Stereocontrolled Synthesis and Rearrangement of Epoxides

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A thesis submitted in partial fulfilment of the requirements
for the degree of Doctor of Philosophy

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Imperial College of Science, Technology and Medicine
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I confirm that this report is my own work and where reference is made to other research this is referenced in text.

Dedicated to my mum and dad for supporting me and encouraging me in fulfilling my academic endeavour and ambitions.

Abstract

This thesis describes two related bodies of work, namely the epoxidation of alkoxydihydropyrans and the synthesis of epoxidation catalysts. For clarity, separate chapters comprising an introduction, results and discussion and conclusion and future work are presented for each.

In Chapter 1, the diastereoselective formation of 4,5-*cis*-tetrahydrofuranones *via* the oxidative rearrangement/Jones oxidation of 2-alkoxy-3,4-dihydro-2*H*-pyrans is described. High levels of stereocontrol were observed with sterically demanding and branched substituents. Furthermore, this oxidative rearrangement method was applied to the synthesis of γ-lactone-containing natural products such as a whisky lactone and a cognac lactone. Additionally, in line with the rearrangement of the heterocycle series, we also investigated an equally rapid route to carbocycles (cyclopentanes) by the cyclopropanation of 2-alkoxy-3,4-dihydro-2*H*-pyrans using diazomalonate and a copper-based catalyst and a mixture of insertion product and rearrangement product was obtained.

The enantioselective formation of tetrahydrofuranones from aryl-substituted alkoxydihydropyrans using an asymmetric epoxidation catalyst (chiral manganese salen catalyst) is presented in Chapter 2. Higher levels of stereocontrol were observed with more sterically demanding and branched alkyl groups, or more electron-donating aryl groups.

In Chapter 3, we describe the synthesis of novel chiral ketone catalysts for the asymmetric epoxidation of alkenes. An oxabicyclic ketone catalyst and an azabicyclic ketone catalyst were synthesised and their reactivity and selectivity of epoxidation were investigated.

Finally, full experimental details and spectra are presented for all novel compounds synthesised in the course of this work in Chapter 4.

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Finally, I would like to thank my parents for their continued support throughout many years as a student.

Abbreviations

^{1}H	Proton
^{13}C	Carbon-13
Å	Angstrom(s)
Ac	Acetyl
acac	Acetylacetone
AIBN	Azobisisobutyronitrile
aq.	Aqueous
Ar	Aryl substituent
bpy	2,2'-Bipyridine
^{i}Bu	*iso*-Butyl
^{n}Bu	*n*-Butyl
^{t}Bu	*tert*-Butyl
Bn	Benzyl
Bz	Benzoyl
Cat.	Catalyst
CI	Chemical ionisation
cod	1,5-Cyclooctadiene
Conc.	Concentrated
Cp	Cyclopentadiene
CSA	Camphorsulfonic acid
cyHex	Cyclohexyl
d	Doublet
dba	Dibenzylideneacetone
DBB	di-*tert*-Butylbiphenylide
DBMP	2,6-di-*tert*-Butyl-4-methylpyridine
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
dd	Doublet of doublets
DET	Diethyl tartrate
DHP	Dihydropyran
DFT	Density functional theory
DMAP	4-(*N*-Dimethylamino)pyridine
DMDO	Dimethyldioxirane
DMF	*N,N'*-Dimethylformamide
DMSO	Dimethyl sulfoxide
DPE	1,2-Bis(diphenylphosphino)ethane
DPPBA	2-(Diphenylphosphino)benzaldehyde
dr	Diastereoisomeric ratio
dt	Doublet of triplets
EDTA	Ethylenediaminetetraacetate
ee	Enantiomeric excess
EPHP	1-Ethylpiperidine hydrophosphite

Eq	Equivalent(s)
Et	Ethyl
FOD	6,6,7,7,8,8,8-Heptafluoro-2,2-dimethyl-3,5-octanedione
g	Gram(s)
h	Hour(s)
HDA	Hetero Diels-Alder
HPLC	High-Performance Liquid Chromatography
hυ	Irradiation (photolysis)
Hz	Hertz
IDCP	Iodonium dicollidine perchlorate
Im	Imidazole
IR	Infrared
J	Coupling constant (in Hz)
LDA	Lithium di-*iso*-propylamide
m	Multiplet
M	Molar
MCBA	*meta*-Chlorobenzoic acid
MCPBA	*meta*-Chloroperbenzoic acid
Me	Methyl
mg	Milligram(s)
MHz	Megahertz
min	Minute(s)
mL	Millilitre(s)
mmol	Millimole(s)
m.p.	Melting point
MS	Molecular sieves
MTO	Methyltrioxorhenium
m/z	Mass/charge ratio (in mass spectrometry)
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
NHC	*N*-Heterocyclic carbene
NHP	*N*-Hydroxyphthalimide
NIS	*N*-Iodosuccinimide
NMO	*N*-Methylmorpholine-*N*-Oxide
NMP	*N*-Methyl pyrrolidinone
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
NOESY	Cross-correlated NOE spectrum
Nu	Nucleophile
PCC	Pyridinium chloro chromate
petrol	Petroleum ether (b.p. 40-60°C)
Ph	Phenyl
Pht	Phthalimide

ppm	Part(s) per million
PPTS	Pyridinium *p*-toluenesulfonate
^{i}Pr	*iso*-Propyl
PTAB	Phenyltrimethylammonium tribromide
py	Pyridine
q	Quartet
rt	Room temperature
s	Singlet
salen	*N,N'*-Bis(salicylidene)ethylenediamine
sat.	Saturated
SCX	Strong cation exchange
skewphos	2,4-bis(diphenyl-phosphino)pentane
t	Triplet
TBAF	Tetra-*n*-butylammonium fluoride
TBAI	Tetra-*n*-butylammonium iodide
TBDPS	*tert*-Butyldiphenylsilyl
TBPA	Tris(4-bromophenyl)aminium
TBS	*tert*-Butyldimethylsilyl
TEA	Triethylamine
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	*N,N,N',N'*-tetramethyl 1,2-ethanediamine
TMS	Trimethylsilyl
p-Tol	*p*-Toluyl
triflate	Trifluoromethanesulfonate
N-Tris	*N*-2,4,6-Triisopropylbenzenesulfonyl
Ts	*p*-Toluenesulfonyl
UHP	Urea hydrogen peroxide

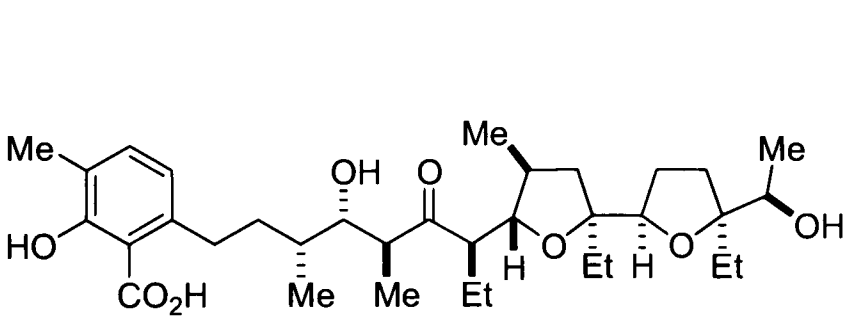
Chapter I. Diastereoselective oxidative rearrangement of 2-alkoxydihydropyrans

1. Introduction

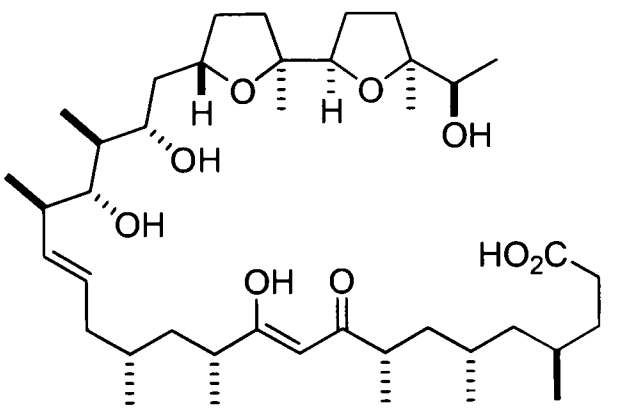
1.1. Tetrahydrofurans in natural products

Substituted tetrahydrofurans (THFs) are frequently encountered in various natural products[1] as well as being versatile synthetic intermediates.[2] Indeed, they feature predominantly in a number of biologically significant molecules such as the polyether antibiotics,[1a] lignans[3] and macrodiolides.[4]

Polyether antibiotics, isolated from fermentation cultures of *Streptomyces*, are distinguished by a linear carbon framework containing THFs and tetrahydro-*2H*-pyrans, multiple centres of asymmetry and a structure often terminating in a carboxylic acid. Representative examples are shown in Fig. 1.



Isolasalocid



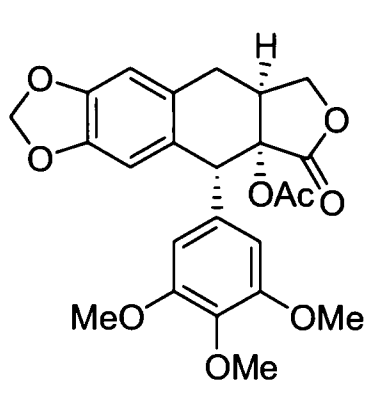
Ionomycin

Fig. 1. Structure of representative polyether antibiotics.

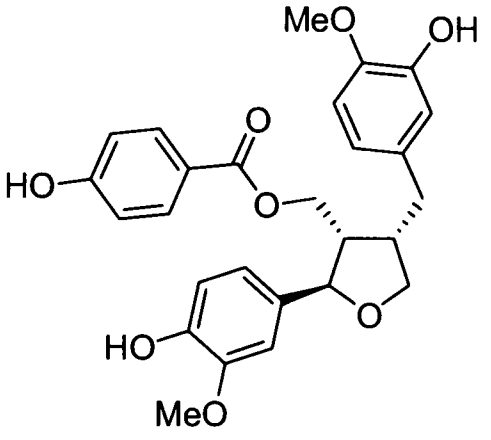
In terms of biological activity, a carboxylate group and oxygen atoms of the antibiotics play a role as ligands for the complexation of the most biologically significant polar cations such as K^+, Na^+, Ca^{2+}, Mg^{2+} and the biogenic amines. Such complexes are exceptionally hydrophobic and the antibiotics can thus assist the transport of these cations across lipid bilayers, inducing a range of biological responses that include ruminant growth promotion, anticoccidial activity, and mammalian cardiovascular effects. Their features and synthesis have been reviewed by Westley in 1982[5] and Huff in 2000.[1a]

Lignans are a class of secondary plant metabolites produced by oxidative dimerization of

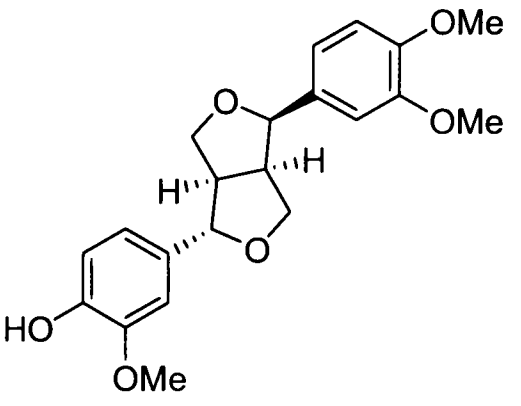
two phenylpropane units. Although their molecular backbone consists only of two phenylpropane units, lignans show an enormous structural diversity. Some examples are shown in Fig. 2. It is known that these compounds show potential anti-apoptotic activity[6] or anti-cancer activity.[7] Such important bioactivities and the potential applications in cancer chemotherapy have fuelled a growing interest in lignans and their synthetic derivatives.[3]



erlangerins C



Agastinol

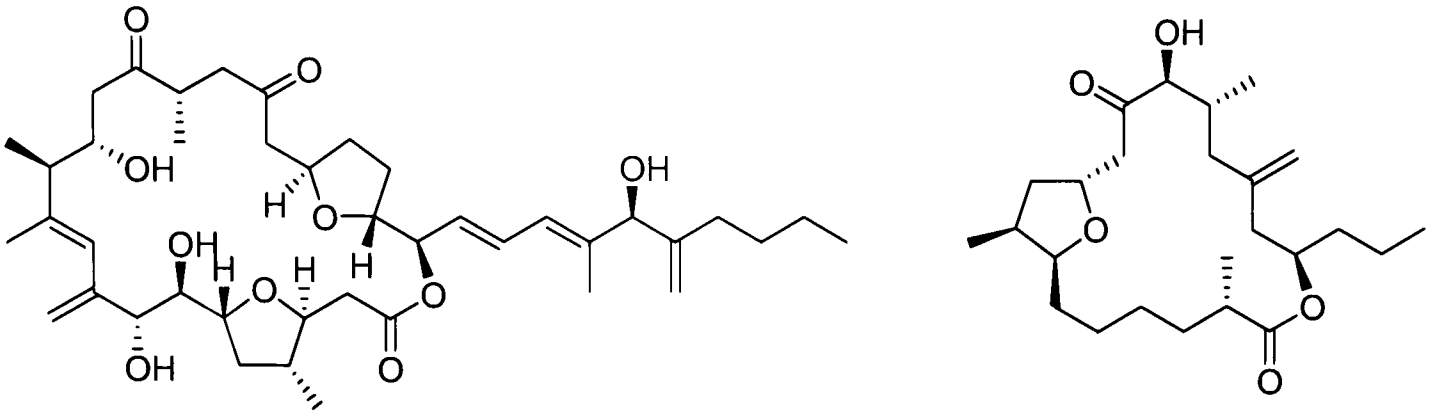


phillygenol

Fig. 2. Structure of representative lignans.

Macrodiolides are an interesting class of natural products exhibiting many different bioactivities. A wide range of total syntheses and biological activities of macrodiolides were reviewed by Lee in 2005.[4] Among the macrodiolides, this section focuses on only amphidinolides bearing THFs because these are of particular interest to our group. These amphidinolides were isolated from symbiotic marine dinoflagellates of the genus *Amphidinium* sp. from inside cells of Okinawa marine flatworms.[1b] Since Yamasu and co-workers found that *Amphidinium* show potent cytotoxic activity (70-90% inhibition at 3 $\mu g \cdot mL^{-1}$) against murine lymphoma L1210 cells and human epidermoid carcinoma KB cells in 1987,[8] *Amphidinium* have been investigated worldwide; Kobayashi has provided a comprehensive review of their isolation, properties and synthesis in 2004.[1b] Currently, our group is interested in Amphidinolide C **1** and T1 **2** (Fig. 3). In terms of structure, Amphidinolide C **1** is a 25-membered macrolide with two THF rings[9] and amphidinolide

T1 **2** is a 19-membered macrolide with one THF ring.[10]



Amphidinolide C **1**

Amphidinolide T1 **2**

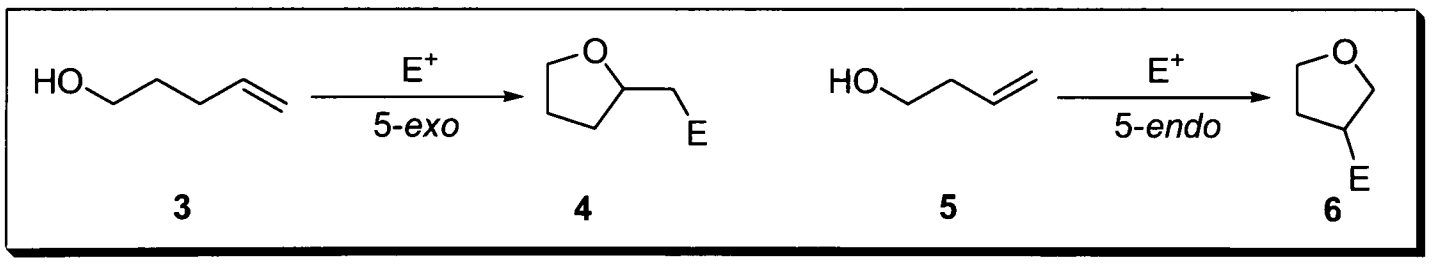
Fig. 3. Structure of representative amphidinolides.

1.2. Previous synthetic routes to tetrahydrofurans

Due to the importance of the THF framework, enormous effort has been devoted towards the development of methods for the synthesis of substituted THFs. There have been several reviews to cover the previous methods reported up to 2001.[11] Thus this section will cover key literature reports showing novel strategies or high levels of stereocontrol from 2002 onwards.

1.2.1. Electrophilic cyclization strategies.

Electrophilic cyclization is one of the most common strategies to construct THF rings. Generally, attack of an alcohol on the alkene moiety of unsaturated alcohols of general structure **3** or **5** is promoted by an electrophile (E^+) to form the THF **4** or **6** respectively (Scheme 1). A wide range of electrophiles have been employed, including halogens, oxygen (epoxide), sulfur or metals. This type of transformation has been widely used for the synthesis of 2,5-disubstituted THFs. An important issue is often the control of *exo*- vesus *endo*-ring closure.

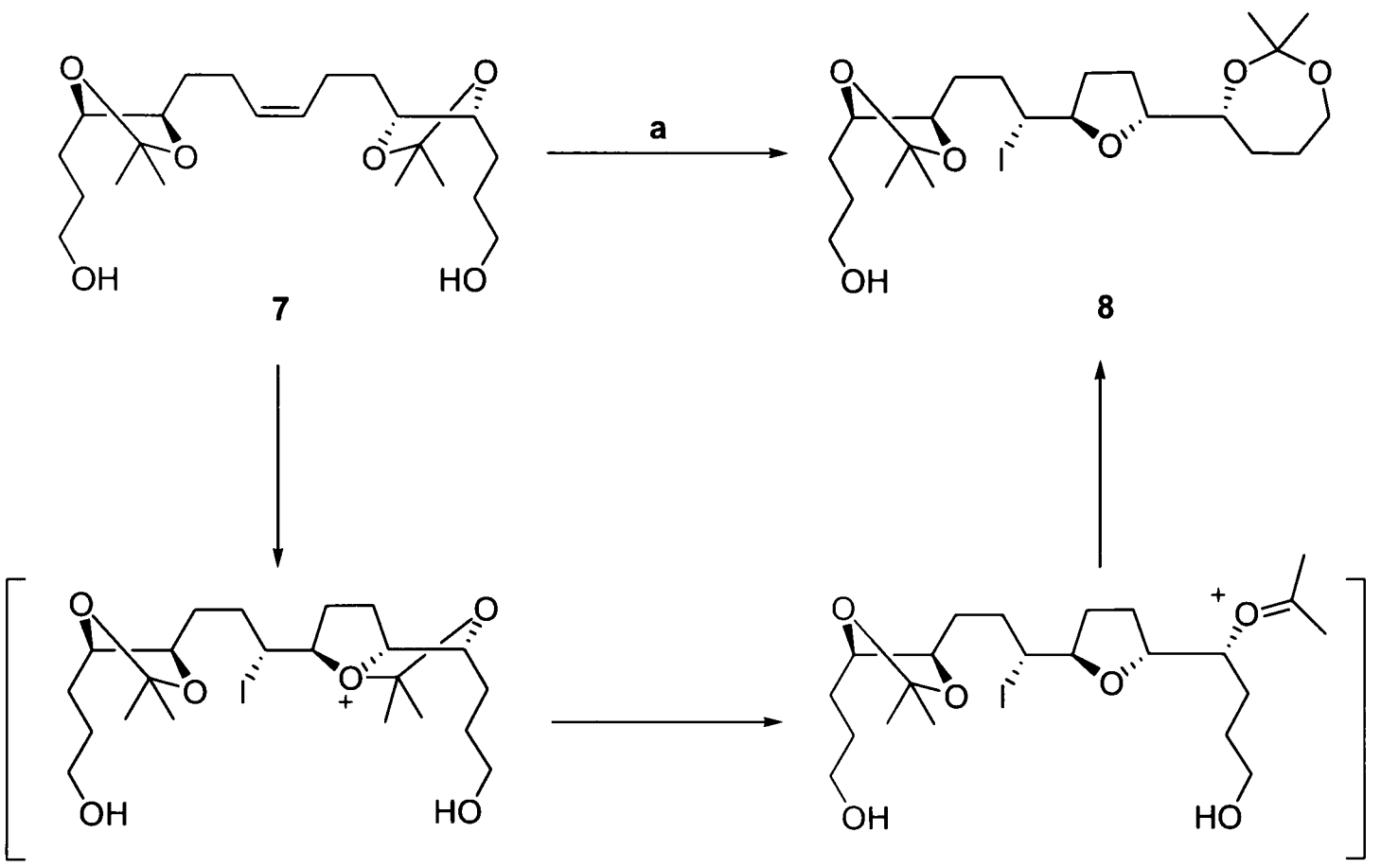


Scheme 1. Formation of THF by electrophilic cyclization.

1.2.1.1. Halocyclisation (E=halogen)

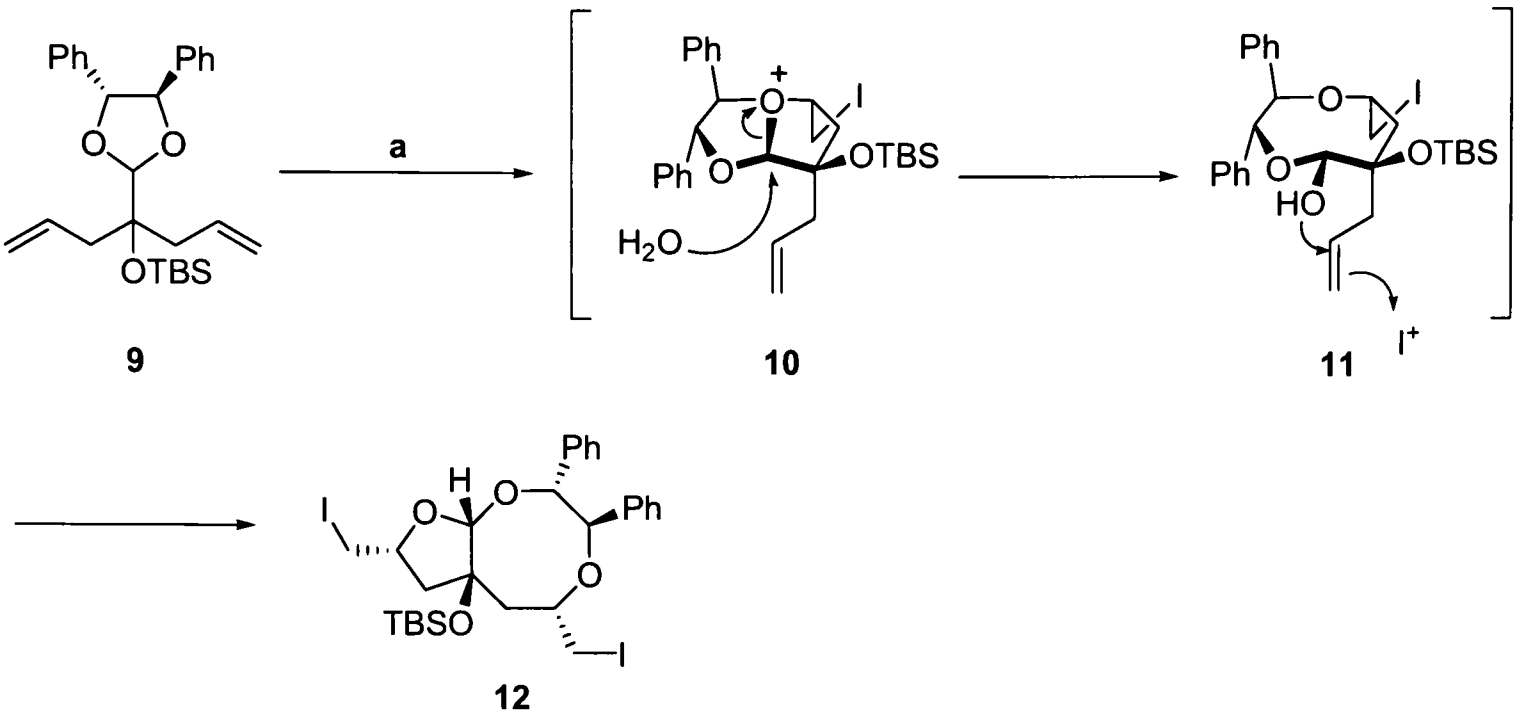
Since Bartlett and co-workers reported the synthesis of 2,5-*cis*-disubstituted THFs by halocyclization using a γ,δ-unsaturated alcohol and I_2 in 1981,[12] it has been extensively studied by several groups. For example, in 2002, Mootoo and co-workers showed the formation of THF rings by iodocylisation using iodonium dicollidine perchlorate (IDCP) in the synthesis of oligo-THFs (Scheme 2).[13] Here, it is noteworthy that the acetal moiety of

bis-acetal **7** is used as a nucleophilic oxygen source instead of the alcohol moiety and THF **8** is obtained as a single 2,5-*trans* isomer in 81% yield. The observed diastereoselectivity could be explained by the cyclic transition state with minimised steric hindrance between the iodoalkyl substituent of the eventual THF and the methyl group of the conformationally restricted acetal.[14]



Scheme 2. Iodoetherification between acetal and alkene using IDCP; (a) IDCP, CH_3CN, 81%.

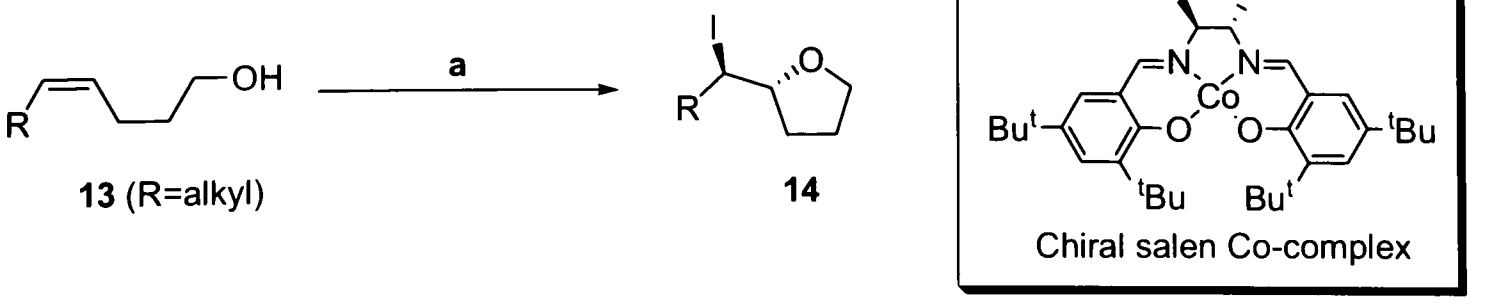
In 2005, Fujioka and co-workers reported a double iodoetherification of a symmetric a diene acetal **9** (Scheme 3).[15] In terms of mechanism, hemiacetal intermediate **11** is obtained *via* oxonium cation **10**; a second intramolecular cyclization then occurs to give THF **12**. In this transformation, four stereogenic centres are defined in a single step and the major isomer **12** is obtained with a diastereoisomeric ratio of 11 to 1 in 84% yield.



Scheme 3. THF formation by double iodoetherification of a symmetric diene acetal; (a) NIS, H_2O, CH_3CN, dr 11:1 (major isomer to other isomers), 84%.

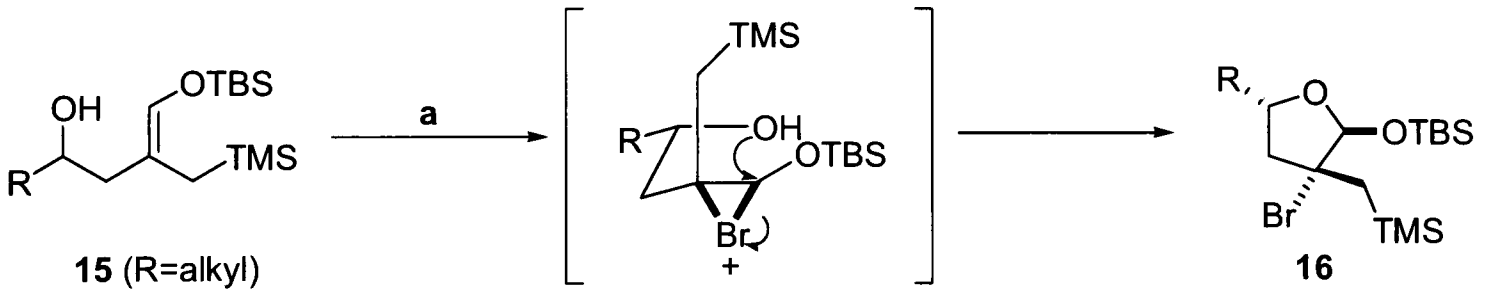
In spite of the widespread use of iodocyclisations, reagent-controlled enantioselective versions of this strategy have rarely been investigated. In 2003, Kang and co-workers reported enantioselective intramolecular iodocyclization of γ-hydroxy-*cis*-alkene **13** to form 2-substituted THFs **14** using chiral salen-Co complexes (Table 1). In this transformation, they obtained THF in over 83% yield and with enantiomeric excesses ranging between 67% and 90%. Higher enantiomeric excesses were observed for substrates with larger substituents R.

Table 1. Enantioselective iodoetherification using chiral salen-Co complexes; (a) I_2 (1.5 eq), chiral salen-Co complex (0.3 eq), NCS (0.8 eq), CH_2Cl_2.



R	Yield (%)	ee (%)
Me	96	67
^{i}Pr	83	73
^{n}Pr	85	85
$(CH_2)_3OTf$	89	90

Similarly, bromocyclisation strategies have been reported. For example, in 2002, Marko and co-workers showed the synthesis of THF **16** by bromocyclisation of β,γ-unsaturated alcohol **15** (Scheme 4).[16] The key difference here is that the THF ring is formed by 5-*endo*-cyclisation whereas all the others have been 5-*exo*-cyclisations because the silyloxy group assists halocyclization by electron donation towards the bromonium ion. They obtained **16** as a single isomer in over 95% yield. The stereoselectivity is explained by stereospecific *anti*-addition to the intermediate bromonium ion with the R substituent occupying a pseudoequatorial position.

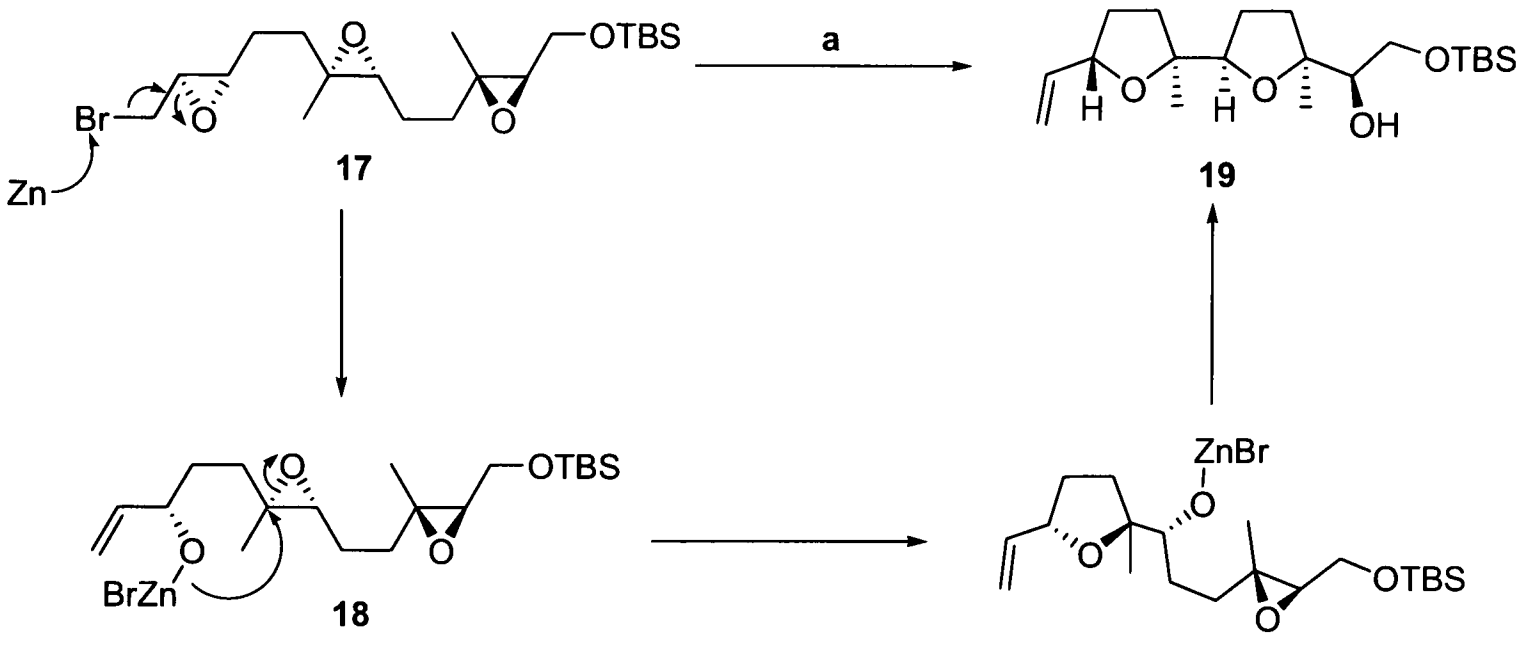


Scheme 4. THF formation by bromocyclisation; (a) NBS, THF, 95%.

1.2.1.2. Electrophilic cyclization *via* epoxyalcohol (E=O).

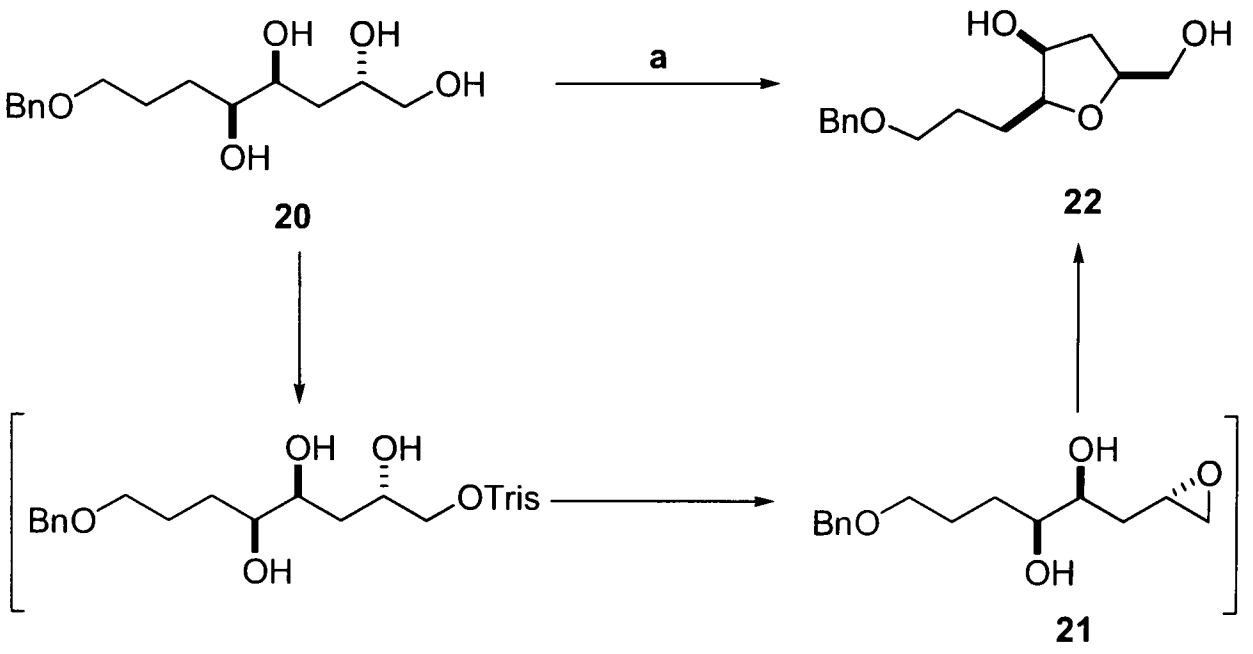
Cyclisation of epoxyalcohols is another well established method for THF synthesis. Traditionally, the epoxyalcohols were prepared by epoxidation of the appropriate unsaturated alcohol. However, some recent examples demonstrate alternative methods for epoxyalcohol generation. For example, as part of a total synthesis of ionomycin, Marshall and co-workers showed the synthesis of *bis*-THFs *via* zinc-initiated triepoxide cascade cyclization in the presence of tetrabutylammonium iodide (TBAI) (Scheme 5).[17] It is

notable that this polyepoxide cascade strategy is quite similar to the proposed biosynthesis of THF-containing polyether antibiotics.[18] In terms of mechanism, the treatment of terminal epoxy bromide **17** with zinc forms a transient allylic alkoxy zinc species **18**. Two sequential 5-*exo*-cyclisations then give *bis*-THF **19** in 62% yield.



Scheme 5. Zinc-initiated triepoxide cascade cyclization; (a) Zn, TBAI, MeOH, 62%.

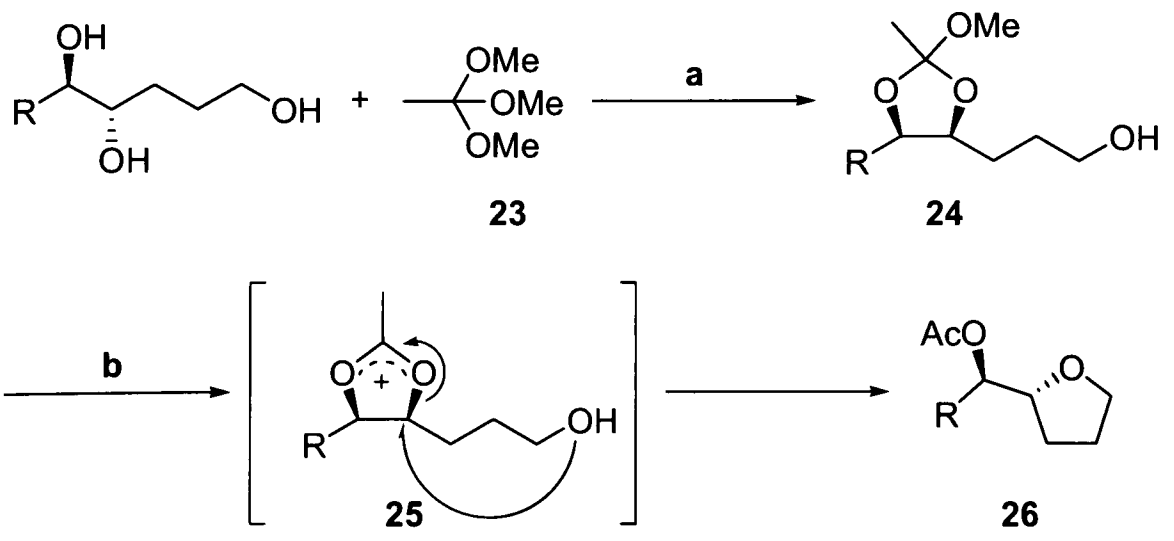
Furthermore, Forsyth and co-workers reported the synthesis of THFs *via* a one-pot polyol cyclization cascade (Scheme 6).[19] Mechanistically, the terminal alcohol in **20** is selectively activated by treatment with *N*-2,4,6-triisopropylbenzenesulfonyl imidazole (*N*-TrisIm). Subsequently, the intramolecular nucleophilic substitution forms epoxide **21** and a second intramolecular nucleophilic substitution gives the THF product **22** in 62% yield.



Scheme 6. Synthesis of THFs *via* one-pot polyol cyclization cascade; (a) KO^{t}Bu, ^{t}BuOH, *N*-TrisIm, 62%.

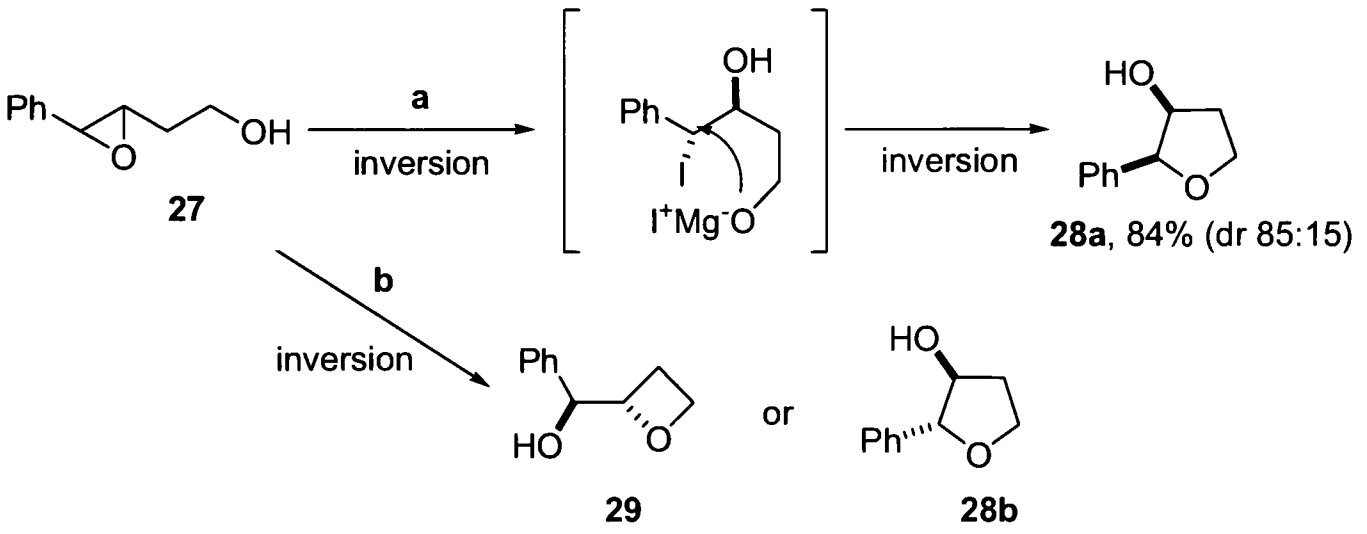
As an alternative electrophile for cyclization, Borhan and co-workers in 2005 reported the cyclization of 1,4,5-triols *via* an acetoxonium intermediate (Table 2). [20] The enantiomerically enriched 1,4,5-triol is obtained by Sharpless asymmetric dihydroxylation. The orthoester **24** is then obtained by reaction with trimethyl orthoacetate **23**. Subsequent ionisation of the orthoester **24** in the presence of Lewis acid gives a reactive acetoxonium species **25** and THF **26** is then formed in up to 98% yield by intramolecular cyclization.

Table 2. Cyclization of 1,4,5-triol; (a) PPTS (cat), (b) $BF_3 \cdot OEt_2$.



R	Yield (%)
^{n}Pent	81
^{n}Bu	82
EtO_2C	62
cyHex	50

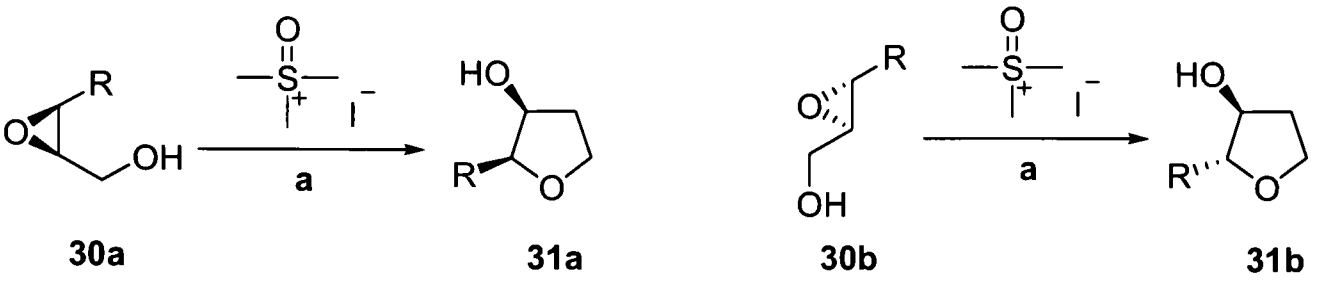
Apart from the cyclization of γ,δ-epoxyalcohols, Karikomi and co-workers reported the synthesis of THFs **28** by the cyclization of β,γ-epoxyalcohols **27** using magnesium halide (Scheme 7).[21] In contrast to the favoured formation of oxetane **29** by base-catalysed 4-*exo* cyclization or the formation of 2,3-*trans*-THF **28b** by acid catalysed 5-*endo* ring-closure, this transformation by magnesium halide gives 2,3-*cis*-THF **28a** *via* two inversions; i) first inversion in epoxide opening by halogen, ii) second inversion by intramolecular halogen displacement by the alcohol. Here, 2,3-*cis*-THFs **28a** were obtained as the major product with 85:15 dr and up to 84% yield.

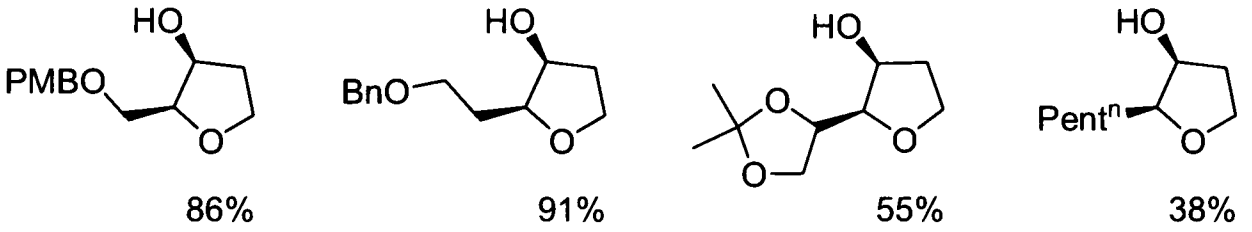


Scheme 7. Cyclization of 3,4-epoxyalcohols using magnesium halide; a) MgI_2, b) acid or base.

Bohran and co-workers reported an interesting new method for the formation of THFs *via* cyclisation of epoxyalcohols **30a** and **30b** using a sulfoxonium ylide (Scheme 8).[22] It is noteworthy that in this strategy the formation of THF is not obtained from direct

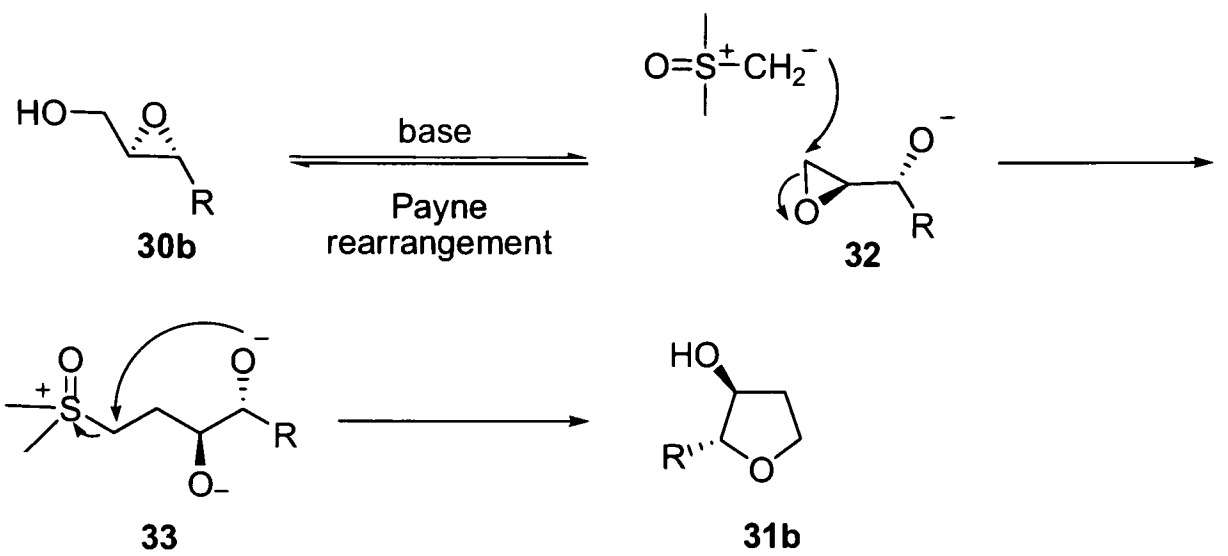
electrophilic cyclization of the starting 2,3-epoxyalcohol but involves Payne rearrangement and nucleophilic substitution of the resulting isomeric epoxide with sulfoxonium ylide. In this transformation, they obtained enantiomerically pure 2,3-*cis*-epoxyalcohol **30a** and 2,3-*trans*-epoxyalcohol **30b** from the Sharpless asymmetric epoxidation of allylic alcohols. The reaction of these epoxyalcohols with trimethylsulfoxonium iodide affords the corresponding 2,3-disubstituted THF in good yield with complete control of stereochemistry. Thus, *cis*-epoxide **30a** gives *cis*-THF **31a** and *trans*-epoxide **30b** gives *trans*-THF **31b**. The selected results are shown in Scheme 8.





Scheme 8. Formation of THF *via* nucleophilic substitution of 2,3-epoxyalcohol using a sulfoxonium ylide; (a) NaH, DMSO, 80 °C.

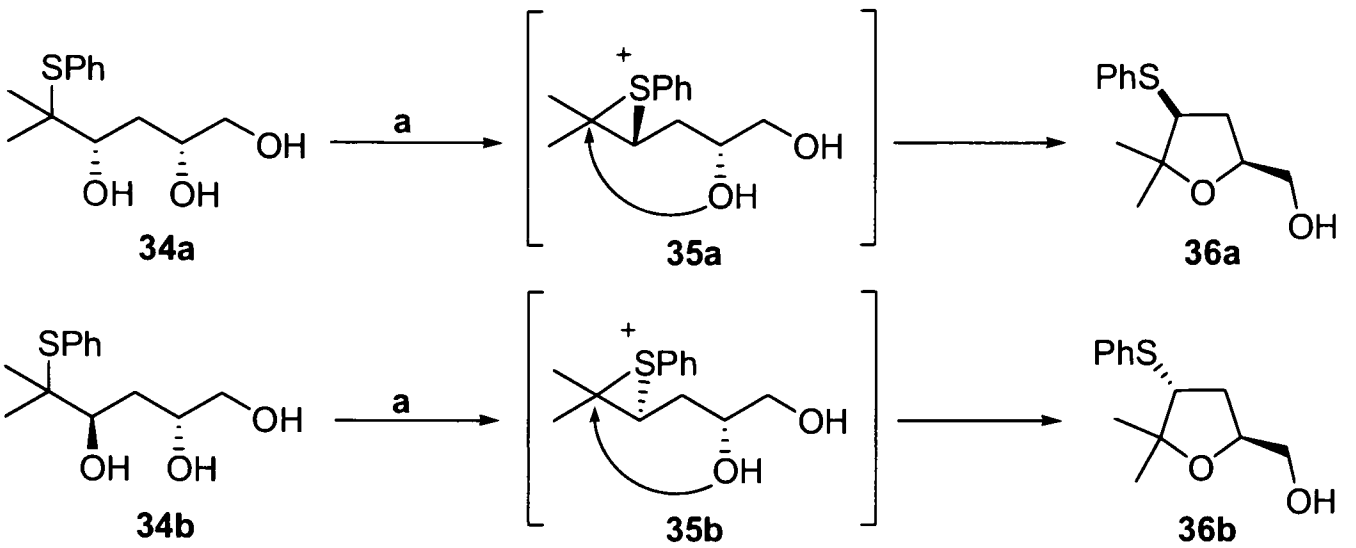
Mechanistically, the reaction is postulated to proceed by an initial Payne rearrangement of epoxyalcohol **30b** to give the more sterically accessible terminal epoxide **32**. This is then attacked by sulfoxonium ylide to form *bis*-alkoxide **33** which subsequently cyclises to THF **31b** by intramolecular nucleophilic substitution (Scheme 9).



Scheme 9. Proposed mechanism of cyclization of 2,3-epoxyalcohol using a sulfoxonium ylide.

1.2.1.3. Electrophilic cyclization *via* phenylsulfanyl migration (E=SPh).

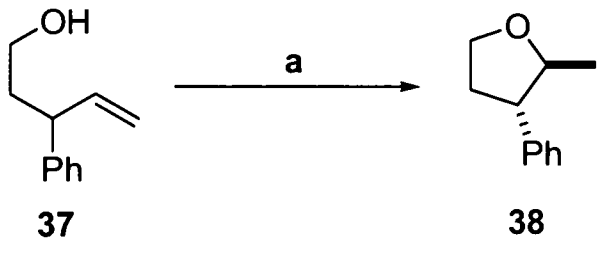
Electrophilic sulphur or selenium reagents can serve to activate alkenes for attack by alcohols in an analogous manner to electrophilic halide. An alternative method for generation of episulfonium ion intermediates starts from β–hydroxysulfides. For example, in 2002, Warren and co-workers reported the synthesis of enantiomerically pure THFs from enantiomerically pure 2,4,5-triols **34a** and **34b** (Scheme 10).[23] They obtained 2,4-*cis*-THF **36a** and 2,4-*trans*-THF **36b** as the major product, respectively, by 1,2-phenylsulfanyl migration *via* the sulfonium ion intermediates **35a** and **35b**; stereoselectivity is decided by the stereochemistry of starting triols **34a** and **34b**. The formation of tetrahydropyran products *via* the attack of the primary alcohol on the sulfonium ion intermediate is competitive to THF formation in this transformation and a mixture of THF and tetrahydropyran is obtained when short reaction times (10 min) are used. However, only THF is obtained (over 83% yield) as the thermodynamic product with longer reaction times (48 h). The favoured formation of THF over that of the tetrahydropyran could be explained by the Thorpe-Ingold effect.



Scheme 10. Synthesis of 2,4-substituted THF by phenylsulfonyl migration; (a) TsOH,CH_2Cl_2, 40 °C, 48 h.

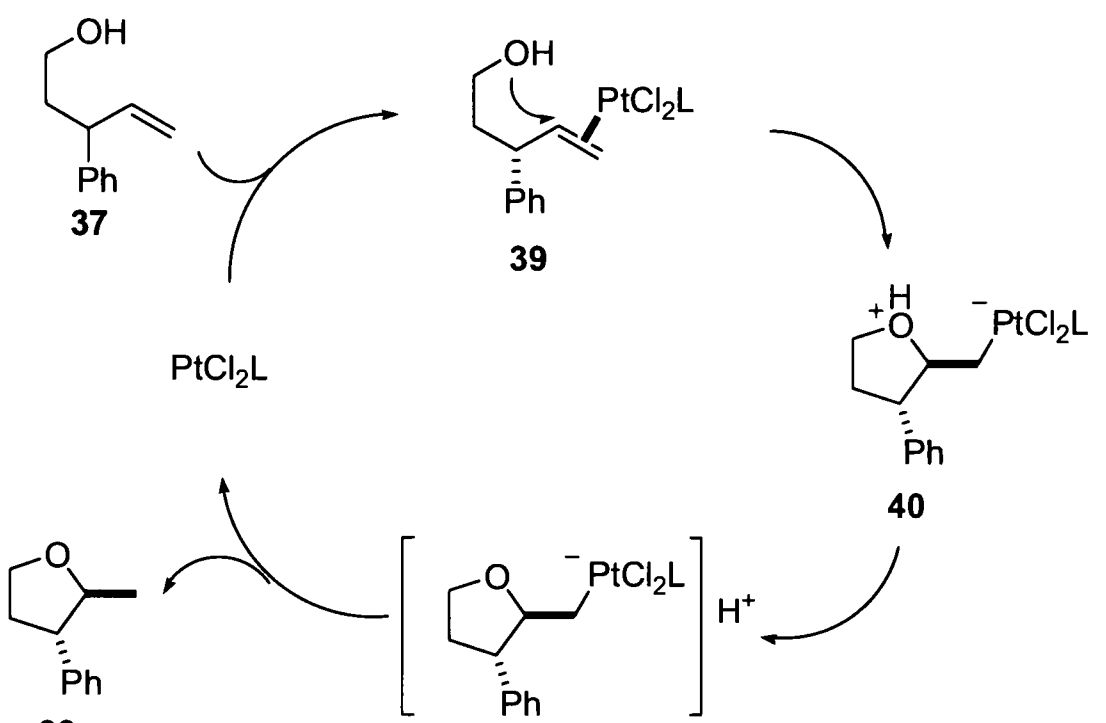
1.2.1.4. Metal-catalysed cyclization (E=metal complex)

Metals have been widely used for electrophilic cyclization. In this type of transformation, the THF framework is constructed by the electrophilic attack of a hydroxyl group on a metal-complexed olefin and the entire reaction is generally terminated by the protonolysis of the metal-carbon bond. For example, in 2004, Widenhoefer and co-workers reported platinum-catalysed intramolecular hydroalkoxylation of γ-hydroxy alkene **37** to regioselectively form THF **38** in up to 98% yield (Scheme 11).[24] The reaction tolerates substitution at the α, β and γ-carbon atoms. Also, the reaction tolerates substitution at the internal and terminal olefin carbons. When alcohol **37** was exposed to the reaction condition, 2,3-*trans* THF **38** was obtained with the best dr of 8:1.



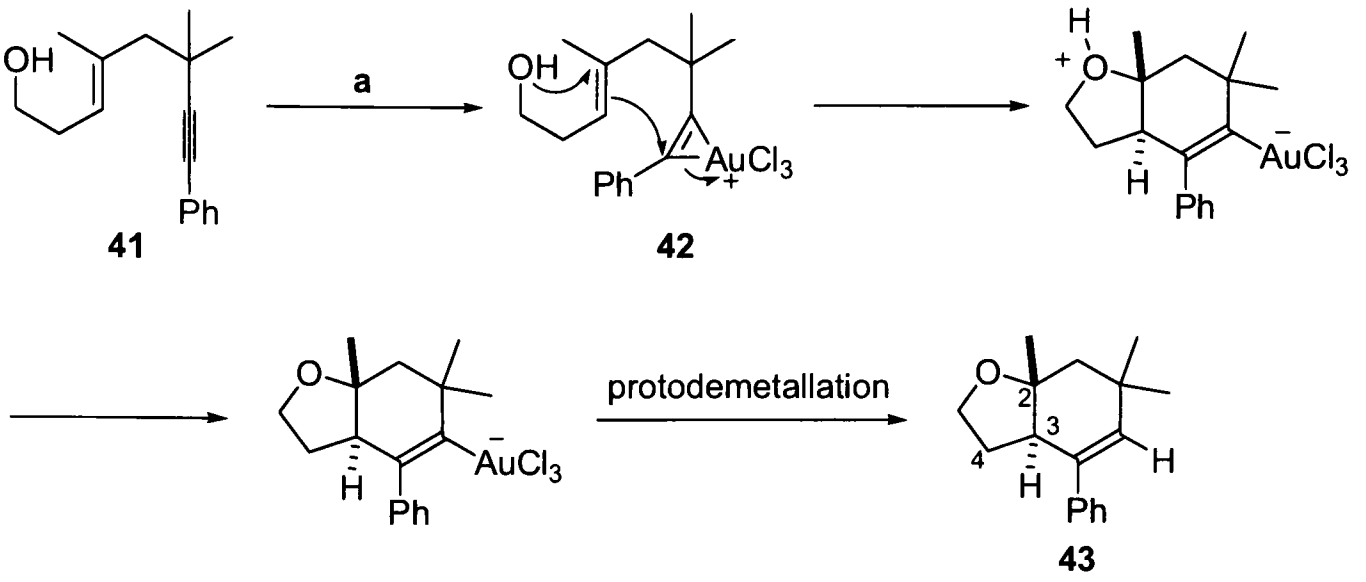
Scheme 11. Platinum-catalysed intramolecular hydroalkoxylation; (a) $[PtCl_2(H_2C{=}CH_2)]_2$ (2.5 mol%), P(4-$C_6H_4CF_3)_3$ (5 mol%), $Cl_2CHCHCl_2$, 70 °C.

The proposed mechanism is shown in Scheme 12. Initially, platinum activates the olefin **37** and the hydroxyl group attacks the platinum-complexed olefin **39** to form zwitterion **40**. Then, the corresponding THF **38** is obtained by proton transfer involving protonolysis of Pt-C bond.



Scheme 12. Proposed mechanism of platinum-catalysed intramolecular hydroalkoxylation.

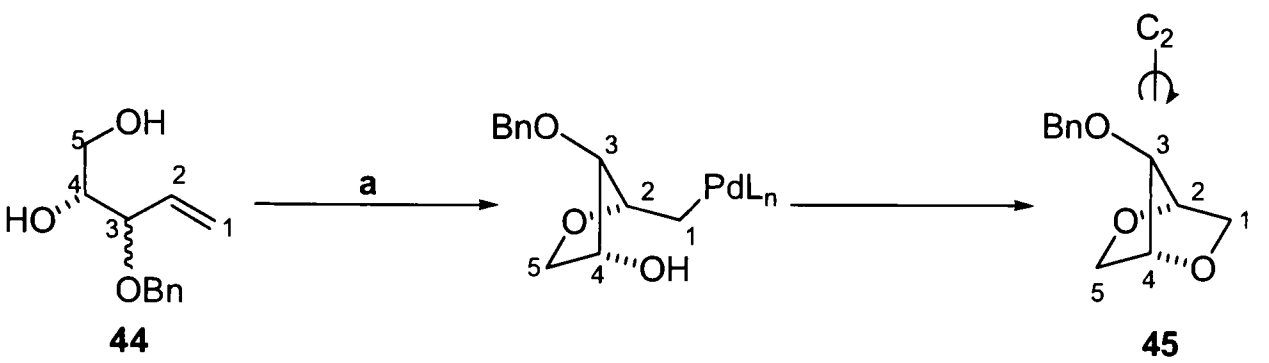
Also, Kozmin and co-workers reported gold-catalysed double cyclization of 1,5-enynes **41** with a nucleophile alcohol substituent (Scheme 13).[25] They obtained bicyclic product **43** in over 86% yield with high diastereoselectivity (dr >97:3). The *cis*/*trans* relationship between C-2 and C-3 stems from the *E*/*Z* geometry of the initial alkene.



Scheme 13. Gold-catalysed double cyclization; (a) $AuCl_3$ (10 mol%), MeCN, 20 °C.

In terms of mechanism, cyclopropenyl gold intermediate **42** is opened by intramolecular attack of oxygen nucleophile initiating a double cyclization; subsequent protodemetallation gives the bicyclic product **43**. In 2005, Duňach and co-workers reported this type of transformation using $Sn(OTf)_4$ as a metal source and 2-monosubstituted THFs were regioselectively obtained in up to 98% yield.[26]

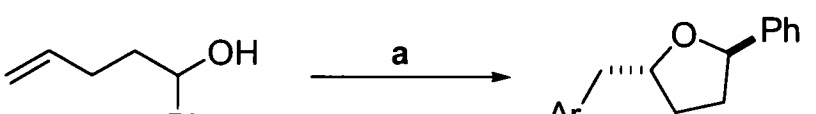
In the preparation of optically pure THFs, Kang and co-workers reported enantioselective mercuriocyclisation of γ-hydroxy-*cis*-alkenes using dimethylmalonate-derived bisoxazoline-Hg(II) complexes.[27] They obtained 2-monosubstituted THFs in up to 95% ee and over 68% yield. In 2005, Gracza and co-workers reported the preparation of enantiomerically pure THFs by a novel "pseudo-*meso*-trick" (Scheme 14).[28] This Pd-catalysed bicyclization of diastereoisomeric dihydroxyl alkene **44** furnished the C_2 symmetrical product **45**. In this transformation, a newly-formed C-O bond is stereospecifically generated with a *cis* relationship to hydroxyl group at C-4. It is remarkable that the enantiomerically pure bicyclic compound **45** is formed from diastereoisomeric mixture **44** (dr 1:1) by the degeneration of the allylic stereogenic centre because of the C_2 symmetry of **45**.



44 **45**

Scheme 14. Preparation of THF by pseudo-*meso*-trick; (a) $PdCl_2$, $CuCl_2$, AcONa, AcOH, 79%.

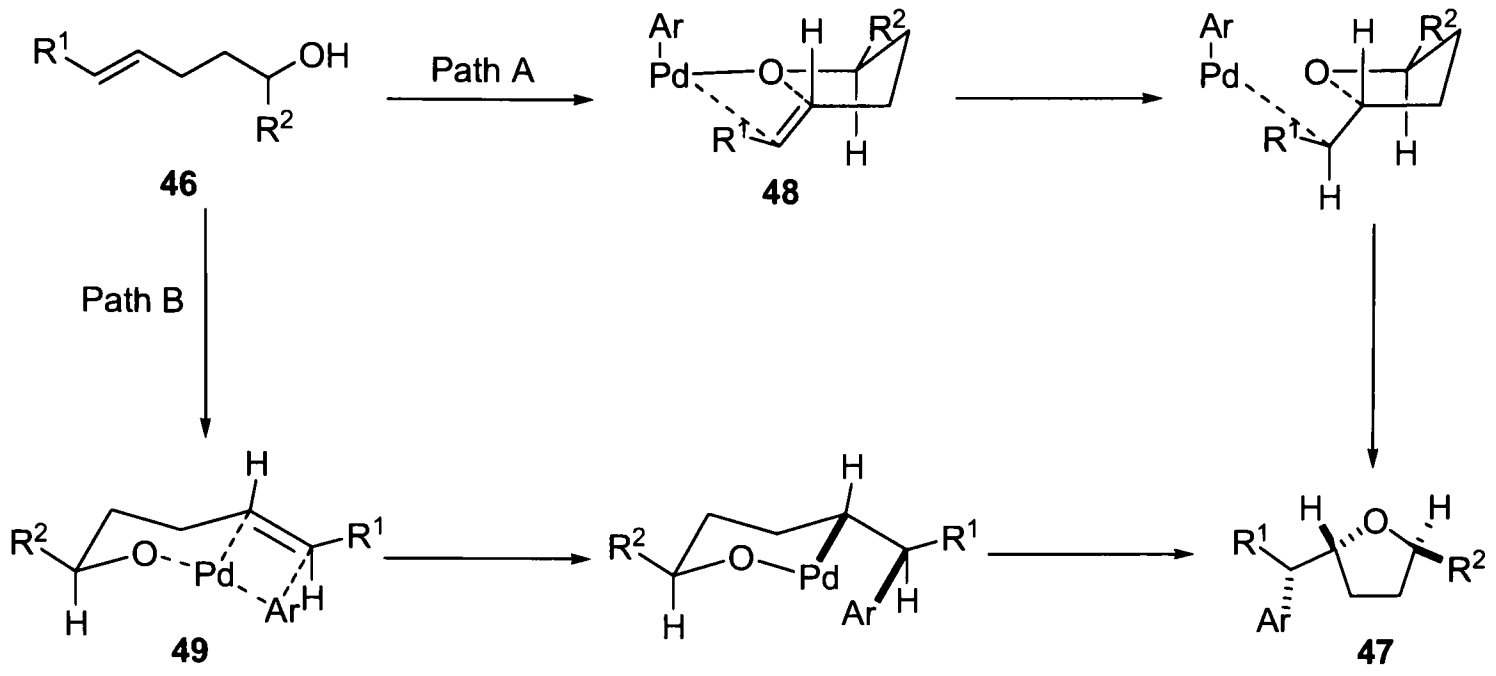
Wolfe and co-workers reported the Pd-catalysed reaction of aryl bromides with γ–hydroxy alkenes to prepare substituted tetrahydrofurans and a representative example is shown in Scheme 15.[29] The 2,5-*trans*-THF **47** was obtained from **46** as the major product with the ratio over 20:1 and in over 60% yield.



46 **47**

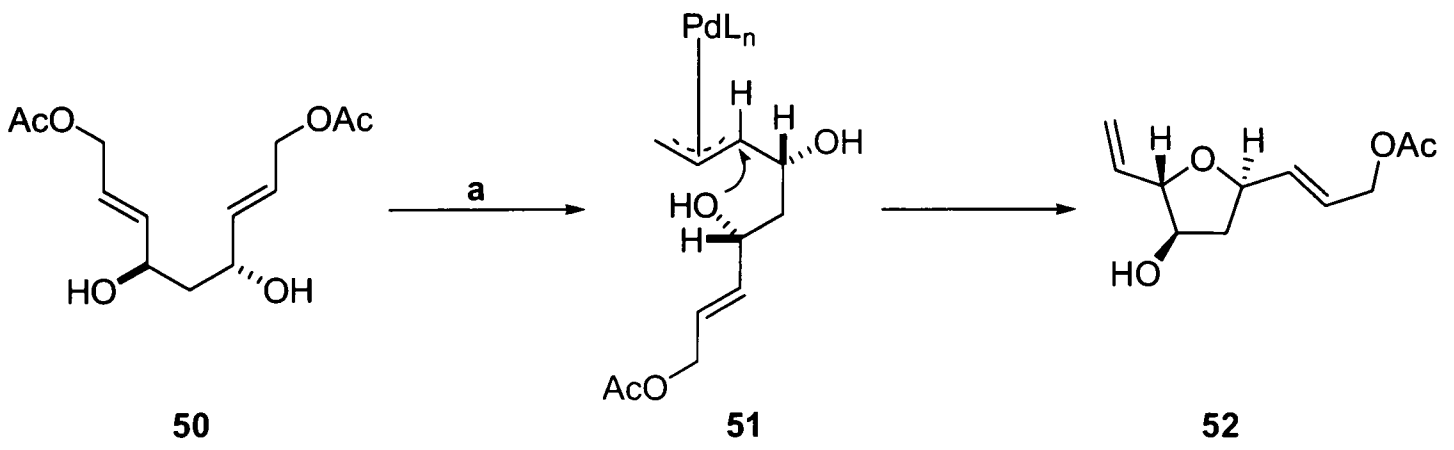
Scheme 15. Pd-catalysed reaction of aryl bromide with γ–hydroxy alkenes to prepare substituted tetrahydrofurans; (a) ArBr (2.0 eq), NaO^tBu (2.0 eq), $Pd_2(dba)_3$ (1 mol%), DPE-Phos (2 mol%), THF (0.25 M), 65 °C.

Two pathways have been proposed to explain the observed stereochemistry (Scheme 16). Firstly, Pd(Ar)(OR) intermediate **48** is formed in path A and it could undergo insertion of the olefin into the Pd-O bond. Then, a C-C bond is formed by reductive elimination to give the product **47**. Alternatively, Pd(Ar)(OR) intermediate **49** is formed in path B and it could undergo insertion of the olefin into the Pd-C bond. Finally, the C-O bond is formed by reductive elimination. The observed diastereoselectivity could be explained by the cyclic transition state, where all substituents occupy pseudoequatorial positions.



Scheme 16. Pathways for Pd-catalysed reaction of aryl bromide with γ–hydroxy alkenes.

In a similar manner, in 2002, Burke showed the construction of THF units by Pd-catalyzed diastereoselective desymmetrisation of C_2 diol acetate **50** in the total synthesis of halichondrin B (Scheme 17).[30] Here, 2,4,5-trisubstituted THF **52** is obtained *via* palladium π–allyl complex **51** in 87% yield and the chiral ligand, DPPBA, controlled the stereoselectivity of desymmetrisation.

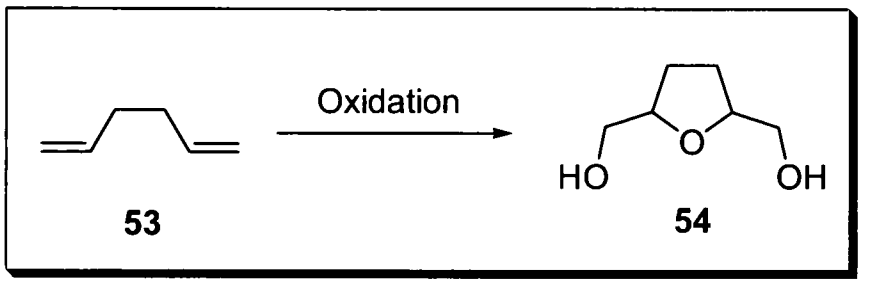


Scheme 17. Pd-catalyzed desymmetrisation of C_2 diol acetate; (a) $Pd_2(dba)_3$, (*R*,*R*)-DPPBA, 0 °C, 87%.

1.2.2. Oxidation strategies.

1.2.2.1. Oxidation of 1,5-dienes.

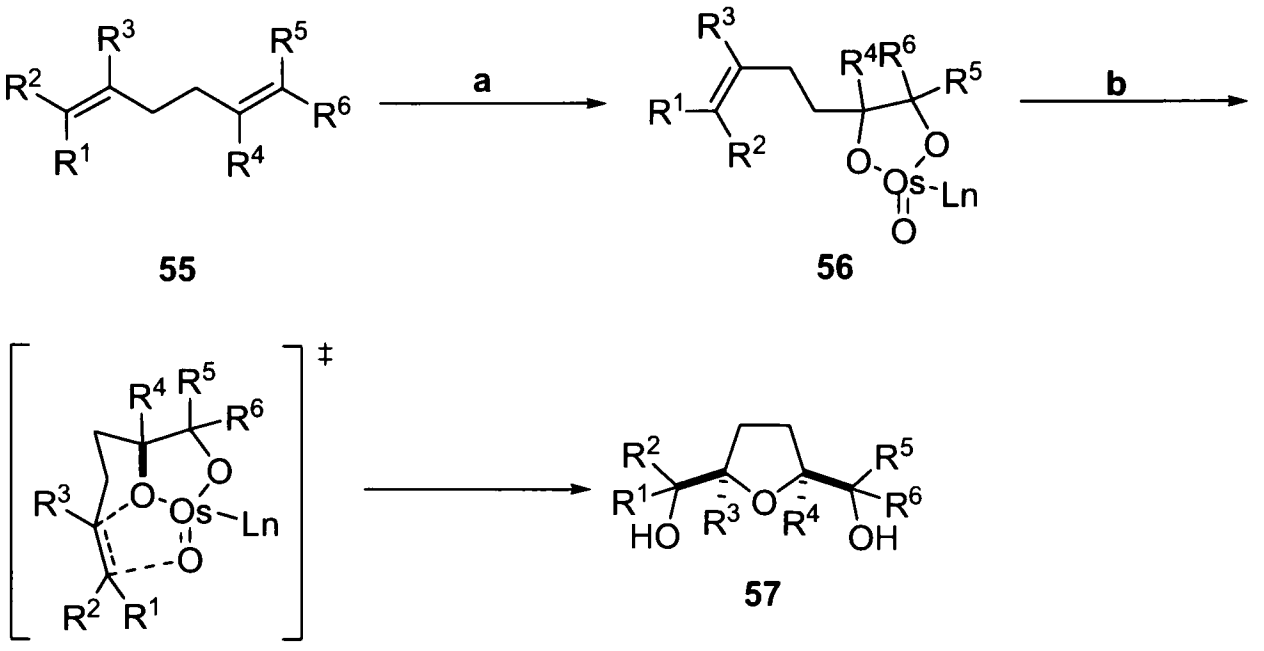
Since Klein and Rojahn reported the oxidative cyclization of 1,5-dienes by $KMnO_4$ in 1965,[31] the cyclization using metal oxides has been the most common oxidation strategy to synthesise THFs. The general transformation from 1,5-dienes **53** to THF **54** is shown in Scheme 18. This transformation usually shows high stereoselectivity although yields are often low. However, it is noteworthy that this kind of cyclisation has been postulated as a possible biosynthetic alternative to the polyepoxide cyclisation hypothesis.[18]



Scheme 18. Oxidation of 1,5-diene.

In a recent example, in 2003, Donohoe and co-workers reported the cyclization of 1,5-dienes by dihydroxylation using catalytic osmium tetroxide instead of $KMnO_4$ (Table 3).[32] The initial dihydroxylation of the diene **55** furnishes an osmate ester **56** which then undergoes cyclisation to give a single diastereoisomer, 2,5-*cis*-THF **57**, in 60-95% yield. Also, for the example of polyTHF, in 2005, Piccialli and co-workers reported the oxidative cyclization of polyalkene to pentafuranyl compound using RuO_4.[33]

Table 3. Oxidative cyclization of 1,5-diene using osmium tetroxide; (a) OsO_4 (0.05 eq), TMEDA (4.0 eq), CH_2Cl_2, (b) CSA (6.0 eq).

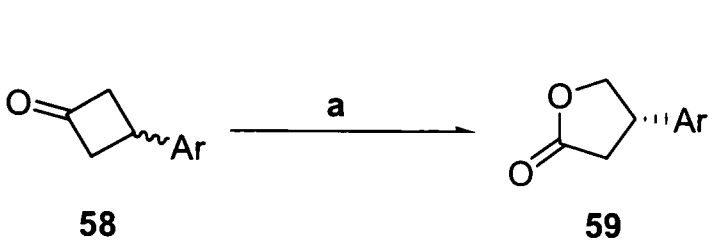


R^1	R^2	R^3	R^4	R^5	R^6	Yield
H	H	H	H	H	H	60%
H	H	Me	Me	H	H	72%
Me	Me	H	Me	H	CH_2OBn	88%
Me	Me	H	Me	CH_2OBn	H	95%
H	$-(CH_2)_4-$	H	H	H	H	71%

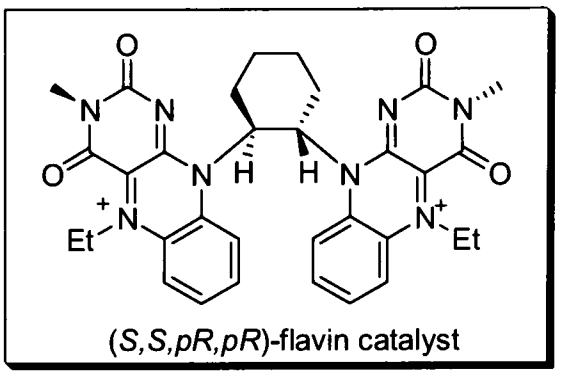
1.2.2.2. Other oxidative strategies.

In 2002, Murahashi and co-workers showed a metal-free flavin-catalysed asymmetric Baeyer-Villiger reaction of aryl substituted cyclobutanone **58** (Table 4).[34] The corresponding lactone **59** can be obtained in up to 67% yield and 74% ee. The asymmetric induction was explained by hydrophobic π–π stacking between the aryl substituent of cyclobutanone and phenyl ring of the flavin catalyst.

Table 4. Bayer-Villiger reaction of cyclobutanone; (a) H_2O_2 (1.5 eq), (*S,S,pR,pR*)-flavin cat. (0.1 eq), AcONa (cat), $CF_3CH_2OH/MeOH/H_2O$.



58 **59**

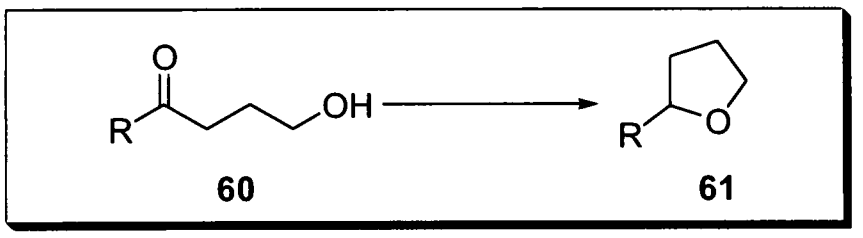


(*S,S,pR,pR*)-flavin catalyst

Ar	Yield (%)	ee (%)
4-MeO-phenyl	67	61 (+)
4-MeO-phenyl	53	62 (+)
Ph	67	63 (*S*)
4-Br-phenyl	28	68 (+)
4-Cl-phenyl	34	66 (*S*)

1.2.3. Reductive strategies.

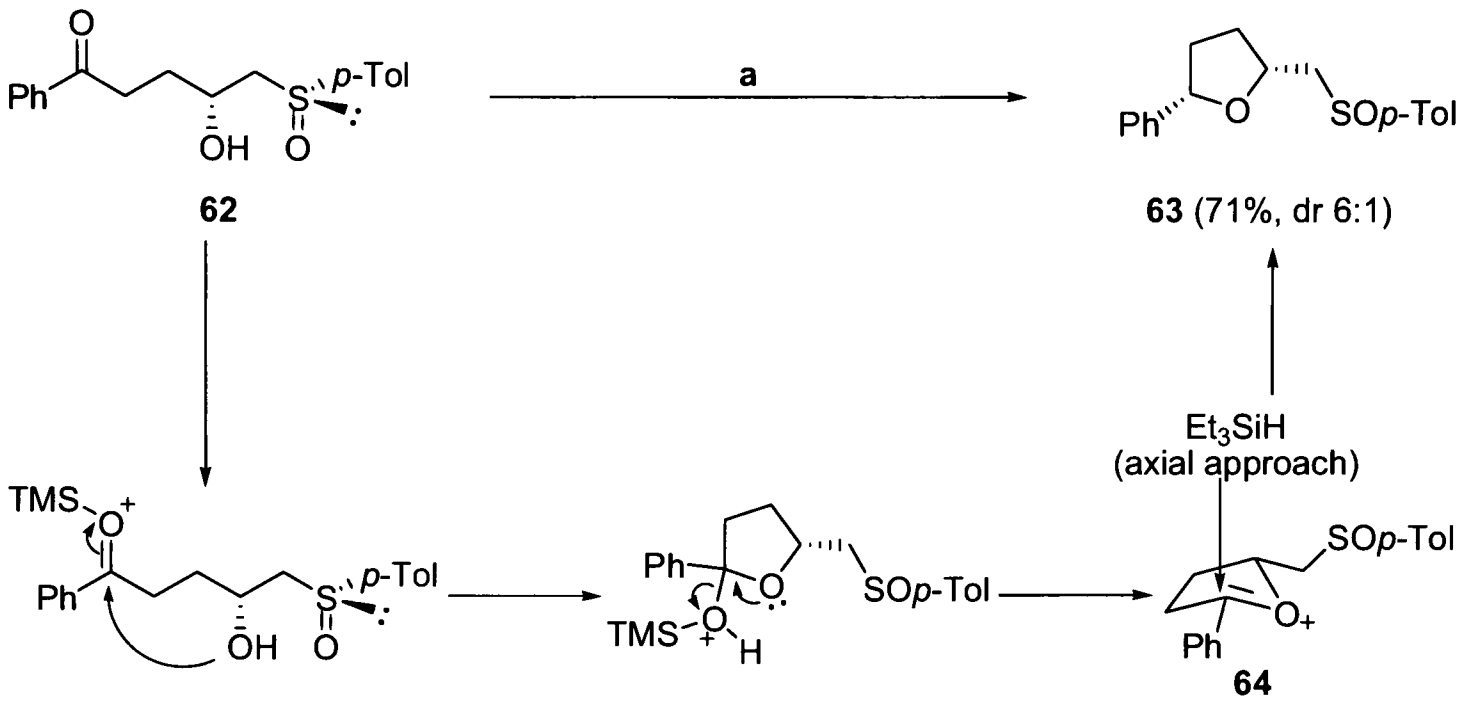
Several strategies for THF synthesis have been reported which entail reductive cyclisation of ketoalcohols **60** to THFs **61** (Scheme 19).



Scheme 19. Synthesis of THF by reductive method.

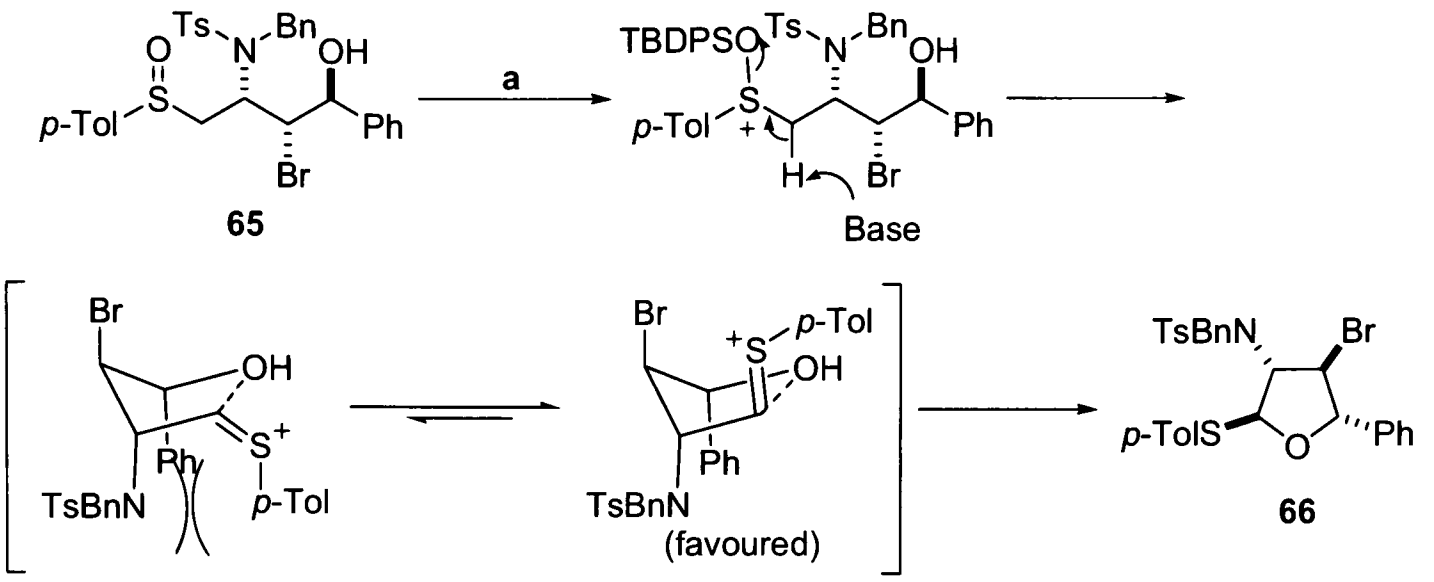
Carreño and co-workers reported reductive cyclization of enantiomerically pure hydroxylsulfinyl ketone **62** to give THF **63** (Scheme 20).[35] Here, they obtained 2,5-*cis*-THF **63** as a major product with 6:1 dr in 71% yield. Activation of the carbonyl group of the hydroxysulfinyl ketone **62** by TMSOTf favours the intramolecular nucleophilic addition

of the OH to give an intermediate mixed acetal precursor of the carboxonium intermediate **64**. The axial approach of Et_3SiH to **64**, affording the *cis*-diastereomer, is favoured because of the lower energy of the resulting cyclic transition state with all substituents in pseudoequatorial positions



Scheme 20. Synthesis of THF by nucleophilic attack of alcohol moiety to ketone; (a) Et_3SiH, TMSOTf, CH_2Cl_2, 0 °C.

Also, in 2003, Raghavan and co-workers reported the use of sulfoxides instead of ketones for this type of transformation. They prepared highly substituted THF **66** *via* silicon-promoted Pummerer type reaction, proceeding in over 82% yield (Scheme 21).[36] In terms of mechanism, the sulfoxide oxygen of **65** coordinates to silicon to give the sulfonium salt, which yields THF **66** by the intramolecular attack of hydroxyl group. The observed stereoselectivity is explained by the transition state with minimised steric interactions between sulfonium moiety and NBnTs group.



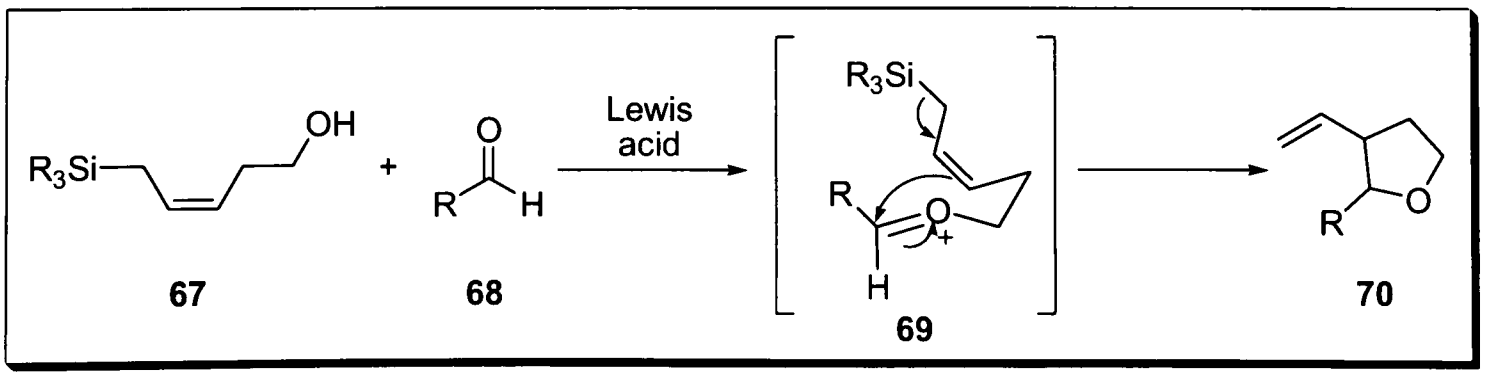
Scheme 21. Preparation of THF *via* silicon promoted Pummerer reaction; (a) TBDPSCl, Imidazole, DMF.

1.2.4. Strategies using allylic silanes and carbonyl compounds.

Various methods involving cyclisation of carbonyl compounds and allylic silanes have been reported. Mechanistically, they can be divided into two main classes; i) cyclisation onto oxonium ion intermediates, ii) cyclisation onto silyl cations.

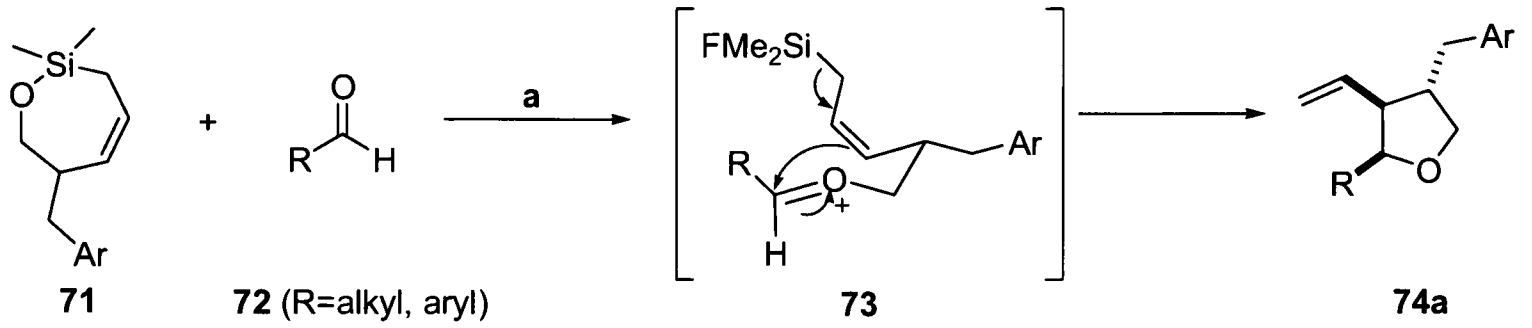
1.2.4.1. Cyclisation of allylic or propargylic silanes onto oxonium ion intermediates

One common strategy in this field is condensation of aldehydes with hydroxyl-containing allylic silanes **67**. The general mechanism is shown in Scheme 22. In this transformation, oxonium ion **69**, obtained from the Lewis acid-mediated condensation of aldehydes **68** with allylic silanes **67**, undergoes cyclization to give THFs **70**.



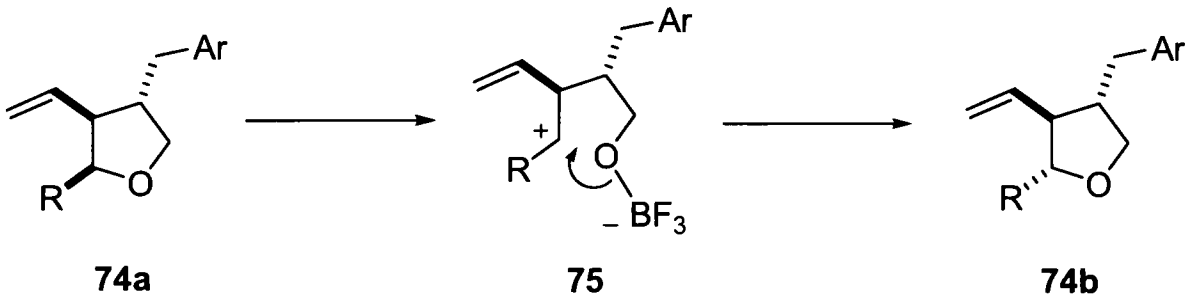
Scheme 22. Nucleophilic addition to oxonium ion using allylic silane.

For example, in 2004, Marsden and co-workers reported the construction of 2,3,4-trisubstituted THFs *via* a Lewis acid-mediated condensation of aldehydes **72** with allylsiloxanes **71** as a synthetic approach to lignans (Scheme 23).[37] Here, they obtained 2,3-*cis*, 3,4-*trans*-isomer **74a** as a major product regardless of aldehyde substituent in the presence of $BF_3.OEt_2$. In terms of mechanism, (*E*)-oxonium ion **73** obtained from the condensation of aldehydes with allylsiloxanes undergoes cyclisation through chair-like transition state with all substituents in an equatorial orientation.



Scheme 23. 2,3,4-Trisubstituted THF *via* a Lewis acid-mediated condensation of aldehydes with allylsiloxanes; (a) $BF_3{\cdot}OEt_2$, CH_2Cl_2, -78 °C, 8 h, then rt.

However, they obtained 2,3-*trans*-, 3,4-*trans*-isomer **74b** *via* reversible ring-opening, when the aldehyde contained electron-rich aryl substituents to stabilise the intermediate benzylic cation **75** (Scheme 24).

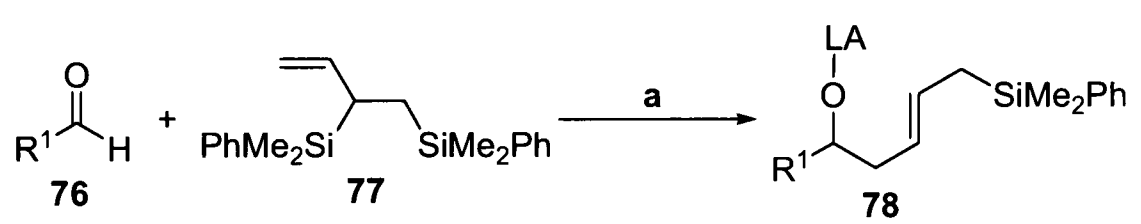


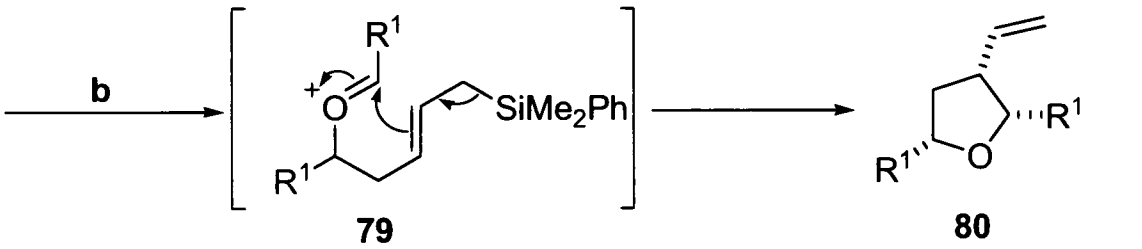
Scheme 24. Formation of thermodynamic product *via* reversible ring-opening.

Furthermore, they showed the application of this method to the synthesis of aryltetralins[38a] and virgatusin.[38b] Also, in 2005, García and co-workers showed the application of this

method to the total synthesis of pterocarpans[39] and negolignans.[40] In a similar manner, Sakar and co-workers reported a one-pot synthesis of 2,3,5-trisubstituted THF *via* a double Sakurai-Hosomi reaction using bis-silyl reagent **77** (Table 5).[41] In the presence of Lewis acid, aldehyde **76** gives allylic silane **78** when treated with *bis*-silyl reagent **77**. Then, the introduction of a second aldehyde **76** into allylic silane **78** gives 2,3,5-trisubstituted THF **80** *via* oxocarbenium ion transition state **79**. Here, the 2,3-*cis*, 2,5-*cis*-isomer was obtained as a major isomer in 48-68% yield.

Table 5. Synthesis of 2,3,5-trisubstituted THF *via* double Sakurai-Hosomi reaction; (a) $BF_3{\cdot}OEt_2$, -78 °C to rt, 8 h, (b) R^1CHO **76**.





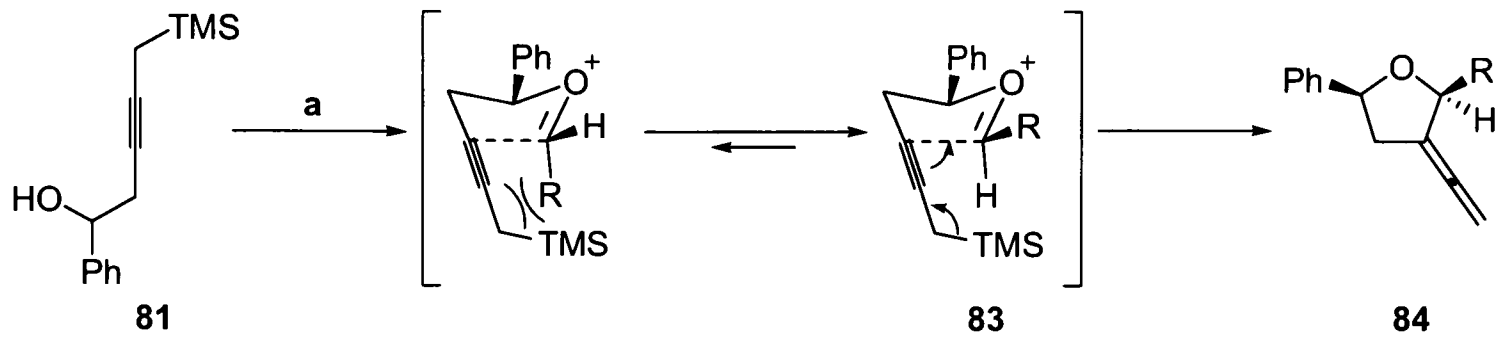
R^1	Yield (%)
BnO	68
$BnO(CH_2)_2$	52
$BnOCHCH_3$	48

[a] Obtained as a diastereomeric mixture (dr 3:1:1).

Similarly, Cho and co-workers reported the preparation of 2,3,5-trisubstituted THFs from condensation of hydroxyalkynes and aldehydes (Table 6).[42] Here, it is notable that they used a propargyl silane instead of an allylic silane. Condensation of alcohol **81** and aldehyde **82** in the presence of Lewis acid furnishes an oxocarbenium ion **83**, which is the more favoured intermediate with less steric hindrance. Subsequently, the oxonium ion is

transformed to 2,3,5-trisubstituted THF **84** *via* a Prins-type cyclization. Here, the resulting THFs are obtained in 63% to 93% yield and 2,5-*cis*-selectivity is observed between Ph and R (over 40:1 dr).

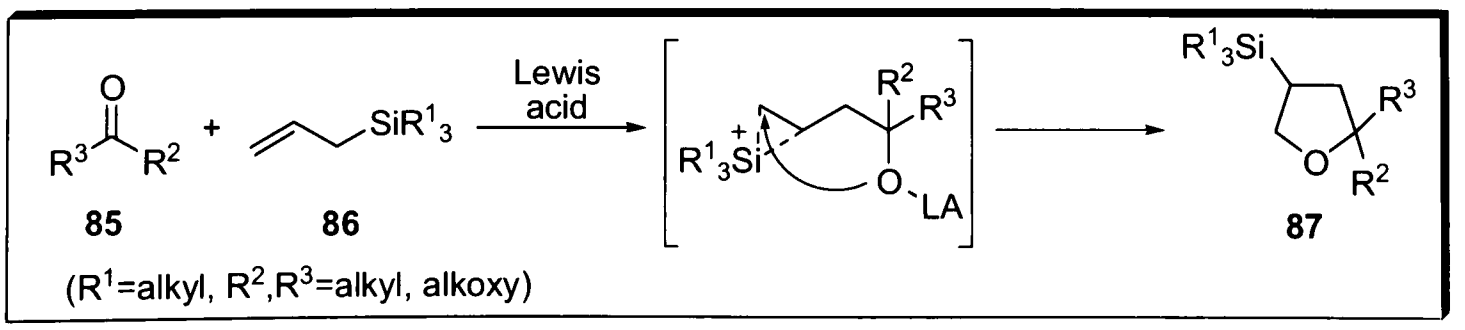
Table 6. Synthesis of 2,3,5-trisubstituted THF *via* Prins-type cyclization; (a) RCHO **82**, TMSOTf, Et_2O.



R	Yield	*cis*/*trans*
Ph	91%	40:1
cyHex	86%	*cis* only
$CH_3(CH_2)_4$	71%	*cis* only
$CH_3COO(CH_2)_3$	82%	*cis* only

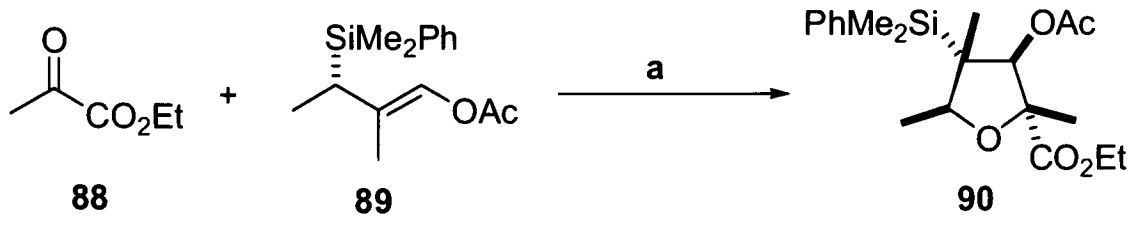
1.2.4.2. Cyclisation onto silyl cations.

