[4+2] And [4+3] Cycloaddition Reactions And Lewis Acid Catalysed Cycloisomerisation of Malonyl Epoxides

By

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Abstract

Donor-acceptor cyclopropanes have been extensively used in synthetic chemistry in [3+2] and [3+3] cycloaddition reactions for the preparation of highly substituted carbo- and heterocyclic products. This methodology is further extended to donor-acceptor cyclobutane in [4+2] and [4+3] cycloaddition reactions for the synthesis of highly substituted carbo- and heterocyclic products. Initial work carried out makes use of cyclobutanes substituted with a metal-alkyne complex towards the synthesis of tetrahydropyrans in good yields and with acceptable diastereoselectivity. The initial aim of the project was to improve and expand the scope of the previous work carried out within the group on [4+2] cycloaddition reaction. For example, [4+2] and [4+3] cycloaddition reaction were carried out by using diester cyclobutanes having an alkene and phenyl π-donors. The [4+3] cycloaddition reaction of cyclobutane with nitrone did not work but [4+2] cycloaddition was successful when aldehydes were used as trapping reagents. Lower yields of the cycloadducts were observed due to formation of (±)-dimethyl-2-methyl-6-phenylcyclohex-3-ene-1,1-dicarboxylate and 2,6-diphenyl-4,8-dipropenylcyclooctane-1,1,5,5-tetracarboxylic acid tetramethyl ester. During the synthesis of a precursor cyclobutane a novel cycloisomerisation of malonyl epoxide under Lewis acidic conditions to 6,8-dioxabicyclo[3.2.1]octane derivatives was developed. This reaction has opened a new pathway for the synthesis of 6,8-dioxabicyclo[3.2.1]octanes in a diastereoselective fashion using malonyl epoxides as precursors. A wide range of malonyl epoxides were cycloisomerised under Lewis acidic conditions and the cycloisomerisation of *syn* and *anti* malonyl epoxides were stereospecific. The diastereoselectivity of the process was proven by nOe and X-ray analysis. The cycloisomerisation of malonyl diepoxide has also been investigated towards the formation of 5,5-dimethoxy-6,6,8,8-tetraoxa4,4-spirobi[bicyclo[3.2.1]octane].

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At the end of my studies I was having a very difficult time when my daughter fell critically ill. At this very difficult time I would really appreciate the help and support provided by the nursing and paediatric staff of Queen's Hospital Burton Upon Trent. Lastly I would like to dedicate this thesis to my daughter Um-E-Raumaan who died at the end of my Ph. D. studies and left her memories with us forever.

Table of Contents

Abbreviations

A	=	acceptor
Ac	=	acetyl
acac	=	acetylacetonate
B.A.	=	Brønsted acid
BDA	=	butane-2,3-diacetal
Bn	=	benzyl group
br	=	broad
^{t}Bu	=	*tert*-butyl
^{n}BuLi or BuLi	=	butyllithium
°C	=	degrees Celcius
cat	=	catalytic
cm^{-1}	=	centimetre
CM	=	complex mixture
CSA	=	camphorsulphonic acid
δ	=	chemical shift
D	=	donor
d	=	doublet
dba	=	dibenzylideneacetone
1,2-DCE	=	1,2-dichloroethane
DCM	=	dichloromethane
dd	=	doublet of doublet
d.e.	=	diastereoisomeric excess
DMF	=	N,N-dimethylformamide
DMS	=	dimethylsulfide
DIBALH	=	diisobutylaluminium hydride
d.r.	=	diastereoisomeric ratio
e.e.	=	enantiomeric excess
EDG	=	electron donating group
EI	=	electron ionisation
ESI	=	electrospray ionisation
eq	=	equivalent(s)

Et	=	ethyl
EtOH	=	ethanol
EWG	=	electron withdrawing group
g	=	gram
hrs	=	hours
Hz	=	Hertz
IR	=	infra-red
L.A.	=	Lewis acid
m-	=	meta
m	=	multiplet or medium
MAD	=	Methyl aluminium bis(2,6-di-*tert*-butyl-4-methylphenoxide)
Me	=	methyl
MHz	=	megahertz
min	=	minute
mL	=	millilitre
mmol	=	millimole
mp	=	melting point
4 Å MS	=	molecular sieves
ms	=	mass spectrometry
MVK	=	methyl vinyl ketone
m/z	=	mass to charge ratio
NMR	=	nuclear magnetic resonance
nOe	=	nuclear overhauser effect
Nu	=	nucleophile
o-	=	ortho
OTf	=	trifluoromethanesulfonate
p-	=	para
Ph	=	phenyl
ppm	=	parts per million
^{i}Pr	=	*iso*-propyl
RT	=	room temperature

s	=	singlet or strong
SM	=	starting material
t	=	triplet or time
T	=	temperature
TBDMS or TBS	=	*tert*-butyldimethylsilyl
TBDPS	=	*tert*-butyldiphenylsilyl
TFA	=	trifluoroacetic acid
Tf	=	trifluoromethanesulfonyl
THF	=	tetrahydrofuran
TLC	=	thin layer chromatography
TMS	=	trimethylsilyl
Tol	=	4-methylphenyl
µL	=	microlitre
w	=	weak

1. Introduction

Cyclopropanes are versatile building blocks in modern synthetic chemistry. In cyclopropane three -CH_2- groups are accommodated in a cyclic arrangement with all C-C-C bond angles equal to 60°.[1] These bond angles are less than the ideal 109.5° bond angle for a sp^3 hybridized orbital, resulting in angular strain. The cyclopropane being coplanar, all C-H bonds are eclipsed, resulting in torsional strain (Figure 1). The bonds in cyclopropane are often referred as "bent" because the three sp^3 hybridized orbitals of the -CH_2- groups are pointed 22° outward from an imaginary line connecting the nuclei, resulting in 20 % less effective overlap than the C-C bond of ethane (Figure 2).

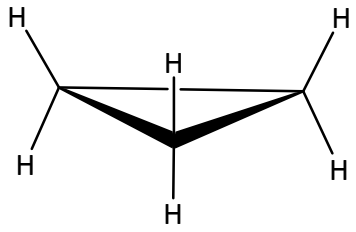


Figure 1

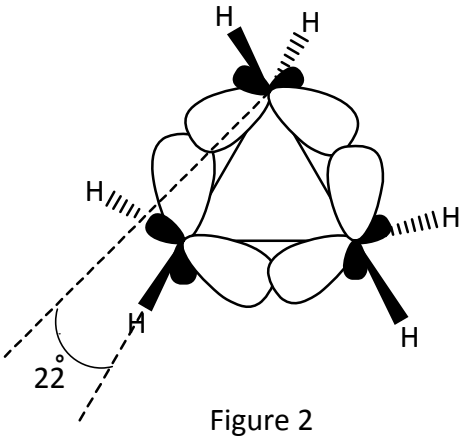
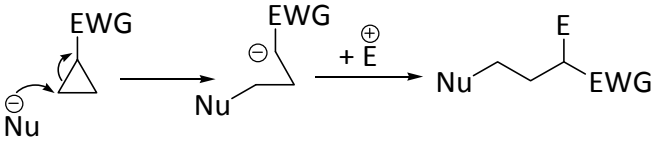


Figure 2

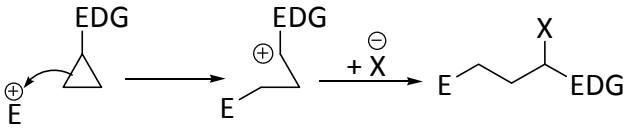
Under the influence of chemical reagents like electrophiles, nucleophiles, radicals and external physical force e.g. heat, the cyclopropane derivatives undergo ring opening reactions.[2] The chemistry of the cyclopropane C-C single bond resembles that of a carbon-carbon double bond. In the presence of electron accepting groups on the ring, the strained cyclopropane react as homo Michael acceptors in nucleophilic ring opening (Scheme 1).



EWG = Electron withdrawing groups : CO_2R, COR, CN, etc.

Scheme 1

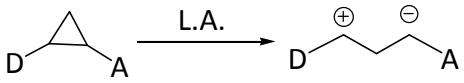
The donor substituted cyclopropanes can be cleaved by electrophiles to afford cation equivalents for further transformations (Scheme 2).



EDG = Electron donating groups : OR, $OSiR_3$, SR etc

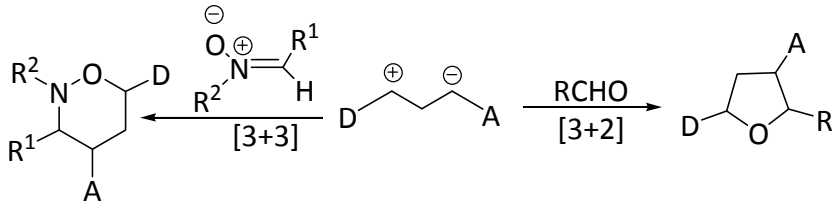
Scheme 2

Cyclopropanes substituted by vicinal donor-acceptor groups are particularly useful synthetic building blocks. The electron donating and withdrawing effects of the substituents further increase the reactivity of cyclopropanes. Under Lewis acidic conditions, the doubly activated cyclopropanes give 1,3-zwitterionic intermediates also known as a 1,3-dipoles (Scheme 3).



Scheme 3

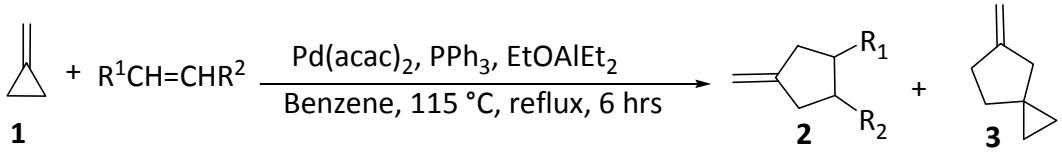
1,3-Zwitterionic intermediates react with various trapping reagents like alkenes,[3] nitrones,[4] aldehydes,[5] imines[6] and diazenes[7] by [3+2] and [3+3] cycloaddition reactions giving a diverse range of five and six membered carbocyclic and heterocyclic compounds (Scheme 4).



Scheme 4

1.1 [3+2] and [3+3] Cycloaddition Reactions

In 1977 Schuchardt successfully demonstrated the use of methylene cyclopropane **1** in cycloaddition reactions with alkenes.[3] Pd(0) catalysed [3+2] cycloaddition of methylene cyclopropane with alkenes resulted in the formation of five membered cycloadducts (Scheme 5, table 1).

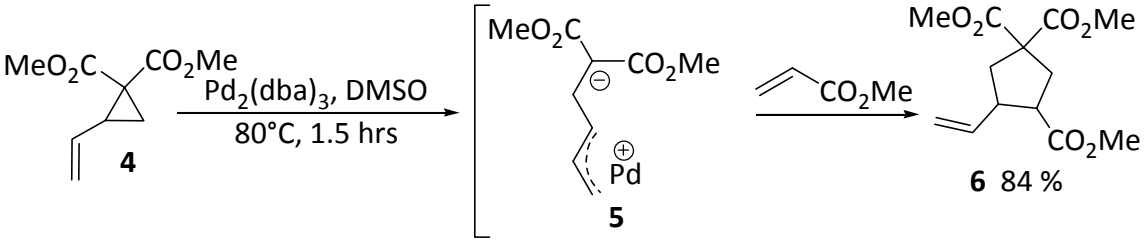


Scheme 5

Entry	R^1	R^2	Temp.°C	Conditions	2 Yield %	3 Yield %	Remarks
1	H	H	115	6 hrs	23	72	
2	H	CO_2Me	100	3 hrs	51	3	
3	CO_2Me	CO_2Me *cis*	100	18 hrs	77	23	60 % *trans*/ 40 % *cis*
4	CO_2Me	CO_2Me *trans*	100	18 hrs	88	4	88 % *trans*/ 12 % *cis*

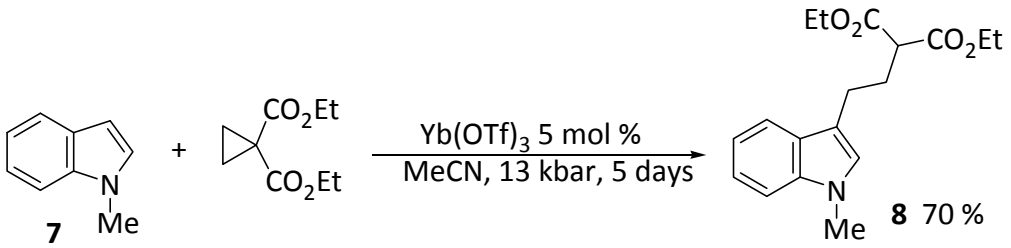
Table 1

Later in 1987 Tsuji performed cycloaddition reactions by using donor acceptor vinylcyclopropanes **4** substituted with two ester groups.[8] Upon treatment with Pd(0), the cyclopropane ring opens to form a zwitterionic π-allylpalladium complex **5**. There are two major factors affecting the reactivity of vinyl cyclopropanes toward an ionic ring opening; one is the ability of an electron withdrawing groups to stabilize an adjacent developing negative charge, and the other is the ability of the electron donating group to engage in proximal stabilization of a developing positive charge. The malonyl moiety stabilises the carbanion and π-allylpalladium complex stabilises the carbocation. This dipolar intermediate is then trapped by α,β-unsaturated esters or ketones to form the corresponding vinylcyclopentane in good yields (Scheme 6).[9]



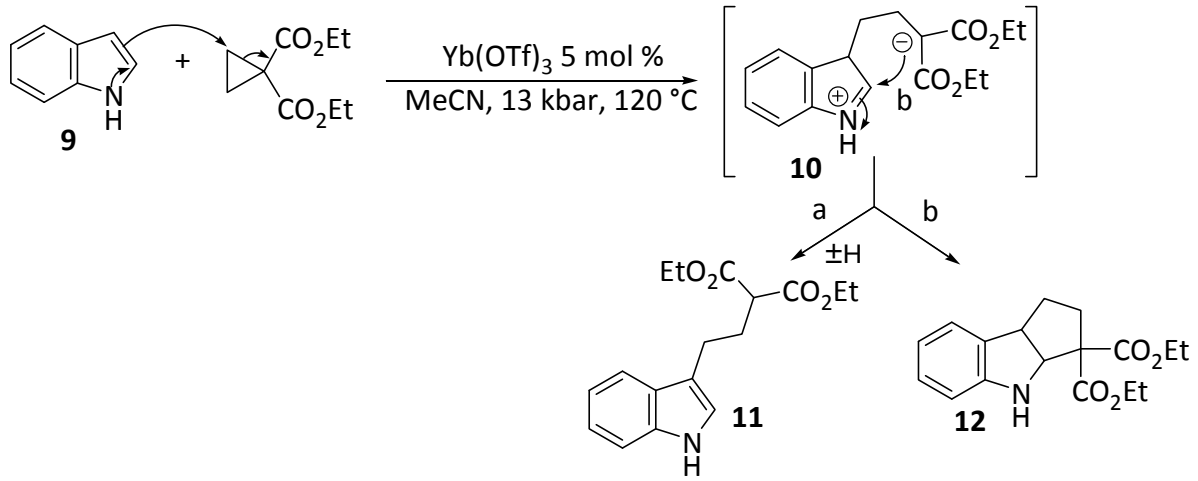
Scheme 6

Kerr discovered while investigating the homo-Michael addition of indoles to cyclopropanes that activated cyclopropanes can undergo [3+2] cyclisation.[10] He reported that alkylation of indoles **7** with cyclopropane-1,1-dicarboxylic acid esters in the presence of $Yb(OTf)_3$ proceed smoothly to give good yields of adduct **8** (Scheme 7).



Scheme 7

However, in the case where there was no substituent on the indole nitrogen, the yield was dramatically lowered and formation of by-product **12** was observed. Full details of the reaction were not reported. The electrophilic iminium ion **10** formed after homo-Michael addition, followed by lose of a proton to restore aromaticity and protonated at malonic enolate to afford adduct **11** whereas, the nucleophilic attack by malonic enolate on the electrophilic iminium ion resulted in cyclisation affording tricyclic pyrolidine derivative **12** (Scheme 8).



Scheme 8

Later, Kerr successfully reported homo [3+2] dipolar cycloaddition using a cyclopropane diester moiety with nitrones.[4] He discovered that 1,1-cyclopropane diester behaved like α,β-unsaturated carbonyl compounds in their ability to react with nucleophiles. The strained bonds in the cyclopropane ring show significant π-character. These bonds can be polarized and further weakened by coordination of a Lewis acid to one or both the ester moieties. Such polarisation can be enhanced by the presence of a carbocation stabilization group e.g. vinyl, phenyl (R^1, R^2) etc. on cyclopropane ring by stabilising developing positive charge (Figure 3).

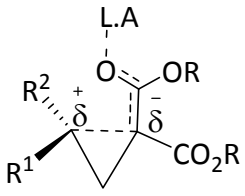
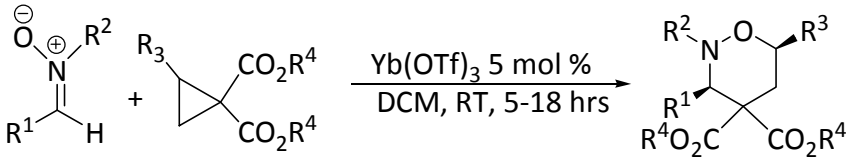


Figure 3

Using this polarisation of the cyclopropane under Lewis acid conditions, Kerr performed the [3+2] cycloaddition between nitrones **13a-e** and substituted cyclopropanes **14a-e** affording

tetrahydro-1,2-oxazines **15a-e** in a *cis*-configuration (Scheme 9, table2). Different nitrones were used for the cycloaddition but better results were obtained with a nitrone having a *p*-tolyl group on the nitrogen atom. The presence of either a vinyl, phenyl or styryl substituent on the cyclopropane unit greatly reduced the reaction time and resulted in better yields. The tetrahydro-1,2-oxiazines were prepared with *cis*-stereochemistry only.



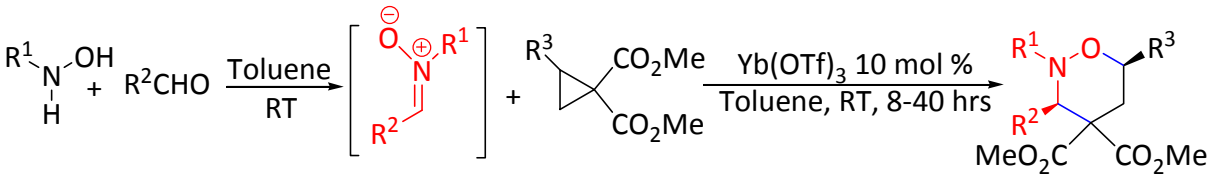
13a-e **14a-e** **15a-e**

Scheme 9

Entry	R^1	R^2	R^3	R^4	Time	Product	Yield %
1	Ph	*p*-tolyl	H	Et	18	**15a**	77
2	Ph	*p*-tolyl	Ph	Me	18	**15b**	94
3	Ph	*p*-tolyl	Styryl	Me	5	**15c**	95
4	Ph	*p*-tolyl	vinyl	Et	42	**15d**	73
5	Ph	Me	Ph	Me	42	**15e**	84

Table 2

Many nitrones are readily available and are stable, some are difficult to prepare and are unstable to isolate or to store for long periods of time. Kerr and Young developed a one-pot protocol, preparing the nitrone *in situ* from the reaction of a hydroxylamine and aldehyde prior to the addition of the cyclopropane, avoiding the isolation of unstable nitrones (Scheme 10).[11]



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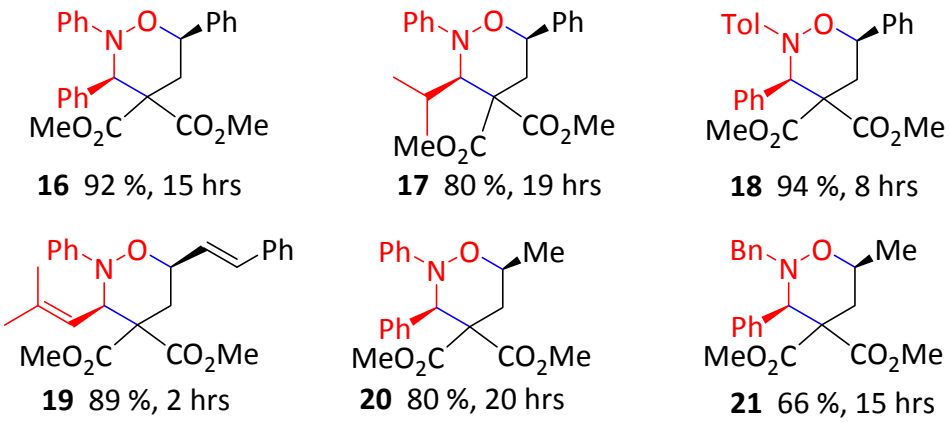
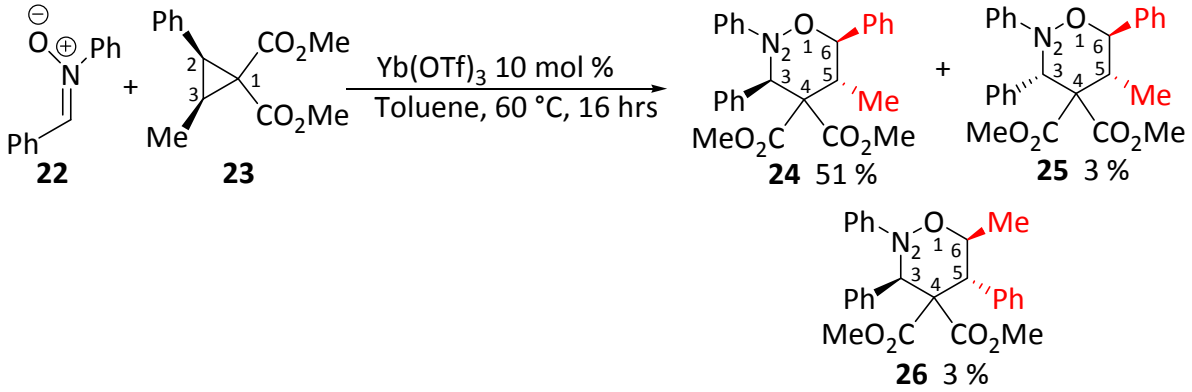
For example:



Scheme 10

The cyclopropanes having a π-donor group such as phenyl or styryl group allowed the synthesis of oxazines in high yield; whereas lower yield was obtained in the case of methyl substituted diester cyclopropanes.

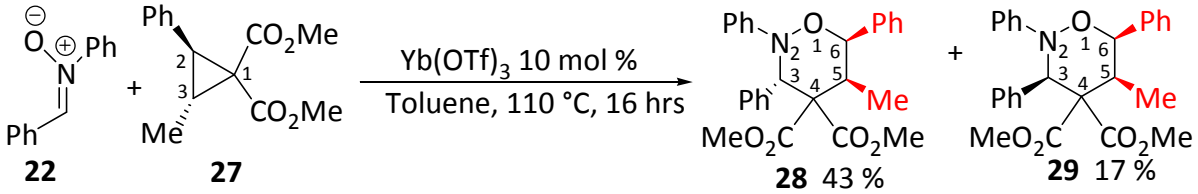
Lastly, Kerr has tried to demonstrate the mechanism of [3+3] dipolar cycloaddition reactions also known as [3+2] dipolar cycloaddition because one of the carbons in the cyclopropane was not electronically involved in the reaction.[12] He has found that reacting nitrone **22** with 2,3-*cis*-disubstituted cyclopropane **23** lead to 5,6-*trans*-oxazines **24**. This observed stereochemical inversion provides evidence for a stepwise mechanism in the preparation of tetrahydro-1,2-oxazines (Scheme 11).



Scheme 11

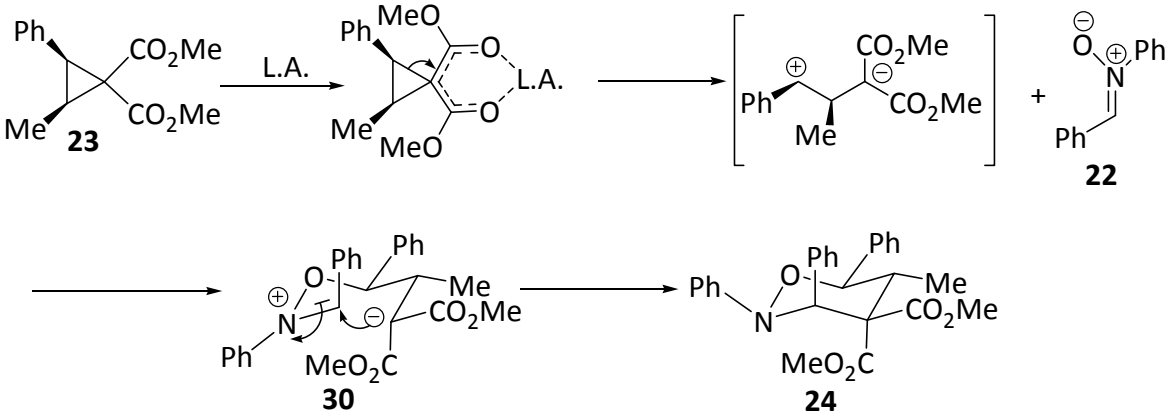
The groups at the 5 and 6 position of tetrahydro-1,2-oxazines **24**, **25** and **26** had a *trans*-relationship, indicating that ring opening of cyclopropane **23** had occurred with inversion of configuration. As expected the 3,6-*cis*-diastereoisomer **24** was the major isomer. 2,3-*Trans*-disubstituted cyclopropane **27** reacted quite differently leading to the 5,6-*cis*-oxazines **28** and **29**, indicating again that the reaction had proceeded with inversion of configuration during the cyclopropane ring opening event. The reaction was performed by heating under

reflux and the yields were lower when compared to the corresponding *cis*-cyclopropane **23**. However, the 3,6-*trans*-diastereoisomer **28** was isolated as a major isomer (Scheme 12) indicating that the extra substituent, which is on a carbon 3 not electronically involved in the reaction, influenced the stereochemical relationship.



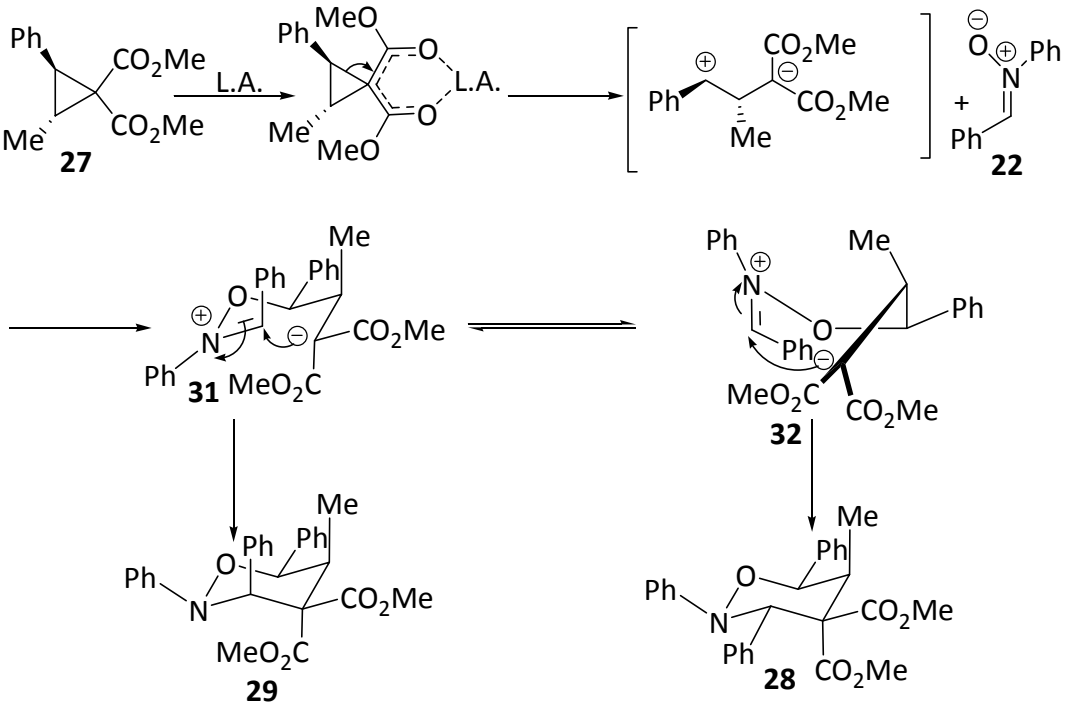
Scheme 12

In case of cyclopropane **23**, nitrone attack on cyclopropane carbon proceeds with inversion of stereochemistry and results in intermediate **30**, in which the phenyl and methyl groups originating from the cyclopropane can both be equatorial in chair like conformation. The intermediate **30** then proceeds to the product with the expected and observed stereochemical outcome (Scheme 13).



Scheme 13

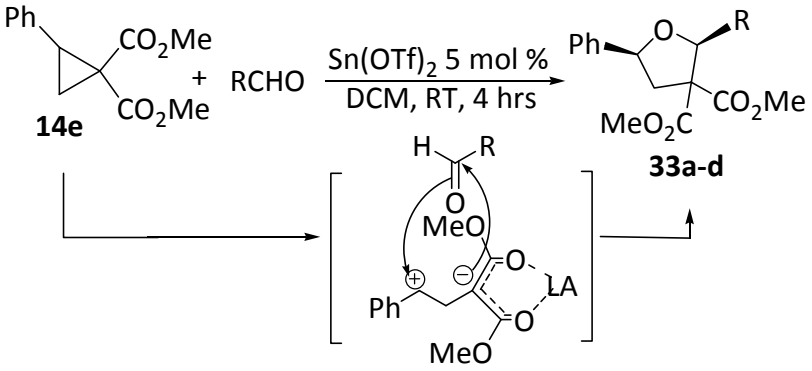
Cyclopropane **27** on the hand would result in intermediate **31** upon reaction with nitrone, putting methyl group in an axial orientation. This should result in an unfavourable 1,3-diaxial interaction with the phenyl substituent from the nitrone. The formation of higher energy intermediate would imply slower rate of reaction. Relief of the unfavourable 1,3-diaxial interaction would be achieved upon changing to a boat conformation **32**. Ring closure from **32** would produce the unusual 3,6-*trans*-tetrahydro-1,2-oxazines **28** as a major diastereoisomer (Scheme 14).



Scheme 14

These observations strengthen the postulation of a stepwise mechanism as being the mode of reaction for the cycloaddition.

Substituted furans can also be synthesised using [3+2] dipolar cycloaddition. Johnson *et al.* reported the synthesis of 2,5-disubstituted tetrahydrofurans from donor-acceptor cyclopropanes and aldehydes using a catalytic amount of tin triflate (Scheme 15, table 3).[5a-b]

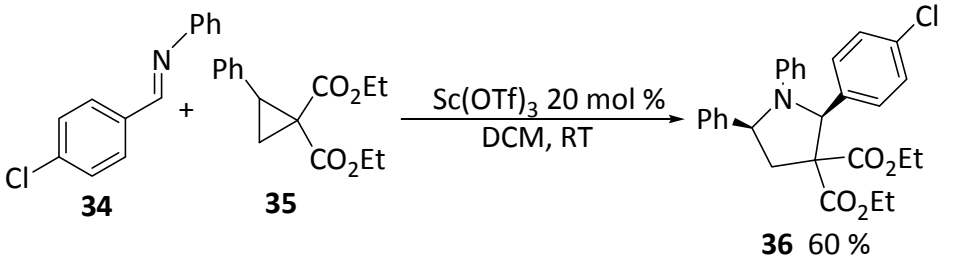


Scheme 15

Entry	R	Time	Product	Yield %
1	Ph	3 hrs	**33a**	100
2	4-ClC_6H_4-	5 hrs	**33b**	96
3	4-MeO C_6H_4-	3 hrs	**33c**	98
4	2-Furyl	3 hrs	**33d**	82

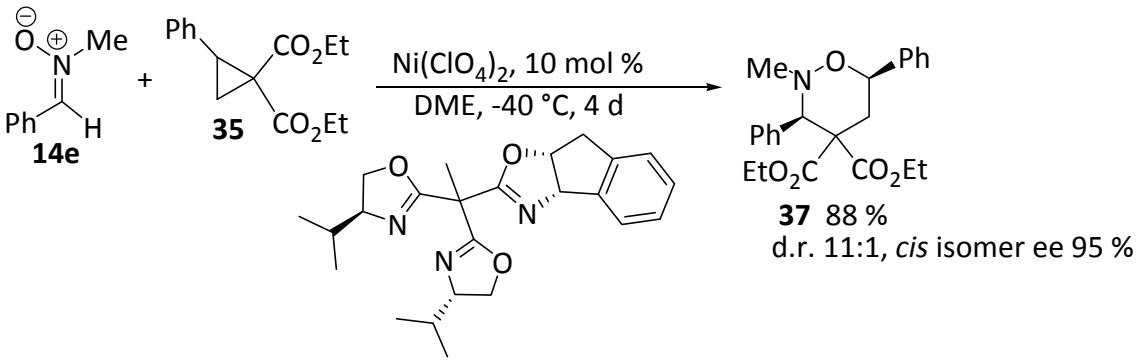
Table 3

Tang *et al.* have described the synthesis of poly substituted pyrrolidine. Dipolar [3+2] cycloaddition of cyclopropane **35** with imine **34** in the presence of a catalytic amount of scandium triflate afforded the pyrrolidine **36** in a good yield (Scheme 16).[6]



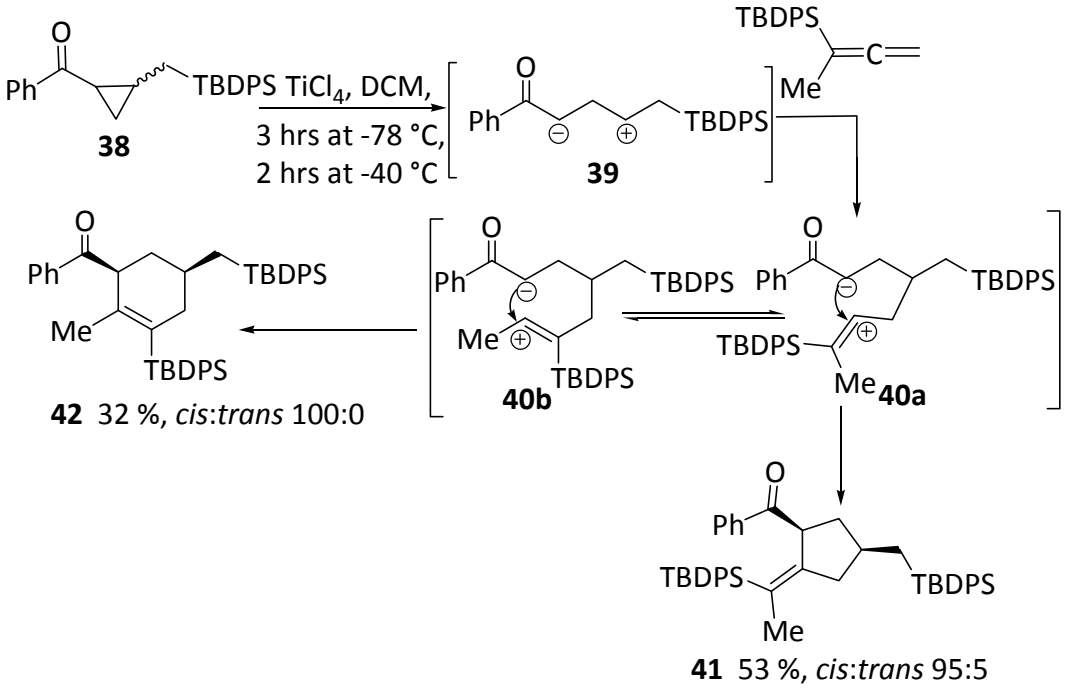
Scheme 16

Sibi and Tang *et al.* have both independently described highly enantioselective and diastereoselective cycloaddition of cyclopropanes with nitrone in the presence of chiral catalyst. In this way the tetrahydro-1,2-oxazine **37** was synthesised in 88 % yield with excellent diastereo and enantioselectivity (Scheme 17).[13a-b]



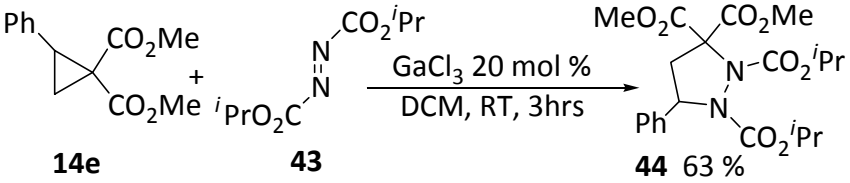
Scheme 17

Similarly, Yadav *et al*. have described dipolar cycloaddition of donor-acceptor substituted cyclopropanes upon allenylsilanes leading to formation of [3+2] and [3+3] cycloadducts. [14a-b] *Tert*-butyldiphenylsilylmethyl substituted cyclopropyl ketone **38** was treated with Lewis acid to reveal 1,3-dipolar synthon **39**. This intermediate was trapped with allenylsilane affording [3+2] and [3+3] cycloadducts with high stereo and regioselectively (Scheme 18). Once the cyclopropane opened, the addition of allenylsilane led to formation of a vinyl cation **40a** which may rearrange to vinyl cation **40b** entailing 1,2-migration of allenylsilicon group. The intermolecular capture of cation **40a** and **40b** by the enolate will culminate in formation of five and six membered carbocycles **41** and **42** respectively.



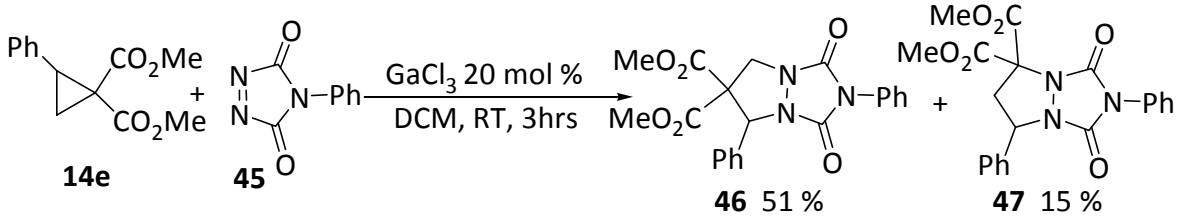
Scheme 18

Recently, Meijere *et al.* have reported the cycloaddition of diazene derivatives onto diester cyclopropanes giving rise to pyrazolidine derivative in a regioselective fashion.[7] When cyclopropane **14e** was reacted with the *trans*-diazene **43** in the presence of a catalytic amount of gallium chloride, only one regioisomer of the pyrazolidine **44** was obtained in 63 % yied (Scheme 19).



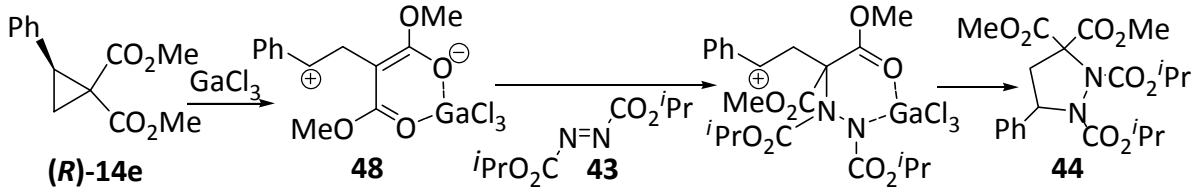
Scheme 19

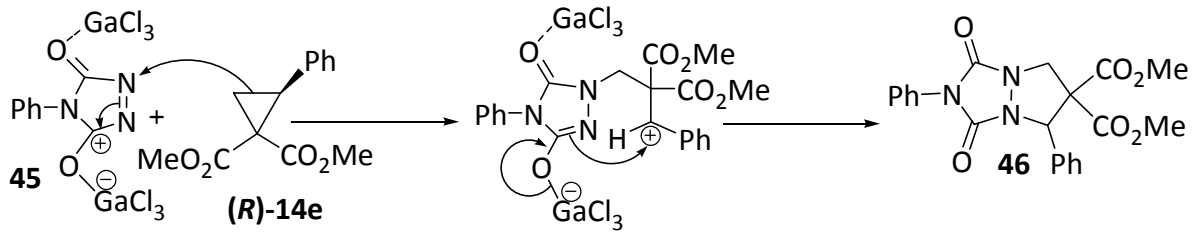
When *cis*-diazene **45** was reacted with cyclopropane **14e** under the same reaction conditions resulting in two regioisomers **46** and **47**. However, the unexpected regioisomer **46** was obtained as a major product (Scheme 20).



Scheme 20

Further experimentation was carried out to find out the reason for the formation of unexpected regioisomer **46** with *cis*-diazene **45**. The reaction of the enantiomerically pure cyclopropane **(*R*)-14e** with *trans*-diazene **43** resulted in racemic product **44** (Scheme 19). Similarly, the reaction of enantiomerically pure cyclopropane **(*R*)-14e** with *cis*-diazene **45** (Scheme 20) also afforded racemic products **46** and **47**. These reactions must proceed via achiral dipolar intermediates. The gallium trichloride, being a powerful Lewis acid, may affect formation of achiral dipolar ring opened intermediate **48** which can add to electron deficient N=N bond. The addition of gallium trichloride to a solution of enantiomerically pure cyclopropane **(*R*)-14e** in dichloromethane in the absence of any diazene did not lead to any racemisation of the residual **(*R*)-14e**, while the net amount of **(*R*)-14e** was decreased. The ring opening of cyclopropane appears to be irreversible. The reaction of cyclopropane **(*R*)-14e** with *trans*-diazene **43** proceeds via an achiral dipolar intermediate **48** affording racemic product **44**. The higher reactivity of *cis*-diazene **45** over the *trans*-diazene **43** probably enables addition to the least sterically congested methylene group of the cyclopropane, affording racemic unexpected regioisomer **46** as the major product.





Scheme 21

1.2 Nicholas carbocations in [3+2] and [3+3] cycloaddition reaction

1.2.1. Alkyne dicobalt hexacarbonyl complexes

Cobalt is in group nine in the periodic table with a [Ar] $4s^2\ 3d^7$ electronic configuration. One of the most important example of Co(0) complexes is $Co_2(CO)_8$.[15] Cobalt needs nine more electrons for formation of an 18-electron species. So to satisfy 18-electron rule cobalt forms a dimer $Co_2(CO)_8$. Each cobalt atom donates an electron to form Co—Co bond. X-Ray

crystallographic studies of $Co_2(CO)_8$ has revealed that two carbon monoxide ligands are bridging between two cobalt atoms (Figure 4). Each of these bridging ligands donates only one electron to each cobalt centre. In terms of hybridization each cobalt centre is sp^3d^2 hybridized resulting in six hybridized orbitals in octahedral environment. Five hybridized orbitals are used for bonding to the CO ligands and remaining one orbital for metal-metal bond formation. The orbitals for Co—Co bond formation do not point directly towards each other and result in bent Co—Co bond.[13]

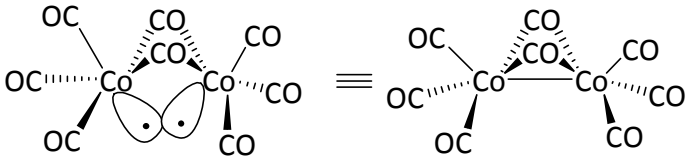


Figure 4

In solution state an equilibrium exists between bridged and non-bridged isomers (Figure 5).[16]

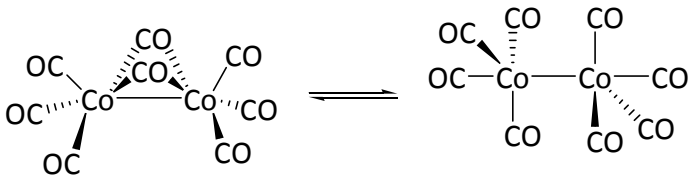
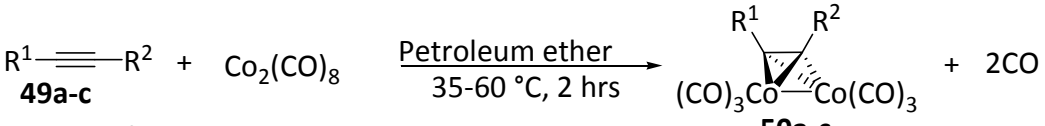


Figure 5

Sternberg *et al.* reported in 1954 that the two bridging carbonyls in $Co_2(CO)_8$ can be replaced by acetylene and substituted acetylene.[17] The reaction proceeds smoothly and quantitatively at room temperature. In this new organometallic complex, the C—C bond originally C≡C is perpendicular to the Co—Co bond (Scheme 22).



49a R^1=Ph; R^2=Ph
49b R^1=Ph; R^2=H
49c R^1=H; R^2= $-CH_2OH$

Scheme 22

Qualitative observations had indicated that many acetylenic dicobalt hexacarbonyl complexes decomposed on exposure to air.[18] Their complexation is easy to perform, simply by means of addition of dicobalt octacarbonyl to a solution of alkyne in a non-polar solvent. The new bimetallic complex is rapidly formed with the loss of two carbon monoxide ligands. The linear geometry of acetylenic carbon atoms in dicobalt hexacarbonyl complex twisted which brings the structure closer to that of an olefin.[19] The angle between acetylenic carbon

atoms and substituents is approximately 142°. The new complex formed is closer to a *Z*-substituted alkene (Figure 6).

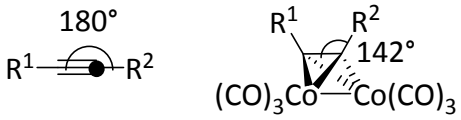
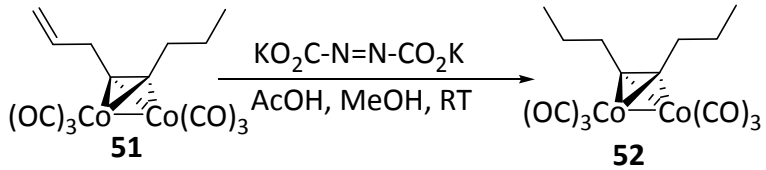


Figure 6

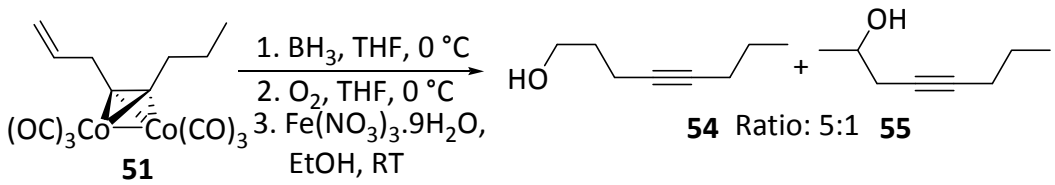
1.2.2. Protection of alkynes

Alkynes are generally very reactive in various addition reactions, such as hydrogenation, acid catalysed hydration, hydroboration and other hydrometallation reactions.[20] Hence protection of carbon-carbon triple bond in polyfunctional organic molecules is essential for selective synthetic transformations. Coordination of alkyne group to dicobalt hexacarbonyl has been most successful approach towards deactivation of triple bond. This method was first presented by Nicholas and Pettit in 1971.[21] They employed $Co_2(CO)_8$ to react with mono- and dialkyl acetylenes to form stable alkyne dicobalt hexacarbonyl complexes. Liberation of alkyne from complex was achieved by oxidative degradation with Fe(III) salts. The reduction of eneyne complex **51** upon addition of $KO_2C–N=N–CO_2K$ and acetic acid in methanol, gave reduced product **52** (Scheme 23).[19]



Scheme 23

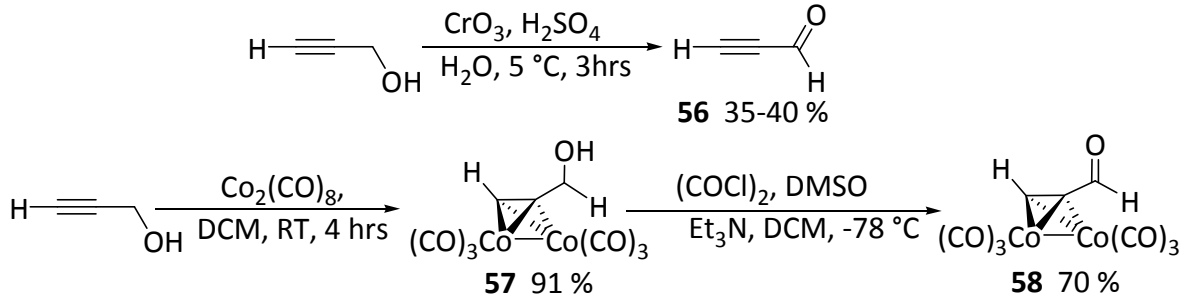
Similarly, hydroboration of enyne complex **51** gave exclusively the product of reaction at the double bond. The complex **51** was treated with BH_3 followed by oxidation under oxygen atmosphere. The dicobalt complex was then removed by oxidation with iron (III) affording alcohols **54** and **55** in 62 % yield in a ratio of 5:1 respectively (Scheme 24)



Scheme 24

The protection of the triple bond has also been used for the preparation of acetylenic aldehydes,[22] which are generally obtained by the oxidation of the corresponding propargylic alcohols using Jones oxidation with 35 to 40 % yield.[23] After complexing the triple bond, the

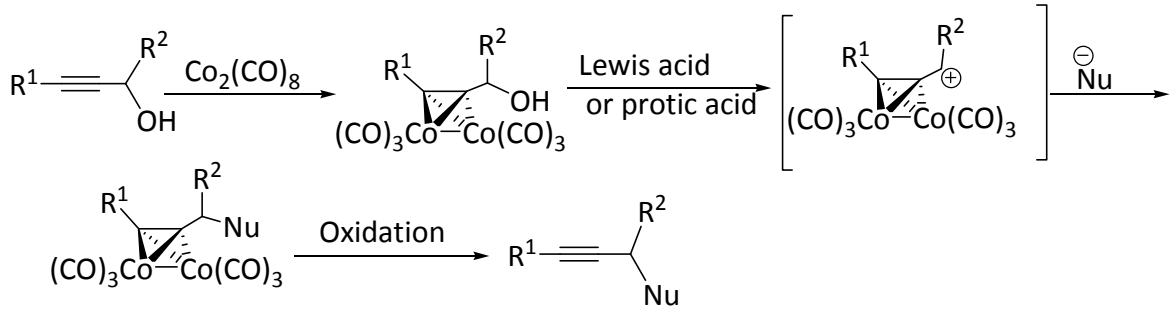
complexed propargyl alcohol **57** can be oxidised by Swern oxidation in good yield.[22] The decomplexation to obtain acetylenic aldehydes can be achieved by oxidation with iron (III) (Scheme 25).[21]



Scheme 25

1.2.3. The Nicholas reaction

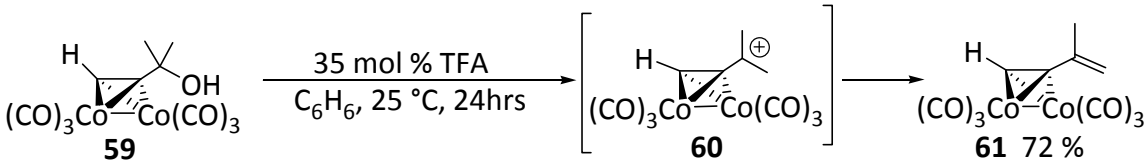
Complexation of alkyne to cobalt stabilises positive charge in the propargylic position. These cobalt stabilised propargyl cations permit synthetically useful reactions with various nucleophiles to give propargylic substitution products without producing allenic by-products. This reaction is known as the Nicholas reaction.[24] The alkynes can be decomplexed by oxidation with iron (III) or with cerium ammonium nitrate to release free alkyne (Scheme 26). The cobalt stabilised propargyl cations can be made from various precursors, especially propargyl alcohols with treatment with a Lewis or a protic acid.[25]



Scheme 26

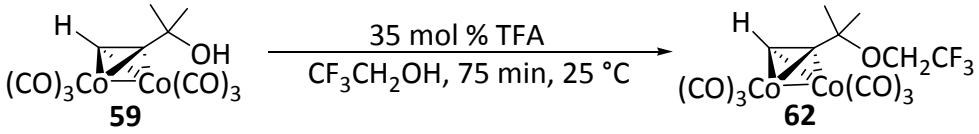
1.2.4. The reaction discovery

Dicobalt complexes enhance the stability of carbonium ions formed from propargyl alcohols and ethers. In 1972 Nicholas and Pettit reported the formation of such propargylic ions.[26] They discovered that tertiary propargyl alcohol complexes readily undergo acid catalysed dehydration to give conjugated enyne complexes. For example, the carbinol complex **59** when treated with 35 mol % of trifluoroacetic acid in benzene was converted to vinyl cobalt complex **61** in 72 % yield in 24 hrs (Scheme 27).



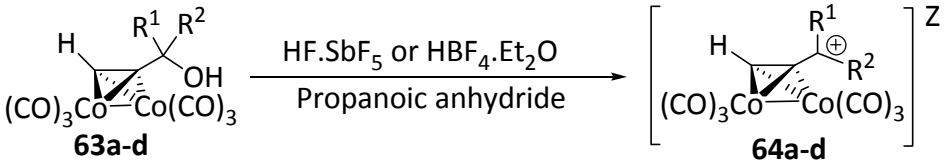
Scheme 27

Under the same reaction conditions the uncomplexed carbinols were unchanged. Dehydration of free tertiary propargyl alcohols requires considerably higher temperatures (80-200 °C) and stronger acidic conditions. Nicholas and Pettit suggested the formation of propargylium intermediate **60**, which was further confirmed by the treatment of the carbinol **59** with a catalytic amount of CF_3CO_2H in trifluoroethanol led to the quantitative formation of trifluoroethylether **62** in 75 minutes at 25 °C (Scheme 28).



Scheme 28

Stabilised carbonium ion salts **64a-d** of SbF_6 or BF_4 were prepared by the treatment of propionic anhydride solution of complexed propargyl alcohols **63a-d** with an excess of $HF.SbF_5$ or $HBF_4.Et_2O$ at -40 °C. Addition of anhydrous ether and filtration at -40 °C under nitrogen afford products in good yield (Scheme 29, table 4).[27]



Scheme 29

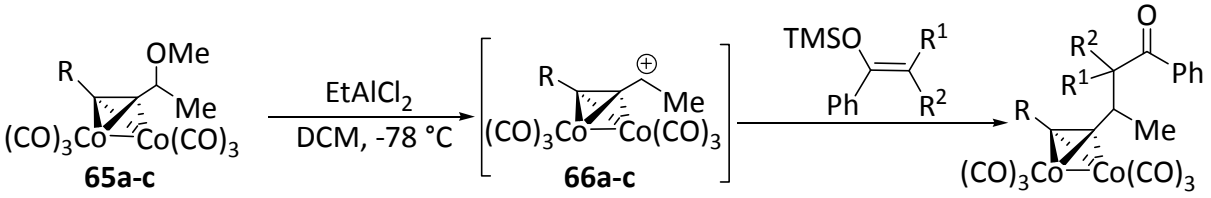
SM	R^1	R^2	Acid	Z	conditions	Product %
63a	Me	Me	$HF.SbF_5$	SbF_6^-	-40 °C	**64a** 78
63b	Ph	Ph	$HF.SbF_5$	SbF_6^-	-40 °C	**64b** 64
63c	Me	H	HBF_4	BF_4^-	-40 °C	**64c** 81
63d	H	H	HBF_4	BF_4^-	-40 °C	**64d** 78

Table 4

The generation of such a carbocation in this position is also possible without complexation although a rearrangement to the corresponding allene is likely to occur.

1.2.5. The generation of Nicholas carbocation

The most commonly used method for generation of Nicholas carbocation is by treatment of propargylic alcohol with a Lewis or a protic acid, but several other methods have been developed for generation of these carbocations.[25] Schreiber investigated a Lewis acid mediated version of this reaction on cobalt complexed propargylic ethers.[28] The cobalt complexed propargylic ethers **65a-c** on treatment with Lewis acid generated the corresponding carbonium intermediates **66a-c**. Then these intermediates were trapped by using nucleophilic enolate of trimethylsilyl enol ether generated *in situ* using $EtAlCl_2$ to yield compounds **67a-c** (Scheme 30).



65a-c

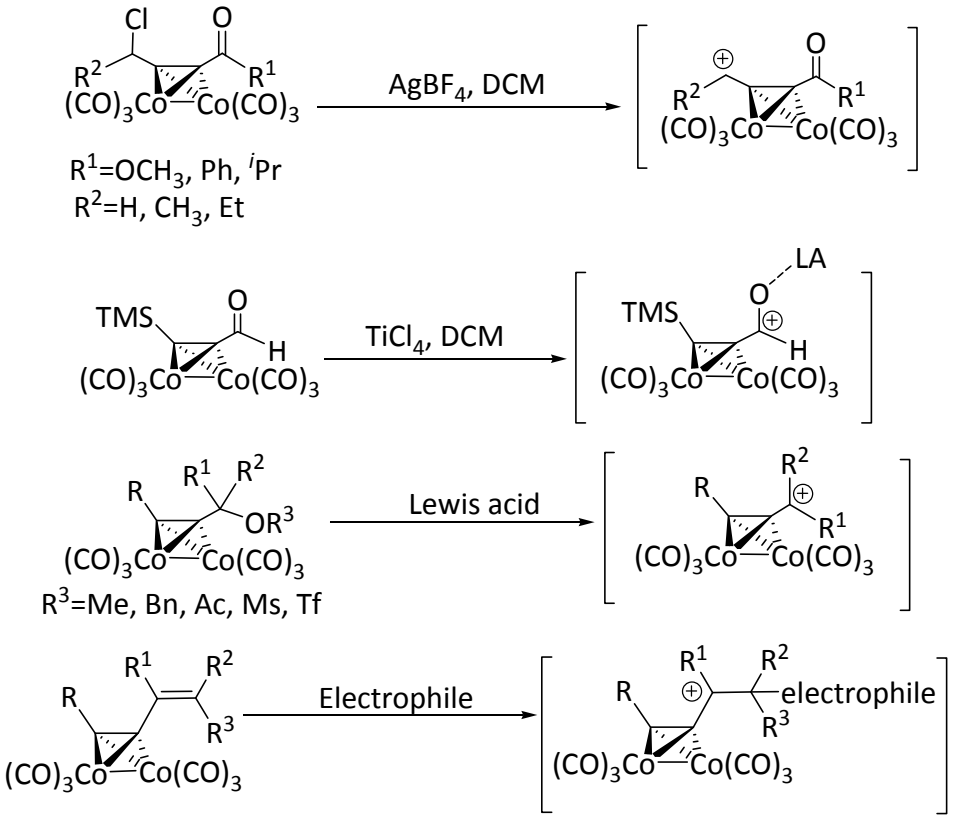
65a R=Ph; R^1=Me; R^2=H
65b R=Ph; R^1=H; R^2=Me
65c R=H; R^1=Me; R^2=H

66a-c

67a-c 85 %

Scheme 30

Some other methods for generation of Nicholas carbocation are summarised in scheme 31. Stabilised carbocations can be generated, starting from various precursors such as chlorides, aldehydes, ethers, esters and electrophilic addition to 1,3-enyne complexes.[29a-d]



Scheme 31

1.2.6. The use of Nicholas carbocation in [3+2] and [3+3] cycloaddition reaction

Dipolar cycloaddition reaction can be used with a dicobalt complex to stabilise the positive charge formed during the ring opening. This variation of the Nicholas reaction has previously been used within the Pritchard and Christie research groups.[30] Upon treatment with Lewis acid dicobalthexacarbonyl complex of 2-ethynylcyclopropane-1,1-dicarboxylic acid dimethyl ester **68** forms a doubly stabilised 1,3-dipole; the cobalt alkyne unit stabilises the propargylic carbocation, while the malonate functionality stabilises the negative charge (Figure 7).[31]

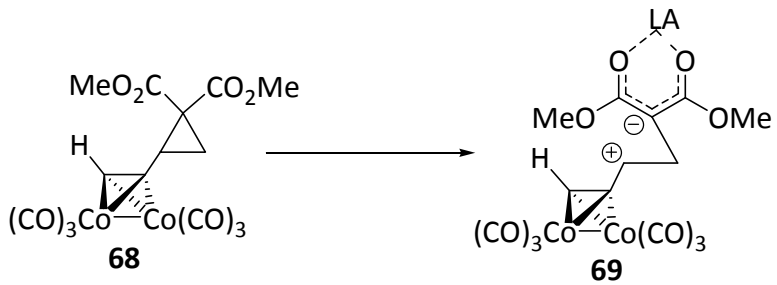
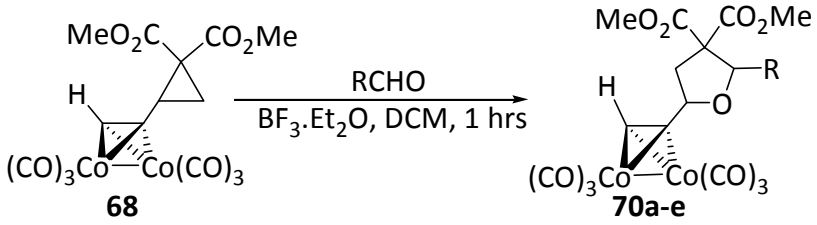


Figure 7

The activated cyclopropane **68** was trapped with various aldehydes in the presence of boron trifluoride etherate affording corresponding tetrahydrofurans (Scheme 32, table 5). Better yields were obtained with electron deficient aromatic aldeyhdes. The *cis* and *trans* isomers were isolated as a 1:1 mixture in most of the reactions.



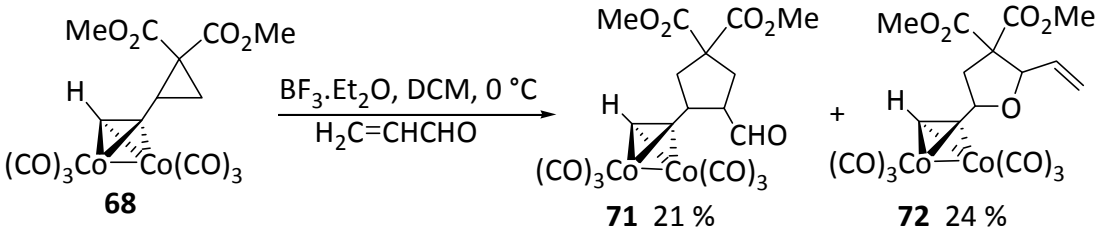
68 **70a-e**

Scheme 32

Entry	R	Temp. °C	Product	Yield %	*Cis/ trans*
1	Ph	25	**70a**	68	1:1
2	4-$MeOC_6H_4$-	0	**70b**	0	n/a
3	4-$NO_2C_6H_4$-	40	**70c**	71	1:2
4	Me	0	**70d**	65	1:1
5	-CO_2Et	40	**70e**	85	1:1

Table 5

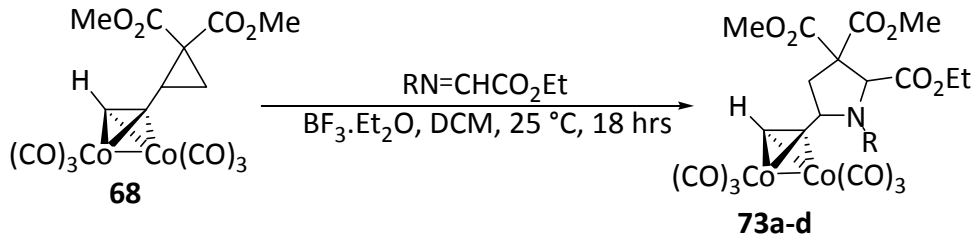
When propenal was used as trapping reagent during cycloaddition of cyclopropane complex **68**, the carbocycle **71** was afforded with an equal amount of corresponding tetrahydrofuran **72**. Cyclopentane **71** was 2:1 ratio of diastereoisomers, while tetrahydrofuran **72** was 1:1 mixture (Scheme 33).[32]



68 **71** 21 % **72** 24 %

Scheme 33

Using similar conditions, imines were reacted to form pyrrolidines. In general yields were good to excellent when an electron withdrawing group was present on the imine of carbon and an electron donating group was present on nitrogen atom (Scheme 34, table 6).

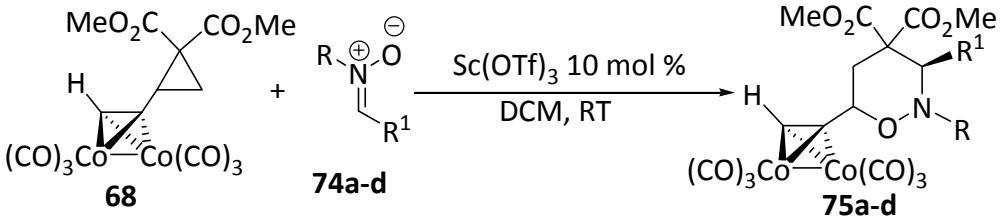


Scheme 34

Entry	R	Temp. °C	Product	Yield %	*Trans*/*cis*
1	4-$MeOC_6H_4$	0	**73a**	91	1:1
2	2,4-$(MeO)_2C_6H_3$	0	**73b**	85	2:1
3	4-MeC_6H_4	25	**73c**	81	1:1
4	2-CNC_6H_4	25	**73d**	72	1:3

Table 6

Kerr *et al*. also reported the Nicholas-type activation of cyclopropanes toward reaction with nitrones in the homo-[3+2]-dipolar cycloaddition.[33] They screened a range of Lewis acids and found that ytterbium triflate and scandium triflate were suitable to promote the reaction; however scandium triflate was the preferred catalyst affording the oxazines in better yields (Scheme 35).



Scheme 35

Entry	R	R^1	Time	Product	Yield %
1	Ph	Ph	3 hrs	**75a**	90
2	Ph	4-$MeOC_6H_4$	5 hrs	**75b**	73
3	Ph	Bn	18 hrs	**75c**	86
4	Bn	4-$NO_2C_6H_4$	6 hrs	**75d**	65

Table 7

1.3 [4+2] Cycloaddition reaction

The use of donor-acceptor cyclopropanes as a precursor in [3+2] and [3+3] cycloaddition reaction described so for is due to their unique reactivity profile. Their value as synthetic building blocks has been demonstrated by the preparation of highly substituted carbon and heterocyclic products via dipolar cycloaddition.[3-14] This methodology has recently been

extended to donor-acceptor cyclobutane.[34] The total ring strain in cyclobutane is almost the same as cyclopropane, but distributed over four carbon atoms. [35] If cyclobutane was planar and square, it would have bond angle 90° and torsional train due to eclipsing interaction of bonds. But unlike cyclopropane, the cyclobutane is not planar. To reduce torsional strain, cyclobutane adopt slightly folded form with bond angles of 88° (Figure 8). These small angles require slightly more angle strain than 90° angles, but the relief of some of torsional strain appears to compensate for a small increase in angle strain. The strain energy of cyclobutane (26.3kcal/mol) is similar to that of cyclopropane (27.5kcal/mol), suggesting that ring opening reactions of cyclobutanes may be possible.[34]

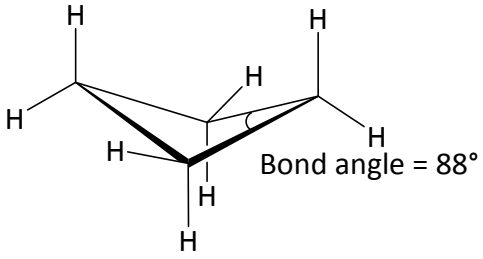
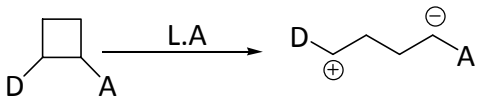


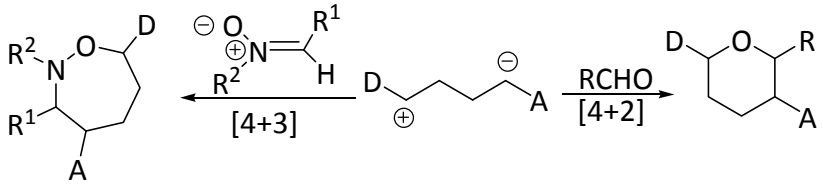
Figure 8

The cyclobutane substituted by vicinal donor-acceptor groups under Lewis acidic conditions, like donor-acceptor cyclopropanes can give 1,4-zwitterionic intermediates (Scheme 36).



Scheme 36

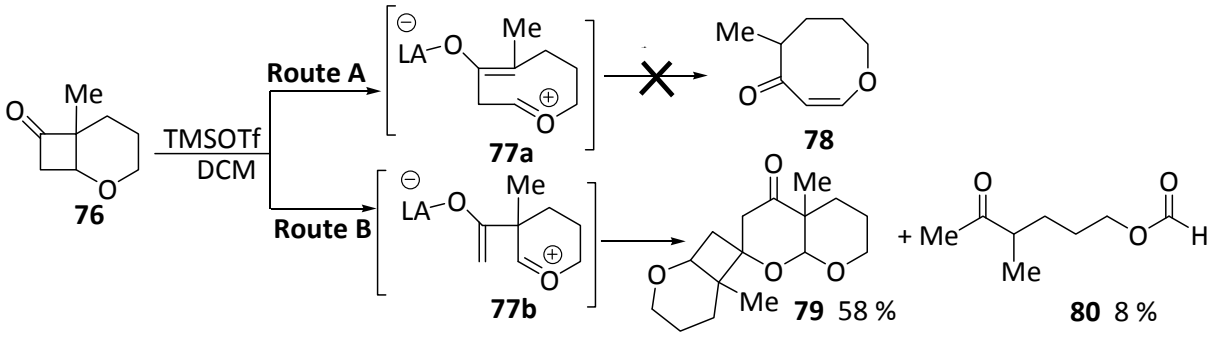
The 1,4-zwitterionic intermediates like 1,3-zwitterionic intermediates can react with various trapping reagents such as aldehydes,[34] ketones,[36] allyltrialkylsilanes,[37] silyl enol ethers,[38] imines,[39] alkenes,[40] and nitrones[42] by [4+2] and [4+3] cycloaddition reactions giving diverse range of six and seven membered carbocyclic and heterocyclic compounds (Scheme 37).



Scheme 37

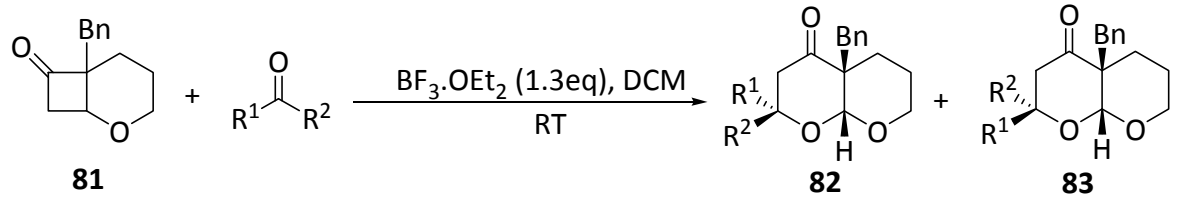
During the course of natural product synthesis, Matsuo *et al*. were trying to prepare eight membered cyclic enone **78** by Lewis acid catalysed ring opening of bicyclocyclobutanone **76**, expecting formation of zwitterionic species **77a** as an intermediate (Scheme 38, route A).[36] However the desired compound was not obtained, whereas tetracyclic compound **79** and

acyclic compound **80** were obtained in 58 % and 8 % yields respectively. These results suggested that ring opening of cyclobutanone **76** proceeded regioselectively to generate zwitterionic species **77b** (Scheme 38, route B). The zwitterion **77b** was trapped with the keto group of starting material cyclobutanone **76** as a result of [4+2] cycloaddition reaction.



Scheme 38

The regioselectivity of ring opening of cyclobutanone **76** can be rationalized by considering that formation of an eight membered ring bearing two double bonds **77a** is energetically unfavourable because of its strain. Therefore, the ring cleaves at the less substituted side of cyclobutanone **76** giving the intermediate **77b** and proceeds to the products. Later, Matsuo successfully reacted tetrahydropyran fused cyclobutanone **81** bearing benzyl group at the bridge-head position with aldehydes and ketones catalysed by boron trifluride etherate in [4+2] cycloaddition reaction. The cycloaddition of acetophenone gave two diastereoisomers. In all cases below, aldehydes and ketones were inserted into the less substituted side of cyclobutanone **81** (Scheme 39, table 8).



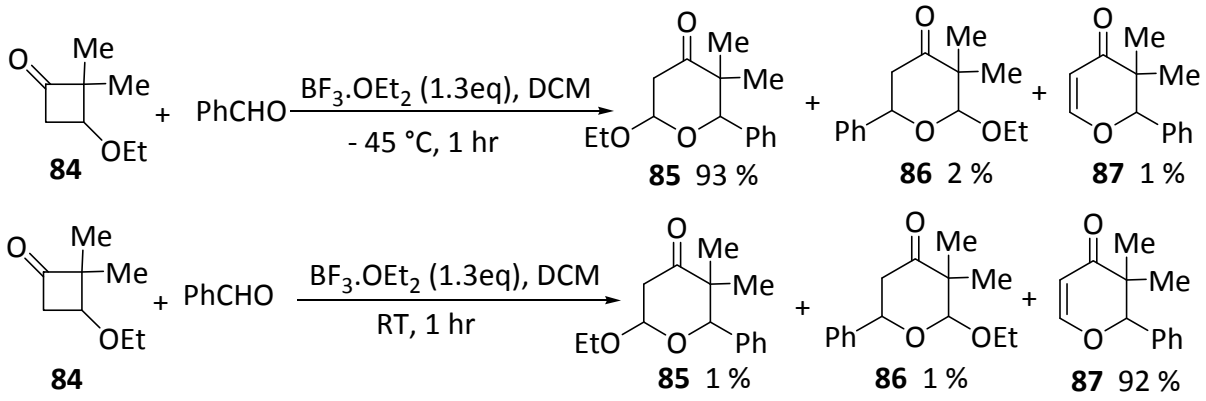
Scheme 39

Entry	R^1	R^2	Time	Tem. °C	82 Yield %	83 Yield %
1	Ph	H	2.5 hrs	RT	73	0
2	^{t}Bu	H	3.5 hrs	RT	85	0
3	Ph	Me	5 hrs	RT	54	31
4	-$(CH_2)_5$-		3.5 hrs	RT	84	0

Table 8

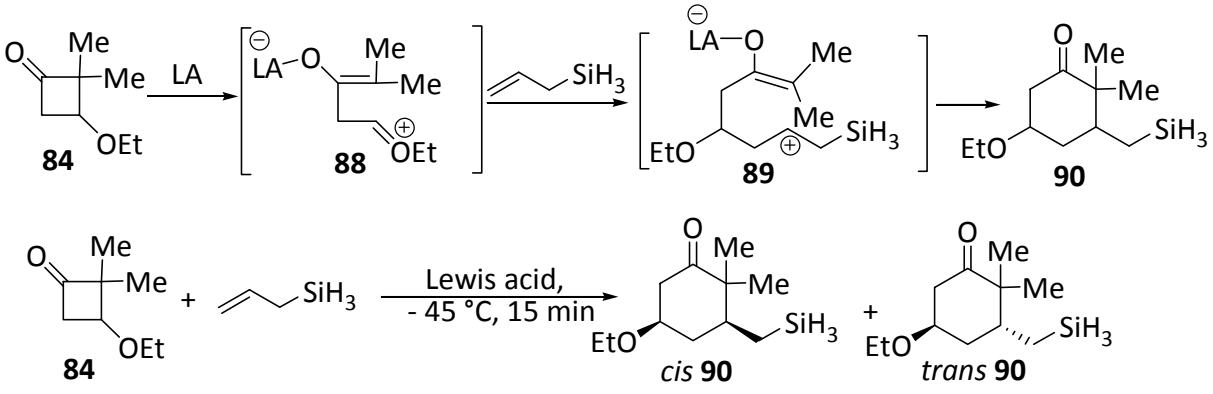
When monocyclic 3-ethoxycyclobutanone **84** was reacted with benzaldehyde at -45 °C under the conditions of boron trifluride etherate in DCM, the cycloadduct **85** was afforded

in 93 % yield (*cis*/*trans*=76/24) along with regioisomer **86** in 2 % and dihydro-γ-pyrone derivative **87** in 1 % yield. When the same reaction was performed at room temperature, dihydro-γ-pyrone derivative **87** was obtained as a major product in 92 % yield. The regioselectivity of cyclobutanone **84** in contrast to cyclobutanones **76** and **81**, benzaldehyde was inserted in to the more substituted side of ring (Scheme 40).



Scheme 40

Since the C—O double bond of the aldehyde was efficiently inserted into the more substituted bond of cyclobutanone ring, next they planned insertion of C—C double bonds into cyclobutanone ring. They successfully reacted the zwitterionic species **88**, generated by Lewis acid mediated ring opening of 3-ethoxycyclobutanone **84** with allylsilane to give a formal [4+2] carbocyclic cycloadduct **90** via a β-silyl cation intrermediate **89**.[37] The allylsilane was regioselectively inserted into the more substituted side of cyclobutanone **84**. Tin (IV) chloride was found most effective Lewis acid. Tin (IV) chloride catalysed cycloaddition reaction also proceeded smoothly in toluene giving the desired cycloadduct **90** in 85 % yield (*cis*/*trans* 71/29). The *cis*/*trans* ratio did not depend on the Lewis acid employed and sterically favoured *cis* stereoisomer was obtained as a major fraction (Scheme 41, table 9).

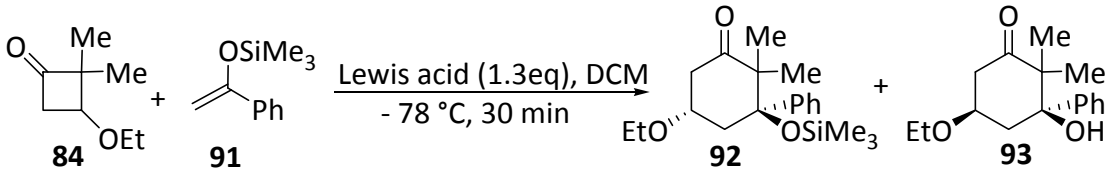


Scheme 41

Entry	Solvent	Lewis acid	90 Yield %	*Cis*/*Trans*
1	DCM	$EtAlCl_2$	53	79/21
2	DCM	$TiCl_4$	57	89/11
3	DCM	$TiBr_4$	6	83/17
4	DCM	$SnCl_4$	80	71/29
5	Toluene	$SnCl_4$	85	71/29
6	DCM	$SnBr_4$	16	69/31

Table 9

After successfully using allylsilane as a trapping reagent for zwitterionic species **88**, they then planned the insertion of the C—C double bond of a silyl enol ether to zwitterionic species **88**.[38] Lewis acid catalysed [4+2] cycloaddition between 2,2-dimethyl-3-ethoxycyclobutanone **84** and 1-phenyl-1-trimethylsilyloxyethene **91** afforded trimethylsilylated cycloadduct **92** along with a trace amount of a desilylated diastereoisomer **93**. During Lewis acid screening, ethylaluminum dichloride was found to be the most effective Lewis acid (Scheme 42, table 10).

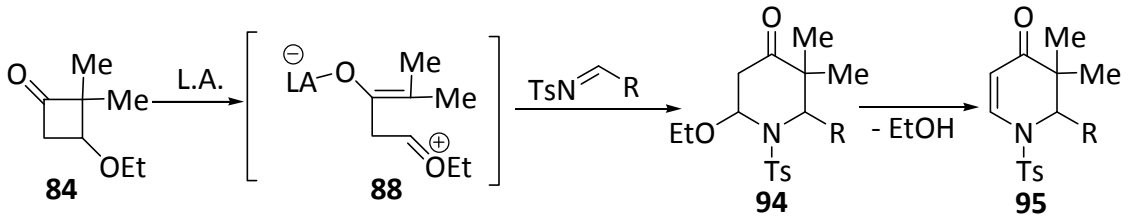


Scheme 42

Entry	Lewis acid	92 Yield %	93 Yield %
1	$EtAlCl_2$	70	traces
2	$SbCl_5$	41	8
3	$SnCl_4$	35	1
4	$Sc(OTf)_3$	26	2
5	$GaCl_3$	22	0

Table 10

2,3-Dihydro-4-pyridones are versatile synthetic intermediates in organic synthesis.[39] The zwitterionic intermediate **88**, generated by Lewis acid mediated ring opening of 3-ethoxycyclobutanone **84** was also trapped by reacting with imines affording dihydropyridones **95**. Titanium (IV) chloride and tin (IV) chloride were found to be the most effective Lewis acids to catalyse the [4+2] cycloaddition between 2,2-dimethyl-3-ethoxycyclobutanone **84** and various N-tosylimines. Tetrahydropyridone **94** was not obtained under these conditions probably due to the participation of nitrogen in the elimination of ethanol (Scheme 43, table 11).

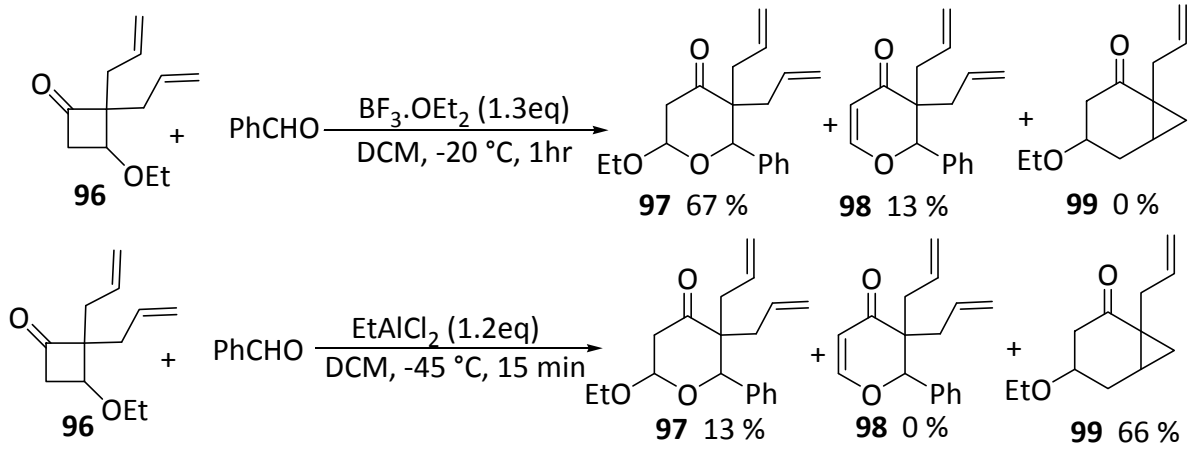


Scheme 43

Entry	R	Solvent	Acid (1.3eq)	Tem. °C	Time	95 yield %
1	Ph	DCM	$TiCl_4$	-45	1 hr	80
2	Ph	DCM	$TiBr_4$	-45	1 hr	56
3	Ph	DCM	$SnBr_4$	-45 to RT	3.5 hrs	74
4	Ph	DCM	$BF_3.OEt_2$	-45 to RT	4 hrs	34
5	Ph	DCM	$EtAlCl_2$	-45 to RT	2 hrs	10
6	4-$MeOC_6H_4$	DCM	$TiCl_4$	0 to RT	30 min	40
7	PhCH=CH-	DCM	$TiCl_4$	-20	1 hr	84
8	^{n}Pr	DCM	$TiCl_4$	-20	1 hr	64

Table 11

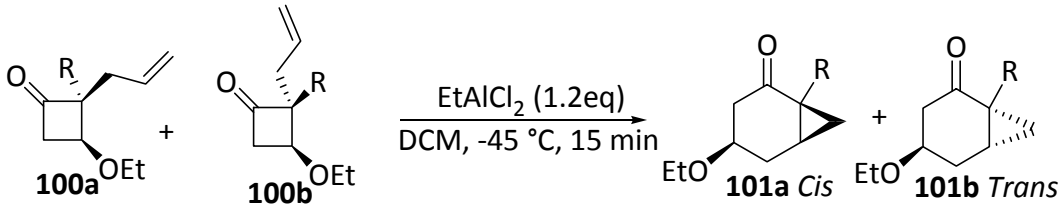
During the reaction of 2,2-diallyl-3-ethoxycyclobutanone **96** and benzaldeyhde, it was found that catalysis with boron trifluride etherate gave expected cycloadducts **97** and **98** in 67 % and 13 % yields respectively, however ethylaluminium dichloride gave intramolecular cycloadduct **99** as major product (Scheme 44).[40]



Scheme 44

The finding of unprecedented intramolecular cycloaddition of an allyl group into cyclobutanone as well as interesting chemoselectivity prompted Matsuo *et al*. to investigate this intramolecular cycloaddition further. Ethylaluminium dichloride was also found to be the most effective Lewis acid to promote intramolecular cycloaddition of the alkenyl group at the 2-position of 3-ethoxycyclobutanone **100a** and **100b** to give *cis* **101a** and *trans* **101b** cycloadduct. *Cis* and *trans* mixture of 2-allylcyclobutanones **100a** and **100b** gave desired

cycloadduct **101a** and **101b** in 88-90 % yields and reaction was found to proceed nonstereospecifically since *cis*/*trans* ratio of cycloadducts **101a** and **101b** did not correspond to the *cis*/*trans* ratios of 3-ethoxycyclobutanone 1**00a** and **100b** (Scheme 45, table 12).

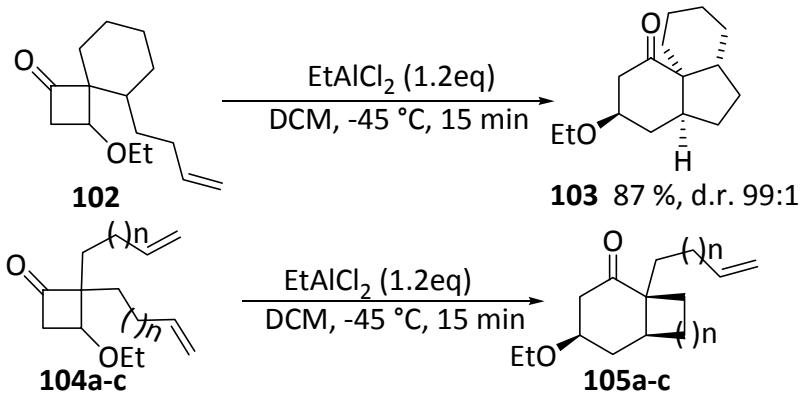


Scheme 45

Entry	R	*Cis*/*Trans*	101a/101b Yield %	*Cis*/*Trans*
1	Allyl	---	92	84/16
2	Me	56/44	72	89/11
3	Bn	34/66	81	85/15
4	^{i}Pr	28/72	88	82/18

Table 12

Preparation of bicyclic and tricyclic compounds was also investigated. Cyclobutanone having a 3-butenyl **104a** or 4-pentenyl group **104b** at the 2-position gave the corresponding cycloadduct as single diastereoisomer. Cyclobutanone **104c** bearing a 5-hexenyl group did not give a cycloadduct. Intramolecular cycloaddition of spirocyclobutanone proceeded smoothly to afford corresponding tricyclic compound (Scheme 46, table 13).

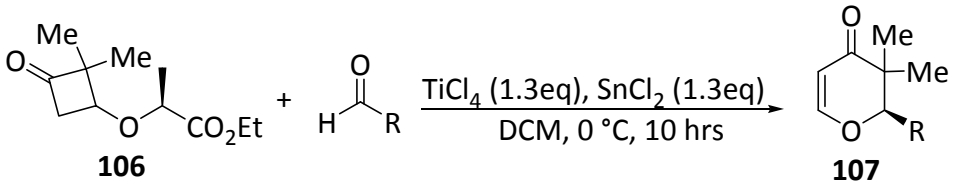


Scheme 46

Entry	104 n	Product	Yield	d.r.
1	n=1	**105a**	18	99:1
2	n=2	**105b**	86	99:1
3	n=3	**105c**	0	----

Table 13

Chiral cyclobutanone **106** which had L-ethyl lactate as chiral auxiliary at the 3-position reacted with aldeyhdes to give 2,3-dihydro-4-pyranones in up to 92 % ee by combined use of titanium (IV) chloride and tin (II) chloride.[41] When electron withdrawing groups were substituted at the *para* position of the phenyl group of benzaldehyde the corresponding 2,3-dihydropyranones **107** were obtained in good yields and high ee's 77-92 %, whereas aldehydes bearing methyl or phenyl group gave lower ee's (Scheme 47, table 14).

