)	2967(20)	87
H(32)	3601(4)	1657(3)	3662(2)	71
H(33)	1117(4)	1038(4)	4584(2)	88
H(34)	1067(5)	-1035(4)	5243(2)	94
H(35)	3514(6)	-2498(4)	5014(2)	88
H(36)	6005(4)	-1900(3)	4101(2)	65

Appendix 4. X-ray crystal structure of 1-methylene-*N*-tetrahydro-(5`*S*)-methyl-(6`*R*)-phenyl-1`,3`-oxazin-2`,4`-dione-7,7-dimethyl-[(3*S*)-*endo*]-hydroxy-bicyclo [2.2.1]heptane 156

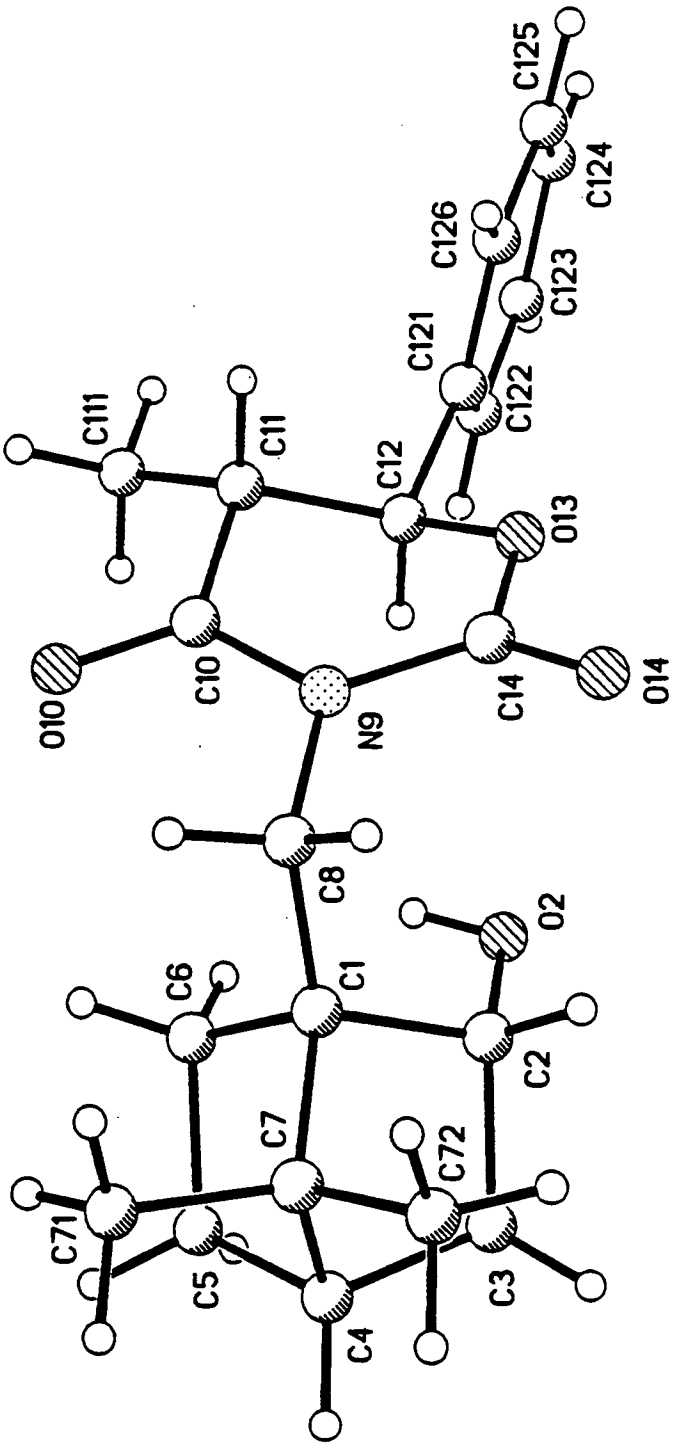


Table 1. Crystal data and structure refinement for ta047b at 220(2) K.

Empirical formula	C21 H27 N O4
Formula weight	357.44
Wavelength	1.54184 A
Crystal system	Monoclinic
Space group	P2(1)
Unit cell dimensions	a = 13.791(3) A alpha = 90 deg. b = 7.041(2) A beta = 108.910(10) deg. c = 20.994(4) A gamma = 90 deg.
Volume	1928.5(8) A^3
Number of reflections for cell	41 (20 < theta < 22 deg.)
Z	4
Density (calculated)	1.231 Mg/m^3
Absorption coefficient	0.683 mm^-1
F(000)	768
Crystal description	Colourless needle
Crystal size	0.77 x 0.04 x 0.04 mm
Theta range for data collection	3.39 to 60.03 deg.
Index ranges	-15<=h<=14, 0<=k<=7, 0<=l<=23
Reflections collected	3532
Independent reflections	3099 [R(int) = 0.1348]
Scan type	omega-2theta with learnt profile
Data / restraints / parameters	3049/574/472 (Full-matrix least-squares on F
Goodness-of-fit on F^2	1.112
Conventional R [F>4sigma(F)]	R1 = 0.0834 [1641 data]
R indices (all data)	R1 = 0.1807, wR2 = 0.2181
Absolute structure parameter	-0.7(8)
Extinction coefficient	0.0012(2)
Final maximum delta/sigma	0.002
Weighting scheme calc w=1/[\s^2^(Fo^2^)+(0.0452P)^2^+2.5041P] where P=(Fo^2^+2Fc^2^)/3	
Largest diff. peak and hole	0.257 and -0.264 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for 1. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
C11	5461(6)	8898(12)	7986(4)	38(2)
C21	5283(6)	6822(13)	8133(5)	46(3)
O21	4949(6)	6640(11)	8711(3)	51(2)
C31	6332(7)	5906(13)	8236(6)	62(3)
C41	6981(7)	7536(14)	8095(5)	60(3)
C51	7243(6)	8812(17)	8721(5)	69(4)
C61	6182(6)	9754(14)	8642(4)	51(3)
C71	6183(6)	8680(14)	7553(5)	49(2)
C711	6598(8)	10588(14)	7382(6)	74(4)
C721	5722(8)	7629(18)	6893(5)	73(4)
C81	4509(6)	10058(14)	7687(4)	50(3)
N91	3792(5)	10093(11)	8073(4)	41(2)
C101	3867(7)	11563(14)	8516(5)	43(2)
O101	4460(6)	12857(11)	8557(4)	65(3)
C111	3127(7)	11495(13)	8905(4)	43(3)
C1111	3535(9)	12650(16)	9554(5)	74(4)
C121	2946(6)	9425(13)	9052(4)	38(2)
O131	2596(5)	8416(10)	8411(3)	47(2)
C141	3091(7)	8606(15)	7958(4)	43(3)
O141	2878(5)	7605(12)	7472(3)	64(3)
C1211	2113(6)	9152(15)	9366(4)	45(3)
C1221	2359(7)	8477(20)	10010(5)	64(4)
C1231	1612(8)	8322(22)	10322(6)	77(4)
C1241	614(8)	8825(21)	9984(6)	72(4)
C1251	362(7)	9457(19)	9324(5)	58(3)
C1261	1115(6)	9631(18)	9026(5)	53(3)
C12	-257(6)	4012(11)	6865(4)	37(2)
C22	765(7)	3892(14)	7429(4)	44(3)
O22	1081(6)	1984(10)	7629(3)	53(2)
C32	567(7)	5014(15)	8007(4)	52(3)
C42	-525(7)	5790(14)	7685(5)	58(3)
C52	-1237(8)	4088(15)	7650(5)	56(3)
C62	-1046(7)	2855(14)	7090(5)	47(3)
C72	-582(7)	6089(12)	6947(5)	49(2)
C712	-1661(6)	6642(16)	6483(5)	61(3)
C722	145(8)	7629(14)	6866(5)	62(3)
C82	-263(6)	3368(14)	6181(4)	43(3)
N92	539(5)	4109(12)	5934(3)	37(2)
C102	1475(6)	3213(15)	6120(5)	42(3)
O102	1646(5)	1822(11)	6480(3)	49(2)
C112	2274(6)	4057(13)	5864(4)	36(2)
C1112	3343(6)	3807(18)	6371(5)	57(3)
C122	2037(6)	6127(13)	5681(5)	45(3)
O132	983(4)	6255(11)	5233(3)	47(2)
C142	222(6)	5471(15)	5420(5)	44(3)
O142	-640(5)	5971(12)	5168(3)	57(2)
C1212	2696(6)	7082(14)	5330(5)	44(3)
C1222	3022(8)	8912(15)	5510(5)	57(3)
C1232	3655(9)	9830(17)	5213(6)	71(4)
C1242	3962(8)	8943(18)	4727(6)	67(4)
C1252	3605(9)	7120(19)	4531(6)	67(4)
C1262	2979(8)	6217(16)	4832(5)	58(3)

Table 3. Bond lengths [A] and angles [deg] for 1.