Another common strategy in this field is Lewis acid-mediated annulation using allylic silanes **86** and carbonyl compounds **85**. This strategy uses the Lewis acid-complexed alkoxide as a nucleophile to attack the intermediate silyl cation, resulting in a 1,2-shift of the silyl moiety to give THF **87**. The general mechanism is shown in Scheme 25.



Scheme 25. Nucleophilic substitution of Lewis acid-compexed alkoxide to silyl cation.

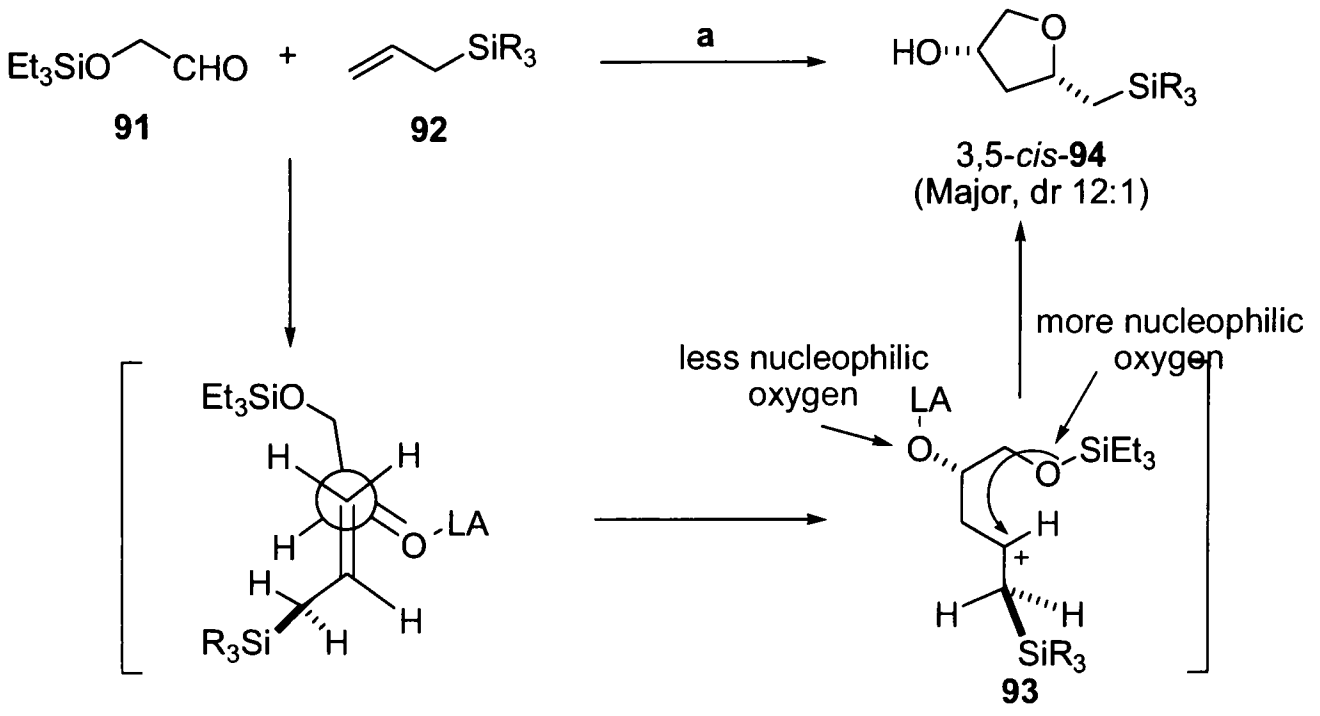
For example, Woerpel and co-workers used the $SnCl_4$-mediated cyclisation between functionalised allylsilane **89** and α–ketoester **88** to prepare multisubstituted THF **90** as a single diastereoisomer in 85% yield (Scheme 26).[43]



88 **89** **90**

Scheme 26. $SnCl_4$ mediated [3+2] cyclisation between allylsilane and α–ketoester; (a) $SnCl_4$, 85%.

As an alternative to the use of a Lewis acid-complexed alkoxide as oxygen nucleophile, Angle and co-workers reported the reaction between aldehyde and allylsilane to prepare 3,5-*cis*-disubstituted THFs (12:1 *cis* to *trans*) in 83% yield (Scheme 27).[44] Allylsilane **92** adds to the Lewis acid-activated aldehyde **91** to form silyl cation **93**. Subsequently, the more nucleophilic triethylsilyl ether participates in the cyclization to give THF **94**. Here, the major isomer shows *cis*-selectivity between the hydroxyl group at C-3 and the silyl methylene substituent at C-5. Furthermore, they prepared various di-, tri- and tetra-substituted THFs using α-substituted aldehydes and crotylsilanes. The observed stereochemistry could be explained by facial selectivity (Felkin-Anh) of the addition of the allylsilane to aldehyde.



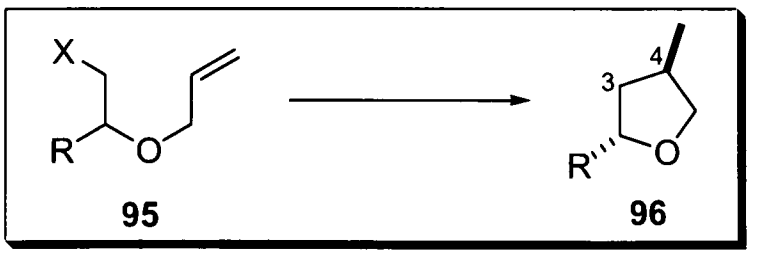
Scheme 27. Reaction between aldehyde and allylsilane to prepare 3,5-*cis* disubstituted THF; (a) $BF_3{\cdot}OEt_2$, DBMP, CH_2Cl_2, -78 °C.

1.2.5. Radical reaction strategies.

Various methods involving radical ring-closing reactions have been reported. There are two main strategies for the synthesis of THFs; i) *via* C-C bond formation, ii) *via* C-O bond formation.

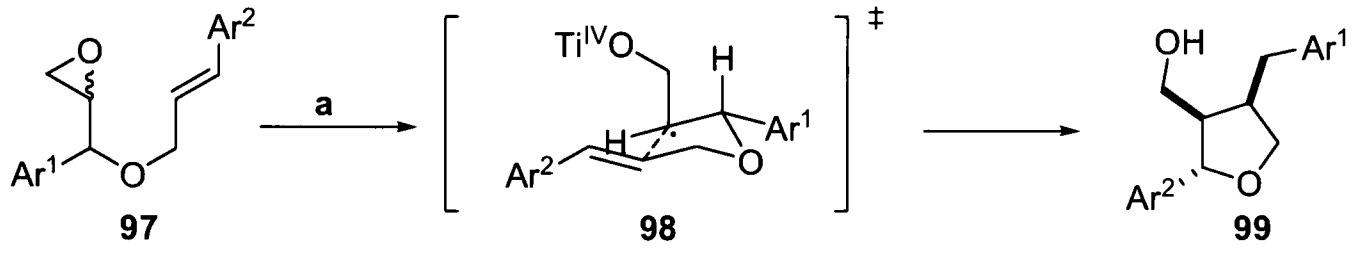
1.2.5.1. C-C bond formation

Numerous methods for the synthesis of THFs involving radical mediated C-C bond formation have been reviewed.[45] However, there appear to be two main strategies. Firstly, the haloalkyl allylic ether **95** is used as a radical precursor and it cyclises *via* the formation of C3-C4 bond in THF **96** by the treatment with a radical initiator (Scheme 28).



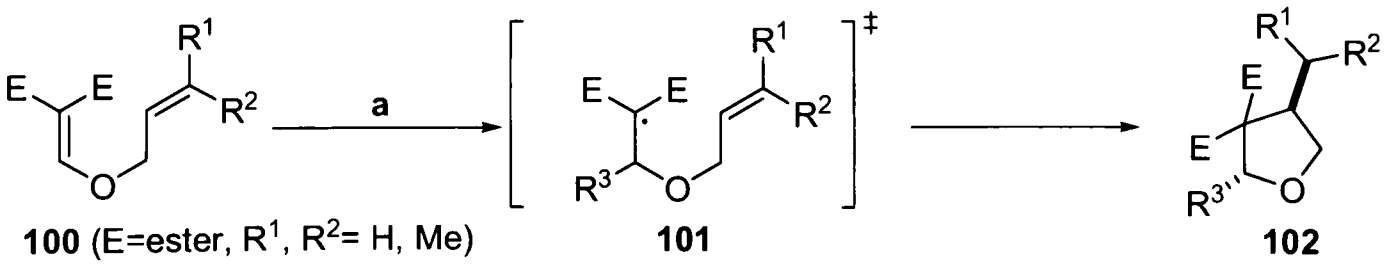
Scheme 28. C-C bond formation by radical precursor with double bond.

In 2002, Roy and co-workers showed this type of C3-C4 bond formation *via* the C-O bond cleavage of an epoxides in the synthesis of furano lignans (Scheme 29).[46] The C-O bond of the epoxide in radical precursor **97** is cleaved using Cp_2TiCl to generate a β–alkoxy-radical. The cyclisation product **99** was obtained as a mixture of diastereoisomers with ratio of 5:1 (3,4-*cis* to 3,4-*trans*) in up to 95% yield. They explained the observed stereoselectivity by suggesting that the chair-like transition state **98** is favoured in which Ar^2 and the alkene adopt pseudoequatorial positions.



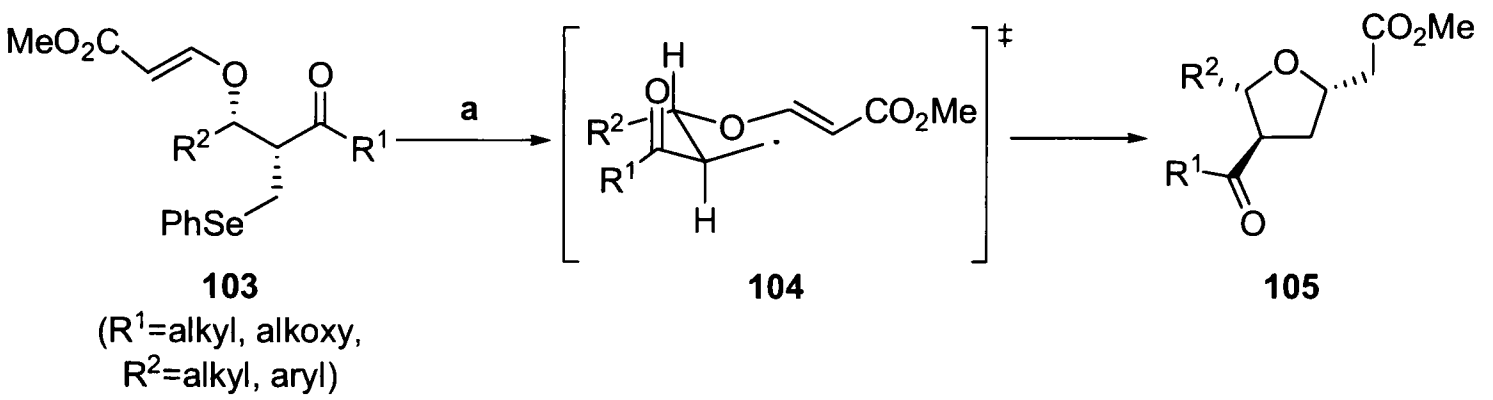
Scheme 29. C-C bond formation *via* epoxide cleavage; (a) i.Cp_2TiCl, THF, rt, ii. H_3O^+.

In 2003, Oshima and co-workers reported this type of chemistry using gallium and indium hydrides as radical initiator instead of toxic tin compounds.[47] In 2004, Sibi and co-workers reported the preparation of substituted THFs using a tandem radical addition-cyclisation reaction (Scheme 30).[48] They used a doubly activated malonate-type β-oxygenated acceptor **100** which underwent addition by a nucleophilic alkyl radical generated *in situ* from a haloalkane. The intermediate malonyl radical **101** could then cyclise onto the unactivated alkene. The product **102** was a diastereoisomeric mixture with 2,4-*trans*-selectivity (up to 50:1) and up to 79% yield.



Scheme 30. C-C bond formation *via* radical addition-cyclization; (a) R^3X (alkyl halide), Bu_3SnH, $Yb(OTf)_3$, Et_3B/O_2, -78 °C.

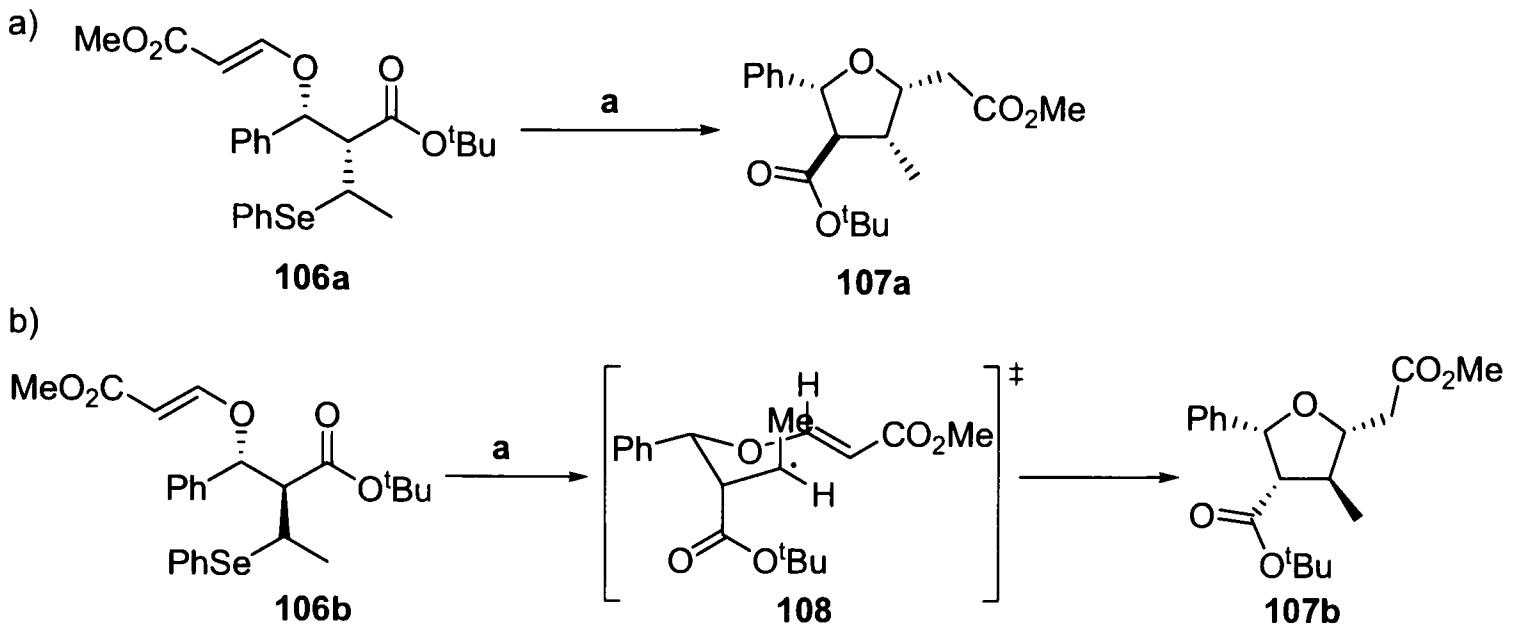
Similarly, in 2002, Kamimura and co-workers reported the preparation of trisubstituted THFs *via* the C2-C3 bond formation from optically active radical precursor **103** (Scheme 31).[49] In the presence of Bu_3SnH and AIBN, the radical precursor smoothly gives a single isomer **105** up to 86% yield *via* radical transition state **104**. They again explained the high stereoselectivity as arising from pseudoequatorial orientation of the substituents in a chair-like transition state.



103 (R¹=alkyl, alkoxy, R²=alkyl, aryl) **104** **105**

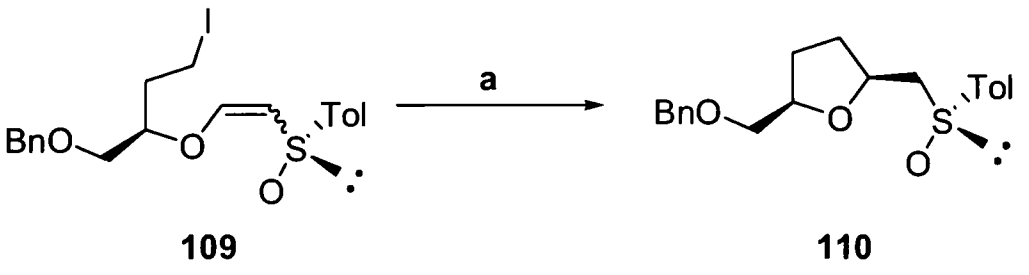
Scheme 31. Synthesis of trisubstituted THF *via* C2-C3 bond formation; (a) Bu_3SnH, AIBN, toluene, 110 °C.

They also applied the method to the synthesis of tetrasubstituted THFs (Scheme 32). When they used radical precursor **106a**, they obtained a diastereoisomeric mixture of tetrasubstituted THF **107a** with the ratio of 3 to 1 (major isomer to other 3 diastereoisomers) in 98% yield (a, Scheme 32). The stereoselectivity was explained in the way as the example in Scheme 31. Also, when they used radical precursor **106b**, they obtained a diastereoisomeric mixture of tetrasubstituted THF **107b** with the ratio of 3 to 1 (major isomer to other 3 diastereoisomers) in 93% yield (b, Scheme 32). However, the stereoselectivity was explained in different manner. When the methyl group at the radical centre is located at a pseudoequatorial position in transition state, there would be unfavoured steric repulsion between the Me group and ^{t}butoxy ester group. However, when the methyl group is located at pseudo-axial position in transition state **108**, there would be no steric repulsion and it would give the major THF **107b**.



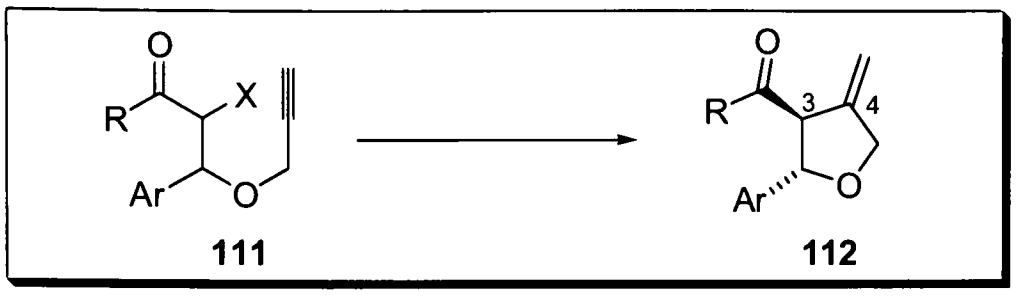
Scheme 32. Synthesis of tetrasubstituted THF *via* C2-C3 bond formation; (a) Bu_3SnH, AIBN, toluene, 110°C.

In 2004, Lee and co-workers showed a similar C4-C5 bond formation *via* the radical cyclization of β–alkoxyvinyl sulfoxides **109** (Scheme 33).[50] They obtained 2,5-*cis*-THF **110** as a major product with the a diastereoisomeric ratio over 92:8 and over 85% yield. Furthermore, they showed the synthesis of allyl carbinols *via* Pummerer rearrangement and subsequent allylation.



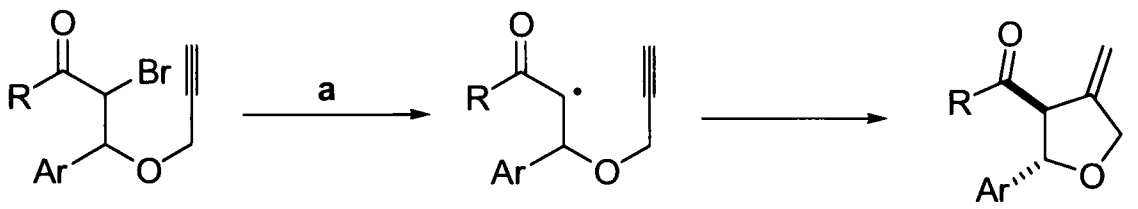
Scheme 33. C4-C5 bond formation *via* the radical cyclization of β–alkoxy vinyl sulfoxides; (a) Bu_3SnH, Et_3B, toluene, -20°C.

The second main strategy uses haloalkyl propargyl ether **111** as a radical precursor and it cyclises *via* the formation of C3-C4 bond in THF **112** (Scheme 34).



Scheme 34. C-C bond formation by radical precursor with triple bond.

In 2002, Roy and co-workers showed the radical-mediated cyclization of bromoalkyne **113** using 1-ethylpiperidine hypophosphite (EPHP) as a radical reducing agent and AIBN (Scheme 35).[51] They obtained trisubstituted THF **115** with 2,3-*trans*-relationship as a single diastereoisomer in 75-89% yield, *via* the formation of radical **114**. They applied this method to the synthesis of (±)-dihydrosesamin. Similarly, the same authors reported the radical cyclization of an α–bromocarbonyl compound using titanocene(III) chlorite as a radical initiator in 2005[52] and Ranu reported the radical cyclization using indium(I) iodide as a radical initiator in 2006.[53]

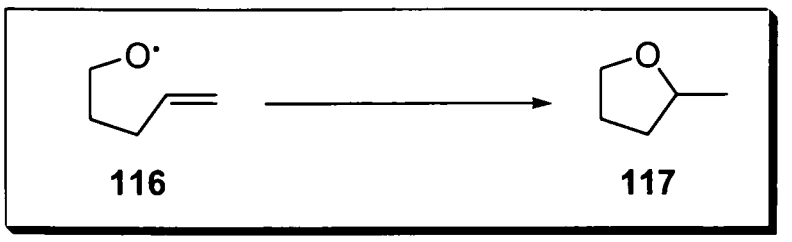


113 (R= alkyl, alkoxy) **114** **115**

Scheme 35. Radical-mediated cyclization of bromoalkyne using EPHP and AIBN; (a) EPHP, AIBN, benzene, reflux.

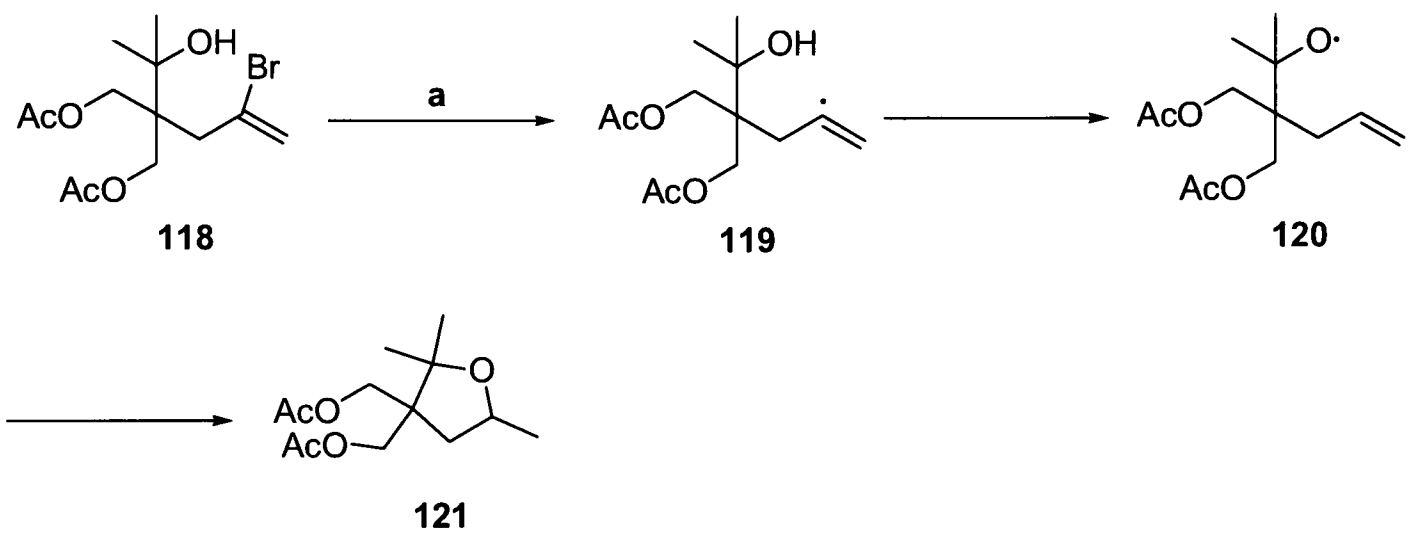
1.2.5.2. C-O bond formation

Various methods for the synthesis of THFs involving radical-mediated C-O bond formation have been reviewed.[54] Most of strategies use alkoxy radical precursor **116** to form the C-O bond in THF **117** (Scheme 36).



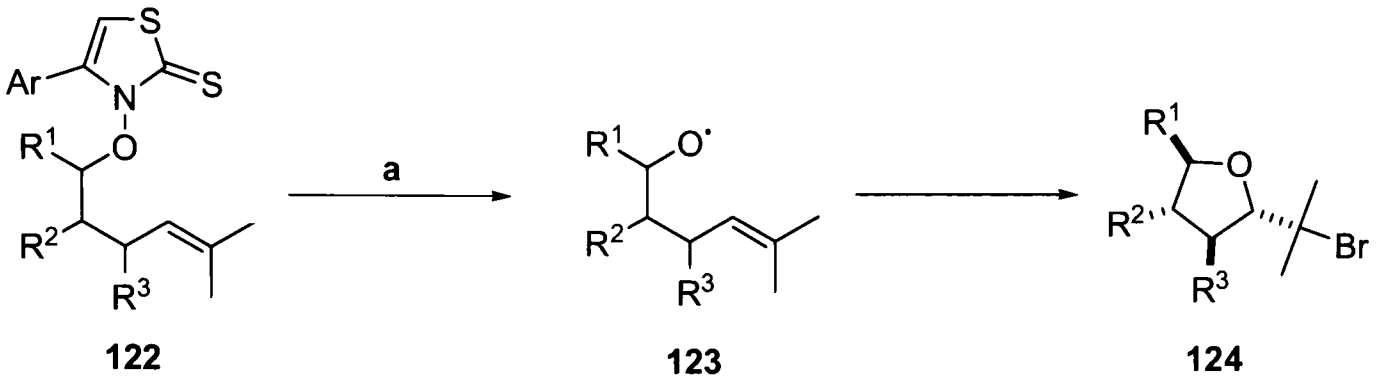
Scheme 36. Formation of C-O bond *via* radical precursor.

In 2003, Ihara and co-workers reported the synthesis of THF **121** *via* alkoxy radical cyclization of hydroxy vinyl bromide **118** using Bu_3SnH and AIBN (Scheme 37).[55] Firstly, alkoxy radical **120** is generated from vinyl radical **119** and it leads to the formation of THF **121** in 55% yield. Here, the hydrogen atom of the hydroxyl group is selectively abstracted in spite of the presence of two methyl groups.



Scheme 37. Synthesis of THF *via* alkoxy radical cyclization of hydroxy vinyl bromide; (a) Bu_3SnH, AIBN, benzene, reflux.

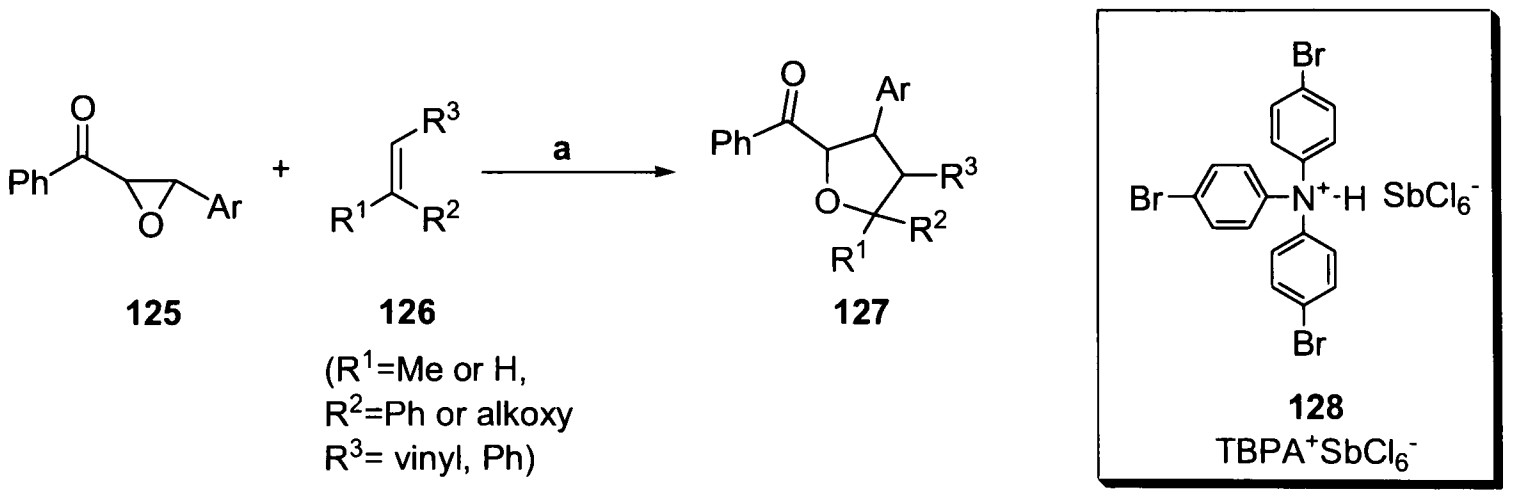
In 2003, Hartung and co-workers reported the synthesis of halogenated THFs **124** *via* bromocyclisation of thione radical precursor **122** (Scheme 38).[56] Radical $\cdot CCl_3$ generated in the reaction mixture induces homolytic cleavage of **122** to give the alkoxy radical **123**; this then undergoes a 5-*exo*-trig cyclisation followed by bromine capture to give THF **124**.



122 **123** **124**

Scheme 38. Bromocyclisation of thione radical precursor; (a) 250 W visible light discharge lamp, $BrCCl_3$, benzene, 15 °C.

When R^1=Ph and R^2, R^3=H, 2,5-*trans*-THF is obtained as a major product in a ratio of 72:28 (*trans*:*cis*) in 87% yield. When R^1, R^2=H and R^3=Ph, 2,3-*trans*-THF is also obtained as a major product in a ratio of 98:2 (*trans*:*cis*) in 90% yield. However, when R^1, R^3=H and R^2 is Ph, 2,4-*cis*-THF is obtained as the major product in a ratio of 68:32 (*cis*:*trans*) in 75% yield. In 2004, Liu reported the synthesis of THFs from cation radical induced [3+2] cycloaddition of electron-rich chalcone epoxide **125** to electron-rich alkene **126** initiated by tris(4-bromophenyl)aminium hexachloroantimonate **128** ($TBPA^+SbCl6^-$, Scheme 39).[57] In this transformation, various multi-substituted THFs **127** were obtained as a mixture of 4 diastereoisomers in 61-82% yield.



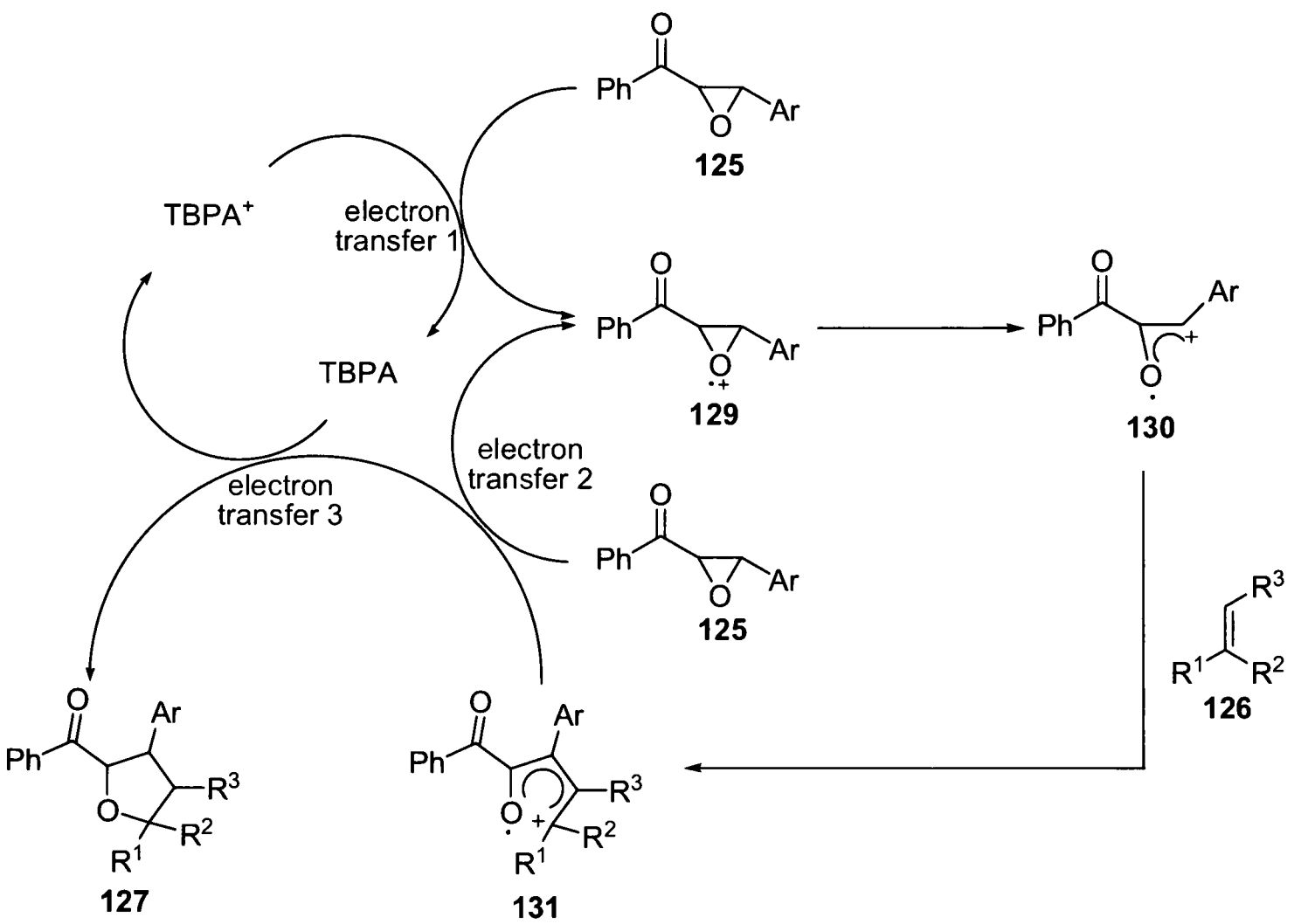
125 **126** **127**

(R^1=Me or H,
R^2=Ph or alkoxy
R^3= vinyl, Ph)

128
$TBPA^+SbCl_6^-$

Scheme 39. Synthesis of THF from cation radical induced [3+2] cycloaddition of chalcone epoxide; (a) $TBPA^+SbCl_6$, CH_2Cl_2.

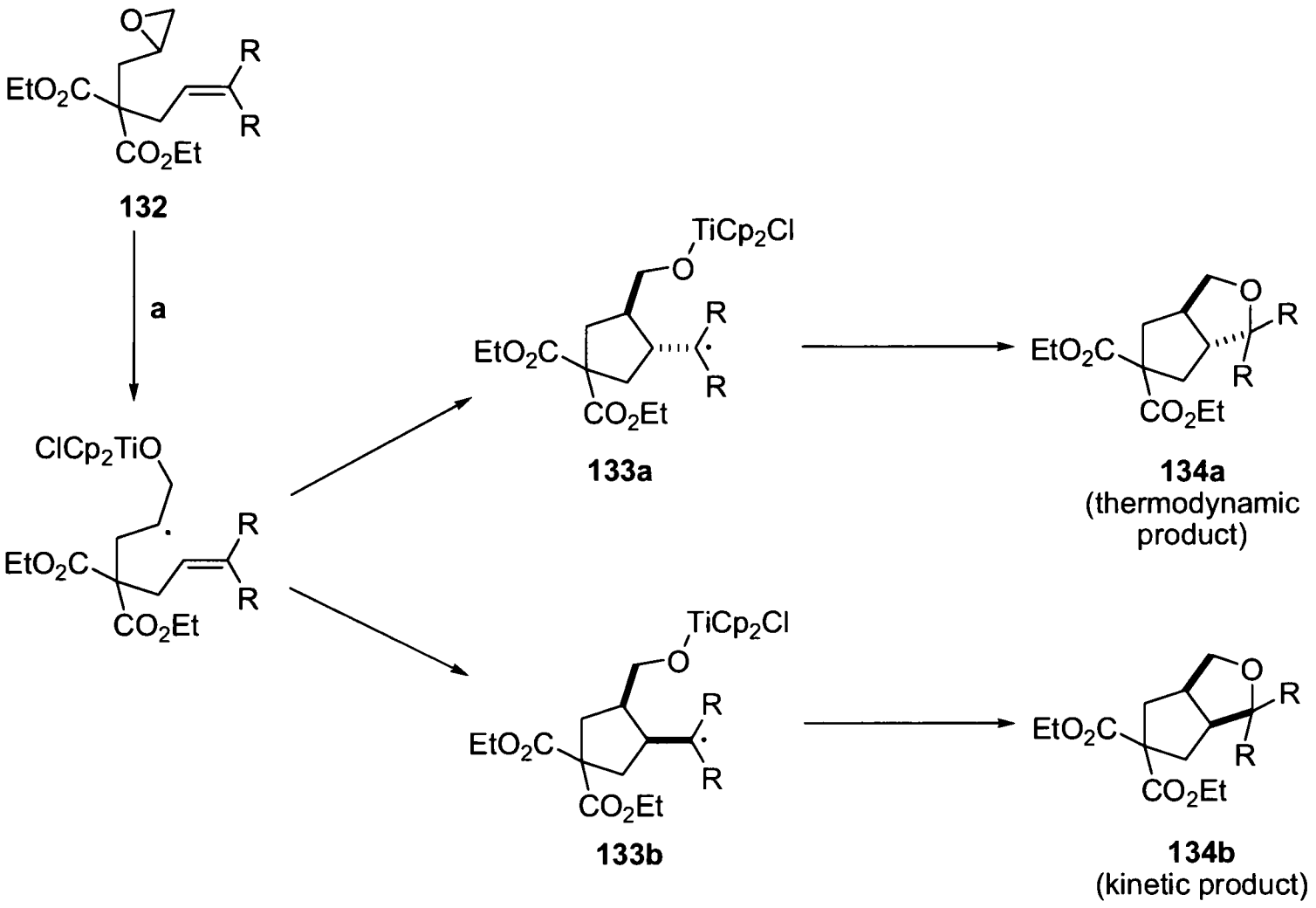
The reaction is believed to proceed *via* firstly, single electron transfer between epoxide **125** and $TBPA^+$ **128** producing the cation radical **129** of epoxide **125** (Scheme 40). Subsequently, selective cleavage of the C_β-O bond gives a new cation radical **130**. Finally, the addition of the cation radical **130** to electron-rich olefin **126** forms cation radical adduct **131**, which undergoes a second electron transfer followed by ring-closure to give THF **127**.



Scheme 40. Mechnism of cation radical induced [3+2] cycloaddition of chalcone epoxide and olefin.

A different example is the synthesis of THFs by C-O bond formation *via* homolytic cleavage of the epoxide C-O bond reported by Gansäuer and co-workers (Scheme 41).[58] Initial reaction between epoxide **132** and Cp_2TiCl forms a Ti-O bond and a carbon-centred radical which undergoes 5-*exo*-cyclisation to give **133**. Homolytic cleavage of the Ti-O bond then generates a new C-O bond to give THFs **134**. The 3,4-*cis*-THFs **134b** were

obtained with high stereoselectivity in up to 73% yield. They explained this high stereoselectivity by density functional theory (DFT) calculations which suggested that 3,4-*cis*-THFs **134b** were the kinetically favoured products, in contrast to the thermodynamically favoured 3,4-*trans*-THFs **134a**.



Scheme 41. Synthesis of THF by the C-O bond formation *via* homolytic cleavage of Ti-O bond; (a) Cp_2TiCl, Mn, HCl, EtOAc.

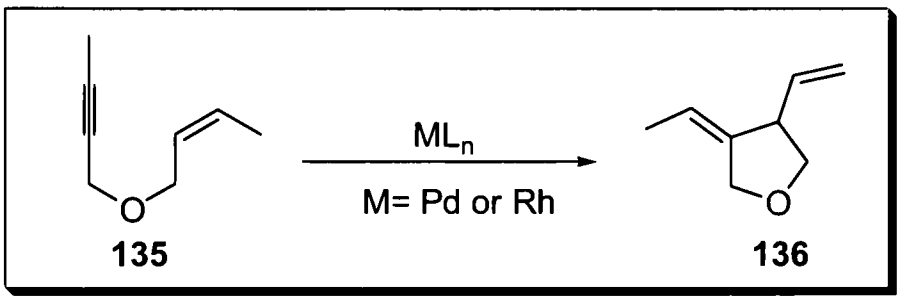
Similar to this titanium-catalysed formation of THFs, Hilt and co-workers have reported the iron-catalysed formation of THFs from the reaction between styrene oxide and unsaturated alkenes *via* electron transfer steps.[59]

1.2.6. C-C bond formation strategies.

Various methods for THF formation involving C-C bond formation have been reported. Ene-type cyclisations are prevalent.

1.2.6.1. Ene-type cyclisation.

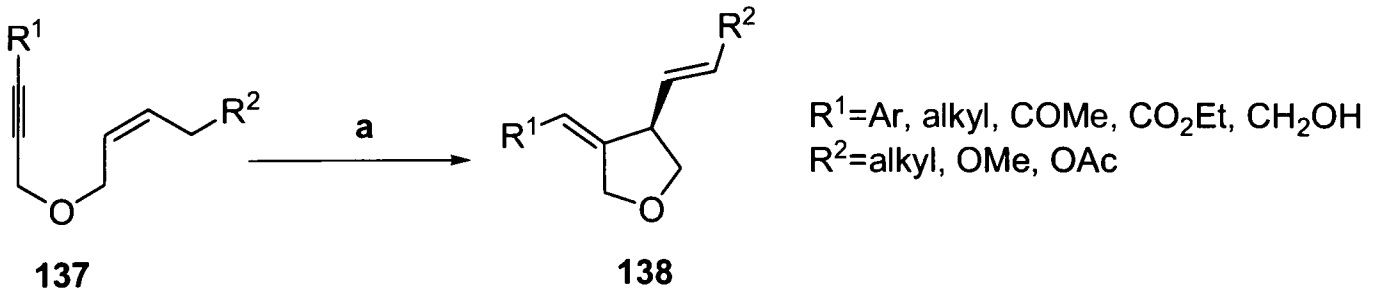
Transition metal catalysed C-C bond formation from 1,6-enynes **135** is frequently used for the formation of the C3-C4 bond in THFs **136** (Scheme 42). This type of transformation has been described in several reviews.[60]



135 136

Scheme 42. C-C bond formation from 1,6-enyne.

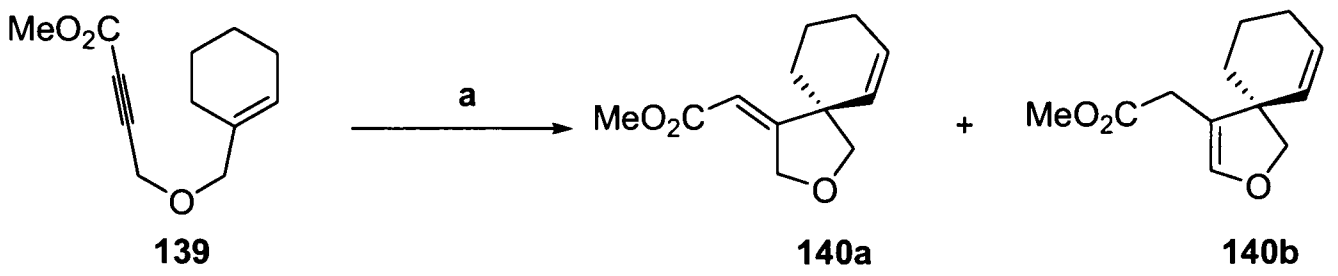
For example, in 2002, Zhang reported a Rh-catalysed Alder-ene reaction for the preparation of a variety of chiral THFs using an air stable [{Rh(cod)Cl}$_2$] precursor with BINAP ligand (Scheme 43).[61] The functionalised THFs **138** were obtained from enyne **137** in over 82% yield and 99% ee for all substrates. Additionally, they reported a highly efficient kinetic resolution of racemic 1,6-enynes bearing alkyl substituent at both the allylic positions.[62]



137 138

Scheme 43. Preparation of THFs by Alder-ene reaction; (a) [{Rh(cod)Cl}$_2$], (*S*)-BINAP, $AgSbF_6$.

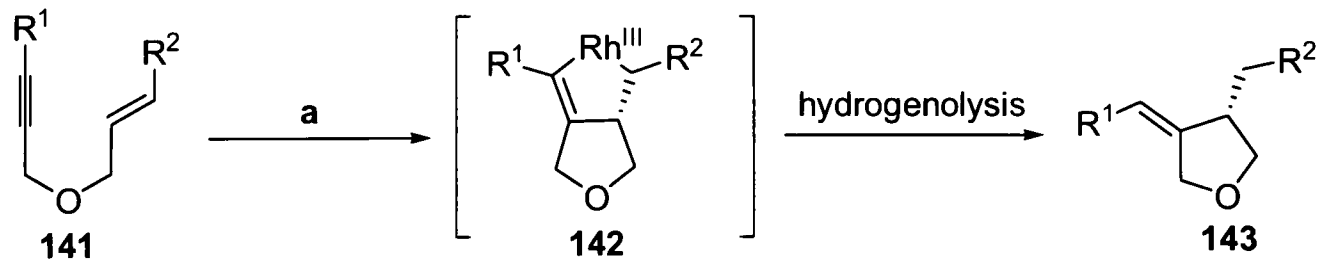
In 2004, Mikami and co-workers showed ene-type carbocyclisation with skewphosrodium complex (Scheme 44).[63] In contrast to Zhang's work, this carbocyclisation of enyne **139** is accompanied by olefin migration, favouring the product **140b** (44% yield, 91% ee) over the product **140a** (4% yield, 67% ee) at a high reaction temperature (80 °C). The high temperature is necessary since it allows dramatically reduced reaction time (40 min), in contrast to the longer reaction time (46 h) at room temperature.



139 **140a** **140b**

Scheme 44. Ene-type carbocyclisation accompanying olefin migration; (a) $[Rh((S,S)\text{-skewphos})]_2(SbF_6)_2$ (5mol%), CH_2Cl_2, 80 °C.

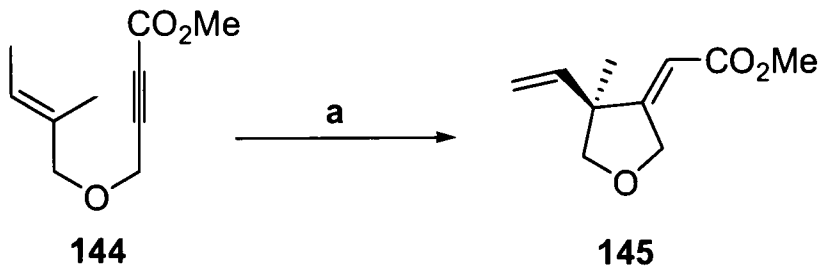
In 2005, Krishe and co-workers reported Rh-catalysed asymmetric cyclisation-hydrogenolysis of 1,6-enynes **141** (Scheme 45).[64] In this transformation, they obtained THF **143** in up to 85% yield and 98% ee. They suggested that the reaction proceeds *via* intermediate **142**.



141 **142** **143**

Scheme 45. Asymmetric hydrogenation of 1,6-enynes; (a) $Rh(cod)_2OTf$ (3-5 mol%), chiral phosphine (3-5 mol%) CH_2Cl_2, 25 °C, H_2 (1 atm), 2-3 h.

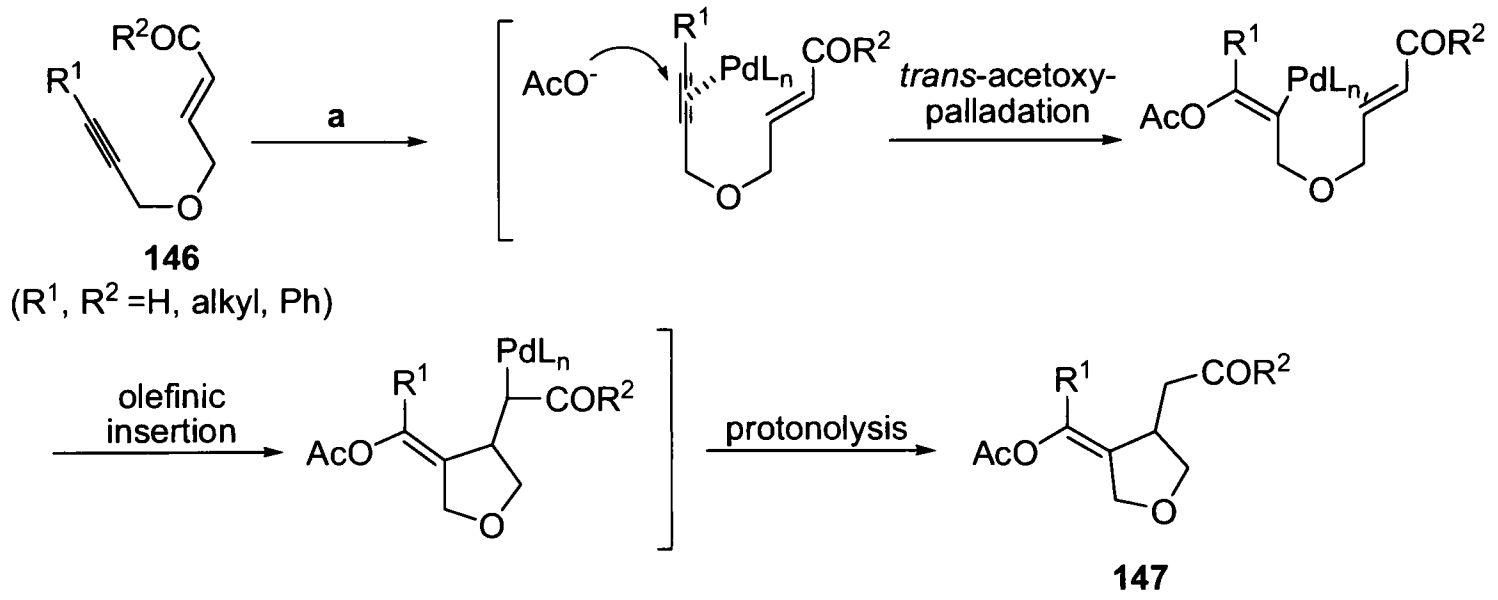
Similarly, Mikami and co-workers reported Pd-catalysed cyclization of 1,6-enynes **144** with a new N,P-ligand bearing an achiral *gem*-dimethyloxazolidine (Scheme 46).[65] They obtained THF **145** in 92% yield and 87% ee.



144 145

Scheme 46. Pd-catalysed cyclization of 1,6-enynes; (a) $[(MeCN)_4Pd](BF_4)_2$ (5 mol%), N,P-ligand (10 mol%), HCOOH (1.0 eq), DMSO, 80 °C.

Lu and co-workers also reported Pd-catalysed cyclization of 1,6-enynes **146** initiated by acetoxypalladation of the alkyne followed by alkene insertion and protonolysis of the carbon palladium bond to give THFs **147** (Scheme 47).[66] When R^1=Ph and R^2=H, the highest yield obtained was 96%. Also, they synthesised enantiomerically enriched THFs using chiral oxazoline ligands in up to 65% yield and 77% ee.



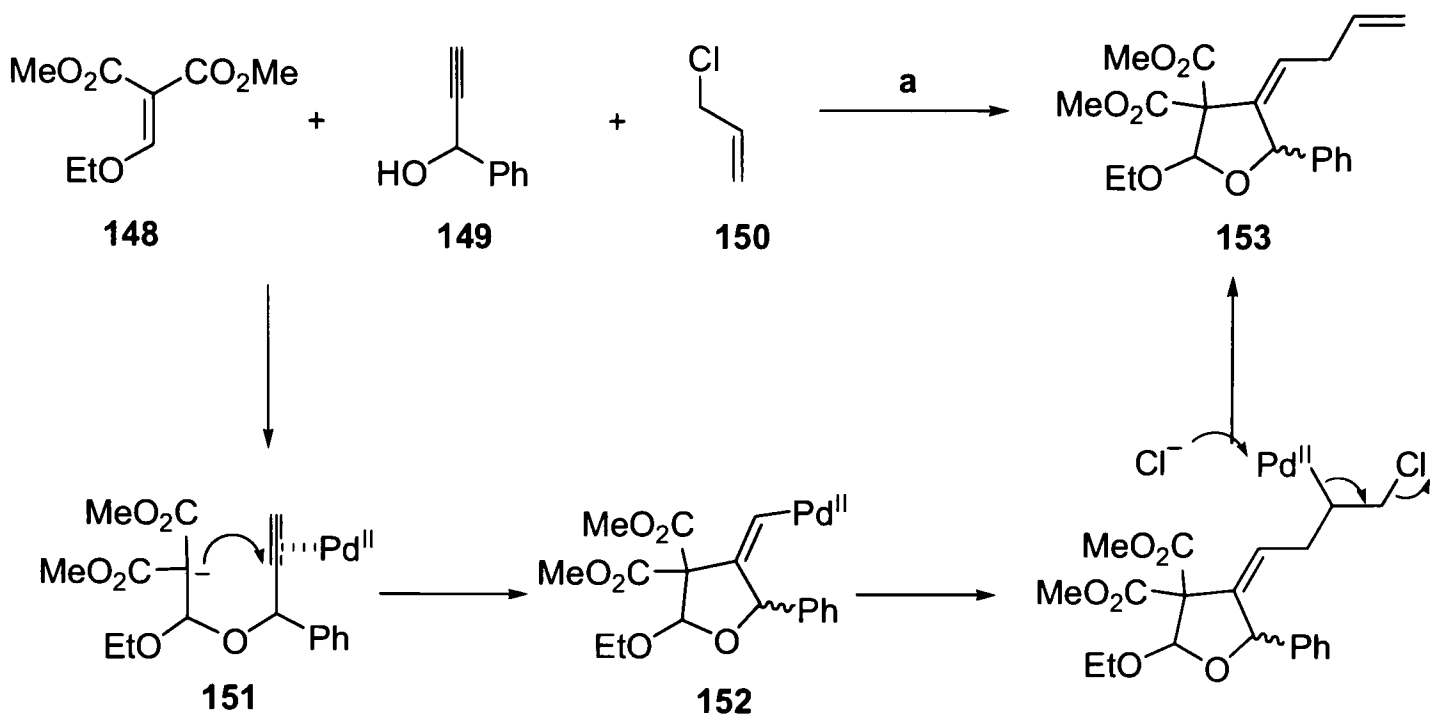
146
(R^1, R^2 =H, alkyl, Ph)

147

Scheme 47. Cyclization *via* acetoxypalladation of 1,6-enynes; (a) $Pd(OAc)_2$/bpy, HOAc, 80 °C.

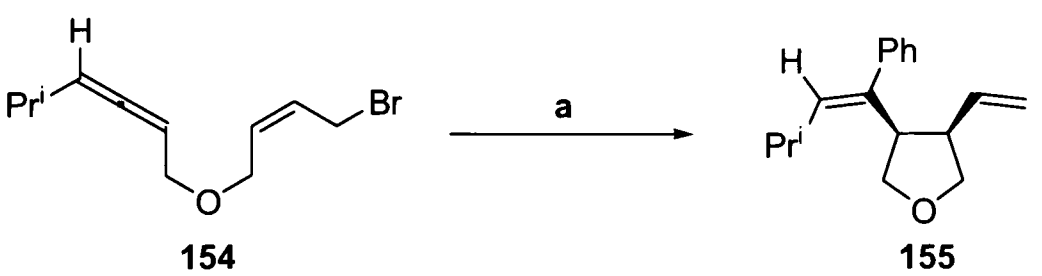
The same authors also reported the synthesis of THFs *via* a divalent palladium-catalysed three- component coupling (Scheme 48).[67] They used methylene malonate **148**, propargyl alcohol **149** and allyl chloride **150** for this one-pot synthesis. Initially, the reaction between methylene malonate **148** and potassium propargylate generated from alcohol **149** by base (^{t}BuOK) gives malonate anion species **151**. Subsequent cyclisation yields palladated THF

152 which then undergoes olefin insertion followed by β–elimination to produce THF **153** as a mixture of two diastereoisomers (2,5-*cis* and *trans*) in up to 75% yield.



Scheme 48. Synthesis of THF *via* a divalent palladium-catalysed three component coupling; (a) ^{t}BuOK, Pd(II)/LiCl, dr 1.1:1 (*cis/trans*), 75%.

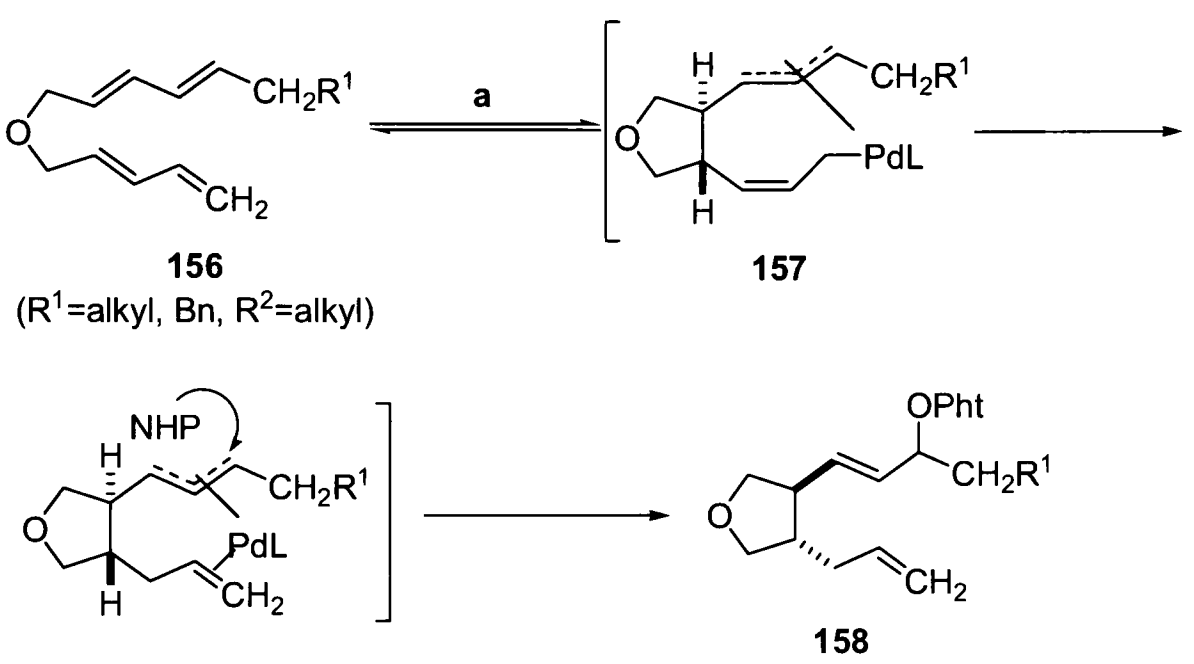
Similarly, in 2004, Nakamura and co-workers reported the use of a Zn(II)/amine catalysed coupling reaction between alkylidenemalonate and propargyl alcohol and they obtained methylene THFs in 70-94% yield.[68] In the same year, Zhang showed palladium-catalysed cyclization using 1,2,7-trienes **154** instead of 1,6-enynes, followed by a Suzuki coupling reaction (Scheme 49).[69] In this tandem process, they obtained 3,4-*cis*-THF **155** as a single diastereoisomer in 59% yield.



Scheme 49. Palladium-catalysed cyclization using 1,2,7-trienes; (a) Aryl boronic acid, $Pd(PPh_3)_4$, $K_3PO_4 \cdot 3H_2O$, toluene, 50 °C, 59%.

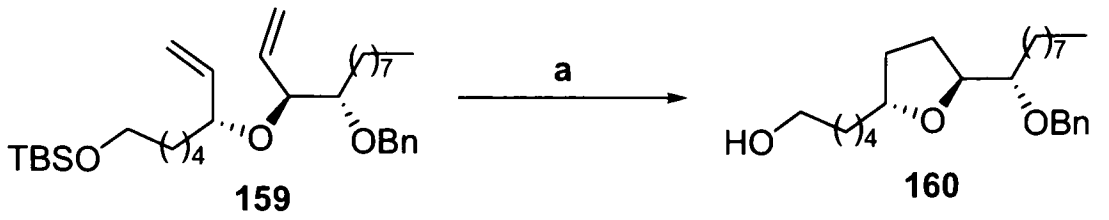
1.2.6.2. Other C-C bond formations.

As a different type of strategy for the C-C bond formation, Takacs and co-workers reported a palladium-catalysed bisdiene carbocyclisation-nucleophilic trapping method in 2003 (Scheme 50).[70] The palladium-mediated oxidative coupling of bisdiene **156** gives palladacycle **157** and then treatment with nucleophilic trapping reagent, *N*-hydroxyphthalimide (NHP), gives the THF **158** as a single diastereoisomer in up to 90% yield.



Scheme 50. Formation of THF by palladium-catalysed bisdiene carbocyclisation-nucleophilic trapping; (a) $Pd_2(dba)_3$, (*o*-biphenyl)P(^{t}Bu)$_2$, NHP, 90%.

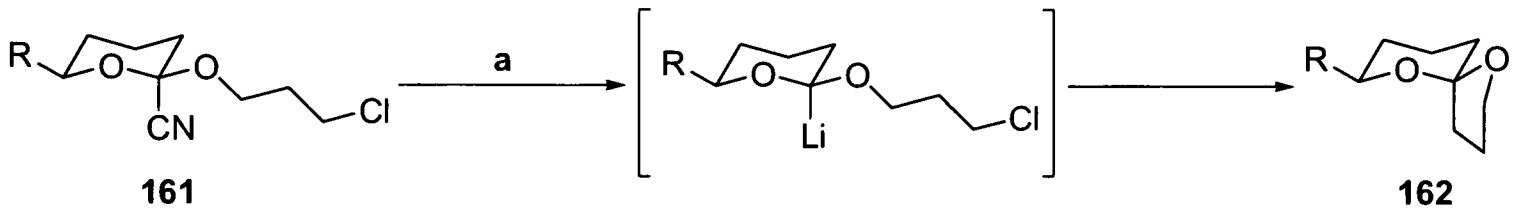
Another different strategy is based on olefin metathesis. In 2004, Evans and co-workers demonstrated the preparation of the THF moiety in this way as part of their total synthesis of Gaur acid (Scheme 51).[71] Olefin metathesis using the ruthenium based Grubbs *N*-heterocyclic carbene catalyst followed by hydrogenation converted diene **159** into THF **160** in 75% yield.



159 160

Scheme 51. Preparation of THF by ring-closing metathesis; (a) i. Grubbs NHC catalyst, DCE, 40 °C, ii. H_2, 70 °C, iii. HCl, MeOH.

Additionally, in 2005, Rychnovsky and co-workers reported the preparation of THF by reductive cyclization (Scheme 52).[72] Reduction of nitrile **161** using lithium di-tert-butylbiphenylide (LiDBB) generates an axial organolithium and the intramolecular alkylation produces spiroacetal **162** as a single diastereoisomer in 63% yield.



161 162

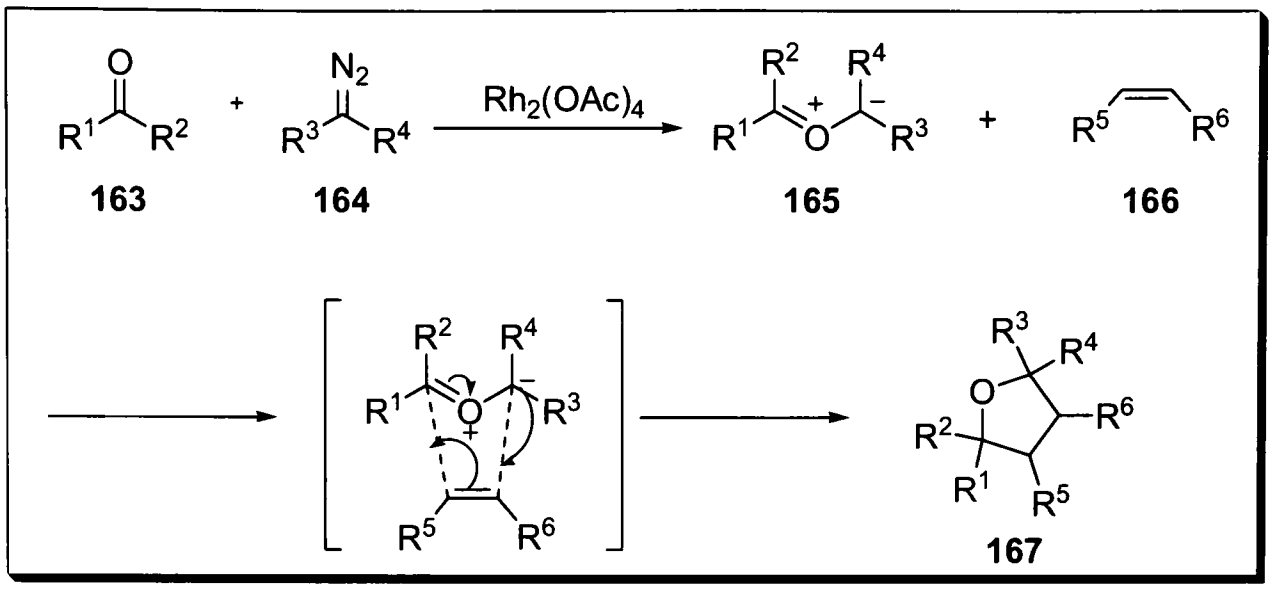
Scheme 52. Preparation of THF by reductive cyclization; (a) LiDBB, THF, -78 °C, 63%.

1.2.7. [3+2] cycloaddition strategy.

Various methods involving [3+2] cycloaddition have been reported. There are two main strategies; i) [3+2] cycloaddition using carbonyl ylides and alkenes, ii) [3+2] cycloaddition using cyclopropanes and aldehydes.

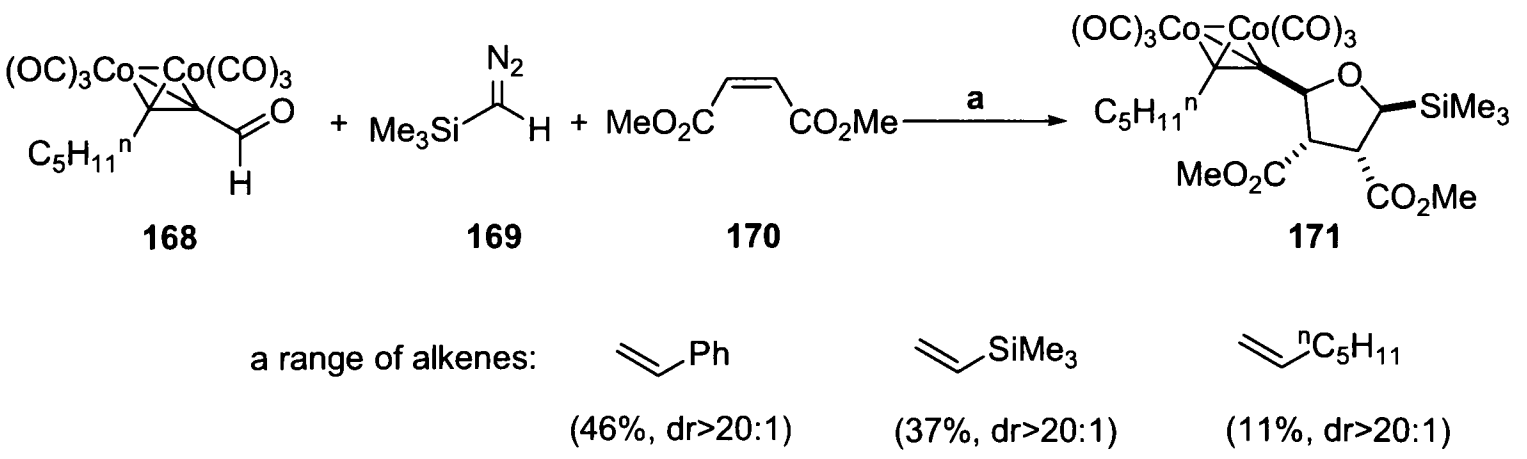
1.2.7.1. [3+2] cycloaddition using carbonyl ylides and alkenes.

A common strategy in this field is the Rh-catalysed [3+2] cycloaddition reaction between a carbonyl ylide and an alkene. The general concept is shown in Scheme 53. Firstly, a carbonyl ylide **165** is prepared from the reaction between carbonyl compound **163** and diazo compound **164** and the THF **167** is formed by the annulation between dipolar ylide **165** and electron-deficient alkene **166**.



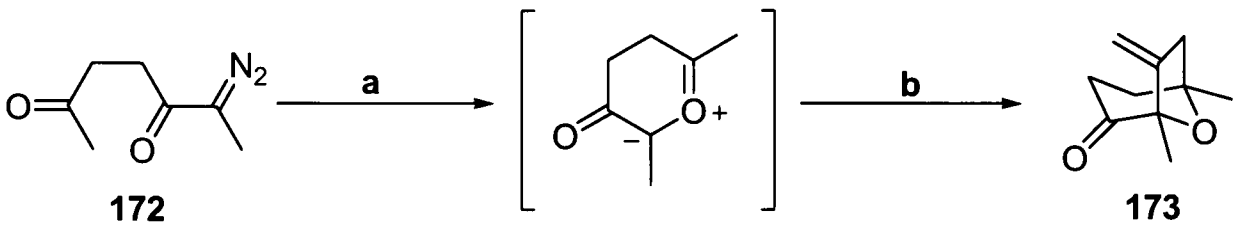
Scheme 53. Rh-catalysed [3+2] annulation between carbonyl ylide and alkene.

For example, in 2002, Jamison and co-workers showed the three-component coupling between diazo compound **169**, alkene **170** and aldehyde **168** bearing a dicobalt hexacarbonyl ($Co_2(CO)_6$) cluster (Scheme 54).[73] This transformation gives a single diastereoisomer **171** in 74% yield. This type of transformation is usually limited to electron-deficient alkenes, so it is notable that the use of the cobalt cluster-bearing aldehyde increases the scope to encompass a wide range of alkenes. For example, when styrene was employed, the corresponding THF was obtained in 46% yield.



Scheme 54. Three-component coupling between diazo compound, alkene and aldehyde bearing cobalt cluster; (a) $Rh_2(OAc)_4$, CH_2Cl_2, 74%, single diastereoisomer.

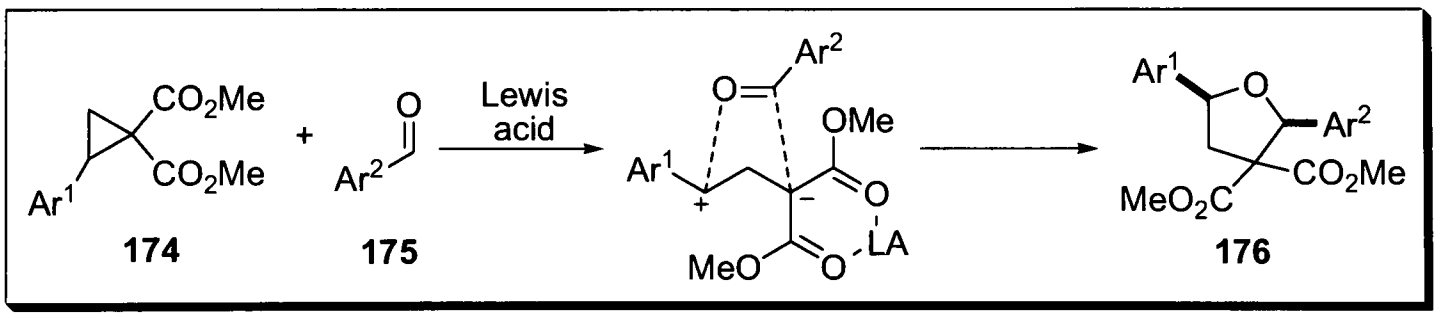
In 2004, Hodgson and co-workers demonstrated the use of allenes for the cycloaddition, in place of electron-deficient alkenes (Scheme 55).[74] They obtained cycloadduct **173** in 77% yield from the reaction between allene and diazocarbonyl compound **172**.



Scheme 55. [3+2] cyclization using allene and carbonyl ylide; (a) $Rh_2(OAc)_4$, (b) allene.

1.2.7.2. [3+2] cycloaddition using cyclopropanes and aldehydes.

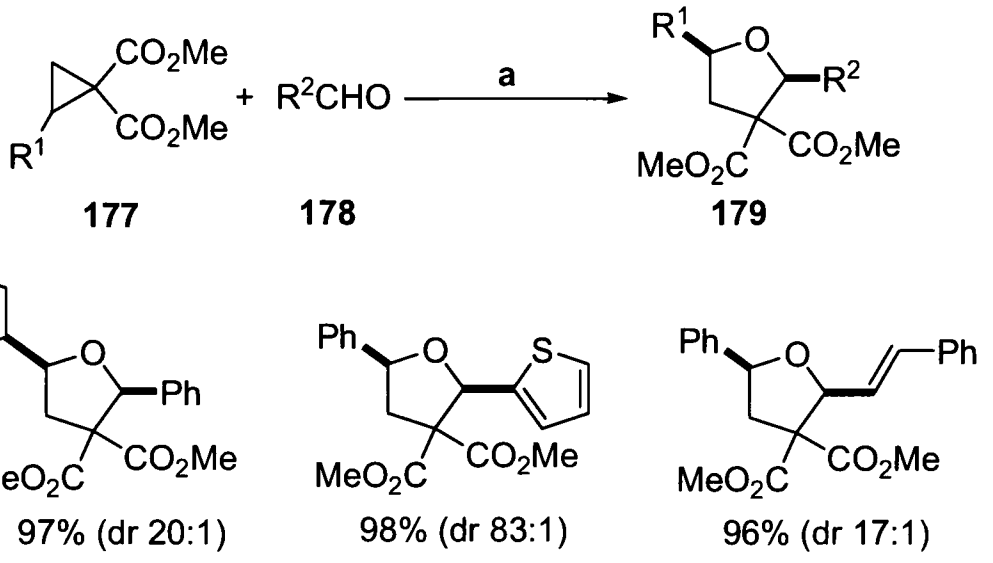
In the general process (Scheme 56), a cyclopropane **174** bearing diester and aryl substituents generates a formal zwitterionic intermediate *via* Lewis acid-mediated ring-opening which is then trapped by aryl aldehyde **175**. In terms of stereochemistry, two Ar groups (Ar^1 and Ar^2) are located pseudoequatorially in the transition state, resulting in the formation of 2,5-*cis*-THF **176**.



Scheme 56. [3+2] annulation using cyclopropane and aldehyde.

Similarly, in 2005, Johnson and co-workers reported the tin-mediated formation of 2,5-*cis*-THFs **179** from aldehydes **178** and cyclopropanes **177** (Scheme 57).[75] Here, they obtained 2,5-*cis*-THFs from benzaldehyde and thienyl cyclopropane with diastereomer ratios of up to 20:1 and in up to 97% yield. Also, they obtained 2,5-*cis*-THF from phenyl cyclopropane

and thienyl aldehyde (83:1 dr and up to 98% yield). However, when they used α,β-unsaturated aldehydes or styrenyl cyclopropanes, they could obtained 2,5-*cis*-THFs with low diastereoselectivity (<17:1), albeit in high yield (over 92%).

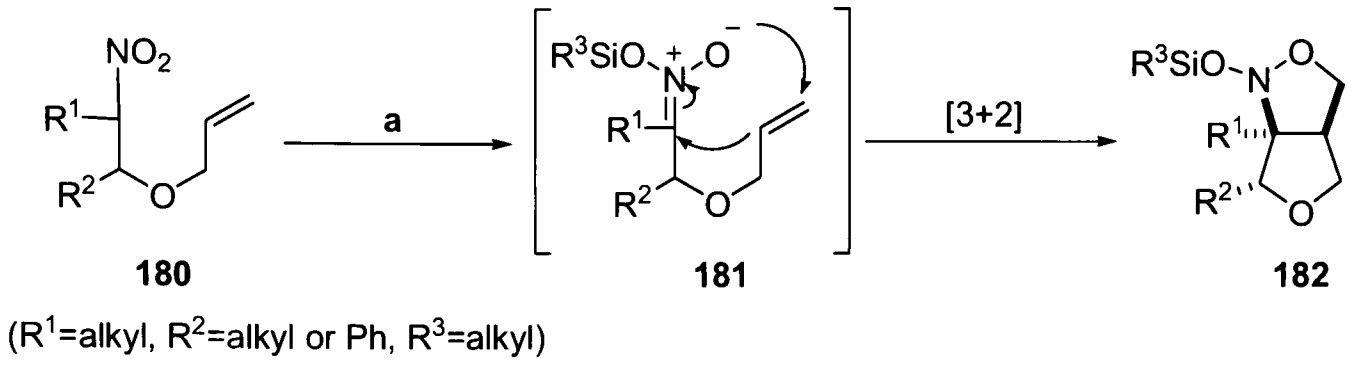


Scheme 57. [3+2] Annulation using cyclopropane and aldehyde; (a) $Sn(OTf)_2$ (5 mol%), CH_2Cl_2.

In 2006, Yadav and co-workers reported scandium-mediated [3+2] cyclization of silylmethyl-substituted cyclopropanes with aryl aldehydes and aryl ketones.[76] The corresponding THFs were obtained with a diastereomeric ratio of 12.5:1 in up to 100% yield. Also, Christie and co-workers have shown [3+2] annulation using aldehydes and cyclopropanes bearing cobalt clusters instead of aryl substituents and a mixture of diastereoisomeric THFs were obtained up to 85% yield.[77]

1.2.7.3. Other [3+2] cycloaddition strategies.

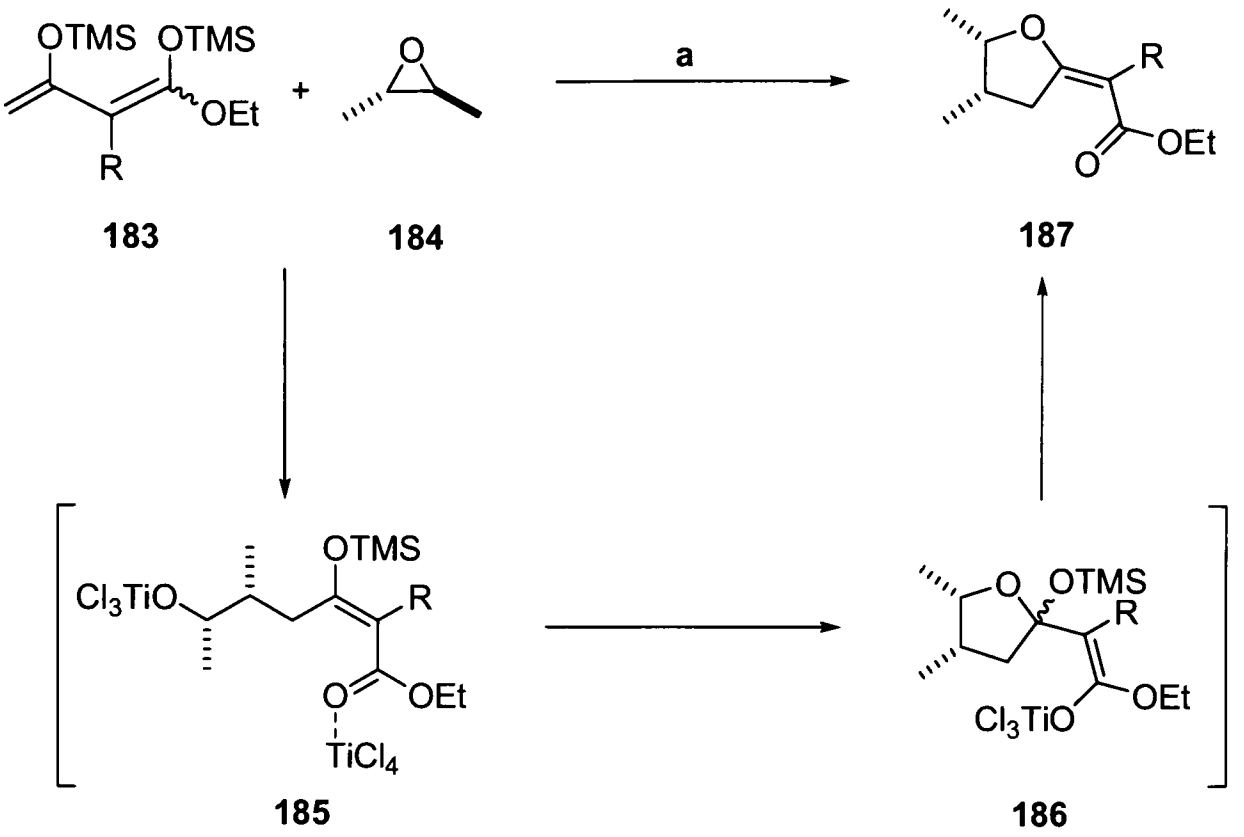
In 2004, Dulcère and co-workeres reported the formation of the THF unit *via* the transformation of nitroalkyl allyl ether **180** into isoxazaolidine **182** (Scheme 58).[78] The nitroalkyl allyl ether **180** first reacts with a trialkylchlorosilane and DBU to give silylnitronate intermediate **181**. Subsequently, an intramolecular [3+2] cycloaddition constructs the THF moiety of isoxazaolidine **182**. In this transformation, the 2,3,4-trisubstituted THF **182** is obtained in 69-100% yield.



Scheme 58. Transformation of silylnitronate into isozaolidine; (a) DBU, R^3SiCl, CH_2Cl_2.

1.2.8. Miscellaneous strategies.

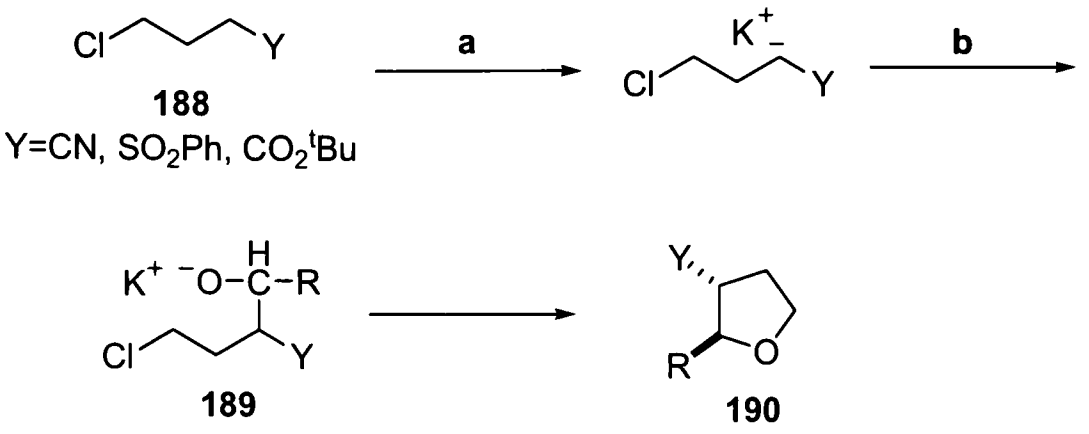
Langer and co-workers have developed the synthesis of THFs using 1,3-dicarbonyl dianion species. They have shown that the Lewis acid-mediated cyclization of epoxides with 1,3-bis(trimethylsilyloxy)-1,3-butadienes as a neutral equivalent of 1,3-dicarbonyl dianion generates 2-alkylidene THFs (Scheme 59).[79] Initial regioselective attack of the terminal alkene of diene **183** on the epoxide **184** furnishes intermediate **185** with inversion of the configuration. The subsequent $TiCl_4$-mediated conjugate addition of the epoxide-derived hydroxy group onto the α,β-unsaturated ester moiety then gives intermediate **186**. Finally, 2-alkylidene THF **187** is obtained by the elimination of silanolate. Thus, *trans*-epoxide affords 4,5-*cis*-THF and *cis*-epoxide affords 4,5-*trans*-THF. Also, *E*-olefin geometry is predominantly observed.



Scheme 59. Lewis acid-mediated cyclization of epoxides with 1,3-bis(trimethylsilyloxy)-1,3-butadienes to form 2-alkylidene THF; (a) $TiCl_4$ (2.0 eq), CH_2Cl_2, 4 Å MS, -78 °C (5 h) then 20 °C (12 h).

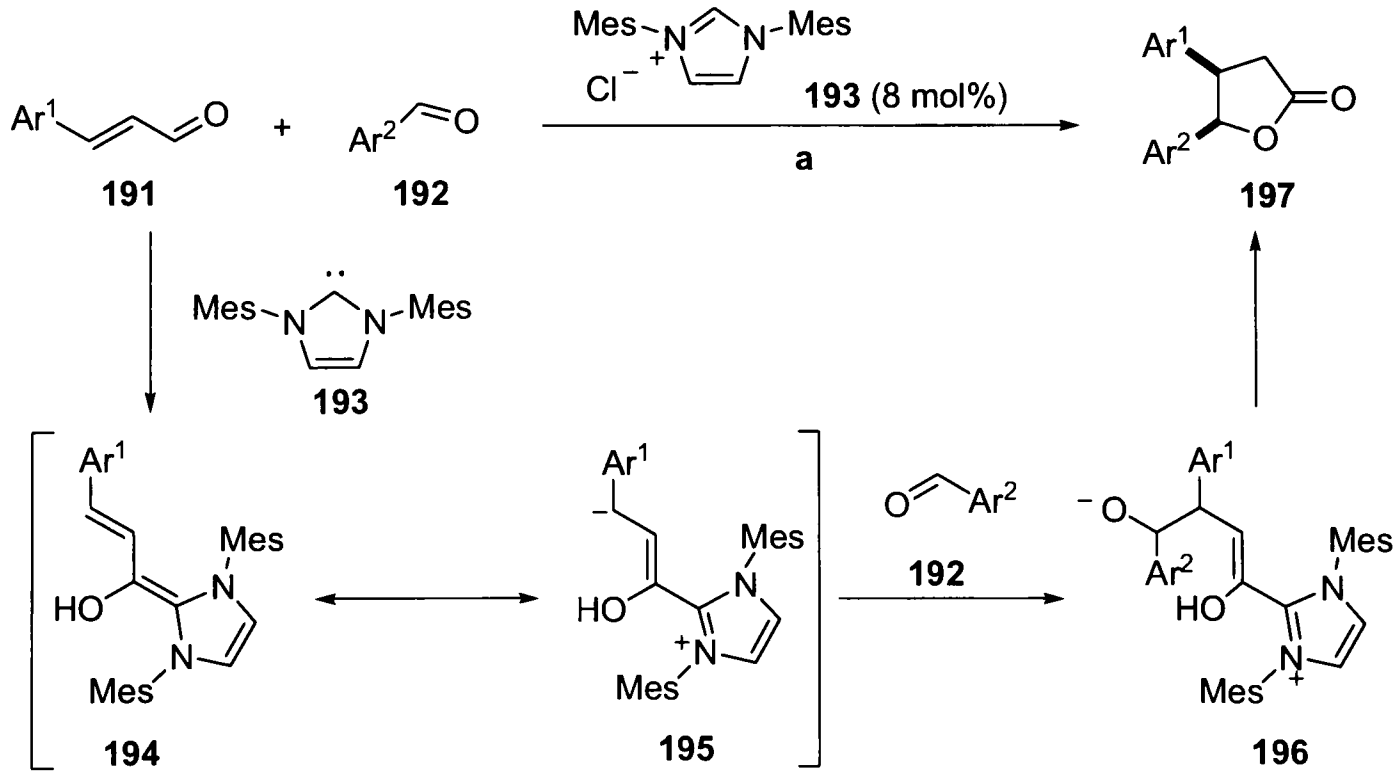
Similarly, these authors reported the preparation of 2-alkylidene THFs *via* LDA mediated generation of dianions from β-ketoesters and subsequent intermolecular cyclization with 1-bromo-2-chloroethane.[80] Also, they showed the preparation of 2-alkylidene THFs by $LiClO_4$-mediated cyclization of β-ketoesters with epibromohydrin.[81]

In 2002, Mącosza and co-workers reported the preparation of 2,3-disubstituted THFs *via* the formation of γ-halocarbanions (Scheme 60).[82] Haloalkane **188** was deprotonated by the treatment of ^{t}BuOK and the resultant anion added to an aldehyde. The resulting γ-halocarbanion **189** cyclized to form 2,3-*trans*-THF **190** as the major product in a diastereoisomeric ratio of 69:31.



Scheme 60. 2,3-disubstituted THF *via* the formation of γ-halocarbanion; (a) ^{t}BuOK, -30 °C, THF, (b) RCHO (R=alkyl, aryl).

In 2004, Bode[83] and Glorius[84] independently developed the synthesis of butyrolactones by direct annulation of enals and aldehydes catalyzed by *N*-heterocyclic carbenes. For example, Bode and co-workers prepared 4,5-*cis*-butyrolactones by this type of transformation as a major product (diastereoisomeric ratio of up to 5:1 and 41-81% yield) (Scheme 61).



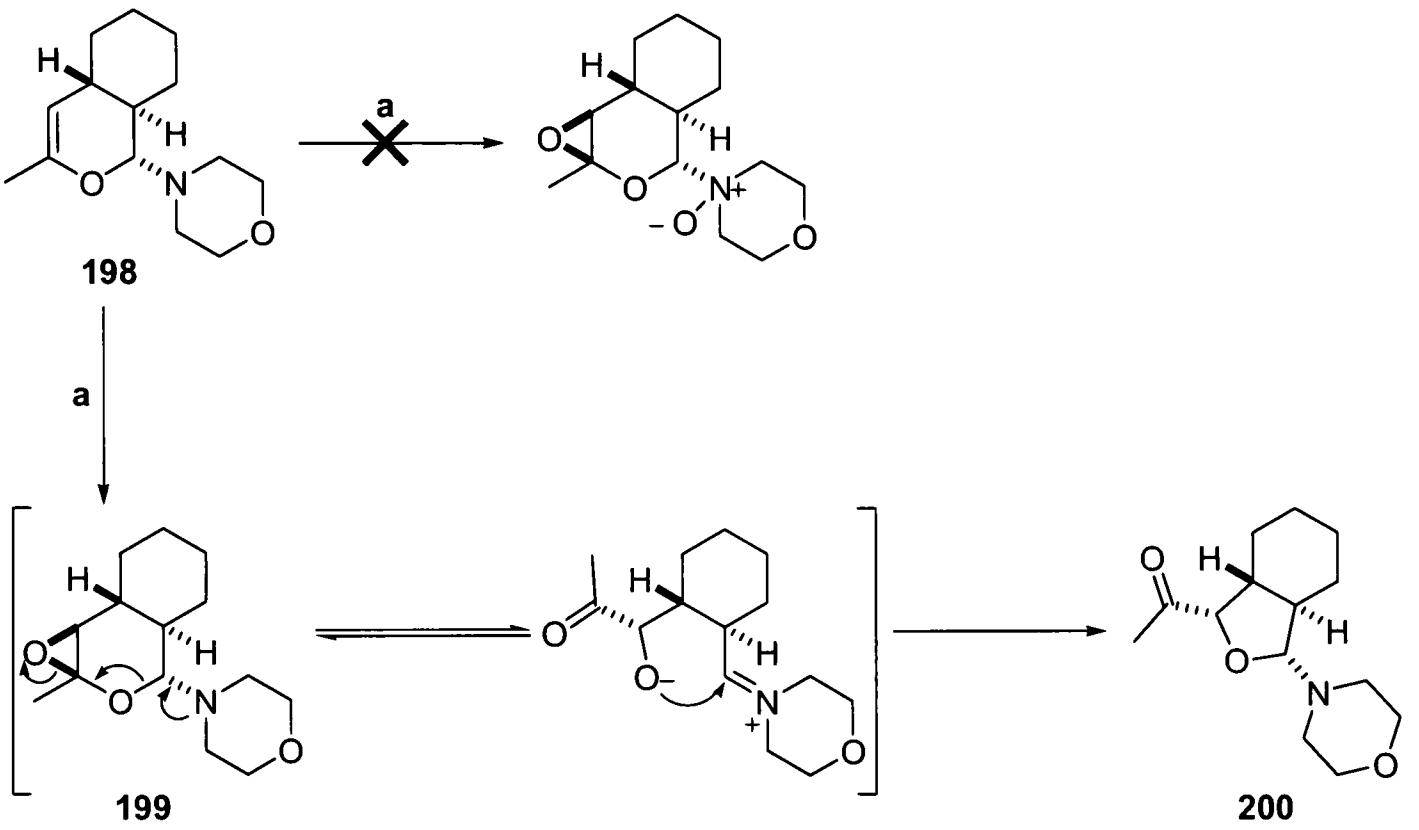
Scheme 61. Synthesis of butyrolactones by direct annulation of enals and aldehydes catalyzed by *N*-heterocyclic carbene; (a) DBU (7 mol%), 1:1 THF/^{t}BuOH, 25 °C.

Initially, α,β-unsaturated aldehyde **191** is attacked by *N*-heterocyclic carbene catalyst **193** to give conjugated acyl anion equivalent **194**, which then tautomerizes to homoenolate **195**. The subsequent addition of homoenolate **195** to aldehyde **192** gives alkoxide **196** which then cyclises to afford lactone **197**.

It can be seen from the above review that numerous methods have been developed for the preparation of THFs. However, it is noteworthy that strategies allowing the synthesis of 2,3-*cis*-disubstituted THFs have rarely been reported. Therefore, the investigation of the synthesis of 2,3-*cis*-disubstituted THFs is certainly desirable and necessary in this field.

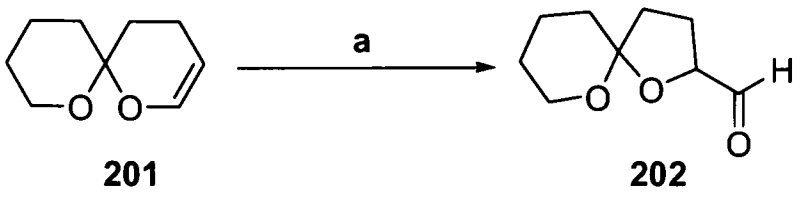
1.3. Background to the project

The idea for this project came from previous research undertaken in the Armstrong group. During work towards the total synthesis of acremolactone A, our group found that the oxidation of the 2-amino dihydropyran (DHP, **198**), which had been expected to result in epoxidation and simultaneous formation of the *N*-oxide for subsequent Cope elimination, instead resulted in the formation of THF **200** (Scheme 62).[85] Presumably, following epoxidation of DHP **198**, the unstable epoxide intermediate **199** underwent ring opening to give an iminium intermediate which then led to the THF **200**.



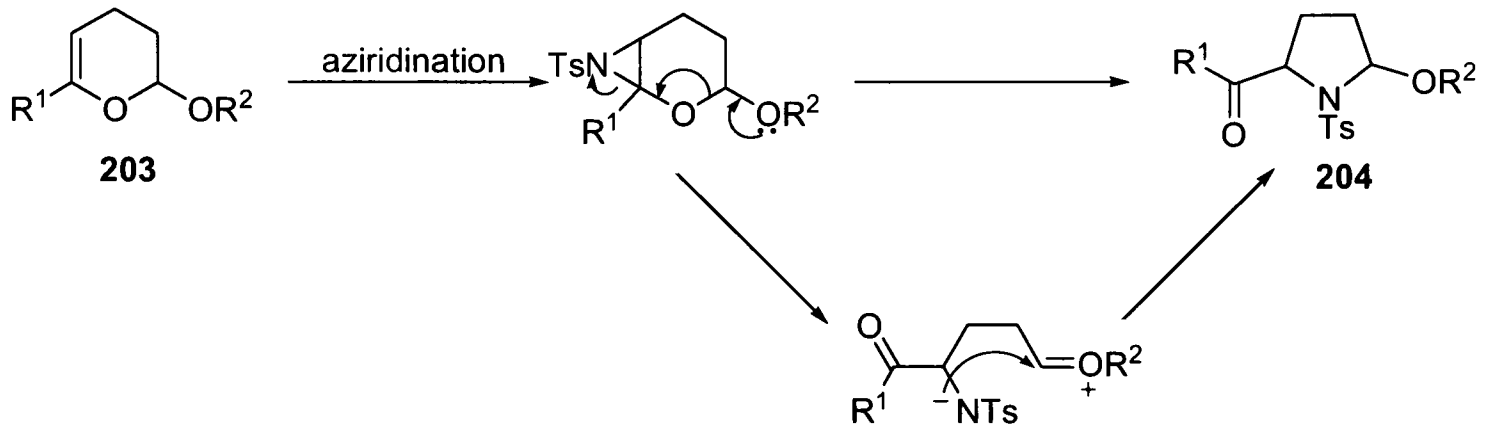
Scheme 62. Oxidation of 2-amino DHP; (a) DMDO

After finding this unexpected rearrangement, our group became aware that Ireland had reported a similar rearrangement in the synthesis of (±)-chalcogran.[86] Ireland showed that the epoxidation of 2-alkoxy DHP **201** resulted in the formation of THF **202** (Scheme 63). However, Ireland focused on only specific spiroketal systems.



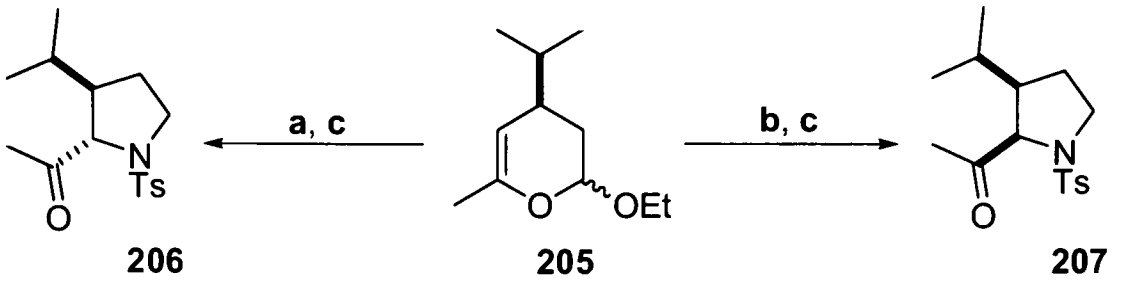
Scheme 63. Oxidative rearrangement of 2-alkoxy DHP by Ireland; (a) MCPBA (1.1 eq), MeOH, -5 °C (2 h) to rt, 82%.

On the basis of these two findings, our group investigated the aziridination of DHP **203** rather than epoxidation. The aziridination successfully effected an analogous rearrangement; leading to the formation of pyrrolidine **204** (Scheme 64).[87]



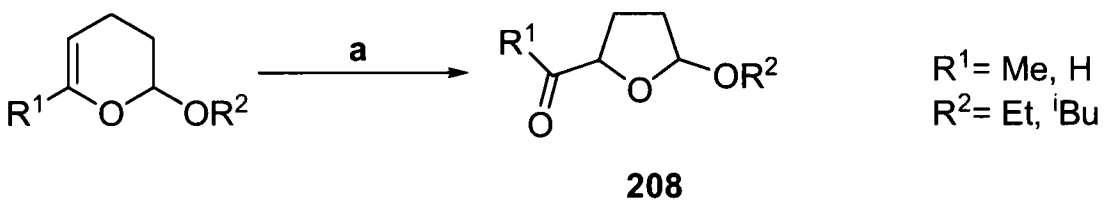
Scheme 64. Aminative rearrangement of 2-alkoxy DHPs by Armstrong.

In this research, our group showed that two different aziridination conditions were able to control the relative stereochemistry of the resulting pyrrolidines; the combination of *N*-bromosuccinimide (NBS) and Chloramine-T (TsNClNa) gave 2,3-*trans*-pyrrolidine **206** and the combination of Cu and PhINTs gave 2,3-*cis*-pyrrolidine **207** (Scheme 65). Using the NBS reagent, DHP **205** was brominated on the less hindered face, *trans* to the isopropyl substituent. Nucleophilic attack of TsNClNa resulted in inversion of configuration, leading to the formation of 2,3-*trans*-pyrrolidine **206**. However, DHP **205** was directly aziridinated on the less hindered face under the Cu-nitrene reagent system, leading to the formation of 2,3-*cis*-pyrrolidine **207**.