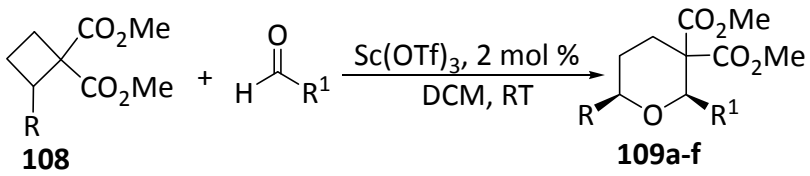


Scheme 47

Entry	R	Time	107 Yield %	% ee
1	4-$CF_3C_6H_4$-	12 hrs	68	89
2	4-FC_6H_4-	10 hrs	67	91
3	4-ClC_6H_4-	8 hrs	75	92
4	4-IC_6H_4-	12 hrs	78	88
5	Me	8 hrs	59	77
6	Ph	12 hrs	70	77

Table 14

Johnson *et al*. have recently reported Lewis acid catalysed [4+2] cycloaddition of malonate derived cylobutanes and aldehydes. Several malonate derived cyclobutanes underwent cycloaddition with cinnamyl and electronically diverse aryl aldehydes affording tetrahydropyrans in high yield and stereoselectivity. $Hf(OTf)_4$ and $Sc(OTf)_3$ were found to be the most effective catalysts.[34]

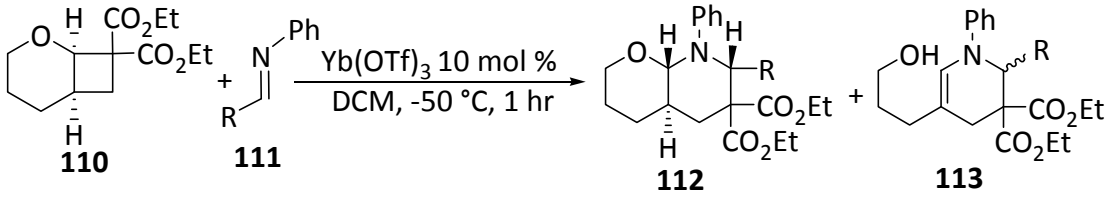


Scheme 48

Entey	R	R^1	Product	Yield %	d.r.
1	Ph	Ph-CH=CH-	**109a**	77	77:23
2	4-$MeOC_6H_4$-	4-MeC_6H_4-	**109b**	96	96:4
3	4-$MeOC_6H_4$-	3-BrC_6H_4-	**109c**	76	96:4
4	4-BrC_6H_4-	4-$CF_3C_6H_4$-	**109d**	90	98:2
5	Ph	4-$MeOC_6H_4$-	**109e**	68	96:4
6	Me-CH=CH-	4-ClC_6H_4-	**109f**	68	94:6

Table 15

Pagenkopf *et al*. have recently reported $Yb(OTf)_3$ catalysed [4+2] cycloaddition of donor-acceptor cyclobutane with imines.[42] Cyclobutane **110** and imine **111** in the presence of a catalytic amount of $Yb(OTf)_3$ at -50 °C gave bicyclic piperidine **112** as a single diastereoisomer and piperideine **113**. However, reaction of imine **111** having nitro group on phenyl ring gave cycloadduct **112** as a 2:1 mixture of diastereoisomers. In order to isolate only piperideine **113**, the reaction was warmed to RT for a further one hour to drive the product from piperidine **112** to the piperideine **113** (Scheme 49, table 16).

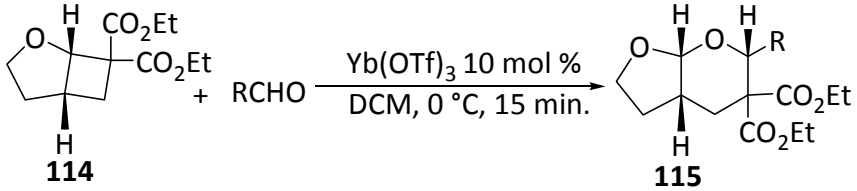


Scheme 49

Entry	R	Time	Temp. °C	112 Yield %	d.r.	113 Yield %
1	Ph	1 hr	-51	17	*cis*	67
2	3-$NO_2C_6H_4$-	1 hr	-50	22	2:1	56
3	Ph	2 hrs	-50 to RT	0	--	83

Table 16

Pagenkopf *et al*. have also reported $Yb(OTf)_3$ catalysed synthesis of fused bicyclic acetals **115** in good yield and excellent diastereoselectivity by the formal [4+2] dipolar cycloaddition of alkoxy substituted donor acceptor cyclobutane **114** with aromatic and aliphatic aldehydes. The fused bicyclic acetal was obtained as a single diastereoisomer (Scheme 50, table 17).[43]

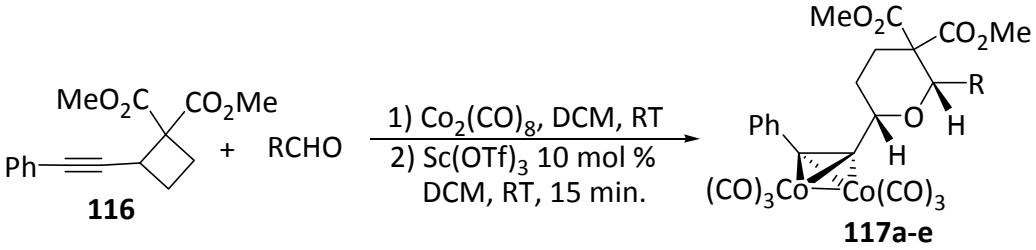


Scheme 50

Entry	R	115 Yield %
1	Ph	78
2	4-$MeOC_6H_4$-	80
3	4-ClC_6H_4-	89
4	4-CNC_6H_4-	88
5	4-$NO_2C_6H_4$-	75
6	Ph-CH=CH-	87
7	Ph-CΞC-	62

Table 17

The use of Nicholas type activated cyclobutanes in [4+2] cycloaddition has been reported within the Pritchard and Christie research group. The dicobalt hexacarbonyl complexed diester cyclobutane **116** in the presence of catalytic amount of scandium triflate reacts with aldehydes to afford the corresponding tetrahydropyran **117a-e** in high yield and excellent diastereoselectivity (Scheme 51, table 18).[44]



116 **117a-e**

Scheme 51

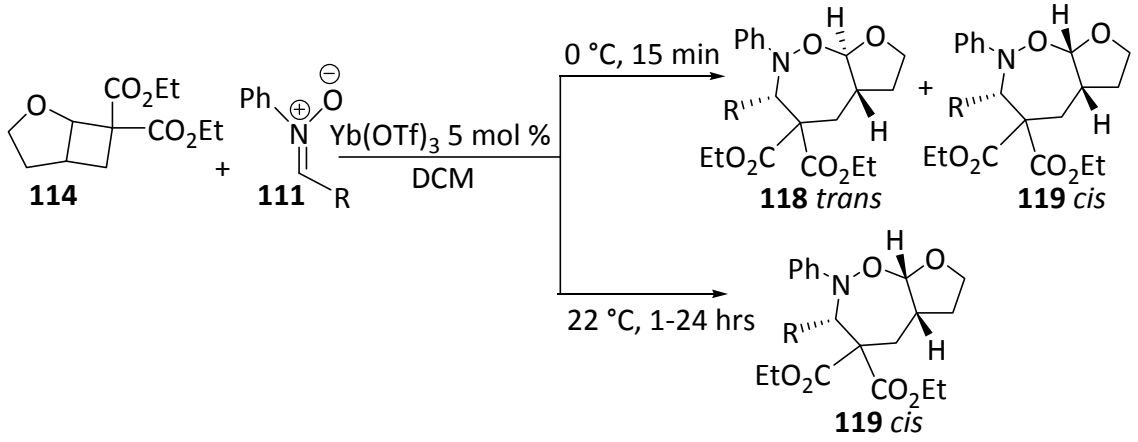
Entry	R	Time	117a-e	Yield %	*Cis/Trans*
1	Ph	24 hrs	**117a**	34	*cis*
2	4-MeC_6H_4-	10 min	**117b**	64	*cis*
3	2-MeC_6H_4-	1 hr	**117c**	47	*cis*
4	Ph-CH=CH-	1 hr	**117d**	82	*cis*
5	2,4-$(MeO)_2C_6H_3$-	10 min	**117e**	92	*cis*
6	3,4-$(MeO)_2C_6H_3$-	10 min	**117f**	92	*cis*

Table 18

1.4. [4+3] Cycloaddition Reaction

Pagenkopf *et al*. have also reported $Yb(OTf)_3$ catalysed [4+3] cycloaddition reactions between donor-acceptor cyclobutane **114** and nitrones **111** affording structurally unique oxazepines **118** and **119**.[45] The addition of cyclobutane **114** to the solution of nitrone in DCM in the presence of 5 mol % $Yb(OTf)_3$ gave a mixture of two diastereoisomers in ten minutes. The diastereoisomeric ratio was reversed when the reaction was performed at 0 °C. In all cases, increasing the reaction time or catalyst loading led ultimately to the single

diastereoisomer. It was found that electron rich nitrone require less than an hour for reaction to yield a single diastereoisomer, where as electron deficient nitrones require extended reaction time up to 24 hrs (Scheme 52, table 19).



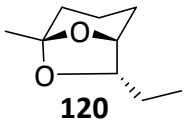
Scheme 52

Entry	R	Time	Temp. °C	118/119 Yield %	d.r. *trans*:*cis*	119 Yield %
1	Ph	15 min	0	91	69:31	--
2	Ph	15 min	22	91	20:80	--
3	Ph	1 hr	22	--	0:100	76
4	4-$MeOC_6H_4$-	15 min	0	88	63:37	--
5	4-$MeOC_6H_4$-	1 hr	22	--	0:100	74
6	4-$NO_2C_6H_4$-	15 min	0	90	83:17	--
7	4-$NO_2C_6H_4$-	24 hrs	22	--	0:100:0	73

Table 19

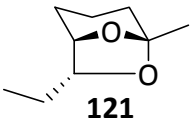
1.5. 6,8-dioxabicyclo[3.2.1]octane derivatives

The 6,8-dioxabicyclo[3.2.1]octane ring system is one of the prevailing motifs among pheromones. Frontalin, *endo*-brevicomin and *exo*-brevicomin have been discovered as the aggregation pheromones of bark beetles, while 3,4-dihydro-*exo*-brevicomin has been identified as sex pheromone produced by the male house mouse. Frontalin has recently been shown to be the sex pheromone of male Asian elephants.[46] Development of new approaches for the construction of 6,8-dioxabicyclo[3.2.1]octane is an attractive goal due to the number of natural products that contain this unit, as insect pheromones or complex natural product.[47] Most of them exhibit promising bioactive profiles, such as fused bicyclic acetal **129** with impressive anticancer properties. Derivatisation of a similar molecule as carbamates **130** brought a significant variation in potency.[48] Cyclodidemniserinol trisulfate **132** is an inhibitor of HIV-1 integrase.[47] Alkylated 6,8-dioxabicyclo[3.2.1]octanes are well known aggregation pheromones isolated from several species of the bark beetles and play an important role in the system of chemical communication amongst them.[49] These beetles infect pine trees causing great ecological and economic damage.



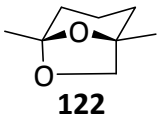
120

(+)-*Endo*-brevicomin



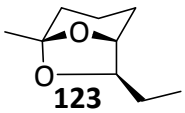
121

(-)-*Endo*-brevicomin



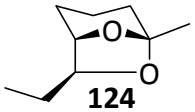
122

(-)-Frontalin
southern pine bettle,
asian elephant



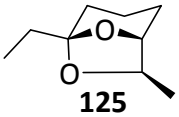
123

(+)-*Exo*-brevicomin
western pine bettle



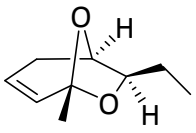
124

(-)-*Exo*-brevicomin



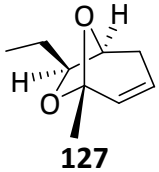
125

(+)-Iso-*exo*-brevicomin
western pine bettle



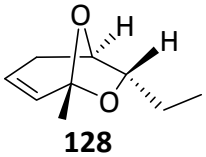
126

(-)-Mus musculus
(-)-3,4-dehydro-*exo*- brevicom
in house mouse



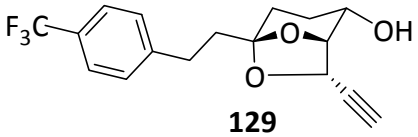
127

(+)-Mus musculus

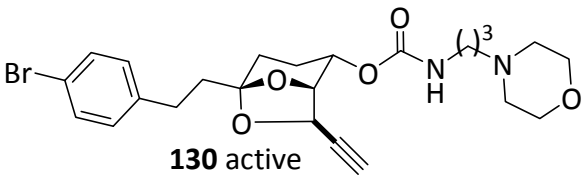


128

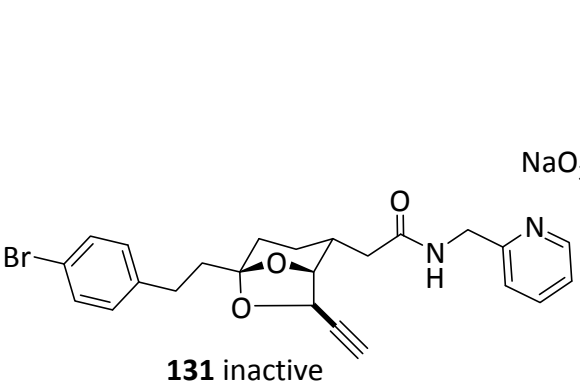
(-)-*Endo* mus musculus



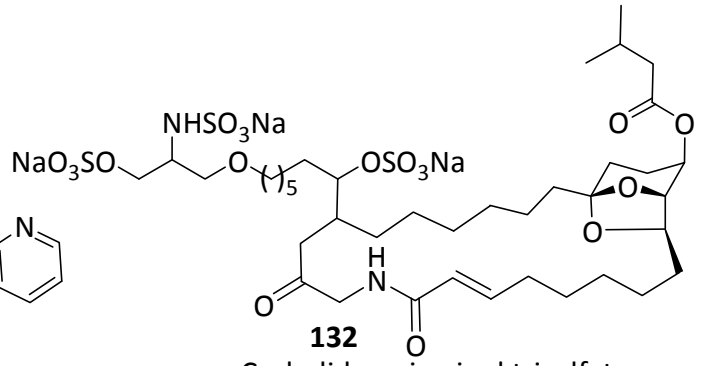
129



130 active



131 inactive

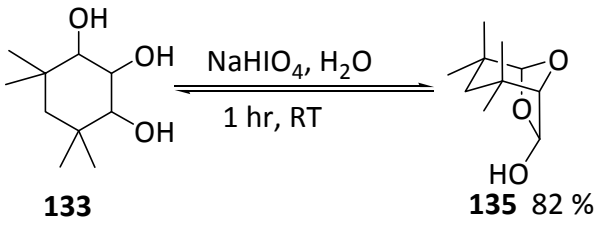


132 Cyclodidemniserinol trisulfate

Various synthetic approaches have been devised for the synthesis of 6,8-dioxabicyclo[3.2.1]octane ring system.

1.5.1. Periodic acid cleavage of 1,2,3-cyclohexane triol

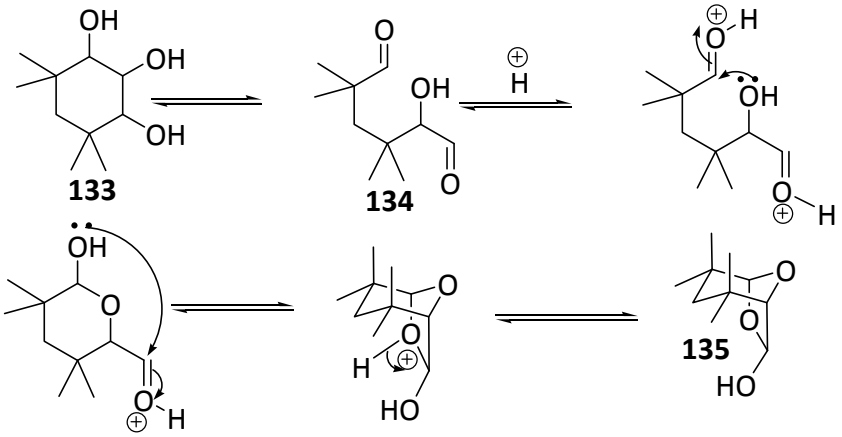
Periodic acid cleavage of 1,2,3-cyclohexane triol **133** gave bicyclic ketal **135** rather than expected 2,2,4,4-tetramethylpentane-1,5-dial **136**.[50a-b]



133 **135** 82 %

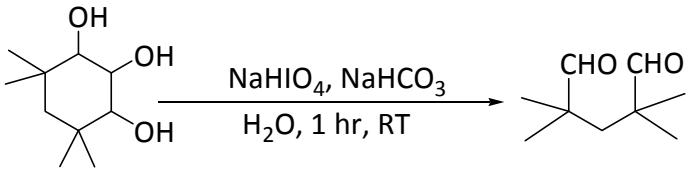
Scheme 53

Bicyclic ketal **135** is formed by incomplete oxidation of 1,2,3-cyclohexane triol **133** to the hydroxydialdehyde **134**. The intramolecular acetalization of hydroxydialdehyde **134** gave bicyclic ketal **135**.



Scheme 54

However, oxidation of 1,2,3-cyclohexane triol **133** in a weakly basic solution containing sodium hydrogen carbonate gave a significant yield of dial **136** (Scheme 55).

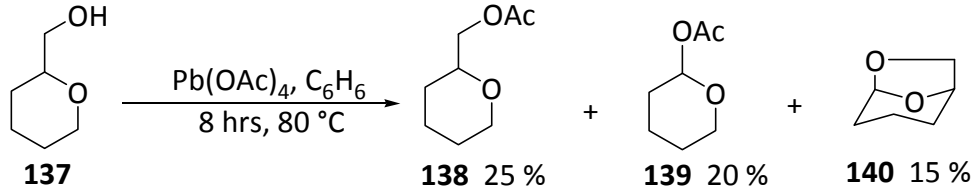


Scheme 55

The oxidation of 1,2,3-cyclohexane triol **133** to dial **136** is faster in basic solution, but it is tremendously slow in acidic solution. In acidic solution acetalization is greatly favoured.

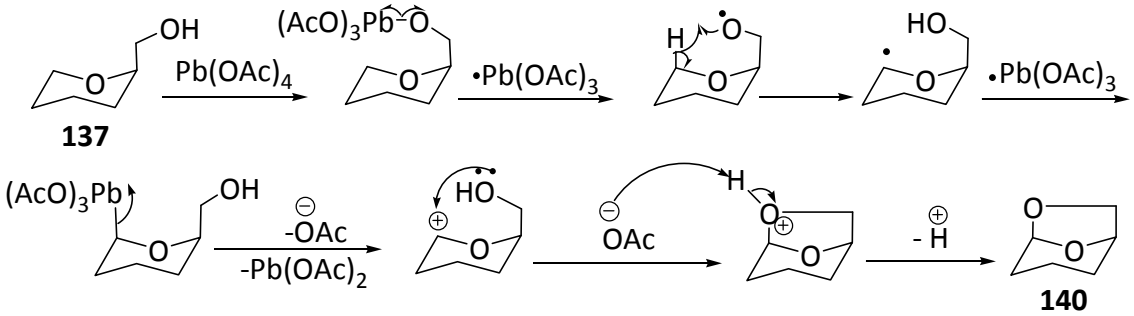
1.5.2. Cyclisation of carbinol

The oxidation of carbinol **137** with lead tetraacetate in refluxing benzene results in cyclisation forming bicyclic ketal **140** in low yield.[51]



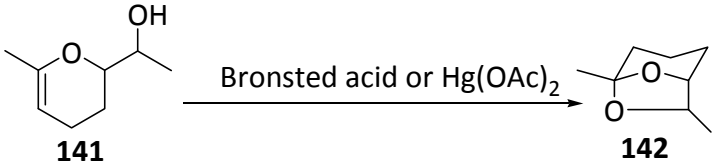
Scheme 56

The cyclization of a carbinol **137** with lead tetraacetate to bicyclic ketal **140** proceeds through a radical mechanism (Scheme 57).



Scheme 57

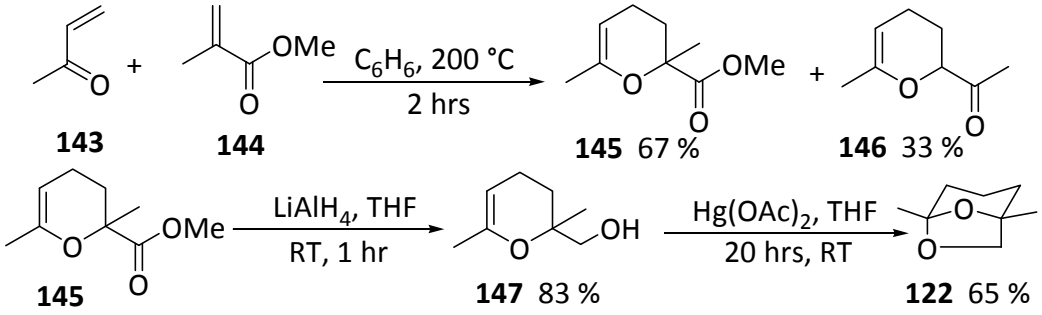
The secondary carbinol **141** can also cyclise to bicyclic ketals **142** by the treatment with Brønsted acid or mercury(II)acetate (Scheme 58).[50a]



Scheme 58

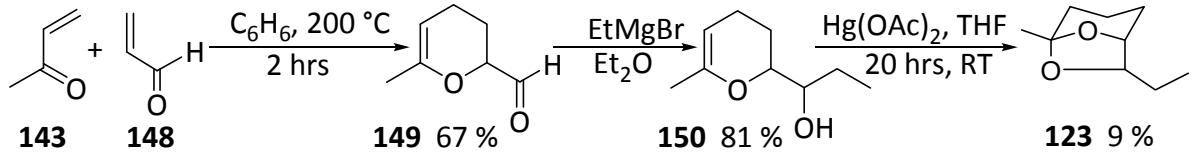
Frontalin, 1,5-dimethyl-6,8-dioxabicyclo[3.2.1]octane **122** is an aggregation pheromone of southern pine bettle, Dendroctonus frontalis. In 1971 Mondy *et al*. had reported its

synthesis from carbinol **147**.[52] A Diels-Alder reaction of methyl vinyl ketone **143** with methylmethacrylate **144** afforded a mixture of the dimer of methyl vinyl ketone **146** and cycloadduct **145**. The reduction of **145** with lithium aluminium hydride in THF gave carbinol **147** and cyclised to frontalin in the presence of mercury acetate (Scheme 59).



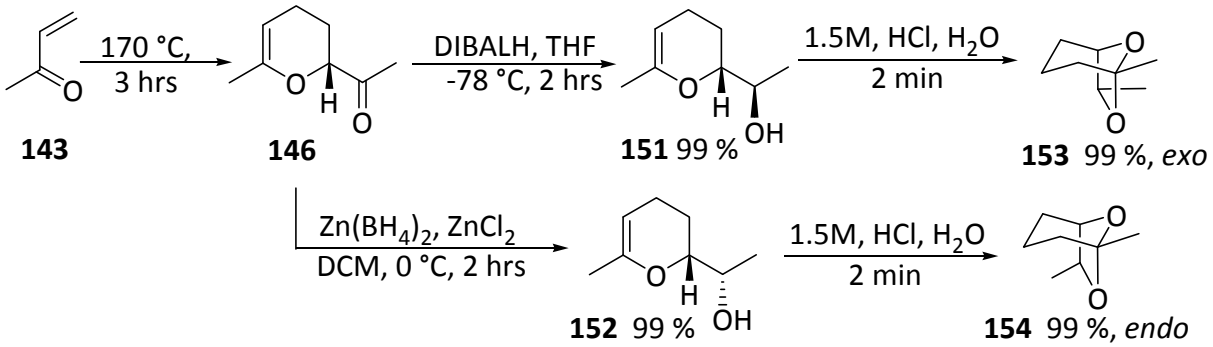
Scheme 59

Similarly, brevicomin a pheromone of western pine bettle, Dendroctonus brevicomin, was prepared (Scheme 60).



Scheme 60

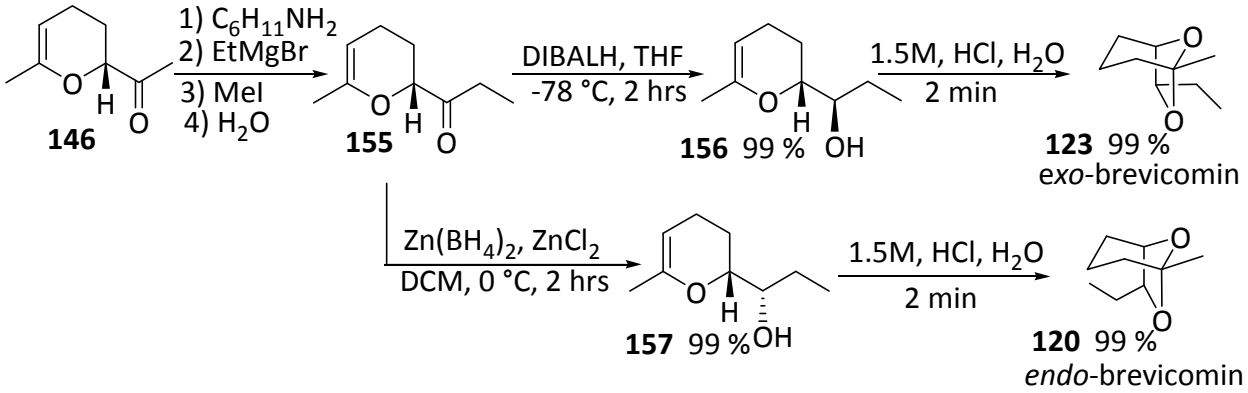
Jun *et al*. have reported stereoselective synthesis of *exo* and *endo* ketals by stereoselective reduction of methyl vinyl ketone dimer **146** to *syn* **151** or *anti* alcohol **152**.[53] The methyl vinyl ketone dimer was prepared by Diels-Alder reaction in an autoclave at 170 °C. A stereoselective reduction of MVK dimer by using a non-chelating, DIBALH in THF at -78 °C, yielded *syn*/*anti* ratio 83:17 and using a chelating system, $Zn(BH_4)_2$ with $ZnCl_2$ in DCM at 0 °C gave *syn*/*anti* ratio 19:81 in quantitative yield respectively. The *syn* and *anti* alcohols were cyclised to *exo* and *endo* ketals during the 1.5M aqueous HCl work up in quantitative yield respectively (Scheme 61).



Scheme 61

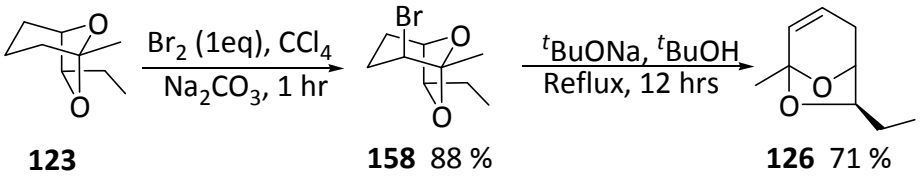
Then using this methodology *exo*-brevicomin and *endo*-brevicomin were prepared. The *exo*-brevicomin is known to be a key component of aggregation pheromone whereas *endo*-brevicomin is a potent inhibitor of aggregation behaviour of southern pine bettle.

MVK dimer **146** was methylated using enamine alkylation and reduced using DIBALH in THF at -78 °C, yielded *syn*/*anti* ratio 86:14 and using a chelating system, $Zn(BH_4)_2$ with $ZnCl_2$ in DCM at 0 °C gave *syn*/*anti* ratio 17:83 in quantitative yield respectively. After acidic work up *syn* and *anti* alcohols were converted to *exo*- and *endo*-brevicomin respectively (Scheme 62).



Scheme 62

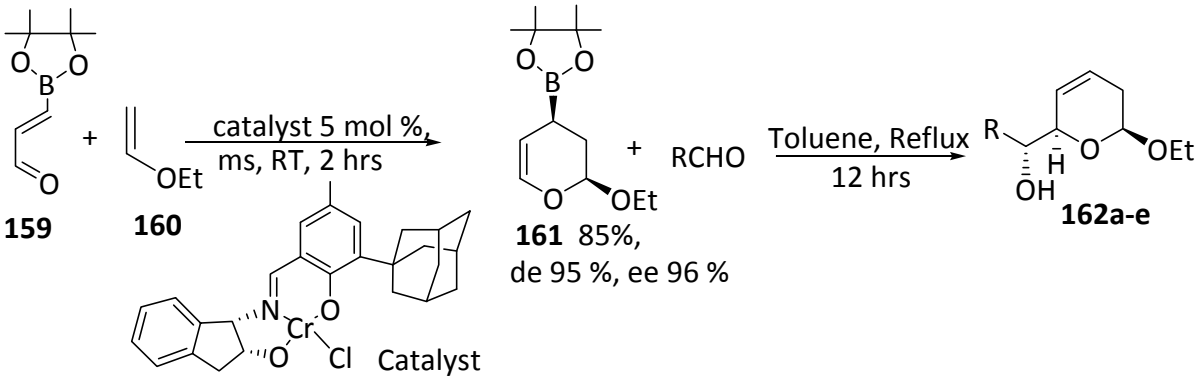
The mouse pheromone has been isolated from urine of the male mouse of the species mus musculus. To synthesise it *exo*-brevicomin **123** was brominated on carbon atom α to ketal functional group in 88 % yield using bromine in CCl_4 for seven hours at RT. With addition of sodium carbonate, the reaction was completed in one hour in quantative yield. The monobrominated product was dehydrobrominated with ^{t}BuONa at reflux over night via an E2 mechanism giving 71 % yield of the mouse pheromone (Scheme 63).



Scheme 63

Carreaux and Hall's groups have recently reported an efficient three component cycloaddition-allylboration sequence using Jacobsen's chiral Cr (III) catalyst to give α-hydroxyalkyl dihydropyrans **162a-e**.[54a-d] This sequence begins by inverse electron-demand hetero [4+2] cycloaddition that affords a cyclic allylboronate **161**, which is then able to react with an aldehyde to give the six membered adduct **162a-e** with two contiguous asymmetric

centres. By using this methodology α-hydroxyalkyl dihydropyran derivatives **162a-e** were prepared with high enantio and diastereoselectivity (Scheme 64, table 20).

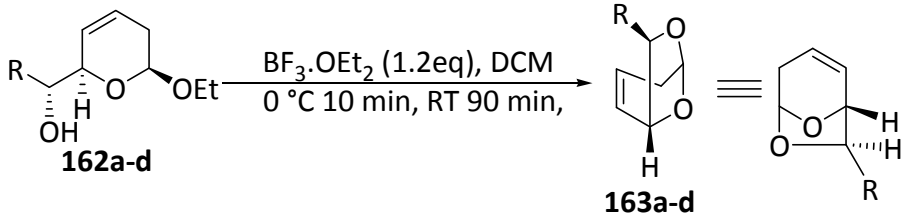


Scheme 64

Entry	R	Yield %	ee %	Product
1	4-$NO_2C_6H_4$-	92	96	**162a**
2	4-ClC_6H_4-	77	93	**162b**
3	Bn-	82	96	**162c**
4	Ph-CH(OTBDPS)	78	95	**162d**
5	Me-	70	95	**162e**

Table 20

Transformation of acetals **162a-d** to bicyclic acetals **163a-d** were carried out by using boron trifluoride etherate as Lewis acid (Scheme 65, table 21).[47]



Scheme 65

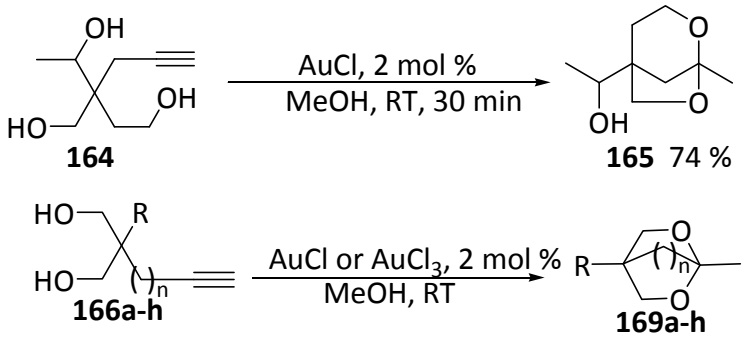
Entry	R	Yield %	Product
1	4-$NO_2C_6H_4$-	92	**163a**
2	4-ClC_6H_4-	93	**163b**
3	Bn-	87	**163c**
4	Ph-CH(OTBDPS)	95	**163d**

Table 21

1.5.3. Cycloisomerisation of alkynediol

Cycloisomerisation of alkynediols with various metals is also an efficient method for the synthesis of strained bicyclic ketals.[55] Bis-homopropargylic diols undergo Au-catalysed cyclisation under extremely mild conditions. Bis-homopropargylic alcohols have shown

interesting cyclisation behaviours in the presence of Pd, W, Ru and Rh catalysts. A general room temperature Au^{I}- and Au^{III}- catalysed cycloisomerisation of bis-homopropargylic diols leading to strained dioxabicyclo[2.2.1], [2.2.2] or [3.2.1] ketals. The diol **164** and **166** were cyclised in the presence of 2 mol % of AuCl or $AuCl_3$ in methanol. The reaction conditions were compatible with various side chains, such as benzyl, phenyl or ^{n}butyl groups. The corresponding bicyclic ketals were obtained in excellent 70-99 % yield and very short reaction time (Scheme 66, table 22).



164 **165** 74 %

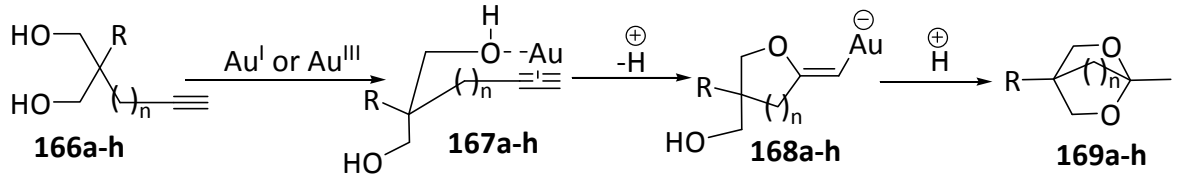
166a-h **169a-h**

Scheme 66

Entry	R	n	Catalyst	Time	Product	Yield %
1	Bn	1	AuCl	30 min	**169a**	99
2	Ph	1	AuCl	30 min	**169b**	99
3	^{n}Bu	1	AuCl	30 min	**169c**	80
4	Cinnamyl	2	AuCl	30 min	**169d**	82
5	Allyl	2	AuCl	30 min	**169e**	91
6	Bn	1	$AuCl_3$	30 min	**169f**	99
7	Ph	1	$AuCl_3$	30 min	**169g**	99
8	Allyl	1	$AuCl_3$	30 min	**169h**	74

Table 22

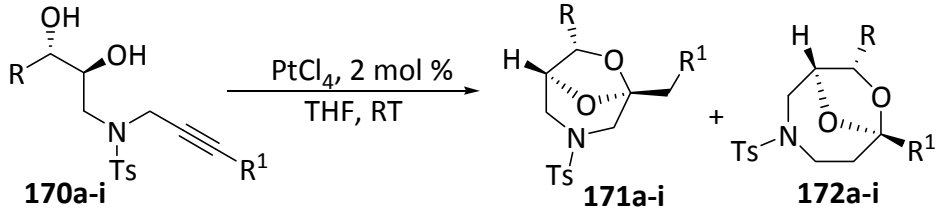
The Au^{I} or Au^{III} catalysed reaction may be initiated by the formation of π-alkynal complex **167a-h** through the complexation of unsaturated triple bond to the Au catalyst. The coordination of triple bond enhances the electrophilicity of the alkyne. The addition of one alcohol may be favoured by an intramolecular complexation of the OH group to the gold catalyst. The enol vinyl gold intermediate **168a-h** may be then protonolysed leading to an enol ether, which then undergoes another intramolecular addition of remaining alcohol leading to the cyclic ketal **169a-h** (Scheme 67).



Scheme 67

The transition metal-catalysed cycloisomerisation reactions of ω-alkynols have been applied to the synthesis of oxygen containing heterocycles. The intramolecular nature of these transformations means that the regio- and stereoselectivities are often excellent, thus permitting the synthesis of single compound after several bond forming reactions.

Ley *et al*. have reported a Lewis acid catalysed cascade cycloisomerisation-hydroalkoxylation reaction of 6-heptyne-1,2-diol derivative towards the synthesis of heteroatom containing fused bicyclic acetal.[56] The intramolecular double alkoxylation of alkyne diols result in the synthesis of [4.2.1] and [3.2.1] fused bicyclic acetals depending on the substitution of the triple bond. Terminal alkynes give the [3.2.1] bicyclic product by a 6-*exo* pathway, whereas arylalkynes undergo a 7-*endo* cyclisation to the [4.2.1] bicycles. After optimization process it was found that the use of 2 mol % $PtCl_4$ in THF solvent afford corresponding bicyclic acetal in good yield (Scheme 68, table 23).



Scheme 68

Entry	Alkyne diol 170a-i	R	R^1	Time	Product 171a-i	171 Yield %	Product 172a-i	172 Yield %
1	**170a**	H	H	2 hrs	**171a**	93	**172a**	0
2	**170b**	CO_2Me	H	2 hrs	**171b**	80	**172b**	0
3	**170c**	H	Ph	16 hrs	**171c**	0	**172c**	77
4	**170d**	H	2-BrC_6H_4-	16 hrs	**171d**	0	**172d**	82
5	**170e**	H	3-ClC_6H_4-	16 hrs	**171e**	0	**172e**	75
6	**170f**	H	3-$MeOC_6H_4$-	16 hrs	**171f**	0	**172f**	81
7	**170g**	H	4-FC_6H_4-	16hrs	**171g**	0	**172g**	89
8	**170h**	H	4-$CF_3C_6H_4$-	16 hrs	**171h**	75[a]	**172h**	[a]
9	**170i**	H	4-$NO_2C_6H_4$-	16 hrs	**171i**	83[b]	**172i**	[b]

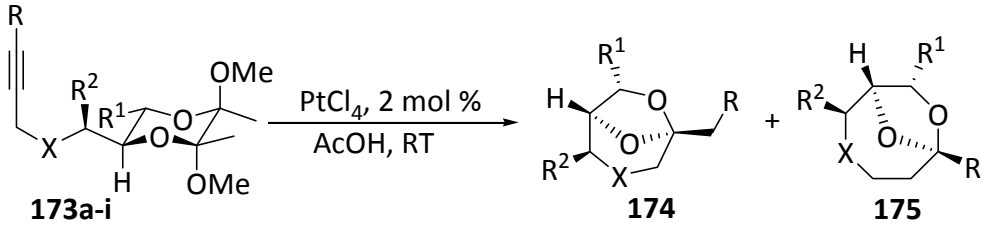
[a] 1 : 2.5 mixture of 171h and 172h , [b] 6 : 1 mixture of 171i and 172i

Table 23

During platinum catalysed double intramolecular hydroalkoxylation reaction, the substrates **170a-b** were cyclised by 6-*exo* cyclisation resulting [3.2.1]bicyclic acetals **171a-b**. Whereas,

the alkyne diols **170c-g** bearing an aryl-substituted triple bond, the internal triple bonds were found to be less reactive than terminal ones. Consequently, a longer reaction time (16 hrs) was required for reactions to complete. The major isolated product in most cases was the [4.2.1]bicyclic acetal **172c-g**, which arises from 7-*endo* cyclisation, instead of the [3.2.1]bicyclic acetals **171c-g** which can be formed by 6-*exo* cyclisation. The reaction proceeded in good yield for substrates without a strong electron withdrawing substituent on aromatic ring **170c-g** and gave the homochiral bicyclic acetals **172c-g**. However, the presence of an electron withdrawing substituent in the *para* position of the aromatic ring diminishes the reactivity and changes the regioselectivity of the cycloisomerisation reaction. Thus in the case of *p*-CF_3 **170h** and *p*-NO_2 **170i** 1:2.5 and 6:1 ratios of 6 *exo* to 7-*endo* products were observed respectively.

They further explored that the platinum catalyst can convert butane-2,3-diacetal protected substrate in to desired bicyclic acetal product by a cascade deprotection hydroalkoxylation sequence. Since acetal protecting groups can be removed by acid treatment, so Lewis acid was used to cleave butane-2,3-diacetal group and generate the diol which then underwent a double intramolecular hydroalkoxylation reaction of the triple bond. 2 Mol % $PtCl_4$ in acetic acid led to complete conversion of the starting material into bicyclic acetal. Although other Lewis acids were able to cleave the butane-2,3-diacetal group and form the diol as well, only $PtCl_4$ and $AuCl_3$ could catalysed the subsequent hydroalkoxylation reaction. The other solvent systems were not as effective for cascade sequence (Scheme 69, table 24).



173a-i **174** **175**

Scheme 69

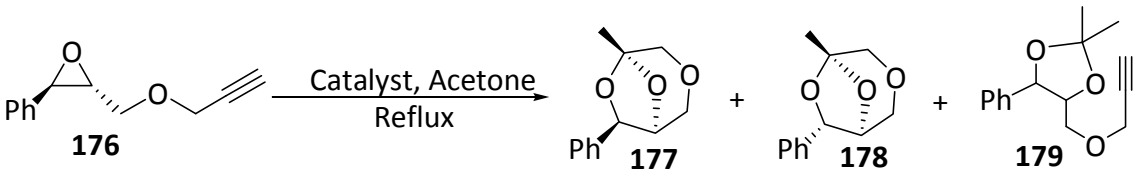
Entry	BDA 173a-i	R	R^1	R^2	X	Product	Yield %	d.r.
1	**173a**	H	H	H	NTs	**174a**	92	
2	**173b**	Ph	H	H	NTs	**175b**	75	
3	**173c**	2-BrC_6H_4-	H	H	NTs	**175c**	77	
4	**173d**	3-ClC_6H_4-	H	H	NTs	**175d**	65	
5	**173e**	4-FC_6H_4-	H	H	NTs	**175e**	78	
6	**173f**	4-$CF_3C_6H_4$-	H	H	NTs	**174f/175f**	63	1:2.5
7	**173g**	H	CH_2OBn	H	O	**174g**	84	
8	**173h**	H	CH_2OTs	H	O	**174h**	85	
9	**173i**	H	H	Bn	O	**174i**	72	

Table 24

The cycloisomerisation step of the cascade reaction proceeded with the same regioselectivity as already observed. The terminal alkyne lead to [3.2.1]bicyclic acetals **174** by a 6-*exo* pathway, where as aryl-substituted alkynes give rise to [4.2.1]bicyclic acetals **175** through a 7-*endo* cyclisation. The yields of isolated products were generally good and comparable to the cycloisomerisations of the corresponding alkyne diols.

1.5.4. Cascade cyclisation of epoxyalkyne

The search for new routes to complex molecules from relatively simple substrates has been one of the major objectives for organic chemists for the last decade.[57] In this regard cascade reactions have been established as a powerful tool to accomplish this goal. The cascade reactions offer highly efficient transformations by allowing the build up of complex structures in fewer steps and increased overall yields. Balamurugan *et al*. have observed the formation of bicyclic ketal **177** and acetonide **179** when epoxy alkyne **176** was heated under reflux in acetone in presence of 2 mol % $AuCl_3$. The improvement in the yield was noted when $AgSbF_6$ was added to $AuCl_3$ (entry 2). Although there was no reaction with Ph_3PAuCl but cationic Au(I) generated from a combination of Ph_3PAuCl and $AgSbF_6$ worked well for the formation of bicyclic ketals in good yields (Scheme 70, table 25).

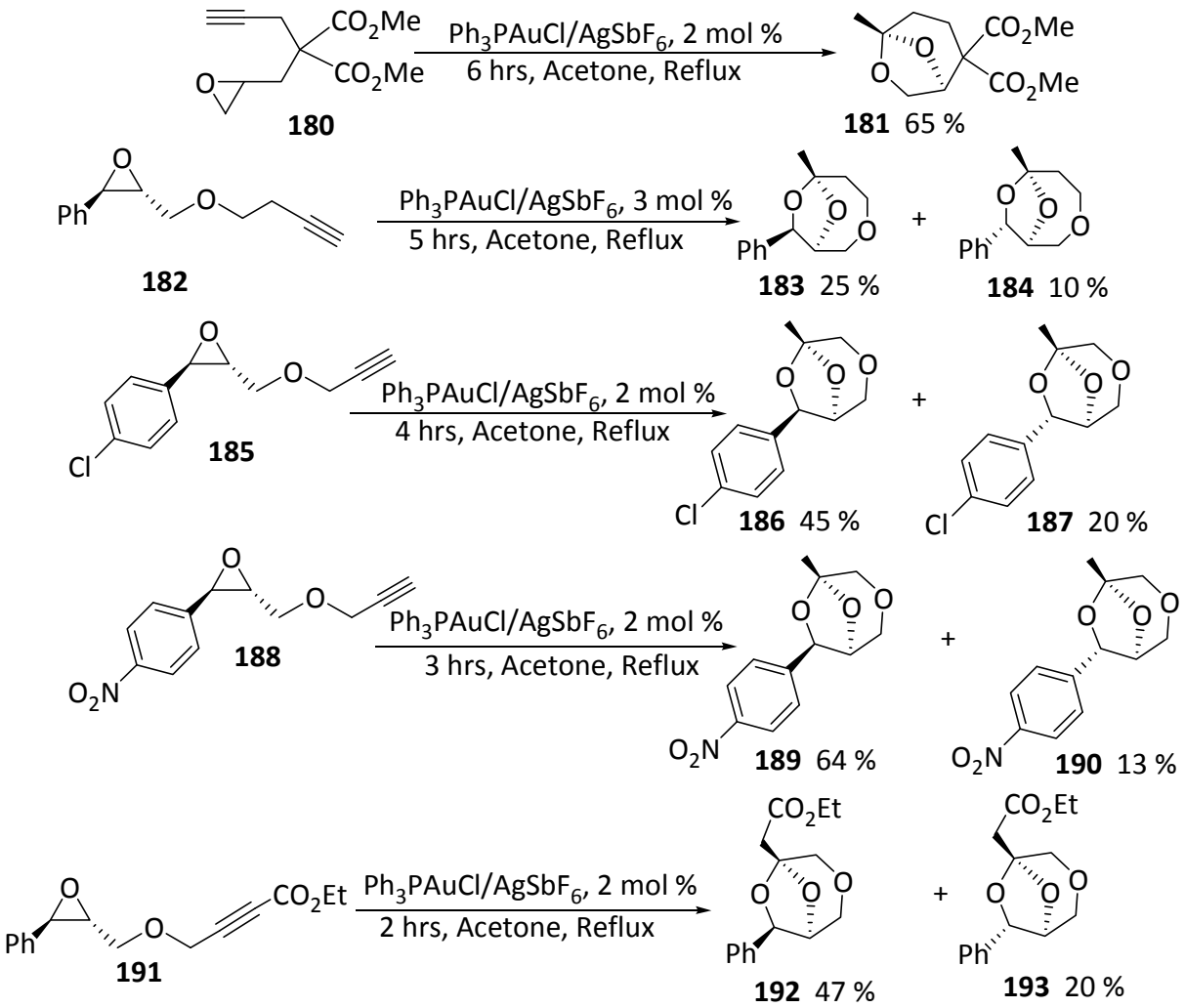


Scheme 70

Entry	Catalyst	Mol %	Time	177 Yield %	178 Yield %	179 Yield %	179 (*cis*:*trans*)
1	$AuCl_3$	2	11 hrs	6	0	85	1 : 1.4
2	$AuCl_3$/ $AgSbF_6$	2	12 hrs	20	7	30	1 : 13
3	Ph_3PAuCl	2	11 hrs	0	0	0	0
4	Ph_3PAuCl/ $AgSbF_6$	2	6 hrs	46	30	3	0 : 1
5	$AgSbF_6$	2	8 hrs	0	0	82	1.2 : 1
6	TfOH	5	5 hrs	0	0	56	1 : 1.9

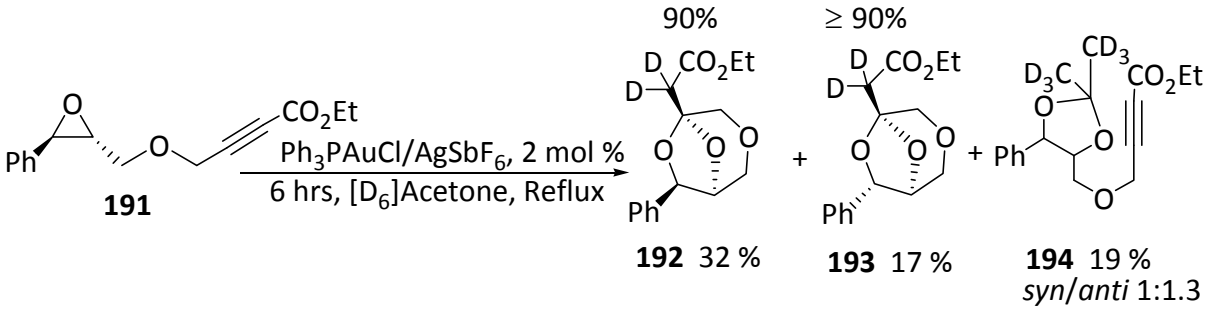
Table 25

A series of epoxy alkyne derivatives with different substitution patterns were synthesised and subjected to cascade cyclisation in the presence of Ph_3PAuCl/ $AgSbF_6$ in acetone under reflux. TLC analysis of the reaction mixtures revealed the formation of acetonide derivatives first and their subsequent transformation into corresponding bicyclic ketal derivatives (Scheme 71).



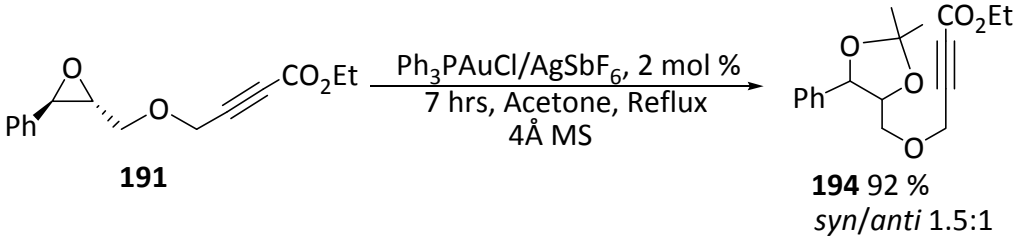
Scheme 71

To establish the mechanism of cyclisation, the gold catalysed cyclisation of epoxy alkyne **191** was carried out in deuterated acetone. This reaction resulted in deuterium incorporation (≥90%) at the methylene carbon α to the ester. These results indicate the involvement of acetone in the protodemetallation during the cyclisation (Scheme 72).



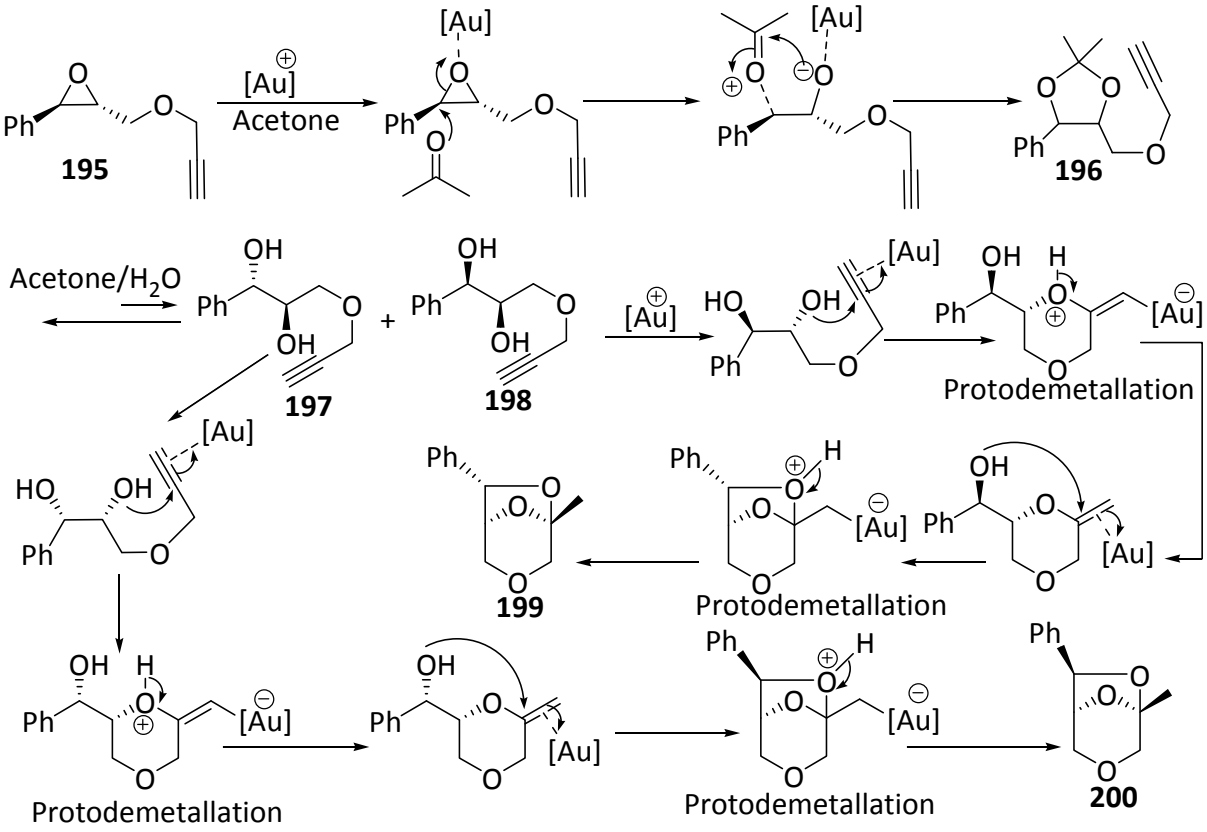
Scheme 72

But when the same reaction was performed in acetone in the presence of molecular sieve (4Å) the reaction stopped at the acetonide stage, indicating that cascade cyclisation proceeds with the assistance of water (Scheme 73).



Scheme 73

All these reaction were performed under anhydrous conditions. Under Lewis acidic conditions there is a great likelihood that the acetone solvent underwent aldol self condensation to generate water. These experiments indicate that water that is slowly formed from acetone plays a vital role in the cyclisation. Deuterium incorporation was observed when reaction was carried out in [D_6] acetone shows that water had come from acetone. The ring opening of epoxy alkyne **195** by acetone catalysed by Lewis acid gives a mixture of *cis* and *trans* acetonide **196**. The acetonide **196** can enter into an equilibrium with *trans* **197** and *cis* diol **198** with assistance of Lewis acid and water generated from acetone. The diol **197** and **198** can catalyse intramolecularly on the triple bonds under gold catalyst resulting in bicyclic ketals **199** and **200** (Scheme 74).

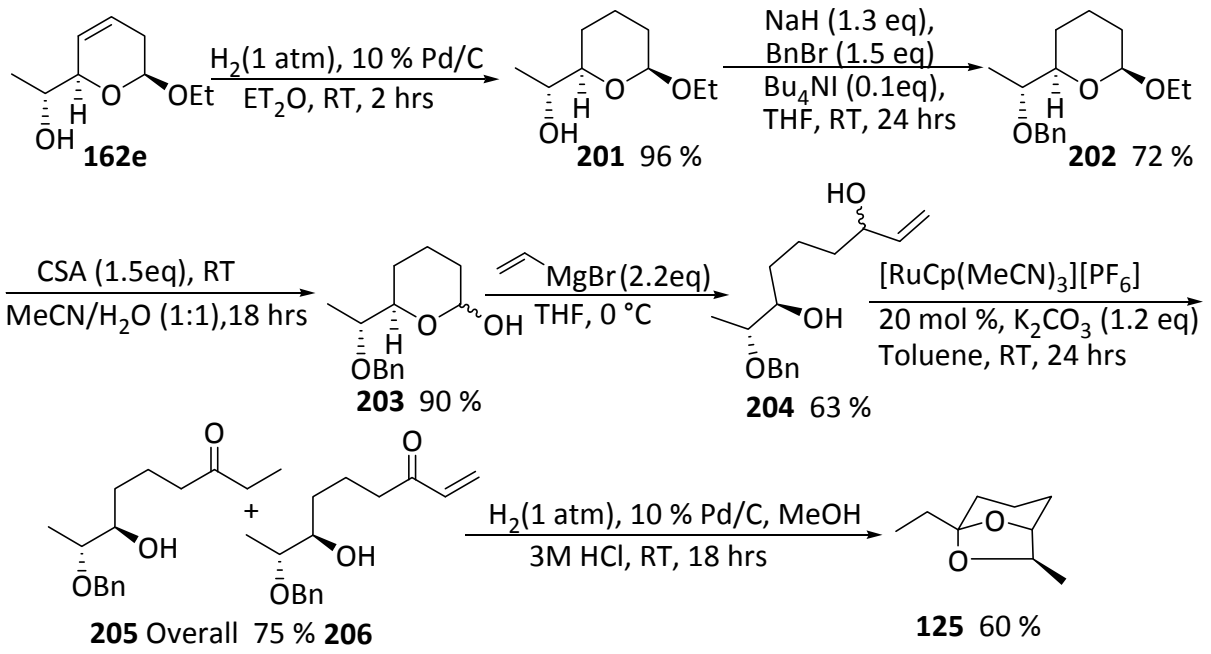


Scheme 74

1.5.5. Intramolecular acetalization of dihydroxy ketone

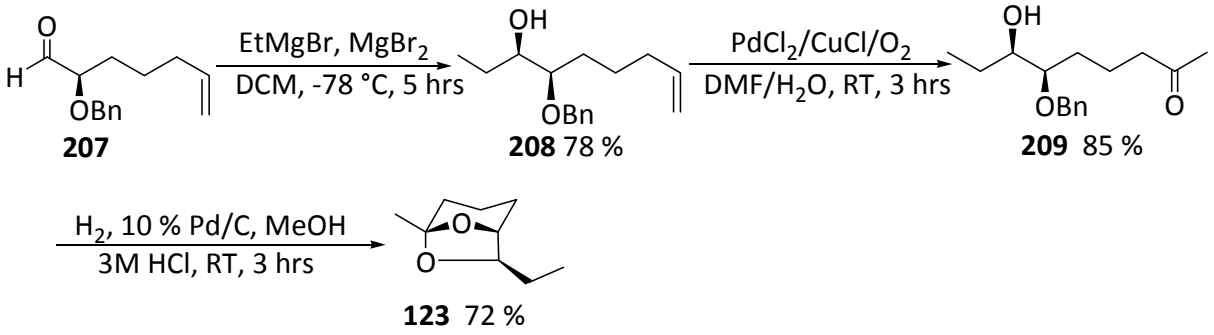
The synthesis of dihydroxy ketone followed by an interamolecular acetalization is the most widely used method for the preparation of 6,8-dioxabicyclo[3.2.1]octane skelton. Various synthetic strategies were employed for the synthesis of dihydroxy ketone.

α-Hydroxyalkyl dihydropyran **162e** could be a good precursor for asymmetric construction of 6,8-dioxabicyclo[3.2.1]octane ring system.[47] Hydrogenation of the double bond in the presence of Pd/C, followed by benzylation of hydroxyl group, afforded benzyl ether **202** with 84 % overall yield for the two steps. Hydrolysis of ethyl lactol **202** was carried out with camphorsulfonic acid in an aqueous medium at RT to give compound **203** which was converted into a mixture of diastereoisomers of allylic alcohol by addition of vinylmagnesium chloride. Redox isomerisation of **204** was carried out with 20 mol % $[RuCp(MeCN)_3][PF_6]$ in toluene at RT giving carbonyl compound **205** and α-β-unsaturated carbonyl compound **206** in a ratio 7:3 respectively, with 75 % overall yield. The hydrogenation of α-β-unsaturated carbonyl compound in the reaction mixture with palladium on charcoal could lead to the formation of the same carbonyl compound **205** and traces of acid resulted in formation of (+)-iso-*exo*-brevicomin in 60 % yield (Scheme 75).



Scheme 75

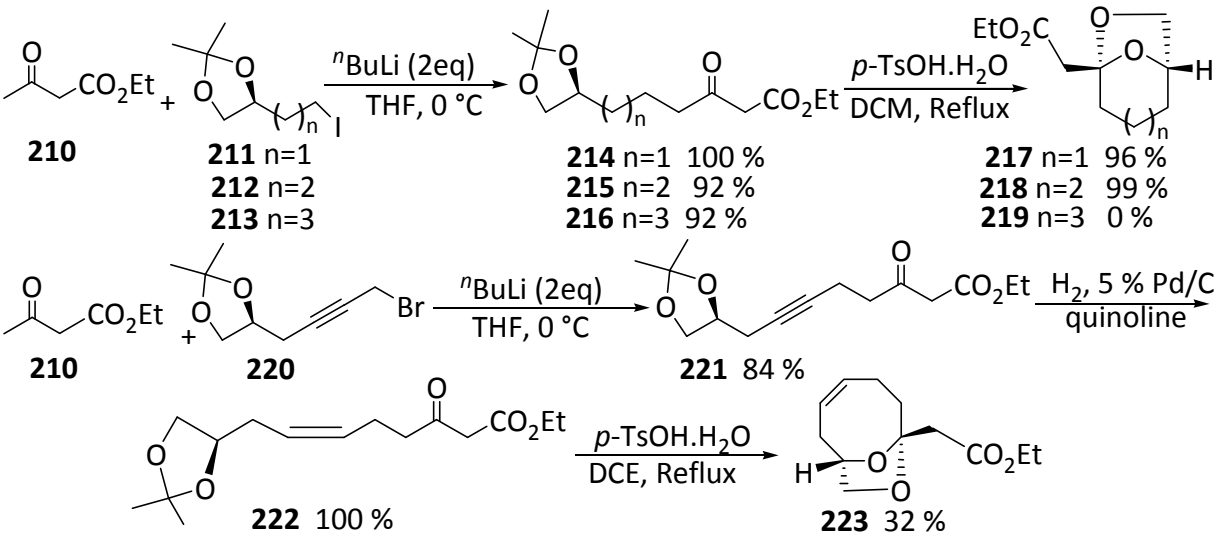
When aldehyde **207** was treated with ethylmagnesium bromide in the presence of magnesium bromide in dichloromethane the corresponding *syn* alcohol **208** was obtained as a single diastereoisomer in 78 % yield.[58a-b] Wacker oxidation of alcohol **208** with $PdCl_2$/CuCl produced ketone **209**. Simultaneous debenzylation and intramolecular acetalization with Pd/C in MeOH and a trace of 3M HCl transformed **209** into (+)-*exo*-brevicomin (Scheme 76).



Scheme 76

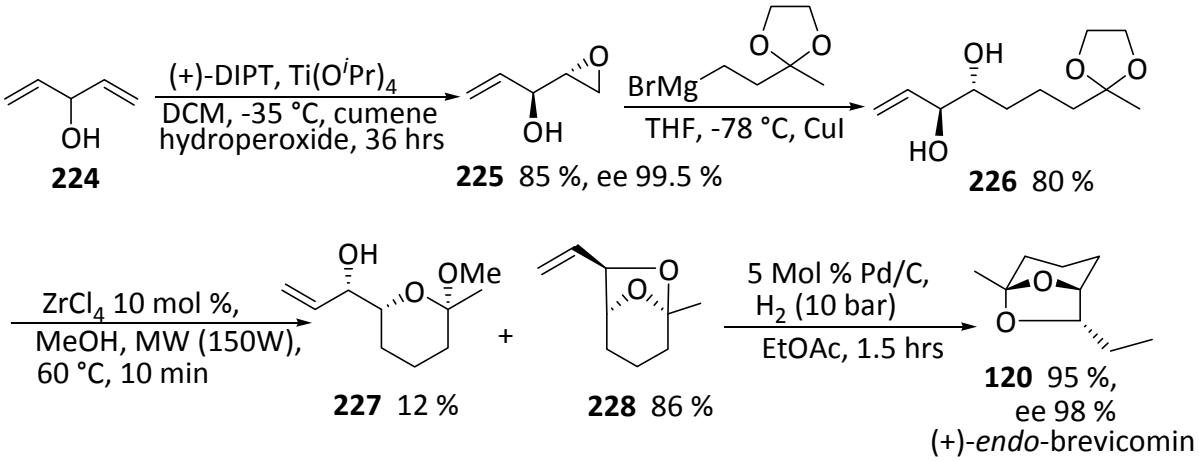
Kotsuki *et al*. have employed intramolecular acetalization of chiral ω-ketodiols for enantioselective construction of bicyclic ketals.[59] The synthesis of chiral ω-ketoacetonide derivatives **214-216** were carried out by condensation of optically active iodides **211-213** with ethylacetoacetate **210**. The subsequent step of bicyclic ketal **217-219** formation under the intramolecular transketalization conditions was found to be rather sensitive to the chain length of the substrates. The transformation of **214** and **215** to the corresponding bicyclic ketals **217-218** proceeded smoothly and in good yield by treatment with a catalytic amount

of *p*-toluenesulfonic acid in refluxing dichloromethane. Under the same conditions **216** did not give ketal **219**. Apparently this difficulty could be due to the unfavourable thermodynamic and conformational reasons. To overcome this difficulty *cis* double bond was introduced in carbon framework and bicyclic ketalization of **222** was effected in refluxing DCE in the presence of *p*-toluenesulfonic acid (0.5eq) (Scheme 77).



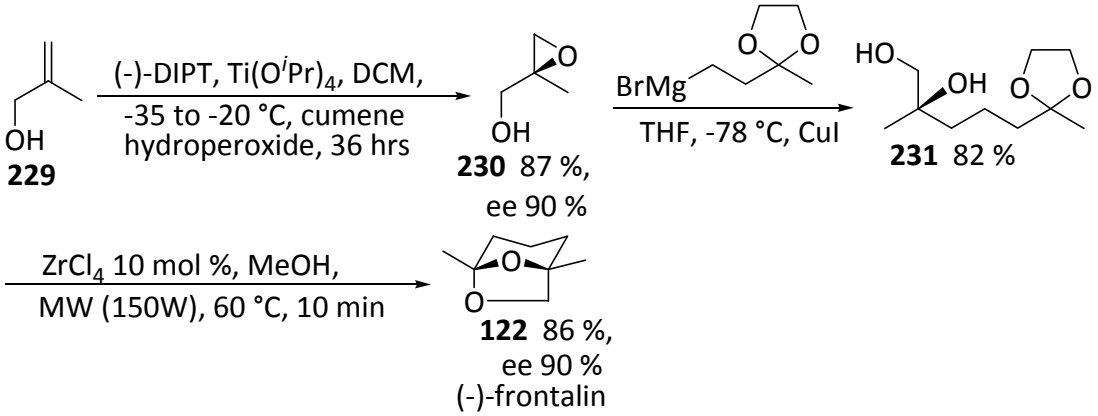
Scheme 77

Guiry *et al*. have employed Lewis acid catalysed deprotection of protected ketone **226** and intramolecular acetalization of dihydroxy ketone gave 6,8-dioxabicyclo[3.2.1]octane ring system.[60] The Sharpless asymmetric epoxidation of alcohol **224** afforded epoxide **225** in 85 % yield and 99.5 % ee. The ring opening of epoxide **225** by the Grignard reagent, in the presence of 10 mol % CuI at -78 °C, afforded diol **226**. The diol **226** was treated with $ZrCl_4$ in methanol under microwave irradiation to give (1*R*,5*S*,7*S*)-5-methyl-7-vinyl-6,8-dioxabicyclo[3.2.1]octane **228** via the formation of (*S*)-1-((2*R*,6*S*)-6-methoxy-6-methyltetrahydro-2H-pyran-2-yl)prop-2-en-1-ol **227**. Acetal **227** could be quantitatively transformed into (1*R*,5*S*,7*S*)-5-methyl-7-vinyl-6,8-dioxabicyclo[3.2.1]octane **228** upon treatment with $ZrCl_4$ in methanol under microwave irradiation. Hydrogenation of **228** in the presence of a catalytic amount of Pd/C gave (+)-*endo*-brevicomin in 95 % yield and 98 % ee (Scheme 78).



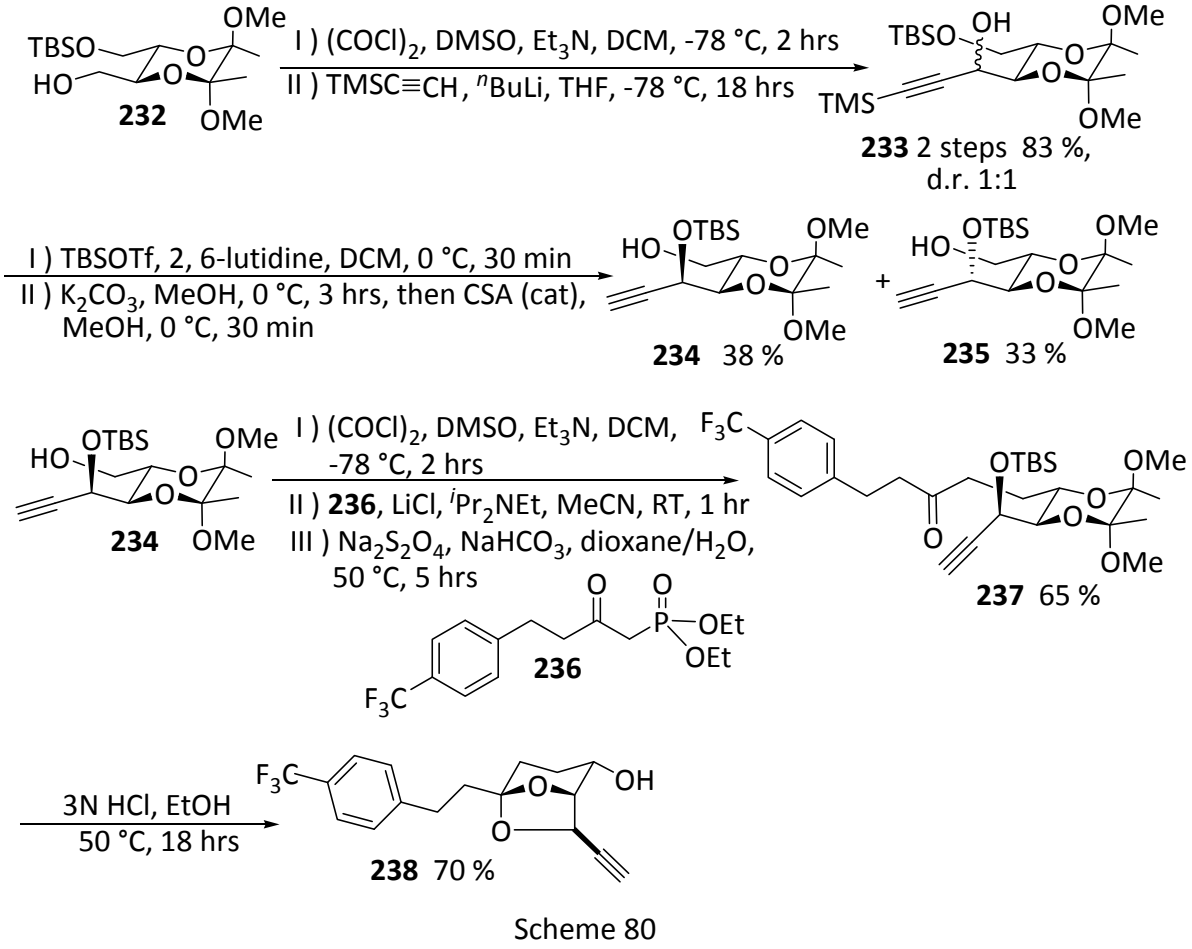
Scheme 78

Similarly (-)-frontalin was synthesised by (+)-epoxide **230** under similar reaction conditions (Scheme 79).[61]



Scheme 79

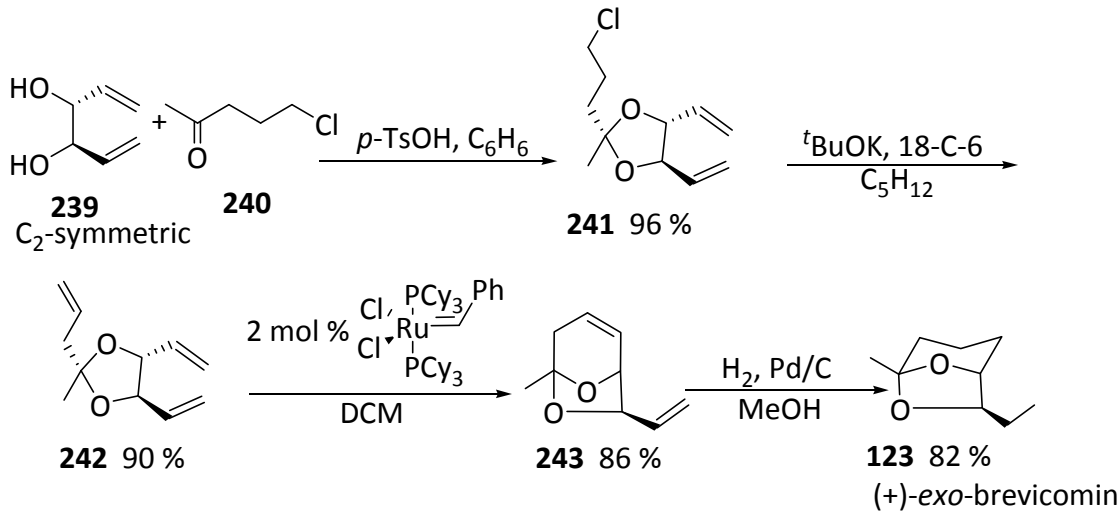
Ley *et al*. have employed butane-2,3-diacetal protected substrate **237** for the synthesis of 6,8-dioxabicyclo[3.2.1]octane ring system.[62] The swern oxidation of known compound **232** and acetylide addition to the resultant aldehyde afforded as a deliberate 1:1 mixture of diastereoisomers **233**. Efficient protecting group manipulation subsequently led to separable diastereoisomeric alcohols **234** and **235**. The Swern oxidation of alcohol **234** gave the aldehyde, which was then reacted with phosphonate diester **236** under Horner-Emmons condition. The use of diverse phosphonate reagents was a convenient way to introduce chemical variation at this end. Reduction of the resulting enone led to the precursor **237** which on treatment with acid, cyclised to afford as a single diastereoisomer **238** (Scheme 80).



Scheme 80

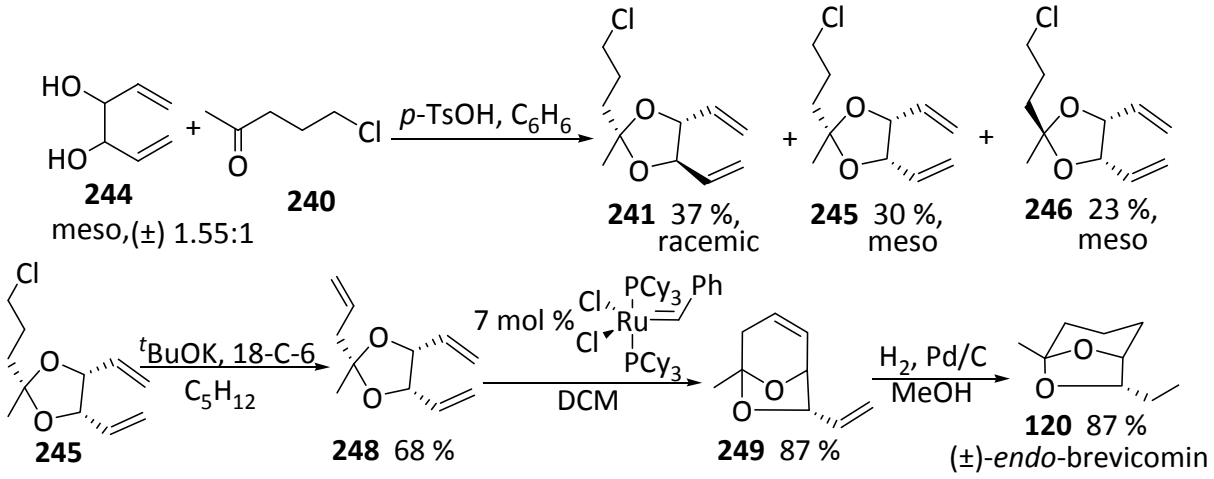
1.5.6. Ring-closing metathesis

Ring-closing metathesis has recently been featured in novel constructions of small, medium and large rings. Burke *et al*. have employed desymmetrization of trienes **242** and **248** derived from diol **239** and **244** with C_2 and meso symmetry via ring-closing metathesis for construction of 6,8-dioxabicyclo[3.2.1]octane ring system.[63] Ketalization of commercially available 5-choloro-2-pentanone **240** with diol **239** under Dean-Stark conditions gave ketal **241** in 96 % yield. Elimination with ^{t}BuOK and catalytic amount of 18-crown-6 afforded the triene **242** together with its internal double bond isomer in an inseparable 14:1 mixture. The minor internal double bond isomer did not react and was separated by flash chromatography. Ring-closing metathesis with 2 mol % of the Grubbs catalyst converted triene **242** to 6,8-dioxabicyclo[3.2.1]octane ring **243**. Catalytic hydrogenation of 6,8-dioxabicyclo[3.2.1]octane ring system **243** afforded (+)-*exo*-brevicomin **123** (Scheme 81).



Scheme 81

Ketalization of 5-choloro-2-pentanone **240** with a 1.55:1 meso, (±) diol **244** afforded three diastereoisomers rac-**241** 37 %, meso-**245** 30 % and meso-**246** 23 % which were separated by flash chromatography. Subjection of meso *cis* ketal **245** to elimination conditions produced triene **248** together with small amount of its internal double bond isomer (45:1, 68 %). The meso triene **248** was desymmetrized to the racemic 6,8-dioxabicyclo[3.2.1]octane skelton **249**, with vinyl group *endo*, via ring closing metathesis using 7 mol % Grubbs catalyst. As before internal double bond isomer did not react and was separated by flash chromatography. Catalytic hydrogenation of 6,8-dioxabicyclo[3.2.1]octane ring system **249** afforded (±)-*endo*-brevicomin **120** (Scheme 82).

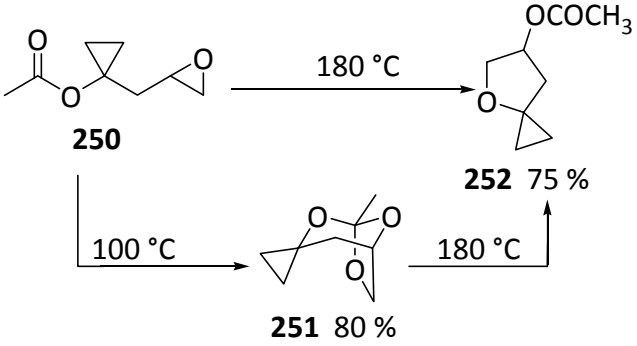


Scheme 82

1.5.7. Cycloisomerisation of carbonyl epoxide

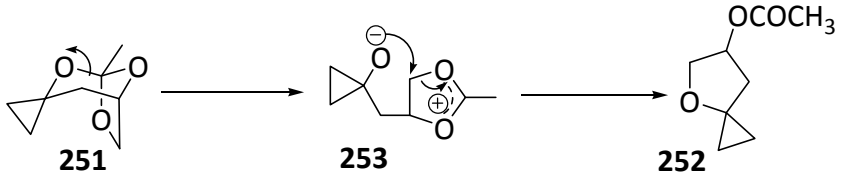
In 1969 Wassermann *et al*. have observed that the epoxide of 1-allylcyclopropyl acetate **250** undergoes a novel thermal rearrangement at 180 °C to yield 2,2-dimethylene-4-

acetoxytetrahydrofuran **252**.[64] The intermediate in this transformation appears to be the orthoester **251**, since **251** may be formed from **250** at a lower temperature of 100 °C. Complete details of the reaction were not reported (Scheme 83).



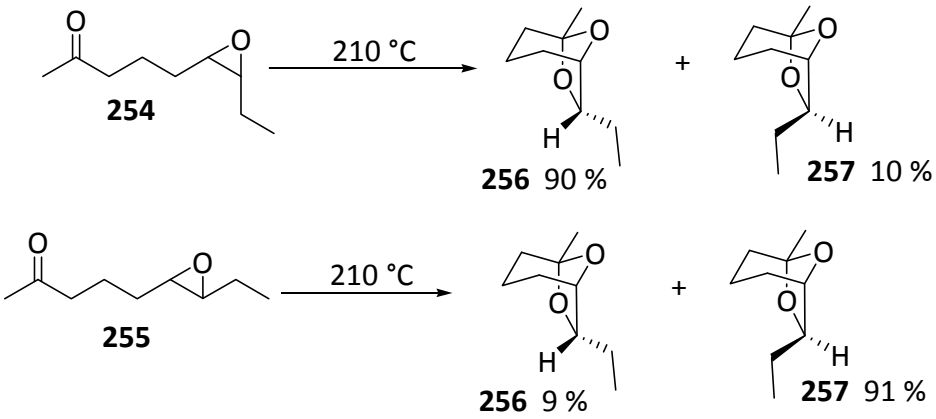
Scheme 83

Conversion of **251** to **252** appears to take place by heterolytic C—O cleavage with formation of intermediate **253** (Scheme 84).



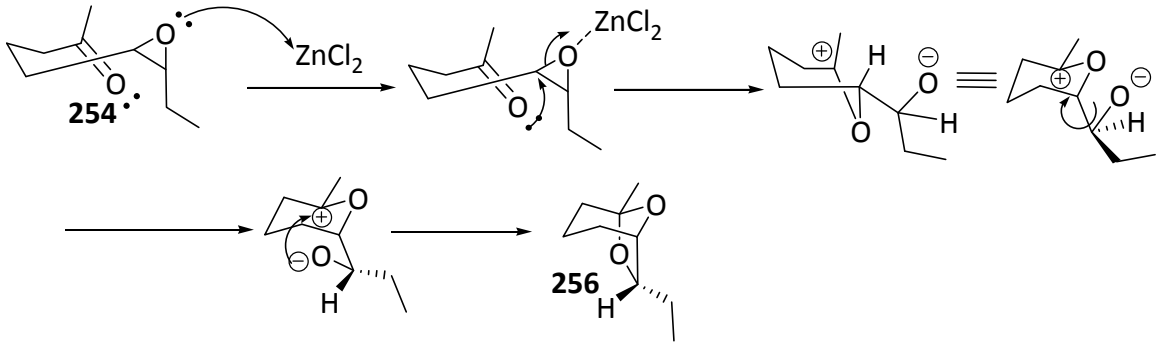
Scheme 84

They further applied the above thermal rearrangement of α-ε-epoxy ketones to a useful synthesis of brevicomin. When *cis*-6,7-epoxynonan-2-one **254** was heated to 210 °C, nearly complete conversion took place to yield a mixture of *exo*-6-ethyl-1-methyl-7,8-dioxabicyclo[3.2.1]octane **256** 90 % and the corresponding *endo* isomer **257** 10 %. Similarly *trans*-6,7-epoxynonan-2-one **255** under the same reaction conditions gave *endo*-6-ethyl-1-methyl-7,8-dioxabicyclo[3.2.1]octane **257** in 91 % yield and the corresponding *exo* isomer **256** in 9 % yield (Scheme 85).



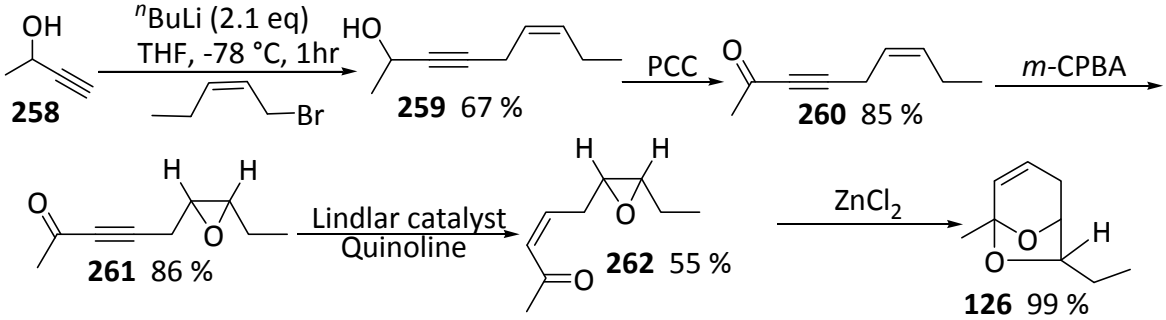
Scheme 85

These reactions were also catalysed by acid and transformation appeared to take place by ring opening of the epoxide by the carbonyl oxygen stereospecifically, with inversion of configuration through a chair like transition state as illustrated in the $ZnCl_2$ catalysed process (Scheme 86).



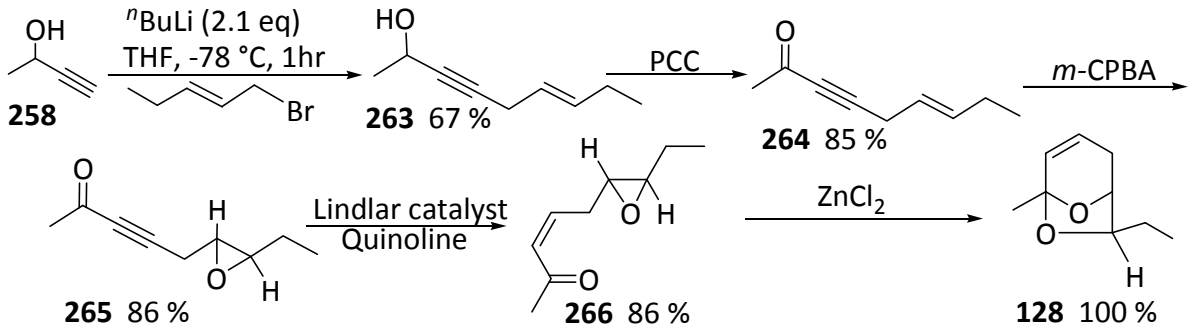
Scheme 86

They further extended this rearrangement to unsaturated analogous, (*Z*)-6,7-epoxy-3-nonen-2-one **262** and (*E*)-6,7-epoxy-3-nonen-2-one **266**.[65] The alkylation of precursor (±) 2-hydroxy-3-butyne **258** with (*Z*)-1-bromo-2-pentene was carried out using ^{n}BuLi, in THF and the alkylated product **259** was oxidised by PCC to the corresponding ketone **260**. The epoxidation of ketone **260** with *m*-CPBA gave (*Z*)-epoxide **261**. Hydrogenation of (*Z*)-epoxide **261** with Lindlar's catalyst afforded (*Z*)-6,7-epoxy-3-nonen-2-one **262**. The rearrangement of (*Z*)-6,7-epoxy-3-nonen-2-one **262** proceeded smoothly in the presence of $ZnCl_2$ and gave (±)-mus musculus pheromone **126** (house mouse pheromone) stereospecifically in quantitative yield (Scheme 87). The reaction was tried with various acids ($BF_3.Et_2O$, *p*-TsOH, silicic acid and $ZnCl_2$). During the screening process $ZnCl_2$ was found to be the most effective Lewis acid.



Scheme 87

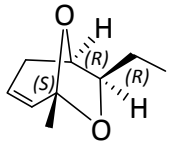
Similarly, (*E*)-6,7-epoxy-3-nonen-2-one **266** was prepared. The treatment of (*E*)-6,7-epoxy-3-nonen-2-one **266** with $ZnCl_2$ afforded (±)-*endo*-derivative **128** as the sole product (Scheme 88).



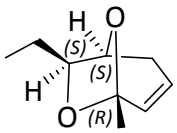
Scheme 88

Intramolecular ring opening of the epoxides **262** and **266** by the carbonyl oxygen take place stereospecifically, with inversion of configuration at the epoxide carbon under the nucleophilic attack.

Later they employed this rearrangement in conjunction with the Sharpless asymmetric epoxidation for efficient synthesis of both enantiomers **126** and **127** of mus musculus pheromone.[66]

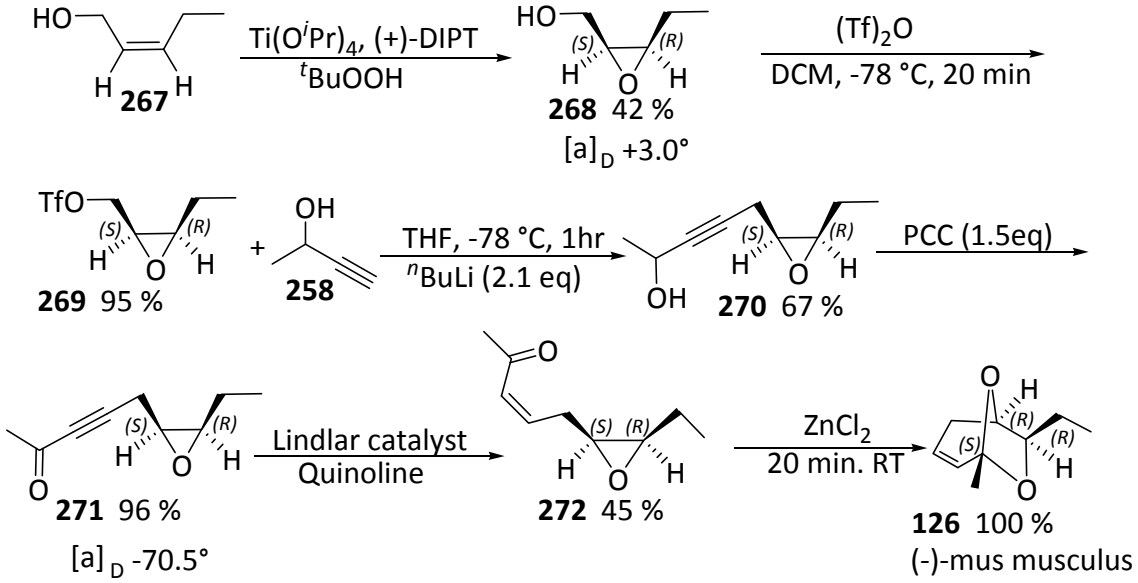


126
(-)-Mus musculus



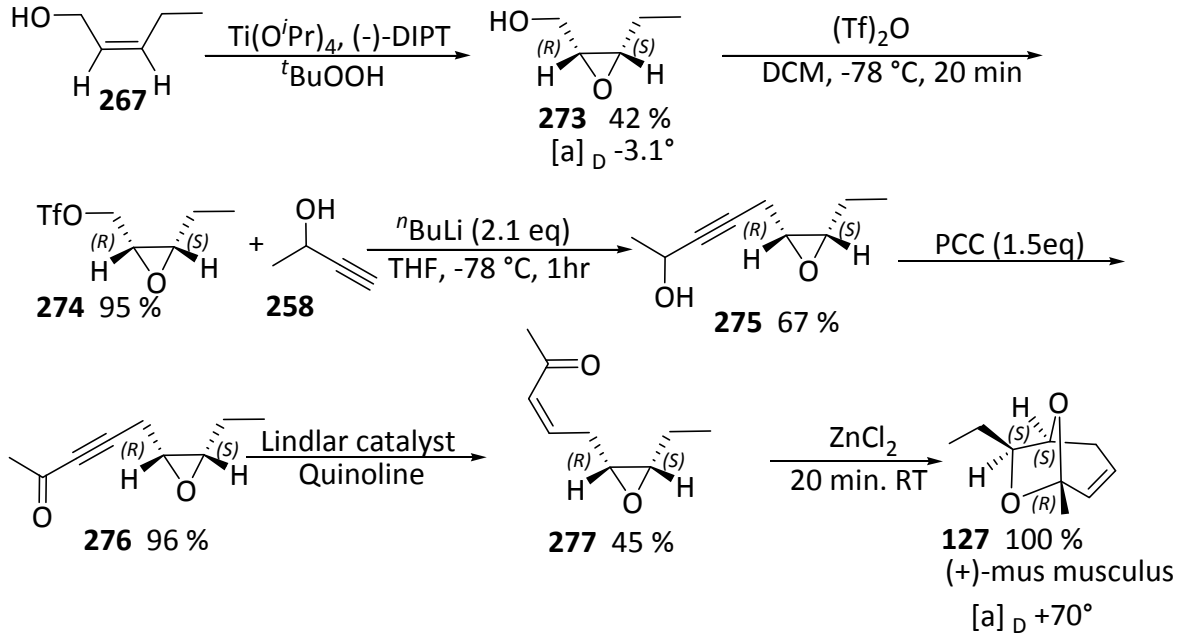
127
(+)-Mus musculus

The (*Z*)-alcohol **267** was epoxidized in the presence of (+)-diisopropyl tartrate and titanium isopropoxide to afford 2(*S*)-3(*R*)-epoxy-1-pentanol **268** in moderate yield 42 % $[\alpha]_D$ +3.0°. The alcohol **268** was immediately treated with trifluoromethylsulfonic anhydride in DCM to yield triflate **269**. The triflate **269** was alkylated with (±) 2-hydroxy-3-butyne **258** in the presence of ^{n}BuLi giving a diastereoisomeric mixture of alcohol **270**, which was oxidized to ketone **271** by PCC. The reduction of acetylenic ketone **271** using Lindler's catalyst afforded 6-(*S*)-7-(*R*)-epoxy-3-nonen-2-one **272** in 45 % yield. When 6-(*S*)-7-(*R*)-epoxy-3-nonen-2-one **272** was treated with $ZnCl_2$ in DCM at RT afforded the pure (-)-mus-musculus pheromone **126** in quantitative yield $[\alpha]_D$ -70.5° (Scheme 89).