C11-C81	1.500(10)
C11-C21	1.529(11)
C11-C61	1.537(10)
C11-C71	1.558(10)
C21-O21	1.437(9)
C21-C31	1.534(10)
C31-C41	1.542(11)
C41-C71	1.530(11)
C41-C51	1.535(11)
C51-C61	1.565(10)
C71-C721	1.517(11)
C71-C711	1.548(11)
C81-N91	1.467(8)
N91-C101	1.374(10)
N91-C141	1.392(10)
C101-O101	1.209(10)
C101-C111	1.500(10)
C111-C121	1.527(12)
C111-C1111	1.529(10)
C121-O131	1.459(9)
C121-C1211	1.511(10)
O131-C141	1.345(9)
C141-O141	1.195(9)
C1211-C1221	1.369(11)
C1211-C1261	1.371(10)
C1221-C1231	1.391(11)
C1231-C1241	1.374(12)
C1241-C1251	1.390(12)
C1251-C1261	1.380(10)
C12-C82	1.503(10)
C12-C22	1.522(10)
C12-C62	1.550(10)
C12-C72	1.555(11)
C22-O22	1.433(10)
C22-C32	1.544(10)
C32-C42	1.537(11)
C42-C52	1.537(11)
C42-C72	1.540(11)
C52-C62	1.553(10)
C72-C722	1.524(11)
C72-C712	1.541(11)
C82-N92	1.462(8)
N92-C102	1.375(10)
N92-C142	1.403(10)
C102-O102	1.213(10)
C102-C112	1.497(10)
C112-C122	1.516(11)
C112-C1112	1.523(10)
C122-O132	1.456(9)
C122-C1212	1.503(10)
O132-C142	1.352(9)
C142-O142	1.187(9)
C1212-C1262	1.371(10)
C1212-C1222	1.377(12)
C1222-C1232	1.387(11)
C1232-C1242	1.373(12)
C1242-C1252	1.389(13)
C1252-C1262	1.379(11)
C81-C11-C21	115.4(7)

C81-C11-C61	112.7(7)
C21-C11-C61	107.1(7)
C81-C11-C71	116.6(6)
C21-C11-C71	101.4(7)
C61-C11-C71	102.2(6)
O21-C21-C11	111.8(7)
O21-C21-C31	112.9(8)
C11-C21-C31	103.0(6)
C21-C31-C41	103.9(7)
C71-C41-C51	104.0(8)
C71-C41-C31	102.2(7)
C51-C41-C31	105.2(8)
C41-C51-C61	101.9(6)
C11-C61-C51	103.9(6)
C721-C71-C41	114.2(8)
C721-C71-C711	106.7(8)
C41-C71-C711	113.5(7)
C721-C71-C11	115.0(7)
C41-C71-C11	93.5(7)
C711-C71-C11	113.9(7)
N91-C81-C11	115.6(6)
C101-N91-C141	125.5(7)
C101-N91-C81	118.1(7)
C141-N91-C81	116.5(7)
O101-C101-N91	121.1(8)
O101-C101-C111	123.3(8)
N91-C101-C111	115.4(8)
C101-C111-C121	108.9(7)
C101-C111-C1111	110.4(7)
C121-C111-C1111	111.4(8)
O131-C121-C1211	105.6(6)
O131-C121-C111	107.8(7)
C1211-C121-C111	114.0(7)
C141-O131-C121	120.8(7)
O141-C141-O131	120.3(8)
O141-C141-N91	123.8(8)
O131-C141-N91	115.8(7)
C1221-C1211-C1261	119.0(8)
C1221-C1211-C121	119.7(8)
C1261-C1211-C121	121.2(8)
C1211-C1221-C1231	120.5(9)
C1241-C1231-C1221	120.5(10)
C1231-C1241-C1251	118.8(9)
C1261-C1251-C1241	120.0(9)
C1211-C1261-C1251	121.1(9)
C82-C12-C22	116.3(6)
C82-C12-C62	110.2(6)
C22-C12-C62	107.4(7)
C82-C12-C72	118.5(7)
C22-C12-C72	101.1(7)
C62-C12-C72	101.8(6)
O22-C22-C12	113.4(7)
O22-C22-C32	111.4(7)
C12-C22-C32	103.2(6)
C42-C32-C22	103.6(7)
C52-C42-C32	105.3(8)
C52-C42-C72	103.6(7)
C32-C42-C72	102.3(6)
C42-C52-C62	102.1(6)
C12-C62-C52	104.2(7)
C722-C72-C42	112.9(8)
C722-C72-C712	106.6(8)
C42-C72-C712	113.2(7)
C722-C72-C12	115.7(7)

C42-C72-C12	93.5(7)
C712-C72-C12	114.9(8)
N92-C82-C12	117.5(7)
C102-N92-C142	124.2(7)
C102-N92-C82	118.9(7)
C142-N92-C82	115.7(6)
O102-C102-N92	121.5(8)
O102-C102-C112	121.8(8)
N92-C102-C112	116.7(8)
C102-C112-C122	110.4(7)
C102-C112-C1112	111.2(7)
C122-C112-C1112	111.6(8)
O132-C122-C1212	106.9(7)
O132-C122-C112	108.2(7)
C1212-C122-C112	116.0(7)
C142-O132-C122	119.5(7)
O142-C142-O132	120.6(8)
O142-C142-N92	124.3(8)
O132-C142-N92	115.1(7)
C1262-C1212-C1222	118.5(8)
C1262-C1212-C122	122.9(8)
C1222-C1212-C122	118.6(8)
C1212-C1222-C1232	120.6(9)
C1242-C1232-C1222	120.8(10)
C1232-C1242-C1252	118.4(9)
C1262-C1252-C1242	120.3(10)
C1212-C1262-C1252	121.3(9)

Symmetry transformations used to generate equivalent atoms:

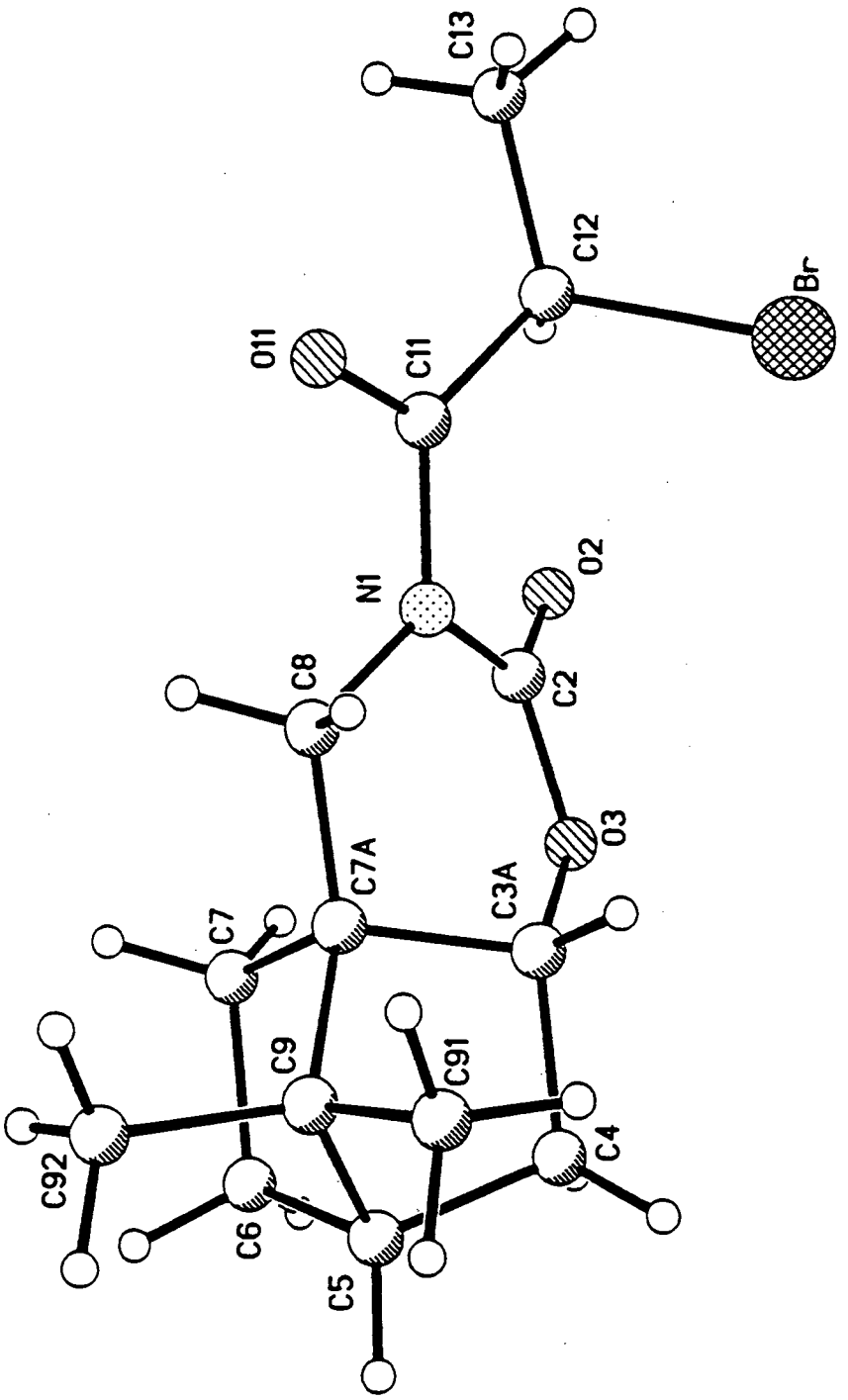
Table 4. Anisotropic displacement parameters (A^2 x 10^3) for 1. The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
C11	41(5)	28(6)	51(5)	-1(5)	22(4)	-3(4)
C21	43(5)	33(6)	66(7)	-1(6)	24(5)	-1(5)
O21	71(5)	32(5)	59(5)	-4(4)	31(4)	-11(5)
C31	56(7)	42(6)	87(8)	0(6)	24(6)	6(5)
C41	43(6)	56(8)	86(7)	-10(6)	28(5)	-3(5)
C51	37(5)	64(9)	101(8)	-15(7)	17(5)	-10(6)
C61	57(6)	34(7)	64(6)	-9(6)	24(5)	-9(5)
C71	43(6)	37(7)	77(6)	-9(5)	35(5)	-13(5)
C711	79(9)	68(9)	102(10)	6(7)	65(8)	-23(7)
C721	71(8)	93(11)	73(7)	-28(8)	47(6)	-12(8)
C81	48(6)	57(8)	53(6)	9(6)	27(5)	5(5)
N91	37(5)	40(5)	48(5)	-2(4)	17(4)	0(4)
C101	41(6)	31(6)	54(6)	2(5)	12(5)	6(5)
O101	71(6)	34(5)	109(7)	-17(5)	57(5)	-13(4)
C111	42(6)	42(6)	50(6)	-5(5)	21(5)	-4(5)
C1111	112(11)	50(9)	68(8)	-25(7)	40(8)	-23(9)
C121	27(5)	41(6)	46(5)	-5(5)	10(4)	-1(5)
O131	46(4)	37(5)	65(4)	-13(4)	27(3)	-12(4)
C141	28(5)	49(7)	45(6)	-3(5)	4(5)	-2(5)
O141	44(5)	77(7)	69(5)	-35(5)	17(4)	-16(5)
C1211	41(5)	35(7)	61(6)	3(6)	22(5)	2(6)
C1221	59(6)	64(10)	69(7)	21(7)	20(5)	-3(7)
C1231	89(8)	70(11)	83(8)	28(8)	43(7)	-2(9)
C1241	78(7)	66(10)	94(8)	10(9)	58(7)	-1(9)
C1251	48(6)	61(10)	74(7)	-12(7)	35(6)	-4(6)
C1261	41(5)	60(9)	65(7)	-1(7)	28(5)	14(6)
C12	39(5)	27(5)	44(5)	-4(5)	13(4)	-7(4)
C22	53(5)	39(6)	43(5)	-3(6)	18(4)	1(5)
O22	63(5)	46(5)	51(5)	5(4)	21(4)	6(4)
C32	56(6)	61(8)	44(5)	-25(6)	24(5)	-18(6)
C42	56(6)	52(8)	75(6)	-23(6)	35(5)	-13(5)
C52	63(6)	52(8)	63(7)	-17(6)	34(6)	-13(7)
C62	46(6)	42(6)	61(7)	-9(6)	29(5)	-7(6)
C72	46(6)	37(6)	73(6)	-9(6)	30(5)	-5(5)
C712	46(6)	42(8)	95(8)	-7(8)	22(6)	8(6)
C722	64(7)	40(7)	89(9)	-4(7)	36(7)	-10(6)
C82	45(5)	46(8)	40(5)	-6(5)	16(4)	-10(6)
N92	39(4)	27(5)	46(5)	-1(4)	15(4)	-1(4)
C102	45(5)	52(7)	29(6)	-1(5)	12(5)	3(5)
O102	56(5)	40(5)	57(5)	10(4)	25(4)	21(4)
C112	32(5)	38(6)	41(6)	-6(5)	16(4)	8(5)
C1112	43(5)	56(9)	59(7)	9(7)	-3(5)	9(6)
C122	34(5)	47(6)	50(6)	4(6)	10(4)	4(5)
O132	33(3)	54(6)	50(4)	11(4)	9(3)	1(4)
C142	33(5)	55(8)	43(6)	6(5)	10(5)	2(5)
O142	35(4)	64(6)	67(5)	18(5)	10(4)	9(4)
C1212	34(5)	48(6)	52(6)	7(6)	16(5)	10(5)
C1222	54(7)	50(7)	75(8)	-7(7)	33(6)	-4(6)
C1232	62(8)	74(9)	84(9)	-6(7)	33(7)	-22(7)
C1242	58(8)	78(9)	77(8)	17(8)	38(7)	0(8)
C1252	63(8)	84(10)	63(8)	-3(8)	31(6)	3(8)
C1262	69(8)	58(8)	54(7)	-7(7)	29(6)	-4(7)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for 1.