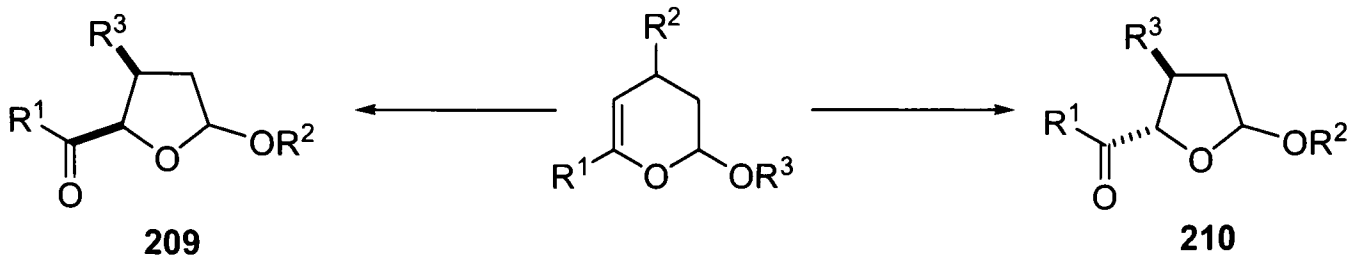
Scheme 65. Stereocontrolled aminative rearrangement of DHP; (a) NBS (20 mol%), TsNClNa (3.0 eq), CH_3CN, rt, 1 h, 64%; (b) $Cu(MeCN)_4PF_6$ (10 mol%), PhINTs (1.1 eq), CH_3CN, 0 °C, 0.5 h, 52%; (c) Et_3SiH (3.0 eq), $BF_3 \cdot Et_2O$ (2.0 eq), -78 to 0 °C, 2 h, >90%.

In an analogous fashion, Hall also reported the epoxidation of DHP and ring contraction, giving 2,5-disubstituted THF **208** (Scheme 66).[88] In this research, Hall suggested a possible mechanism for the formation of THF **208** by ring-opening related to the epoxidation. However, this study only focused on the formation of THFs with substitution in the 6-position (R^1=Me, H and R^2=Et, ^{i}Bu) and there was no further study of stereoselectivity or alternative reaction conditions.



Scheme 66. Oxidative rearrangement of DHP by Hall; (a) MCPBA (1.0 eq), CH_2Cl_2, 0-10 °C, 20-90%.

Consequently, we decided to investigate the possibility of using this oxidative rearrangement for the stereocontrolled synthesis of substituted THFs. In particular, we would investigate the stereocontrolled formation of 2,3-disubstituted THFs **209** and **210** by this oxidative rearrangement because of the relative lack of methods for the synthesis of 2,3-disubstituted THFs (Scheme 67).



Scheme 67. Stereocontrolled formation of 2,3-disubstituted THFs.

2. Results and discussion

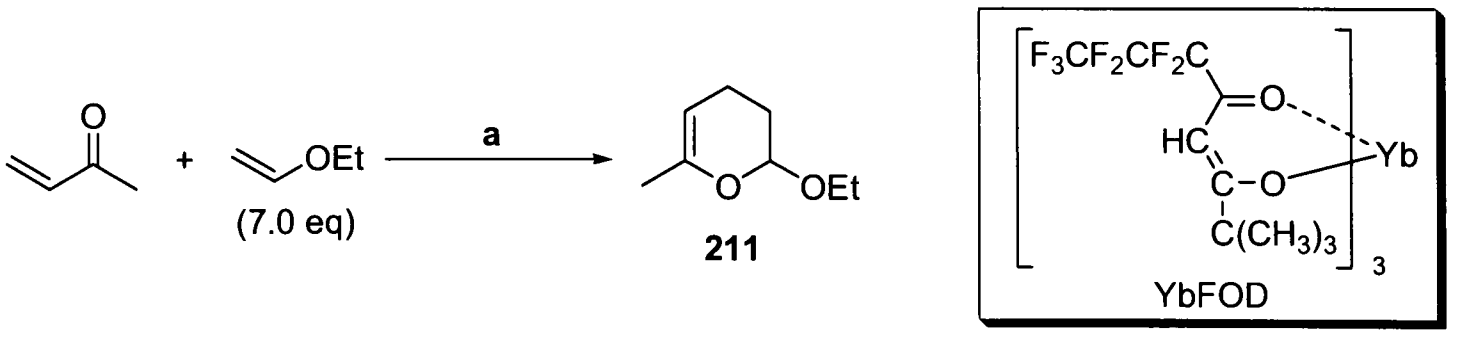
We first planned to optimise the reaction conditions for the oxidative rearrangement by screening several alternative oxidants. If we were able to optimise the conditions, we could then investigate the diastereoselectivity of the rearrangement by application of the conditions to various substituted DHPs. Furthermore, we could apply our method to natural product synthesis.

2.1. Optimisation of the oxidative rearrangement

2.1.1. Preparation of dihydropyrans by hetero Diels-Alder reaction

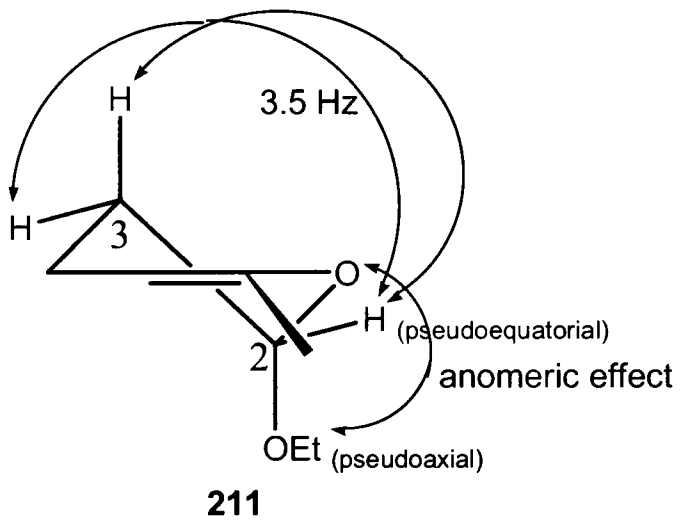
The hetero Diels-Alder (HDA) reaction of heterodienes with enol ethers using lanthanide catalysts is a short and attractive route to make dihydropyrans. Moreover, the mildness of the lanthanide catalyst is a notable feature which allows fragile but valuable functionality in both the diene and the cycloadduct to survive. In addition to this, only a few mole percent of catalyst suffices for reasonable reaction rates at room temperature. Because of these attractions, the HDA was considered as a suitable method to prepare DHPs as a starting material for the oxidative rearrangement.

Firstly, we prepared a simple DHP **211** by Danishefsky's method (Scheme 68).[89] The excess of enol ether (7.0 eq) to diene (1.0 eq) was used because the enol ether played a role as both the dieneophile and the solvent. A catalytic amount of YbFOD was sufficient to give a reasonable yield (70%). However, if the pressure tube was opened during the reaction for TLC analysis it caused a decrease of the yield from 70% to 40%.



Scheme 68. HDA reaction of heterodiene; (a) YbFOD (5 mol%), 45 °C, pressure tube, 3 d, yield 70%.

In terms of spectral data, the proton NMR spectrum for DHP **211** shows two characteristic peaks for an OC*H*O proton and an alkene C*H* proton. Each appears to be a triplet, centred at δ 4.96 ppm and δ 4.50 ppm respectively, with a vicinal coupling constant in both cases of 3.5 Hz. These two peaks were important to identify the oxidative rearrangement products in the next stage as well as other DHPs by comparing the chemical shift and multiplicities of these peaks. The ^{3}J value of 3.5 Hz between two coupled protons at C-2 and C-3 suggests a small dihedral angle and hence that the proton at C-2 is in an approximately pseudoequatorial position (Fig. 4). Thus, the ethoxy group in C-2 is in a pseudoaxial position as would be expected based on the anomeric effect.



211

Fig. 4. Suggested conformation of DHP **211**.

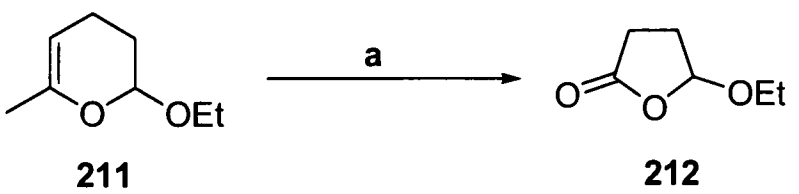
2.1.2. Choice of oxidants for epoxidation

After the preparation of simple DHP **211**, several oxidants such as MCPBA, DMDO, methyl(trifluoromethyl)dioxirane and the combination of hydrogen peroxide with MTO were tested in the desired epoxidation/rearrangement process.

2.1.2.1. MCPBA

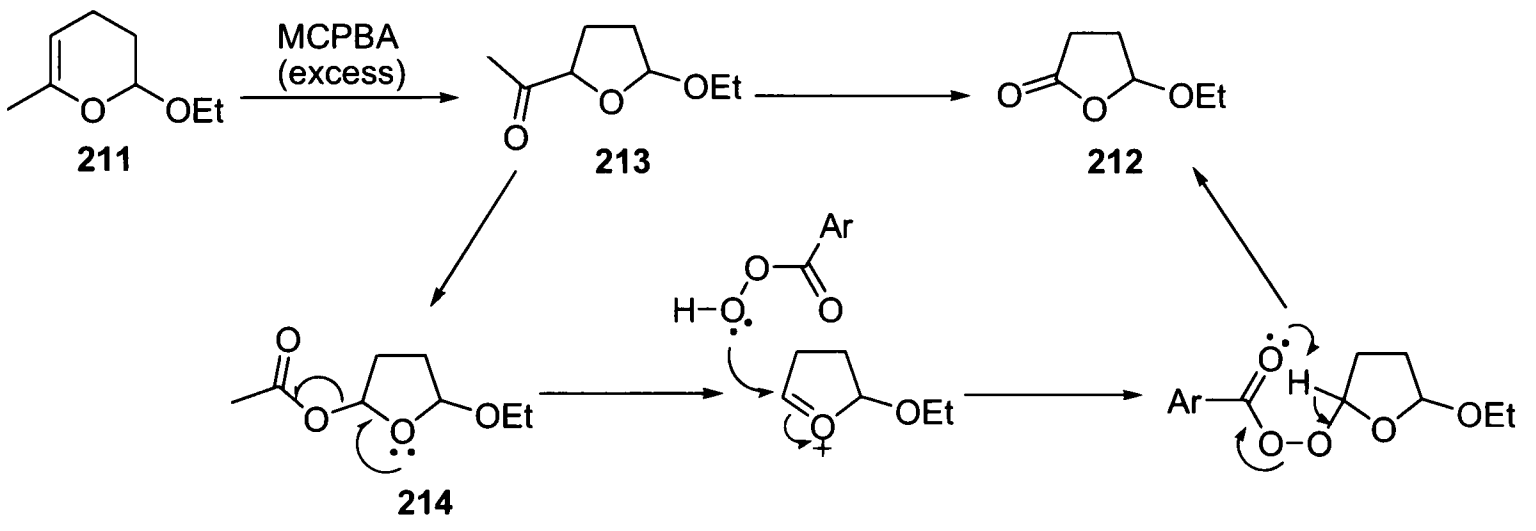
Firstly, MCPBA was adopted for the rearrangement, since it can be regarded as a "standard" reagent for alkene epoxidation.[90] Before use, commercial MCPBA (55%) was washed with phosphate buffer (pH=7.5)[91] to remove MCBA, followed by the iodometric

titration of MCPBA.[92] However, the reaction of DHP **211** with MCPBA (1.0 eq) gave the unexpected five-membered ring lactone **212** (18%) as the only isolated product, after the evaporation of solvent (Scheme 69).



Scheme 69. Oxidation of DHP by excess of MCPBA; (a) MCPBA (1.0 eq), CH_2Cl_2, 0 °C to rt, 2 h, 18%.

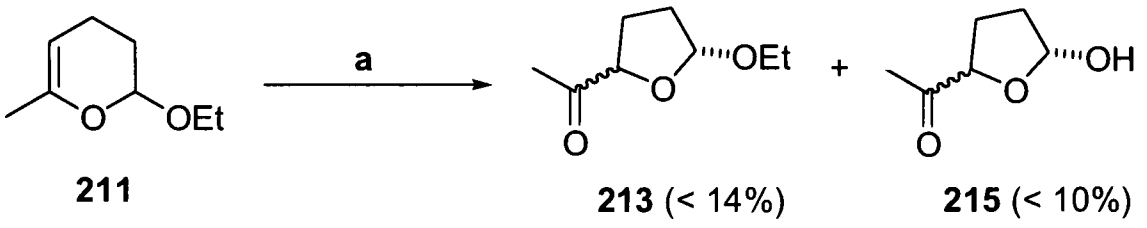
The result was proved by the spectral data; for example, only 6 peaks were observed in the ^{13}C NMR. Other experimental data such as IR spectral data[93] and ^{1}H NMR spectral data[94] also matched literature values. A possible mechanism is shown in Scheme 70. Initial formation of the desired rearrangement product **213** could be followed by Baeyer-Villiger rearrangement to give **214** and subsequent peracid-mediated oxidation to the lactone **212**. To support this proposed mechanism, we reacted the lactol ether **213**[†] with MCPBA (≤5.0 eq) for 1 d and we obtained the lactone **212** in quantitive yield.



Scheme 70. Proposed mechanism of Baeyer-Villiger rearrangement.

[†] The preparation of the lactol ether **213** (*vide infra*)

This formation of the lactone **212** may be occuring because the MCPBA had inadvertently been used in excess. Therefore, we decided to use commercial MCPBA (77%) without any prior purification and titration for this epoxidation, using 1.0 eq of MCPBA assuming that the quoted 77% purity was correct (Scheme 71). Pleasingly, TLC analysis suggested that the DHP **211** was completely consumed and NMR analysis indicated the formation of lactol ether **213** and lactol **215**. The lactol ether **213** and lactol **215** could be separated by column purification. However, the diastereoisomers of the lactol ether **213** and the lactol **215** were not separable by column purification in either case.



Scheme 71. Epoxidation of DHP by MCPBA; (a) MCPBA (≤1.0 eq), CH_2Cl_2, 45 °C, 2 h.

From the ^{1}H NMR analysis, we found that the major product was a mixture of diastereoisomeric lactol ethers **213** (2:1 ratio). The minor product was a mixture of diastereoisomeric lactols **215** (1:1 ratio), presumably formed by hydrolysis of lactol ether **213** under the acidic reaction conditions. The structures of the rearrangement products are supported by ^{1}H NMR. The peak for the olefinic proton at C-5 in DHP **211** at δ 4.50 ppm is now absent. A new dd at δ 4.45 ppm and a new triplet at δ 4.32 ppm suggest the formation of lactol ether **213**. The ^{13}C NMR spectrum strongly supported the presence of the ketone functional group because of the characteristic resonance at δ 170.3 ppm (Fig. 5). Also, the formation of lactol **215** is supported by the absence of the peaks for the ethyl group in the ^{1}H NMR spectrum.

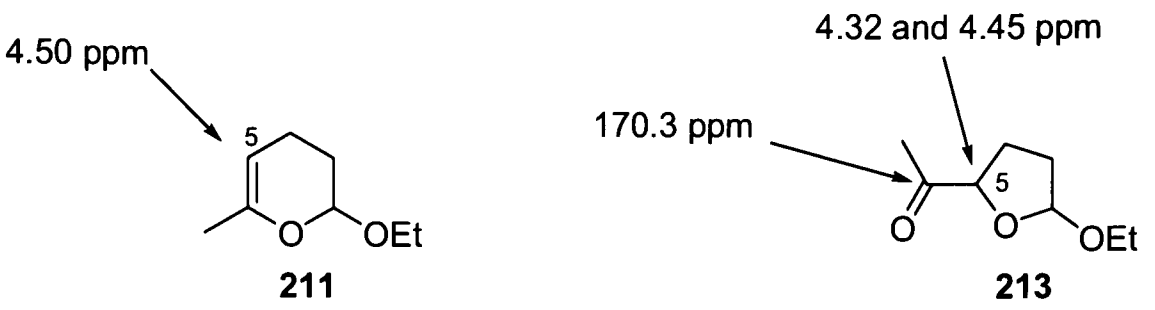


Fig. 5. Chemical shifts of DHP **211** and lactol ether **213**.

Additionally, there was ^{1}H NMR evidence that lactol **215** existed as a mixture of lactol **215** and open-chain aldehyde form **216**, with the former predominating (Fig. 6).[95] The existence of open-chain form **216** can be found in the trace of aldehyde 1H (around 9 ppm) in the ^{1}H NMR spectrum and the low integration of this aldehyde proton proves that the cyclic lactol **215** is a more stable form than open-chain **216**.

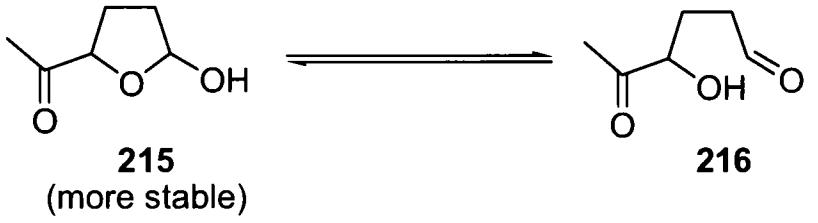
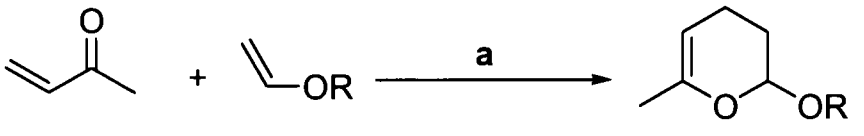


Fig. 6. Equilibrium between cyclic lactol **215** and open-chain **216**.

However, the isolated yield of the products was extremely low (14% for lactol ether **213** and 10% for lactol **215**) and we suspected that the lactol ether **213** may be volatile. We investigated this by placing the pure product **213** under high vacuum for 1 hour; the weight of product was reduced from 74 mg to 6 mg. This indicated that DHP **211** was not an ideal test substrate for the oxidative rearrangement because the rearrangement product **213** was volatile. In order to solve the volatility problem, we decided to increase the product's molecular weight by using a longer-chain ether. Thus, heavier DHPs **217** and **218** were also prepared by the same HDA procedure as before (Table 7).

Table 7. HDA reaction of heterodiene and butyl vinyl ethers; (a) YbFOD (5 mol%), pressure tube.

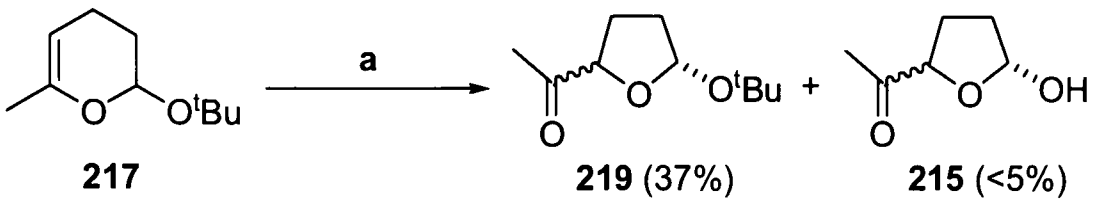


Product	R	Ratio[a]	Time	Temp.	Yield
217	^{t}Bu	1:1	5 d	70 °C	5%
		3:1	8 d	90 °C	20%
218	^{n}Bu	2:1	6 d	90 °C	55%
			6 d	110 °C	N/A

[a] The ratio of enol ether to diene.

The preparation of both DHPs **217** and **218** required more vigorous conditions (6-8 days and 90 °C) than DHP **211** (3 days and 45 °C). Unfortunately, the yield of the synthesis of DHP **217** was extremely poor (20%), in spite of the use of longer reaction time, higher temperature and a large excess of dienophile. However, DHP **218** was obtained in a reasonable yield (55%) at 90 °C while higher reaction temperature (110 °C) resulted in the decomposition of the HDA product.

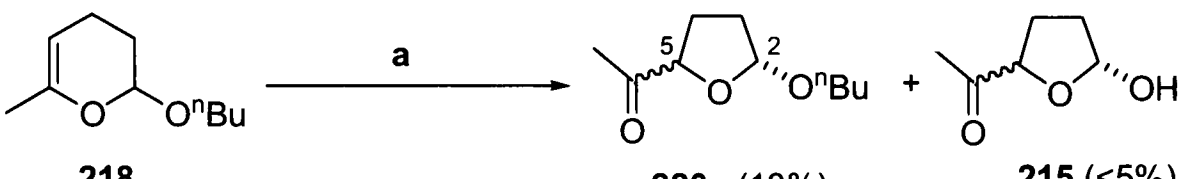
After the preparation of less volatile DHPs, they were used for the epoxidation/rearrangement process. When DHP **217** was employed, the reaction with MCPBA was completed in 4 hours by TLC analysis. The yield of the expected rearrangement product, lactol ether **219**, increased to 37% (Scheme 72). However, the yield of the lactol **215** was reduced. The lactol **215** was only detected by TLC analysis and in the ^{1}H crude NMR spectrum of the crude product. We could not isolate it by column purification. The major rearrangement product, lactol ether **219**, was obtained as inseparable mixture of diastereoisomers in a 1:1 ratio.



217 **219** (37%) **215** (<5%)

Scheme 72. Oxidative rearrangement of DHP **217**; (a) MCBPA (55%, 1.0 eq), CH_2Cl_2, 0 °C to rt, 4 h.

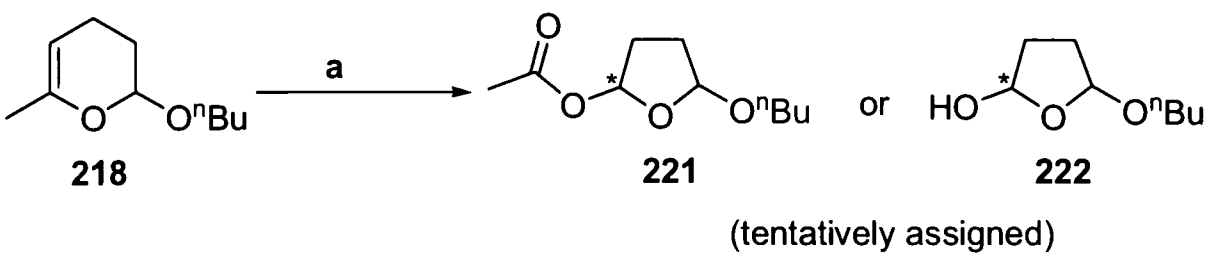
When DHP **218** was reacted with 1.0 eq of MCPBA, the reaction gave the anticipated lactol ether **220** (Scheme 73). In this case, ^{1}H NMR analysis of the crude reaction showed a 2:1 diastereomeric mixture of lactol ether **220** as the major product and a 1:1 mixture of lactol **215** as the minor product. In this case, the two pure isomers **220a** (13%) and **220b** (26%) of unassigned relative configuration could be separated by column chromatography.



218 **220a** (13%) **215** (<5%)
220b (26%)

Scheme 73. Oxidative rearrangement of DHP **218**; (a) MCBPA (55%, 1.0 eq), CH_2Cl_2, 0 °C to rt, 3 h.

In an attempt to reduce the reaction time, the number of equivalents of MCPBA was increased from 1.0 to 1.5 (Scheme 74). However, it seemed that the use of excess MCPBA caused Baeyer-Villiger rearrangement because the peaks for the proton at C-5 of the tentatively assigned products (**221** or **222**) appear as two peaks at low field (δ 5.15 and 5.47 ppm). Further isolation and characterisation were not undertaken for these compounds.

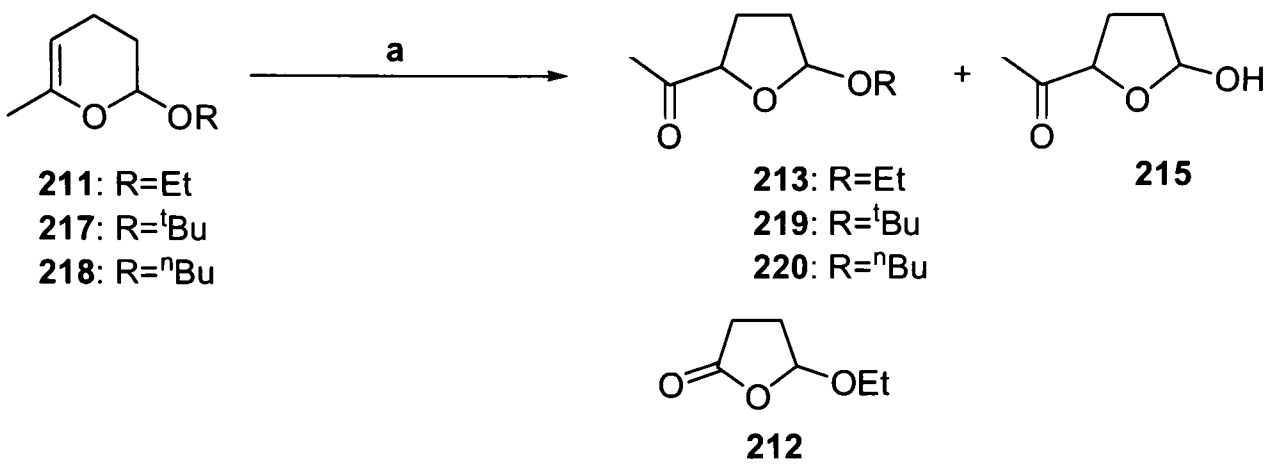


218 **221** **222**
(tentatively assigned)

Scheme 74. Baeyer-Villiger rearrangement of DHP **218**; (a) MCBPA (1.5 eq), CH_2Cl_2, 0 °C to rt, 3 h.

The results of MCPBA oxidation are summarised in Table 8.

Table 8. Results of oxidative rearrangement by MCPBA; (a) MCBPA (1.0eq), CH_2Cl_2, 0 °C to rt.



211: R=Et
217: R=^{t}Bu
218: R=^{n}Bu

213: R=Et
219: R=^{t}Bu
220: R=^{n}Bu

215

212

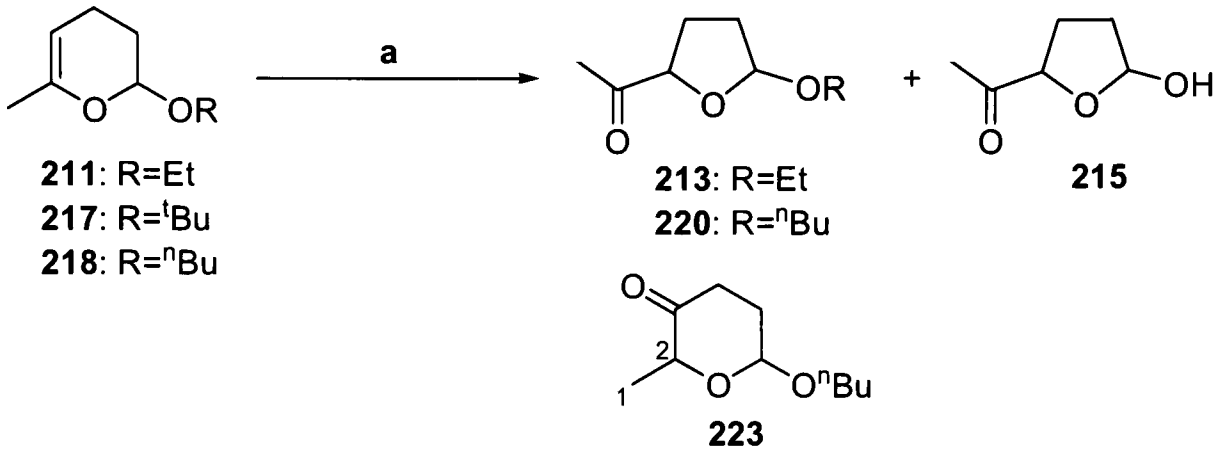
DHP	Time	Major product (yield, dr)	Minor product (yield, dr)
211	2 h	**213** (14%, 2:1 [a])	**215** (10%, 1:1 [a])
	2 h	**212**[b] (18%, N/A)	N/A
217	4 h	**219** (37%, 1:1 [a])	**215** (<5%, 1:1 [a])
218	3 h	**220** (39%, 2:1[c])	**215** (<5%, 1:1 [a])

[a] Isomers were inseparable. [b] An excess of MCPBA (> 5.0 eq) was used. [c] Isomers were separable.

2.1.2.2. DMDO

The second choice for the epoxidation was DMDO and this was prepared by distillation from a mixture of acetone and Oxone®.[96] After isolation, the solution of DMDO in acetone was titrated using acetic acid, saturated KI solution and aqueous $Na_2S_2O_3$ solution (0.002 M). The concentration of DMDO was found to be approximately 0.03 M. DHPs **211**, **217** and **218** (as previously tested with MCPBA) were used for the oxidative rearrangement by DMDO. For the reaction, 1.0 eq of DMDO was reacted with the DHPs in DCM at 0 °C, with the reaction being slowly allowed to warm to room temperature. The DHPs were consumed completely within 2-4 h according to TLC analysis. The results are summarised in Table 9.

Table 9. Results of oxidative rearrangement by DMDO; (a) DMDO (1.0 eq), CH_2Cl_2, 0 °C to rt.



211: R=Et
217: R=^{t}Bu
218: R=^{n}Bu

213: R=Et
220: R=^{n}Bu

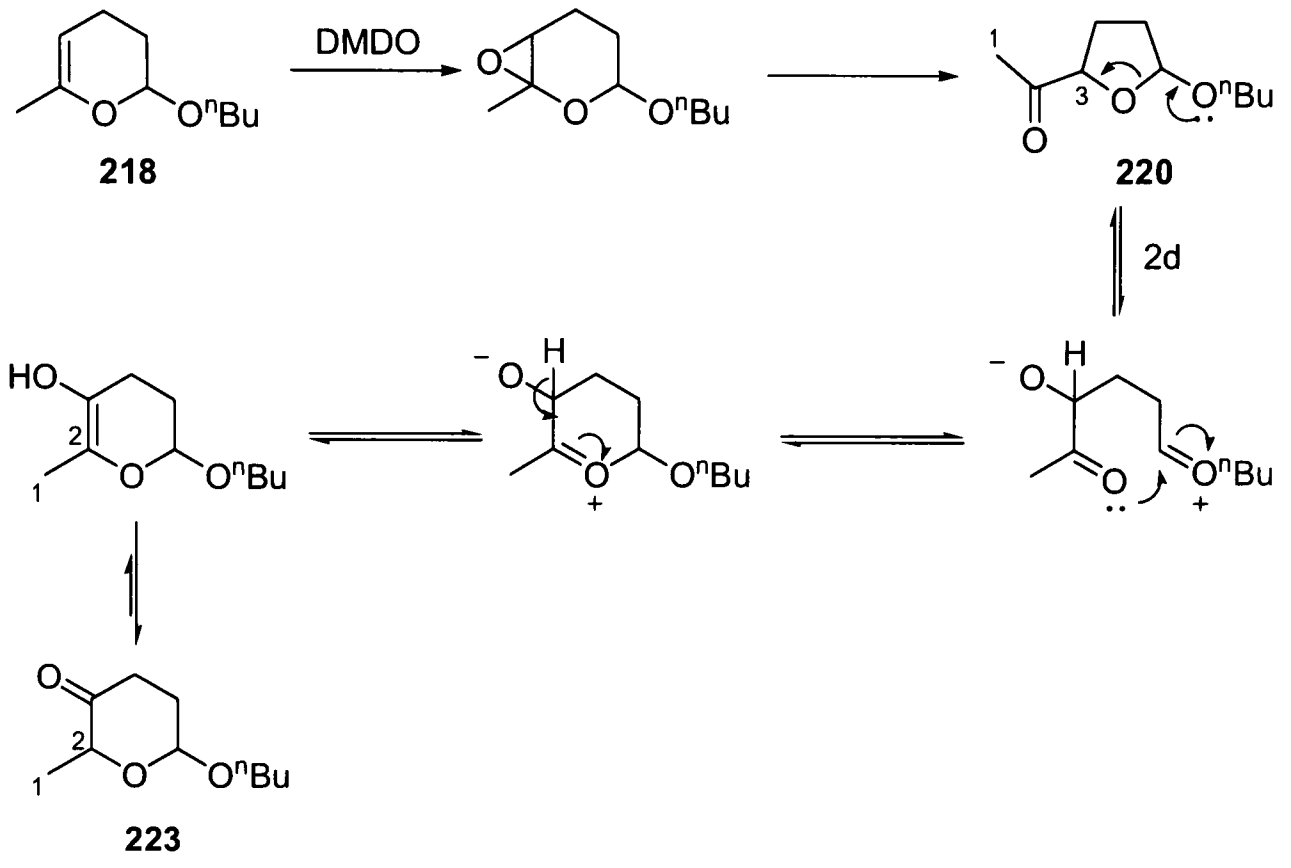
215

223

DHP	Time	Major product (yield, dr)	Minor product (yield, dr)
211	3 h	**215** (53%, 1:1[a])	**213** (N/A, 2:1 [a])
217	3 h	**215** (72%, 1:1 [a])	N/A
218	3 h	**215** (64%, 1:1 [a])	**220** (9%, 2:1 [b])
	2 d	**215** (32%, 1:1 [a])	**223** (10%, N/A)

[a] Isomers were inseparable. [b] Isomers were separable.

Interestingly, all reactions gave lactol **215** as major products, rather than the lactol ethers **213**, **219** and **220**. This result suggested the presence of water in the DMDO solution. The formation of the lactols from the lactol ethers had already been observed in the previous reaction with MCPBA. In terms of yield, the combined yield of lactols and lactol ethers (**213**+**215** = 53%, **215**+**219** = 72%, **215**+**220** = 73%) from DMDO reaction was notably higher than the combined yield (**213**+**215** = 24%, **215**+**219** <42%, **215**+**220** <44%) from MCPBA reaction. During the optimisation, we obtained an interesting product when longer reaction time (2 days) was used for the oxidation of DHP **218** with DMDO. Although the major product was the lactol **215** (32%), the minor product was dihydropyranone **223** (10%, found as one diastereoisomer) and there was no lactol ether **220** in the reaction mixture (Scheme 75).



Scheme 75. Proposed mechanism for formation of dihydropyranone **223**.

Thus, we postulated that the lactol ether **220** converted into dihydropyranones **223** upon prolonged exposure to the reaction conditions. Dihydropyranone **223** was detected by IR analysis as the value of 1715 cm^{-1} for the ketone functional group. The ^{1}H NMR also showed that a doublet at δ 1.32 ppm for the protons of the C-1 methyl group, and a quartet at δ 4.21 ppm for the proton at C-2. Regarding the relative configuration of the single diastereoisomer **223**, ^{1}H NMR suggested that **223** has ^{n}BuO in an axial orientation because the ^{3}J value of 3.0 Hz between two coupled protons in C-5 and C-6 suggests that H-6 is equatorial (Fig. 7). Although this was not proven conclusively, it is likely that the Me group will be in an equatorial position to avoid an unfavourable 1,3-diaxial interaction with the alkoxy substituent; hence the *trans*-diastereomer is preferred.

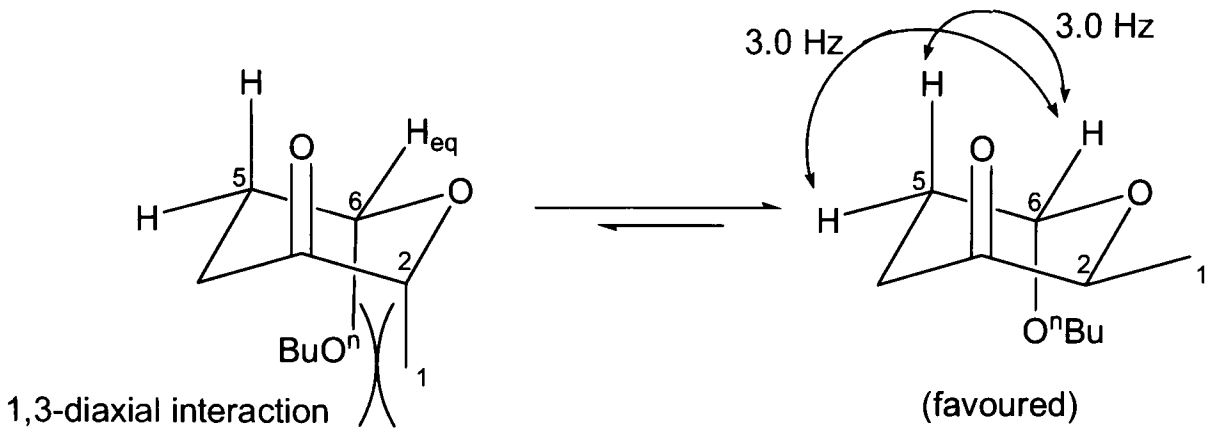
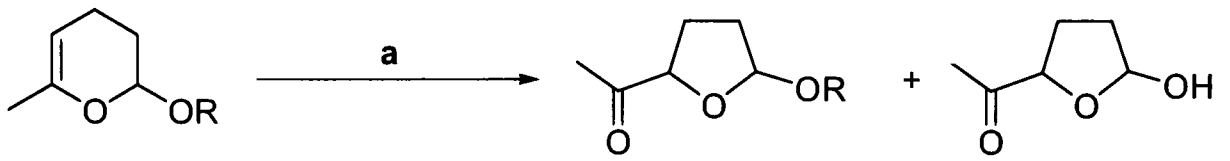


Fig. 7. Expected configuration of dihydropyranone **223**.

2.1.2.3. DMDO generated *in situ*

Acetone solutions of DMDO are useful and powerful oxidants. However, their use suffers from disadvantages such as low concentration of oxidant and inefficient preparation. Thus, the use of DMDO generated *in situ* was potentially an attractive alternative. Therefore we tried the oxidative rearrangement of DHPs **211**, **217** and **218** with DMDO generated from the mixture of Oxone® and $NaHCO_3$ *in situ* at pH 7.5, based on a literature procedure.[97] The oxidative rearrangement by this method gave lactol ethers **213** and **220** as major products and lactol **215** as a minor product (Table 10). Strangely, the oxidation of substrate **217** did not give lactol ethers **219** or lactol **215**, showing the formation of a number of minor products by TLC analysis. The combined yield (13%) of lactol ethers **213** and lactols **215** was considerably lower than the yield of the reaction using isolated DMDO (53%). The low yield of reaction is due partly to the volatility of lactol ether **213**. The combined yield (76%) of lactol ether **220** and lactol **215** were slightly higher than the yield of DMDO reaction (73%). However, this method required a much longer reaction time than other methods. The results of the rearrangement using DMDO generated *in situ* are summarised in Table 10.

Table 10. Results of oxidative rearrangement by DMDO generated *in situ*; (a) Oxone®/acetone, $NaHCO_3$, Na_2EDTA (pH=7.5), CH_2Cl_2, 0 °C to rt, 1 d.



211: R=Et
217: R=^{t}Bu
218: R=^{n}Bu

213: R=Et
220: R=^{n}Bu

215

DHP	Major product (yield, d.r.)	Minor product (yield, d.r.)
211	**213** (13%, 2:1 [a])	**215** (N/A, 1:1 [a])
217	N/A	
218	**220** (46%, 2:1 [b])	**215** (30 %, 1:1 [a])

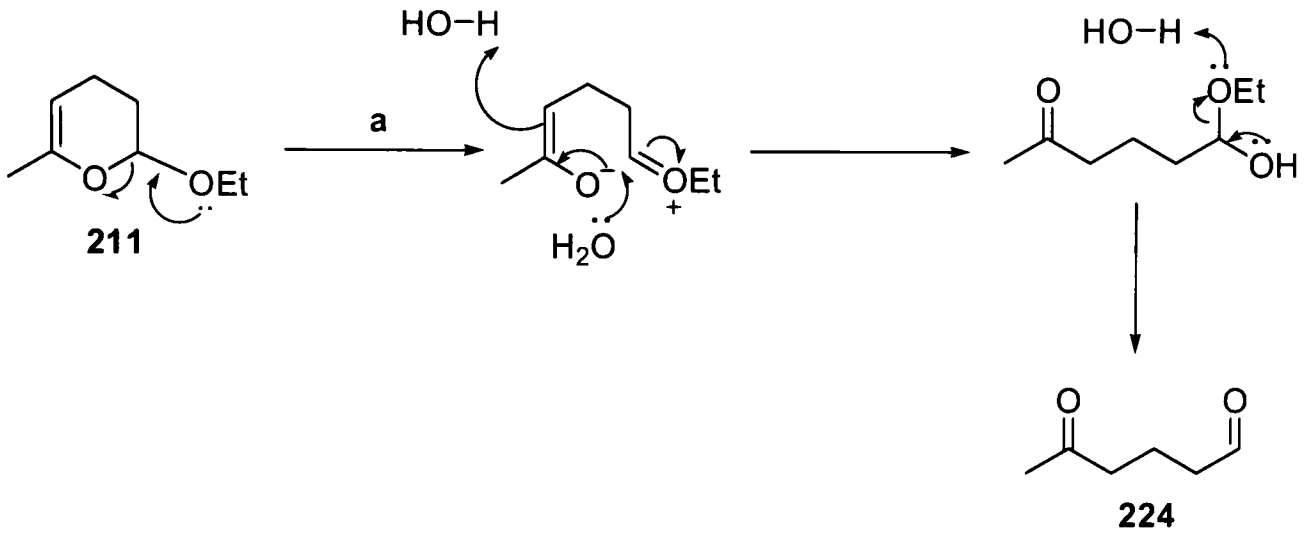
[a] Isomers were inseparable. [b] Isomers were separable.

2.1.2.4. Methyl(trifluoromethyl)dioxirane generated *in situ*

This method was developed by Yang to overcome the low epoxidation rate of dioxiranes generated *in situ* since methyl(trifluoromethyl)dioxirane formed from trifluoroacetone and Oxone® is highly reactive.[98] Thus, we attempted this method with DHP **218** and the substrate was consumed extremely quickly (<30 min). However, TLC analysis showed the formation of a number of impurities and only small amounts of the desired product **220**. Therefore this chemistry was not investigated further.

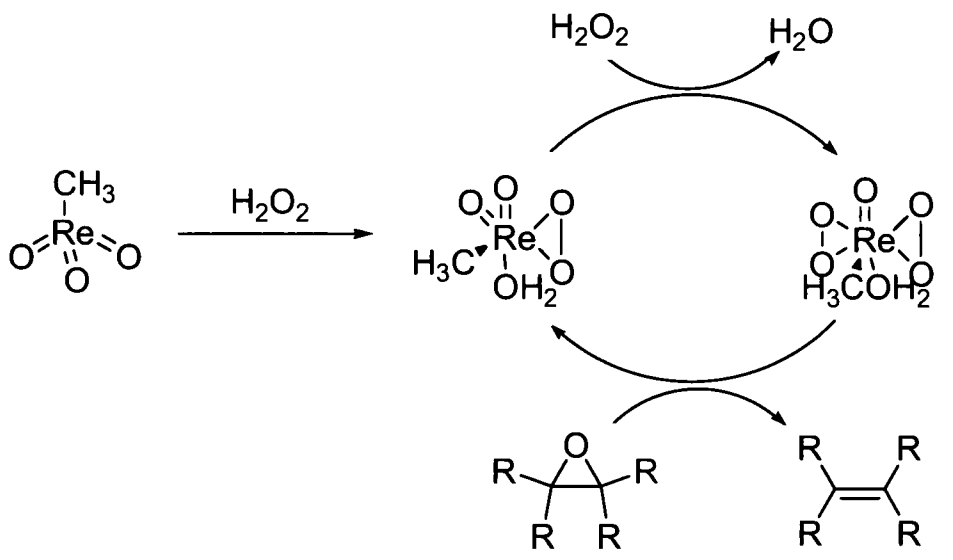
2.1.2.5. Hydrogen peroxide with MTO

Initially, we tried the oxidative rearrangement of DHP **211** with only hydrogen peroxide (aq, 27% w/w). However, this resulted in formation of ketoaldehyde **224** in 20% yield. This is effectively the product of hydrolysis of **211**; a likely mechanism is shown in Scheme 76.



Scheme 76. Proposed mechanism for formation of ketoaldehyde **224**; (a) H_2O_2 (27% w/w, 1.0 eq), CH_3CN, 15 h, 20%.

However, no oxidation/rearrangement product was observed. Thus, we explored the methyltrioxorhenium(VII)-catalysed epoxidation with hydrogen peroxide.[99] A generally accepted catalytic cycle for the epoxidation using hydrogen peroxide with MTO is described in Scheme 77.[99a]



Scheme 77. Epoxidation of olefin by combination of hydrogen peroxide and MTO.

We also used pyridine as additive, which is known to effect ligand acceleration.[99b] When DHP **211** was exposed to these conditions overnight, the reaction did not give the desired

rearrangement product. The ^{1}H NMR spectrum of the crude mixture suggested the product could be an epoxide **225**, not the rearrangement product, due to the presence of a triplet at δ 4.34 ppm with a *J* value of 3.0 Hz which could conceivably correspond to the epoxide proton (indicated by * in Fig. 8). It is possible that pyridine (which was still present by ^{1}H NMR) prevented acid-mediated decomposition of the epoxide.

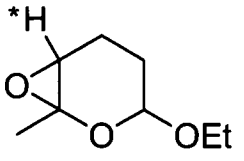


Fig. 8. Tentatively assigned epoxide **225**.

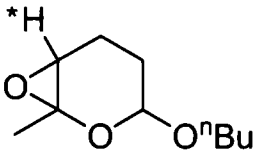
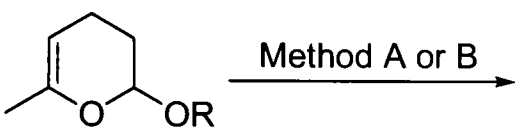


Fig. 9. Tentatively assigned epoxide **226**.

Additionally, TLC analysis showed this tentatively assigned epoxide was less polar than the rearrangement products **213** and **215**. To investigate the conversion of this putative epoxide to the rearrangement product, we added a trace of CSA to the NMR tube and also tried to heat the epoxide to effect the desired reaction. However, in neither case could we see the formation of rearrangement product by ^{1}H NMR. The oxidation of DHP **218** under MTO/H_2O_2 conditions also gave the tentatively assigned epoxide **226**. The epoxide proton (indicated by * in Fig. 9) for the peak of epoxide proton appears as a triplet at δ 4.46 ppm with a *J* value of 3.0 Hz. Interestingly, the reaction of DHP **218** gave a trace of rearrangement product, lactol ether **220**, as a minor product after column chromatography. However, we could not effect transformation of the tentatively assigned epoxides **225** and **226** to the desired rearrangement products. Therefore, this chemistry was not investigated further. The results of MTO oxidation with hydrogen peroxide are summarised in Table 11.

Table 11. Results of oxidative rearrangement by H_2O_2 and MTO; (a) Method A: H_2O_2 (1.0 eq, 27% w/w), CH_3CN, rt, 1 d, (b) Method B: MTO (0.5 mol%), pyridine (12 mol%), H_2O_2 (1.5 eq, 27% w/w), CH_2Cl_2, rt, 1 d.

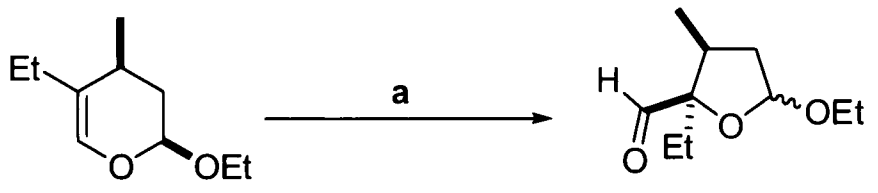


211: R=Et
218: R=^{n}Bu

DHP	Method	Product (yield)
211	A	**224** (20%)
211	B	Tentatively assigned epoxide **225** (>95%[a])
218	B	Tentatively assigned epoxide **226** (major, >95%) **220** (minor, N/A)

[a] Crude yield.

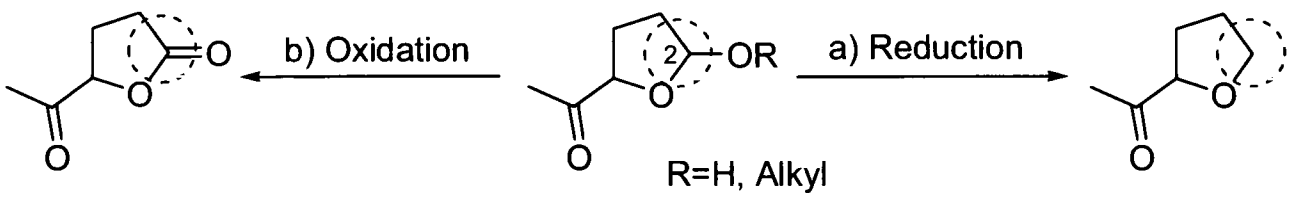
Later work by a co-worker showed that the combination of urea hydrogenperoxide (UHP), imidazole and MTO could give the rearrangement product **228** (Scheme 78).[100]



Scheme 78. Oxidative rearrangement using MTO and UHP; (a) MTO (4 mol%), UHP (3.0 eq), ImH (0.5 eq), CH_2Cl_2, then acid, 55%

2.1.3. Product manipulation to simplify stereochemical analysis

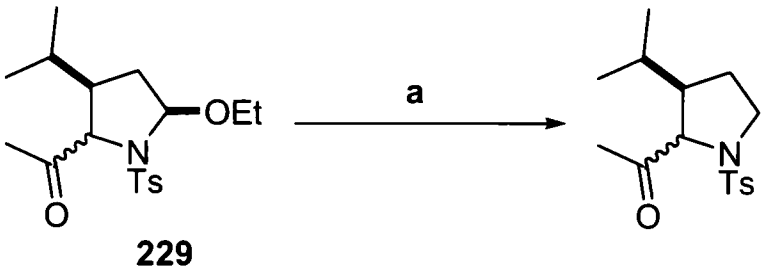
Based on the results so far, we decided to use DMDO as the reagent of choice for the oxidative rearrangement. The rearrangement by DMDO generally gave a mixture of lactol and lactol ether as products, with the former predominating. Because the purpose of this project was the investigation of stereocontrolled formation of 4,5-disubstituted THFs, we needed to simplify the product mixture by converging the lactol and lactol ether to a common product, and removing the lactol/lactol ether stereocentre. We considered two approaches; reduction and oxidation (Scheme 79).



Scheme 79. Two ideas to remove stereocentre.

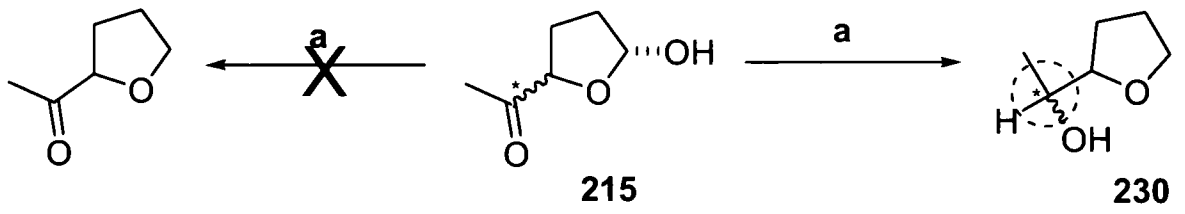
2.1.3.1. Acetal reduction

In the related aminative rearrangement work, we had shown that it was possible to selectively reduce the hemiacetal **229** in in the presence of the ketone with Et_3SiH and $BF_3{\cdot}Et_2O$ (Scheme 80).[87]



Scheme 80. Reduction of alkoxy pyrrolidine; (a) Et_3SiH (3.0 eq), $BF_3{\cdot}Et_2O$ (2.0 eq), -78 to 0 °C, 2 h, >90%.

Therefore we initially attempted the reduction of lactol **215** under these conditions. If it were successful, the other rearrangement product (lactol ether) could potentially be hydrolyzed to the lactol and reduced in the same way, or reduced directly under the same conditions. However, the reduction of lactol **215** with Et_3SiH and $BF_3{\cdot}Et_2O$ did not give the expected result: unwanted additional reduction of the ketone functional group was observed, with consequent formation of a further stereocentre in the product **230** (Scheme 81).



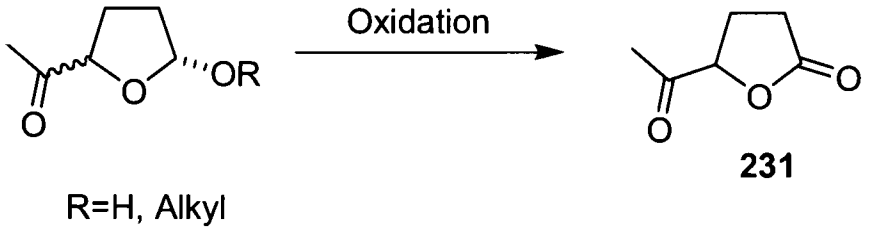
Scheme 81. Attempted reduction of lactol **215**; (a) Et_3SiH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, -78 °C to rt, 4 h.

Evidence for this came from the ^1H NMR spectrum, notably the disappearance of the singlet for the methyl group next to the ketone and the appearance of a new Me-doublet. Additionally, the IR spectrum showed disappearance of the C=O stretch at 1716 cm^{-1} and a new O-H stretch at 2936 cm^{-1}. This data confirmed the reduction of the ketone to the

secondary alcohol. In view of this result, we turned our attention to oxidation of the lactol as an alternative.

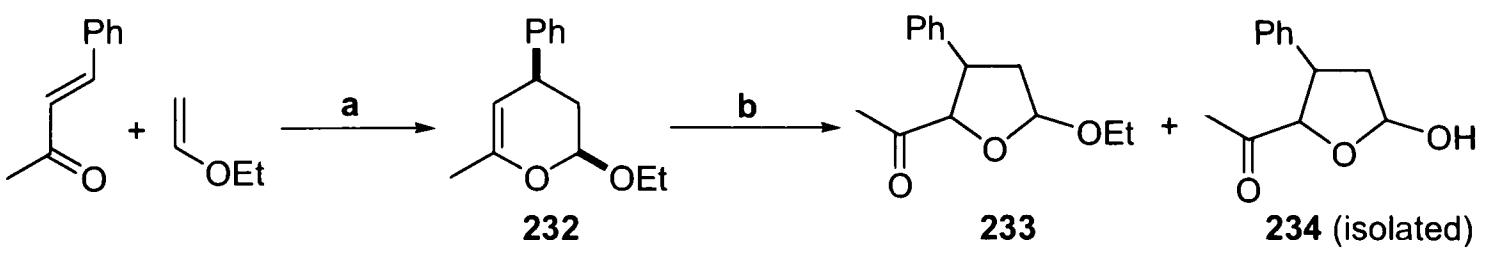
2.1.3.2. Acetal oxidation

It was aimed to effect oxidation of the mixture of lactols and lactol ethers to a single lactone product **231** (Scheme 82).



Scheme 82. Idea to remove stereocentre by oxidation.

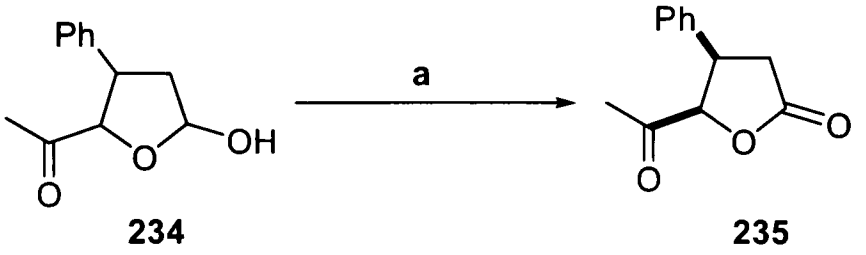
Firstly, Dess Martin oxidation conditions[101] were tested for oxidation of lactol **215**. However, TLC analysis suggested formation of a complex product mixture. Next, we investigated the use of PCC. Additionally, we adopted a phenyl substituted lactol in order to facilitate TLC analysis under UV. To prepare phenyl substituted lactol **234**, we prepared DHP **232** by HDA reaction in 50% yield and DHP **232** was transformed by oxidative rearrangement with DMDO (Scheme 83). In this case only the major product lactol **234** was isolated, in 80% yield.



Scheme 83. The preparation of lactol ether **233** and lactol **234**; (a) YbFOD (5 mol%), pressure tube, 65 °C, 5 d, 50%, (b) DMDO (1.0 eq), CH_2Cl_2, 0 °C to rt, 80% (yield of **234**).

The oxidation of phenyl substituted lactol **234** with PCC[102] showed an excellent

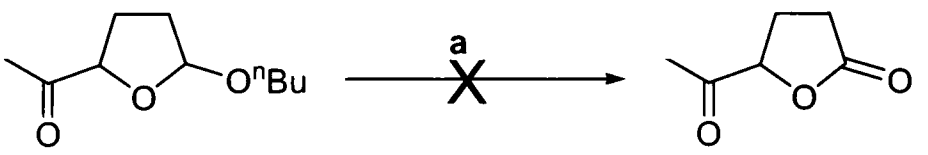
conversion to the corresponding lactone **235** as a single diastereoisomer in 88% yield (Scheme 84).



234 **235**

Scheme 84. Oxidation of lactol **234** to lactone **235**; (a) PCC (3.0 eq), CH_2Cl_2, rt, overnight, 88%.

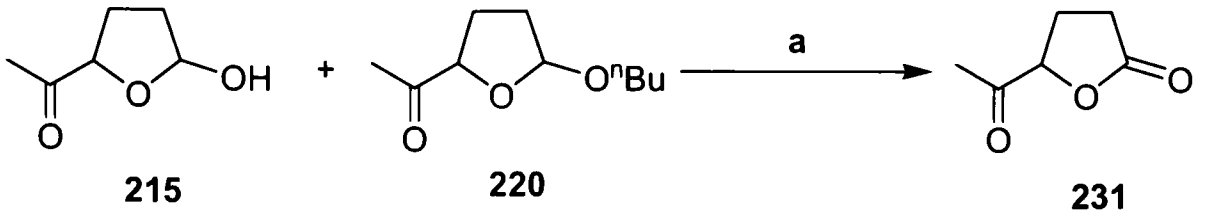
Ideally we required an oxidant that could effect oxidation of both lactols and lactol ethers to lactones. After the successful oxidation of the lactol **234**, we considered the oxidation of lactol ethers **233** under these conditions. The lactol ether **220** was employed alternatively, because the lactol ether **233** was isolated in very low yield (<5%). However, the same PCC oxidation could not oxidise lactol ether **220** to the corresponding lactone (Scheme 85).



220 **231**

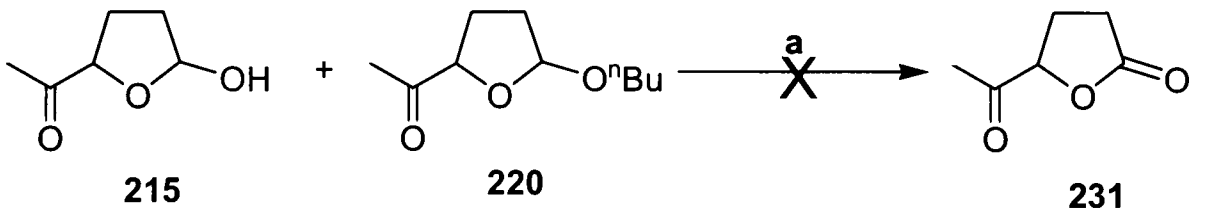
Scheme 85. Attempted oxidation of lactol ether **220**; (a) PCC (3.0 eq), CH_2Cl_2, rt, overnight.

In order to oxidise lactol and lactol ether at the same time, we needed a different oxidant. We decided to use another chromium based oxidant, Jones oxidant,[103] because literature precedent showed the Jones oxidation of both lactols[104] and lactol ethers[105] gave the corresponding lactones. So, we tried to oxidize simultaneously the mixture of lactol **215** and lactol ether **220** (7:1) under Jones oxidation conditions. Pleasingly, it gave the corresponding lactone **231** as sole product in 60% yield (Scheme 86).



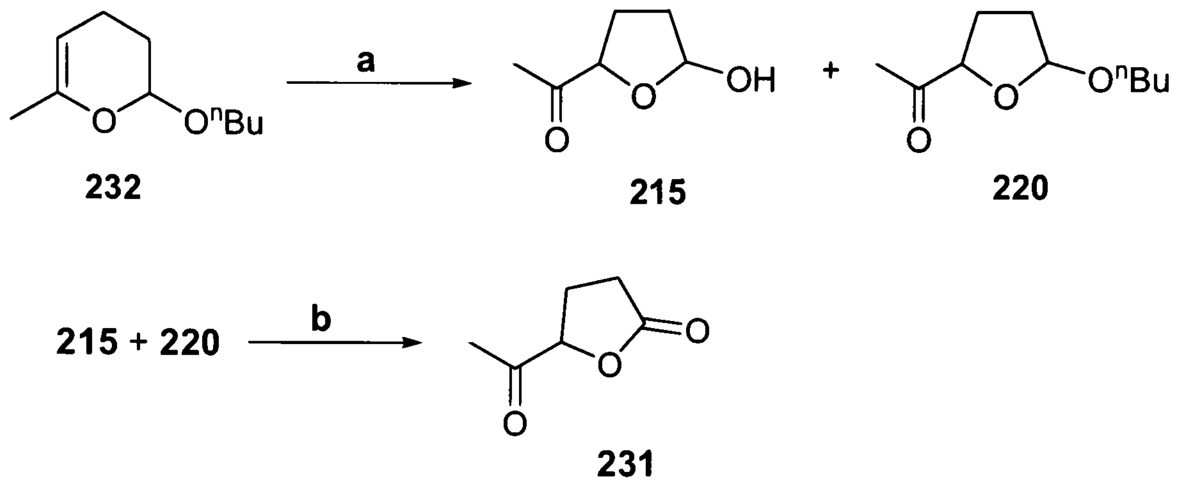
Scheme 86. Convergence of rearrangement products; (a) Jones reagent (3.0 eq), acetone, 0 °C to rt, 60%.

In spite of the successful Jones oxidation, we needed to consider other cleaner oxidants because the Jones reagent is based on toxic chromium. From a literature search, we were able to find an oxidation method for conversion of lactol ethers into lactones using hydrogen peroxide with aqueous HCl as catalyst.[106] We assumed that this reaction may proceed *via* initial hydrolysis to the lactol, and so would also be applicable to oxidation of the lactol/lactol ether mixture. The mixture of lactol **215** and lactol ether **220** was therefore tested under with these conditions (Scheme 87). However, TLC analysis suggested formation of a complex product mixture.



Scheme 87. Attempted convergence of rearrangement products by H_2O_2 and HCl; (a) H_2O_2, HCl, rt, overnight.

Because only Jones oxidation had so far given the desired result, we decided to utilise it in further studies. Furthermore, we wanted to combine our oxidative rearrangement and Jones oxidation. For this, DHP **218** was selected as a model. After the rearrangement of DHP **218** to lactol ether **220** and lactol **215**, the crude product mixture was simultaneously oxidized by the Jones reagent to give lactone **231** in 69% yield over 2 steps (Scheme 88).



Scheme 88. Model study to generalise the oxidative rearrangement; (a) DMDO (1.0 eq), CH_2Cl_2, 0 °C to rt, 73%, (b) Jones reagent (3.0 eq), acetone, 0 °C to rt, 94%.

After this successful model study we decided to apply our method to various substrates and to investigate the stereoselectivity of the oxidative rearrangement.

2.2. Application of oxidative rearrangement to dihydropyrans

2.2.1. Preparation of dihydropyrans

To apply our oxidative rearrangement to various DHPs and to investigate the stereochemistry of the resulting products, various DHPs were synthesised using the HDA reaction (Fig. 10).

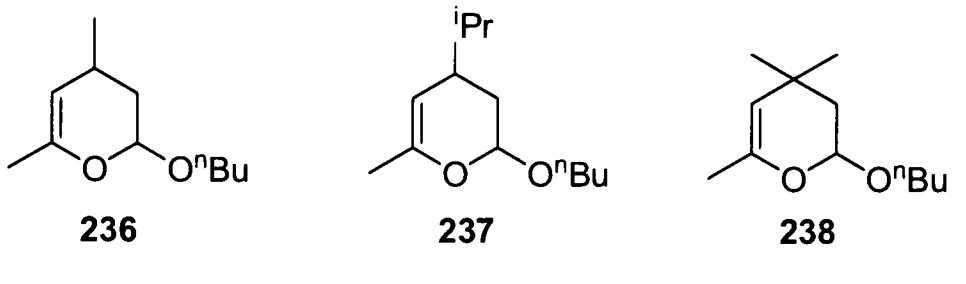
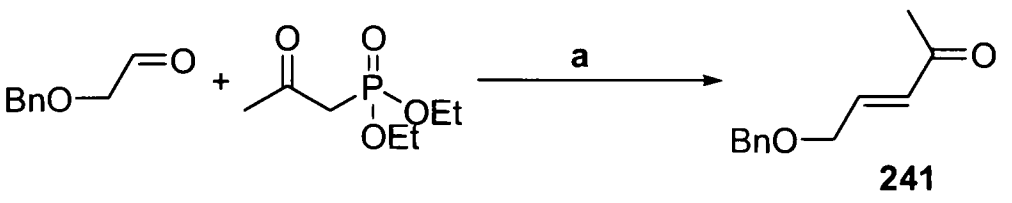


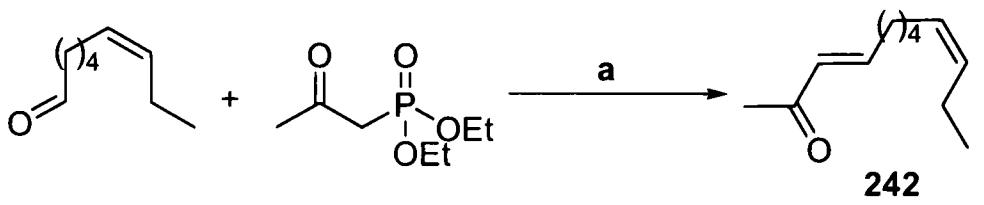
Fig 10. Various DHP substrates.

Although most of the substrate enones were commercially available, *(E)-5-benzyloxy-pent-3-en-2-one* **241** and *(3E, 9Z)-dodecadien-2-one* **242** were not. We prepared these enones by Horner-Wadsworth-Emmons reaction of diethyl(2-oxopropyl) phosphonate and the appropriate aldehydes. The olefination of benzyloxyacetaldehyde gave selectively *(E)-5-benzyloxy-pent-3-en-2-one* **241** in reasonable yield (Scheme 89).



Scheme 89. Horner-Wadsworth-Emmons reaction of benzyloxyacetaldehyde; (a) LiCl (1.2 eq), DBU (1.0 eq), CH_3CN/THF (1:1), rt, overnight, 59%.

The olefination of *cis*-6-nonenal also gave only (*E*)–isomer, *(3E, 9Z)-dodecadien-2-one* **242** (Scheme 90).



Scheme 90. Horner-Wadsworth-Emmons reaction of *cis*-6-nonenal; (a) LiCl (1.2 eq), DBU (1.0 eq), CH_3CN/THF(1:1), rt, overnight, 66%.

After we prepared the enones, the DHPs (**232** and **236-240**) were simply obtained in a reasonable yield (40-75%) from thermal HDA reaction (in a pressure tube) of the appropriate dienes and vinyl ethers in the presence of the Lewis acid catalyst YbFOD (Table 12)

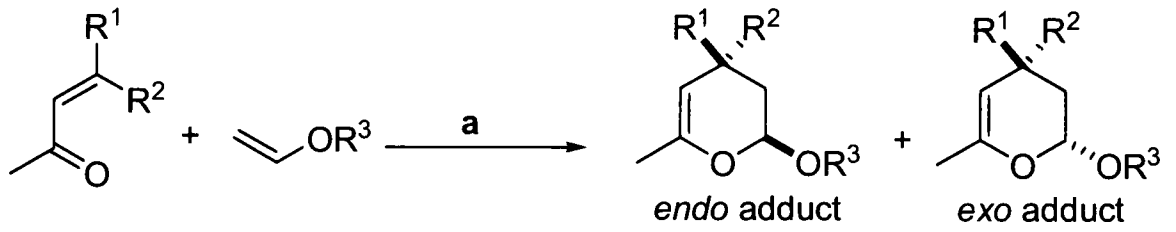


Table 12. Preparation of various DHP by HDA reaction; (a) YbFOD (5 mol%), pressure tube, 3 d.

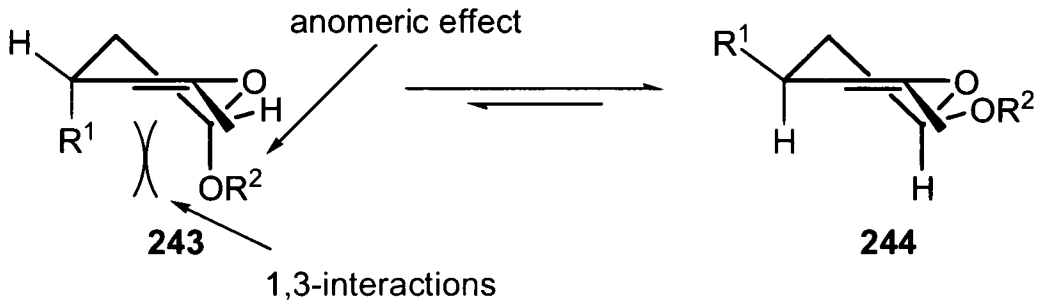
R^1	R^2	R^3	Ratio[a]	Time	Temp.	Product (yield[b])	dr[c]
Me	H	^{n}Bu	1:2	10 d	50 °C	**236** (40%)	6:1
^{i}Pr	H	^{n}Bu	1:2	3 d	55 °C	**237** (75%)	6:1
Me	Me	^{n}Bu	1:5	5 d	100 °C	**238** (54%)	N/A
Ph	H	Et	1:5	5 d	65 °C	**232** (50%)	-[d]
CH_2OBn	H	Et	1:10	1 d	55 °C	**239** (67%)	-[d]
$(CH_2)_4CH{=}CHEt$	H	Et	1:10	5 d	55 °C	**240** (56%)	4:1

[a] The ratio of heterodiene to enol ether. [b] Combined yield of two diastereoisomers. [c] The ratio of *endo* to *exo* determined by ^{1}H NMR. [d] *Endo* product only .

^{1}H NMR analysis showed that the HDA reactions generally afforded a mixture of two diastereoisomers with one predominant (>4:1). Since it is known that these reactions are generally *endo* selective,[85, 89] the major isomers were assigned as the 2,4-*cis* isomers.

The conformations of these 4-substituted-2-alkoxydihydropyrans are of interest. The dihydropyrans exist as rapidly inverting half-chair forms and the conformational equilibrium seems to be governed by two factors[107]: (a) the anomeric effect which forces the C-2 alkoxy group into the axial position, (b) the conformational free enthalpy of the C-4 substituent which prefers the pseudoequatorial position to minimise 1,3-interactions (particularly when bulkier groups are involved). In order to identify the conformations adopted, we investigated the coupling constants in the ^{1}H NMR spectra. Particularly, the interactions between C-2 proton and C-3 protons were studied. The conformation of the major *endo* products and the corresponding coupling constants are shown in Table 13.

Table 13. Conformation of major *endo* isomers and coupling constants.



DHPs	R^1	R^2	$J_{C2\text{-}C3}{}^a$ (Hz)	$J_{C2\text{-}C3}{}^b$ (Hz)
236	Me	^{n}Bu	7.0	3.0
237	^{i}Pr	^{n}Bu	9.5	2.0
232	Ph	Et	9.0	2.0
239	CH_2OBn	Et	7.5	1.0
240	$(CH_2)_4CH{=}CHEt$	Et	9.0	2.0

[a] di-axial coupling constants, [b] axial/equatorial coupling constants.

The C-2 protons of the DHPs appear around 4.82-5.01 ppm as a doublet of doublets with two coupling constants: (a) 7.0-9.5 Hz for the di-axial coupling between the H_{axial} at C-2

and the H_{axial} at C-3, (b) 1.0-3.0 Hz for the axial/equatorial coupling between the H_{axial} at C-2 and the $H_{equatorial}$ at C-3. This suggests that the substituent at C-2 is located in a pseudoequatorial position. If the major *endo* products have a 2,4-*cis* relationship as reported in the literature, the substituent at C-4 is also located in a pseudoequatorial position and the conformational equilibrium between conformer **243** and conformer **244** favours conformer **244**. This suggests that the conformational equilibrium for the *endo* product is mainly governed by the 1,3-interactions. However, these di-axial coupling constants are not as large as could be expected because a small portion of conformer **243** still exists in this equilibrium, and because of the presence of sp^2-centres in the ring.

The conformation of the minor *exo* compounds for the DHPs (**236**, **237** and **240**) was also investigated. The C-2 protons of these DHPs appear around 4.99-5.01 ppm as a triplet with a small coupling constant (2.5-3.0 Hz), signifying that the C-2 proton occupies an pseudoequatorial position. Since the minor *exo* products are believed to have the 2,4-*trans* relationship, the proton at C-4 would then be located in an axial position and the conformer **246** is favoured in the conformational equilibrium (Fig. 11).

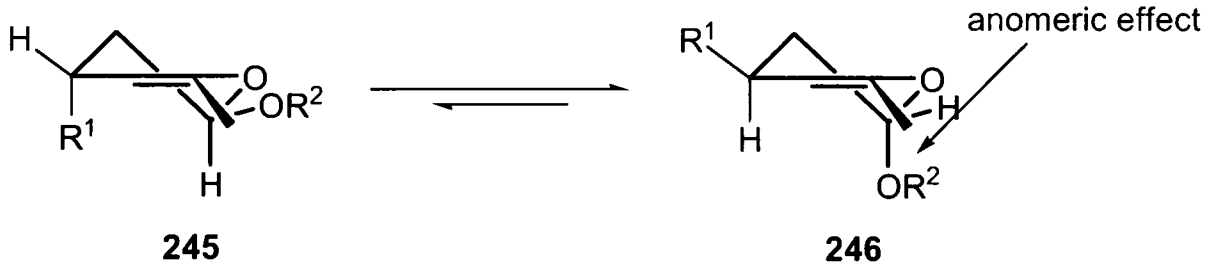
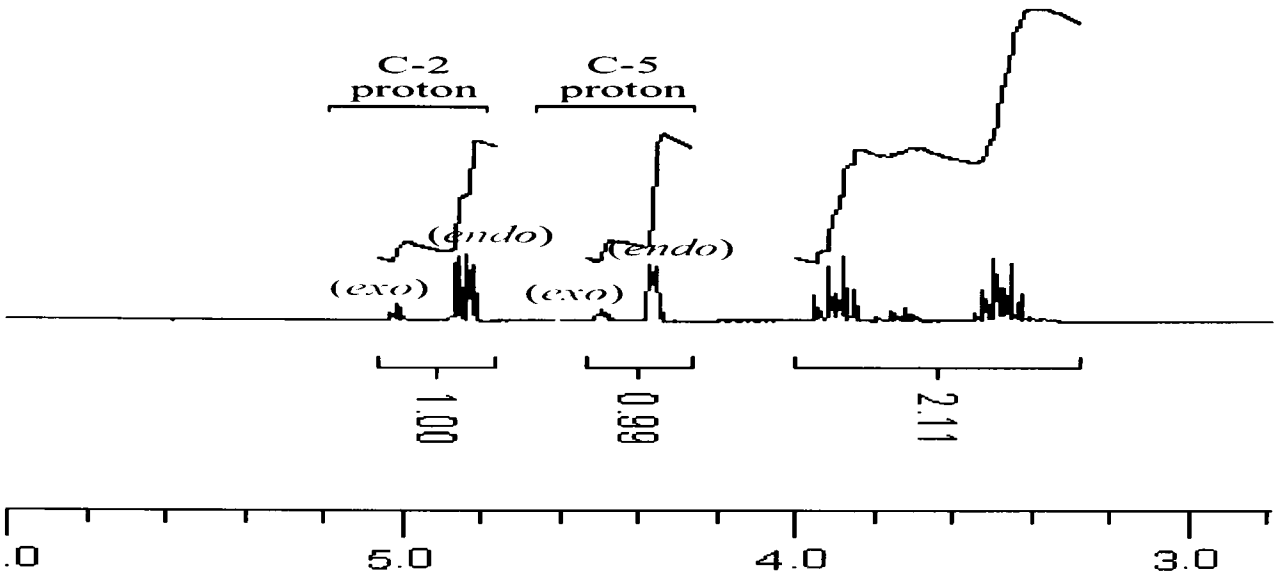


Fig. 11. Conformation of minor *exo* isomers.

Interestingly, ^{1}H NMR analysis showed that the *endo* product **236a** was epimerised to *exo* product **236b** (6:1 to 1:3, Fig. 12), when the diastereomeric mixture was kept in $CDCl_3$ at room temperature for 1 d.

a) ^{1}H NMR spectrum of DHP **236**.



b) ^{1}H NMR spectrum of DHP **236** after 1 d.

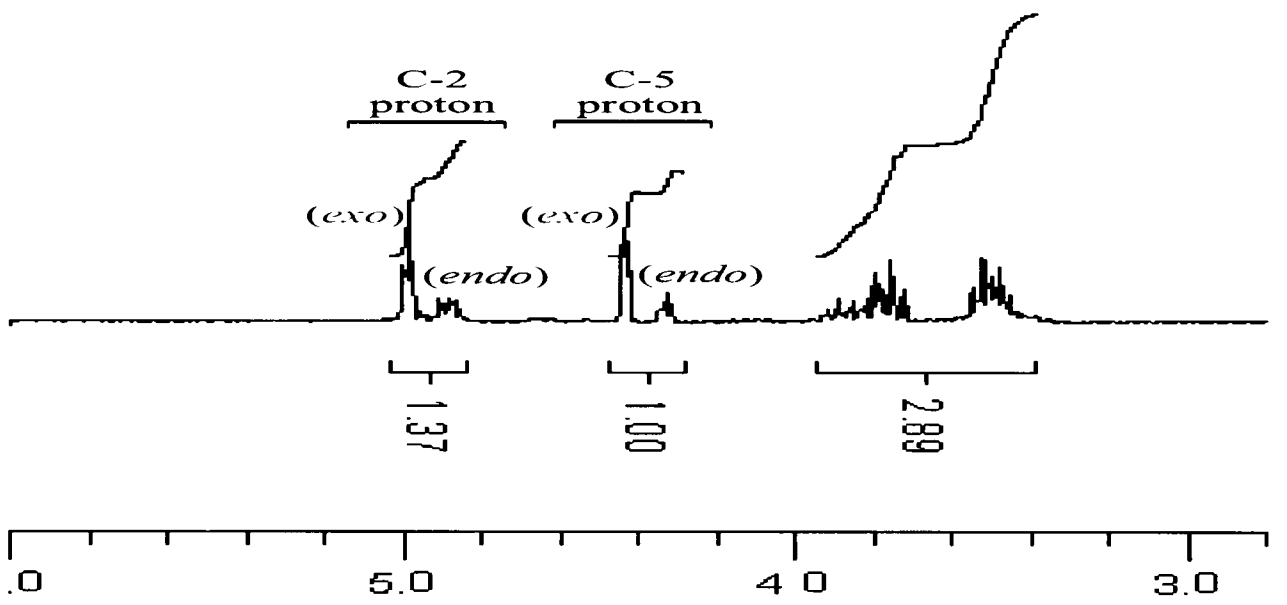
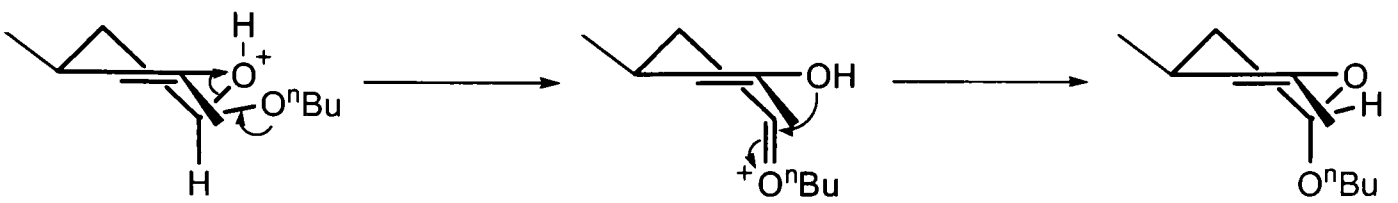


Fig. 12. Epimerisation of DHP **236**.

This epimerisation from **236a** to **236b** can be explained by the formation of acyclic oxonium species **247** and the subsequent ring closure (Scheme 91). This observation suggests that the DHP **236b** is the thermodynamic isomer with a pseudoaxial substituent at C-2 preserved by the anomeric effect as well as the C4-substituent being in the preferred pseudoequatorial orientation.



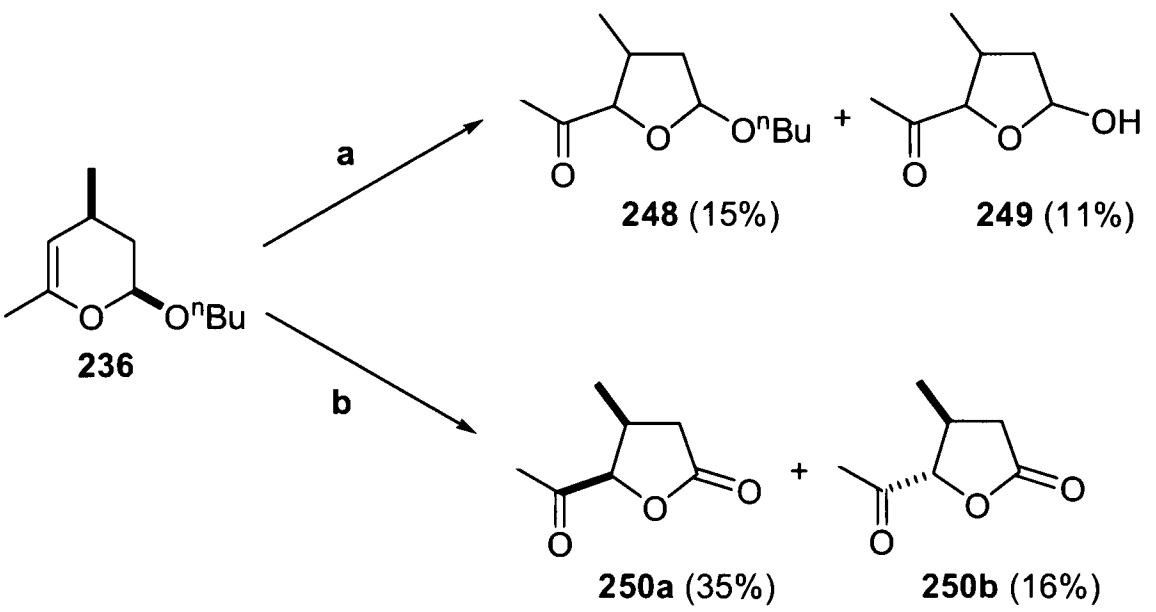
236a **247** **236b**

Scheme 91. Epimerization of *endo* DHP **236a** to *exo* DHP **236b**.

2.2.2. Diastereoselective formation of 2,3-*cis*-tetrahydrofurans

After having prepared various DHPs (**232** and **236-240**), we applied our DMDO oxidative rearrangement/Jones oxidation sequence. Because the initial oxidative rearrangement by DMDO could potentially give a mixture of eight products (four diastereoisomeric lactols and four diastereomeric lactol ethers), we generally effected Jones oxidation of the crude product from the DMDO step without attempting to separate the intermediates.

DHP **236** was examined first. Oxidative rearrangement with DMDO followed by direct Jones oxidation of the crude product mixture (Scheme 92) gave a 3:1 mixture of diastereoisomeric lactones according to ^{1}H NMR analysis. Column chromatography allowed separation of lactone **250a** (35% over the two steps from DHP **236**) and **250b** (16%).



Scheme 92. Oxidative rearrangement of DHP **236**; (a) DMDO (1.0 eq), CH_2Cl_2, 0 °C to rt, (b) i. DMDO (1.0 eq), CH_2Cl_2, 0 °C to rt, ii. Jones reagent (3.0 eq), acetone, 0 °C to rt.

The identity of the lactone products was supported by the values of 1787, 1723 cm^{-1} for the carboxyl and carbonyl groups, respectively, in the IR spectra. The stereochemistry of each diastereoisomer was identified by NOESY experiments, showing the key correlations between the protons at C-4 and C-5 for 4,5-*cis*-lactones **250a** (Fig. 13) and the key correlation between the proton at C-5 and the proton in methyl group at C-4 for 4,5-*trans*-lactones **250b** (Fig. 14).

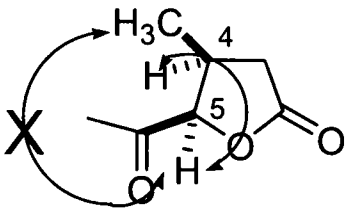


Fig. 13. NOESY of 4,5-*cis*-lactones **250a**

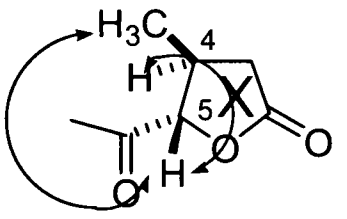
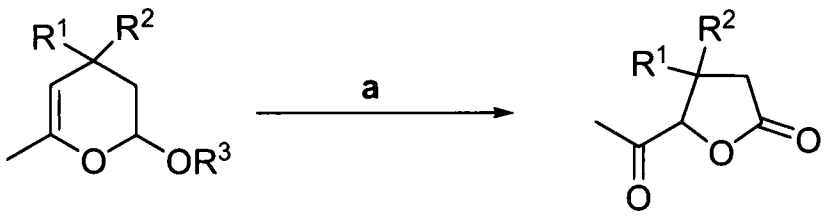


Fig. 14. NOESY of 4,5-*trans*-lactones **250b**

Therefore, the NOESY experiment proved the favoured formation of *cis* isomer between 4,5-*cis*-lactones **250a** and 4,5-*trans*-lactones **250b**. After we obtained this result, we investigated the possible epimerisation between lactone **250a** and **250b** to confirm that this stereoselective process reflected a kinetic product ratio. Firstly, we re-submitted **250a** and **250b** respectively under the Jones oxidation conditions overnight. Secondly, we kept each of the pure lactone in chloroform for one week at room temperature. However, neither diastereoisomer showed epimerisation under these conditions.

Other DHPs (**232** and **237-240**) were also oxidized by DMDO, followed by direct Jones oxidation to give the corresponding lactones (**235** and **251-254**) without the purification of the rearrangement products. The results for the DMDO oxidative rearrangement followed by Jones oxidation are summarised in Table 14.

Table 14. Diastereoselective oxidative rearrangement; (a) i. DMDO (1.0 eq), CH_2Cl_2, 0 °C to rt, ii. Jones reagent (3.0 eq), acetone, 0 °C to rt.



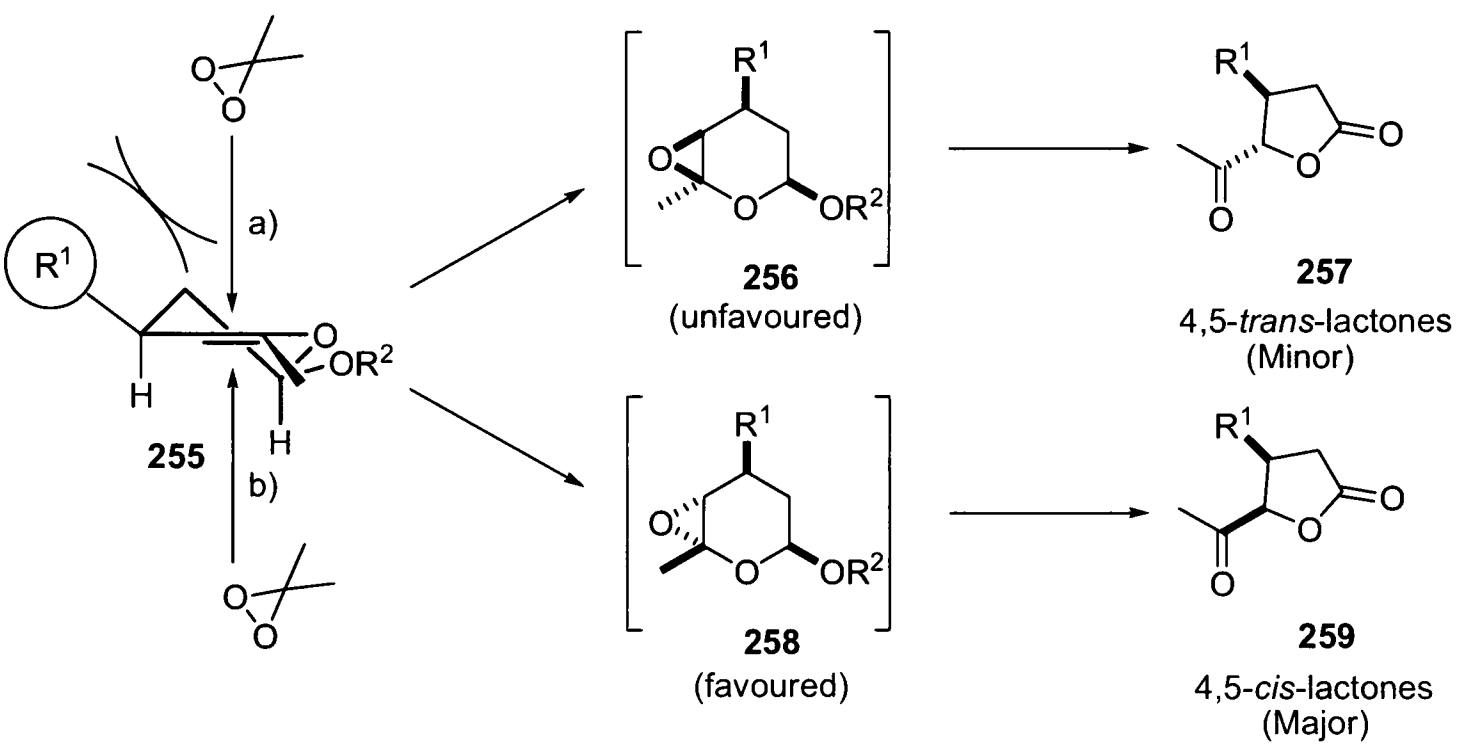
DHP	R^1	R^2	R^3	Tetrahydrofuranone (yield[a], dr[b])	
218	H	H	^{n}Bu	**231**	(69%, N/A)
236	Me	H	^{n}Bu	**250a, 250b**	(53%, 3:1)
237	^{i}Pr	H	^{n}Bu	**251a, 251b**	(63%, 9:1)
238	Me	Me	^{n}Bu	**252**	(50%, N/A)
232	Ph	H	Et	**235**	(65%, -[c])
239	CH_2OBn	H	Et	**253a, 253b**	(48%, 95:5[d])
240	$(CH_2)_4CH{=}CHEt$	H	Et	**254**	(64%, -[c])

[a] Yield over two steps. [b] The ratio of 4,5-*cis*-lactone to 4,5-*trans* lactone (based on ^{1}H NMR analysis). [c] 4,5-*cis*-product only. [d] Estimated from the ^{1}H NMR spectrum.

The yields over two steps were generally reasonable (48-69%). Additionally, lactone **253a** was isolated from the mixture of diastereoisomers whereas **253b** could not be isolated because of the low yield. It was notable that during the oxidative rearrangement and Jones oxidation, the benzylic ether moiety in lactone **253** was tolerated and the DHP **240** bearing an isolated olefin was selectively oxidised. In terms of stereoselectivity, product lactones (**235**, **251**, **254**) showed excellent diastereoselectivity (dr >9:1) and higher levels of stereocontrol were observed with more sterically demanding and branched R^1 substituents. The ratio of the two isomers was determined from the ^{1}H NMR of the mixture and NOESY experiments indicated the favoured formation of 4,5-*cis*-lactones (**235**, **251a**, **253a**, **254**).

2.2.3. Explanation of observed stereochemistry

After we found excellent diastereoselectivity in our oxidative rearrangement method, it was necessary to explain this observed stereoselectivity. It was already mentioned that higher levels of stereocontrol were observed with more sterically demanding and branched R^1 substituents. Thus, we believed that the stereoselectivity would be related to the approach of DMDO. A model for our explanation is shown in Scheme 93.



Scheme 93. Proposed explanation of observed stereochemistry.

As previously explained, the major cycloadduct from the HDA reaction is the *endo* DHP with 2,4-pseudoequatorial substituents. In order to explain the observed stereochemistry, this conformer **255** should be adopted. When the DMDO was delivered from top-face (a) of the DHP **255**, there would be steric hindrance between DMDO and the substituent R^1 of the DHP. Therefore, the formation of epoxide **256** would be less favourable and the 4,5-*trans*-lactone would be the minor product **257**. However, when the DMDO was delivered from the bottom-face (b) of the DHP **255**, there would be no steric hindrance between DMDO and substituent R^1 of the DHP. Therefore, the formation of epoxide **258** would be favoured and it would undergo rearrangement to give the major 4,5-*cis*-lactone **259**.

2.3. Synthesis of Quercus Lactone species

To apply our oxidative rearrangement method to natural product synthesis, we focused on a simple target molecule, Quercus lactone species. Structurally, Quercus lactones are 4,5-disubstituted tetrahydrofuranones and so they were ideal for our purpose. Quercus lactones consist of whisky lactone **260** (Fig. 15) and cognac lactone **261** (Fig. 16).

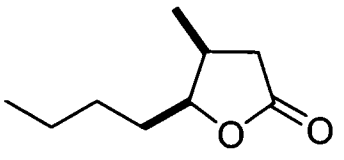


Fig. 15. 4,5-*cis*-whisky lactone **260**

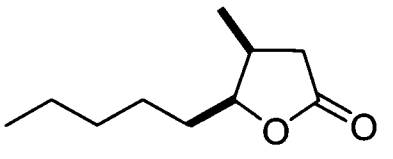
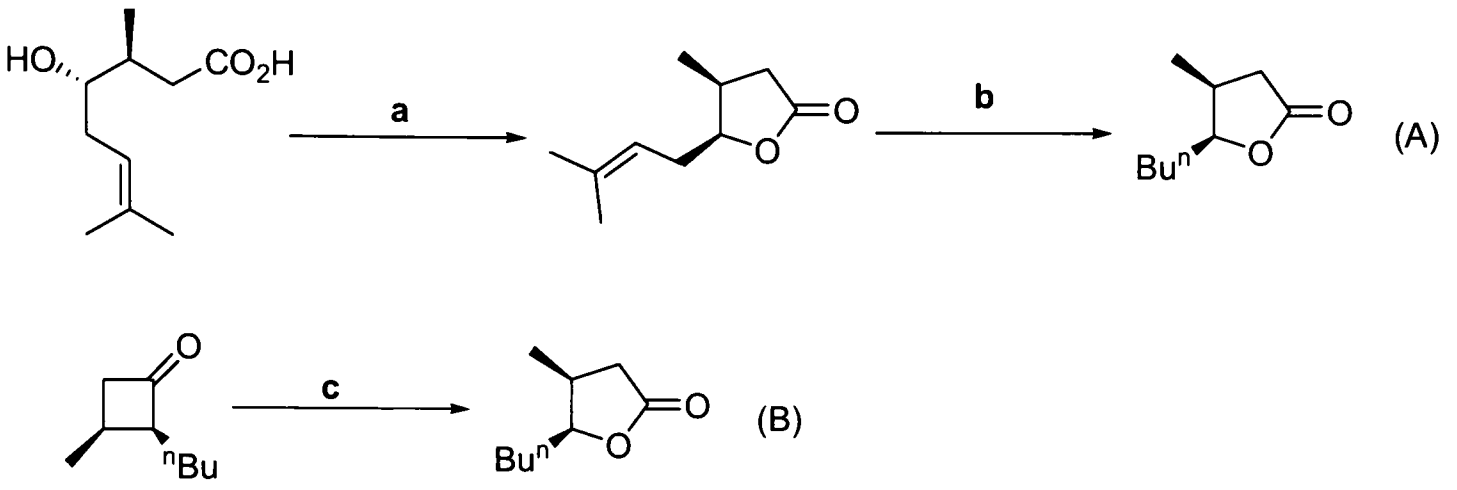


Fig. 16. 4,5-*cis*-cognac lactone **261**

These lactones were isolated from different types of wood and they were identified as key flavours of aged alcoholic beverages such as whisky, brandy, wine and cognac.[108] Especially, the *cis* diastereoisomer defines the "vanilla", "coconut", and "chocolate" notes in Chardonnay and Cabernet Sauvignon wines.[109] Additionally, the Taylor group reported the synthesis of the four possible stereoisomers of whisky lactone.[110]

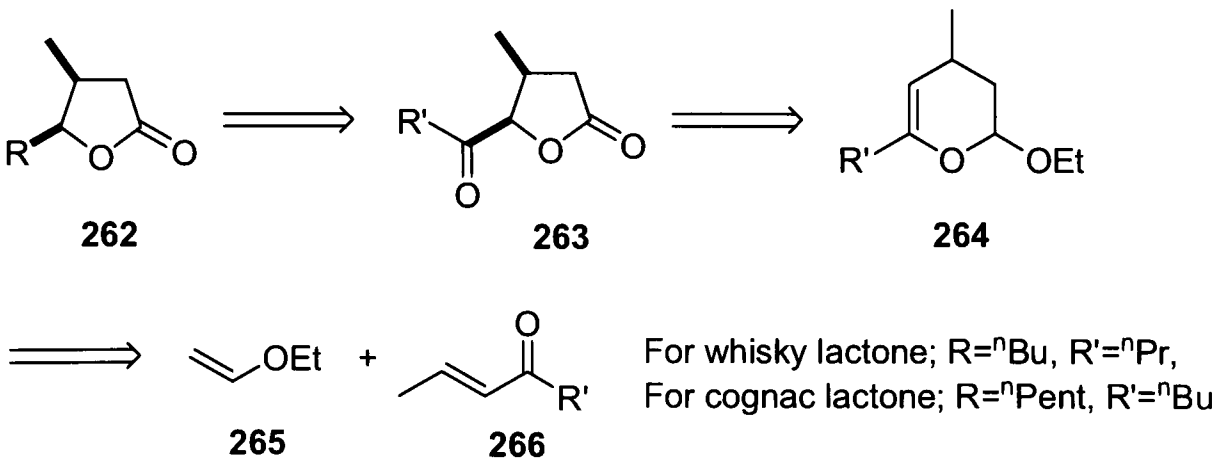
2.3.1. Proposed synthesis of Quercus lactones

A variety of syntheses of racemic whisky lactone[111] and cognac lactone[112] have been reported in the literature. Additionally, a few examples of the enantioselective synthesis of *cis*-Quercus lactones have been reported.[111l, 111n, 113] Representative methods are shown in Scheme 94. The Suzuki group prepared (4*S*,5*S*)-*cis*-whisky lactone by a route involving the synthesis of THFs and manipulation of the side chain (A, Scheme 94).[111n] Also, the Chevtchouk group reported the synthesis of both (4*S*,5*S*)-*cis* and (4*S*,5*R*)-*trans* isomers by Baeyer-Villiger oxidation of cyclobutanones (B, Scheme 94).[113a]



Scheme 94. Representative examples of previous Quercus lactone synthesis; (a) Benzene, heat, (b) i. $NaNO_2$, $AcOH{\cdot}H_2O$, 0 °C, ii. H_2, Pd/C, EtOAc, (c) MCPBA.

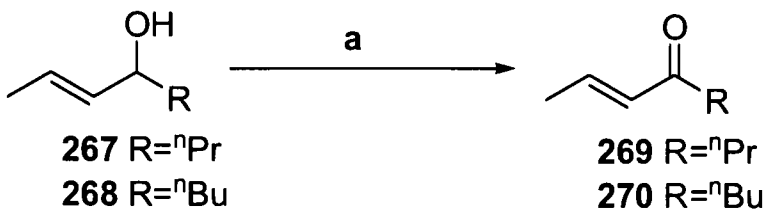
Compared to previous synthetic approaches, it seemed that our oxidative rearrangement method would give a relatively short synthetic route toward Quercus lactones. Our strategy is shown in Scheme 95. The target molecule, Quercus lactone **262**, could be obtained from the reduction of the ketone functional group of disubstituted lactone **263** and, for this purpose, we considered Wolff-Kishner reduction or Barton-McCombie deoxygenation of the derived alcohols. The lactone **263** would be easily synthesised by the oxidative rearrangement of DHP **264** with DMDO and subsequent Jones oxidation. The DHP **264** also would be made from the HDA reaction of enones **265** and enol ether **266**.



Scheme 95. Retrosynthesis for Quercus lactones.

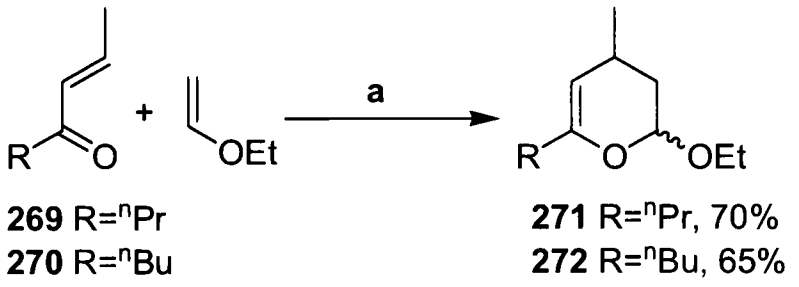
2.3.2. Synthesis of tetrahydrofuranone precursors

According to our synthetic strategy, we prepared heterodienes **269** and **270** by Swern oxidation of the commercially available alcohols **267** and **268** (Scheme 96).