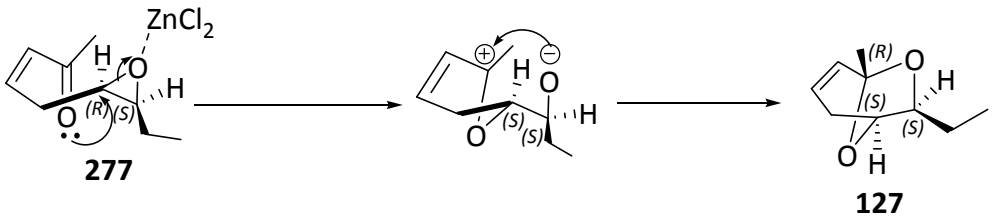
Scheme 89

Using (-)-diisopropyl tartrate in the asymmetric epoxidation, epoxy alcohol **273** was prepared $[\alpha]_D$ -3.1°. Then using epoxy alcohol **273** by following the same synthetic steps as in scheme 89 the pure (+)-mus musculus pheromone **127** was prepared in quantitative yield $[\alpha]_D$ +70.4° (Scheme 90).



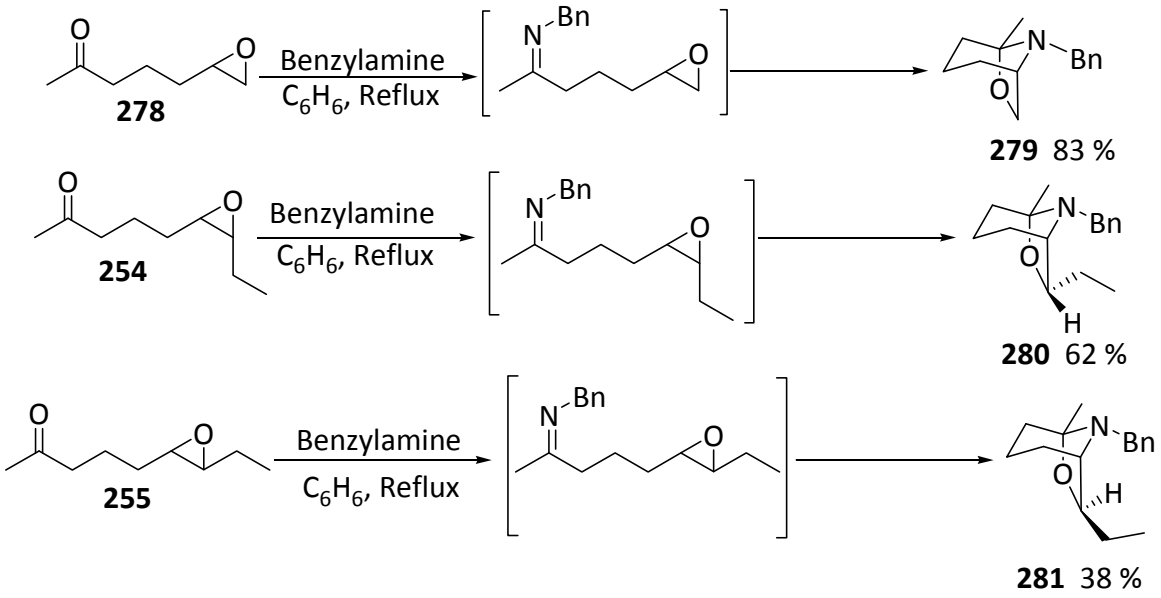
Scheme 90

As observed previously on carbonyl epoxide rearrangement, the reaction takes place stereospecifically with epoxide ring opening by the ketone carbonyl group with inversion of configuration (Scheme 91).



Scheme 91

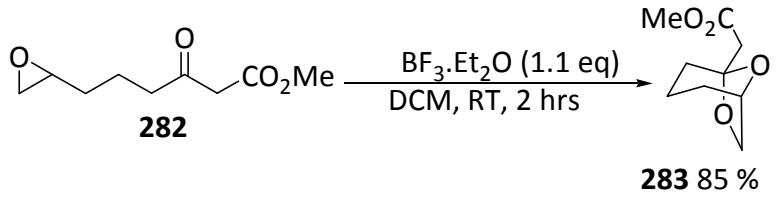
After successfully using α-ε-epoxy ketones for synthesis of 6,8-dioxabicyclo[3.2.1]octane derivatives, they further extended this reaction to α-ε-epoxy imines, leading to 6-oxa-8-azabicyclo[3.2.1]octanes by an analogous stereospecific epoxide ring opening.[67] Treatment of 6,7-epoxy-2-heptanone **278** with benzyl amine in refluxing benzene led directly to the 6-oxa-8-azabicyclo[3.2.1]octane **279** in 83 % yield. Under the same conditions, *cis*-6,7-epoxy-2-nonanone **254** was reacted with benzyl amine to give N-benzyl-*exo*-7-ethyl-5-methyl-6-oxa-8-azabicyclo[3.2.1]octanes **280** as the exclusive product. *Trans*-6,7-epoxy-2-nonanone **255** gave only the corresponding *endo* isomer **281** (Scheme 92).



Scheme 92

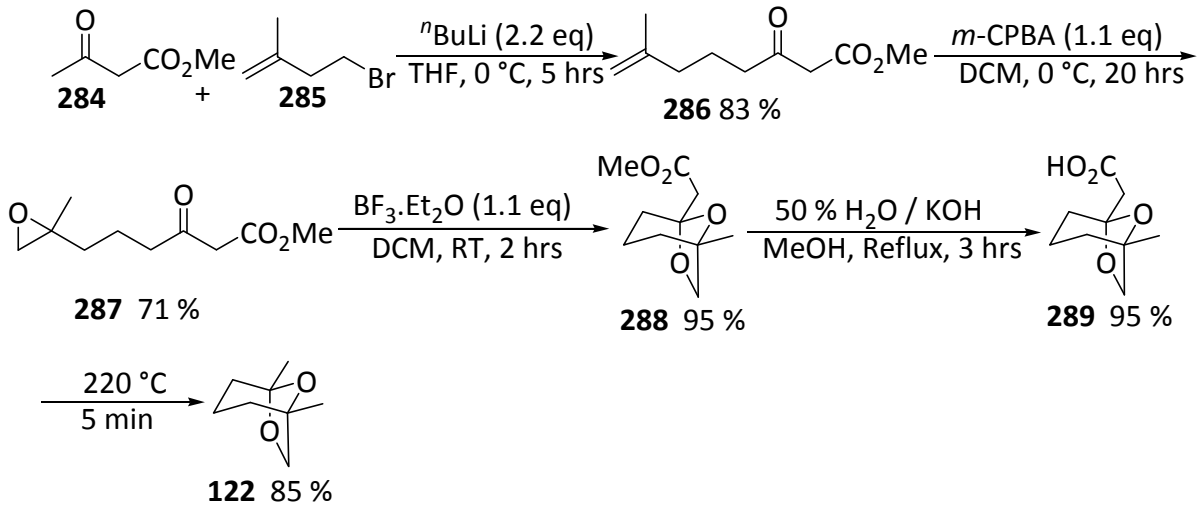
The cycloisomerisation of α-ε-epoxy ketones and α-ε-epoxy imines to 6,8-dioxabicyclo[3.2.1]octane and 6-oxa-8-azabicyclo[3.2.1]octane shows that this cycloisomerisation could be extended to α-ε-epoxy ester, α-ε-epoxy amides etc.

Sum and co-workers have also reported Lewis acid catalysed isomerisation of epoxide **282** affording 6,8-dioxabicyclo[3.2.1]octane **283** in 85 % yield (Scheme 93).[68]



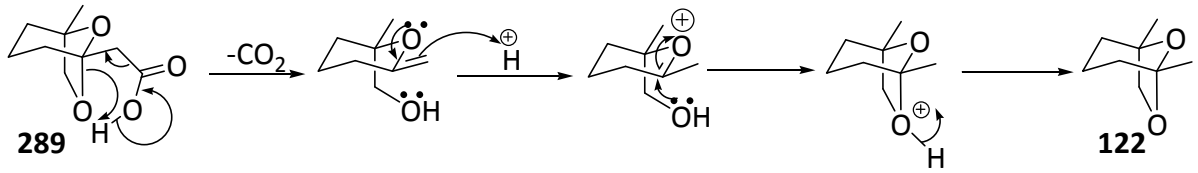
Scheme 93

Then they successfully used this strategy for the construction of insect pheromones. In the synthesis of frontalin the methylacetoacetate **284** was alkylated with 4-bromo-2-methyl-1-butene **285** to afford 83 % of the γ-alkylated product **286**. The epoxidation was carried by *m*-chloroperbenzoic acid. The $BF_3.Et_2O$ catalysed cyclisation of **287** afforded 6,8-dioxabicyclo[3.2.1]octane **288** in 95 % yield. The ester **288** was hydrolysed with 50 % aqueous alkaline solution in methanol and resulting carboxylic acid **289** underwent smooth thermal decarboxylation to give an 85 % yield of (±)-frontaline **122** (Scheme 94).



Scheme 94

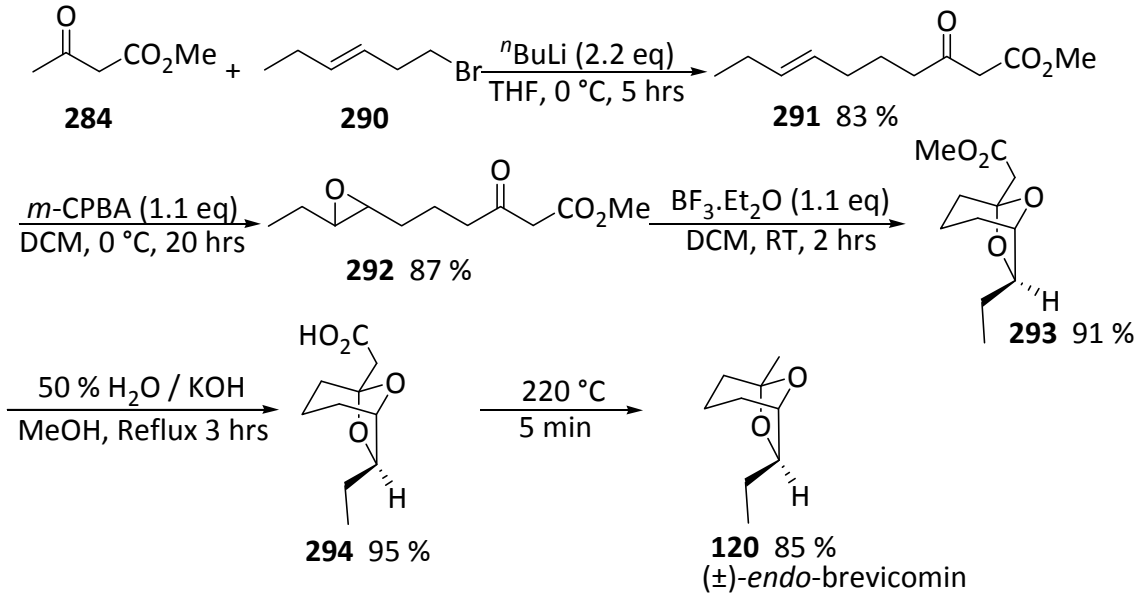
The facile decarboxylation of acid **289** may be due to the participation of one of the ketal oxygens (Scheme 95).



Scheme 95

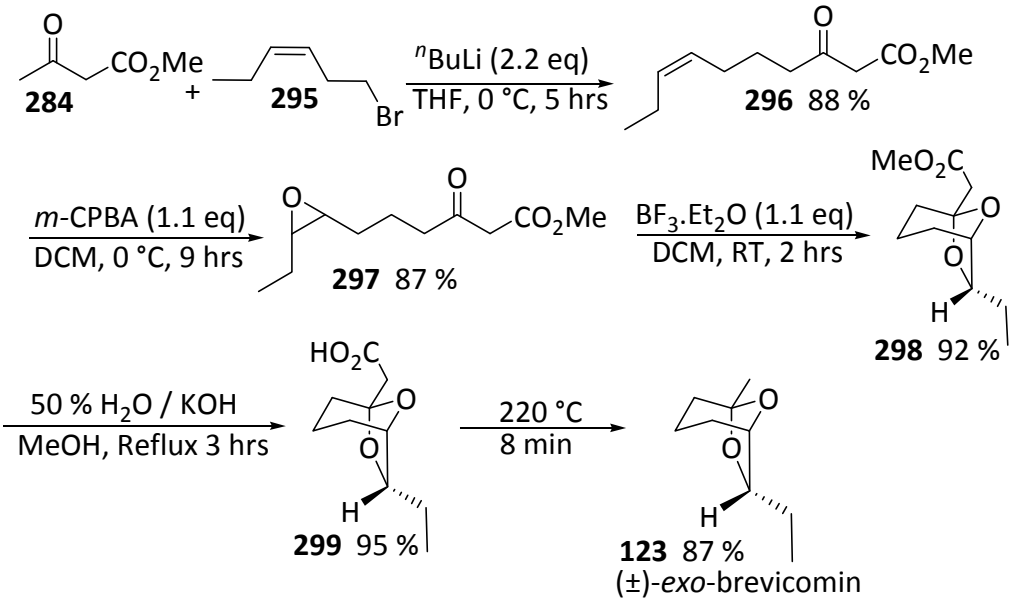
The synthesis of *endo*-brevicomin **120** was also accomplished along similar lines as that of frontalin **122**. Lewis acid catalysed cyclisation of epoxide **292** afforded 6,8-dioxabicyclo[3.2.1]octane **293** in 91 % yield. There was no isomeric *exo*-isomer in this cyclisation as found in case of epoxide **254** and **255** (Scheme 85). Epoxide **254** and **255**

under these conditions produced mixture of *endo* and *exo* isomers. The high stereospecificity in the cyclisation of epoxide **292** may be related to significantly higher enol content of β-keto ester relative to a simple ketone. The ketal ester **293** was converted into *endo*-brevicomin by hydrolysis and thermal decarboxylation (Scheme 96).



Scheme 96

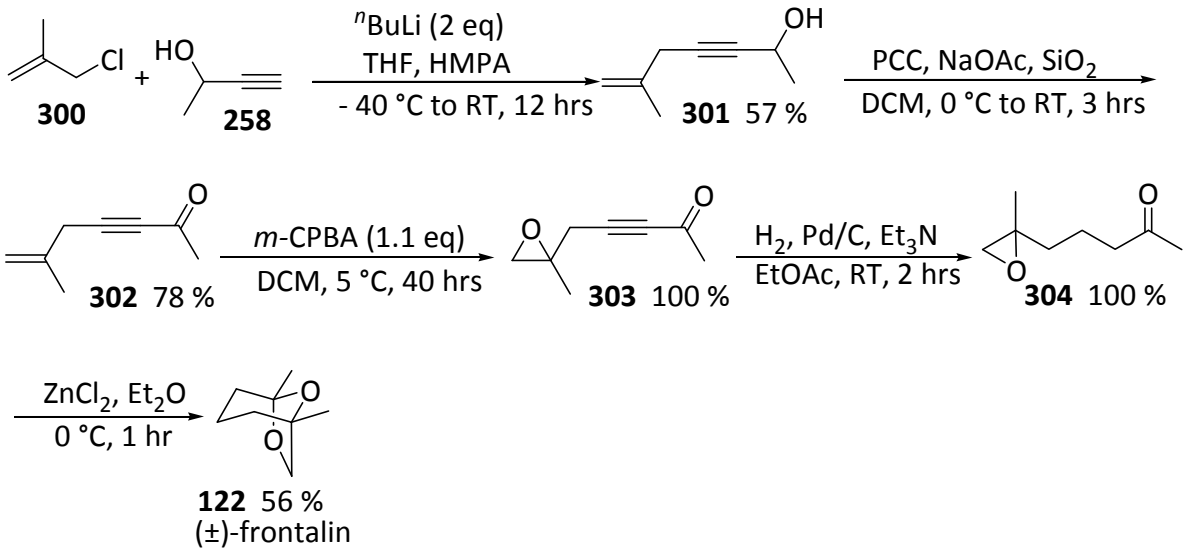
The synthesis of *exo*-brevicomin was carried out similarly by using (*Z*)-1-bromo-3-hexene (Scheme 97).



Scheme 97

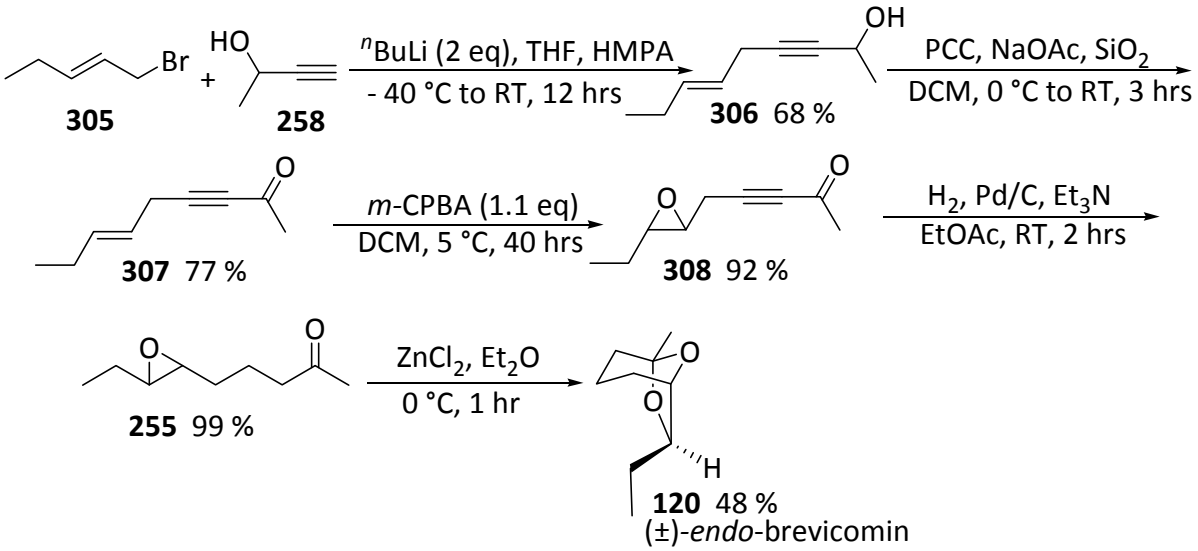
Mori *et al*. have also recently employed carbonyl epoxide rearrangement for the synthesis of 6,8-dioxabicyclo[3.2.1]octane ring system.[46] For the synthesis of (±)-frontalin, the carbon framework was constructed by alkylating the dianion of (±)-2hydroxy-3-butyne **258** with

methallyl chloride **300**. The oxidation of (±)-**301** with pyridinum chlorochromate afforded acetylenic ketone **302**. Selective epoxidation of the double bond was carried out by *m*-CPBA. The epoxy ketone **303** was then hydrogenated over palladium-charcoal in the presence of small amount of triethylamine to give epoxy ketone **304**. Epoxy ketone **304** when reacted in presence of zinc chloride in diethyl ether, yielded (±)-frontalin **122** (Scheme 98).



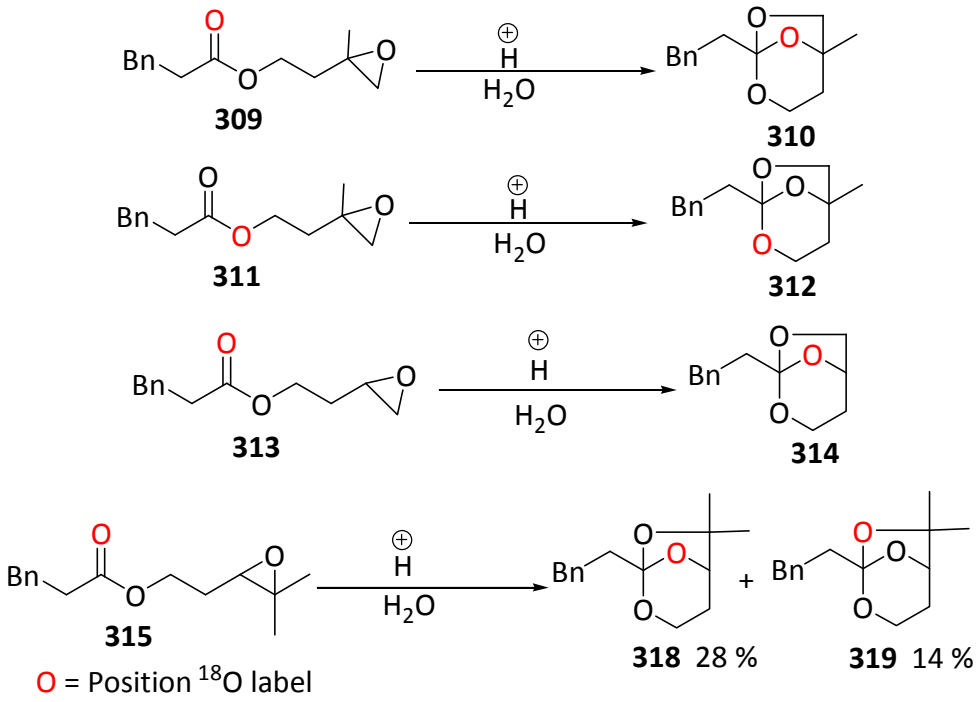
Scheme 98

The synthesis of (±)-*endo*-brevicomin started with lachrymatory bromide (Scheme 99). The subsequent steps were carried out under the same reaction conditions as reported in (Scheme 98).



Scheme 99

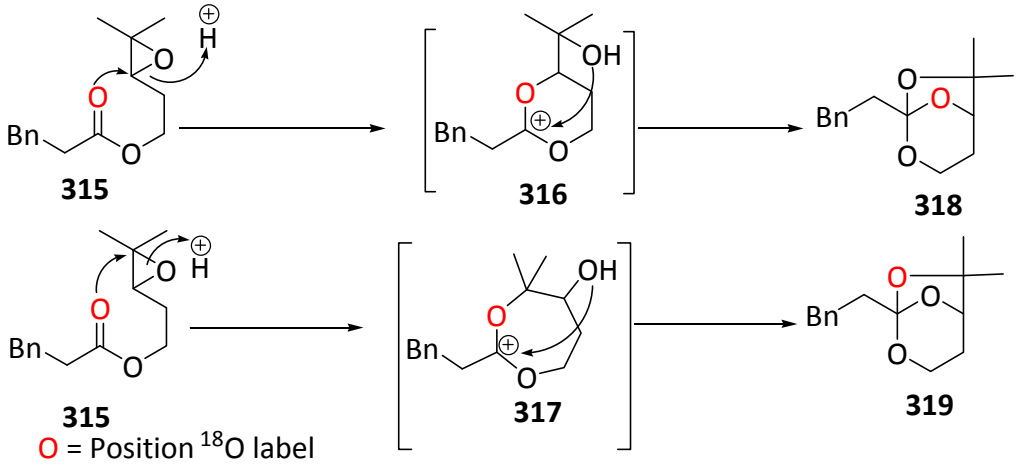
The carbonyl epoxide rearrangements described so far take place through a 6-*exo*-*tet* cyclisation. Giner *et al*. have used ^{13}C NMR-detected ^{18}O-labelling to show that the epoxy ester rearrangement takes place preferentially via 6-*exo* cyclisation, although the 7-*endo* process competes when the distal centre of the epoxide is disubstituted.[69] In the rearrangement of epoxy esters **309** and **313** to orthoesters **310** and **314**, the ^{18}O-label was found exclusively in the position connecting the orthoester carbon with the bridge centre. Upon rearrangement of epoxy ester **315**, orthoester was found to have ^{18}O-label in two different positions, with 28 % ^{18}O-labelling of the bridgehead carbon **318** and 14 % ^{18}O-labelling of the dimethyl substituted carbon **319** (Scheme 100).



Scheme 100

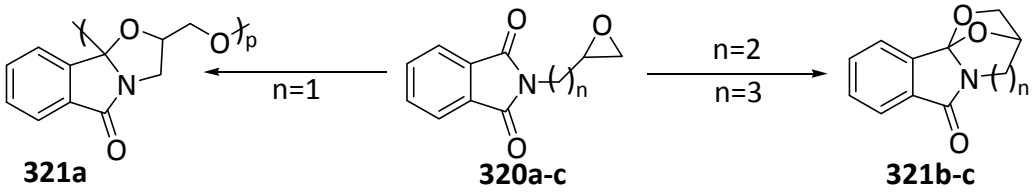
The ^{18}O-labelling experiments provide insight into the course of the rearrangement reactions. The rearrangements of ^{18}O-labeled epoxy esters **309** and **313** to orthoesters **310** and **314** were found to occur entirely via 6-*exo* cyclisation to an intermediate six membered dioxonium ion. However, the rearrangement product of ^{18}O-labeled epoxy ester **315** showed ^{18}O-label in two positions **318** and **319**, indicating a 2:1 ratio of 6-*exo* and 7-*endo* cyclisation pathways. The pathway via the six-membered dioxonium ion **316** remains preferred, however 7-*endo* cyclisation via seven membered dioxonium ion **317** is also

observed, apparently because alkyl substitution activates the distal centre of the intermediate protonated epoxide by stabilising a partial positive charge (Scheme 101).



Scheme 101

Kanoh *et al*. have also reported Lewis acid promoted isomerisation of oxiranes and oxetanes having carbonyl functional groups to different heterocyclic compounds.[70] The relative position of the carbonyl oxygen in oxirane phthalimides results in polymerisation or isomerisation. In the reaction of 1,5-positioned carbonyl oxygen **320a**, polymerisation occurs predominately to give the polyacetal **321a** with a five membered 4,5-dihydro-oxazole ring in the main chain. In the reaction of 1,6-positioned **320b** and 1,7-positioned **320c** carbonyl oxygen isomerisation occurs to give the bicyclic acetal **321b** and **321c**. All of these products including the polyacetal are formed as a result of *exo* attack (Scheme 102, table 26).



Scheme 102

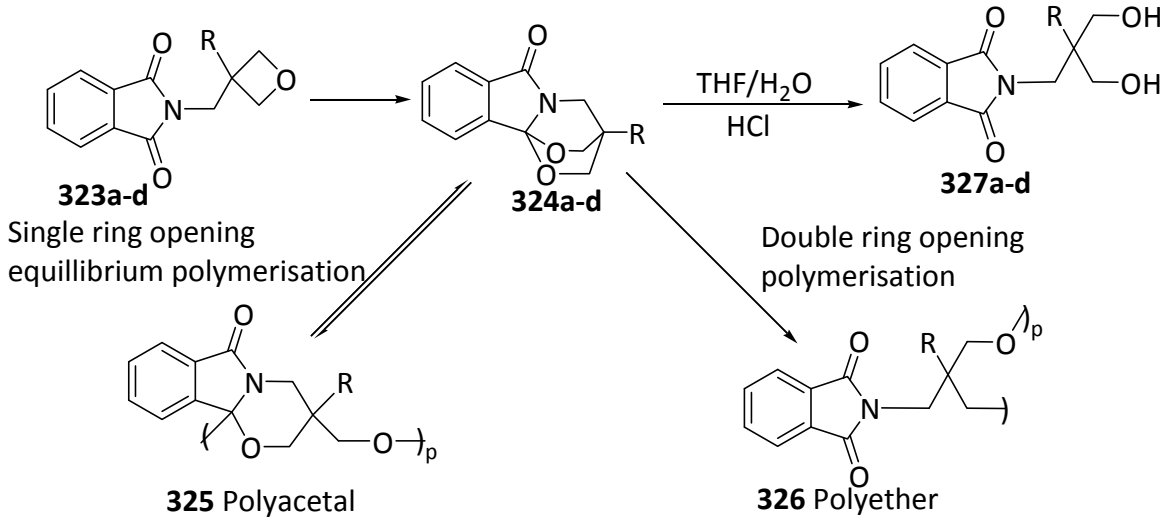
Entry	n	Solvent	Acid mol %	Tem. °C	Time	Product	Yield %
1	1	Toluene	MAD 5 mol %	25	70	**321a**	70
2	2	Toluene	MAD 5 mol %	25	72	**321b**	84
3	3	DCM	$BF_3.Et_2$ 250 mol %	25	72	**321c**	90

Table 26

1.6. Cycloisomerisation and polymerisation of carbonyl oxetanes

The oxetane having a cyclic imide at the 3-position also undergoes isomerisation and polymerisation under acidic conditions. The polymerisation gave two kinds of polymers with different structures depending on the temperature. One is polyacetal **325** containing tetrahydro-1,3-oxazine rings in the main chain and the other is polyether **326** carrying pendant imide groups.

The oxetane imides **323a-d** undergo isomerisation prior to polymerisation resulting in bicyclic acetals **324a-d** which cationically polymerise by single ring opening at low temperature or by double ring opening at high temperature (< 80 °C). Both Lewis acids and Brønsted acids were effective catalysts for isomerisation and polymerisation. The isomerisation took place above -10 °C and proceeded more rapidly at higher temperature. To obtain bicyclic acetals **324a-d** in high yields, it was necessary to use weak Lewis acids, such as trimethyl aluminium (Me_3Al) and methyl aluminium bis(2,6-di-*tert*-butyl-4-methylphenoxide (MAD), neither of which initiate polymerisation. The nature of the cyclic imide had little or no effect on the isomerisation yield. The choice of catalyst was not so crucial since the ring opening polymerisation is an equilibrium phenomenon. If the polyacetals are formed, dilution of the reaction mixture allows regeneration of **324** through depolymerisation. Bicyclic acetals **324a-d** were readily hydrolysed in aqueous THF containing a small amount of dilute HCl at RT, to give 2-(imidomethyl-substituted)propane-1,3-diols **327a-d** almost quantitatively (Scheme 103, table 27).

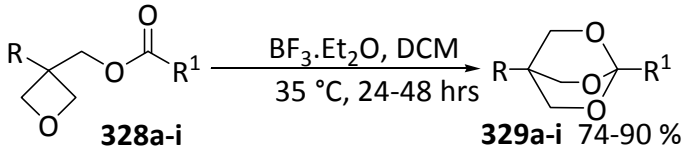


Scheme 103

Entry	R	Solvent	Acid	Tem. °C	Time	324a-d Yield %
1	Me	PhCl	Me_3Al	120	12 hrs	**324a** 96
2	Me	PhCl	MAD	120	12 hrs	**324a** 91
3	Me	PhCl	TMSOTf	120	3 hrs	**324a** 74
4	CH_2Ph	PhCl	$BF_3.Et_2O$	35	72 hrs	**324b** 74
5	Et	PhCl	Me_3Al	120	3 hrs	**324c** 77
6	Ph	PhCl	TFA	80	10min	**324d** 82

Table 27

Similarly oxetanes having an ester substituent such as **328a-i** undergo isomerisation. In contrast to the cases **324a-d** the isomerisation of **328** was not accompanied by polymerisation. The isomerisation of **328** with $BF_3.Et_2O$ in DCM at 35 °C gave **329** in good yield (Scheme 104, table 28).



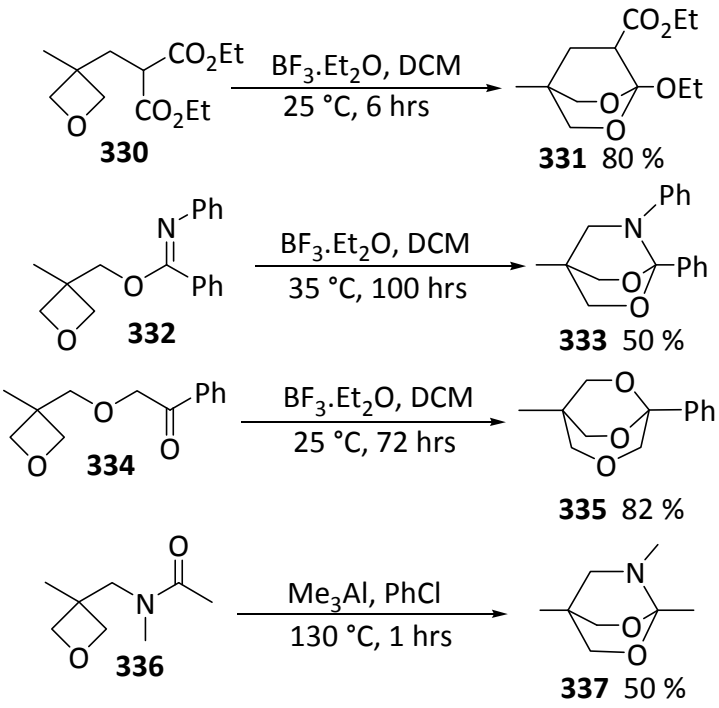
328a-i **329a-i** 74-90 %

Scheme 104

Entry	R	R^1	329a-i
1	Me	Et	**329a**
2	Me	^{n}Pr	**329b**
3	Me	4-$MeOC_6H_4$-	**329c**
4	C_6H_5-	C_6H_5-	**329d**
5	Me	4-$NO_2OC_6H_4$-	**329f**
6	Me	$CH=CH_2$-	**329g**
7	Me	Me-$CH=CH_2$-	**329i**

Table 28

This isomerisation was also applicable to oxetanes linked with esters **330**, benzimidate **332**, ketone **334** and *tert*-amides **336** (Scheme 105).



Scheme 105

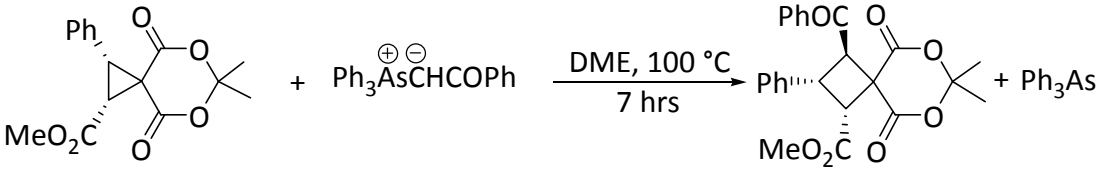
From these examples it appear that like epoxides, oxetanes are also equally favourable towards Lewis acid promoted isomerisation.

2. Results and discussions

The use of donor-acceptor cyclobutanes having different stabilising groups as precursors in cycloaddition reactions have recently been reported in the literature.[34-45] The use of Nicholas type activated cyclopropanes and cyclobutanes in [3+2] (Scheme 32, page 18)[30] and [4+2] (Scheme 51, page 28)[44] cycloadditions were already reported within the Pritchard and Christie research groups prior to the commencement of my Ph. D. studies.

Lewis acid catalysed dipolar cycloaddition involving donor-acceptor cyclopropanes are well documented and have been employed in [3+2] and [3+3] cycloaddition reactions with alkenes,[3] nitrones,[4] aldehydes,[5] and imines[6] for the preparation of a range of heterocycles. The aim of our research project was to further extend this methodology to donor-acceptor cyclobutanes in [4+2] and [4+3] cycloaddition reactions with various reagents such as aldehydes, alkenes, nitrones and imines for the preparation of different heterocycles, which could lead to the natural product synthesis.

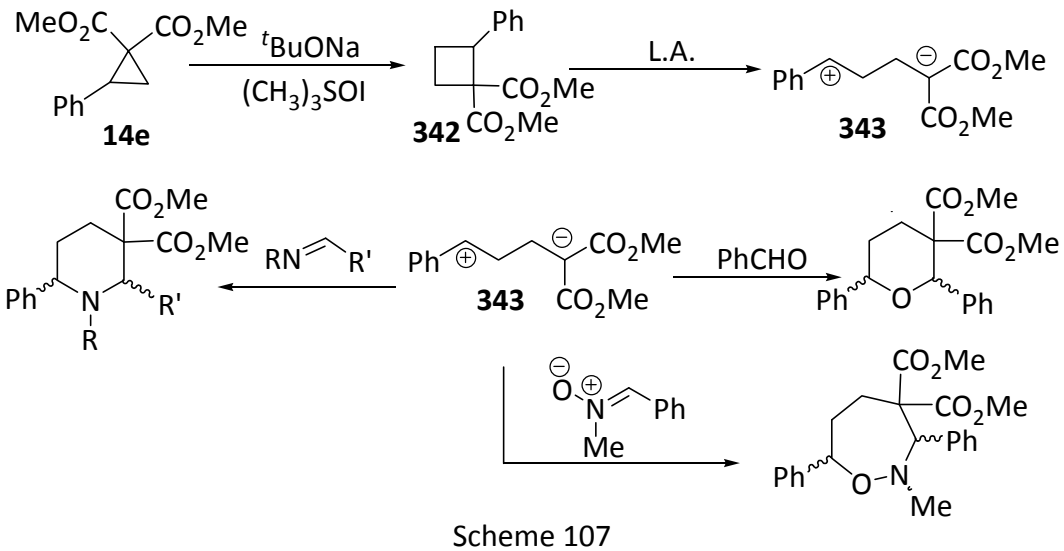
Chen *et al*. have reported that electron-deficient cyclopropane derivatives react with an arsonium ylide, a weak carbon containing nucleophile, to form new carbon-carbon bonds with high stereoselectivity (Scheme 106).[71]



338 **339** **340** 50-60 % **341**

Scheme 106

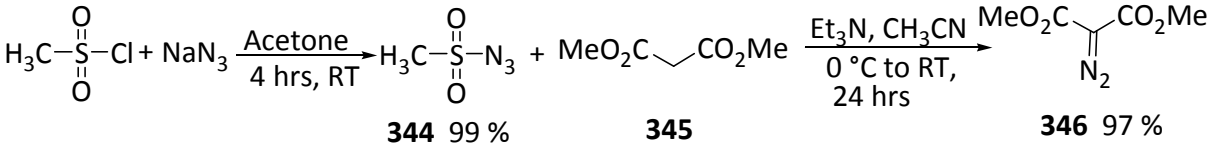
These conditions could be employed to synthesise the precursor donor-acceptor cyclobutanes for cycloaddition reactions. The donor-acceptor cyclobutane **342** could be synthesised from electron deficient diester cyclopropane **14e** by using a ylide reaction. The cyclobutane **342** upon cycloaddition reactions in the presence of Lewis acid could then give a 1,4-dipole **343** which would be trapped with various reagents like aldehydes, nitrones and imines to give diverse range of heterocycles (Scheme 107).



Scheme 107

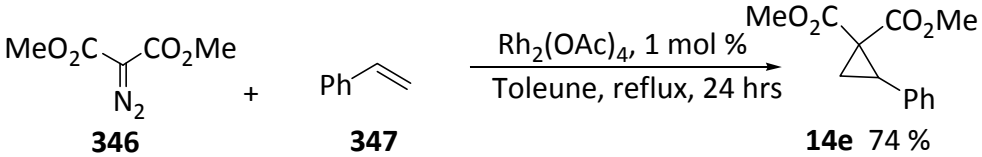
2.1. Synthesis of dimethyl-2-phenylcyclopropane-1,1-dicarboxylate

Dimethyl-2-phenylcyclopropane-1,1-dicarboxylate **14e** could be an ideal precursor for the synthesis of donor-acceptor cyclobutane **342**. The synthesis of dimethyl-2-phenylcyclopropane-1,1-dicarboxylate **14e** starts from methanesulfonyl chloride which is converted to mesyl azide **344** using 1.2 equivalents of sodium azide in acetone at RT. Mesyl azide **344** is then reacted with dimethylmalonate **345** in the presence of triethylamine to obtain the diazo dimethyl malonate **346** in 97 % yield (Scheme 108).[72]



Scheme 108

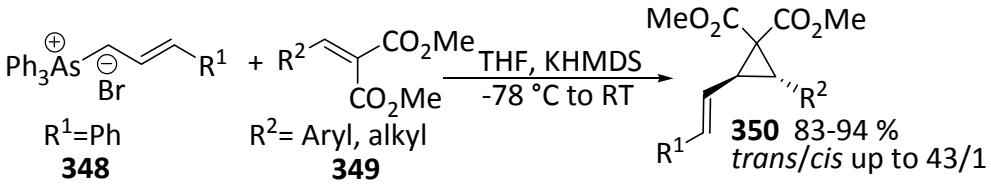
Styrene was then reacted with diazo dimethylmalonate **346** in toluene in the presence of $Rh_2(OAc)_4$ under refluxing conditions to give the desired cyclopropane **14e** in 74 % yield (Scheme 109).



Scheme 109

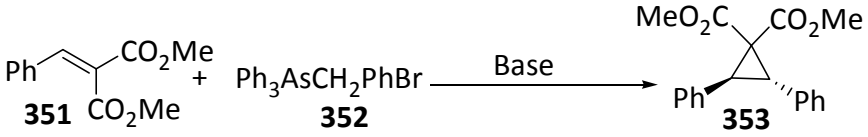
2.2. Attempted synthesis of dimethyl-2,3-diphenylcyclopropane-1,1-dicarboxylate

Tang and co-workers have reported that alkylidene or arylidene malonates react with arsonium allylides to give *trans* disubstituted cyclopropane-1,1-dicarboxylate with high stereoselectivity in high yields (Scheme 110).[73]



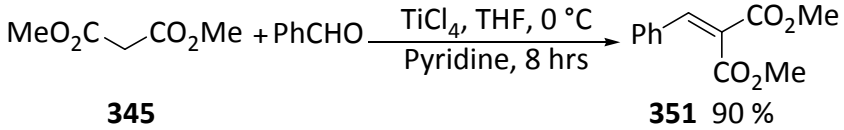
Scheme 110

Similarly, we believe the cyclopropane **353** could be prepared by the reaction of phenylidene dimethyl malonates **351** with an arsonium ylide generated *in situ* from benzyltriphenylarsonium bromide **352** under basic conditions (Scheme 111).



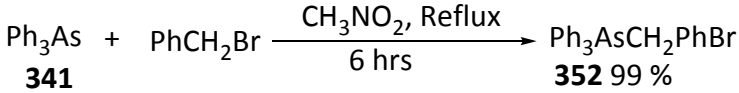
Scheme 111

The precursor phenylidene dimethyl malonate **351** for the synthesis of cyclopropane **353** was prepared by a known literature procedure reported by Cardillo *et al*.[74] By following their procedure, the desired product **351** was prepared in 90 % yield by the condensation of dimethyl malonate and benzaldehyde in the presence of $TiCl_4$ and pyridine in THF (Scheme 112).



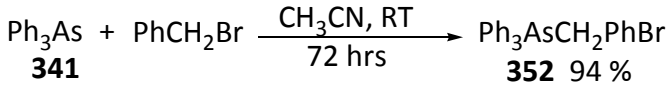
Scheme 112

Cheng *et al.* have reported the synthesis of benzyltriphenylarsonium bromide.[75] Triphenyl arsine and benzyl bromide were reacted in nitromethane under reflux for six hours to give white precipitate of benzyltriphenylarsonium bromide (Scheme 113).



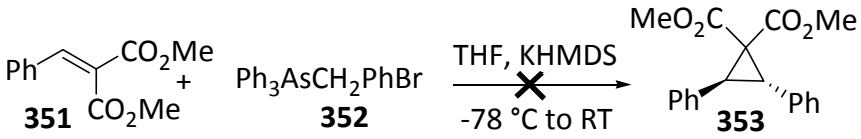
Scheme 113

Similarly, benzyltriphenylarsonium bromide salt was prepared by the reaction of triphenyl arsine and benzyl bromide in CH_3CN, under nitrogen atmosphere, at RT (Scheme 114).



Scheme 114

An attempt was made for the preparation of cyclopropane **353** by the reaction of phenylidene dimethyl malonates **351** with an arsonium ylide generated *in situ* from benzyltriphenylarsonium bromide **352** under basic condition (Scheme 115).

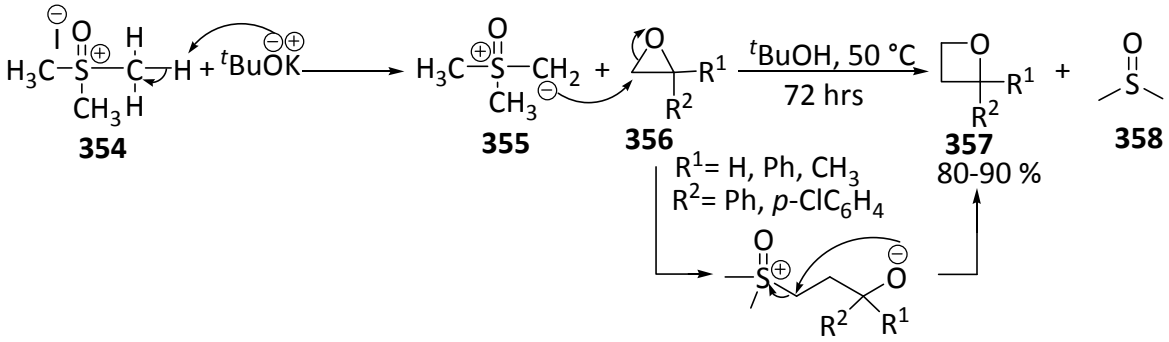


Scheme 115

Unfortunately, by using these reaction conditions we did not get the desired product. Further experiments were required to understand the reason why the reaction was not working.

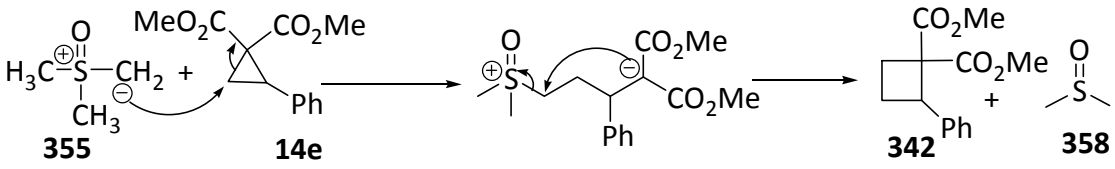
2.3. Attempted synthesis of dimethyl-2-phenylcyclobutane-1,1-dicarboxylate by using a sulfur ylide

Dimethyloxosulfonium methylide **355** generated *in situ* from trimethyloxosulfonium iodide **354** under basic conditions is reported to be an efficient methylene transfer reagent in reactions with epoxides affording the corresponding oxetanes **357** in good yields (scheme 116).[76]



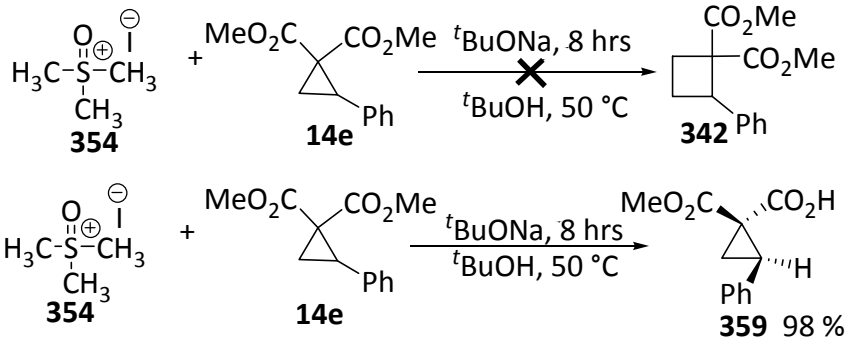
Scheme 116

Similarly, the reaction of cyclopropane **14e** with dimethyloxosulfonium methylide **355** could give the cyclobutane **342** (Scheme 117).



Scheme 117

These conditions were applied in attempts to synthesise donor-acceptor cyclobutane **342** from cyclopropane **14e**. On completion of the reaction, the aqueous work up gave only traces of the cyclopropane **14e**. But, when the aqueous medium was acidified, it gave *syn*-1-methoxycarbonyl-2-phenylcyclopropanecarboxylic acid **359** as a sole product. A variety of conditions were attempted but in all cases cyclopropane **359** was obtained as a major product (Scheme 118, table 29).



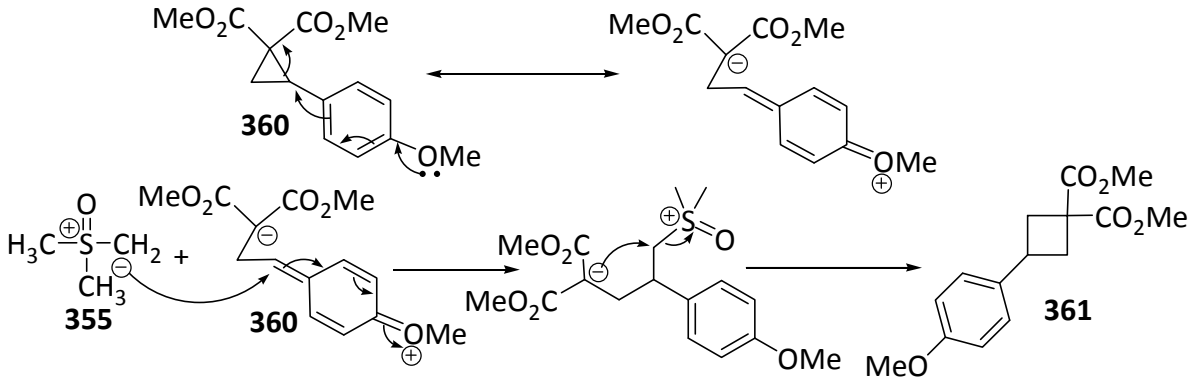
Scheme 118

Entry	14e (eq)	^{t}BuONa (eq)	Solvent	Time	Temp °C	359 Yield
1	1	2	^{t}BuOH	8 hrs	40	**98 %**
2	1	2	THF	8 hrs	RT	**98 %**
3	1	2	THF	8 hrs	67	**98 %**
4	1	2	DMSO	8 hrs	80	**96 %**

Table 29

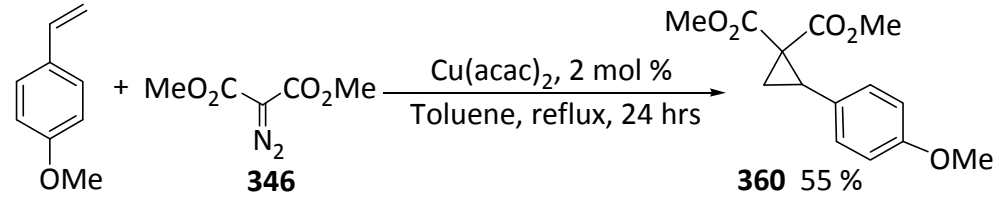
In all the cases one ester of the cyclopropane **14e** was hydrolysed to an acid. These reactions were carried out under anhydrous conditions. The ester hydrolysis of the cyclopropane **14e** is due to the interference of water during aqueous work up.

To make this reaction work, it was thought to change the reactivity of cyclopropane **14e** by adding electron donating group on phenyl ring. EDG (OCH_3) on phenyl ring could promote the ring opening of the cyclopropane **360** and reaction with dimethyloxosulfonium methylide **355** could give the cyclobutane **361** (Scheme 119).



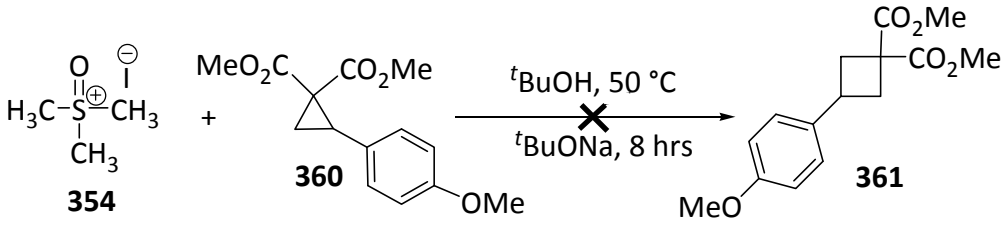
Scheme 119

Similar to cyclopropane **14e** the precursor cyclopropane **360** with EDG (OCH_3) on phenyl ring was made. 4-Vinylanisole was reacted with diazo dimethylmalonate **346** in toluene, in the presence of $Cu(acac)_2$, under refluxing conditions to afford the desired cyclopropane **360** in 55 % yield (Scheme 120).



Scheme 120

The attempts were made for the synthesis of cyclobutane **361** by reacting trimethyloxosulfonium iodide **354** under ^{t}BuONa basic conditions with cyclopropane **360**. The reaction resulted in complex mixture in both DMSO and ^{t}BuOH solvents (Scheme 121).

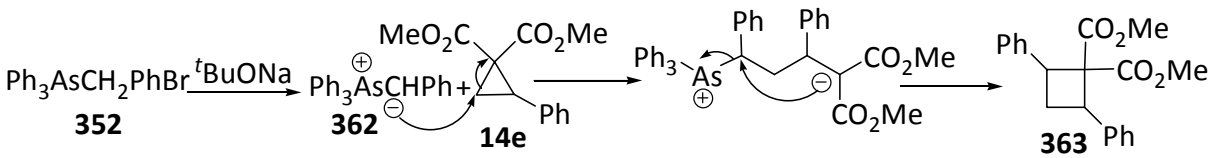


Scheme 121

We did not succeed in the synthesis of the requisite cyclobutane **361** with electron donating group on the phenyl ring of cyclopropane **360**. At this point it was thought to use a different type of ylide in the synthesis of the proposed cyclobutane.

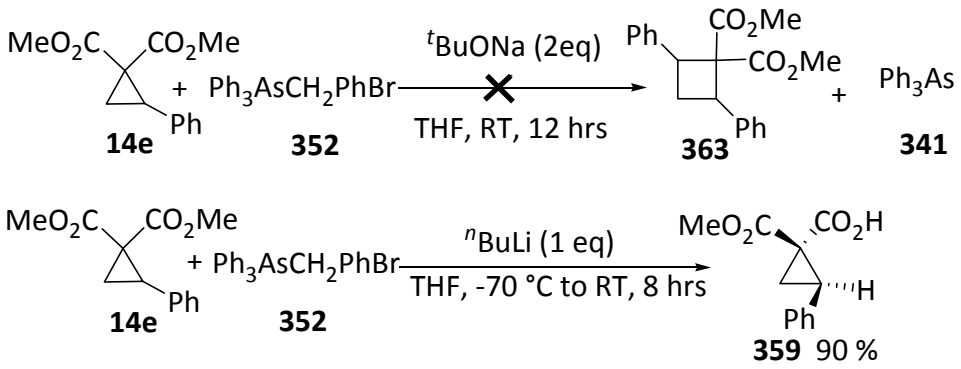
2.4. Attempted synthesis of dimethyl-2,4-diphenylcyclobutane-1,1-dicarboxylate

Chen *et al.* have reported the synthesis of cyclobutane **340** by reacting electron deficient cyclopropane **388** with an arsonium ylide **339** (Scheme 106, page 61).[71] Similarly, the cyclopropane **14e** upon reaction with an arsonium ylide **362** generated *in situ* from benzyltriphenylarsonium bromide **352** under basic condition could give cyclobutane **363** (Scheme 122).



Scheme 122

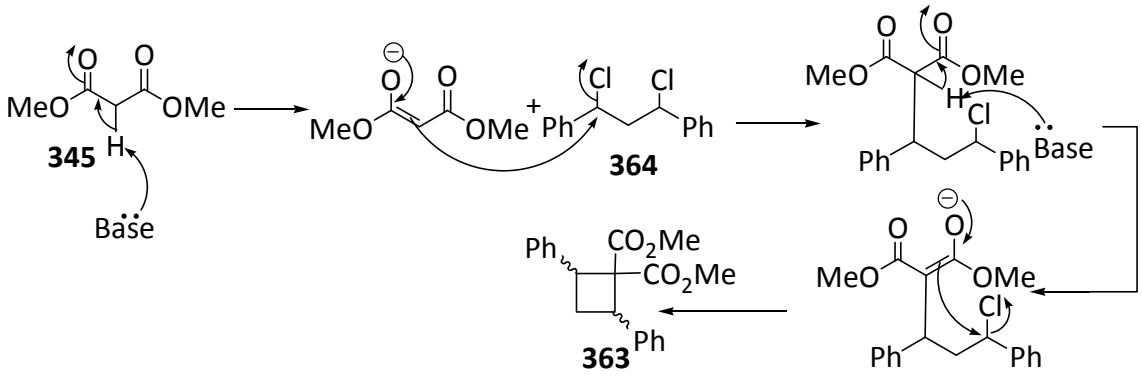
Attempts were made for the synthesis of cyclobutane **363** by reacting cyclopropane **14e** with an arsonium ylide generated *in situ* from benzyltriphenylarsonium bromide under basic condition (Scheme 123)



Scheme 123

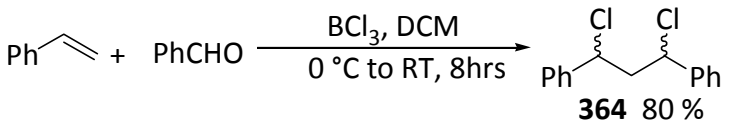
The reaction of cyclopropane **14e** with benzyltriphenylarsonium bromide under the conditions of ^{t}BuONa resulted in complex mixture. But, when the same reaction was repeated under the conditions of ^{n}BuLi, gave the cyclopropane **359** in 90 % yield, like sulfur ylide reaction (Scheme 118, page 65). This is due to the interference of water in aqueous work up. The exact reason why only one ester was hydrolysed to an acid is not known. Further experiments are required to understand the reason for ester hydrolysis. The reactions between cyclopropane **14e** and ylides were unsuccessful. So, we decided to synthesise donor-acceptor cyclobutane **363** by using different precursors.

Dimethyl-2,4-diphenylcyclobutane-1,1-dicarboxylate **363** could be prepared by reacting dimethyl malonate **345** under basic conditions with 1,3-dichloro-1,3-diphenylpropane **364** (scheme 124).



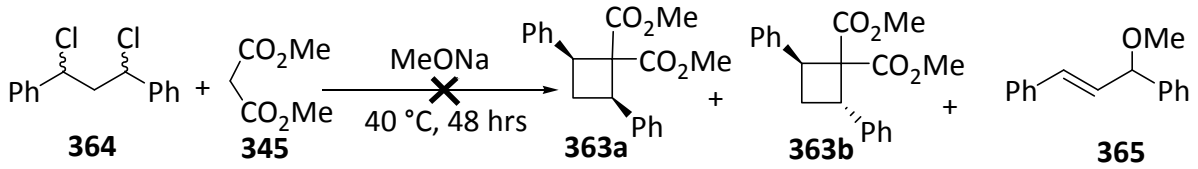
Scheme 124

The precursor 1,3-dichloro-1,3-diphenylpropane **364** was prepared by following a report from Kabalka *et al*.[77] The desired product was prepared as a diastereomeric mixture (1:1) in 80 % yield (scheme 125).



Scheme 125

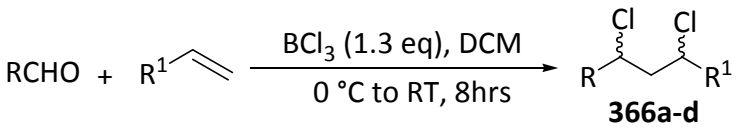
An attempt was made to synthesise the cyclobutane **363** by reacting with dimethylmalonate under basic conditions with 1,3-dichloro-1,3-diphenylpropane **364** (Scheme 126).



Scheme 126

On completion of the reaction three different products were isolated. The ^{1}H and ^{13}C NMR spectra of the minor fraction suggested that it could be 1,3-diphenyl-3-methoxy-1-propene **365**, which was later confirmed by mass spectrometry. The ^{1}H NMR spectra of the two major fractions suggested that they could be the two diastereoisomers of dimethyl-2,4-diphenylcyclobutane-1,1-dicarboxylate **363a** and **363b** having requisite chemical shifts for all twenty protons. However, the ^{13}C NMR spectra of both fractions were having the carbon chemical shifts for one phenyl ring with one aromatic quaternary carbon atom. The chemical shifts for the quaternary carbon atoms of carbonyl groups and the cyclobutane rings **363a** and **363b** were missing in both spectra. The rest of chemical shifts for one CH_2, two CH and two OMe carbons were present.

From the ^{13}C NMR spectra of both fractions it appeared that both organic molecules are symmetrical. To break the symmetry in the molecules it was decided to synthesise more derivatives by using the precursor 1,3-dichloro-1,3-diphenylpropane **366a-c** with substitution on one of the phenyl rings or 1,3-dichloropropane **366d** with different rings (phenyl and furan). Various attempts were made to prepare analogues of propane **364** with substitution on phenyl ring **376a-c** or with one ring other than phenyl ring **366d** (Scheme 127, table 33).



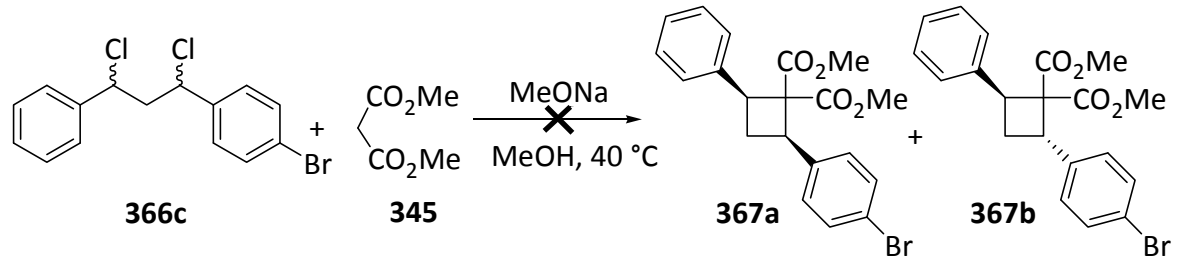
Scheme 127

Entry	R (eq)	R^1 (eq)	Time	Product	Yield %
1	Ph- (1)	4-$OMeC_6H_4$- (1)	8hrs	**366a**	CM
2	4-$MeOC_6H_4$- (1)	Ph- (1)	8hrs	**366b**	CM
3	4-BrC_6H_4- (1)	Ph- (1)	8hrs	**366c**	54
4	2-Fur- (1)	Ph- (1)	8hrs	**366d**	CM

Table 33

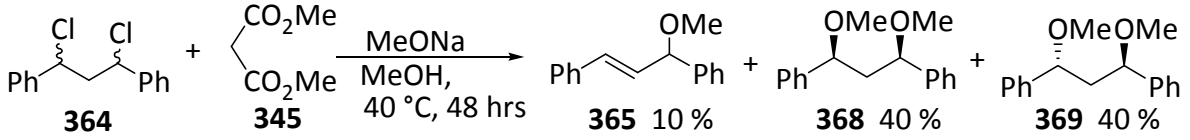
The only successful attempt to get substitution on one of phenyl ring was reaction between 4-bromobenzaldehyde and styrene to afford 1-bromo-4-(1,3-dichloro-3-phenylpropyl)benzene **366c** as a diastereomeric mixture (1:1) in 54 % yield.

Then propane **366c** was reacted under basic conditions with dimethylmalonate **345**. When the reaction was complete two products were isolated which could be the diastereoisomers of dimethyl-2-(4-bromophenyl)-4-phenylcyclobutane-1,1-dicarboxylate **367a** and **367b** (Scheme 128).

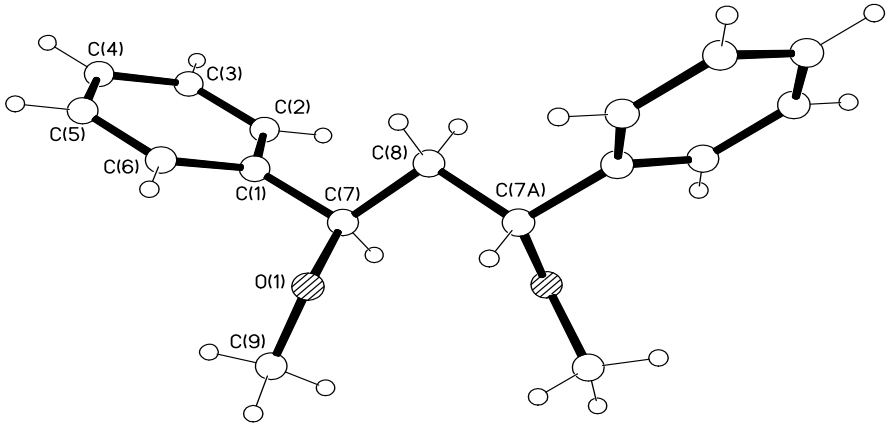


Scheme 128

Due to substitution of bromine on one of the phenyl rings the symmetry in both molecules has been broken and carbon chemical shifts for both phenyl rings were present in both spectra. The chemical shifts for the quaternary carbon atoms of carbonyl groups and the cyclobutane rings **367a** and **367b** were again missing in both spectra. The ^{13}C NMR spectra of the isolated products did not correspond to compounds **367a** and **367b**. This means that both isolated products were not diastereoisomers of dimethyl-2-(4-bromophenyl)-4-phenylcyclobutane-1,1-dicarboxylate **367a** and **367b**. An X-ray crystal structure of **363b** revealed that the compound was actually 1,3-dimethoxy-1,3-diphenylpropane **369** which was also confirmed by mass spectrometry. The other fraction **363a** was (meso) 1,3-dimethoxy-1,3-diphenylpropane **368** and their relative stereochemistry is shown in scheme 129.

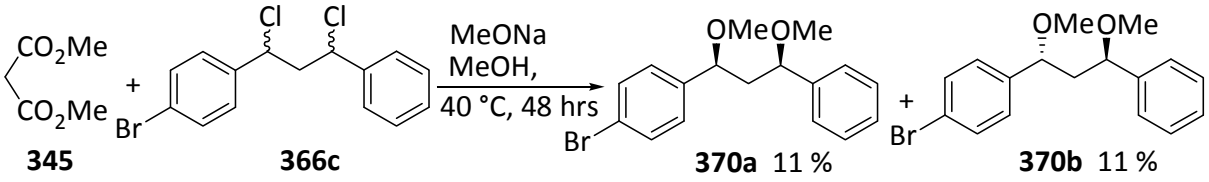


Scheme 129



369

Similarly **367a** and **367b** were actually 1-bromo-4-(1,3-dimethoxy-3-phenylpropyl)benzene **370a** and **370b** with their relative stereochemistry shown in scheme 130.

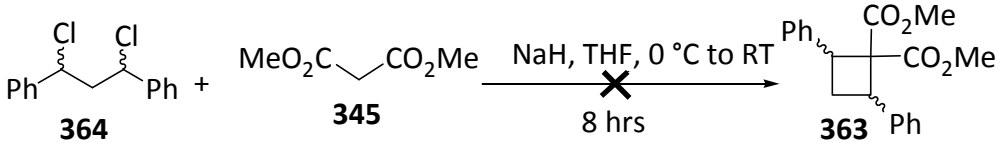


345 **366c** **370a** 11 % **370b** 11 %

Scheme 130

The products **368**, **369**, **370a** and **370b** are formed by the nucleophilic substitution (S_N2 mechanism) of both chlorine atoms in propanes **364** and **366c** by sodium methoxide. The product **365** was formed by E2 elimination or S_N2' mechanism.

Sodium methoxide, instead of deprotonating dimethylmalonate, had reacted as a nucleophile. In order to make the reaction work, it was decided to use non-nucleophilic bases to deprotonate dimethyl malonate. So various attempts were made to synthesise dimethyl-2,4-diphenylcyclobutane-1,1-dicarboxylate **363** by using NaH, ^{t}BuONa and Et_3N bases in a range of solvents, at different temperatures but all in vain (Scheme 131).



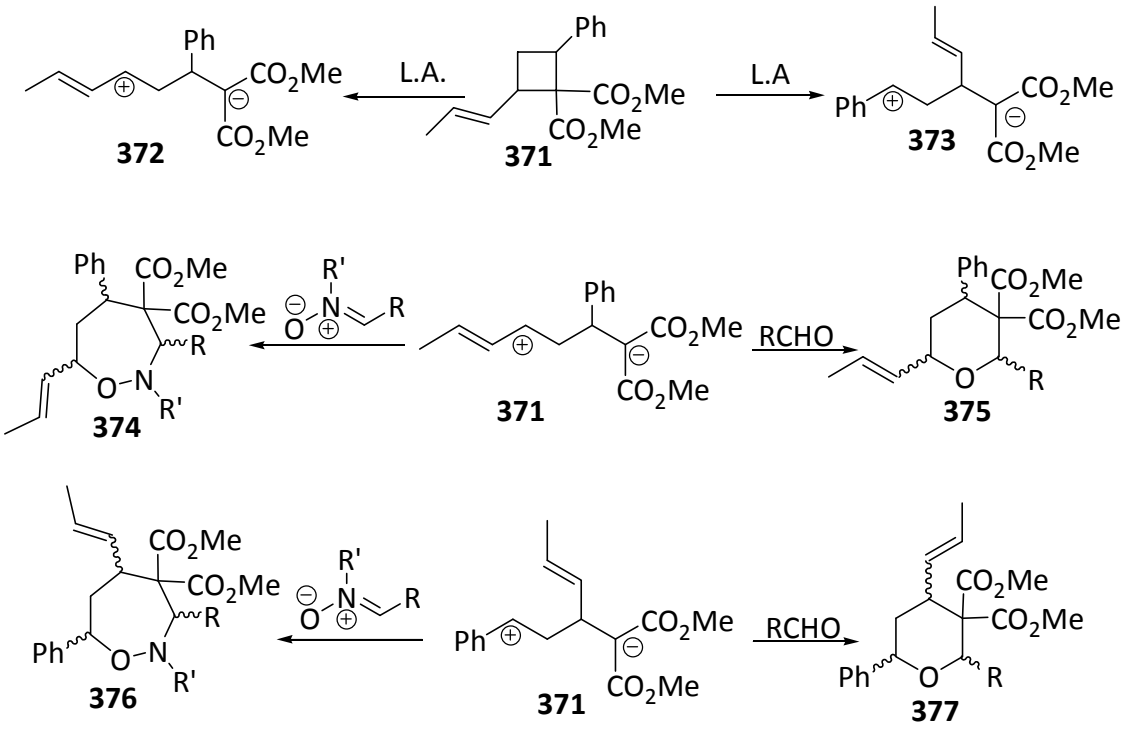
364 **345** **363**

Scheme 131

As result of these reactions we could not get the desired product, so an alternative direction was required.

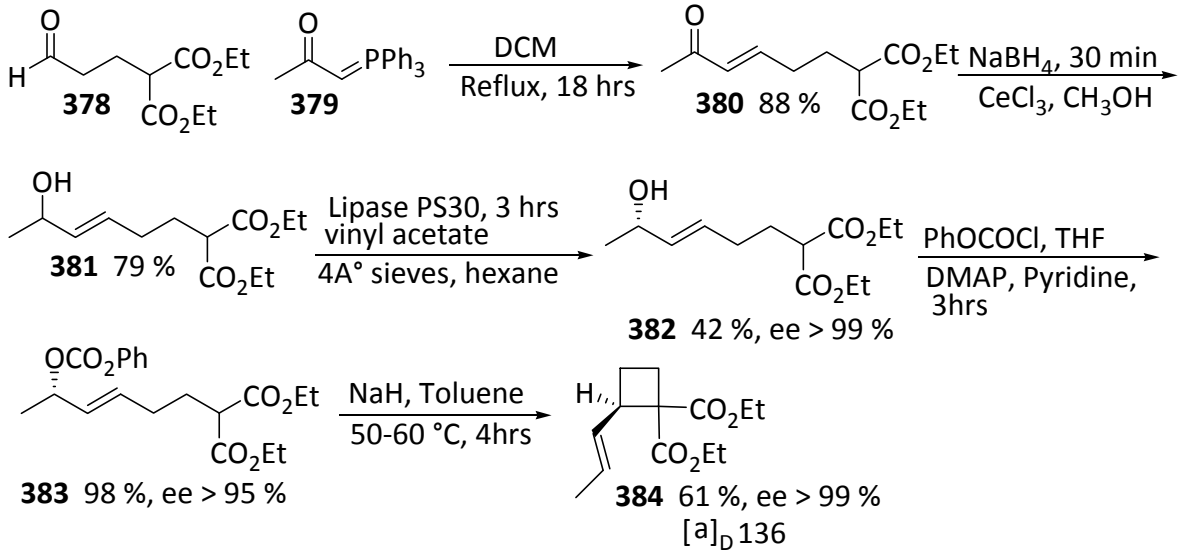
2.5. Synthesis of 1,1-dimethoxycarbonyl-2-phenyl-4-(*E*)-propenyl cyclobutane

So far we had not succeeded in the synthesis of requisite diester cyclobutane having suitable π donor group. It was decided to synthesise the cyclobutane **371** having an alkene and phenyl π-donor groups. Under Lewis acidic conditions the regioselective ring opening could occur either on phenyl or alkene end and could give rise two possible zwitterions **372** and **373**. These zwitterions could be trapped with various reagents to synthesise different organic compounds (Scheme 132).



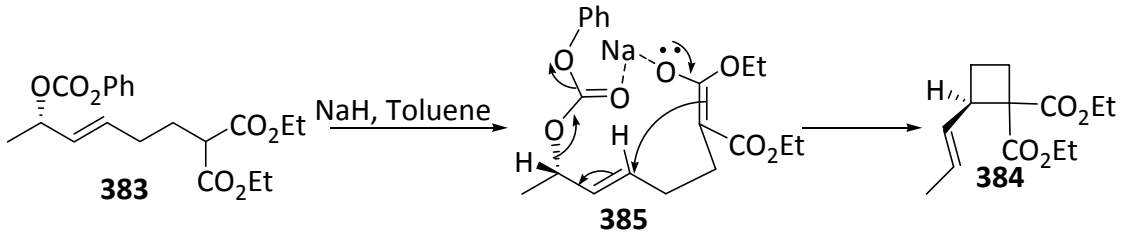
Scheme 132

Boeckman and Reeder have successfully reported the synthesis of cyclobutane diesters **384** via highly π facially selective *syn* S_N2' ring closure of acyclic substrates **383**.[78] The known aldehyde **378** was converted to enone **380** and allylic alcohol **381** using standard methods in 65-75 % overall yields. The (*S*)-alcohol **382** was isolated in 42 % yield upon exposure to Lipase PS30. The corresponding (*S*)-phenyl carbonate **383** was prepared in 98 % yield. The (*S*)-phenyl carbonate **383** was cyclised by using NaH in Toluene at 50-60 °C to afford cyclobutane diester **384** in 61 % yield (Scheme 133).



Scheme 133

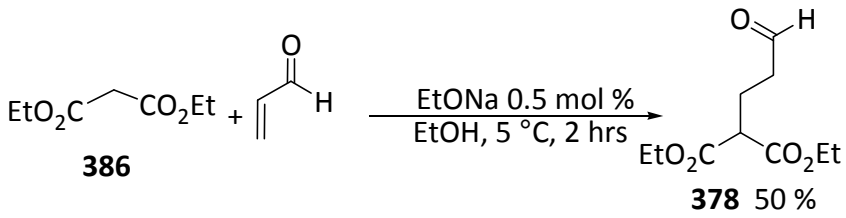
The stereochemical outcome observed for the cyclisation of acyclic substrate **383** is due to S_N2' substitution occurring *syn* to the departing group. The high stereoselectivity seen in S_N2' cyclisation of acyclic substrate **383** motivated Boeckman and Reeder to determine the mechanism of cyclisation. When the base was changed to KH or LDA in toluene, only deacylation product was observed. Addition of 18-crown-6 to the anion prepared from acyclic substrate **383** using NaH in toluene at RT gave no ring closure, but upon heating gave deacylation product. It appears that both the malonate anion and leaving group must be associated with the counter ion to observe cyclisation in the non polar medium. The complex **385** could account for the observed results, since such a complex is geometrically constrained to afford only *syn* substitution (Scheme 134).



Scheme 134

However our target was the synthesis of 1,1-dimethoxycarbonyl-2-phenyl-4-(*E*)-propenyl cyclobutane **371** which has additional phenyl group.

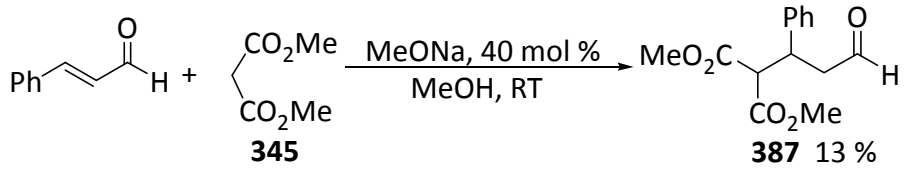
For the preparation of cyclobutane **371**, the precursor aldehyde **387** was required. Warner *et al*. have reported that 1,4-addition of ethyl malonate and acrolein proceeds in the presence of an alkaline catalyst to afford the aldehyde **378** in 50 % yield.[79]



386 **378** 50 %

Scheme 135

A similar attempt was made to react dimethylmalonate and *trans*-cinnamaldehyde in the presence of an alkaline catalyst to prepare aldehyde **387** (Scheme 136).

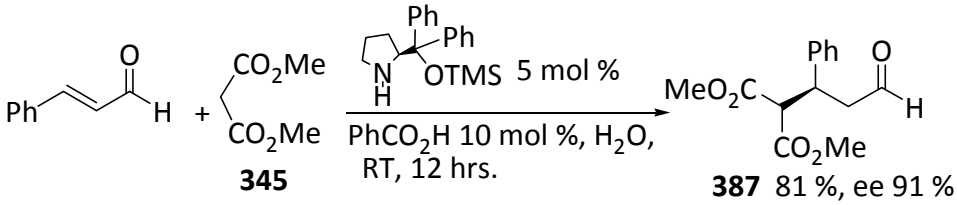


345 **387** 13 %

Scheme 136

The crude product was purified by Kugelrohr distillation. The distillate obtained at 210 °C under vacuum was a complex mixture containing a small amount of the desired aldehyde **387**. The distillate was further purified by column chromatography to afford the aldehyde **387** in 13 % yield. The further purification of the distillate obtained by Kugelrohr distillation was difficult and time consuming therefore the route was abandoned.

Ma *et al*. have also reported the enantioselective synthesis of the precursor aldehyde **387.**[80] The Michael addition of malonate to aromatic α,β-unsaturated aldehyde could be achieved with good yield and enantioselectivity by using O-TMS protected diphenylprolinol and benzoic acid in water at RT. A reaction is reported in the paper between dimethyl malonate and *trans*-cinnamaldehyde at RT using additive benzoic acid (10 mol %) and diphenyl-2-pyrrolindine methanol trimethyl silyl ether (5 mol %) in water affording the aldehyde **387** in 81 % yield and 91% ee (Scheme 137).

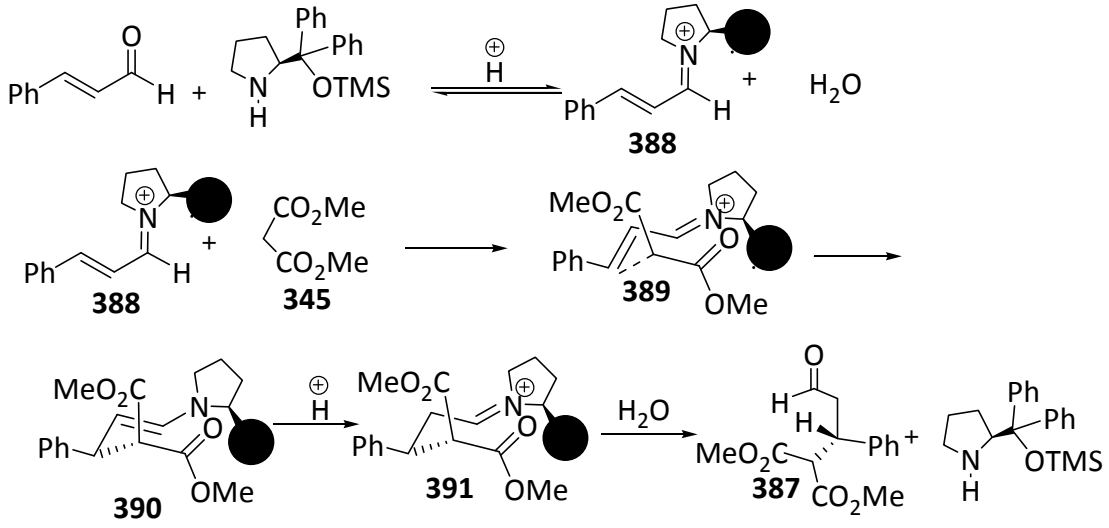


345 **387** 81 %, ee 91 %

Scheme 137

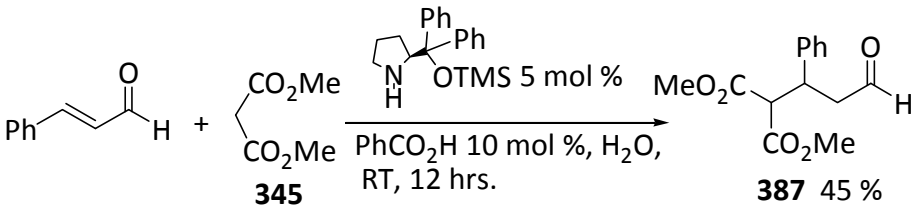
The reaction proceeds through an iminium ion mechanism.[81] The reversible condensation of *trans*-cinnamaldehyde with chiral catalyst forms α, β-unsaturated chiral iminium ion **388**. The face-selective nucleophilic attack by malonate to β carbon atom of α, β-unsaturated

iminium ion **388** gives an enamine **390** which reacts with an electrophile to give an iminium ion **391.** The iminium ion **391** on hydrolysis gives the β-chiral carbonyl compound **387** (Scheme 138).



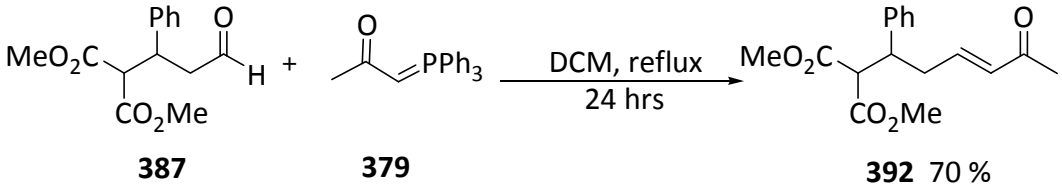
Scheme 138

When the reaction was performed between dimethyl malonate and *trans*-cinnamaldehyde using the same reaction conditions, the aldehyde **387** was obtained in 45 % yield showing no sign of optical rotation (Scheme 139). Further experimentations were required to elucidate the loss of enantioselectivity under similar reaction conditions.



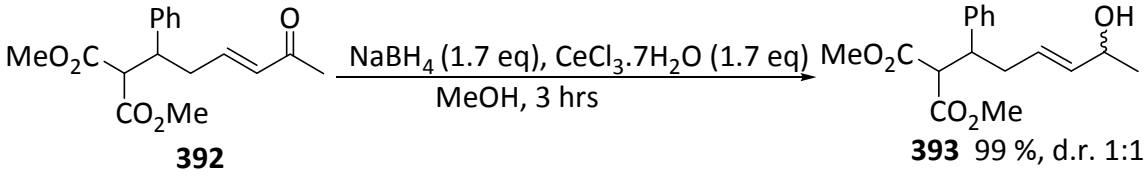
Scheme 139

Wittig reaction was applied to aldehyde **387** using acetylmethylene triphenylphosphorane **379** to afford ketone **392** in 70 % yield (Scheme 140).



Scheme 140

Ketone **392** was reduced to an alcohol using commercially available cerium trichloride heptahydrate and sodium borohydride in MeOH, giving (1:1) mixture of inseparable diastereoisomers **393** in 99 % yield (Scheme 141).

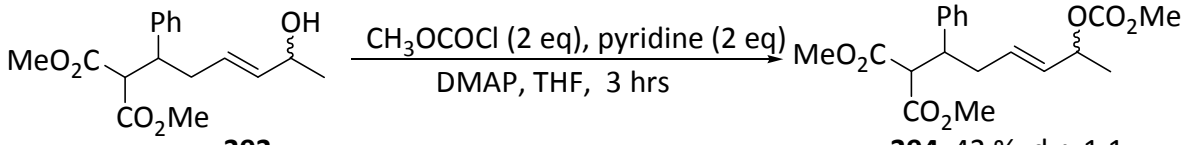


392

393 99 %, d.r. 1:1

Scheme 141

Then methyl carbonate **394** was prepared, when a solution of alcohol **393** in THF at 0 °C, with pyridine and DMAP (cat) were reacted with methyl chloroformate to give a (1:1) mixture of inseparable diastereoisomers in 42 % yield (Scheme 142).

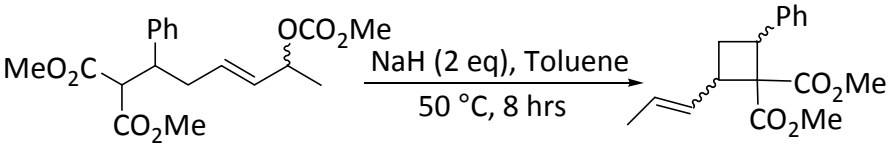


393

394 42 %, d.r. 1:1

Scheme 142

The cyclisation of methyl carbonate **394** by an internal S_N2' type reaction was carried out in toluene using sodium hydride to give a (3:1) mixture of inseparable diastereoisomers of desired diester cyclobutane **371** in 26 % yield (Scheme 143).

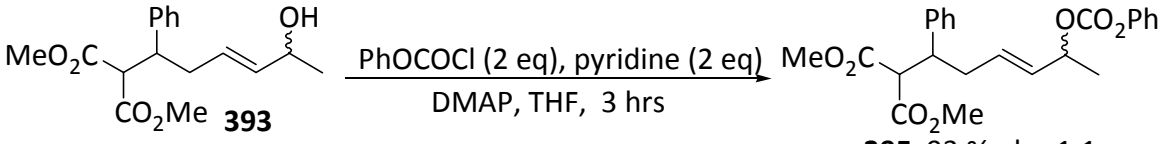


394

371 26 %, d.r. 3:1

Scheme 143

In the literature phenyl carbonate **383** is known to give a higher yield of cyclobutane **384**.[78] So phenyl carbonate **395** was prepared, when solution of alcohol **393** in THF at 0 °C, with pyridine and DMAP (cat) were reacted with phenyl chloroformate to give a (1:1) mixture of inseparable diastereoisomers in 93 % yield (Scheme 144).

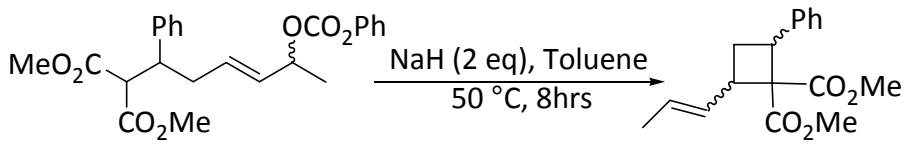


393

395 93 %, d.r. 1:1

Scheme 144

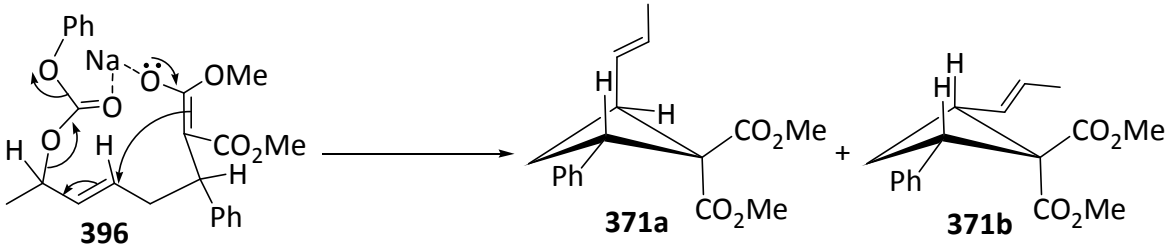
Phenyl carbonate **395** upon cyclisation in toluene with sodium hydride gave (3:1) mixture of inseparable diastereoisomers of diester cyclobutane **371** in 88 % yield (Scheme 145).



395 **371** 88 %, d.r. 3:1

Scheme 145

The nOe experiments were not conclusive to find out the exact structures of the diastereoisomers of cyclobutane **371**. We believe the phenyl group is controlling the stereoselectivity in the cyclisation of acyclic substrate **395** to the cyclobutane **371**. The cyclisation of acyclic complex **396** could give a less favoured *trans*-cyclobutane **371a** having phenyl group equatorial and propenyl group axial resulting in unfavourable 1,3-diaxial interactions and a more favoured *cis*-cyclobutane **371b** having both phenyl and propenyl groups equatorial with less 1,3-diaxial interactions. Hence one cyclobutane is formed as a major diastereoisomer (Scheme 146).