	x	y	z	U(eq)
H21	4766(6)	6252(13)	7735(5)	55
H2A1	5122(83)	7598(79)	8952(32)	77
H3A1	6275(7)	4853(13)	7920(6)	74
H3B1	6631(7)	5432(13)	8697(6)	74
H41	7580(7)	7121(14)	7968(5)	72
H5A1	7759(6)	9765(17)	8718(5)	82
H5B1	7490(6)	8064(17)	9136(5)	82
H6A1	5952(6)	9440(14)	9025(4)	61
H6B1	6221(6)	11138(14)	8607(4)	61
H71A1	6901(8)	11310(14)	7792(6)	111
H71B1	6040(8)	11309(14)	7077(6)	111
H71C1	7113(8)	10341(14)	7169(6)	111
H72A1	5225(8)	8439(18)	6576(5)	110
H72B1	5385(8)	6485(18)	6971(5)	110
H72C1	6260(8)	7292(18)	6710(5)	110
H8A1	4713(6)	11367(14)	7635(4)	60
H8B1	4146(6)	9566(14)	7236(4)	60
H111	2467(7)	12052(13)	8625(4)	52
H11A1	3049(9)	12593(16)	9800(5)	111
H11B1	3628(9)	13961(16)	9444(5)	111
H11C1	4187(9)	12130(16)	9830(5)	111
H121	3594(6)	8856(13)	9345(4)	46
H1221	3037(7)	8115(20)	10244(5)	77
H1231	1791(8)	7871(22)	10766(6)	92
H1241	111(8)	8742(21)	10197(6)	86
H1251	-320(7)	9765(19)	9080(5)	69
H1261	940(6)	10086(18)	8582(5)	63
H22	1300(7)	4543(14)	7289(4)	53
H2A2	1307(84)	1490(57)	7346(31)	79
H3A2	607(7)	4181(15)	8388(4)	63
H3B2	1062(7)	6050(15)	8161(4)	63
H42	-685(7)	6931(14)	7908(5)	69
H5A2	-1955(8)	4488(15)	7526(5)	67
H5B2	-1049(8)	3405(15)	8080(5)	67
H6A2	-768(7)	1609(14)	7265(5)	56
H6B2	-1682(7)	2671(14)	6714(5)	56
H71A2	-2152(6)	5696(16)	6519(5)	92
H71B2	-1663(6)	6707(16)	6021(5)	92
H71C2	-1847(6)	7871(16)	6618(5)	92
H72A2	78(8)	7758(14)	6393(5)	92
H72B2	845(8)	7284(14)	7120(5)	92
H72C2	-25(8)	8826(14)	7032(5)	92
H8A2	-217(6)	1979(14)	6187(4)	52
H8B2	-928(6)	3709(14)	5855(4)	52
H112	2252(6)	3368(13)	5448(4)	43
H11A2	3845(6)	4365(18)	6192(5)	86
H11B2	3487(6)	2465(18)	6454(5)	86
H11C2	3378(6)	4433(18)	6789(5)	86
H122	2095(6)	6843(13)	6098(5)	54
H1222	2814(8)	9546(15)	5838(5)	68
H1232	3878(9)	11074(17)	5345(6)	85
H1242	4402(8)	9556(18)	4532(6)	80
H1252	3792(9)	6498(19)	4192(6)	81
H1262	2741(8)	4984(16)	4692(5)	70

Appendix 5. X-ray crystal structure of [6(*S*)-*endo*]-*N*-α-(*R*)-bromopropionyl-3-aza-11,11-dimethyl-5-oxatricyclo[6.2.1.0^{1,6}]undecan-4-one 164