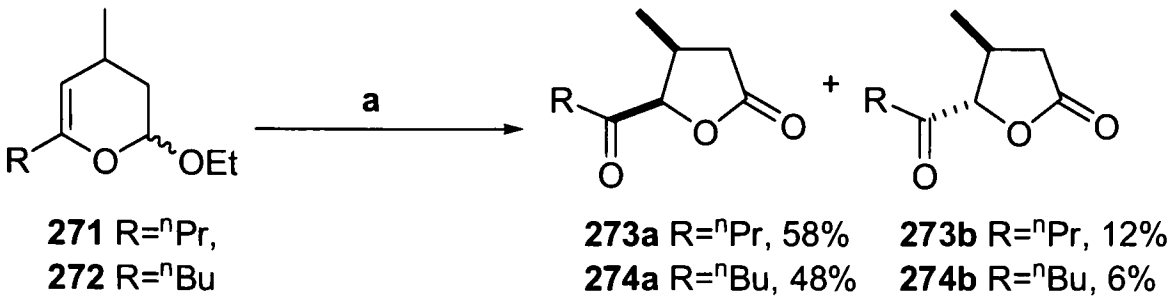
Scheme 96. Typical Swern oxidation to prepare enone **269** and **270**; (a) i. DMSO, CH_2Cl_2, $(COCl)_2$ (1.1 eq), 10 min, ii. Et_3N, 30 min.

Having prepared the enones, we synthesised DHPs **271** and **272** by HDA reaction (Scheme 97).



Scheme 97. Preparation of DHPs from enones **269** and **270**; (a) YbFOD (5 mol%), pressure tube, 5 d.

DHP **271** was isolated in 70% yield and DHP **272** was isolated in 65% yield. Based on ^1H NMR analysis, the ratio of *endo*:*exo* compounds was 4:1 for in both cases. After the preparation of the DHPs **271** and **272**, we subjected them to the oxidative rearrangement/Jones oxidation conditions (Scheme 98).



Scheme 98. Diastereoselective oxidative rearrangement of DHPs **271** and **272**; (a) i. DMDO (1.0 eq), CH_2Cl_2, 0 °C to rt, ii. Jones reagent (3.0 eq), acetone, 0 °C to rt.

Both substrates afforded a mixture of two lactone diastereoisomers. ^{1}H NMR analysis of the crude reaction mixture showed a ratio of 5:1 for lactones **273a** and **273b**, and a ratio of 8:1 for lactones **274a** and **274b**. After column purification of the mixture **273a** and **273b**, the lactone **273a** was isolated in 58% yield and the lactone **273b** was isolated in 12% yield. Similarly, after column purification of the mixture **274a** and **274b**, the lactone **274a** was isolated in 48% yield and the lactone **274b** was isolated in 6% yield. The stereochemistry of each diastereoisomer was proved by NOESY experiments. 4,5-*cis*-Lactones **273a** and **274a** showed the key NOE relationship between two protons at C-4 and C-5 and did not show the NOE relationship between the proton at C-5 and the proton in methyl group of C-4 (Fig. 17). However, 4,5-*trans*-lactones **273b** and **274b** showed the key NOE relationship between the proton at C-5 and the proton in methyl group of C-4 and did not show the relationship between two protons at C-4 and C-5 (Fig. 18).

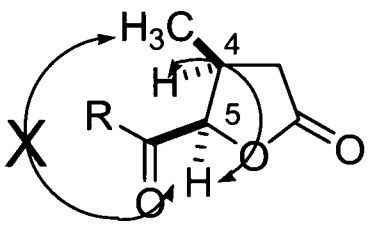


Fig. 17. NOESY of 4,5-*cis*-lactones **273a** (R=^{n}Pr) and **274a** (R=^{n}Bu).

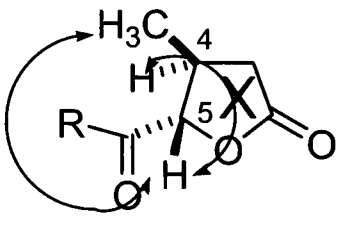
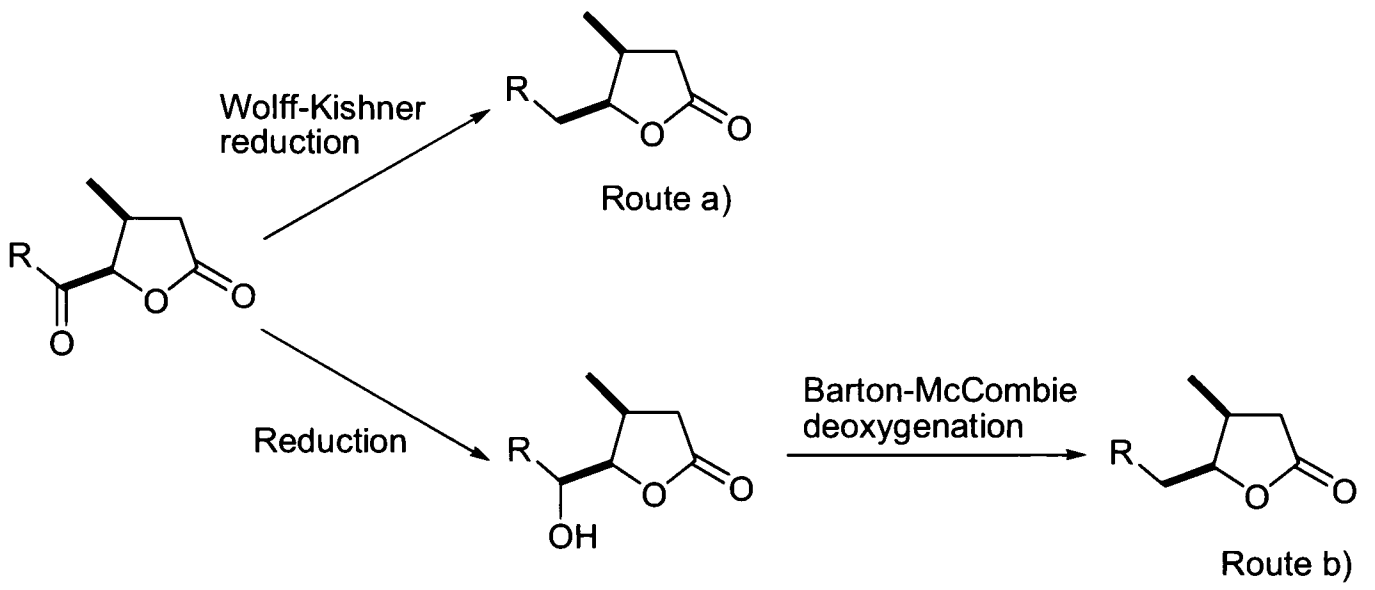


Fig. 18. NOESY of 4,5-*trans*-lactones **273b** (R=^{n}Pr) and **274b** (R=^{n}Bu).

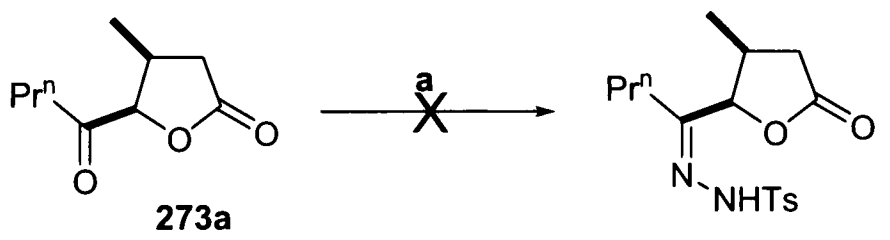
2.3.3. Quercus lactones

To obtain the natural products, 4,5-*cis*-Quercus lactones, it was necessary to reduce the ketone functional group of lactones **273a** and **274a**. We considered two reduction method methods, Wolff-Kishner reduction (route a in Scheme 99) and Barton-McCombie deoxygenation of the derived alcohols (route b in Scheme 99).



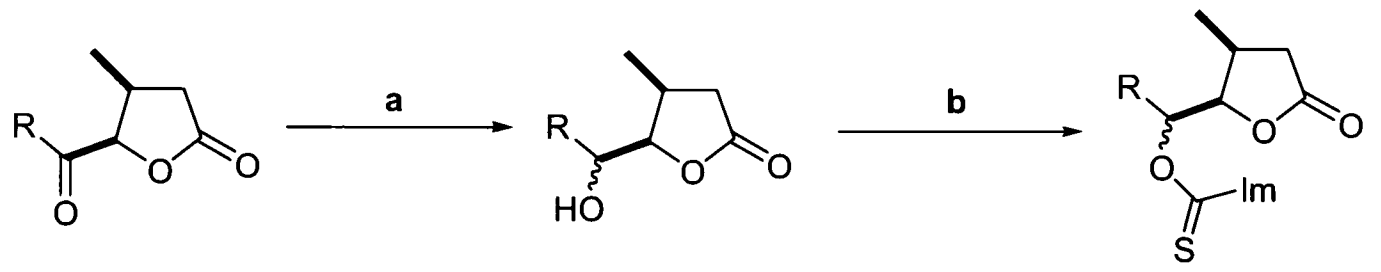
Scheme 99. Two ideas for reduction of ketone moiety.

From literature precedent, we found that a wide range of carbonyl functions could be reduced by modified Wolff-Kishner conditions using $NaBH_3CN$ reduction of tosylhydrazones.[114] We therefore attempted to form the tosylhydrazone of the 4,5-*cis*-lactone **273a** (Scheme 100).



Scheme 100. Attempted Wolff-Kishner reduction; (a) $TsNHNH_2$, EtOH, rt, 2 d.

However, the reaction showed little conversion even after 2 d at room temperature. Only a trace of the hydrazone product was detected by the TLC and ^{1}H NMR analysis. Thus, we moved our attention to Barton-McCombie deoxygenation.[115] Before the deoxygenation, we needed to prepare thiocarbonyl compounds from the ketone **273a** and **274a**. The reduction of the ketones **273a** and **274a** with $NaBH_4$ successfully gave the alcohols **275** and **276** as a 1:1 mixture of diastereoisomers. Subsequently, the diastereoisomeric alcohols **275** and **276** were converted into the thiocarbonyl compounds **277** and **278** by treatment with thiocarbonylimidazole at 80 °C (Scheme 101).



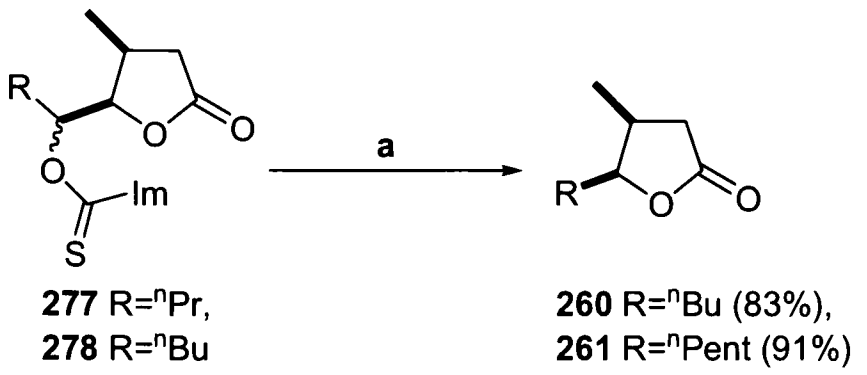
273a R=^{n}Pr, **274a** R=^{n}Bu

275 R=^{n}Pr (87%) **276** R=^{n}Bu (70%)

277 R=^{n}Pr (50%) **278** R=^{n}Bu, (77%)

Scheme 101. Preparation of thiocarbonyl compounds; (a) $NaBH_4$ (1.0 eq), MeOH, rt, overnight, (b) thiocarbonyldiimidazole (1.5 eq), DCE, 80-100 °C, overnight.

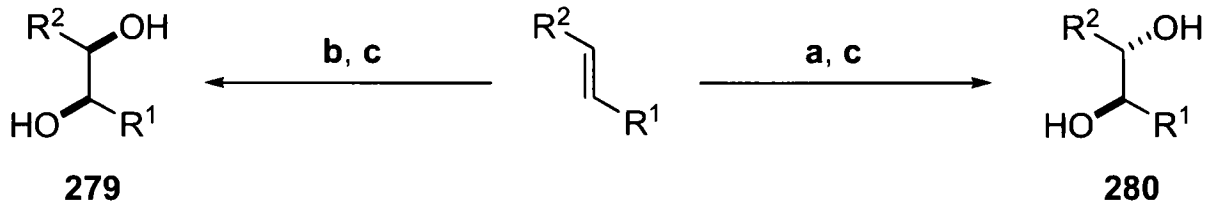
Finally, Barton-McCombie deoxygenation of thiocarbonyl compounds **277** and **278** gave 4,5-*cis*-whisky lactone **260** in 83% yield and cognac lactone **261** in 91% yield (Scheme 102) and the spectral data of two lactones **260** and **261** matched the literature data.[112f, 116] Thus, we had successfully applied our oxidative rearrangement method to synthesise 4,5-*cis*-whisky lactone **260** and 4,5-*cis*-cognac lactone **261**. Because of this successful result, we were encouraged to try to widen the scope of our oxidative rearrangement method for the preparation of 4,5-*trans*-THFs.



Scheme 102. Barton-McCombie deoxygenation; (a) $^{n}Bu_3SnH$ (1.1 eq), (0.1 eq), toluene, rt, overnight.

2.4. Attempted Prevost *trans*-dihydroxylation

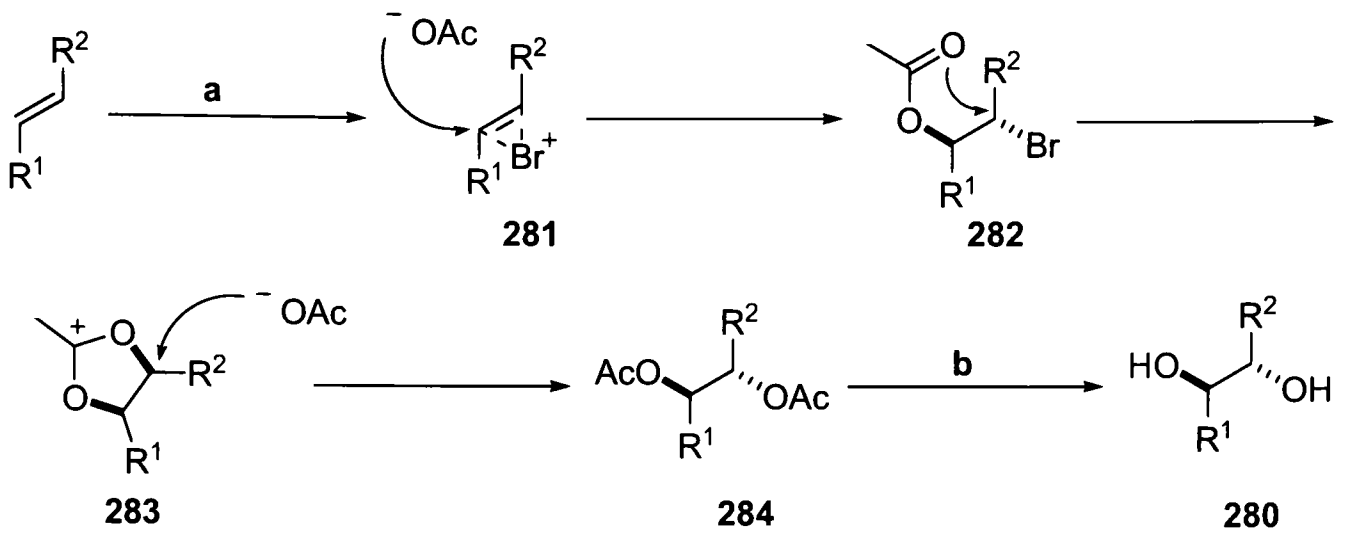
In spite of the successful synthesis of 4,5-*cis*-tetrahydrofuranones by our novel rearrangement method, it would be desirable to be able to synthesise 4,5-*trans*-tetrahydrofuranones to make this method more universal. Because DMDO epoxidation conditions gave the *cis* tetrahydrofuranone as a major product, we would need alternative oxidation conditions. Towards the end of this project, we found that Sudalai *et.al.* reported Prevost *trans* dihydroxylation of olefins mediated by $PhI(OAc)_2$ and LiBr (Scheme 103).[117] In this paper, they controlled the formation of *syn* diol **279** with $NaIO_4$ and LiBr and *anti* diol **280** with $PhI(OAc)_2$ and LiBr.



279 **280**

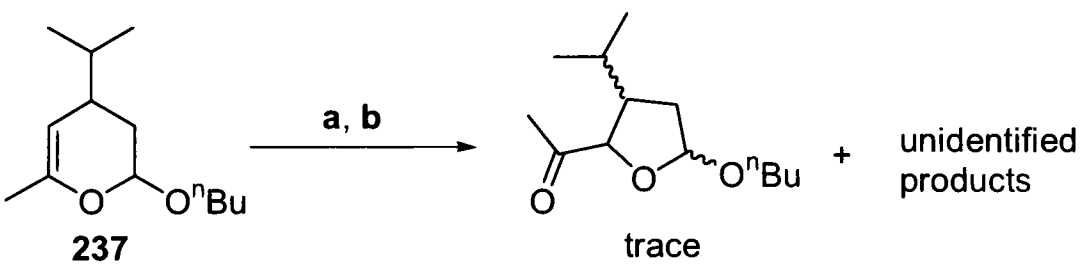
Scheme 103. Prevost-Woodward reaction; (a) $PhI(OAc)_2$ (1.0 eq), LiBr (20 mol%), AcOH, 95 °C, 18 h, (b) $NaIO_4$ (30 mol%), LiBr (20 mol%), AcOH, 95 °C, 18 h, (c) K_2CO_3, MeOH, 25 °C, 24 h.

Mechanistically, the alkene reacts with bromine, generated *in situ* from alkali metal halides by oxidation with $NaIO_4$ or $PhI(OAc)_2$, and undergoes bromoacetoxylation *via* bromonium ion **281**. The intermediate species **283** from the acetal formation of *trans*-1,2-bromoacetoxylation **282** gives the *anti* diol **280** by the ring opening with acetic acid (Scheme 104). Also, the ring opening of intermediate species **283** by water gives the *syn* diol **279** without the inversion of configuration.



Scheme 104. The formation of *anti* diol **280**; (a) $PhI(OAc)_2$ (1.0 eq), LiBr (20 mol%), AcOH, 95 °C, 18 h, (b) K_2CO_3, MeOH, 25 °C, 24 h.

Although this chemistry does not proceed *via* an epoxide, we speculated that intermediates similar to **283**, or the 1,2-diols, might be able to undergo a similar rearrangement leading to a THF product. Moreover, the initial attack of bromine on the less hindered face followed by opening of the brominium ion with inversion should lead to formation of the *trans*-THF, by analogy to the NBS-mediated aziridination process developed earlier in the group. We therefore undertook a test reaction with DHP **237** under these *trans*-dihydroxylation conditions using $PhI(OAc)_2$ and LiBr (Scheme 105).



Scheme 105. Attempted Prevost dihydroxylation; (a) $PhI(OAc)_2$ (1.0 eq), LiBr (20 mol%), AcOH, 95 °C, 18 h, (b) K_2CO_3, MeOH, 25 °C, 24 h.

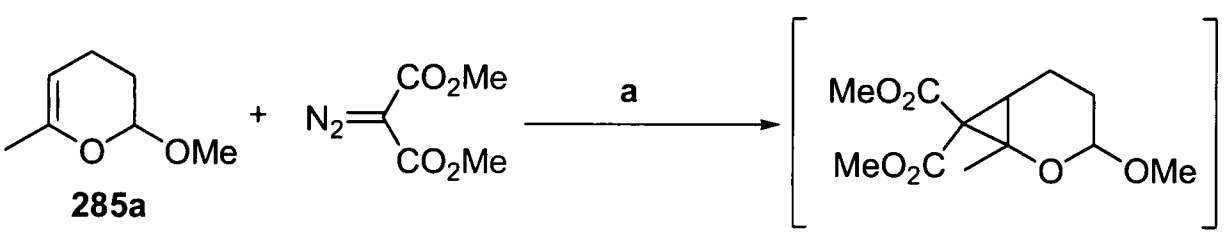
Unfortunately, the reaction gave only a trace of rearrangement products along with several other unidentified products. Additionally, we could not determine the stereochemistry because of the complexity of the ^1H NMR spectrum caused by the presence of three

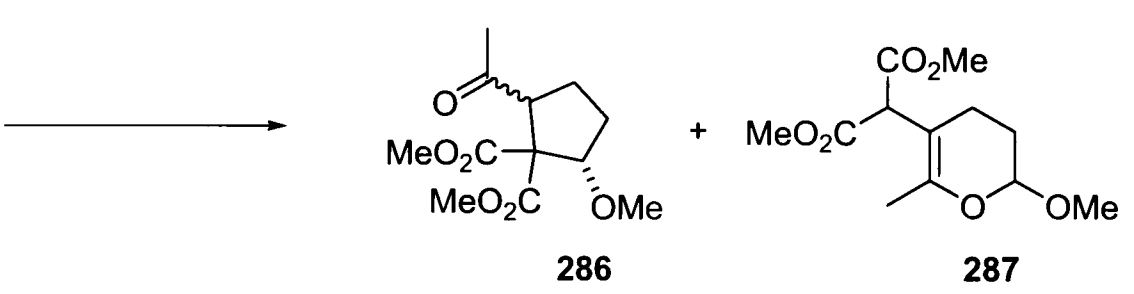
stereocentres in the product. However, the formation of THFs at least to some extent was a promising result and this process could potentially be optimised as part of future work.

2.5. Preparation of cyclopentanes by cyclopropanation/ rearrangement

2.5.1. Previous work in this field

Using the same rearrangement concept, we reasoned that reaction of DHPs with other electrophiles rather than oxygen and nitrogen could give a wide range of 5-membered ring products, and one possible reaction was the rearrangement of DHP by cyclopropanation leading to cyclopentanes. In fact, there was a literature precedent supporting this idea. Alonso and co-workers studied addition/rearrangement of dimethyl diazomalonate to DHPs (Scheme 106).[118] In this work they showed this reaction gave a diastereoisomeric mixture of rearrangement products **286** as minor products and insertion product **287** as a major product (1:2.5) and they proposed both products could arise from the ring opening of common cyclopropane intermediate.

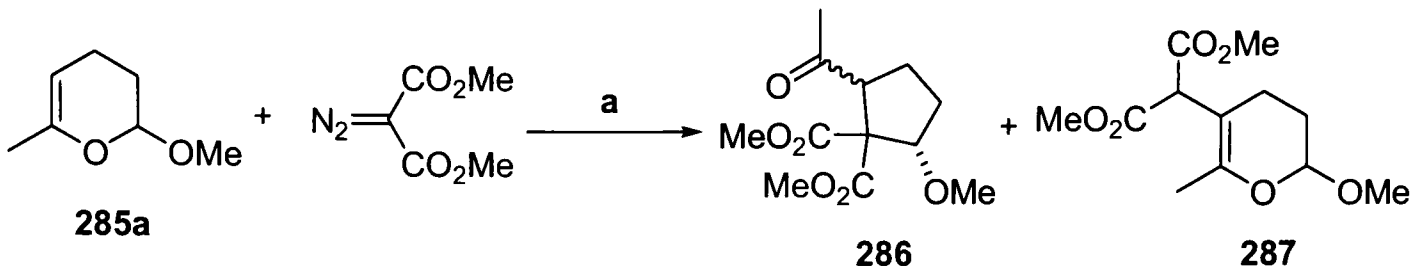




Scheme 106. Addition/rearrangement of dimethyl diazomalonate to DHP **285a** by Alonso; (a) $Cu(F_6acac)_2$, benzene, 1: 2.5 (the ratio of **286** to **287**), 81% (total yield).

Also, Alonso and co-workers reported the influence of catalysts such as copper based catalysts and rhodium based catalysts on product composition [119] and selected representative examples are shown in Table 15. In this work, they found that the rearrangement product **286** was obtained as the major compound (52%, mixture of diastereoisomers) when $Cu(F_6acac)_2$ was used as a catalyst (entry 2) and other catalysts gave the rearrangement product as a minor product (entry 1 and 3).

Table 15. Influence of catalyst on composition of products in cyclopropanation; (a) ML_n, fluorobenzene.

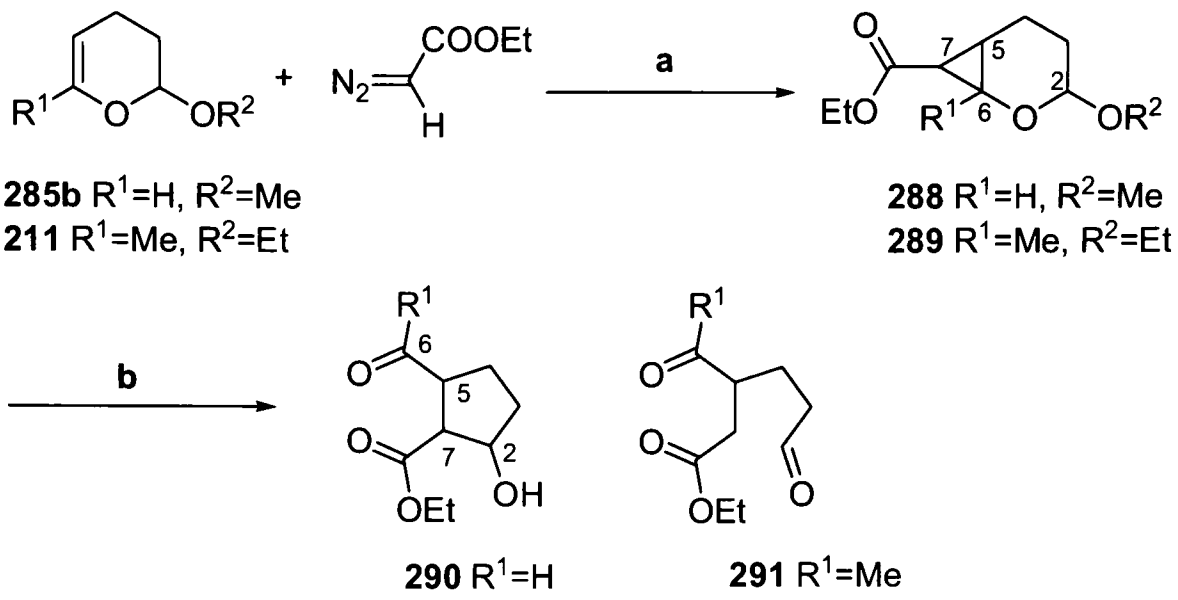


Entry	ML_n	Time	Yield of **286**[a]	Yield of **287**
1	$Cu(acac)_2$	8.5 h	5%	75%
2	$Cu(F_6acac)_2$	4.0 h	52%	41%
3	Rh_2OAc_4	2.5 h	12%	39%

[a] For the mixture of diastereoisomers.

Apart from Alonso's work, there were some earlier preliminary studies in our group (Table 16).[120] Firstly, our group undertook the reaction of DHPs (**285b** and **211**) with ethyl diazoacetate and catalytic $Cu(acac)_2$ to give cyclopropanes (**288** and **289**) in a reasonable yield (67-72%). The resulting cyclopropanes were then treated with HCl to promote the rearrangement and the cyclopropane **288** rearranged to the cyclopentane **290** in 68% yield. However, the cyclopropane **289** did not rearrange to give the cyclopentane and the ring system was opened to give **291** under these acidic conditions. Additionally, the unnecessary stereocentres at C-2 and C-7 in cyclopropanes (**288**, **289**) and cyclopentane **290** caused difficulty in the stereochemical analysis and the reaction did not seem to be diastereoselective. Therefore, we decided to use dimethyl diazomalonate for the cyclopropanation as this would remove one unnecessary stereocentre at C-7. Furthermore, it was expected that two electron withdrawing ester moieties in diazomalonate might increase the reactivity of the cyclopropanation and the rearrangement to the cyclopentane.

Table 16. Cyclopropanation of DHP; (a) $Cu(acac)_2$ (0.05 mol%), CH_2Cl_2, 90 °C, (b) 1M HCl (aq), CH_3CN, rt, 20 min.



285b R^1=H, R^2=Me
211 R^1=Me, R^2=Et

288 R^1=H, R^2=Me
289 R^1=Me, R^2=Et

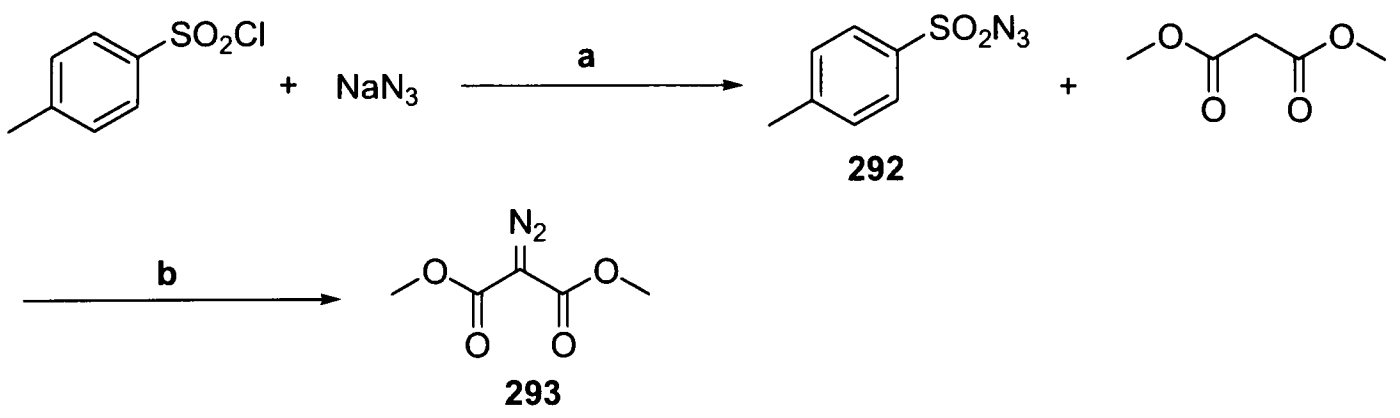
290 R^1=H

291 R^1=Me

DHPs	Cyclopropane (yield, dr)	Rearrangement product (yield)
285b	**288** (67%, 1:1.3)	**290** (68%)
211	**289** (72%,1:1.4)	**291** (74%)

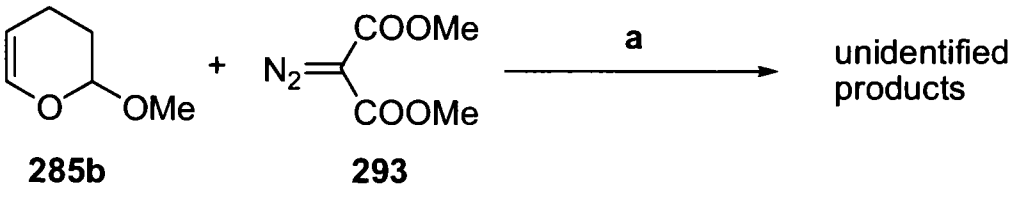
2.5.2. Attempted cyclopropanation with diazomalonate

In contrast to ethyl diazoacetate, dimethyl diazomalonate **293** was not commercially available and we therefore synthesised it using a known procedure (Scheme 107).[121]



Scheme 107. Synthesis of dimethyl diazomalonate; (a) acetone/water (1:1), 40 °C, 3 h, (b) Diethylamine, Et_2O, 0 °C.

Firstly, *p*-toluenesulfonyl azide **292** was prepared *via* the reaction between *p*-toluenesulfonyl chloride and sodium azide in 80% yield and it was identified by mass spectroscopy (215 for $M+NH_4$). Subsequently, *p*-toluenesulfonyl azide **292** reacted with dimethyl malonate to give dimethyl diazomalonate **293** in 60% yield and the product's spectroscopic data were in accordance with those in the literature.[121b] The diazomalonate **293** was then applied to the cyclopropanation of the commercially available DHP **285b** (Scheme 108). The reaction conditions were exactly same as in the previous procedure (condition a, Table 16) except that diazomalonate was used.



Scheme 108. Attempted cyclopropanation with diazomalonate; (a) $Cu(acac)_2$ (0.05 mol%), CH_2Cl_2, 90 °C.

The reaction was monitored by TLC and DHP **285b** was completely consumed within 4 h. Although TLC analysis indicated the formation of four major products, only two of them could be isolated by chromatography. Unfortunately, ^1H and ^{13}C NMR spectral data were not clean. However, from ^1H NMR analysis, we could see singlets at 3.74 ppm and 3.78 ppm indicating that the dimethyl malonate portion had been incorporated. Additionally, in mass spectroscopic analysis, we observed m/z at 245 (100%) for both fractions and this value matches to M+H for the 3 possible products in Fig. 19.

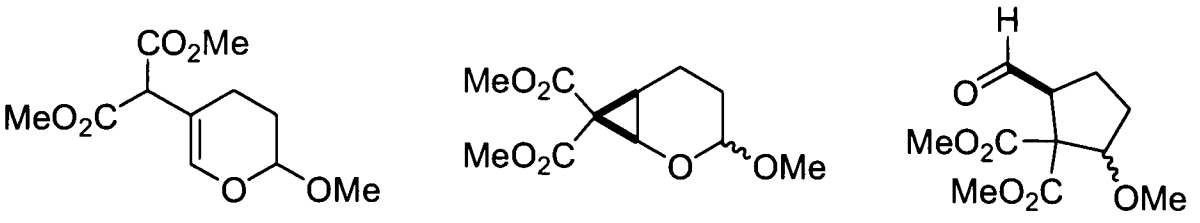
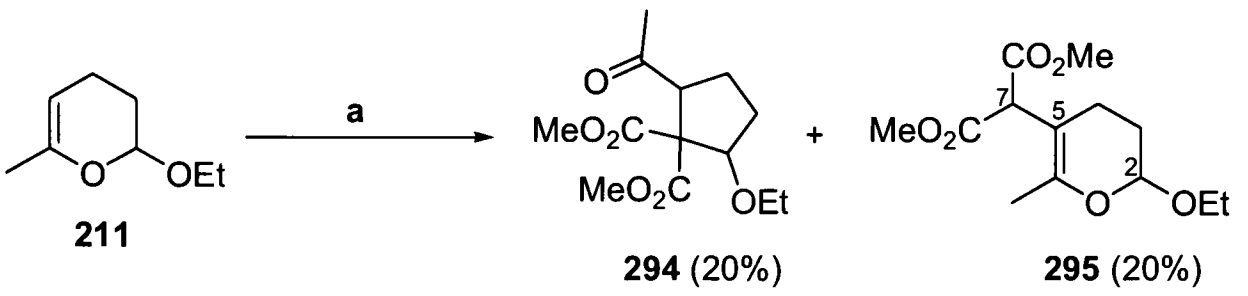


Fig. 19. Three possible isomers from cyclopropanation.

Since Alonso showed the formation of cyclopentane from DHP **211** with $Cu(F_6acac)_2$ in resonable yield (52%), we decided to change our reaction conditions (Scheme 109). DHP **285b** and $Cu(acac)_2$ were changed to DHP **211** and $Cu(F_6acac)_2$.

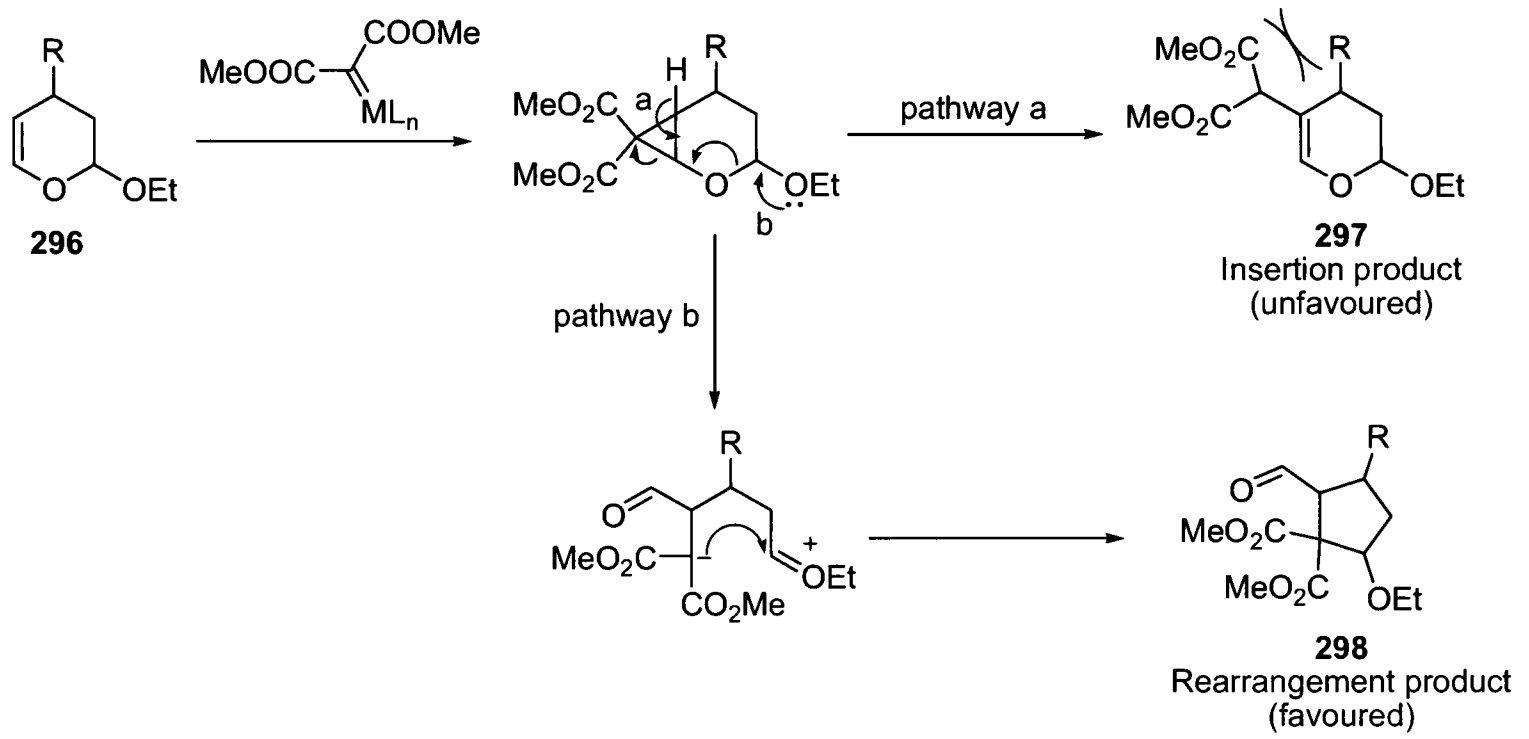


Scheme 109. Cyclopropanation of DHP **211** catalysed by $Cu(F_6acac)_2$; (a) diazomalonate (1.2 eq), $Cu(F_6acac)_2$ (0.05 mol%), 75 °C, 4 h.

The cyclopentane **294** was obtained as a mixture of stereoisomers (1:1) in ca. 20% yield and the insertion product **295** was obtained in ca. 20% yield. The combined yield (ca. 40%) might be increased by the use of more equivalents of diazomalonate because Alonso used 2.0 eq of diazomalonate to 1.0 eq of DHP and obtained a combined yield of 93%. We could not obtain completely clean spectral data for compounds **294** and **295** even though they were isolated as one single spot by TLC analysis. However, we could find some evidence supporting their structures. For compound **294**, two carboxyl group at 169.7 and 169.4 and one carbonyl group at 167.1 were found in ^{13}C NMR analysis and 273 (M+H) was found in the mass spectrum. For compound **295**, a triplet with J=3.5 Hz for the proton at C-2 was found at 5.00 ppm and singlet for the proton at C-7 was found at 4.32 in ^{1}H NMR analysis. Moreover, two carbons in double bond at 147.1 and 109.8 and two carboxyl group at 169.2 and 168.9 were found in ^{13}C NMR analysis and the mass spectrum again showed a peak at 273 (M+H). In fact, the ^{1}H NMR spectrum of product **294** also showed a trace of aldehyde, suggesting that the product **294** could be ring-opened under the slightly acidic $CDCl_3$ conditions.

At this stage, we decided to suspend this cyclopropanation/rearrangement project because of the difficulties in obtaining pure products and we therefore turned our attention to the enantioselective oxidation/rearrangement. However, this process is potentially useful to

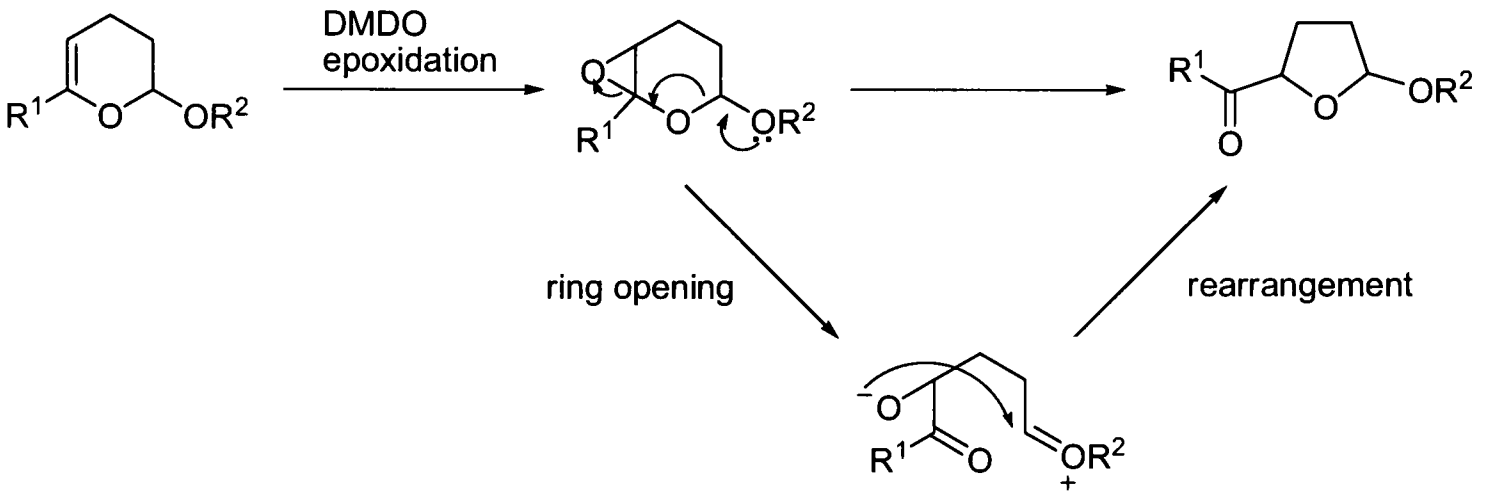
synthesise cyclopentanes and could merit further investigation. For example, the modification of the substrate DHP may be effective to favour the formation of the rearrangement product. In the cyclopropanation, the formation of the rearrangement product would be competitive with the insertion product and we may need DHP **296** containing bulky substituent such as Ph (Scheme 110). Sterically bulky DHP **296** may prevent the formation of addition product **297** by steric hindrance (pathway a) and would favour the formation of rearrangement product **298** (pathway b). So, this cyclopropanation of DHP containing bulky substituent should be pursued further for the future work.



Scheme 110. Idea to obtain rearrangement product **298**.

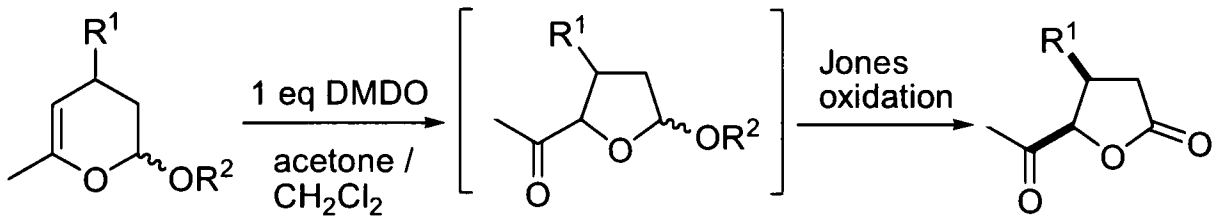
3. Conclusions.

The initial aim of this project was the preparation of THFs by the epoxidation of DHPs and the subsequent rearrangement of epoxide intermediates. Fortunately, we were able to optimise the reaction conditions and this oxidative rearrangement successfully gave THFs in good yield using DMDO as oxidant (Scheme 111).



Scheme 111. Idea of oxidative rearrangement.

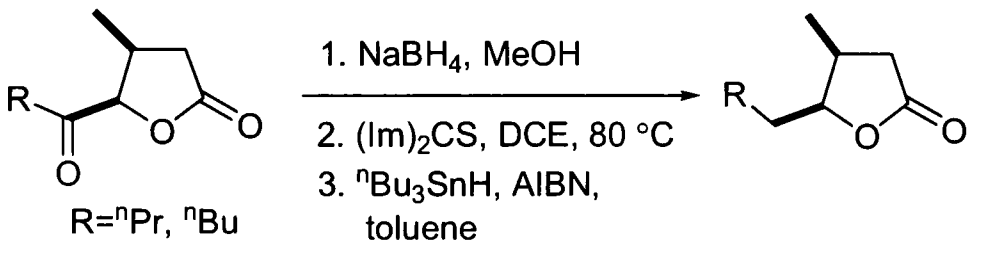
Furthermore, we investigated the diastereoselectivity of the oxidative rearrangement. For this study, we needed to remove the unnecessary lactol stereocentre from the 2,5-disubstituted THFs and this was achieved *via* Jones oxidation, giving 5-substituted tetrahydrofuranones. After we established this typical procedure for the synthesis of tetrahydrofuranones from DHPs, we were able to synthesise various 4.5-disubstituted tetrahydrofuranones (Scheme 112).



Scheme 112. Diastereoselective synthesis of 4,5-*cis*-tetrahydrofuranone.

Higher levels of stereocontrol were observed with more sterically demanding and branched

R^1 substituents and NOE studies indicated that the 4,5-*cis*-tetrahydrofuranones were the major product. This diastereoselectivity was explained by the size of substituent R^1 and the direction of the approach of DMDO to the olefin. Finally, we applied our novel oxidative rearrangement to the synthesis of natural products, the Quercus lactones. After the isolation of 4,5-*cis*-tetrahydrofuranones, we successfully synthesised whisky lactone (36% over 3 steps) and cognac lactone (49% over 3 steps) by the reduction of tetrahydrofuranones, followed by Barton-McCombie deoxygenation of derived alcohols (Scheme 113).



Scheme 113. Synthesis of Quercus lactones.

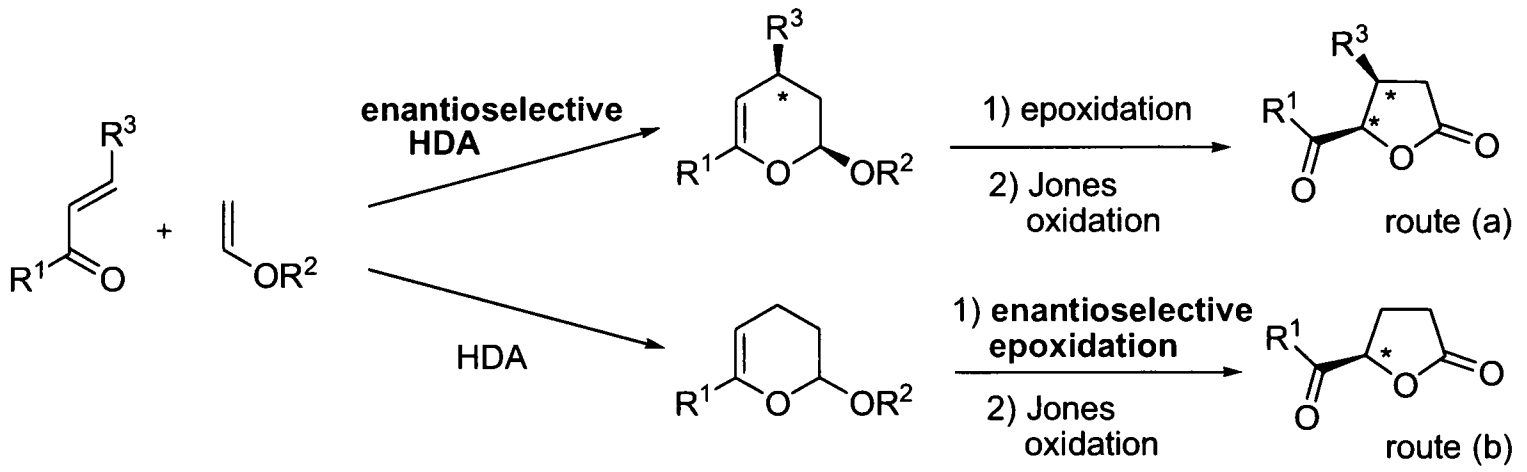
Additionally, we attempted the synthesis of 4,5-*trans*-THF using Prevost dihydroxylation method and we also adapted our rearrangement concept for the synthesis of cyclopentanes: attempted cyclopropanation of DHPs gave mixtures of the insertion product and the rearrangement product.

This whole section dealt with racemic material. Extension of the chemistry to enantioselective synthesis was an important goal and this will be discussed in chapter II.

Chapter II. Enantioselective oxidative rearrangement of 2-alkoxydihydropyrans

1. Introduction

Previously, we discussed the diastereoselective formation of tetrahydrofuranones using oxidative rearrangement of DHPs. In this chapter, the enantioselective formation of tetrahydrofuranones will be discussed. We considered two possible routes to synthesise tetrahydrofuranones enantioselectively. Firstly, enantiomerically pure tetrahydrofuranones could potentially be obtained by using an enantioselective HDA reaction, followed by the established oxidative rearrangement method by DMDO (Scheme 114. route a). Secondly, the enantiomerically pure tetrahydrofuranones could be obtained by using an enantioselective epoxidation step after the formation of racemic DHPs (Scheme 114. route b).



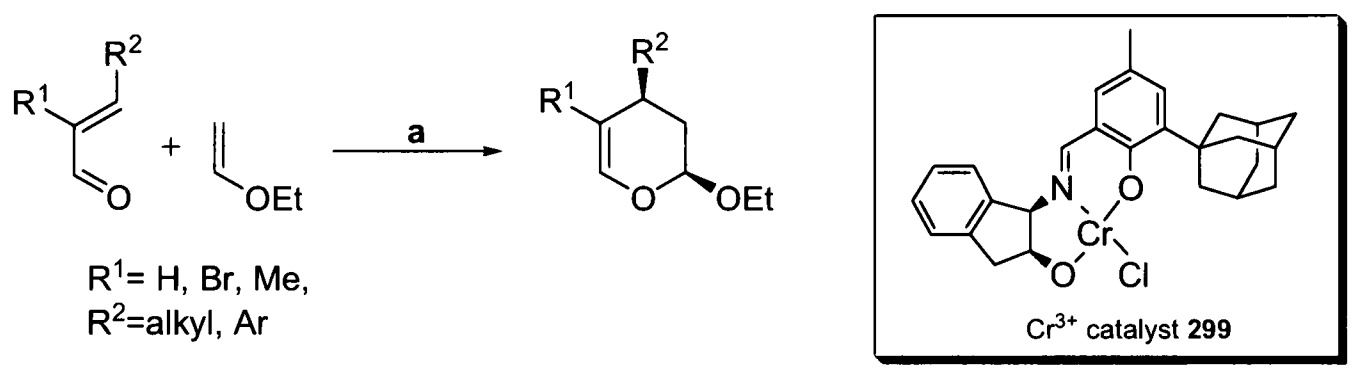
Scheme 114. Two ideas for enantioselective synthesis of tetrahydrofuranone.

1.1. Asymmetric HDA reaction

It is really attractive to synthesise chiral tetrahydrofuranones *via* the preparation of chiral DHPs by asymmetric HDA because the chiral DHP precursors could afford disubstituted tetrahydrofuranones containing two chiral centres in the oxidative rearrangement. From a literature search, we found two asymmetric HDA reactions catalysed by chiral Lewis acids which may be appropriate for our purpose.

1.1.1. Hetero Diels-Alder reaction under Cr^{3+} catalysis

Recently, the Jacobsen group reported an enantioselective HDA reaction between ethyl vinyl ether and a range of α,β-unsaturated aldehydes affording the product DHP in 70-95% yield and 89-98% ee using Cr^{3+} catalyst **299** (Scheme 115).[122]

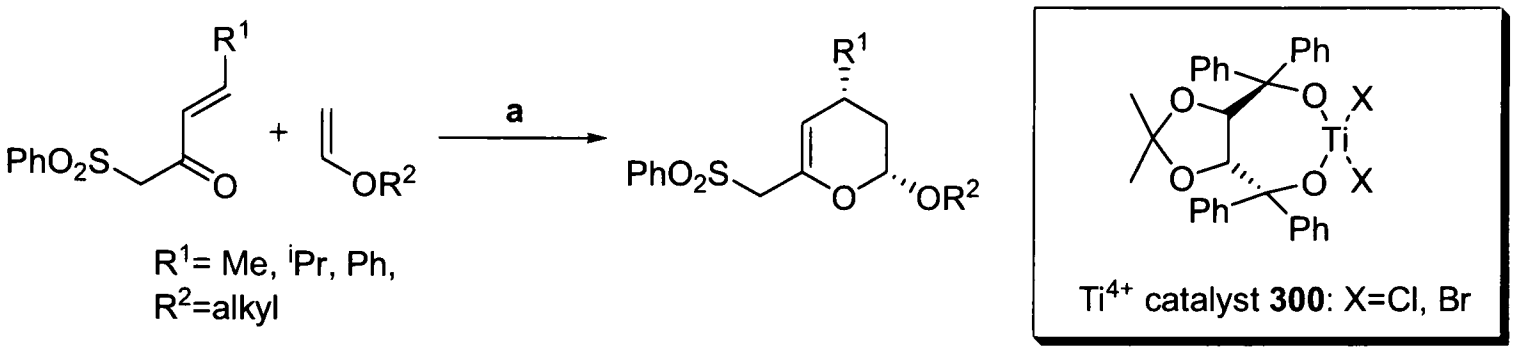


Scheme 115. Hetero-Diels-Alder reactions by Cr^{3+} catalysis; (a) Cr^{3+} catalyst (5 mol%), neat, rt, yield 70-95%, ee 89-98%.

However, the reaction was only performed with α,β-unsaturated aldehydes and we could not find any examples for its application to α,β-unsaturated ketones. For the diastereoselective oxidative rearrangement, most of our DHP substrates were prepared from α,β-unsaturated ketones and some DHPs from α,β-unsaturated aldehydes were found not to undergo the rearrangement. Thus, we would need to investigate the application of Jacobsen's HDA reaction to α,β-unsaturated ketones, if we wanted to adopt this method

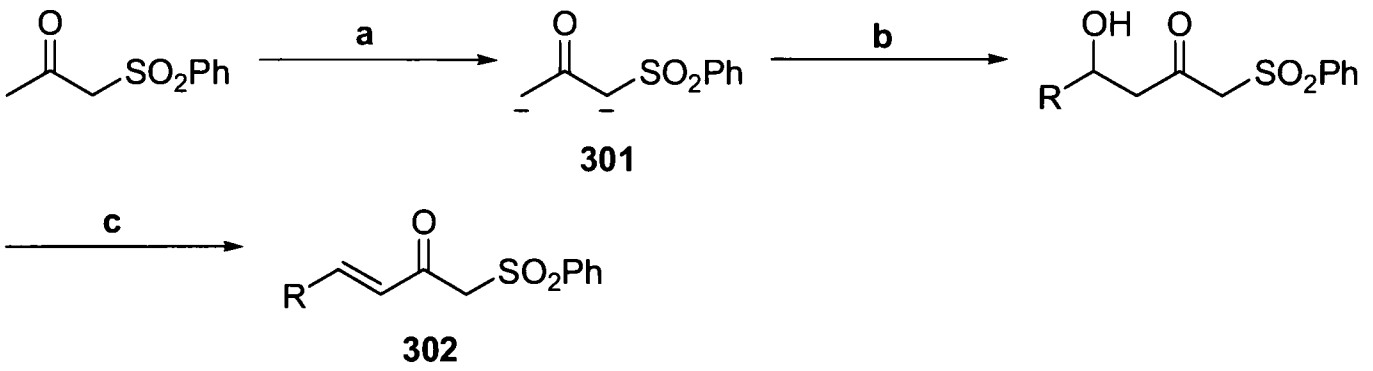
1.1.2. Hetero Diels-Alder reaction of phenylsulfonyl enones under Ti^{4+} catalysis

The Wada group reported an enantioselective HDA reaction between a range of vinyl ethers and α,β-unsaturated phenylsulfonyl ketones affording the product DHP in 77-96% yield and 59-97 % ee, using Ti^{4+} catalyst **300** (Scheme 116).[123]



Scheme 116. Hetero Diels-Alder reactions by Ti^{4+} catalysis; (a) Ti^{4+} catalyst (5-10 mol%), MS 4Å, CH_2Cl_2, 30, -50 or -78 °C, yield 77-96%, ee 59-97%.

The reaction was successfully performed with α,β-unsaturated ketones but the scope was limited to phenylsulfonyl ketones and it would be necessary to prepare phenylsulfonyl enones **302** *via* the reaction of dianion **301** with aldehydes (Scheme 117).



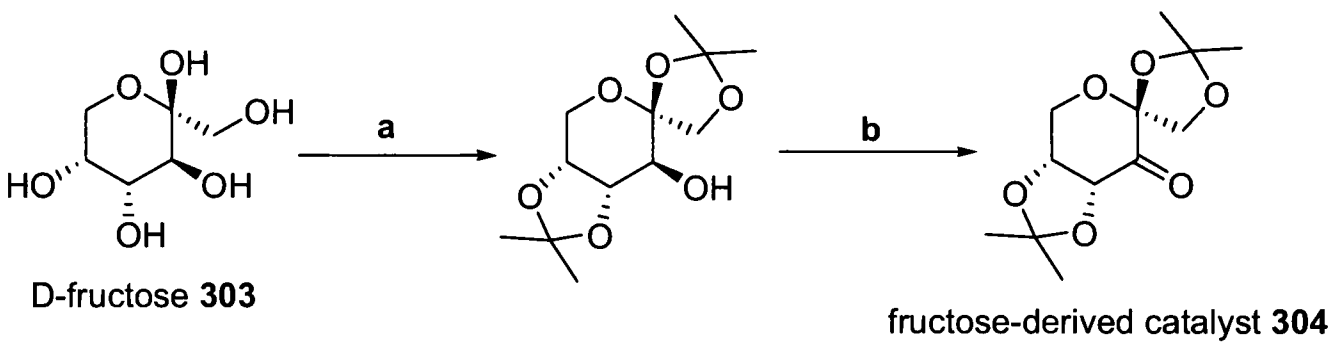
Scheme 117. Preparation of phenylsulfonyl enone; (a) LDA (2.0 eq), 0 °C, THF, (b) RCHO, -78 °C, (c) *p*-TsOH, reflux, C_6H_6.

1.2. Asymmetric epoxidation methods

For the enantioselective oxidative rearrangement, chiral tetrahydrofuranones could be still obtained by asymmetric epoxidation method even though it would result in the formation of only one stereocentre, in contrast to the formation of two stereocentres by the asymmetric HDA route. For the asymmetric epoxidation, we considered two representative catalysts for the asymmetric epoxidation of DHP substrates. They were a fructose-derived chiral ketone catalyst by Shi[124] and a chiral salen manganese catalyst by Jacobsen[125] because both catalysts are commercially available and show good reactivity and enantioselectivity with a variety of olefins.

1.2.1. Fructose-derived chiral ketone catalyst by Shi.

In 1996, a fructose-derived ketone **304** was developed as an effective epoxidation catalyst by the Shi group.[126] This catalyst is readily obtained from commercial sources or from very inexpensive D-fructose **303** by ketalisation and oxidation (Scheme 118).



Scheme 118. Preparation of fructose-derived ketone catalyst; (a) acetone, 0 °C, 53%, (b) PCC, CH_2Cl_2, rt, 93%.

The structural feature of the catalyst is that stereocentres are close to the reacting centre allowing control of the approach of an olefin to the reacting dioxirane by sterically blocking one face. The stereochemistry of epoxidation can then be explained by *spiro* transition states, in which π–electrons of the olefin attack the σ^*–orbital of the dioxirane and the lone-paired electrons of oxygen interact with the π^*–orbital of the olefin to give the epoxide (Fig. 20).[127]

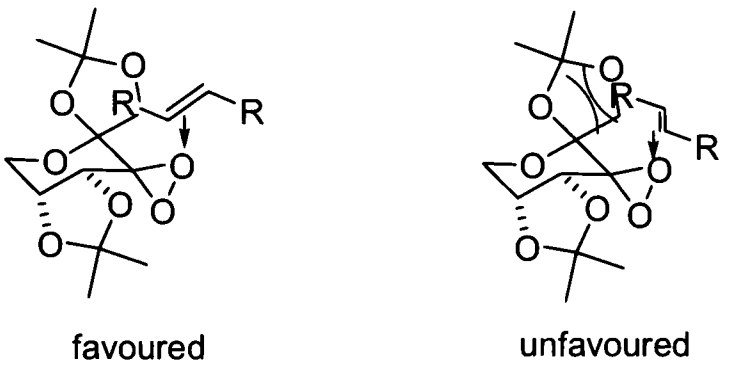
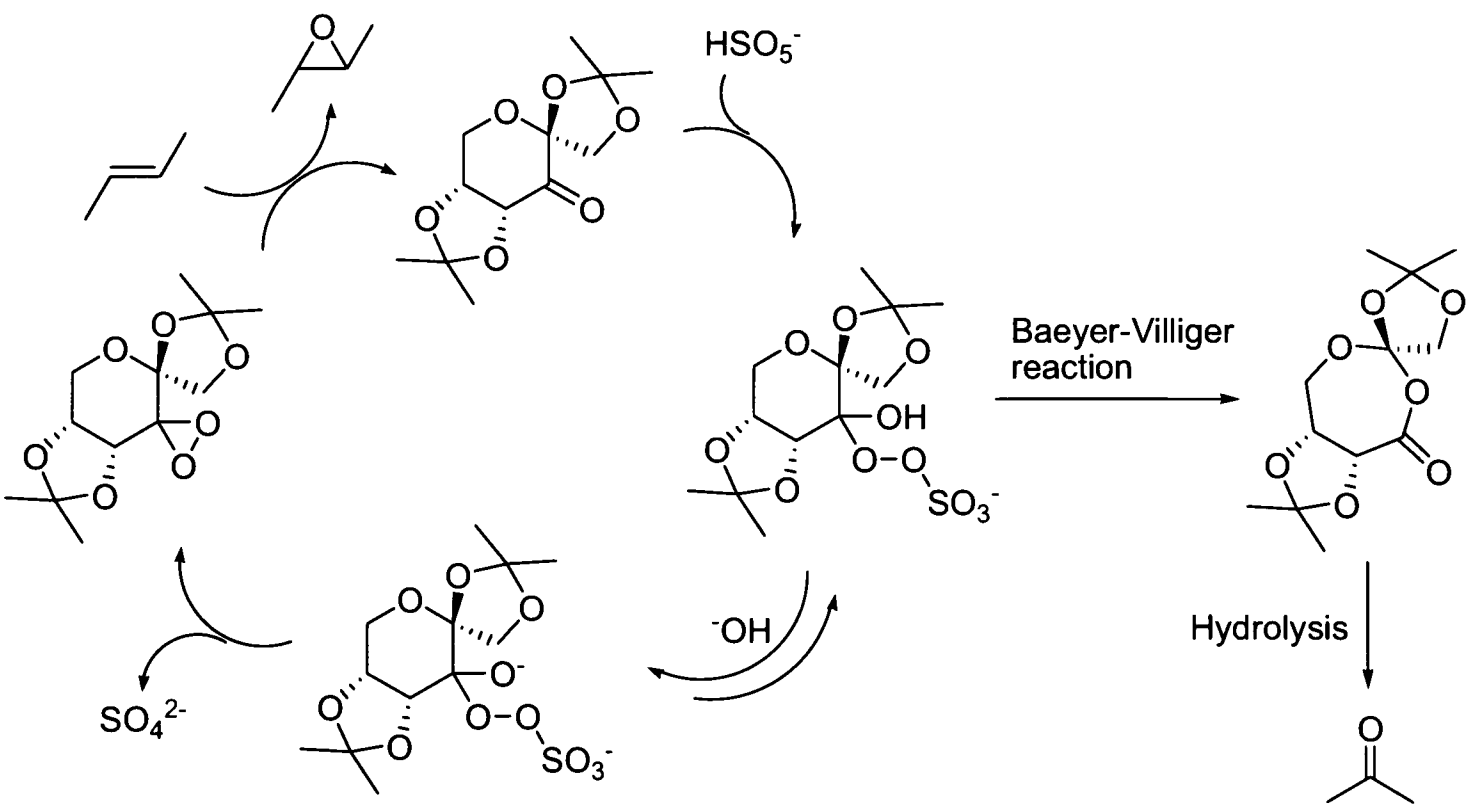


Fig. 20. Two *spiro* transition states to explain stereochemistry of epoxidation.

Additionally, the fused ring and quaternary centre at the α-position to the ketone prevents the epimerisation of the stereocentre and the inductively electron withdrawing substituent increases the catalytic activity.

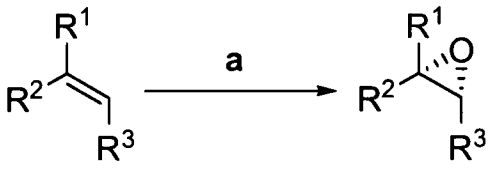
The catalyst's efficiency often shows high dependence on the reaction pH due to the sensitivity of the catalyst to decomposition *via* Baeyer-Villiger reaction (Scheme 119), control of pH (typically pH 7-8) can minimise this side-reaction.[128]



Scheme 119. Decomposition of catalyst *via* Baeyer-Villiger reaction.[129]

Under controlled pH conditions, the fructose-derived ketone **304** shows excellent catalytic activity and enantioselectivity in the epoxidation of a wide range of olefins.[129] Representative results are shown in Table 17.

Table 17. Representative result of epoxidation by fructose derived chiral ketone **304**; (a) catalyst **304** (30 mol%), Oxone, H_2O/Me_3CN.

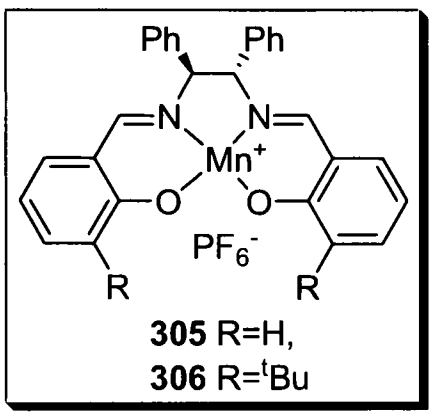


Entry	R^1	R^2	R^3	Yield (%)	ee (%)
1	Ph	H	Ph	78	99
2	Ph	H	Me	94	96
3	Ph	H	CH_2OTBS	83	95
4	Ph	H	$C_2H_4CO_2Me$	76	91
5	Ph	Me	Me	89	97
6	$C_{10}H_{21}$	Me	Me	97	87
7	^{t}Bu	Me	Me	35	91
8	Ph	$(CH_2)_4$		94	98
9	Me	$(CH_2)_4$		77	81
10	H	Ph	H	90	24
11	H	C_8H_{17}	H	80	27
12	H	$^i Pr_3SiCH_2$	H	92	35
13	Me	Ph	H	81	28
14	H	$(CH_2)_4$		85	32

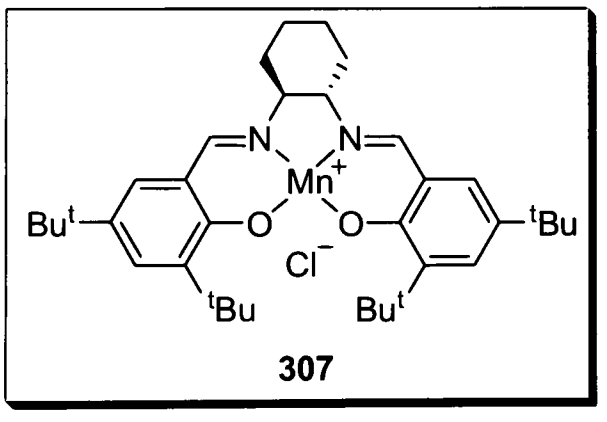
The catalyst works well with *trans*-disubstituted olefins (entries 1-4) and trisubstituted olefins (entries 5-9). Additionally, the reaction tolerates enol silylethers (entry 3), α,β-unsaturated esters (entry 4) and cyclic olefins (entries 8-9). However, the epoxidation of *cis*-disubstituted olefins (entries 10-13) and terminal olefins (entry 14) gave low ee.

1.2.2. Chiral manganese salen catalysts.

Since Jacobsen[130] and Katsuki[131] independently reported asymmetric epoxidation of conjugated olefins catalysed by chiral salen manganese catalysts in 1990, various salen manganese complexes (**305-307**) have been further improved (Fig. 21). The structural features of the catalyst are C_2-symmetry and two sp^3 carbon stereocentres at the ethylenediamine moiety. The catalysts show excellent catalytic activity and enantioselectivity in the epoxidation of a wide range of olefins and representative examples of the asymmetric epoxidation by chiral salen manganese catalysts from Jacobsen are shown in Table 18.



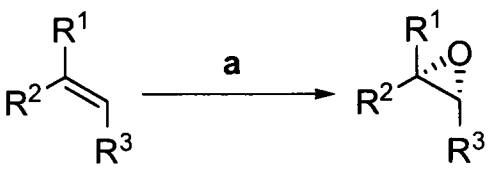
305 R=H,
306 R=^{t}Bu



307

Fig. 21. Salen manganese catalysts.

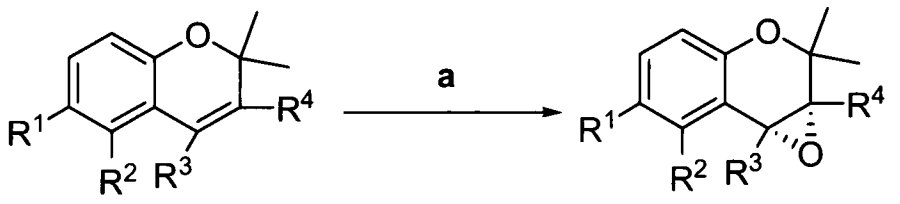
Table 18. Representative results from epoxidation by chiral salen manganese catalyst; catalyst (<8 mol%), additives (0-20 mol%), oxidant (NaOCl or ArIO).



Entry	catalyst	R^1	R^2	R^3	Yield	ee
1	B	H	Ph	Me	73%	84%
2	C	H	Ph	CO_2Et	96%	93%
3	A	Ph	H	Ph	63%	33%
4	A	Ph	H	Me	93%	20%
5	B	Ph	H	H	75%	57%
6	B	Ph	Me	H	36%	30%
7	C	Ph	Me	Ph	69%	93%
8	C	Ph	Ph	Ph	97%	92%
9	C	Ph	Ph	Me	91%	95%
10	C	Ph	$(CH_2)_3$		75%	86%

The catalyst works well with *cis*-disubstituted olefins (entries 1[130]-2[132]) and trisubstituted

olefins (entries 7-10).[133] The reaction also tolerates cyclic olefins (entry 10) and enoates give a high level of enantioselectivity (entry 2). However, the epoxidation of *trans*-disubstituted olefins is slow and a loss of selectivity is reported (entries 3-4) and also terminal olefins (entries 5-6) are poor substrates.[130] Additionally, the epoxidation of various chromene derivatives by salen manganese catalyst **307** shows excellent enantioselectivity (Scheme 120).[134]



Scheme 120. Epoxidation of chromene derivatives by chiral salen manganese catalyst; (a) catalyst **307** (4 mol%, Fig. 2), NaOCl, yield 51-96%, ee 94-98%.

The enantioselectivity is induced through the interaction between the chiral salen ligand and the incoming olefin (Fig. 22). In most cases, the observed stereoselectivities are explained well by a side-on approach of the olefin (Fig. 22, a).

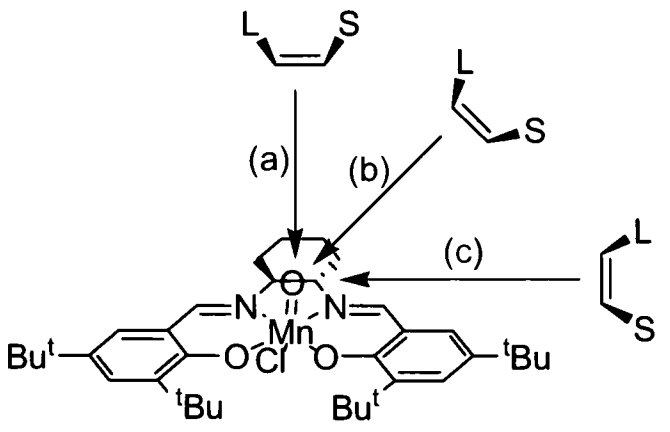
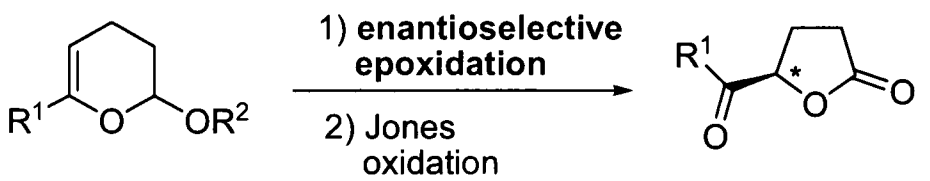


Fig. 22. Plausible olefin approaches.

1.3. Concept of this project

For the enantioselective oxidative rearrangement, we chose to study the asymmetric epoxidation pathway to prepare chiral tetrahydrofuranones (Scheme 121) rather than the asymmetric HDA reaction, because the epoxidation methodology was straightforward to use, whereas the HDA reaction would either have to be extended (Cr^{3+} catalysis) or would require substrate synthesis (Ti^{4+} catalysis).



Scheme 121. Concept of enantioselective oxidative rearrangement *via* asymmetric epoxidation.

As mentioned above, the chiral ketone catalyst by Shi shows excellent catalytic activity and ee for the epoxidation of trisubstituted cyclic olefins. The salen manganese catalyst also gives good results with these substrates. Additionally, these catalysts are either commercially available or easy to prepare. Thus, we decided to adopt these two catalysts for our oxidative rearrangement.

2. Results and discussion

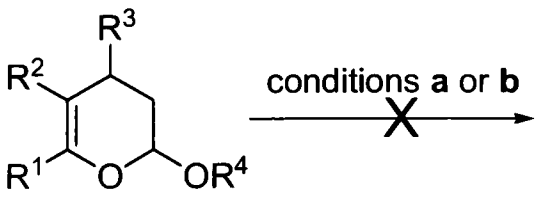
2.1. Optimisation of enantioselective oxidative rearrangement

2.1.1. Enantioselective epoxidation by Shi's catalyst.

Given the earlier successful oxidative rearrangement using DMDO, the use of chiral ketone catalysts for formation of chiral dioxiranes was an attractive possibility. The Armstrong group has developed several enantioselective chiral ketone catalysts, but earlier work has shown that these generally give very poor enantiomeric excesses for epoxidation of enol ethers.[135] Hence we elected to use Shi's catalyst **304** because of its ability to epoxidise enantioselectively various olefin systems, including enol ethers and esters.[126, 129, 136] Shi's catalyst was commercially available as a D-epoxone® from Alfa Aesar.

The results from attempted epoxidation of DHPs with D-epoxone® is shown in Table 19. The DHP substrates were available from the previous diastereoselective oxidative rearrangement studies (DHP **211** and **237**) or were easily synthesised using the HDA reaction (DHP **308**). After the preparation of these DHPs, we tested epoxidation under two different pH conditions because Shi's catalyst is known to be sensitive to this parameter.

Table 19. Attempted epoxidation of DHPs with Shi's catalyst **304**; (a) Oxone® (5.0 eq), $NaHCO_3$ (15.5 eq), Shi's catalyst (3.0 eq), CH_3CN, 0 °C, (b) Oxone® (1.4 eq), $NaHCO_3$ (5.0 eq), Shi's catalyst (0.3 eq), $^nBu_4NHSO_3$ (0.04 eq), CH_3CN, 0 °C.



Entry	DHP	Conditions[a]	R^1	R^2	R^3	R^4
1	**211**	a	Me	H	H	Et
2	**211**	b	Me	H	H	Et
3	**237**	b	Me	H	^{i}Pr	^{n}Bu
4	**308**	b	Ph	H	H	Et

[a] Conditions a: pH~7, Conditions b: pH~10.5

Initially, we carried out the epoxidation of DHP under pH~7 (entry 1, conditions a).

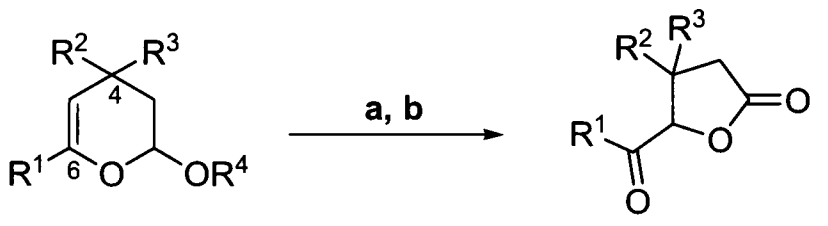
However, this was not successful because TLC analysis showed largely starting material with several unidentified weak spots (entry 1). In line with literature precedent,[129] we assumed that catalyst decomposition by Baeyer-Villiger reaction at the pH employed was a potential cause of the poor results. In an attempt to solve this problem, we initially increased the amount of catalyst from 3.0 eq up to 5.0 eq and the reaction time up to overnight. However, the desired product was still not observed. Thus, we changed the reaction pH to 10.5~11.0 (entries 2-4, conditions b) because higher pH conditions are known to prevent the decomposition of the catalyst.[129] Unfortunately, higher pH conditions still did not give any of the desired product, showing the same outcome on TLC inspection (entry 2). Other DHPs containing a tri-substituted olefin were also attempted (entries 3-4) but they also did not give the expected products, although they had previously been epoxidised under DMDO conditions in good yield. Especially, it was disappointing that the substrate with a phenyl-substituted alkene (entry 4) was not epoxidised, because aryl alkenes are generally good substrates for Shi epoxidation.[129] In view of these disappointing results, we decide to turn our attention to the Jacobsen epoxidation.

2.1.2. Enantioselective epoxidation by Jacobsen's catalyst.

The Jacobsen chiral manganese salen catalyst is able to epoxidise a wide range of olefin systems.[125] Both enantiomers of Jacobsen's catalyst are commercially available from Strem and we adopted (*R*,*R*)-Jacobsen's catalyst **307** for the epoxidation. Because we would epoxidise a trisubstituted olefin in our DHPs, we followed the procedure for the epoxidation of trisubstituted olefins by Jacobsen.[133] 1.5 eq of NaOCl was used as co-oxidant and 0.2 eq of pyridine oxide was used as an additive (Table 20) because this generally increased both ee and yield in Jacobsen's studies. Pleasingly, the oxidised rearrangement products, tetrahydrofuranones (**231**, **252**, **309**), were obtained after the epoxidation of DHPs with Jacobsen's catalyst followed by Jones oxidation. Perhaps not surprisingly, the simple substrate **211** afforded essentially racemic product **231**, as indicated by its optical rotation. At this stage, we postulated that either the replacement of the proton at C-4 with a sterically bulkier group or the replacement of the methyl at C-6 with an

aromatic group may lead to improved enantioselectivity. Firstly, we attempted the epoxidation of DHP **238** bearing two methyl substituents at C-4 (entry 2). However, this still gave racemic product **252**, as indicated by its optical rotation, as well as a low yield (16%). In spite of this unfavourable result, we attempted the epoxidation of DHP **308** with a phenyl substituent at C-6. Pleasingly, we could obtain tetrahydrofuranone **309** with 38% ee in 55% yield (entry 4). This result suggested the importance of the Ph substituent at C-6 which was adjacent to the olefin, rather than the bulkiness of substituent at C-4, which was one carbon away from the olefin.

Table 20. Epoxidation of DHPs with Jacobsen's catalyst **307**; (a) 4-phenyl pyridine N-oxide (0.2 eq), (*R*,*R*)-Jacobsen's cat (0.05 eq), NaOCl (1.5 eq), CH_2Cl_2, 0 °C to rt, (b) Jones reagent (3.0 eq), acetone, 0 °C to rt.



Entry	DHP	R^1	R^2	R^3	R^4	Tetrahydrofuranone (Yield[a])	ee
1	**211**	Me	H	H	Et	**231** (40%)	0%[b]
2	**238**	Me	Me	Me	^{n}Bu	**252** (16%)	0%[b]
3	**308**	Ph	H	H	Et	**309** (55%)	38%[c]

[a] Over 2 steps. [b] Based on the optical rotation observation. [c] Based on HPLC analysis.

2.2. Enantioselective oxidative rearrangement by Jacobsen's catalyst.

After finding the importance of the phenyl substituent at C-6, we decided to investigate more closely the effect of the DHP substituents on the product ee (Fig. 23). Specially, we wished to explore the electronic effect of the aryl substituent at C-6 and the steric effect of bulky substituents at C-4. For this goal, we first needed to synthesise various phenyl enones to allow access to the DHP substrates *via* HDA chemistry.

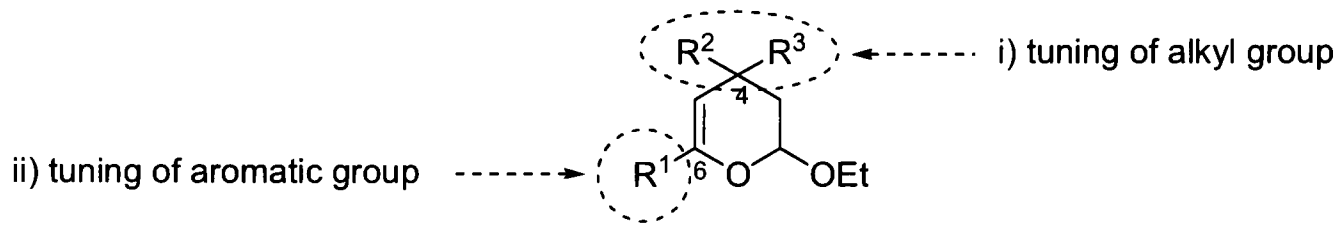


Fig. 23. Idea for tuning of DHP.

2.2.1. Preparation of various phenyl enones

The required aryl enones were synthesised through various routes such as Mukaiyama aldol reaction, Friedel-Crafts acylation, the combination of Grignard reaction and oxidation and Rupe rearrangement (Fig. 24).

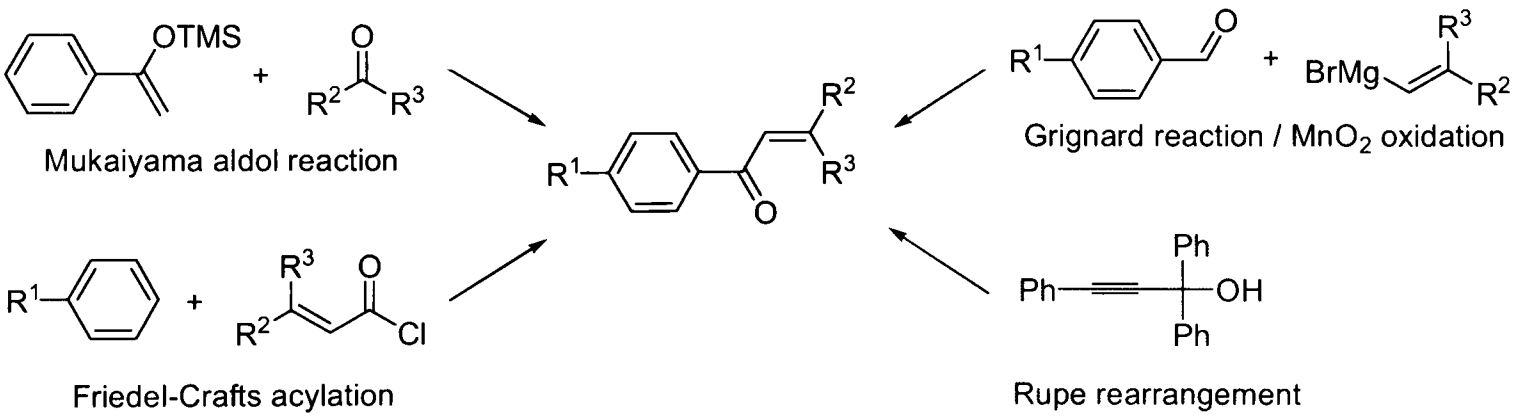
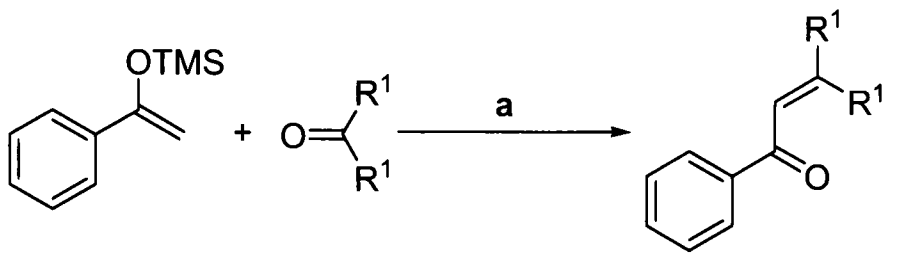


Fig. 24. Various routes toward synthesis of various enones.

In the beginning, we were interested in the effect of the bulkiness of substituents at C-4 of DHPs. From a literature search, we found that Mukaiyama aldol reaction gave various

bulky enone systems in a one-pot procedure[137] and we prepared enones **310-312** in 44-65% yield (Table 21).

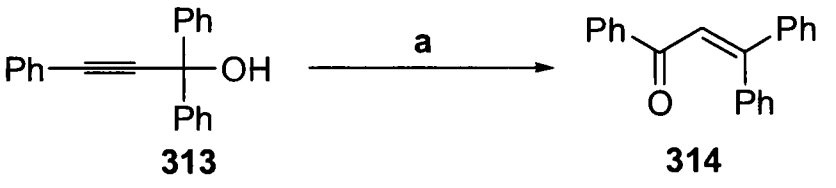
Table 21. Mukaiyama aldol reaction; (a) i. $TiCl_4$ (1.0 eq), CH_2Cl_2, rt, 2 h; ii. TFAA (1.0 eq), rt, 1 h; iii. TEA (2.0 eq), rt, 2 h, iv. H_2O



Entry	R^1	Product (yield)
1	Me	**310** (44%)
2	Et	**311** (50%)
3	cyHex	**312** (65%)
4	^{i}Pr	N/A[a]
5	Ph	N/A[a]

[a] No reaction

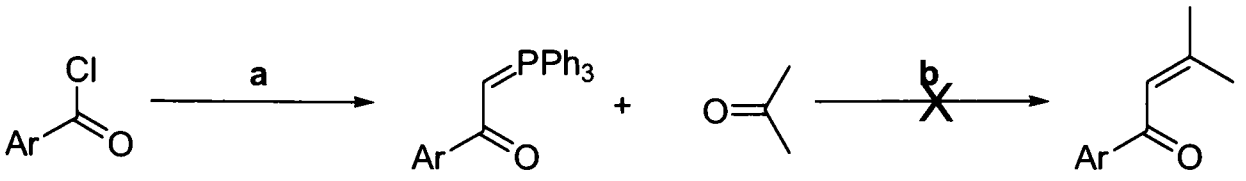
However, extremely bulky substrates (entry 4 and 5) did not give the corresponding product. For the synthesis of bulky substrate **314**, Rupe rearrangement[138] provided an alternative method. Commercially available tertiary α–acetylenic alcohol **313** was successfully isomerised to α,β-unsaturated carbonyl compound **314** *via* a 1,3-shift (Scheme 122).



Scheme 122. Rupe Rearrangement; (a) H_2SO_4 (1.5 eq), AcOH, 110 °C, 1 d, 55%.

After the preparation of phenyl enones (**310-312** and **314**), we needed a further set of enones to investigate the electronic effect of various substituents on the aromatic ring. However, neither Mukaiyama aldol reaction nor Rupe rearrangement seemed to be a good choice because of the difficulty in the preparation of the requisite stating materials. At this stage, we considered an alternative approach using Wittig olefination (Table 22).

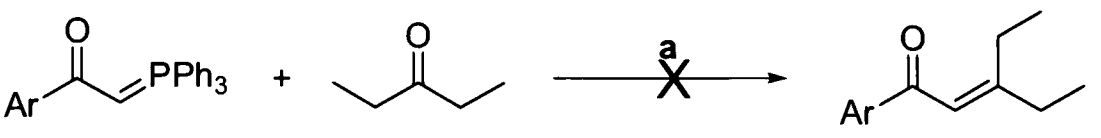
Table 22. Attempted Wittig olefination; (a) CH_3PPh_3Br (3.0 eq), PhLi solution in Et_2O (1.80 M, 3.0 eq), THF, -78 °C to rt, overnight, (b) acetone (excess), toluene, 110 °C.



Entry	Ar	Ylide (yield)
1	*p*-methoxyphenyl	**315** (95%)
2	*p*-chlorophenyl	**316** (60%)

To prepare the representative examples of electron poor aryl enone and electron rich aryl enones, we synthesised ylides **315** and **316** in reasonable yield from two different benzoyl chlorides bearing aryl Cl and MeO substituents. Subsequently, the ylides were used in a Wittig reaction with acetone. However, neither ylide underwent the desired reaction. To examine optimal conditions, we used an excess of acetone as it was used as both solvent and reactant (ketone). Additionally, the reaction temperature was increased from 0 °C to 50 °C and also longer reaction time was given up to 36 h. However, no product was observed. Thus, the solvent was changed from acetone to toluene to allow the application of higher reaction temperature (110 °C) and also the ketone was changed to pentan-3-one with higher boiling point than acetone (Table 23). Unfortunately, none of the above attempts gave any expected product from either ylide **315** or **316**. TLC inspection showed that the reaction mixture mainly consisted of starting materials.

Table 23. Attempted Wittig olefination with pentan-3-one; (a) acetone (excess), toluene, 110 °C.

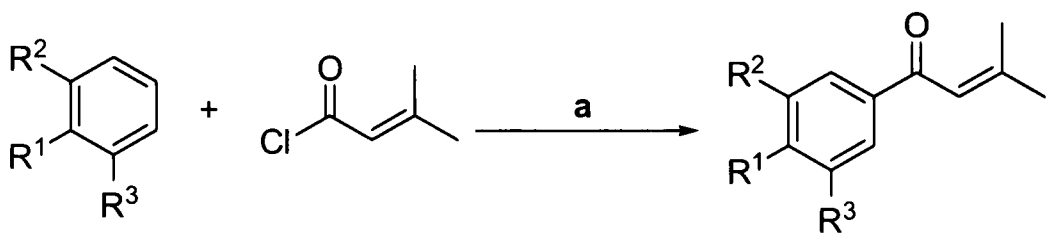


Entry	Ylide	Product
1	*p*-methoxyphenyl **315**	N/A[a]
2	*p*-chlorophenyl **316**	N/A[a]

[a] No reaction

Thus, we needed to consider other alternatives and a literature search suggested the application of Friedel-Crafts acylation to the synthesis of enones with electron rich phenyl rings in the presence of the Lewis acid $AlCl_3$.[139] According to literature procedures, we synthesised enones with mono-, di- and tri-methoxy substituted phenyl moieties in good yield (Table 24). However, the acylation did not work for the aryl system with a methyl substituent (entry 5) nor with an electron withdrawing group (Cl, entry 4) at the *para* position. It was suspected that these substrates might not be sufficiently electron-rich to undergo the acylation.

Table 24. Friedel-Crafts acylation; (a) $AlCl_3$, CS_2, 0 °C to rt, 1 d.



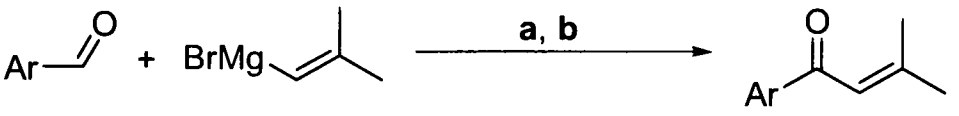
Entry	R^1	R^2	R^3	Product (yield)
1	MeO	H	H	**317** (75%)
2	MeO	MeO	H	**318** (80%)
3	MeO	MeO	MeO	**319** (80%)
4	Cl	H	H	N/A[a]
5	Me	H	H	N/A[a]

[a] No reaction.

For the preparation of aryl enones with electron poor substituents, we employed Grignard

reaction between the appropriate aromatic aldehyde and a vinyl Grignard reagent, followed by MnO_2 oxidation of the resulting alcohol (Table 25).

Table 25. Grignard reaction and oxidation strategy; (a) 0.5 M Grignard reagent in THF (1.2 eq), Et_2O, rt, 5 h, (b) acetone, MnO_2 (20.0 eq) rt.



Entry	Ar	Product (yield[a])
1	*p*-chloroxyphenyl	**320** (53%)
2	*p*-nitrophenyl	**321** (13%)
3	*p*-methylphenyl	**322** (62%)
4	2-Naph	**323** (69%)

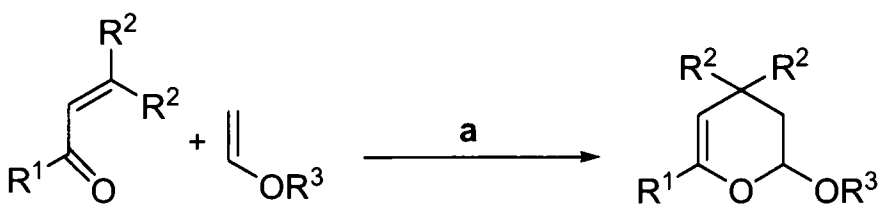
[a] Over two steps

For the MnO_2 oxidation, we used the crude mixture of the alcohol from the Grignard reaction without purification. In addition to the synthesis of aryl enones with electron poor substituents such as chloro (**320**) and nitro (**321**), we prepared tolyl enone (**322**) and naphthalenyl enone (**323**) in reasonable yield over 2 steps.

2.2.2. Preparation of various DHPs

After having prepared a wide range of enones, we used them in the synthesis of various DHPs (Table 26). At this stage, we adopted microwave technology to promote the HDA reaction rather than using a pressure tube. In spite of its limitations for large scale reaction, the use of microwaves dramatically reduced the reaction time from a few days to a few hours.

Table 26. Preparation of various DHPs; (a) YbFOD (0.05 mol%), microwaves.



Entry	R^1	R^2	R^3	DHP (yield)
1	Ph	H	Et	**308** (48%)
2	Ph	Me	Et	**324** (41%)
3	Ph	Et	Et	**325** (12%)
4	Ph	cyHex	Et	**326** (30%)
5	Ph	Ph	Et/^{n}Bu	N/A (0%)
6	*p*-MeO phenyl	Me	Et	**327** (27%)
7	*m,p*-MeO phenyl	Me	Et/^{n}Bu	N/A (0%)
8	*m,m,p*-MeO phenyl	Me	Et/^{n}Bu	N/A (0%)
9	Naph	Me	Et	**328** (41%)
10	*p*-Me phenyl	Me	Et	**329** (40%)
11	*p*-Cl phenyl	Me	Et	**330** (44%)
12	*p*-NO_2 phenyl	Me	Et	**331** (58%)

From the results above, we found that bulky enone ß-substituents slowed down the cycloaddition (entries 1-5). The yield gradually decreased as the size of substituent R^2 became larger. In the case of extremely bulky substrates, the reaction did not give any cycloadduct and the product mixture was complex (entry 5). We assumed that the bulky R^2 substituents would disfavour the s-*cis*-enone form which is required for cycloaddition, and the enone would exist predominantly in the s-*trans*-enone form (Fig. 25).

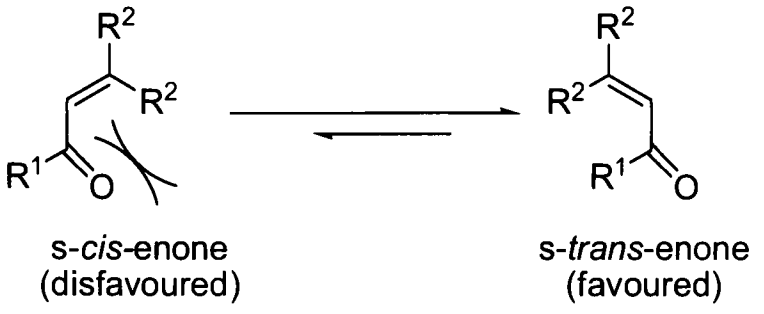


Fig. 25. s-*cis*-enone and s-*trans*-enone.

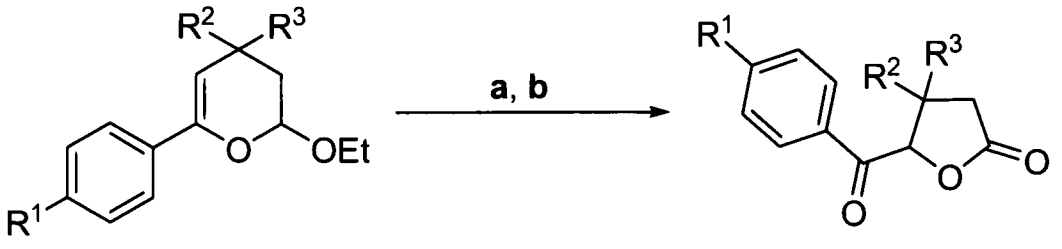
We also found a trend caused by the electronic effect of the substituents in the aryl ring. When the aryl group was electron-rich, the yield of cycloaddition was decreased (entries 6-8 and 10). In the case of the reaction between aryl enones bearing dimethoxy (entry 7) and trimethoxy substituents (entry 8) and an enol ether, we could not observe any cycloadduct and the reaction mixture was complex. However, we obtained the highest yield (58%) for the *p*-NO_2 substituted phenyl enone (entry 12). These trends are as expected for reaction with an electron rich dienophile (the enol ether). Finally, we synthesised an interesting DHP bearing a naphthalenyl moiety in 41% yield (entry 9).

Consequently, even though some of the HDA reactions gave a low yield or did not give the cycloadduct, we had been able to prepare a wide range of DHPs for testing in the next step, the oxidative rearrangement.

2.2.3. Enantioselective formation of THFs

After the preparation of various DHPs, we synthesised the racemic tetrahydrofuranones *via* the previously established oxidative rearrangement method using DMDO followed by Jones oxidation (Table 27). These racemic compounds were required in order to establish conditions for eventual determination of enantiomeric excess by chiral HPLC. Conversion was complete by TLC inspection and all DHPs were smoothly transformed to tetrahydrofuranones in a reasonable yield over two steps (49-69%). After we obtained the racemic tetrahydrofuranones, we were able in each case to resolve the two enantiomers by chiral HPLC.

Table 27. Synthesis of racemic tetrahydrofuranones; (a) DMDO (1.0 eq), CH_2Cl_2, 0 °C to rt, (b) Jones reagent (3.0 eq), acetone, 0 °C to rt.

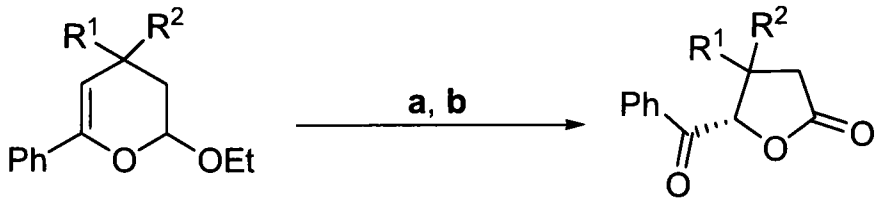


Entry	R^1	R^2 (=R^3)	Tetrahydrofuranone (yield[a])
1	H	H	(±)-**309** (50%)
2	H	Me	(±)-**332** (69%)
3	H	Et	(±)-**333** (59%)
4	H	cyHex	(±)-**334** (55%)
5	MeO	Me	(±)-**335** (50%)
6	Me	Me	(±)-**336** (69%)
7	Cl	Me	(±)-**337** (53%)
8	NO_2	Me	(±)-**338** (49%)
9	Naph	Me	(±)-**339** (53%)

[a] Over 2 steps.

After the preparation of the racemic tetrahydrofuranones, we undertook the enantioselective oxidative rearrangement *via* asymmetric epoxidation with Jacobsen's catalyst followed by Jones oxidation. Firstly, we investigated the effect of substituent size at C-4 of the DHP in the rearrangement (Table 28). The reactions were complete by TLC inspection and gave tetrahydrofuranones in reasonable yield (40-55%). However, the yield gradually decreased as the size of substituent R^1 and R^2 became larger. In terms of enantiomeric excess, higher levels of stereocontrol up to 80% ee (entry 4) were observed with more sterically demanding and branched R^1 and R^2 groups.

Table 28. Enantioselective synthesis of tetrahydrofuranones I; (a) 4-phenyl pyridine *N*-oxide (0.2 eq), (*R,R*)-Jacobsen's catalyst **307** (0.05 eq), NaOCl (1.5 eq), CH_2Cl_2, 0 °C to rt, (b) Jones reagent (3.0 eq), acetone, 0 °C to rt.

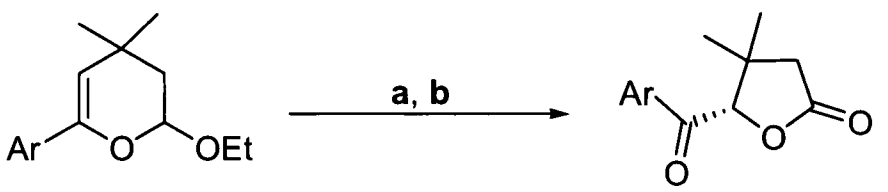


Entry	R^1 (=R^2)	Tetrahydrofuranone (yield[a])	ee[b]
1	H	(*S*)-**309** (55%)	38%
2	Me	(*S*)-**332** (49%)	58%
3	Et	(*S*)-**333** (45%)	69%
4	cyHex	(*S*)-**334** (40%)	80%

[a] Over 2 steps, [b] Determined by HPLC analysis)

Secondly, we investigated the electronic effect of the aryl substituent at C-6 of the DHP in the rearrangement (Table 29).