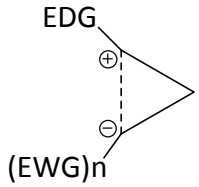
396 **371a** + **371b**

Scheme 146

2.6. Use of cyclobutane towards [4+2] and [4+3] dipolar cycloaddition reactions

After successful synthesis of the precursor donor-acceptor cyclobutane **371**, our next mission was to further employ cyclobutane **371** in [4+2] and [4+3] cycloaddition reaction.

[3+2] And [3+3] cycloaddition reactions with three membered rings have been extensively used in organic chemistry to synthesise tetrahydro-1,2-oxazines,[4] tetrahydrofurans[5] and pyrrolidines.[6] There are two major factors affecting the reactivity of donor-acceptor cyclopropanes toward an ionic ring opening.[33] One is the ability of electron withdrawing groups to stabilize an adjacent developing negative charge, and the other is the ability of the electron donating groups to engage in proximal stabilization of a developing positive charge (Figure 9).

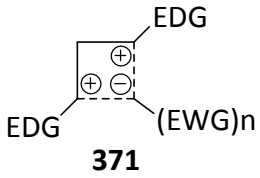


Donor-acceptor cyclopropanes

Figure 9

The suitable π-donor such as phenyl group, alkenes are particularly effective in stabilization a developing positive charge and as a result the cyclopropanes show much increased reactivity in the cycloaddition.

Similar reactivity is expected from diester cyclobutane **371**. The two π-donor group phenyl and alkene are present in cyclobutane **371** which are particularly effective in stabilization a developing positive charge and malonyl moiety stabilise the carbanion. Under Lewis acidic conditions the regioselective ring opening could occur either on phenyl or alkene end of cyclobutane **371** (Figure 10).

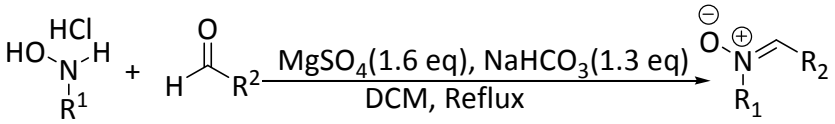


371

Donor acceptor cyclobutane

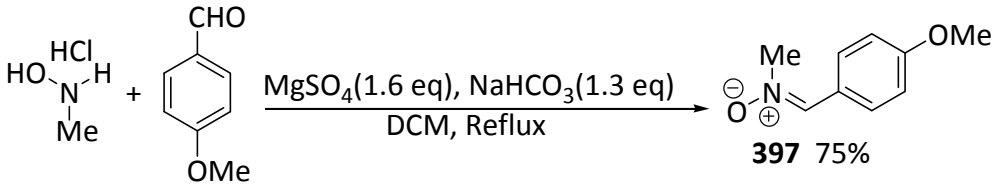
Figure 10

At the onset of this project dipolar [4+3] cycloaddition onto cyclobutane was not reported in literature. Nitrones are well known dipolarophiles in [3+3] cycloaddition reactions with donor-acceptor cyclopropanes for synthesis of heterocyclic compounds.[4] So, nitrone could be an ideal dipolarophile for [4+3] cycloaddition reaction. Several nitrones were prepared in relatively high yields from corresponding hydroxylamine hydrochlorides and aldehydes in anhydrous DCM in presence of $MgSO_4$ and $NaHCO_3$ under reflux (Scheme 147).[72]



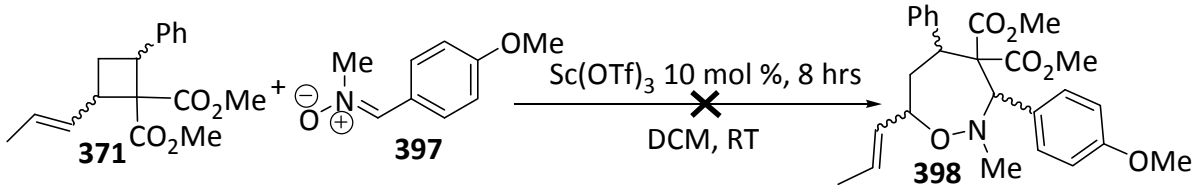
Scheme 147

N-Methyl-(4-methoxybenzylidene)amine-N-oxide **397** was prepared from N-methylhydroxylamine hydrochloride and *p*-anisaldehyde in 75 % yield (Scheme 148).



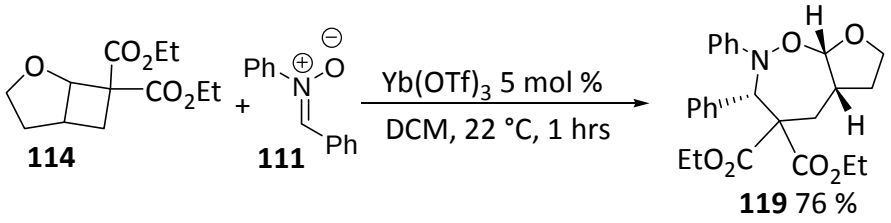
Scheme 148

Various attempts were made for dipolar [4+3] cycloaddition by reacting cyclobutane **371** and nitrones **397** using different reaction conditions $Sc(OTf)_3$, $Yb(OTf)_3$, range of solvents and reaction temperatures to form seven membered heterocycles. Unfortunately none of these conditions afforded the desired product **398** but gave starting material back (Scheme 149).



Scheme 149

Pagenkopf *et al*. have recently reported [4+3] cycloaddition reaction between donor-acceptor cyclobutane **114** and nitrones **111** catalysed by $Yb(OTf)_3$ affording oxazepines **119** in high yield (Scheme 150).[45]

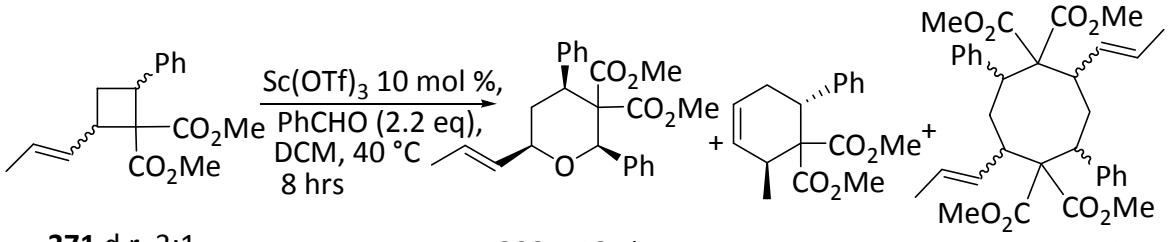


Scheme 150

The fused cyclobutane **114** has a fused ring strain. The ring opening in cyclobutane **114** is favoured under Lewis acidic conditions to release the fused ring strain and the non bonding electrons on the oxygen stabilise developing positive charge. Whereas, the cyclobutane **371** lack such fused ring strain and has alkene and phenyl groups to stabilise positive charge. The cyclobutane **371** under similar reaction conditions failed to show [4+3] cycloaddition reaction, may be due to lack of fused ring strain and the different nature of π-donor groups.

[4+2] Dipolar cycloaddition onto a cyclobutane has also been recently reported in the literature.[34-45] At the onset of this project the use of Nicholas type activated cyclobutane in [4+2] cycloaddition (Scheme 51, page 28) was already known within the Pritchard and Christie research groups.[44]

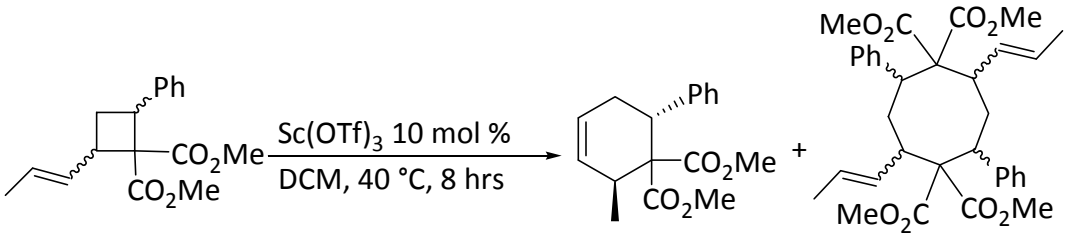
Similarly, [4+2] cycloaddition reaction was applied to the cyclobutane **371**. The cyclobutane **371** on reaction with benzaldehyde, in presence of scandium triflate gave (±)-dimethyl-2,4-diphenyl-6-(*E*-propenyl)dihydro-2H-pyran-3,3(4H)-dicarboxylate **399a** in 18 % yield, (±)-dimethyl-2-methyl-6-phenylcyclohex-3-ene-1,1-dicarboxylate **400** in 25 % yield and 2,6-diphenyl-4,8-dipropenylcyclooctane-1,1,5,5-tetracarboxylic acid tetramethyl ester **401** in 2 % yield with their relative stereochemistry as shown in scheme 151.



371 d.r. 3:1 **399a** 18 % **400** 20 % **401** 2 %

Scheme 151

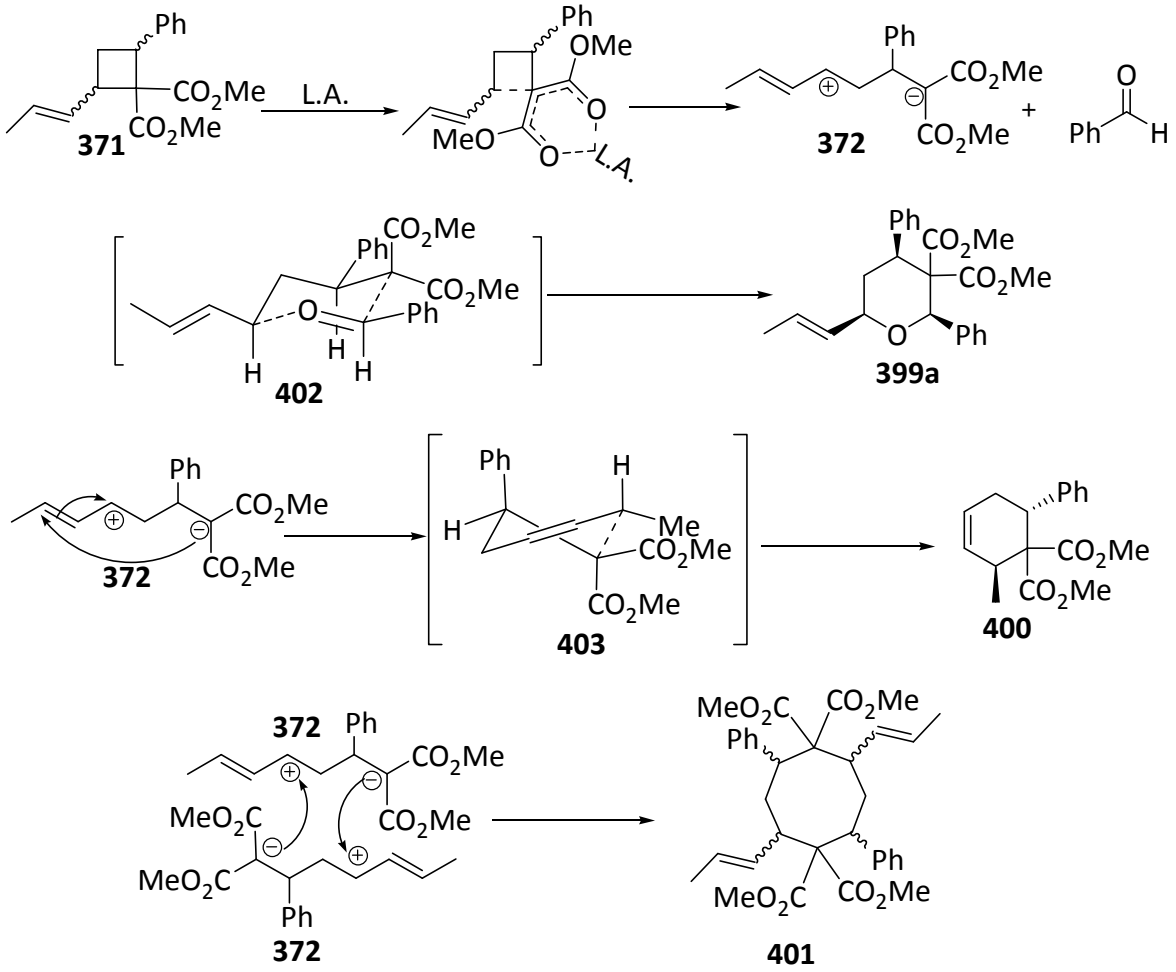
The products (±)-dimethyl-2-methyl-6-phenylcyclohex-3-ene-1,1dicarboxylate **400** and 2,6-diphenyl-4,8-dipropenylcyclooctane-1,1,5,5-tetracarboxylic acid tetramethyl ester **401** seems to originate solely from the cyclobutane **371**. To further confirm, the cyclobutane **371** was refluxed in DCM, under Lewis acidic conditions (Scheme 152).



371 d.r. 3:1 **400** 30 % **401** 8 %

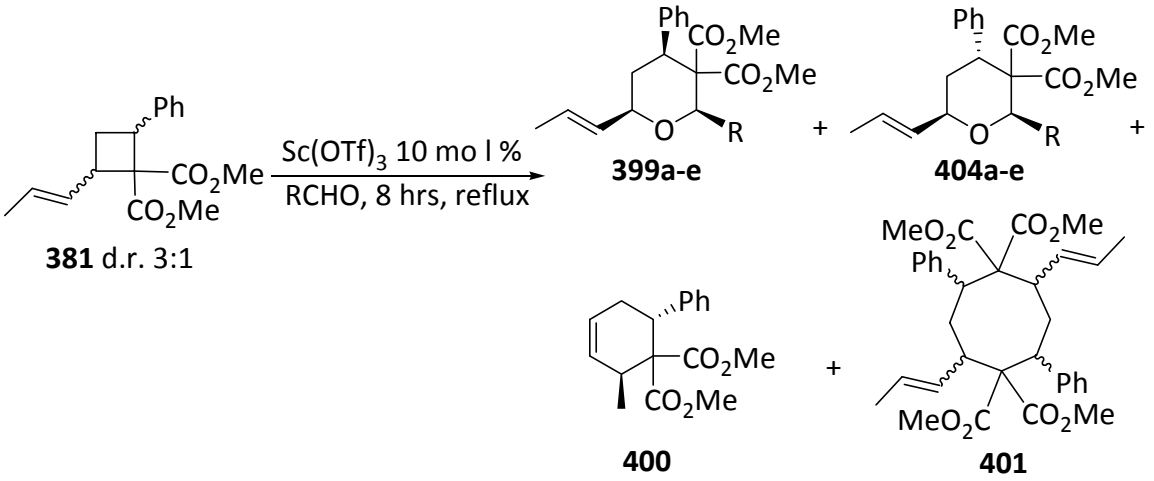
Scheme 152

The products **400** and **401** were observed in low yield due to formation of complex mixture as a major fraction. The ring opening of cyclobutane **371** under Lewis acidic conditions gave zwitterion **372**. The zwitterion **372** was trapped with benzaldehyde and gave the transition state **402**. The transition state **402** led to cycloadduct **399a** by [4+2] cycloaddition reaction. The zwitterion **372** also gave the transition state **403** leading to ring expansion product **400** and even two zwitterions **372** dimerised to afford a dimer **401** (Scheme 153).



Scheme 153

Following this success a range of aldehydes were screened in attempts to form the corresponding tetrahydropyrans by using different conditions (Scheme 154, table 34).

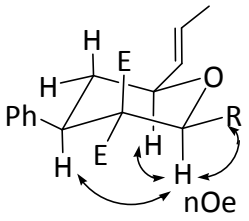


Scheme 154

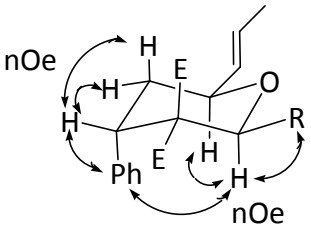
Entry	RCHO (eq)	Solvent	Temp. °C	399a-d Yield %	400 Yield %	401 Yield %	404a-d Yield%
1	PhCHO (1.2)	DCM	Reflux	**399a** 18	20	0	**404a** 0
2	PhCHO (1.2)	Toluene	Reflux	**399a** 0	25	0	**404a** 0
3	PhCHO (2.2)	DCM	Reflux	**399a** 18	25	2	**404a** 0
4	4-$MeOC_6H_4CHO$ (1)	DCM	Reflux	**399b** Traces	0	0	**404b** 0
5	4-$MeOC_6H_4CHO$ (1)	DCE	Reflux	**399b** 0	0	0	**404b** 0
6	4-$MeOC_6H_4CHO$ (1)	DCE	Reflux	**399c** 0	25	0	**404c** 0
7	4-$NO_2C_6H_4CHO$ (1.2)	DCM	Reflux	**399c** 0	33	0	**404c** 0
8	Ph-CH=CHCHO (1.2)	DCM	Reflux	**399d** 27	10	3	**404d** 9
9	CH_2=CH-CHO (3)	DCM	Reflux	**399e** 12	15	2	**404e** 8

Table 34

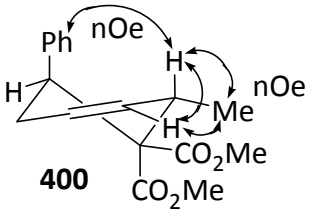
When *trans*-cinnamaldehyde and acrolein were used as trapping reagent (entry 8 and 9) two diastereoisomers of the cycloadduct tetrahydropyran **399d-e** and **404d-e** were obtained. The relative stereochemistry of tetrahydropyrans **399a-e**, **404d-e** and cyclohexene **400** were identified by nOe expirements. Irradiation of the proton next to the R substituents in cycloadduct **399a-e** leads to an nOe to the protons next to the phenyl and propenyl groups, and to the protons on the R substituents. This suggests that the three protons are on the same side of the molecule. When the proton next to the phenyl substituent in **404d-e** was irradiated, there was clear nOe to the neighbouring CH_2 protons and to the aromatic protons. However, irradiation of the proton next to the R substituents in cycloadduct **404d-e** leads to an nOe between the proton next to propenyl group and the aromatic protons, and to the protons on the R substituents. This suggests that the two protons and the phenyl substituent are on the same side of the molecule. Irradiation to the methyl group in cyclohexene **400** showed a strong nOe to the proton next to methyl substituent and to one of the neighbouring alkene protons. Irradiation of the proton next to the methyl substituent showed a strong nOe to the methyl substituent, the neighbouring alkene proton, and a moderate nOe to the phenyl group. This suggests that the proton next to methyl substituent and the phenyl group are on the same side of molecule.



399a R = Ph
399d R = Ph-CH=CH-
399e R = CH_2=CH-



404d R = Ph-CH=CH-
404e R = CH_2=CH-



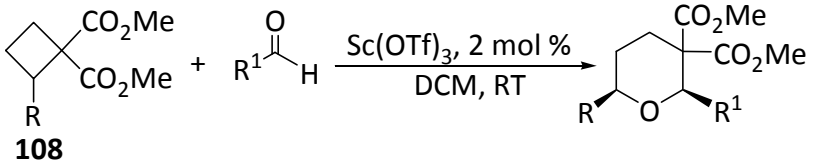
400

Low yields of desired cycloadduct tetrahydropyran **399a** and **404a** were observed due to formation of a complex mixture of side products in each case. To increase the yield of desired product it was decided to further optimise the reaction conditions by increasing the amount of aldehyde, decreasing the amount of solvent and trying different Lewis acids and solvents. By varying these conditions a slightly higher yield of the product was seen only when $Sc(OTf)_3$ was used as Lewis acid in DCM solvent (Entry 1). The reaction did not work in polar solvents like DMSO, DMF and THF due to decrease in Lewis acidity of the Lewis acids in these polar solvents and gave the starting material back (Table 35).

Entry	RCHO (eq)	Solvent	Temp °C	Catalyst 10 mol %	399a Yield %	400 Yield %	401 Yield %	404a Yield %
1	PhCHO (5)	DCM	40	$Sc(OTf)_3$	47	17	0	0
2	PhCHO (5)	toluene	40	$Sc(OTf)_3$	17	10	0	0
3	PhCHO (5)	DMSO	40	$Sc(OTf)_3$	0	0	0	0
4	PhCHO (5)	DMF	40	$Sc(OTf)_3$	0	0	0	0
5	PhCHO (5)	THF	40	$Sc(OTf)_3$	0	0	0	0
6	PhCHO (5)	DCE	40	$Sc(OTf)_3$	0	17	0	0
7	PhCHO (5)	DCM	40	$ZnBr_2$	2	2	0	0
8	PhCHO (5)	DCM	40	$FeCl_3$	25	10	0	0

Table 35

Lewis acid catalysed [4+2] cycloaddition of cylobutanes and aldehydes reported by Johnson *et al*. afforded tetrahydropyrans in high yield and stereoselectivity (Scheme 155).[34]



108

R = Ph R^1 = Ph-CH=CH-
R = Me-CH=CH- R^1 = 4-ClPh

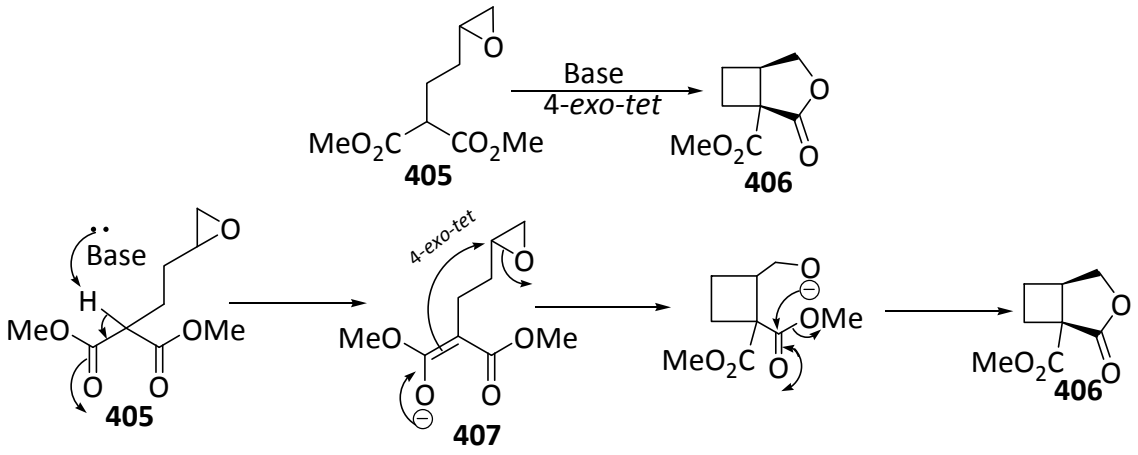
109a 77 %
109f 68 %

Scheme 155

The cyclobutane **108** when having only phenyl substituent or an alkene substituent underwent [4+2] cycloaddition reaction with aldehydes in high yields. But in the case of cyclobutane **371**, having an alkene and a phenyl π-donor groups, the ring opening on alkene end and formation of side products in each case resulted in lower yield of the desired cycloadduct. So at this point we decided to synthesise more complex cyclobutane, than that being reported by Johnson, in order to expand the scope of the chemistry.

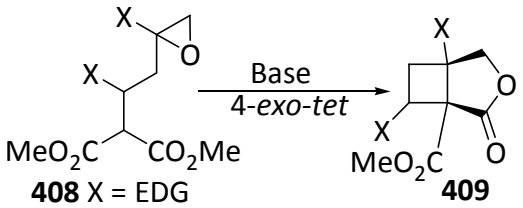
2.7. Attempted synthesis of 2-oxo-3-oxabicyclo[3.2.0]heptanes-1-carboxylic acid methyl ester

The 2-(2-oxiranylethyl) malonic acid dimethylester **405** under basic conditions could cyclise by 4-*exo-tet* cyclisation to fused cyclobutane **406** having a lactone ring and ester moiety on bridgehead position (Scheme 156).



Scheme 156

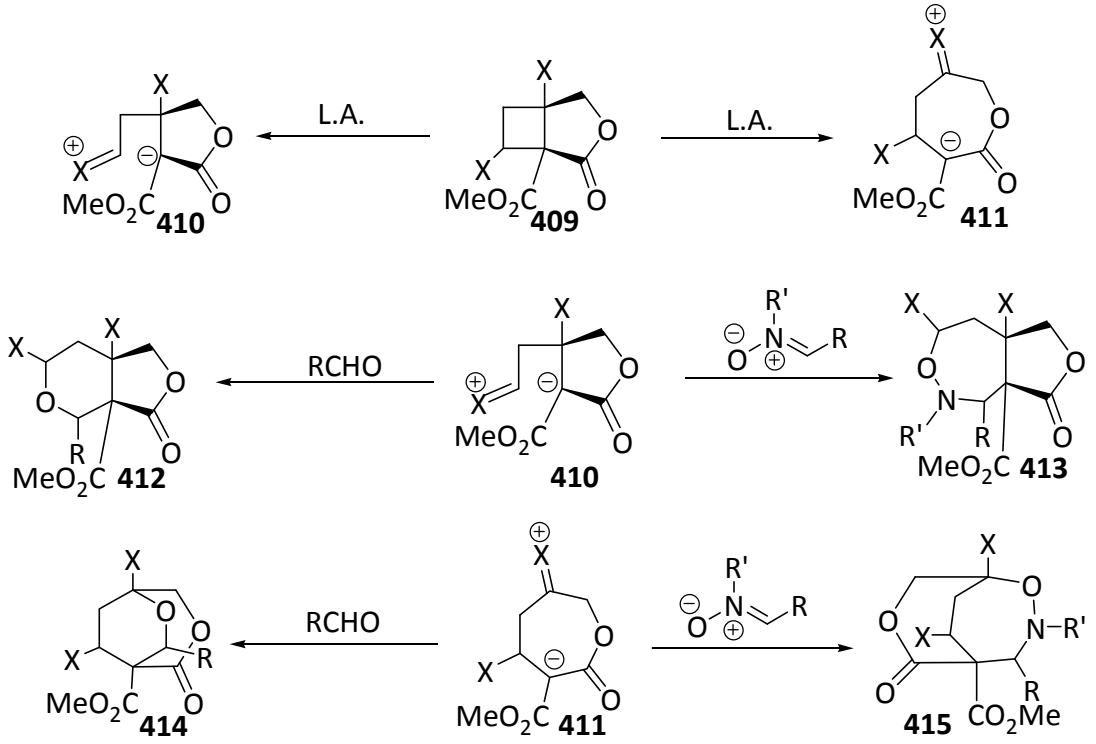
The idea was to further synthesise the analogous donor-acceptor cyclobutane **409** with electron donating group on the cyclobutane ring or at the bridgehead position (Scheme 157).



Scheme 157

The donor-acceptor cyclobutane **409** could be used as a precursor in a cycloaddition reaction. The cyclobutane **409** under Lewis acidic conditions could give two possible

zwitterions **410** and **411** which would be trapped with different reagents like aldehydes and nitrones for the preparation of heterocyclic compounds (Scheme 158).



Scheme 158

The deprotonatation of the acidic proton of 2-(2-oxiranylethyl) malonic acid dimethylester **405** under basic conditions could give the malonic enolate **407** (Figure 11)**.** There are two nucleophilic sites in the malonic enolate **407** (C and O) which could intramolecularly attack the epoxide ring and cyclise by *exo-tet* and *endo-tet* cyclisation to the corresponding *C*- or *O*-alkylated products. According to the Baldwin's rules, "all *exo-tet* cyclisations are favoured and 5- and 6-*endo-tet* cyclisation are disfavoured."[82] In *exo-tet* cyclisations, the lone pair of anion and C—O σ* has no stereoelectronic problem to overlap successfully irrespective of the ring size.[83] According to Baldwin's rules, in malonic enolate **407** 4- and 6-*exo-tet* cyclisation are favoured over 5- and 7-*endo-tet* cyclisations.

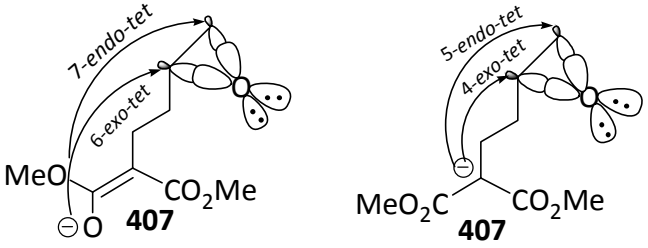
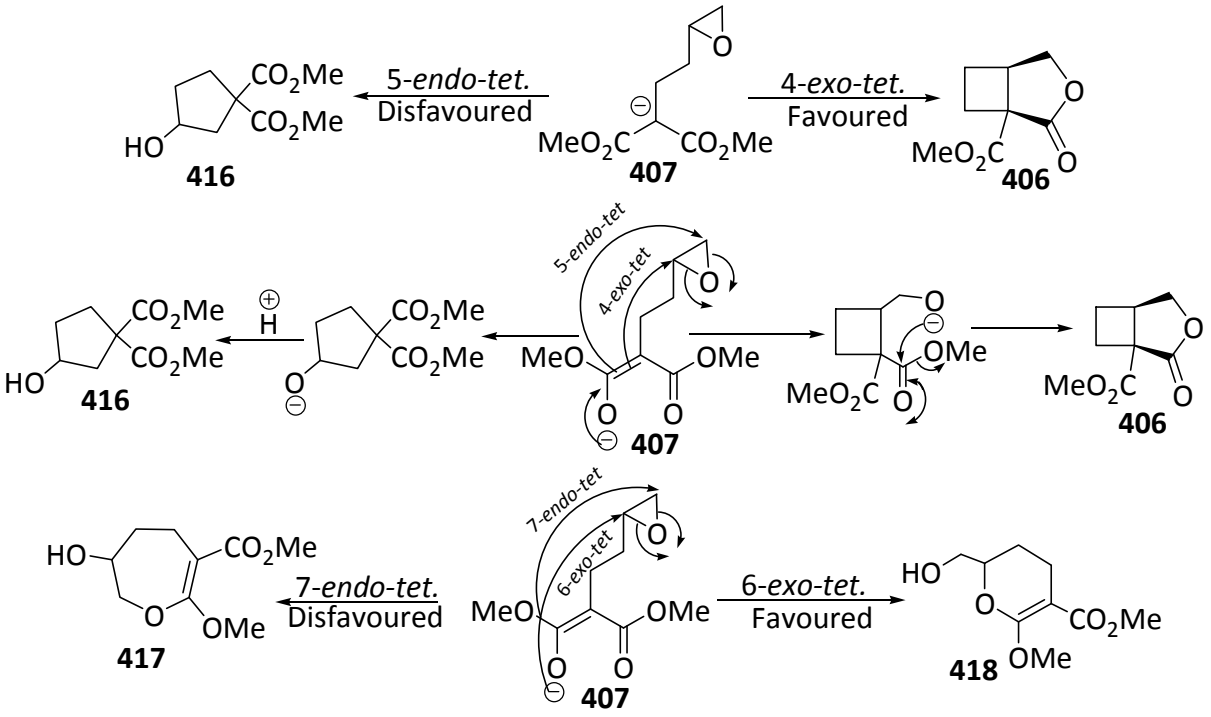


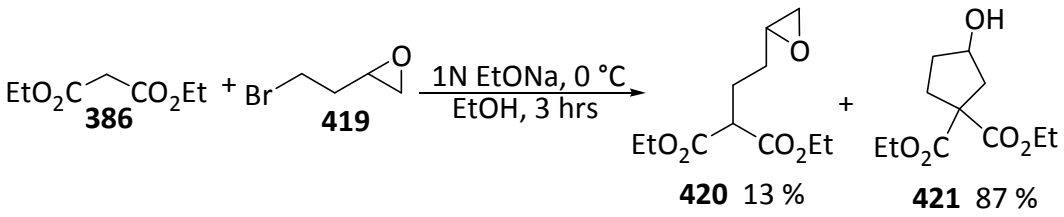
Figure 11

The rate of formation of significantly strained four membered rings is slow as compared to the less strained five, six and seven membered rings.[83] The activation energy barrier $\Delta G^{\ddagger}$ for a reaction depends upon the enthalpy of activation $\Delta H^{\ddagger}$ and entropy of activation $\Delta S^{\ddagger}$. The enthalpy of activation $\Delta H^{\ddagger}$ is the energy required to bring atoms together against the strain and repulsive forces. Whereas, the entropy of activation $\Delta S^{\ddagger}$ tells how easy it is to form an ordered transition state from a wriggling and randomly rotating molecule. For small strained three and four membered rings the enthalpy of activation $\Delta H^{\ddagger}$ is large because more energy is needed to bend the molecule into the strained small ring conformations. The long chain has more disorder and it has to give up a lot of freedom to get its ends to meet and react. To form an ordered transition state from a long chain is hard compared to a small chain and the entropy of activation $\Delta S^{\ddagger}$ is higher in a long chain. For medium and large rings $\Delta S^{\ddagger}$ is large and negative and contributing to a large $\Delta G^{\ddagger}$ and slow reactions. For four membered rings, the activation energy barrier ($\Delta G^{\ddagger}$) is large because the enthalpy of activation $\Delta H^{\ddagger}$ and entropy of activation $\Delta S^{\ddagger}$ are large. So, four membered rings are formed slowly. There is less strain in five; six and seven membered rings and enthalpy of activation $\Delta H^{\ddagger}$ is small. The rate of formation for five membered rings is the fastest. The activation energy barrier $\Delta G^{\ddagger}$ for five membered rings is small compared to four, six and seven membered rings. The enthalpy of activation $\Delta H^{\ddagger}$ in five membered rings is small due to less strain in five membered rings and activation energy barrier $\Delta G^{\ddagger}$ for five membered rings is mainly due to entropy of activation $\Delta S^{\ddagger}$. There is less strain in six and seven membered rings and the enthalpy of activation $\Delta H^{\ddagger}$ is small but, the rate of the formation of six and seven membered rings is slow due to increase in entropy of activation $\Delta S^{\ddagger}$ which ultimately increase the activation energy barrier $\Delta G^{\ddagger}$. Although five membered rings are formed faster than six membered rings, they are usually less stable (kinetic product) than six membered ring (thermodynamic product). The cyclisation of the malonic enolate **407** by 4-*exo*-*tet* and 6-*exo*-*tet* cyclisation to four **406** and six **418** membered rings are favoured according to the Baldwin's rules but the rate of formation of four membered rings is slow compared to six membered rings. 5-*endo*-*tet* or seven-*endo*-*tet* cyclisation to the five **416** and seven **417** membered rings are disfavoured according to the Baldwin's rules but the rate of formation of five, six and seven membered rings are higher than four membered rings. The cyclisation of malonic enolate **407** could give the following possible products (Scheme 159).



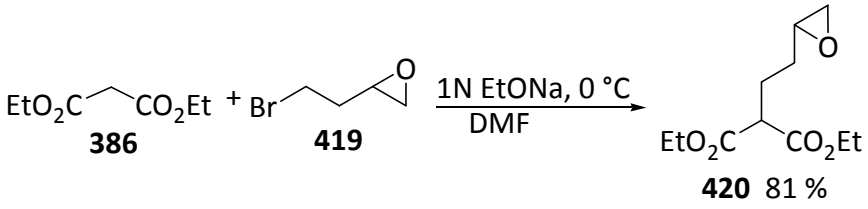
Scheme 159

In 1969 Cruickshank and Fishman reported the reaction of diethylmalonate and 4-bromo-1,2-epoxybutane **419** in 1N ethanolic sodium ethoxide solution affording 2-(2-oxiranylethyl) malonic acid diethylester **420** as a minor and 3-hydroxycyclopentane-1,1-dicarboxylic acid diethyl ester **421** as a major product (Scheme 160).[84]



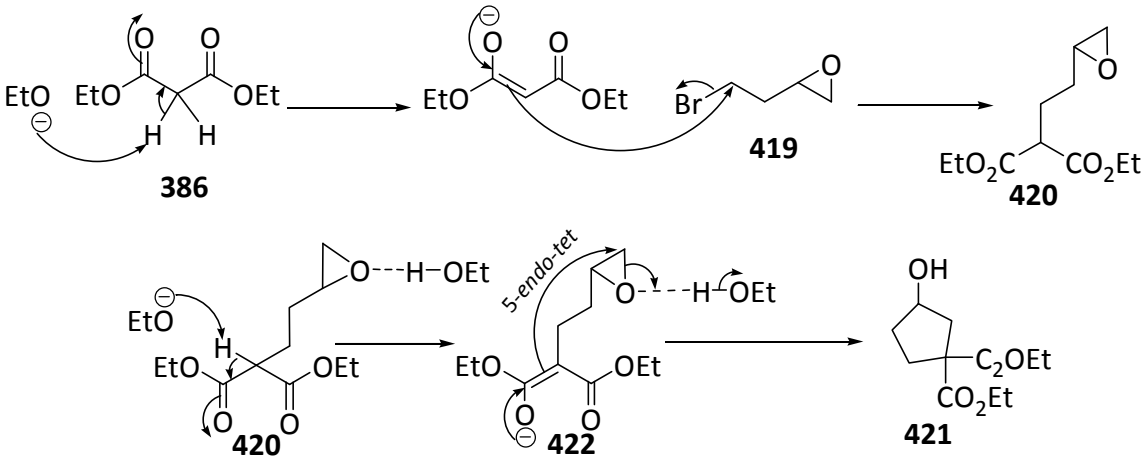
Scheme 160

When the same reaction was carried out in aprotic solvent 2-(2-oxiranylethyl) malonic acid diethylester **420** was obtained as the sole product (Scheme 161).



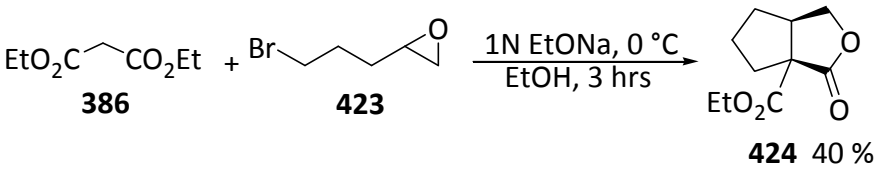
Scheme 161

In 4-bromo-1,2-epoxybutane **419** both reactive sites are primary carbon atoms. In aprotic solvent the carbon-bromine bond is more susceptible to nucleophilic attack and in protic solvents hydrogen bonding at the epoxide ring weakens the carbon-oxygen bond and the nucleophilic attack at this site becomes favoured. The reaction of diethylmalonate and 4-bromo-1,2-epoxybutane under basic conditions in aprotic solvent gave epoxyalkyl product **420** as expected. However, when the same reaction was carried in alcoholic media epoxyalkyl product **420** and 3-hydroxycyclopentane-1,1-dicarboxylic acid diethyl ester **421** were obtained as products. The solvent effect does not seem to be important in the reaction of diethyl malonate and 4-bromo-1,2-epoxybutane in protic solvents. The nucleophile attacks at the less solvated carbon-bromine bond resulting in formation of epoxyalkyl product **420**. Under basic conditions 2-(2-oxiranylethyl) malonic acid diethylester **420** gives malonic enolate **422**, which intramolecularly attacks less hindered primary carbon atom of the solvated epoxide ring and cyclises through 5-*endo-tet* cyclisation affording 3-hydroxycyclopentane-1,1-dicarboxylic acid diethyl ester **421** as a major product. The cyclisation of 2-(2-oxiranylethyl) malonic acid diethylester **420** deviates from the Baldwin's rules and cyclisation to the five membered ring **421** was observed due to higher rate of formation of five membered rings compared to four membered rings (Scheme 162).[83]



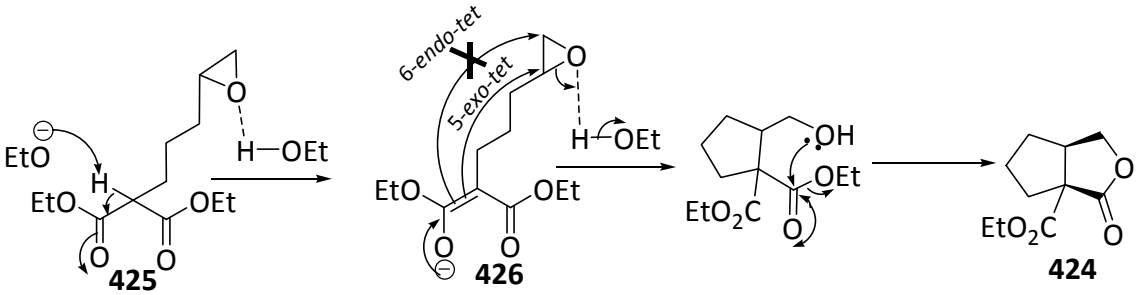
Scheme 162

When the reaction was carried out between diethylmalonate and 5-bromo-1,2-epoxypentane **423** under the same reaction conditions in ethanol, 3-oxotetrahydrocyclopenta[c]furan-3a-carboxylic acid ethyl ester **424** was obtained in 40 % yield (Scheme 163).[84]



Scheme 163

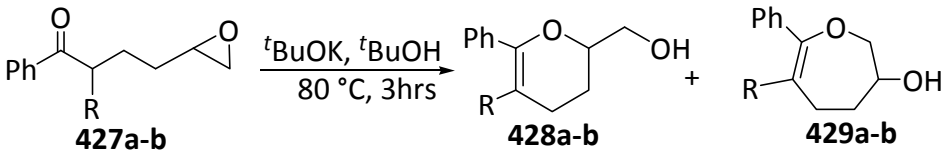
The reaction results in the formation of 2-(3-oxiranylpropyl)malonic acid diethyl ester **425** by a similar mechanism as described in scheme 162. The deprotonation of the acidic proton of 2-(3-oxiranylpropyl)malonic acid diethyl ester **425** under basic conditions gives malonic enolate **426**. The nucleophilic malonic enolate **426** attacks on solvated epoxide ring at more hindered secondary carbon atom and cyclises through 5-*exo*-*tet* cyclisation affording 3-oxotetrahydrocyclopenta[c]furan-3a-carboxylic acid ethyl ester **424**. The cyclisation of malonic enolate **426** follows Baldwin's rules and cyclisation results in the formation of five membered fused cyclopentane **424** because the activation energy barrier $\Delta G^{\mp}$ for five membered rings is low and their rate of formation is higher compared to six membered rings (Scheme 164).[83]



Scheme 164

The reaction resulted in fused cyclopentane **424** whereas, a similar reaction between diethylmalonate and 4-bromo-1,2-epoxybutane failed to give fused cyclobutane. The activation energy barrier $\Delta G^{\mp}$ for four membered rings is large and their rate of formation is slow therefore fused cyclobutane was not formed under a similar reaction between diethylmalonate and 4-bromo-1,2-epoxybutane and the reaction resulted in five membered 3-hydroxycyclopentane-1,1-dicarboxylic acid diethyl ester **421**.

Crotti *et al*. have reported the cyclisation of epoxy ketones **427a-b** under basic conditions affording *O*-alkylated products **428a-b** and **429a-b** formed by 6-*exo*-*tet* and 7-*endo*-*tet* cyclisation (Scheme 165, table 36).[85]



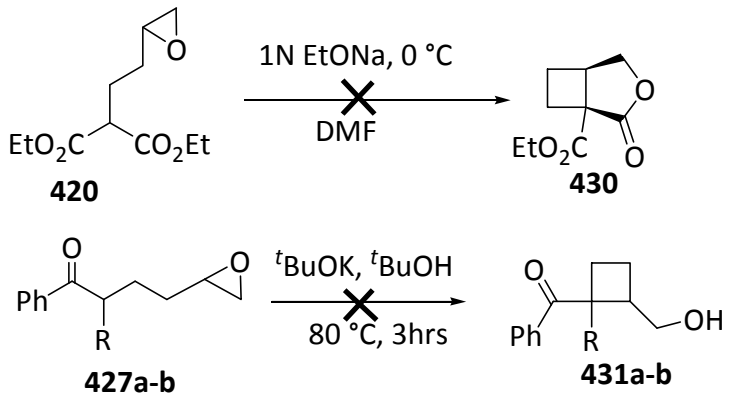
Scheme 165

Entry	427	R	Time	Temp.°C	428 %	429 %	Yield %
1	**427a**	H	3 hrs	80	**428a** 77	**429a** 23	84
2	**427b**	Me	3 hrs	80	**428b** 83	**429b** 17	75

Table 36

The reaction of epoxy ketone **427a-b** afforded only *O*-alkylated six and seven membered products and corresponding *C*-alkylated four and five membered products were not observed at all.

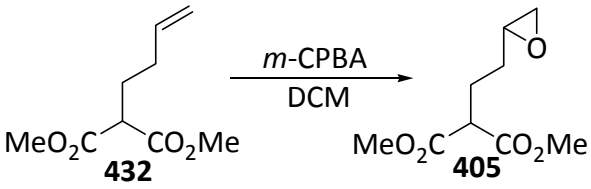
The formation of four membered rings **430** and **431** were not observed by the cyclisation of 2-(2-oxiranylethyl) malonic acid diethylester **420** and epoxy ketones **427a-b** under basic conditions (Scheme 166).



Scheme 166

A variety of other basic conditions could be try in an attempt to cyclise 2-(2-oxiranylethyl) malonic acid dimethylester **405** to fused cyclobutane **406**. So, it was decided to go ahead with the synthesis of 2-(2-oxiranylethyl) malonic acid diethylester **405** and subsequent cyclisation under basic conditions.

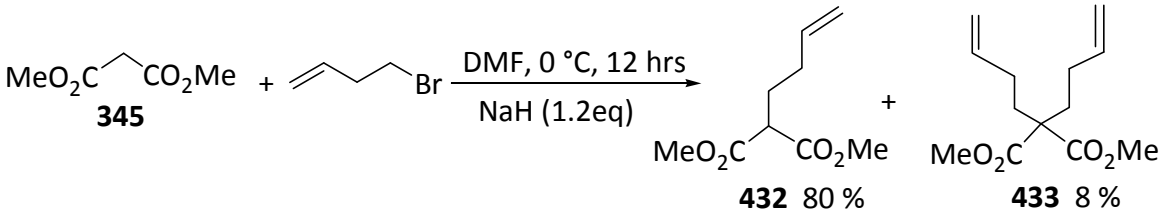
The route we planned for the synthesis of 2-(2-oxiranylethyl) malonic acid dimethylester **405** was the epoxidation of 2-but-3-enylmalonic acid dimethyl ester **432** (Scheme 167).



432 **405**

Scheme 167

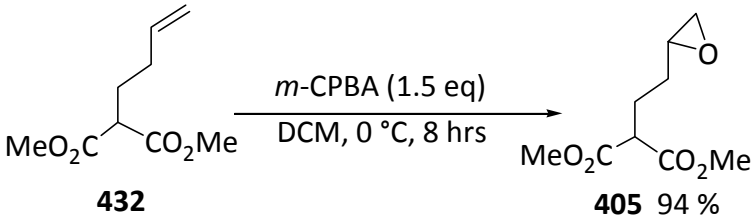
Prestat and Poli have reported the synthesis of 2-but-3-enylmalonic acid dimethyl ester **432**.[86] By following their procedure the allylic alkylation of dimethylmalonate was carried out in a suspension of NaH in DMF at 0 °C with 4-bromo-1-butene giving requisite 2-but-3-enylmalonic acid dimethyl ester **432** in 80 % yield. The dialkylated product **433** was also obtained in 8 % yield as a side product (Scheme 168).



432 80 % **433** 8 %

Scheme 168

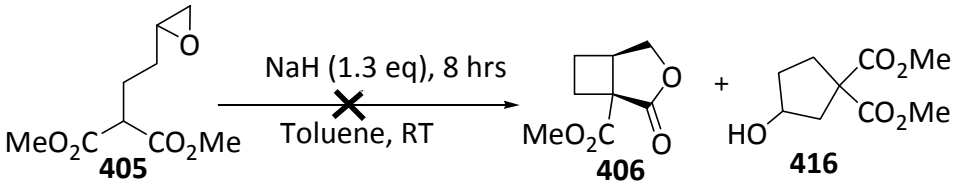
The next step was the epoxidation of 2-but-3-enylmalonic acid dimethyl ester **432**, which was carried out in DCM, using *m*-CPBA, at 0 °C, affording 94 % yield of the desired epoxide **405** (Scheme 169).



432 **405** 94 %

Scheme 169

Attempts were then made to cyclise the epoxide **405** under basic conditions to the fused cyclobutane **406** and 3-hydroxycyclopentane-1,1-dicarboxylic acid dimethyl ester **416** (Scheme 170).

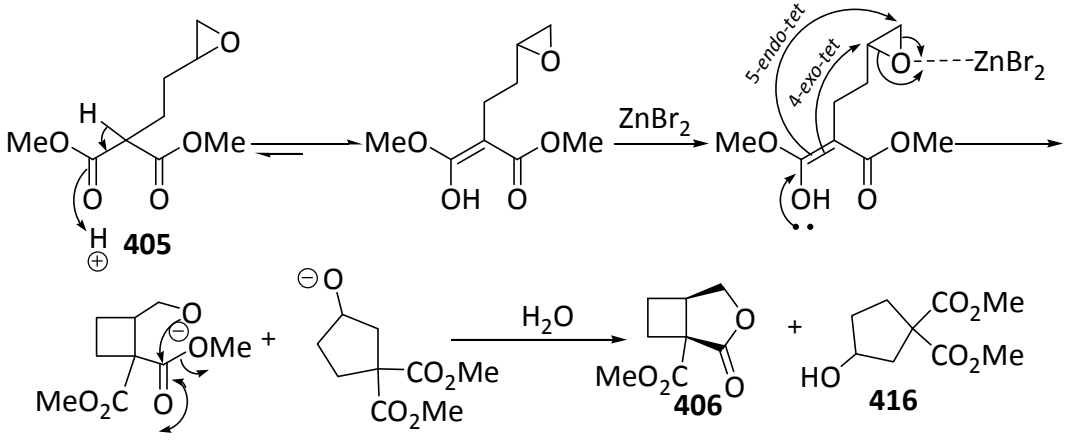


405 **406** **416**

Scheme 170

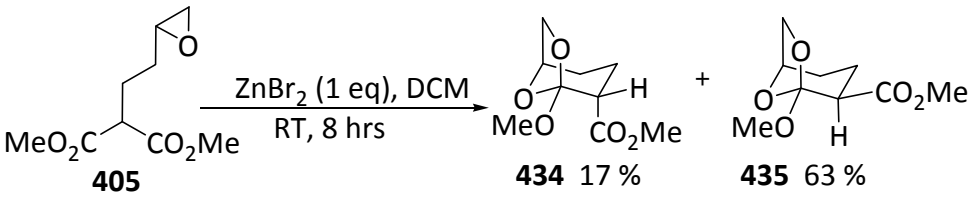
We observed decomposition of epoxide **405** in a range of solvents when employing NaH as the base. Fishman *et al.* have reported the formation of 2-(2-oxiranylethyl) malonic acid

diethylester **420** and its cyclisation into 3-hydroxycyclopentane-1,1-dicarboxylic acid diethyl ester **421** in a 1N ethanolic sodium ethoxide solution (Scheme 160).[84] In 1N ethanolic sodium ethoxide solution 2-(2-oxiranylethyl) malonic acid diethylester **420** was stable. So an attempt was made to cyclise epoxide **405** in methanolic sodium methoxide solution. When the reaction was performed under similar conditions, a mixture of three inseparable compounds was obtained. The mass recovery of the product was low compared to the starting material. The NMR data was not helpful to work out the exact structures of these inseparable compounds. The mass spectrum showed presence of a compound $C_{10}H_{17}O_6$ which differs from $C_9H_{14}O_5$ **405** by CH_3O unit indicating that base is acting as nucleophile. Then it was decided to perform reaction by using non nucleophilic base. Various attempts were made by using non nucleophilic bases (^{t}BuONa, Et_3N and DBU) in a range of solvents and reaction temperatures but all in vain. We did not succeed in synthesising the desired cyclobutane **406** or cyclopentane **416** under basic conditions, at this stage it was decided to perform the reaction under Lewis acidic conditions. It was suggested that Lewis acidic conditions could cyclise 2-(2-oxiranylethyl) malonic acid dimethylester **405** to the same fused cyclobutane **406** and cyclopentane **416** (Scheme 171).



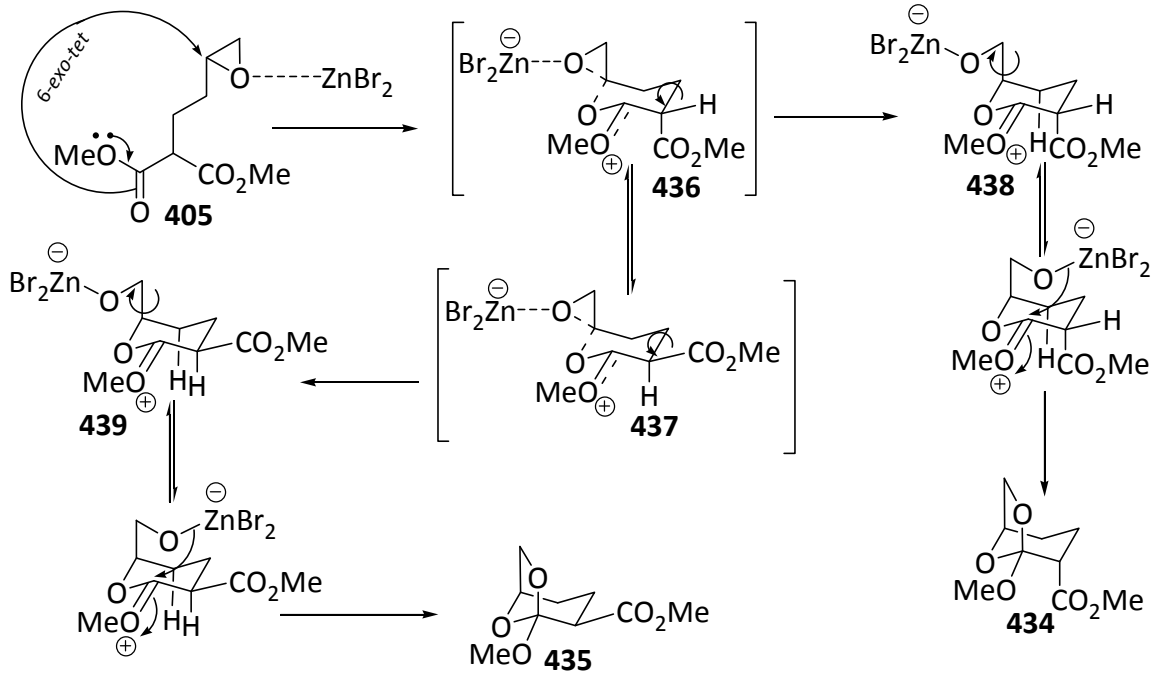
Scheme 171

When the epoxide **405** was reacted with zinc bromide in DCM, at room temperature, none of the desired fused cyclobutane **406** or cyclopentane **416** were observed, but the reaction gave two diastereoisomers of 5-methoxy-6,8-dioxabicyclo[3.2.1]octane-4-carboxylic acid methyl ester **434** and **435** as products (Scheme 172).



Scheme 172

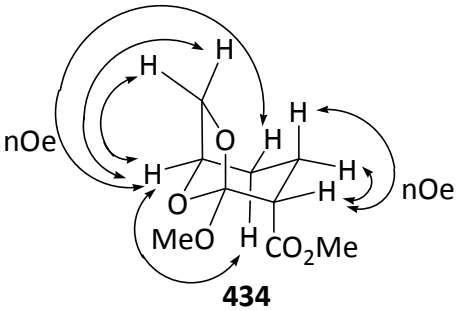
The reaction appears to proceed through nucleophilic ring opening of the epoxide **405** by the carbonyl oxygen lone pair performing an internal S_N2 type reaction (Scheme 173).



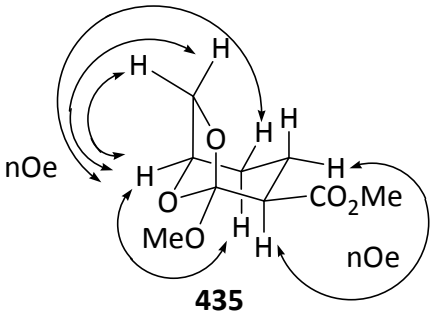
Scheme 173

The Lewis acid coordinates with oxygen lone pair of the epoxide ring and makes the epoxide ring electrophilic. Nucleophilic attack of the lone pair of the carbonyl oxygen to the epoxide and subsequent 6-*exo*-*tet* cyclisation give rise two chair-like transition states **436** and **437** leading to the intermediates **438** and **439** respectively. In intermediate **438** the ester group is in an axial orientation, which results in an unfavourable 1,3-diaxial interaction with hydrogen atom. Ring closure of the higher energy intermediate **438** to 5-methoxy-6,8-dioxabicyclo[3.2.1]octane-4-carboxylic acid methyl ester **434** results in the minor isomer. Whereas, in intermediate **439** the ester group is in an equatorial position and hence is a more stable conformation. The ring closure of this more stable intermediate **439** to 5-methoxy-6,8-dioxabicyclo[3.2.1]octane-4-carboxylic acid methyl ester **435** results in major isomer.

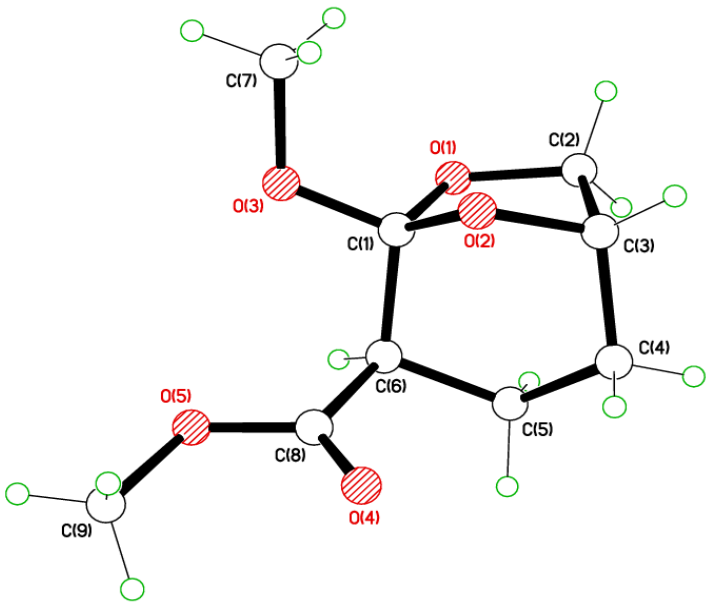
The relative stereochemistry of **434** and **435** was proven by nOe experiments and X-ray crystallography. In compounds **434** and **435** irradiation of the protons to the bridge-head position show strong nOe to both CH_2 protons on the bridge and axial and equatorial protons of neighbouring CH_2 group. Irradiation of the proton next to ester group in **434** leads clear nOe to neighbouring axial and equatorial CH_2 protons. This suggests that the proton next to ester group is in equatorial position in **434**. In compound **435** irradiation of the proton next to ester group leads clear nOe to only equatorial proton of neighbouring CH_2 group suggesting that the proton is in axial position.



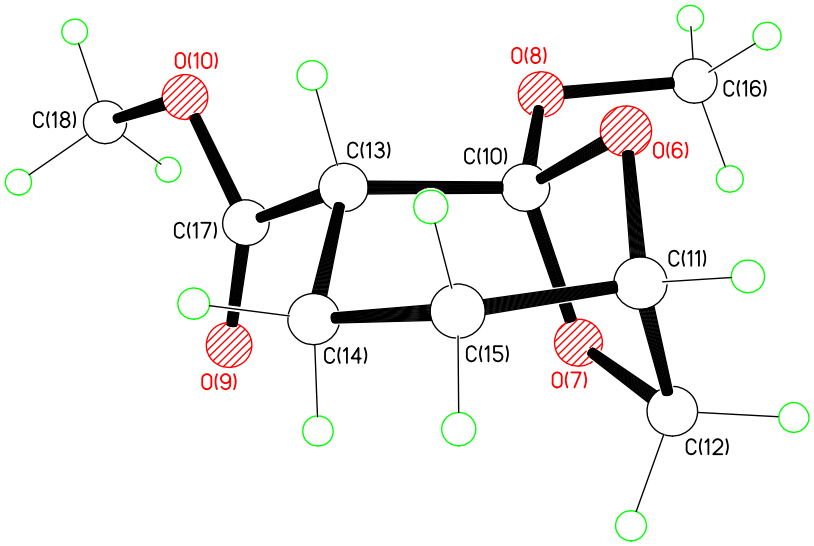
434



435



434



435

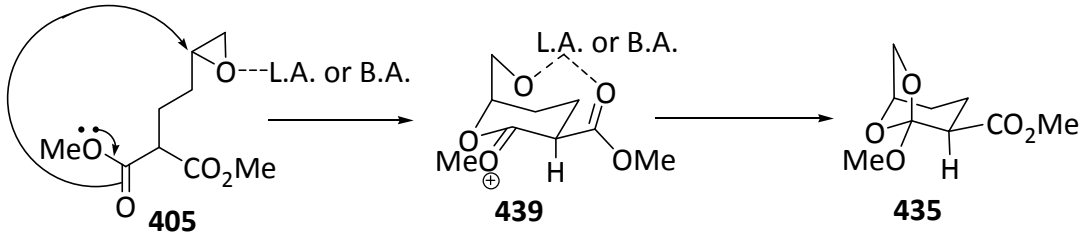
To explore the reaction a variety of Lewis and Brønsted acids were tried in stoichiometric and catalytic amounts using different solvents and conditions (Table 37).

Entry	solvent	Lewis acid	Eq /mol %	Temp.°C	Time	434 isolated yield %	435 isolated Yield %	Total yield %
1	DCM	$ZnBr_2$	10 mol %	Reflux	12 hrs	30	50	80
2	DCM	$MgBr_2$	1 eq	RT	10 hrs	---	---	---
3	DCM	$MgBr_2$	10 mol %	RT	10 hrs	---	---	---
4	DCE	$ZnBr_2$	10 mol %	50	12 hrs	30	60	90
5	DCE	$ZnBr_2$	1 eq	RT	8 hrs	30	60	90
6	Toluene	$ZnBr_2$	10 mol %	40	18 hrs	24	34	58
7	THF	$ZnBr_2$	10 mol %	RT	12 hrs	---	---	---
8	THF	$ZnBr_2$	1 eq	60	6 hrs	---	---	---
9	DCM	$BF_3.OEt_2$	10 mol %	RT	1 hrs	---	---	---
10	DCM	$Yt(OTf)_3$	10 mol %	Reflux	8 hrs	Traces	75	75
11	DCM	$Sc(OTf)_3$	10 mol %	RT	2 hrs	---	---	---
12	DCM	$Sc(OTf)_3$	1 mol %	RT	18 hrs	---	Traces	---
13	DCM	$Sc(OTf)_3$	1 mol %	Reflux	20 min	---	30	30
14	DCM	*p*-TsOH	1 mol %	RT	1 hrs	---	60	60

Table 37

During the screening process $ZnBr_2$ was found most effective Lewis acid in DCM and DCE solvents. The $Yt(OTf)_3$ and *p*-TsOH gave better selectivity affording only 5-methoxy-6,8-dioxabicyclo[3.2.1]octane-4-carboxylic acid methyl ester **435**. The observed selectivity

during the cyclisation of epoxide **405** in the presence of strong Lewis and Brønsted acids [$Yt(OTf)_3$, $Sc(OTf)_3$ and *p*-TsOH] can be rationalized due to the chelation of Lewis or Brønsted acid with the oxygen atoms of epoxide ring and carbonyl group of the ester resulting in most stable conformation **439** and affording **435** as a major product (Scheme 174).



Scheme 174

Under Lewis and Brønsted acidic conditions we did not succeed in getting the desired cyclobutane **406** but the synthesis of 6,8-dioxabicyclo[3.2.1]octane ring system **434** and **435** from epoxide **405** is novel to the best our knowledge. The cycloisomerisation of α-ε-epoxy ketones[64] (Scheme 85, page 48) and α-ε-epoxy imines[67] (Scheme 92, page 52) for the synthesis of 6,8-dioxabicyclo[3.2.1]octane and 6-oxa-8-azabicyclo[3.2.1]octanes derivatives are known in literature. The 6,8-dioxabicyclo[3.2.1]octane ring system is found in insect pheromones and complex natural products (Figure 12).[42-49] Most of them are biologically active, such as cyclodidemniserinol trisulfate, which is an inhibitor of HIV-1 integrase.

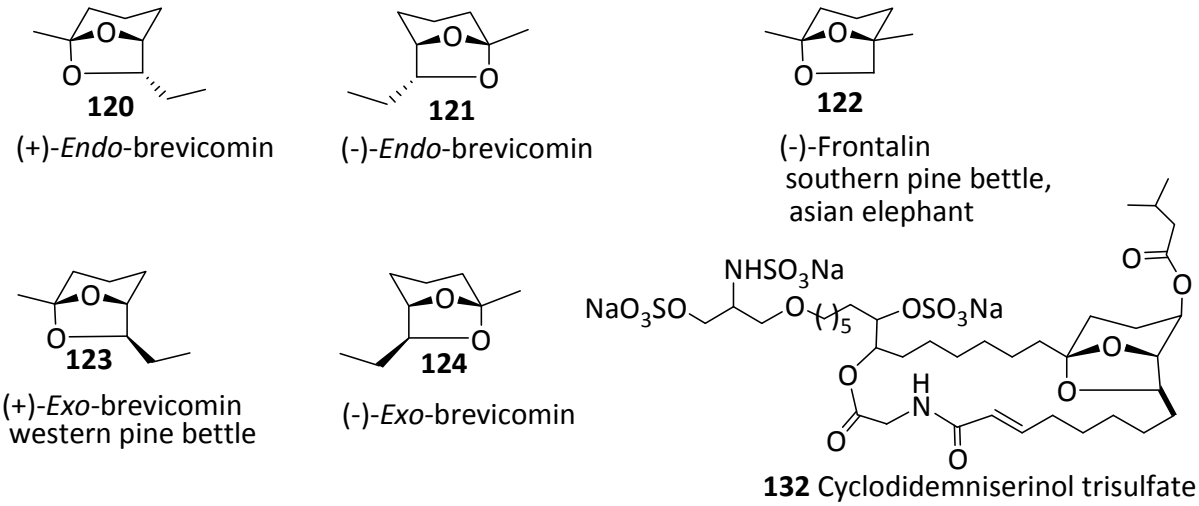
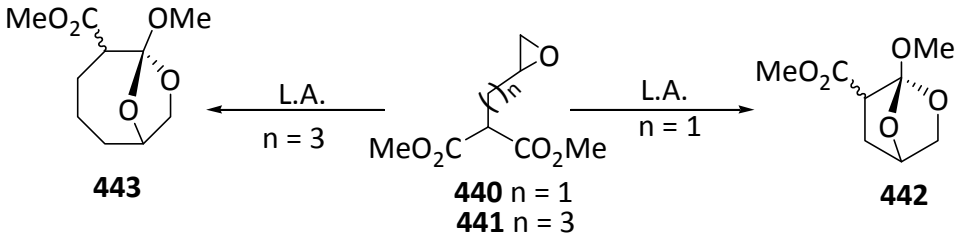


Figure 12 Insect pheromones and cyclodidemniserinol trisulfate

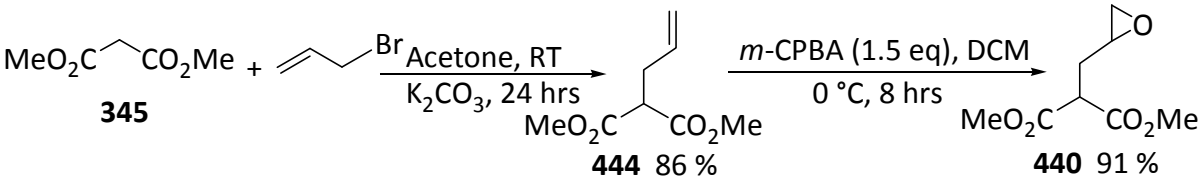
2.8. Attempted synthesis of 1-methoxy-2,7-dioxabicyclo[2.2.1]heptanes-6-carboxylic acid methyl ester and 6-methoxy-7,9-dioxabicyclo[4.2.1]nonane-5-carboxylic acid methyl ester

Due to the importance of 6,8-dioxabicyclo[3.2.1]octanes it was decided to extend the scope of this reaction by increasing or decreasing the carbon chain length of the epoxide **405** by a CH_2 unit to synthesise smaller and larger ring systems. Attempts were made to synthesise 2,7-dioxabicyclo[2.2.1]heptane **442** and 7,9-dioxabicyclo[4.2.1]nonane **443** bicyclic compounds by varying number of carbon in the epoxide **405** chain. The epoxides **440** and **441** differ from the epoxide **405** in carbon chain length and under Lewis acidic conditions could give similar cycloisomerised products (Scheme 175).



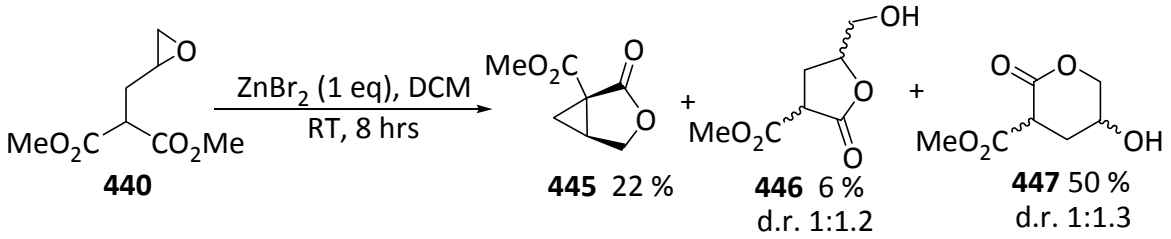
Scheme 175

Our next target was the synthesis of the required epoxides **440** and **441**. The requisite precursor 2-allylmalonic acid dimethyl ester **444** for the preparation of epoxide **440** was prepared by a procedure reported by Prestat and Poli.[86] By following their procedure dimethylmalonate and 3-bromoprop-1-ene were reacted in a suspension of potassium carbonate in acetone, at RT, for 24 hours, to get desired 2-allylmalonic acid dimethyl ester **444** in 86 % yield. The epoxidation of 2-allylmalonic acid dimethyl ester **444** was carried out in DCM, at 0 °C, with *m*-CPBA (1.5 eq) and gave 91 % yield of the desired epoxide **440** in eight hours (Scheme 176).



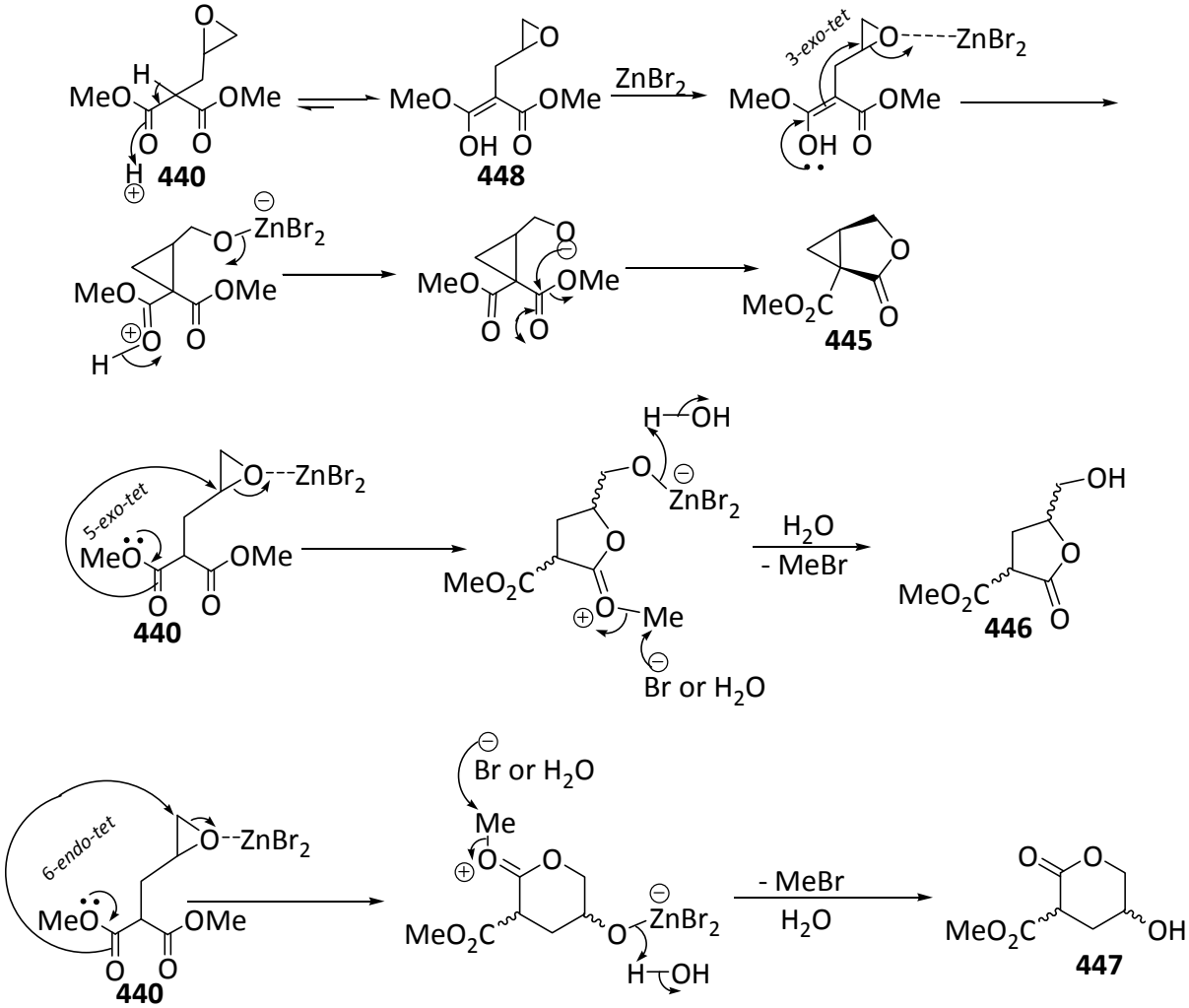
Scheme 176

When epoxide **440** was reacted with zinc bromide in DCM at RT, the desired 2,7-dioxabicyclo[2.2.1]heptane **442** was not obtained but fused cyclopropane **445**, a mixture of inseparable diastereoisomers (1:1.2) tetrahydrofuran **446** and a mixture of inseparable diastereoisomers (1:1.3) of tetrahydropyran **447** were obtained as products (Scheme 177).



Scheme 177

The epoxide **440** has the same functionalities as epoxide **405** but one less CH_2, reacted differently under the similar reaction conditions. The epoxide **440** gave three, five and six membered rings under the reaction conditions. The reaction mechanism we suggested below (Scheme 178).

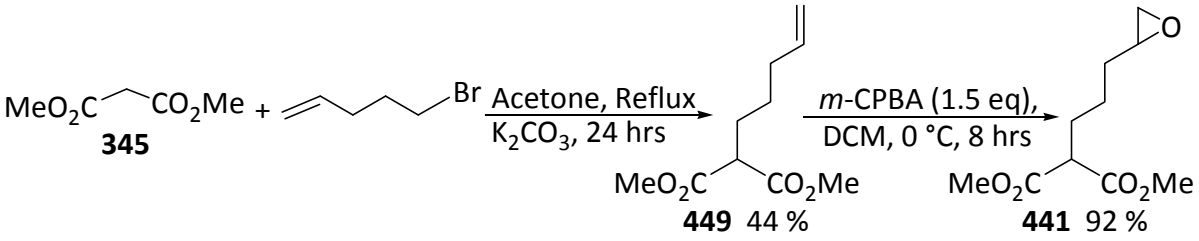


Scheme 178

The coordination of oxygen lone pair of the epoxide **440** with the Lewis acid makes the epoxide ring electrophilic. The nucleophilic enol form **448** (Scheme 178) of the epoxide **440** intramolecularly attacks the epoxide ring and 3-*exo-tet* cyclisation leads to the fused

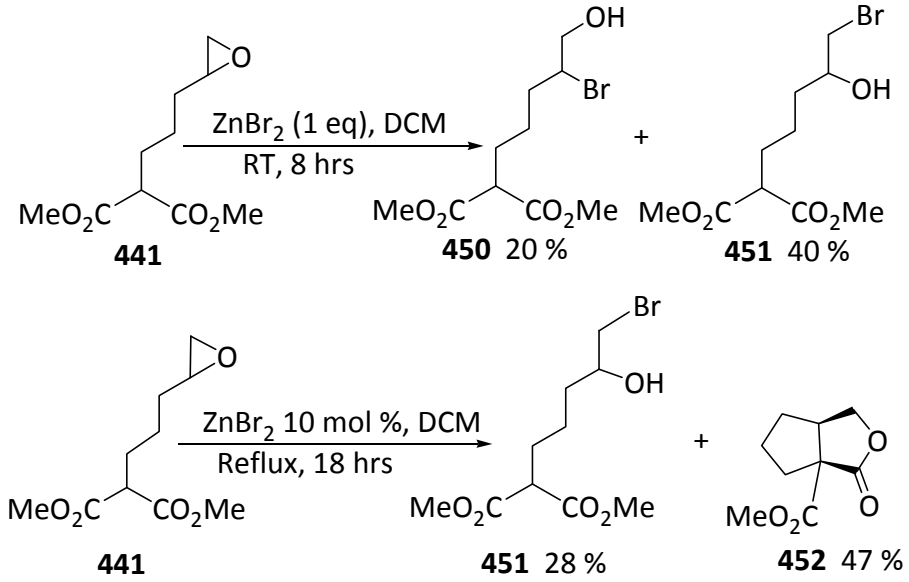
cyclopropane **445**. Three membered rings are more strained then four membered rings.[83] The epoxide **440** cyclised to three membered fused cyclopropane **445** whereas, the epoxide **405** under similar reaction conditions fail to give fused cyclobutane **406.** Three and four membered rings are both strained and have large enthalpy of activation $\Delta H^{\mp}$. The epoxide **440** has small carbon chain length, the reacting atoms are very close together and entropy of activation $\Delta S^{\mp}$ is very small. To cyclise the epoxide **440** to three membered cyclopropane the enthalpy of activation $\Delta H^{\mp}$ is large and entropy of activation $\Delta S^{\mp}$ is small. The overall activation energy barrier $\Delta G^{\mp}$ is small compared to four membered rings and so the epoxide **440** is cyclised to fused cyclopropane **445**. The reacting atoms are for apart in the epoxide **405** compared to the epoxide **440** due to increase in carbon chain length and the entropy of activation $\Delta S^{\mp}$ is large. To cyclise the epoxide **405** in to four membered ring the enthalpy of activation $\Delta H^{\mp}$ and entropy of activation $\Delta S^{\mp}$ are both large. The overall activation energy barrier $\Delta G^{\mp}$ to form four membered ring from the epoxide **405** is large and therefore fused cyclobutane **406** was not formed under similar reaction condition. The lone pair of carbonyl oxygen also attacks the epoxide ring and cyclises through 5-*exo*-*tet* and 6-*endo*-*tet* cyclisation to the corresponding five and six membered tetrahydrofuran **446** and tetrahydropyran **447** respectively. The cyclisation of the epoxide **440** has no stereoelectronic problem to cyclise through 5-*exo*-*tet* cyclisation to tetrahydrofuran **446** and the rate of formation of five membered rings is higher. However the cyclisation of the epoxide **440** through 6-*endo*-*tet* cyclisation is disfavoured according to the Baldwin's rules but six membered terrahydropyran **447** (thermodynamic product) was obtained as a major product.

The requisite precursor **449** for the preparation of epoxide **441** was prepared by allylic alkylation of dimethylmalonate in suspension of potassium carbonate in acetone, at reflux, with 5-bromo-1-pentene, affording 2-pent-4-enyl malonic acid dimethylester **449** in 44 % yield as a sole product.[86] The epoxidation of 2-pent-4-enyl malonic acid dimethylester **449** was carried out in DCM, at 0 °C, with *m*-CPBA (1.5 eq), in eight hours, giving 92 % yield of the desired epoxide **441** (Scheme 179).



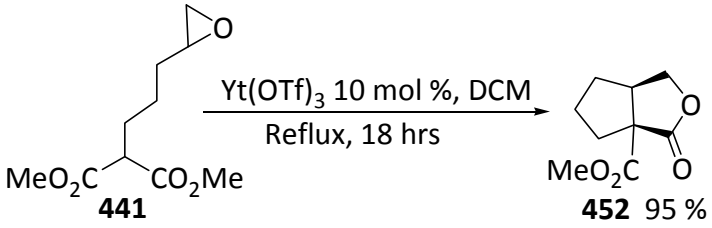
Scheme 179

When the epoxide **441** was reacted with $ZnBr_2$, in DCM, the desired bicyclic compounds **443** was not obtained. The epoxide **441** under stoichiometric amount of Lewis acidic in DCM showed opening of epoxide ring by bromide ion giving regioisomers **450** and **451**. When the reaction conditions were further changed to 10 mol % of zinc bromide at refluxing conditions the bromide **451** and fused cyclopentane **452** were obtained as products (Scheme 180).



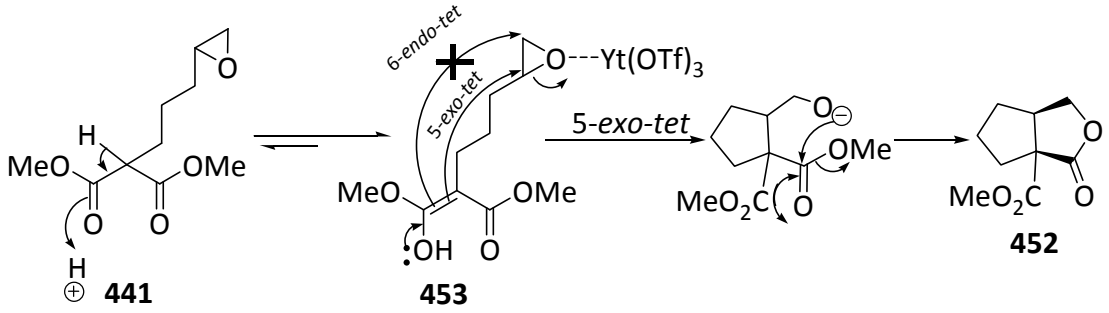
Scheme 180

When the same reaction was tried in the presence of catalytic amount of non nucleophilic Lewis acid $Yt(OTf)_3$ the fused cyclopentane **452** was obtained as a sole product (Scheme 181).



Scheme 181

Under Lewis acidic conditions the enol form **453** of the epoxide **441** is cyclised by *5-exo-tet* cyclisation to fused cyclopentane **452**. The suggested mechanism of formation of fused cyclopentane **452** is given below (Scheme 182).



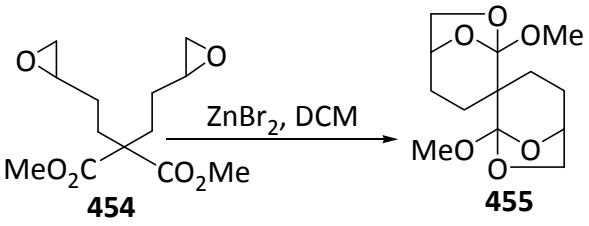
Scheme 182

The epoxides **440** and **441** are cyclised under Lewis acidic conditions to fused propane **445** and cyclopentane **452** whereas the epoxide **405** failed to give fused cyclobutane **406**. The epoxide **441** is longer in chain length compared to the epoxide **405** and has large entropy of activation $\Delta S^{\mp}$. Five membered rings are less strained compared to four membered rings and the enthalpy of activation $\Delta H^{\mp}$ is small.[83] To cyclise the epoxide **441** to five membered ring the enthalpy of activation $\Delta H^{\mp}$ is small and entropy of activation $\Delta S^{\mp}$ is large. The overall activation energy barrier $\Delta G^{\mp}$ for five membered rings is small compared to four membered rings and therefore epoxide **441** is cyclised to fused cyclopentane **452**. The activation energy barrier $\Delta G^{\mp}$ for for five membered rings is also small compared to six membered rings and five membered rings are formed faster than six membered rings. The *5-exo-tet* cyclisation is favoured over *6-endo-tet* cyclisation.

By varying the number of carbon atoms in epoxide chain we did not succeed in the synthesis of the required bicyclic compounds. It was then decided to synthesise a range of different 6,8-dioxabicyclo[3.2.1]octane derivatives.

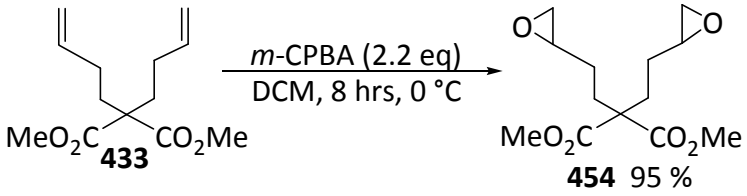
2.9. Synthesis of 5,5-dimethoxy-6,6,8,8-tetraoxa-4,4-spirobi[bicyclo[3.2.1]octane]

The cycloisomerisation of epoxide **405** under Lewis acidic conditions to the diastereoisomers of 5-methoxy-6,8-dioxabicyclo[3.2.1]octane-4-carboxylic acid methyl ester **434** and **435** motivated us to look at 2,2-bis-(2-oxiranylethyl)malonic acid dimethyl ester **454** having two epoxide rings and two esters. Under Lewis acidic conditions both carbonyl ends of 2,2-bis-(2-oxiranylethyl)malonic acid dimethyl ester **454** could cyclise on both epoxide rings (Scheme 183).



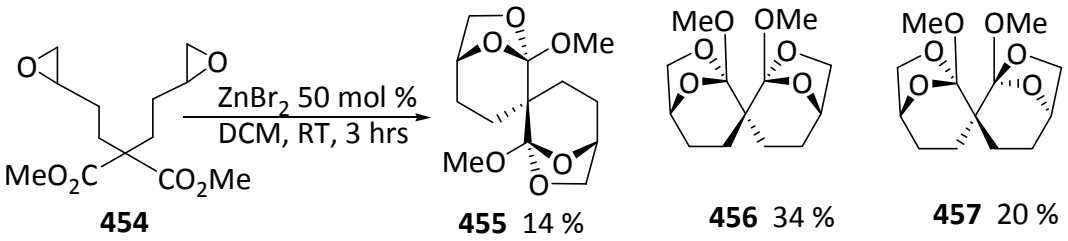
Scheme 183

2,2-Dibut-3-enylmalonic acid dimethyl ester **433** had been obtained as a side product during allylic alkylation of dimethylmalonate with 4-bromo-1-butene in 8 % yield (Scheme 168 page 90), so we decided to use this material. (±)-2,2-Bis-(2-oxiranylethyl)malonic acid dimethyl ester **454** was prepared by the epoxidation of 2,2-di-but-3-enylmalonic acid dimethyl ester **433** with of *m*-CPBA (2.2 eq), at 0 °C, in DCM (Scheme 184).



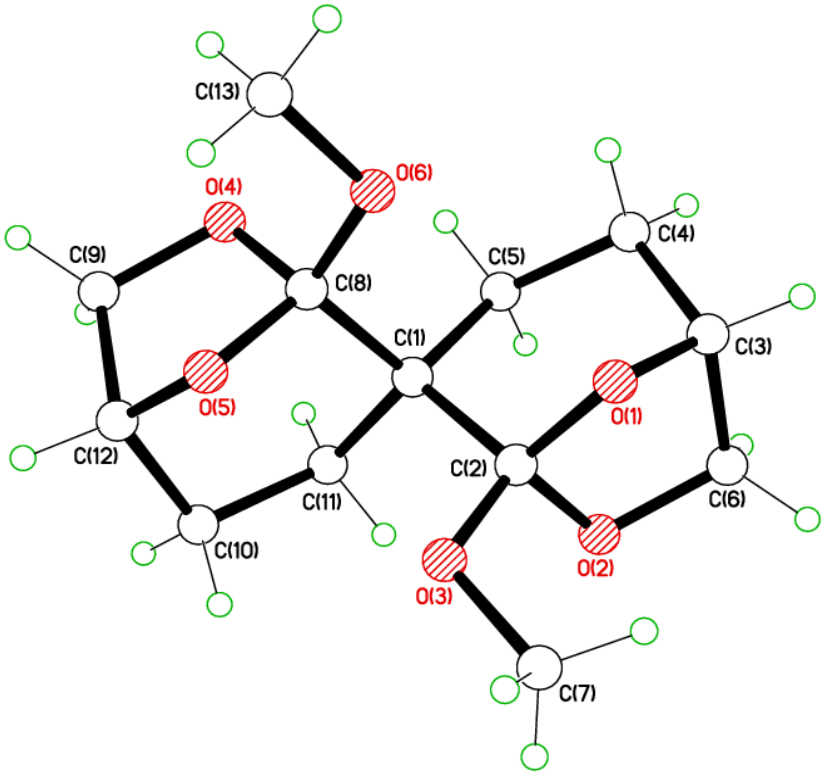
Scheme 184

When (±)-2,2-bis-(2-oxiranylethyl)malonic acid dimethyl ester **454** was reacted with 50 mol % of zinc bromide, in DCM, three diastereoisomers of (±)-5,5-dimethoxy-6,6,8,8-tetraoxa-4,4-spirobi[bicyclo[3.2.1]octane] **455**, **456** and **457** were isolated (Scheme 185).