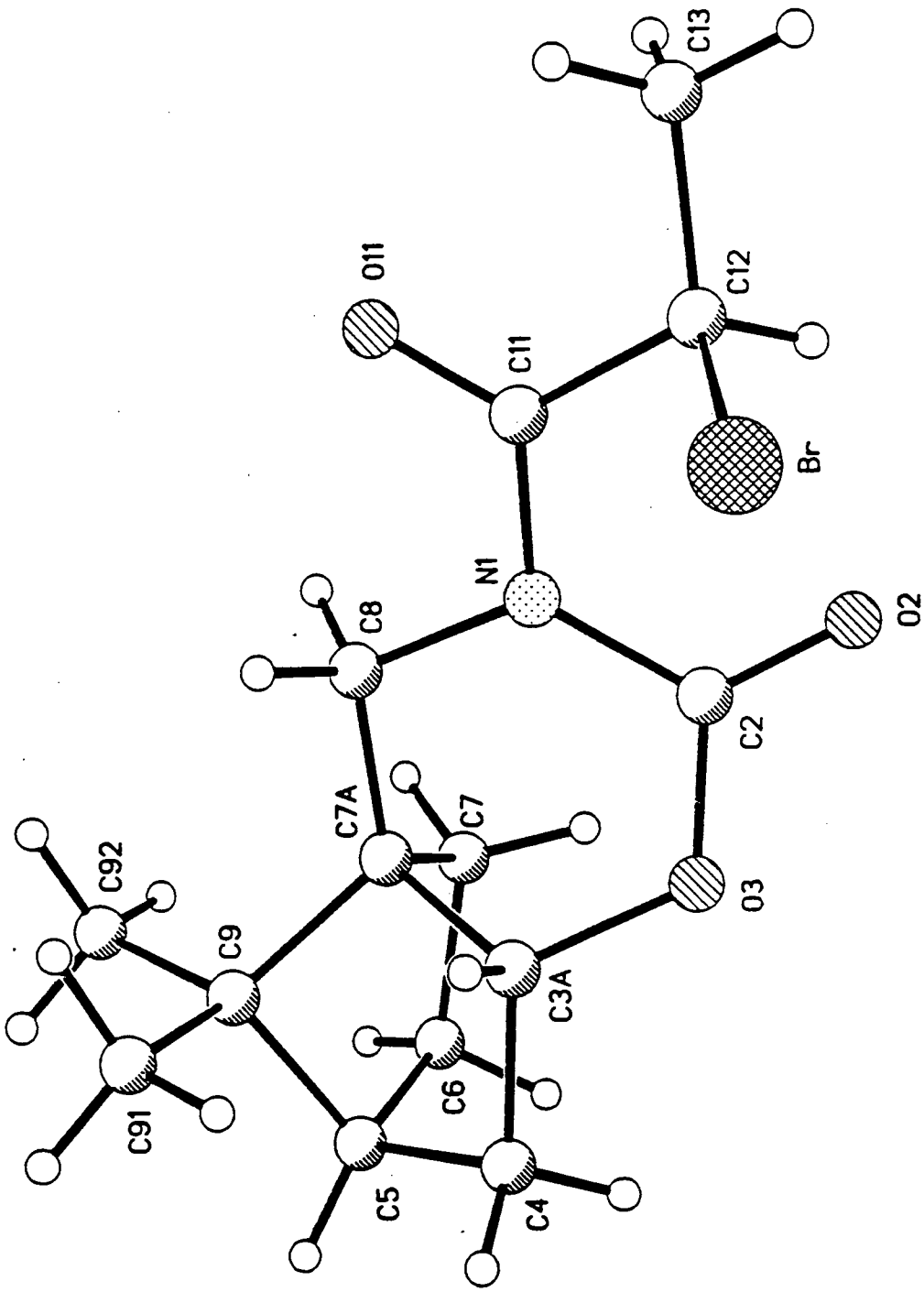

C13
O11
C12
C11
Br
N1
C8
O2
C2
C7A
C7
C92
O3
C9
C3A
C6
C91
C5
C4

Table 1. Crystal data and structure refinement for tal5oc at 220(2) K.

Empirical formula	C14 H20 Br N O3
Formula weight	330.22
Wavelength	1.54178 A
Crystal system	Orthorhombic
Space group	P212121
Unit cell dimensions	a = 9.5393(10) A alpha = 90 deg. b = 10.5986(12) A beta = 90 deg. c = 14.586(2) A gamma = 90 deg.
Volume	1474.7(3) A^3
Number of reflections for cell	60 (20 < theta < 22 deg.)
Z	4
Density (calculated)	1.487 Mg/m^3
Absorption coefficient	3.840 mm^-1
F(000)	680
Crystal description	Colourless column
Crystal size	0.33 x 0.12 x 0.12 mm
Theta range for data collection	5.16 to 69.95 deg.
Index ranges	-11<=h<=11, -1<=k<=12, 0<=l<=17
Reflections collected	3383
Independent reflections	2666 [R(int) = 0.0199]
Scan type	Omega-theta with learnt profile (Clegg)
Absorption correction	Psi-scans (Tmin= 0.390, Tmax=0.310)
Data / restraints / parameters	2662/0/173 (Full-matrix least-squares on F^2
Goodness-of-fit on F^2	1.059
Conventional R [F>4sigma(F)]	R1 = 0.0386 [2345 data]
R indices (all data)	R1 = 0.0466, wR2 = 0.0897
Absolute structure parameter	-0.04(3)
Extinction coefficient	0.0040(2)
Final maximum delta/sigma	0.000
Weighting scheme calc w=1/[\s^2^(Fo^2^)+(0.0307P)^2^+0.8051P] where P=(Fo^2^+2Fc^2^)/3	
Largest diff. peak and hole	0.400 and -0.422 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for 1. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
N(1)	314(3)	5314(3)	3622(2)	31(1)
C(11)	1019(3)	5751(3)	4405(2)	35(1)
O(11)	453(2)	6519(2)	4890(2)	45(1)
C(12)	2455(3)	5240(4)	4654(2)	42(1)
C(13)	3165(4)	6001(4)	5380(3)	62(1)
Br	2127(1)	3515(1)	5076(1)	88(1)
O(2)	2192(2)	4520(3)	2817(2)	54(1)
C(2)	955(3)	4546(3)	2959(2)	36(1)
O(3)	115(2)	3798(2)	2458(2)	38(1)
C(3A)	-1362(3)	3823(3)	2685(2)	35(1)
C(4)	-2292(4)	3227(3)	1943(3)	46(1)
C(5)	-3366(4)	4273(4)	1756(2)	45(1)
C(6)	-2614(4)	5233(4)	1142(3)	58(1)
C(7)	-1532(4)	5818(4)	1810(2)	45(1)
C(7A)	-1846(3)	5183(3)	2737(2)	31(1)
C(8)	-1167(3)	5779(3)	3551(2)	35(1)
C(9)	-3466(3)	4987(3)	2685(2)	39(1)
C(91)	-4093(4)	4174(4)	3447(3)	53(1)
C(92)	-4289(4)	6219(4)	2648(3)	62(1)

Table 3. Bond lengths [A] and angles [deg] for 1.

N(1)-C(11)	1.403(4)
N(1)-C(2)	1.405(4)
N(1)-C(8)	1.499(4)
C(11)-O(11)	1.206(4)
C(11)-C(12)	1.517(4)
C(12)-C(13)	1.495(5)
C(12)-Br	1.954(4)
O(2)-C(2)	1.198(4)
C(2)-O(3)	1.344(4)
O(3)-C(3A)	1.447(4)
C(3A)-C(7A)	1.516(4)
C(3A)-C(4)	1.536(5)
C(4)-C(5)	1.535(5)
C(5)-C(6)	1.534(5)
C(5)-C(9)	1.555(5)
C(6)-C(7)	1.550(5)
C(7)-C(7A)	1.539(4)
C(7A)-C(8)	1.492(4)
C(7A)-C(9)	1.561(4)
C(9)-C(92)	1.525(5)
C(9)-C(91)	1.527(5)
C(11)-N(1)-C(2)	122.8(3)
C(11)-N(1)-C(8)	113.6(2)
C(2)-N(1)-C(8)	123.5(2)
O(11)-C(11)-N(1)	119.0(3)
O(11)-C(11)-C(12)	120.3(3)
N(1)-C(11)-C(12)	120.7(3)
C(13)-C(12)-C(11)	112.7(3)
C(13)-C(12)-Br	110.7(3)
C(11)-C(12)-Br	105.4(2)
O(2)-C(2)-O(3)	118.7(3)
O(2)-C(2)-N(1)	124.2(3)
O(3)-C(2)-N(1)	117.2(3)
C(2)-O(3)-C(3A)	116.4(2)
O(3)-C(3A)-C(7A)	109.0(3)
O(3)-C(3A)-C(4)	113.2(3)
C(7A)-C(3A)-C(4)	104.5(3)
C(5)-C(4)-C(3A)	102.3(3)
C(6)-C(5)-C(4)	105.7(3)
C(6)-C(5)-C(9)	102.4(3)
C(4)-C(5)-C(9)	103.7(3)
C(5)-C(6)-C(7)	102.1(3)
C(7A)-C(7)-C(6)	104.4(3)
C(8)-C(7A)-C(3A)	108.0(3)
C(8)-C(7A)-C(7)	115.4(3)
C(3A)-C(7A)-C(7)	108.2(3)
C(8)-C(7A)-C(9)	121.6(3)
C(3A)-C(7A)-C(9)	99.9(2)
C(7)-C(7A)-C(9)	102.1(3)
C(7A)-C(8)-N(1)	109.0(2)
C(92)-C(9)-C(91)	107.9(3)
C(92)-C(9)-C(5)	114.6(3)
C(91)-C(9)-C(5)	112.5(3)
C(92)-C(9)-C(7A)	113.4(3)
C(91)-C(9)-C(7A)	115.4(3)
C(5)-C(9)-C(7A)	92.7(3)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for 1. The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
N(1)	26(1)	39(2)	28(1)	-4(1)	-1(1)	1(1)
C(11)	34(2)	39(2)	31(2)	2(1)	-2(1)	-7(2)
O(11)	49(1)	53(1)	34(1)	-11(1)	-3(1)	1(1)
C(12)	38(2)	48(2)	39(2)	-1(2)	-7(1)	0(2)
C(13)	56(2)	70(3)	59(2)	-9(2)	-29(2)	-6(2)
Br	126(1)	48(1)	89(1)	17(1)	-37(1)	2(1)
O(2)	28(1)	91(2)	43(1)	-16(1)	4(1)	0(1)
C(2)	29(2)	49(2)	30(2)	-6(2)	0(1)	4(2)
O(3)	28(1)	43(1)	43(1)	-14(1)	-1(1)	4(1)
C(3A)	26(1)	38(2)	40(2)	0(1)	2(1)	0(1)
C(4)	42(2)	40(2)	56(2)	-12(2)	-2(2)	-8(2)
C(5)	40(2)	52(2)	43(2)	-7(2)	-12(2)	-4(2)
C(6)	62(3)	67(3)	44(2)	6(2)	-13(2)	-6(2)
C(7)	50(2)	43(2)	42(2)	5(2)	-4(2)	-5(2)
C(7A)	28(2)	30(2)	34(2)	-2(1)	-1(1)	1(1)
C(8)	27(2)	41(2)	38(2)	-8(2)	1(1)	5(1)
C(9)	29(2)	44(2)	45(2)	-3(2)	-6(1)	4(2)
C(91)	31(2)	66(3)	61(2)	1(2)	4(2)	-3(2)
C(92)	42(2)	54(3)	90(3)	-5(2)	-15(2)	18(2)