Table 29. Enantioselective synthesis of tetrahydrofuranones II; (a) 4-phenyl pyridine N-oxide (0.2 eq), (*R,R*)-Jacobsen's catalyst **307** (0.05 eq), NaOCl (1.5 eq), CH_2Cl_2, 0 °C to rt, (b) Jones reagent (3.0 eq), acetone, 0 °C to rt.



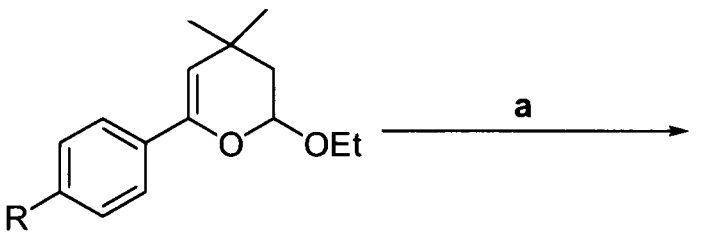
Entry	Ar	Tetrahydrofuranone (yield[a])	ee[b]
1	*p*-MeO phenyl	(*S*)-**335** (35%)	79%
2	Naph	(*S*)-**339** (41%)	71%
3	*p*-Me phenyl	(*S*)-**336** (43%)	70%
4	Ph	(*S*)-**332** (49%)	58%
5	*p*-Cl phenyl	(*S*)-**337** (40%)	76%
6	*p*-NO_2 phenyl	(*S*)-**338** (64%)	46%

[a] Over 2 steps, [b] Determined by HPLC analysis.

The reactions were again complete by TLC analysis and gave tetrahydrofuranones in reasonable yield (40-64%) in most cases (entries 2-6). Additionally, we found that the yield was generally higher when the aryl substituent was an electron-withdrawing group (entries 1, 3, 4, 6) In terms of enantiomeric excess, higher levels of stereocontrol (up to 79 % ee, entry 1) were generally observed with electron-donating aryl substituents (compare entries 1, 3, 6). In view of those results, the high ee observed for the oxidative rearrangement of *p*-Cl-substituted aryl DHP (76% ee, entry 5) hinted that the electron-donating effect of the Cl-substituent by resonance rather than its inductive effect was a major influence on the enantioselectivity.

At this stage, we wondered whether the differing ee results could be partly due to differing levels of background epoxidation for the various substrates. If NaOCl without Jacobsen's catalyst could epoxidise the DHPs, it would affect the product ee because of the competing formation of racemic products. Thus, we needed to check the background reaction without catalyst. We chose three representative DHP examples and applied the same epoxidation conditions in the absence of Jacobsen's catalyst (Table 30).

Table 30. Background reaction without Jacobsen's catalyst **307**; (a) 4-phenyl pyridine *N*-oxide (0.2 eq), NaOCl (1.5 eq), CH_2Cl_2, 0 °C to rt.



Entry	DHP (R)	Time	Product
1	**327** (MeO)	3.5 h	S.M. disappeared[a] (no rearrangement product[b])
2	**324** (H)	3.5 h	S.M. disappeared[a] (no rearrangement product[b])
3	**331** (NO_2)	3.5 h	No reaction[a,b]

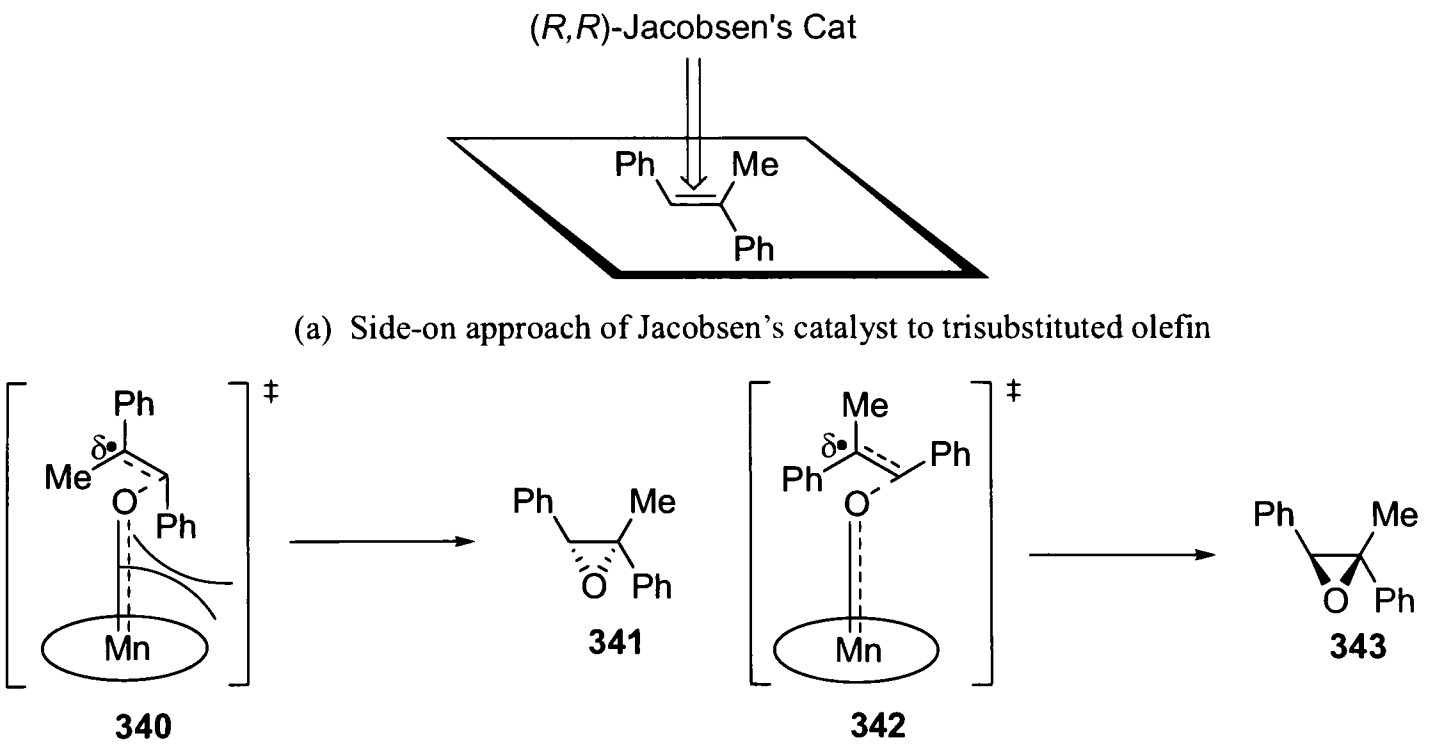
[a] Determined by TLC analysis. [b] Determined by ^{1}H NMR analysis.

However, we could not find any rearranged product by epoxidation from the background reactions of electron-rich aryl substituted DHP (entry 1), phenyl substituted DHP (entry 2)

and electron poor aryl substituted DHP (entry 3). This suggested that the product ee values would not be affected by background oxidation. Additionally, the result showed that the electron-rich aryl substituted DHP (entry 1) is more reactive to NaOCl than the electron-poor aryl substituted DHP (entry 3). This could explain the lower yields observed in the epoxidation/rearrangement of the former substrates.

2.2.4. Determination of product configuration

After observing promising levels of enantioselectivity in the enantioselective formation of tetrahydrofuranones, it was necessary to determine and explain the observed product configuration. Jacobsen reported that the enantioselectivity in the epoxidation can be evaluated according to a general skewed side-on approach transition state model (Scheme 123).[133] The transition state **340** leads to severe steric repulsion between ligand and olefin and the formation of the corresponding epoxide **341** will be disfavoured (Scheme 123, b). However, such interactions are avoided in competing transition state **342** and it leads to the formation of the expected epoxide **343** (Scheme 123, c).



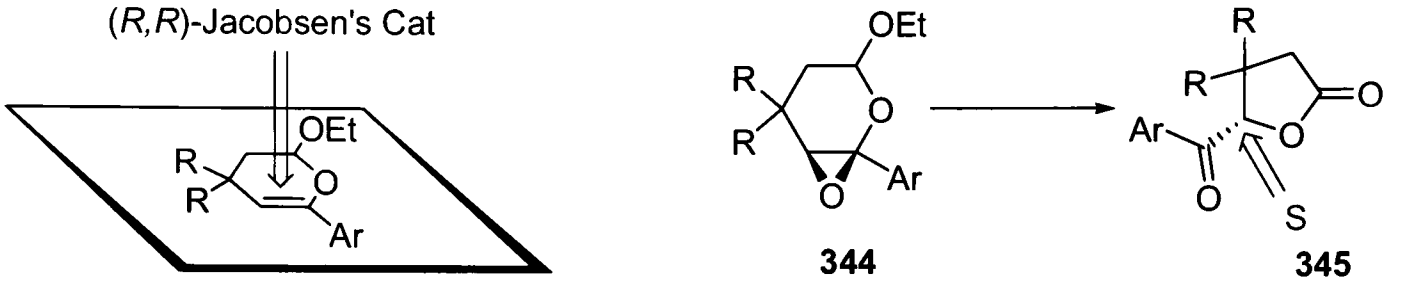
(a) Side-on approach of Jacobsen's catalyst to trisubstituted olefin

(b) Disfavoured transition state.

(c) Favoured transition state.

Scheme 123. Enantioselectivity explained by Jacobsen's model study.

On the basis of Jacobsen's model study, we expected the (*S*)-configuration of the resulting tetrahydrofuranone **345** from the formation of the favoured epoxide **344** (Scheme 124).

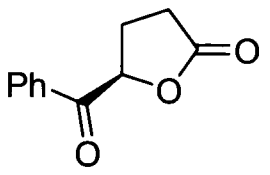


(a) Side-on approach of Jacobsen's catalyst to DHP. (b) (*S*)-Tetrahydrofuranone from favoured epoxide.

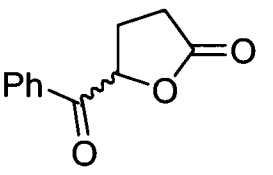
Scheme 124. Applcation of Jacobsen's model study to our DHP system.

In spite of our prediction for the observed configuration, we still needed evidence to confirm it. From a literature search, we found that Ghisalberti reported the optical rotation value of enantiomerically pure (*R*)-5-benzoyl-tetrahydrofuranone (*R*)-**309** as $[\alpha]_D$= +4.2 in acetone and +9 in $CHCl_3$ (Table 31).[140]

Table 31. Comparison of (*R*)-5-benzoyl-tetrahydrofuranone **309** and our result.



(*R*)-**309**

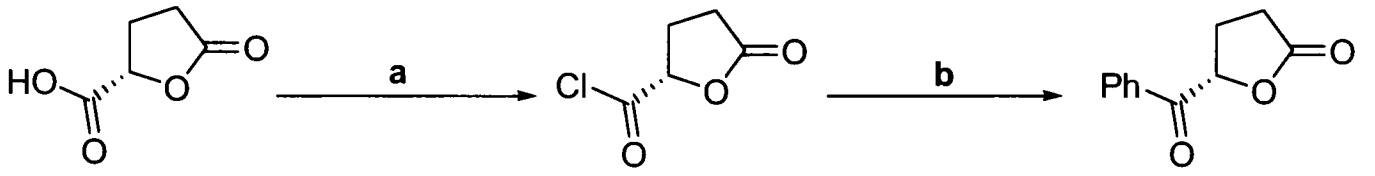


309

	Ghisalberti's result (*R*)-**309**	Our observation **309**
configuration	(*R*)	(Unknown)
ee	>99%	38%
$[\alpha]_D$	+4.2° in acetone (+9° in $CHCl_3$)	0° in $CHCl_3$

If our prediction was correct, our product should give a negative optical rotation value because we expected our major product would have the (*S*)-configuration. However, we

could not use optical rotation values to assign configuration because the observed optical rotation for our sample of 38% ee was essentially zero ($[\alpha]_D$=0 (*c* 0.03, $CHCl_3$)). This would be due to the low ee (38%) of our product and the small magnitude of the optical rotation for the enantiomerically pure compound. We therefore considered the comparison of chiral HPLC retention times between enantiomerically pure benzoyl-tetrahydrofuranone (*R*)-**309** and our product **309**. However, to obtain chiral HPLC data for the optically pure benzoyl-tetrahydrofuranone, we needed to synthesise it. From a literature search, we found that Cahiez has reported a synthesis of (*S*)-benzoyl-tetrahydrofuranone (*S*)-**309** (Scheme 125).[140, 141]

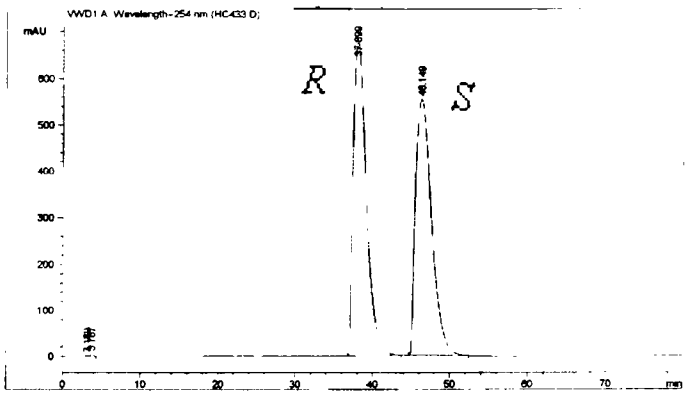


346 (*S*)-**309**

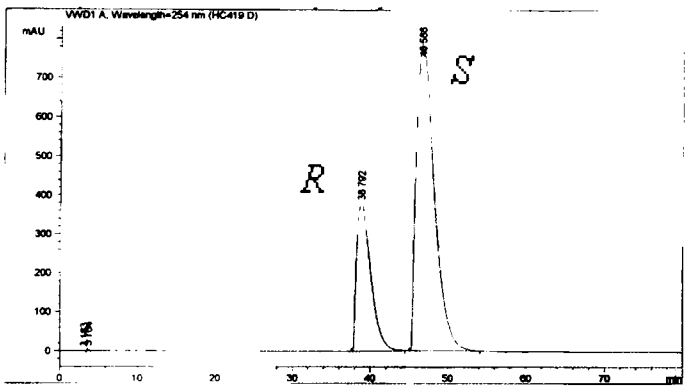
Scheme 125. Synthetic route toward (*S*)-5-benzoyl-dihydrofuranone by Cahiez; (a) $(COCl)_2$, DMF, CH_2Cl_2, (b) PhMnCl, THF, -78 °C, 3h.

According to Cahiez's procedure, we synthesised (*S*)-5-benzoyl-tetrahydrofuranone **309**. Firstly, crude acid chloride was obtained by the reaction of commercially available (*S*)-5-oxo-tetrahydrofuran-2-carboxylic acid **346** and oxalyl chloride in the presence of DMF as a catalyst. Subsequently, the addition of phenylmanganese chloride gave (*S*)-5-benzoyl-tetrahydrofuranone (*S*)-**309** in 99% ee and 10% yield over 2 steps. We compared the chiral HPLC data to those of our sample **309** (Fig. 26). This provided the evidence to support our proposed configuration, showing that the major enantiomer from our Jacobsen's epoxidation/rearrangement indeed had the (*S*)-configuration

a) Racemic mixture from the oxidative rearrangement by DMDO.



b) Chiral tetrahydrofuranone (38% ee) from the oxidative rearrangement by Jacobsen's catalyst.



c) Chiral tetrahydrofuranone (<99% ee) from Cahiez's synthesis.

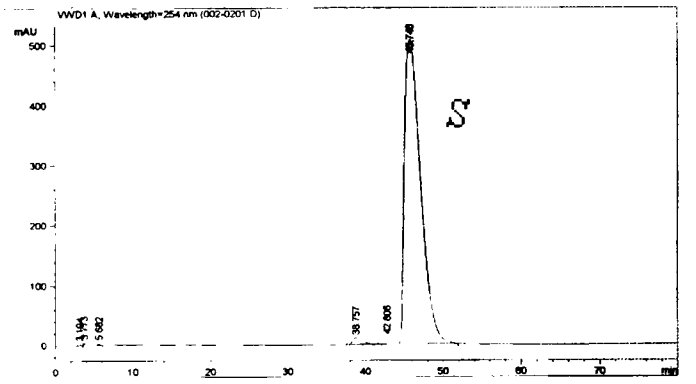
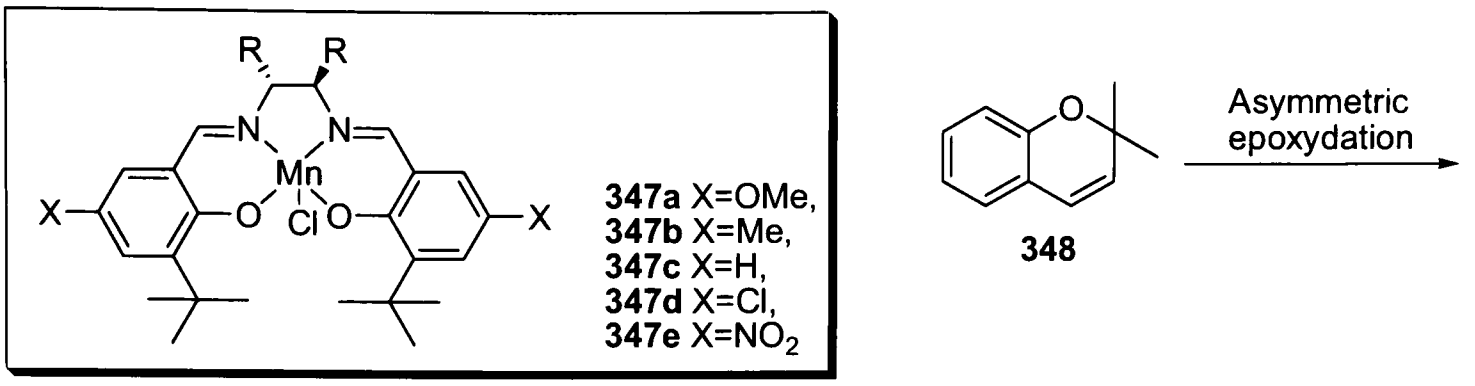


Fig. 26. Comparison of HPLC data for 5-benzoyl-tetrahydrofuranone **309**.

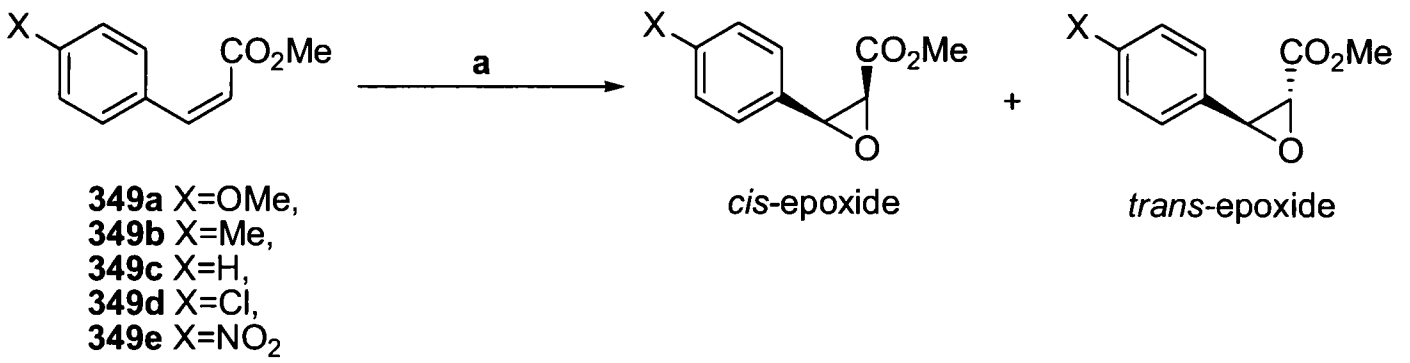
We next decided to examine more closely the observed electronic effect of the aryl substituent on enantioselectivity. From a literature search, we found previous studies on electronic effects in asymmetric epoxidation using Jacobsen catalysts. Firstly, we found that Jacobsen and co-workers showed a linear Hammett relationship between the value of the substituent constant σ_{para} for the catalyst and the enantiomeric excess in the epoxidation of (*Z*)-1,2-disubstituted alkene **348** (Scheme 126).[142]



Scheme 126. Electronic tuning of Mn(salen) catalyst

In this study, they found that the simple change of the substituent (X) of the catalyst resulted in a dramatic change of the enantiomeric excess from 22% (**347e**, X=NO_2) to 96% (**347a**, X=OMe). However, they only focussed on the tuning of the catalyst and they did not study the electronic tuning of the alkene substrate.

Secondly, we found that Jacobsen and co-workers also found a good linear relationship between the electronic properties of (*Z*)-cinnamate esters (**349a-349e**) and the ratio of *cis*/*trans*-epoxides using a Hammett plot and the value of the substituent constant σ_{para} (Scheme 127).[132]

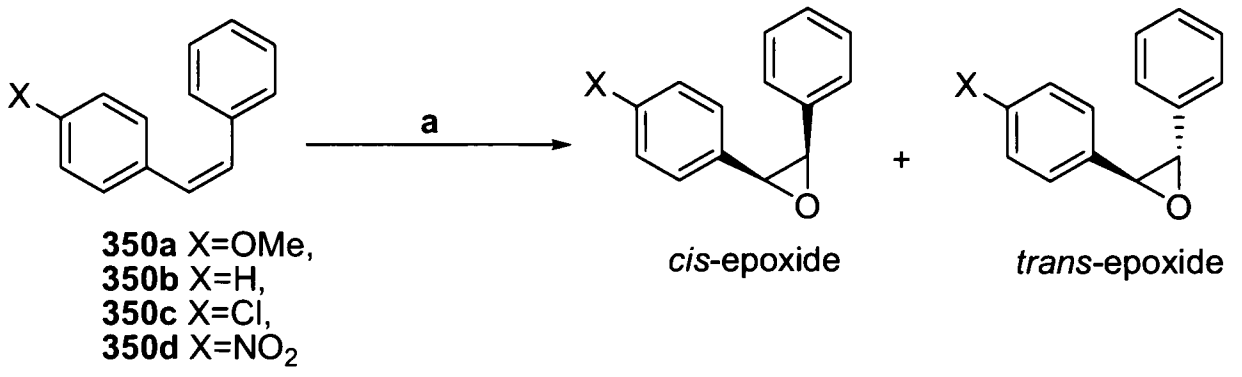


Scheme 127. Asymmetric epoxidation of (*Z*)-cinnamate esters; (a) (*R*,*R*)-Jacobsen's catalyst **307**.

In this study, they found that changing the substituent (X) of the (*Z*)-cinnamate ester **349** resulted in a dramatic change of the ratio of *cis*/*trans*-epoxides from 0.3 (**349e**, X=NO_2) to 11.7 (**349a**, X=OMe). Furthermore, they obtained facial selectivity (61-82%) by the equation (Eq. 1).

$$\text{Facial selectivity} = (ee_{cis} \times \%cis) + (ee_{trans} \times \%trans) \qquad \text{(Eq. 1)}$$

However, this facial selectivity did not show a Hammett correlation to the substituent's electronic properties. Additionally, Linde and co-workers showed a good relationship between the electronic property of (*Z*)-stilbenes **350** and the ratio of *cis*/*trans*-epoxides using a Hammett plot and the value of the modified substituent constant σ_{para}^{+} (Scheme 128).[143]



350a X=OMe,
350b X=H,
350c X=Cl,
350d X=NO_2

cis-epoxide

trans-epoxide

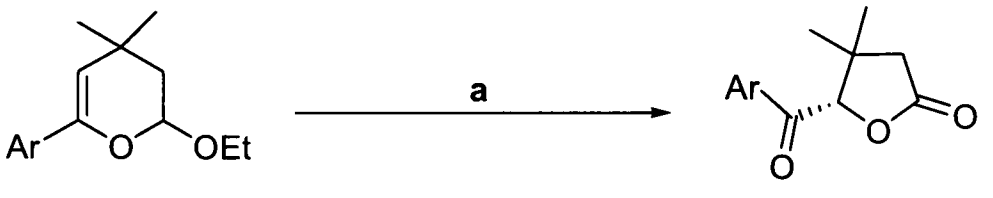
Scheme 128. Asymmetric epoxidation of (*Z*)-stilbenes **350**; (a) (*R*,*R*)-Jacobsen's catalyst **307**.

In this study, they found that changing the substituent (X) of (*Z*)-stilbenes **350** resulted in a change of the ratio of *cis*/*trans*-epoxides from 0.2 (**350d**, X=NO_2) to 2.2 (**350a**, X=OMe). They also suggested that the modified substituent constant σ_{para}^{+} was more suitable to explain the selectivity of *cis*/*trans*-epoxides than the substituent constant σ_{para} in the epoxidation of (*Z*)-stilbenes. However, Jacobsen and Linde focused on the correlation between the electronic tuning of olefins and the selectivity of *cis*/*trans*-epoxides. Their study was therefore not appropriate to explain the epoxidation of our DHPs for two reasons. Firstly, the epoxidation of the unique olefin in a rigid ring system (DHP) only gave the *cis* epoxide and there was no issue of *cis*/*trans*-selectivity. Secondly, we were interested in the correlation between the electronic tuning of olefins and the enantiomeric excess of the *cis* epoxides. Thus, we decided to examine a Hammett plot based on our results.

For our own Hammett plots, we used the value of the substituent constant σ_{para} and the

modified substituent constant σ_{para}^{+} and log (*S*/*R*). Log (*S*/*R*) values were obtained from the observed enantiomeric excess (Table 32).

Table 32. Values for Hammett plots; (a) i. oxidative rearrangement; ii. Jones oxidation.[144]



Entry	THF	Ar	σ_{para}	σ_{para}^{+}	ee	%*S*[a]	%*R*[b]	log (*S*/*R*)[c]
1	**335**	*p*-MeO phenyl	-0.27	-0.78	79%	89.5	10.5	0.931
2	**336**	*p*-Me phenyl	-0.17	-0.31	70%	85.0	15.0	0.753
3	**332**	Ph	0	0	58%	79.0	21.0	0.575
4	**337**	*p*-Cl phenyl	0.23	0.11	75%	87.5	12.5	0.845
5	**338**	*p*-NO_2 phenyl	0.78	0.79	46%	73.0	27.0	0.432

[a] % of *S* enantiomer. [b] % of *S* enantiomer. [c] *S*/*R* = (% of *S* enantiomer) / (% of *R* enantiomer)

Firstly, we plotted log (*S*/*R*) against the substituent constant σ_{para} (Fig. 27). The black line shows the best linear fit to the data produced by software‡.

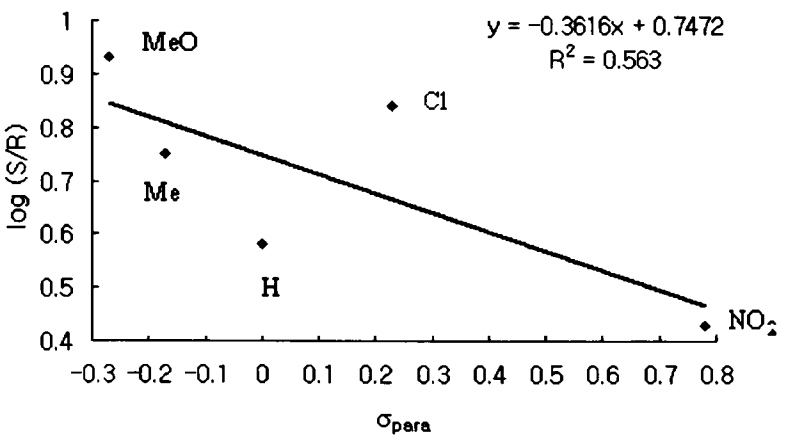


Fig. 27. Correlation of the enantioselectivity of epoxidation against σ_{para}.

‡ Microsoft Office Excel 2003

Clearly, these values did not show a reasonable correlation. So, we decided to plot log (*S*/*R*) against the modified substituent constant σ_{para}^{+} and the correlation was indeed improved (a, Fig. 28). Because the result with the chloro-substituent appeared to be furthest from the best-fit line, we decided to examine the effect of omitting this data point. Indeed, this modified data set now gave a reasonable straight line correlation (b, Fig. 28).

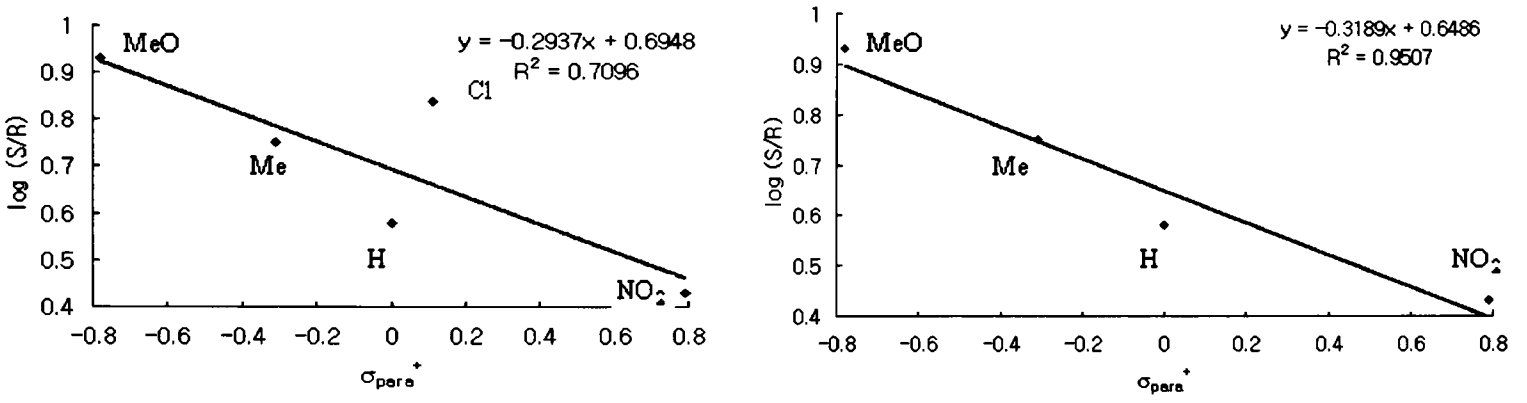
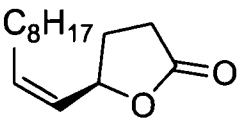


Fig. 28. Correlation of the enantioselectivity of epoxidation against σ_{para}^{+}.

From our Hammett plots, we were able to see σ_{para}^{+} provided a better correlation to our results than σ_{para}. The σ_{para}^{+} parameter is derived from a study of the rates of S_N1 hydrolysis of substituted aryl halides, which proceed *via* a benzylic carbocation. A good correlation of ee to this parameter suggests that the transition state leading to the major enantiomer has a larger degree of benzylic cation character than the transition state leading to the minor enantiomer.

2.2.5. Attempted manipulation of DHPs by Baeyer-Villiger reaction

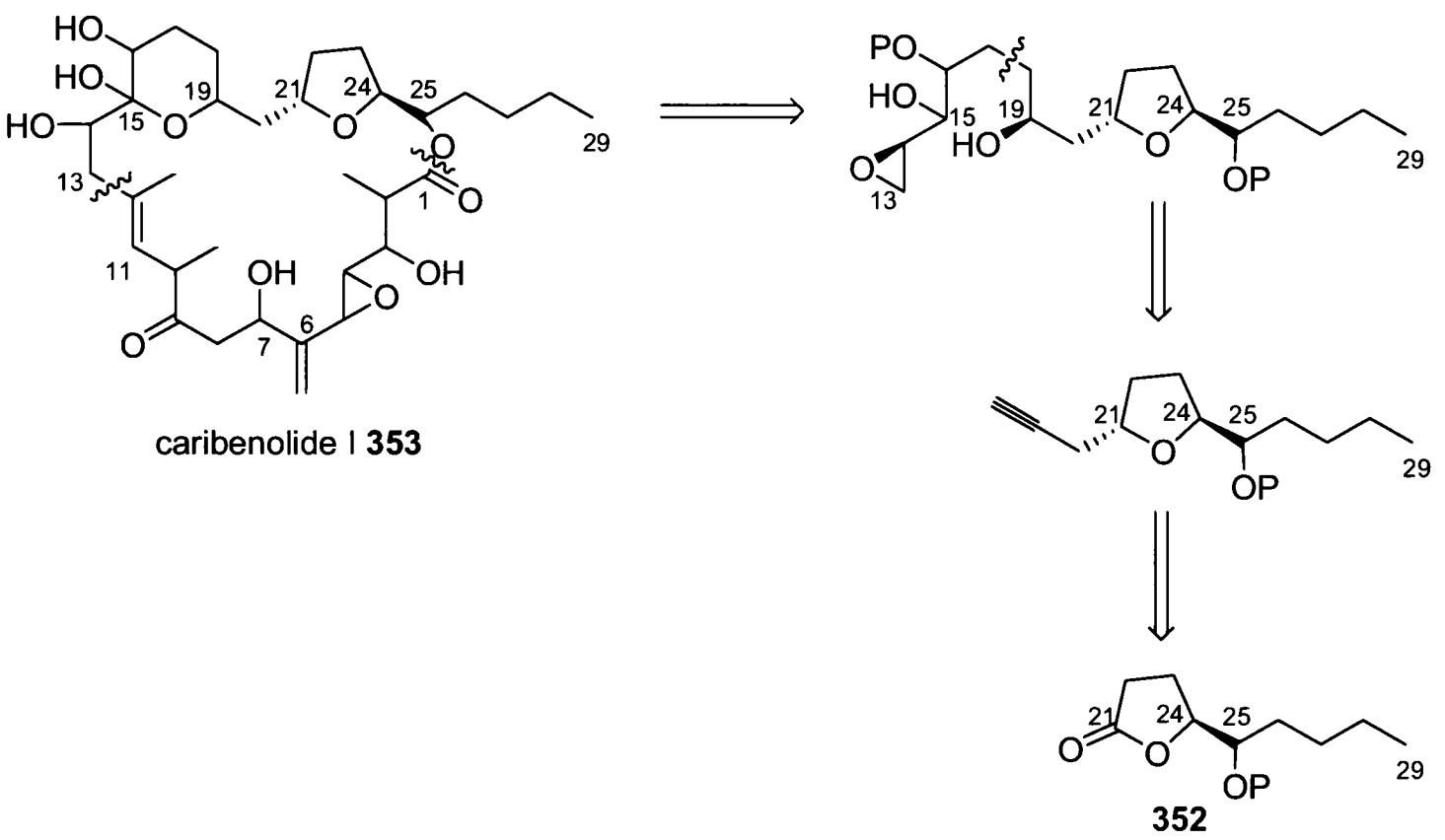
Having established a method for the enantioselective synthesis of tetrahydrofuranones, it would be desirable to apply our method to the synthesis of target molecules. From a literature search, we found that tetradecenolide **351** (Fig. 29) would be a suitable target molecule because of the structural similarity to our tetrahydrofuranones. This molecule was known to have pheromone activity, stimulating oviposition of mosquitos.[145]



351

Fig 29. Structure of tetradecenolide **351**.

Another possible target was the THF **352**, an intermediate in a synthesis of the C13-C29 fragment of caribenolide I (**353**) by Figadère and co-workers (Scheme 129).[146]



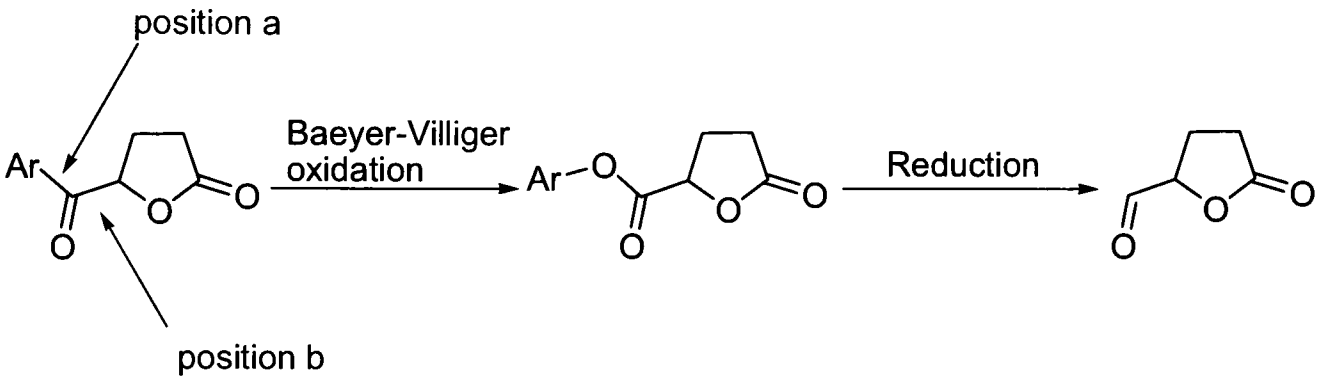
caribenolide I **353**

352

Scheme 129. Retrosynthesis of caribenolide I **353**.

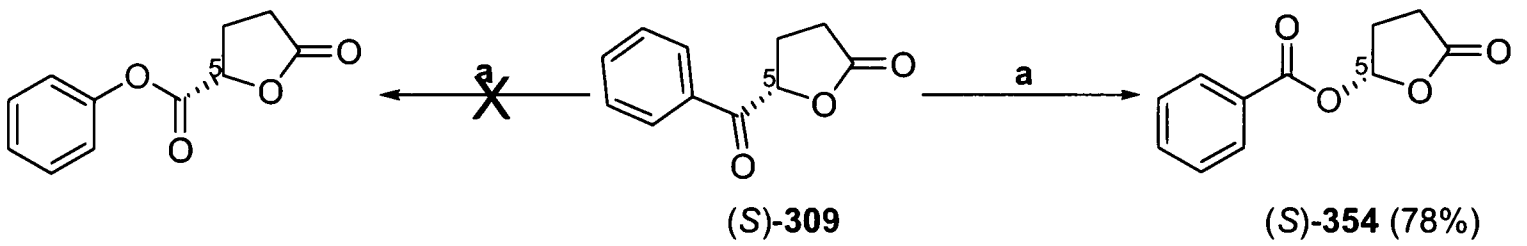
However, both of these targets would need substrates with no substituents at C-4 of the tetrahydrofuranone and these could not be prepared in good enantiomeric excess by our oxidative rearrangement method. To apply our method to the enantioselective synthesis of various target molecules or various synthetic intermediates as shown above, we would need to be able to manipulate the exocyclic ketone functional group. At this stage, we considered Baeyer-Villiger oxidation to the corresponding ester which could be reduced to the aldehyde functional group. The aldehyde functional group could then easily be transformed

into various functional groups and this would provide routes towards natural products or useful synthetic intermediates (Scheme 130).



Scheme 130. Idea for manipulation of tetrahydrofuranone.

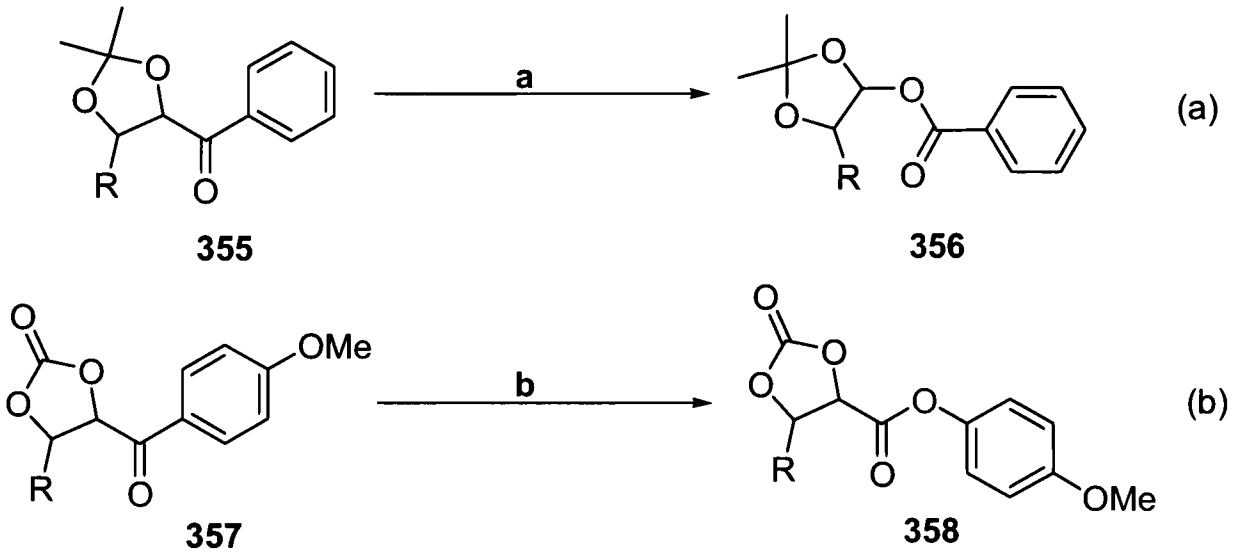
However, there was an issue about the regiochemistry in the migration of the Baeyer-Villiger reaction: we wanted to insert oxygen into between the aryl group and the ketone (position a), not between the lactone and the ketone (position b). Initially, we attempted Baeyer-Villiger oxidation of phenyl ketone (*S*)-**309** with MCPBA at 80 °C (Scheme 131).



Scheme 131. Attempted Baeyer-Villiger reaction of phenyl ketone; (a) MCPBA (2.0 eq), $C_2H_4Cl_2$, 80 °C, 2 d.

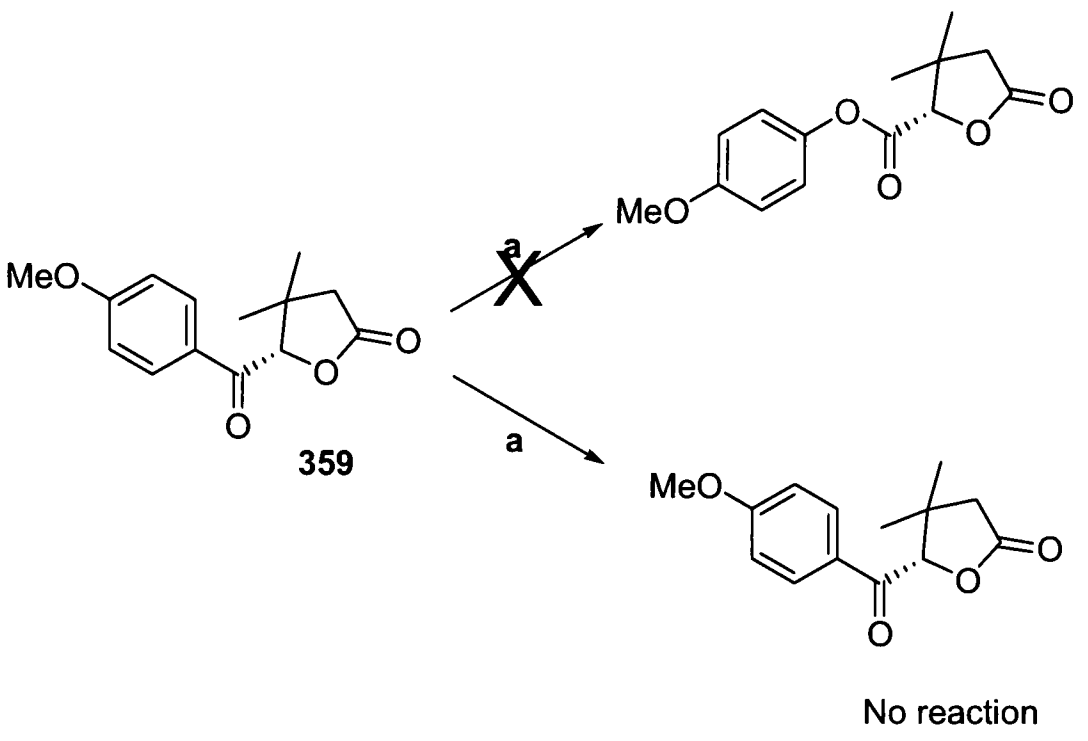
However, NMR analysis showed the value of the chemical shift for the proton at C-5 had moved from 5.79 ppm for the ketone (*S*)-**309** to 6.90 ppm in the product. Additionally, in the ^{13}C NMR spectrum, C-5 moved from 78.3 ppm for the ketone (*S*)-**309** to 95.8 ppm in the product. These observations suggested that the product was ester **354** with the unwanted regioselectivity because the observed large shifts downfield would not match with the desired phenyl ester. We speculated that addition of electron donating substituents to the

phenyl group may favour the desired regioselectivity. Indeed, we could find literature precedent for this tactic. Thus, Baeyer-Villiger of phenyl ketone **355** is reported to give the ester **356**, whereas the *p*-methoxyphenyl variant **357** is reported to afford the aryl ester **358** (Scheme 132).[147] The strategy would be especially attractive because methoxy-substituents on the aryl ring had earlier been found to improve the enantioselectivity of the epoxidation.



Scheme 132. Effect of electronic tuning on Baeyer-Villiger oxidation; (a) MCPBA, rt, 91%, (b) MCPBA, 50 °C, 87%.

We therefore attempted the Baeyer-Villiger oxidation of the more electron-rich aryl ketone **359** bearing a MeO group (Scheme 133). Unfortunately, however, the electron rich ketone did not react with MCPBA, even after 2 d at 80 °C. So, this reaction was not investigated further at this stage.

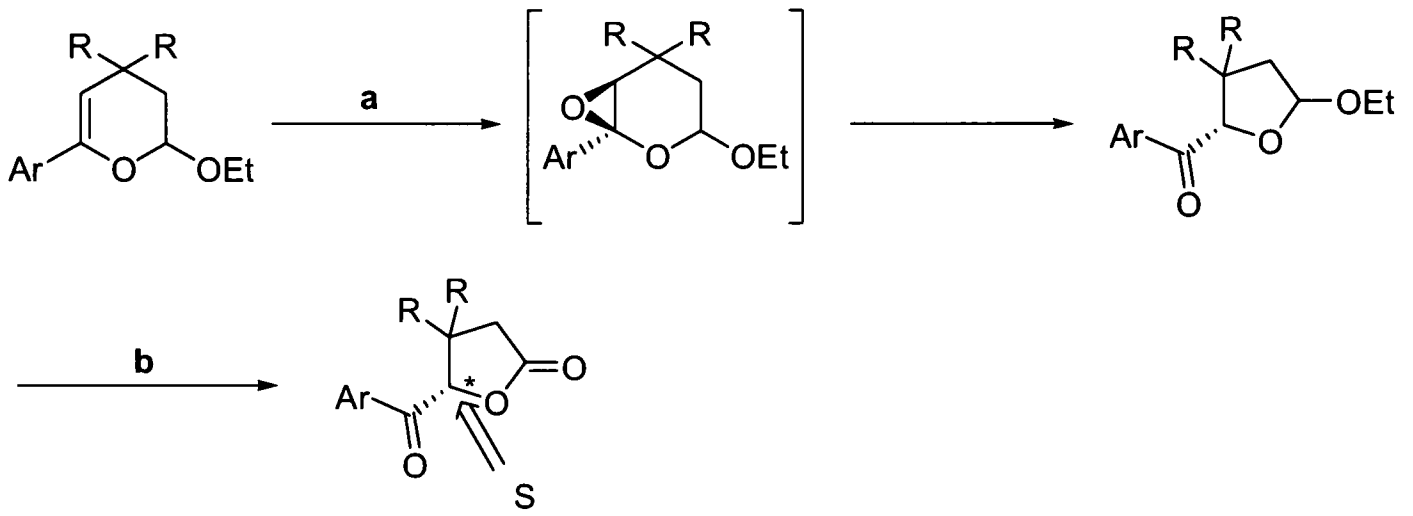


Scheme 133. Attempted Baeyer-Villiger oxidation of electron rich aryl ketone **359**; (a) MCPBA (2.0 eq), $C_2H_4Cl_2$, 80 °C, 2 d.

3. Conclusions and future work

3.1. Conclusions

In this Chapter, we investigated the enantioselective oxidative rearrangement of various aryl substituted DHPs to synthesise tetrahydrofuranones and this was achieved *via* asymmetric epoxidation with Jacobsen's catalyst (Scheme 134). The best result (80% ee) was obtained for tetrahydrofuranone **334** with a cyclohexyl moiety.

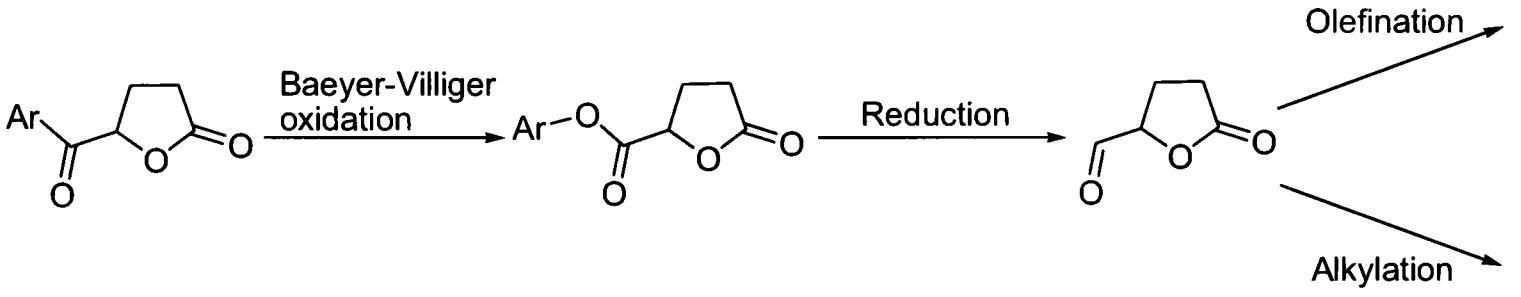


Scheme 134. Enantioselective oxidative rearrangement; (a) Asymmetric epoxidation by (*R*,*R*)-Jacobsen's catalyst **307**, (b) Jones reagent (3.0 eq), acetone, 0 °C to rt.

We proved the configuration of our products by comparison to a known tetrahydrofuranone and the observed enantioselectivity was in accordance with that observed previously for Jacobsen epoxidation of trisubstituted alkenes. Additionally, we investigated the electronic effect on the asymmetric epoxidation by Jacobsen's catalyst *via* tuning of the aryl moiety. A Hammett plot using σ_{para}^{+} values suggested the importance of conjugation to the aryl substituent in the asymmetric epoxidation. Furthermore, we attempted the manipulation of the tetrahydrofuranone *via* Baeyer-Villiger oxidation. However, it did not give the desired aryl ester.

3.2. Future work

Future work would include the investigation of alternative oxidants for Baeyer-Villiger oxidation. If this were successful, we could prepare the corresponding aryl ester which could then be reduced to the aldehyde functional group (Scheme 135). Furthermore, the aldehyde functional group could then easily be transformed into various functional groups by olefination or alkylation and this would provide routes towards natural product targets or valuable synthetic intermediates.



Scheme 135. Manipulation of tetrahydrofuranones.

This whole section dealt with enantioselective oxidative rearrangement by metal-based asymmetric epoxidation catalysis. In the next phase of the project, we explored the development of a catalyst for metal-free asymmetric epoxidation and the results of this will be discussed in Chapter III.

Chapter III. Synthesis of novel chiral ketone catalysts for enantioselective epoxidation of alkenes

1. Introduction

1.1. Previous chiral ketone catalyst in our group

Asymmetric epoxidation is important in organic synthesis because epoxides can react with various nucleophiles to provide ring-opened products stereospecifically. Use of enantiomerically enriched epoxides allows control of the absolute configuration of the resulting products to afford useful building blocks for asymmetric synthesis. Enantioselective synthesis of epoxides by epoxidation of alkenes has been intensively studied.[124] Amongst non-metal mediated methods, epoxidation catalysed by chiral ketones in the presence of Oxone® as an oxidant is particularly attractive. Shi's carbohydrate-derived catalyst **304** is the best known chiral ketone to date (see Chapter II), but several other classes of ketone have also been developed. In particular, new ketones that can be used in low loadings and that will work with a wider range of alkene substitution patterns are still required. Especially, the epoxidation of terminal alkenes with high enantioselectivity and electron-poor alkenes such as unsaturated esters with fast conversion are still remaining challenges. Shi and co-workers showed the improvement of ee in the epoxidation of *cis* olefins and terminal olefins with modified carbohydrate-derived catalyst **360** by the modification of the spirocyclic substituent (Fig. 30).[136d, 136e, 148] However, 1,1-disubstituted alkenes still give poor ee.

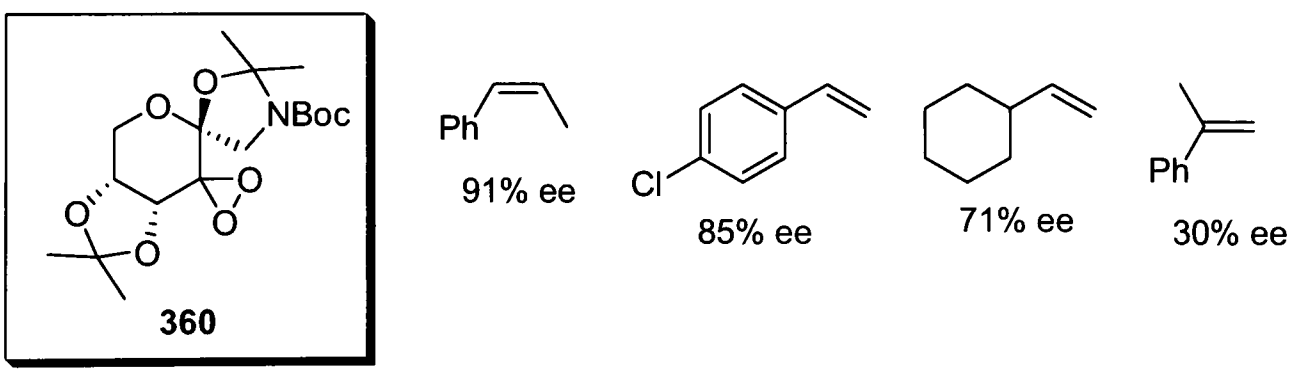
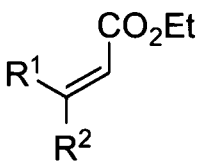


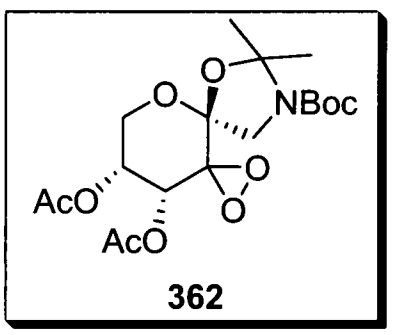
Fig. 30. Epoxidation of alkenes with catalyst **360**.

For the epoxidation of electron-poor alkenes, Shi and co-workers reported improved

catalytic reactivity and enantioselectivity by the replacement of the acetonide unit with more electron-withdrawing ester groups (Fig. 31) because the electrophilicity of electrophilic oxidant, dioxirane, can be increased by this replacement and it can prevent the decomposition of the catalyst by Baeyer-Villiger reaction.[149] This ketone **362** gives very good ee for α,β-trisubstituted unsaturated esters (**361a-361c**).



361a R^1=H, R^2=Ph (96% ee),
361b R^1=Me, R^2=Ph (96% ee),
361c R^1=R^2=Me (82% ee)



362

Fig. 31. Epoxidation of enolates with catalyst **362**.

Previously, the Armstrong group has synthesised various [3.2.1]-bicyclic ketone systems and tested them as catalysts for the asymmetric epoxidation with Oxone® (Fig 32).[150]

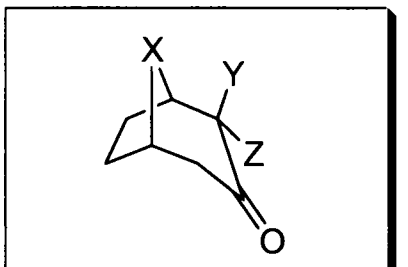
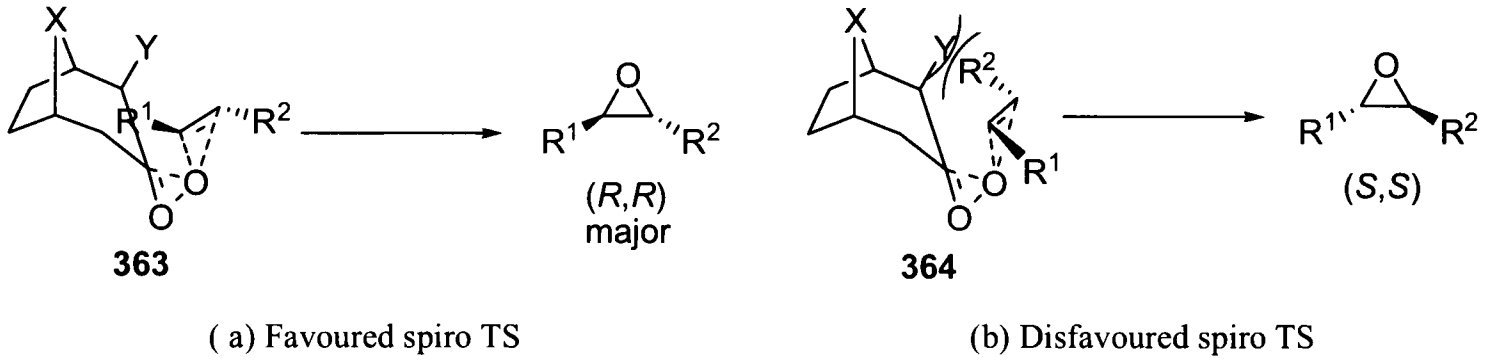


Fig. 32. Structure of [3.2.1] bicyclic ketones.

Much work has been done in the group on the effect of structure on the epoxidation enantioselectivity. Firstly, the bridgehead atom (X, Fig. 32) plays an important role in determining the activity and selectivity of the catalyst. *Oxa*-bicyclic ketones (X=O)

generally give higher enantiomeric excess than *aza*-bicyclic ketones (X=NCO_2Et).[151] Secondly, the electron-withdrawing substituent at the α-position (Y, Fig. 32) makes the ketone more electrophilic, activating it toward attack from Oxone®. The catalyst also becomes more stable to possible side reaction such as the Baeyer-Villiger decomposition. Thirdly, various α-monosubstituted ketones have been synthesised (Y = F, Cl, OAc, OCOR and Z = H) and axial substituted derivatives represent the best catalysts to date in the series (93% ee for *E*-stilbene when X = O, Y = OAc and Z = H).[152] The observed stereochemistry can be explained by a *spiro* transition state (Scheme 136). The major enantiomers can be obtained *via* the transition state **363** with less steric repulsion rather than the competing transition state **364** with severe steric repulsion between the olefin and substituent Y of the catalyst. Thus *trans*- and tri-substituted olefins are expected to give high enantioselectivity and terminal olefins are expected to give lower ee.

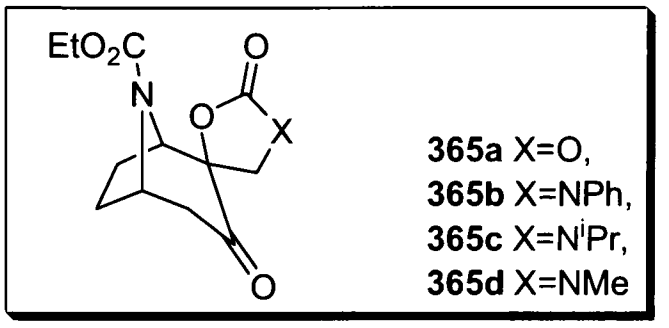


(a) Favoured spiro TS (b) Disfavoured spiro TS

Scheme 136. Explanation of stereochemistry from *spiro* transition state.

Very recently, our group has investigated the synthesis of 1,1-spirocyclic disubstituted ketones (**365a-365d**, Table 33) because Shi and co-workers found that the replacement of the spiroketal unit in fructose-derived ketone **365a** with an oxazolidinone gave improved enantioselectivity in the epoxidation of styrene.[148] Representative results are shown in Table 33.[153] This replacement could provide enantioselectivity of up to 59% ee in the epoxidation of styrene with catalyst **365b**. However, in terms of conversion, the oxazolidinone series (**365b-365d**) generally showed lower conversion than dioxolanone **365a**.

Table 33. Epoxidation catalysed by ketones **365a-365d**; Reaction conditions: alkene (1.0 eq), catalyst (0.1 eq), Oxone® (10.0 eq), $NaHCO_3$ (15.5 eq), CH_3CN, aq. Na_2EDTA (0.4 mM solution).



	365a		365b		365c		365d	
	Conv.[a]	ee	Conv.[a]	ee	Conv.[a]	ee	Conv.[a]	ee
E-Stilbene	100%	89%	76%	87%	90%	87%	85%	92%
Styrene	100%	46%	93%	59%	35%	54%	79%	58%
E-Ethylcinnamate	55%	74%	40%	82%	N/A	N/A	41%	80%

[a] Conversion (determined by ^1H NMR)

1.2. Concept of this project

As descrived above, the tropinone-derived spirocyclic catalysts (**365a–365d**) had given promising results. Because previous work in the group had shown that *oxa*-bicyclic catalysts generally give higher enantioselectivities than the tropinone derivatives, it seemed appropriate to study the effect of this modification on the spirocyclic catalysts. Therefore, in this project, a new *spiro*-cyclic ketone (Fig. 33) with an oxygen bridgehead would be synthesised and this catalyst would tested with various alkenes in the asymmetric epoxidation process to allow comparison of the results with its tropinone counterpart.

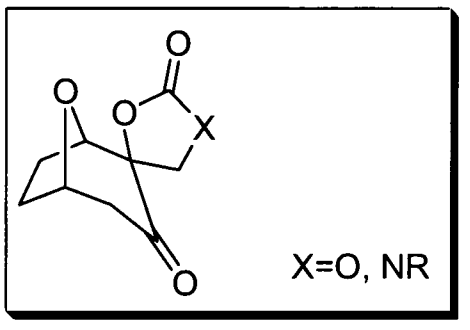


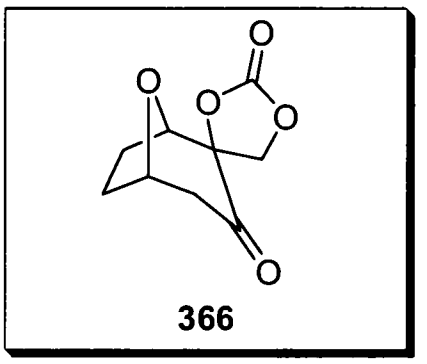
Fig. 33. Structure of new spirocyclic ketone system.

2. Results and discussion

2.1. *Oxa*-bicyclic ketone catalyst

2.1.1. Synthesis of racemic *oxa*-bicyclic ketone.

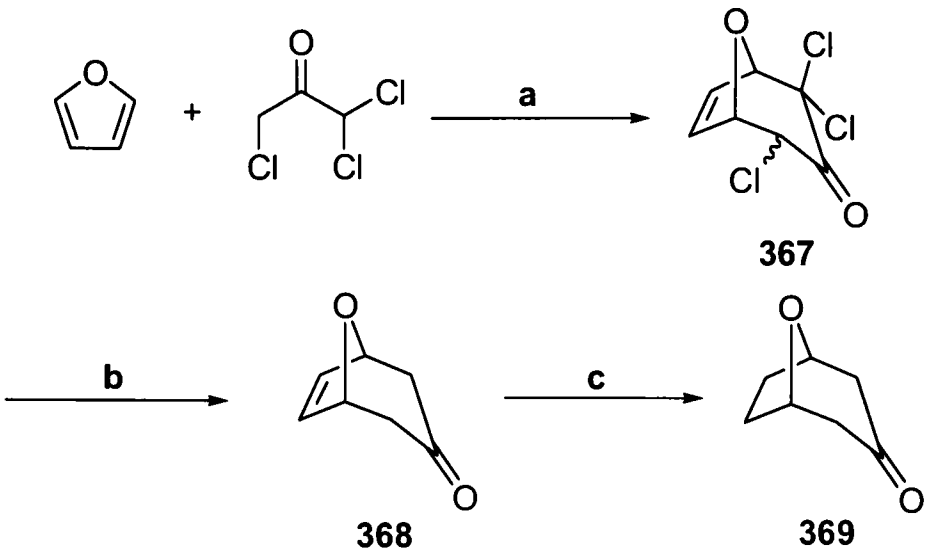
The first target molecule was the *oxa*-bicyclic ketone **366** containing a 1,1-fused cyclic carbonate (Fig. 34) using a synthetic strategy similar to that previously used for the tropinone series in our group.[153]



366

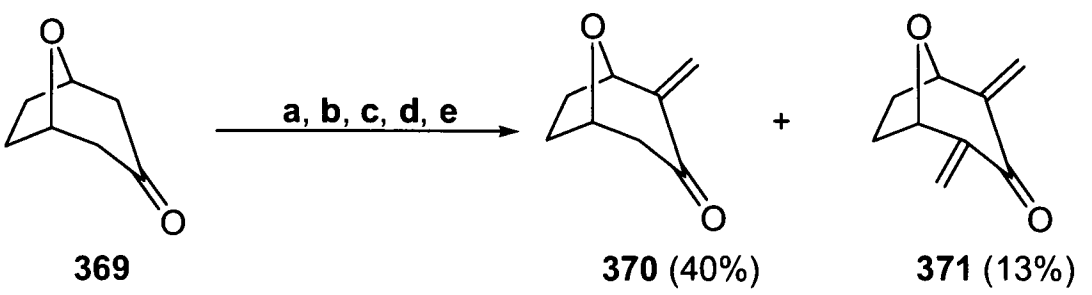
Fig. 34. *Oxa*-bicyclic ketone catalyst **366**.

To synthesise the target molecule, the parent *oxa*-bicylic ketone **369** was first synthesised using a known procedure (Scheme 137). Thus, 1,3-dipolar cycloaddition between furan and 1,1,3-trichloroacetone gave the *oxa*-bicycle **367** and subsequent treatment with an excess of zinc powder and copper (I) iodide effected complete dechlorination. The olefin in the oxabicycle **368** was then reduced by catalytic hydrogenation.



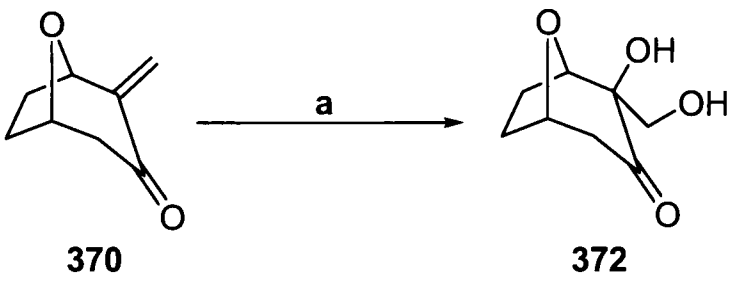
Scheme 137. Synthesis of parent *oxa*-bicyclic ketone; (a) CF_3CH_2OH, Et_3N, 5 °C to rt, overnight, (b) Zn powder (2.1 eq), CuI (0.7 eq), benzene/MeOH, 0 °C to overnight, 45% (over 2 steps), (C) H_2, 10% Pd/C, MeOH, rt, overnight, 98%.

After the preparation of parent ketone **369**, the introduction of the *exo*-methylene unit on the *oxa*-bicyclic ketone **369** was successfully achieved using a Mannich reaction analogous to that employed in the tropinone series (Scheme 138).[135] Thus, the ketone **369** was deprotonated with LiHMDS at -78 °C and then treated with TMSCl. The resulting silyl enol ether was then reacted with Eschenmoser's salt to give the Mannich base which was then methylated with MeI. Elimination of trimethylamine was achieved by heating in the presence of $NaHCO_3$. Interestingly, the formation of dimethylene **371** was competitive with the formation of desired methylene ketone **370**, resulting in a moderate yield of methylene ketone **370**.



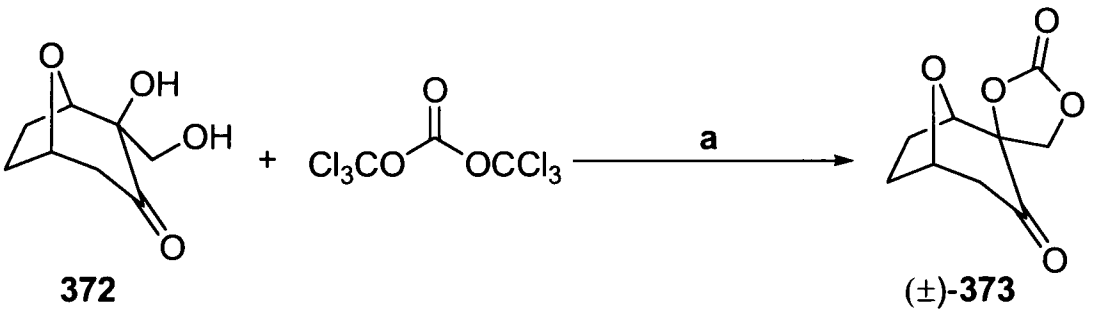
Scheme 138. Introduction of *exo*-methylene unit on *oxa*-bicyclic ketone by Mannich reaction; (a) 1.0 M LiHMDS (1.0 eq), THF, -78 °C, 30 min, (b) TMSCl (1.5 eq), -78 to 0 °C, 30 min, (c) Eschenmoser's salt (1.0 eq), DMF, pressure tube, rt, 1.5 h, (d) MeI (5.0 eq), 50 °C, overnight, (e) $NaHCO_3$ (7.0 eq), DMF, 95 °C, overnight.

The exocyclic enone **370** was then dihydroxylated with a catalytic quantity of $K_2OsO_4 \cdot 2H_2O$ and co-oxidant NMO in acetone/water using quinuclidine as the ligand (Scheme 139).[135]



Scheme 139. Dihydroxylation of methylene **370**; (a) $K_2OsO_4 \cdot 2H_2O$ (0.01 eq), quinuclidine (0.05 eq), NMO (1.9 eq), acetone/H_2O, rt, 3 d, 71%.

We assumed that the reaction occurred stereoselectively on the less hindered *exo*-face, in accordance with the stereochemical outcome in the tropinone series, which was proven by NOESY studies.[153] The diol **372** was then cyclised with triphosgene to give the dioxolanone **373** (Scheme 140).



Scheme 140. Cyclisation of diol **372** to dioxolanone **373**; (a) Pyridine, CH_2Cl_2, O °C to rt, 8 h, 72%.

2.1.2. Epoxidation by racemic *oxa*-bicyclic ketone

After we prepared racemic catalyst (±)-**373**, its potential catalytic efficiency towards the epoxidation of (*E*)-stilbene was evaluated using the standard Yang one-phase conditions (Table 34). Compared to tropinone derivative catalyst (entry 1), *oxa*-bicyclic ketone (±)-**373** clearly showed better catalytic reactivity. The epoxidation of (*E*)-stilbene was complete

using only 10 mol% loading of catalyst in 10 minutes. The reaction also proved that the catalyst was stable to the reaction conditions, since we were able to see the peaks for the catalyst in the ^{1}H NMR spectrum of the crude mixture.

Table 34. Epoxidation of *E*-stilbene catalysed by ketone (±)-**373**; Reaction conditions: alkene (1.0 eq), catalyst (0.1 eq), Oxone® (10.0 eq), $NaHCO_3$ (15.5 eq), CH_3CN, aq. Na_2EDTA (0.4 mM solution).

Entry	Alkene	Catalyst	Time	Epoxide (conversion[a])
1	(*E*)-Stilbene	(±)-**373**	<10 min	(±)-**374** (100%)
2		Tropinone **365a**	30 min	(±)-**374** (86%)

[a] Determined by crude ^{1}H NMR.

As a consequence of this encouraging result, we investigated the epoxidation of various olefins (Table 35).

Table 35. Epoxidation catalysed by ketone (±)-**373**; Reaction conditions: alkene (1.0 eq), catalyst (0.1 eq), Oxone® (10.0 eq), $NaHCO_3$ (15.5 eq), CH_3CN, aq. Na_2EDTA (0.4 mM solution).

Entry	Alkene	Catalyst	Time	Epoxide (conversion[a])
1	Styrene	(±)-**373**	1 h	(±)-**375** (100%)
2		Tropinone **365a**	1 h	(±)-**375**(100%)
3	α-Methylstyrene	(±)-**373**	1 h	(±)-**376** (100%)
4		Tropinone **365a**	1 h	(±)-**376** (100%)
5	(*E*)-β-Methylstyrene	(±)-**373**	1 h	(±)-**377** (100%)
6		Tropinone **365a**	1 h	(±)-**377** (100%)
7	Phenylcyclohexene	(±)-**373**	1 h	(±)-**378** (100%)
8		Tropinone **365a**	1 h	(±)-**378** (100%)
9	(*E*)-Ethylcinnamate	(±)-**373**	18 h	(±)-**379** (33%)
10		Tropinone **365a**	18 h	(±)-**379** (55%)

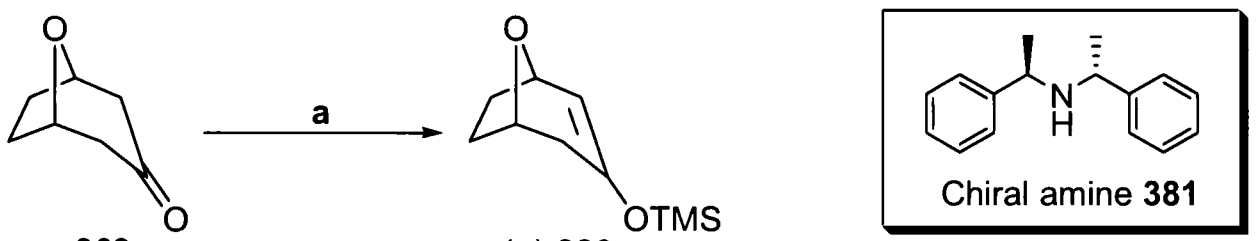
[a] Determined by crude ^{1}H NMR.

In all cases except (*E*)-ethylcinnamate, *oxa*-bicylic ketone (±)-**373** showed excellent

catalytic reactivity. The epoxidation of olefins was complete with only 10 mol% loading of catalyst in 1 h (entries 1-8). However, the ketone (±)-**373** showed extremely low catalytic reactivity in the epoxidation of (*E*)-ethylcinnamate (entry 9). The epoxidation of (*E*)-ethylcinnamate by ketone (±)-**373** showed 33% conversion in 18 h and this represented even lower conversion than the 55% observed with the tropinone catalyst (entry 10).

2.1.3. Synthesis of enantiomerically enriched *oxa*-bicyclic ketone

Since racemic ketone (±)-**373** generally showed excellent catalytic reactivity, we decide to investigate its synthesis in non-racemic form. In line with earlier studies in the group,[152, 154] we decided to employ desymmetrisation of parent ketone **369** *via* the formation of silyl enol ether with (*R*,*R*)-chiral amine **381** (Scheme 141).[155]



Scheme 141. Desymmetrisation of parent ketone (+)-**369**; (a) (+)-Bis[(*R*)-α-methylbenzyl]amine **381** (1.5 eq), ^{n}BuLi (1.5 eq), TMSCl (5.0 eq), THF, >40%.

The low yield of silyl enol ether **380** was caused by difficulties in removing the chiral amine. The amine was not completely removed by washing with $CuSO_4$ (aq, sat) several times. Use of an SCX column successfully removed the amine, but resulted in some hydrolysis of **380** to starting ketone **369**. After the desymmetrisation, we followed the reaction sequence previously employed for the synthesis of the racemic catalyst. Thus, Mannich reaction on (+)-**380** followed by dihydroxylation of the resulting olefin **370** with K_2OsO_4 and NMO gave diol **372**. Subsequently, reaction with triphosgene gave the chiral ketone catalyst (+)-**373**. To find out the enantiomeric purity of chiral catalyst (+)-**373**, we attempted to use chiral HPLC to separate the racemic ketone (±)-**373** with OD(H), OJ(H), OC, AD(H) and AS(H) columns with UV detection at 206 nm or 280 nm. However,

satisfactory resolution could not be achieved. As an alternative, we used ^{1}H NMR spectroscopy in the presence of the shift reagent Eu(hfc)$_3$. Pleasingly, when 30 mol% of the shift reagent was used, a clear separation for the racemic ketone (±)-**373** was detected around 3.10-3.60 ppm by ^{1}H NMR (b, Fig. 35). The same conditions were used for the chiral ketone (+)-**373** and the enantiomeric excess of catalyst (+)-**373** was evaluated as 68% ee because the ratio of two enantiomers was 5.3 to 1.0 by the investigation of the corresponding integral in the ^{1}H NMR spectrum (Fig. 35, c).

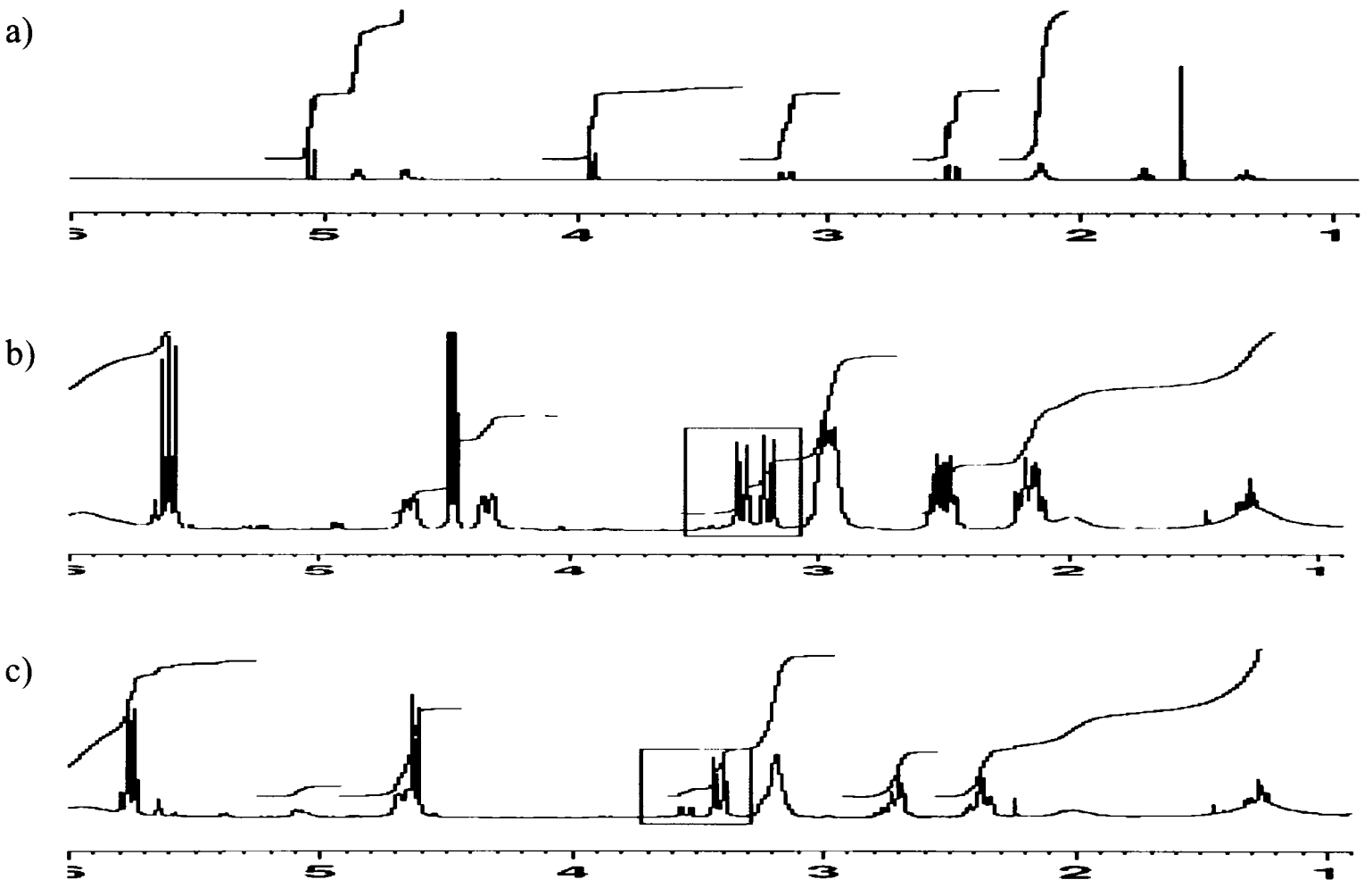


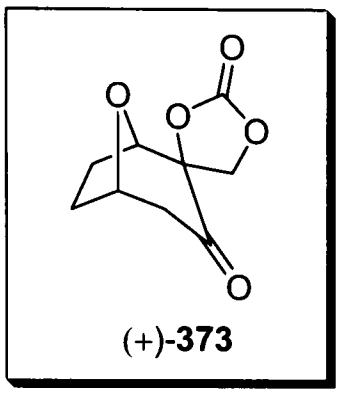
Fig 35. ^{1}H NMR of catalyst **373**; a) Racemic catalyst (±)-**373** ; b) Racemic catalyst (±)-**373** with 30 mol% shift reagent, c) Chiral catalyst (+)-**373** with 30 mol% shift reagent.

2.1.4. Epoxidation by enantiomerically enriched *oxa*-bicyclic ketone

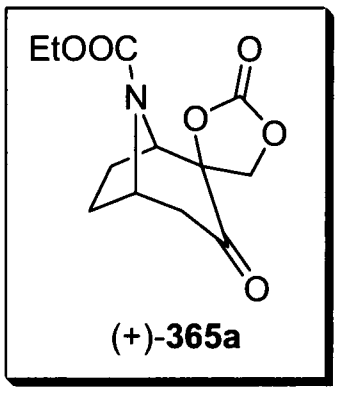
After having prepared enantioenriched chiral catalyst (+)-**373**, it was tested in the asymmetric epoxidation of various olefins and the results were compared to the tropinone

series (Table 36).

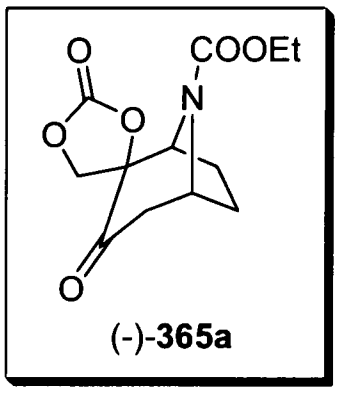
Table 36. Epoxidation catalysed by chiral ketone (+)-**373**; Reaction conditions: alkene (1.0 eq), catalyst (0.1 eq), Oxone® (10.0 eq), $NaHCO_3$ (15.5 eq), CH_3CN, aq. Na_2EDTA (0.4 mM solution).



(+)-**373**



(+)-**365a**



(-)-**365a**

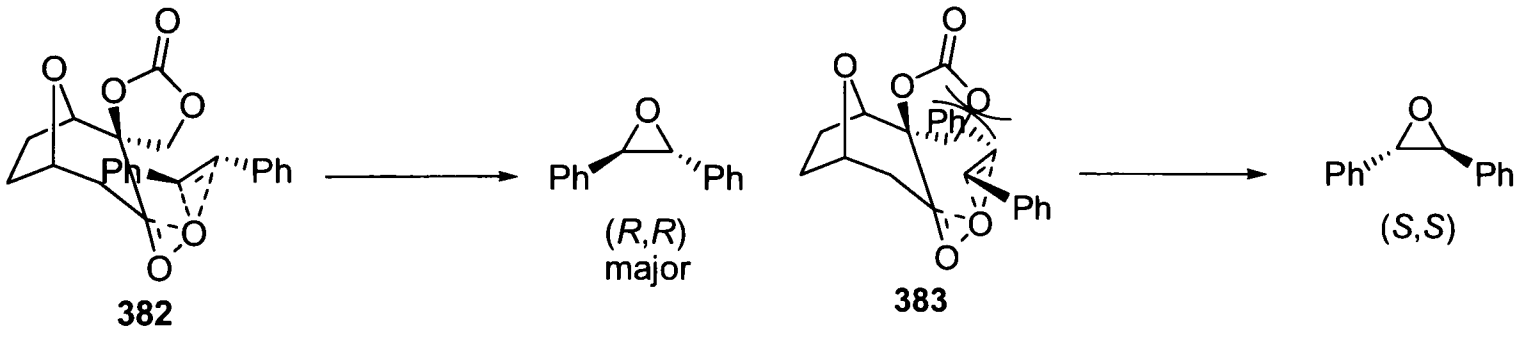
Entry	Alkene	Catalyst	ee_{obs} [a]	ee_{max} [b]	Epoxide [c]
1	(*E*)-Stilbene	(+)-**373**	62	91	(*R*,*R*)-**374**
2		(-)-Tropinone **365a**	86	N/A	(*S*, *S*)-**374**
3	Styrene	(+)-**373**	28	41	(*R*)-**375**
4		(-)-Tropinone **365a**	46	N/A	(*S*)-**375**
5	α-Methylstyrene	(+)-**373**	1	<1	(*R*)-**376**
6		(-)-Tropinone **365a**	19	N/A	(*S*)-**376**
7	(*E*)-β-Methylstyrene	(+)-**373**	48	71	(*R*,*R*)-**377**
8		(-)-Tropinone **365a**	63	N/A	(*S*, *S*)-**377**
9	Phenylcyclohexene	(+)-**373**	55	81	(*R*,*R*)-**378**
10		(-)-Tropinone **365a**	73	N/A	(*S*,*S*)-**378**
11	(*E*)-Ethylcinnamate	(+)-**373**	46	68	(2*S*, 3*R*)-**379**
12		(-)-Tropinone **365a**	74	N/A	(2*R*, 3*S*)-**379**

[a] %, Determined by chiral HPLC, [b] %, $ee_{max} = ee_{obs} \times 100 / 68$, [c] Configuration of major isomer.

Although we obtained the enantiomeric excess from the asymmetric epoxidation of various olefins, it could not be directly compared to the enantiomeric excess from the epoxidation by the tropinone derivative (-)-**365a** because the chiral ketone catalyst (+)-**373** was not

enantiomerically pure (ee = 68%) and the tropinone derivative had been used in enantiomerically pure form. So, we assumed that there would be a linear relationship between the enantiomeric excess of catalyst and the enantiomeric excess of the resulting epoxides and we calculated the ee_{max} by the equation; $ee_{max} = ee_{obs} \times 100 / 68$. Previous work in the group with *oxa*-bicylic chiral ketone catalysts has demonstrated that this linear relationship is valid.[152] With the calculated ee_{max} value, we compared our results to the tropinone catalyst. For di- and trisubstituted aryl alkenes, the *oxa*-bicycle (+)-**373** (entries 1, 7 and 9) did indeed generally afford higher enantioselectivity than its tropinone counterpart (entries 2, 8 and 10). The highest enantiomeric excess was found for (*E*)-stilbene (91%, entry 1). However, ketone catalyst (+)-**373** did not give any ee for the epoxidation of the challenging substrate, α-methylstyrene (<1%, entry 5), and gave slightly lower ee than the tropinone derivative (-)-**365a** for epoxidation of styrene and (*E*)-ethylcinnamate.

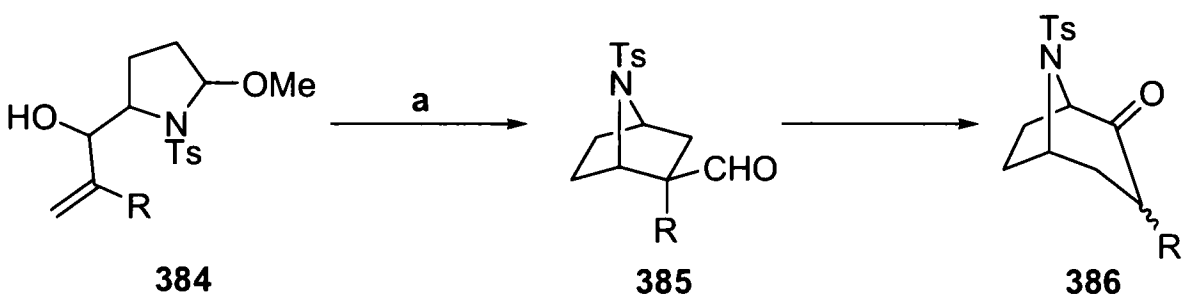
The observed stereoselectivity could be explained by the previously mentioned *spiro* transition state model. In general, the configuration of major enantiomers fits with with less steric repulsion in one transition state (Scheme 142, **382**) compared to the competing transition state **383** with severe steric repulsion. Thus the *trans*- and trisubstituted olefins (entries 1, 7, 9 and 11, Table 36) give high enantioselectivity whilst terminal olefins (entries 3 and 5, Table 36) give lower ee because they can more easily attack the dioxirane in two different *spiro* transition states leading to both enantiomers.



Scheme 142. Transition state for formation of both enantiomers of (*E*)-stilbene oxide.

2.2. *Aza*-bicyclic ketone catalyst

Recently, our group has reported a novel rearrangement sequence for the synthesis of *aza*-bicyclic ketones (Scheme 143).[156] Alkoxy-pyrrolidine **384** (obtained by addition of a vinyl Grignard reagent to the product of DHP aziridination/rearrangement) can give the 7-*aza*-bicyclo[2.2.1]heptane ring system **385** *via* an unusual *aza*-Prins-pinacol reaction mediated by $SnCl_4$. On further exposure to Lewis acid, the [2.2.1]heptane ring expands to the isomeric [3.2.1]tropane **386**.



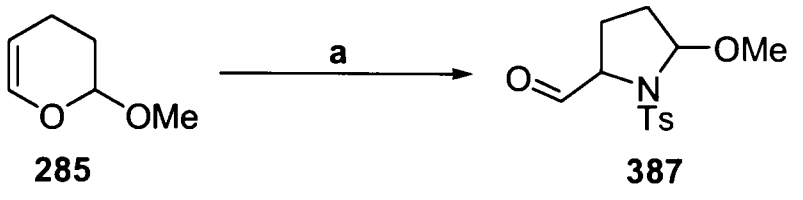
384 **385** **386**

Scheme 143. Rearrangement of pyrrolidine **384** to *aza*-bicyclic ketone **386**; (a) $SnCl_4$ (1.0 M in heptane, 10.0 eq). CH_2Cl_2, 0 °C to rt, 16 h.

We reasoned that the catalyst **386** could potentially be an interesting new class of ketone catalyst which may display complementary reactivity and selectivity to our previous bicyclic ketones. Thus, we decided to synthesise a representative ketone of this type and to test it for the epoxidation of various olefins.

2.2.1. Synthesis of racemic *aza*-bicyclic ketone catalyst

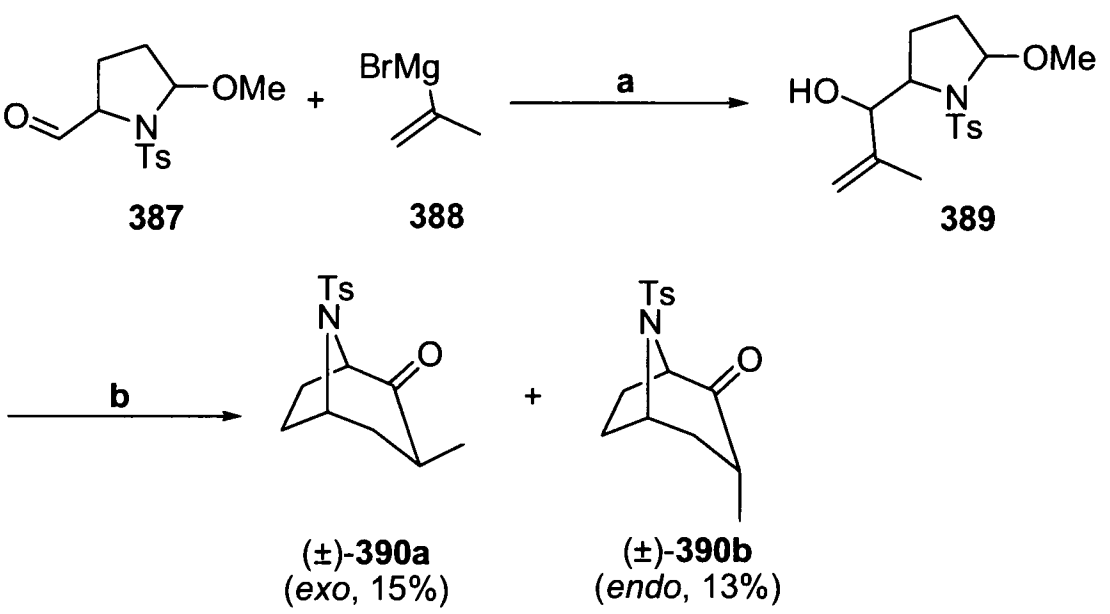
Firstly, commercially available DHP **285** was aziridinated by Chloramine-T in the presence of NBS to effect rearrangement to the corresponding pyrrolidine **387** (Scheme 144).



285 **387**

Scheme 144. Rearrangement of DHP **285** to pyrrolidine **387**; (a) Chloramine-T (1.2 eq), NBS (0.2 eq), CH_3CN, rt, 2 h, 50%.

Addition of the vinyl Grignard reagent **388** then gave alcohol **389** as a mixture of diastereoisomers. Subsequent reaction with $SnCl_4$ gave the *aza*-bicyclic ketone (±)-**390a** and (±)-**390b** as a separable mixture of isomers (Scheme 145). Both isomers were identified by the comparison of ^{1}H-NMR spectrum to the prevous results in the group.[157] The low yield was caused by incomplete ring-expansion from [2.2.1]heptane ring to [3.2.1]tropane.



Scheme 145. Synthesis of *aza*-bicyclic ketone (±)-**390a** and (±)-**390b**; (a) Et_2O, 0 °C to rt, 10 min, (b) $SnCl_4$ (1.0 M in heptane, 10.0 eq). CH_2Cl_2, 0 °C to rt, 16 h,

2.2.2. Epoxidation by racemic *aza*-bicyclic ketone catalyst

After the synthesis of racemic ketone (±)-**390a** and **390b**, we tested the *exo-aza*-bicyclic ketone (±)-**390a** to investigate its catalytic activity for the epoxidation of olefins. Initially, we adopted (*E*)-stilbene as the olefin to be oxidised because it showed the highest reactivity in the epoxidation with *oxa*-bicyclic ketone catalyst (±)-**373** (Table 37). However, *exo-aza*-bicyclic ketone catalyst (±)-**390a** showed inferior catalytic activity to *oxa*-bicylic ketone (±)-**373** in all cases. The epoxidation of (*E*)-stilbene showed extremely low conversion after 18 h (entry 1). Interestingly, the epoxidation of styrene by ketone catalyst (±)-**390a** still showed lower activity than *oxa*-bicylic ketone (±)-**373**. However, the reaction was completed in 5 h (entry 4). Additionally, we attempted the epoxidation of (*E*)-stilbene by *endo-aza*-bicyclic ketone catalyst (±)-**390b** (entry 2). However, the catalytic activity of

endo-aza-bicyclic ketone (±)-**390b** was slightly inferior to the *exo-aza*-bicyclic ketone **390a** (entry 2). We assumed that the low catalytic activity for both might be caused by the methyl substituent next to the ketone moiety because it could prevent the access of olefin to dioxirane by steric hindrance. These preminary studies showed that these ketones can act as catalysts, albeit less effectively than the earlier ones for stilbene epoxidation.

Table 37. Epoxidation of olefins by ketone (±)-**390a**; Reaction conditions: alkene (1.0 eq), catalyst (0.1 eq), Oxone® (10.0 eq), $NaHCO_3$ (15.5 eq), CH_3CN, aq. Na_2EDTA (0.4 mM solution).

Entry	Alkene	Catalyst	time	Conversion (%)[a]
1	(*E*)-Stilbene	(±)-**390a**	18 h	18
2		(±)-**390b**	18 h	15
3		(±)-**373**	<10 min	100
4	Styrene	(±)-**390a**	5 h	>99
5		(±)-**373**	1 h	100

[a] Determined by crude ^1H NMR

3. Conclusions and future work

In this project, we synthesised several novel bicyclic ketone catalysts and we investigated them as catalysts for alkene epoxidation using Oxone®. Firstly, *oxa*-bicyclic ketone catalyst **373** generally showed better catalytic reactivity and enantioselectivity than tropinone derivative ketone catalyst **365a**. However, this catalyst could not overcome the low catalytic activity in the epoxidation of (*E*)-ethylcinnamate and the low enantioselectivity in the epoxidation of α-methylstyrene. Secondly, a different class of bicyclic ketone **390** was synthesised but it showed low catalytic activity in the epoxidation. Therefore, we would still need to investigate different type of catalysts for the epoxidation of challenging olefins such as (*E*)-ethylcinnamate and α-methylstyrene. For the future work, further manipulation of the *oxa*-bicyclic ketone catalyst **373** and the *aza*-bicyclic ketone catalyst **390** would be desirable. Firstly, it is possible to replace the *spiro* ketal in *oxa*-bicyclic ketone **373** because Shi and co-workers found that the replacement of the *spiro* ketal in fructose derivatives with an oxazolidinone gave catalysts that provided very good ee in the epoxidation of styrenes[149] and our group also found that oxazolidinones can give good selectivity (*vide ante*). Thus, the *spiro* ketal moiety in *oxa*-bicyclic ketone **373** could be replaced with an oxazolidinone (Fig. 36) to potentially improve the epoxidation enantioselectivity.

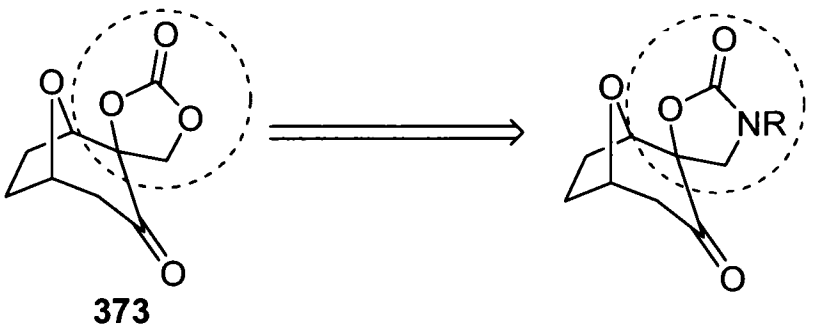
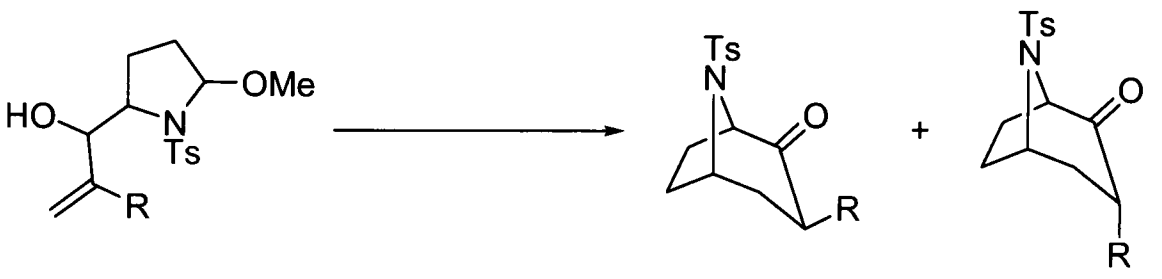


Fig 36. *Oxa*-bicyclic ketone bearing oxazolidinone moiety

Secondly, the replacement of the methyl group at the α-position of *aza*-bicyclic ketone **390** with other alkyl or aryl substituents would be interesting because the diverse property of catalyst can be easily obtained by the tuning of α-substituent (Scheme 146). Especially,

electron-withdrawing substituents would be desirable because they should increase the reactivity.



Scheme 146. Tuning of α-substituent in *aza*-bicyclic ketone **390**.

Chapter IV. Experimental procedures and data

General details

Solvents were freshly distilled before use from sodium benzophenone (diethyl ether, THF, toluene) or CaH_2 (dichloromethane). Liquids reagents were distilled prior to use, while other commercial solids were used as supplied. Reactions were run under a positive pressure of nitrogen. Reaction temperatures were recorded as bath temperatures. Flash column chromatography was performed using BDH F_{254} silica gel. Analytical thin layer chromatography was performed on pre-coated Merck silica gel 60 F_{254} glass backed plates and visualised by either UV light (254 nm) or reactive stain reagents as appropriate.

NMR analyses were performed on Bruker AC 250 MHz, AV 400 MHz or DX 400 MHz instruments; Chemical shifts are quoted in ppm relative to TMS (as referenced to residual $CHCl_3$ δ_H=7.26 or $CDCl_3$ δ_C=77.0), with coupling constants quoted in Hz. Splitting patterns are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) and combinations of the above. Infrared analyses were recorded on NaCl plates. A Mattson Satellite FTIR spectrometer was employed in the absorption range of 4000-600 cm^{-1}. Microwave reactions were carried out using a CEM Discover instrument. Chemical Ionisation Mass Spectrometry was carried out with ammonia reagent gas using a Micromass Autospec-Q spectrometer at the Imperial College Mass Spectrometry Service. Melting points were determined using a Reichert hot stage microscope apparatus. Optical rotations were recorded on an Optical-Activity AA-5 Polarimeter, with a path length of 10 cm in chloroform unless stated otherwise. $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Concentrations (*c*) are given in grams per 100 cm^3. Chiral HPLC was performed on Hewlett Packard Series 1100 HPLC system with Chiralcel columns using ^{i}PrOH/hexane as eluent. For HPLC, retention times are quoted in minutes.