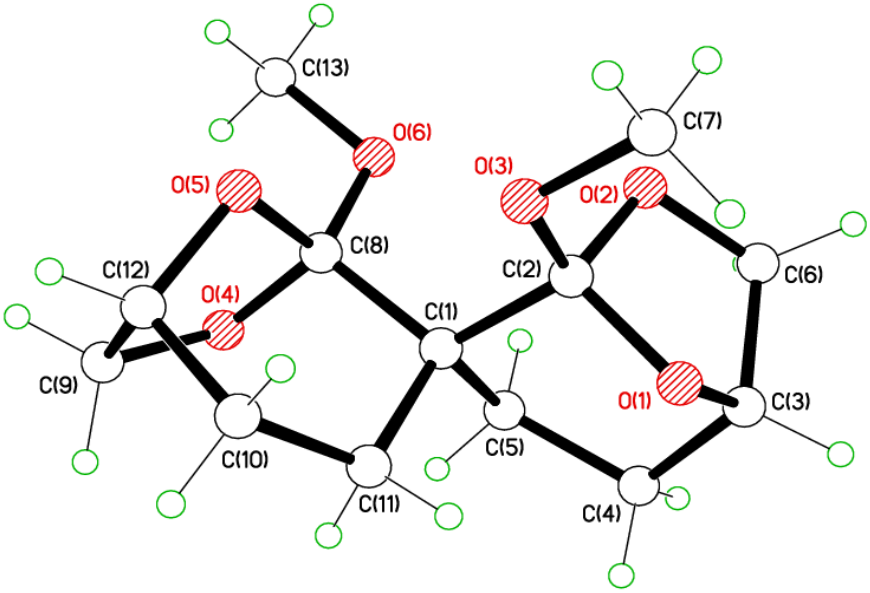


Scheme 185

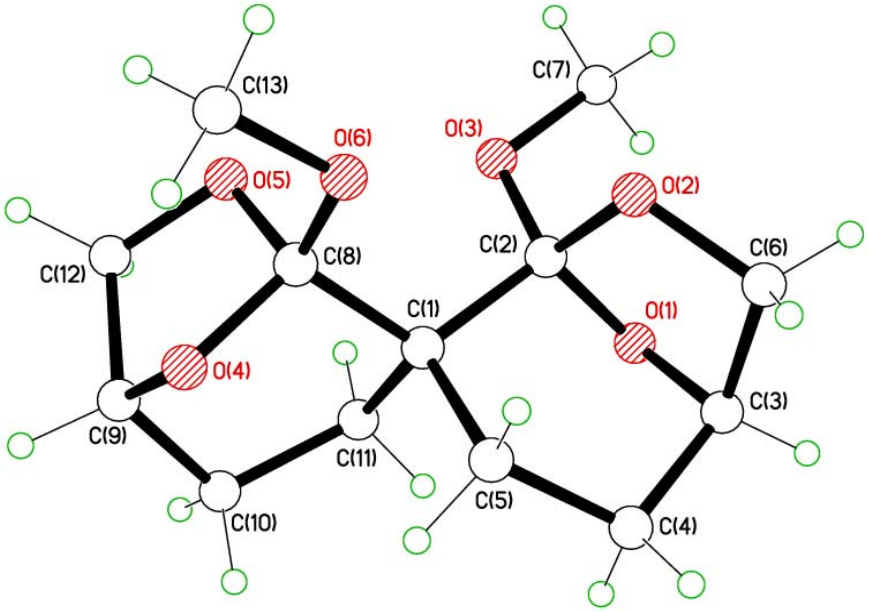
Their structures were identified by X-Ray crystallography. The ^{13}C NMR spectra of **455** and **457** were symmetrical showing seven carbon atoms, where as ^{13}C NMR spectrum of **456** was unsymmetrical showing thirteen carbon atoms.


C(13)
O(6)
O(4)
C(9)
C(8)
C(5)
C(4)
C(1)
C(3)
O(5)
O(1)
C(12)
C(2)
C(6)
C(11)
C(10)
O(2)
O(3)
C(7)

455


C(13)
O(6)
C(7)
O(5)
O(3)
O(2)
C(8)
C(12)
C(2)
C(6)
O(4)
C(1)
C(9)
O(1)
C(3)
C(5)
C(10)
C(11)
C(4)

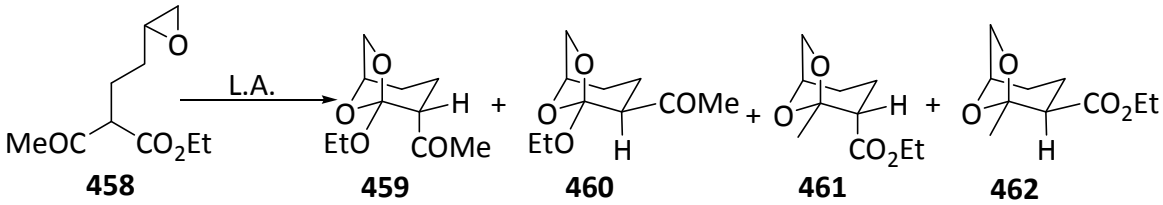
456



457

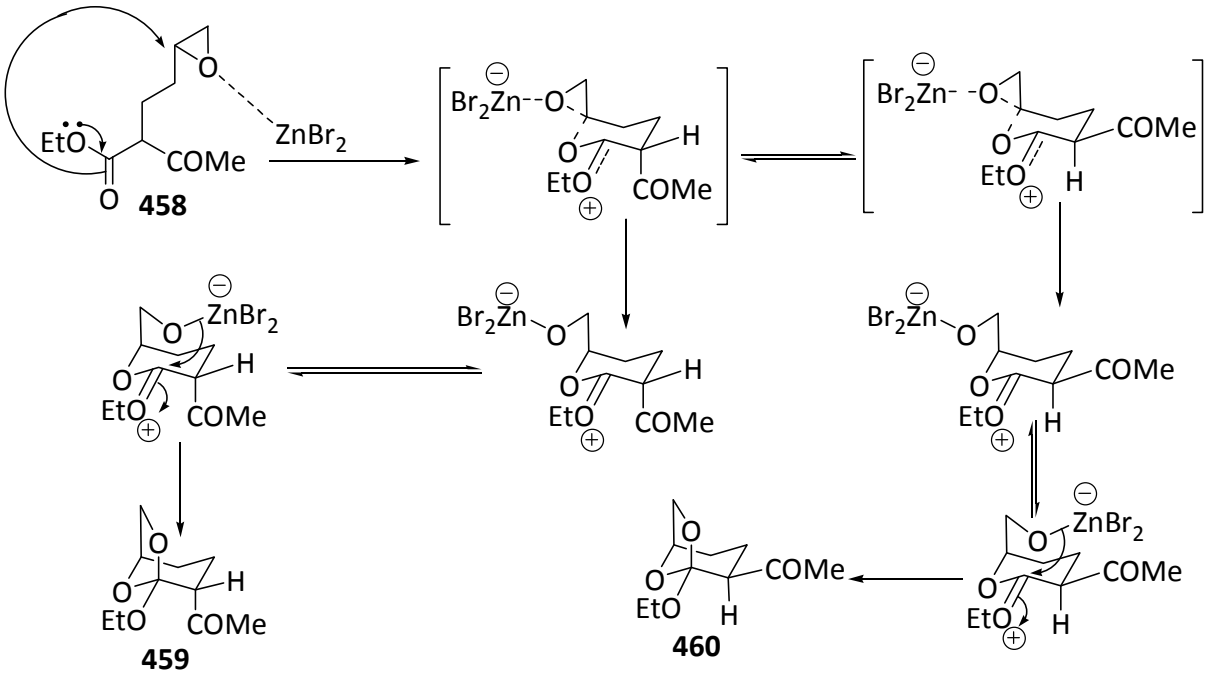
2.10. Synthesis of different derivatives of 6,8-dioxabicyclo[3.2.1]octane

In order to look at the chemoselectivity in the reaction it was devised to cyclise 2-(2-oxiranylethyl)-3-oxobutyric acid ethyl ester **458** having ester and keto functionalities under Lewis acidic conditions. The epoxide **458** being a (1:1) mixture of diastereoisomers and due to the difference in nucleophilicity of ester and ketone carbonyl group, the nucleophilic ring opening of epoxide could take place by carbonyl oxygen of ketone or ester giving rise to four possible derivatives of 6,8-dioxabicyclo[3.2.1]octane (Scheme 186).



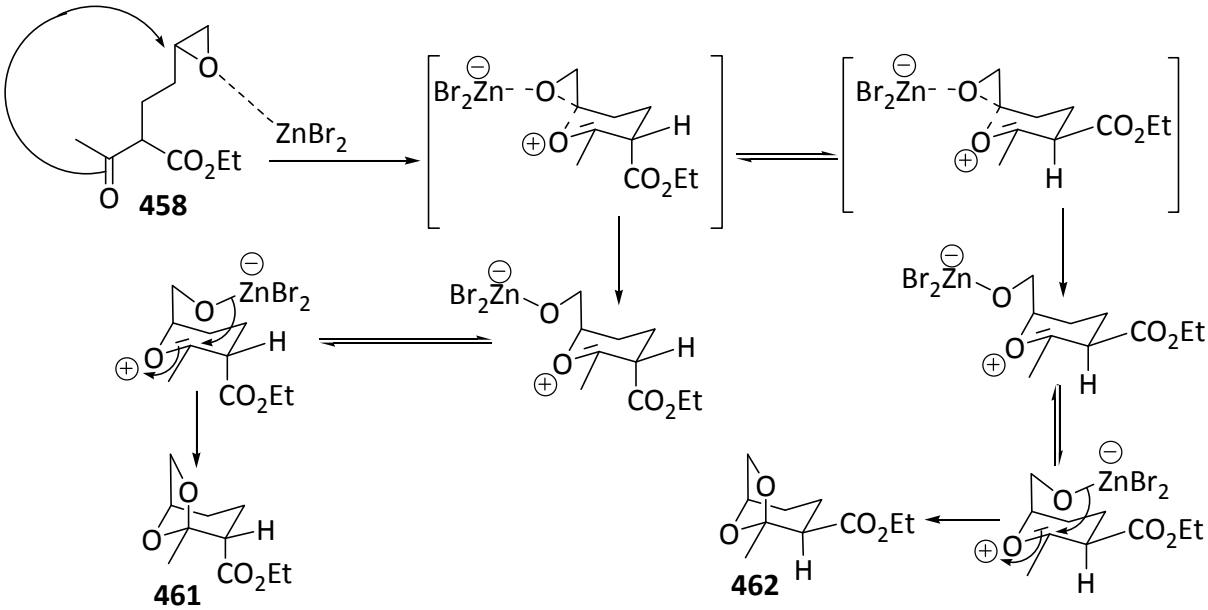
Scheme 186

If the nucleophilic ring opening of epoxide **458** is through carbonyl group of the ester it goes through following mechanism (Scheme 187).



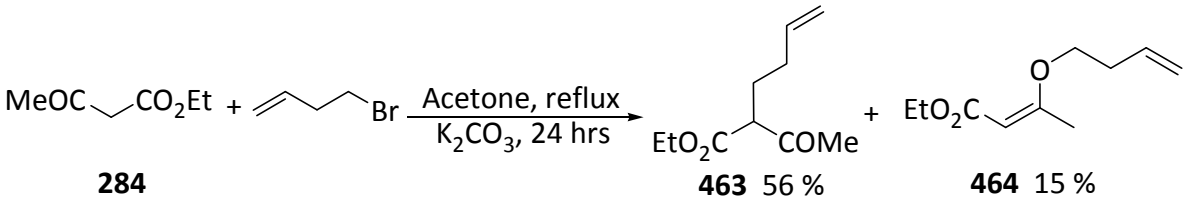
Scheme 187

If the nucleophilic ring opening of epoxide **458** is through carbonyl group of the ketone it goes through following mechanism (Scheme 188).



Scheme 188

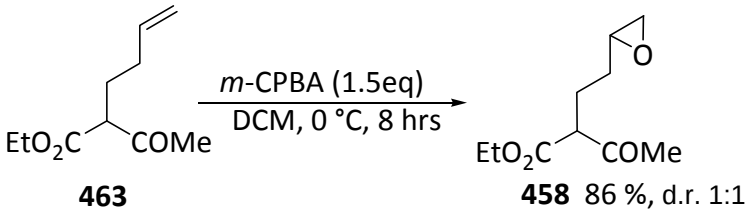
For the synthesis of (±)-2-(2-oxiranylethyl)-3-oxobutyric acid ethyl ester **458** the precursor 2-acetylhex-5-enoic acid ethyl ester **463** was required. The allylic alkylation of ethylacetoacetate **284** was carried out in suspension of K_2CO_3, in acetone, with 4-bromo-1-butene, under refluxing conditions (Scheme 189).



284 **463** 56 % **464** 15 %

Scheme 189

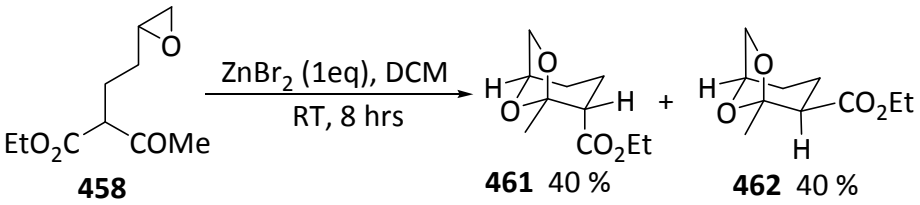
Then 2-acetylhex-5-enoic acid ethyl ester **463** was oxidized by *m*-CPBA in DCM, at 0 °C, affording 86 % of the desired product as a mixture (1:1) of diastereoisomers of **458** (Scheme 190).



463 **458** 86 %, d.r. 1:1

Scheme 190

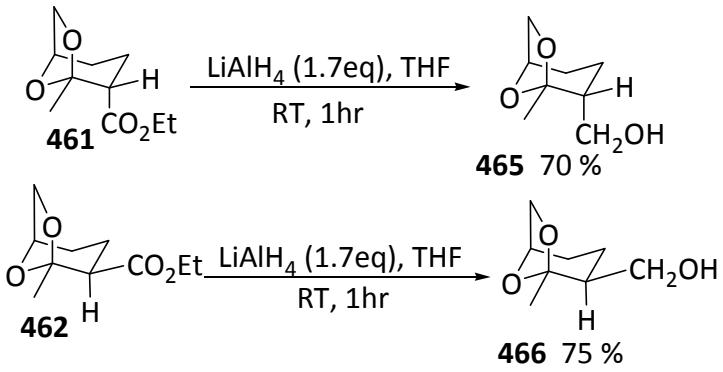
When epoxide **458** was reacted with $ZnBr_2$ in DCM, two diastereoisomers of 6,8-dioxabicyclo[3.2.1]octane **461** and **462** were isolated as product in a 1:1 ratio (Scheme 191).



458 **461** 40 % **462** 40 %

Scheme 191

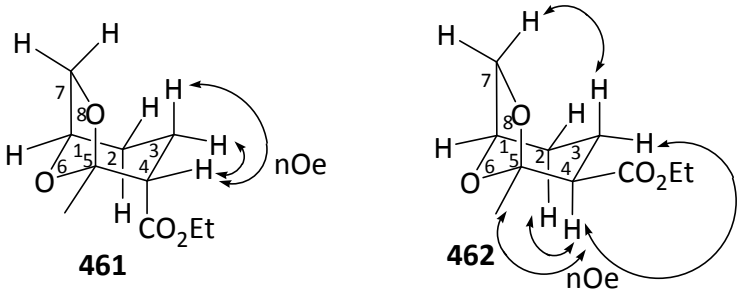
The ^{13}C NMR spectra of the both isolated diastereoisomers of 6,8-dioxabicyclo[3.2.1]octane **461** and **462** have the carbonyl peak of the ester at 172 ppm. The carbonyl peak of the ketone at 202 ppm was missing in both spectra, suggesting that the cyclisation of epoxide **458** has occurred on ketone carbonyl group. To further confirm, the reduction of these two isolated diastereoisomers were carried out by $LiAlH_4$ in THF, at RT and (5-methyl-6,8-dioxabicyclo[3.2.1]oct-4-yl)methanol **465** and **466** were obtained as products (Scheme 192).



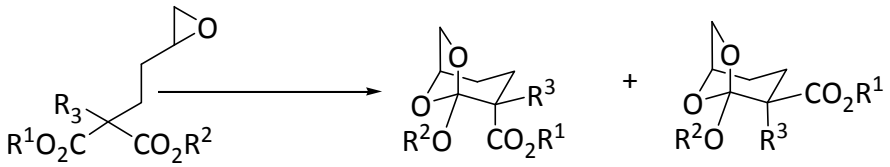
Scheme 192

These experiments have confirmed that the cyclisation of epoxide **458** had occurred on ketone group even though carbonyl oxygen of ester is more nucleophilic than ketone group.[89] In contrast to epoxide **405** the cyclisation of epoxide **458** is non diastereoselective affording 1:1 ratio of the diastereoisomers **461** and **462**.

The relative stereochemistry of 5-methyl-6,8-dioxabicyclo[3.2.1]octane-4-carboxylic acid ethyl ester **461** and **462** were proven by nOe experiments. Irradiation of the proton next to ester group in **461** leads strong nOe to the neighbouring axial and equatorial CH_2 protons. This suggests that the proton next to ester group is in equatorial position in **461**. In compound **462** irradiation of the proton next to ester group leads strong nOe to the equatorial proton of neighbouring CH_2 group on C3, axial proton on C2 and methyl protons on bridge-head carbon C5 suggesting that the proton is in axial position.



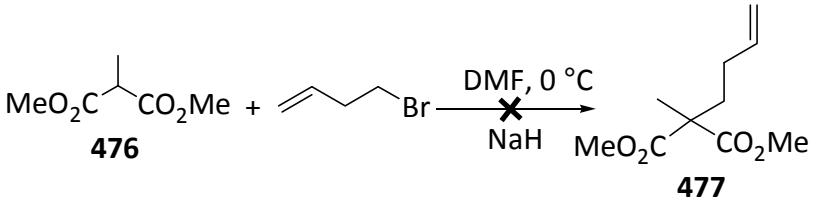
It was devised to synthesise epoxides **467**, **470** and **473** substituted with different size substituent R_3 (methyl, benzyl, phenyl) and cyclise these epoxides under Lewis acidic conditions in order to incorporate these substituents (methyl, benzyl, phenyl) in 6,8-dioxabicyclo[3.2.1]octane derivatives and to increase steric bulk at the ester centre. By increasing the size of substituent R_3 and competition between ester and R_3 for axial and equatorial orientation in 6,8-dioxabicyclo[3.2.1]octane derivatives could affect the diastereoselectivity and the yield of the reaction (Scheme 193).



467 R^1, R^2, R^3 = Me **468** **469**
470 R^1, R^2 = Me; R^3 = Bn **471** **472**
473 R^1, R^2 = Et; R^3= Ph **474** **475**

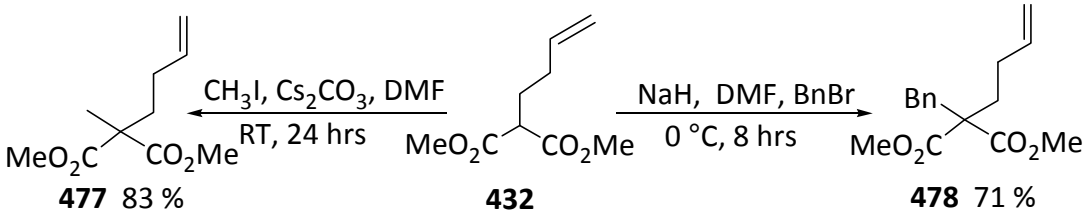
Scheme 193

To synthesise epoxide **467** the precursor 2-but-3-enyl-2-methylmalonic acid dimethyl ester **477** was required. An attempt was made to synthesise the required precursor **477** by allylic alkylation of 2-methylmalonic acid dimethyl ester **476** in a suspension of NaH in DMF, at 0 °C, by reacting with 4-bromo-1-butene (Scheme 194).[86]



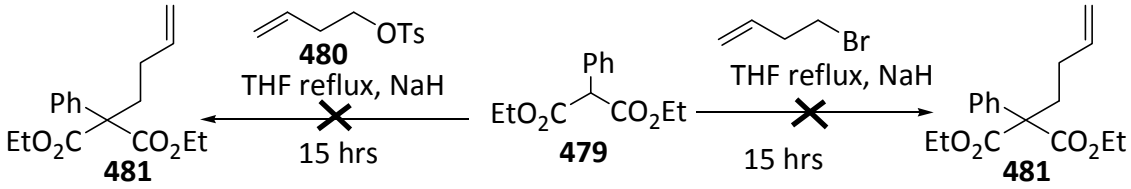
Scheme 194

The reaction resulted in decomposition of 4-bromo-1-butene giving back the malonate. Kojima *et al*. have reported the synthesis of 2-but-3-enyl-2-methylmalonic acid dimethyl ester **477**. [87] By following their procedure the precursor **477** was prepared by reacting 2-but-3-enylmalonic acid dimethyl ester **432** with methyl iodide in a suspension of cesium carbonate in DMF, at room temperature, in 83 % yield. The precursor **478** for epoxide **470** was made by reacting of 2-but-3-enylmalonic acid dimethyl ester **432** in a suspension of NaH, in DMF, using benzyl bromide (Scheme 195).



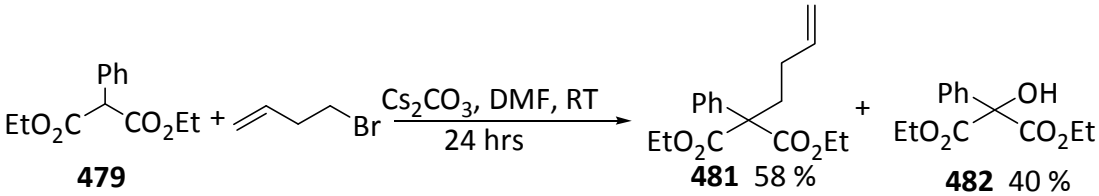
Scheme 195

For the synthesis of epoxide **473** the precursor 2-but-3-enyl-2-phenylmalonic acid diethyl ester **481** was required. The attempts were made for synthesis of 2-but-3-enyl-2-phenylmalonic acid diethyl ester **481** by reacting diethylphenylmalonate **479** with 4-bromo-1-butene and tosylate **480** using NaH in THF at reflux (Scheme 196).[86]



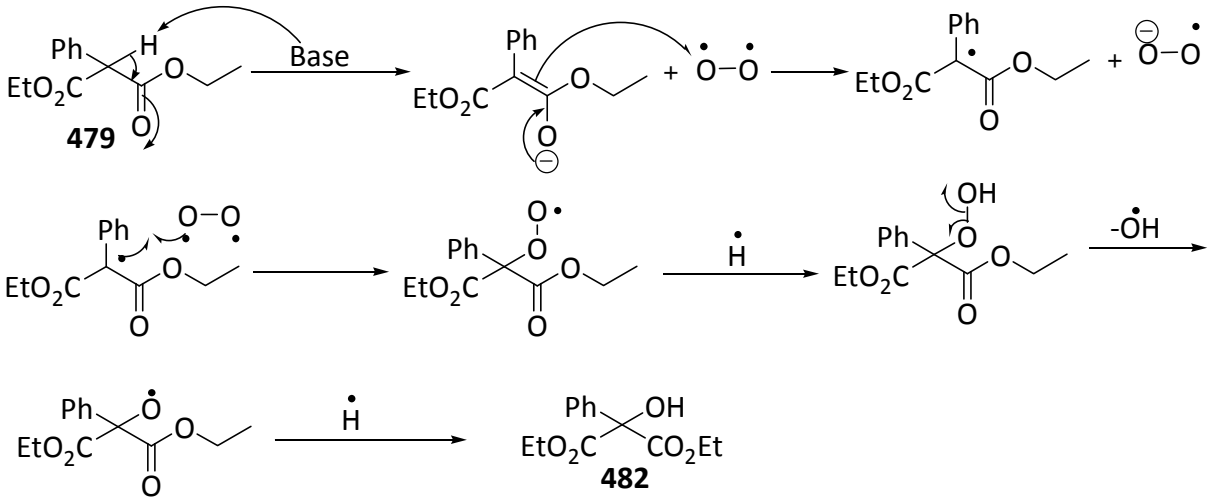
Scheme 196

When the reaction was performed using diethylphenylmalonate **479** and 4-bromo-1-butene in DMF at RT, using cesium carbonate, 58 % of the desired product **481** was obtained along with 2-hydroxy-2-phenylmalonic acid diethyl ester **482** in 40 % yield (Scheme 197).[87]



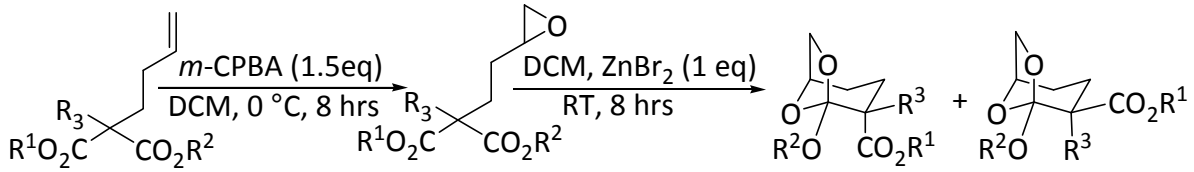
Scheme 197

The formation of 2-hydroxy-2-phenylmalonic acid diethyl ester **482** may be due to the interference of oxygen in the reaction, a mechanism is suggested below (Scheme 198).



Scheme 198

The oxidation of these precursors **477**, **478** and **481** to corresponding epoxides **467**, **470** and **473** were carried out by *m*-CPBA in DCM, at 0 °C affording 97-98 % of the each epoxide. When these epoxides were reacted with zinc bromide in DCM, the corresponding 6,8-dioxabicyclo[3.2.1]octane derivatives were obtained (Scheme 199).



477 R^1, R^2, R^3 = Me
478 R^1, R^2 = Me; R^3 = Bn
481 R^1, R^2 = Et; R^3= Ph

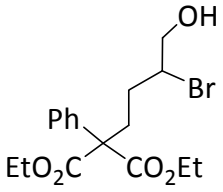
467 97 %
470 98 %
473 98 %

468 17 %
471 15 %
474 9 %

469 63 %
472 63 %
475 30 %

Scheme 199

The cyclisation of epoxides **467**, **470** and **473** successfully incorporated methyl, benzyl and phenyl (R^3) substituents to 6,8-dioxabicyclo[3.2.1]octane derivatives. The diastereoisomers having ester group in axial and R^3 in equatorial position were obtained as minor products, whereas diastereoisomers having ester group in equatorial and R^3 in axial position were obtained as major products. The steric bulk of the substituents R^3 had little effect on the configuration of the major products, although the diastereoselectivity was not the same in each case. The lower yield of both diastereoisomers of 5-ethoxy-4-phenyl-6,8-dioxabicyclo[3.2.1]octane-4-carboxylic acid ethyl ester **474** and **475** was observed due to the ring opening of the epoxide **473** by the bromide ion and formation of the side product 2-(3-bromo-4-hydroxy-butyl)-2-phenylmalonic acid diethyl ester **483** in 17 % yield.

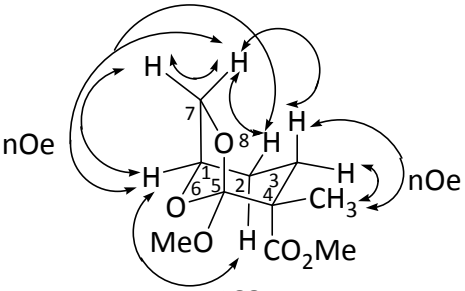


483

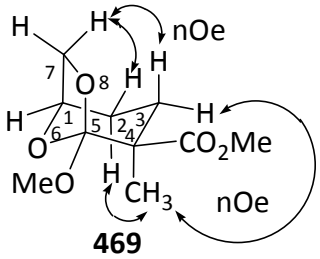
The relative stereochemistry of 6,8-dioxabicyclo[3.2.1]octane derivatives were proven by nOe experiments and crystal structures.

In compound **468** irradiation of the proton to the bridge-head position C1 show strong nOe to both CH_2 protons on the bridge and weak nOe to axial and equatorial protons of neighbouring CH_2 group on C2. Irradiation to the CH_2 proton on the bridge C7 at 3.80 ppm leads strong nOe to neighbouring CH_2 proton on bridge, the equatorial CH_2 proton on C2 and axial proton on C3. Irradiation of the methyl protons next to ester group in **468** leads clear nOe to neighbouring axial and equatorial CH_2 protons on C3. This suggests that methyl group is in equatorial position in **468**. In compound **469** irradiation to the CH_2 proton on the bridge at 3.91 ppm leads strong nOe to the equatorial CH_2 proton on C2 and axial proton on C3. Irradiation of the methyl protons next to ester group leads strong nOe to equatorial

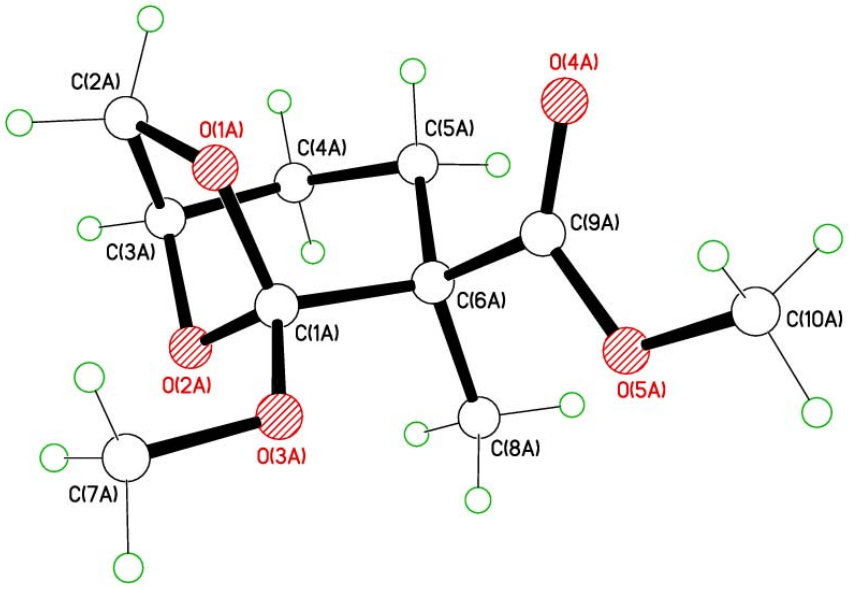
proton of neighbouring CH_2 group on C3 and axial proton on C2 suggesting that the methyl group is in axial position in **469**.



468

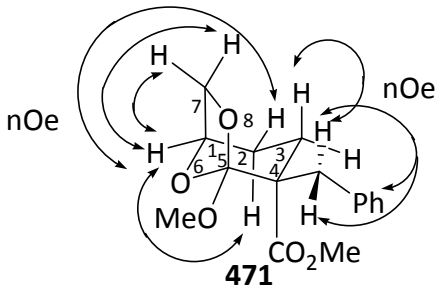


469

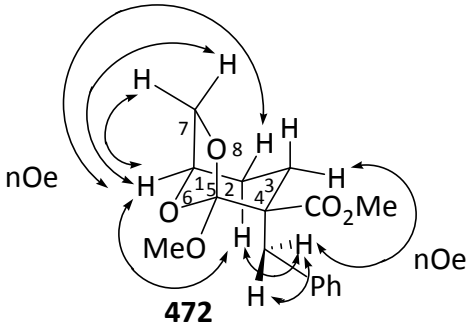


469

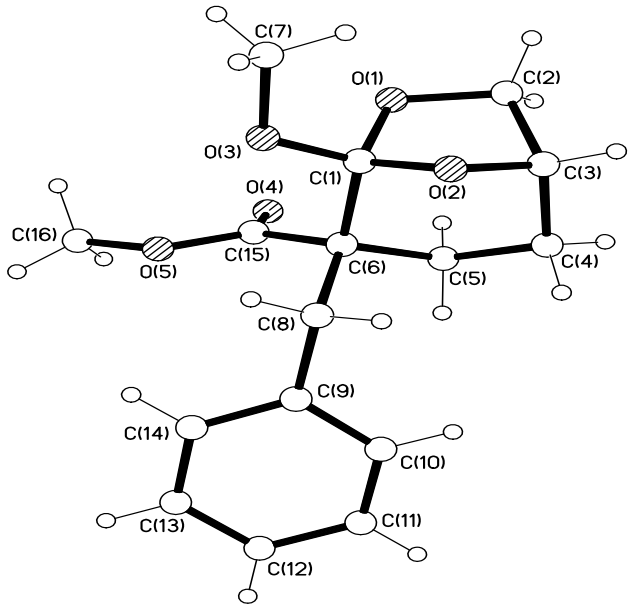
In compounds **471** and **472** irradiation of the protons to the bridge-head position show strong nOe to both CH_2 protons on the bridge and axial and equatorial protons of neighbouring CH_2 group on C2. Irradiation to the CH_2 proton of benzyl group at 2.70 ppm in **471** leads strong nOe to the neighbouring CH_2 proton of benzyl group at 3.59 ppm, axial proton on C3 and to aromatic protons. This suggests that the benzyl group is in equatorial position in **471**. In compound **472** irradiation of CH_2 proton of the benzyl group at 3.10 ppm leads strong nOe to the neighbouring CH_2 proton of benzyl group at 3.54 ppm, axial proton on C2 and equatorial proton on C3. This suggests that the benzyl group is in axial position in **472**.



471

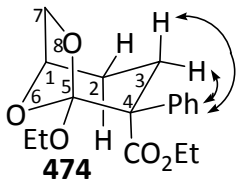


472

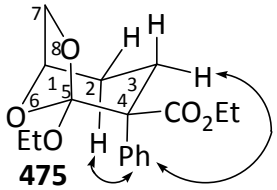


472

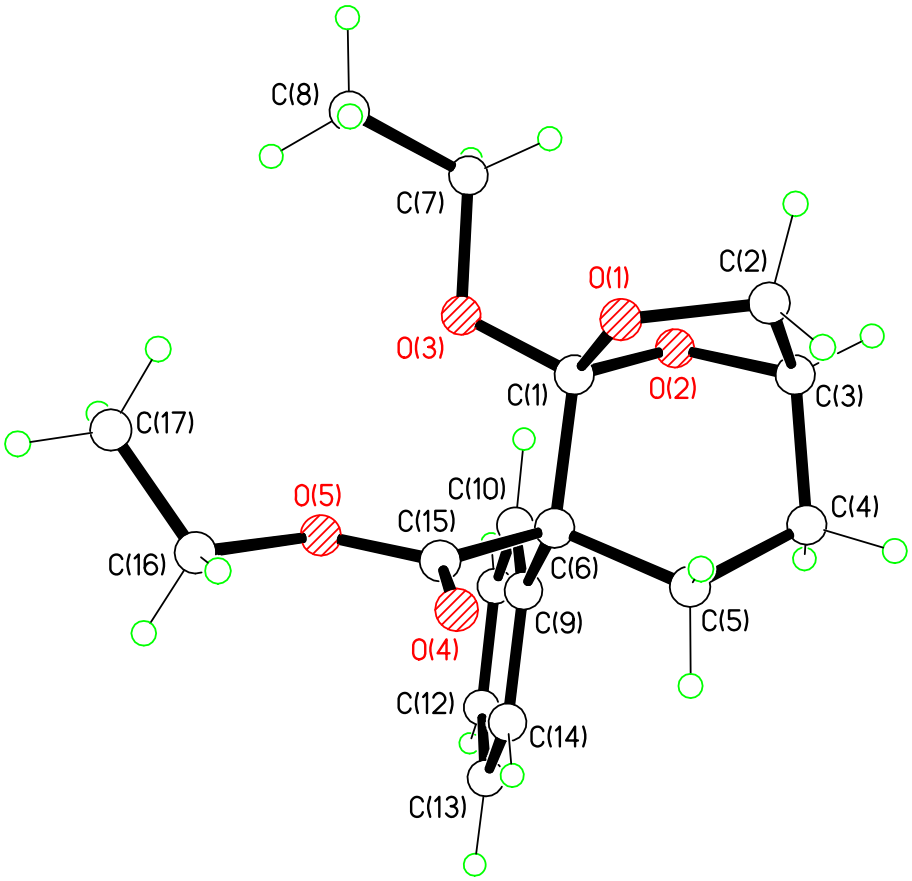
Irradiation of the aromatic protons in **474** leads strong nOe to neighbouring axial and equatorial CH_2 protons on C3. This suggests that phenyl group is in equatorial position in **474**. In compound **475** irradiation of the aromatic protons leads clear nOe to equatorial proton of neighbouring CH_2 group on C3 and axial proton of CH_2 group on C2 suggesting that the phenyl group is in axial position.



474

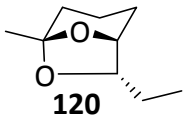


475

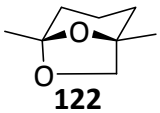


475

After successful incorporation of methyl, benzyl and phenyl group at the ester chiral centre, it was then decided to incorporate the methyl group at bridgehead position. Many natural products have methyl substituent at bridgehead position e.g. (+)-*endo*-brevicomin **120** and (-)-frontalin **122**.[46]

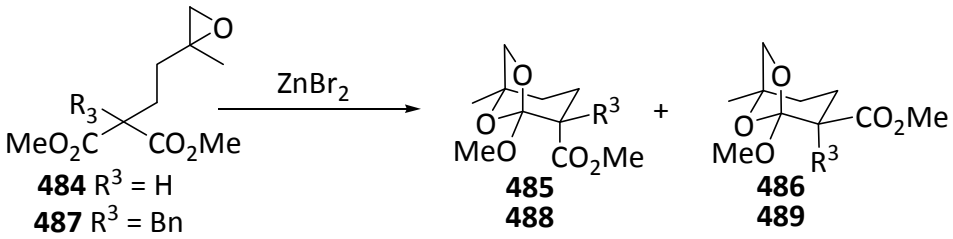


120
(+)-*Endo*-brevicomin



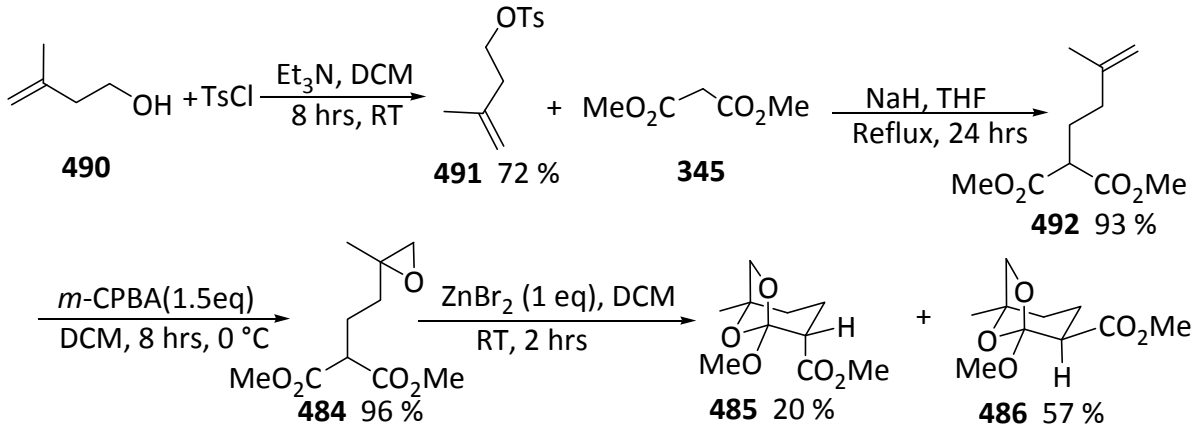
122
(-)-Frontalin
southern pine bettle,
asian elephant

The epoxides **484** and **487** could cyclise and incorporate a methyl group at bridgehead position of 6,8-dioxabicyclo[3.2.1]octane derivatives (Scheme 200).



Scheme 200

The required precursor **492** for the synthesis of epoxide **484** was made in 93 % yield by a known method reported by Kojima et al.[87] Oxidation of 2-(3-methylbut-3-enyl)malonic acid dimethyl ester **492** was carried out in DCM, using *m*-CPBA (1.5eq) at 0 °C. When 2-[2-(2-methyloxiranyl)ethyl]malonic acid dimethyl ester **484** was reacted with $ZnBr_2$ in DCM, at RT, 5-methoxy-1-methyl-6,8-dioxa-bicyclo[3.2.1]octane-4-carboxylic acid methyl ester **485** and **486** were obtained as products in two hours. If the reaction time exceeds more than two hours complex mixture was obtained, resulting in lower yields of the desired compounds (Scheme 201).

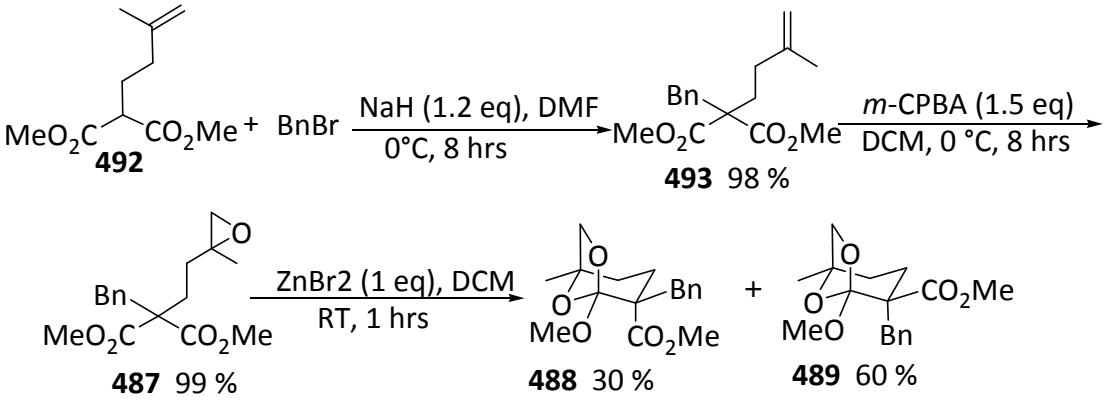


Scheme 201

The diastereoisomer **485** having ester group in axial and proton in equatorial position was obtained as minor product, whereas **486** having ester group in equatorial and proton in axial position was obtained as major product. The cyclisation of epoxide **484** successfully incorporated a methyl substituent at bridgehead position of 6,8-dioxabicyclo[3.2.1]octane derivatives **485** and **486**. It was then decided to incorporate methyl group at bridgehead position and benzyl group at ester end of the 6,8-dioxa-bicyclo[3.2.1]octane derivative in order to look that these different sized substituents could be incorporated in the 6,8-dioxa-bicyclo[3.2.1]octane derivatives and could affect the diastereoselectivity of the reaction.

The precursor for the synthesis of epoxide **487** was made by alkylation of 2-(3-methyl-but-3-enyl)malonic acid dimethyl ester **492** with benzyl bromide, in DMF, at 0 °C. Epoxidation of

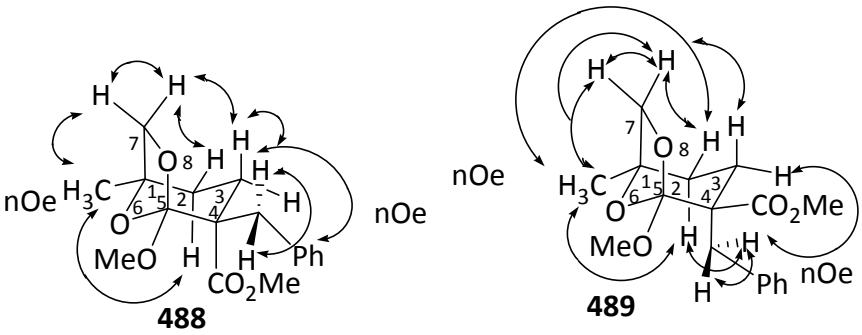
2-benzyl-2-(3-methylbut-3-enyl)malonic acid dimethyl ester **493** was carried out in DCM, with *m*-CPBA (1.5 eq), at 0 °C. When 2-benzyl-2-[2-(2-methyloxiranyl)ethyl]malonic acid dimethyl ester **487** was reacted with $ZnBr_2$ in DCM, at RT, 4-benzyl-5-methoxy-1-methyl-6,8-dioxabicyclo[3.2.1]octane-4-carboxylic acid methyl ester **488** and **489** were obtained as products in one hour (Scheme 202).



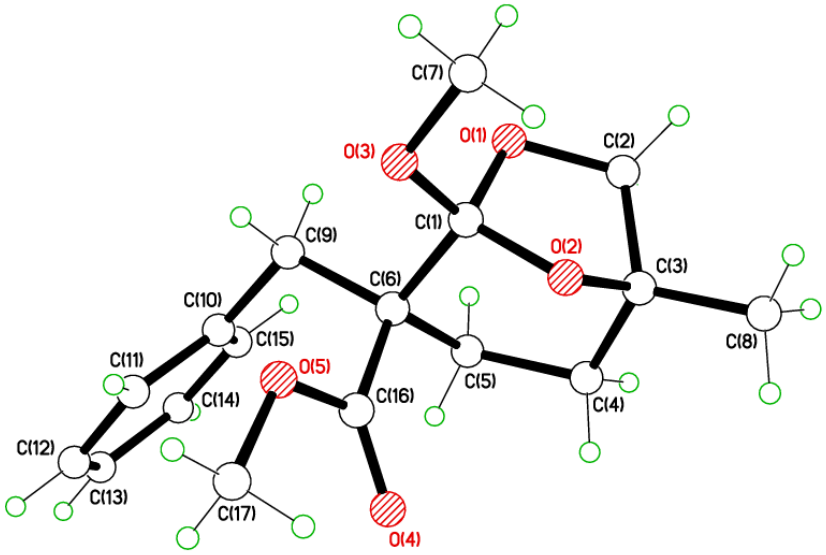
Scheme 202

Both methyl and benzyl groups were incorporated into the 6,8-dioxabicyclo[3.2.1]octane derivatives **488** and **489**. The steric bulk of the benzyl group at ester chiral centre and methyl at the bridge-head position had little effect on the configuration of the major product and reaction resulted in slightly higher yield and diastereoselectivity. The diastereoisomer **488** having ester group in axial and benzyl group in equatorial position was obtained as minor product, whereas **489** having ester group in equatorial and benzyl group in axial position was obtained as major product.

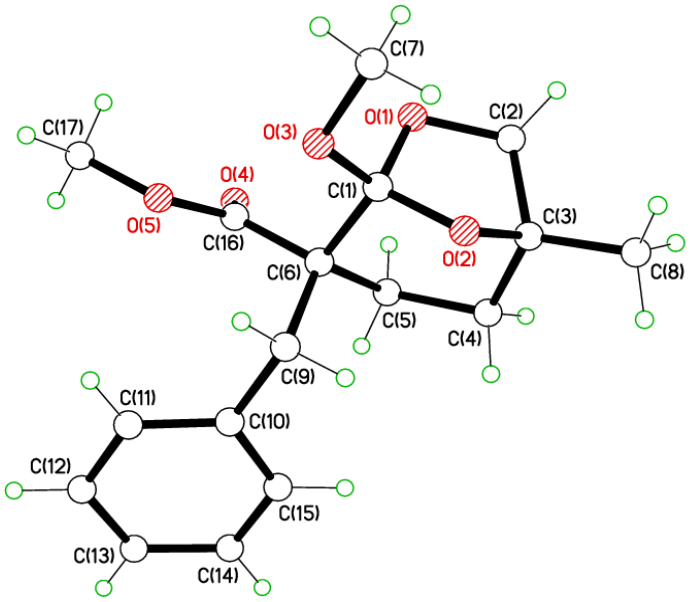
Their stereochemistry was proven by nOe experiments and crystal structures. In compounds **488** irradiation of the CH_2 proton on the bridge carbon C7 at 3.86 ppm show nOe to the other neighbouring CH_2 proton on the bridge at 3.61 ppm, the equatorial proton of CH_2 group on C2 and axial protons on C3. Irradiation of the CH_2 proton of benzyl group at 2.67 ppm in **488** leads strong nOe to axial proton on C3 and aromatic protons. This suggests that the benzyl group is in equatorial position in **488**. In compound **489** irradiation of the CH_3 protons to the bridge-head position C1 show strong nOe to the CH_2 protons on the bridge C7 and axial and equatorial protons of neighbouring CH_2 group on C2. The irradiation of CH_2 proton of the benzyl group leads strong nOe to axial proton on C2 and equatorial proton on C3. This suggests that the benzyl group is in the axial position in **489**.



488 **489**

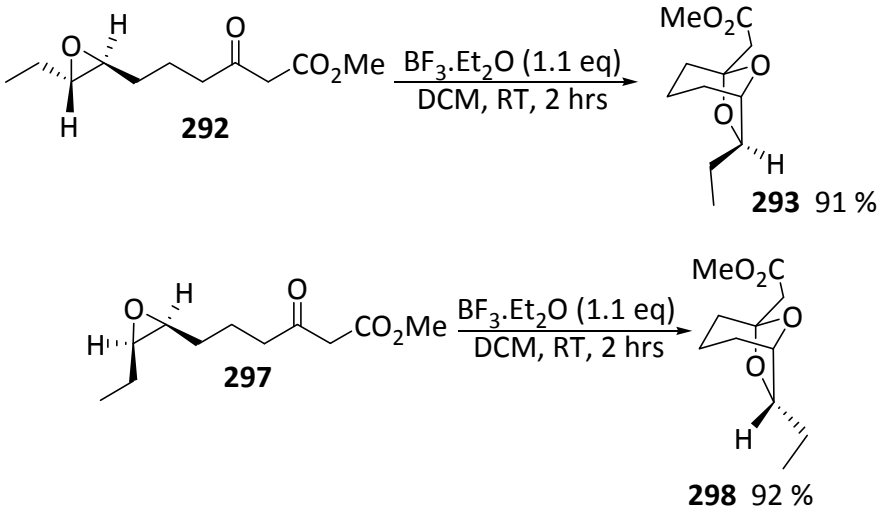


488



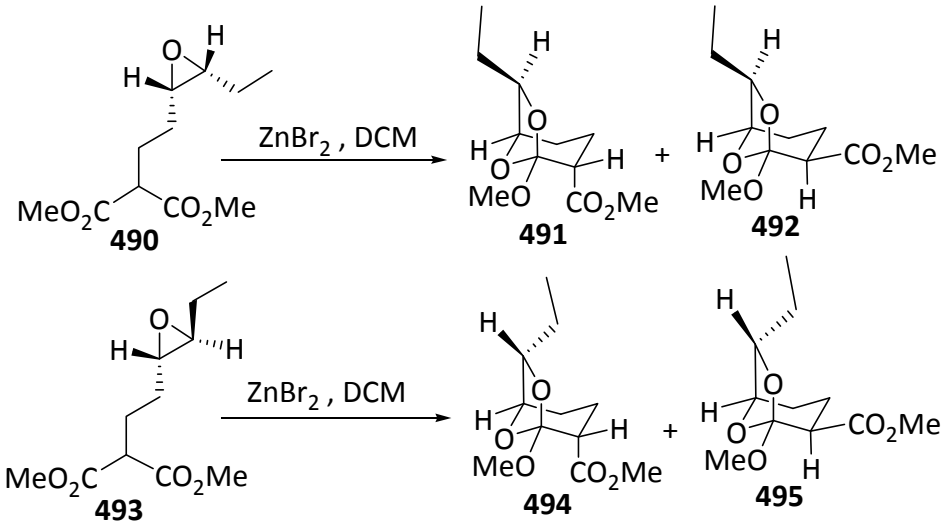
489

In order to look at the stereochemical path of cyclisation it was decided to cyclise *syn*- and *anti*-2-[2-(3-ethyloxiranyl)ethyl]malonic acid dimethyl ester **490** and **493** under Lewis acidic conditions to 6,8-dioxabicyclo[3.2.1]octane derivatives (Scheme 204). Sum and co-workers have reported Lewis acid catalysed isomerisation of epoxide **292** and **297** affording *endo*- and *exo*-6,8-dioxabicyclo[3.2.1]octane **293** and **298**. These reactions take place stereospecifically with epoxide ring opening by the ketone carbonyl group with inversion of configuration (Scheme 203).[68]



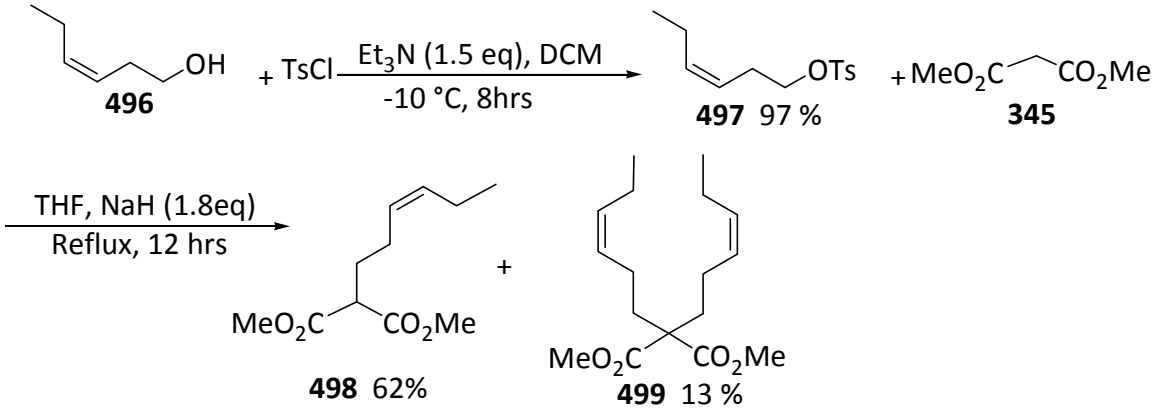
Scheme 203

Similarly the cyclisation of *syn*- and *anti*-2-[2-(3-ethyloxiranyl)ethyl]malonic acid dimethyl ester **490** and **493** under Lewis acidic conditions to *exo*- and *endo*-6,8-dioxabicyclo[3.2.1]octane derivatives could be stereospecific (Scheme 204).



Scheme 204

We planned to synthesise *syn*- and *anti*-2-[2-(3-ethyloxiranyl)ethyl]malonic acid dimethyl ester **490** and **493** by using *cis*-3-hexen-1-ol **496** and *trans*-3-hexen-1-ol **504**. For synthesis of *syn*-2-[2-(3-ethyloxiranyl)ethyl]malonic acid dimethyl ester **490** the requsite precursor (*Z*)-2-hex-3-enylmalonic acid dimethyl ester **498** was prepared by converting *cis*-3-hexen-1-ol **496** into a tosylate **497** which then was reacted with dimethylmalonate **345** in a suspension of NaH, in THF and the desired precursor **498** was obtained in 62 % yield (Scheme 205).

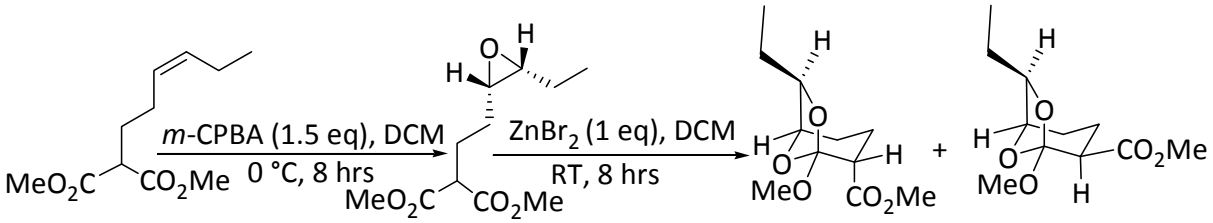


496 **497** 97 % **345**

498 62% **499** 13 %

Scheme 205

The epoxidation of (*Z*)-2-hex-3-enylmalonic acid dimethyl ester **498** was carried out in DCM, with *m*-CPBA, at 0 °C, in eight hours affording *syn*-2-[2-(3-ethyloxiranyl)ethyl]malonic acid dimethyl ester **490** in 98 % yield. When *Syn*-2-[2-(3-ethyloxiranyl)ethyl]malonic acid dimethyl ester **490** was reacted with zinc bromide in DCM, two diastereoisomers *exo*-7-ethyl-5-methoxy-6,8-dioxabicyclo[3.2.1]octane-4-carboxylic acid methyl ester **491** and **492** were isolated with relative stereochemistry as shown in scheme 206.

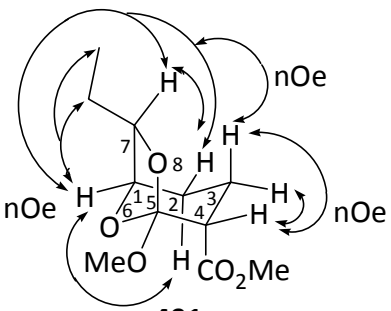


498 **490** 98 % **491** 10 % **492** 50 %

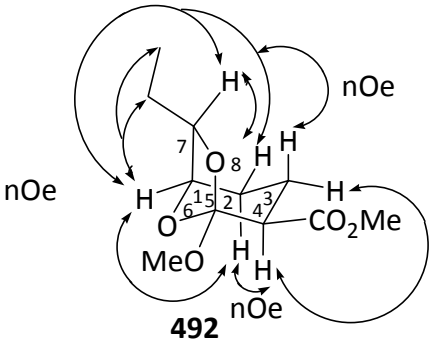
Scheme 206

The relative stereochemistry of *exo*-7-ethyl-5-methoxy-6,8-dioxabicyclo[3.2.1]octane-4-carboxylic acid methyl ester **491** and **492** were proven by nOe experiments. In compounds **491** and **492** irradiation of the protons to the bridge-head position C1 show nOe to the CH_3, CH_2 protons of the ethyl group, proton next to ethyl group on the bridge and axial and equatorial protons of neighbouring CH_2 group on C2. In both compounds irradiation of the proton next to ethyl group on C7 leads nOe to equatorial proton on C2 and axial proton of

C3. This suggests that the proton next to ethyl group is closer to C2 and C3 protons. Irradiation of the proton next to ester group in **491** leads nOe to neighbouring axial and equatorial protons on C3. This suggests that the proton next to ester group is in equatorial position in **491**. In compound **492** irradiation of the proton next to ester group leads nOe to equatorial proton of neighbouring CH_2 group on C3 and axial proton on C2 suggesting that the proton is in axial position.

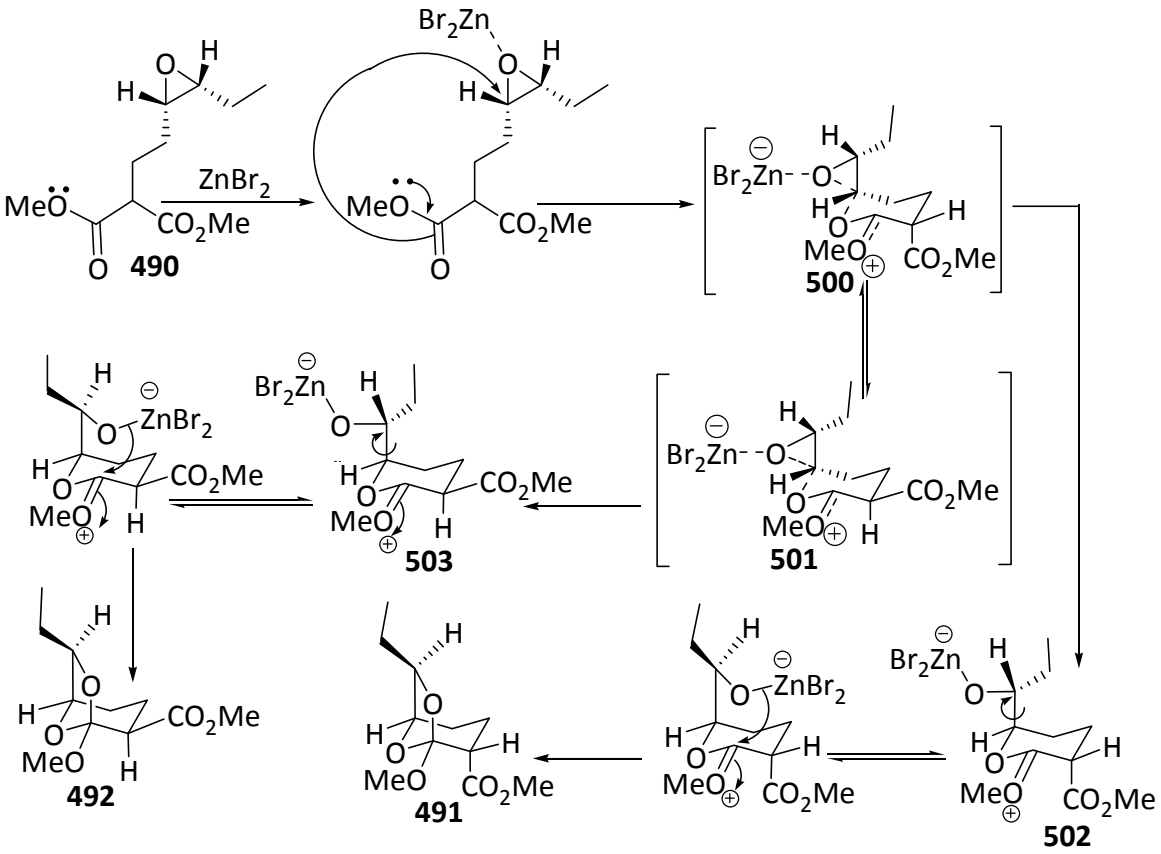


491



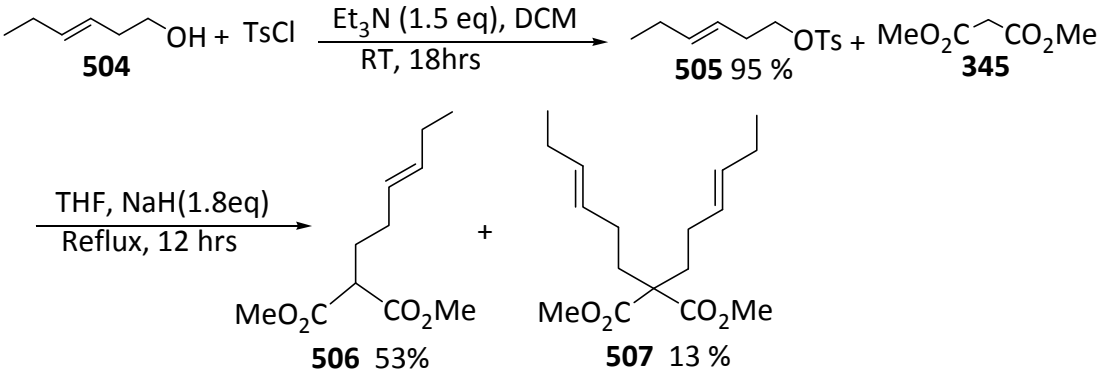
492

The nucleophilic ring opening of epoxide **490** under Lewis acidic conditions by carbonyl oxygen is through an internal S_N2 type mechanism with inversion of stereochemistry at the epoxide carbon under the nucleophilic attack. 6-*Exo*-*tet* cyclisation results in two transition states **500** and **501** in chair conformations and leads to the intermediates **502** and **503** respectively. The further ring closure of these intermediates **502** and **503** proceed stereospecifically to give *exo*-7-ethyl-5-methoxy-6,8-dioxabicyclo[3.2.1]octane-4-carboxylic acid methyl ester **491** and 4**92** (Scheme 207).



Scheme 207

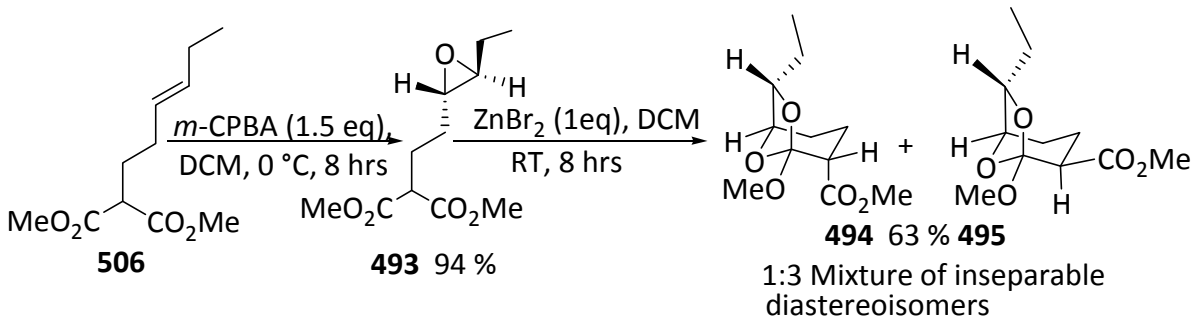
For the synthesis of (*E*)-2-hex-3-enylmalonic acid dimethyl ester **506**, *trans*-3-hexen-1-ol **504** was converted into a tosylate **505**, which then was reacted with dimethylmalonate **345** in the a suspension of NaH, in THF, to afford the desired precursor **506** in 53 % yield (Scheme 208).



Scheme 208

The epoxidation of (*E*)-2-hex-3-enylmalonic acid dimethyl ester **506** was carried out in DCM, with *m*-CPBA, at 0 °C in eight hours affording *anti*-2-[2-(3-ethyloxiranyl)ethyl]malonic acid dimethyl ester **493** in 94 % yield. When *anti*-2-[2-(3-ethyloxiranyl)ethyl]malonic acid

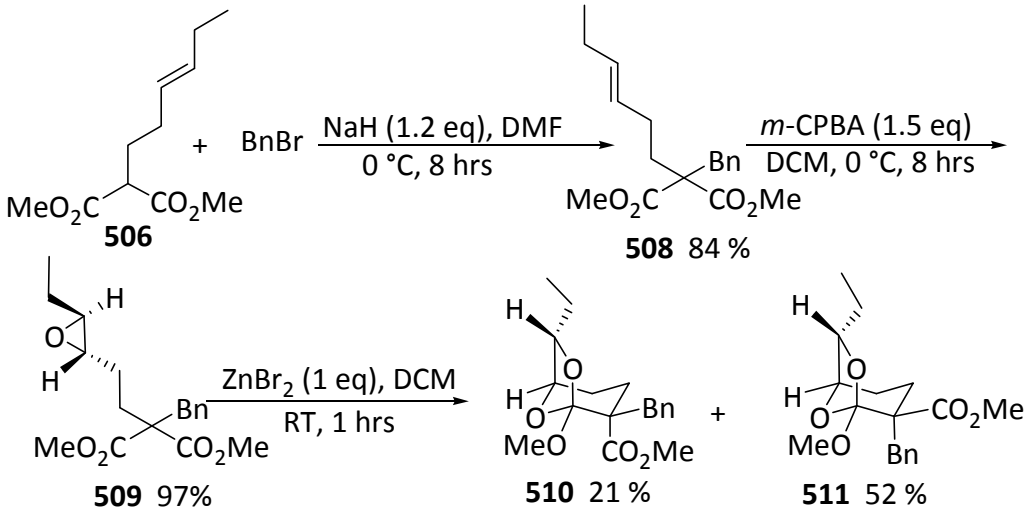
dimethyl ester **493** was reacted with zinc bromide in DCM, a mixture (1:3) of inseparable diastereoisomers of **494** and **495** was obtained in 63 % yield (Scheme 209).



Scheme 209

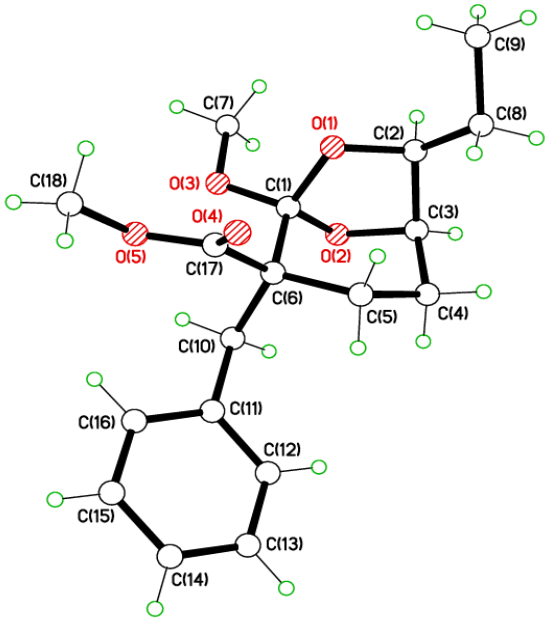
The diastereoisomers **494** and **495** were inseparable by chromatography. It was decided to synthesis more derivatives of *endo*- and *exo*-7-ethyl-5-methoxy-6,8-dioxabicyclo[3.2.1]octane-4-carboxylic acid methyl ester and attempt to isolate both diastereoisomers, in order to get a clear picture of the reaction. So, *anti* and *syn*-2-benzyl-2-[2-(3-ethyloxiranyl)ethyl]malonic acid dimethyl ester **509** and **515** were cyclised under Lewis acidic conditions to *endo*- and *exo*-4-benzyl-7-ethyl-5-methoxy-6,8-dioxa-bicyclo[3.2.1]octane-4-carboxylic acid methyl ester derivatives (Schemes 210 & 212).

To synthesise *anti*-2-benzyl-2-[2-(3-ethyloxiranyl)ethyl]malonic acid dimethyl ester **509** the alkylation of (*E*)-2-hex-3-enylmalonic acid dimethyl ester **506** was carried out in a suspension of NaH in DMF, at 0 °C with benzyl bromide. The epoxidation of (*E*)-2-benzyl-2-hex-3-enylmalonic acid dimethyl ester **508** was carried out in DCM, with *m*-CPBA, at 0 °C, for eight hours. When *anti*-2-benzyl-2-[2-(3-ethyloxiranyl)ethyl]malonic acid dimethyl ester **509** was reacted with $ZnBr_2$, in DCM, a mixture of chromatographically inseparable diastereoisomers of *endo*-4-benzyl-7-ethyl-5-methoxy-6,8-dioxabicyclo[3.2.1]octane-4-carboxylic acid methyl **510** and **511** was obtained. The major diastereoisomer **511** was isolated from the mixture by crystallisation (Scheme 210).



Scheme 210

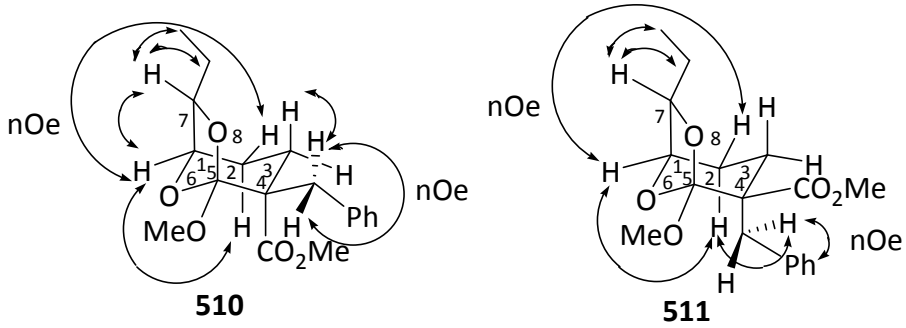
Their relative stereochemistry was proven by crystal structure and nOe experiments.



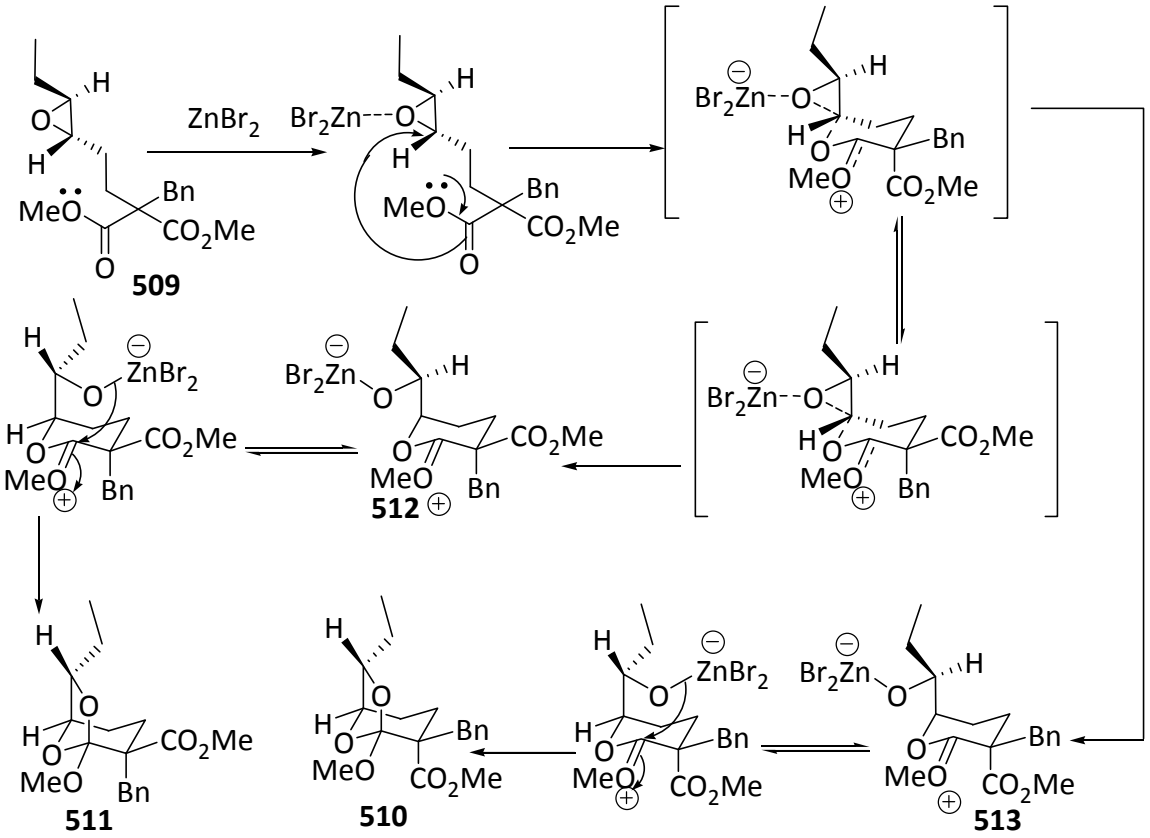
511

In compounds **510** and **511** irradiation of the protons to the bridge-head position C1 show nOe to the proton next to ethyl group on the bridge and axial and equatorial protons of neighbouring CH_2 group on C2. In both compounds irradiation of the protons next to ethyl group on C7 leads to a nOe between CH_3 and CH_2 protons of the ethyl group and proton to the bridge-head position C1. This suggests that the proton next to ethyl group is closer to bridge-head protons on C1. Irradiation of the CH_2 proton of benzyl group in **510** leads nOe to axial proton on C3. This suggests that the benzyl group is in equatorial position in **510**. In

compound **511** the irradiation of CH_2 proton of the benzyl group leads an nOe to axial proton on C2. This suggests that the benzyl group is in axial position in **511**.

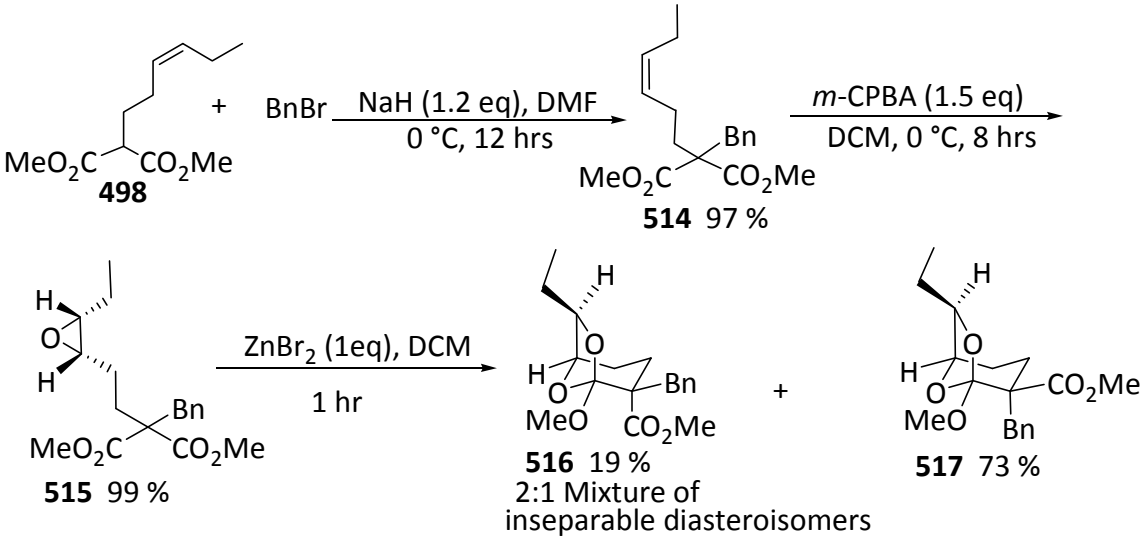


These results further confirm that the nucleophilic ring opening of epoxide **509** by carbonyl oxygen of ester is through an internal S_N2 type mechanism with inversion of stereochemistry at the epoxide carbon under nucleophilic attack. The intermediates formed through 6-*exo*-*tet* cyclisation and ring closure proceeded stereospecifically to give *endo*-7-ethyl-5-methoxy-6,8-dioxabicyclo[3.2.1]octane-4-carboxylic acid methyl ester **510** and **511** (Scheme211).



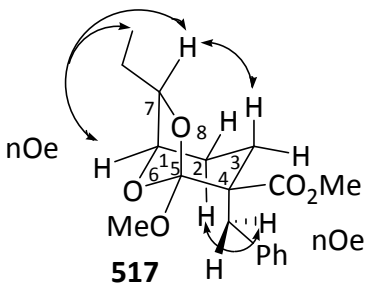
Scheme 211

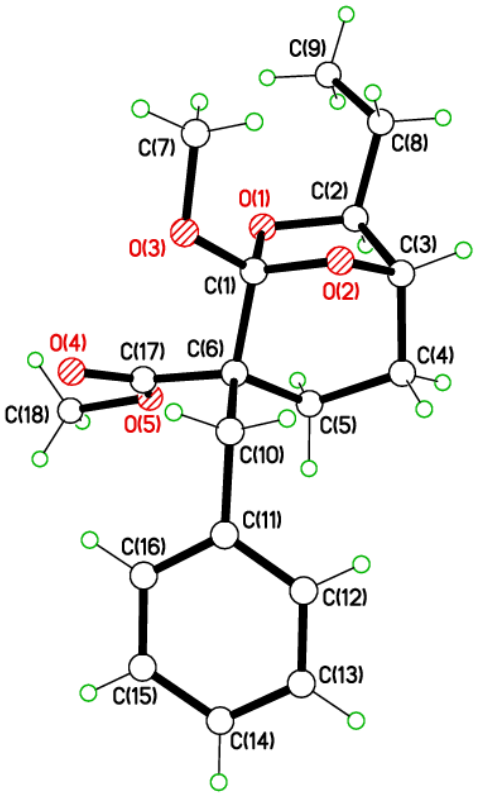
Similarly, *syn*-2-benzyl-2-[2-(3-ethyloxiranyl)ethyl]malonic acid dimethyl ester **515** was prepared by using (*Z*)-2-hex-3-enylmalonic acid dimethyl ester **498.** When *syn*-2-benzyl-2-[2-(3-ethyloxiranyl)ethyl]malonic acid dimethyl ester **515** was reacted with zinc bromide in DCM, a mixture of chromatographically inseparable diastereoisomers of *exo*-4-benzyl-7-ethyl-5-methoxy-6,8-dioxabicyclo[3.2.1]octane-4-carboxylic acid methyl **516** and **517** was obtained. The major diastereoisomer **517** was partially isolated from the mixture by crystallisation and the remaining mixture (2:1) of the diastereoisomers was containing higher concentration of minor diastereoisomer **516** (Scheme 212). Their relative stereochemistry is shown in the scheme below.



Scheme 212

The relative stereochemistry of the major diastereoisomer was proven by nOe experiment and crystal structure. In compound **517** the irradiation of protons to the bridge-head position C1 show nOe to the proton next to ethyl group on the bridge and CH_3 protons of the ethyl group. Irradiation of proton next to ethyl group on C7 leads nOe to axial proton of C3. This suggests that the proton next to ethyl group is closer to proton on C3. Irradiation of the CH_2 proton of benzyl group leads nOe to axial proton on C2. This suggests that the benzyl group is in axial position.



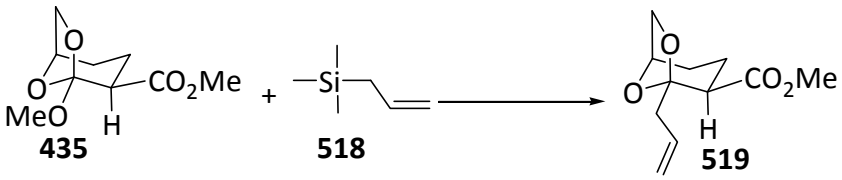


517

The cyclisation of *syn* and *anti* malonyl epoxides have proved that the ring opening of the epoxides by ester carbonyl oxygen is through inversion of stereochemistry at the epoxide carbon under the nucleophilic attack. Once the epoxide ring is opened the further cyclisation proceeded stereospecifically.

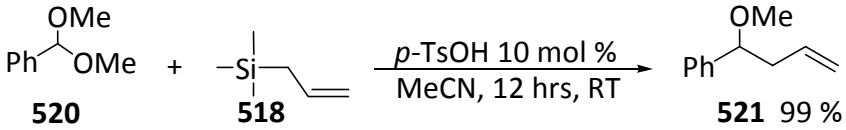
2.11. Attempted synthesis of 5-allyl-6,8-dioxabicyclo[3.2.1]octane-4-carboxylic acid methyl ester

To further extend the chemistry it was decided to substitute the methoxy group of 5-methoxy-6,8-dioxabicyclo[3.2.1]octane-4-carboxylic acid methyl ester **435** with an allyl group in a carbon-carbon bond forming reaction on 6,8-dioxabicyclo[3.2.1]octane ring system (Scheme 213).



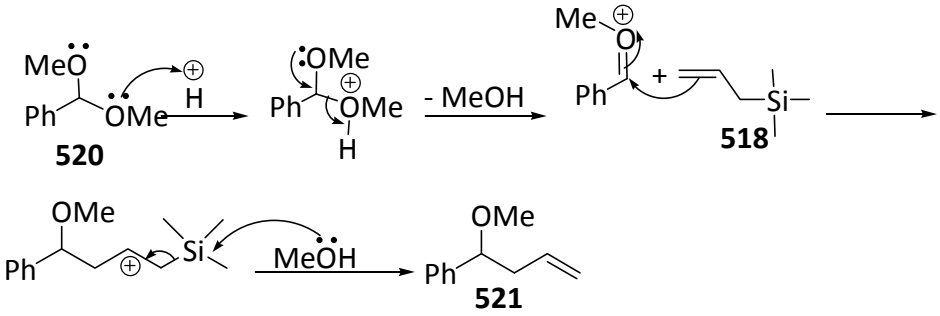
Scheme 213

List *et al*. have reported Hosomi-Sakurai reaction of acetals **520** with allyltrimethylsilane **518** catalysed by Brønsted acid to furnish homoallylic ether **521** in excellent yield. The reaction is also catalysed by Lewis acids (Scheme 214).[89a-b]



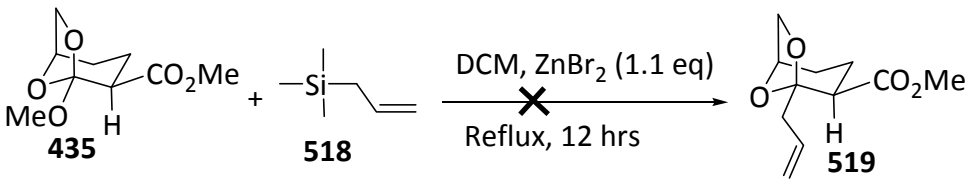
Scheme 214

The protonation of acetal with Brønsted acid gives an oxonium ion. Its reaction with allyltrimethylsilane and methanol librated during the reaction leads to the product in a stepwise mechanism (Scheme 215).



Scheme 215

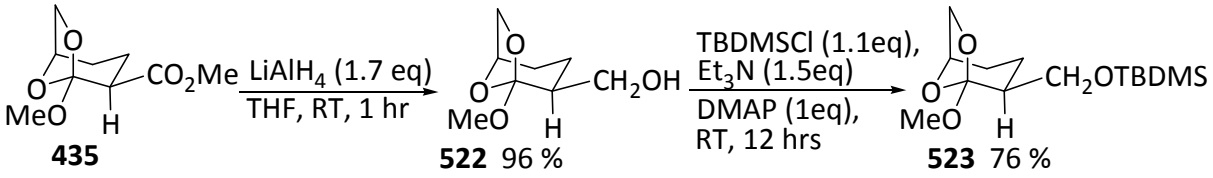
These conditions could be applied for the allylic substitution of methoxy group of 5-methoxy-6,8-dioxabicyclo[3.2.1]octane-4-carboxylic acid methyl ester **435**. The attempts were made for the substitution of methoxy group of **435** with allylic group of allyltrimethylsilane **518** under the conditions of Brønsted acids (CH_3CO_2H, TFA, *p*-TsOH) and Lewis acids ($ZnBr_2$, $BF_3.Et_2O$, $TiCl_4$, $CuCl_2$, $Yt(OTf)_3$, TMSOTf) in a range of solvents and reaction conditions. Unfortunately none of these conditions afforded the desired product but resulted in complex mixture or gave the starting material back (Scheme 216).



Scheme 216

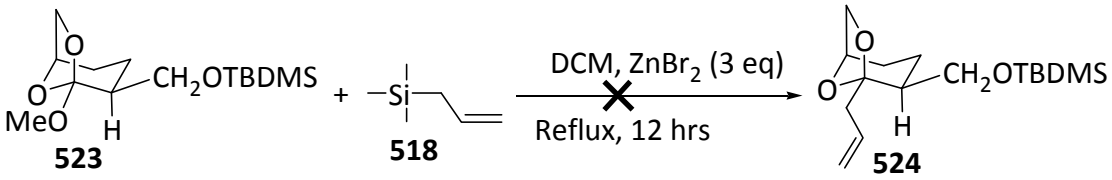
To see if it was the ester group of 5-methoxy-6,8-dioxabicyclo[3.2.1]octane-4-carboxylic acid methyl ester **435** interfering in the reaction, it was decided to reduce the ester group to an alcohol and to protect it. 5-Methoxy-6,8-dioxa-bicyclo[3.2.1]octane-4-carboxylic acid

methyl ester **435** was reduced with $LiAlH_4$, in THF, at RT and then was protected with *tert*-butyldimethyl silyl chloride to afford **523** in 76 % yield (Scheme 217).



Scheme 217

The attempts for the substitution of methoxy group of *tert*-butyl-(5-methoxy-6,8-dioxabicyclo[3.2.1]oct-4-ylmethoxy)dimethylsilane **523** with allyl group of allyltrimethylsilane **518** under range of conditions with zinc bromide were unsuccessful (Scheme 218).



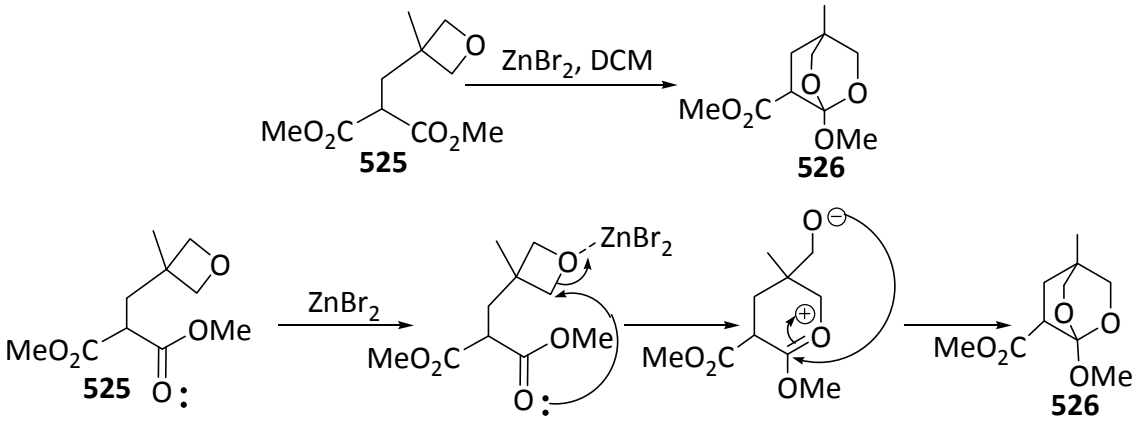
Scheme 218

The lack of success in allylic substitution of methoxy group under a range of conditions is may be due to the poor participation of non-bonding electrons of neighbouring oxygen atoms in 6,8-dioxabicyclo[3.2.1]octane rigid ring system.

The attempts for allylic substitution of 5-methoxy-6,8-dioxabicyclo[3.2.1]octane-4-carboxylic acid methyl ester **435** under a range of conditions did not work, so the above reaction was abandoned.

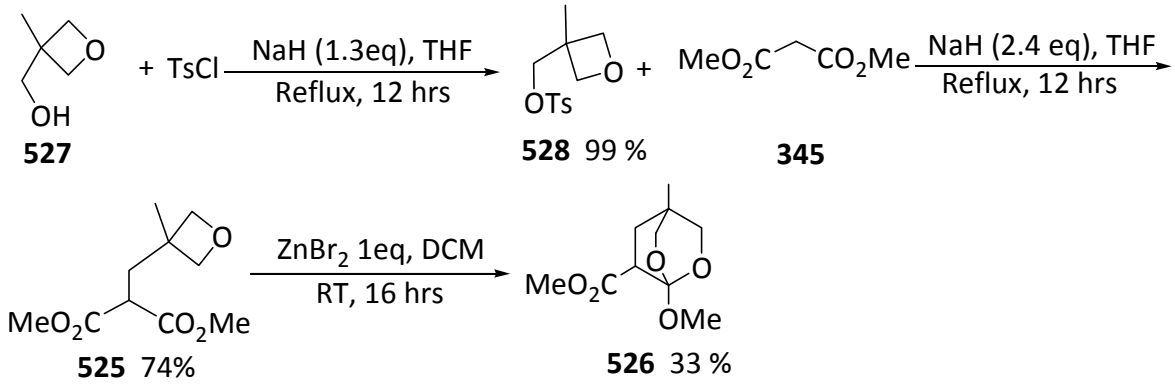
2.12. Synthesis of 1-methoxy-4-methyl-2,6-dioxabicyclo[2.2.2]octane-7-carboxylic acid methyl ester

After successfully using malonate derived epoxides in synthesis of 6,8-dioxabicyclo[3.2.1]octane derivatives it was decided to extend this methodology to oxetanes for the synthesis of similar smaller and larger ring system. The malonate derived oxetane **525** could cyclise under Lewis acidic conditions to 1-methoxy-4-methyl-2,6-dioxabicyclo[2.2.2]octane-7-carboxylic acid methyl ester **526** (Scheme 219).