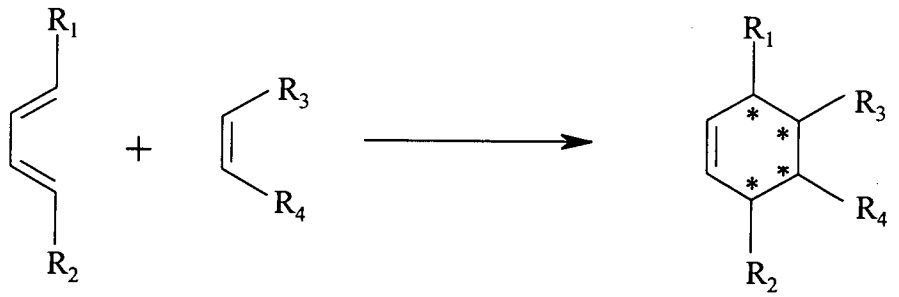
Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for 1.

	x	y	z	U(eq)
H(12A)	3051(3)	5220(4)	4099(2)	50
H(13A)	4075(4)	5636(4)	5514(3)	92
H(13B)	2597(4)	6000(4)	5932(3)	92
H(13C)	3286(4)	6861(4)	5167(3)	92
H(3AA)	-1522(3)	3398(3)	3281(2)	42
H(4A)	-1750(4)	3026(3)	1391(3)	55
H(4B)	-2748(4)	2458(3)	2167(3)	55
H(5A)	-4276(4)	3971(4)	1513(2)	54
H(6A)	-3265(4)	5872(4)	908(3)	69
H(6B)	-2150(4)	4817(4)	624(3)	69
H(7A)	-572(4)	5635(4)	1611(2)	54
H(7B)	-1653(4)	6734(4)	1851(2)	54
H(8A)	-1686(3)	5559(3)	4108(2)	42
H(8B)	-1174(3)	6699(3)	3485(2)	42
H(91A)	-3585(4)	3382(4)	3484(3)	79
H(91B)	-5071(4)	4006(4)	3312(3)	79
H(91C)	-4020(4)	4617(4)	4027(3)	79
H(92A)	-3909(4)	6753(4)	2168(3)	93
H(92B)	-4215(4)	6649(4)	3233(3)	93
H(92C)	-5266(4)	6039(4)	2518(3)	93

Appendix 6. Attempts to correlate the diastereotopicity imparted by chiral auxiliaries in asymmetric Diels-Alder reactions and the chemical shift differences of the diastereotopic protons in the attached *N*-propionyl moiety

A ^{1}H NMR spectroscopic study of the prochiral protons H_a and H_b in the methylene group of the *N*-propionyl derivatives of various chiral auxiliaries has been carried out with the aim of determining the extent, if any, to which the diastereotopicity imparted by the chiral auxiliary in asymmetric Diels-Alder reaction of the corresponding acrylate derivatives with cyclopentadiene is reflected in the NMR parameters. Before making any attempt at correlation, it is worth while to outline the key aspects of the Diels-Alder reaction and its stereochemical outcome.

Since its discovery in 1928[102], the Diels-Alder reaction has become a very powerful tool in organic synthesis. Its great importance is based on the creation of a six membered ring in one step by reaction of an appropriately substituted diene and dienophile with the simultaneous generation of up to four chiral centres (Scheme 73).



Scheme 73

It suffices to point out that there are four possible isomers which can form in this reaction, *viz.* two *endo* and two *exo* isomers, although, only one *endo* and one *exo* isomer can form from each face of the alkene.

During the last few years huge quantities of papers on the use of this reaction in asymmetric synthesis have been published and this topic (in regard to chiral auxiliaries) has been reviewed by Oppolzer[103].

An important development of this reaction over recent years has been the increased use of Lewis acid catalysts, *e.g.* Et_2AlCl (diethylaluminium chloride).These catalysed reactions as well as proceeding at a much faster rate, also exhibit increased regio- and stereo-selectivities compared with non-catalysed reactions.

The effect of the catalyst on the course of the reaction has been rationalised by the application of frontier molecular orbital theory[104]. Thus, in a normal Diels-Alder reaction (that is one involving an electron deficient dienophile and an electron-rich diene), the most important interaction is that between the lowest unoccupied molecular orbital (LUMO) of the dienophile and the highest occupied molecular orbital (HOMO) of the diene (Fig. 16). Electron-withdrawing groups on the dienophile, or the coordination of a Lewis acid with a suitable electron donor on the dienophile, lowers the energy of the LUMO (dienophile) relative to that of the HOMO (diene), and thus decreases the energy separation between the LUMO (dienophile) and the HOMO (diene), leading to a greatly accelerated reaction. The increased regio- and stereo-selectivities in these catalysed reactions arises from the changes in the size of the frontier orbital coefficients.

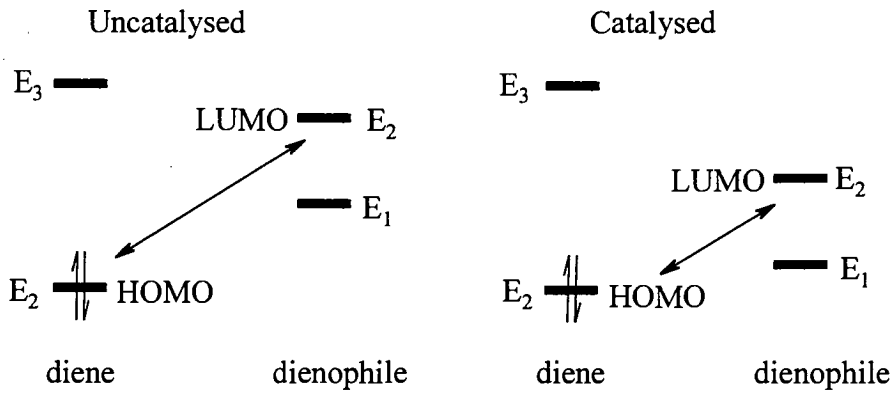
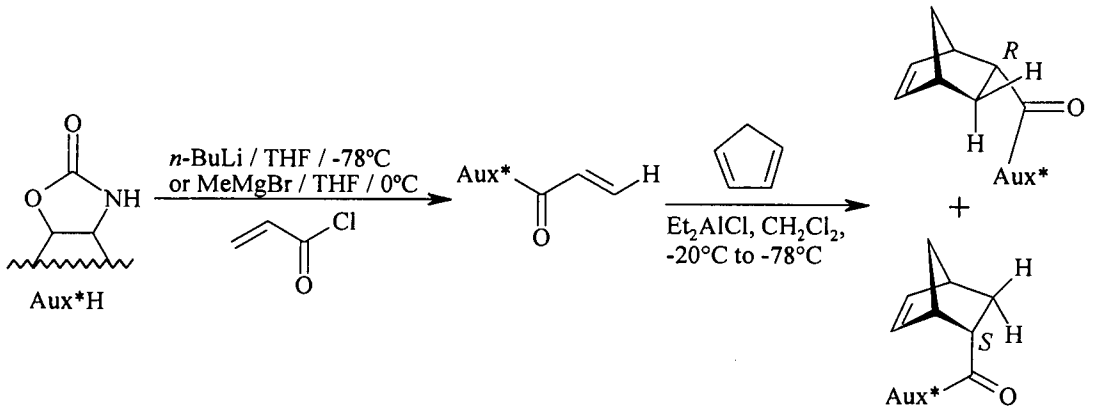


Figure 16

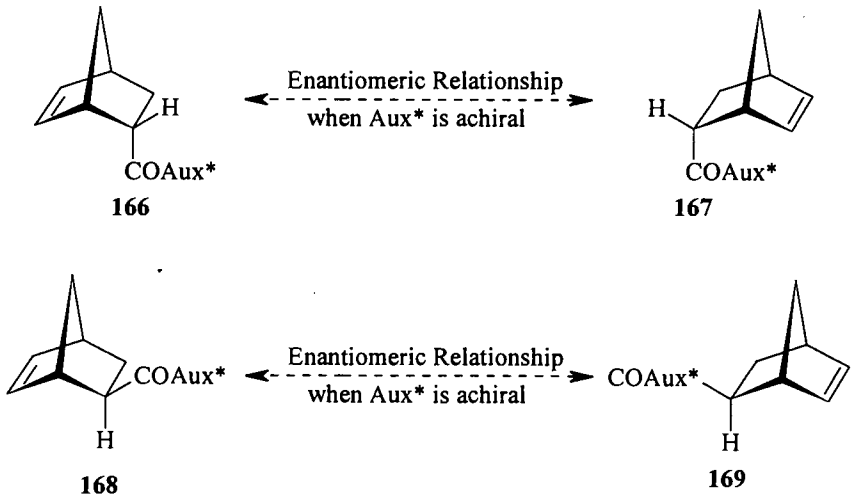
In a study of number of Lewis acids, Evans *et al*[23] noted that diethylaluminium chloride was the most effective in respect to the Diels-Alder reaction. It was also found that the degree of selectivity increased when greater than one equivalent of catalyst was used.

The employment of various chiral auxiliaries in an asymmetric Diels-Alder reactions with cyclopentadiene, and diethylaluminium chloride as the Lewis acid catalyst, is shown in Scheme 74.



Scheme 74

When an acrylate reacts with cyclopentadiene, the formation of four isomers is possible. These are the two kinetically favoured *endo* adducts **166** and **167** and the two thermodynamically favoured *exo* adducts **168** and **169** (Scheme 75).



Scheme 75

Because the auxiliary is homochiral, the two *endo* isomers are not mirror images of each other. This is also true for the two *exo* isomers. Hence all four isomers are diastereomers of each other. Thus, all of the signals in the ^{1}H NMR spectrum of the

mixture will not necessarily have the same chemical shift (but can have) and this fact can be used to determine the ratio of the isomers formed.

If approach of the diene to the C_α-*si* face is severely restricted by steric interactions, only the C_α-*re* face is open to reaction (Fig. 17). Hence this would be compelling evidence that the two isomers formed are the *endo* and the *exo* isomers, shown below, as only one *endo* and one *exo* isomer can form from one face of the alkene (Scheme 76).