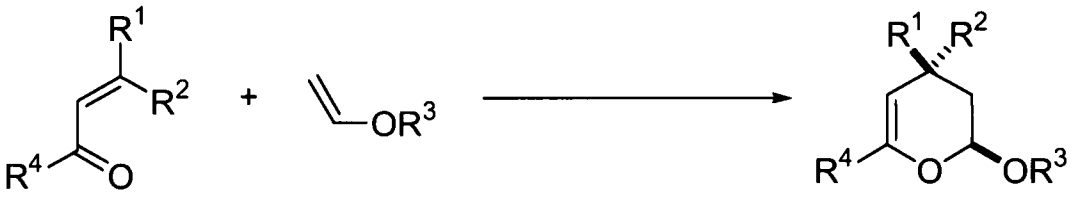
Nomenclature and numbering

The names of the compounds were determined according to IUPAC rules and Autonom 4.01.304 when applicable.

1. Compounds from Chapter 1.

General procedure for hetero Diels-Alder reaction using pressure tube[89]

To vinyl ether (2.0-10.0 eq) at room temperature in the pressure tube was added diene (1.0 eq) and YbFOD (0.05 eq). The solution was allowed to stir at the corresponding temperature (45-100 °C) for 1- 10 days. The reaction mixture allowed to room temperature. Column chromatography eluting with a diethyl ether/petrol gave alkoxydihydropyrans.



Product	R^1	R^2	R^3	R^4
211	H	H	Et	Me
217	H	H	^{t}Bu	Me
218	H	H	^{n}Bu	Me
236	Me	H	^{n}Bu	Me
237	^{i}Pr	H	^{n}Bu	Me
238	Me	Me	^{n}Bu	Me
232	Ph	H	Et	Me
239	CH_2OBn	H	Et	Me
240	(*Z*)-$(CH_2)_4CH$=CHEt	H	Et	Me
271	Me	H	Et	^{n}Pr
272	Me	H	Et	^{n}Bu

2-Ethoxy-6-methyl-3,4-dihydro-2H-pyran **211**[158]: Prepared by the general procedure (1.0 eq of diene, 8.0 eq of vinyl ether, 0.05 eq of Yb catalyst, 45 °C, 3 d) to give **211** (2.35 g, 70%) as a pale yellow oil. ν_{max} ($CHCl_3$)/cm^{-1} 2978 (CH), 2254, 1713, 1643 (C=C); δ_H (250 MHz, $CDCl_3$) 4.96 (1H, t, *J* 3.5, OCHO), 4.50 (1H, t, *J* 3.5, C=CH), 3.83 (1H, dq, *J* 10.0, 7.0, OC*H*H), 3.55 (1H, dq, *J* 10.0, 7.0, OCH*H*), 2.17-1.70 (4H, m, CH_2CH_2), 1.70 (3H, s,

CCH_3), 1.19 (3H, t, *J* 7.0, CH_2CH_3); *m/z* (CI) 114 (100%), 143 (MH^+), 160 (MNH_4^+), Found: MH^+, 143.1069. $C_8H_{14}O_2$ requires MH^+, 143.1072.

2-tert-Butoxy-6-methyl-3,4-dihydro-2H-pyran **217**: Prepared by the general procedure (1.0 eq of diene, 3.0 eq of vinyl ether, 0.05 eq of Yb catalyst, 90 °C, 8 d) to give **217** (0.80 g, 20%) as a pale yellow oil. ν_{max} ($CHCl_3$)/cm^{-1} 1682 (C=C); δ_H (250 MHz, $CDCl_3$) 5.18 (1H, t, *J* 4.0, OCHO), 4.45 (1H, t, *J* 4.0, C=CH), 2.18-1.81 (4H, m, CH_2CH_2), 1.64 (3H, s, CCH_3) 1.18 (9H, s, 3 x CCH_3); ^{13}C could not be obtained due to the rapid decomposition of the sample in $CDCl_3$. *m/z* (CI) 171 (MH^+), Found: MH^+, 171.1383. $C_{10}H_{18}O_2$ requires MH^+, 171.1385.

2-Butoxy-6-methyl-3,4-dihydro-2H-pyran **218**[159]: Prepared by the general procedure (1.0 eq of diene, 2.0 eq of vinyl ether, 0.05 eq of Yb catalyst, 90 °C, 6 d) to give **218** (2.80 g, 55%) as a pale yellow oil. ν_{max} ($CHCl_3$)/cm^{-1} 2958-2936 (CH), 1721, 1687 (C=C); δ_H (250 MHz, $CDCl_3$) 4.97 (1H, t, *J* 3.5, OCHO), 4.52 (1H, t, *J* 3.5, C=CH), 3.78 (1H, dt, *J* 9.5, 6.5, OC*H*H), 3.50 (1H, dt, *J* 9.5, 6.5, OCH*H*), 2.20-1.69 (4H, m, CH_2CH_2), 1.68-1.48 (2H, m, CH_2), 1.42-1.24 (2H, m, CH_2), 1.71 (3H, s, CCH_3), 0.90 (3H, t, *J* 7.5, CH_2CH_3); δ_C (125 MHz, $CDCl_3$) 147.4 (C), 97.4 (CH), 96.1 (CH), 67.9 (CH_2), 31.8 (CH_2), 26.4 (CH_2), 19.9 (CH_3), 19.3 (CH_2), 17.0 (CH_2), 13.8 (CH_3); *m/z* (CI) 140, 171 (MH^+), 197, Found: MH^+, 171.1387. $C_{10}H_{18}O_2$ requires MH^+, 171.1385

(*2S*,4S**)-*2-Butoxy-4,6-dimethyl-3,4-dihydro-2H-pyran* **236**: Prepared by the general procedure (1.0 eq of diene, 2.0 eq of vinyl ether, 0.05 eq of Yb catalyst, 50 °C, 10 d) to give **236** (1.90 g, 40%) in a 3:1 inseparable mixture as a colourless oil. ν_{max} ($CHCl_3$)/cm^{-1} 2960-2873 (CH), 1719, 1674 (C=C); δ_H (250 MHz, $CDCl_3$) 4.99 ($1H_{major}$, t, *J* 3.0, OCHO), 4.88 ($1H_{minor}$, dd, *J* 7.0, 3.0, OCHO), 4.43 ($1H_{major}$, d, *J* 1.0, C=CH), 4.33 ($1H_{minor}$, d, *J* 1.0, C=CH), 3.82 ($2H_{both}$, m, 2 x OC*H*H), 3.47 ($2H_{both}$, m, 2 x OCH*H*), 2.39 ($2H_{both}$, m, 2 x CH_3CH), 1.92-1.25 ($12H_{both}$, 6 x CH_2), 1.72 ($6H_{both}$, s, 2 x CCH_3), 1.02-0.88 ($6H_{both}$, m, 2 x $CHCH_3$, 2 x CH_2CH_3); ^{13}C δ_C (100 MHz, $CDCl_3$) 147.5 $(C)_{major}$, 146.1 $(C)_{minor}$, 103.1

$(CH)_{minor}$, 102.3 $(CH)_{major}$, 99.8 $(CH)_{major}$, 96.8 $(CH)_{minor}$, 68.4 $(CH_2)_{major}$, 67.7 $(CH_2)_{minor}$, 36.2 $(CH)_{major}$, 35.0 $(CH)_{minor}$, 31.9 $(CH_2)_{minor}$, 31.8 $(CH_2)_{major}$, 26.2$(CH_2)_{both}$, 21.5 $(CH_3)_{major}$, 21.4 $(CH_3)_{minor}$, 19.7 $(CH_3)_{minor}$, 19.5 $(CH_3)_{major}$, 19.4 $(CH_2)_{minor}$, 19.2 $(CH_2)_{major}$, 13.7 $(CH_3)_{both}$; *m/z* (CI) 185 (MH^+), Found: MH^+, 185.1538. $C_{11}H_{20}O_2$ requires MH^+, 185.1541.

(*2S*,4R**)-*2-Butoxy-4-isopropyl-6-methyl-3,4-dihydro-2H-pyran* **237**: Prepared by the general procedure (1.0 eq of diene, 2.0 eq of vinyl ether, 0.05 eq of Yb catalyst, 55 °C, 3 d) to give **237** (3.77 g, 75%) in a 6:1 inseparable mixture as a pale yellow oil. ν_{max} $(CHCl_3)/cm^{-1}$ 2958-2873 (CH), 1721, 1678 (C=C); δ_H (250 MHz, $CDCl_3)_{major}$ 4.84 (1H, dd, *J* 9.5, 2.0, OCHO), 4.36 (1H, d, *J* 1.5, C=CH), 3.90 (1H, dt, *J* 9.5, 6.5, OCH*H*), 3.47 (1H, dt, *J* 9.5, 6.5, OC*H*H), 2.08 (1H, dqq, *J* 12.5, 4.0, 1.5, $(CH_3)_2CH$), 1.86 (1H, ddt, *J* 12.5, 6.5, 1.7, $(CH_3)_2CHCH$), 1.71 (3H, s, CCH_3), 1.64-1.25 (6H, m, 3 x CH_2), 0.94-0.82 (9H, 3 x CH_3); δ_C (125 MHz, $CDCl_3)_{major}$ 146.8 (C), 99.9 (CH), 97.1 (CH), 67.8 (CH_2), 33.1 (CH), 31.8 (CH), 31.7 (CH_2), 31.5 (CH_2), 19.8, 19.6 (2 x CH_3), 19.2 (CH_3), 19.1 (CH_2), 13.8 (CH_3); *m/z* (CI) 213 (MH^+, 100%), Found: MH^+, 213.1860. $C_{13}H_{24}O_2$ requires MH^+, 213.1854.

2-Butoxy-4,4,6-trimethyl-3,4-dihydro-2H-pyran **238**[87]: Prepared by the general procedure (1.0 eq of diene, 5.0 eq of vinyl ether, 0.05 eq of Yb catalyst, 100 °C, 5 d) to give **238** (1.60 g, 54%) as a pale yellow oil. ν_{max} $(CHCl_3)/cm^{-1}$ 2958-2872 (CH), 1676 (C=C); δ_H (250 MHz, $CDCl_3$) 4.88 (1H, dd, *J* 7.5, 3.0, OCHO), 4.32 (1H, s, C=CH), 3.88 (1H, dt, *J* 9.5, 6.5, OC*H*H), 3.48 (1H, dt, *J* 9.5, 6.5, OCH*H*), 1.76-1.25 (6H, m, CH_2, CH_2CH_2), 1.71 (3H, s, $C=CCH_3$), 1.02 (3H, s, CH_3), 1.00 (3H, s, CH_3), 0.92 (3H, t, *J* 7.5, CH_2CH_3); δ_C (63 MHz, $CDCl_3$) 145.9 (C), 107.4 (CH), 98.4 (CH), 68.6 (CH_2), 41.7 (CH_2), 31.8 (CH_2), 31.4 (CH_3), 30.5 (CH_3), 29.6 (C), 19.7 (CH_3), 19.3 (CH_2), 13.8 (CH_3); *m/z* (CI) 199 (MH^+, 100%), Found: MH^+, 199.1695. $C_{12}H_{22}O_2$ requires MH^+, 199.1698.

(*2S*,4R**)-*2-Ethoxy-6-methyl-4-phenyl-3,4-dihydro-2H-pyran* **232**[87]: Prepared by the

general procedure (1.0 eq of diene, 5.0 eq of vinyl ether, 0.05 eq of Yb catalyst, 65 °C, 5 d) to give **232** (210 mg, 50%) as a pale yellow oil. ν_{max} ($CHCl_3$)/cm^{-1} 3067-2872 (CH), 1677 (C=C); δ_H (250 MHz, $CDCl_3$) 7.20-7.00 (5H, m, Ph), 4.82 (1H, dd, *J* 9.0, 2.0, OCHO), 4.50 (1H, m, C=CH), 3.34-3.93 (3H, m, OCH_2, C*H*CH_3), 2.11-1.94 (2H, m, CHC*H*$_2$), 1.77 (3H, s, CCH_3), 1.15 (3H, t, *J* 7.0 , CH_2CH_3); *m/z* (CI) 219 (*MH*$^+$, 100%), Found: MH^+, 219.1384. $C_{14}H_{18}O_2$ requires MH^+, 219.1385.

(*2S**,*4S**)-*2-Benzyloxymethyl-2-ethoxy-6-methyl-3,4-dihydro-2H-pyran* **239**[87]: Prepared by the general procedure (1.0 eq of diene, 10.0 eq of vinyl ether, 0.05 eq of Yb catalyst, 55 °C, 1 d) to give **239** (0.60 g, 67%) as a pale yellow oil. ν_{max} ($CHCl_3$)/cm^{-1} 2976-2857 (CH), 1714, 1643 (C=C); δ_H (250 MHz, $CDCl_3$) 7.38-7.23 (5H, Ph), 5.01 (1H, dd, *J* 7.5, 1.0, OCHO), 4.55-4.51 (3H, CH_3C=C*H*, $PhCH_2$), 4.00 (1H, dq, *J* 9.5, 7.0, OC*H*HCH_3), 3.60 (1H, dq, *J* 9.5, 7.0, OCH*H*CH_3), 3.43 (2H, d, *J* 7.0, $BnOCH_2$), 2.73-2.55 (1H, m, $BnOCH_2$C*H*), 2.09 (1H, ddd, *J* 13.0, 6.5, 2.0, CHC*H*$_2$CH), 1.77 (3H, s, CCH_3), 1.67 (1H, ddd, *J* 13.0, 6.5, 2.0, CHC*H*$_2$CH), 1.26 (3H, t, *J* 7.0, CH_2CH_3); *m/z* (CI) 263 (*MH*$^+$, 100%), 280 (*MNH*$_4^+$), Found: MH^+, 263.1652. $C_{16}H_{22}O_3$ requires MH^+, 263.1647.

(*2S**,*4S**)-*2-Ethoxy-6-methyl-4-(Z-octen-5-yl)-3,4-dihydro-2H-pyran* **240**[87]: Prepared by the general procedure (1.0 eq of diene, 10.0 eq of vinyl ether, 0.05 eq of Yb catalyst, 55 °C, 5 d) to give **240** (0.55 g, 56%) in a 4:1 inseparable mixture as a pale yellow oil. ν_{max} ($CHCl_3$)/cm^{-1} 3002-2855 (CH), 1719, 1652 (C=C); δ_H (250 MHz, $CDCl_3$) 5.40-5.24 ($4H_{both}$, m, 2 x CH=CH), 5.01 ($1H_{minor}$, t, *J* 3.0, OCHO), 4.88 ($1H_{major}$, dd, *J* 9.0, 2.0, OCHO), 4.51-4.48 ($1H_{minor}$, m, C=CH), 4.49-4.36 ($1H_{major}$, m, C=CH), 4.01-3.77 ($2H_{both}$, dt, *J* 9.5, 7.0, 2 x OC*H*H), 3.63-3.50 ($2H_{both}$, 2 x OCH*H*), 2.32-1.80 ($10H_{both}$, m, 2 x C=CHC*H*CH_2, 2 x CH_2, 2 x CH_2), 1.72 ($6H_{both}$, s, 2 x CH=CC*H*$_3$), 1.52-1.12 ($22H_{both}$, m, 8 x CH_2, 2 x OCH_2CH_3), 0.94 ($6H_{both}$, t, *J* 7.5, 2 x CH_2CH_3); *m/z* (CI) 253 (*MH*$^+$, 100%), 270 (*MNH*$_4^+$, 100%), Found: MH^+, 253.2172. $C_{16}H_{28}O_2$ requires MH^+, 253.2168

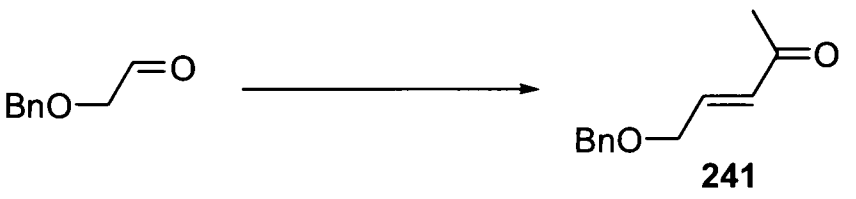
(*2S**,*4S**)-*2-Ethoxy-4-methyl-6-propyl-3,4-dihydro-2H-pyran* **271**: Prepared by the general

procedure (1.0 eq of diene, 5.0 eq of ethyl vinyl ether, 0.05 eq of Yb catalyst, 55 °C, 5 d) to give **271** (0.55 g, 70%) in a 4:1 inseparable mixture as a colourless oil. ν_{max} ($CHCl_3$)/cm^{-1} 2961-2873 (CH), 1675 (C=C); δ_H (250 MHz, $CDCl_3$) 5.00 ($1H_{minor}$, t, *J* 3.0, OCHO), 4.88 ($1H_{major}$, dd, *J* 8.5, 2.0, OCHO), 4.44 ($1H_{minor}$, d, *J* 1.0, C=CH), 4.33 ($1H_{major}$, d, *J* 1.0, C=CH), 3.93 ($1H_{major}$, dq, *J* 9.5, 7.0, OC*H*H), 3.56 ($1H_{major}$, dq, *J* 9.5, 7.0, OCH*H*), 2.48-2.28 ($2H_{both}$, m 2 x C*H*CH_3), 2.03-1.90 ($4H_{both}$, m, 2 x CH_2), 1.55-1.14 ($8H_{both}$, 2 x CH_2, 2 x CH_2), 1.23 ($3H_{major}$, t, *J* 7.0, OCH_2CH_3), 0.99 ($3H_{major}$, d, *J* 7.0, $CHCH_3$), 0.89 ($3H_{major}$, t, *J* 7.5, $CH_2CH_2CH_3$), ^{13}C could not be obtained due to the rapid decomposition of the sample in $CDCl_3$; *m/z* (CI) 185 (MH^+,100%), Found: MH^+, 185.1550. $C_{11}H_{20}O_2$ requires MH^+, 185.1542.

(*2S*,4S**)-*6-Butyl-2-ethoxy-4-methyl-3,4-dihydro-2H-pyran* **272**: Prepared by the general HDA procedure (1.0 eq of diene, 5.0 eq of ethyl vinyl ether, 0.05 eq of Yb catalyst, 55 °C, 3h, microwave) to give **272** (1.01 g, 65%) in a 4:1 inseparable mixture as a colourless oil. ν_{max} ($CHCl_3$)/cm^{-1} 2957-2872 (CH), 1673 (C=C); δ_H (250 MHz, $CDCl_3$) 5.02 ($1H_{major}$, t, *J* 3.0, OCHO), 4.90 ($1H_{minor}$, dd, *J* 8.5, 2.0, OCHO), 4.45 ($1H_{major}$, d, *J* 0.5, C=CH), 4.35 ($1H_{minor}$, d, *J* 1.0, C=CH), 3.85 ($1H_{major}$, dq, *J* 9.5, 7.0, OC*H*H), 3.58 ($1H_{major}$, dq, *J* 9.5, 7.0, OCH*H*), 2.48-2.33 ($1H_{major}$, m C*H*CH_3), 2.09-1.95 ($2H_{major}$, m, CH_2), 1.51-1.18 ($18H_{both}$, m, 2 x CH_2, 2 x CH_2, 2 x CH_2, 2 x OCH_2CH_3), 1.01 ($3H_{minor}$, d, *J* 7.0, $CHCH_3$), 1.00 ($3H_{major}$, d, *J* 7.0, $CHCH_3$), 0.92 ($3H_{major}$, t, *J* 7.0, $CHCH_3$); δ_C (125 MHz, $CDCl_3$) 151.2 $(C)_{minor}$, 149.8 $(C)_{major}$, 102.7 $CH)_{major}$, 102.0 $(CH)_{minor}$, 96.7 $(CH)_{major}$, 99.8 $(CH)_{minor}$, 64.1 $(CH_2)_{minor}$, 63.5 $(CH_2)_{major}$, 36.7 $(CH_2)_{minor}$, 35.2 $(CH2)_{major}$, 33.7 $(CH_2)_{minor}$ 33.4 $(CH_2)_{major}$, 29.2 $(CH_2)_{major}$, 29.1 $(CH_2)_{minor}$, 26.4 $(CH)_{minor}$, 22.1 $(CH)_{major}$, 21.7 $(CH_2)_{major}$, 21.6 $(CH_2)_{minor}$, 15.3 $(CH_3)_{major}$, 15.2 $(CH_3)_{major}$, 13.9 $(CH_3)_{major}$, 13.9 $(CH_3)_{minor}$ [22 out of 24 carbons observed]; *m/z* (CI) 199 (MH^+,100%) Found: MH^+, 199.1697. $C_{12}H_{22}O_2$ requires MH^+, 199.1698.

Preparation of enone systems

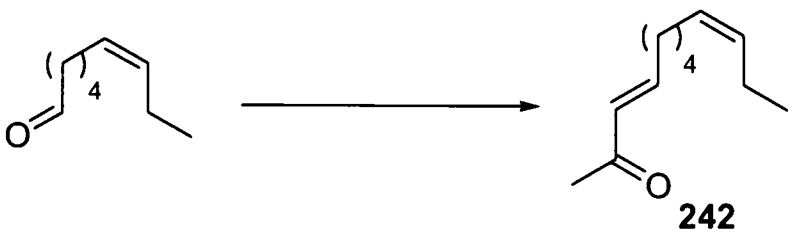
(E)-5-Benzyloxy-pent-3-en-2-one **241**[160]:



241

To a solution of LiCl (0.30 g, 7.2 mmol) in MeCN (55 mL) at room temperature under N_2 was added a solution of diethyl(2-oxopropyl)phosphonate (1.40 g, 7.2 mmol) in MeCN (10 mL). To the reaction mixture was added DBU (0.9 ml, 6.0 mmol) dropwise and then a solution of benzyloxyacetaldehyde (0.9 g, 6.0 mmol) in THF/MeCN (1/1, 30 mL) was added. After stirring overnight, the reaction mixture was quenched with water/brine (1/1, total volume 200 mL). The organic phases were separated and extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and concentrated to afford the crude product. Column chromatography eluting with EtOAc/petrol (1/3) gave **241** (0.67 g, 59%) as a colourless oil. δ_H (250 MHz, $CDCl_3$) 7.38-7.30 (5H, m, Ph), 6.81 (1H, dt, *J* 16.0, 4.5, $BnOCH_2CH$), 6.35 (1H, dt, *J* 16.0, 2.0, $CHC(O)CH_3$), 4.58 (2H, s, OCH_2Ph), 4.21 (2H, dd, *J* 4.5, 2.0, CH_2OBn), 2.28 (3H, s, CH_3); *m/z* (CI) 191 (MH^+), 208 (MNH_4^+, 100%) Found: MH^+, 191.1063. $C_{12}H_{14}O_2$ requires MH^+, 191.1072.

(3E, 9Z)-Dodecadien-2-one **242**[87]:

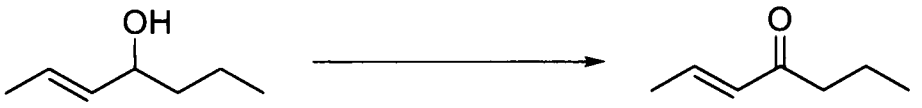


242

To a solution of LiCl (0.50 g, 12.0 mmol) MeCN (90 mL) at room temperature under N_2

was added diethyl(2-oxopropyl)phosphonate (2.70 g, 12.0 mmol) in MeCN (20 mL). To the reaction mixture was added DBU (1.50 g, 10.0 mmol) dropwise and then a solution of *cis*-6-nonenal (1.40 g, 10.0 mmol) in THF:MeCN (1/1, 40 mL) was added. After stirring for overnight, the reaction mixture was quenched with water/brine (1:1, total volume 200 mL). The phases were separated and extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and concentrated to afford the crude product. Column chromatography eluting with EtOAc/petrol (3/7) gave **242** (1.20 g, 66%) as a colourless oil. δ_H (250 MHz, $CDCl_3$) 6.79 (1H, dt, *J* 16.0, 7.0, C*H*=CHC(O)CH_3), 6.05 (1H, dt, *J* 16.0, 1.5, CH=C*H*C(O)CH_3), 5.42-5.22 (2H, m, CH_2C*H*=C*H*CH_2), 2.26-2.16 (2H, m, CH_2), 2.22 (3H, s, $COCH_3$), 2.08-1.95 (4H, m, 2 x CH_2), 1.54-1.29 (4H, m, 2 x CH_2), 0.94 (3H, t, *J* 7.5, CH_2CH_3); *m/z* (CI) 181 (MH^+), 198 (MNH_4^+).

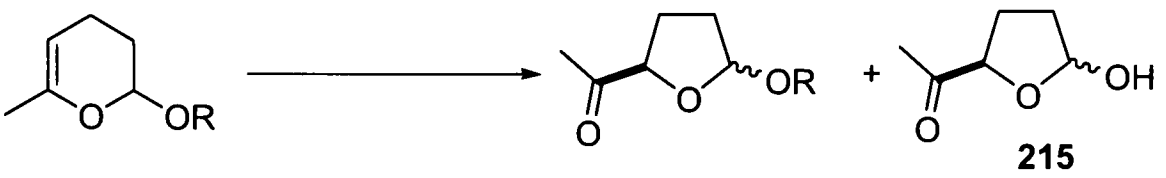
(E)-Hept-2-en-4-one **269**[161]:



269

To a solution of DMSO in CH_2Cl_2 (25 mL) at -78 °C was added to a solution of 2.0 M of oxalyl chloride in CH_2Cl_2 (5 mL) dropwise. After stirring for 20 min, a solution of alcohol (1.00 g, 8.70 mmol) in CH_2Cl_2 (10 mL) was added dropwise. After stirring for 10 min, Et_3N was added dropwise and the reaction mixture allowed to warm to room temperature. After stirring for 30 min, the reaction mixture was quenched by the addition of H_2O. The organic layer was extracted, dried over $MgSO_4$ and concentrated to give yellow oil. Column chromatography eluting with EtOAc/petrol (1/4) gave **269** (0.49 g, 50%) as yellow oil. δ_H (250 MHz, $CDCl_3$) 6.80 (1H, dq, *J* 13.0, 6.5, CH=C*H*CH_3), 6.09 (1H, d, *J* 13.0, C*H*=CHCH_3), 2.47 (2H, t, *J* 7.5, CH_2C(O)CH), 1.86 (3H, d, *J* 6.5, CHCH_3), 1.68-1.51 (2H, m, CH_3CH_2), 0.90 (3H, t, *J* 7.5, CH_2CH_3); *m/z* (CI) 113 (MH^+), 130 (MNH_4^+, 100%).

General procedure for the oxidative rearrangement using MCPBA



215

Dihydropyrans	R	Product	
		lactol ether	lactol
211	Et	**213**	**215**
217	^{t}Bu	**219**	**215**
218	^{n}Bu	**220**	**215**

To a solution of 2-alkoxydihydropyrans (**211**, **217**, **218**, 1.0 eq) in CH_2Cl_2, 77% MCPBA (1.0 eq, max) in CH_2Cl_2 at 0 °C under N_2 was added dropwise. After stirring at room temperature, the white precipitate was filtered off from the reaction mixture and then phosphate buffer solution was added for the work-up. The reaction mixture was quenched with aqueous saturated $NaHCO_3$ solution, dried with $MgSO_4$ and filtered. Column chromatography eluting with EtOAc/petrol (1/4→1/1) gave lactol ether (**213**, **217**, **220**) in a mixture of diastereoisomers for the major product as a colourless oil and volatile lactol **215** in an inseparable mixture (1:1) for the minor product as a colourless oil.

(2R,5R*)-1-(5-Hydroxy-tetrahydro-furan-2-yl)-ethanone* and *(2R*,5S*)-1-(5-hydroxy-tetrahydro-furan-2-yl)-ethanone* **215**[95a]: ν_{max} ($CHCl_3$)/cm^{-1} 2959 (CH), 1716 (C=O), 1649; δ_H (250 MHz, $CDCl_3$) 5.60 ($1H_{one}$, t, *J* 2.5, C*H*OH), 5.53 ($1H_{another}$, t, *J* 2.5, C*H*OH), 5.11 ($2H_{both}$, s, 2 x OH), 4.53 ($1H_{one}$, dd, *J* 9.0, 5.0, C(O)CH), 4.36 ($1H_{another}$, t, *J* 8.0, C(O)CH), 2.53-1.72 ($8H_{both}$, m, 4 x CH_2), 2.15 ($3H_{one}$, s, CH_3), 2.08 ($3H_{another}$, s, CH_3); δ_C (125 MHz, $CDCl_3$) 210.5, 209.2 (C), 99.4, 99.2 (CH), 84.0, 82.5 (CH), 33.3, 32.2 (CH_2), 26.5, 25.9 (CH_3), 25.5, 25.1 (CH_2); *m/z* (CI) 148 (*MNH*$_4^+$, 100%), Found: MNH_4^+, 148.0975. $C_6H_{10}O_3$ requires MNH_4^+, 148.0974.

(2R,5R*)-1-(5-Ethoxy-tetrahydro-furan-2-yl)-ethanone* and *(2R*,5S*)-1-(5-ethoxy-tetrahydro-furan-2-yl)-ethanone* **213**[88]: Prepared by the general procedure (1.4 mmol of 2-alkoxydihydropyran, 1.4 mmol MCPBA, 2 h) to give **213** (32 mg, > 14%) in an inseparable mixture (2:1) as a colourless oil. ν_{max} ($CHCl_3$)/cm^{-1} 2979 (CH), 2254, 1716 (C=O); δ_H (250 MHz, $CDCl_3$) 5.25 ($1H_{minor}$, t, *J* 3.5, OCHO), 5.18 ($1H_{major}$, t, *J* 3.5, OCHO), 4.45 ($1H_{minor}$, dd, *J* 9.0, 5.5, C(O)CH), 4.32 ($1H_{major}$, t, *J* 8.0, C(O)CH), 3.85 ($2H_{both}$, dq, *J* 9.5, 7.0, 2 x OC*H*H), 3.46 ($2H_{both}$, dq, *J* 9.5, 7.0, 2 x OCH*H*), 2.42-1.80 ($8H_{both}$, m, 4 x CH_2), 2.22 ($3H_{major}$, s, $C(O)CH_3$), 2.18 ($3H_{minor}$, s, $C(O)CH_3$), 1.17 ($3H_{minor}$, t, *J* 7.0, CH_2CH_3), 1.20 ($3H_{major}$, t, *J* 7.0, CH_2CH_3); δ_C (125 MHz, $CDCl_3$) 105.0, 104.6 (CH), 84.7, 82.4 (CH), 63.2, 61.2 (CH_2), 32.9, 31.6 (CH_3), 26.9, 26.7 (CH_2), 25.5, 19.1 (CH_2), 15.0, 15.2 (CH_3).

(2R,5R*)-1-(5-tert-Butoxy-tetrahydro-furan-2-yl)-ethanone* and *(2R*,5R*)-1-(5-tert-butoxy-tetrahydro-furan-2-yl)-ethanone* **219**: Prepared by the general procedure (1.2 mmol of 2-alkoxydihydropyran, 1.2 mmol MCPBA, 4 h) to give **219** (82 mg, 37%) as an inseparable mixture (2:1) in a pale yellow oil. ν_{max} ($CHCl_3$)/cm^{-1} 2962-2875 (CH), 1714 (C=O), 1641; δ_H (250 MHz, $CDCl_3$) 5.68 ($1H_{minor}$, t, *J* 3.0, OCHO), 5.45 ($1H_{major}$, t, *J* 3.0, OCHO), 4.50 ($1H_{minor}$, t, *J* 8.0, C(O)CH), 4.18 ($1H_{major}$, t, *J* 8.0, C(O)CH), 2.32-1.65 ($14H_{both}$, m, 2 x $C(O)CH_3$, 4 x CH_2), 1.15 ($18H_{both}$, s, 6 x C*C*H_3); δ_C (125 MHz, $CDCl_3$) 212.2 $(C)_{major}$, 209.6 $(C)_{minor}$, 99.8 $(CH)_{major}$, 99.8 $(CH)_{minor}$, 84.5 $(CH)_{major}$, 82.0 $(CH)_{minor}$, 74.3 $(C)_{both}$, 33.8 $(CH_3)_{major}$, 31.2 $(CH_3)_{minor}$, 28.8 (3 x $CH_3)_{minor}$, 28.7 (3 x $CH_3)_{major}$, 27.2 $(CH_2)_{major}$, 27.0 $(CH_2)_{minor}$, 26.1$(CH_2)_{both}$; *m/z* (CI) 204 (*M*NH_4^+), Found: MNH_4^+, 204.1595. $C_{10}H_{18}O_3$ requires MNH_4^+, 204.1560.

(2R,5R*)-1-(5-Butoxy-tetrahydro-furan-2-yl)-ethanone* and *(2R*,5S*)-1-(5-butoxy-tetrahydro-furan-2-yl)-ethanone* **220**: Prepared by the general procedure (3.0 mmol of 2-alkoxydihydropyran, 3.0 mmol MCPBA, 3h) to give major compounds **220a** (74 mg, 13%) and **220b** (146 mg, 26%) as a separable mixture (2:1) in a colourless oil (220 mg, **220a**+**220b**=39%).

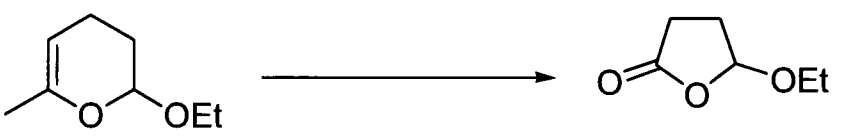
220a (major): ν_{max} ($CHCl_3$)/cm^{-1} 2962-2876 (CH), 1722 (C=O), 1644; δ_H (250 MHz,

$CDCl_3$) 5.28 (1H, t, *J* 2.0, OCHO), 4.49 (1H, dd, *J* 9.0, 6.0, C(O)CH), 3.70 (1H, dt, *J* 9.5, 6.5, OC*H*H), 3.42 (1H, dt, *J* 9.5, 6.5, OCH*H*), 2.40-1.79 (4H, m, CH_2, CH_2), 2.19 (3H, s, CCH_3), 1.62-1.42 (2H, m, CH_2), 1.42-1.25 (2H, m, CH_2), 0.91 (3H, t, *J* 7.5, CH_2CH_3); δ_C (125 MHz, $CDCl_3$), 209.0 (C), 104.8 (CH), 82.4 (CH), 67.4 (CH_2), 31.7 (CH_2), 31.6 (CH_2), 26.9 (CH_2), 26.1 (CH_3), 19.3 (CH_2), 13.8 (CH_3); *m/z* (CI) 171 (MH^+), Found: MNH_4^+, 204.1595. $C_{10}H_{18}O_3$ requires MNH_4^+, 204.1560.

220b (minor): ν_{max} ($CHCl_3$)/cm^{-1} 2962-2876 (CH), 1721 (C=O), 1642; δ_H (250 MHz, $CDCl_3$) 5.19 (1H, dd, *J* 4.5, 1.5, OCHO), 4.34 (1H, t, *J* 8.0, C(O)CH), 3.80 (1H, dt, *J* 9.5, 6.5, OC*H*H), 3.43 (1H, dt, *J* 9.5, 6.5, OCH*H*), 2.25 (3H, s, CH_3), 2.22-1.87 (4H, m, CH_2, CH_2), 1.62-1.43 (2H, m, CH_2), 1.42-1.22 (2H, m, CH_2), 0.92 (3H, t, *J* 6.5, CH_2CH_3); δ_C (125 MHz, $CDCl_3$), 211.0 (C), 105.3 (CH), 84.7 (CH), 67.7 (CH_2), 32.8 (CH_2), 31.7 (CH_2), 26.7 (CH_2), 25.5 (CH_3), 19.4 (CH_2), 13.9 (CH_3); *m/z* (CI) 171 (MH^+), Found: MNH_4^+, 204.1595. $C_{10}H_{18}O_3$ requires MNH_4^+, 204.1560.

Oxidation of *2-ethoxy-6-methyl-3,4-dihydro-2H-pyran* 211 using an excess of MCPBA

5-Ethoxy-dihydro-furan-2-one **212**[93, 94]:

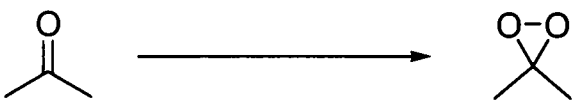


212

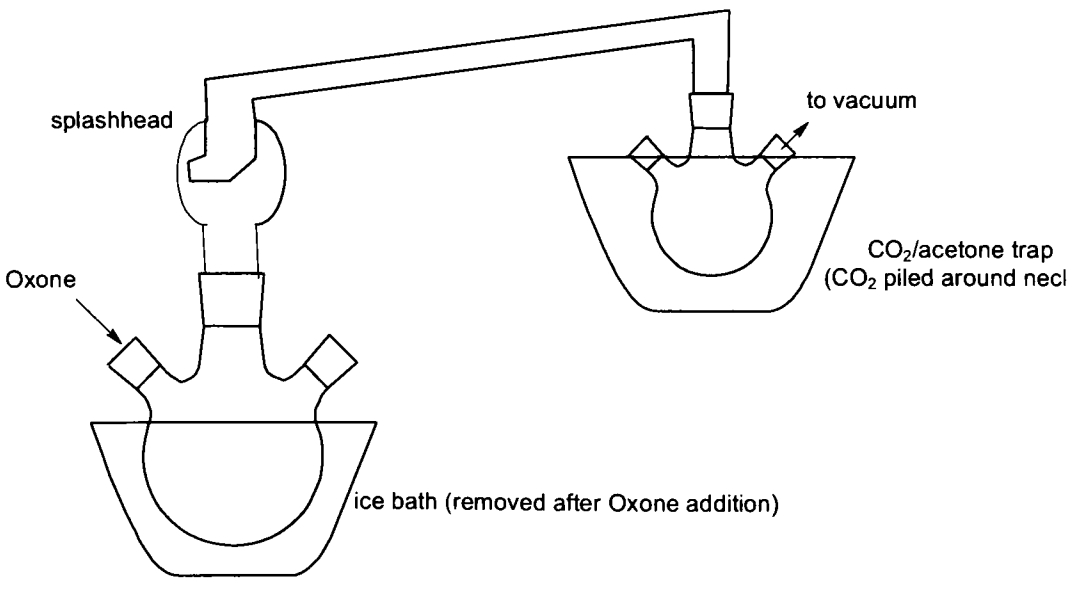
To a solution of 2-alkoxydihydropyran **211** (200 mg, 1.4 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added the excess of MCPBA. After stirring at room temperature under N_2 for 2 h, the reaction mixture was filtered and the solvent removed under reduced pressure. Column chromatography eluting with EtOAc/Et_3N/petrol (1/0.2/4) gave dihydrofuranone **212** (40 mg, 18%) as a pale yellow oil, ν_{max} ($CHCl_3$)/cm^{-1} 1783 (C=O); δ_H (270 MHz, $CDCl_3$) 5.55 (1H, d, *J* 3.5, OCHO), 3.86 (1H, dq, *J* 9.5, 7.0, OC*H*H), 3.66 (1H, dq, *J* 9.5, 7.0, OCH*H*), 2.75-2.05 (4H, m, CH_2CH_2,), 1.18 (3H, t, *J* 7.0, CH_3); δ_C (68 MHz, $CDCl_3$) 176.6 (C),

104.0 (CH), 64.0 (CH_2), 28.8 (CH_2), 26.8 (CH_2), 14.9 (CH_3); *m/z* (CI) 148 (MNH_4^+, 100%), Found: MH^+, 131.0714. $C_6H_{10}O_3$ requires MH^+, 131.0708.

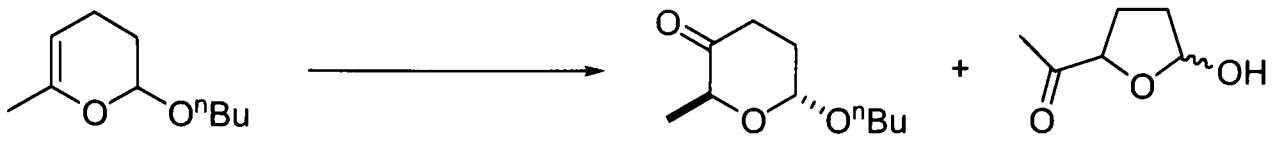
Preparation of DMDO[97]



A mixture of $NaHCO_3$ in acetone and water (3:4, 446 mL) was cooled down in ice bath. Oxone® (120 g) was added portionwise (over 5 times, at 3 minutes intervals) with stirring. After the last Oxone® addition, the vacuum pump was slowly opened until the mixture became foaming. The ice bath was removed. The distillation lasted until no more foaming was observed under high vacuum pressure. DMDO in acetone was collected as a yellow liquid by dry ice trap. The DMDO/acetone solution was dried with K_2CO_3 and filtered. For the titration of DMDO, DMDO/acetone (1 mL) with the unknown concentration, the mixture of acetic acid and acetone (3:2, 2 mL) and saturated KI solution (2 mL) was mixed to give a brown solution. The mixture (1 mL) was titrated with aqueous $Na_2S_2O_3$ solution (0.002 M). The concentration of DMDO was approximately 0.03 M.



Exposure of *2-Butoxy-6-methyl-3,4-dihydro-2H-pyran* 218 to DMDO for 2 d

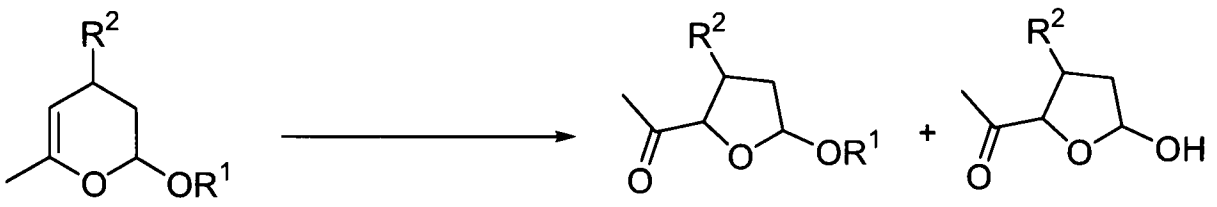


218 **223** **215**

To solution of 2-alkoxydihydropyran **218** (100 mg, 0.6 mmol) in CH_2Cl_2 (5 mL) was added 0.013 M DMDO/acetone (48 ml, 0.6 mmol). After stirring for 30 min at 0 °C, the reaction mixture allowed to be stirred at room temperature for 2 d. Column chromatography eluting with diethyl ether/petrol (1/1→4/1) gave the major product **215** as colourless oil (25 mg, 32%) and the minor product **223** as a colourless oil (10 mg, 10%).

(2S,6R*)-6-Butoxy-2-methyl-dihydro-2H-pyran-3(4H)-one* **223**: ν_{max} ($CHCl_3$)/cm^{-1} 1715 (C=O); δ_H (250 MHz, $CDCl_3$) 4.92 (1H, t, *J* 3.0, OCHO), 4.21 (1H, q, *J* 9.0, C(O)CH), 3.71 (1H, dt, *J* 9.5, 6.5, OC*H*H), 3.42 (1H, dt, *J* 9.5, 6.5, OCH*H*), 2.59-1.88 (4H, m, CH_2, CH_2), 1.65-1.10 (4H, m, CH_2, CH_2), 1.32 (3H, d, *J* 9.0, CHCH_3), 0.85 (3H, t, *J* 6.5, CH_2CH_3); δ_C (125 MHz, $CDCl_3$), 210.6 (C), 96.5 (CH), 70.8 (CH), 67.6 (CH_2), 33.7, 31.7, 29.2, 29.0 (4 x CH_2), 14.9 (CH_3), 13.8 (CH_3); *m/z* (CI) 187 (*MH*$^+$, 100%) and 204 (*MNH*$_4^+$), Found: MH^+, 187.1338. $C_{10}H_{18}O_3$ requires MNH_4^+, 187.1334.

General procedure for the oxidative rearrangement using DMDO/acetone



R^1	R^2	Product	
		lactol ether	lactol
Et	H	**213**	**215**
^{t}Bu	H	**219**	**215**
^{n}Bu	H	**220**	**215**
^{n}Bu	Me	**248**	**249**
Et	Ph	N/A	**234**

To solution of 2-alkoxydihydropyran in CH_2Cl_2 at 0 °C was added a DMDO/acetone solution. After stirring for 30 min, the reaction mixture was allowed to stir at room temperature. Column chromatography eluting with diethyl ether/petrol gave lactols as major products and lactol ethers as minor products.[§]

1-(5-Hydroxy-tetrahydro-furan-2-yl)-ethanone **215** and *1-(5-ethoxy-tetrahydro-furan-2-yl)-ethanone* **213**: Prepared by the general procedure (3.5 mmol of 2-alkoxydihydropyran, 0.04 M DMDO/acetone 90 mL, 3 h) to give **215** (263 mg, >53%) as a major product.

1-(5-Hydroxy-tetrahydro-furan-2-yl)-ethanone **215** and *1-(5-tert-butoxy-tetrahydro-furan-2-yl)-ethanone* **219**: Prepared by the general procedure (1.2 mmol of 2-alkoxydihydropyran, 0.03 M DMDO/acetone 40 mL, 3 h) to give **215** (109 mg, >72%) as a major product.

1-(5-Hydroxy-tetrahydro-furan-2-yl)-ethanone **215** and *1-(5-butoxy-tetrahydro-furan-2-yl)-*

[§] For the spectral data of products **213**, **215**, **219**, **220**; see MCPBA reaction.

ethanone **220**: Prepared by the general procedure (0.6 mmol of 2-alkoxydihydropyran, 0.013 M DMDO/acetone 48 mL, 3 h) to give **215** (50 mg, >64%) as a major product and **220** (10 mg, 9%).

1-(5-Butoxy-3-methyl-tetrahydro-furan-2-yl)-ethanone **248** and *1-(5-hydroxy-3-methyl-tetrahydro-furan-2-yl)-ethanone* **249**: Prepared by the general procedure (1.1 mmol of 2-alkoxydihydropyrans, 0.075 M DMDO/acetone 15 mL, 3 h) to give lactols **249** (15%) in a mixture of 4 diastereoisomers as colourless oil and give lactol ethers **248** (17 mg, 11%) in a mixture of 4 diastereoisomers as a colourless oil.

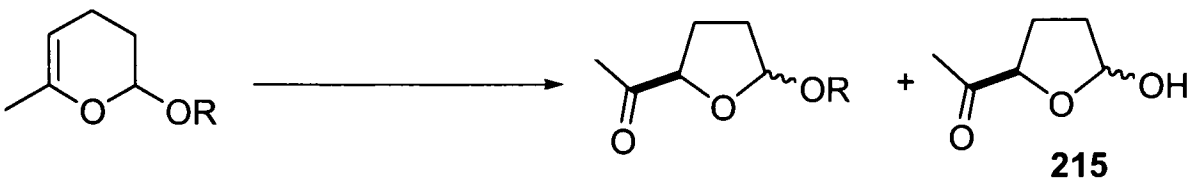
1-(5-Butoxy-3-methyl-tetrahydro-furan-2-yl)-ethanone **248**: ν_{max} ($CHCl_3$)/cm^{-1} 2962-2875 (CH), 1714 (C=O), 1641; δ_H (250 MHz, $CDCl_3$)$_{major}$ 5.14 (1H, dd, *J* 5.0, 5.0, OCHO), 3.98 3.80 (1H, d, *J* 9.5, C(O)CH), 3.86-3.35 (2H, m, OCH_2), 2.52-1.80 (3H, m, CH, CH_2), 2.24 (3H, s, $COCH_3$), 1.70-1.31 (4H, m, CH_2, CH_2), 1.13 (3H, d, *J* 6.5, $CHCH_3$), 0.92 (3H, t, *J* 7.5, CH_2CH_3); δ_C (125 MHz, $CDCl_3$)$_{major}$ 211.1 (C), 104.7 (CH), 92.6 (CH), 67.7 (CH_2), 41.5 (CH_2), 35.6 (CH_2), 31.7 (CH), 25.2 (CH_3), 19.4 (CH_2), 17.0 (CH_3), 13.8 (CH_3); *m/z* (CI) 218 (MNH_4^+), Found: MNH_4^+, 218.1753. $C_{11}H_{20}O_3$ requires MNH_4^+, 218.1756.

1-(5-Hydroxy-3-methyl-tetrahydro-furan-2-yl)-ethanone **249**: ν_{max} ($CHCl_3$)/cm^{-1} 3414 (OH) , 2921-2850 (CH), 2091, 1644; δ_H (250 MHz, $CDCl_3$)$_{major}$ 5.59 (1H, t, *J* 4.5, C(O)CH), 3.97 (1H, d, *J* 8.0, OCHCO), 2.57-2.03 (1H, m, CH_3CH), 2.27 (3H, s, $COCH_3$) , 1.77-1.53 (2H, m, CH_2), 1.21 (3H, d, *J* 6.5, $CHCH_3$); δ_C (125 MHz, $CDCl_3$)$_{major}$ 210.4 (C), 99.6 (CH), 90.7 (CH), 42.3 (CH_2), 35.4 (CH), 25.8 (CH_3), 17.9 (CH_3); *m/z* (CI) 144 (*M*, 100%), 162 (MNH_4^+), Found: MNH_4^+, 162.1129. $C_7H_{12}O_3$ requires MNH_4^+, 162.1130.

1-(5-Hydroxy-3-phenyl-tetrahydro-furan-2-yl)-ethanone **234**: Prepared by the general procedure (0.7 mmol of 2-alkoxydihydropyran, 0.025 M DMDO/acetone 29 mL, 3 h) to give major product, lactols **234** (80%), in a mixture of 4 diastereoisomers as a colourless oil. ν_{max} ($CHCl_3$)/cm^{-1} 3445 (OH), 2944 (CH), 1780, 1714(C=O), 1645; δ_H (250 MHz,

$CDCl_3)_{major}$ 7.38-7.11 (5H, Ph), 5.99 (1H, dd, *J* 5.0, 2.5, OC*H*OH), 4.96 (1H, d, *J* 7.5, C(O)CH), 4.02-3.77 (1H, m, PhCH), 2.47-2.11 (2H, m, CH_2), 1.64 (3H, s, $C(O)CH_3$); ^{13}C NMR could not be recorded due to the complexity of spectrum; *m/z* (CI) 206 (*M*, 100%), 224 (MNH_4^+), Found: MNH_4^+, 224.1281. $C_{12}H_{14}O_3$ requires MNH_4^+, 224.1287.

General procedure for the oxidative rearrangement using DMDO generated *in situ*



215

Dihydropyrans	R	Product	
		lactol ether	lactol
211	Et	**213**	**215**
218	^{n}Bu	**220**	**215**

To a solution of acetone (> 20.0 eq) and 2-alkoxydihydropyrans (1.0 eq) in CH_2Cl_2 at 0 ℃ was added 0.4 mM Na_2EDTA (aq). After the mixture of Oxone® (2.5 eq) and $NaHCO_3$ (4.0 eq) was ground, it was added to the reaction mixture over 30 minutes. After stirring vigorously at room temperature for overnight, the organic layer was separated by extraction with aqueous saturated $NaHCO_3$ solution, dried with $MgSO_4$ and filtered. Column chromatography eluting with diethyl ether/petrol (3:2) gave lactol ether as a major compound and give lactol as a minor compound.**

1-(5-Hydroxy-tetrahydro-furan-2-yl)-ethanone **215** and *1-(5-ethoxy-tetrahydro-furan-2-yl)-ethanone* **213**: Prepared by the general procedure (60.0 mmol of acetone, 3.5 mmol of 2-alkoxydihydropyran **211**, 8.8 mmol of Oxone® and 14.0 mmol of $NaHCO_3$) to give lactolether **213** in a mixture of diastereoisomers (1:1) as a colourless oil (74 mg, 13%) and give a minor compound **215**.

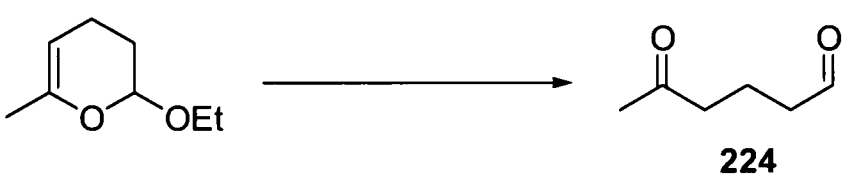
1-(5-Hydroxy-tetrahydro-furan-2-yl)-ethanone **215** and *1-(5-butoxy-tetrahydro-furan-2-yl)-*

** For the spectral data of lactol **215** and lactol ether **213** and **220**; see the oxidative rearrangement using MCPBA.

ethanone **220**: Prepared by the general procedure (60.0 mmol of acetone, 1.8 mmol of 2-alkoxydihydropyran **218**, 4.5 mmol of Oxone® and 7.2 mmol of $NaHCO_3$) to give lactol ether **220** in a mixture of diastereoisomers (1:1) as a colourless oil (74 mg, 13%) and give a minor compound **215**.

Attempted oxidation of *2-ethoxy-6-methyl-3,4-dihydro-2H-pyran* 211 using hydrogen peroxide

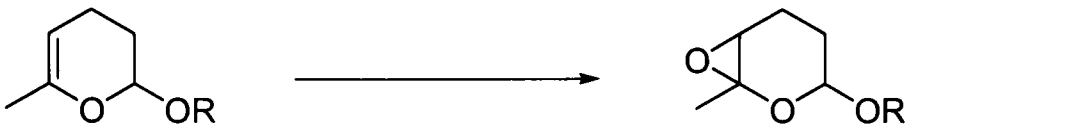
5-Oxo-hexanal **224**[162]:



224

To solution of 2-alkoxydihydropyran **211** (200 mg, 1.4 mmol) in MeCN (3 mL) was added a solution of 27 % hydrogen peroxide (176 mg, 1.4 mmol) in MeCN (3 mL). After the reaction mixture stirred at room temperature for 15 h, saturated aqueous sodium sulfite was used for the work-up. The reaction mixture was dried with $MgSO_4$, filtered and concentrated. Column chromatography eluting with diethyl ether/petrol (4:1) to give a pale yellow oil **224** (37 mg, 20%). ν_{max} ($CHCl_3$)/cm^{-1} 1720 (C=O), 1730 (C=O); δ_H (500 MHz, $CDCl_3$) 9.75 (1H, s, C(O)H), 2.55-2.35 (4H, 2 x CH_2), 2.10 (3H, s, $C(O)CH_3$), 1.86-1.80 (2H, m, CH_2); δ_C (125 MHz, $CDCl_3$) 208.0 (C), 43.0 (CH_2), 42.3 (CH_2), 30.0 (CH_3), 16.0 (CH_2) [5 out of 6 carbons observed]; *m/z* (CI) 115 (*M*), 131, 132 (MNH_4^+), 148 (100%), Found: MNH_4^+ 132.1030 $C_6H_{10}O_2$ requires MNH_4^+ 132.1025.

General procedure for the epoxidation of dihydropyrans using hydrogen peroxide and MTO[99d]



Tentatively assigned products

Dihydropyrans	R	Product
211	Et	**225**
218	^{n}Bu	**226**

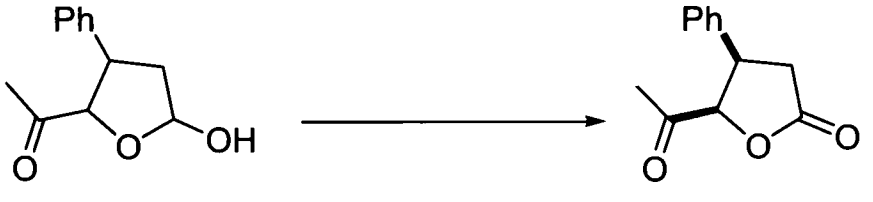
To the mixture of MTO (0.03 eq) and pyridine (0.6 eq) in CH_2Cl_2 was added 27 % hydrogen peroxide (3.0 eq). To a solution of 2-alkoxydihydropyran (1.0 eq) in CH_2Cl_2 was added the solution of the oxidant dropwise at room temperature under N_2 condition. After the reaction mixture stirred for 8 h, saturated aqueous $NaHCO_3$ was used for the work-up. The reaction mixture was dried with $MgSO_4$, filtered and concentrated to give the crude as a pale yellow oil.

Tentatively assigned product, *3-ethoxy-1-methyl-2,7-dioxa-bicyclo[4,1,0]heptane*: Prepared by the general procedure (0.02 mmol of MTO, 0.8 mmol of pyridine, 10.5 mmol of 27% hydrogen peroxide and 3.5 mmol of 2-alkoxydihydropyran **211**) to give the crude **225** as a pale yellow oil. δ_H (250 MHz, $CDCl_3$) 4.85 (1H, t, *J* 3.0, OCHO), 4.30 (1H, t, *J* 3.0, $CH_{epoxide}$), 3.71 (1H, dq, *J* 9.5, 7.0, OC*H*H), 3.40 (1H, dq, *J* 9.5, 7.0, OCH*H*), 2.05-1.35 (7H, m, CCH_3, CH_2, CH_2); 1.00 (3H, t, *J* 7.0, CH_2CH_3); ^{13}C NMR could not be recorded due to the rapid decomposition of the sample.

Tentatively assigned product, *3-butoxy-1-methyl-2,7-dioxa-bicyclo[4,1,0]heptane*: Prepared by the general procedure (0.02 mmol of MTO, 0.8 mmol of pyridine, 10.5 mmol of 27% hydrogen peroxide and 3.5 mmol of 2-alkoxydihydropyran **218**) to give the crude **226** as a

pale yellow oil. δ_H (250 MHz, $CDCl_3$) 4.92 (1H, t, *J* 3.0, OCHO), 4.46 (1H, t, *J* 3.0, $CH_{epoxide}$), 3.73 (1H, dt, *J* 9.5, 6.5, OC*H*H), 3.43 (1H, dt, *J* 9.5, 6.5, OCH*H*), 2.10-1.19 (8H, m, CH_2, CH_2, CH_2, CH_2), 1.66 (3H, s, CCH_3), 0.85 (3H, t, *J* 7.5, CH_2CH_3); ^{13}C NMR could not be recorded due to the rapid decomposition of the sample.

Oxidation of *1-(5-Hydroxy-3-phenyl-tetrahydro-furan-2-yl)-ethanone* using PCC



234 **235**

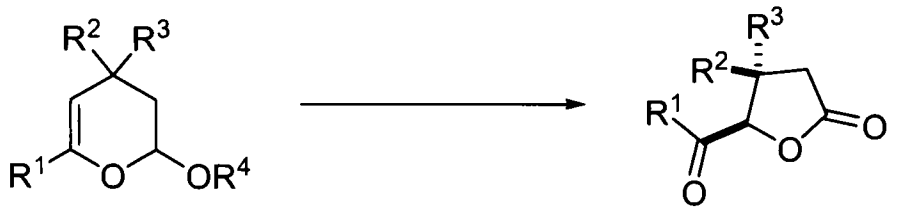
To a solution of *1-(5-hydroxy-3-phenyl-tetrahydro-furan-2-yl)-ethanone* **234** (116 mg, 0.56 mmol) in CH_2Cl_2 (10 ml) was added a suspension of PCC (361 mg, 1.68 mmol) and neutral alumina (815 mg, 8.9 mmol) in CH_2Cl_2 (20 mL). After stirring at room temperature for overnight, the solution was filtered through a short pad of Florisil and the solid residue was washed several times with diethyl ether. The solvent was removed under reduced pressure to give a yellow solid. The colour of the solution turned into dark brown. Column chromatography eluting with the EtOAc/petrol (3/7) gave *(4R*,5R*)-5-acetyl-4-phenyl-dihydro-furan-2-one* **235** as a white solid (100 mg, 88%).[††]

The preparation of 3.0 M Jones oxidant[103]

To a solution of CrO_3 (67.0 g) in H_2O (125 mL) was added carefully a solution of concentrated H_2SO_4 (58 mL). The precipitated salts were dissolved by adding an additional minimal quantity of water (total volume was 225 mL) to give 3.0 M Jones oxidant.

[††] For the spectral data; see the rearrangement / Jones oxidation of alkoxydihydropyrans.

General procedure for rearrangement / Jones oxidation of alkoxydihydropyrans



Product	R^1	R^2	R^3	R^4
231	Me	H	H	^{n}Bu
250	Me	Me	H	^{n}Bu
251	Me	^{i}Pr	H	^{n}Bu
252	Me	Me	Me	^{n}Bu
235	Me	Ph	H	Et
253	Me	CH_2OBn	H	Et
254	Me	$(CH_2)_4CH=CHEt$	H	Et
273	^{n}Pr	Me	H	Et
274	^{n}Bu	Me	H	Et

To solution of 2-alkoxydihydropyran in CH_2Cl_2 at 0 °C was added DMDO/acetone solution. After stirring for 30 min, the reaction mixture was allowed to warm to room temperature. After the crude was extracted with saturated aqueous $NaHCO_3$ solution, it was concentrated to give the mixture of lactol and lactol ether. The crude mixture from oxidative rearrangement was dissolved into acetone at 0 °C and 3.0 M Jones reagent (3.0 eq to initial 2-alkoxydihydropyran) was added dropwise. After being stirred, the excess of oxidants was quenched by the addition of 2-propanol until the brown colour of the mixture turned to green. The reaction mixture was diluted with diethyl ether and the precipitated chromium salts were dissolved by the addition of saturated aqueous NH_4Cl solution. The organic layer was separated and the aqueous layer was extracted with diethyl ether. Column chromatography gave 4,5-*cis*-lactones as major products and 4,5-*trans*-lactones as minor products. Structures of 4,5-*cis*-isomers and 4,5-*trans*-isomers were assigned by NOESY

experiment.[‡‡]

5-Acetyl-dihydro-furan-2-one **231**[163]: Prepared by the general procedure (0.9 mmol of 2-alkoxydihydropyran, 0.013 M DMDO 70 mL, 3.0 M Jones reagent 0.9 mL, 3 h for DMDO oxidation, 30 min for Jones oxidation) to give lactone **231** as a pale yellow oil (80 mg, 69% over 2 steps). ν_{max} ($CHCl_3$)/cm^{-1} 1767 (lactone), 1723 (C=O), 1634; δ_H (250 MHz, $CDCl_3$) 4.81 (1H, t, *J* 7.5, CH), 2.62-2.18 (4H, m, CH_2CH_2) 2.30 (3H, s, CH_3); δ_C (125 MHz, $CDCl_3$), 205.4 (C), 175.7 (C), 82.0 (CH), 27.4 (CH_2), 26.2 (CH_3), 24.4 (CH_2); *m/z* (CI) 146 (*MNH_4^+*, 100%) Found: MNH_4^+, 146.0814. $C_6H_8O_3$ requires MNH_4^+, 146.0817.

(4S,5R*)-5-Acetyl-4-methyl-dihydro-furan-2-one* **250a** and *(4S*,5R*)-5-acetyl-4-methyl-dihydro-furan-2-one* **250b**[164]: Prepared by the general procedure (0.9 mmol of 2-alkoxydihydropyran, 0.013 M DMDO 70 mL, 3.0 M Jones reagent 0.9 mL, 3 h for DMDO oxidation, 30 min for Jones oxidation) to give lactone **250** in a 3:1 mixture[§§]; **250a** (45 mg, 35% over 2 steps) as a major product in pale yellow oil and **250b** (20 mg, 16 % over 2 steps) as a minor product in a pale yellow oil.

(4R,5R*)-5-Acetyl-4-methyl-dihydro-furan-2-one* **250a**: ν_{max} ($CHCl_3$)/cm^{-1} 3058-2989 (CH), 1791 (lactone), 1720 (C=O), 1643; δ_H (250 MHz, $CDCl_3$) 4.80 (1H, d, *J* 7.0, OCH), 3.02-2.82 (1H, m, C*H*CH_3), 2.75 (1H, dd, *J* 17.0, 8.0, C*H*H), 2.29 (1H, dd, *J* 17.0, 8.0, CH*H*), 2.27 (3H, s, C(O)CH_3), 1.02 (3H, d, *J* 7.0, $CHCH_3$); δ_C (125 MHz, $CDCl_3$), 205.7 (C), 175.4 (C), 85.1 (CH), 36.4 (CH_2), 33.0 (CH), 28.5 (CH_3), 14.8 (CH_3); *m/z* (CI) 160 (*MNH_4^+*, 100%), Found: MNH_4^+, 160.0972. $C_7H_{10}O_3$ requires MNH_4^+, 160.0974.

(4S,5R*)-5-Acetyl-4-methyl-dihydro-furan-2-one* **250b**: ν_{max} ($CHCl_3$)/cm^{-1} 1787 (lactone), 1723 (C=O), 1613; δ_H (250 MHz, $CDCl_3$) 4.33 (1H, d, *J* 7.0, OCH), 2.72 (1H, dd, *J* 17.0, 8.5, CH_2), 2.23 (1H, dd, *J* 17.0, 8.5, CH_2), 2.55 (1H, m, CH), 2.28 (3H, s, C(O)CH_3), 1.28 (3H, d, *J* 6.5, $CHCH_3$); δ_C (125 MHz, $CDCl_3$), 205.4 (C), 175.1 (C), 88.1 (CH), 35.9 (CH_2), 33.6 (CH), 26.2 (CH_3), 18.4 (CH_3); *m/z* (CI) 160 (*MNH_4^+*, 100%), Found: MNH_4^+,

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[‡‡] For NOESY spectra; see appendix.

[§§] Ratio determined by ^{1}H-NMR

160.0972. $C_7H_{10}O_3$ requires MNH_4^+, 160.0974.

(4R,5R*)-5-Acetyl-4-isopropyl-dihydro-furan-2-one* **251a** and *(4S*,5R*)-5-acetyl-4-isopropyl-dihydro-furan-2-one* **251b**: Prepared by the general procedure (0.9 mmol of 2-alkoxydihydropyran, 0.045 M DMDO 20 mL, 3.0 M Jones reagent 0.9 mL, 3 h for DMDO oxidation, 30 min for Jones oxidation) to give an inseparable mixture of diastereoisomers, **251a** and **251b** in a 9:1 ratio (96 mg, 63% over 2 steps), as a colourless oil. ν_{max} ($CHCl_3$)/cm^{-1} 2965-2879 (CH), 1787 (lactone), 1720 (C=O), 1644; δ_H (250 MHz, $CDCl_3$) 4.88 ($1H_{major}$, d, *J* 7.0, OCH), 4.56 ($1H_{minor}$, d, *J* 5.0, OCH) 2.64-2.34 ($6H_{both}$, m, 2 x CH_2, 2 x COCH), 2.29 ($3H_{major}$, s, $C(O)CH_3$), 2.26 ($3H_{minor}$, s, $C(O)CH_3$), 1.90 ($1H_{minor}$, m, C*H*CH_3), 1.68 ($1H_{major}$, m, C*H*CH_3), 0.99 ($3H_{major}$, d, *J* 6.5, CHC*H*$_3$), 0.96 ($3H_{minor}$, d, *J* 2.0, CHC*H*$_3$), 0.94 ($3H_{minor}$, d, *J* 2.0, CHC*H*$_3$), 0.87 ($3H_{major}$, d, *J* 6.5, CHC*H*$_3$); δ_C (125 MHz, $CDCl_3$)$_{major}$, 205.7 (C), 175.4 (C), 84.3 (CH), 46.4 (CH_2), 31.3 (CH), 29.1 (CH), 27.6 (CH_3), 21.4 (CH_3), 20.0 (CH_3); *m/z* (CI) 188 (*MNH*$_4^+$, 100%), Found: MNH_4^+, 188.1289. $C_9H_{14}O_3$ requires MNH_4^+, 188.1287.

5-Acetyl-4,4-dimethyl-dihydrofuran-2(3H)-one **252**[165]: Prepared by the general procedure (1.8 mmol of 2-alkoxydihydropyran, 0.035 M DMDO 50 mL, 3.0 M Jones reagent 2.3 mL, 3 h for DMDO oxidation, 30 min for Jones oxidation) to give lactone **252** as a colourless oil (136 mg, 50% over 2 steps). ν_{max} ($CHCl_3$)/cm^{-1} 2969-2878 (CH), 2358, 1789 (lactone), 1714 (C=O), 1634; δ_H (250 MHz, $CDCl_3$) 4.40 (1H, s, OCH), 2.43 (2H, d, *J* 3.5, CH_2), 2.27 (3H, s, $C(O)CH_3$), 1.35 (3H, s, CH_3), 1.05 (3H, s, CH_3); δ_C (125 MHz, $CDCl_3$), 206.1 (C), 174.7 (C), 89.7 (CH), 43.9 (CH_2), 40.7 (C), 28.4, 26.2, 22.1 (3 x CH_3); *m/z* (CI) 174 (*MNH*$_4^+$, 100%), Found: MNH_4^+, 174.1130. $C_8H_{12}O_3$ requires MNH_4^+, 174.1130.

(4R,5R*)-5-Acetyl-4-phenyl-dihydro-furan-2-one* **235**: Prepared by the general procedure (0.9 mmol of 2-alkoxydihydropyran, 0.045 M DMDO 20 mL, 3.0 M Jones reagent 2.7 mL, 3 h for DMDO oxidation, 30 min for Jones oxidation) to give the only one diastereoisomer lactone **235** as a white solid (120 mg, 65% over 2 steps). mp 92-93 °C; ν_{max} ($CHCl_3$)/cm^{-1}

3035-2877 (CH), 1772 (lactone), 1721 (C=O), 1650; δ_H (250 MHz, $CDCl_3$) 7.35-7.13 (5H, m, Ph), 5.09 (1H, d, *J* 8.0, OCH), 4.05 (1H, dt, *J* 8.0, 6.0, CH), 2.96 (1H, dd, *J* 17.5, 8.5, C*H*H), 2.88 (1H, dd, *J* 17.5, 6.0, CH*H*), 1.64 (3H, s, CH_3); δ_C (125 MHz, $CDCl_3$), 205.0 (C), 175.6 (C), 135.8 (C), 129.2 (2 x CH), 128.4 (CH), 127.6 (2 x CH), 85.6 (CH), 44.0 (CH), 34.5 (CH_2), 28.0 (CH_3); *m/z* (CI) 222 (*MNH_4^+*, 100%), Found: MNH_4^+, 222.1127. $C_{12}H_{12}O_3$ requires MNH_4^+, 222.1130

(4R,5R*)-5-Acetyl-4-(benzyloxymethyl)-dihydrofuran-2(3H)-one* **253**: Prepared by the general procedure (0.8 mmol of 2-alkoxydihydropyran, 0.02 M DMDO 40 mL, 3.0 M Jones reagent 2.4 mL, 3 h for DMDO oxidation, 30 min for Jones oxidation) to give the only one diastereoisomer **253** (>95:5) as a colourless oil (96 mg, 48% over 2 steps). ν_{max} ($CHCl_3$)/cm^{-1} 2874 (CH), 2089, 1780 (lactone), 1645; δ_H (250 MHz, $CDCl_3$), 7.39-7.19 (5H, m, Ph), 4.80 (1H, d, *J* 8.0, C(O)CH), 4.40 (1H, d, *J* 21.5, $PhCH_2$), 4.36 (1H, d, *J* 21.5, $PhCH_2$), 3.53 (1H, dd, *J* 9.5, 3.0, $BnOCH_2$), 3.38 (1H, dd, *J* 9.5, 3.0, $BnOCH_2$), 3.03 (1H, dtt, *J* 8.0, 9.5, 3.0, $BnOCH_2CH$), 2.72 (1H, dd, *J* 17.5, 9.5, $C(O)CH_2$), 2.55 (1H, dd, *J* 17.5, 4.0, $C(O)CH_2$), 2.23 (3H, s, $C(O)CH_3$); δ_C (125 MHz, $CDCl_3$) 206.5 (C), 175.5 (C), 136.9 (C), 128.4 (2 x CH), 127.9 (CH), 127.6 (2 x CH), 83.1 (CH), 73.1, 68.0 (2 x CH_2), 38.1 (CH_2), 32.2 (CH), 28.1 (CH_3); *m/z* (CI) 266 (*MNH_4^+*, 100%), Found: MNH_4^+, 266.1395. $C_{14}H_{16}O_4$ requires MNH_4^+, 266.1392.

(4S,5R*,Z)-5-Acetyl-4-(oct-5-enyl)-dihydrofuran-2(3H)-one* **254**: Prepared by the general procedure (1.2 mmol of 2-alkoxydihydropyran, 0.03 M DMDO 40 mL, 3.0 M Jones reagent 2.5 mL, 3 h for DMDO oxidation, 30 min for Jones oxidation) to give the only one diastereoisomer **254** as a colourless oil (130 mg, 64% over 2 steps). ν_{max} ($CHCl_3$)/cm^{-1} 3007-2858 (CH), 2358, 2330, 1790 (lactone), 1717 (C=O); δ_H (250 MHz, $CDCl_3$) 5.47-5.14 (2H, m, CH=CH), 4.82 (1H, d, *J* 7.5, C(O)CH), 2.86-2.65 (1H, m, C(O)CHC*H*), 2.65 (1H, dd, *J* 17.0, 8.0, $C(O)CH_2CH$), 2.37 (1H, dd, *J* 17.0, 6.0, $C(O)CH_2CH$), 2.26 (3H, s, $C(O)CH_3$), 2.07-1.96 (2H, m, CH_2CH_3), 1.52-1.02 (8H, m, 4 x CH_2), 0.94 (3H, t, *J* 7.5, CH_2CH_3); δ_C (125 MHz, $CDCl_3$) 205.8 (C), 175.5 (C), 132.2, 128.3 (2 x CH), 84.9 (CH),

38.7 (CH_2), 33.6 (CH), 29.3, 28.8, 28.7, 27.1, 26.7 (5 x CH_2), 20.5 (CH_3), 14.3 (CH_3); *m/z* (CI) 256 (MNH_4^+, 100%), Found: MNH_4^+, 256.1907. $C_{14}H_{22}O_3$ requires MNH_4^+, 256.1913 Structure of **2,3-*cis*-254** was assigned by NOESY.

(4S,5R*)-4-Methyl-5-pentanoyl-dihydrofuran-2(3H)-one* **273a** and *(4R*,5R*)-4-methyl-5-pentanoyl-dihydrofuran-2(3H)-one* **273b**: Prepared by the general procedure (2.6 mmol of 2-alkoxydihydropyran, 0.03 M DMDO 90 mL, 3.0 M Jones reagent 3.0 mL, 3 h for DMDO oxidation, 30 min for Jones oxidation) to give **273** in a 5:1 mixture[***]; **273a** (290 mg, 58%) and **273b** (60 mg, 12%) as a pale yellow oil.

273a (major): ν_{max} ($CHCl_3$)/cm^{-1} 2255, 1788 (lactone), 1719 (C=O); δ_H (250 MHz, $CDCl_3$), 4.80 (1H, d, *J* 7.0, OCH), 3.08-2.82 (1H, m, CH_3CH), 2.73 (1H, dd, *J* 17.0, 8.0, C(O)CH_2CH), 2.29 (1H, dd, *J* 17.0, 4.5, C(O)CH_2CH), 2.78-2.32 (2H, m, $CH_2CH_2CH_3$), 1.71-1.56 (2H, m, $CH_2CH_2CH_3$), 1.00 (3H, d, *J* 7.0, $CHCH_3$), 0.94 (3H, t, *J* 7.5, CH_2CH_3); δ_C (125 MHz, $CDCl_3$), 207.8 (C), 175.6 (C), 84.9 (CH), 42.9 (CH_2), 36.4 (CH), 33.1, 16.0 (2 x CH_2), 14.8, 13.6 (2 x CH_3); *m/z* (CI) 188 (MNH_4^+, 100%) Found: MNH_4^+, 188.1289. $C_9H_{14}O_3$ requires MNH_4^+, 188.1286.

273b (minor): ν_{max} ($CHCl_3$)/cm^{-1} 2255, 1788 (lactone), 1719 (C=O); δ_H (250 MHz, $CDCl_3$), 4.32 (1H, d, *J* 7.0, OCH), 2.68 (1H, dd, *J* 17.0, 8.5, C(O)CH_2), 2.19 (1H, dd, *J* 17.0, 7.5, C(O)CH_2), 2.60-2.43 (3H, m, $CH_2CH_2CH_3$,CH_3CH), 1.61 (2H, tq, *J* 11.0, 6.5, $CH_2CH_2CH_3$), 1.26 (3H, d, *J* 6.5, $CHCH_3$), 0.91 (3H, t, *J* 6.5, CH_2CH_3); δ_C (125 MHz, $CDCl_3$), 207.8 (C), 175.0 (C), 87.9 (CH), 40.4, 35.8 (2 x CH_2), 33.6 (CH), 18.5 (CH_2), 16.2, 13.6 (2 x CH_3); *m/z* (CI) 188 (MNH_4^+, 100%), Found: MNH_4^+, 188.1284. $C_9H_{14}O_3$ requires MNH_4^+, 188.1284.

(4S,5R*)-4-Methyl-5-pentanoyl-dihydrofuran-2(3H)-one* **274a** and *(4S*,5S*)-4-methyl-5-pentanoyl-dihydrofuran-2(3H)-one* **274b**: Prepared by above general procedure (2.8 mmol of 2-alkoxydihydropyran, 0.07 M DMDO 40 mL, 3.0 M Jones reagent 3.0 mL, 3 h for

[***] Ratio determined by ^{1}H-NMR

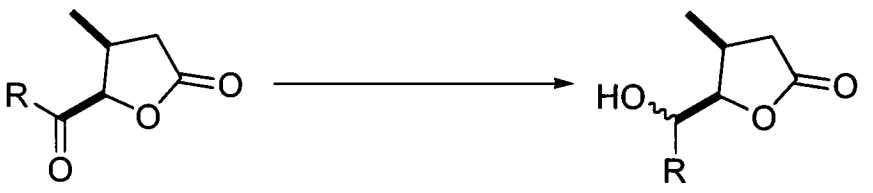
DMDO oxidation, 30 min for Jones oxidation) to give **274** in a 8:1 mixture[†††]; **274a** (250 mg, 48%) and **274b** (31 mg, 6%) in a 8:1 ratio in a pale yellow oil.

274a (major): ν_{max} ($CHCl_3$)/cm^{-1} 2254, 1789 (lactone), 1716 (C=O); δ_H (250 MHz, $CDCl_3$), 4.80 (1H, d, *J* 10.0, OCH), 2.94 (1H, m, CH_3CH), 2.72 (1H, dd, *J* 17.5, 8.0, $C(O)CH_2CH$), 2.73-2.40 (2H, m, CH_2 in ^nBu), 2.28 (1H, dd, *J* 17.5, 4.5, $C(O)CH_2CH$), 1.62-1.54 (2H, m, CH_2 in ^nBu), 1.38-1.28 (2H, m, CH_2 in ^nBu), 0.99 (3H, d, *J* 7.0, $CHCH_3$), 0.91 (3H, t, *J* 7.5, CH_2CH_3); δ_C (125 MHz, $CDCl_3$), 207.8 (C), 175.6 (C), 84.9 (CH), 40.7 (CH_2), 36.4 (CH_2), 36.4 (CH), 24.6, 22.2 (2 x CH_2), 14.8, 13.8 (2 x CH_3); *m/z* (CI) 202 (MNH_4^+, 100%), Found: MNH_4^+, 202.1447. $C_{10}H_{16}O_3$ requires MNH_4^+, 202.1443.

274b (minor): ν_{max} ($CHCl_3$)/cm^{-1} 2254, 1789 (lactone), 1716 (C=O); δ_H (250 MHz, $CDCl_3$), 4.33 (1H, d, *J* 9.5, OCH), 2.69 (1H, dd, *J* 17.5, 8.5, $C(O)CH_2CH$), 2.62-2.48 (3H, m, CH_3CH, CH_2 in ^nBu), 2.20 (1H, dd, *J* 17.5, 4.5, $C(O)CH_2CH$), 1.61-1.53 (2H, m, CH_2 in ^nBu), 1.37-1.26 (2H, m, CH_2 in ^nBu), 1.27 (3H, d, *J* 6.5, $CHCH_3$), 0.90 (3H, t, *J* 7.5, CH_2CH_3); δ_C (125 MHz, $CDCl_3$), 207.4 (C), 175.3 (C), 88.0 (CH), 38.3, 35.8 (2 x CH_2), 33.6 (CH), 24.8, 22.2 (2 x CH_2), 18.5, 13.8 (2 x CH_3); *m/z* (CI) 202 (MNH_4^+, 100%), Found: MNH_4^+, 202.1438. $C_{10}H_{16}O_3$ requires MNH_4^+, 202.1443.

[†††] Ratio determined by ^{1}H-NMR

General procedure for the reduction of ketone using $NaBH_4$[166]



Ketones	R	Alcohols
273a	^{n}Pr	**275**
274a	^{n}Bu	**276**

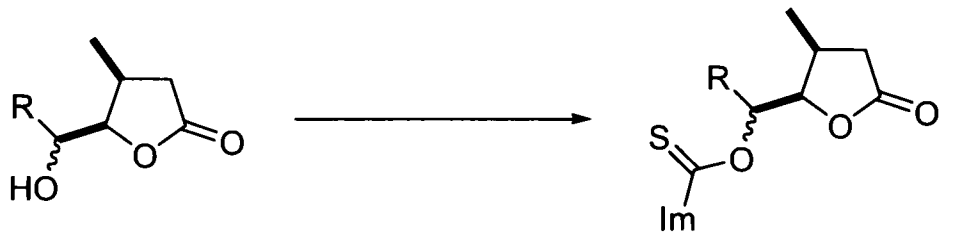
To a solution of ketone (1.0 eq) in MeOH was added a solution of $NaBH_4$ (1.0 eq) in EtOH. After stirring at room temperature under N_2 for overnight, H_2O was used for the workup. Column chromatography eluting with EtOAc/petrol (1/1) gave diastereoisomeric mixture of alcohols as colourless oil.

(4S,5R*)-5-(1-Hydroxybutyl)-4-methyl-dihydrofuran-2(3H)-one*: Prepared by the general procedure (148 mg of ketone **273a**, 33 mg of $NaBH_4$) to give alcohol **275** (2:1 diastereoisomeric mixture) as a colourless oil (130 mg, 87%). ν_{max} ($CHCl_3$)/cm^{-1} 3458 (OH), 2964 (CH), 2254, 1777 (lactone); δ_H (250 MHz, $CDCl_3$)$_{major}$, 4.17 (1H, dd, *J* 8.5, 5.0, C*H*CHCH$_3$), 3.80 (1H, dt, *J* 8.5, 3.0, HOC*H*), 2.78-2.68 (2H, m, CH$_3$C*H*, CH$_3$CHC*H*$_2$), 2.24 (1H, dd, *J* 5.5, 5.5, CH$_3$CHC*H*$_2$), 1.81-1.38 (4H, m, 2 x CH_2 in ^{n}Pr), 1.13 (3H, d, *J* 7.0, CH*CH*$_3$), 0.97 (3H, t, *J* 7.0, CH$_2$C*H*$_3$); δ_C (125 MHz, $CDCl_3$)$_{major}$, 176.7 (C), 84.4 (CH), 69.5 (CH), 38.0, 36.8, 18.3 (3 x CH_2), 32.0 (CH), 14.2, 14.0 (2 x CH_3); *m/z* (CI) 190 (*MNH*$_4^+$, 100%), Found: MNH_4^+, 190.1441. $C_9H_{16}O_3$ requires MNH_4^+, 190.1443.

(4S,5R*)-5-(1-Hydroxypentyl)-4-methyl-dihydrofuran-2(3H)-one*: Prepared by the general procedure (280 mg of ketone **274a**, 69 mg of $NaBH_4$) to give alcohol **276** (2:1 diastereoisomeric mixture) as a colourless oil (197 mg, 70%). ν_{max}/cm^{-1} 3446 (OH), 2254, 1776 (lactone), 1642; δ_H (250 MHz, $CDCl_3$)$_{major}$, 4.28 (1H, dd, *J* 8.5, 4.0, C*H*CHCH$_3$), 3.77

(1H, dt, *J* 8.5, 3.5, HOC*H*), 2.96-2.84 (1H, m, CH_3CH), 2.78-2.41 (4H, m, CH_3CHCH_2, $HOCHCH_2CH_2$), 1.92-1.25 (4H, m, 2 x CH_2 in ^nBu), 1.15 (3H, d, *J* 7.0, $CHCH_3$), 0.91 (3H, t, *J* 6.5, CH_2CH_3); δ_C (125 MHz, $CDCl_3$) 177.2 $(C)_{major}$, 176.7 $(C)_{minor}$, 84.8 $(CH)_{major}$, 84.4 $(CH)_{minor}$, 70.6 $(CH)_{major}$, 69.6 $(CH)_{minor}$, 38.06, 34.4, 27.2, 22.6 (4 x $CH_2)_{minor}$, 37.1, 33.0, 27.6, 22.5 (4 x $CH_2)_{major}$, 32.5 $(CH)_{major}$, 32.0 $(CH)_{minor}$, 14.0, 13.9 (2 x $CH_3)_{both}$ [18 out of 20 carbons observed] *m/z* (CI) 204 (MNH_4^+, 100%) Found: MNH_4^+, 204.1594. $C_{10}H_{18}O_3$ requires MNH_4^+, 204.1599.

General procedure for the synthesis of thiocarbonylimidazolides[115c]



Alcohols	R	thiocarbonylimidazolides
275	^nPr	**277**
276	^nBu	**278**

To a solution of alcohol (1.0 eq) in DCE at room temperature under N_2 was added thiocarbonyldiimidazole (1.5 eq). The reaction mixture was stirred and the temperature was gradually increased to 80-100 °C. After stirring overnight, H_2O was used for the workup. Column chromatography eluting with EtOAc/petrol (3:7) gave thiocarbonylimidazolides as a diastereoisomeric mixture.[‡‡‡]

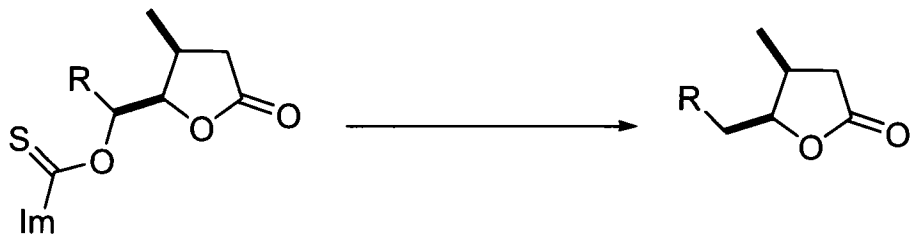
O-1-((2R,3S*)-3-Methyl-5-oxo-tetrahydrofuran-2-yl)butyl 1H-imidazole-1-carbothioate*: Prepared by the general procedure (130 mg of alcohol, 203 mg of thiocarbonyldiimidazole,

[‡‡‡] NMR assignment; only for the major product.

80 °C) to give thiocarbonylimidazolide **277** (2:1 diastereoisomeric mixture) as a pale yellow oil (80 mg, 50%). ν_{max} ($CHCl_3$)/cm^{-1} 3432, 2254, 1787 (lactone), 1714; δ_H (250 MHz, $CDCl_3)_{major}$ 8.37, 7.66, 7.09 (3H, m, 3 x CH in Im), 5.81 (1H, dt, *J* 6.5, 4.0, Im(S)COCH), 4.74 (1H, dd, *J* 6.5, 6.0, CH_3CHCH), 2.90-1.37 (7H, m, CH_3CH, CH_3CHCH_2, 2 x CH_2 in ^nPr), 1.12 (3H, d, *J* 6.5, $CHCH_3$), 0.95 (3H, t, *J* 7.5, CH_2CH_3); δ_C (125 MHz, $CDCl_3)_{major}$ 175.7 (C), 175.4 (C), 81.4, 81.3, 79.2 (3 x CH), 81.1 (CH), 80.6 (CH), 37.0, 32.5, 17.8 (3 x CH_2), 32.2 (CH_3), 14.7, 14.0 (CH_3, CH_3); *m/z* (CI) 283 (MH^+, 100%), Found: MH^+, 283.1116. $C_{13}H_{18}N_2O_3S$ requires MH^+, 283.1116.

O-1-((2R,3S*)-3-Methyl-5-oxo-tetrahydrofuran-2-yl)pentyl 1H-imidazole-1-carbothioate*: Prepared by the general procedure (197 mg of alcohol, 267 mg of thiocarbonyldiimidazole, 100 °C) to give thiocarbonylimidazolide **278** (2:1 diastereoisomeric mixture) as a pale yellow oil (250 mg, 77%). ν_{max} ($CHCl_3$)/cm^{-1} 2959, 2253, 1776 (lactone), δ_H (250 MHz, $CDCl_3)_{major}$, 8.45, 7.57, 7.09 (3H, 3 x CH in Im), 5.79 (1H, dt, *J* 6.5, 4.0, Im(S)COCH), 4.70 (1H, dd, *J* 7.0, 4.0, CH_3CHCH), 2.92-2.76 (1H, m, CH_3CH), 2.00-1.84 (2H, m, CH_2 in ^nBu), 2.69 (1H, dd, *J* 17.5, 8.5, CH_3CHCH_2), 2.18 (1H, dd, *J* 17.5, 8.0, CH_3CHCH_2), 1.47-1.29 (4H, m, 2 x CH_2 in ^nBu), 1.12 (3H, d, *J* 7.0, $CHCH_3$), 0.92 (3H, t, *J* 7.5, CH_2CH_3); δ_C (125 MHz, $CDCl_3)_{major}$, 182.2 (C), 175.6 (C), 137.0, 130.3, 117.6 (3 x CH), 81.0 (CH), 81.3 (CH), 36.6, 29.8, 27.0, 22.5 (4 x CH_2), 32.2 (CH), 14.1, 13.8 (2 x CH_3); *m/z* (CI) 297 (MH^+), Found: MH^+, 297.1277. $C_{14}H_{20}N_2O_3S$ requires MH^+, 297.1279.

General procedure for the synthesis of *Quercus lactones*



thiocarbonylimidazolides	R	*Quercus lactones*
277	^{n}Pr	**260**
278	^{n}Bu	**261**

To a refluxing solution of *n*-BuSnH (1.1 eq) and AIBN (0.1 eq) in toluene at room temperature under N_2 was added dropwise a solution of thiocarbonylimidazolides (1.0 eq) in toluene. After stirring for overnight, column purification eluting with EtOAc/petrol (1/1) gave *Quercus lactones*.

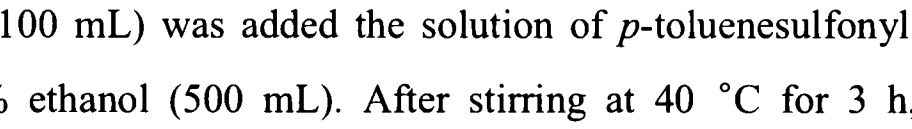
(4S,5S*)-5-Butyl-4-methyl-dihydrofuran-2(3H)-one* **260**[116, 167]: Prepared by the general procedure (92 mg of *n*-BuSnH, 5 mg of AIBN, 80 mg of thiocarbonylimidazolide) to give *whisky lactone* as a brown oil (37 mg, 83%). ^{1}H NMR (250 MHz, $CDCl_3$) 4.44 (1H, dt, *J* 6.0, 4.5, CH_3CHCH), 2.70 (1H, dd, *J* 16.5, 8.0, C(O)C*H*H), 2.65-2.52 (1H, m, CH_3CH), 1.80-2.20 (1H, dd, *J* 16.5, 3.5, C(O)CH*H*), 1.80-1.27 (6H, m, 3 x CH_2 in ^{n}Bu), 1.01 (3H, d, *J* 7.0, CH_3CH), 0.92 (3H, t, *J* 7.0, CH_2CH_3); δ_C (125 MHz, $CDCl_3$) 176.9 (C), 83.7 (CH), 37.6 (CH_2), 33.0 (CH), 29.6, 28.0, 22.5 (3 x CH_2), 13.9, 13.8 (2 x CH_3); *m/z* (CI) 174 (MNH_4^+, 100%), Found: MNH_4^+, 174.1493. $C_9H_{16}O_2$ requires MNH_4^+, 174.1494.

(4S,5S*)-4-Methyl-5-pentyl-dihydrofuran-2(3H)-one* **261** [168]: Prepared by the general procedure (407 mg of *n*-BuSnH, 57 mg of AIBN, 205 mg of thiocarbonylimidazolide) to give *cognac lactone* as a brown oil (108 mg, 91%). ^{1}H NMR (250 MHz, $CDCl_3$) 4.40 (1H, dd, *J* 6.0, 4.5, CH_3CHCH), 2.66 (1H, dd, *J* 17.0, 8.0, $C(O)CH_2$), 2.60-2.50 (1H, m, CH_3CH),

2.16 (1H, dd, *J* 17.0, 4.0, C(O)CH_2), 1.69-1.26 (8H, m, 4 x CH_2 in ^{n}Pent), 0.98 (3H, d, *J* 7.0, CH_3CH), 0.87 (3H, t, *J* 7.0, CH_2CH_3); δ_C (125 MHz, $CDCl_3$) 176.8 (C), 83.6 (CH), 37.6 (CH_2), 33.0 (CH), 31.6, 29.8, 25.6, 22.5 (4 x CH_2), 25.1, 13.9 (2 x CH_3); *m/z* (CI) 171 (MH^+), 188 (MNH_4^+, 100%), Found: MNH_4^+, 188.1648. $C_{10}H_{18}O_2$ requires MNH_4^+, 188.1650.

Synthesis of *Dimethyl diazomalonate*

p-Toluenesulfonyl azide **292**[121a]:



292

To a solution of sodium azide (17.9 g, 0.28 mol) in the mixture of water (50 mL) and 90% aqueous ethanol (100 mL) was added the solution of *p*-toluenesulfonyl chloride (47.6 g, 0.25 mol) in 99% ethanol (500 mL). After stirring at 40 °C for 3 h, the solvent was removed at 40 °C under reduced pressure. The oily sulfonyl azide was washed with water and organic layer was separated. It was dried over Na_2SO_4 and the solvent was removed at 40 °C under reduced pressure to give **292** as a colourless oil (38.0 g, 80%). δ_H (400 MHz, $CDCl_3$) 7.85 (2H, d, *J* 8.5, 2 x CH in Ph), 7.42 (2H, d, *J* 8.5, 2 x CH in Ph), 2.50 (3H, s, CH_3); *m/z* (CI) 189, 215 (MNH_4^+).

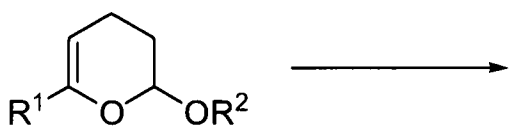
Dimethyl diazomalonate **293**[121b]:



293

To a solution of tosylazide (18.90 g, 96.0 mmol) and dimethyl malonate (11.4 mL, 0.10 mol) in benzene (85 mL) at room temperature was added triethylamine (13.7 mL, 0.10 mol). After stirring for 15 h, the mixture was vacuum filtered and concentrated *in vacuo*. Column chromatography eluting with EtOAc and hexane (1/3) gave **293** as a pale yellow oil (9.10 g, 60%). δ_H (400 MHz, $CDCl_3$) 3.82 (6H, s, 2 x CH_3).

Attempted cyclopropanation[118, 119]



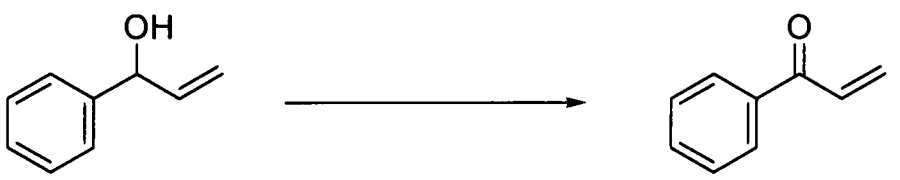
285b R^1=H, R^2=Me,
211 R^1=Me, R^2=Et

To a solution of *bis*(hexafluoroacetoacetonato)copper(II) (0.02 eq) in benzene at reflux temperature (75 °C) under Ar was added dropwise (over 2 h) a solution of dimethyl diazomalonate (1.05 eq) and 2-alkoxydihydropyran (1.00 eq) in benzene. After stirring at 75 °C for 4 h, the reaction mixture was cooled down to room temperature. The cold reaction mixture was passed through a pad of neutral alumina to remove catalyst and solvents were removed. Column chromatography eluting with EtOAc/hexane (3/7) gave colourless oil. The ^{1}H NMR spectrum indicated a complex product mixture.

2. Compounds from Chapter 2.

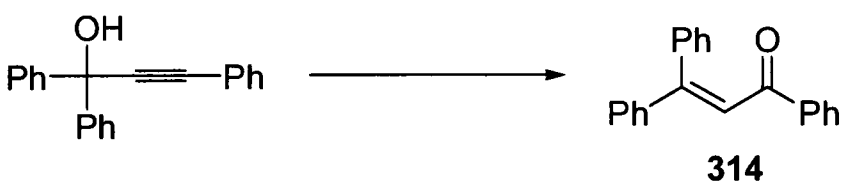
Synthesis of enone systems

1-Phenylprop-2-en-1-one[169]:



To a mixture of CrO_3 (0.04 g, 0.4 mmol) in CH_2Cl_2 (20 mL) was added sequentially aq 70 % ^tBuOOH (3.00 g, 23.0 mmol) and 1-phenylprop-2-en-1-ol (1.00 g, 7.5 mmol). The reaction mixture was stirred vigorously under an air atmosphere for overnight. After filtration on alumina and evaporation of solvent, column chromatography eluting with diethyl ether/petrol (1/9) gave a pale yellow oil (0.41 g, 42%). δ_H (250 MHz, $CDCl_3$) 7.97-7.93 (2H, m, 2 x CH in Ph), 7.48-7.58 (3H, m, 3 x CH in Ph), 7.16 (1H, dd, *J* 17.0, 10.5, C*H*=CH_2), 6.43 (1H, dd, *J* 17.0, 2.0, CH=C*H*H), 5.93 (1H, dd, *J* 10.5, 2.0, CH=CH*H*); *m/z* (CI) 133 (MH^+), 150 (MNH_4^+, 100%).

1,3,3-Triphenylprop-2-en-1-one **314**[138]:

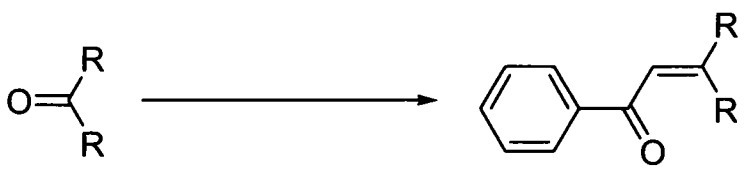


314

To a solution of propargyl alcohol (2.00 g, 7.0 mmol) in AcOH was added dropwise conc. H_2SO_4 (1.03 g, 10.5 mmol). After stirring vigorously at 110 °C under N_2 for overnight, the reaction mixture was quenched by the addition of $NaHCO_3$ (sat, aq). The organic layer was extracted by ether and water and recrystallization with MeOH gave **314** as a yellow solid (1.10 g, 55%). mp 92-93 °C [lit. mp 86-87 °C[170]]; δ_H (250 MHz, $CDCl_3$) 7.94 (2H, d, *J* 7.0, 2 x CH in PhCO), 7.50 (1H, t, *J* 7.5, CH in PhCO), 7.35-7.45 (7H, m, 7 x CH in Ph), 7.26-

7.32 (3H, m, 3 x CH in Ph), 7.18-7.24 (2H, m, 2 x CH in Ph), 7.15 (1H, s, CCH); *m/z* (CI) 285 (MH^+, 100%).

General procedure for the preparation of enones by Mukaiyama-aldol reaction[137]



R	Enones
Me	**310**
Et	**311**
cyHex	**312**

To a solution of ketone and $TiCl_4$ (1.0 eq) in CH_2Cl_2 was added dropwise the solution of silyl enol ether (1.0 eq) in CH_2Cl_2. After stirring vigorously at r.t. under N_2 for 2 h, TFAA (1.0 eq) was added dropwise. After stirring vigorously for an additional 1 h, TEA (2.0 eq) was added. After stirring for an additional 2 h, the reaction was quenched by the addition of H_2O and the organic layer was extracted by ether and NH_4Cl (aq). Column chromatography eluting with diethyl ether/petrol (1/9) gave enones.

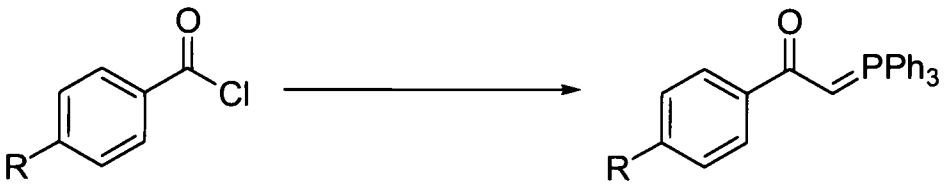
3-Methyl-1-phenylbut-2-en-1-one **310**[171]: Prepared by the general procedure (1.00 g of silyl enol ether, 0.30 g of acetone) to give enone **310** (0.36 g, 44%) as a yellow oil. δ_H (400 MHz, $CDCl_3$) 7.92-7.94 (2H, m, 2 x CH in Ph), 7.41-7.56 (3H, m, 3 x CH in Ph), 6.76 (1H, s, CCH), 2.22 (3H, s, CH_3), 2.02 (3H, s, CH_3); *m/z* (CI) 161 (MH^+), 178 (MNH_4^+, 100%).