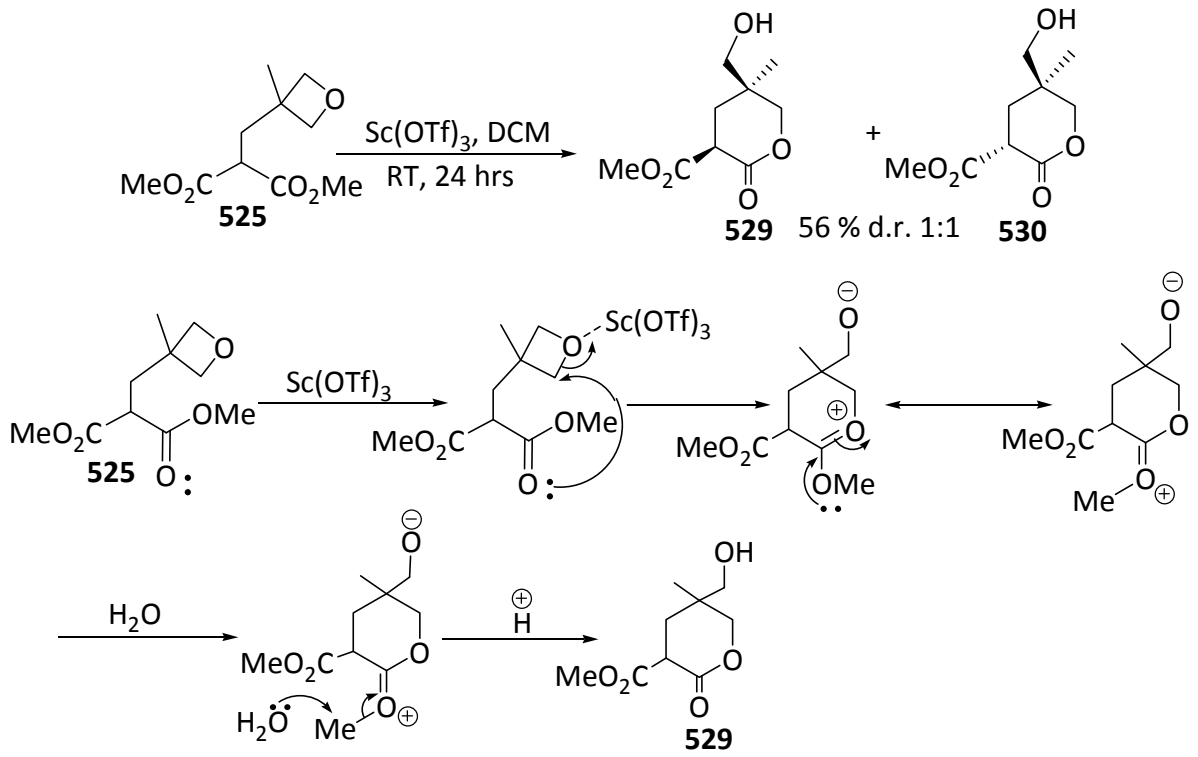
Scheme 219

The precursor 2-(3-methyloxetan-3-ylmethyl)malonic acid dimethyl ester **525** was synthesised by converting commercially available 3-methyl-3-oxetane methanol **527** into the tosylate **528** and which then was reacted with dimethylmalonate **345** in a suspension of NaH, in THF, to afford the desired precursor in 74 % yield. Under the condition of zinc bromide in DCM 2-(3-methyloxetan-3-ylmethyl)malonic acid dimethyl ester **525** was cyclised to 1-methoxy-4-methyl-2,6-dioxabicyclo[2.2.2]octane-7-carboxylic acid methyl ester **526** in 33 % yield. The same reaction resulted in complex mixture under the conditions of *p*-TsOH in DCM (Scheme 220).



Scheme 220

When reaction was performed using 10 mol % of scandium triflate, (±) 5-hydroxymethyl-5-methyl-2-oxotetrahydropyran-3-carboxylic acid methyl ester **529** and **530** was obtained as a mixture of inseparable diastereoisomers (1:1), which is may be due to the interference of water in the reaction (Scheme221).



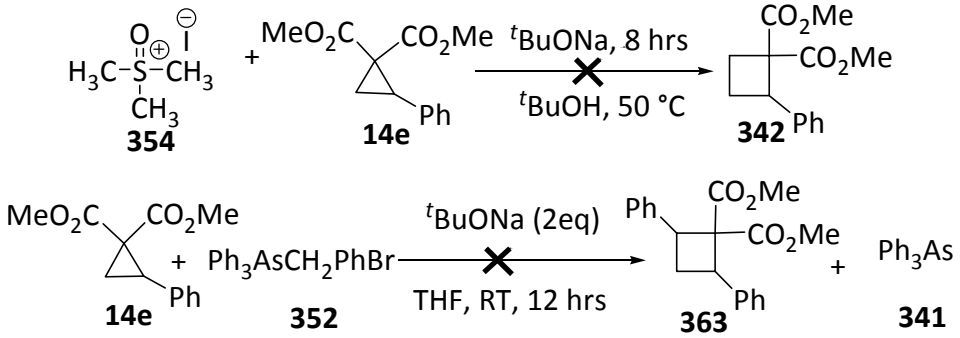
Scheme 221

We later found that Kanoh *et al*. had reported a Lewis acid promoted isomerisation of oxetanes having carbonyl functional group to different heterocyclic compounds. The isomerisation is applicable to oxetane linked with esters **330**, benzimidate **332**, ketone **334** and *tert*-amides **336** (Scheme 105, page 60).[70]

Like epoxides, oxetanes are also equally favourable towards Lewis acid promoted isomerisation.

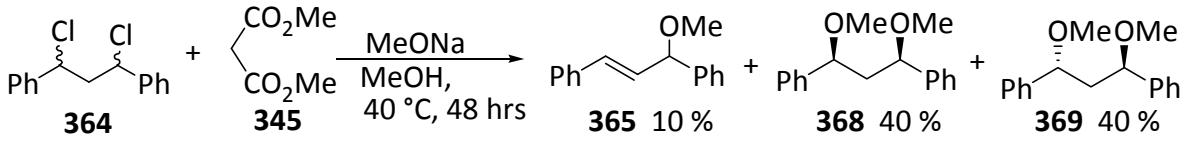
3. Conclusion

The attempts to synthesise donor-acceptor cyclobutanes **342** and **363** from donor-acceptor cyclopropane **14e** were unsuccessful by using both sulfur and arsonium ylide (Scheme 222).



Scheme 222

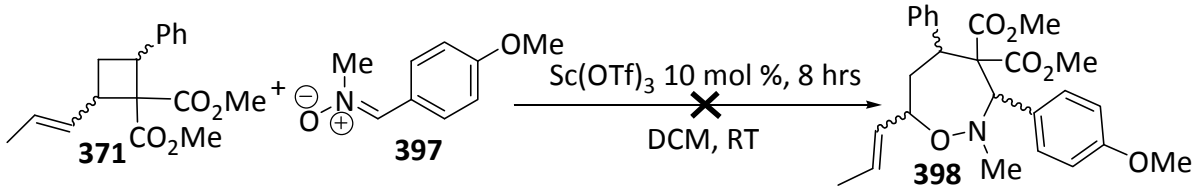
The attempt to synthesise dimethyl-2,4-diphenylcyclobutane-1,1-dicarboxylate **363** by the reaction of 1,3-dichloro-1,3-diphenylpropane **364** and dimethyl malonate under basic conditions was also unsuccessful. The reaction afforded 1,3-diphenyl-3-methoxy-1-propene **365**, (meso)-1,3-dimethoxy-1,3-diphenylpropane **368** and (±)-1,3-dimethoxy-1,3-diphenylpropane **369** as products (scheme 223).



Scheme 223

The donor-acceptor cyclobutanes **371** having an alkene and phenyl π donor groups were successfully synthesised in five steps, in 26 % overall yield.

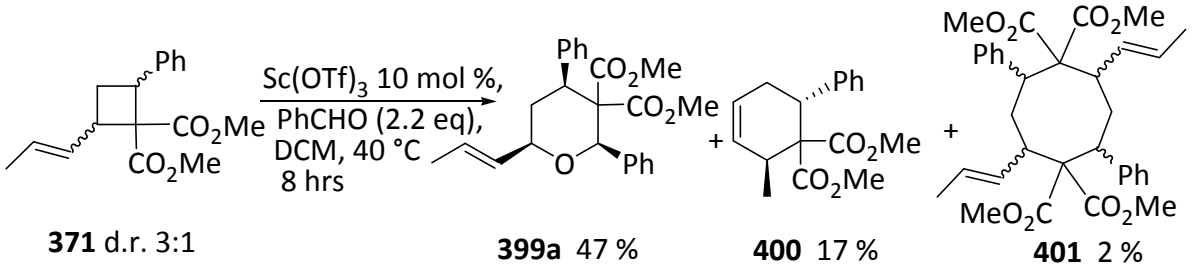
The attempts for dipolar [4+3] cycloaddition reaction between cyclobutane **371** and nitrones **397** were unsuccessful (Scheme 224).



Scheme 224

However, [4+2] cycloaddition reactions between the donor-acceptor cyclobutane **371** and aldehydes, in the presence of scandium triflate were successful and afforded tetrahydropyrans in 47 % yield, dimethyl-2-methyl-6-phenylcyclohex-3-ene-1,1-dicarboxylate in 17 % yield and 2,6-diphenyl-4,8-dipropenyl-cyclooctane-1,1,5,5-

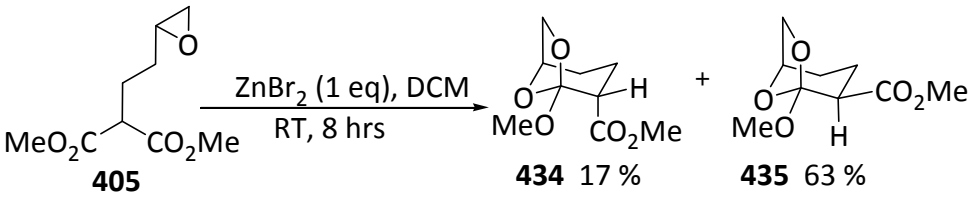
tetracarboxylic acid tetramethyl ester in 2 % yield (Scheme 225). The low yield of desired cycloadduct tetrahydropyran was observed due to formation of undesired side products.



371 d.r. 3:1 **399a** 47 % **400** 17 % **401** 2 %

Scheme 225

During attempts to synthesise a requisite cyclobutane a novel cycloisomerisation was observed with malonyl epoxide **405** under Lewis acidic conditions affording two diastereoisomers of 5-methoxy-6,8-dioxabicyclo[3.2.1]octane-4-carboxylic acid methyl ester **434** and **435** (Scheme 226).



434 17 % **435** 63 %

Scheme 226

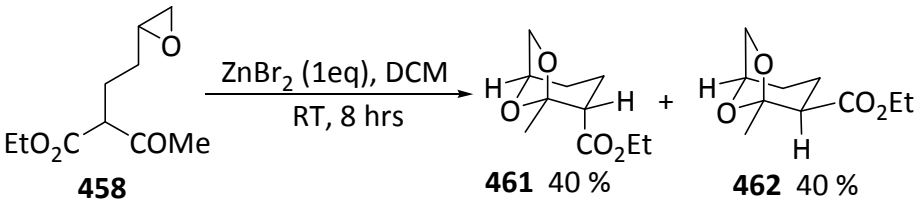
Development of new routes for the construction of 6,8-dioxabicyclo[3.2.1]octane is an attractive challenge for organic chemists, because a number of natural products contain this unit, for example several insect pheromones. This reaction has opened a new path for the synthesis of 6,8-dioxabicyclo[3.2.1]octane in a diastereoselective fashion using malonyl epoxide as a precursor. A wide range of malonyl epoxides were cycloisomerised under Lewis acidic conditions.

The attempts to synthesise similar smaller and larger ring systems by increasing or decreasing the carbon chain length of epoxide **405** by CH_2 unit were unsuccessful.

The cycloisomerisation of malonyl diepoxide **454** has also been investigated towards the formation of 5,5-dimethoxy-6,6,8,8-tetraoxa4,4-spirobi[bicyclo[3.2.1]octane] **455**. When 2,2-bis-(2-oxiranylethyl)malonic acid dimethyl ester was reacted under Lewis acidic condition afforded three diastereoisomers of (±)-5,5-dimethoxy-6,6,8,8-tetraoxa4,4-spirobi[bicyclo[3.2.1]octane] ring system in 68 % overall yield.

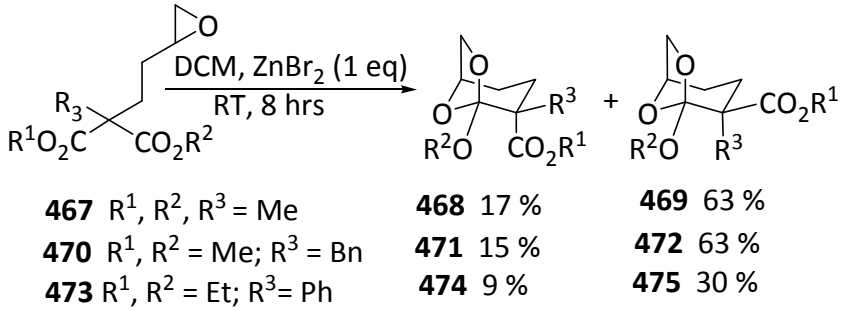
The Lewis acid catalysed chemoselective cyclisation of epoxide **458** was found to occur on the ketone carbonyl group in non diastereoselective fashion and afforded the

diastereoisomers 5-methyl-6,8-dioxabicyclo[3.2.1]octane-4-carboxylic acid ethyl ester **461** and **462** in 1:1 ratio (Scheme 227).



Scheme 227

Successful incorporation of methyl, benzyl and phenyl substituent in 6,8-dioxabicyclo[3.2.1]octane derivatives was achieved. The size of these substituents has little effect on the configuration of the major diastereoisomers and the diastereoselectivity was not same in each case (Scheme 228).



Scheme 228

The cycloisomerisation of *syn* and *anti* malonyl epoxides have proved that the nucleophilic ring opening of epoxides by the carbonyl oxygen of the ester was through an internal S_N2 type mechanism with inversion of stereochemistry at the epoxide carbon under the nucleophilic attack and subsequent ring closure proceeded strereospecifically to afford *exo*- and *endo*-6,8-dioxabicyclo[3.2.1]octane derivatives.

The attempts for allylic substitution of methoxy group of 5-methoxy-6,8-dioxa-bicyclo[3.2.1]octane-4-carboxylic acid methyl ester **435** with allyl group of allyltrimethylsilane **518** were unsuccessful under various Brønsted and Lewis acidic conditions, may be due to poor participation of non bonding electrons of neighbouring oxygen atoms.

Malonyl epoxides and malonyl oxetanes are also equally favourable towards Lewis acid promoted isomerisation.

4. Experimental

General information

All reactions herein were carried out in one of the following solvents, which were dried and purified, or purchased by the following procedures.

Acetone	Purchased from Aldrich (99.8 %), and used without further purification.
Acetonitrile	Purchased from Aldrich (99.8 %), Sure/seal^{TM} anhydrous quality.
Dichloromethane	For general use, DCM was distilled over boiling chips or CaH_2 for anhydrous reactions.
Diethyl ether	Purchased from Fischer Scientific (99+ %) used without purification for general use.
Ethyl acetate	Distilled over $CaCl_2$ for general use.
Light petroleum	Distilled over boiling chips for general use, collecting the fraction distilling below 60 °C.
Tetrahydrofuran	Distilled over sodium and benzophenone.

Anhydrous reactions were carried out in oven-dried glassware and under an atmosphere of nitrogen.

All chemicals used in the reactions were bought from Alfa Aesar or Sigma Aldrich.

Analysis of the compounds created herein was made using a number of the following instruments and procedures.

High-resolution mass spectroscopy was carried out on a Thermo Scientific Exactive machine, used atmospheric pressure ionisation (API) technique to form gas phase sample ions from sample molecule, analysed by an orbitrap mass analyser. For ESI spectroscopy the compounds under investigation were dissolved in 1 % solution of acetic acid in methanol prior to ionisation.

Nuclear magnetic resonance spectroscopy was carried out using a Brucker DPX 400 instrument. The spectra were calibrated to the signals of tetramethylsilane or the small quantity of $CHCl_3$ present in $CDCl_3$. The coupling constants (J) are shown denoting the

multiplicity as a singlet (s), doublet (d), triplet (t), quartet (q), sixtet (Sixt) multiplet (m), or broad signal (br). The size of the coupling constant is given in Hertz (Hz).

Fourier transformation Infra Red spectroscopy was recorded using a Spectrum 65 Perkin Elmer FT-IR spectrophotometer in the range of 600-3800 cm^{-1} following a standard background correction. The intensity of IR peak is reported as broad (br), medium (m), strong (s) or weak (w).

Flash silica column chromatography was used as a standard purification procedure using Fluka Kieselgel 60, 0.04-0.063 mm particle size. Thin layer chromatography was used where possible as a standard procedure for monitoring the course and rate of a given reaction. TLC plates used were Merck aluminium backed sheets with Kieselgel 60 F_{254} silica coating.

X-ray Experimental

Diffraction data were collected using a Bruker APEX 2 CCD diffractometer at 150 K using sealed tube MoKα (λ = 0.71073 Å) graphite monochromated radiation[92]. Data were corrected for absorption by multi-scan technique and for Lp effects[92]. Structure solutions were by direct methods and refinement on F^2 with SHELXTL.[93,94] All non-H atoms were refined anisotropically. H atoms were constrained using a riding model. For the non-centrosymmetric structures the absolute structure could not be reliably determined due to the lack of a heavy enough anomalous scatterer.

In **369** half a molecule was unique, lying on a two-fold axis. There was evidence of unresolved twinning. The crystal quality was poor.

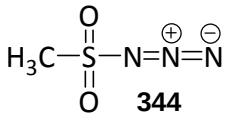
In **469** there are four molecules in the asymmetric unit. The diffraction data were twinned via a 180° rotation about reciprocal axis 0.012, -0.477, 1.0. Approximately de-twinned (SHELX HKLF 4 format) data were employed in the refinement.

In **469**, **456, 475** and **511** the Friedel pairs were merged.

The diffraction data for **489** and **455** were both two-fold twinned via a 180° rotation about reciprocal axis 0 0 1 with the major domain = 62.16(12) for **489** and 72.59(10) % for **455**.

There are two molecules in the asymmetric unit of **435**.

Methyl sulfonyl azide 344.[72]



344

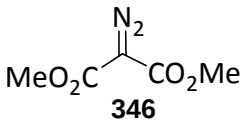
Under a nitrogen atmosphere methane sulfonyl chloride (15.00 g, 130 mmol) was dissolved in acetone (100 mL). To this sodium azide (10.14 g, 156 mmol) was added in small proportions over a 30 minute period. The reaction was left to stir at room temperature for additional four hours. Once the reaction was complete, water (100 mL) was added to the reaction. The organic layer was extracted using diethyl ether (2×50 mL) and washed with brine and dried over $MgSO_4$. The excess solvents were removed under reduced pressure to obtain the desired compound as a colourless liquid (15.57 g, 120 mmol, 99 %).

V_{max} (film)/cm^{-1} 3032w, 2935w, 2374br (N=N=N), 2141s, 1357s, 1166s, 966s, 729s.

δH (400 MHz; $CDCl_3$) 3.27 (3H, s, C$\underline{H}_3$).

δC (100 MHz; $CDCl_3$), 42.85 ($\underline{C}H_3$).

Diazo dimethyl malonate 346.[72]



346

In a dry round bottom flask, dimethylmalonate (4.96 g, 37.56 mmol) and mesyl azide (5.00 g, 41.42 mmol) were dissolved in anhydrous acetonitrile (60 mL). The reaction mixture was cooled with an ice bath and trimethylamine (8.36 g, 82.64 mmol) was added drop wise under nitrogen atmosphere. The reaction mixture was allowed to stir at room temperature under nitrogen atmosphere for 24 hours. The solution was concentrated in *vacuo* and residue was dissolved in a solution of petrol: chloroform (1:1, 40 mL), where precipitation of methanesulfonamide salt took place. The filtrate was concentrated in *vacuo* to afford the desired compound as light yellow oil (5.74 g, 36.33 mmol, 97 %).

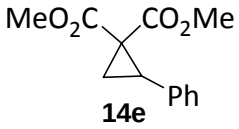
V_{max} (film)/cm^{-1} 2956m, 2140s, (NΞN), 1761s (C=O), 1695s (C=O), 1438s, 1334s, 1276s, 1192s, 1102s, 762s.

δH (400 MHz; $CDCl_3$) 3.85 (6H, s, OC$\underline{H}_3$).

δC (100 MHz; $CDCl_3$) 52.49, (O$\underline{C}H_3$), 65.64 ($\underline{C}$N), 161.43 ($\underline{C}O_2$Me).

General procedure for preparation of cyclopropanes 14e and 360.

Dimethyl-2-phenylcyclopropane-1,1-dicarboxylate 14e.[72]



14e

In a round bottom flask, styrene (1.00 g, 9.60 mmol) was dissolved in anhydrous toluene (20 mL). Diazo malonate **346** (2.50 g, 16 mmol) and a catalytic amount of rhodium acetate dimmer (46 mg, 0.10 mmol) were added. The reaction mixture was refluxed under a nitrogen atmosphere for 24 hours. The mixture was filtered through a pad of celite and silica gel. The crude product was purified by flash chromatography on silica gel using petroleum: ethyl acetate (9:1) as eluent to afford the desired product as light yellow oil (1.70 g, 7.20 mmol, 74 %).

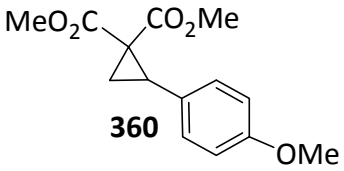
V_{max} (film)/cm^{-1} 3027w, 2951m, 1728s (C=O), 1498w, 1436s, 1335s, 1278s, 1218s, 1130s, 1097w, 892w, 792m, 749m.

δH (400 MHz; $CDCl_3$) 1.74 (1H, dd, J 5.2 Hz, 9 Hz, C$\underline{H}_2$), 2.20 (1H, dd, J 5.2 Hz, 9 Hz, C$\underline{H}_2$), 3.23 (1H, t, J 9 Hz, C$\underline{H}$), 3.35 (3H, s, OC$\underline{H}_3$), 3.79 (3H, s, OC$\underline{H}_3$), 7.18-7.29 (5H, m, ArC$\underline{H}$).

δC (100 MHz; $CDCl_3$) 19.11 (C$\underline{H}_2$), 32.56 (C$\underline{H}$), 37.25 (C$\underline{}$), 52.21 (OC$\underline{H}_3$), 52.81 (OC$\underline{H}_3$), 127.41 (ArC$\underline{H}$), 128.18 (ArC$\underline{H}$), 128.44 (ArC$\underline{H}$), 134.58 (ArC$\underline{}$), 167.04 ($\underline{C}O_2CH_3$), 170.25 ($\underline{C}O_2CH_3$).

m/z (ESI) Calculated for $C_{13}H_{14}O_4(Na^+)$ requires 257.0784; found 257.0782 and $C_{13}H_{14}O_4(H^+)$ requires 235.0965 found 235.0964.

Dimethyl-2-(4-methoxyphenyl)cyclopropane-1,1-dicarboxylate 360.[72]



360

4-vinylanisole (1.00 g, 7.40 mmol), toluene (25 mL), diazo malonate **346** (2.00 g, 12.40 mmol) and $Cu(acac)_2$ (40 mg, 0.07 mmol).

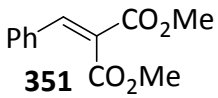
The crude product was purified by flash chromatography on silica gel using petroleum: diethyl ether (1:1) as eluent to afford the desired product as light yellow oil (1.10 g, 4.10 mmol, 55 %).

V_{max} (film)/cm^{-1} 3005w, 2954w, 2837s, 1737s (C=O), 1611m, 1516s, 1439m, 1250s, 1176m, 1147w, 1032m, 836m, 756w.

δH (400 MHz; $CDCl_3$) 1.73 (1H, dd, J 5.2 Hz, 10.4 Hz, C$\underline{H}_2$), 2.16 (1H, dd, J 5.2 Hz, 10.4 Hz, C$\underline{H}_2$), 3.19 (1H, t, J 10.4 Hz, C$\underline{H}$), 3.39 (3H, s, OC$\underline{H}_3$), 3.77 (3H, s, OC$\underline{H}_3$), 3.78 (3H, s, OC$\underline{H}_3$), 6.80 (2H, d, J 8.6 Hz, ArC$\underline{H}$), 7.11 (2H, d, J 8.6 Hz, ArC$\underline{H}$).

δC (100 MHz; $CDCl_3$) 19.29 ($\underline{C}H_2$), 32.23 ($\underline{C}$H), 37.09 ($\underline{C}$), 52.26 (O$\underline{C}H_3$), 52.76 (O$\underline{C}H_3$), 55.21 (O$\underline{C}H_3$), 113.59 (Ar$\underline{C}$H), 126.45 (Ar$\underline{C}$), 129.61 (Ar$\underline{C}$H), 158.90 (Ar$\underline{C}$), 167.18 ($\underline{C}O_2CH_3$), 170.35 ($\underline{C}O_2CH_3$).

Methyl-2-methoxycarbonyl-3-phenyl-2-propenoate 351.[74]



351

To a chilled solution of $TiCl_4$ (14.40 g, 76.00 mmol) in THF (50 mL), at 0 °C, under a nitrogen atmosphere, dimethylmalonate (5.00 g, 38.00 mmol) and benzaldehyde (4.00 g, 38.00 mmol) were added. After 40 minutes of stirring, pyridine (12.00 g, 152 mmol) was added and reaction mixture was stirred overnight, slowly warm to room temperature. The reaction was then quenched with saturated solution of $NaHCO_3$ (30 mL) and extracted with ethyl acetate (3×30 mL). The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2, 9:1, light petrol: ethyl acetate) to afford methyl-2-methoxycarbonyl-3-phenyl-2-propenoate (7.40 g, 32.16 mmol, 90 %) as a light yellow oil.

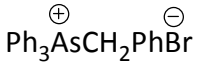
V_{max} (film)/cm^{-1} 3058m, 3027m, 3000m, 2951s, 2844w, 2357w, 1733s (C=O), 1627s (C=C), 1601w, 1575w, 1496w, 1436s, 1374s, 1322s, 1265br, 1222br, 1082s, 1064s, 1025w, 1001w, 940w, 830m, 769s, 692s.

δH (400 MHz; $CDCl_3$) 3.85 (6H, s, OC$\underline{H}_3$), 7.38-7.44 (5H, m, ArC$\underline{H}$), 7.78 (1H, s, C$\underline{H}$).

δC (100 MHz; $CDCl_3$) 52.72 (O$\underline{C}H_3$), 125.48 ($\underline{C}$), 128.91 (Ar$\underline{C}$H), 129.41 (Ar$\underline{C}$H), 130.72 (Ar$\underline{C}$H), 132.77 (Ar$\underline{C}$), 142.98 ($\underline{C}$H), 164.51 ($\underline{C}O_2CH_3$), 167.16 ($\underline{C}O_2CH_3$).

m/z (ESI) Calculated for $C_{12}H_{12}O_4(Na^+)$ requires 243.0628; found 243.0625 and $C_{12}H_{12}O_4(H^+)$ requires 221.0808 found 221.0807.

Benzyl triphenyl arsonium bromide 352.[75]



352

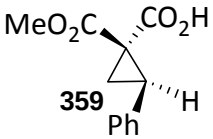
Triphenyl arsine (5.00 g, 16.32 mmol) was dissolved in CH_3CN (50 mL) and benzyl bromide (3.35 g, 19.59 mmol) was added under nitrogen. The mixture was protected from light with an aluminium foil and allowed to stir for three days. Benzyl triphenyl arsonium bromide salt (7.30 g, 15.30 mmol, 94 %) was separated by filtration and washed with diethyl ether: light petrol (1:1) mixture. m.p. 183.5-184.8 °C, literature m.p. 172-172.5 °C. The spectral data were in agreement with literature.

δH (400 MHz; $CDCl_3$) 5.47 (2H, s, C$\underline{H}_2$), 7.12-7.25 (5H, m, ArC$\underline{H}$), 7.59-7.74 (15H, m, ArC$\underline{H}$).

δC (100 MHz; $CDCl_3$) 33.62 (C$\underline{H}_2$), 120.93 (Ar$\underline{C}$), 128.15 (Ar$\underline{C}$), 128.53 (Ar$\underline{C}$H), 128.95 (Ar$\underline{C}$H), 130.66 (Ar$\underline{C}$H), 131.01 (Ar$\underline{C}$H), 133.41 (Ar$\underline{C}$H), 134.01 (Ar$\underline{C}$H).

m/z (ESI) Calculated for $C_{25}H_{22}As$ requires 397.0932; found 397.0925.

Syn-1-(Methoxycarbonyl)-2-phenylcyclopropanecarboxylic acid 359.



To a solution of trimethyloxosulfonium iodide (1.90 g, 8.50 mmol) in ^{t}BuOH (40 mL) was added ^{t}BuONa (0.80 g, 8.50 mmol) at 50 °C. After 30 minutes of stirring, the solution of cyclopropane **14e** (1.00 g, 4.00 mmol) in ^{t}BuOH (10 mL) was added drop wise to this solution. After 12 hours of stirring the resulting suspension was washed with water (20 mL) and extracted with ethylacetate (3×30 mL) to isolate unreacted cyclopropane **14e** (0.10 g, 0.02 mmol). The pH of aqueous medium was changed to 2 and extracted with ethyl acetate (3×30 mL). The combined organic layer was dried over $MgSO_4$, filtered and solvent evaporated under reduced pressure to afford *syn*-1-(methoxycarbonyl)-2-phenylcyclopropanecarboxylic acid (0.50 g, 4.12 mmol, 98 %) as light yellow solid. m.p. 112.5-113.9 °C, literature m.p. 94-96 °C.[90] The spectral data were in agreement with literature.

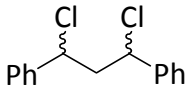
V_{max} (film)/cm^{-1} 3030br (O-H), 2952m, 1734s (C=O), 1436s, 1332s, 1218s, 1141s, 696s.

δH (400 MHz; $CDCl_3$) 2.33 (1H, dd, J 4.8 Hz, 9.2 Hz, C$\underline{H}_2$), 2.42 (1H, dd, J 4.8 Hz, 9.2 Hz, C$\underline{H}_2$), 3.26 (3H, s, OC$\underline{H}_3$), 3.42 (1H, t, J 9.2 Hz, C$\underline{H}$), 7.23-7.33 (5H, m, ArC$\underline{H}$).

δC (100 MHz; $CDCl_3$) 21.31 ($\underline{C}H_2$), 33.52 ($\underline{C}$), 40.97 ($\underline{C}H$), 52.52 ($O\underline{C}H_3$), 127.94 (Ar$\underline{C}$H), 128.31 (Ar$\underline{C}$H), 129.18 (Ar$\underline{C}$H), 134.04 (Ar$\underline{C}$), 170.36 ($\underline{C}O_2CH_3$), 173.66 ($\underline{C}O_2H$).

m/z (ESI) Calculated for $C_{12}H_{12}O_4(Na^+)$ requires 243.0628; found 243.0627 and $C_{12}H_{12}O_4(H^+)$ requires 221.0808 found 221.0808.

1,3-Dichloro-1,3-diphenylpropane 364.[77]



364

Benzaldehyde (1.00 g, 9.60 mmol) and styrene (1.00 g, 9.60 mmol) were dissolved in DCM (50 mL) at room temperature in a dry flask maintained under nitrogen atmosphere. The solution was cooled to 0 °C in an ice bath and BCl_3 (1.50 g, 12.50 mmol, 12.50 mL of a 1M DCM solution) was added via syringe. The reaction was allowed to stir at 0 °C for 2 hours and then at room temperature for 8 hours, during which time the reaction solution turned purple. Water (30 mL) was added and product extracted with DCM (3×30 mL). The combined organic layer was dried over $MgSO_4$ and solvent removed under reduced pressure. The crude product was purified by column chromatography (hexane, silica gel) to afford a diastereomeric mixture (1:1) of the desired product (2.00 g, 7.54 mmol, 80 %) as colourless oil.

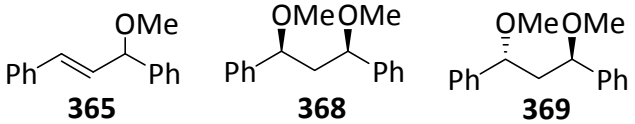
V_{max} (film)/cm^{-1} 3085m, 3061s, 3030s, 2966w, 2912w, 1950w, 1600w, 1585w, 1492s, 1452s, 1296s, 1264m, 1239s, 1197m, 1028m, 1017m, 911m, 847m, 789w, 767s.

δH (400 MHz; $CDCl_3$) 2.63-2.72 (1.5H, m, C$\underline{H}_2$), 2.93-3.00 (0.5H, m, C$\underline{H}_2$), 4.78 (1H, dd, J 6.8 Hz, 8 Hz, C$\underline{H}$), 5.20 (1H, dd, J 6.4 Hz, 7.6 Hz, C$\underline{H}$), 7.29-7.42 (10H, m, ArC$\underline{H}$).

δC (100 MHz; $CDCl_3$) 49.47 ($\underline{C}H_2$), 49.62 ($\underline{C}H_2$), 60.12 ($\underline{C}$H), 60.76 ($\underline{C}$H), 127.02 (Ar$\underline{C}$H), 127.08 (Ar$\underline{C}$H), 128.66 (Ar$\underline{C}$H), 128.78 (Ar$\underline{C}$H), 128.84 (Ar$\underline{C}$H), 128.89 (Ar$\underline{C}$H), 140.10 (Ar$\underline{C}$), 140.76 (Ar$\underline{C}$).

1,3-Diphenyl-3-methoxy-1-propene 365,

1,3-Dimethoxy-1,3-diphenylpropane 368 and 369.



365 **368** **369**

Sodium metal (0.30 g, 13.04 mmol) was added in methanol (50 mL) at room temperature and allowed it to stir until become homogeneous. Dimethylmalonate (1.20 g, 9.10 mmol) was added to the solution and heated to 40 °C under reflux. After half an hour **364** (2.00 g, 7.50 mmol) was added to the reaction flask and the reaction left under reflux for two days. Once the reaction was completed by TLC, the excess solvent was removed under reduced pressure. Water (40 mL) was added to the residue remaining, and product was extracted with ethyl acetate (3×30 mL). The organic layer was dried over $MgSO_4$, filtered and solvent removed in *vacuo*. The crude product was purified by flash chromatography (SiO_2, 50:1, light petrol: diethyl ether) to give 1,3-diphenyl-3-methoxy-1-propene **365** (0.20 g, 0.89 mmol, 10 %) as light yellow oil, (meso)-1,3-dimethoxy-1,3-diphenylpropane **368** (0.80 g, 3.12 mmol, 40 %) as colourless oil and (±)-1,3-dimethoxy-1,3-diphenylpropane **369** (0.80 g, 3.12 mmol, 40 %) as white crystalline solid m.p. 61-62 °C.

365 **V_{max} (film)/cm^{-1}** 3080w, 3058m, 3025s, 2979w, 2930m, 2818s, 1599w, 1492s, 1448s, 1308br, 1187m, 1084m, 966s, 744s, 697s.

δH (400 MHz; $CDCl_3$) 3.38 (3H, s, OC<u>H</u>$_3$), 4.80 (1H, d, J 7 Hz, C<u>H</u>), 6.29 (1H, dd, J 7 Hz, 16 Hz, C<u>H</u>), 6.63 (1H, d, J 16 Hz, C<u>H</u>), 7.20-7.38 (10H, m, ArC<u>H</u>).

δC (100 MHz; $CDCl_3$) 56.46 (O<u>C</u>H$_3$), 84.32 (<u>C</u>H), 126.59 (Ar<u>C</u>H), 126.85 (Ar<u>C</u>H), 127.73 (Ar<u>C</u>H), 128.53 (Ar<u>C</u>H), 130.12 (<u>C</u>H), 131.48 (<u>C</u>H), 136.57 (Ar<u>C</u>), 141.01 (Ar<u>C</u>).

m/z (FAB) 224(70), 223 (70), 193 (100), 147 (60), 121 (90), 115 (75).

368 **V_{max} (film)/cm^{-1}** 3082s, 3060s, 3027s, 2976s, 2925s, 2884s, 1601w, 1491s, 1453s, 1438s, 1363s, 1329m, 1304m, 1259m, 1230s, 1191s, 1165s, 1107s, 1002s, 900s, 860s, 913s, 877m.

δH (400 MHz; $CDCl_3$) 1.79-1.87 (1H, m, C<u>H</u>$_2$), 2.44 (1H, dt, J 7 Hz, 14 Hz, C<u>H</u>$_2$), 3.14 (6H, s, OC<u>H</u>$_3$), 4.05 (2H, t, J 7 Hz, C<u>H</u>), 7.25-7.37 (10H, m, ArC<u>H</u>).

δC (100 MHz; $CDCl_3$) 46.11 (<u>C</u>H$_2$), 56.39 (O<u>C</u>H$_3$), 80.90 (<u>C</u>H), 126.86 (Ar<u>C</u>H), 127.68 (Ar<u>C</u>H), 128.42 (Ar<u>C</u>H), 141.67 (Ar<u>C</u>).

m/z (ESI) Calculated for $C_{17}H_{20}O_2(Na^+)$ requires 279.1356; found 279.1353.

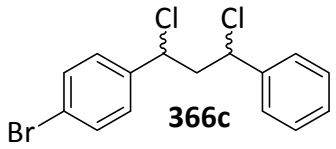
369 **V_{max} (film)/cm^{-1}** 3090w, 3070w, 3010s, 2990s, 2803w, 1601w, 1500w, 1490m, 1450s, 1430s, 1360s.

δH (400 MHz; $CDCl_3$) 1.98 (2H, dd, J 6, 7.6 Hz, C<u>H</u>$_2$), 3.26 (6H, s, OC<u>H</u>$_3$), 4.41 (2H, dd, J 6 Hz, 7.6 Hz, C<u>H</u>), 7.24-7.35 (10H, m, ArC<u>H</u>).

δC (100 MHz; $CDCl_3$) 47.58 ($\underline{C}H_2$), 56.80 ($O\underline{C}H_3$), 80.06 ($\underline{C}H$), 126.60 (Ar$\underline{C}$H), 127.49 (Ar$\underline{C}$H), 128.40 (Ar$\underline{C}$H), 142.31 (Ar$\underline{C}$).

m/z (ESI) Calculated for $C_{17}H_{20}O_2(Na^+)$ requires 279.1356; found 279.1353.

1-Bromo-4-(1,3-dichloro-3-phenylpropyl)benzene 366c.[77]



366c

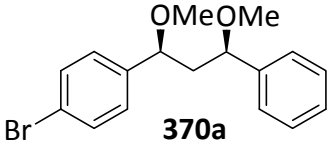
4-Bromobenzaldehyde (1.80 g, 9.60 mmol) and styrene (1.00 g, 9.60 mmol) were dissolved in DCM (50 mL) at room temperature in a dry flask maintained under nitrogen atmosphere. The solution was cooled to 0 °C in an ice bath and BCl_3 (1.46 g, 12.50 mmol, 12.50 mL of a 1M CH_2Cl_2 solution) was added via syringe. The reaction was allowed to stir at 0 °C for 2 hours and then at room temperature for 8 hours, during which time the reaction solution turned purple. Water (30 mL) was added and product extracted with DCM (3×30 mL). The combined organic layer was dried over $MgSO_4$ and solvent removed under reduced pressure. The crude product was purified by column chromatography (hexane, silica gel) to afford a diastereomeric mixture (1:1) of the desired product (1.80 g, 4.93 mmol, 54 %) as colourless oil.

ν_{max} (film)/cm^{-1} 3061w, 3029w, 1590m, 1488s, 1453s, 1406s, 1239w, 1197w, 1105w, 1072s, 1010s, 924s, 865w, 824s, 764m, 716s, 697s.

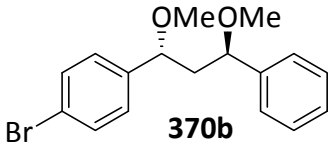
δH (400 MHz; $CDCl_3$) 2.58-2.67 (1.5 H, m, $C\underline{H}_2$), 2.90-2.97 (0.5H, m, $C\underline{H}_2$), 4.72-4.77 (1H, m, C$\underline{H}$), 5.14-5.20 (1H, m, C$\underline{H}$), 7.23-7.28 (2H, m, ArC$\underline{H}$), 7.31-7.40 (5H, m, ArC$\underline{H}$), 7.48-7.53 (2H, m, ArC$\underline{H}$).

δC (100 MHz; $CDCl_3$) 49.40 ($\underline{C}H_2$), 49.55 ($\underline{C}H_2$), 59.26 ($\underline{C}$H), 59.93 ($\underline{C}$H), 59.96 ($\underline{C}$H), 60.61 ($\underline{C}$H), 122.62 (Ar$\underline{C}$), 122.78 (Ar$\underline{C}$), 127.01 (Ar$\underline{C}$H), 127.07 (Ar$\underline{C}$H), 128.75 (Ar$\underline{C}$H), 128.83 (Ar$\underline{C}$H), 128.78 (Ar$\underline{C}$H), 128.92 (Ar$\underline{C}$H), 128.97 (Ar$\underline{C}$H), 132.03 (Ar$\underline{C}$H), 132.10 (Ar$\underline{C}$H), 139.14 (Ar$\underline{C}$H), 139.82 (Ar$\underline{C}$), 139.20 (Ar$\underline{C}$), 140.58 (Ar$\underline{C}$).

1-Bromo-4-(1,3-dimethoxy-3-phenylpropyl)benzene 370a and 370b.



370a



370b

Sodium metal (0.10 g, 4.35 mmol) was added in methanol (30 mL) at room temperature and allowed it to stir until become homogeneous. Dimethylmalonate (0.50 g, 3.78 mmol) was added to the solution and heated to 40 °C under reflux. After half an hour **366c** (1.00 g, 2.90 mmol) was added to the reaction flask and the reaction left under reflux for two days. Once the reaction was completed, the excess solvent was removed under reduced pressure. Water was (30 mL) added to the residue remaining, and product was extracted with ethyl acetate (3×30 mL). The organic layer was dried over $MgSO_4$, filtered and solvent removed in *vacuo*. The crude product was purified by flash chromatography (SiO_2, 50:1, light petrol: diethyl ether) to afford (±)-1,3-dimethoxy-1,3-diphenylpropane **370a** (0.10 g, 0.30 mmol, 11 %) as colourless oil and (±)-1-bromo-4-(1,3-dimethoxy-3-phenylpropyl)benzene **370b** (0.10 g, 0.30 mmol, 11 %) as light yellow crystalline solid m.p. 62-63 °C.

370a V_{max}/cm^{-1} 3082w, 3060m, 3027m, 2976m, 2925m, 2884w, 1601m, 1491w, 1453s, 1438s, 1363s, 1329s, 1304s, 1259s, 1230w, 1191s, 1165s, 1107s, 1002s, 900w, 860s, 913m, 877s.

δH (400 MHz; $CDCl_3$) 1.67-1.73 (1H, m, C$\underline{H}_2$), 2.33 (1H, dt, J 7 Hz, 14, C$\underline{H}_2$), 3.06 (6H, s, OC$\underline{H}_3$), 3.94 (2H, q, J 7 Hz, C$\underline{H}$), 7.07 (2H, d, J 8.4 Hz, ArC$\underline{H}$), 7.17-7.31 (5H, m, ArC$\underline{H}$), 7.14 (2H, d, J 8.4 Hz, ArC$\underline{H}$).

δC (100 MHz; $CDCl_3$) 46.05 (C$\underline{H}_2$), 56.41 (OC$\underline{H}_3$), 56.51 (OC$\underline{H}_3$), 80.31 (C$\underline{H}$), 80.73 (C$\underline{H}$), 121.48 (Ar$\underline{C}$Br), 126.84 (Ar$\underline{C}$H), 127.81 (Ar$\underline{C}$H), 128.51 (Ar$\underline{C}$H), 128.60 (Ar$\underline{C}$H), 131.62 (Ar$\underline{C}$H), 140.81 (Ar$\underline{C}$), 141.44 (Ar$\underline{C}$).

m/z (ESI) Calculated for $C_{17}H_{19}O_2Br^{79}(Na^+)$ requires 357.0461; found 357.0461.

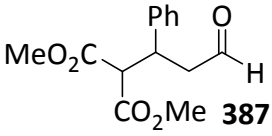
370b V_{max}/cm^{-1} 3090w, 3070m, 3010m, 2990s, 2803m, 1601s, 1500s, 1490m, 1450m, 1430s, 1360s.

δH (400 MHz; $CDCl_3$) 1.86 (2H, t, J 7.2 Hz, C$\underline{H}_2$), 3.17 (3H, s, OC$\underline{H}_3$), 3.18 (3H, s, OC$\underline{H}_3$), 4.29-4.35 (2H, m, C$\underline{H}$), 7.11 (2H, d, J 8.4 Hz, ArC$\underline{H}$), 7.17-7.30 (5H, m, ArC$\underline{H}$), 7.38 (2H, d, J 10.8 Hz, ArC$\underline{H}$).

δC (100 MHz; $CDCl_3$) 47.52 (C$\underline{H}_2$), 56.82 (OC$\underline{H}_3$), 56.91 (OC$\underline{H}_3$), 79.51 (C$\underline{H}$), 79.92 (C$\underline{H}$), 121.25 (Ar$\underline{C}$Br), 126.55 (Ar$\underline{C}$H), 127.60 (Ar$\underline{C}$H), 128.34 (Ar$\underline{C}$H), 128.48 (Ar$\underline{C}$H), 131.57 (Ar$\underline{C}$H), 141.45 (Ar$\underline{C}$), 142.10 (Ar$\underline{C}$).

m/z (ESI) Calculated for $C_{17}H_{19}O_2Br^{79}(Na^+)$ requires 357.0461; found 357.0252.

Dimethyl-2-methoxycarbonyl-3-phenyl-5-oxopentonate 387.[80]



387

To a mixture of cinnamaldehyde (1.00 g, 7.60 mmol), dimethylmalonate (2.00 g, 15.10 mmol), benzoic acid (93 mg, 0.08 mmol) and (*S*)-α,α-diphenyl-2-pyrrolidine methanol trimethylsilyl ether (0.12 g, 0.38 mmol) was added distilled water (2 mL) in a round bottom flask, at room temperature. The reaction flask was allowed to stir for 12 hours. The resulting mixture was extracted with DCM (3×20 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent removed in *vacuo*. The resulting crude product was purified by flash chromatography (SiO_2, 9:1 light petrol: EtOAc) to afford methyl-2-methoxycarbonyl-3-phenyl-5-oxopentanoate **387** (0.90 g, 45 %) as a light yellow oil $[\alpha]_d = 0$.

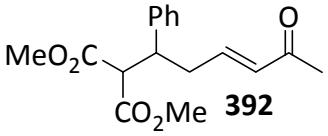
V_{max} (film)/cm^{-1} 3029w, 2953m, 2730w, 1731s (C=O), 1602w, 1583w, 1495m, 1453m, 1434m, 1317s, 1253s, 1158s, 1071w, 1024w, 702s.

δH (400 MHz; $CDCl_3$) 2.91-2.94 (2H, m, C<u>H</u>$_2$), 3.50 (3H, s, OC<u>H</u>$_3$), 3.75 (3H, s, OC<u>H</u>$_3$), 3.74 (1H, d, J 4.8 Hz, C<u>H</u>), 4.00-4.10 (1H, m, C<u>H</u>), 7.21-7.32 (5H, m, ArC<u>H</u>), 9.60 (1H, t, J 1.6 Hz , C<u>H</u>O).

δC (100 MHz ; $CDCl_3$) 39.50 (<u>C</u>H), 47.21 (<u>C</u>H$_2$), 52.51 (O<u>C</u>H$_3$), 52.79 (O<u>C</u>H$_3$), 57.27 (<u>C</u>H), 127.59 (Ar<u>C</u>H), 127.97 (Ar<u>C</u>H), 128.79 (Ar<u>C</u>H), 139.68 (Ar<u>C</u>), 167.84 (<u>C</u>O$_2$CH$_3$), 168.38 (<u>C</u>O$_2$CH$_3$), 199.97 (<u>C</u>HO).

m/z (ESI) Calculated for $C_{14}H_{16}O_5(Na^+)$ requires 287.0890; found 287.0885.

(*E*)-Methyl-2-methoxy carbonyl-3phenyl-7-oxo-5-octenoate 392.[78]



392

To a stirred solution of acetomethylenetriphenylphosphorane **379** (0.40 g, 1.30 mmol) in DCM (20 mL) was added aldehyde **387** (0.30 g, 1.60 mmol) at room temperature. The reaction mixture was heated under reflux for twenty four hours. The reaction mixture was cooled at room temperature, filtered and the filtrate was concentrated in *vacuo*. The residue was purified by flash chromatography (SiO_2, 2:8 EtOAc: light petrol) to afford (*E*)-methyl-2-methoxycarbonyl-7-oxo-5-octenoate **392** (0.35 g, 70 %) as a light yellow oil.

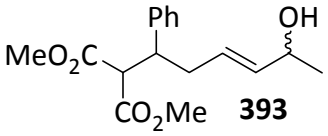
V_{max}(DCM)/cm^{-1} 3038w, 3003w, 2844w, 1731s (C=O), 1673s (C=O), 1626m, 1495w, 1453s, 1434s, 1361s, 1253br, 1156s, 1022w, 981m, 765w, 702s.

δH(400 MHz; $CDCl_3$) 2.11 (3H, s, C$\underline{H}_3$), 2.58-2.70 (2H, m, C$\underline{H}_2$), 3.46 (3H, s, OC$\underline{H}_3$), 3.55-3.61 (1H, m, C$\underline{H}$), 3.74 (1H, d , J 8.8 Hz, C$\underline{H}$), 3.77 (3H, s, OC$\underline{H}_3$), 5.94 (1H, d, J 15.6 Hz, C$\underline{H}$), 6.50 (1H, dt, J 7.2 Hz, 15.6 Hz C$\underline{H}$), 7.16-7.32 (5H, m, ArC$\underline{H}$).

δC (100 MHz; $CDCl_3$) 26.80 (C$\underline{H}_3$), 36.78 (C$\underline{H}_2$), 44.71 (C$\underline{H}$), 52.44 (OC$\underline{H}_3$), 52.77 (OC$\underline{H}_3$), 57.64 (C$\underline{H}$), 127.51 (ArC$\underline{H}$), 127.97 (ArC$\underline{H}$), 128.69 (ArC$\underline{H}$), 133.10 (C$\underline{H}$), 139.41 (Ar$\underline{C}$), 144.36 (C$\underline{H}$), 167.81 ($\underline{C}O_2CH_3$), 168.49 ($\underline{C}O_2CH_3$), 198.26 ($\underline{C}$=O).

m/z (ESI) Calculated for$C_{17}H_{20}O_5(Na^+)$ requires 327.1196; found 327.1193; $C_{17}H_{20}O_5(H^+)$ requires 305.1377; found 305.1376.

(*E*)-Methyl-2-methoxycarbonyl-3-phenyl-7-hydroxy-5-octenoate 393.[78]



393

Cerium trichloride hepahydrate (0.20 g, 0.56 mmol) was added to methanol (30 mL) at room temperature and stirred until homogeneous. To the solution was added ketone **392** (0.10 g, 0.33 mmoles) followed by portion wise addition of sodium borohydride (0.20 g, 0.56 mmol). The reaction mixture was stirred for further three hours to give white precipitate in a light yellow solution. The reaction mixture was quenched with 10 % aqueous HCl solution and extracted with DCM (3×25 mL). The combined organic layer was washed with saturated NaCl solution (25 ml). The organic phases were dried over $MgSO_4$, filtered and solvent removed in *vacuo* to afford a (1:1) mixture of two diastereoisomers of (*E*)-methyl-2-methoxy carbonyl-3-phenyl-7-hydroxy-5-octenoate **393** (99 mg, 99 %) as a light yellow oil.

V_{max} film/cm^{-1} 3212br (O-H), 3028w, 2952m, 1754s (C=O), 1736s (C=O), 1602w, 1494w, 1453m, 1434m, 1366w, 1317w, 1248w, 1195w, 1134w, 1058w, 970w, 763w, 701m.

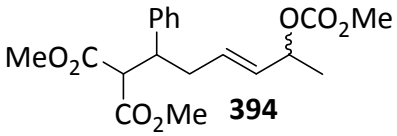
δH (400 MHz; $CDCl_3$) 1.07 (3H, d, 6.4 Hz C$\underline{H}_3$), 1.12 (3H, d, 6.4 Hz, C$\underline{H}_3$), 2.36-2.47 (4H, m, C$\underline{H}_2$), 3.44 (6H, s, OC$\underline{H}_3$), 3.45-3.50 (2H, m, C$\underline{H}$), 3.70 (1H, d, J 1.2 Hz, C$\underline{H}$), 3.73 (1H, d, J 1.2 Hz, C$\underline{H}$), 3.78 (6H, s, OC$\underline{H}_3$), 4.06-4.13 (2H, m, C$\underline{H}$), 5.35-5.39 (4H, m, C$\underline{H}$), 7.15-7.30 (10H, m, ArC$\underline{H}$).

δC (100 MHz; $CDCl_3$) 23.06 (C$\underline{H}_3$), 23.17 (C$\underline{H}_3$), 36.60 (C$\underline{H}_2$), 36.66 (C$\underline{H}_2$), 45.44 (C$\underline{H}$), 45.52 (C$\underline{H}$), 52.32 (OC$\underline{H}_3$), 52.68 (OC$\underline{H}_3$), 57.62 (C$\underline{H}$), 57.66 (C$\underline{H}$), 68.49 (C$\underline{H}$), 68.58 (C$\underline{H}$), 126.79 (C$\underline{H}$), 126.87 (C$\underline{H}$), 127.05 (ArC$\underline{H}$), 127.08 (ArC$\underline{H}$), 128.22 (ArC$\underline{H}$), 128.25 (ArC$\underline{H}$), 128.35

(Ar<u>C</u>H), 128.36 (Ar<u>C</u>H), 137.08 (<u>C</u>H), 137.11 (<u>C</u>H), 140.22(Ar<u>C</u>), 140.23 (Ar<u>C</u>), 168.10 (<u>C</u>O_2CH_3), 168.11 (<u>C</u>O_2CH_3), 168.75 (<u>C</u>O_2CH_3), 168.76 (<u>C</u>O_2CH_3).

m/z (ESI) Calculated for $C_{17}H_{22}O_5(Na^+)$ requires 329.1359; found 329.1352.

(*E*)-Methyl-2-methoxycarbonyl-3-phenyl-7-O-(methoxycarbonyl)-5-octenoate 394.[78]



394

Alcohol **393** (0.20 g, 0.65 mmol) was dissolved in THF (3 mL) and cooled to 0 °C. Pyridine (0.10 g, 1.30 mmol) and DMAP (16 mg, 0.13 mmol) were added followed by drop wise addition of methyl chloroformate (0.12 g, 1.30 mmol). During the addition a thick white precipitate formed. The mixture was stirred at 0 °C for 30 minutes and then allowed to warm to room temperature for four hours. The reaction mixture was quenched with 10 % aqueous HCl solution (15 mL) and extracted with EtOAc (3×10 mL). The organic phase was washed successively with 10 % aqueous HCl solution (2×10 mL) and 10 % aqueous NaOH solution (2×10mL). The organic layer was dried over $MgSO_4$, filtered and solvent removed in *vacuo* to give crude product as light yellow oil. The crude product was purified by flash chromatography (SiO_2, 8:2 light petrol: EtOAc) to afford a (1:1) mixture of diastereoisomers of (*E*)-methyl-2-methoxycarbonyl-7-O-(methoxycarbonyl)-5-octenoate **394** (0.10 g, 42 %) as colourless oil.

V_{max} (film)/cm^{-1} 3028w, 2996w, 2953m, 1737s (C=O), 1602w, 1495w, 1438s, 1327s, 1266s, 1146m, 1037m, 970w, 940w, 862w, 792w, 764w.

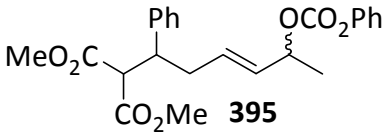
δH (400 MHz ; $CDCl_3$) 1.14 (3H, d J 6.8 Hz, C<u>H</u>$_3$), 1.22 (3H, d J 6.8 Hz, C<u>H</u>$_3$), 2.35-2.45 (4H, m , C<u>H</u>$_2$), 3.43 (3H, s , OC<u>H</u>$_3$), 3.44 (3H, s , OC<u>H</u>$_3$), 3.46 (1H, d, J 0.8 Hz, C<u>H</u>), 3.50 (1H, d, J 0.8 Hz, C<u>H</u>), 3.71 (1H, d, J 0.8 Hz , C<u>H</u>), 3.74 (1H, d, J 0.8 Hz, C<u>H</u>), 3.76 (6H, s, OC<u>H</u>$_3$), 3.77 (6H, s, OC<u>H</u>$_3$), 4.97-5.02 (2H, m, C<u>H</u>), 5.29-5.39 (2H, m, C<u>H</u>), 5.44-5.50 (2H, m, C<u>H</u>), 7.13-7.29 (10H, m, ArC<u>H</u>).

δC (100 MHz; $CDCl_3$) 20.15 (<u>C</u>H$_3$), 20.25 (<u>C</u>H$_3$), 36.65 (<u>C</u>H$_2$), 45.23 (<u>C</u>H), 45.34 (<u>C</u>H), 52.32 (O<u>C</u>H$_3$), 52.67 (O<u>C</u>H$_3$), 52.68 (O<u>C</u>H$_3$), 54.47 (O<u>C</u>H$_3$), 54.49 (O<u>C</u>H$_3$), 57.40 (<u>C</u>H), 57.45 (<u>C</u>H), 74.85 (<u>C</u>H), 75.02 (<u>C</u>H), 127.07 (Ar<u>C</u>H), 128.18 (Ar<u>C</u>H), 128.22 (Ar<u>C</u>H), 128.35 (Ar<u>C</u>H), 128.37 (Ar<u>C</u>H), 129.97 (<u>C</u>H), 130.01 (<u>C</u>H), 131.68 (<u>C</u>H), 131.87 (<u>C</u>H), 139.99 (Ar<u>C</u>), 140.00 (Ar<u>C</u>),

154.96 ($\underline{C}O_2CH_3$), 154.99 ($\underline{C}O_2CH_3$), 168.05 ($\underline{C}O_2CH_3$), 168.07 ($\underline{C}O_2CH_3$), 168.67 ($\underline{C}O_2CH_3$), 168.69 ($\underline{C}O_2CH_3$).

m/z (ESI) Calculated for $C_{19}H_{24}O_7(Na^+)$ requires 387.1414; found 387.1406.

(*E*)-Methyl-2-methoxycarbonyl-3-phenyl-7-O-(phenoxycarbonyl)-5-octenoate 395.[78]



395

Alcohol **393** (3.10 g, 10.13 mmol) was dissolved in THF (60 mL) and cooled to 0 °C. Pyridine (1.60 g, 20.25 mmol) and DMAP (0.25 g, 2.03 mmol) were added followed by drop wise addition of phenyl chloroformate (3.10 g, 20.25 mmol). During the addition thick white precipitate formed. The mixture was stirred at 0 °C for 30 minutes and then allowed to warm to room temperature for four hours. The reaction mixture was quenched with 10 % aqueous HCl solution (40 mL) and extracted with EtOAc (3×30 mL). The organic phase was washed successively with 10 % aqueous HCl solution (2×30 mL) and 10 % aqueous NaOH solution (2×30 mL). The organic layer was dried over $MgSO_4$, filtered and solvent removed in *vacuo* to give crude product as light yellow oil. The crude product was purified by flash chromatography (SiO_2, 9:1 light petrol: EtOAc) to afford a (1:1) mixture of diastereoisomers of (*E*)-methyl-2-methoxycarbonyl-7-O-(phenoxycarbonyl)-5-octenoate **395** (4.00 g, 9.40 mmol, 93 %) as colourless oil.

V_{max} (film)/cm^{-1} 3060w, 3028w, 2983w, 2951w, 1756s (C=O), 1736s (C=O), 1591w, 1494m, 1453m, 1434m, 1324m, 1252s, 1210s, 1146m, 1041m, 971w, 921w, 779m.

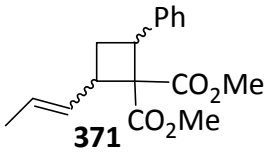
δH (400 MHz; $CDCl_3$) 1.22 (3H, d, J 6.4 Hz, C$\underline{H}_3$), 1.31 (3H, d, J 6.4 Hz, C$\underline{H}_3$), 2.37-2.50 (4H, m, C$\underline{H}_2$), 3.44 (3H, s, OC$\underline{H}_3$), 3.45 (3H, s, OC$\underline{H}_3$), 3.46-3.53 (2H, m, C$\underline{H}$), 3.73 (1H, d, J 4.8 Hz, C$\underline{H}$), 3.76 (1H, d, J 4.8 Hz, C$\underline{H}$), 3.78 (3H, s , OC$\underline{H}_3$), 3.79 (3H, s, OC$\underline{H}_3$), 5.07-5.12 (2H, m, C$\underline{H}$), 5.36-5.46 (2H, m, C$\underline{H}$), 5.50, 5.57 (2H, m, 5C$\underline{H}$), 7.12-7.28 (20H, m, ArC$\underline{H}$).

δC (100 MHz; $CDCl_3$) 20.13 ($\underline{C}H_3$), 20.20 ($\underline{C}H_3$), 36.65 ($\underline{C}H_2$), 45.17 ($\underline{C}H$), 45.27 ($\underline{C}H$), 52.34 (O$\underline{C}H_3$), 52.70 (O$\underline{C}H_3$), 57.33 ($\underline{C}H$), 57.45 ($\underline{C}H$), 75.88 ($\underline{C}H$), 76.02 ($\underline{C}H$), 121.09 (Ar$\underline{C}H$), 121.10 (Ar$\underline{C}H$), 125.87 (Ar$\underline{C}H$), 127.11 (Ar$\underline{C}H$), 128.16 (Ar$\underline{C}H$), 128.21, (Ar$\underline{C}H$), 128.38 (Ar$\underline{C}H$), 128.42 (Ar$\underline{C}H$), 129.38 (Ar$\underline{C}H$), 129.40 (Ar$\underline{C}H$), 130.65 ($\underline{C}H$), 130.71 ($\underline{C}H$), 131.26 ($\underline{C}H$), 131.42 ($\underline{C}H$),

139.95 (Ar<u>C</u>), 151.11 (Ar<u>C</u>), 152.80 (<u>C</u>O_2Ph), 152.82 (<u>C</u>O_2Ph), 168.03 (<u>C</u>O_2CH_3), 168.05 (<u>C</u>O_2CH_3), 168.67 (<u>C</u>O_2CH_3), 168.68 (<u>C</u>O_2CH_3).

m/z (ESI) Calculated for $C_{24}H_{26}O_7(Na^+)$ requires 449.1571; found 449.1563.

1,1-Dimethoxycarbonyl-2-phenyl-4-(*E*)-propenylcyclobutane 371.[78]



371

Carbonate **395** (2.00 g, 4.68 mmol) was dissolved in anhydrous toluene (50 mL) and cooled to 0 °C. Sodium hydride (0.17 g, 60 % dispersion in mineral oil, 7.02 mmol) was added portion wise to the stirred solution of carbonate. The resulting mixture was allowed to warm to room temperature for 20 minutes and then heated to 50 °C for further 8 hours. The resulting reaction mixture was cooled to room temperature and then poured into water (50 mL). It was extracted with ethyl acetate (3×40 mL). The organic layer was dried over $MgSO_4$ and filtered. The solvent was removed in *vacuo* to give a residue which was purified by flash chromatography (SiO_2, 9:1 light petrol: EtOAc). This gave a (3:1) mixture of diastereoisomers of the 1,1-dimethoxycarbonyl-2-phenyl-4-(*E*)-propenylcyclobutane **371** (1.20 g, 4.16 mmol, 88 %) as colourless oil.

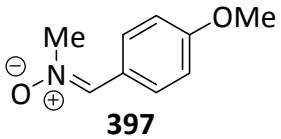
V_{max} (film)/cm^{-1} 3085w, 3058m, 3026m, 2949s, 2915m, 1730s (C=O), 1603w, 1496w, 1448m, 1433s, 1370, 1271s, 1199s, 1074s, 968s, 880w, 766w, 698s.

δH (400 MHz; $CDCl_3$) 1.69-1.71 (6H, m C<u>H</u>$_3$), 2.29-2.36 (2H, m, C<u>H</u>$_2$), 2.69-2.77 (2H, m, C<u>H</u>$_2$), 3.19 (3H, s , OC<u>H</u>$_3$), 3.24-3.30 (2H, m, C<u>H</u>), 3.31 (3H, s, OC<u>H</u>$_3$), 3.71 (3H, s, OC<u>H</u>$_3$), 3.83 (3H, s, OC<u>H</u>$_3$), 4.01-4.13 (2H, m, 2C<u>H</u>), 5.60-5.75 (4H, m, C<u>H</u>), 7.18-7.30 (10H, m, ArC<u>H</u>).

δC (100 MHz; $CDCl_3$) 18.01 (<u>C</u>H$_3$), 27.42 (<u>C</u>H$_2$), 28.48, (<u>C</u>H$_2$), 41.71 (<u>C</u>H), 42.22, (<u>C</u>H), 42.44 (<u>C</u>H), 42.77 (<u>C</u>H), 51.53 (O<u>C</u>H$_3$), 51.58 (O<u>C</u>H$_3$), 52.41 (O<u>C</u>H$_3$), 52.48 (O<u>C</u>H$_3$), 65.00 (<u>C</u>), 65.22 (<u>C</u>), 126.60 (Ar<u>C</u>H), 126.67 (Ar<u>C</u>H), 127.33 (Ar<u>C</u>H), 127.35 (Ar<u>C</u>H), 127.50 (Ar<u>C</u>H), 127.98 (Ar<u>C</u>H), 128.10 (<u>C</u>H), 128.38 (<u>C</u>H), 128.86 (<u>C</u>H), 129.00 (<u>C</u>H), 139.01 (Ar<u>C</u>), 139.11 (Ar<u>C</u>), 168.34 (<u>C</u>O_2CH_3), 168.46 (<u>C</u>O_2CH_3), 172.17 (<u>C</u>O_2CH_3), 172.24 (<u>C</u>O_2CH_3).

m/z (ESI) Calculated for$C_{17}H_{20}O_4$ (Na^+) requires 311.1254; found 311.1246.

N-Methyl(4-methoxybenzylidene)amine-N-oxide 397.[72]



397

To anhydrous DCM (40 mL) under a nitrogen atmosphere was added $MgSO_4$ (1.20 g, 9.60 mmol) and $NaHCO_3$ (0.70 g, 7.80 mmol). To this suspension N-methylhydroxylamine hydrochloride (0.50 g, 6.0 mmol) was added, followed by *p*-anisaldehyde (0.82 g, 6.00 mmol) and the mixture was stirred and refluxed under nitrogen for 72 hours. The mixture was then filtered to remove the $MgSO_4$ and the filtrate was concentrated under vacuum to afford a viscous oil, which crystallised when placed in an ice bath. The crude product was purified by recrystallisation, using mixture of DCM and light petrol (1:1) at 0 °C to give the desired compound as a white crystalline solid (0.75 g, 4.54 mmol, 75 %) m.p. 62-63 °C, literature m.p. 99.8-103.4 °C. The spectral data were in agreement with literature.

V_{max} (DCM)/cm^{-1} 2837m, 2760w, 1602s, 1568s, 1507s, 1463s, 1441s, 1415s, 1322s, 1305s, 1257s, 1161s, 1027s, 943s.

δH (400 MHz; $CDCl_3$) 3.86 (6H, s, C<u>H</u>$_3$), 6.95 (2H, d, J 8.8 Hz, ArC<u>H</u>), 7.32 (1H, s, C<u>H</u>), 8.22 (2H, d, J 8.8 Hz, ArC<u>H</u>).

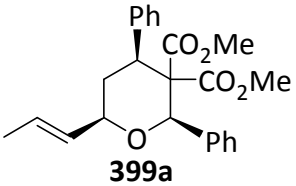
δC (100 MHz; $CDCl_3$) 53.94 (<u>C</u>H$_3$), 55.36 (<u>C</u>H$_3$), 113.85 (Ar<u>C</u>H), 123.45 (Ar<u>C</u>), 130.45 (Ar<u>C</u>H), 134.99 (<u>C</u>H), 161.08 (Ar<u>C</u>).

m/z (ESI) Calculated for $C_9H_{11}O_2N(Na^+)$ requires 188.0682; found 188.0682.

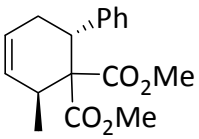
General procedure for [4+2] cycloaddition reaction between cyclobutane 371 and aldehydes.

Under a nitrogen atmosphere, cyclobutane **371** and aldehydes were dissolved in anhydrous DCM and $Sc(OTf)_3$ was added to this. The reaction was left to stir at 40 °C for 8 hours. Then the mixture was filtered through a pad of celite and silica gel and washed with small amount of DCM. The excess solvent was removed in *vacuo* to afford crude product.

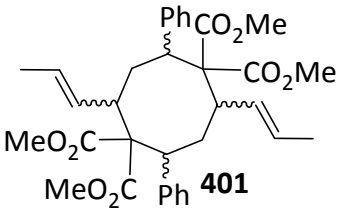
(±)-Dimethyl-2,4-diphenyl-6-(*E*)-propenyldihydro-2H-pyran-3,3(4H)dicarboxylate 399a, (±)-dimethyl-2-methyl-6-phenylcyclohex-3-ene-1,1-dicarboxylate 400, 2,6-diphenyl-4,8-dipropenylcyclooctane-1,1,5,5-tetracarboxylic acid tetramethyl ester 401.



399a



400



401

Cyclobutane **371** (0.40 g, 1.39 mmol), benzaldehyde (0.18 g, 1.67 mmol), DCM (20 mL) and $Sc(OTf)_3$ (68 mg, 0.14 mmol).

The crude product was purified by flash chromatography (SiO_2, 99:1, light petrol: ethyl acetate) to give (±)-dimethyl-2,4-diphenyl-6-(*E*)-propenyldihydro-2H-pyran-3,3(4H)-dicarboxylate **399a** (0.10 g, 0.25 mmol, 18 %) as colourless oil, (±)-dimethy-2-methyl-6-phenylcyclohex-3-ene-1,1-dicarboxylate **400** (80 mg, 0.28 mmol, 20 %) as a colourless oil and 2,6-diphenyl-4,8-dipropenylcyclooctane-1,1,5,5-tetracarboxylic acid tetramethyl ester **401** (33 mg, 0.05 mmol, 2 %) as colourless oil.

399a V_{max}(film)/cm^{-1} 3029w, 2948w, 1741s (C=O), 1715s (C=O), 1495w, 1454w, 1432w, 1375w, 1266s, 1209m, 1094m, 1073m, 1018w.

δH (400 MHz; $CDCl_3$) 1.72 (3H, d, J 6.4 Hz, C$\underline{H}_3$), 1.82 (1H, ddd, J 2.8 Hz, 3.6 Hz, 13.2 Hz, C$\underline{H}_2$), 2.92 (1H, dt, J 11.2 Hz, 13.2 Hz, C$\underline{H}_2$), 3.36 (3H, s, OC$\underline{H}_3$), 3.42 (3H, s, OC$\underline{H}_3$), 3.53 (1H, dd, J 3.6 Hz, 13.2 Hz, C$\underline{H}$), 4.25-4.28 (1H, m, C$\underline{H}$), 5.26 (1H, s, C$\underline{H}$), 5.66-5.83 (2H, m, C$\underline{H}$), 7.20-7.41 (10H, m, ArC$\underline{H}$).

δC (100 MHz; $CDCl_3$) 17.86 (C$\underline{H}_3$), 33.33 (C$\underline{H}_2$), 50.43 (OC$\underline{H}_3$), 50.88 (OC$\underline{H}_3$), 51.70 (C$\underline{H}$), 64.87 (C$\underline{}$), 79.66 (C$\underline{H}$), 83.56 (C$\underline{H}$), 127.28 (ArC$\underline{H}$), 127.34 (ArC$\underline{H}$), 127.44 (ArC$\underline{H}$), 127.66 (ArC$\underline{H}$), 127.67 (ArC$\underline{H}$), 127.93 (ArC$\underline{H}$), 129.14 (C$\underline{H}$), 131.17 (C$\underline{H}$), 139.41 (ArC$\underline{}$), 140.46 (ArC$\underline{}$), 167.45 (C$\underline{}O_2CH_3$), 170.60 (C$\underline{}O_2CH_3$)**.**

m/z (ESI) Calculated for $C_{24}H_{26}O_5(Na^+)$ requires 417.1672; found 417.1662.

400 V_{max} (film)/cm^{-1} 3025w, 2948w, 2838w, 1731s (C=O), 1601w, 1493m, 1454m, 1432m, 1246s, 1211s, 1125m, 1059m.

δH (400 MHz; $CDCl_3$) 1.13 (3H, d, J 7.2 Hz, C$\underline{H}_3$), 2.27 (1H, dsixt, J 1.6 Hz, 17.2 Hz, C$\underline{H}_2$), 2.94-2.97 (1H, m, C$\underline{H}$), 3.07-3.14 (1H, m, C$\underline{H}_2$), 3.56 (3H, s, OC$\underline{H}_3$), 3.64 (1H, dd, J 2.4 Hz, 7.2 Hz, C$\underline{H}$), 3.69 (3H, s, OC$\underline{H}_3$), 5.57 (1H, dq, J 2 Hz, 10.4 Hz, C$\underline{H}$), 5.86-5.89 (1H, m, C$\underline{H}$), 7.18-7.26 (5H, m, ArC$\underline{H}$).

δC (100 MHz; $CDCl_3$) 18.25 ($\underline{C}H_3$), 30.86 ($\underline{C}H$), 30.88 ($\underline{C}H_2$), 42.79 ($\underline{C}H$), 51.74 ($O\underline{C}H_3$), 51.81 ($O\underline{C}H_3$)**,** 60.41 ($\underline{C}$), 126.05 ($Ar\underline{C}H$), 127.07 ($\underline{C}H$), 128.07 ($Ar\underline{C}H$), 128.57 ($Ar\underline{C}H$), 130.05 ($\underline{C}H$), 142.68 ($Ar\underline{C}$), 170.59 ($\underline{C}O_2CH_3$), 170.80 ($\underline{C}O_2CH_3$)**.**

m/z (ESI) Calculated for $C_{17}H_{20}O_4(Na^+)$ requires 311.1254; found 311.1247.

401 V_{max} (film)/cm^{-1} 2950m, 1729s (C=O), 1434s, 1267m, 1200w, 1104s, 968s, 745s, 700s.

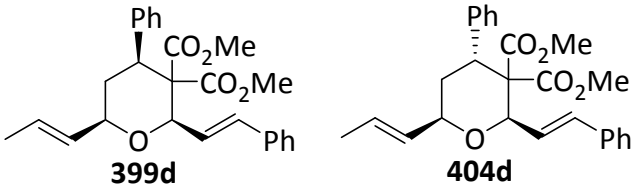
δH (400 MHz; $CDCl_3$) 1.67 (3H, dd, J 1.6 Hz, 6.8 Hz, $C\underline{H}_3$), 1.70 (3H, dd, J 1.2 Hz, 6.4Hz, $C\underline{H}_3$), 2.01-2.07 (1H, m, $C\underline{H}_2$), 2.16-2.22 (1H, m, $C\underline{H}_2$), 2.68 (1H, dt, J 9 Hz, 11.6 Hz, $C\underline{H}_2$), 2.81 (1H, dt, J 9.4 Hz, 11.2 Hz, $C\underline{H}_2$), 3.18 (3H, s, $OC\underline{H}_3$), 3.19 (3H, s, $OC\underline{H}_3$), 3.68 (1H, s, $C\underline{H}$), 3.69 (3H, s, $OC\underline{H}_3$), 3.71 (3H, s, $OC\underline{H}_3$), 4.00 (1H, dt, J 4.4 Hz, 12 Hz, $C\underline{H}$), 4.39 (1H, t, J 9.2 Hz, $C\underline{H}$), 4.48 (1H, t, J 9.2 Hz, $C\underline{H}$), 5.50-5.69 (4H, m, $C\underline{H}$), 7.19-7.31 (10H, m, $ArC\underline{H}$).

δC (100 MHz; $CDCl_3$) 13.29 ($\underline{C}H_3$), 17.99 ($\underline{C}H_3$), 26.61 ($\underline{C}H_2$), 28.03 ($\underline{C}H_2$), 34.77 ($\underline{C}H$), 39.95 ($\underline{C}H$), 42.21 ($\underline{C}H$), 42.26 ($\underline{C}H$), 51.84 ($O\underline{C}H_3$), 52.18 ($O\underline{C}H_3$), 64.21 ($\underline{C}$), 64.41 ($\underline{C}$), 126.99 ($Ar\underline{C}H$), 127.01 ($Ar\underline{C}H$), 127.74 ($Ar\underline{C}H$), 127.76 ($Ar\underline{C}H$), 128.03 ($Ar\underline{C}H$), 128.09 ($Ar\underline{C}H$), 128.40 ($\underline{C}H$), 128.94 ($\underline{C}H$), 129.15 ($\underline{C}H$), 129.21 ($\underline{C}H$), 139.06 ($Ar\underline{C}$), 139.10 ($Ar\underline{C}$), 169.56 ($\underline{C}O_2CH_3$), 169.61 ($\underline{C}O_2CH_3$), 170.13 ($\underline{C}O_2CH_3$), 170.27 ($\underline{C}O_2CH_3$).

m/z (ESI) Calculated for $C_{34}H_{40}O_8(Na)^+$ requires 599.2615; found 599.2599.

(±)-4-Phenyl-6-propenyl-2-styryldihydropyran-3,3-dicarboxylic acid dimethyl ester 399d,

(±)-4-Phenyl-6-propenyl-2-styryldihydropyran-3,3-dicarboxylic acid dimethyl ester 404d.



399d **404d**

Cyclobutane **371** (0.30 g, 1.04 mmol), *trans*-cinnamaldehyde (0.18 g, 1.25 mmol), DCM (15 mL) and $Sc(OTf)_3$ (51 mg, 0.10 mmol).

The crude product was purified by flash chromatography (SiO_2, 95:5, light petrol: ethyl acetate) to give (±)-4-phenyl-6-propenyl-2-styryldihydropyran-3,3-dicarboxylic acid dimethyl ester **399d** (0.12 g, 0.29 mmol, 27 %) as light yellow oil, (±)-4-phenyl-6-propenyl-2-styryldihydropyran-3,3-dicarboxylic acid dimethyl ester **404d** (40 mg, 0.10 mmol, 9 %) as light yellow oil, (±)-dimethy-2-methyl-6-phenylcyclohex-3-ene-1,1dicarboxylate **400** (30 mg,

0.10 mmol, 10 %) as a colourless oil and 2,6-diphenyl-4,8-dipropenylcyclooctane-1,1,5,5-tetracarboxylic acid tetramethyl ester **401** (20 mg, 0.03 mmol, 3 %) as colourless oil.

399d V_{max} (film)/cm^{-1} 3027m, 2951s, 2852m, 2361s, 1728s, 1494m, 1436m, 1258m, 1067m, 968m.

δH (400 MHz; $CDCl_3$) 1.73 (3H, d, J 6.4 Hz, C$\underline{H}_3$), 1.83 (1H, dt, J 3.2 Hz, 13.6 Hz, C$\underline{H}_2$), 2.70 (1H, dt, J 11.6 Hz, 13.6 Hz, C$\underline{H}_2$), 3.46 (1H,dd, J 3.2 Hz, 13.6 Hz, C$\underline{H}$), 3.49 (3H, s, OC$\underline{H}_3$), 3.62 (3H, s, OC$\underline{H}_3$), 4.21 (1H, t, J 7.6 Hz, C$\underline{H}$), 4.71 (1H, d, 6 Hz, C$\underline{H}$), 5.63-5.69 (1H, m, C$\underline{H}$), 5.77-5.84 (1H, m, C$\underline{H}$), 6.38 (1H, dd, J 6.2 Hz, 15.6 Hz, C$\underline{H}$), 6.65 (1H, d, J 16 Hz, C$\underline{H}$), 7.19-7.38 (10H, m, ArC$\underline{H}$).

δC (100 MHz; $CDCl_3$) 17.87 (C$\underline{H}_3$), 33.17 (C$\underline{H}_2$), 49.53 (C$\underline{H}$), 51.49 (OC$\underline{H}_3$), 51.93 (OC$\underline{H}_3$), 63.99 (C$\underline{C}$), 79.48 (C$\underline{H}$), 83.32 (C$\underline{H}$), 126.62 (Ar$\underline{C}$H), 126.68 (Ar$\underline{C}$H), 127.20 (C$\underline{H}$), 127.54 (Ar$\underline{C}$H), 127.80 (Ar$\underline{C}$H), 128.42 (Ar$\underline{C}$H), 128.49 (C$\underline{H}$), 129.17 (Ar$\underline{C}$H), 131.04 (C$\underline{H}$), 131.57 (C$\underline{H}$), 136.97 (Ar$\underline{C}$), 140.38 (Ar$\underline{C}$), 167.79 ($\underline{C}O_2CH_3$), 170.35 ($\underline{C}O_2CH_3$).

m/z (ESI) Calculated for $C_{26}H_{28}O_5(Na^+)$ requires 443.1829; found 433.1817.

404d V_{max} (film)/cm^{-1} 2951m, 1726s, 1507m, 1477m, 1460m, 1262s, 1050s, 900s.

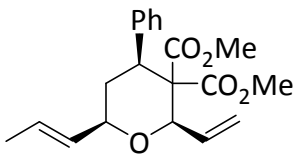
δH (400 MHz; $CDCl_3$) 1.71 (3H, d, J 6.4 Hz, C$\underline{H}_3$), 1.87 (1H, dt, J 2.8 Hz, 13.6 Hz, C$\underline{H}_2$), 2.55-2.63 (1H, m, C$\underline{H}_2$), 3.26 (3H, s, OC$\underline{H}_3$), 3.66 (3H, s, OC$\underline{H}_3$), 3.94 (1H, dd, J 2 Hz, 6.8 Hz, C$\underline{H}$), 4.55-4.59 (1H, m, C$\underline{H}$), 5.15 (1H, dd, J 1.6 Hz, 4.4 Hz, C$\underline{H}$), 5.54-5.60 (1H, m, C$\underline{H}$), 5.71-5.84 (1H, m, C$\underline{H}$), 6.45 (1H,dd, J 4.8 Hz, 16 Hz, C$\underline{H}$), 6.72 (1H, d, J 16 Hz, C$\underline{H}$), 7.17-7.38 (10H, m, ArC$\underline{H}$).

δC (100 MHz; $CDCl_3$) 17.87 (C$\underline{H}_3$), 33.82 (C$\underline{H}_2$), 43.69 (C$\underline{H}$), 51.65 (OC$\underline{H}_3$), 52.19 (OC$\underline{H}_3$), 60.75 (C$\underline{C}$), 74.95 (C$\underline{H}$), 75.50 (C$\underline{H}$), 126.49 (Ar$\underline{C}$H), 127.06 (Ar$\underline{C}$H), 127.13 (Ar$\underline{C}$H), 127.22 (Ar$\underline{C}$H), 127.47 (C$\underline{H}$), 128.07 (C$\underline{H}$), 128.39 (Ar$\underline{C}$H), 128.44 (Ar$\underline{C}$H), 128.90 (Ar$\underline{C}$H), 129.06 (Ar$\underline{C}$H), 129.99 (C$\underline{H}$), 131.56 (C$\underline{H}$), 137.40 (Ar$\underline{C}$), 142.30 (Ar$\underline{C}$), 169.32 ($\underline{C}O_2CH_3$), 169.56 ($\underline{C}O_2CH_3$).

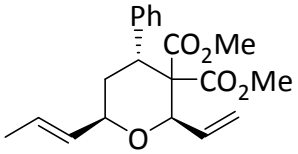
m/z (ESI) Calculated for $C_{26}H_{28}O_5(Na^+)$ requires 443.1829; found 433.1819.

(±)-4-Phenyl-6-propenyl-2-vinyldihydropyran-3,3-dicarboxylic acid dimethyl ester 399e,

(±)-4-Phenyl-6-propenyl-2-vinyldihydropyran-3,3-dicarboxylic acid dimethyl ester 404e.



399e



404e

Cyclobutane **371** (0.20 g, 0.69 mmol), acrolein (0.12 g, 2.10 mmol), DCM (10 mL) and $Sc(OTf)_3$ (34 mg, 0.07 mmol).

The crude product was purified by flash chromatography (SiO_2, 124:1, light petrol : ethyl acetate) to afford (±)-4-phenyl-6-propenyl-2-vinyldihydropyran-3,3-dicarboxylic acid dimethyl ester **399e** (60 mg, 0.17 mmol, 12 %) as colourless oil, (±)-4-Phenyl-6-propenyl-2-vinyldihydropyran-3,3-dicarboxylic acid dimethyl ester **404e** (20 mg, 0.06 mmol, 8 %) as colourless oil, (±)-dimethy-2-methyl-6-phenylcyclohex-3-ene-1,1-dicarboxylate **400** (0.03g, 0.10 mmol, 15 %) as a colourless oil and 2,6-diphenyl-4,8-dipropenylcyclooctane-1,1,5,5-tetracarboxylic acid tetramethyl ester **401** (8 mg, 0.02 mmol, 2 %) as colourless oil.

399e V_{max} (film)/cm^{-1} 3455w, 2951s, 2852s, 1728s, 1635s, 1603s, 1495m, 1440s, 1370s, 1258s, 1062s, 928m, 834w, 769s.

δH (400 MHz; $CDCl_3$) 1.69 (3H, d, J 6.4, C$\underline{H}_3$), 1.82 (1H, dt, J 3.2 Hz, 14 Hz, C$\underline{H}_2$), 2.51-2.59 (1H, m, C$\underline{H}_2$), 3.25 (3H, s, OC$\underline{H}_3$), 3.72 (3H, s, OC$\underline{H}_3$), 3.90 (1H, dd, J 2 Hz, 6.8 Hz, C$\underline{H}$), 4.49-4.54 (1H, m, C$\underline{H}$), 4.94-4.97 (1H, m, C$\underline{H}$), 5.16 (1H, dt, J 2 Hz, 10.8 Hz, C$\underline{H}_2$), 5.41 (1H, dt, J 1.8 Hz, 17.2 Hz, C$\underline{H}_2$), 5.48-5.55 (1H, m, C$\underline{H}$), 5.70-5.79 (1H, m, C$\underline{H}$), 6.06-6.14 (1H, m, C$\underline{H}$), 7.20-7.36 (5H, m, ArC$\underline{H}$).

δC (100 MHz; $CDCl_3$) 17.85 (C$\underline{H}_3$), 33.85 (C$\underline{H}_2$), 43.65 (C$\underline{H}$), 51.59 (OC$\underline{H}_3$), 51.97 (OC$\underline{H}_3$), 60.41 (C$\underline{C}$), 74.18 (C$\underline{H}$), 75.59 (C$\underline{H}$), 115.53 (C$\underline{H}_2$), 127.10 (C$\underline{H}$), 127.83 (ArC$\underline{H}$), 128.41 (ArC$\underline{H}$), 129.05 (ArC$\underline{H}$), 131.60 (C$\underline{H}$), 135.59 (C$\underline{H}$), 142.30 (ArC$\underline{C}$), 169.35 (C$\underline{C}O_2CH_3$), 169.55 (C$\underline{C}O_2CH_3$).

m/z (ESI) Calculated for $C_{20}H_{24}O_5(Na^+)$ requires 367.1516; found 367.1508.

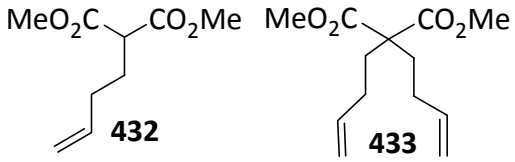
404e V_{max} (film)/cm^{-1} 3455w, 2952s, 2852s, 1725s, 1636s, 1602m, 1495m, 1436s, 1370s, 1258s, 1064s, 991s, 928s, 834s, 769s.

δH (400 MHz; $CDCl_3$) 1.71 (3H, d, J 6.4 Hz, C$\underline{H}_3$), 1.80 (1H, dt, J 3.2 Hz, 13.2 Hz, C$\underline{H}_2$), 2.64 (1H, dt, J 11.6 Hz, 13.2 Hz, C$\underline{H}_2$), 3.42 (1H, dd, J 3.6 Hz, 13.2 Hz, C$\underline{H}$), 3.53 (3H, s, OC$\underline{H}_3$), 3.64 (3H, s, OC$\underline{H}_3$), 4.16 (1H, t, J 7.6 Hz, C$\underline{H}$), 4.52 (1H, d, J 6 Hz, C$\underline{H}$), 5.16 (1H, d, J 10.8 Hz, C$\underline{H}$), 5.34 (1H, d, J 17.2 Hz, C$\underline{H}$), 5.61 (1H, dd, J 5.6 Hz, 6 Hz, C$\underline{H}$), 5.74-5.81 (1H, m, C$\underline{H}$), 5.90-6.07 (1H, m, C$\underline{H}$), 7.20-7.30 (5H, m, ArC$\underline{H}$).