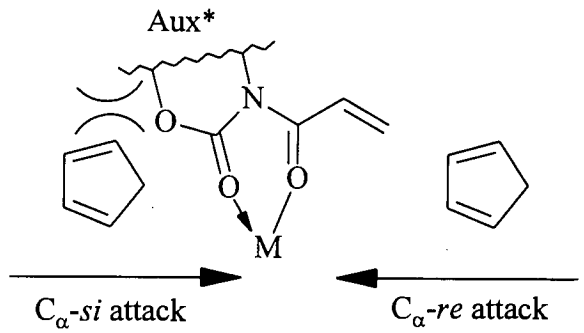
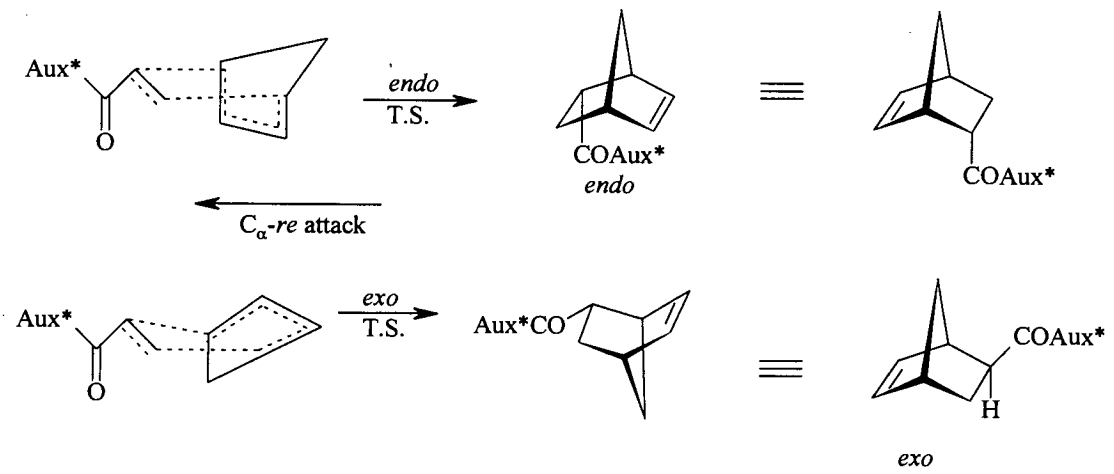


Figure 17



Scheme 76

The aforementioned acrylate dienophile is easily prepared by treating the auxiliary with *n*-butyllithium at -78°C in tetrahydrofuran, followed by acylation with acryloyl chloride, or treated with methylmagnesium bromide followed by acylation with acryloyl chloride to afford the desired acrylate.

Asymmetric Diels-Alder reactions are conducted usually by adding a solution of diethylaluminium chloride catalyst (1.4 equivalents) to a cooled, stirred mixture of the dienophile and freshly cracked cyclopentadiene (10 equivalents) in dichloromethane solvent. After completion of the reaction, the crude products are subjected to flash column chromatography in order to remove excess cyclopentadiene. The resulting material is then analysed by ^{1}H NMR spectroscopy to determine the diastereoselectivity of the reaction.

The signal of interest in these spectra is the doublet of doublets in the chemical shift range 5.50-6.50 ppm, arising from the olefinic protons of the Diels-Alder cycloadducts. Integration of these signals allows the *endo/exo* selectivity and the diastereomeric excess to be determined.

Table 5 depicts the relationship between the stereochemical outcome, *i.e.* diastereomeric excess (*d.e.* %) for the Diels-Alder reactions of the various acrylate derivatives of different chiral auxiliaries with cyclopentadiene and the difference in chemical shift ($\Delta\delta$) of the prochiral methylene protons H_a and H_b in the *N*-propionyl derivatives of these chiral auxiliaries. From an inspection of the data, it can be seen that Et_2AlCl served as the most efficient catalyst Lewis acid for this reaction and yielded the highest values of diastereomeric excess (*d.e.* %) of all the reagents employed. For example, Evans chiral auxiliary **31** achieves levels of diastereoselection of 79% in Diels-Alder reaction when Et_2AlCl is used as a Lewis acid, but very poor diastereoselection (24%) when $TiCl_4$,$Ti(O^iPr)_4$ is employed. By comparison, Chirabornox **60** achieves almost the same levels of diastereoselection of 60% and 33% for Et_2AlCl and $TiCl_4$,$Ti(O^iPr)_4$ respectively, whilst only 3% of diastereoselection is achieved without catalyst. On the other hand, Oppolzer`s chiral sultam **43** achieves excellent levels of diastereoselection of 93% and 94% respectively when Et_2AlCl and $TiCl_4$ serve as the Lewis acid.

The diastereomeric excess (*d.e.* %) obtained in these cycloaddition reactions has been plotted against the chemical shift separation ($\Delta\delta$) of the diastereotopic protons H_a and H_b in the corresponding *N*-propionyl derivatives. Fig. 18 shows that in these systems there is no correlation between the diastereotopicity imparted by the chiral auxiliary and $\Delta\delta$.

For example, in the case of Oppolzer's chiral sultam **43**, $\Delta\delta$ is only 0.04 ppm, but this auxiliary achieves levels of diastereoselection of 93% in Diels-Alder reactions. By comparison, Chiracamphox **67** gives the same levels of diastereoselection, but $\Delta\delta$ in this case is 0.19 ppm.

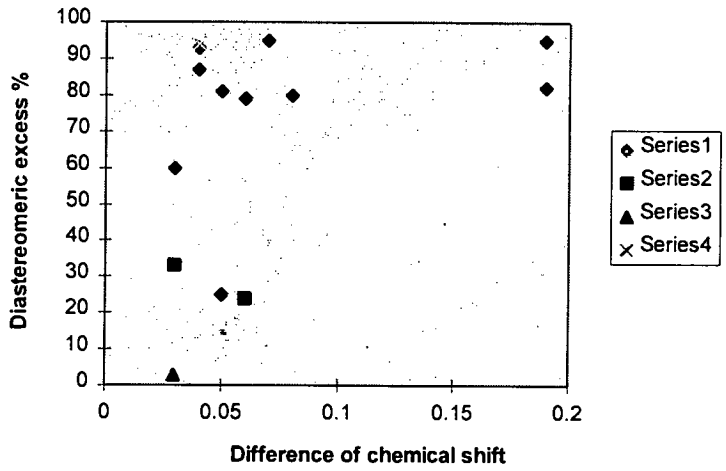


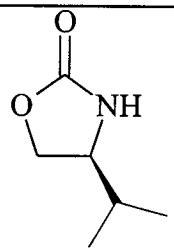
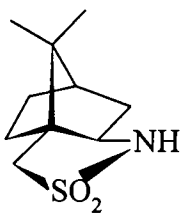
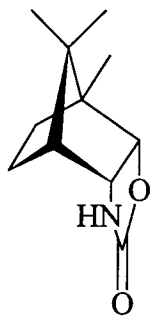
Figure 18. Relationship between diastereomeric excess (*d.e.* %) obtained in the Diels-Alder reaction of the corresponding acrylate derivatives with cyclopentadiene and $\Delta\delta$ of H_a and H_b in the corresponding *N*-propionyl derivative under 4 different series (Series 1 : Et_2AlCl, Series 2 : $TiCl_2(OPr^i)_2$, Series 3 : no catalyst, Series 4 : $TiCl_4$).

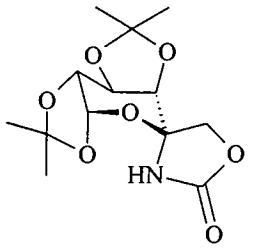
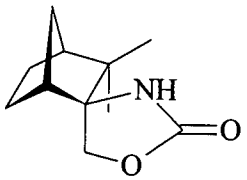
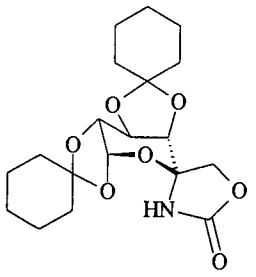
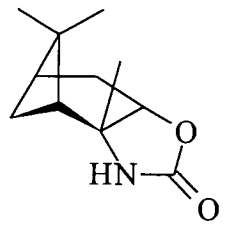
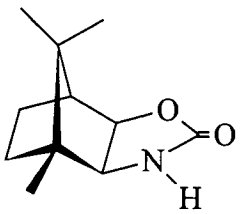
Equally illuminating is the observation that $\Delta\delta$ for the *endo*-auxiliary **60** is 0.03 ppm, and that this auxiliary achieves levels of diastereoselection of only 60% in Diels-Alder reactions. On the other hand, the exo isomer **100** brings about a much higher diastereoselection (*d.e.* = 81%), but $\Delta\delta$ in this case is equally small, *i.e.* 0.05 ppm. Similarly, Chirafructox **105** and the auxiliary from di-*O*-isopropylidene-2-keto-L-gulonic acid **103** produce almost the same levels of diastereoselection of (87% for **105**) and (82% for **103**), but notably they have markedly different $\Delta\delta$, *viz.* 0.04 ppm for **105** and 0.19 ppm for **103**.