3-Ethyl-1-phenylpent-2-en-1-one **311**[172]: Prepared by the general procedure (3.00 g of silylenolether, 1.34 g of pentanone) to give enone **311** (1.47 g, 50%) as a brown oil. δ_H (400 MHz, $CDCl_3$) 7.92-8.00 (2H, m, 2 x CH in Ph), 7.43-7.56 (3H, m, 3 x CH in Ph), 6.68 (1H,

s, CCH), 2.61 (2H, q, *J* 7.5, CH_2CH_3), 2.30 (2H, q, *J* 7.5, CH_2CH_3), 1.16 (3H, t, *J* 7.5, CH_2CH_3), 1.13 (3H, t, *J* 7.5, CH_2CH_3); *m/z* (CI) 189 (MH^+), 203, 220 (100%).

2-Cyclohexylidene-1-phenylethanone **312**[173]: Prepared by the general procedure (3.00 g of silylenolether, 1.53 g of cyclohexanone) to give enone **312** (2.04 g, 65%) as a brown oil. δ_H (400 MHz, $CDCl_3$) 7.93-8.00 (2H, m, 2 x CH in Ph), 7.43-7.58 (3H, m, 3 x CH in Ph), 5.58 (1H, s, CCH), 1.98-2.07 (4H, m, 2 x CH_2 in CyHex), 1.53-1.68 (6H, m, 3 x CH_2 in CyHex); *m/z* (CI) 201 (MH^+), 215, 232 (100%).

General procedure for the preparation of ylides



R	Ylides
MeO	**315**
Cl	**316**

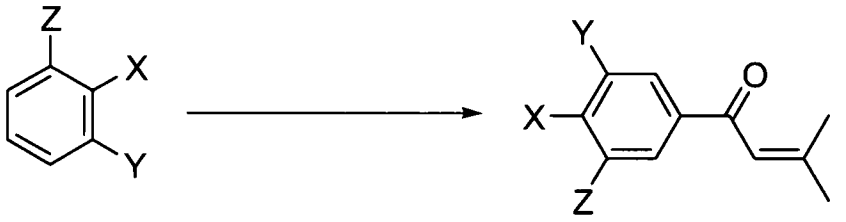
To a solution of CH_3PPh_3Br (3.0 eq) in THF at 0 °C under N_2 was added PhLi solution in Et_2O (1.80 M, 3.0 eq). After allowing to warm up to room temperature over 2 h, the reaction mixture (methylenetriphenylphosphorane) was cooled down to -78 °C. To the reaction mixture was added a solution of benzoyl chloride (1.0 eq) in THF. After stirring vigorously for overnight, the reaction mixture was quenched by the addition of water and the organic layer was extracted by EtOAc and NaCl (aq). Column chromatography eluting with EtOAc gave ylides.

1-(4-Methoxyphenyl)-2-(triphenylphosphanylidene)-ethanone **315**[174]: Prepared by the general procedure (5.79 g of CH_3PPh_3Br, 9 mL of 1.80 M PhLi and 0.92 g of benzoyl

chloride) to give ylide **315** (2.11 g, 95%) as a white solid. mp 156-158 °C; δ_H (400 MHz, $CDCl_3$) 7.96 (2H, d, *J* 8.5, 2 x CH in Ph), 7.69-7.74 (6H, m, 6 x CH in Ph_3), 7.41-7.53 (9H, m, 9 x CH in Ph_3), 6.86 (2H, d, *J* 8.5, 2 x CH in Ph), 4.40 (1H, s, P=CH), 3.76 (3H, s, OCH_3); *m/z* (CI) 263, 279 (100%) , 411 (MH^+).

1-(4-Chlorophenyl)-2-(triphenylphosphanylidene)-ethanone **316**[175]: Prepared by the general procedure (5.79 g of CH_3PPh_3Br, 9 mL of 1.80 M PhLi and 0.94 g of benzoyl chloride) to give ylide **316** (1.35 g, 60%) as a white solid. mp 198-199 °C [lit. mp 196-198 °C[176]]; δ_H (400 MHz, $CDCl_3$) 7.92 (2H, d, *J* 8.5, 2 x CH in Ph), 7.68-7.73 (6H, m, 6 x CH in Ph_3), 7.44-7.58 (9H, m, 9 x CH in Ph_3), 7.29 (2H, d, *J* 8.5, 2 x CH in Ph), 4.40 (1H, s, P=CH); *m/z* (CI) 217, 279 (100%), 415 (MH^+), 433 (MNH_4^+).

General procedure for the preparation of enones by Friedel-Crafts acylation[177]



X	Y	Z	Enones
MeO	H	H	**317**
MeO	MeO	H	**318**
MeO	MeO	MeO	**319**

To a solution of acid chloride in CS_2 at 0 °C were added slowly $AlCl_3$. After being stirred for 5 min, benzene was added dropwise. After stirring at room temperature, CS_2 was removed *in vacuo* and the residue was decomposed by the addition of cold diluted HCl (0.1 M). Column chromatography eluting with EtOAc/petrol (1/9) gave a corresponding product.

1-(4-Methoxyphenyl)-3-methylbut-2-en-1-one **317**[178]: Prepared by the general procedure

(12 mL of anisole, 5.00 g of $AlCl_3$, 4.00 g of acid chloride and 20 mL of CS_2) to give a corresponding product **317** as a yellow oil. δ_H (400 MHz, $CDCl_3$) 7.95 (2H, d, *J* 8.5, 2 x CH in Ph), 6.92 (2H, d, *J* 8.5, 2 x CH in Ph), 6.73 (1H, s, CH), 3.85 (3H, s, OCH_3), 2.20 (3H, s, CH_3), 2.00 (3H, s, CH_3); *m/z* (CI) 191 (MH^+, 100%).

1-(3,4-Dimethoxyphenyl)-3-methylbut-2-en-1-one **318**: Prepared by the general procedure (12 mL of anisole, 5.00 g of $AlCl_3$, 4.00 g of acid chloride and 20 mL of CS_2) to give a corresponding product **318** as a yellow oil. ν_{max} ($CHCl_3$)/cm^{-1} 2935 (CH), 1656 (α, β-unsaturated C=O); δ_H (400 MHz, $CDCl_3$) 7.60 (1H, d, *J* 2.0, CH in Ph), 7.57 (1H, dd, *J* 8.0, 2.0, CH in Ph), 6.90 (1H, d, *J* 8.0, CH in Ph), 6.75 (1H, s, CH), 3.97 (6H, s, 2 x OCH_3), 2.21 (3H, s, CH_3), 2.04 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 190.2 (C), 155.5 (C), 152.7 (C), 149.0 (C), 132.3 (C), 122.6 (CH), 121.0 (CH), 110.5 (CH), 109.9 (CH), 56.1 (CH_3), 56.0 (CH_3), 28.0 (CH_3), 21.1 (CH_3); *m/z* (CI) 221 (MH^+,100%), Found: MH^+ 221.1183, $C_{13}H_{16}O_3$ requires MH^+ 221.1178.

3-Methyl-1-(3,4,5-trimethoxyphenyl)but-2-en-1-one **319**: Prepared by the general procedure (12 mL of anisole, 5.00 g of $AlCl_3$, 4.00 g of acid chloride and 20 mL of CS_2) to give a corresponding product **319** as a yellow oil. ν_{max} ($CHCl_3$)/cm^{-1} 2938 (CH), 1658 (α, β-unsaturated C=O); δ_H (400 MHz, $CDCl_3$) 7.41 (1H, d, *J* 9.0, CH in Ph), 6.73 (1H, d, *J* 9.0, CH in Ph), 6.67 (1H, s, CH), 3.91 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 2.22 (3H, s, CH_3), 1.99 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 191.4 (C), 156.5(C), 154.6(C), 125.5(CH), 125.2(CH), 107.1 (CH), 61.9, 61.0, 56.1 (3 x CH_3), 27.9, 27.2 (2 x CH_3); *m/z* (CI) 250 (MH^+,100%), Found: MH^+ 251.1283, $C_{14}H_{18}O_4$ requires MH^+ 251.1283.

General procedure for the preparation of enones by Grignard reaction / MnO_2 Oxidation



Ar	Enones
p-Me Phenyl	**320**
p-Cl phenyl	**321**
p-NO_2 phenyl	**322**
2-Naph	**323**

To a solution of aryl aldehyde (1.0 eq) in dried Et_2O at room temperature under N_2 was added 0.5 M (2-methylprop-1-enyl)magnesium bromide (in THF, 1.2 eq). After stirring for 5 h, the reaction was quenched with NH_4Cl (aq). It was then extracted with Et_2O and $NaHCO_3$ (aq) followed by brine. The organic layer was dried by $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was dissolved in acetone and MnO_2 (20.0 eq) was added to the mixture. After stirring at room temperature for overnight, Mn residues were removed by filtration and the resulting product was evaporated to give the crude product. Column chromatography eluting with Et_2O/petrol (1/9) gave a corresponding product.

3-Methyl-1-p-tolylbut-2-en-1-one **320**: Prepared by the general procedure (40 mL of Grignard reagent, 2.00 g of aldehyde and 29.00 g of MnO_2) to give a corresponding product **320** as a yellow oil (1.80 g, 62%). ν_{max} ($CHCl_3$)/cm^{-1} 3030-2914 (CH), 1661 (α, β-unsaturated C=O), δ_H (400 MHz, $CDCl_3$) 7.86 (2H, d, *J* 8.0, 2 x CH in Ph), 7.26 (2H, d, *J* 8.0, 2 x CH in Ph), 6.76 (1H, s, CH), 2.42 (3H, s, CH_3), 2.22 (3H, s, CH_3), 2.03 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 191.2 (C), 156.0 (CH), 143.0 (C), 136.7 (C), 129.1 (2 x CH), 128.3 (2 x CH), 121.3 (C), 28.0 (CH_3), 21.6 (CH_3), 21.1 (CH_3); *m/z* (CI) 175 (MH^+,100%),

Found: MH^+, 175.1122, $C_{12}H_{14}O$ requires MH^+, 175.1123.

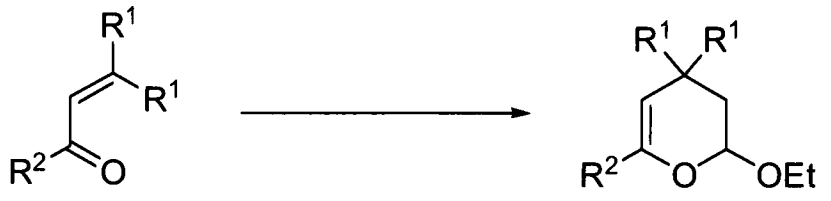
1-(4-Chlorophenyl)-3-methylbut-2-en-1-one **321**: Prepared by the general procedure (34 mL of Grignard reagent, 2.00 g of aldehyde and 30.00 g of MnO_2) to give a corresponding product **321** as a yellow oil (1.45 g, 53%). $\nu_{max}(CHCl_3)/cm^{-1}$ 2976-2913 (CH), 1662 (α, β-unsaturated C=O); δ_H (400 MHz, $CDCl_3$) 7.89 (2H, d, *J* 8.5, 2 x CH in Ph), 7.43 (2H, d, *J* 8.5, 2 x CH in Ph), 6.72 (1H, s, CH), 2.23 (3H, s, CH_3), 2.04 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 190.1 (C), 157.7 (CH), 138.6 (C), 137.6 (C), 129.6 (2 x CH), 128.7 (2 x CH), 120.7(C), 28.1 (CH_3), 21.3 (CH_3); *m/z* (CI) 195 (*MH*$^+$,100%), Found: MH^+, 195.0577, $C_{11}H_{11}OCl$ requires MH^+, 195.0577.

1-(4-Nitrophenyl)-3-methylbut-2-en-1-one **322**: Prepared by the general procedure (31 mL of Grignard reagent, 2.00 g of aldehyde and 29.00 g of MnO_2) to give a corresponding product **322** as a yellow solid (0.35 g, 13%); mp 114-116 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 2947-2903 (CH), 2853, 1656 (α, β-unsaturated C=O), 1613 (NO_2); δ_H (400 MHz, $CDCl_3$) 8.32 (2H, d, *J* 9.0, 2 x CH in Ph), 8.08 (2H, d, *J* 9.0, 2 x CH in Ph), 6.78 (1H, s, CH), 2.30 (3H, s, CH_3), 2.10 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 189.3 (C), 160.4 (CH), 149.8 (C), 144.1 (C), 129.1 (2 x CH), 123.7 (2 x CH), 120.4 (C), 28.3 (CH_3), 21.6 (CH_3); *m/z* (CI) 206 (*MH*$^+$,100%), Found: MH^+, 206.0816, $C_{11}H_{11}NO_3$ requires MH^+, 206.0817.

3-Methyl-1-(naphthalen-2-yl)but-2-en-1-one **323**: Prepared by the general procedure (40 mL of Grignard reagent, 2.00 g of aldehyde and 32.00 g of MnO_2) to give a corresponding product **323** as a yellow solid (1.38 g, 69%). mp 102-104 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 3057-2911 (CH), 1658 (α, β-unsaturated C=O); δ_H (400 MHz, $CDCl_3$) 8.45 (1H, s, CH in Naph), 8.07 (1H, d, *J* 8.5, CH in Naph), 7.99 (1H, d, *J* 8.0, CH in Naph), 7.91 (2H, t, *J* 8.5, CH in Naph), 7.50-7.62 (2H, m, 2 x CH in Naph), 6.94 (1H, s, CH), 2.29 (3H, s, CH_3), 2.10 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 191.5 (C), 156.7 (C), 136.6 (C), 135.3 (C), 132.6 (C), 129.5 (CH), 128.3 (CH), 128.1 (CH), 127.8 (CH), 126.6 (CH), 124.4 (CH), 121.3 (CH), 28.1 (CH_3), 21.3 (CH_3) [14 out of 15 carbons observed]; *m/z* (CI) 211 (*MH*$^+$,100%) Found: MH^+,

211.1128, $C_{15}H_{14}O$ requires MH^+, 211.1123

General procedure for Hetero Diels-Alder reaction using microwave



R^1	R^2	DHPs
H	Ph	**308**
Me	Ph	**324**
Et	Ph	**325**
cyHex	Ph	**326**
Me	2-Naph	**328**
Me	*p*-MeO phenyl	**327**
Me	*p*-Me Phenyl	**329**
Me	*p*-Cl phenyl	**330**
Me	*p*-NO_2 phenyl	**331**

To ethyl vinyl ether (5.0 eq) was added enone (1.0 eq) and YbFOD (0.05 eq). After the reaction in microwave at the corresponding temperature (55-80 °C) for 2-10 h, Column chromatography eluting with diethyl ether/petrol (5/95 to 1/9) gave 2-alkoxydihydropyrans.

2-Ethoxy-6-phenyl-3,4-dihydro-2H-pyran **308**: Prepared by the general HDA procedure (0.41 g of diene, 0.11 g of vinyl ether, 0.16 g of Yb catalyst, 55 °C, 2 h) to give alkoxydihydropyran **308** (0.30 g, 48%) as a pale yellow oil. ν_{max} ($CHCl_3$)/cm^{-1} 2974 (CH), 1722, 1684 (C=C); δ_H (400 MHz, $CDCl_3$) 7.60 (2H, d, *J* 8.0, 2 x CH in Ph), 7.37-7.27 (3H, m, 3 x CH in Ph), 5.45 (1H, dd, *J* 3.5, 4.5, OCHO), 5.26 (1H, t, *J* 3.5, C=CH), 4.01 (1H, dq, *J* 9.5, 7.0, OC*H*H), 3.72 (1H, dq, *J* 9.5, 7.0, OCH*H*), 2.44-2.15 (2H, m, CH_2), 1.97-1.90

(2H, m, CH_2), 1.28 (3H, t, *J* 7.0, CH_3); δ_C (125 MHz, $CDCl_3$) 148.1 (C), 136.0 (C), 128.1, 127.7, 124.3 (5 x CH), 98.0 (CH) 97.6 (CH), 63.8 (CH_2), 26.5 (CH_2), 17.6(CH_2), 15.3 (CH_3); *m/z* (CI) 205 (*MH*$^+$,100%), Found: MH^+, 205.1225. $C_{13}H_{16}O_2$ requires MH^+, 205.1228.

2-Ethoxy-4,4-dimethyl-6-phenyl-3,4-dihydro-2H-pyran **324**: Prepared by the general procedure (1.00 g of diene, 3.0 ml of vinyl ether, 0.33 g of Yb catalyst, 55 °C, 4 h) to give alkoxydihydropyran **324** (0.60 g, 41%) as a yellow oil. ν_{max} ($CHCl_3$)/cm^{-1} 3058-2957 (CH), 2250, 1649 (C=C); δ_H (500 MHz, $CDCl_3$) 7.62-7.65 (2H, m, 2 x CH in Ph), 7.28-7.39 (3H, m, 3 x CH in Ph), 5.26 (1H, s, CCHC), 5.14 (1H, dd, *J* 2.5, 8.0, OCHO), 4.15 (1H, dt, *J* 9.5, 7.0, OC*H*H), 3.74 (1H, dt, *J* 9.5, 7.0, OCH*H*), 1.85-1.89 (1H, m, CH_2), 1.77-1.81 (1H, m, CH_2), 1.35 (3H, t, *J* 7.0, CH_2CH_3), 1.21 (3H, s, CH_3) 1.19 (3H, s, CH_3); δ_C (125 MHz, $CDCl_3$) 146.6 (C), 135.7 (C), 128.1, 127.8, 124.6 (5 x CH), 108.6 (CH), 98.7 (CH), 64.6 (CH_2), 42.0 (CH_2), 31.5 (CH_3), 30.6 (CH_3), 30.5 (C), 15.4 (CH_3); *m/z* (CI) 233 (*MH*$^+$,100%), Found: MH^+, 233.1537. $C_{15}H_{20}O_2$ requires MH^+, 233.1542.

2-Ethoxy-4,4-diethyl-6-phenyl-3,4-dihydro-2H-pyran **325**: Prepared by the general procedure (1.20 g of diene, 2.30 g of vinyl ether, 0.34 g of Yb catalyst, 70-80 °C, 4 h) to give alkoxydihydropyran **325** (0.20 g, 12%) as a pale yellow oil. ν_{max} ($CHCl_3$)/cm^{-1} 2968 (CH), 2254, 1713, 1650(C=C); δ_H (400 MHz, $CDCl_3$) 7.58-7.61 (2H, m, 2 x CH in Ph), 7.24-7.35 (3H, m, 3 x CH in Ph), 5.20 (1H, s, CCHC), 5.06 (1H, dd, *J* 2.5, 8.5, OCHO), 4.14 (1H, dt, *J* 9.5, 7.0, OC*H*H), 3.70 (1H, dt, *J* 9.5, 7.0, OCH*H*), 1.68-1.80 (2H, m, CH_2), 1.39-1.54 (4H, 2 x CCH_2CH_3), 1.32 (3H, t, *J* 7.0, OCH_2CH_3), 0.88 (3H, t, *J* 7.5, CH_3) 0.85 (3H, t, *J* 7.5, CH_3); δ_C (125 MHz, $CDCl_3$) 147.9 (C), 135.8 (C), 128.1, 127.9, 124.6 (5 x CH), 106.1 (CH), 98.9 (CH), 64.6 (CH_2), 37.5 (CH_2), 36.7 (C), 33.6 (CH_2), 31.5 (CH_2), 15.4 (CH_3), 8.3 (2 x CH_3); *m/z* (CI) 261 (*MH*$^+$,100%) Found: MH^+, 261.1851. $C_{17}H_{24}O_2$ requires MH^+, 261.1854.

4-Ethoxy-2-phenyl-3-oxa-spiro[5,5]undec-1-ene **326**: Prepared by the general procedure

(1.85 g of diene, 3.31 g of vinyl ether, 0.49 g of Yb catalyst, 65 °C, 6 h) to give alkoxydihydropyran **326** (0.75 g, 30%) as a pale yellow oil. ν_{max} ($CHCl_3$)/cm^{-1} 2927 (CH), 2251, 1648 (C=C); δ_H (400 MHz, $CDCl_3$) 7.58-7.62 (2H, m, CH in Ph), 7.24-7.34 (3H, m, CH in Ph), 5.38 (1H, s, CCHC), 5.07 (1H, dd, *J* 2.5, 8.5, OCHO), 4.12 (1H, dt, *J* 9.5, 7.0, OC*H*H), 3.69 (1H, dt, *J* 9.5, 7.0, OCH*H*), 2.00 (1H, d, *J* 13.0, 1H in CH_2), 1.38-1.68 (11H, m, 1H in CH_2, 5 x CH_2 in CyHex), 1.31 (3H, t, *J* 7.0, CH_2CH_3); δ_C (100 MHz, $CDCl_3$) 146.8 (C), 135.8 (C), 128.6, 128.0, 124.6 (5 x CH), 107.1 (CH), 98.5 (CH), 64.5 (CH_2), 39.4 (CH_2), 39.3 (CH_2), 36.6 (C), 33.6 (CH_2), 26.0(CH_2), 22.0 (CH_2), 21.5 (CH_2), 15.3 (CH_3); *m/z* (CI) 273 (*MH*$^+$,100%), Found: MH^+, 273.1849. $C_{18}H_{24}O_2$ requires MH^+, 273.1854.

2-Ethoxy-6-(4-methoxyphenyl)-4,4-dimethyl-3,4-dihydro-2H-pyran **327**: Prepared by the general procedure (1.00 g of diene, 1.91 g of vinyl ether, 0.29 g of Yb catalyst, 60 °C, 5 h) to give alkoxydihydropyran **327** (0.38 g, 27%) as a yellow oil. ν_{max} ($CHCl_3$)/cm^{-1} 3380, 2960 (CH), 2360, 2054, 1646 (C=C), 1622; δ_H (400 MHz, $CDCl_3$) 7.55 (2H, d, *J* 8.5, 2 x CH in Ph), 6.89 (2H, d, *J* 8.5, 2 x CH in Ph), 5.11-5.13 (2H, m, CCHC, OCHO), 4.14 (1H, dt, *J* 15.0, 7.5, 1H in OC*H*H), 3.84 (3H s, OCH_3), 3.73 (1H, dt, *J* 15.0, 7.5, 1H in OCH*H*), 1.89-1.70 (2H, m, CH_2), 1.34 (3H, t, *J* 7.0, CH_2CH_3), 1.18 (3H, s, CCH_3) 1.16 (3H, s, CCH_3); δ_C (100 MHz, $CDCl_3$) 159.4 (C), 146.4 (C), 128.4 (C), 125.9 (2 x CH), 113.5 (2 x CH), 107.0 (CH), 98.7 (CH), 64.5 (CH_2), 55.3 (CH_3), 42.1 (CH_2), 31.6 (CH_3), 30.7 (CH_3), 30.4 (C), 15.4 (CH_3); *m/z* (CI) 263 (*MH*$^+$,100%), Found: MH^+, 263.1642. $C_{16}H_{22}O_3$ requires MH^+, 263.1647.

2-Ethoxy-4,4-dimethyl-6-p-tolyl-3,4-dihydro-2H-pyran **329**: Prepared by the general procedure (2.00 g of diene, 4.10 g of vinyl ether, 0.61 g of Yb catalyst, 65 °C, 3 h) to give alkoxydihydropyran **329** (1.13 g, 40%) as a yellow oil. ν_{max} ($CHCl_3$)/cm^{-1} 2956-2926 (CH), 2867, 1649 (C=C); δ_H (400 MHz, $CDCl_3$) 7.50 (2H, d, *J* 8.0, 2 x CH in Ph), 7.15 (2H, d, *J* 8.0, 2 x CH in Ph), 5.19 (1H, s, C=CH), 5.11 (1H, dd, *J* 2.5, 8.0, OCHO), 4.13 (1H, dt, *J* 9.5, 7.0, OC*H*H), 3.72 (1H, dt, *J* 9.5, 7.0, OCH*H*), 2.37 (3H, s, CH_3Ph), 1.73-1.86 (2H, m,

CH_2), 1.33 (3H, t, *J* 7.0, CH_2CH_3), 1.18 (3H, s, CH_3) 1.16 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 146.6 (C), 137.6 (C), 132.9 (C), 128.8 (2 x CH), 124.4 (2 x CH), 107.8 (CH), 98.6 (CH), 64.5 (CH_2), 42.0 (CH_2), 31.5, 30.6 (2 x CH_3), 30.5 (C), 21.2 (CH_3), 15.4 (CH_3); *m/z* (CI) 247 (MH^+,100%), Found: MH^+, 247.1689, $C_{16}H_{22}O_2$ requires MH^+, 247.1685.

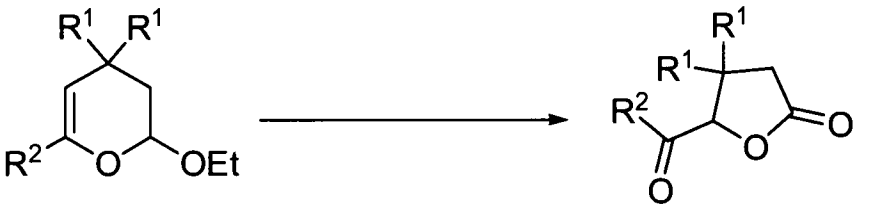
6-(4-chlorophenyl)-2-ethoxy-4,4-dimethyl-3,4-dihydro-2H-pyran **330**: Prepared by the general procedure (1.00 g of diene, 1.90 g of vinyl ether, 0.28 g of Yb catalyst, 65 °C, 5 h) to give alkoxydihydropyran **330** (0.60 g, 44%) as a yellow oil. ν_{max} ($CHCl_3$)/cm^{-1} 2958-2926 (CH), 2867, 1648 (C=C); δ_H (400 MHz, $CDCl_3$) 7.54 (2H, d, *J* 8.5, 2 x CH in Ph), 7.31 (2H, d, *J* 8.5, 2 x CH in Ph), 5.23 (1H, s, CCHC), 5.12 (1H, dd, *J* 8.0, 2.5, OCHO), 4.11 (1H, dt, *J* 9.5, 7.0, OC*H*H), 3.71 (1H, dt, *J* 9.5, 7.0, OCH*H*), 1.72-1.87 (2H, m, CH_2), 1.33 (3H, t, *J* 7.0, CH_2CH_3), 1.19 (3H, s, CCH_3) 1.17 (3H, s, CCH_3); δ_C (100 MHz, $CDCl_3$) 145.7 (C), 134.2 (C), 133.5 (C), 128.2 (2 x CH), 125.8 (2 x CH), 109.0 (CH), 98.8 (CH), 64.6 (CH_2), 41.8 (CH_2), 31.4 (CH_3), 30.5 (C, CH_3), 15.4 (CH_3); *m/z* (CI) 267 (MH^+,100%), Found: MH^+, 267.1149. $C_{15}H_{19}O_2Cl$ requires MH^+, 267.1152.

6-(4-Nitrophenyl)-2-ethoxy-4,4-dimethyl-3,4-dihydro-2H-pyran **331**: Prepared by the general procedure (0.32 g of diene, 0.56 g of vinyl ether, 0.09 g of Yb catalyst, 65 °C, 5 h) to give alkoxydihydropyran **331** (0.25 g, 58%) as a yellow oil. ν_{max} ($CHCl_3$)/cm^{-1} 3466, 2254, 1640 (C=C), 1518 (NO_2); δ_H (400 MHz, $CDCl_3$) 8.20 (2H, d, *J* 9.0, 2 x CH in Ph), 7.74 (2H, d, *J* 9.0, 2 x CH in Ph), 5.46 (1H, s, CCHC), 5.16 (1H, dd, *J* 7.5, 2.5, OCHO), 4.05-4.15 (1H, m, OC*H*H), 3.68-3.77 (1H, m, OCH*H*), 1.90-1.77 (2H, m, CH_2), 1.32 (3H, t, *J* 7.0, CH_2CH_3), 1.22 (3H, s, CH_3) 1.19 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 147.1 (C), 145.0 (C) , 141.8 (C) , 125.0 (2 x CH), 123.5 (2 x CH), 112.8 (CH), 98.9 (CH), 64.8 (CH_2), 41.5 (CH_2), 31.2 (CH_3), 30.6 (C), 30.2 (CH_3), 15.3 (CH_3); *m/z* (CI) 278 (MH^+,100%), Found: MH^+, 278.1405. $C_{15}H_{19}NO_4$ requires MH^+, 278.1392.

2-Ethoxy-4,4-dimethyl-6-(naphthalen-2-yl)-3,4-dihydro-2H-pyran **328**: Prepared by the general procedure (1.00 g of diene, 1.73 g of vinyl ether, 0.25 g of Yb catalyst, 65 °C, 5 h)

to give alkoxydihydropyran **328** (0.55 g, 41%) as a yellow oil. ν_{max} ($CHCl_3$)/cm^{-1} 3057-2926 (CH), 2868, 1643 (C=C), 1626; δ_H (400 MHz, $CDCl_3$) 8.09 (1H, s, CH in Naph), 7.79-7.90 (3H, m, 3 x CH in Naph), 7.71 (1H, dd, *J* 8.5, 1.5, CH in Naph), 7.45-7.51 (2H, m, 2 x CH in Naph), 5.41 (1H, s, CCHC), 5.21 (1H, dd, *J* 2.5, 8.0, OCHO), 4.22 (1H, dt, *J* 9.5, 7.0, OC*H*H), 3.79 (1H, dt, *J* 9.5, 7.0, OCH*H*), 1.82-1.94 (2H, m, CH_2), 1.38 (3H, t, *J* 7.0, CH_2CH_3), 1.24 (3H, s, CH_3) 1.21 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 146.6 (C), 133.3 (C), 133.0 (C), 132.9 (C), 128.4 (CH), 127.63 (CH), 127.55 (CH), 126.1 (CH), 125.9 (CH), 123.3 (CH), 122.8 (CH), 109.4 (CH) 98.8 (CH), 64.7 (CH_2), 42.0 (CH_2), 31.5 (CH_3), 30.65 (CH_3), 30.63 (C), 15.4 (CH_3); *m/z* (CI) 283 (MH^+,100%), Found: MH^+, 283.1691. $C_{19}H_{22}O_2$ requires MH^+, 283.1698.

General procedure for rearrangement / Jones oxidation of alkoxydihydropyrans[179]



R^1	R^2	Tetrahydrofuranones
H	Ph	(±)-**309**
Me	Ph	(±)-**332**
Et	Ph	(±)-**333**
cyHex	Ph	(±)-**334**
Me	Naph	(±)-**339**
Me	*p*-MeO phenyl	(±)-**335**
Me	*p*-Me Phenyl	(±)-**336**
Me	*p*-Cl phenyl	(±)-**337**
Me	*p*-NO_2 phenyl	(±)-**338**

To solution of 2-alkoxydihydropyran in CH_2Cl_2 at 0 °C was added DMDO/acetone solution. After stirring for 30 min, the reaction mixture was allowed to be stirred at room temperature. After the crude was extracted with saturated aqueous $NaHCO_3$ solution, it was concentrated to give the mixture of lactol and lactol ether. The crude mixture from oxidative rearrangement was dissolved in acetone at 0 °C and 3.0 M Jones reagent (3.0 eq to initial 2-alkoxydihydropyran) was added dropwise. After stirring, the excess of oxidants was quenched by the addition of 2-propanol until the brown colour of the mixture turned to be green. The reaction mixture was diluted with diethyl ether and the precipitated chromium salts were dissolved by the addition of saturated aqueous NH_4Cl solution. After the organic layer was separated and the aqueous layer was extracted with diethyl ether, column chromatography gave a corresponding lactone as a product.

(±)-*5-Benzoyl-dihydrofuran-2(3H)-one* **309**[140, 141]: Prepared by the general procedure (4.0 mmol of 2-alkoxydihydropyran, 0.088 M DMDO 50 mL, 3.0 M Jones reagent 4 mL, 2 h for DMDO oxidation, 1 h for Jones oxidation) to give lactone (±)-**309** as a white crystal (380 mg, 50% over 2 steps). mp 79-80 °C [lit. mp 78-79 °C[180]]; δ_H (500 MHz, $CDCl_3$) 8.02-7.48 (5H, m, Ph), 5.82-5.76 (1H, m, CH_2CH), 2.65-2.44 (4H, m, 2 x CH_2); *m/z* (CI) 208 (MNH_4^+, 100%), 398 Found: MNH_4^+, 208.0972 $C_{11}H_{10}O_3$ requires MNH_4^+, 208.0974.

(±)-*5-Benzoyl-4,4-dimethyl-dihydrofuran-2(3H)-one* **332**: Prepared by the general procedure (0.43 mmol of 2-alkoxydihydropyran, 0.12 M DMDO 3.9 mL, 3.0 M Jones reagent 0.7 mL, 2 h for DMDO oxidation, 2 h for Jones oxidation) to give lactone (±)-**332** as colourless oil (65 mg, 69% over 2 steps). ν_{max} ($CHCl_3$)/cm^{-1} 2969 (CH), 2343, 1789 (lactone), 1690 (C=O); δ_H (500 MHz, $CDCl_3$) 7.96 (2H, d, *J* 8.5, 2 x CH in Ph), 7.67 (1H, dd, *J* 8.5, 7.5, CH in Ph), 7.55 (2H, d, *J* 7.5, 2 x CH in Ph), 5.55 (1H, s, OCH), 2.60 (1H, d, *J* 17.0, CH_2), 2.36 (1H, d, *J* 17.0, CH_2), 1.40 (3H, s, CCH_3), 1.00 (3H, s, CCH_3); δ_C (100 MHz, $CDCl_3$), 195.7 (C), 175.7 (C), 135.8 (C), 134.3 (CH), 129.1 (2 x CH), 128.6 (2 x CH) 85.5 (CH), 41.8 (CH_2), 40.7 (C), 28.3, 23.5 (CH_3, CH_3); *m/z* (CI) 236 (MNH_4^+, 100%) Found: MNH_4^+, 236.1285. $C_{13}H_{14}O_3$ requires MNH_4^+, 236.1287.

(±)-*5-Benzoyl-4,4-diethyl-dihydrofuran-2(3H)-one* **333**: Prepared by the general procedure (0.35 mmol of 2-alkoxydihydropyran, 0.12 M DMDO 3 mL, 3.0 M Jones reagent 0.6 mL, 3 h for DMDO oxidation, 2 h for Jones oxidation) to give lactone (±)-**333** as colourless oil (51 mg, 59% over 2 steps). ν_{max} ($CHCl_3$)/cm^{-1} 3444, 2342, 1788 (lactone), 1649 (C=O); δ_H (500 MHz, $CDCl_3$) 7.96 (2H, d, *J* 8.5, 2 x CH in Ph), 7.68 (1H, dd, *J* 8.5, 7.5, CH in Ph), 7.55 (2H, d, *J* 7.5, 2 x CH in Ph), 5.71 (1H, s, OCH), 2.63 (1H, d, *J* 17.0, C(O)C*H*H), 2.30 (1H, d, *J* 17.0, C(O)CH*H*), 1.73-1.80 (1H, m, C*H*HCH_3), 1.60-1.68 (1H, m, CH*H*CH_3), 1.38- 1.46 (1H, m, C*H*HCH_3), 1.12-1.22 (1H, m, CH*H*CH_3), 1.09 (3H, s, *J* 7.5, CH_3), 0.76 (3H, s, *J* 7.5, CH_3); δ_C (125 MHz, $CDCl_3$), 196.6 (C), 176.3 (C), 136.0 (C), 134.3 (CH), 129.1 (2 x CH), 128.4 (2 x CH) 82.2 (CH), 48.0 (C), 38.7 (CH_2), 28.8 (CH_2), 26.2 (CH_2), 9.1 (CH_3), 8.4 (CH_3); *m/z* (CI) 264 (*M*NH_4^+, 100%) Found: MNH_4^+, 264.1596. $C_{15}H_{18}O_3$ requires MNH_4^+, 264.1600.

(±)-*1-Benzoyl-2-oxa-spiro[4,5]decan-3-one* **334**: Prepared by the general procedure (0.7 mmol of 2-alkoxydihydropyran, 0.12 M DMDO 6 mL, 3.0 M Jones reagent 1.2 mL, 3 h for DMDO oxidation, 2 h for Jones oxidation) to give lactone (±)-**334** as a colourless oil (100 mg, 55% over 2 steps). ν_{max} ($CHCl_3$)/cm^{-1} 3434, 2931 (CH), 2338, 1787 (lactone), 1685 (C=O); δ_H (400 MHz, $CDCl_3$) 7.94 (2H, d, *J* 9.0, 2 x CH in Ph), 7.65 (1H, dd, *J* 9.0, 7.5, CH in Ph), 7.53 (2H, d, *J* 7.5, 2 x CH in Ph), 5.53 (1H, s, OCH), 2.55 (2H, s, CH_2), 1.07-1.89 (10H, m, 5 x CH_2 in CyHex); δ_C (100 MHz, $CDCl_3$), 196.2 (C), 175.9 (C), 136.2 (C), 134.2 (CH), 129.1 (2 x CH), 128.5 (2 x CH), 85.4 (CH), 45.0 (C), 37.3 (CH_2), 36.3, 32.9, 25.2, 23.1, 22.2 (5 x CH_2); *m/z* (CI) 276 (*M*NH_4^+, 100%), Found: MNH_4^+, 276.1588. $C_{16}H_{18}O_3$ requires MNH_4^+, 276.1600.

(±)-*5-(4-Methoxybenzoyl)-4,4-dimethyl-dihydrofuran-2(3H)-one* **335**: Prepared by the general procedure (0.76 mmol of 2-alkoxydihydropyran, 0.12 M DMDO 7.0 mL, 3.0 M Jones reagent 1.3 mL, 3 h for DMDO oxidation, 2 h for Jones oxidation) to give lactone (±)-**335** as colourless oil (95 mg, 50% over 2 steps). ν_{max} ($CHCl_3$)/cm^{-1} 2965-2931 (CH),

1788 (lactone), 1677 (C=O); δ_H (400 MHz, $CDCl_3$) 8.00 (2H, d, *J* 9.0, 2 x CH in Ph), 7.01 (2H, d, *J* 9.0, 2 x CH in Ph), 5.48 (1H, s, OC*H*), 3.92 (3H, s, CH_3), 2.62 (1H, d, *J* 17.0, CH_2), 2.33 (1H, d, *J* 17.0, CH_2), 1.40 (3H, s, CCH_3), 1.00 (3H, s, CCH_3), δ_C (100 MHz, $CDCl_3$), 193.8 (C), 175.9 (C), 164.4 (C), 131.0 (2 x CH), 128.8 (C), 114.3 (2 x CH) 85.3 (CH), 55.6 (CH_3), 41.8 (CH_2), 40.6 (C), 28.4 (CH_3), 23.5 (CH_3); *m/z* (CI) 266 (*MNH*$_4^+$, 100%) Found: MNH_4^+, 266.1403. $C_{14}H_{16}O_4$ requires MNH_4^+, 266.1392.

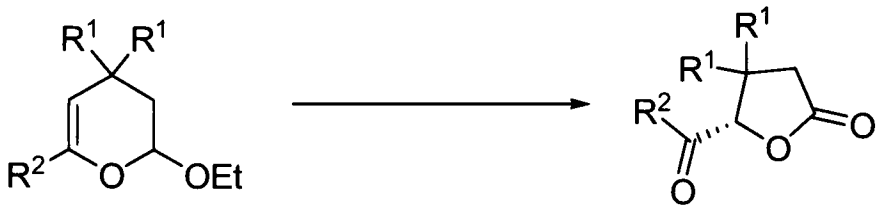
(±)-*4,4-Dimethyl-5-(4-methylbenzoyl)-dihydrofuran-2(3H)-one* **336**: Prepared by the general procedure (0.62 mmol of 2-alkoxydihydropyran, 0.12 M DMDO 6.0 mL, 3.0 M Jones reagent 1.0 mL, 4 h for DMDO oxidation, 1 h for Jones oxidation) to give lactone (±)-**336** as white solid (102 mg, 69% over 2 steps). mp 134-136 °C; ν_{max} ($CHCl_3$)/cm^{-1} 2967-2931 (CH), 2874, 1788 (lactone), 1682 (C=O), 1606; δ_H (400 MHz, $CDCl_3$) 7.86 (2H, d, *J* 8.0, 2 x CH in Ph), 7.34 (2H, d, *J* 8.0, 2 x CH in Ph), 5.53 (1H, s, OCH), 2.61 (1H, d, *J* 17.0, CH_2), 2.46 (3H, s, CH_3Ph), 2.34 (1H, d, *J* 17.0, CH_2), 1.40 (3H, s, CCH_3), 0.99 (3H, s, CCH_3); δ_C (100 MHz, $CDCl_3$), 195.2 (C), 175.9 (C), 145.5 (C), 133.3 (C), 129.8 (2 x CH), 128.7 (2 x CH), 85.4 (CH), 41.8 (CH_2), 40.6 (C), 28.4, 23.5, 21.8 (3 x CH_3); *m/z* (CI) 250 (*MNH*$_4^+$, 100%), Found: MNH_4^+, 250.1432. $C_{14}H_{16}O_3$ requires MNH_4^+, 250.1443.

(±)-*5-(4-Chlorobenzoyl)-4,4-dimethyl-dihydrofuran-2(3H)-one* **337**: Prepared by the general procedure (0.75 mmol of 2-alkoxydihydropyran, 0.12 M DMDO 7.0 mL, 3.0 M Jones reagent 1.2 mL, 3 h for DMDO oxidation, 1 h for Jones oxidation) to give lactone (±)-**337** as white crystal (103 mg, 53% over 2 steps). mp 132-134 °C; ν_{max} ($CHCl_3$)/cm^{-1} 2963 (CH), 2874, 1789 (lactone), 1690 (C=O); δ_H (400 MHz, $CDCl_3$) 7.92 (2H, d, *J* 8.5, 2 x CH in Ph), 7.53 (2H, d, *J* 8.5, 2 x CH in Ph), 5.46 (1H, s, OCH), 2.59 (1H, d, *J* 17.0, CH_2), 2.38 (1H, d, *J* 17.0, CH_2), 1.45 (3H, s, CH_3), 1.00 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$), 194.7 (C), 175.4 (C), 141.0 (C), 134.1 (C), 130.0 (2 x CH), 129.5 (2 x CH), 85.6 (CH), 41.9 (CH_2), 40.8 (C), 28.2, 23.5 (2 x CH_3); *m/z* (CI) 270 (*MNH*$_4^+$, 100%) Found: MNH_4^+, 270.0893. $C_{13}H_{13}O_3Cl$ requires MNH_4^+, 270.0897.

(±)-*4,4-Dimethyl-5-(4-nitrobenzoyl)-dihydrofuran-2(3H)-one* **338**: Prepared by the general procedure (0.43 mmol of 2-alkoxydihydropyran, 0.12 M DMDO 4.0 mL, 3.0 M Jones reagent 0.7 mL, 3 h for DMDO oxidation, 1 h for Jones oxidation) to give lactone (±)-**338** as colourless oil (55 mg, 49% over 2 steps). ν_{max} ($CHCl_3$)/cm^{-1} 2980 (CH), 2939, 1790 (lactone), 1698 (C=O), 1603; δ_H (400 MHz, $CDCl_3$) 8.39 (2H, d, *J* 9.0, 2 x CH in Ph), 8.15 (2H, d, *J* 9.0, 2 x CH in Ph), 5.44 (1H, s, OCH), 2.57 (1H, d, *J* 17.0, CH_2), 2.43 (1H, d, *J* 17.0, CH_2), 1.44 (3H, s, CCH_3), 1.02 (3H, s, CCH_3); δ_C (100 MHz, $CDCl_3$), 195.1 (C), 174.9 (C), 150.8 (C), 140.2 (C), 129.8 (2 x CH), 124.2 (2 x CH), 86.2 (CH), 42.0 (CH_2), 41.1 (C), 27.9, 23.4 (2 x CH_3); *m/z* (CI) 250 (MNH_4^+, 100%) Found: MNH_4^+, 281.1141. $C_{13}H_{13}NO_5$ requires MNH_4^+, 281.1137.

(±)-*5-(2-Naphthoyl)-4,4-dimethyl-dihydrofuran-2(3H)-one* **339**: Prepared by the general procedure (0.71 mmol of 2-alkoxydihydropyran, 0.12 M DMDO 7.0 mL, 3.0 M Jones reagent 1.2 mL, 3 h for DMDO oxidation, 1 h for Jones oxidation) to give lactone (±)-**339** as colourless oil (101 mg, 53% over 2 steps). ν_{max} ($CHCl_3$)/cm^{-1} 2962-2926 (CH), 1788 (lactone), 1681 (C=O), 1627; δ_H (400 MHz, $CDCl_3$) 8.48 (1H, s, CH in NapH), 7.93-8.04 (4H, m, 4 x CH in Naph), 7.62-7.71 (2H, 2 x CH in Naph), 5.71 (1H, s, OCH), 2.66 (1H, d, *J* 17.0, CH_2), 2.39 (1H, d, *J* 17.0, CH_2), 1.46 (3H, s, CH_3), 1.03 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$), 195.6 (C), 175.8 (C), 136.0 (C), 133.2 (C), 132.4 (C), 130.7 (CH), 129.8 (CH), 129.3 (CH), 129.2 (CH), 127.9 (CH), 127.3 (CH), 123.7 (CH), 85.5 (CH), 41.9 (CH_2), 40.8 (C), 28.4, 23.6 (2 x CH_3); *m/z* (CI) 286 (MNH_4^+, 100%); Found: MNH_4^+, 286.1437. $C_{17}H_{16}O_3$ requires MNH_4^+, 286.1443.

General procedure for enantioselective rearrangement / Jones oxidation of alkoxydihydropyrans using Jacobsen's catalyst



R^1	R^2	Tetrahydrofuranones
H	Me	**231**
Me	Me	**252**
H	Ph	(*S*)-**309**
Me	Ph	(*S*)-**332**
Et	Ph	(*S*)-**333**
cyHex	Ph	(*S*)-**334**
Me	Naph	(*S*)-**339**
Me	*p*-MeO phenyl	(*S*)-**335**
Me	*p*-Me Phenyl	(*S*)-**336**
Me	*p*-Cl phenyl	(*S*)-**337**
Me	*p*-NO_2 phenyl	(*S*)-**338**

A mixture of alkoxydihydropyran (1.0 eq) pre-dissolved in CH_2Cl_2, *Jacobsen* catalyst (0.05-0.1 eq) and 4-phenyl pyridine *N*-oxide (0.2 eq) was cooled down to 0 °C. Buffered bleach (1.5-3.0 eq, pH~11.5) pre-cooled to 0 °C was added to the mixture and the reaction was stirred at 0 °C. The reaction mixture was diluted with DCM, extracted with water and dried with Na_2SO_4. Short column purification was performed to remove Mn species with the solvent system of EtOAc/petrol (1/1). After the reaction mixture was dissolved in acetone, Jones reagent (3.0 eq to initial 2-alkoxydihydropyran) was added dropwise. After stirring, the excess of oxidants was quenched by the addition of 2-propanol until the brown

colour of the mixture turned to green. The reaction mixture was diluted with diethyl ether. After the organic layer was separated and the aqueous layer was extracted with diethyl ether, column chromatography gave a corresponding lactone as a product.

Acetyl-dihydro-furan-2-one **231**: Prepared by the general procedure (300 mg of 2-alkoxydihydropyran, 40 mg of Jacobsen's catalyst, 48 mg of pyridine *N*-oxide, 0.7 ml of NaOCl, 1.5 mL of 3.0 M Jones reagent, 10 h for epoxidation, 3 h for Jones oxidation) to give lactone **231** as colourless oil (108 mg, 40% over 2 steps). $[\alpha]_D^{20}$ 0 (*c* 0.03, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 4.81 (1H, t, *J* 7.5, CH), 2.62-2.18 (4H, m, CH_2CH_2) 2.30 (3H, s, CH_3).

Acetyl-4,4-dimethyl-dihydrofuran-2(3H)-one **252**: Prepared by the general procedure (250 mg of 2-alkoxydihydropyran, 40 mg of Jacobsen's catalyst, 43 mg of pyridine *N*-oxide, 1.0 mL of NaOCl, 1.5 mL of 3.0 M Jones reagent, 10 h for epoxidation, 3 h for Jones oxidation) to give lactone **252** as colourless oil (32 mg, 16% over 2 steps). $[\alpha]_D^{20}$ 0 (*c* 0.03, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 4.40 (1H, s, OCH), 2.43 (2H, d, *J* 3.5, CH_2), 2.27 (3H, s, $C(O)CH_3$), 1.35 (3H, s, CH_3), 1.05 (3H, s, CH_3).

(S)-5-Benzoyl-dihydrofuran-2(3H)-one **309**: Prepared by the general procedure (276 mg of 2-alkoxydihydropyran, 30 mg of Jacobsen's catalyst, 51 mg of pyridine *N*-oxide, 1.0 mL of NaOCl, 1.4 mL of 3.0 M Jones reagent, 6 h for epoxidation, 3 h for Jones oxidation) to give lactone (*S*)-**309** as white crystal (140 mg, 55 % over 2 steps). mp 189-191 °C; ee 38% (HPLC analysis: OD-H column, 254 nm, flow 1.0 ml/m, ^{i}PrOH/hexane (5/95), t_m=37.90 min, t_M=46.15 min); $[\alpha]_D^{20}$ 0 (*c* 0.03, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 8.02-7.48 (5H, m, Ph), 5.82-5.76 (1H, m, CH_2CH), 2.65-2.44 (4H, m, 2 x CH_2)

(+)-(S)-5-Benzoyl-4,4-dimethyl-dihydrofuran-2(3H)-one **332**: Prepared by the general procedure (300 mg of 2-alkoxydihydropyran, 80 mg of Jacobsen's catalyst, 50 mg of pyridine *N*-oxide, 2 mL of NaOCl, 2.2 mL of 3.0 M Jones reagent, 6 h for epoxidation, 3 h

for Jones oxidation) to give lactone (*S*)-**332** as white crystal (140 mg, 49% over 2 steps). mp 113-115 °C; ee 58% (HPLC analysis: OD column, 254 nm, flow 0.5 ml/m, 5 % ^{i}PrOH/hexane (5/95), t_M=53.24 min, t_m=58.21 min); $[\alpha]_D^{20}$ +42.0 (*c* 0.01, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 7.96 (2H, d, *J* 8.5, 2 x CH in Ph), 7.67 (1H, dd, *J* 8.5, 7.5, CH in Ph), 7.55 (2H, d, *J* 7.5, 2 x CH in Ph), 5.55 (1H, s, OCH), 2.60 (1H, d, *J* 17.0, CH_2), 2.36 (1H, d, *J* 17.0, CH_2), 1.40 (3H, s, CCH_3), 1.00 (3H, s, CCH_3).

(+)-(S)-5-Benzoyl-4,4-diethyl-dihydrofuran-2(3H)-one **333**: Prepared by the general procedure (100 mg of 2-alkoxydihydropyran, 26 mg of Jacobsen's catalyst, 21 mg of pyridine *N*-oxide, 1.2 mL of NaOCl, 0.7 mL of 3.0 M Jones reagent, 6 h for epoxidation, 3 h for Jones oxidation) to give lactone (*S*)-**333** as colourless oil (44 mg, 45% over 2 steps). ee 69% (HPLC analysis: OD-H column, 254 nm, flow 0.5 ml/m, ^{i}PrOH/hexane (2/98), t_M=49.18 min, t_m=60.11 min); $[\alpha]_D^{20}$ +47.0 (*c* 0.01, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 7.96 (2H, d, *J* 8.5, 2 x CH in Ph), 7.68 (1H, dd, *J* 8.5, 7.5, CH in Ph), 7.55 (2H, d, *J* 7.5, 2 x CH in Ph), 5.71 (1H, s, OCH), 2.63 (1H, d, *J* 17.1, $C(O)CH_2$), 2.30 (1H, d, *J* 17.0, $C(O)CH_2$), 1.73-1.80 (1H, m, C*H*HCH_3), 1.60-1.68 (1H, m, CH*H*CH_3), 1.38-1.46 (1H, m, C*H*HCH_3), 1.12-1.22 (1H, m, CH*H*CH_3),1.09 (3H, s, *J* 7.5, CH_3), 0.76 (3H, s, *J* 7.5, CH_3).

(+)-(S)-1-Benzoyl-2-oxa-spiro[4,5]decan-3-one **334**: Prepared by the general procedure (300 mg of 2-alkoxydihydropyran, 70 mg of Jacobsen's catalyst, 50 mg of pyridine *N*-oxide, 2 mL of NaOCl, 1.8 mL of 3.0 M Jones reagent, 6 h for epoxidation, 3 h for Jones oxidation) to give lactone (*S*)-**334** as colourless oil (120 mg, 40 % over 2 steps). ee 80% (HPLC analysis: OD column, 254 nm, flow 0.5 ml/m, ^{i}PrOH/hexane (5/95), t_m=57.82 min, t_M=79.09 min); $[\alpha]_D^{20}$ +29.2 (*c* 0.01, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.94 (2H, d, *J* 9.0, 2 x CH in Ph), 7.65 (1H, dd, *J* 9.0, 7.5, CH in Ph), 7.53 (2H, d, *J* 7.5, 2 x CH in Ph), 5.53 (1H, s, OCH), 2.55 (2H, s, CH_2), 1.07-1.89 (10H, m, 5 x CH_2 in CyHex).

(+)-(S)-5-(4-Methoxybenzoyl)-4,4-dimethyl-dihydrofuran-2(3H)-one **335**: Prepared by the general procedure (140 mg of 2-alkoxydihydropyran, 40 mg of Jacobsen's catalyst, 25 mg

of pyridine *N*-oxide, 1.0 mL of NaOCl, 1.0 mL of 3.0 M Jones reagent, 6 h for epoxidation, 3 h for Jones oxidation) to give lactone (*S*)-**335** as colourless oil (35 mg, 35% over 2 steps). ee 79% (HPLC analysis: OD column, 254 nm, flow 0.5 ml/m, ^{i}PrOH/hexane (5/95), t_m=104.08 min, t_M=119.72 min); $[\alpha]_D^{20}$ +56.0 (*c* 0.01, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 8.00 (2H, d, *J* 9.0, 2 x CH in Ph), 7.01 (2H, d, *J* 9.0, 2 x CH in Ph), 5.48 (1H, s, OCH), 3.92 (3H, s, CH_3), 2.62 (1H, d, *J* 17.0, CH_2), 2.33 (1H, d, *J* 17.0, CH_2), 1.40 (3H, s, CCH_3), 1.00 (3H, s, CCH_3).

(+)-(S)-4,4-Dimethyl-5-(4-methylbenzoyl)-dihydrofuran-2(3H)-one **336**: Prepared by the general procedure (157 mg of 2-alkoxydihydropyran, 38 mg of Jacobsen's catalyst, 38 mg of pyridine *N*-oxide, 1.3 mL of NaOCl, 1.1 mL of 3.0 M Jones reagent, 15 h for epoxidation, 1 h for Jones oxidation) to give lactone (*S*)-**336** as white solid and oil (64 mg, 43% over 2 steps). mp 157-160 °C; ee 70% (HPLC analysis: OJ column, 254 nm, flow 1.2 ml/m, ^{i}PrOH/hexane (2/98), t_m=33.14 min, t_M=45.97 min); $[\alpha]_D^{20}$ +37.0 (*c* 0.02, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.86 (2H, d, *J* 8.0, 2 x CH in Ph), 7.34 (2H, d, *J* 8.0, 2 x CH in Ph), 5.53 (1H, s, OCH), 2.61 (1H, d, *J* 17.0, CH_2), 2.46 (3H, s, CH_3Ph), 2.34 (1H, d, *J* 17.0, CH_2), 1.40 (3H, s, CCH_3), 0.99 (3H, s, CCH_3).

(+)-(S)-5-(4-Chlorobenzoyl)-4,4-dimethyl-dihydrofuran-2(3H)-one **337**: Prepared by the general procedure (200 mg of 2-alkoxydihydropyran, 51 mg of Jacobsen's catalyst, 39 mg of pyridine *N*-oxide, 2.0 mL of NaOCl, 1.2 mL of 3.0 M Jones reagent, 15 h for epoxidation, 1 h for Jones oxidation) to give lactone (*S*)-**337** as white crystal (56 mg, 30% over 2 steps). mp 155-158 °C; ee 76% (HPLC analysis: OD-H column, 254 nm, flow 0.5 ml/m, ^{i}PrOH/hexane (5/95), t_m=60.54 min, t_M=74.56 min); $[\alpha]_D^{20}$ +25.0 (*c* 0.01, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.92 (2H, d, *J* 8.5, 2 x CH in Ph), 7.53 (2H, d, *J* 8.5, 2 x CH in Ph), 5.46 (1H, s, OCH), 2.59 (1H, d, *J* 17.0, CH_2), 2.38 (1H, d, *J* 17.0, CH_2), 1.45 (3H, s, CH_3), 1.00 (3H, s, CH_3).

(+)-(S)-4,4-Dimethyl-5-(4-nitrobenzoyl)-dihydrofuran-2(3H)-one **338**: Prepared by the

general procedure (90 mg of 2-alkoxydihydropyran, 19 mg of Jacobsen's catalyst, 17 mg of pyridine *N*-oxide, 1.0 mL of NaOCl, 0.5 mL of 3.0 M Jones reagent, 15 h for epoxidation, 3 h for Jones oxidation) to give lactone (*S*)-**338** as colourless oil (54 mg, 64% over 2 steps). ee 46% (HPLC analysis: OD-H column, 254 nm, flow 1.5 ml/m, ^{i}PrOH/hexane (10/90), t_m=35.79 min, t_M=43.31 min); $[\alpha]_D^{20}$ +14.0 (*c* 0.01, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 8.39 (2H, d, *J* 9.0, 2 x CH in Ph), 8.15 (2H, d, *J* 9.0, 2 x CH in Ph), 5.44 (1H, s, OCH), 2.57 (1H, d, *J* 17.0, CH_2), 2.43 (1H, d, *J* 17.0, CH_2), 1.44 (3H, s, CCH_3), 1.02 (3H, s, CCH_3).

(+)-(S)-5-(2-Naphthoyl)-4,4-dimethyl-dihydrofuran-2(3H)-one **339**: Prepared by the general procedure (200 mg of 2-alkoxydihydropyran, 45 mg of Jacobsen's catalyst, 38 mg of pyridine *N*-oxide, 2.0 mL of NaOCl, 1.2 mL of 3.0 M Jones reagent, 15 h for epoxidation, 1 h for Jones oxidation) to give lactone (*S*)-**339** as colourless oil (78 mg, 41% over 2 steps). ee 71% (HPLC analysis: AD-H column, 254 nm, flow 1.8 ml/m, ^{i}PrOH/hexane (4/96), t_m=64.66 min, t_M=69.32 min); $[\alpha]_D^{20}$ +31.0 (*c* 0.01, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 8.48 (1H, s, CH in NapH), 7.93-8.04 (4H, 4 x CH in Naph), 7.62-7.71 (2H, 2 x CH in Naph), 5.71 (1H, s, OCH), 2.66 (1H, d, *J* 17.0, CH_2), 2.39 (1H, d, *J* 17.0, CH_2), 1.46 (3H, s, CH_3), 1.03 (3H, s, CH_3).

Bayer-Villiger oxidation of *5-benzoyl-dihydrofuran-2(3H)-one*[147a]

5-Oxo-tetrahydrofuran-2-yl benzoate **354**:



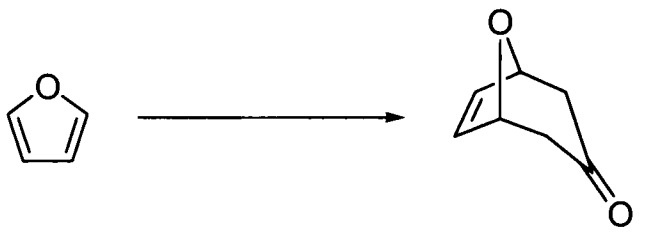
354

To a solution of lactone (100 mg) in 1,2-dichloroethane (20 mL) at room temperature were added NaH_2PO_4 (252 mg) and MCPBA (277 mg). After stirring at 80° C for 2 d, the reaction mixture was quenched by sat. $Na_2S_2O_3$ (aq). The resulting mixture were extracted with diethyl ether and washed with $NaHCO_3$ (aq) and brine. The organic layer was dried over Na_2SO_4. After the evaporation of solvent, column chromatography eluting with EtOAc/petrol (1/1) gave **354** as a colourless oil (84 mg, 78%). ν_{max} ($CHCl_3$)/cm^{-1} 3433, 2360, 1798 (lactone), 1733 (C=O), 1601; δ_H (400 MHz, $CDCl_3$) 8.06 (2H, d, *J* 7.0, 2 x CH in Ph), 7.63, (1H, t, *J* 7.5, CH in Ph), 7.49 (2H, dd, *J* 7.0, 7.5, 2 x CH in Ph), 6.90 (1H, dd, *J* 5.5, 1.0, OCHO), 2.40-2.89 (4H, m, C*H*$_2$C*H*$_2$); δ_C (100 MHz, $CDCl_3$) 175.4 (C), 164,7 (C), 133.9 (CH), 129.9 (2 x CH), 128.8 (C), 128.6 (2 x CH), 95.8 (CH), 28.1, 25.9 (2 x CH_2); *m/z* (CI) 224 (MNH_4^+, 100 %); Found: MNH_4^+, 224.0922. $C_{11}H_{10}O_4$ requires: MNH_4^+, 224.0923.

3. Compounds from Chapter 3.

Synthesis of *oxa*-bicyclic ketone catalyst

(±)-*8-Oxa-bicyclo[3.2.1]oct-6-en-3-one* **368**[181]:

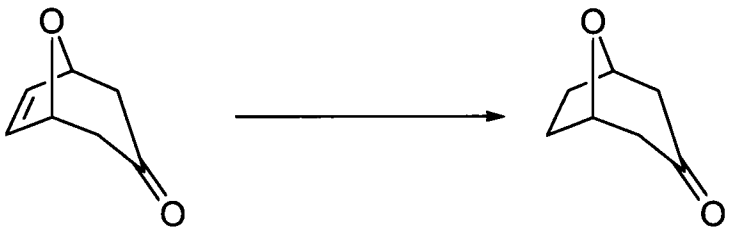


368

To a rapidly stirring solution of furan (11.3 mL, 150.0 mmol) and trifluoroethanol (30 mL) at 5 °C under Ar was added 1,1,3-trichloroacetone. To this stirring mixture was then added triethylamine (8.6 mL, 62.0 mmol) dropwise. After stirring at room temperature for overnight, the reaction was quenched by water (100 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Short column chromatography eluting with diethyl ether and petrol (1/1) removed dark brown impurity.

To zinc powder (20.3 g, 310.0 mol) and copper (I) iodide (19.6 g, 100.0 mmol) was added methanol (30 mL) and benzene (30 mL). After stirring for 20 min, the reaction mixture from the previous step was then added dropwise at 0 °C to avoid a large exotherm. The resulting reaction mixture was stirred for overnight under Ar, quenched by addition of saturated Na_2EDTA solution (30 mL) and then left for 1 hour. The slurry obtained was filtered through a filter paper and washed with CH_2Cl_2. The filtrate was dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography eluting with diethylether and petrol (1/1) gave **368** as a pale yellow solid (1.7 g, 45% over 2 steps), δ_H (400 MHz, $CDCl_3$) 5.95 (2H, s, 2 x CH_{bridge}), 4.69 (2H, d, *J* 5.0, CH=CH), 2.39 (2H, dd, *J* 17.0, 5.0, 2 x $CH_{2ax}C{=}O$), 1.95 (2H, d, *J* 17.0, 2 x $CH_{2eq}C{=}O$); *m/z* (CI) 125 (MH^+), 142 (MNH_4^+, 100%), 202, Found: MNH_4^+, 142.0869, $C_7H_8O_2$ requires MNH_4^+, 142.0868.

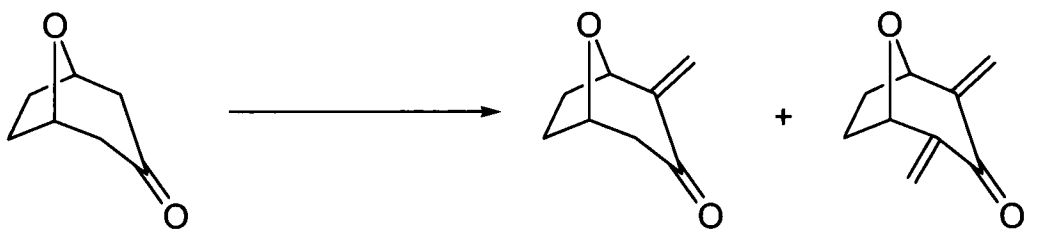
(±)-*8-Oxa-bicyclo[3.2.1]octan-3-one* **369**[155]:



369

To a solution of oxabicycle **368** (200 mg, 1.0 mmol) in MeOH (5 mL) was added 10 % Pd/C (20 mg). The reaction system was evacuated in the presence of hydrogen to leave a positive pressure of hydrogen. After stirring for 24 h at room temperature, the reaction mixture filtered through a short pad of Celite™ and the filtrate was evaporated to dryness under reduced pressure to yield crude pale yellow oil. Column chromatography eluting with diethylether and petrol (1/1) gave **369** as a pale yellow solid (198 mg, 98%), δ_H (400 MHz, $CDCl_3$) 4.67 (2H, s, 2 x CH_{bridge}), 2.69 (2H, dd, *J* 15.5, 2.5, 2 x $CH_{2ax}C{=}O$), 2.23 (2 H, d, *J* 15.5, 2 x $CH_{2eq}C{=}O$), 2.05-1.95 (2H, 2 x $CH_{2eq}CH_2$), 1.75-1.65 (2H, 2 x $CH_{2ax}CH_2$).

(±)-*2-Methylene-8-oxa-bicyclo[3.2.1]octan-3-one* **370** and *2,4-dimethylene-8-oxa-bicyclo[3.2.1]octan-3-one* **371**:



(±)-370 **371**

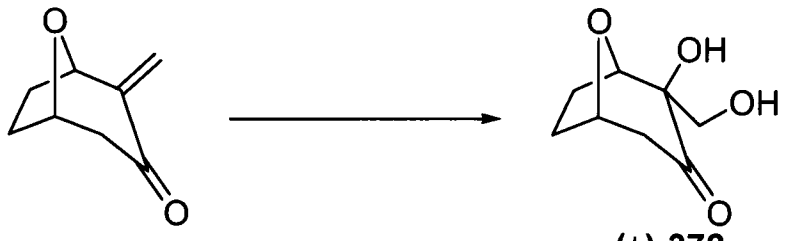
To a stirred solution of the parent ketone (1.25 g, 9.9 mmol) in THF (15 mL) cooled to -78 °C under Ar was added dropwise LiHMDS 1.0 M in THF (9.9 mL, 9.9 mmol). After stirring at -78 °C for 30 min, Me_3SiCl (1.9 mL, 13.6 mmol) was added. After stirring for 30 min, the reaction mixture was quenched with a saturated solution of NH_4Cl (50 mL) at 0 °C.

The organic layer was diluted with EtOAc (100 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with a saturated solution of $NaHCO_3$ (50 mL), dried over $MgSO_4$ and concentrated. To the solution of silyl enol ether in DMF (15 mL) in a sealed tube under Ar was added Eschenmoser's salt (1.83 g, 9.9 mmol). After stirring at room temperature for 1.5 h, MeI (2.9 mL, 47.5 mmol) was added. After stirring at 50 °C for overnight, $NaHCO_3$ (5.81 g, 69.2 mmol) was added and the reaction mixture diluted with DMF (10 mL). After stirring at 95 °C for overnight, the reaction mixture cooled to room temperature. The reaction mixture was diluted with EtOAc (100 mL), washed with H_2O (50 mL), extracted with EtOAc (3 x 30 mL) and separated. The combined organics were dried over $MgSO_4$ and concentrated. Column chromatography eluting with EtOAc and Hexane (1/1) gave methylene (±)-**370** (0.54 g, 40% over 2 steps) as pale yellow oil and dimethylene **371** (200 mg, 13% over 2 steps) as pale yellow oil.

(±)-*2-Methylene-8-oxa-bicyclo[3.2.1]octan-3-one* (±)-**370**: ν_{max} ($CHCl_3$)/cm^{-1} 2963 (CH), 1697 (C=O), 1629 (C=C); δ_H(400 MHz, $CDCl_3$) 5.95 (1H, s, C=CH_2), 5.20 (1H, s, C=CH_2), 5.01 (1H, d, *J* 6.5, OCH_{bridge}), 4.77 (1H, t, *J* 6.5, OCH_{bridge}), 2.81 (1H, dd, *J* 6.0, 18.0, $CH_{2ax}CO$), 2.43 (1H, d, *J* 18.0, $CHCH_{2eq}CO$), 2.18-2.31 (2H, m, $CHCH_{2exo}CH_{2exo}CH$), 1.75-1.93 (2H, m, $CHCH_{2endo}CH_{2endo}CH$); δ_c (100 MHz, $CDCl_3$) 197.7 (C=O), 146.7 (C), 118.5 (CH_2), 78.4 (CH) , 74.0 (CH), 48.1 (CH_2), 32.1 (CH_2), 29.3 (CH_2); *m/z* (CI) 156 (MNH_4^+, 100%), Found: MNH_4^+, 156.1026, $C_8H_{10}O_2$ requires MNH_4^+, 156.1025.

2,4-Dimethylene-8-oxa-bicyclo[3.2.1]octan-3-one **371**: ν_{max} ($CHCl_3$)/cm^{-1} 3425, 2957, 1626 (C=C, C=O); δ_H(400 MHz, $CDCl_3$) 6.15 (2 H, s, C=CH_2), 5.32 (2 H, s, C=CH_2), 5.01 (2H, dd, *J* 5.0, 3.0, OCH_{bridge}), 2.36-2.27 (2H, m, $CHCH_{2exo}$), 1.86 (2H, d, *J* 7.0, $CHCH_{2endo}CH$); δ_c (100 MHz, $CDCl_3$) 186.1 (C=O), 146.2 (C), 120.0 (CH_2), 78.8 (CH) , 31.0 (CH_2); *m/z* (CI) 168 (MNH_4^+, 100 %), Found: MNH_4^+, 168.1021, $C_9H_{10}O_2$ requires MNH_4^+, 168.1025

(1R,2R*,5S*)*-(±)-*2-Hydroxy-2-(hydroxymethyl)-8-oxa-bicyclo[3.2.1]octan-3-one* **372**:

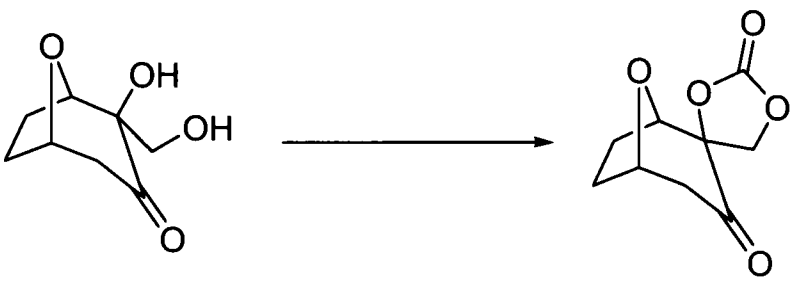


(±)-372

To a stirred suspension of $K_2OsO_4 \cdot 2H_2O$ (11 mg, 0.03 mmol), quinuclidine (22 mg, 0.15 mmol) and *N*-methylmorpholine-*N*-oxide (680 mg, 5.8 mmol) in H_2O (3 mL) was added a solution of olefin (400 mg, 2.9 mmol) in acetone (6 mL). After stirring vigorously at room temperature for 3 d, solid sodium metabisulfite (~3.00 g) was added. After vigorous stirring for a further hour, the reaction mixture was diluted with DCM (10 mL). The solid was removed by filtration though a pad of Celite™ and washed with DCM (20 mL). The combined filtrate and washings were evaporated to dryness. Column chromatography eluting with methanol and dichloromethane (5/95) gave (±)-**372** as a white solid (354 mg, 71%), mp (racemate) 108-110 °C; ν_{max} ($CHCl_3$)/cm^{-1} 3469 (OH), 2988 (CH), 1719 (C=O); δ_H(400 MHz, $CDCl_3$) 4.75 (1H, t, *J* 5.5, OCH_{bridge}), 4.50 (1 H, d, *J* 7.5, OCH_{bridge}), 4.01 (1 H, d, *J* 12.5, CCH*H*OH), 3.59 (1H, d, *J* 12.5, CC*H*HOH), 3.16 (1H, dd, *J* 15.0, 5.5, $CHCH_{2ax}CO$), 2.21 (1H, d, *J* 15.0, $CHCH_{2eq}CO$), 2.05-2.13 (2H, m, $CHCH_{2exo}CH_{2exo}CH$), 1.70-1.78 (2H, m, $CHCH_{2endo}CH_{2endo}CH$); δ_C (100 MHz, $CDCl_3$) 207.6 (C=O), 80.2 (C), 78.4 (CH_2), 75.6 (CH), 61.7 (CH), 46.3 (CH_2), 28.6 (CH_2), 23.4 (CH_2); *m/z* (CI) 190 (MNH_4^+, 100%), Found: MNH_4^+, 190.1077, $C_8H_{12}O_4$ requires MNH_4^+, 190.1079.

(1R,2R,5S)-(-)-*2-Hydroxy-2-(hydroxymethyl)-8-oxa-bicyclo[3.2.1]octan-3-one* (-)-**372**: A white solid, mp (non-racemic) 108-110 °C, $[\alpha]_D^{20}$ -39.7 (*c* 0.01, $CHCl_3$); δ_H(400 MHz, $CDCl_3$) 4.75 (1H, t, *J* 5.5, OCH_{bridge}), 4.50 (1 H, d, *J* 7.5, OCH_{bridge}), 4.01 (1 H, d, *J* 12.5, CCH*H*OH), 3.59 (1H, d, *J* 12.5, CC*H*HOH), 3.16 (1H, dd, *J* 15.0, 5.5, $CHCH_{2ax}CO$), 2.21 (1H, d, *J* 15.0, $CHCH_{2eq}CO$), 2.05-2.13 (2H, m, $CHCH_{2exo}CH_{2exo}CH$), 1.70-1.78 (2H, m, $CHCH_{2endo}CH_{2endo}CH$).

(1R,2R*,5S*)-(±)-2',3-Dioxo-8-2',3-dioxo-8H-spiro [8-oxabicyclo[3.2.1]octane -2,4'-[1,3] dioxolane]* **373**:

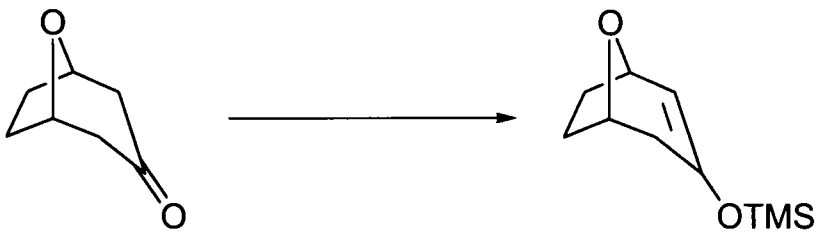


(±)-373

To a stirred solution of diol (200 mg, 1.2 mmol) and pyridine (1.0 mL, 12.0 mmol) in DCM (10 mL) at 0 °C under Ar was added a solution of triphosgene in DCM (5 mL). After stirring between 0 °C and room temperature for 8 hours, it was quenched with H_2O (5 mL). The organic phase was diluted with DCM, separated, dried over $MgSO_4$ and concentrated. Column chromatography eluting with ethylacetate and hexane (1/1) gave **(±)-373** as a white solid (171 mg, 72%), mp (racemate) 117-119 °C; ν_{max} ($CHCl_3$)/cm^{-1} 3449, 2254, 1813 (C=O), 1638 (C=O), 1265 (C-O); δ_H(400 MHz, $CDCl_3$) 5.06 (1H, d, *J* 9.0, CCH_2O), 4.87 (1H, t, *J* 5.5, OCH_{bridge}), 4.68 (1H, d, *J* 7.0, OCH_{bridge}), 3.94 (1H, d, *J* 9.0, CCH_2O), 3.17 (1H, dd, *J* 15.0, 5.5, $CHCH_{2ax}CO$), 2.51 (1H, d, *J* 15.0, $CHCH_{2eq}CO$), 2.12-2.25 (2H, m, $CHCH_{2exo}CH_{2exo}CH$), 1.75 (1H, t, *J* 9.0, $CH_2CHCH_{2endo}CH_{2endo}CH$), 1.35 (1H, t, *J* 9.0, $CH_2CHCH_{2endo}CH_{2endo}CHC$); δ_C(100 MHz, $CDCl_3$) 199.0 (C=O), 152.7 (C=O), 84.3 (C), 79.8 (CH_2), 76.0 (CH), 64.6 (CH), 47.5 (CH_2), 28.2 (CH_2), 23.6 (CH_2); *m/z* (CI) 216 (MNH_4^+, 100 %), Found: MNH_4^+, 216.0877, $C_9H_{10}O_5$ requires MNH_4^+, 216.0872

(1R,2R,5S)-(+)-2',3-Dioxo-8-2',3-dioxo-8H-spiro [8-oxabicyclo[3.2.1]octane -2,4'-[1,3] dioxolane] **(+)-373**: A white solid, mp (chiral) 118-119 °C; $[\alpha]_D^{20}$ +15.7 (*c* 0.01, $CHCl_3$), ee 68% (Shift reagent $Eu(hfc)_3$); δ_H(400 MHz, $CDCl_3$) 5.06 (1H, d, *J* 9.0, CCH_2O), 4.87 (1H, t, *J* 5.5, OCH_{bridge}), 4.68 (1H, d, *J* 7.0, OCH_{bridge}), 3.94 (1H, d, *J* 9.0, CCH_2O), 3.17 (1H, dd, *J* 15.0, 5.5, $CHCH_{2ax}CO$), 2.51 (1H, d, *J* 15.0, $CHCH_{2eq}CO$), 2.12-2.25 (2H, m, $CHCH_{2exo}CH_{2exo}CH$), 1.75 (1H, t, *J* 9.0, $CH_2CHCH_{2endo}CH_{2endo}CH$), 1.35 (1H, t, *J* 9.0, $CH_2CHCH_{2endo}CH_{2endo}CHC$).

(+)-(8-Oxa-bicyclo[3.2.1]oct-2-en-3-yloxy)trimethylsilane **380**[155]:

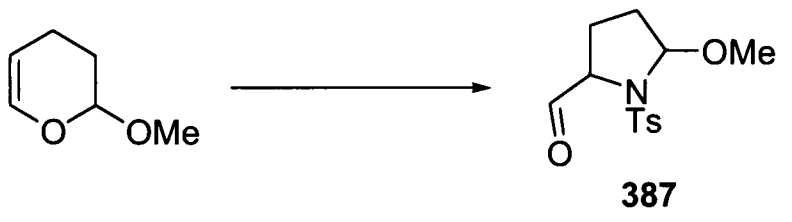


(+)-380

To a solution of the chiral amine (722 mg, 5.7 mmol) in THF at -78 °C under Ar was added dropwise ^{n}BuLi (6.6 mL of 1.33 M solution in hexane, 8.7 mmol). After 5 min the solution was allowed to warm to room temperature and then recooled to -78 °C. TMSCl (3.9 mL, 43.1 mmol) was added, and after 45 min at -78 °C the reaction was quenched with $NaHCO_3$ (sat, aq), the two phase separated and the aqueous layer extracted with petrol. The organic phase was washed with $CuSO_4$, dried and evaporated to give enol silane (+)-**380** as colourless oil (1200 mg, >95%), δ_H (400 MHz, $CDCl_3$) 5.08 (1H, d, *J* 5.0, CH=C), 4.58 (1H, d, *J* 6.0, OCH_{bridge}), 4.52 (1H, t, *J* 5.0, OCH_{bridge}), 2.71 (1H, dd, *J* 5.0, 16.5, $CH_{2ax}CO$), 2.17-2.08 (1H, m, $CHCH_{2eq}CO$), 2.03-1.88 (2H, m, $CHCH_{2exo}CH_{2exo}CH$), 1.78-1.69 (2H, m, $CHCH_{2endo}CH_{2endo}CH$), 0.20 (9H, s, 3 x CH_3); *m/z* (CI) 90, 199 (MH^+), 226, 216 (MNH_4^+), Found: MNH_4^+, 199.1153, $C_9H_{18}O_2$ requires MNH_4^+, 199.1154

Synthesis of *aza*-bicyclic ketone catalyst

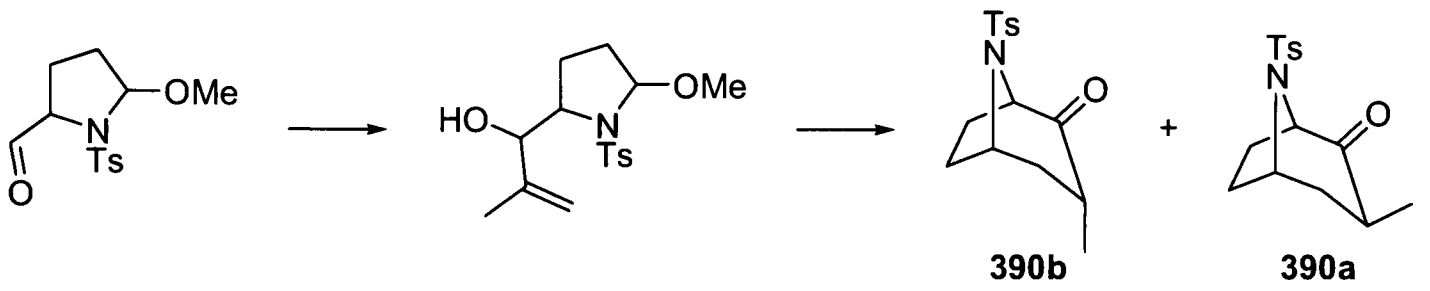
(2R, 5R*)-5-Methoxy-1-tosylpyrrolidine-2-carbaldehyde* and *(2R*, 5S*)-5-methoxy-1-tosylpyrrolidine-2-carbaldehyde* **387**[87]:



387

To a solution of dried Chloramine-T (13.65 g, 60 mmol, 1.2 eq) in acetonitrile (250 mL) at room temperature was added the 2-alkoxydihydropyran (5.7 mL, 5.70 g 50 mmol, 1.0 eq). After stirring for 5 min, NBS (1.78g, 10 mmol, 0.2 eq) was added. After stirring for 2 h, the reaction mixture passed through a plug of Et_3N-washed silica, flushing with EtOAc. The resulting solution was concentrated *in vacuo* to give a dark orange oil. Column chromatography eluting with ethylacetate and hexane (1/1) gave pale yellow oil **387** as a mixture (6.99, 50 %) of 2 diastereisomers (1:1), δ_H (400 MHz, $CDCl_3$) 9.70 ($1H_{trans}$, d, *J* 3.0, CHO), 9.54 ($1H_{cis}$, d, *J* 3.0, CHO), 7.77 ($2H_{trans}$, d, *J* 8.5, ArH), 7.69 ($2H_{cis}$, d, *J* 8.0, ArH), 7.33 ($2H_{cis}$, d, *J* 8.0, ArH), 7.29 ($2H_{trans}$, d, *J* 8.5, ArH), 5.32 ($1H_{trans}$, d, *J* 4.0, NCH(OMe)), 5.12 ($1H_{cis}$, d, *J* 5.0, NCH(OMe)), 3.87-3.84 ($1H_{trans}$, m, C*H*CHO), 3.81 ($1H_{cis}$, td, *J* 8.5, 3.0, C*H*CHO), 3.48 ($3H_{cis}$, s OMe), 3.28 ($3H_{trans}$, s, OMe), 2.43 ($3H_{trans}$, s, $ArCH_3$), 2.41 ($3H_{cis}$, s, $ArCH_3$), 2.11-2.07 ($4H_{both}$, m, 2 x C*H*HCHCHO), 1.96-1.94 ($4H_{both}$, m, 2 x CH*H*CHCHO), 1.90-1.85 ($4H_{both}$, m, 2 x C*H*HCH(OMe)), 1.29-1.21 ($4H_{both}$, m, 2 x CH*H*CH(OMe)).

(±)-(1R, 3S*, 5S*)-3-Methyl-8-(toluene-4-sulfonyl)-8-aza-bicyclo[3.2.1]octan-2-one* **390b and** *(±)-(1R*, 3R*, 5S*)-3-methyl-8-(toluene-4-sulfonyl)-8-aza-bicyclo[3.2.1]octan-2-one* **390a**:



390b **390a**

To a solution of aldehyde (4.63 g, 16.3 mmol, 1.0 eq) in Et_2O (50 mL) at 0 °C was added Grignard reagent (0.5 M in THF, 50.0 mL, 1.5 eq). The reaction was allowed to warm to room temperature for 10 min before being quenched by the addition of saturated aqueous NH_4Cl solution (100 mL). The mixture was extracted into diethyl ether (2 x 100 mL). The combined organics washed with brine and then dried over Na_2SO_4. Column chromatography eluting with diethyl ether and petrol (2/3) gave the rearrangement precursor as a mixture of diastereoisomers as a pale yellow oil (1.69 g). *m/z* (CI) 343 (MNH_4^+).

To a solution of rearrangement precursor (1.69 g, 1.0 eq) in DCM (50 mL) at 0 °C was added $SnCl_4$ solution (1.0 M in heptanes, 10.4 mL). The mixture was allowed to warm to room temperature and stirred for 16 h. The reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ (50 mL). The mixture was extracted into chloroform and combined organics dried over Na_2SO_4. Column chromatography eluting with diethyl ether and petrol (1/1) gave isomeric tropanes *endo* **390b** (0.20 g, 13 %) and *exo* **390a** (0.23 g, 15 %) as pure compounds.

endo product **390b**: δ_H(400 MHz, $CDCl_3$) 7.74 (2H, d, *J* 8.0, 2 x SO_2CCH), 7.30 (2H, d, *J* 8.0, ArH), 4.51-4.42 (1H, m, NC*H*$(CH_2)_2$), 4.38-4.32 (1H, m, NCHC=O), 2.80-2.62 (1H, m, C*H*CH_3), 2.43 (3H, s, $ArCH_3$), 1.83-0.86 (6H, m, CCH_2C), 1.04 (3H, d, *J* 6.5, CHC*H*$_3$); *m/z* (CI) 294 (MH^+), 311 (MNH_4^+, 100%), Found: MH^+, 294.1155, $C_{15}H_{19}NO_3S$ requires MH^+,

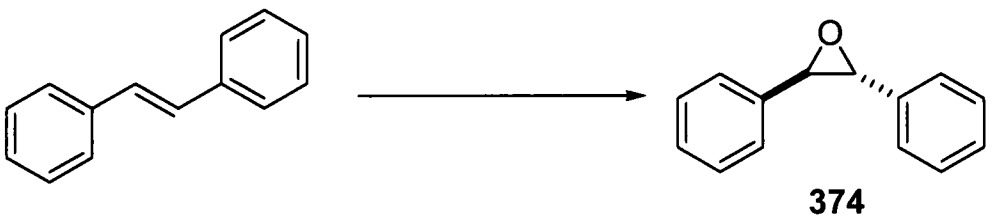
294.1164.

exo product **390a**: δ_H(400 MHz, $CDCl_3$) 7.74 (2H, d, *J* 8.0, 2 x SO_2CCH), 7.30 (2H, d, *J* 8.0, ArH), 4.48-4.40 (1H, m, NC*H*$(CH_2)_2$), 4.29-4.23 (1H, m, NCHC=O), 2.51-2.34 (1H, m, CHMe), 2.43 (3H, s, $ArCH_3$), 2.03-1.66 (6H, m, CCH_2C), 0.97 (3H, d, *J* 6.5, $CHCH_3$); *m/z* (CI) 294 (MH^+), 311 (MNH_4^+, 100%), Found: MNH_4^+, 311.1432, $C_{15}H_{19}NO_3S$ requires MNH_4^+, 311.1429.

General procedure for one-phase epoxidation system – Yang pH 7.5

To a solution of ketone catalyst (0.1 eq) and alkene (1.0 eq) in acetonitrile (6.0 ml) was added aqueous Na_2EDTA solution (4.0 ml of a 0.4 mM aqueous solution). Oxone® (10.0 eq) and $NaHCO_3$ (15.5 eq) were added in portions simultaneously over 30 minutes. The reaction was stirred vigorously until completion (by TLC analysis) or for 18 hours, then diluted with water. The reaction mixture was extracted into diethyl ether (30 mL x 3). The combined organic extracts were dried over Na_2SO_4, filtered and evaporated to dryness under reduced pressure. Column chromatography eluting with diethyl ether and hexane previously washed with 1% triethylamine gave the relevant epoxides.

(2R,3R*)-2,3-Diphenyloxirane* **374**[182]:

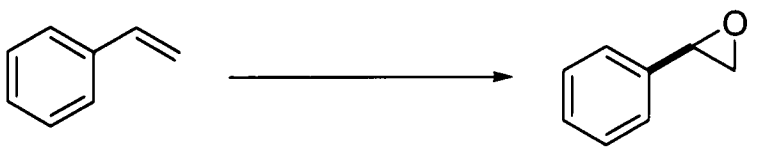


374

White solid; m.p. 68-70 °C; δ_H(400 MHz, $CDCl_3$) 7.36-7.45 (10H, m, 2 x Ph), 3.91 (2H, s, 2 x CH); *m/z* (CI) 214 (MNH_4^+, 100 %); *m/z* (CI) 197 (MH^+), 214 (MNH_4^+, 100%), Found: MNH_4^+, 214.1239. $C_{14}H_{12}O$ requires MNH_4^+, 214.1232.

(2R,3R)-2,3-Diphenyloxirane: white solid; m.p. 68-70 °C; ee_{obs} 62%; ee_{max} 91%; $[\alpha]_D^{20}$ +60.0 (*c* 0.01, $CHCl_3$).

2-Phenyloxirane **375**[183]:

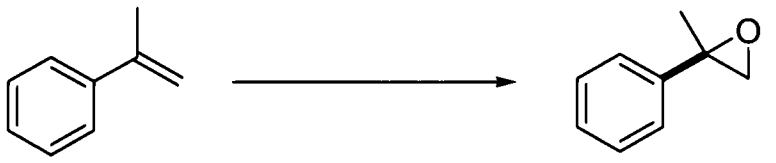


375

Colourless oil; δ_H (400 MHz, $CDCl_3$) 7.40-7.28 (5H, m, Ph), 3.89 (1H, dd, *J* 2.5, 4.0, CH), 3.17 (1H, dd, *J* 4.0, 5.5, C*H*H), 2.83 (1H, dd, *J* 2.5, 5.5, CH*H*).

(R)-2-Phenyloxirane: colourless oil; ee_{obs} 28%; ee_{max} 41%; $[\alpha]_D^{20}$ +2.0 (*c* 0.01, $CHCl_3$).

2-Methyl-2-phenyloxirane **376**[184]:



376

Colourless oil; δ_H (400 MHz, $CDCl_3$) 7.48-7.28 (5H, m, Ph), 3.80 (1H, d, *J* 11.0, C*H*H), 3.64 (1H, d, *J* 11.0, CH*H*), 1.54 (3H, s, CH_3); *m/z* (CI) 152 (MNH_4^+), 170, Found: MNH_4^+, 152.1077, $C_9H_{10}O$ requires MH^+, 152.1075.

(R)-2-Methyl-2-phenyloxirane: colourless oil; ee_{obs} <1%; ee_{max} <1%; $[\alpha]_D^{20}$ +20.0 (*c* 0.01, $CHCl_3$).

(2R,3R*)-2-Methyl-3-phenyloxirane* **377**[185]:

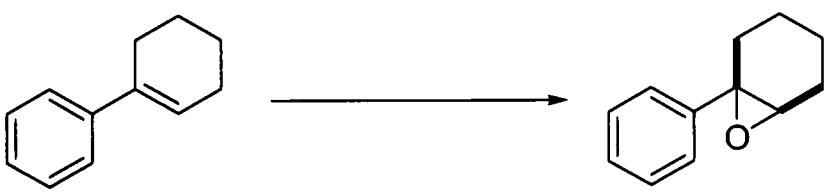


377

Colourless oil; δ_H (400 MHz, $CDCl_3$) 7.39-7.26 (5H, m, Ph), 3.60 (1H, d, *J* 2.0, CH), 3.06 (1H, dq, *J* 2.0, 5.0, C*H*CH_3), 1.48 (3H, d, *J* 5.0, CH_3); *m/z* (CI) 152 (MNH_4^+, 100 %), Found: MNH_4^+, 152.1077, $C_9H_{10}O$ requires MH^+, 152.1075.

(2R,3R)-2-Methyl-3-phenyloxirane: colourless oil; ee_{obs} 48%; ee_{max} 71%; $[\alpha]_D^{20}$ +4.6 (*c* 0.02, $CHCl_3$).

(1R,6R*)-1-Phenyl-7-oxa-bicyclo[4.1.0]heptane* **378**[184]:

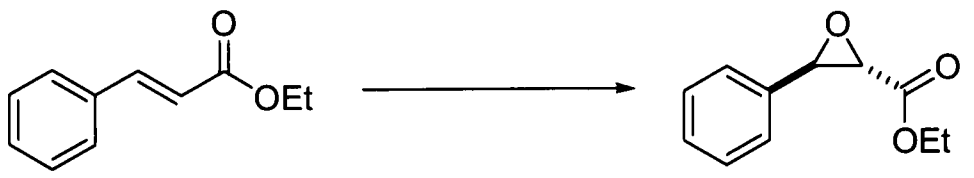


378

Colourless oil, δ_H (400 MHz, $CDCl_3$) 7.56-7.28 (5H, m, Ph), 4.03 (1H, d, *J* 11.0, CH), 1.94-1.37 (8H, 4 x CH_2); *m/z* (CI) 175(MH^+), 192, Found: MNH_4^+, 175.1124, $C_{12}H_{14}O_2$ requires MH^+, 175.1123.

(1R,6R)-1-Phenyl-7-oxa-bicyclo[4.1.0]heptane: colourless oil; ee_{obs} 55%; ee_{max} 81%; $[\alpha]_D^{20}$ +110.0 (*c* 0.01, $CHCl_3$).

(2S,3R*)-Ethyl 3-phenyloxirane-2-carboxylate* **379**[186]:



379

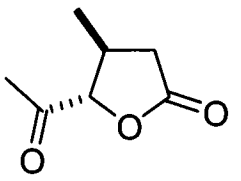
Colourless oil; 7.42-7.30 (5H, m, Ph), 4.30 (2H, q, *J* 7.0, OCH_2), 4.11 (1H, d, *J* 1.5, PhCH), 3.53 (1H, d, *J* 1.5, CH), 1.35 (3H, d, *J* 7.0, CH_3); *m/z* (CI) 210 (MNH_4^+, 100 %), Found: MNH_4^+, 210.1131, $C_{11}H_{12}O_3$ requires MH^+, 210.1130.

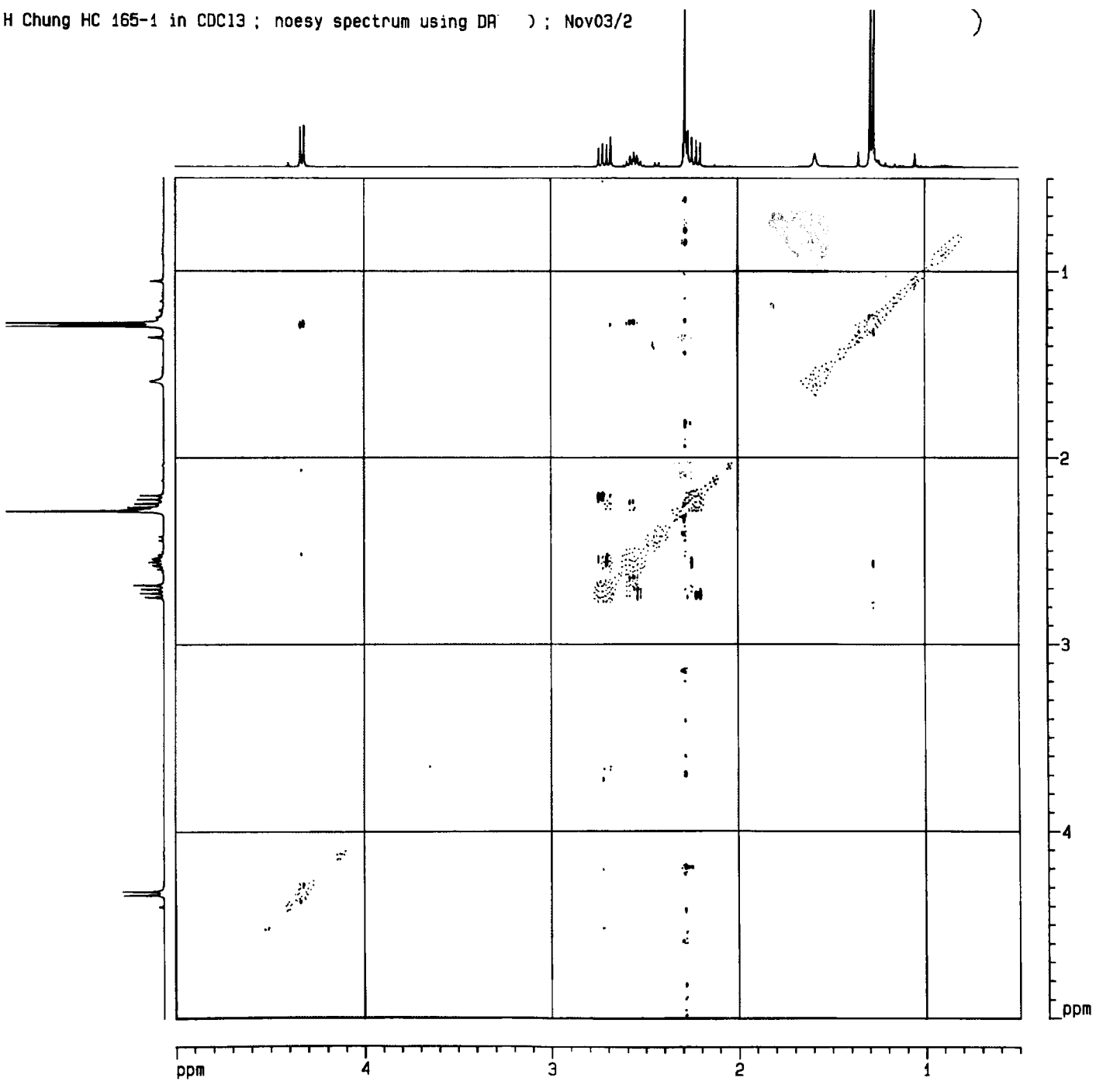
(2S,3R)-ethyl 3-phenyloxirane-2-carboxylate: colourless oil; ee_{obs} 46%; ee_{max} <68%; $[\alpha]_D^{20}$ +40.0 (*c* 0.01, $CHCl_3$).

Appendix

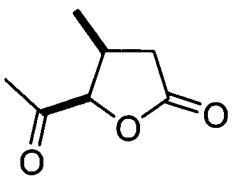
1. NOESY spectra from Chapter 1.