δC (100 MHz; $CDCl_3$) 17.87 ($\underline{C}H_3$), 33.17 ($\underline{C}H_2$), 49.41 ($\underline{C}H$), 51.37 ($O\underline{C}H_3$), 51.90 $O\underline{C}H_3$), 63.78 ($\underline{C}$), 79.33 ($\underline{C}H$), 83.60 ($\underline{C}H$), 116.92 ($\underline{C}H_2$), 127.19 (Ar$\underline{C}H$), 127.80 (Ar$\underline{C}H$), 128.27 ($\underline{C}H$), 129.16 (Ar$\underline{C}H$), 131.08 ($\underline{C}H$), 135.17 ($\underline{C}H$), 140.37 (Ar$\underline{C}$), 167.81 ($\underline{C}O_2CH_3$), 170.31 ($\underline{C}O_2CH_3$).

m/z (ESI) Calculated for $C_{20}H_{24}O_5(Na^+)$ requires 367.1516; found 367.1509.

2-But-3-enylmalonic acid dimethyl ester 432 and 2,2-dibut-3-enylmalonic acid dimethyl ester 433.[86]



432 **433**

To a suspension of sodium hydride (0.67 g, 17.80 mmol, 60 % in mineral oil) in (25 mL) DMF at 0 °C, dimethyl malonate (2.00 g, 14.80 mmol) was added drop wise. The mixture was allowed to warm up to room temperature and 4-bromobut-1-ene (2.20 g, 16.30 mmol) was added. The reaction mixture was allowed to stir for twenty hours at room temperature and then quenched with saturated solution of ammonium chloride. The organic layer was separated and the aqueous layer extracted with ethyl acetate (2×30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in *vacuo*. The crude product was purified by flash chromatography on silica gel eluting with light petrol/EtOAc 200: 1 affording 2-but-3-enylmalonic acid dimethyl ester **432** (2.00 g, 12.35 mmol, 83 %) as light yellow oil and 2,2-dibut-3-enylmalonic acid dimethyl ester **433** (0.30 g, 1.24 mmol, 8 %) as light yellow oil.

432 V_{max} (film)/cm^{-1} 3070w, 2955m, 2848w, 2361w, 1737s, 1641w, 1437m, 1231s, 1156s, 1018w, 917w.

δH (400 MHz; $CDCl_3$) 1.99-2.14 (4H, m, $C\underline{H}_2$), 3.42 (1H, t, J 7.4 Hz, C$\underline{H}$), 3.76 (6H, s, $OC\underline{H}_3$), 5.01-5.08 (2H, m, $C\underline{H}_2$), 5.72-5.83 (1H, m, C$\underline{H}$).

δC (100 MHz; $CDCl_3$) 27.91 ($\underline{C}H_2$), 31.28 ($\underline{C}H_2$), 50.85 ($\underline{C}H$), 52.48 ($O\underline{C}H_3$), 116.03 ($\underline{C}H_2$), 136.74 ($\underline{C}H$), 169.81 ($\underline{C}O_2CH_3$).

m/z (ESI) Calculated for $C_9H_{14}O_4(Na^+)$ requires 209.0784; found 209.0781 and $C_9H_{14}O_4(H^+)$ requires 187.0965 found 187.0962.

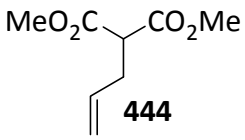
433 V_{max} (film)/cm^{-1} 3077w, 2953m, 1736s, 1642w, 1436m, 1266s, 1206s, 1146s, 1027s, 995w, 914m,795w.

δH (400 MHz; $CDCl_3$) 1.93-2.03 (8H, m, C$\underline{H}_2$), 3.73 (6H, s, OC$\underline{H}_3$), 4.96 (2H, dd, J 1.6 Hz, 10.8 Hz, C$\underline{H}_2$), 5.03 (2H, dd, J 1.6 Hz, 17.2 Hz, C$\underline{H}_2$) 5.73-5.83 (2H, m, C$\underline{H}$).

δC (100 MHz; $CDCl_3$) 28.40 (C$\underline{H}_2$), 31.78 (C$\underline{H}_2$), 52.37 (OC$\underline{H}_3$), 57.06 (C$\underline{C}$), 115.12 (C$\underline{H}_2$), 137.42 (C$\underline{H}$), 171.95 (C$\underline{O}_2CH_3$).

m/z (ESI) Calculated for $C_{13}H_{20}O_4(Na^+)$ requires 263.1254; found 263.1250.

2-Allylmalonic acid dimethyl ester 444.[86]



444

Dimethylmalonate (3.30 g, 24.80 mmol) and 3-bromoprop-1-ene (2.00 g, 16.50 mmol) were added to a suspension of potassium carbonate (5.00 g, 49.50 mmol) in (45 mL) acetone. The reaction mixture was allowed to stir for twenty four hours at room temperature and then quenched with a saturated solution of ammonium chloride (40 mL). The organic layer was separated and the aqueous layer extracted with DCM (3×30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with light petrol / ethylacetate (99:1) affording 2-allylmalonic acid dimethyl ester (2.40 g, 13.94 mmol, 86 %) as colourless oil.

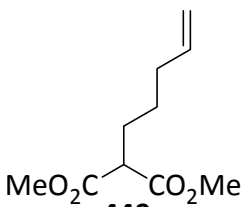
V_{max} (film)/cm^{-1} 3080m, 3010m, 2960m, 2850m, 1753s, 1737s, 1416s, 1239s, 1196s, 887m.

δH (400 MHz; $CDCl_3$) 2.65 (2H, t, J 7.6 Hz, C$\underline{H}_2$), 3.47 (1H, t, J 7.6 Hz, C$\underline{H}$), 3.74 (6H, s, OC$\underline{H}_3$), 5.05-5.16 (2H, m, C$\underline{H}_2$), 5.72-5.82(1H, m, C$\underline{H}$).

δC (100 MHz; $CDCl_3$) 32.98 (C$\underline{H}_2$), 51.42 (C$\underline{H}$), 52.52 (OC$\underline{H}_3$), 117.68 (C$\underline{H}_2$), 133.94 (C$\underline{H}$), 169.30 (C$\underline{O}_2CH_3$).

m/z (ESI) Calculated for $C_8H_{12}O_4(Na^+)$ requires 195.0628; found 195.0629.

2-Pent-4-enylmalonic acid dimethyl ester 449.[86]



449

Dimethylmalonate (1.33 g, 10.10 mmol) and 5-bromopent-1-ene (1.00 g, 6.71 mmol) were added to a suspension of potassium carbonate (2.00 g, 20.10 mmol) in (25 mL) acetone. The

reaction mixture was allowed to stir for twenty four hours at reflux and then quenched with a saturated solution of ammonium chloride. The organic layer was separated and aqueous layer extracted with DCM (3×30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with light petrol/ethylacetate (19:1) affording **449** 2-pent-4-enylmalonic acid dimethyl ester (0.80 g, 3.99 mmol, 44 %) as light yellow oil.

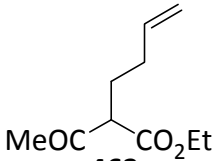
V_{max} (film)/cm^{-1} 3078w, 3000w, 2955m, 2863w, 1754s, 1737s, 1436m, 1343w, 1271m, 1219m, 1155m, 1057m, 1003w, 914w.

δH (400 MHz; $CDCl_3$) 1.37-1.46 (2H, m, C$\underline{H}_2$), 1.91 (2H, q, J 7.6 Hz, 16 Hz, C$\underline{H}_2$), 2.08 (2H, q, J 7.6 Hz, 16 Hz, C$\underline{H}_2$), 3.37 (1H, t, J 7.6 Hz, C$\underline{H}$), 3.74 (6H, s, OC$\underline{H}_3$), 4.95-5.00 (2H,m, C$\underline{H}_2$), 5.72-5.83 (1H, m, C$\underline{H}$).

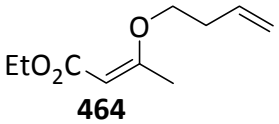
δC (100 MHz; $CDCl_3$) 26.54 (C$\underline{H}_2$), 28.28 (C$\underline{H}_2$), 33.23 (C$\underline{H}_2$), 51.56 (C$\underline{H}$), 52.44 (OC$\underline{H}_3$), 115.07 (C$\underline{H}_2$), 137.86 (C$\underline{H}$), 169.83 (C$\underline{O}_2CH_3$).

m/z (ESI) Calculated for $C_{10}H_{16}O_4(Na^+)$ requires 223.0941; found 223.0937.

2-Acetylhex-5-enoic acid ethyl ester 463 and 3-but-3-enyloxybut-2-enoic acid ethyl ester 464.



463



464

Ethylacetoacetate (2.10 g, 16.30 mmol) and 4-bromo-1-butene (2.00 g, 14.80 mmol) were added to a suspension of potassium carbonate (4.40 g, 44.40 mmol) in (55 mL) acetone. The reaction mixture was allowed to stir for twenty four hours at reflux and then quenched with a saturated solution of ammonium chloride (50 mL). The organic layer was separated and aqueous layer extracted with (3×30 mL) DCM. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with light petrol/EtO_2 (98:2) affording 2-acetylhex-5-enoic acid ethyl ester **463** (1.50 g, 8.15 mmol, 56 %) as colourless oil and 3-but-3-enyloxybut-2-enoic acid ethyl ester **464** (0.40 g, 2.17 mmol, 15 %) as colourless oil.

463 V_{max} (film)/cm^{-1} 3078w, 2980m, 1741s, 1716s, 1641s, 1448w, 1359m, 1244m, 1181m, 1150m, 1026w, 915w.

δH (400 MHz; $CDCl_3$) 1.28 (3H, t, J 7 Hz, C<u>H</u>$_3$), 1.96-2.01 (2H, m, C<u>H</u>$_2$), 2.03-2.08 (2H, m, C<u>H</u>$_2$), 2.23 (3H, s, C<u>H</u>$_3$), 3.45 (1H, t, J 7.2 Hz, C<u>H</u>), 4.20 (2H, q, J 7 Hz, C<u>H</u>$_2$), 5.00-5.06 (2H, m, C<u>H</u>$_2$), 5.71-5.80 (1H, m, C<u>H</u>).

δC (100 MHz; $CDCl_3$) 14.09 (<u>C</u>H$_3$), 27.12 (<u>C</u>H$_2$), 28.98 (<u>C</u>H$_3$), 31.35 (<u>C</u>H$_2$), 58.88 (<u>C</u>H), 61.35 (<u>C</u>H$_2$), 115.97 (<u>C</u>H$_2$), 137.01 (<u>C</u>H), 169.73 (<u>C</u>O$_2$Et), 203.08 (<u>C</u>OCH$_3$).

m/z (ESI) Calculated for $C_{10}H_{16}O_3(Na^+)$ requires 207.0992; found 207.0992 and $C_{10}H_{16}O_3(H^+)$ requires 185.1172 found 185.1173.

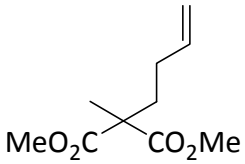
464 V_{max} (film)/cm^{-1} 3080w, 2981m, 2934m, 1712s, 1625s, 1432w, 1402w, 1381w, 1344w, 1276m, 1140s, 1055s, 993w, 817w.

δH (400 MHz; $CDCl_3$) 1.27 (3H, t, J 6.8 Hz, CH_3), 2.29 (3H, s, CH_3), 2.46 (2H, q, J 6.8 Hz, CH_2), 3.81 (2H, t, J 6.8 Hz, CH_2), 4.13 (2H, q, J 6.8 Hz, CH_2), 5.01 (1H, s, CH), 5.07-5.16 (2H, m, CH_2), 5.76-5.87 (1H, m, CH).

δC (100 MHz; $CDCl_3$) 14.44 (CH_3), 19.04 (CH_3), 32.96 (CH_2), 59.30 (CH_2), 67.27 (CH_2), 91.31 (CH), 117.26 (CH_2), 133.92 (CH), 167.99 (C-O), 172.29 (CO_2Et).

m/z (ESI) Calculated for $C_{10}H_{16}O_3(Na^+)$ requires 207.0992; found 207.0993 and $C_{10}H_{16}O_3(H^+)$ requires 185.1172 found 185.1173.

2-But-3-enyl-2-methylmalonic acid dimethyl ester 477.[87]



477

To a suspension of cesium carbonate (1.90 g, 5.80 mmol) in DMF (20 mL) was added a solution of 2-but-3-enylmalonic acid dimethyl ester **432** (0.90 g, 4.80 mmol) in DMF (5 mL) at RT and mixture was stirred for fifteen minutes. Methyl iodide (2.70 g, 19.33 mmol) was added to the reaction mixture. After 24 hours the reaction mixture was quenched with saturated ammonium chloride (20 mL) and aqueous layer extracted with ethylacetate (3×50 mL). The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography on silica gel eluting with light petrol/EtOAc (98:2) affording 2-but-3-enyl-2-methylmalonic acid dimethyl ester **477** (0.80 g, 4.00 mmol, 83 %) as a colourless oil.

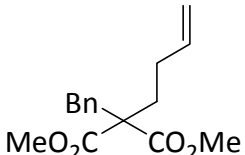
V_{max} (film)/cm^{-1} 3078w, 2978m, 2954s, 2846w, 1737s, 1318s, 1345s, 1318s, 1240s, 1204s, 1156s, 1116s, 998s, 917m, 876w.

δH (400 MHz; $CDCl_3$) 1.44 (3H, s, C$\underline{H}_3$), 1.95-2.02 (4H, m, C$\underline{H}_2$), 3.72 (6H, s, OC$\underline{H}_3$), 4.97 (1H, d, J 10.4Hz, C$\underline{H}_2$), 5.05 (1H, d, J 10.4 Hz, C$\underline{H}_2$), 5.73-5.82 (1H, m, C$\underline{H}$).

δC (100 MHz; $CDCl_3$) 20.00 (C$\underline{H}_3$), 28.64 (C$\underline{H}_2$), 34.85 (C$\underline{H}_2$), 52.46 (OC$\underline{H}_3$), 53.44 (C$\underline{C}$), 115.04 (C$\underline{H}_2$), 137.54 (C$\underline{H}$), 172.67 (C$\underline{O}_2CH_3$).

m/z (ESI) Calculated for $C_{10}H_{16}O_4(Na^+)$ requires 223.0941; found 223.0938 and $C_{10}H_{16}O_4(H^+)$ requires 201.1121 found 201.1119.

2-Benzyl-2-but-3-enylmalonic acid dimethyl ester 478.



478

2-But-3-enylmalonic acid dimethyl ester **432** (1.40 g, 7.52 mmol) was added drop wise to a suspension of sodium hydride (0.40 g, 9.02 mmol, 60 % in mineral oil) in DMF (70 mL), at 0 °C, under a nitrogen atmosphere. The mixture was allowed to warm up to room temperature and benzyl bromide (1.40 g, 8.30 mmol) was introduced. The reaction mixture was allowed to stir for fourteen hours at room temperature and then quenched with a saturated solution of ammonium chloride (50 mL). The organic layer was separated and the aqueous layer extracted with ethyl acetate (3×40 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in *vacuo*. The crude product was purified by flash chromatography on silica gel eluting with light petrol/EtOAc (99:1) affording 2-benzyl-2-but-3-enylmalonic acid dimethyl ester **478** (1.5 g, 5.43 mmol, 71 %) as colourless oil.

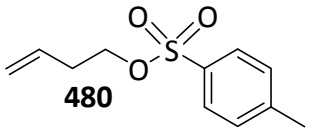
V_{max} (film)/cm^{-1} 3065w, 3030w, 2952m, 1735s, 1641w, 1604w, 1496w, 1453m, 1433m, 1269s, 1236s, 1206s, 1178s, 1085w, 996w, 702m.

δH (400 MHz; $CDCl_3$) 1.86-1.90 (2H, m, C$\underline{H}_2$), 2.02-2.09 (2H, m, C$\underline{H}_2$), 3.26 (2H, s, C$\underline{H}_2$), 3.71 (6H, s, OC$\underline{H}_3$), 4.97 (1H, dq, J 1.2 Hz, C$\underline{H}_2$), 5.04 (1H, dq, J 1.6 Hz, C$\underline{H}_2$), 5.71-5.80 (1H, m, C$\underline{H}$), 7.05 (2H, dd, J 1.4 Hz, 4.4 Hz, ArC$\underline{H}$), 7.20-7.28 (3H, m, ArC$\underline{H}$).

δC (100 MHz; $CDCl_3$) 28.57 (C$\underline{H}_2$), 31.15 (C$\underline{H}_2$), 38.45 (C$\underline{H}_2$), 52.35 (OC$\underline{H}_3$), 58.66 (C$\underline{C}$), 115.16 (C$\underline{H}_2$), 127.05 (Ar$\underline{C}$H), 128.35 (Ar$\underline{C}$H), 129.81 (Ar$\underline{C}$H), 135.92(Ar$\underline{C}$), 137.26 (C$\underline{H}$), 171.56 (C$\underline{O}_2CH_3$).

m/z (ESI) Calculated for $C_{16}H_{20}O_4(Na^+)$ requires 299.1254; found 299.1250.

Toluene-4-sulfonic acid but-3-enyl ester 480.



480

Triethyl amine (4.20 g, 41.55 mmol) was added to the solution of 3-buten-1-ol (2.00 g, 27.70 mmol) in DCM (120 mL). The mixture was allowed to stir for fifteen minutes and *p*-toluenesulfonyl chloride (5.30 g, 27.70 mmol) was added to the reaction mixture. The reaction mixture was allowed to stir for twelve hours at room temperature and then quenched with water (60 mL). The organic layer was separated and aqueous layer extracted with (3×30 mL) DCM. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with light petrol/EtOAc (99:1) to afford toluene-4-sulfonic acid but-3-enyl ester **480** (5.30 g, 23.44 mmol, 84 %) as a colourless oil.

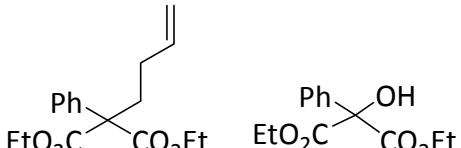
V_{max} (film)/cm^{-1} 3080w, 2983m, 2925w, 1643w, 1598m, 1495w, 1431w, 1359s, 1307w, 1198s, 1211s, 1097w, 920m.

δH (400 MHz; $CDCl_3$) 2.40 (2H, q, J 6.8 Hz, C$\underline{H}_2$), 2.45 (3H, s, C$\underline{H}_3$), 4.06 (2H, t, J 6.8 Hz, C$\underline{H}_2$), 5.05-5.09 (2H, m, C$\underline{H}_2$), 5.62-5.73 (1H, m, C$\underline{H}$), 7.34 (2H, d, J 8.4 Hz, ArC$\underline{H}$), 7.78 (2H, d, J 8.4 Hz ArC$\underline{H}$).

δC (100 MHz; $CDCl_3$) 21.64 (C$\underline{H}_3$), 33.14 (C$\underline{H}_2$), 69.44 (C$\underline{H}_2$), 118.22 (C$\underline{H}_2$), 127.91 (ArC$\underline{H}$), 129.84 (ArC$\underline{H}$), 132.42 (C$\underline{H}$), 133.09 (ArC), 144.79 (ArC).

m/z (ESI) Calculated for $C_{11}H_{14}O_3S(Na^+)$ requires 249.0556; found 249.0559.

2-But-3-enyl-2-phenylmalonic acid diethyl ester 481 and 2-hydroxy-2-phenylmalonic acid diethyl ester 482.[87]



481 **482**

To a stirred suspension of cesium carbonate (1.92 g, 6.00 mmol) in DMF (50 mL) at RT was added diethyl phenyl malonate (1.00 g, 4.20 mmol) and 4-bromo-1-butene (2.30 g, 16.90 mmol). After 24 hours the reaction mixture was quenched with saturated ammonium chloride and aqueous layer extracted with ethylacetate (3×50 mL). The organic layer was

washed with brine, dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography on silica gel eluting with light petrol/EtOAc (249:1) affording 2-but-3-enyl-2-phenylmalonic acid diethyl ester **481** (0.70 g, 2.41 mmol, 58 %) as a colourless oil and 2-hydroxy-2-phenylmalonic acid diethyl ester **482** (0.40 g, 1.59 mmol 40 %) as colourless oil.

481 V_{max} (film)/cm^{-1} 2980w, 2950w, 1732s, 1615w, 1447w, 1366w, 1230s, 1027m, 913w, 696w.

δH (400 MHz; $CDCl_3$) 1.24 (6H, t, J 7.2 Hz, CH_3), 1.95-2.02 (2H, m, CH_2), 2.36-2.41 (2H, m, CH_2), 4.18-4.27 (4H, m, C$\underline{H}_2$), 4.96 (1H, dq, J 1.2 Hz, C$\underline{H}_2$), 5.02 (1H, dq, J 1.6 Hz, C$\underline{H}_2$), 5.74-5.85 (1H, m, C$\underline{H}$), 7.26-7.36 (3H, m, ArC$\underline{H}$), 7.41-7.43 (2H, m, ArC$\underline{H}$).

δC (100 MHz; $CDCl_3$) 13.99 (C$\underline{H}_3$), 28.99 (C$\underline{H}_2$), 34.92 (C$\underline{H}_2$), 61.53 (C$\underline{H}_2$), 62.34 ($\underline{C}$), 114.93 ($\underline{C}H_2$), 127.49 (Ar$\underline{C}$H), 128.04 (Ar$\underline{C}$H), 128.14 (Ar$\underline{C}$H), 136.88 (Ar$\underline{C}$), 137.67 ($\underline{C}$H), 170.63 ($\underline{C}O_2CH_2CH_3$).

m/z (ESI) Calculated for $C_{17}H_{22}O_4(Na^+)$ requires 313.1410; found 313.1405 and $C_{17}H_{22}O_4(H^+)$ requires 291.1591 found 291.1587.

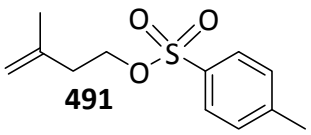
482 V_{max} (film)/cm^{-1} 3475br, 2983w, 2938w, 1736s, 1466w, 1449w, 1391w, 1368w, 1263s, 1191m, 1178m, 1123w, 1072w, 860w.

δH (400 MHz; $CDCl_3$) 1.29 (6H, t, J 7 Hz, C$\underline{H}_3$), 4.23-4.37 (4H, m, C$\underline{H}_2$), 7.34-7.40 (3H, m, ArC$\underline{H}$), 7.64-7.66 (2H, m, ArC$\underline{H}$).

δC (100 MHz; $CDCl_3$) 13.95 ($\underline{C}H_3$), 63.01 ($\underline{C}H_2$), 79.98 ($\underline{C}$) 126.64 (Ar$\underline{C}$H), 127.98 (Ar$\underline{C}$H), 128.61 (Ar$\underline{C}$H), 135.92 (Ar$\underline{C}$), 169.91 ($\underline{C}O_2CH_2CH_3$).

m/z (ESI) Calculated for $C_{13}H_{16}O_5(Na^+)$ requires 275.0890; found 275.0886 and $C_{13}H_{16}O_5(H^+)$ requires 253.1071 found 253.1068.

Toluene-4-sulfonic acid 3-methyl-but-3-enyl ester 491



491

Triethylamine (2.29 g, 22.64 mmol) was added to the solution of 3-methyl-3-buten-1-ol (1.30 g, 15.09 mmol) in DCM (50 mL), at RT. The reaction mixture was allowed to stir for ten minutes and then *p*-toluenesulfonyl chloride (4.03 g, 21.13 mmol) was added. The reaction mixture was allowed to stir for eighteen hours and then quenched with water (60 mL). The organic layer was separated and aqueous layer extracted with DCM (3×30 mL). The

combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with light petrol/EtOAc (99:1) to afford toluene-4-sulfonic acid 3-methyl-but-3-enyl ester **491** (2.60 g, 10.82 mmol, 72 %) as colourless oil.

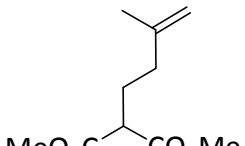
V_{max} (film)/cm^{-1} 3078m, 2971s, 1652m, 1598s, 1495m, 1448m, 1359s, 1307w, 1291w, 1175s, 1097s, 1020s, 964s, 904s, 816s, 778s.

δH (400 MHz; $CDCl_3$) 1.66 (3H, s, C$\underline{H}_3$), 2.35 (2H, t, J 6.8 Hz, C$\underline{H}_2$), 2.45 (3H, s, C$\underline{H}_3$), 4.12 (2H, t, J 6.8 Hz, C$\underline{H}_2$), 4.68 (1H, s, C$\underline{H}_2$), 4.79 (1H, s, C$\underline{H}_2$), 7.34 (2H, d, J 8 Hz, ArC$\underline{H}$), 7.79 (2H, d, J 8, ArC$\underline{H}$).

δC (100 MHz; $CDCl_3$) 21.65 (C$\underline{H}_3$), 22.34 (C$\underline{H}_3$), 36.76 (C$\underline{H}_2$), 68.76 (C$\underline{H}_2$), 113.11 (C$\underline{H}_2$), 127.92 (Ar$\underline{C}$H), 129.82 (Ar$\underline{C}$H), 133.18 ($\underline{C}$), 140.14 (Ar$\underline{C}$), 144.74 (Ar$\underline{C}$).

m/z (ESI) Calculated for $C_{12}H_{16}O_3S(Na^+)$ requires 263.0712; found 263.0714.

2-(3-Methylbut-3-enyl)malonic acid dimethyl ester 492.[87]



492

To a suspension of NaH (0.43 g, 10.82 mmol, 60 % in mineral oil) in THF (70 mL), at 0 °C, under nitrogen, dimethylmalonate (1.65 g, 12.48 mmol) was added. The reaction mixture was stirred for fifteen minutes and then a solution of 3-methyl-3-butenyl tosylate **491** (2.00 g, 8.32 mmol) in THF (4 mL) was added. The solution was allowed to warm to RT and refluxed for twenty hours. The reaction mixture was quenched with saturated ammonium chloride and extracted with EtOAc (3×40 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography on silica gel eluting with light petrol/EtOAc (99:1) affording 2-(3-methylbut-3-enyl)-malonic acid dimethyl ester **492** (1.55 g, 7.75 mmol, 93 %) as a colourless oil.

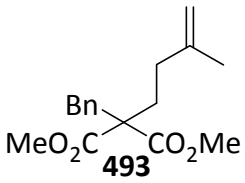
V_{max} (film)/cm^{-1} 3076w, 2995s, 1736s, 1650m, 1436s, 1376w, 1325s, 1346s, 1200br, 1152s, 1059m, 1014m, 968s.

δH (400 MHz; $CDCl_3$) 1.72 (3H, s, C$\underline{H}_3$), 2.05-2.07 (4H, m, C$\underline{H}_2$), 3.38 (1H, t, J 6.8 Hz C$\underline{H}$), 3.74 (6H, s, OC$\underline{H}_3$), 4.69 (1H, s, C$\underline{H}_2$), 4.76 (1H, s, C$\underline{H}_2$).

δC (100 MHz; $CDCl_3$) 22.14 (C$\underline{H}_3$), 26.66 (C$\underline{H}_2$), 35.19 (C$\underline{H}_2$), 50.96 (C$\underline{H}$), 52.44 (OC$\underline{H}_3$), 111.21 (C$\underline{H}_2$), 143.92 ($\underline{C}$), 169.82 ($\underline{C}O_2CH_3$).

m/z (ESI) Calculated for $C_{10}H_{16}O_4(Na^+)$ requires 223.0941; found 223.0943 and $C_{10}H_{17}O_4(H^+)$ requires 201.1121 found 201.1124.

2-Benzyl-2-(3-methylbut-3-enyl)malonic acid dimethyl ester 493.



493

2-(3-Methylbut-3-enyl)malonic acid dimethyl ester **492** (1.50g, 7.50mmol) was added drop wise to a suspension of sodium hydride (0.36 g, 8.99 mmol, 60 % in mineral oil), in DMF (75 mL), at 0 °C, under nitrogen atmosphere. The mixture was allowed to warm up to room temperature and benzyl bromide (1.41 g, 8.25 mmol) was introduced. The reaction mixture was allowed to stir for ten hours at room temperature and then quenched with saturated solution of ammonium chloride (50 mL). The organic layer was separated and the aqueous layer extracted with ethyl acetate (3×40 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in *vacuo*. The crude product was purified by flash chromatography on silica gel eluting with light petrol/EtOAc (99:1) affording 2-benzyl-2-(3-methylbut-3-enyl)malonic acid dimethyl ester **493** (2.15 g, 7.41 mmol, 98 %) as white crystalline solid m.p. 58-59.6 °C.

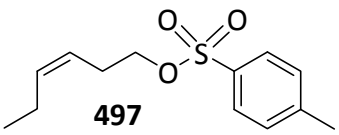
V_{max} (film)/cm^{-1} 3068w, 2967m, 2951m, 1735s, 1603w, 1496m, 1453s, 1434s, 1363w, 1331w, 1230s, 1190s, 1081m, 1030w, 966w.

δH (400 MHz; $CDCl_3$) 1.71 (3H, s, C$\underline{H}_3$), 1.92-1.97 (2H, m, C$\underline{H}_2$), 1.92-1.97 (2H, m, C$\underline{H}_2$), 3.27 (2H, s, C$\underline{H}_2$), 3.72 (6H, s, OC$\underline{H}_3$), 4.70 (2H, d, J 10 Hz, C$\underline{H}_2$), 7.05-7.08 (2H, m, ArC$\underline{H}$), 7.20-7.27 (3H, m, ArC$\underline{H}$).

δC (100 MHz; $CDCl_3$) 22.51 (C$\underline{H}_3$), 30.19 (C$\underline{H}_2$), 32.33 (C$\underline{H}_2$), 38.32 (C$\underline{H}_2$), 52.33 (OC$\underline{H}_3$), 58.76 ($\underline{C}$), 110.47 (C$\underline{H}_2$), 127.04 (ArC$\underline{H}$), 128.33 (ArC$\underline{H}$), 129.82 (ArC$\underline{H}$), 135.95 (Ar$\underline{C}$), 144.60 ($\underline{C}$), 171.61 ($\underline{C}O_2CH_3$).

m/z (ESI) Calculated for $C_{17}H_{22}O_4(Na^+)$ requires 313.1410; found 313.1407.

Toluene-4-sulfonic acid-(*Z*)-hex-3-enyl ester 497.



497

Triethylamine (1.82 g, 17.97 mmol) was added to the solution of *cis*-3-hexen-1-ol (1.2 g, 11.98 mmol) in DCM (60 mL), at -10 °C. The reaction mixture was allowed to stir for ten minutes and then *p*-toluenesulfonyl chloride (2.70 g, 14.40 mmol) was added. The reaction mixture was allowed to stir for eighteen hours at -10 °C and then quenched with water (60 mL). The organic layer was separated and aqueous layer extracted with (3×30 mL) DCM. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with light petrol/EtOAc (199:1) to give toluene-4-sulfonic acid-(*Z*)-hex-3-enyl ester **497** (2.90 g, 11.41 mmol, 97 %).

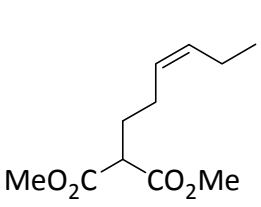
V_{max} (film)/cm^{-1} 3066w, 3012m, 2964s, 2933s, 2874s, 1598s, 1495s, 1400s, 1307s, 1188s, 1177s, 1097s, 1019s, 965s, 918s, 815s, 773s.

δH (400 MHz; $CDCl_3$) 0.93 (3H, t, J 7.4 Hz, C$\underline{H}_3$), 1.94-2.02 (2H, m, C$\underline{H}_2$), 2.40 (2H, q, J 7.2 Hz, C$\underline{H}_2$), 2.45 (3H, s, C$\underline{H}_3$), 4.00 (2H, t, J 7 Hz, C$\underline{H}_2$), 5.16-5.22 (1H, m, C$\underline{H}$), 5.45-5.51 (1H, m, C$\underline{H}$), 7.34 (2H, d, J 8 Hz, ArC$\underline{H}$), 7.79 (2H, d, J 8 Hz, ArC$\underline{H}$).

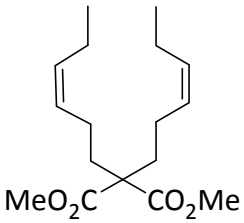
δC (100 MHz; $CDCl_3$) 14.08 (C$\underline{H}_3$), 20.61 (C$\underline{H}_2$), 21.65 (C$\underline{H}_3$), 26.98 (C$\underline{H}_2$), 69.83 (C$\underline{H}_2$), 122.06 (C$\underline{H}$), 127.91 (ArC$\underline{H}$), 129.81 (ArC$\underline{H}$), 133.19 (ArC$\underline{C}$), 135.54 (C$\underline{H}$), 144.71 (ArC$\underline{C}$).

m/z (ESI) Calculated for $C_{13}H_{18}O_3S(Na^+)$ requires 277.0869; found 277.0865 and $C_{13}H_{18}O_3S(H^+)$ requires 255.1049; found 255.1048.

(*Z*)-2-Hex-3-enylmalonic acid dimethyl ester 498, (*Z*)-2,2-di-hex-3-enylmalonic acid dimethyl ester 499.



498



499

To a suspension of NaH (0.60 g, 14.20 mmol, 60 % in mineral oil), in THF (75 mL), at 0 °C under nitrogen, dimethylmalonate (1.80 g, 13.38 mmol) was added. The reaction mixture was stirred for fifteen minutes and then a solution of toluene-4-sulfonic acid-(*Z*)-hex-3-enyl ester **497** (2.00 g, 7.87 mmol) in THF (5 mL) was added. The solution was allowed to warm to RT and refluxed for twelve hours. The reaction mixture was quenched with saturated ammonium chloride and extracted with EtOAc (3×40 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The crude product was

purified by flash chromatography on silica gel eluting with light petrol/EtOAc (125:1) affording (*Z*)-2-hex-3-enyl-malonic acid dimethyl ester **498** (1.05 g, 4.90 mmol, 62 %) as a colourless oil and (*Z*)-2,2-di-hex-3-enyl-malonic acid dimethyl ester **499** (0.30 g, 1.01 mmol, 13 %) as colourless oil.

498 V_{max} (film)/cm^{-1} 3006m, 2960s, 2936s, 2849m, 1754s, 1737s, 1436s, 1345s, 1200s, 1155s, 1070s, 1047s, 1011s, 969m.

δH (400 MHz; $CDCl_3$) 0.95 (3H, t, J 7.6 Hz, C$\underline{H}_3$), 1.96-2.04 (4H, m, C$\underline{H}_2$), 2.08 (2H, q, J 7.2 Hz, C$\underline{H}_2$), 3.39 (1H, t, J 7.2 Hz, C$\underline{H}$), 3.74 (6H, s, OC$\underline{H}_3$), 5.24-5.32 (1H, m, C$\underline{H}$), 5.40-5.46 (1H, m, C$\underline{H}$).

δC (100 MHz; $CDCl_3$) 14.20 (C$\underline{H}_3$), 20.48 (C$\underline{H}_2$), 24.75 (C$\underline{H}_2$), 28.77 (C$\underline{H}_2$), 50.94 (C$\underline{H}$), 52.45 (OC$\underline{H}_3$), 126.84 (C$\underline{H}$), 133.49 (C$\underline{H}$), 169.88 (C$\underline{O}_2CH_3$).

m/z (ESI) Calculated for $C_{11}H_{18}O_4(Na^+)$ requires 237.1097; found 237.1092 and $C_{11}H_{18}O_4(H^+)$ requires 215.1278 found 215.1274(-1.6216ppm).

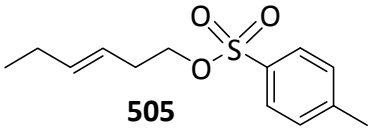
499 V_{max} (film)/cm^{-1} 3006m, 2961s, 2874m, 1735s, 1454m, 1435m, 1243m, 1178m, 1153w, 1070w, 968w.

δH (400 MHz; $CDCl_3$) 0.95 (6H, t, J 7.2 Hz, C$\underline{H}_3$), 1.93-1.99 (8H, m, C$\underline{H}_2$), 2.03 (4H, q, J 7.2 Hz, C$\underline{H}_2$), 3.72 (6H, s, OC$\underline{H}_3$), 5.28-5.32 (2H, m, C$\underline{H}$), 5.37-5.40 (2H, m, C$\underline{H}$).

δC (100 MHz; $CDCl_3$) 14.23 (C$\underline{H}_3$), 20.44 (C$\underline{H}_2$), 22.03 (C$\underline{H}_2$), 32.66 (C$\underline{H}_2$), 52.28 (OC$\underline{H}_3$), 57.36 (C$\underline{}$), 127.54 (C$\underline{H}$), 132.57 (C$\underline{H}$), 172.05 (C$\underline{O}_2CH_3$).

m/z (ESI) Calculated for $C_{17}H_{28}O_4(Na^+)$ requires 319.1880; found 319.1873 and $C_{17}H_{28}O_4(H^+)$ requires 297.2060 found 297.2055.

Toluene-4-sulfonic acid-(*E*)-hex-3-enyl ester 505.



505

Triethylamine (1.52 g, 14.97 mmol) was added to the solution of *trans*-3-hexen-1-ol (1.00 g, 9.98 mmol) in DCM (50 mL), at RT. The reaction mixture was allowed to stir for ten minutes and then *p*-toluenesulfonyl chloride (2.30 g, 11.98 mmol) was added. The reaction mixture was allowed to stir for eighteen hours at RT and then quenched with water (50 mL). The organic layer was separated and aqueous layer extracted with DCM (3×30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with

light petrol/EtOAc (199:1) to afford toluene-4-sulfonic acid-(*E*)-hex-3-enyl ester **505** (2.40 g, 9.44 mmol, 95 %).

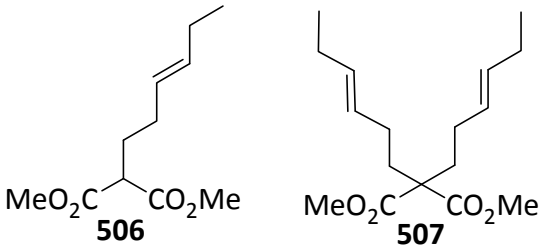
V_{max} (film)/cm^{-1} 3033w, 2963s, 2932m, 2874w, 1598m, 1461w, 1360s, 1198s, 1177s, 1097s, 966s, 919s, 815s.

δH (400 MHz; $CDCl_3$) 0.93 (3H, t, J 7.6 Hz, C$\underline{H}_3$), 1.92-2.00 (2H, m, C$\underline{H}_2$), 2.32 (2H, q, J 6.8 Hz, C$\underline{H}_2$), 2.45 (3H, s, C$\underline{H}_3$), 4.01 (2H, t, J 6.8 Hz, C$\underline{H}_2$), 5.20-5.27 (1H, m, C$\underline{H}$), 5.48-5.55 (1H, m, C$\underline{H}$), 7.34 (2H, d, J 8 Hz, ArC$\underline{H}$), 7.79 (2H, d, J 8 Hz, ArC$\underline{H}$).

δC (100 MHz; $CDCl_3$) 13.50 (C$\underline{H}_3$), 21.62 (C$\underline{H}_3$), 25.52 (C$\underline{H}_2$), 32.07 (C$\underline{H}_2$), 70.16 (C$\underline{H}_2$), 122.51 (C$\underline{H}$), 127.90 (ArC$\underline{H}$), 129.79 (ArC$\underline{H}$), 133.26 (ArC$\underline{}$), 136.07 (4C$\underline{H}$), 144.67 (ArC$\underline{}$).

m/z (ESI) Calculated for $C_{13}H_{18}O_3S(Na^+)$ requires 277.0869; found 277.0863.

(*E*)-2-hex-3-enylmalonic acid dimethyl ester 506, (*E*)-2,2-di-hex-3-enylmalonic acid dimethyl ester 507.



506 **507**

To a suspension of NaH (0.60 g, 14.20 mmol, 60 % in mineral oil) in THF (75 mL), at 0 °C, under a nitrogen atmosphere, dimethylmalonate (1.80 g, 13.38 mmol) was added. The reaction mixture was stirred for fifteen minutes and then a solution of toluene-4-sulfonic acid-(*E*)-hex-3-enyl ester **505** (2.00 g, 7.87 mmol) in THF (5 mL) was added. The solution was allowed to warm to RT and refluxed for twelve hours. The reaction mixture was quenched with saturated ammonium chloride and extracted with EtOAc (3×40 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography on silica gel eluting with light petrol/EtOAc (300:1) affording (*E*)-2-hex-3-enylmalonic acid dimethyl ester **506** (0.90 g, 4.20 mmol, 53 %) as a colourless oil and (*E*)-2,2-di-hex-3-enylmalonic acid dimethyl ester **507** (0.30 g, 1.01 mmol, 13 %) as colourless oil.

506 V_{max} (film)/cm^{-1} 2959s, 2873m, 2848m, 1733s, 1435s, 1443m, 1242s, 1222s, 966m, 814w.

δH (400 MHz; $CDCl_3$) 0.97 (3H, t, J 3.8 Hz, C$\underline{H}_3$), 1.94-2.03 (6H, m, C$\underline{H}_2$), 3.39 (1H, t, J 7.2 Hz, C$\underline{H}$), 3.74 (6H, s, OC$\underline{H}_3$), 5.28-5.38 (1H, m, C$\underline{H}$), 5.45-5.52 (1H, m, C$\underline{H}$).

δC (100 MHz; $CDCl_3$) 13.77 ($\underline{C}H_3$), 25.53 ($\underline{C}H_2$), 28.61 ($\underline{C}H_2$), 30.13 ($\underline{C}H_2$), 50.88 ($\underline{C}H$), 52.44 ($O\underline{C}H_3$), 126.93 ($\underline{C}H$), 133.94 ($\underline{C}H$), 169.92 ($\underline{C}O_2CH_3$).

m/z (ESI) Calculated for $C_{11}H_{18}O_4(Na^+)$ requires 237.1097; found 237.1095.

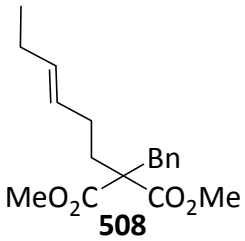
507 V_{max} (film)/cm^{-1} 3021m, 2961s, 2935s, 2874s, 2849s, 1736s, 1455s, 1434s, 1260s, 1195s, 1178s, 1142s, 1092m, 967s, 903w.

δH (400 MHz; $CDCl_3$) 0.96 (6H, t, J 7.4 Hz, $C\underline{H}_3$), 1.80-1.90 (4H, m, $C\underline{H}_2$), 1.93-2.00 (8H, m, $C\underline{H}_2$), 3.71 (6H, s, $OC\underline{H}_3$), 5.30-5.38 (2H, m, $C\underline{H}$), 5.42-5.52 (2H, m, $C\underline{H}$).

δC (100 MHz; $CDCl_3$) 13.73 ($\underline{C}H_3$), 25.52 ($\underline{C}H_2$), 27.21 ($\underline{C}H_2$), 32.43 ($\underline{C}H_2$), 52.28 ($O\underline{C}H_3$), 57.20 ($\underline{C}$), 127.73 ($\underline{C}H$), 132.83 ($\underline{C}H$), 172.12 ($\underline{C}O_2CH_3$).

m/z (ESI) Calculated for $C_{17}H_{28}O_4(Na^+)$ requires 319.1880; found 319.1875 and $C_{17}H_{28}O_4(H^+)$ requires 297.2060 found 297.2057.

2-Benzyl-(*E*)-2-hex-3-enyl-malonic acid dimethyl ester 508.



508

To a solution of (*E*)-2-hex-3-enylmalonic acid dimethyl ester **506** (0.80 g, 3.73 mmol) under nitrogen, in DMF (40 mL), at 0 °C, was added to sodium hydride (0.18 g, 4.48 mmol, 60 % in mineral oil). The mixture was allowed to warm up to room temperature and benzyl bromide (0.77 g, 4.48 mmol) was introduced. The reaction mixture was allowed to stir for ten hours at room temperature and then quenched with saturated solution of ammonium chloride (40 mL). The organic layer was extracted with ethyl acetate (3×30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in *vacuo*. The crude product was purified by flash chromatography on silica gel eluting with light petrol/EtOAc (99:1) affording 2-benzyl-(*E*)-2-hex-3-enylmalonic acid dimethyl ester **508** (0.95 g, 3.12 mmol, 84 %) as colourless oil.

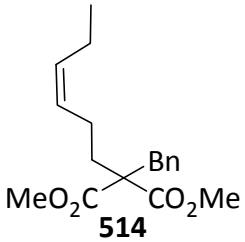
V_{max} (film)/cm^{-1} 3087w, 3063w, 3030s, 2959s, 2873w, 2847w, 1736s, 1604w, 1496m, 1454s, 1434s, 1265s, 1228s, 1197s, 1086s, 967s, 742m.

δH (400 MHz; $CDCl_3$) 0.95 (3H, t, J 7.4 Hz, $C\underline{H}_3$), 1.84-1.87 (2H, m, $C\underline{H}_2$), 1.96-2.00 (4H, m, $C\underline{H}_2$), 3.25 (2H, s, $C\underline{H}_2$), 3.70 (6H, s, $OC\underline{H}_3$), 5.30-5.40 (1H, m, $C\underline{H}$), 5.45-5.53 (1H, m, $C\underline{H}$), 7.05 (2H, d, J 7.6 Hz, $ArC\underline{H}$), 7.21-7.26 (3H, m, $ArC\underline{H}$).

δC (100 MHz; $CDCl_3$) 13.74 ($\underline{C}H_3$), 25.53 ($\underline{C}H_2$), 27.39 ($\underline{C}H_2$), 31.89 ($\underline{C}H_2$), 38.38 ($\underline{C}H_2$), 52.28 ($O\underline{C}H_3$), 58.76 ($\underline{C}$), 126.98 (Ar$\underline{C}$H), 127.51 ($\underline{C}$H), 128.30 (Ar$\underline{C}$H), 129.83 (Ar$\underline{C}$H), 132.92 ($\underline{C}$H), 136.05 (Ar$\underline{C}$), 171.63 ($\underline{C}O_2CH_3$).

m/z (ESI) Calculated for $C_{18}H_{24}O_4(Na^+)$ requires 327.1567; found 327.1562 and $C_{18}H_{24}O_4(H^+)$ requires 305.1747 found 305.1744.

2-Benzyl-(*Z*)-2-hex-3-enyl-malonic acid dimethyl ester 514.



514

(*Z*)-2-Hex-3-enylmalonic acid dimethyl ester **498** (1.10 g, 5.14 mmol) was added drop wise to a suspension of sodium hydride (0.25 g, 6.20 mmol, 60 % in mineral oil) in DMF (60 mL), at 0 °C, under nitrogen atmosphere. The mixture was allowed to warm up to room temperature and benzyl bromide (1.05 g, 6.20 mmol) was introduced. The reaction mixture was allowed to stir for ten hours at room temperature and then quenched with saturated solution of ammonium chloride (50 mL). The organic layer was extracted with ethyl acetate (3×30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in *vacuo*. The crude product was purified by flash chromatography on silica gel eluting with light petrol/EtOAc (99:1) affording 2-benzyl-(*E*)-2-hex-3-enylmalonic acid dimethyl ester **514** (1.55 g, 5.10 mmol, 99 %) as colourless oil.

V_{max} (film)/cm^{-1} 3087w, 3064w, 3030s, 3006s, 2960s, 2874s, 1732s, 1604w, 1496s, 1434s, 1267br, 1198s, 1085s, 1068s, 1029w, 943w.

δH (400 MHz; $CDCl_3$) 0.96 (3H, t, J 7.6 Hz, C$\underline{H}_3$), 1.80-1.84 (2H, m, C$\underline{H}_2$), 1.99-2.05 (4H, m, C$\underline{H}_2$), 3.27 (2H, s, C$\underline{H}_2$), 3.72 (6H, s, OC$\underline{H}_3$), 5.23-5.30 (1H, m, C$\underline{H}$), 5.35-5.41 (1H, m, C$\underline{H}$), 7.06 (2H, d, J 8 Hz, ArC$\underline{H}$), 7.23-7.26 (3H, m, ArC$\underline{H}$).

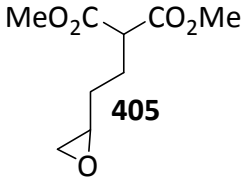
δC (100 MHz; $CDCl_3$) 14.26 ($\underline{C}H_3$), 20.54 ($\underline{C}H_2$), 22.17 ($\underline{C}H_2$), 32.09 ($\underline{C}H_2$), 38.45 ($\underline{C}H_2$), 52.31 ($O\underline{C}H_3$), 58.83 ($\underline{C}$), 127.01 (Ar$\underline{C}$H), 127.41 ($\underline{C}$H), 128.33 (Ar$\underline{C}$H), 129.80 (Ar$\underline{C}$H), 132.55 ($\underline{C}$H), 135.99 (Ar$\underline{C}$), 171.63 ($\underline{C}O_2CH_3$).

m/z (ESI) Calculated for $C_{18}H_{24}O_4(Na^+)$ requires 327.1567; found 327.1559 and $C_{18}H_{24}O_4(H^+)$ requires 305.1747 found 305.1742.

General procedure for the epoxidation of malonic olefins.

To a solution of malonic olefins in DCM, at 0 °C, *m*-CPBA was added. The reaction mixture was allowed to stir for eight hours at 0 °C and then quenched with 0.1M NaOH solution (80 mL). The organic layer was separated and aqueous layer extracted with DCM (2×25 mL). The combined organic layers were washed again with 0.1M NaOH (2×50 mL) solution, dried over $MgSO_4$, filtered and concentrated under *vacuo* to afford neat epoxides.

The epoxidation of 2-but-3-enylmalonic acid dimethyl ester 432.



405

2-But-3-enylmalonic acid dimethyl ester **432** (1.50 g, 8.10 mmol), DCM (60 mL), *m*-CPBA (4.20 g, 12.08 mmol, 50 % H_2O by weight).

Pure 2-(2-oxiranylethyl)malonic acid dimethyl ester **405** (1.50 g, 7.42 mmol, 92 %) was obtained as colourless oil.

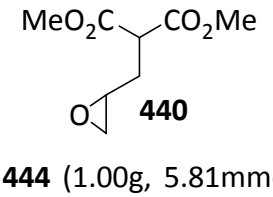
V_{max} (film)/cm^{-1} 2923s, 2853s, 1738s, 1458m, 1375w, 1268w.

δH (400 MHz; $CDCl_3$) 1.53-1.66 (2H, m, C$\underline{H}_2$), 2.05-2.12 (2H, m, C$\underline{H}_2$), 2.49 (1H, dd, J 2.8 Hz, 4.8 Hz, C$\underline{H}_2$), 2.76 (1H, t, J 4.4 Hz, C$\underline{H}_2$), 2.91-2.94 (1H, m, C$\underline{H}$), 3.45 (1H, t, J 7.4 C$\underline{H}$), 3.75 (6H, s, OC$\underline{H}_3$).

δC (100 MHz; $CDCl_3$) 25.28 (C$\underline{H}_2$), 30.08 (C$\underline{H}_2$), 46.80 (C$\underline{H}_2$), 51.11 (C$\underline{H}$), 51.51 (C$\underline{H}$), 52.61 (OC$\underline{H}_3$), 52.62 (OC$\underline{H}_3$), 169.55 (C$\underline{O}_2CH_3$), 169.57 (C$\underline{O}_2CH_3$).

m/z (ESI) Calculated for $C_9H_{14}O_5(Na^+)$ requires 225.0733; found 225.0728 and $C_9H_{14}O_5(H^+)$ requires 203.0914 found 203.0910.

The epoxidation of 2-allylmalonic acid dimethyl ester 444.



440

2-Allylmalonic acid dimethyl ester **444** (1.00g, 5.81mmol), DCM (55 mL), *m*-CPBA (3.00 g, 8.70 mmol, 30 % H_2O by weight).

Pure 2-oxiranylmethylmalonic acid dimethyl ester **440** (1.00 g, 5.31 mmol, 91 %) was obtained as colourless oil.

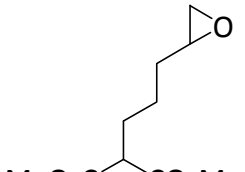
V_{max} (film)/cm^{-1} 3002w, 2956m, 1735s, 1437s, 1345s, 1200s, 1112w, 1060w, 1023s, 918w, 694w.

δH (400 MHz; $CDCl_3$) 1.96-2.03 (1H, m, C<u>H</u>$_2$), 2.27-2.34 (1H, m, C<u>H</u>$_2$), 2.52 (1H, dd, J 2.4 Hz, 4.4 Hz, C<u>H</u>$_2$), 2.78 (1H, t, J 4.4 Hz, C<u>H</u>$_2$), 3.00-3.03 (1H, m, C<u>H</u>), 3.58 (1H, dd, J 6 Hz, 9 Hz, C<u>H</u>), 3.76 (3H, s, OC<u>H</u>$_3$), 3.77 (3H, s, OC<u>H</u>$_3$).

δC (100 MHz; $CDCl_3$) 31.72 (<u>C</u>H$_2$), 47.17 (<u>C</u>H$_2$), 48.60 (<u>C</u>H), 49.71 (<u>C</u>H), 52.70 (O<u>C</u>H$_3$), 52.74 (O<u>C</u>H$_3$), 169.19 (<u>C</u>O$_2$CH$_3$), 169.27 (<u>C</u>O$_2$CH$_3$).

m/z (ESI) Calculated for $C_8H_{12}O_5(Na^+)$ requires 211.0577; found 211.0574 and $C_8H_{12}O_5(H^+)$ requires 189.0757 found 189.0755.

The epoxidation of 2-pent-4-enylmalonic acid dimethyl ester 449.



441

2-Pent-4-enylmalonic acid dimethyl ester **449** (0.60 g, 3.00 mmol), DCM (17 mL), *m*-CPBA (0.80 g, 4.50 mmol, 30 % H_2O by weight).

Pure 2-(3-oxiranylpropyl)malonic acid dimethyl ester **441** (0.60 g, 2.77 mmol, 92 %) was obtained as colourless oil.

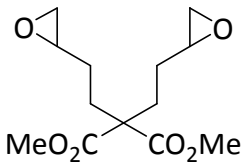
V_{max} (film)/cm^{-1} 2996s, 2955s, 2865s, 1737s, 1482w, 1458s, 1436s, 1413w, 1345s, 1275br, 1052m, 1015m, 831m.

δH (400 MHz; $CDCl_3$) 1.48-1.61 (4H, m, C<u>H</u>$_2$), 1.96 (2H, q, J 7.6 Hz, C<u>H</u>$_2$), 2.74 (1H, dd, J 2.8 Hz, 4.8 Hz, C<u>H</u>$_2$), 2.75 (1H, t, J 4.8 Hz, C<u>H</u>$_2$), 2.89-2.92 (1H, m, C<u>H</u>), 3.39 (1H, t, J 7.6 Hz, C<u>H</u>), 3.75 (6H, s, OC<u>H</u>$_3$).

δC (100 MHz; $CDCl_3$) 32.81 (<u>C</u>H$_2$), 28.51 (<u>C</u>H$_2$), 32.01 (<u>C</u>H$_2$), 46.93 (<u>C</u>H$_2$), 51.50 (<u>C</u>H), 51.80 (<u>C</u>H), 52.49 (O<u>C</u>H$_3$), 169.67 (<u>C</u>O$_2$CH$_3$).

m/z (ESI) Calculated for $C_{10}H_{16}O_5(Na^+)$ requires 239.0890; found 239.0884 and $C_{10}H_{16}O_5(H^+)$ requires 217.1071 found 217.1067.

The epoxidation of 2,2-di-but-3-enylmalonic acid dimethyl ester 433.



454

2,2-Di-but-3-enylmalonic acid dimethyl ester **433** (1.00 g, 4.10 mmol), DCM (50 mL), *m*-CPBA (2.20 g, 9.00 mmol, 30 % H_2O by weight).

2,2-Bis-(2-oxiranylethyl)malonic acid dimethyl ester **454** (1.05 g, 3.86 mmol, 95 %) as colourless oil.

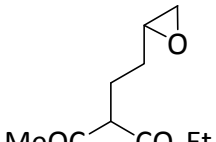
V_{max} (film)/cm^{-1} 3030w, 2997s, 2905m, 2890w, 1732s, 1455m, 1435m, 1266s, 1235s, 1207s.

δH (400 MHz; $CDCl_3$) 1.37-1.55 (4H, m, C$\underline{H}_2$), 2.00-2.08 (4H, m, C$\underline{H}_2$), 2.47 (2H, dd, J 2.6 Hz, 4.4 Hz, C$\underline{H}_2$), 2.75 (2H, t, J 4.4 Hz, C$\underline{H}_2$), 2.86-2.92 (2H, m, C$\underline{H}$), 3.72 (3H, s, OC$\underline{H}_3$), 3.73 (3H, s, OC$\underline{H}_3$).

δC (100 MHz; $CDCl_3$) 27.41 (C$\underline{H}_2$), 27.45 (C$\underline{H}_2$), 29.04 (C$\underline{H}_2$), 29.08 (C$\underline{H}_2$), 46.90 (C$\underline{H}_2$), 46.93 (C$\underline{H}_2$), 51.77 (C$\underline{H}$), 51.80 (C$\underline{H}$), 52.56 (OC$\underline{H}_3$), 56.79 (C$\underline{C}$), 171.58 (C$\underline{O}_2CH_3$).

m/z (ESI) Calculated for $C_{13}H_{20}O_6(Na^+)$ requires 295.1152; found 295.1144.

The epoxidation of 2-acetylhex-5-enoic acid ethyl ester 463.



458

2-Acetylhex-5-enoic acid ethyl ester **463** (1.30 g, 7.10 mmol), DCM (60 mL), *m*-CPBA (2.60 g, 10.60 mmol, 30 % H_2O by weight).

The crude product was purified by flash chromatography on silica gel eluting with light petrol/EtO_2 (9:1) to afford a mixture (1:1) of inseparable diastereoisomers 2-(2-oxiranylethyl)-3-oxobutyric acid ethyl ester **458** (1.20 g, 6.00 mmol, 86 %) as colourless oil.

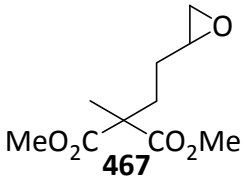
V_{max} (film)/cm^{-1} 2983m, 2936m, 1740s, 1715s, 1621w, 1447w, 1361w, 1246m, 1151m, 1097w, 1069w, 856w, 837w.

δH (400 MHz; $CDCl_3$) 1.28 (6H, t, J 7.2 Hz, C$\underline{H}_3$), 1.42-1.50 (2H, m, C$\underline{H}_2$), 1.62-1.68 (2H, m, C$\underline{H}_2$), 2.02 (4H, q, J 7.6 Hz, C$\underline{H}_2$), 2.25 (3H, s, C$\underline{H}_3$), 2.26 (3H, s, C$\underline{H}_3$), 2.45-2.48 (2H, m, C$\underline{H}_2$), 2.74 (2H, t, J 4.4 Hz, C$\underline{H}_2$), 2.87-2.93 (2H, m, C$\underline{H}$), 3.52 (2H, dt, J 7.2 Hz, 21.6 Hz, C$\underline{H}$), 4.20 (4H, q, J 7.2 Hz, C$\underline{H}_2$).

δC (100 MHz; $CDCl_3$) 14.03 (C$\underline{H}_3$), 24.39 (C$\underline{H}_2$), 24.43 (C$\underline{H}_2$), 28.83 (C$\underline{H}_3$), 29.21 (C$\underline{H}_3$), 29.89 (C$\underline{H}_2$), 30.19 (C$\underline{H}_2$), 46.62 (C$\underline{H}_2$), 46.72 (C$\underline{H}_2$), 51.53 (C$\underline{H}$), 51.61 (C$\underline{H}$), 58.75 (C$\underline{H}$), 59.16 (C$\underline{H}$), 61.40 (C$\underline{H}_2$), 169.43 (C$\underline{O}_2$Et), 202.63 (C$\underline{O}CH_3$), 202.70 (C$\underline{O}CH_3$).

m/z (ESI) Calculated for $C_{10}H_{16}O_4(Na^+)$ requires 223.0941; found 223.0941 and $C_{10}H_{16}O_4(H^+)$ requires 201.1121 found 201.1121.

The epoxidation of 2-but-3-enyl-2-methylmalonic acid dimethyl ester 477.



467

2-But-3-enyl-2-methylmalonic acid dimethyl ester **477** (1.00 g, 5.00 mmol), DCM (40 mL), *m*-CPBA (1.80 g, 7.50 mmol, 30 % H_2O by weight).

Pure 2-methyl-2-(2-oxiranylethyl)malonic acid dimethyl ester **467** (1.05 g, 4.86 mmol, 97 %) was obtained as colourless oil.

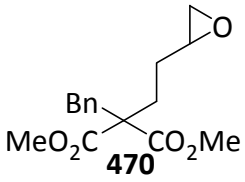
V_{max} (film)/cm^{-1} 2970m, 2954s, 1731s, 1434m, 1380w, 1236br, 1115m, 876w.

δH (400 MHz; $CDCl_3$) 1.42 (3H, s, C$\underline{H}_3$), 1.48-1.54 (2H, m, C$\underline{H}_2$), 1.95-2.06 (2H, m, C$\underline{H}_2$), 2.47 (1H, dd, J 2.8 Hz, 4.8 Hz, C$\underline{H}_2$), 2.75 (1H, t, J 4.8 Hz, C$\underline{H}_2$), 2.89-2.94 (1H, m, C$\underline{H}$), 3.73 (6H, s, OC$\underline{H}_3$).

δC (100 MHz; $CDCl_3$) 20.01 (C$\underline{H}_3$), 27.65 (C$\underline{H}_2$), 31.86 (C$\underline{H}_2$), 46.90 (C$\underline{H}_2$), 51.86 (C$\underline{H}$), 52.52 (OC$\underline{H}_3$), 52.54 (OC$\underline{H}_3$), 53.24 (C$\underline{}$), 172.42 (C$\underline{O}_2CH_3$), 172.46 (C$\underline{O}_2CH_3$).

m/z (ESI) Calculated for $C_{10}H_{16}O_5(Na^+)$ requires 239.0890; found 239.0886.

The epoxidation of 2-benzyl-2-but-3-enylmalonic acid dimethyl ester 478.



470

2-Benzyl-2-but-3-enylmalonic acid dimethyl ester **478** (1.15 g, 4.20 mmol), DCM (54 mL), *m*-CPBA (1.50 g, 6.25 mmol, 30 % H_2O by weight).

Pure 2-benzyl-2-(2-oxiranylethyl)malonic acid dimethyl ester **470** (1.20 g, 4.11 mmol, 98 %) was obtained as colourless oil.

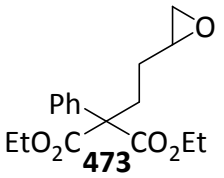
V_{max} (film)/cm^{-1} 3086w, 3061w, 3031w, 2995w, 2952m, 2869w, 1734s, 1496w, 1434s, 1327s, 1269s, 1207s, 1179s, 1157s, 1123s, 1092w, 1031w.

δH (400 MHz; $CDCl_3$) 1.51-1.57 (2H, m, C$\underline{H}_2$), 1.87-2.03 (2H, m, C$\underline{H}_2$), 2.46 (1H, dd, J 2.8 Hz, 4.8 Hz, C$\underline{H}_2$), 2.74 (1H, t, J 4.8 Hz, C$\underline{H}_2$), 2.87-2.90 (1H, m, C$\underline{H}$), 3.24 (2H, s, C$\underline{H}_2$), 3.71 (3H, s, OC$\underline{H}_3$), 3.72 (3H, s, OC$\underline{H}_3$), 7.04-7.07 (2H, m, ArC$\underline{H}$), 7.23-7.29 (3H, m, ArC$\underline{H}$).

δC (100 MHz; $CDCl_3$) 27.68 ($\underline{C}H_2$), 28.35 ($\underline{C}H_2$), 38.62 ($\underline{C}H_2$), 46.96 ($\underline{C}H_2$), 51.83 ($\underline{C}H$), 52.45 ($O\underline{C}H_3$), 52.46 ($O\underline{C}H_3$), 58.52 ($\underline{C}$), 127.15 (Ar$\underline{C}$H), 128.41 (Ar$\underline{C}$H), 129.79 (Ar$\underline{C}$H), 135.67 (Ar$\underline{C}$), 171.35 ($\underline{C}O_2CH_3$), 171.43 ($\underline{C}O_2CH_3$).

m/z (ESI) Calculated for $C_{16}H_{20}O_5(Na^+)$ requires 315.1203; found 315.1197 and $C_{16}H_{20}O_5(H^+)$ requires 293.1384 found 293.1379.

The epoxidation of 2-but-3-enyl-2-phenylmalonic acid diethyl ester 481.



473

2-But-3-enyl-2-phenylmalonic acid diethyl ester **481** (0.60 g, 2.10 mmol), DCM (30 mL), *m*-CPBA (0.80 g, 3.10 mmol, 30 % H_2O by weight).

Pure 2-(2-oxiranyl-ethyl)-2-phenyl-malonic acid diethyl ester **473** (0.63g, 2.06 mmol, 98 %) was obtained as colourless oil.

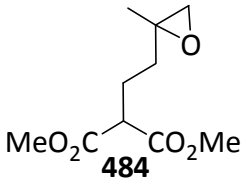
V_{max} (film)/cm^{-1} 3058w, 2982s, 2937m, 1732s, 1499m, 1447s, 1412m, 1389m, 1367w, 1184s, 1122m, 1049m, 943w, 916w, 841m.

δH (400 MHz; $CDCl_3$) 1.24 (6H, t, J 7.2 Hz, $C\underline{H}_3$), 1.43-1.59 (2H, m, $C\underline{H}_2$), 2.37-2.53 (3H, m, $C\underline{H}_2$), 2.72 (1H, t, J 4.4 Hz, $C\underline{H}_2$), 2.88-2.91 (1H, m, C$\underline{H}$), 4.21-4.27 (4H, m, $C\underline{H}_2$), 7.26-7.40 (5H, m, ArC$\underline{H}$).

δC (100 MHz; $CDCl_3$) 13.98 ($\underline{C}H_3$), 27.98 ($\underline{C}H_2$), 32.02 ($\underline{C}H_2$), 46.92 ($\underline{C}H_2$), 51.97 ($\underline{C}H$), 61.65 ($\underline{C}H_2$), 62.19 ($\underline{C}$), 127.58 (Ar$\underline{C}$H), 127.95 (Ar$\underline{C}$H), 128.21 (Ar$\underline{C}$H), 136.66 (Ar$\underline{C}$), 170.47 ($\underline{C}O_2Et$), 170.51 ($\underline{C}O_2CH_2CH_3$).

m/z (ESI) Calculated for $C_{17}H_{22}O_5(Na^+)$ requires 329.1359; found 329.1359 (-0.1010ppm) and $C_{17}H_{22}O_5(H^+)$ requires 307.1540 found 307.1541 (0.3416ppm).

The epoxidation of 2-(3-methylbut-3-enyl)malonic acid dimethyl ester 492.



484

2-(3-Methylbut-3-enyl)malonic acid dimethyl ester **492** (1.50 g, 7.50 mmol), DCM (90 mL), *m*-CPBA (2.80 g, 11.20 mmol, 30 % H_2O by weight).

Pure 2-[2-(2-methyloxiranyl)ethyl]malonic acid dimethyl ester **484** (1.55 g, 7.17 mmol, 96 %) was obtained as colourless oil.

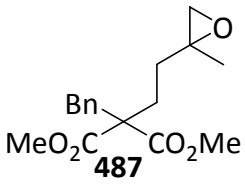
V_{max} (film)/cm^{-1} 2956m, 1735s, 1436s, 1346s, 1227br, 1157s, 1101w, 1042w, 892w, 806w.

δH (400 MHz; $CDCl_3$) 1.33 (3H, s, C$\underline{H}_3$), 1.54-1.63 (2H, m, C$\underline{H}_2$), 2.01 (2H, q, J 7.2 Hz, C$\underline{H}_2$), 2.58 (1H, d, J 4.6 Hz, C$\underline{H}_2$) 2.63 (1H, d, J 4.6 Hz, C$\underline{H}_2$), 3.39 (1H, t, J 7.2 Hz, C$\underline{H}$), 3.74 (3H, s, OC$\underline{H}_3$), 3.75 (3H, s, OC$\underline{H}_3$).

δC (100 MHz; $CDCl_3$) 20.79 (C$\underline{H}_3$), 24.48 (C$\underline{H}_2$), 34.10 (C$\underline{H}_2$), 51.29 (C$\underline{H}$), 52.54 (OC$\underline{H}_3$), 52.56 (OC$\underline{H}_3$), 53.48 (C$\underline{H}_2$), 56.32 (C$\underline{C}$), 169.55 (C$\underline{C}O_2CH_3$), 169.58 (C$\underline{C}O_2CH_3$).

m/z (ESI) Calculated for $C_{10}H_{16}O_5(Na^+)$ requires 239.0890; found 239.0888 and $C_{10}H_{16}O_5(H^+)$ requires 217.1071 found 217.1069.

The epoxidation of 2-benzyl-2-(3-methylbut-3-enyl)malonic acid dimethyl ester 493.



487

2-Benzyl-2-(3-methylbut-3-enyl)malonic acid dimethyl ester **493** (1.50 g, 5.20 mmol), DCM (90 mL), *m*-CPBA (1.90 g, 7.75 mmol, 30 % H_2O by weight).

Pure 2-benzyl-2-[2-(2-methyloxiranyl)ethyl]malonic acid dimethyl ester **487** (1.60 g, 5.23 mmol, 99 %) was obtained as colourless oil.

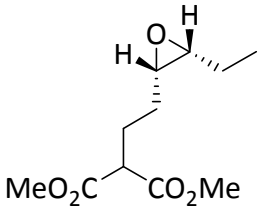
V_{max} (film)/cm^{-1} 3087w, 3061w, 3031s, 2952s, 2886w, 2844w, 1734s, 1604w, 1496s, 1435s, 1392m, 1328m, 1231s, 1198s, 1177s, 1109s, 1024s, 976s, 900m.

δH (400 MHz; $CDCl_3$) 1.29 (3H, s, C$\underline{H}_3$), 1.43-1.50 (1H, m, C$\underline{H}_2$), 1.56-1.60 (1H, m, C$\underline{H}_2$), 1.86-1.90 (2H, m, C$\underline{H}_2$), 2.56 (2H, q, J 5 Hz, C$\underline{H}_2$), 3.23 (2H, s, C$\underline{H}_2$), 3.71 (3H, s, OC$\underline{H}_3$), 3.72 (3H, s, OC$\underline{H}_3$), 7.05-7.07 (2H, m, ArC$\underline{H}$), 7.20-7.30 (3H, m, ArC$\underline{H}$).

δC (100 MHz; $CDCl_3$) 20.83(C$\underline{H}_3$), 27.59 (C$\underline{H}_2$), 31.58 (C$\underline{H}_2$), 38.37 (C$\underline{H}_2$), 52.42 (OC$\underline{H}_3$), 53.61 (C$\underline{H}_2$), 56.54 (C$\underline{C}$), 58.54 (C$\underline{C}$), 127.13 (Ar$\underline{C}$H), 128.38 (Ar$\underline{C}$H), 129.78 (Ar$\underline{C}$H), 135.72 (Ar$\underline{C}$), 171.38 (C$\underline{C}O_2CH_3$), 171.42 (C$\underline{C}O_2CH_3$).

m/z (ESI) Calculated for $C_{17}H_{22}O_5(Na^+)$ requires 329.1359; found 329.1357 and $C_{17}H_{22}O_5(H^+)$ requires 307.1540 found 307.1539.

The epoxidation of (*Z*)-2-Hex-3-enylmalonic acid dimethyl ester 498.



490

(*Z*)-2-hex-3-enyl-malonic acid dimethyl ester **498** (0.80 g, 3.73 mmol), DCM (40 mL), *m*-CPBA (1.40 g, 5.60 mmol, 30 % H_2O by weight).

Pure *syn*-2-[2-(3-ethyloxiranyl)ethyl]malonic acid dimethyl ester **490** (0.80 g, 3.48 mmol, 93 %) was obtained as colourless oil.

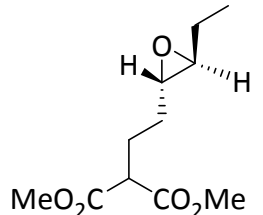
V_{max} (film)/cm^{-1} 2970s, 2878m, 2848w, 1752s, 1736s, 1436s, 1346s, 1288s, 1255s, 1229s, 1157s, 1105w, 1064w, 1013m, 910m, 815m.

δH (400 MHz; $CDCl_3$) 1.04 (3H, t, J 7.4 Hz, C$\underline{H}_3$), 1.49-1.60 (4H, m, C$\underline{H}_2$), 2.07-2.11 (2H, m, C$\underline{H}_2$), 2.87-2.94 (1H, m, C$\underline{H}$), 2.87-2.94 (1H, m, C$\underline{H}$), 3.46 (1H, t, J 7.4 Hz, C$\underline{H}$), 3.75 (6H, s, OC$\underline{H}_3$).

δC (100 MHz; $CDCl_3$) 10.58 (C$\underline{H}_3$), 21.03 (C$\underline{H}_2$), 25.57 (C$\underline{H}_2$), 25.92 (C$\underline{H}_2$), 51.23 (C$\underline{H}$), 52.56 (OC$\underline{H}_3$), 52.60 (OC$\underline{H}_3$), 56.37 (C$\underline{H}$), 58.21 (C$\underline{H}$), 169.56 (C$\underline{O}_2CH_3$), 169.78 (C$\underline{O}_2CH_3$).

m/z (ESI) Calculated for $C_{11}H_{18}O_5(Na^+)$ requires 253.1046; found 253.1042 and $C_{11}H_{18}O_5(H^+)$ requires 231.1227 found 231.1223.

The epoxidation of (*E*)-2-hex-3-enylmalonic acid dimethyl ester 506.



493

(*E*)-2-hex-3-enyl-malonic acid dimethyl ester **506** (0.74 g, 3.45mmol), DCM (40 mL), *m*-CPBA (1.30 g, 5.18 mmol, 30 % H_2O by weight).

Pure *anti*-2-[2-(3-ethyloxiranyl)ethyl]malonic acid dimethyl ester **493** (0.74 g, 3.21 mmol, 94 %) was obtained as colourless oil.

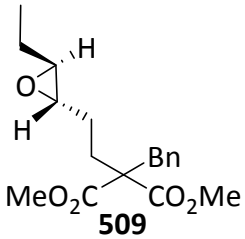
V_{max} (film)/cm^{-1} 2967s, 2877s, 2845s, 1744s, 1437s, 1164br, 1012s, 891s, 806s, 779w, 732w, 708w.

δH (400 MHz; $CDCl_3$) 0.99 (3H, t, J 7.4 Hz, C$\underline{H}_3$), 1.52-1.63 (4H, m, C$\underline{H}_2$), 2.02-2.09 (2H, m, C$\underline{H}_2$), 2.64-2.71 (2H, m, C$\underline{H}$), 3.44 (1H, t, J 7.4 Hz, C$\underline{H}$), 3.74 (3H, s, OC$\underline{H}_3$), 3.75 (3H, s, OC$\underline{H}_3$).

δC (100 MHz; $CDCl_3$) 9.80 ($\underline{C}H_3$), 24.95 ($\underline{C}H_2$), 25.34 ($\underline{C}H_2$), 29.69 ($\underline{C}H_2$), 51.11 ($\underline{C}H$), 52.51 ($O\underline{C}H_3$), 52.52 ($O\underline{C}H_3$), 57.48 ($\underline{C}H$), 59.58 ($\underline{C}H$), 169.53 ($\underline{C}O_2CH_3$), 169.55 ($\underline{C}O_2CH_3$).

m/z (ESI) Calculated for $C_{11}H_{18}O_5(Na^+)$ requires 253.1046; found 253.1042 and $C_{11}H_{18}O_5(H^+)$ requires 231.1227 found 231.1223.

The epoxidation of 2-benzyl-(*E*)-2-hex-3-enyl-malonic acid dimethyl ester 508.



509

2-Benzyl-(*E*)-2-hex-3-enylmalonic acid dimethyl ester **508** (0.57 g, 1.87 mmol), DCM (30 mL), *m*-CPBA (0.70 g, 2.81 mmol, 30 % H_2O by weight).

Pure *anti*-2-benzyl-2-[2-(3-ethyloxiranyl)ethyl]malonic acid dimethyl ester **509** (0.57 g, 1.78 mmol, 97 %) was obtained as colourless oil.

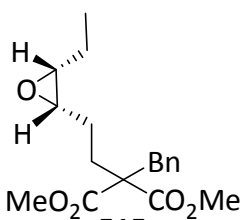
V_{max} (film)/cm^{-1} 3087w, 3063w, 3030w, 2968s, 2876w, 2844w, 1735s, 1604w, 1496w, 1455s, 1434s, 1269s, 1232s, 1203s, 1179s, 1097w, 892w.

δH (400 MHz; $CDCl_3$) 0.97 (3H, t, J 7.6 Hz, $C\underline{H}_3$), 1.49-1.58 (4H, m, $C\underline{H}_2$), 1.85-1.98 (2H, m, $C\underline{H}_2$), 2.62-2.66 (2H, m, $C\underline{H}$), 3.24 (2H, s, $C\underline{H}_2$), 3.71 (3H, s, $OC\underline{H}_3$), 3.72 (3H, s, $OC\underline{H}_3$), 7.06 (2H, d, J 8 Hz, $ArC\underline{H}$), 7.23-7.28 (3H, m, $ArC\underline{H}$).

δC (100 MHz; $CDCl_3$) 9.83 ($\underline{C}H_3$), 24.99 ($\underline{C}H_2$), 27.34 ($\underline{C}H_2$), 28.42 ($\underline{C}H_2$), 38.58 ($\underline{C}H_2$), 52.41 ($O\underline{C}H_3$), 57.83 ($\underline{C}H$), 58.56 ($\underline{C}$), 59.80 ($\underline{C}H$), 127.12 ($Ar\underline{C}H$), 128.38 ($Ar\underline{C}H$), 129.80 ($Ar\underline{C}H$), 135.72 ($Ar\underline{C}$), 171.36 ($\underline{C}O_2CH_3$), 171.42 ($\underline{C}O_2CH_3$).

m/z (ESI) Calculated for $C_{18}H_{24}O_5(Na^+)$ requires 343.1527; found 343.1509 and $C_{18}H_{24}O_5(H^+)$ requires 321.1707 found 321.1691.

The epoxidation of 2-Benzyl-(*Z*)-2-hex-3-enyl-malonic acid dimethyl ester 514.



515

2-Benzyl-(*E*)-2-hex-3-enylmalonic acid dimethyl ester **514** (1.56 g, 5.13 mmol), DCM (90 mL), *m*-CPBA (1.89 g, 7.60 mmol, 30 % H_2O by weight).

Pure *syn*-2-benzyl-2-[2-(3-ethyloxiranyl)ethyl]malonic acid dimethyl ester **515** (1.62 g, 5.12 mmol, 99 %) was obtained as colourless oil.

V_{max} (film)/cm^{-1} 3087m, 3063s, 3030s, 2970s, 2877s, 2844m, 1732s, 1604w, 1454s, 1434s, 1389s, 1309s, 1203br, 1108s, 1031s, 818s.

δH (400 MHz; $CDCl_3$) 1.02 (3H, t, J 7.6 Hz, C$\underline{H}_3$), 1.42-1.59 (4H, m, C$\underline{H}_2$), 1.85-2.02 (2H, m, C$\underline{H}_2$), 2.84-2.88 (2H, m, C$\underline{H}$), 3.26 (2H, s, C$\underline{H}_2$), 3.72 (3H, s, OC$\underline{H}_3$), 3.73 (3H, s, OC$\underline{H}_3$), 7.07 (2H, d, J 8 Hz, ArC$\underline{H}$), 7.21-7.29 (3H, m, ArC$\underline{H}$).

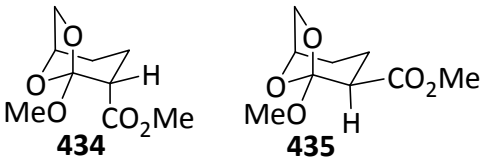
δC (100 MHz; $CDCl_3$) 10.61 (C$\underline{H}_3$), 21.00 (C$\underline{H}_2$), 23.08 (C$\underline{H}_2$), 28.96 (C$\underline{H}_2$), 38.68 (C$\underline{H}_2$), 52.43 (C), 56.68 (OC$\underline{H}_3$), 58.39 (C$\underline{H}$), 58.66 (C$\underline{H}$), 127.13 (ArC$\underline{H}$), 128.41 (ArC$\underline{H}$), 129.78 (ArC$\underline{H}$), 135.69 (ArC), 171.36 ($\underline{C}O_2CH_3$), 171.45 ($\underline{C}O_2CH_3$).

m/z (ESI) Calculated for $C_{18}H_{24}O_5(Na^+)$ requires 343.1516; found 343.1510 and $C_{18}H_{24}O_5(H^+)$ requires 321.1697 found 321.1693.

General procedure for Lewis acid catalysed cyclisation of malonyl epoxides.

To the solution of malonyl epoxide in DCM was added zinc bromide. The reaction mixture was allowed to stir at room temperature for eight hours and then quenched with water. The organic layer was separated and aqueous layer extracted with (3×30 mL) DCM. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure.

Lewis acid catalysed cyclisation of 2-(2-oxiranylethyl)malonic acid dimethyl ester 405.



434 **435**

2-(2-Oxiranylethyl)malonic acid dimethyl ester **405** (0.30 g, 1.50 mmol), DCM (15mL), zinc bromide (0.30 g, 1.50 mmol).

The crude product was purified by flash chromatography on silica gel eluting with light petrol/EtOAc (9:1) affording two diastereoisomers of 5-methoxy-6,8-dioxabicyclo[3.2.1]octane-4-carboxylic acid methyl ester **434** (50 mg, 0.25 mmol, 17 %) as

white crystalline solid, recrystallised from MeOH at 0 °C m.p. 69-71 °C and **435** (0.19 g, 0.94 mmol, 63 %) as white crystalline solid, recrystallised from MeOH at 0 °C m.p. 65.5 °C.

434 V_{max} (film)/cm^{-1} 2953s, 2894m, 2863w, 1735s, 1434m, 1369m, 1329m, 1290s, 1218s, 1138s, 1003, 1025s, 920s.

δH (400 MHz; $CDCl_3$) 1.46 (1H, dd, J 5.8 Hz, 14 Hz, C$\underline{H}_2$), 1.89 (1H,dd, J 6.2 Hz, 14 Hz, C$\underline{H}_2$), 1.99-2.07 (1H, m, C$\underline{H}_2$), 2.32-2.36 (1H, m, C$\underline{H}_2$), 2.92 (1H, d, J 6.2 Hz, C$\underline{H}$), 3.41 (3H, s, OC$\underline{H}_3$), 3.72 (3H, s, OC$\underline{H}_3$), 3.86 (1H, d, J 7 Hz, C$\underline{H}_2$), 4.00 (1H, t, J 7 Hz, C$\underline{H}_2$), 4.72 (1H, s, C$\underline{H}$).

δC (100 MHz; $CDCl_3$) 21.17 ($\underline{C}H_2$), 25.59 ($\underline{C}H_2$), 47.35 ($\underline{C}H$), 49.02 (O$\underline{C}H_3$), 51.92 (O$\underline{C}H_3$), 68.14 ($\underline{C}H_2$), 75.57 ($\underline{C}H$), 118.90 ($\underline{C}$), 171.80 ($\underline{C}O_2CH_3$).

m/z (ESI) Calculated for $C_9H_{14}O_5(Na^+)$ requires 225.0733; found 225.0729.

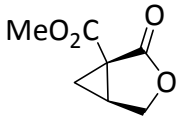
435 V_{max} (DCM)/cm^{-1} 2993m, 2954m, 2922m, 2900s, 2853m, 1741s, 1490s, 1435s, 1362s, 1341m, 1291m, 1227m, 1162s, 994s, 960s.

δH (400 MHz; $CDCl_3$) 1.62 (1H, dd, J 6 Hz, 12.4 Hz, C$\underline{H}_2$), 1.86-1.93 (1H, m, C$\underline{H}_2$), 1.86-1.93 (1H, m, C$\underline{H}_2$), 2.15-2.24 (1H, m, C$\underline{H}_2$), 2.94 (1H, dd, J 4.8 Hz, 12.4 Hz, C$\underline{H}$), 3.40 (3H, s, OC$\underline{H}_3$), 3.71 (3H, s, OC$\underline{H}_3$), 3.96 (1H, d, J 7 Hz, C$\underline{H}_2$), 4.05 (1H, t, J 7 Hz, C$\underline{H}_2$), 4.63 (1H, s, C$\underline{H}$).

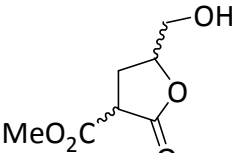
δC (100 MHz; $CDCl_3$) 21.66 ($\underline{C}H_2$), 27.71 ($\underline{C}H_2$), 48.92 ($\underline{C}H$), 49.85 (O$\underline{C}H_3$), 51.93 (O$\underline{C}H_3$), 69.12 ($\underline{C}H_2$), 74.73 ($\underline{C}H$), 119.08 ($\underline{C}$), 171.79 ($\underline{C}O_2CH_3$).

m/z (ESI) Calculated for $C_9H_{14}O_5(Na^+)$ requires 225.0733; found 225.0732.

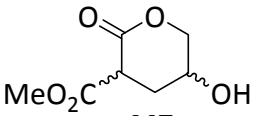
Lewis acid catalysed cyclisation of 2-oxiranylmethylmalonic acid dimethyl ester 440.



445



446



447

2-Oxiranylmethylmalonic acid dimethyl ester **440** (0.60 g, 3.20 mmol), DCM (30mL), zinc bromide (0.72 g, 3.20 mmol).

The crude product was purified by flash chromatography on silica gel eluting with light petrol/EtOAc (7:3) affording 2-oxo-3-oxabicyclo[3.1.0]hexane-1-carboxylic acid methyl ester **445** (0.11 g, 0.70 mmol 22 %) as colourless oil, (±)-5-hydroxymethyl-2-oxotetrahydrofuran-3-carboxylic acid methyl ester **446** (38 mg, 0.23 mmol, 7 %) as colourless oily mixture (1:1.2) of inseparable diastereoisomers and (±)-5-hydroxy-2-oxotetrahydropyran-3-carboxylic acid

methyl ester **447** (0.27 g, 1.55 mmol, 49 %) as colourless oily mixture (1:1.3) of inseparable diastereoisomers.

445 V_{max} (film)/cm^{-1} 3099w, 2958w, 2913w, 1780s, 1728s, 1441s, 1385s, 1318s, 1271s, 1204s, 1174s, 1115s, 1048s, 968s, 926s, 790s.

δH (400 MHz; $CDCl_3$) 1.42 (1H, t, J 4.8 Hz, C$\underline{H}_2$), 2.10 (1H, dd, J 4.8 Hz, 8 Hz, C$\underline{H}_2$), 2.78 (1H, m, C$\underline{H}$), 3.81 (3H, s, OC$\underline{H}_3$), 4.20 (1H, d, J 9.6 Hz, C$\underline{H}_2$), 4.38 (1H, dd, J 4.8 Hz, 9.6 Hz, C$\underline{H}_2$).

δC (100 MHz; $CDCl_3$) 20.95 (C$\underline{H}_2$), 28.11 (C$\underline{H}$), 29.30 (C$\underline{}$), 52.89 (OC$\underline{H}_3$), 67.12 (C$\underline{H}_2$), 167.26 (C$\underline{}$=O), 170.59 (C$\underline{}$=O).

m/z (ESI) Calculated for $C_7H_8O_4(Na^+)$ requires 179.0315; found 179.0312 and $C_7H_8O_4(H^+)$ requires 157.0495 found 157.0494.

446 V_{max} (film)/cm^{-1} 3457br, 2956w, 1782s, 1736s, 1437w, 1347w, 1260w, 1157s, 1016w, 933w.

δH (400 MHz; $CDCl_3$) 2.36-2.44 (1H, m, C$\underline{H}_2$), 2.50-2.58 (1H, m, C$\underline{H}_2$), 2.68-2.75 (1H, m, C$\underline{H}_2$), 2.80-2.87 (1H, m, C$\underline{H}_2$), 3.52-3.65 (4H, m, C$\underline{H}_2$), 3.72 (1H, t, J 10 Hz, C$\underline{H}$), 3.77 (1H, dd, J 6Hz, 10Hz, C$\underline{H}$), 3.82 (3H, s, OC$\underline{H}_3$), 3.83 (3H, s, OC$\underline{H}_3$), 4.67-4.74 (1H, m, C$\underline{H}$), 4.90-1.95 (1H, m, C$\underline{H}$).

δC (100 MHz; $CDCl_3$) 30.20 (C$\underline{H}_2$), 30.57 (C$\underline{H}_2$), 32.45 (C$\underline{H}_2$), 34.11 (C$\underline{H}_2$), 46.54 (C$\underline{H}$), 46.76 (C$\underline{H}$), 53.28 (OC$\underline{H}_3$), 53.32 (OC$\underline{H}_3$), 76.99 (C$\underline{H}$), 77.09 (C$\underline{H}$), 167.80 (C$\underline{}$=O), 167.90 (C$\underline{}$=O), 170.67 (C$\underline{}$=O), 170.91 (C$\underline{}$=O).

m/z (ESI) Calculated for $C_7H_{10}O_5(Na^+)$ requires 197.0420; found 197.0417.

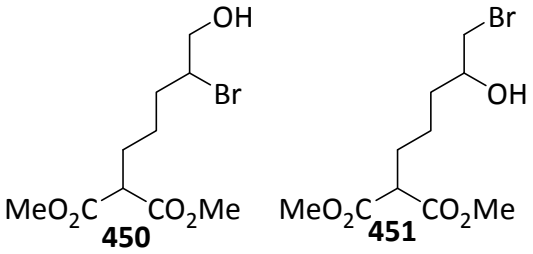
447 V_{max} (film)/cm^{-1} 3491br, 2957w, 1776s, 1737s, 1438m, 1355m, 1282m, 1165m, 1097m, 1044m, 937w, 896s, 776w.