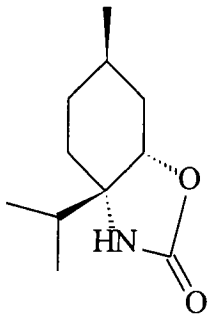
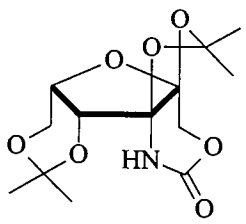
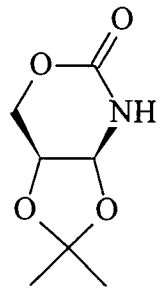
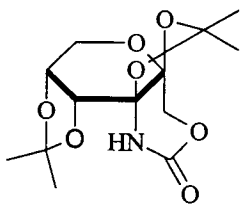
From Fig. 18, it is evident that there is a random scatter with poor levels of diastereoselection unless a Lewis-acid catalyst, especially diethylaluminium chloride (Et_2AlCl) is employed. For example, Evans chiral auxiliary **31** produced levels of

diastereoselection of 79% when Et_2AlCl is used as a Lewis acid, but very poor diastereoselection (24%) with $TiCl_4$,$Ti(O^iPr)_4$. On the other hand, Chirabornox **60** achieved only 3% of diastereoselection without catalyst, but it achieved higher levels of diastereoselection of 60% and 33% for Et_2AlCl and $TiCl_4$,$Ti(O^iPr)_4$ respectively.

Table 5. Diastereomeric excess (*d.e.* %) of asymmetric Diels-Alder reaction of acrylate derivative with cyclopentadiene, together with $\Delta\delta$ of H_a and H_b in the corresponding *N*-propionyl derivative for various chiral auxiliaries.

Auxiliary Aux*H	Diastereomeric excess (*d.e.* %) of Diels-Alder of acrylate derivative with cyclopentadiene	$\Delta\delta$ of H_a and H_b in *N*-propionyl derivative (ppm)
 **31**	24% ($TiCl_4$,$Ti(OPr^i)_4$) CH_2Cl_2 / -78°C ------ 79% (Et_2AlCl) CH_2Cl_2 / -78°C	δH_a =2.93 δH_b =2.87 $\Delta\delta$ =0.06
 **43**	94% ($TiCl_4$) CH_2Cl_2 / -78°C ------ 93% (Et_2AlCl) CH_2Cl_2 / -78°C	δH_a =2.75 δH_b =2.71 $\Delta\delta$ =0.04
 **60**	3% (no catalyst) CH_2Cl_2 / 0°C ------ 33% ($TiCl_2(OPr^i)_2$) CH_2Cl_2 / -78°C ------ 60% (Et_2AlCl) CH_2Cl_2 / -78°C	δH_a =2.97 δH_b =2.94 $\Delta\delta$ =0.03

 **64**	80% (Et_2AlCl) CH_2Cl_2 / -78°C	δH_a =2.96 δH_b =2.88 $\Delta\delta$ =0.08
 **67**	95% (Et_2AlCl) CH_2Cl_2 / -78°C	δH_a =2.99 δH_b =2.80 $\Delta\delta$ =0.19
 **97**	95% (Et_2AlCl) CH_2Cl_2 / -78°C	δH_a =2.95 δH_b =2.88 $\Delta\delta$ =0.07
 **98**	25% (Et_2AlCl) CH_2Cl_2 / -78°C	δH_a =2.93 δH_b =2.88 $\Delta\delta$ =0.05
 **100**	81% (Et_2AlCl) CH_2Cl_2 / -78°C	δH_a =2.91 δH_b =2.86 $\Delta\delta$ =0.05

 **102**	see footnote a	δH_a =2.93 δH_b =2.85 $\Delta\delta$ =0.08
 **103**	82% (Et_2AlCl) CH_2Cl_2 / -78°C	δH_a =2.92 δH_b =2.73 $\Delta\delta$ =0.19
 **104**	see footnote a	δH_a =3.03 δH_b =2.63 $\Delta\delta$ =0.40
 **105**	87% (Et_2AlCl) CH_2Cl_2 / -78°C	δH_a =2.78 δH_b =2.74 $\Delta\delta$ =0.04

[a] The applications of compound **102** were not pursued, because attempts at functionalising these compounds resulted in the formation of thick gums which proved extremely difficult to purify, and applications of **104** have not been investigated in any great detail.

Pergamon

Tetrahedron Letters, Vol. 38, No. 27, pp. 4917-4920, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01058-7

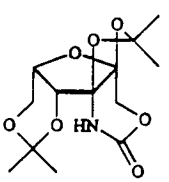
Intramolecular Ring Cleavage of Chiral Terpenoid-derived Oxazinone *via* Asymmetric *anti*-Aldol Reaction : Unexpected Entry to a *N*-Substituted Tetrahydro-1,3-oxazine-2,4-dione Derivative

Tariq R. Abbas[a], J.I.G. Cadogan[b], Allan A. Doyle[a], Ian Gosney[a], Philip K.G. Hodgson[c], Garnet E. Howells[a], Alison N. Hulme[a], Simon Parsons[a] and Ian H. Sadler[a]

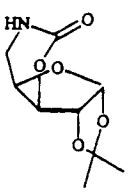
[a] Department of Chemistry, The University of Edinburgh,
West Mains Road, Edinburgh EH9 3JJ, Scotland
[b] Department of Chemistry, Imperial College of Science, Technology and Medicine,
South Kensington, London SW7 2AY, England
[c] B.P.Chemicals Ltd, Research Laboratory, Dunstan Building, Chertsey Road, Sunbury-on-Thames,
Middlesex TW16 7LN, England

Abstract : In the presence of excess Bu_2BOTf to promote *anti*-selectivity, an asymmetric aldol reaction with a homochiral terpenoid-derived 1,3-oxazin-2-one as the chiral control element results unexpectedly in ring cleavage by an intramolecular process to form a *N*-substituted tetrahydro-1,3-oxazine-2,4-dione in virtually quantitative yield. © 1997 Elsevier Science Ltd.

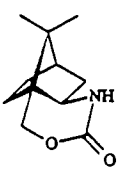
Compared to homochiral oxazolidin-2-ones[1], the use of the six-membered 1,3-oxazin-2-one ring system as a stoichiometric chiral control element has received scant attention[2] despite having the essential features necessary to control asymmetric transformations, *viz.* an easily functionalised nitrogen atom, carbonyl group for chelation control, and importantly, conformational immobility to provide the necessary stereochemical bias . So far, mainly carbohydrates have provided the necessary stereogenic centres for construction of chiral 1,3-oxazin-2-ones, *e.g.* 2-keto-L-gulonic acid for **1**[3], and xylofuranose which serves as a chiral source for the variant **2**[4]. The only terpenoid-based oxazinone to be used as a chiral auxiliary is camphor-derived **3**[5],



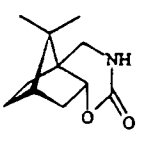
1



2



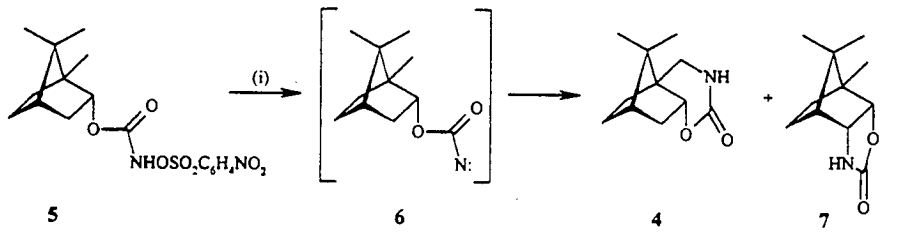
3



4

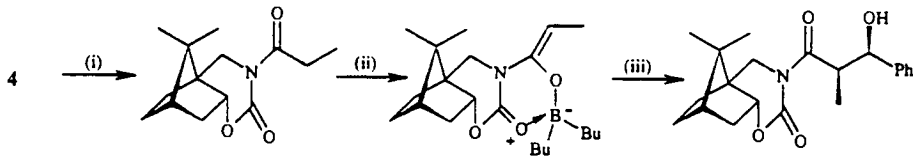
which imparted considerable diastereoselectivity in titanium-mediated "chelation-controlled" aldol reactions to give only *syn*-products. In this Letter, we wish to report the use of the 1,3-oxazin-2-one **4**, a structural isomer of **3**, as a chiral control element, and secondly, the unexpected cleavage of the fused ring system during attempts to stereoregulate the aldol reaction of its *N*-propionyl imide derivative leading to a tetrahydro-1,3-oxazine-2,4-dione[6] by a novel rearrangement process.

The oxazinone auxiliary **4** was synthesised as a *ca.* 1:1 mixture with the tricyclic oxazolidin-2-one **7**[7] by application of the INIR (Intramolecular Nitrene Insertion Reaction) method to the optically-active nitrene **6** which was generated from carbamate precursor **5** as shown in Scheme 1 in a two-phase system.



Scheme 1. *Reagents and conditions:* (i), benzyltriethylammonium chloride, sodium hydrogen carbonate, CH_2Cl_2-water, 25°C.

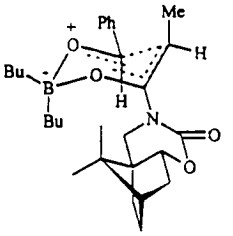
Separation of the isomeric products was easily achieved by flash chromatography on silica (cyclohexane:ethylacetate) which furnished well-formed crystals of the chiral oxazinone **4** in an enantiomerically pure form [(mp 170-171°C; $[\alpha]_D^{23}$= +72.1°; c = 5.1(ethanol) (*cf.* **3**, mp 240-242°C; $[\alpha]_D$= -155°; c = 0.85 (chloroform)] in 36% yield. The stereochemical control imparted by **4** in diastereoselective aldol processes with the enolate **9** derived from the *N*-propionyl imide **8** is reflected in the realisation of nearly complete asymmetric induction in boron-mediated aldol reaction[8] with benzaldehyde (Scheme 2).



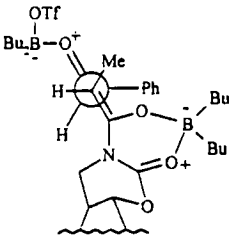
Scheme 2. *Reagents and conditions:* (i), EtMgBr, then CH_3CH_2COCl, THF, -78°C; (ii), Bu_2BOTf, Pr^i_2NEt, CH_2Cl_2, 0°C; (iii), PhCHO, CH_2Cl_2, -78°C.