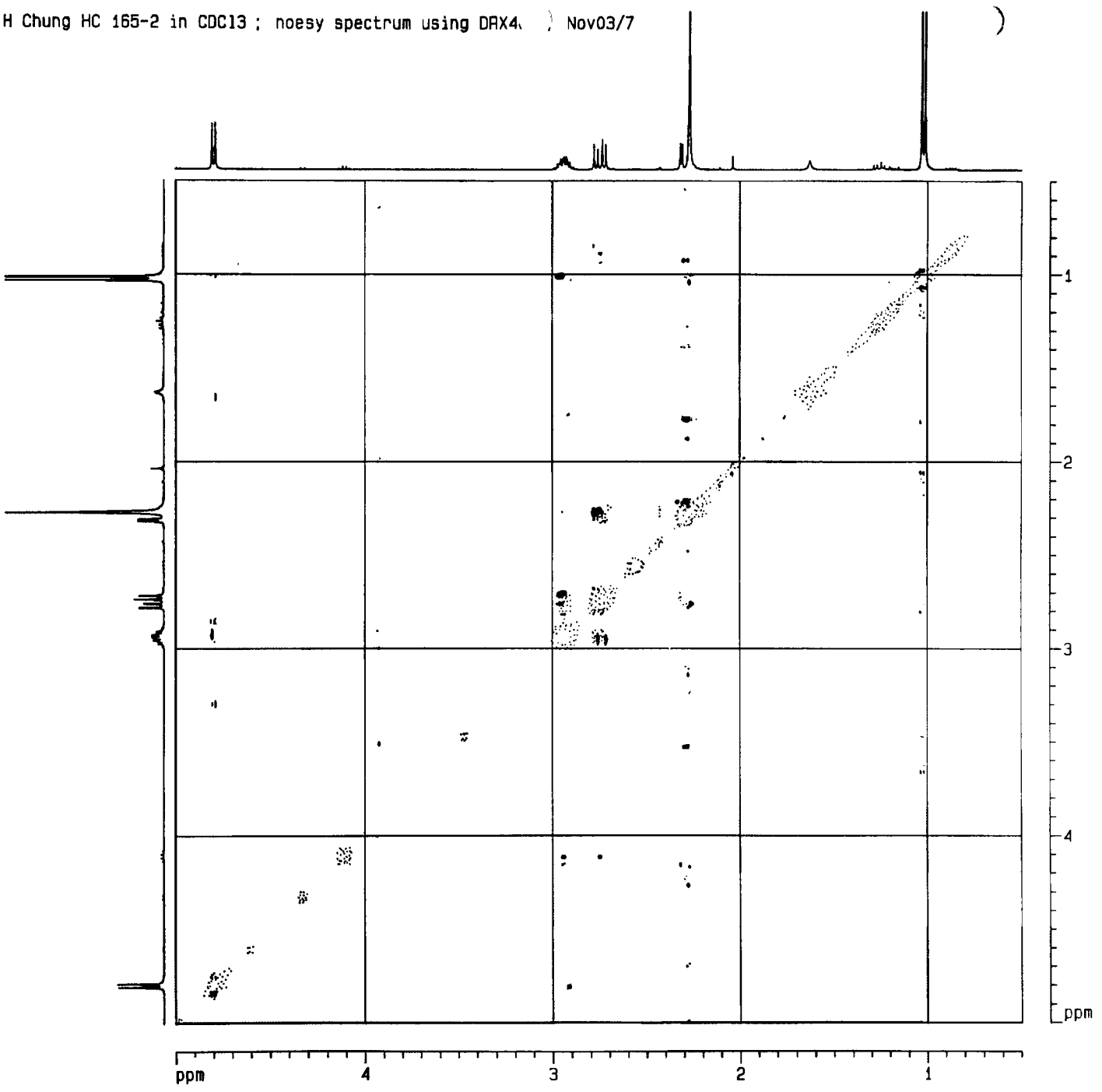
(4*S**,5*S**)-5-Acetyl-4-methyl-dihydrofuran-2(3*H*)-one **250b**



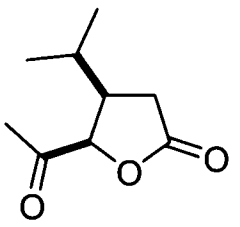


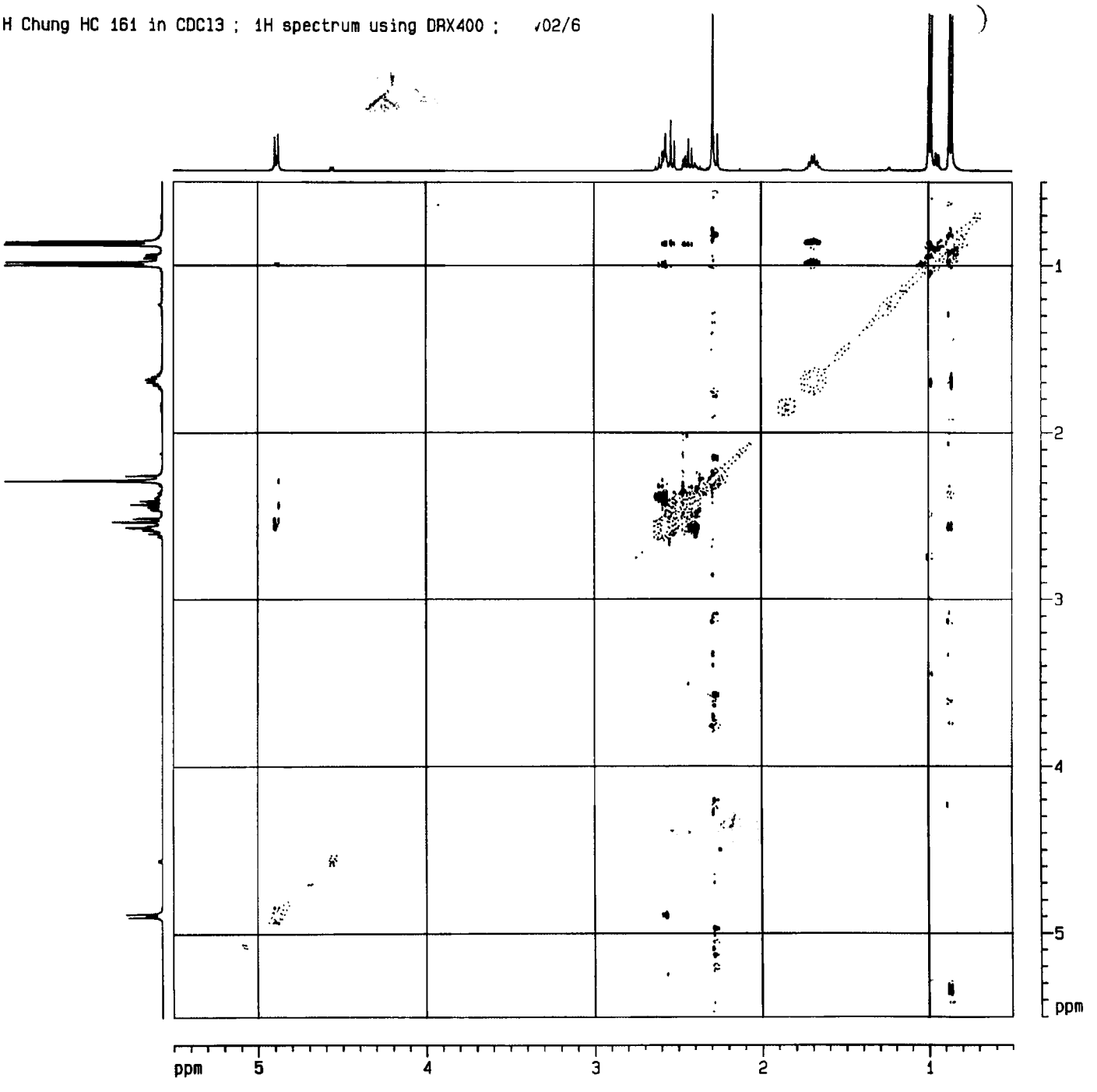
(4*S**,5*R**)-5-Acetyl-4-methyl-dihydrofuran-2(3*H*)-one **250a**



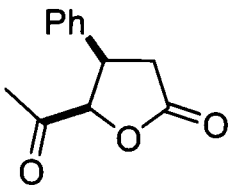


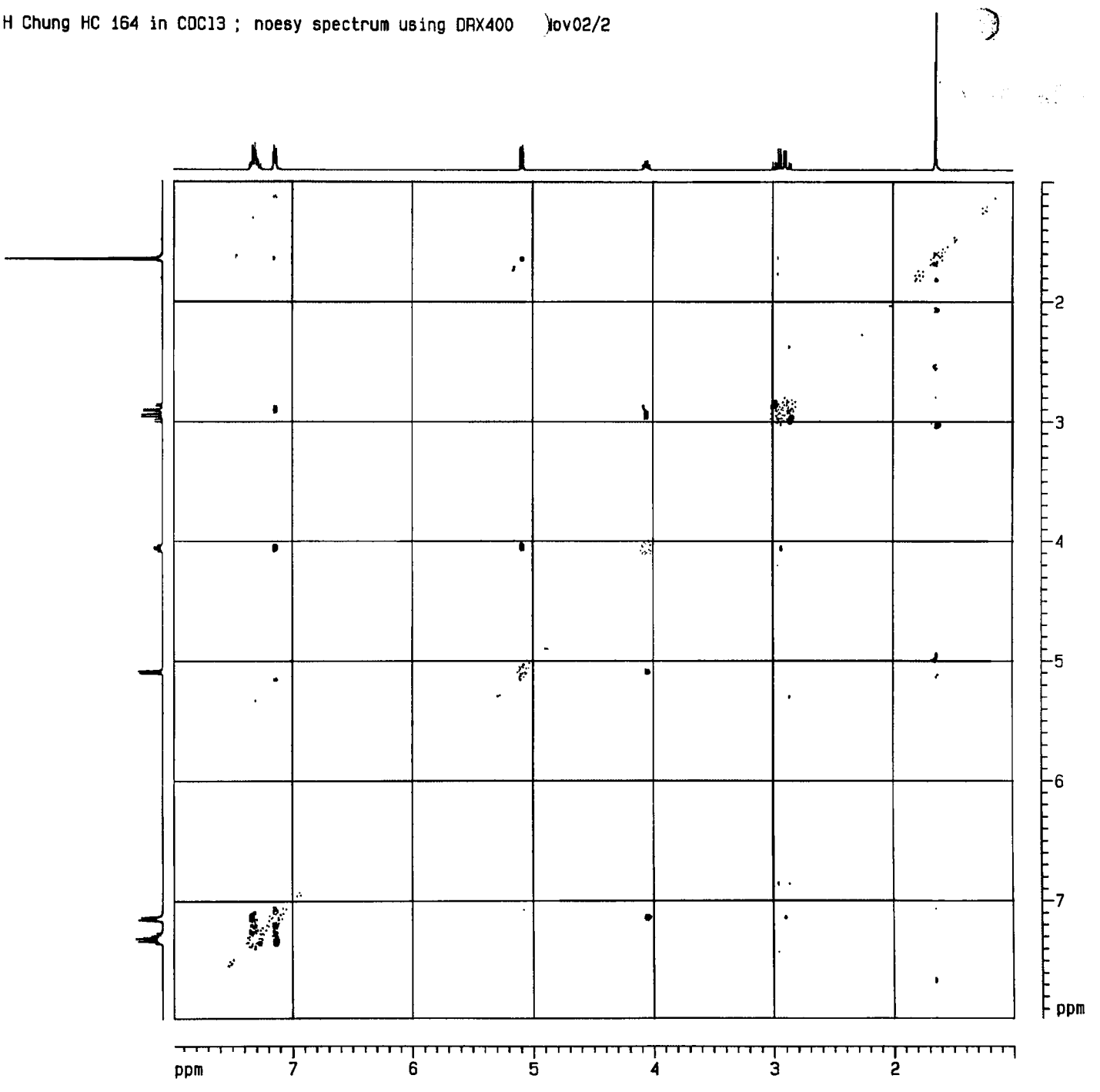
(4*R**,5*R**)-5-Acetyl-4-isopropyl-dihydrofuran-2(3*H*)-one **251a**



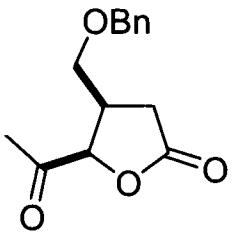


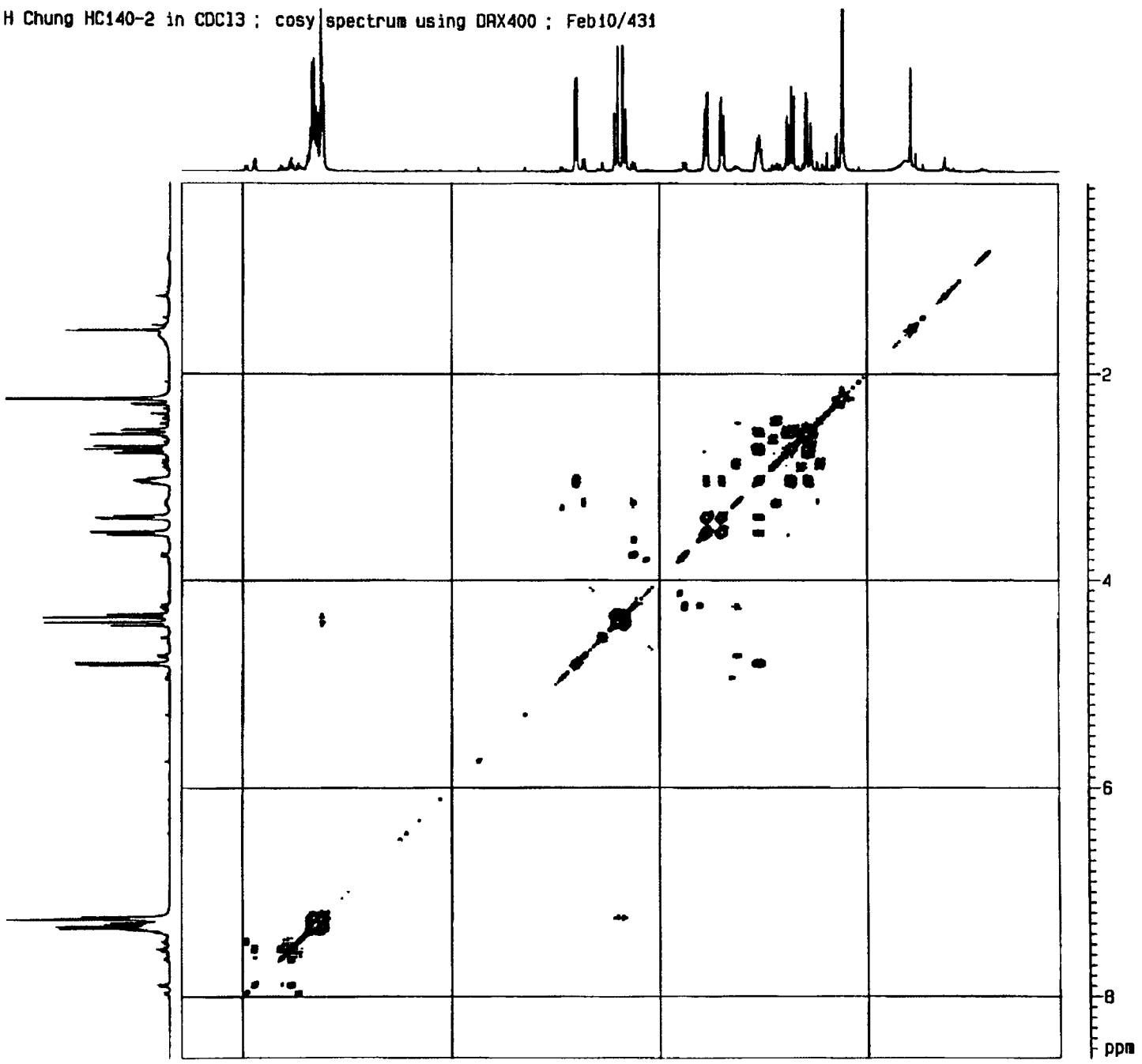
(4*R**,5*R**)-5-Acetyl-4-phenyl-dihydrofuran-2(3*H*)-one **235**



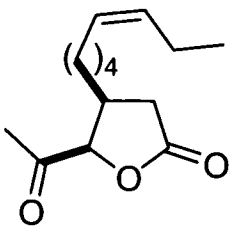


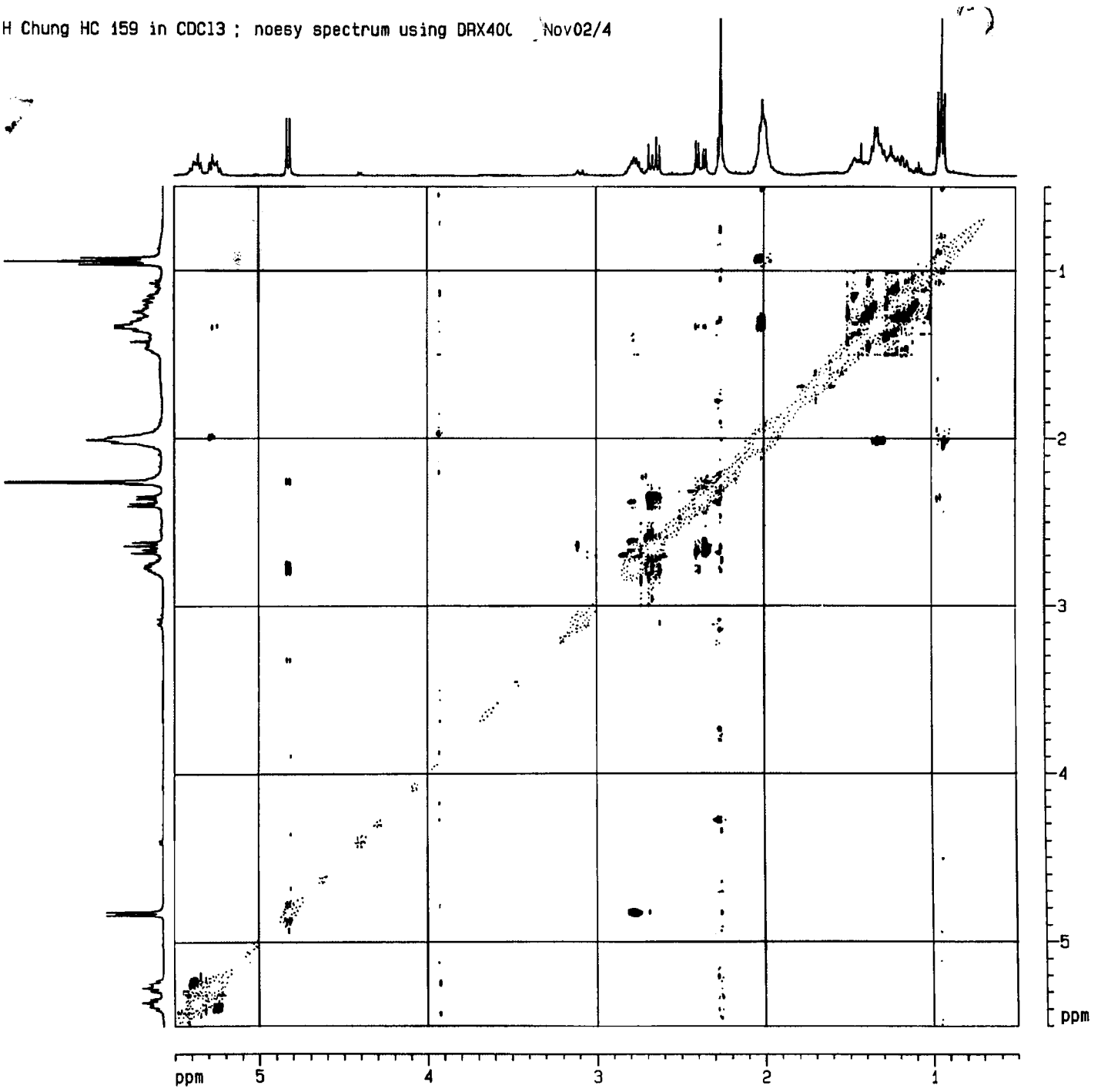
(4*R**,5*R**)-5-Acetyl-4-(benzyloxymethyl)-dihydrofuran-2(3*H*)-one **253**



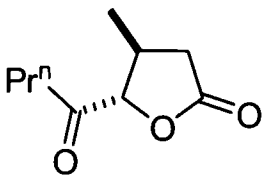


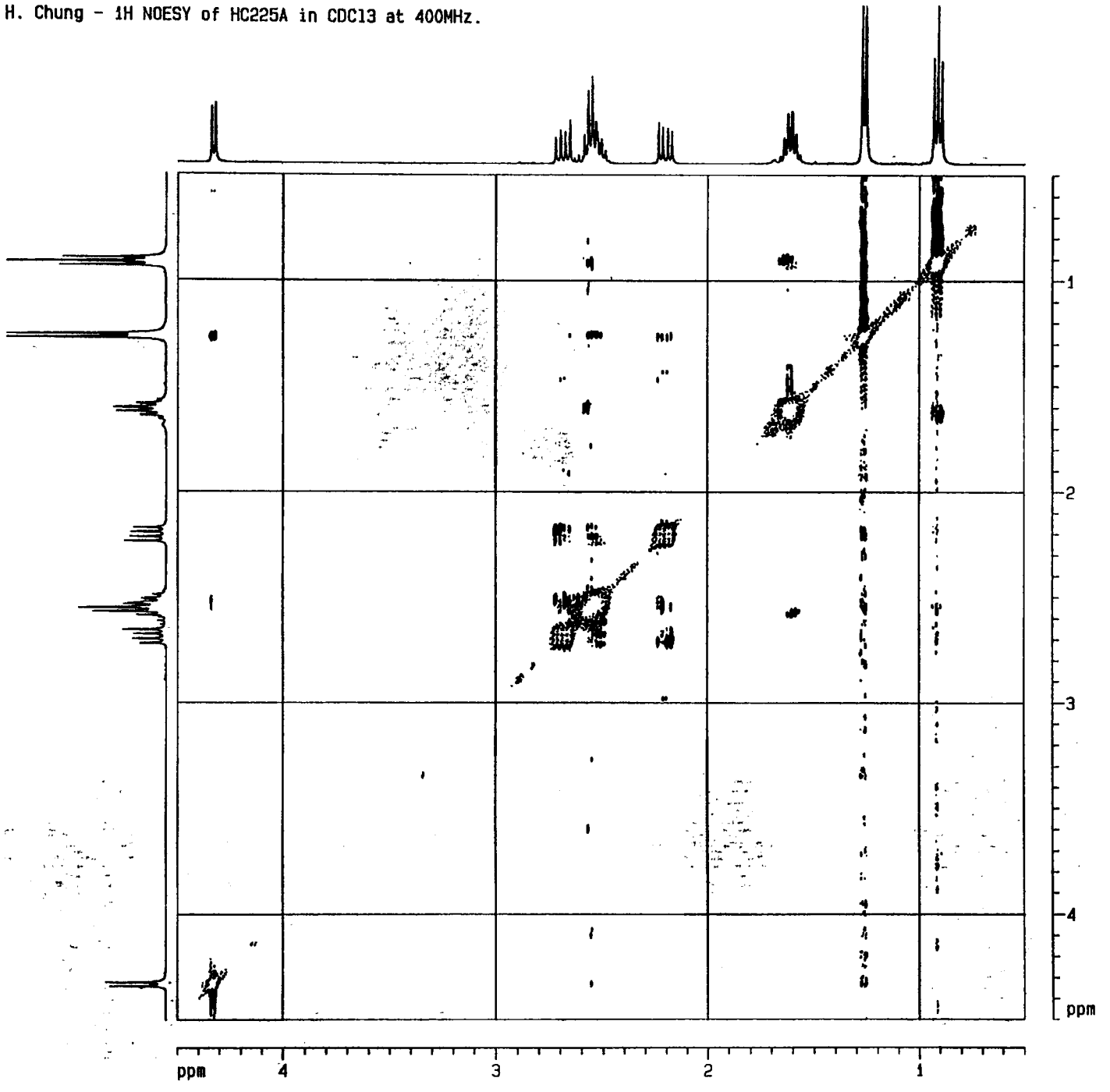
(4*S**,5*R**,*E*)-5-Acetyl-4-(oct-5-enyl)-dihydrofuran-2(3*H*)-one **254**



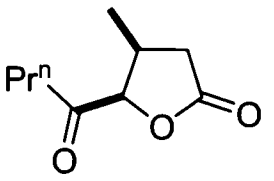


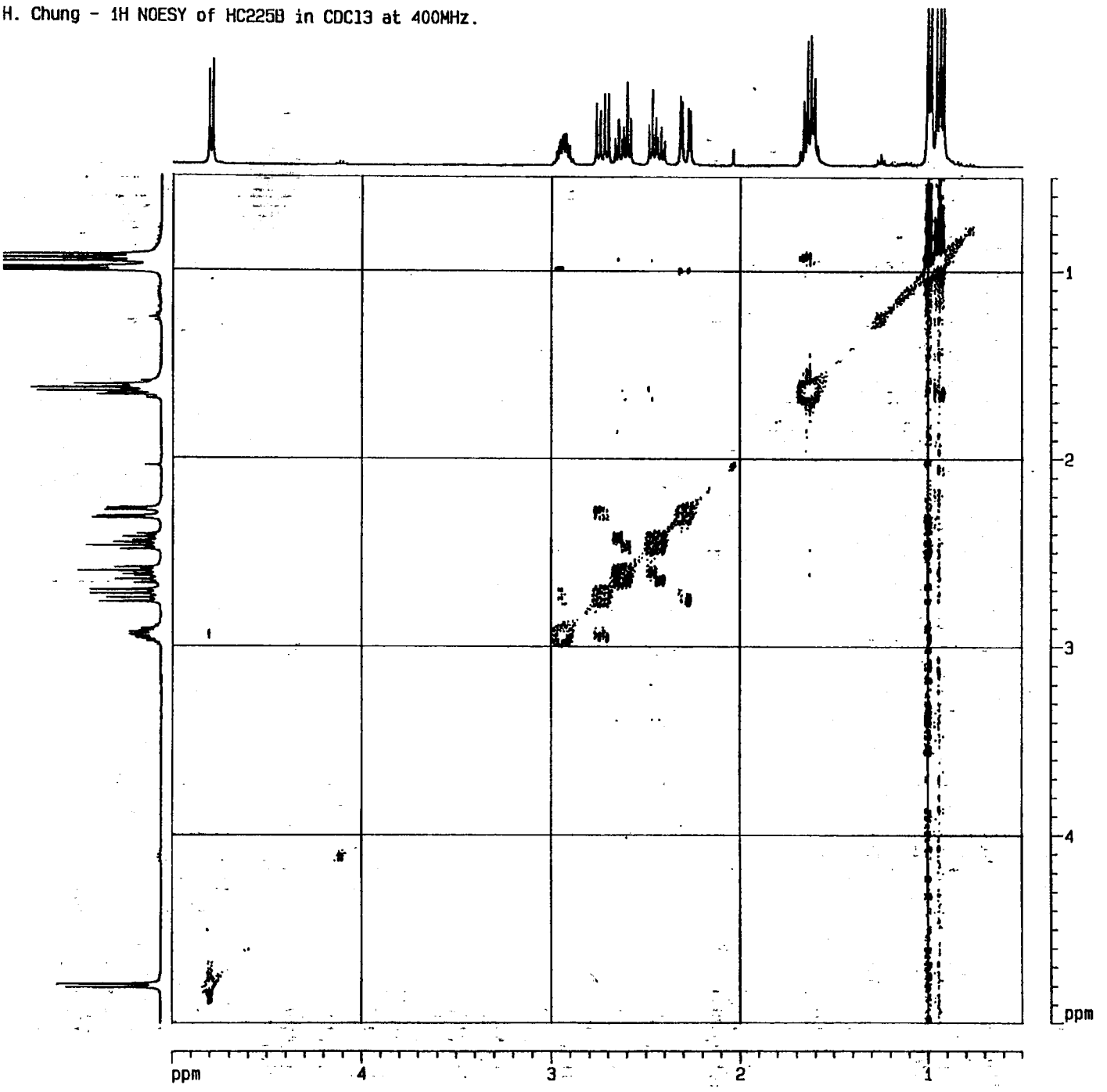
(4*S**,5*S**)-5-Butyryl-4-methyl-dihydrofuran-2(3*H*)-one **273b**



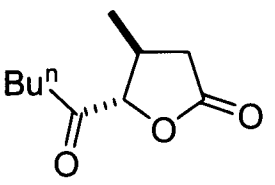


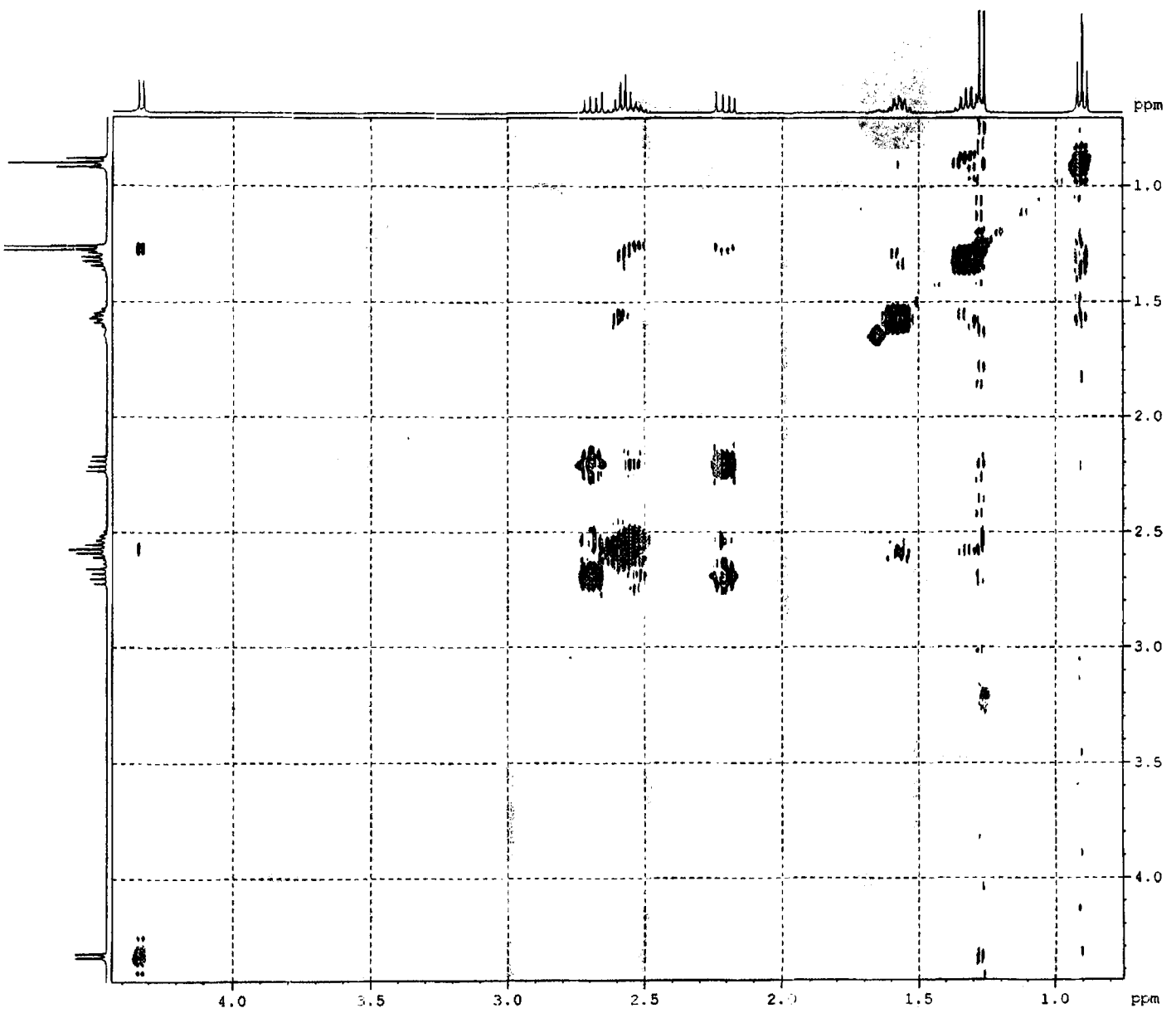
(4*S**,5*R**)-5-Butyryl-4-methyl-dihydrofuran-2(3*H*)-one **273a**



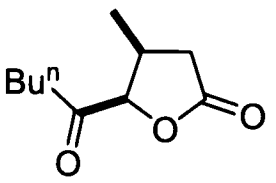


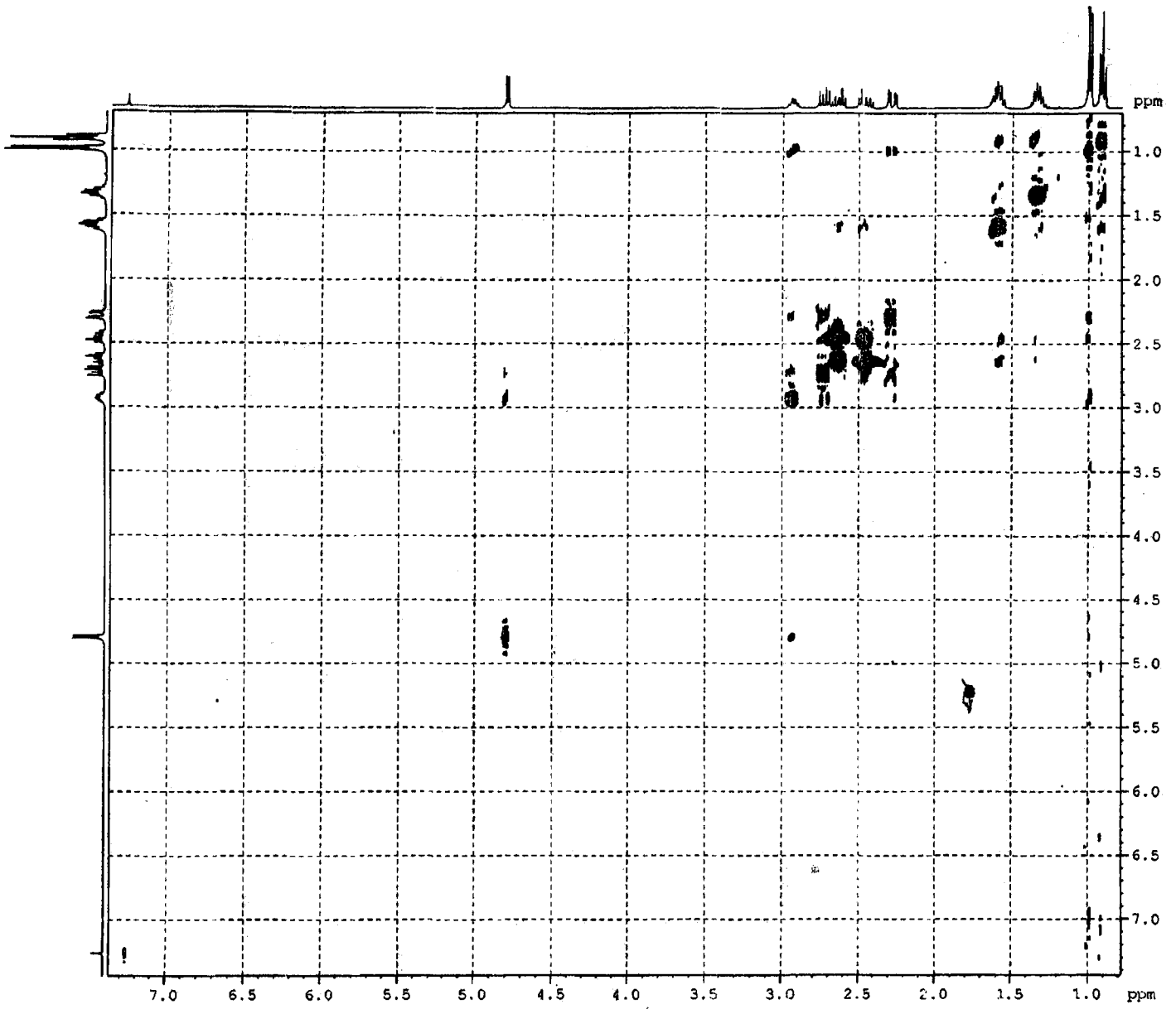
(4*S*,5*S*)-4-Methyl-5-pentanoyl-dihydrofuran-2(3*H*)-one **274b**





(4*S*,5*R*)-4-Methyl-5-pentanoyl-dihydrofuran-2(3*H*)-one **274a**

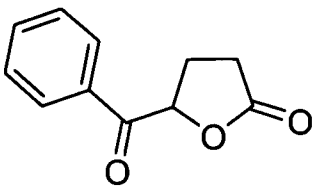


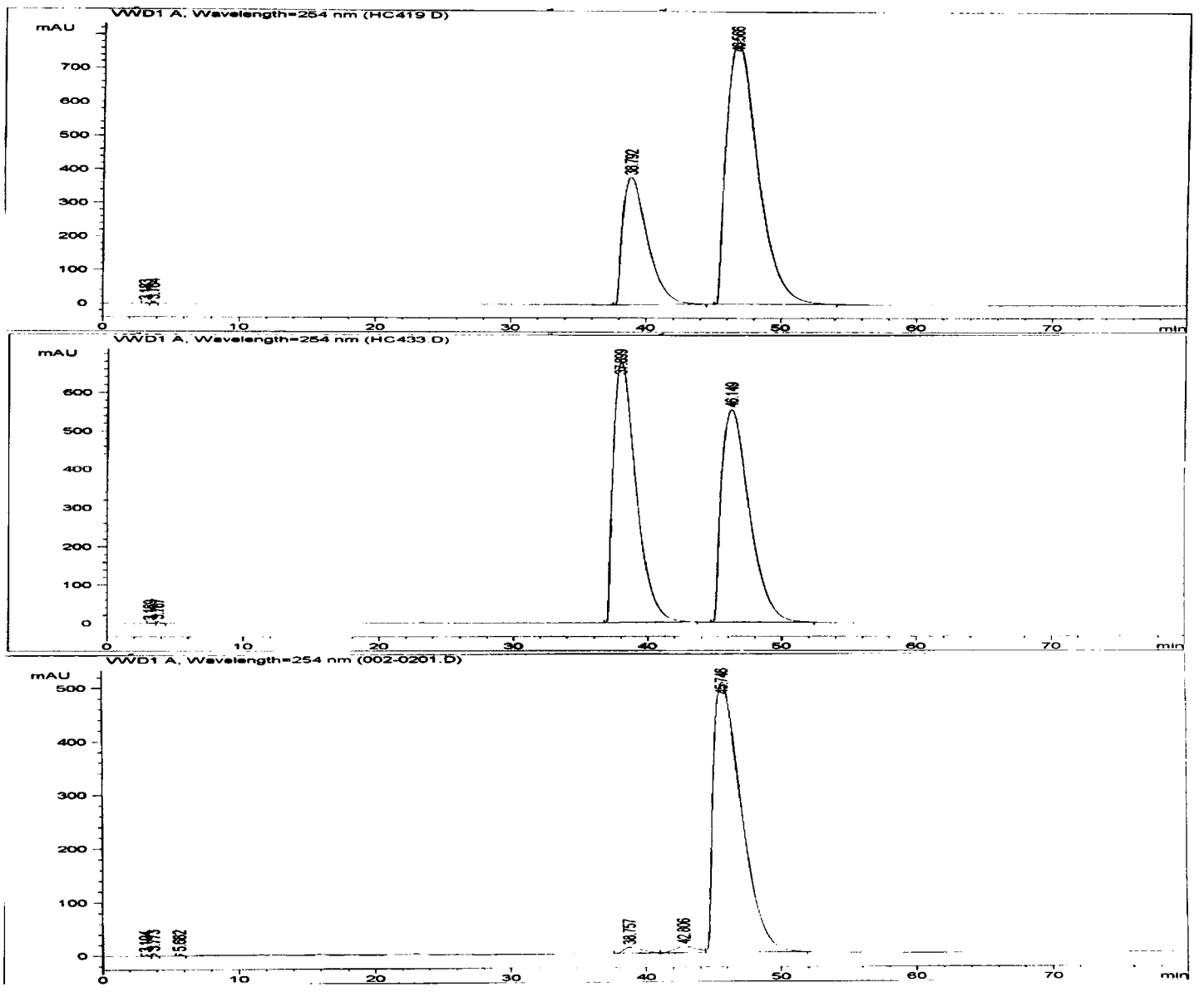


2. HPLC chromatograms from Chapter 2.

HPLC conditions and results for measuring the configurations.

5-Benzoyl-dihydrofuran-2(3*H*)-one **309**

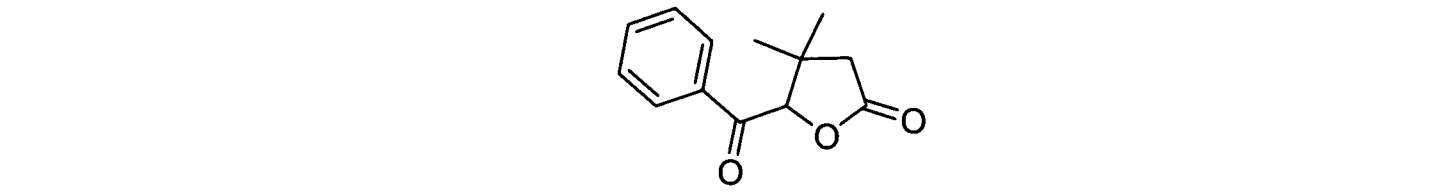


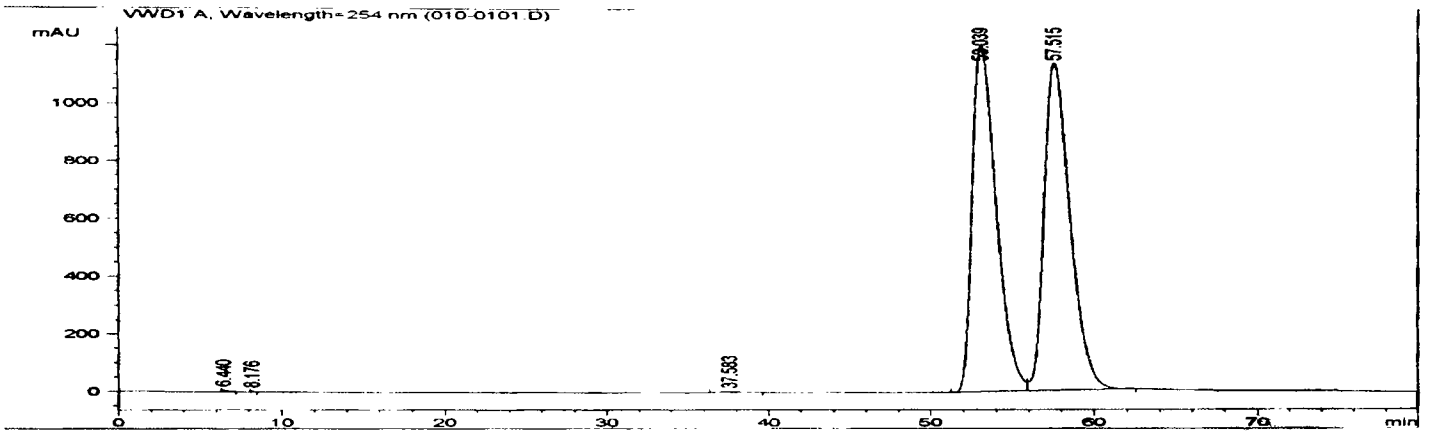


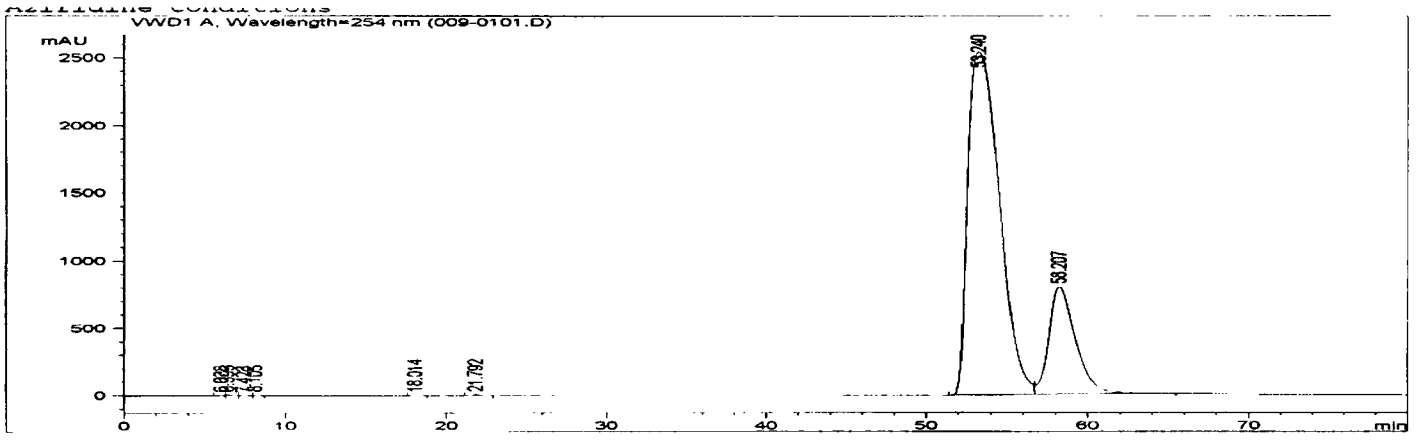
Column	Conditions[a]	t_m[b] (configuration)	t_M[c] (configuration)
Chiralcel OD-H	254; 5/95; 1.0	37.90 (*R*)	46.15 (*S*)

[a] wavelength (nm); eluent system (^{i}PrOH/hexane); flow rate (mL/min), [b] retention time (minor compound), [c] retention time (major compound).

5-Benzoyl-4,4-dimethyl-dihydrofuran-2(3*H*)-one **332**



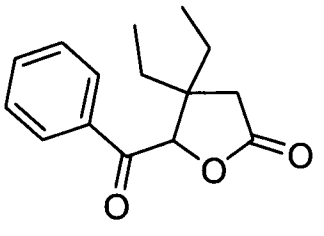


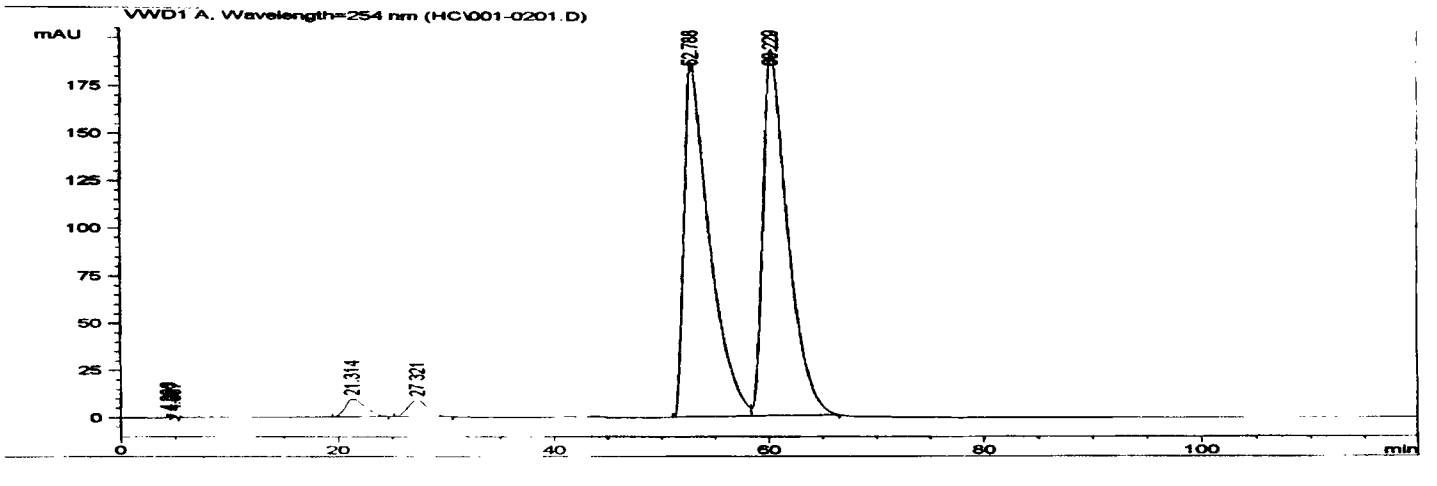


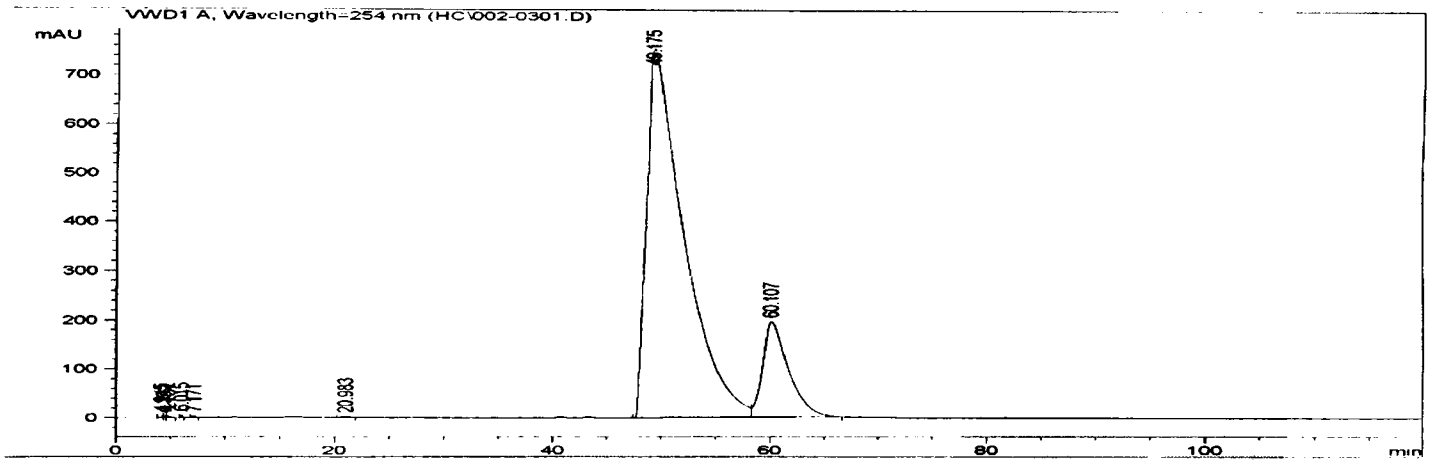
Column	Conditions[a]	t_m[b] (configuration)	t_M[c] (configuration)
Chiralcel OD	254; 5/95; 0.5	58.21 (*R*)	53.24 (*S*)

[a] wavelength (nm); eluent system (^{i}PrOH/hexane); flow rate (mL/min), [b] retention time (minor compound), [c] retention time (major compound).

5-Benzoyl-4,4-diethyl-dihydrofuran-2(3*H*)-one **333**





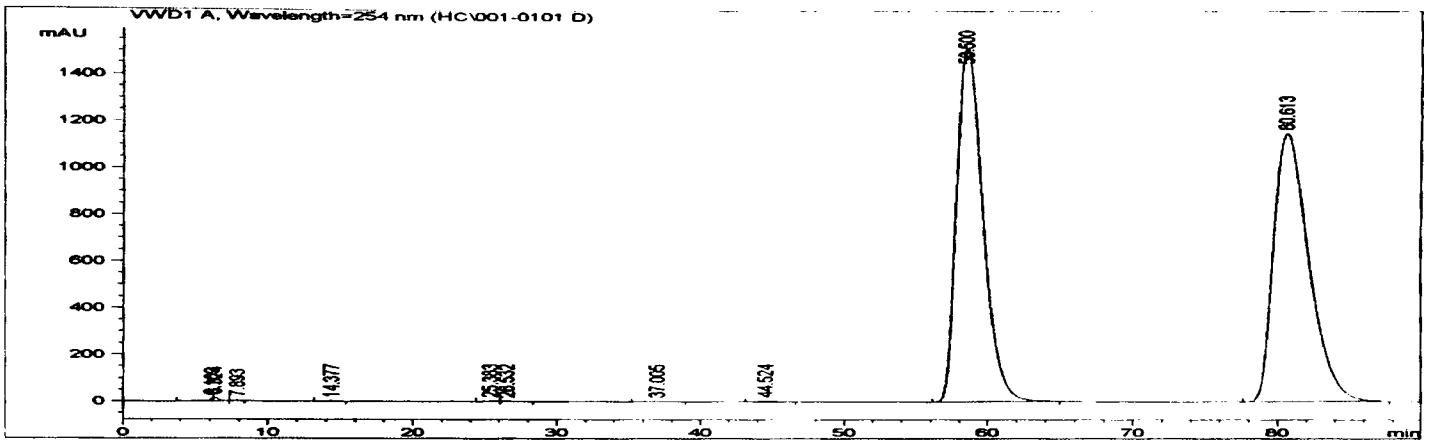


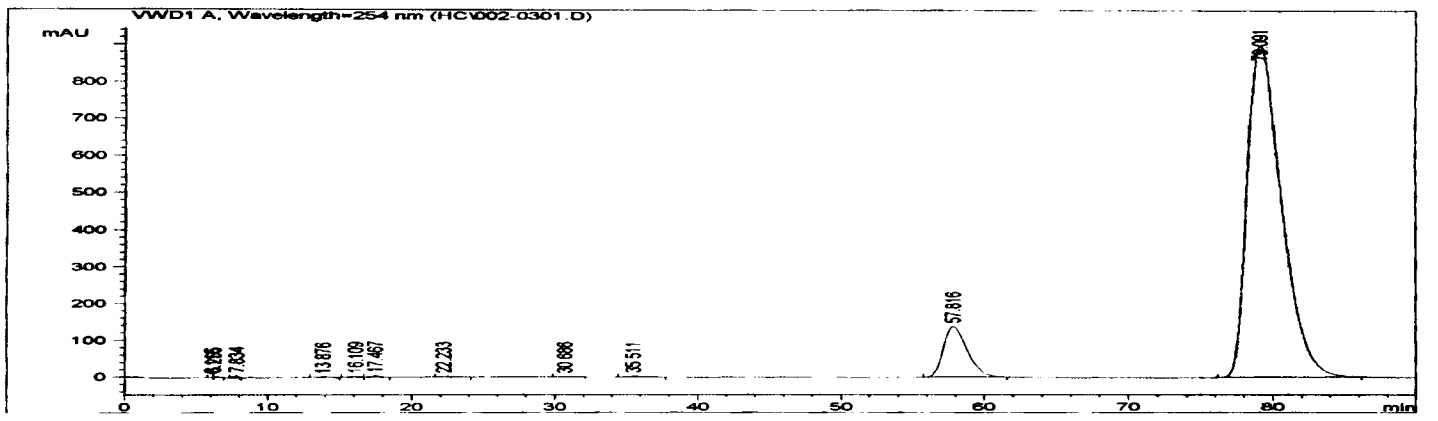
Column	Conditions[a]	t_m[b] (configuration)	t_M[c] (configuration)
Chiralcel OD-H	254; 2/98; 0.5	60.11 (*R*)	49.18 (*S*)

[a] wavelength (nm); eluent system (^{i}PrOH/hexane); flow rate (mL/min), [b] retention time (minor compound), [c] retention time (major compound).

1-Benzoyl-2-oxa-spiro[4,5]decan-3-one **334**



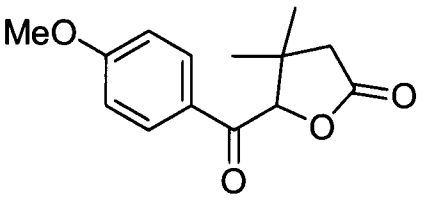


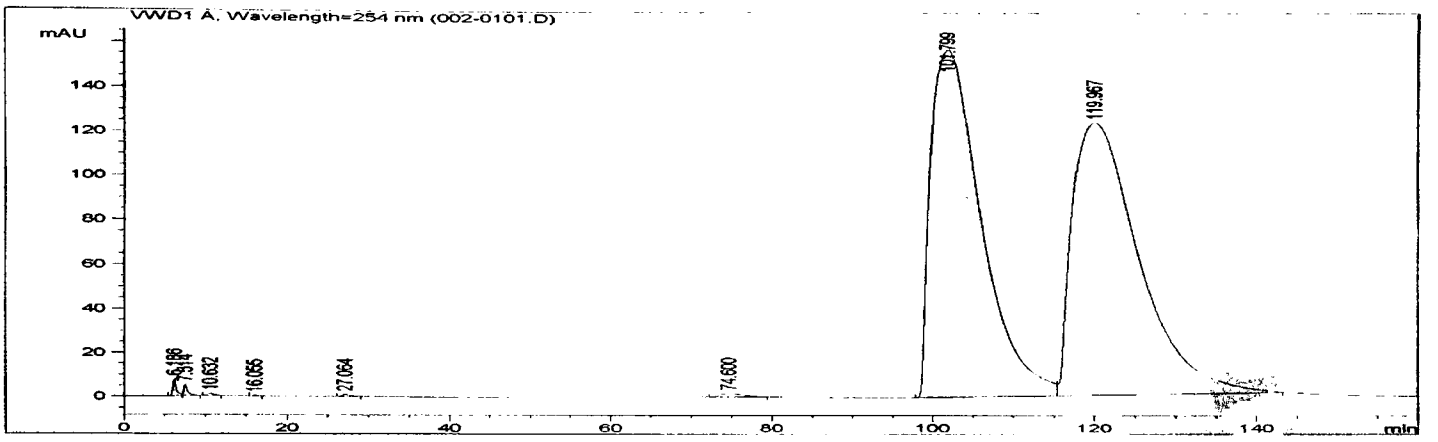


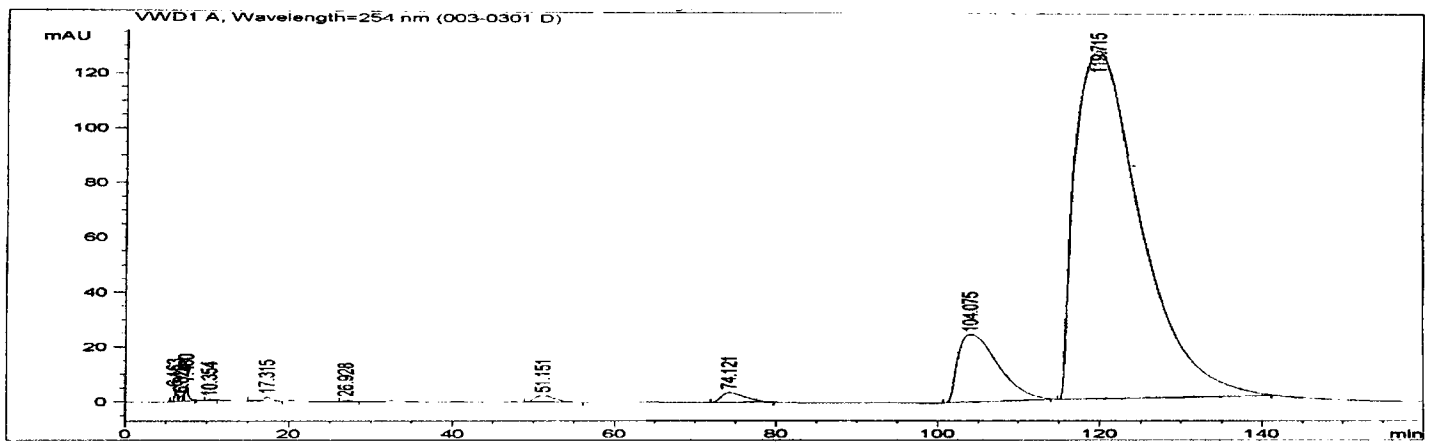
Column	Conditions[a]	t_m[b] (configuration)	t_M[c] (configuration)
Chiralcel OD	254; 5/95; 0.5	57.82 (*R*)	79.09 (*S*)

[a] wavelength (nm); eluent system (^{i}PrOH/hexane); flow rate (mL/min), [b] retention time (minor compound), [c] retention time (major compound).

5-(4-Methoxybenzoyl)-4,4-dimethyl-dihydrofuran-2(3*H*)-one **335**



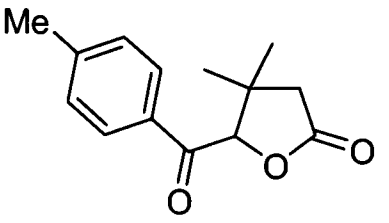


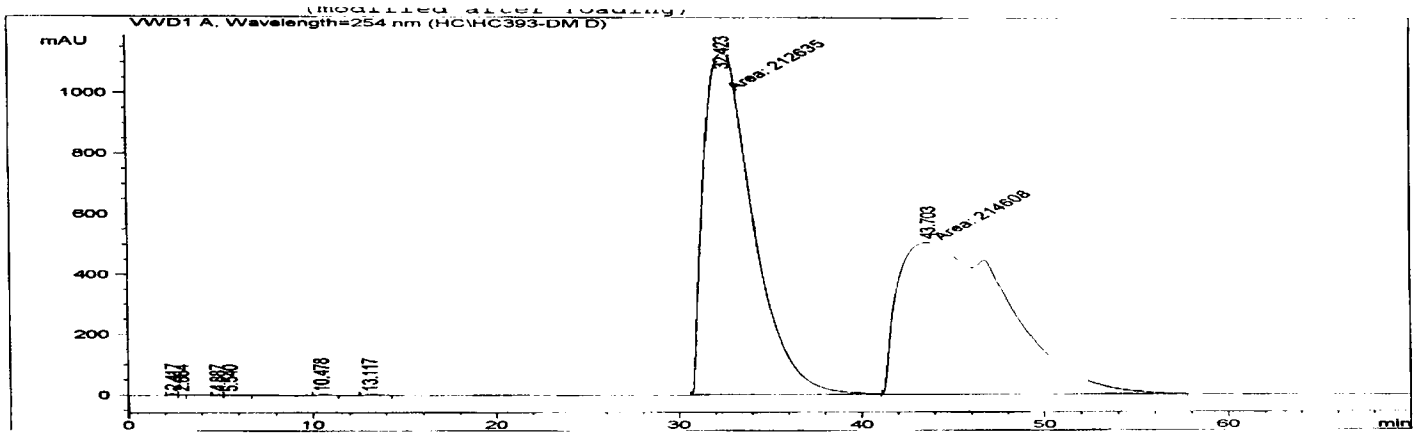


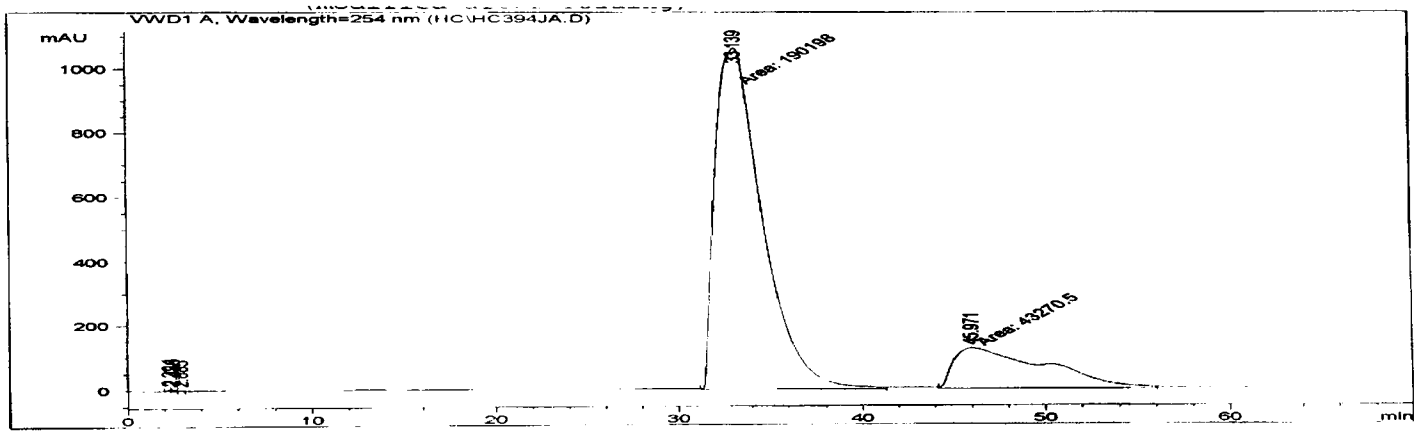
Column	Conditions[a]	t_m[b] (configuration)	t_M[c] (configuration)
Chiralcel OD	254; 5/95; 0.5	104.08 (*R*)	119.72 (*S*)

[a] wavelength (nm); eluent system (^{i}PrOH/hexane); flow rate (mL/min), [b] retention time (minor compound), [c] retention time (major compound).

4,4-Dimethyl-5-(4-methylbenzoyl)-dihydrofuran-2(3*H*)-one **336**



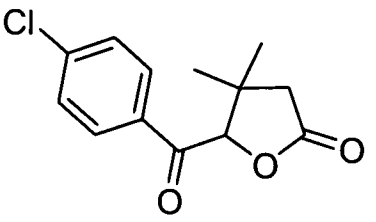


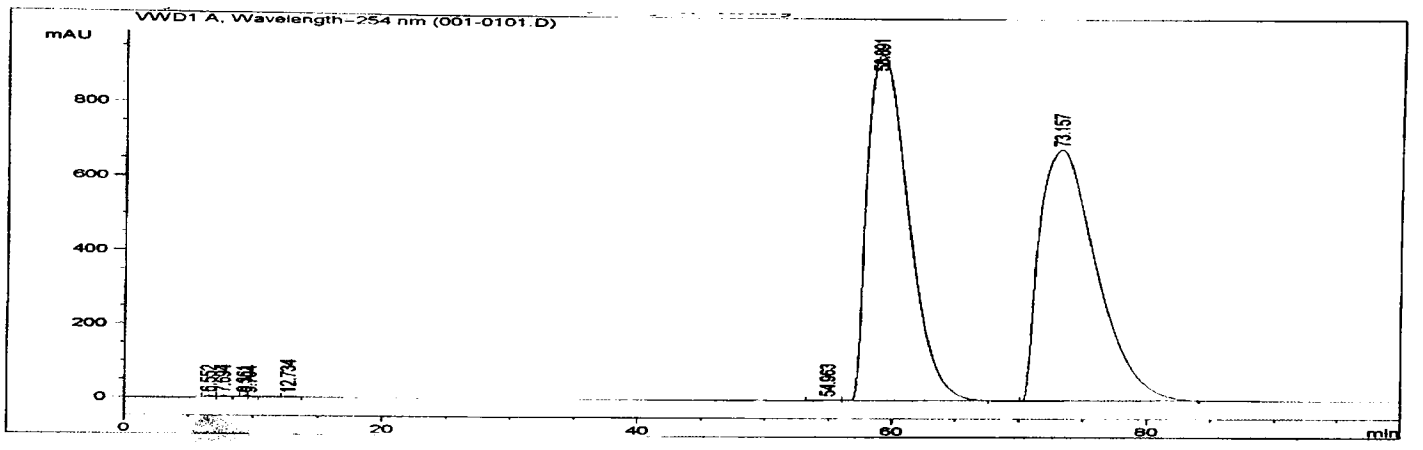


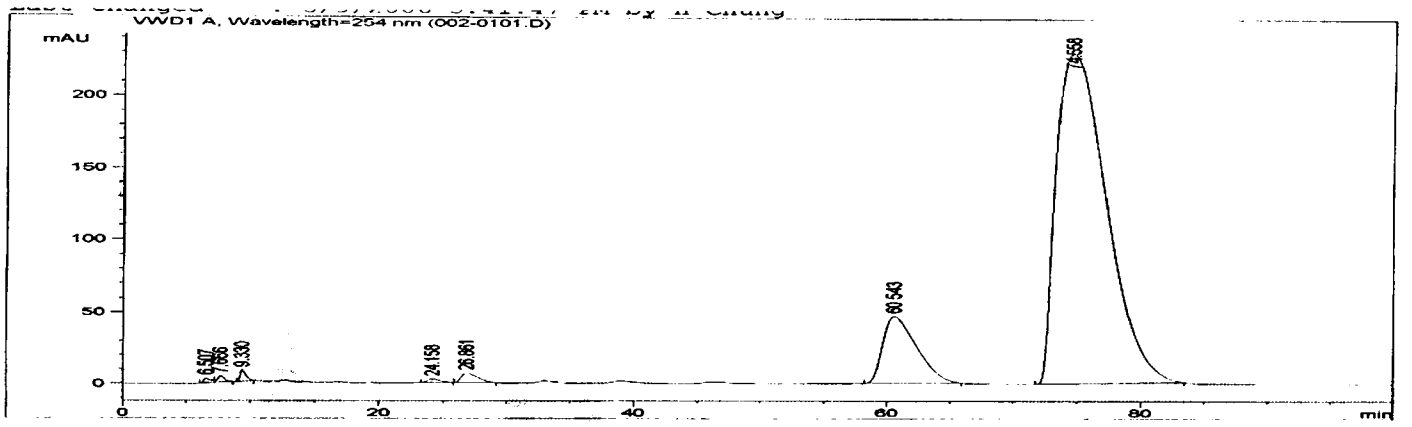
Column	Conditions[a]	t_m[b] (configuration)	t_M[c] (configuration)
Chiralcel OJ	254; 5/95; 0.5	45.97 (*R*)	33.14 (*S*)

[a] wavelength (nm); eluent system (^{i}PrOH/hexane); flow rate (mL/min), [b] retention time (minor compound), [c] retention time (major compound).

5-(4-Chlorobenzoyl)-4,4-dimethyl-dihydrofuran-2(3*H*)-one **337**



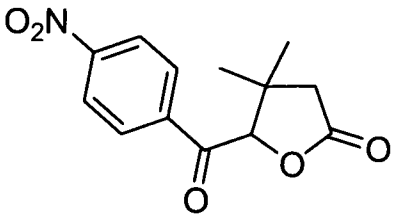


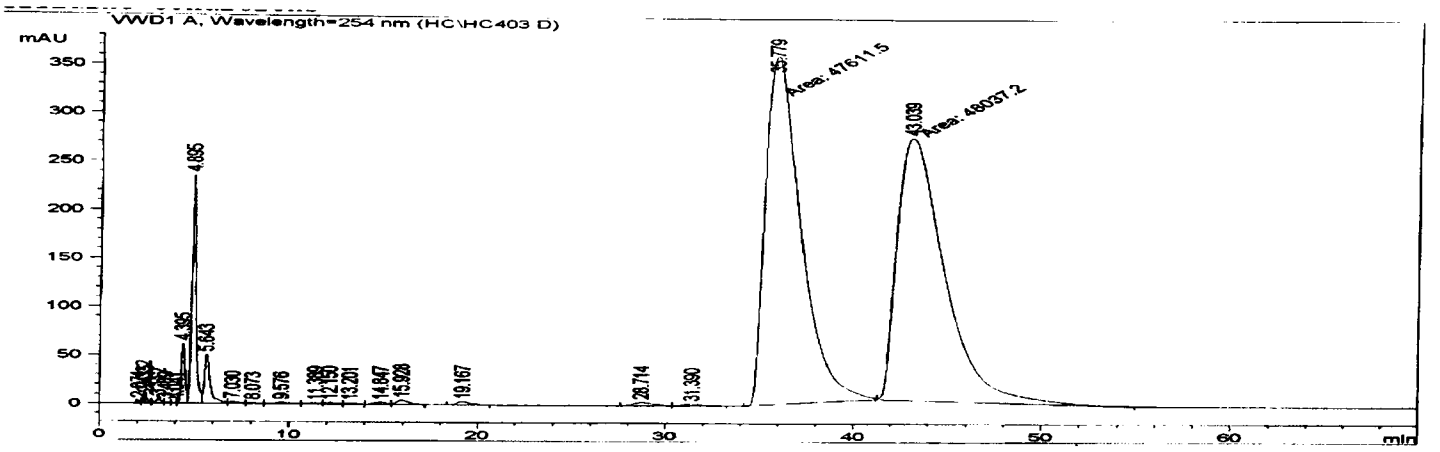


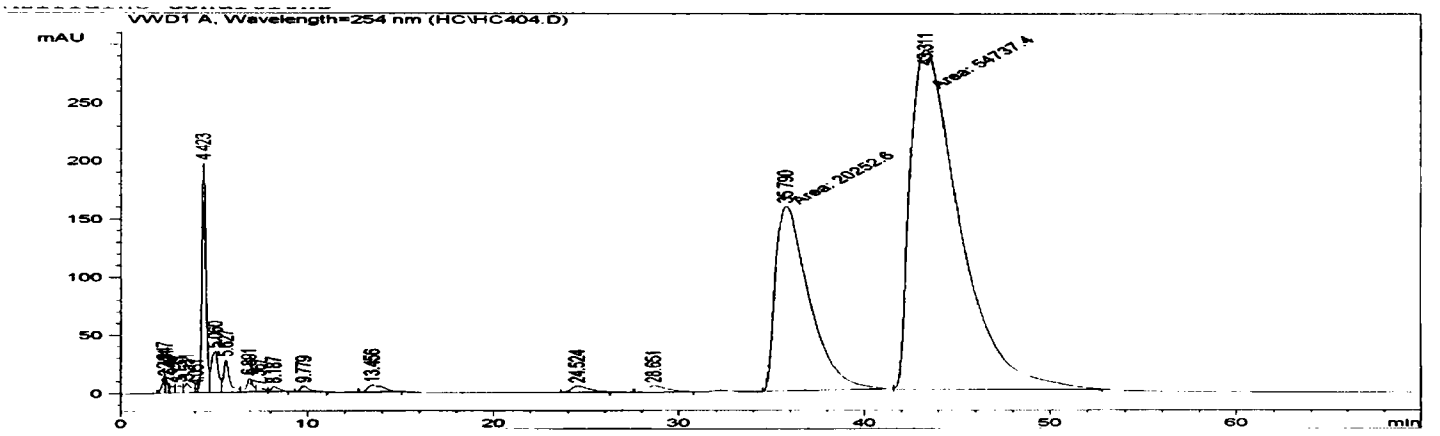
Column	Conditions[a]	t_m[b] (configuration)	t_M[c] (configuration)
Chiralcel OD-H	254; 5/95; 0.5	60.54 (*R*)	74.56 (*S*)

[a] wavelength (nm); eluent system (^{i}PrOH/hexane); flow rate (mL/min), [b] retention time (minor compound), [c] retention time (major compound).

4,4-Dimethyl-5-(4-nitrobenzoyl)-dihydrofuran-2(3*H*)-one **338**



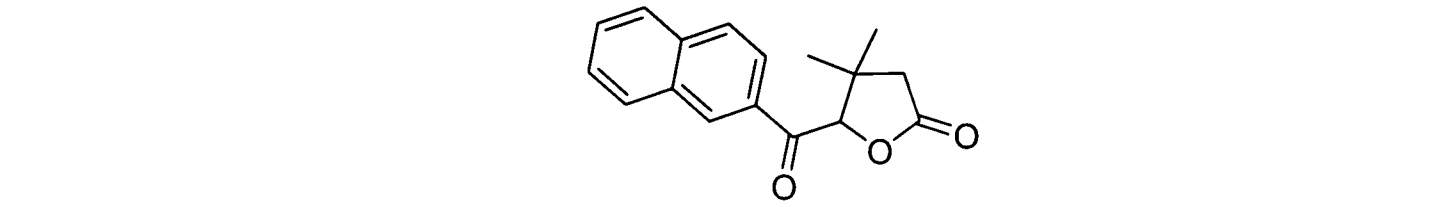


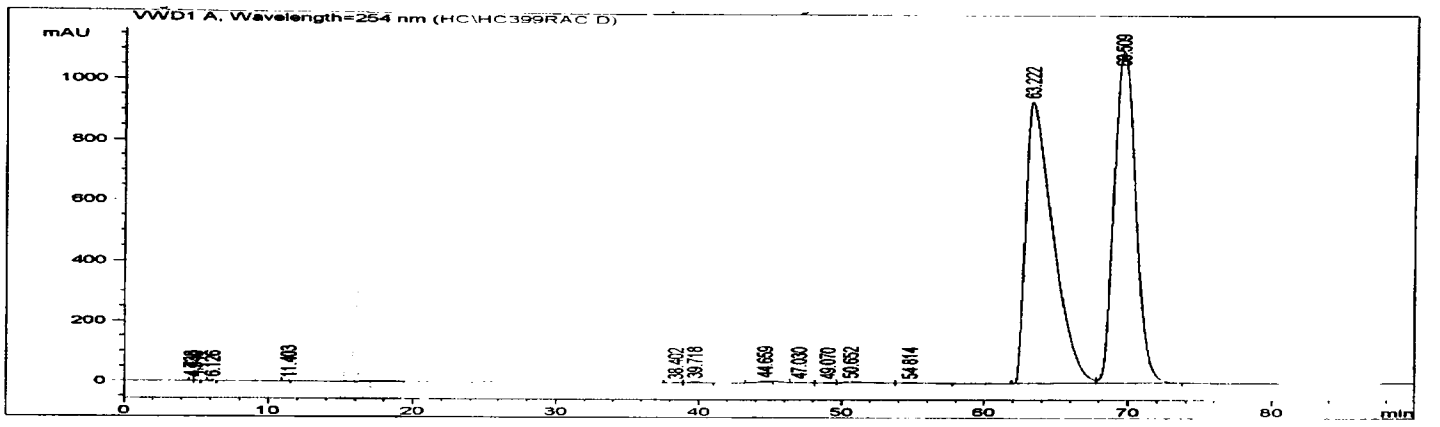


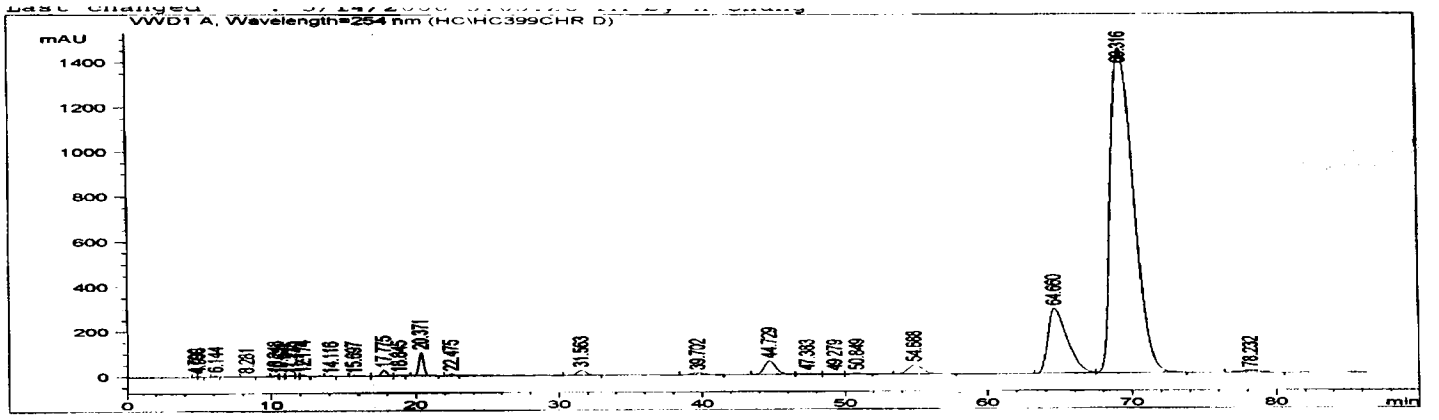
Column	Conditions[a]	t_m[b] (configuration)	t_M[c] (configuration)
Chiralcel OD-H	254; 10/90; 1.5	35.79 (*R*)	43.31 (*S*)

[a] wavelength (nm); eluent system (^{i}PrOH/hexane); flow rate (mL/min), [b] retention time (minor compound), [c] retention time (major compound).

5-(2-Naphthoyl)-4,4-dimethyl-dihydrofuran-2(3*H*)-one **339**





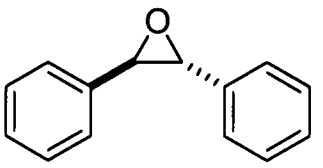


Column	Conditions[a]	t_m[b] (configuration)	t_M[c] (configuration)
Chiralcel AD-H	254; 10/90; 1.5	35.79 (*R*)	43.31 (*S*)

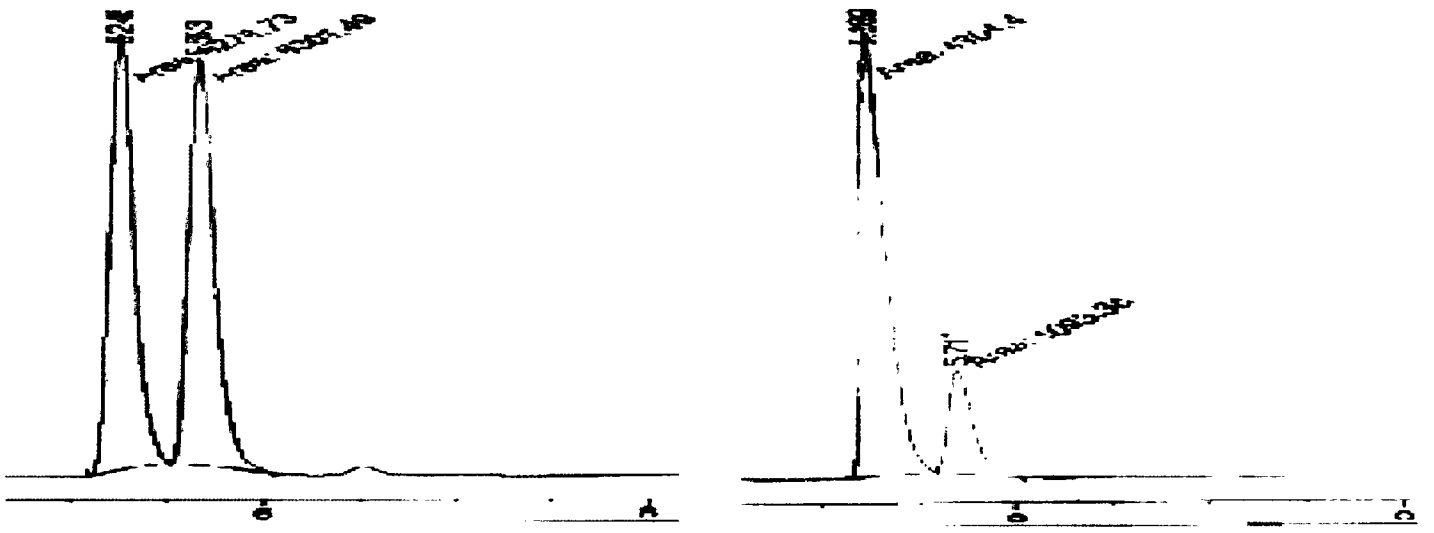
[a] wavelength (nm); eluent system (^{i}PrOH/hexane); flow rate (mL/min), [b] retention time (minor compound), [c] retention time (major compound).

3. HPLC chromatograms from Chapter 3.

HPLC conditions and results for measuring the enantiomeric excesses and the configurations; common conditions for the HPLC; (a) column=chiralcel AS-H, (b) wave length=220 nm.

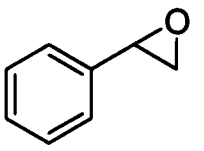


trans-2,3-Diphenyloxirane **374**

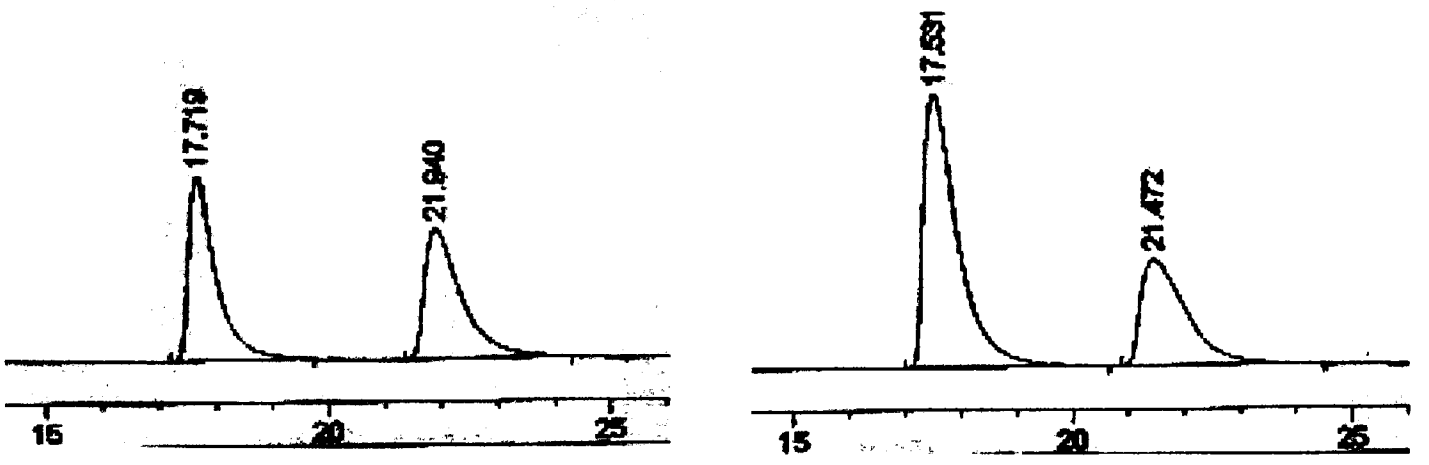


Conditions[a]	t[b] (configuration)	
3/97; 1.0	5.29 (*R*)	5.72 (*S*)

[a] eluent system (^{i}PrOH/hexane); flow rate (mL/min), [b] retention time (min)

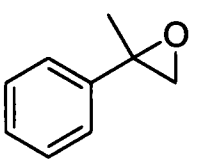


2-Phenyloxirane **375**

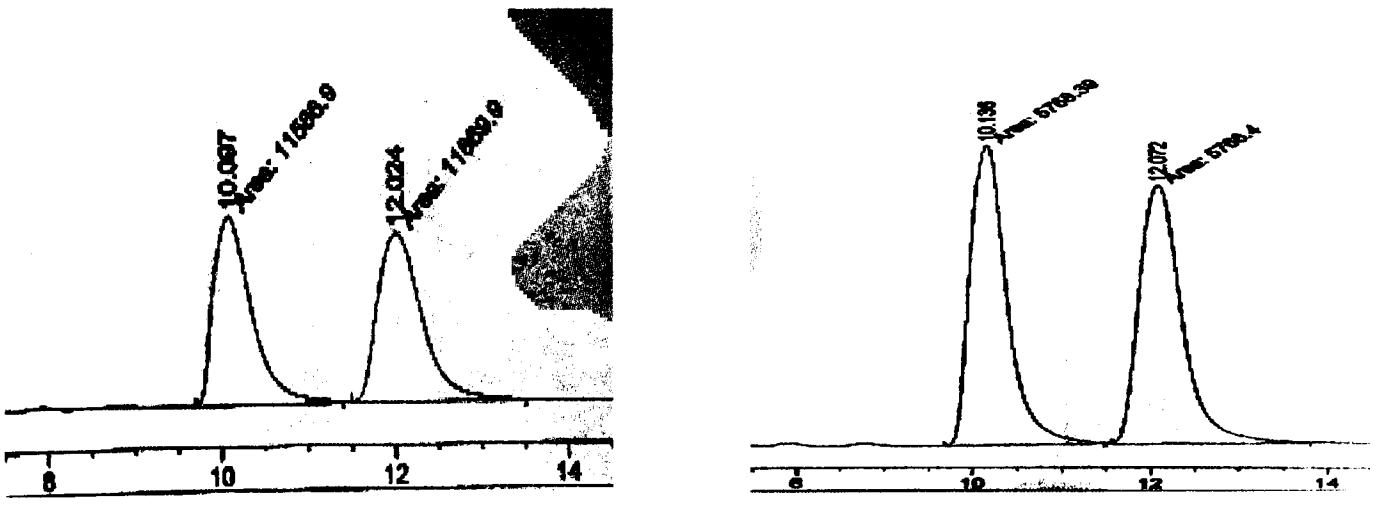


Conditions[a]	t[b] (configuration)	
0.1/99.9; 0.8	17.53 (*R*)	21.47 (*S*)

[a] eluent system (^{i}PrOH/hexane); flow rate (mL/min), [b] retention time (min)

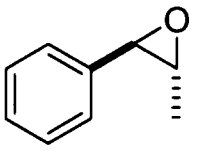


2-Methyl-2-phenyloxirane **376**

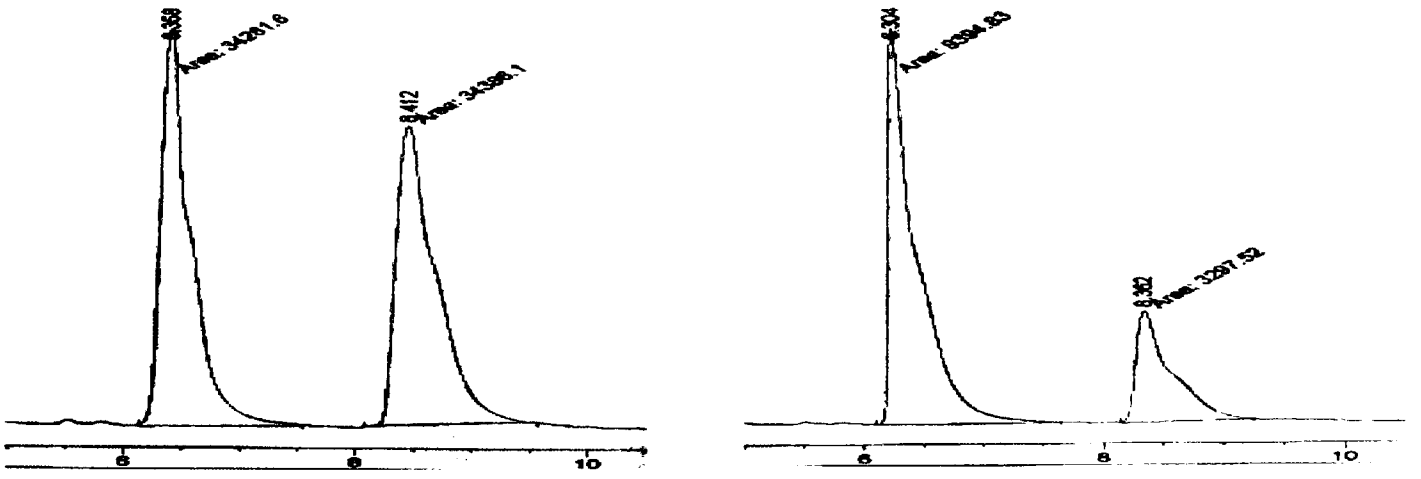


Conditions[a]	t[b] (configuration)	
7/93; 1.2	10.10 (*R*)	12.02 (*S*)

[a] eluent system (^{i}PrOH/hexane); flow rate (mL/min), [b] retention time (min)

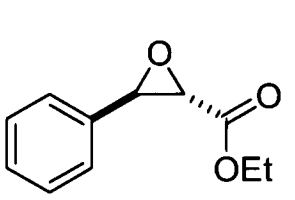


trans-2-Methyl-3-phenyloxirane **377**

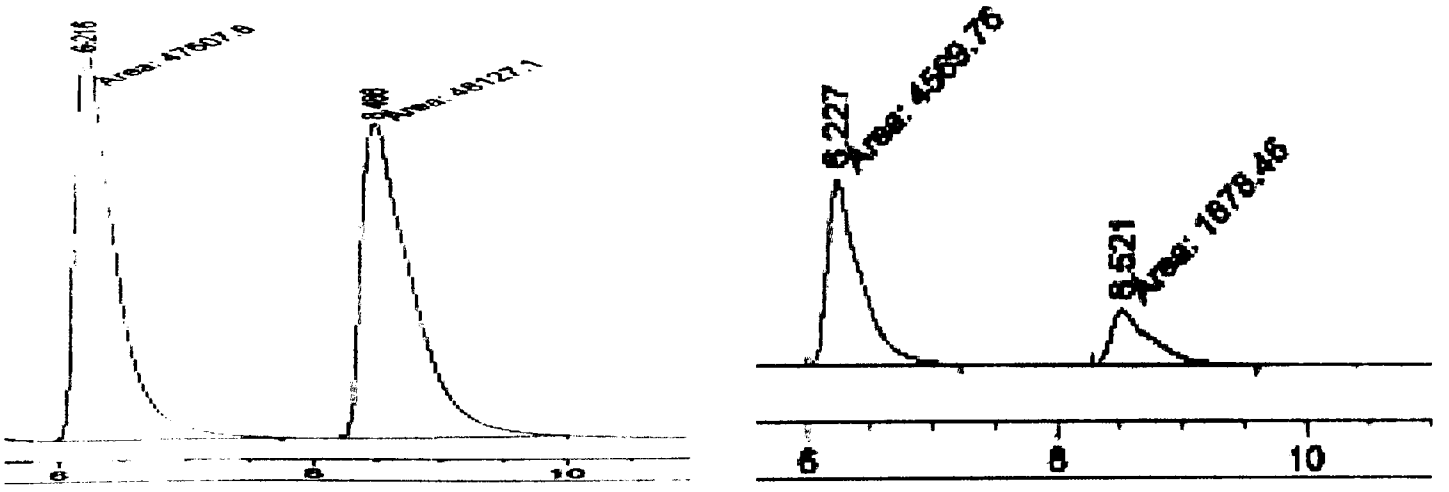


Conditions[a]	t[b] (configuration)	
1/99; 1.0	6.36 (*R,R*)	8.41 (*S,S*)

[a] eluent system ([i]PrOH/hexane); flow rate (mL/min), [b] retention time (min)

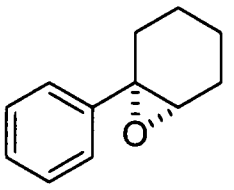


trans-Ethyl 3-phenyloxirane-2-carboxylate **379**

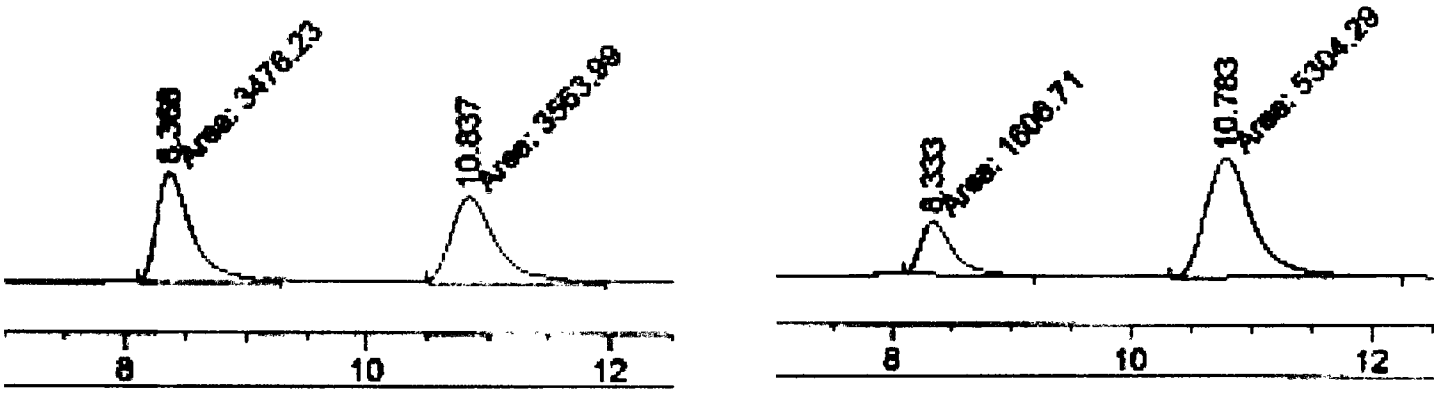


Conditions[a]	t[b] (configuration)	
10/90; 1.0	6.23 (*S,S*)	8.52 (*R,R*)

[a] eluent system ([i]PrOH/hexane); flow rate (mL/min), [b] retention time (min)



1-Phenyl-7-oxa-bicyclo[4.1.0]heptane **378**

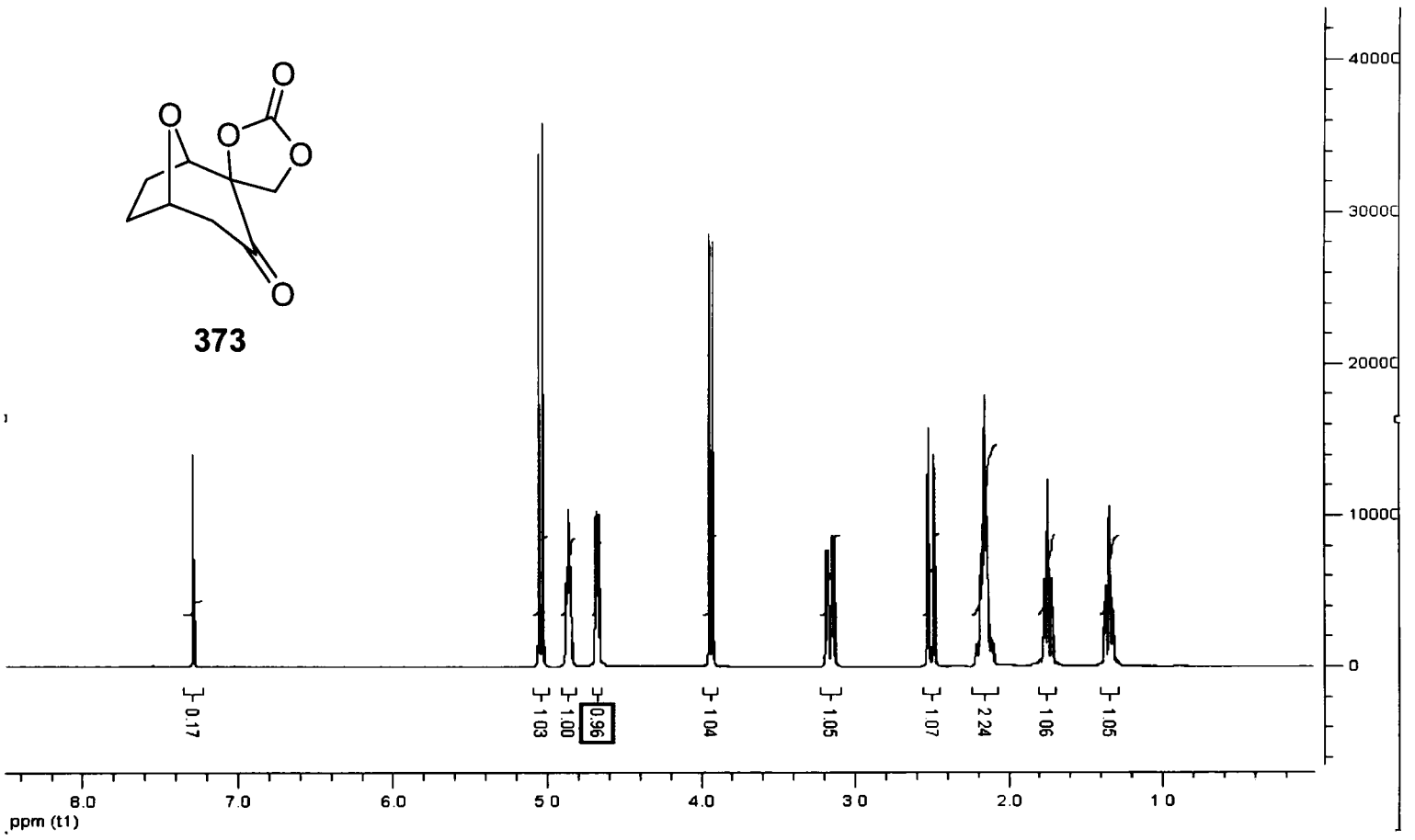


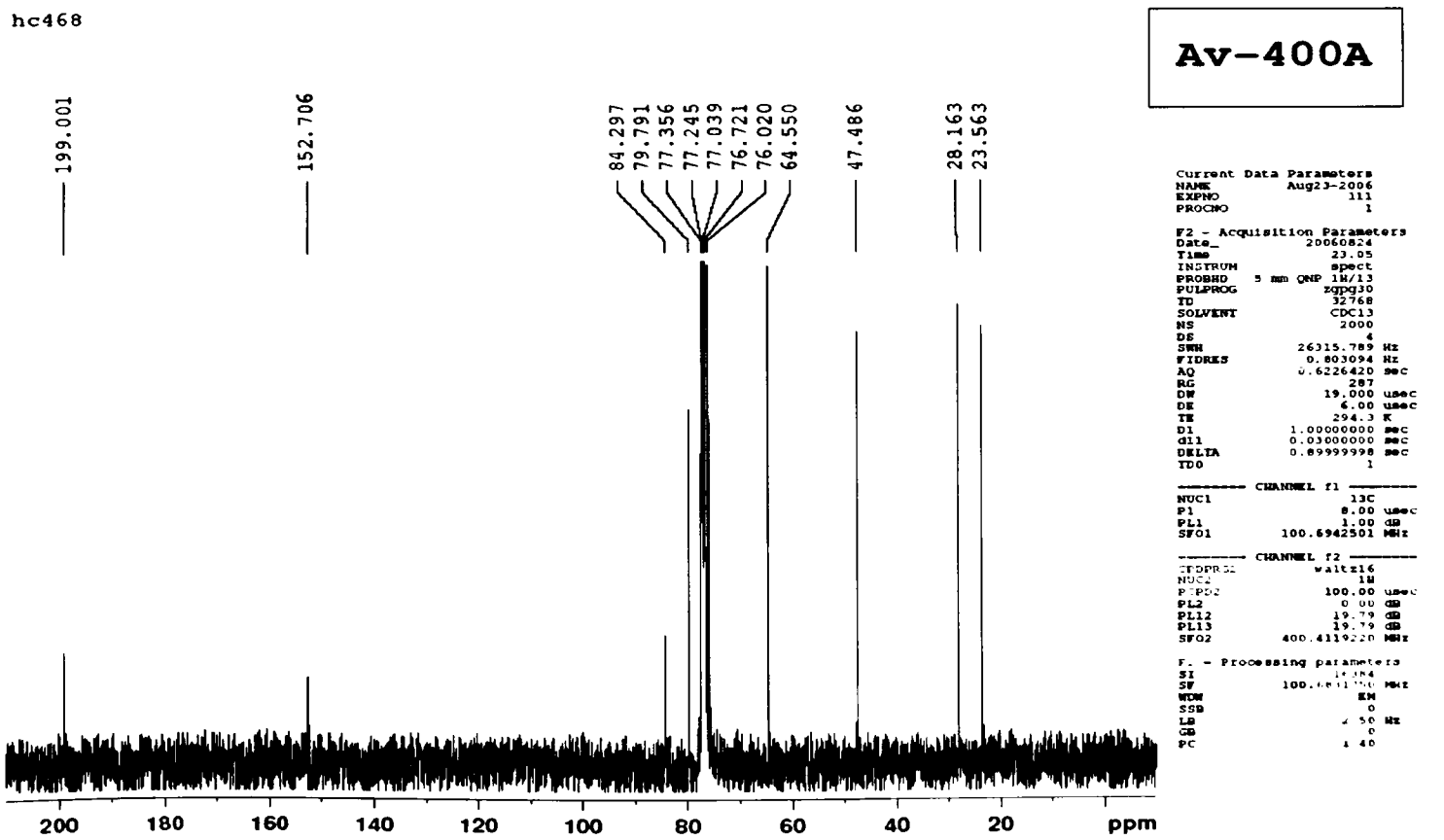
Conditions[a]	t[b] (configuration)	
7/93; 1.2	8.37 (2*S*, 3*R*)	10.84 (2*R*, 3*S*)

[a] eluent system (^{i}PrOH/hexane); flow rate (mL/min), [b] retention time (min)

4. NMR spectra for *oxa*-bicyclic catalyst from Chapter 3.

(1R*,2S*,5S*)-(±)-2',3-Dioxo-8-2',3-dioxo-8H-spiro [8-oxabicyclo[3.2.1]octane-2,4'-[1,3] dioxolane] **373**





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