^{13}C-NMR spectroscopy showed unequivocally that only one product had been formed, whilst *syn*-stereochemistry was assigned on the basis of its small ^{1}H-NMR (250 MHz) vicinal coupling constants (J =2.6Hz) and only one doublet at 5.27 ppm arising from the PhC*H*(OH) proton[9]. The X-ray structure shown in **Fig.1a** confirms the absolute stereochemistry of the two newly formed chiral centres to be *syn* as depicted in compound **10**. This sense of diastereofacial selectivity is similar to that reported for the corresponding aldol reaction of **3** *via* the boron enolate under the original Evans' conditions[5], but in this case, *anti*-isomers were also formed. The high level of asymmetric induction imparted by oxazinone **4** in the

model aldol reaction can be explained by formation of the six-membered Zimmerman-Traxler transition state **11** with tetraco-ordinate boron in which attack of the aldehyde occurs on the C_α-*re* face of the enolate since the bulk of auxiliary shields the C_α-*si* face.



11



12

In an attempt to induce *anti*-selectivity with well defined facial bias, we had occasion to investigate the outcome of the same aldol reaction using Heathcock's protocol[10] with an excess of dibutylboron triflate (2.2 equiv). Indeed, the same behaviour gratifyingly seemed to occur under these conditions, but to our surprise, the product isolated in virtually quantitative yield proved to be the rearranged compound **14** (Scheme 3). Further crystallisation from cyclohexane furnished colourless crystals of the enantiopure tetrahydro-1,3-oxazine-2,4-dione **14** (mp 125-127°C) whose structure was confirmed by microanalysis, mass spectral and NMR data[11]. X-Ray diffraction analysis confirmed the stereochemical integrity of **14** and has shown that the absolute configuration of the chiral centres at C(3) and C(4) is (5*S*,6*R*) (**Fig.1b**).

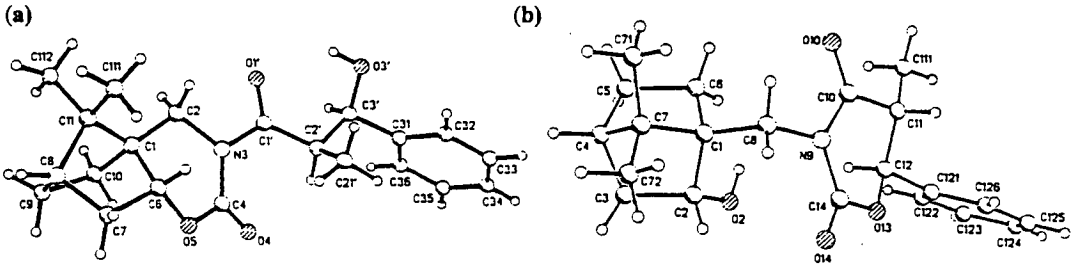
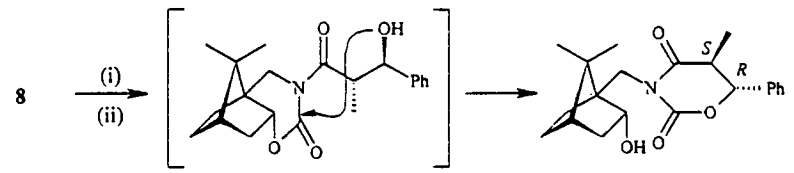


Figure 1. (**a**) Molecular structure of *syn*-aldol **10**, and (**b**) of tetrahydro-1,3-oxazine-2,4-dione **14**

From a mechanistic viewpoint, such an outcome provides strong support for the intermediacy of the *anti*-adduct **13** arising from a transition state like **12** where the enolate boron is chelated to the oxazinone carbonyl to give not only the correct sense of diastereofacial selectivity, but also to facilitate ring cleavage of the oxazinone ring. To our knowledge, this seems to be the first example of such a transformation and it is conceivable that the reaction may be extended to related systems under the influence of a Lewis acid. Further work in this area is in progress and will be reported in due course. In the meantime, it is worth noting that treatment of the *syn*-aldol product **10** with excess boron triflate under Heathcock's conditions gave 1,3-oxazine-2,4-dione **14** with *anti*-stereochemistry exclusively, pointing to realisation of a *retro*-aldol reaction or else α-epimerisation before rearrangement.



13 14

Scheme 3. *Reagents and conditions:* (i), excess Bu_2BOTf, Pr^i_2NEt, CH_2Cl_2, 0°C; (ii), PhCHO, CH_2Cl_2, -78°C.

References and notes

1. For a review, see Cadogan, J.I.G.; Doyle, A.A.; Gosney, I.; Hodgson, P.K.G.; Thorburn, P.; *Enantiomer*, **1997**, *2(2)*, 81-98.
2. See in particular, Kunz, H.; Ruck, K.; *Angew. Chem. Int. Ed. Engl.*, **1993**, *32*, 336-358, and references cited therein.
3. Banks, M.R.; Cadogan, J.I.G.; Gosney, I.; Gaur, S.; Hodgson, P.K.G.; *Tetrahedron Asymmetry*, **1994**, *5*, 2447-2458.
4. Ref. 2, page 346.
5. Anh, H.K.; Lee, S.; Lim, A.; *J. Org. Chem.*, **1992**, *52*, 5065-5066.
6. For pertinent references to the synthesis of tetrahydro-1,3-oxazine-2,4-diones, see Barton, D.H.R.; Liu, W.; *J. Chem. Soc. Chem. Commun.*, **1997**, 571-572.
7. Banks, M.R.; Blake, A.J.; Cadogan, J.I.G.; Dawson, I.M.; Gosney, I.; Grant, K.J.; Gaur, S.; Hodgson, P.K.G.; Knight, K.S.; Smith, G.W.; Stevenson, D.E.; *Tetrahedron*, **1992**, *48*, 7979-8006.
8. See ref. 6, and references cited therein.
9. All compounds exhibited spectral data consistent with their structures. Selected spectroscopic data for compound **10** : FTIR (nujol) ν_{max} : 3560(OH), 1732(C=O), 1674(C=O) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.44-7.20(5H, cm, Ph), 5.27(1H, d, *J* =2.6Hz, C*H*OH), 4.56-4.49(1H, ddd, *J* =4.0,2.4,2.0Hz, C*H*O), 4.10(1H, dq, *J* =7.1, 2.6Hz, C*H*CH_3), 3.59(1H, d, *J* =12.2Hz, CH_2N), 3.48(1H, d, *J* =12.2Hz, CH_2N), 2.73(1H, broad s, O*H*), 2.31-2.21(1H, m, C*H* bridgehead), 1.99-1.24(6H, cm, 3CH_2), 1.02(3H, d, *J* =7.1Hz, CH_3CH), 1.02(3H, s, CH_3), 0.99(3H, s, CH_3) ppm; ^{13}C NMR (63 MHz, $CDCl_3$) δ 181.16(C=O), 152.67(C=O), 141.26(Ar C), 127.94(Ar 2CH), 127.01(Ar CH), 125.95(Ar 2CH), 80.84(CH), 72.64(CH), 48.34(CH_2), 46.99(quat C), 46.38(CH), 45.85(quat C + CH), 32.48(CH_2), 27.44(CH_2), 25.00(CH_2), 19.75(CH_3), 18.61(CH_3), 10.58(CH_3) ppm; MS(FAB) m/z 55(29%), 95(11), 117(64), 135(80), 145(base), 178(7), 240(3), 296(12), 340(68), 358(11); Accurate mass (FAB); Found : 358.20073; $C_{21}H_{28}NO_4$ (M+H) requires 358.20183.
10. Danda, H.; Hansen, M.M.; Heathcock, C.H.; *J. Org. Chem.*, **1990**, *55*, 173-181.
11. Selected spectroscopic data for compound **14** : FTIR (nujol) ν_{max} : 3485(OH), 1765(C=O), 1677(C=O) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.43-7.25(5H, cm, Ph), 4.99(1H, d, *J* =11.6Hz, PhC*H*O), 4.24(1H, dd, *J* =8.9,2.1Hz, C*H*OH), 3.96(2H, s, CH_2N), 2.88(1H, dq, *J* =11.6,7.0Hz, C*H*CH_3), 2.31-2.13(2H, cm, O*H* and C*H* bridgehead), 2.06-1.70(2H, cm, CH_2), 1.59-1.23(4H, cm, 2CH_2), 1.06(3H, d, *J* =7.0Hz, CH_3CH), 1.02(3H, s, CH_3), 0.90(3H, s, CH_3) ppm; ^{13}C NMR (63 MHz, $CDCl_3$) δ 171.87(C=O), 152.07(C=O), 135.09(Ar C), 129.50(Ar CH), 128.79(Ar CH), 128.62(Ar CH), 126.97(Ar CH), 125.28(Ar CH), 80.84(CH), 73.76(CH), 52.59(quat C), 48.54(quat C), 46.04(CH), 42.18(CH_2), 41.81(CH), 37.82(CH_2), 27.75(CH_2), 23.45(CH_2), 20.08(CH_3), 18.99(CH_3), 11.43(CH_3) ppm; MS(FAB) m/z 41(base), 55(53%), 95(20), 117(50), 135(44), 145(97), 178(27), 240(6), 296(11), 340(68), 358(13); Accurate mass (FAB); Found : 358.20129; $C_{21}H_{28}NO_4$ (M+H) requires 358.20183.

(*Received in UK* 28 *April* 1997; *revised* 27 *May* 1997; *accepted* 30 *May* 1997)