δH (400 MHz; C_6D_6) 1.64-1.71 (1H, m, C$\underline{H}_2$), 1.91-1.98 (1H, m, C$\underline{H}_2$), 2.28-2.36 (2H, m, C$\underline{H}_2$), 3.09 (1H, d, J 12 Hz, C$\underline{H}_2$), 3.21 (1H, t, J 10.2 Hz, C$\underline{H}$), 3.29 (1H, dd, J 4.6 Hz, 12.8 Hz, C$\underline{H}_2$), 3.41 (3H, s, OC$\underline{H}_3$), 3.45 (3H, s, OC$\underline{H}_3$), 3.46-3.52 (2H, m, C$\underline{H}_2$), 3.68 (1H, dd, J 7.2 Hz, 10.8 Hz, C$\underline{H}$), 3.93-3.95 (1H, m, C$\underline{H}$), 4.19-4.22 (1H, m, C$\underline{H}$).

δC (100 MHz; C_6D_6) 27.19 (C$\underline{H}_2$), 27.70 (C$\underline{H}_2$), 46.95 (C$\underline{H}$), 47.07 (C$\underline{H}$), 52.39 (OC$\underline{H}_3$), 52.44 (OC$\underline{H}_3$), 63.41 (C$\underline{H}_2$), 63.66 (C$\underline{H}_2$), 79.40 (C$\underline{H}$), 79.51 (C$\underline{H}$), 168.57 (C$\underline{}$=O), 168.82 (C$\underline{}$=O), 171.69 (C$\underline{}$=O), 172.38 (C$\underline{}$=O).

m/z (ESI) Calculated for $C_7H_{10}O_5(Na^+)$ requires 197.0420; found 197.0418 and $C_7H_{10}O_5(H^+)$ requires 175.0601 found 175.0599.

Lewis acid catalysed ring opening of 2-(3-oxiranylpropyl)malonic acid dimethyl ester 441.



2-(3-Oxiranylpropyl)malonic acid dimethyl ester **441** (0.23 g, 1.10 mmol), DCM (13 mL), zinc bromide (0.24 g, 1.10 mmol).

The crude product was purified by flash chromatography on silica gel eluting with light petrol/EtOAc (9:1) affording 2-(4-bromo-5-hydroxypentyl)malonic acid dimethyl ester **450** (60 mg, 0.20 mmol, 20 %) as colourless oil and 2-(5-bromo-4-hydroxypentyl)malonic acid dimethyl ester **451** (0.14 g, 0.47 mmol, 40 %) as colourless oil.

450 V_{max} (film)/cm^{-1} 3509br, 2954m, 2920w, 1734s, 1436m, 1236br, 1050br.

δH (400 MHz; $CDCl_3$) 1.30-1.64 (2H, m, C$\underline{H}_2$), 1.30-1.64 (1H, m, C$\underline{H}_2$), 1.80-1.96 (1H, m, C$\underline{H}_2$), 1.80-1.96 (2H, m, C$\underline{H}_2$), 2.19 (1H, s, O$\underline{H}$), 3.38 (1H, t, J 7.4 Hz, C$\underline{H}$), 3.72-3.81 (2H, m, C$\underline{H}_2$), 3.75 (6H, s, OC$\underline{H}_3$), 4.06-4.15 (1H, m, C$\underline{H}$).

δC (100 MHz; $CDCl_3$) 25.19 (C$\underline{H}_2$), 28.09 (C$\underline{H}_2$), 34.29 (C$\underline{H}_2$), 51.39 (C$\underline{H}$), 52.57 (OC$\underline{H}_3$), 58.56 (C$\underline{H}$), 67.07 (C$\underline{H}_2$), 169.64 (C$\underline{O}_2CH_3$), 169.66 (C$\underline{O}_2CH_3$).

m/z (ESI) Calculated for $C_{10}H_{17}O_5Br^{79}(Na^+)$ requires 319.0152; found 319.0145.

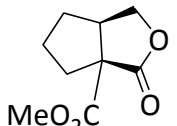
451 V_{max} (film)/cm^{-1} 3508br, 2954s, 2866w, 1733s, 1436s, 1248br, 1157s, 1107w, 1063w, 828w.

δH (400 MHz; $CDCl_3$) 1.35-1.53 (2H, m, C$\underline{H}_2$), 1.53-1.61 (2H, m, C$\underline{H}_2$), 1.91-1.97 (2H, m, C$\underline{H}_2$), 2.36 (1H, d, J 5.2 Hz, O$\underline{H}$), 3.36-3.40 (1H, m, C$\underline{H}_2$), 3.36-3.40 (1H, m, C$\underline{H}$), 3.51 (1H, dd, J 3.6 Hz, 10.4 Hz, C$\underline{H}_2$), 3.74 (6H, s, OC$\underline{H}_3$), 3.76-3.84 (1H, m, C$\underline{H}$).

δC (100 MHz; $CDCl_3$) 23.42 (C$\underline{H}_2$), 28.51 (C$\underline{H}_2$), 34.54 (C$\underline{H}_2$), 40.17 (C$\underline{H}_2$), 51.49 (C$\underline{H}$), 52.55 (OC$\underline{H}_3$), 70.56 (C$\underline{H}$), 169.73 (C$\underline{O}_2CH_3$), 169.75 (C$\underline{O}_2CH_3$).

m/z (ESI) Calculated for $C_{10}H_{17}O_5Br^{79}(Na^+)$ requires 319.0152; found 319.0146.

Lewis acid catalysed cyclisation 2-(3-oxiranylpropyl)malonic acid dimethyl ester 441.



452

To the solution of 2-(3-oxiranylpropyl)malonic acid dimethyl ester **441** (0.10 g, 0.46 mmol) in DCM (5 mL) was added ytterbium triflate (29 mg, 0.05 mmol). The reaction mixture was allowed to stir for eighteen hours at reflux. Then the reaction mixture was filtered through a pad of celite and silica gel. The filtrate was concentrated in *vacuo* to afford 3-oxotetrahydro-cyclopenta[c]furan-3a-carboxylic acid methyl ester **452** (81 mg, 0.44 mmol, 95 %) as colourless oil.

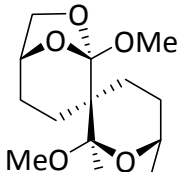
V_{max} (film)/cm^{-1} 2955m, 1773s, 1741s, 1435w, 1380w, 1256s, 1204s, 1147s, 1116s, 1055w, 1012w.

δH (400 MHz; $CDCl_3$) 1.64-1.70 (2H, m, C$\underline{H}_2$), 1.79-1.88 (1H, m, C$\underline{H}_2$), 2.03-2.12 (1H, m, C$\underline{H}_2$), 2.24-2.30 (1H, m, C$\underline{H}_2$), 2.34-2.39 (1H, m, C$\underline{H}_2$), 3.07-3.14 (1H, m, C$\underline{H}$), 3.78 (3H, s, OC$\underline{H}_3$), 4.08 (1H, dd, J 2.4 Hz, 9.2 Hz, C$\underline{H}_2$), 4.56 (1H, dd, J 7.4 Hz, 9.2 Hz, C$\underline{H}_2$).

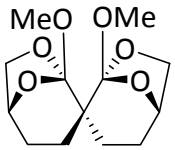
δC (100 MHz; $CDCl_3$) 25.86 (C$\underline{H}_2$), 34.08 (C$\underline{H}_2$), 34.66 (C$\underline{H}_2$), 45.57 (C$\underline{H}$), 53.10 (OC$\underline{H}_3$), 61.54 (C), 72.99 (C$\underline{H}_2$), 170.49 (C=O), 176.41 (C=O).

m/z (ESI) Calculated for $C_9H_{12}O_4(Na^+)$ requires 207.0628; found 207.0633 and $C_9H_{12}O_4(H^+)$ requires 185.0808 found 185.0813.

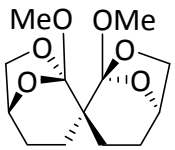
Lewis acid catalysed cyclisation of 2,2-bis-(2-oxiranylethyl)malonic acid dimethyl ester 454.



455



456



457

To solution of 2,2-bis-(2-oxiranylethyl)malonic acid dimethyl ester **454** (0.55 g, 2.02 mmol) in DCM (30 mL) was added zinc bromide (0.23 g, 1.01 mmol). The reaction mixture was allowed to stir at room temperature for three hours and then quenched with water (30 mL). The organic layer was separated and aqueous layer extracted with DCM (2×30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with light petrol/EtOAc (9:1) affording (±)-5,5-dimethoxy-6,6,8,8-tetraoxa4,4-

spirobi[bicyclo[3.2.1]octane] **455** (80 mg, 0.29 mmol, 14 %) as white crystalline solid recrystallised from methanol at 0 °C m.p. 115-117 °C. After the isolation of first fraction **455** from column the polarity of solvent system was raised petrol/EtOAc (8:2) affording **456** (0.19 g, 0.70 mmol, 34 %) as white crystalline solid recrystallised from methanol at 0 °C m.p. 128-130 °C and after the isolation of second fraction **456** from column the polarity of solvent system was raised petrol/EtOAc (7:3) affording **457** (0.11 g, 0.40 mmol, 20 %) as white crystalline solid recrystallised from methanol at 0 °C m.p. 116-118 °C.

455 V_{max} (film)/cm^{-1} 2950m, 2930w, 1233s, 1183s, 1142s, 1045s, 1018m, 976s, 889s.

δH (400 MHz; $CDCl_3$) 1.25-1.34 (4H, m, C$\underline{H}_2$), 1.90 (2H, dd, J 6.4 Hz, 14 Hz, C$\underline{H}_2$), 2.18-2.30 (2H, m, C$\underline{H}_2$), 3.41 (6H, s, OC$\underline{H}_3$), 3.70 (2H, d, J 5.6 Hz, C$\underline{H}_2$), 3.87-3.90 (2H, m, C$\underline{H}_2$), 4.61-4.64 (2H, m, C$\underline{H}$).

δC (100 MHz; $CDCl_3$) 27.36 (C$\underline{H}_2$), 28.92 (C$\underline{H}_2$), 48.58 (OC$\underline{H}_3$), 49.05 (C$\underline{C}$), 67.70 (C$\underline{H}_2$), 75.14 (C$\underline{H}$), 122.14 (C$\underline{C}$).

m/z (ESI) Calculated for $C_{13}H_{20}O_6(Na^+)$ requires 295.1152; found 295.1145.

456 V_{max} (film)/cm^{-1} 2950s, 2887m, 1726m, 1438m, 1329m, 1285m, 1260s, 1236s, 1195m, 1147s, 1129s, 1040s, 995s, 925m.

δH (400 MHz; $CDCl_3$) 1.32-1.54 (4H, m, C$\underline{H}_2$), 1.85-1.94 (1H, m, C$\underline{H}_2$), 2.18-2.30 (2H, m, C$\underline{H}_2$), 2.41 (1H, dd, 6 Hz, 13.6 Hz, C$\underline{H}_2$), 3.41 (6H, s, OC$\underline{H}_3$), 3.74 (1H, d, 6.8 Hz, C$\underline{H}_2$), 3.85 (1H, d, J 6.8 Hz, C$\underline{H}_2$), 3.88-3.91 (1H, m, C$\underline{H}_2$), 3.96-3.99 (1H, m, C$\underline{H}_2$), 4.52 (1H, s, C$\underline{H}$), 4.65 (1H, s, C$\underline{H}$).

δC (100 MHz; $CDCl_3$) 25.60 (C$\underline{H}_2$), 26.99 (C$\underline{H}_2$), 27.03 (C$\underline{H}_2$), 28.11 (C$\underline{H}_2$), 48.59 (OC$\underline{H}_3$), 48.85 (OC$\underline{H}_3$), 50.53 (C$\underline{C}$), 67.57 (C$\underline{H}_2$), 68.81 (C$\underline{H}_2$), 74.76 (C$\underline{H}$), 75.04 (C$\underline{H}$), 121.53 (C$\underline{C}$), 122.26 (C$\underline{C}$).

m/z (ESI) Calculated for $C_{13}H_{20}O_6(Na^+)$ requires 295.1152; found 295.1142 and $C_{13}H_{20}O_6(H^+)$ requires 373.1254 found 373.1324.

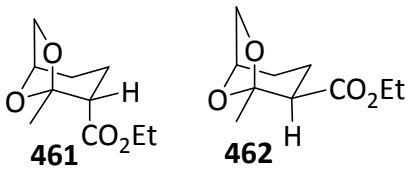
457 V_{max} (film)/cm^{-1} 2951m, 2883w, 1460w, 1436w, 1326w, 1266s, 1237s, 1176s, 1148s, 1130s, 1042s, 1030s, 1013s, 956s, 906m, 938w.

δH (400 MHz; $CDCl_3$) 1.44 (2H, dd, J 6 Hz, 12 Hz, C$\underline{H}_2$), 1.85 (2H, dd, J 6 Hz, 12 Hz, C$\underline{H}_2$), 1.87-1.97 (2H, m, C$\underline{H}_2$), 2.00-2.07 (2H, m, C$\underline{H}_2$), 3.40 (6H, s, OC$\underline{H}_3$), 3.86 (2H, d, J 6.8 Hz, C$\underline{H}_2$), 3.95-3.98 (2H, m, C$\underline{H}_2$), 4.48-4.52 (2H, m, C$\underline{H}$).

δC (100 MHz; $CDCl_3$) 22.55 (C$\underline{H}_2$), 26.11 (C$\underline{H}_2$), 48.78 (OC$\underline{H}_3$), 51.37 (C$\underline{C}$), 96.03 (C$\underline{H}_2$), 74.66 (C$\underline{H}$), 122.06 (C$\underline{C}$).

m/z (ESI) Calculated for $C_{13}H_{20}O_6(Na^+)$ requires 295.1152; found 295.1143 and $C_{13}H_{20}O_6(H^+)$ requires 373.1254 found 373.1324.

Lewis acid catalysed cyclisation of 2-(2-oxiranylethyl)-3-oxobutyric acid ethyl ester 458.



(±)-2-(2-Oxiranylethyl)-3-oxobutyric acid ethyl ester **458** (1.00 g, 4.50 mmol), DCM (55 mL), zinc bromide (1.10 g, 4.50 mmol).

The crude product was purified by flash chromatography on silica gel eluting with light petrol/Et_2O (19:1) affording 5-methyl-6,8-dioxabicyclo[3.2.1]octane-4-carboxylic acid ethyl ester **461** (0.40 g, 2.00 mmol, 40 %) as colourless oil, **462** (0.40 g, 2.00 mmol, 40 %) as colourless oil.

461 V_{max} (film)/cm^{-1} 2978s, 2942s, 2889s, 1734s, 1479w, 1449m, 1372s, 1324s, 1253s, 1243s, 1324s, 1204s, 1154s, 1112s, 1067s, 891s, 876s.

δH (400 MHz; $CDCl_3$) 1.28 (3H, t, J 7.2 Hz, C$\underline{H}_3$), 1.43 (1H, dd, J 6 Hz, 14 Hz, C$\underline{H}_2$), 1.54 (3H, s, C$\underline{H}_3$), 1.85 (1H, dd, J 6 Hz, 14 Hz, C$\underline{H}_2$), 1.98-2.08 (1H, m, C$\underline{H}_2$), 2.25-2.36 (1H, m, C$\underline{H}_2$), 2.65 (1H, d, J 6, C$\underline{H}$), 3.86-3.90 (2H, m, C$\underline{H}_2$), 4.12-4.22 (2H, m, C$\underline{H}_2$), 4.61 (1H, s, C$\underline{H}$).

δC (100 MHz; $CDCl_3$) 14.18 (C$\underline{H}_3$), 20.05 (C$\underline{H}_2$), 23.60 (C$\underline{H}_3$), 25.55 (C$\underline{H}_2$), 48.45 (C$\underline{H}$), 60.41 (C$\underline{H}_2$), 68.48 (C$\underline{H}_2$), 75.58 (C$\underline{H}$), 106.34 (C$\underline{}$), 172.23 (C$\underline{O}_2$Et).

m/z (ESI) Calculated for $C_{10}H_{16}O_4(Na^+)$ requires 223.0941; found 223.0938 and $C_{10}H_{16}O_4(H^+)$ requires 201.1121 found 201.1119.

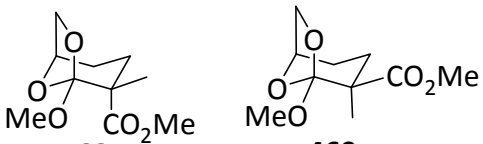
462 V_{max} (film)/cm^{-1} 2979s, 2941s, 2891m, 1736s, 1448w, 1384s, 1337s, 1257s, 1154s, 1036s, 943s, 867w, 829w.

δH (400 MHz; $CDCl_3$) 1.26 (3H, t, J 7.2 Hz, C$\underline{H}_3$), 1.49 (3H, s, C$\underline{H}_3$), 1.59 (1H, dd, J 6 Hz, 13.6 Hz, C$\underline{H}_2$), 1.80-1.87 (1H, m, C$\underline{H}_2$), 1.80-1.87 (1H, m, C$\underline{H}_2$), 2.10-2.20 (1H, m, C$\underline{H}_2$), 2.69 (1H, dd, J 5 Hz, 11.8 Hz, C$\underline{H}$), 3.90-3.94 (1H, m, C$\underline{H}_2$), 3.99 (1H, d, J 6.8 Hz, C$\underline{H}_2$), 4.10-4.20 (2H, m, C$\underline{H}_2$), 4.55 (1H, s, C$\underline{H}$).

δC (100 MHz; $CDCl_3$) 14.21 (C$\underline{H}_3$), 20.52 (C$\underline{H}_2$), 22.91 (C$\underline{H}_3$), 27.80 (C$\underline{H}_2$), 50.95 (C$\underline{H}$), 60.45 (C$\underline{H}_2$), 69.57 (C$\underline{H}_2$), 74.53 (C$\underline{H}$), 106.40 (C$\underline{}$), 172.33 (C$\underline{O}_2$Et).

m/z (ESI) Calculated for $C_{10}H_{16}O_4(Na^+)$ requires 223.0941; found 223.0937 and $C_{10}H_{16}O_4(H^+)$ requires 201.1121 found 201.1118.

Lewis acid catalysed cyclisation of 2-methyl-2-(2-oxiranylethyl)malonic acid dimethyl ester 467.



468 **469**

2-Methyl-2-(2-oxiranylethyl)malonic acid dimethyl ester **467** (1.00 g, 4.63 mmol), DCM (50 mL), zinc bromide (1.00 g, 4.63 mmol).

The crude product was purified by flash chromatography on silica gel eluting with light petrol/EtOAc (97:3) affording 5-methoxy-4-methyl-6,8-dioxabicyclo[3.2.1]octane-4-carboxylic acid methyl ester **468** (0.17 g, 0.79 mmol, 17 %) as colourless oil and **469** (0.63 g, 2.92 mmol, 63 %) as white crystalline solid recrystallised in MeOH at 0 °C. m.p. 42.5 °C.

468 V_{max} (film)/cm^{-1} 2976s, 2950s, 2891m, 2844w, 1728s, 1459m, 1438m, 1375w, 1339w, 1233s, 1282s, 1262s, 1203s, 1168s, 1130s, 1042s, 836w, 648w.

δH (400 MHz; $CDCl_3$) 1.26 (3H, s, C$\underline{H}_3$), 1.45 (1H, dd, J 6 Hz, 13.6 Hz, C$\underline{H}_2$), 1.63 (1H, dt, J 6 Hz, 13.6 Hz, C$\underline{H}_2$), 2.03 (1H, dd, J 6 Hz, 13.6 Hz, C$\underline{H}_2$), 2.23-2.35 (1H, m, C$\underline{H}_2$), 3.38 (3H, s, OC$\underline{H}_3$), 3.71 (3H, s, OC$\underline{H}_3$), 3.80 (1H, d, J 7.2 Hz, C$\underline{H}_2$), 3.99 (1H, t, J 7.2 Hz, C$\underline{H}_2$), 4.66 (1H, s, C$\underline{H}$).

δC (100 MHz; $CDCl_3$) 20.81 (C$\underline{H}_3$), 27.42 (C$\underline{H}_2$), 30.09 (C$\underline{H}_2$), 48.87 (OC$\underline{H}_3$), 50.99 (C$\underline{}$), 52.02 (OC$\underline{H}_3$), 68.54 (C$\underline{H}_2$), 75.45 (C$\underline{H}$), 120.71 (C$\underline{}$), 173.97 (C$\underline{O}_2CH_3$).

m/z (ESI) Calculated for $C_{10}H_{16}O_5(Na^+)$ requires 239.0890; found 239.0888.

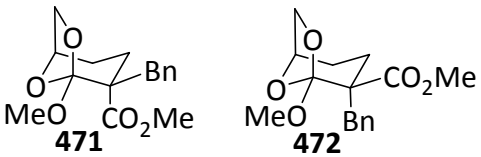
469 V_{max} (film)/cm^{-1} 2984s, 2951s, 2893m, 2843w, 1729s, 1465s, 1438w, 1338w, 1329s, 1262s, 1239s, 1198s, 1182s, 1129s, 1070s.

δH (400 MHz; $CDCl_3$) 1.38 (3H, s, C$\underline{H}_3$), 1.49-1.57 (2H, m, C$\underline{H}_2$), 1.95-2.05 (1H, m, C$\underline{H}_2$), 2.41-2.52 (1H, m, C$\underline{H}_2$), 3.36 (3H, s, OC$\underline{H}_3$), 3.71 (3H, s, OC$\underline{H}_3$), 3.91 (1H, d, J 7.2 Hz, C$\underline{H}_2$), 3.99-4.03 (1H, m, C$\underline{H}_2$), 4.61 (1H, s, C$\underline{H}$).

δC (100 MHz; $CDCl_3$) 17.95 (C$\underline{H}_3$), 25.23 (C$\underline{H}_2$), 28.35 (C$\underline{H}_2$), 48.88 (OC$\underline{H}_3$), 50.96 (C$\underline{}$), 52.09 (OC$\underline{H}_3$), 68.53 (C$\underline{H}_2$), 57.07 (C$\underline{H}$), 120.88 (C$\underline{}$), 174.17 (C$\underline{O}_2CH_3$).

m/z (ESI) Calculated for $C_{10}H_{16}O_5(Na^+)$ requires 239.0890; found 239.0890.

Lewis acid catalysed cyclisation 2-benzyl-2-(2-oxiranylethyl)malonic acid dimethyl ester 470.



2-Benzyl-2-(2-oxiranylethyl)malonic acid dimethyl ester **470** (1.00 g, 3.40 mmol), DCM (50 mL), zinc bromide (0.77 g, 3.40 mmol).

The crude product was purified by flash chromatography on silica gel eluting with light petrol/EtOAc (97:3) affording 4-benzyl-5-methoxy-6,8-dioxa-bicyclo[3.2.1]octane-4-carboxylic acid methyl ester **471** (0.15 g, 0.51 mmol, 15 %) as colourless oil and **472** (0.63 g, 2.16 mmol, 63 %) as white crystalline solid recrystallised from MeOH at 0 °C. m.p. 98.2-99.7 °C.

471 V_{max} (film)/cm^{-1} 3085m, 3061m, 3028s, 2974s, 2949s, 2891s, 2843m, 1728s, 1603m, 1495s, 1439s, 1343s, 1231br, 1201s, 1075s, 690s, 945s,869m.

δH (400 MHz; $CDCl_3$) 1.43 (1H, dd, J 6 Hz, 13.6 Hz, C$\underline{H}_2$), 1.60-1.69 (1H, m, C$\underline{H}_2$), 1.76 (1H, dd, J 6 Hz, 13.6 Hz, C$\underline{H}_2$), 2.15-2.26 (1H, m, C$\underline{H}_2$), 2.69 (1H, d, J 13.6 Hz, C$\underline{H}_2$), 3.44 (3H, s, OC$\underline{H}_3$), 3.55 (1H, d, J 13.6 Hz, C$\underline{H}_2$), 3.72 (3H, s, OC$\underline{H}_3$), 3.85 (1H, d, J 6.8 Hz, C$\underline{H}_2$), 4.03 (1H, t, J 6.8 Hz, C$\underline{H}_2$), 4.64 (1H, s, C$\underline{H}$), 7.08 (2H, d, J 7.2 Hz, ArC$\underline{H}$), 7.17-7.25 (3H, m, ArC$\underline{H}$).

δC (100 MHz; $CDCl_3$) 27.22 (C$\underline{H}_2$), 27.36 (C$\underline{H}_2$), 39.74 (C$\underline{H}_2$), 49.09 (OC$\underline{H}_3$), 51.85 (OC$\underline{H}_3$), 56.47 (C$\underline{C}$), 69.04 (C$\underline{H}_2$), 75.77 (C$\underline{H}$), 120.69 (C$\underline{C}$), 126.46 (ArC$\underline{H}$), 128.09 (ArC$\underline{H}$), 130.01 (ArC$\underline{H}$), 136.84 (ArC$\underline{H}$), 172.53 (C$\underline{C}O_2CH_3$).

m/z (ESI) Calculated for $C_{16}H_{20}O_5(Na^+)$ requires 315.1203; found 315.1206 and $C_{16}H_{20}O_5(H^+)$ requires 293.1384 found 293.1387.

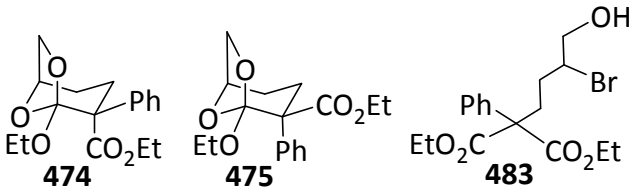
472 V_{max} (film)/cm^{-1} 3085w, 3061w, 3027w, 2950s, 2892m, 2847w, 1727s, 1496w, 1455m, 1437m, 1310w, 1254m, 1195s, 1178s, 994s.

δH (400 MHz; $CDCl_3$) 1.50 (1H, dd, J 5.6 Hz, 14 Hz, C$\underline{H}_2$), 1.59 (1H, dd, J 5.6 Hz, 14 Hz, C$\underline{H}_2$), 2.00-2.11 (1H, m, C$\underline{H}_2$), 2.24-2.38 (1H, m, C$\underline{H}_2$), 3.09 (1H, d, J 14, C$\underline{H}_2$), 3.42 (3H, s, OC$\underline{H}_3$), 3.52 (1H, d, J 14 Hz, C$\underline{H}_2$), 3.71 (3H, s, OC$\underline{H}_3$), 3.91 (1H, d, J 7 Hz, C$\underline{H}_2$), 4.02 (1H, t, J 7 Hz, C$\underline{H}_2$), 4.67 (1H, s, C$\underline{H}$), 7.12 (2H, d, J 7.2 Hz, ArC$\underline{H}$), 7.18-7.26 (3H, m, ArC$\underline{H}$).

δC (100 MHz; $CDCl_3$) 21.07 (C$\underline{H}_2$), 22.32 (C$\underline{H}_2$), 35.79 (C$\underline{H}_2$), 49.18 (OC$\underline{H}_3$), 52.06 (OC$\underline{H}_3$), 56.37 (C$\underline{C}$), 68.72 (C$\underline{H}_2$), 75.15 (C$\underline{H}$), 121.02 (C$\underline{C}$), 126.43 (ArC$\underline{H}$), 128.19 (ArC$\underline{H}$), 130.15 (ArC$\underline{H}$), 138.01 (ArC$\underline{C}$), 172.59 (C$\underline{C}O_2CH_3$).

m/z (ESI) Calculated for $C_{16}H_{20}O_5(Na^+)$ requires 315.1203; found 315.1206 and $C_{16}H_{20}O_5(H^+)$ requires 293.1384 found 293.1387.

Lewis acid catalysed cyclisation of 2-(2-oxiranylethyl)-2-phenylmalonic acid diethyl ester 473.



2-(2-Oxiranylethyl)-2-phenylmalonic acid diethyl ester **473** (0.50 g, 1.60 mmol), DCM (25 mL), zinc bromide (0.40 g, 1.60 mmol).

The crude product was purified by flash chromatography on silica gel eluting with light petrol/EtOAc (97:3) affording 5-ethoxy-4-phenyl-6,8-dioxabicyclo[3.2.1]octane-4-carboxylic acid ethyl ester **474** (44 mg, 0.16 mmol, 9 %) as colourless oil, **475** (0.15 g, 0.49 mmol, 30 %) as white crystalline solid recrystallised from MeOH at 0 °C m.p. 84.5-85.6 °C and 2-(3-bromo-4-hydroxybutyl)-2-phenylmalonic acid diethyl ester **483** (0.10 g, 0.26 mmol, 17 %) as colourless oil.

474 V_{max} (film)/cm^{-1} 2978s, 2896m, 1720s, 1602w, 1499m, 1445m, 1366m, 1262s, 1225s, 1185s, 1154s, 1044s, 1003s, 1056s, 974s, 950m, 770w.

δH (400 MHz; $CDCl_3$) 1.20-1.25 (6H, m, C$\underline{H}_3$), 1.53 (1H, ddt, J 1.4 Hz, 4.8 Hz, 13.2 Hz, C$\underline{H}_2$), 1.95-2.03 (1H, m, C$\underline{H}_2$), 2.27-2.37 (1H, m, C$\underline{H}_2$), 2.45 (1H, ddt, J, 1.4 Hz, 4.8 Hz, 13.2 Hz, C$\underline{H}_2$), 3.75-3.86 (2H, m, C$\underline{H}_2$), 3.89 (1H, d, J 6.8 Hz, C$\underline{H}_2$), 4.05-4.08 (1H, m, C$\underline{H}_2$), 4.13-4.21 (1H, m, C$\underline{H}_2$), 4.24-4.33 (1H, m, C$\underline{H}_2$), 4.69 (1H, t, J 4 Hz, C$\underline{H}$), 7.18-7.22 (1H, m, ArC$\underline{H}$), 7.25-7.30 (2H, m, ArC$\underline{H}$), 7.43-7.45 (2H, m, ArC$\underline{H}$).

δC (100 MHz; $CDCl_3$) 14.06 (C$\underline{H}_3$), 15.58 (C$\underline{H}_3$), 27.83 (C$\underline{H}_2$), 32.34 (C$\underline{H}_2$), 57.62 (C$\underline{H}_2$), 60.70 (C$\underline{H}_2$), 61.08 (C$\underline{H}_2$), 69.17 (C$\underline{H}_2$), 75.56 (C$\underline{H}$), 120.99 (C$\underline{H}$), 126.66 (ArC$\underline{H}$), 127.15 (ArC$\underline{H}$), 128.12 (ArC$\underline{H}$), 140.56 (ArC$\underline{H}$), 172.12 (C$\underline{O}_2CH_2CH_3$).

m/z (ESI) Calculated for $C_{17}H_{22}O_5(Na^+)$ requires 329.1359; found 329.1350 and $C_{17}H_{22}O_5(H^+)$ requires 307.1540 found 307.1532.

475 V_{max} (film)/cm^{-1} 2978m, 1720s, 1606w, 1445w, 1365w, 1251s, 1160m, 1088m, 1028s, 995m, 938w, 753s.

δH (400 MHz; $CDCl_3$) 1.15 (3H, t, J 7.2 Hz, C$\underline{H}_3$), 1.24 (3H, t, J 7.2 Hz, C$\underline{H}_3$), 1.52 (1H, ddt, J 1.6 Hz, 5.6 Hz, 14 Hz, C$\underline{H}_2$), 1.82-1.90 (1H, m, C$\underline{H}_2$), 2.23 (1H, ddt, J 1.6 Hz, 5.6 Hz, 14.4 Hz, C$\underline{H}_2$), 2.71-2.79 (1H, m, C$\underline{H}_2$), 3.79-3.89 (2H, m, C$\underline{H}_2$), 3.94 (1H, d, J 7.2 Hz, C$\underline{H}_2$), 4.00-4.03 (1H, m,

C<u>H</u>$_2$), 4.07-4.20 (2H, m, C<u>H</u>$_2$), 4.61 (1H, t, J 3.6 Hz, C<u>H</u>), 7.19-7.24 (1H, m, ArC<u>H</u>), 7.26-7.31 (2H, m, ArC<u>H</u>), 7.54-7.57 (2H, m, ArC<u>H</u>).

δC (100 MHz; $CDCl_3$) 14.02 (<u>C</u>H$_3$), 15.41 (<u>C</u>H$_3$), 26.25 (<u>C</u>H$_2$), 29.65 (<u>C</u>H$_2$), 57.51 (<u>C</u>H$_2$), 59.49 (<u>C</u>), 60.95 (<u>C</u>H$_2$), 68.41 (<u>C</u>H$_2$), 74.97 (1<u>C</u>H), 120.70 (<u>C</u>), 126.53 (Ar<u>C</u>H), 127.66 (Ar<u>C</u>H), 128.79 (Ar<u>C</u>H), 139.28 (Ar<u>C</u>), 172.55 (<u>C</u>O$_2$CH$_2$CH$_3$).

m/z (ESI) Calculated for $C_{17}H_{22}O_5(Na^+)$ requires 329.1359; found 329.1352 and $C_{17}H_{22}O_5(H^+)$ requires 307.1540 found 307.1533.

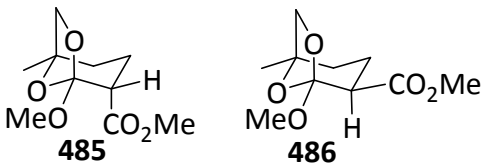
483 V_{max} (film)/cm^{-1} 3523br, 2980m, 1730s, 1604w, 1447m, 1367w, 1236s, 1095m, 1027m, 860w, 697w.

δH (400 MHz; $CDCl_3$) 1.81 (6H, t, J 7.2 Hz, C<u>H</u>$_3$), 1.65-1.81 (2H, m, C<u>H</u>$_2$), 2.23-2.34 (1H, m, C<u>H</u>$_2$), 2.47-2.56 (1H, m, C<u>H</u>$_2$), 3.55-3.80 (2H, m, C<u>H</u>$_2$), 4.00-4.06 (1H, m, C<u>H</u>), 4.12-4.21 (4H, m, C<u>H</u>$_2$), 7.19-7.33 (5H, m, ArC<u>H</u>).

δC (100 MHz; $CDCl_3$) 13.98 (<u>C</u>H$_3$), 29.98 (<u>C</u>H$_2$), 33.55 (<u>C</u>H2), 58.52 (<u>C</u>H), 61.78 (<u>C</u>H$_2$), 62.21 (<u>C</u>), 66.79 (<u>C</u>H$_2$), 127.68 (Ar<u>C</u>H), 127.88 (Ar<u>C</u>H), 128.30 (Ar<u>C</u>H), 136.65 (Ar<u>C</u>), 170.49 (<u>C</u>O$_2$Et), 170.56 (<u>C</u>O$_2$CH$_2$CH$_3$).

m/z (ESI) Calculated for $C_{17}H_{23}O_5Br^{79}(Na^+)$ requires 409.0621; found 409.0615 and $C_{17}H_{23}O_5Br(H^+)$ requires 387.0802 found 387.0795.

Lewis acid catalysed cyclisation of 2-[2-(2-methyloxiranyl)ethyl]malonic acid dimethyl ester 484.



485 **486**

2-[2-(2-Methyloxiranyl)ethyl]malonic acid dimethyl ester **484** (0.30 g, 1.39 mmol), DCM (13 mL), zinc bromide (0.30 g, 1.39 mmol), reaction time 2 hours.

The crude product was purified by flash chromatography on silica gel eluting with light petrol/Et_2O (97:3) affording 5-methoxy-1-methyl-6,8-dioxabicyclo[3.2.1]octane-4-carboxylic acid methyl ester **485** (60 mg, 0.28 mmol, 20 %) as colourless oil, and **486** (0.17 g, 0.79 mmol, 57 %) as colourless oil.

485 V_{max} (film)/cm^{-1} 2951s, 2884s, 2846m, 1736s, 1437s, 1361m, 1323s, 1300, 1242s, 1160s, 1140s, 1100s, 994s, 973s, 894s, 795m.

δH (400 MHz; $CDCl_3$) 1.41 (3H, s, C<u>H</u>$_3$), 1.48-1.53 (1H, m, C<u>H</u>$_2$), 1.91-1.94 (1H, m, C<u>H</u>$_2$), 1.98-2.08 (1H, m, C<u>H</u>$_2$), 2.11-2.20 (1H, m, C<u>H</u>$_2$), 2.88 (1H, d, J 6 Hz, C<u>H</u>), 3.42 (3H, s, OC<u>H</u>$_3$), 3.56 (1H, dd, J 1.8 Hz, 6.8 Hz, C<u>H</u>$_2$), 3.71 (3H, s, OC<u>H</u>$_3$), 3.86 (1H, d, J 6.8 Hz, C<u>H</u>$_2$).

δC (100 MHz; $CDCl_3$) 22.18 (<u>C</u>H$_2$), 22.36 (<u>C</u>H$_3$), 31.45 (<u>C</u>H$_2$), 46.40 (<u>C</u>H), 48.88 (O<u>C</u>H$_3$), 51.87 (O<u>C</u>H$_3$), 73.38 (<u>C</u>H$_2$), 81.37 (<u>C</u>), 119.33 (<u>C</u>), 171.77 (<u>C</u>O$_2$CH$_3$).

m/z (ESI) Calculated for $C_{10}H_{16}O_5(Na^+)$ requires 239.0890; found 239.0888 and $C_{10}H_{16}O_5(H^+)$ requires 217.1071 found 217.1069.

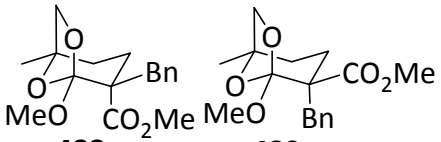
486 V_{max} (film)/cm^{-1} 2951s, 2884s, 2846m, 1736s, 1437s, 1382s, 1364s, 1321s, 1256s, 1235s, 1210s, 1170s, 1106s, 1044s, 1012s, 978m, 922s, 893s.

δH (400 MHz; $CDCl_3$) 1.38 (3H, s, C<u>H</u>$_3$), 1.65-1.70 (2H, m, C<u>H</u>$_2$), 1.88-1.93 (1H, m, C<u>H</u>$_2$), 2.15-2.25 (1H, m, C<u>H</u>$_2$), 2.88 (1H, dd, J 5.2 Hz, 12 Hz, C<u>H</u>), 3.41 (3H, m, OC<u>H</u>$_3$), 3.63 (1H, dd, J 1.2 Hz, 7 Hz, C<u>H</u>$_2$), 3.71 (3H, s, OC<u>H</u>$_3$), 3.98 (1H, d, J 7 Hz, C<u>H</u>$_2$).

δC (100 MHz; $CDCl_3$) 22.15 (<u>C</u>H$_3$), 22.84 (<u>C</u>H$_2$), 33.61 (<u>C</u>H$_2$), 48.79 (<u>C</u>H), 49.09 (O<u>C</u>H$_3$), 51.92 (O<u>C</u>H$_3$), 74.35 (<u>C</u>H$_2$), 80.48 (<u>C</u>), 119.38 (<u>C</u>), 171.97 (<u>C</u>O$_2$CH$_3$).

m/z (ESI) Calculated for $C_{10}H_{16}O_5(Na^+)$ requires 239.0890; found 239.0887 and $C_{10}H_{16}O_5(H^+)$ requires 217.1071 found 217.1069.

Lewis acid catalysed cyclisation of 2-benzyl-2-[2-(2-methyloxiranyl)ethyl]malonic acid dimethyl ester 487.



488 **489**

2-Benzyl-2-[2-(2-methyloxiranyl)ethyl]malonic acid dimethyl ester **487** (0.90 g, 2.94 mmol), DCM (45 mL), zinc bromide (0.70 g, 2.94 mmol), reaction time 1 hour.

The crude product was purified by flash chromatography on silica gel eluting with light petrol/Et_2O (97:3) affording 4-benzyl-5-methoxy-1-methyl-6,8-dioxa-bicyclo[3.2.1]octane-4-carboxylic acid methyl ester **488** (0.27 g, 0.88 mmol, 30 %) as white crystalline solid recrystallised from methanol at 0 °C m.p. 79.2-80.2 °C, and **489** (0.60 g, 1.96 mmol, 60 %) as white crystalline solid recrystallised from methanol at 0 °C m.p. 86.6-87.2 °C.

488 V_{max} (film)/cm^{-1} 3061w, 3029w, 2974s, 2948s, 2881m, 2843w, 1730s, 1604w, 1480w, 1382m, 1374s, 1318s, 1296m, 1228s, 1214s, 1157s, 1103s, 1080s, 971s.

δH (400 MHz; $CDCl_3$) 1.35 (3H, s, C<u>H</u>$_3$), 1.45-1.50 (1H, m, C<u>H</u>$_2$), 1.63-1.71 (1H, m, C<u>H</u>$_2$), 1.75-1.81 (1H, m, C<u>H</u>$_2$), 1.95-2.05 (1H, m, C<u>H</u>$_2$), 2.67 (1H, d, J 13.6 Hz, C<u>H</u>$_2$), 3.46 (3H, s, OC<u>H</u>$_3$), 3.53 (1H, d, J 13.6 Hz, C<u>H</u>$_2$), 3.61 (1H, dd, J 2.4 Hz, 6.8 Hz, C<u>H</u>$_2$), 3.71 (3H, s, OC<u>H</u>$_3$), 3.86 (1H, d, J 6.8 Hz, C<u>H</u>$_2$), 7.08 (2H, d, J 7.6 Hz, ArC<u>H</u>), 7.18-7.25 (3H, m, ArC<u>H</u>).

δC (100 MHz; $CDCl_3$) 21.88 (<u>C</u>H$_3$), 28.17 (<u>C</u>H$_2$), 33.22 (<u>C</u>H$_2$), 39.54 (<u>C</u>H$_2$), 48.95 (O<u>C</u>H$_3$), 51.81 (O<u>C</u>H$_3$), 55.52 (<u>C</u>), 74.17 (<u>C</u>H$_2$), 81.58 (<u>C</u>), 120.20 (<u>C</u>), 126.44 (Ar<u>C</u>H), 128.07 (Ar<u>C</u>H), 129.97 (Ar<u>C</u>H), 136.99 (Ar<u>C</u>), 172.47 (<u>C</u>O$_2$CH$_3$).

m/z (ESI) Calculated for $C_{17}H_{22}O_5(Na^+)$ requires 329.1359; found 329.1351 and $C_{17}H_{22}O_5(H^+)$ requires 307.1540 found 307.1533.

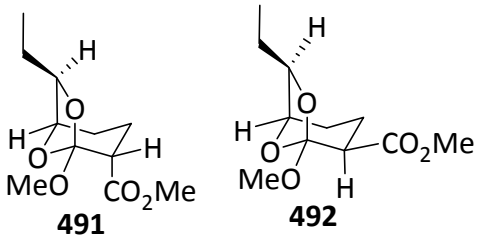
489 V_{max} (film)/cm^{-1} 3086w, 3061w, 3027m, 2975s, 2949s, 2884s, 2844s, 1728s, 1603w, 1496s, 1436s, 1382s, 1293s, 1258s, 1109s, 1093s, 1010s, 990s, 955m, 902m.

δH (400 MHz; $CDCl_3$) 1.43 (3H, s, C<u>H</u>$_3$), 1.53-1.64 (1H, m, C<u>H</u>$_2$), 1.53-1.64 (1H, m, C<u>H</u>$_2$), 1.80-1.89 (1H, m, C<u>H</u>$_2$), 2.30-2.40 (1H, m, C<u>H</u>$_2$), 3.05 (1H, d, J 14 Hz, C<u>H</u>$_2$), 3.44 (3H, s, OC<u>H</u>$_3$), 3.52 (1H, d, J 14 Hz, C<u>H</u>$_2$), 3.60 (1H, dd, J 2 Hz, 6.8 Hz, C<u>H</u>$_2$), 3.71 (3H, s, OC<u>H</u>$_3$), 3.93 (1H, d, J 6.8 Hz, C<u>H</u>$_2$), 7.13 (2H, d, J 7.6 Hz, ArC<u>H</u>), 7.16-7.25 (3H, m, ArC<u>H</u>).

δC (100 MHz; $CDCl_3$) 22.18 (<u>C</u>H$_3$), 23.40 (<u>C</u>H$_2$), 31.59 (<u>C</u>H$_2$), 35.71 (<u>C</u>H$_2$), 49.04 (O<u>C</u>H$_3$), 52.03 (O<u>C</u>H$_3$), 55.46 (<u>C</u>), 73.93 (<u>C</u>H$_2$), 80.93 (<u>C</u>), 121.27 (<u>C</u>), 126.39 (Ar<u>C</u>H), 128.16 (Ar<u>C</u>H), 130.15 (Ar<u>C</u>H), 138.05 (Ar<u>C</u>), 172.66 (<u>C</u>O$_2$CH$_3$).

m/z (ESI) Calculated for $C_{17}H_{22}O_5(Na^+)$ requires 329.1359; found 329.1351 and $C_{17}H_{22}O_5(H^+)$ requires 307.1540 found 307.1533.

Lewis acid catalysed cyclisation of *syn*-2-[2-(3-ethyloxiranyl)ethyl]malonic acid dimethyl ester 490.



491 **492**

Syn-2-[2-(3-ethyloxiranyl)ethyl]malonic acid dimethyl ester **490** (0.30 g, 1.30 mmol), DCM (15 mL), zinc bromide (0.29 g, 1.30 mmol).

The crude product was purified by flash chromatography on silica gel eluting with light petrol/EtOAc (9:1) affording, *exo*-7-ethyl-5-methoxy-6,8-dioxa-bicyclo[3.2.1]octane-4-

carboxylic acid methyl ester **491** (30 mg, 0.13 mmol, 10 %) as colourless oil and **492** (0.15 g, 0.65 mmol, 50 %) as colourless oil.

491 V_{max} (film)/cm^{-1} 2953s, 2879m, 2847m, 1738s, 1461s, 1437s, 1349m, 1322m, 1289s, 1190s, 1178s, 1162s, 1144s, 1041s, 1022s, 977s, 964s, 927s.

δH (400 MHz; $CDCl_3$) 0.97 (3H, t, J 7.2 Hz, C$\underline{H}_3$), 1.41-1.46 (1H, m, C$\underline{H}_2$), 1.55-1.72 (2H, m, C$\underline{H}_2$), 1.86-1.92 (1H, m, C$\underline{H}_2$), 2.00-2.10 (1H, m, C$\underline{H}_2$), 2.26-2.38 (1H, m, C$\underline{H}_2$), 2.89 (1H, d, J 6 Hz, C$\underline{H}$), 3.41 (3H, s, OC$\underline{H}_3$), 3.71 (3H, s, OC$\underline{H}_3$), 3.81 (1H, t, J 7.2 Hz, C$\underline{H}$), 4.29 (1H, s, C$\underline{H}$).

δC (100 MHz; $CDCl_3$) 9.81 (C$\underline{H}_3$), 21.32 (C$\underline{H}_2$), 25.36 (C$\underline{H}_2$), 27.65 (C$\underline{H}_2$), 47.14 (C$\underline{H}$), 48.90 (OC$\underline{H}_3$), 51.85 (OC$\underline{H}_3$), 78.77 (C$\underline{H}$), 79.85 (C$\underline{H}$), 119.18 (C$\underline{}$), 171.91 (C$\underline{O}_2CH_3$).

m/z (ESI) Calculated for $C_{11}H_{18}O_5(Na^+)$ requires 253.1046; found 253.1045.

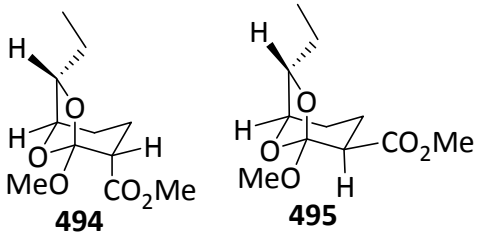
492 V_{max} (film)/cm^{-1} 2953s, 2879m, 2847w, 1738s, 1461m, 1437s, 1349w, 1322m, 1289s, 1231s, 1178s, 1144s, 1041s, 1022s, 977s.

δH (400 MHz; $CDCl_3$) 0.96 (3H, t, J 7.2 Hz, C$\underline{H}_3$), 1.53-1.62 (2H, m, C$\underline{H}_2$), 1.69-1.76 (1H, m, C$\underline{H}_2$), 1.83-1.91 (1H, m, C$\underline{H}_2$), 1.83-1.91 (1H, m, C$\underline{H}_2$), 2.14-2.22 (1H, m, C$\underline{H}_2$), 2.90 (1H, dd, J 4.6 Hz, 12.2 Hz, C$\underline{H}$), 3.40 (3H, s, OC$\underline{H}_3$), 3.71 (3H, s, OC$\underline{H}_3$), 3.92 (1H, t, J 7.2 Hz, C$\underline{H}$), 4.22 (1H, s, C$\underline{H}$).

δC (100 MHz; $CDCl_3$) 9.84 (C$\underline{H}_3$), 22.01 (C$\underline{H}_2$), 27.52 (C$\underline{H}_2$), 27.67 (C$\underline{H}_2$), 48.91 (C$\underline{H}$), 49.63 (OC$\underline{H}_3$), 51.92 (OC$\underline{H}_3$), 77.82 (C$\underline{H}$), 80.90 (C$\underline{H}$), 119.42 (C$\underline{}$), 171.91 (C$\underline{0}_2CH_3$).

m/z (ESI) Calculated for $C_{11}H_{18}O_5(Na^+)$ requires 253.1046; found 253.1043 and $C_{11}H_{18}O_5(H^+)$ requires 231.1227 found 231.1223.

Lewis acid catalysed cyclisation of *Anti*-2-[2-(3-ethyloxiranyl)ethyl]malonic acid dimethyl ester 493.



494 **495**

Anti-2-[2-(3-ethyloxiranyl)ethyl]malonic acid dimethyl ester **493** (0.40 g, 1.70 mmol), DCM (20 mL), zinc bromide (0.39 g, 1.70 mmol).

The crude product was purified by flash chromatography on silica gel eluting with light petrol/EtOAc (19:1) affording a mixture of inseparable diastereoisomers (1:3) of *endo*-7-

ethyl-5-methoxy-6,8-dioxa-bicyclo[3.2.1]octane-4-carboxylic acid methyl ester **494** and **495** (0.25 g, 1.09 mmol, 63 %) as colourless oil.

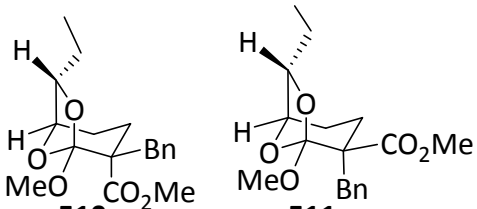
V_{max} (film)/cm^{-1} 2953s, 2879s, 1736s, 1437s, 1369m, 1348m, 1312s, 1290s, 1231s, 1159s, 1128s, 1040s, 1015s, 870w, 825w.

δH (400 MHz; $CDCl_3$) 0.99 (3H, t, J 7.6 Hz, C$\underline{H}_3$), 1.01 (3H, t, J 7.6 Hz, C$\underline{H}_3$), 1.50-2.30 (12H, m, C$\underline{H}_2$), 2.89 (1H, d, J 6.8 Hz, C$\underline{H}$), 2.93 (1H, dd, J 5.2 Hz, 12 Hz, C$\underline{H}$), 3.41 (3H, s, OC$\underline{H}_3$), 3.42 (3H, s, OC$\underline{H}_3$), 3.69 (3H, s, OC$\underline{H}_3$), 3.72 (3H, s, OC$\underline{H}_3$), 4.06-4.12 (1H, m, C$\underline{H}$), 4.13-4.18 (1H, m, C$\underline{H}$), 4.38 (1H, t, J 3.8 Hz, C$\underline{H}$), 4.46 (1H, t, J 3.8 Hz, C$\underline{H}$).

δC (100 MHz; $CDCl_3$) 10.48 (C$\underline{H}_3$), 10.50 (C$\underline{H}_3$), 21.37 (C$\underline{H}_2$), 21.99 (C$\underline{H}_2$), 22.16 (C$\underline{H}_2$), 22.20 (C$\underline{H}_2$), 22.75 (C$\underline{H}_2$), 23.47 (C$\underline{H}_2$), 46.84 (OC$\underline{H}_3$), 48.73 (OC$\underline{H}_3$), 48.81 (OC$\underline{H}_3$), 49.02 (C$\underline{H}$), 51.89 (OC$\underline{H}_3$), 77.15 (C$\underline{H}$), 78.00 (C$\underline{H}$), 81.19 (C$\underline{H}$), 82.25 (C$\underline{H}$), 118.55 (C$\underline{}$), 118.80 (C$\underline{}$), 171.85 (C$\underline{}O_2CH_3$), 172.25 (C$\underline{}O_2CH_3$).

m/z (ESI) Calculated for $C_{11}H_{18}O_5(Na^+)$ requires 253.1046; found 253.1042 and $C_{11}H_{18}O_5(H^+)$ requires 231.1227 found 231.1224.

Lewis acid catalysed cyclisation of *anti*-2-Benzyl-2-[2-(3-ethyloxiranyl)ethyl]malonic acid dimethyl ester 509.



510 **511**

Anti-2-benzyl-2-[2-(3-ethyloxiranyl)ethyl]-malonic acid dimethyl ester **509** (0.52 g, 1.62 mmol), DCM (22 mL), zinc bromide (0.37 g, 1.62 mmol).

The crude product was purified by flash chromatography on silica gel eluting with light petrol/EtOAc (19:1) affording a chromatographically inseparable mixture of diastereoisomers of *endo*-4-benzyl-7-ethyl-5-methoxy-6,8-dioxabicyclo[3.2.1]octane-4-carboxylic acid methyl ester **510** and **511.** The mixture of diastereoisomers **510** and **511** were separated by recrystallization from hexane at 0 °C affording **510** (0.11g, 0.34 mmol, 21 %) as colourless oil and **511** (0.27 g, 0.84 mmol, 52 %) as white granules which were further recrystallized from methanol at 0 °C m.p. 92-94 °C.

510 V_{max} (film)/cm^{-1} 3085w, 3061w, 3028w, 2967s, 2949s, 1730s, 1603w, 1496w, 1453s, 1277s, 1177s, 1134s, 1115s, 1072s, 1012s, 914s, 868w, 807w.

δH (400 MHz; $CDCl_3$) 1.02 (3H, t, J 7.4 Hz, C$\underline{H}_3$), 1.50-1.58 (2H, m, C$\underline{H}_2$), 1.66-1.71 (2H, m, C$\underline{H}_2$), 1.80-1.87 (1H, m, C$\underline{H}_2$), 2.11-2.20 (1H, m, C$\underline{H}_2$), 2.65 (1H, d, J 13.6 Hz, C$\underline{H}_2$), 3.46 (3H, s, OC$\underline{H}_3$), 3.55 (1H, d, J 13.6 Hz, C$\underline{H}_2$), 3.72 (3H, s, OC$\underline{H}_3$), 4.10-4.14 (1H, m, C$\underline{H}$), 4.40 (1H, t, J 3.8 Hz, C$\underline{H}$), 7.07 (2H, d, J 6.8 Hz, ArC$\underline{H}$), 7.17-7.25 (3H, m, ArC$\underline{H}$).

δC (100 MHz; $CDCl_3$) 10.50 (C$\underline{H}_3$), 22.06 (C$\underline{H}_2$), 22.86 (C$\underline{H}_2$), 28.38 (C$\underline{H}_2$), 39.51 (C$\underline{H}_2$), 48.85 (OC$\underline{H}_3$), 51.83 (OC$\underline{H}_3$), 55.87 (C$\underline{C}$), 78.05 (C$\underline{C}$H), 81.72 (C$\underline{C}$H), 120.12 (C$\underline{C}$), 126.38 (ArC$\underline{C}$H), 128.05 (ArC$\underline{C}$H), 130.01 (ArC$\underline{C}$H), 136.97 (ArC$\underline{C}$), 172.89 (C$\underline{C}O_2CH_3$).

m/z (ESI) Calculated for $C_{18}H_{24}O_5(Na^+)$ requires 343.1516; found 343.1510 and $C_{18}H_{24}O_5(H^+)$ requires 321.1697 found 321.1692.

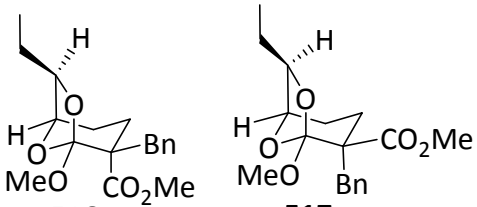
511 V_{max} (film)/cm^{-1} 3085w, 3061w, 3027m, 2967s, 2949s, 2878s, 2842w, 1728s, 1603w, 1496s, 1433s, 1272s, 1227s, 1127s, 1114s, 957s.

δH (400 MHz; $CDCl_3$) 0.98 (3H, t, J 7.2 Hz, C$\underline{H}_3$), 1.52-1.63 (3H, m, C$\underline{H}_2$), 1.83-1.88 (1H, m, C$\underline{H}_2$), 1.90-2.02 (1H, m, C$\underline{H}_2$), 2.34-2.43 (1H, m, C$\underline{H}_2$), 3.10 (1H, d, J 14 Hz, C$\underline{H}_2$), 3.44 (3H, s, OC$\underline{H}_3$), 3.52 (1H, d, J 14 Hz, C$\underline{H}_2$), 3.70 (3H, s, OC$\underline{H}_3$), 4.11-4.17 (1H, m, C$\underline{H}$), 4.43 (1H, t, J 4 Hz, C$\underline{H}$), 7.12 (2H, d, J 7.6 Hz, ArC$\underline{H}$), 2.16-2.26 (3H, m, ArC$\underline{H}$).

δC (100 MHz; $CDCl_3$) 10.54 (C$\underline{H}_3$), 21.60 (C$\underline{H}_2$), 21.82 (C$\underline{H}_2$), 23.34 (C$\underline{H}_2$), 36.33 (C$\underline{H}_2$), 48.95 (OC$\underline{H}_3$), 51.96 (OC$\underline{H}_3$), 55.68 (C$\underline{C}$), 77.34 (C$\underline{C}$H), 81.98 (C$\underline{C}$H), 120.58 (C$\underline{C}$), 126.36 (ArC$\underline{C}$H), 128.15 (ArC$\underline{C}$H), 130.19 (ArC$\underline{C}$H), 138.27 (ArC$\underline{C}$), 172.57 (C$\underline{C}O_2CH_3$).

m/z (ESI) Calculated for $C_{18}H_{24}O_5(Na^+)$ requires 343.1516; found 343.1510.

Lewis acid catalysed cyclisation of *syn*-2-benzyl-2-[2-(3-ethyloxiranyl)ethyl]malonic acid dimethyl ester 515.



516 **517**

Syn-2-benzyl-2-[2-(3-ethyloxiranyl)ethyl]-malonic acid dimethyl ester **515** (0.52 g, 1.62 mmol), DCM (22 mL), zinc bromide (0.37 g, 1.62 mmol).

The crude product was purified by flash chromatography on silica gel eluting with light petrol/EtOAc (19:1) affording a chromatographically inseparable mixture of diastereoisomers of *exo*-4-benzyl-7-ethyl-5-methoxy-6,8-dioxabicyclo[3.2.1]octane-4-carboxylic acid methyl ester **516** and **517.** The mixture of diastereoisomers **516** and **517**

were partially separated by recrystallization in hexane at 0 °C affording a 2:1 mixture of **516** and **517** (0.10 g, 0.31 mmol, 19 %) as colourless oil and **506** (0.38 g, 1.19 mmol, 73 %) as white solid which was further recrystallized from methanol at 0 °C m.p. 100-101 °C.

516 and 517 V_{max} (film)/cm^{-1} 3086w, 3062w, 3028m, 2951s, 2253w, 1731s, 1603w, 1496s, 1437s, 1337s, 1225br, 1131s, 913s, 849w, 809w, 735w.

δH (400 MHz; $CDCl_3$) 0.95 (3H, t, J 7.2 Hz, C$\underline{H}_3$), 0.98 (3H, t, J 7.2 Hz, C$\underline{H}_3$), 1.39-1.44 (1H, m, C$\underline{H}_2$), 1.46-1.51 (1H, m, C$\underline{H}_2$), 1.56-1.76 (7H, m, C$\underline{H}_2$), 2.01-2.06 (1H, m, C$\underline{H}_2$), 2.14-2.23 (1H, m, C$\underline{H}_2$), 2.29-2.38 (1H, m, C$\underline{H}_2$), 2.68 (1H, d, J 14 Hz, C$\underline{H}_2$), 3.08 (1H, d, J 14 Hz, C$\underline{H}_2$), 3.43 (3H, s, OC$\underline{H}_3$), 3.45 (3H, s, OC$\underline{H}_3$), 3.56 (2H, d, J 14 Hz, C$\underline{H}_2$), 3.70 (3H, s, OC$\underline{H}_3$), 3.71 (3H, s, OC$\underline{H}_3$), 3.80 (1H, t, J 7 Hz, C$\underline{H}$), 3.87 (1H, t, J 7 Hz, C$\underline{H}$), 4.23 (1H, t, J 1.8 Hz, C$\underline{H}$), 4.26 (1H, t, 1.8 Hz, C$\underline{H}$), 7.08-7.24 (10H, m, ArC$\underline{H}$).

δC (100 MHz; $CDCl_3$) 9.89 ($\underline{C}H_3$), 9.95 ($\underline{C}H_3$), 22.42 ($\underline{C}H_2$), 25.43 ($\underline{C}H_2$), 27.25 ($\underline{C}H_2$), 27.55 ($\underline{C}H_2$), 27.57 ($\underline{C}H_2$), 35.71 ($\underline{C}H_2$), 39.70 ($\underline{C}H_2$), 49.02 (O$\underline{C}H_3$), 49.07 (O$\underline{C}H_3$), 51.80 (O$\underline{C}H_3$), 52.02 (O$\underline{C}H_3$), 56.00 ($\underline{C}$), 56.09 ($\underline{C}$), 78.24 ($\underline{C}$H), 78.82 ($\underline{C}$H), 80.44 ($\underline{C}$H), 80.74 ($\underline{C}$H), 120.90 ($\underline{C}$), 121.28 ($\underline{C}$), 126.39 (Ar$\underline{C}$H), 126.41 (Ar$\underline{C}$H), 128.06 (Ar$\underline{C}$H), 128.17 (Ar$\underline{C}$H), 130.03 (Ar$\underline{C}$H), 130.14 (Ar$\underline{C}$H), 136.97 (Ar$\underline{C}$), 138.10 (Ar$\underline{C}$), 172.63 ($\underline{C}O_2CH_3$).

m/z (ESI) Calculated for $C_{18}H_{24}O_5(Na^+)$ requires 343.1516; found 343.1512 and $C_{18}H_{24}O_5(H^+)$ requires 321.1697 found 321.1694.

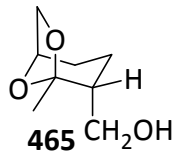
517 V_{max} (film)/cm^{-1} 3085w, 3061w, 3027s, 2950s, 2877s, 2843m, 1723s, 1603m, 1495s, 1436, 1335s, 915s, 865w, 817w, 796m.

δH (400 MHz; $CDCl_3$) 0.95 (3H, t, J 7.6 Hz, C$\underline{H}_3$), 1.46-1.51 (1H, m, C$\underline{H}_2$), 1.54-1.61 (2H, m, C$\underline{H}_2$), 1.68-1.75 (1H, m, C$\underline{H}_2$), 1.96-2.08 (1H, m, C$\underline{H}_2$), 2.28-2.39 (1H, m, C$\underline{H}_2$), 3.08 (1H, d, J 14 Hz, C$\underline{H}_2$), 3.43 (3H, s, OC$\underline{H}_3$), 3.52 (1H, d, J 14 Hz, C$\underline{H}_2$), 3.71 (3H, s, OC$\underline{H}_3$), 3.87 (1H, t, J 7 Hz, C$\underline{H}$), 4.26 (1H, t, J 1.6 Hz, C$\underline{H}$), 7.12 (2H, d, J 7.6 Hz, ArC$\underline{H}$), 7.17-7.25 (3H, m, ArC$\underline{H}$).

δC (100 MHz; $CDCl_3$) 9.89 ($\underline{C}H_3$), 22.42 ($\underline{C}H_2$), 25.43 ($\underline{C}H_2$), 27.55 ($\underline{C}H_2$), 35.72 ($\underline{C}H_2$), 49.07 (O$\underline{C}H_3$), 52.02 (O$\underline{C}H_3$), 56.00 ($\underline{C}$), 78.24 ($\underline{C}$H), 80.44 ($\underline{C}$H), 121.28 ($\underline{C}$), 126.38 (Ar$\underline{C}$H), 128.17 (Ar$\underline{C}$H), 130.14 (Ar$\underline{C}$H), 138.10 (Ar$\underline{C}$), 172.67 ($\underline{C}O_2CH_3$).

m/z (ESI) Calculated for $C_{18}H_{24}O_5(Na^+)$ requires 343.1516; found 343.1511.

(5-Methyl-6,8-dioxabicyclo[3.2.1]oct-4-yl)methanol 465.



465

To the solution of 5-methyl-6,8-dioxabicyclo[3.2.1]octane-4-carboxylic acid ethyl ester **461** (0.25 g, 1.25 mmol) in THF (13 mL) at RT was added $LiAlH_4$ (80 mg, 2.10 mmol). The reaction mixture was allowed to stir for one hour and then quenched with methanol (5 mL) and washed with water (10 mL). The organic layer was extracted with DCM (2×20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure affording (5-methyl-6,8-dioxabicyclo[3.2.1]oct-4-yl)methanol **465** (0.14 g, 0.86 mmol, 70 %) as colourless oil.

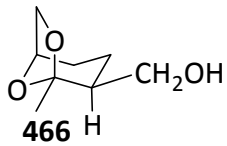
V_{max} (film)/cm^{-1} 3400br, 2940s, 1457s, 1384s, 1327s, 1295s, 1190s, 1168s, 1116s, 1015s, 950s, 887s, 847s.

δH (400 MHz; $CDCl_3$) 1.41-1.44 (1H, m, C$\underline{H}_2$), 1.48 (3H, s, C$\underline{H}_3$), 1.72-1.79 (2H, m, C$\underline{H}$, C$\underline{H}_2$), 1.99-2.09 (2H, m, C$\underline{H}_2$), 2.37 (1H, s, O$\underline{H}$), 3.73 (1H, dd, J 3.6 Hz, 11.2 Hz, C$\underline{H}_2$), 3.80 (1H, dd, J 6 Hz, 11.2 Hz, C$\underline{H}_2$), 3.85-3.91 (2H, m, C$\underline{H}_2$), 4.56 (1H, m, C$\underline{H}$).

δC (100 MHz; $CDCl_3$) 20.06 (C$\underline{H}_2$), 22.78 (C$\underline{H}_3$), 25.88 (C$\underline{H}_2$), 44.39 (C$\underline{H}$), 63.83 (C$\underline{H}_2$), 68.35 (C$\underline{H}_2$), 75.64 (C$\underline{H}$), 108.52 (C$\underline{H}$).

m/z (ESI) Calculated for $C_8H_{14}O_3(Na^+)$ requires 181.0835; found 181.0832 and $C_8H_{14}O_3(H^+)$ requires 159.1016 found 159.1013.

(5-Methyl-6,8-dioxabicyclo[3.2.1]oct-4-yl)methanol 466.



466

To the solution of 5-methyl-6,8-dioxabicyclo[3.2.1]octane-4-carboxylic acid ethyl ester **462** (0.20 g, 0.10 mmol) in THF (10 mL) at RT was added $LiAlH_4$ (64 mg, 1.70 mmol). The reaction mixture was allowed to stir for one hour and then quenched with methanol (5 mL) and washed with water (10 mL). The organic layer was extracted with DCM (2×20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure.

The crude product was purified by flash chromatography on silica gel eluting with light petrol/EtOAc (8:1) affording (5-methyl-6,8-dioxabicyclo[3.2.1]oct-4-yl)methanol **466** (0.12 g, 0.86 mmol, 75 %) as colourless oil.

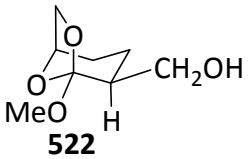
V_{max} (film)/cm^{-1} 3434br, 2940s, 2888s, 1484m, 1453s, 1384s, 1333s, 1213s, 1170s, 1121s, 1074s, 1016s, 959s, 889s, 849s, 739w.

δH (400 MHz; $CDCl_3$) 1.51 (3H, s, C$\underline{H}_3$), 1.58-1.68 (2H, m, C$\underline{H}_2$), 1.81-1.95 (3H, m, C$\underline{H}_2$, C$\underline{H}$), 2.41 (1H, s, O$\underline{H}$), 3.50 (1H, d, J 10.4 Hz, C$\underline{H}_2$), 3.74 (1H, dd, J 3.6 Hz, 11.2 Hz, C$\underline{H}_2$), 3.85-3.90 (2H, m, C$\underline{H}_2$), 4.54-4.55 (1H, m, C$\underline{H}$).

δC (100 MHz; $CDCl_3$) 19.64 (C$\underline{H}_2$), 22.25 (C$\underline{H}_3$), 28.50 (C$\underline{H}_2$), 44.80 (C$\underline{H}$), 63.64 (C$\underline{H}_2$), 68.87 (C$\underline{H}_2$), 74.60 (C$\underline{H}$), 109.14 (C$\underline{H}$).

m/z (ESI) Calculated for $C_8H_{14}O_3(Na^+)$ requires 181.0835; found 181.0835 and $C_8H_{14}O_3(H^+)$ requires 159.1016 found 159.1016.

(5-Methoxy-6,8-dioxabicyclo[3.2.1]oct-4-yl)methanol 522.



522

To the solution of 5-methoxy-6,8-dioxabicyclo[3.2.1]octane-4-carboxylic acid methyl ester **435** (0.66 g, 3.30 mmol) in dry THF (65 mL), at RT, $LiAlH_4$ (0.21 g, 5.60 mmol) was added slowly. The reaction mixture was allowed to stir for one hour and then quenched with methanol. The organic layer was washed with water (80 mL) and extracted with DCM (3x30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford (5-methoxy-6,8-dioxabicyclo[3.2.1]oct-4-yl)methanol **522** (0.55 g, 3.16 mmol, 96 %) as colourless oil.

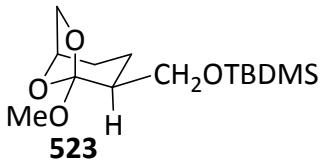
V_{max} (film)/cm^{-1} 3423br, 2950s, 2981s, 1438m, 1334m, 1238s, 1214s, 1184s, 1154s, 1112s, 1098s, 1052s, 1026s, 1016s, 972s, 929m, 901m.

δH (400 MHz; $CDCl_3$) 1.40-1.50 (1H, m, C$\underline{H}_2$), 1.51-1.58 (1H, m, C$\underline{H}_2$), 1.60-1.68 (1H, m, C$\underline{H}_2$), 1.85-1.96 (1H, m, C$\underline{H}_2$), 2.10-2.18 (1H, m, C$\underline{H}$), 2.65 (1H, dd, J 3.2 Hz, 9.2 Hz, O$\underline{H}$), 3.36-3.42 (1H, m, C$\underline{H}_2$), 3.42 (3H, s, OC$\underline{H}_3$), 3.59-3.65 (1H, m, C$\underline{H}_2$), 3.78 (1H, d, J 7.2 Hz, C$\underline{H}_2$), 3.96-3.99 (1H, m, C$\underline{H}_2$), 4.60 (1H, s, C$\underline{H}$).

δC (100 MHz; $CDCl_3$) 20.35 (C$\underline{H}_2$), 28.15 (C$\underline{H}_2$), 45.27 (C$\underline{H}$), 48.47 (OC$\underline{H}_3$), 63.62 (C$\underline{H}_2$), 68.46 (C$\underline{H}_2$), 74.52 (C$\underline{H}$), 121.76 (C$\underline{H}$).

m/z (ESI) Calculated for $C_8H_{14}O_4(Na^+)$ requires 197.0784; found 197.0783 and $C_8H_{14}O_4(H^+)$ requires 175.0965 found 175.0964.

Tert-butyl-(5-methoxy-6,8-dioxabicyclo[3.2.1]oct-4-ylmethoxy)dimethyl silane 523.



523

To the solution of (5-methoxy-6,8-dioxa-bicyclo[3.2.1]oct-4-yl)methanol **522** (0.28 g, 1.60 mmol) in DCM (28 mL) was added triethylamine (0.24 g, 2.40 mmol) and DMAP (0.20 g, 1.60 mmol). The reaction mixture was allowed to stir for five minutes and then *tert*-butyldimethylsilylchloride (0.27 g, 1.80 mmol) was added. The reaction mixture was allowed to stir for twelve hours at RT and the quenched with water (40 mL). The organic layer was separated and aqueous layer extracted with DCM (2×20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with light petrol/EtOAc (124:1) affording *tert*-butyl-(5-methoxy-6,8-dioxabicyclo[3.2.1]oct-4-ylmethoxy)dimethylsilane **523** (0.35 g, 1.37 mmol, 76 %) as colourless oil.

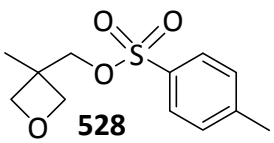
V_{max} (film)/cm^{-1} 2951s, 2930s, 2886s, 2858s, 1495w, 1330w, 1239s, 1219s, 1182s, 1146s, 1125s, 1024s, 980s, 901s, 859s, 775m.

δH (400 MHz; $CDCl_3$) 0.03 (6H, s, C$\underline{H}_3$), 0.87 (9H, s, C$\underline{H}_3$), 1.33-1.47 (1H, m, C$\underline{H}_2$), 1.55 (1H, dd, J 5.6 Hz, 13.6 Hz, C$\underline{H}_2$), 1.80-1.89 (1H, m, C$\underline{H}_2$), 1.96-2.03 (1H, m, C$\underline{H}_2$), 2.09-2.18 (1H, m, C$\underline{H}$), 3.32 (1H, t, J 10 Hz, C$\underline{H}_2$), 3.33 (3H, s, OC$\underline{H}_3$), 3.78 (1H, d, J 6.8 Hz, C$\underline{H}_2$), 3.94 (2H, dd, J 6.8 Hz, 10 Hz, C$\underline{H}_2$), 4.56 (1H, s, C$\underline{H}$).

δC (100 MHz; $CDCl_3$) -5.43 (C$\underline{H}_3$), -5.32 (C$\underline{H}_3$), 18.32 (C$\underline{}$), 22.37 (C$\underline{H}_2$), 25.94 (C$\underline{H}_3$), 28.62 (C$\underline{H}_2$), 46.04 (C$\underline{H}$), 48.29 (OC$\underline{H}_3$), 63.38 (C$\underline{H}_2$), 68.44 (C$\underline{H}_2$), 74.52 (C$\underline{H}$), 120.72 (C$\underline{}$).

m/z (ESI) Calculated for $C_{14}H_{28}O_4Si(Na^+)$ requires 311.1649; found 311.1644.

Toluene-4-sulfonic acid 3-methyloxetan-3-ylmethyl ester 528.[91]



528

Under a nitrogen atmosphere, to the suspension of NaH (1.00 g, 25.50 mmol, 60 % in mineral oil), in THF (100 mL), was added 3-methyl-3-oxetane methanol (2.00 g, 19.60 mmol). The mixture was allowed to stir for five minutes and *p*-toluenesulfonyl chloride

(4.10 g, 21.50 mmol) was added to the reaction mixture. The reaction mixture was allowed to stir for twelve hours at reflux and then quenched with water (50 mL). The organic layer was separated and aqueous layer extracted with DCM (3×50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with light petrol/EtOAc (8:2) to afford toluene-4-sulfonic acid 3-methyloxetan-3-ylmethyl ester **528** (5.00 g, 19.53 mmol, 99 %) as white crystalline solid m.p. 59-61.5 °C, literature m.p. 49-51 °C.[91] The spectral data were in agreement with literature.

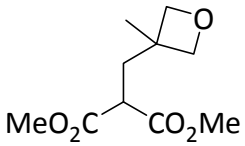
V_{max} (film)/cm^{-1} 3047w, 2938s, 2874s, 1597m, 1492m, 1483m, 1462s, 1394s, 1373s, 1271s, 1178s, 1120s, 1096s, 976s, 839s, 663s.

δH (400 MHz; $CDCl_3$) 1.31 (3H, s, C$\underline{H}_3$), 2.46 (3H, s, C$\underline{H}_3$), 4.11 (2H, s, C$\underline{H}_2$), 4.35 (4H, q, J 6.2 Hz, C$\underline{H}_2$), 7.38 (2H, d, J 8.4 Hz, ArC$\underline{H}$), 7.81 (2H, d, J 8.4 Hz, ArC$\underline{H}$).

δC (100 MHz; $CDCl_3$) 20.67 (C$\underline{H}_3$), 21.68 (C$\underline{H}_3$), 39.25 (C$\underline{C}$), 74.28 (C$\underline{H}_2$), 78.96 (C$\underline{H}_2$), 127.97 (Ar$\underline{C}$H), 129.99 (Ar$\underline{C}$H), 132.61 (Ar$\underline{C}$), 145.12 (Ar$\underline{C}$).

m/z (ESI) Calculated for $C_{12}H_{16}O_4S(Na^+)$ requires 279.0662; found 279.0655, $C_{12}H_{16}O_4S(H^+)$ requires 257.0842; found 257.0836.

2-(3-Methyloxetan-3-ylmethyl)malonic acid dimethyl ester 525.



525

To a suspension of NaH (1.00g, 25.30 mmol, 60 % in mineral oil) in THF (170 mL), at 0 °C, under nitrogen, dimethylmalonate (2.40 g, 17.90 mmol) was added. The reaction mixture was stirred for fifteen minutes and then toluene-4-sulfonic acid 3-methyloxetan-3-ylmethyl ester **528** (2.70 g, 10.54 mmol) was added to the reaction mixture. The solution was allowed to warm to RT and refluxed for twelve hours. The reaction mixture was quenched with saturated ammonium chloride and extracted with EtOAc (3×40 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography on silica gel eluting with light petrol/EtOAc (9:1) affording 2-(3-methyloxetan-3-ylmethyl)malonic acid dimethyl ester **525** (1.70 g, 7.87 mmol, 74 %) as a colourless oil.

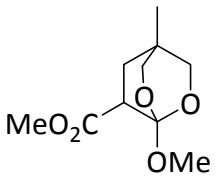
V_{max} (film)/cm^{-1} 2956s, 2869s, 1744s, 1437s, 1219br, 1029s, 980s, 930m, 830m, 703w, 659w.

δH (400 MHz; $CDCl_3$) 1.34 (3H, s, C$\underline{H}_3$), 2.31 (2H, d, J 7.2 Hz, C$\underline{H}_2$), 3.40 (1H, t, J 7.2 Hz, C$\underline{H}$), 3.74 (6H, s, OC$\underline{H}_3$), 4.28 (2H, d, J 6 Hz, C$\underline{H}_2$), 4.42 (2H, d, J 6 Hz, C$\underline{H}_2$).

δC (100 MHz; $CDCl_3$) 22.74 (C$\underline{H}_3$), 37.24 (C$\underline{C}$), 38.40 (C$\underline{H}_2$), 48.03 (C$\underline{H}$), 52.74 (OC$\underline{H}_3$), 82.34 (C$\underline{H}_2$) 169.79 (C$\underline{O}_2$CH$_3$).

m/z (ESI) Calculated for $C_{10}H_{16}O_5(Na^+)$ requires 239.0890; found 239.0887 and $C_{10}H_{16}O_5(H^+)$ requires 217.1071 found 217.1068.

1-Methoxy-4-methyl-2,6-dioxabicyclo[2.2.2]octane-7-carboxylic acid methyl ester 526.



526

To solution of 2-(3-methyloxetan-3-ylmethyl)malonic acid dimethyl ester **525** (0.30 g, 1.39 mmol) in DCM (15 mL) was added zinc bromide (0.30 g, 1.39 mmol). The reaction mixture was allowed to stir at room temperature for twenty hours and then quenched with water (20 mL). The organic layer was separated and aqueous layer extracted with DCM (2×20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with light petrol/EtOAc (9:1) giving 1-methoxy-4-methyl-2,6-dioxa-bicyclo[2.2.2]octane-7-carboxylic acid methyl ester **526** (0.09 g, 0.42 mmol, 30 %) as colourless oil.

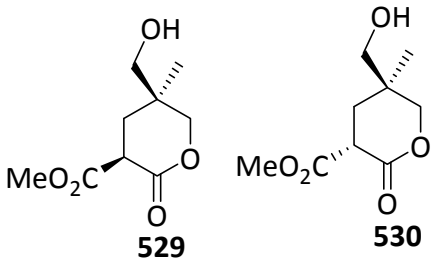
V_{max} (film)/cm^{-1} 2954s, 2876s, 1737s, 1438s, 1357s, 1321s, 1304s, 1275s, 1234s, 1166s, 1113s, 1052s, 1026s, 990s, 886w, 793w.

δH (400 MHz; $CDCl_3$) 0.85 (3H, s, C$\underline{H}_3$), 1.89-1.96 (1H, m, C$\underline{H}_2$), 2.14-2.20 (1H, m, C$\underline{H}_2$), 3.16 (1H, dd, J 5 Hz, 11 Hz, C$\underline{H}$), 3.42 (3H, s, OC$\underline{H}_3$), 3.74 (3H, s, OC$\underline{H}_3$), 3.87 (1H, dd, J 3.6 Hz, 8.4 Hz, C$\underline{H}_2$), 3.91 (1H, dd, J 3.2 Hz, 8 Hz, C$\underline{H}_2$), 3.96 (1H, dd, 3 Hz, 8.2 Hz, C$\underline{H}_2$), 4.13 (1H, dd, J 3.6 Hz, 8 Hz, C$\underline{H}_2$).

δC (100 MHz; $CDCl_3$) 17.65 (C$\underline{H}_3$), 28.87 (C$\underline{C}$), 34.28 (C$\underline{H}_2$), 47.12 (C$\underline{H}$), 49.99 (OC$\underline{H}_3$), 52.28 (OC$\underline{H}_3$), 75.66 (C$\underline{H}_2$), 75.88 (C$\underline{H}_2$), 108.82 (C$\underline{C}$), 172.46 (C$\underline{O}_2$CH$_3$).

m/z (ESI) Calculated for $C_{10}H_{16}O_5(Na^+)$ requires 239.0890; found 239.0886 and $C_{10}H_{16}O_5(H^+)$ requires 217.1071 found 217.1068.

5-Hydroxymethyl-5-methyl-2-oxotetrahydropyran-3-carboxylic acid methyl ester 529 and 530.



Under nitrogen to the solution of 2-(3-methyloxetan-3-ylmethyl)malonic acid dimethyl ester **525** (0.10 g, 0.46 mmol) in DCM (10 mL) was added ytterbium triflate (23 mg, 0.05 mmol). The reaction mixture was allowed to stir for twenty four hours at RT. Then the reaction mixture was filtered through a pad of celite and silica gel. The filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with light petrol/EtOAc (1:1) affording inseparable mixture (1:1) of *syn* and *anti* 5-hydroxymethyl-5-methyl-2-oxotetrahydropyran-3-carboxylic acid methyl ester **529** and **530** (50 mg, 0.25 mmol, 56 %) as colourless oil.

V_{max} (film)/cm^{-1} 3519br, 2957s, 2879s, 1736s, 1459s, 1437s, 1235br, 1042s, 870w, 786w, 734w.

δH (400 MHz; $CDCl_3$) 1.07 (3H, s, C$\underline{H}_3$), 1.08 (3H, s, C$\underline{H}_3$), 1.87 (1H, dd, J 8 Hz, 14 Hz, C$\underline{H}_2$), 2.00 (1H, dd, J 10 Hz, 14 Hz, C$\underline{H}_2$), 2.12-2.18 (2H, m, C$\underline{H}_2$), 2.37 (2H, s, O$\underline{H}$), 3.43-3.54 (4H, m, C$\underline{H}_2$), 3.60-3.68 (2H, m, C$\underline{H}$), 3.79 (3H, s, OC$\underline{H}_3$), 3.80 (3H, s, OC$\underline{H}_3$), 3.99 (2H, dd, J 11.6 Hz, 20.4 Hz, C$\underline{H}_2$), 4.29 (2H, dd, J 7.6 Hz, 11.6 Hz, C$\underline{H}_2$).

δC (100 MHz; $CDCl_3$) 20.67 (C$\underline{H}_3$), 22.14 (C$\underline{H}_3$), 31.42 (C$\underline{H}_2$), 31.64 (C$\underline{H}_2$), 34.68 (C), 34.95 (C), 44.70 (C$\underline{H}$), 45.43 (C$\underline{H}$), 52.92 (OC$\underline{H}_3$), 52.96 (OC$\underline{H}_3$), 67.29 (C$\underline{H}_2$), 67.47 (C$\underline{H}_2$), 73.74 (C$\underline{H}_2$), 74.14 (C$\underline{H}_2$), 168.89 (C=O), 169.05 (C=O), 169.49 (C=O), 169.52 (C=O).

m/z (ESI) Calculated for $C_9H_{14}O_5(Na^+)$ requires 225.0733 found 225.0728 and $C_9H_{14}O_5(H^+)$ requires 203.0914 found 203.0909.

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6. Appendices

Appendix I X-Ray crystallographic data for 369.

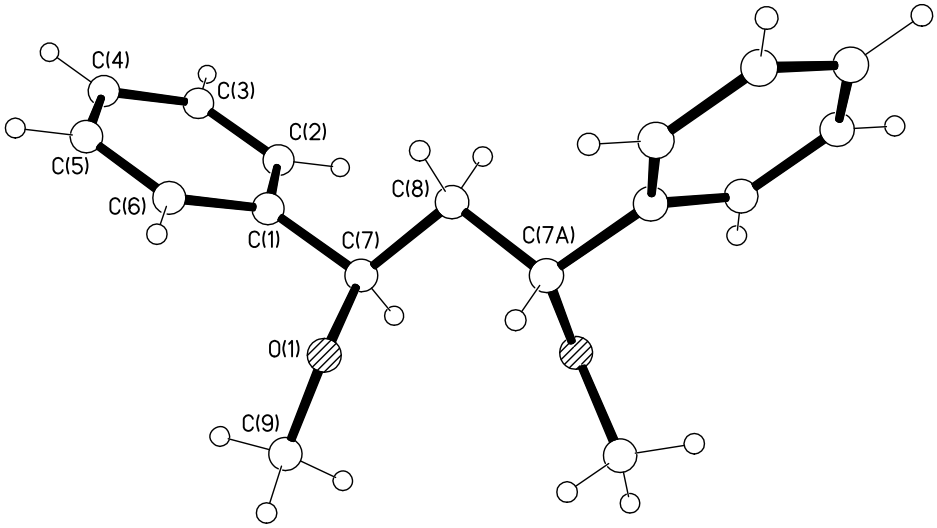


Table 1. Crystal data and structure refinement for 369.

Identification code	gp13	
Chemical formula	$C_{17}H_{20}O_2$	
Formula weight	256.34	
Temperature	150(2) K	
Radiation, wavelength	MoK, 0.71073 Å	
Crystal system, space group	orthorhombic, Aba2	
Unit cell parameters	a = 21.133(6) Å	□ = 90°
	b = 10.020(3) Å	□ = 90°
	c = 6.6268(18) Å	□ = 90°
Cell volume	1403.2(7) $Å^3$	
Z	4	
Calculated density	1.213 g/cm^3	
Absorption coefficient □	0.078 mm^{-1}	
F(000)	552	
Crystal colour and size	colourless, 1.10 × 0.25 × 0.10 mm^3	
Reflections for cell refinement	5409 (□ range 3.69 to 30.54°)	
Data collection method	Bruker APEX 2 CCD diffractometer	
	□ rotation with narrow frames	
□ range for data collection	1.93 to 27.49°	
Index ranges	h −27 to 27, k −12 to 12, l −8 to 8	
Completeness to □ = 27.49°	99.2 %	
Intensity decay	0%	
Reflections collected	6103	
Independent reflections	874 (R_{int} = 0.0597)	
Reflections with F^2>2□	861	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.919 and 0.992	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting parameters a, b	0.1722, 11.0542	
Data / restraints / parameters	874 / 1 / 88	
Final R indices [F^2>2□]	R1 = 0.1179, wR2 = 0.3127	
R indices (all data)	R1 = 0.1187, wR2 = 0.3134	
Goodness-of-fit on F^2	1.137	
Largest and mean shift/su	0.000 and 0.000	
Largest diff. peak and hole	1.500 and −0.508 e $Å^{-3}$	

Absolute structure could not be determined from the diffraction data. Friedel pairs were merged.

Table 2. Atomic coordinates and equivalent isotropic displacement parameters ($Å^2$) for 369. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
C(1)	0.3888(3)	0.0956(7)	0.5732(10)	0.0193(13)
C(2)	0.3472(3)	0.0103(6)	0.4733(11)	0.0245(15)
C(3)	0.2981(3)	0.0623(8)	0.3579(12)	0.0284(16)
C(4)	0.2907(3)	0.1992(8)	0.3427(12)	0.0284(16)
C(5)	0.3313(3)	0.2822(7)	0.4409(12)	0.0270(15)
C(6)	0.3801(3)	0.2317(7)	0.5564(13)	0.0266(15)
C(7)	0.4442(3)	0.0425(6)	0.6983(10)	0.0176(13)
C(8)	0.5000	0.0000	0.5657(15)	0.0191(17)
O(1)	0.4665(2)	0.1389(4)	0.8403(7)	0.0158(10)
C(9)	0.4318(4)	0.1393(7)	1.0226(11)	0.0252(16)

Table 3. Bond lengths [Å] and angles [°] for 369.

C(1)–C(6)	1.381(9)	C(1)–C(2)	1.393(10)
C(1)–C(7)	1.529(8)	C(2)–C(3)	1.390(10)
C(3)–C(4)	1.385(11)	C(4)–C(5)	1.360(11)
C(5)–C(6)	1.381(10)	C(7)–O(1)	1.428(8)
C(7)–C(8)	1.532(8)	C(8)–C(7')	1.532(8)
O(1)–C(9)	1.414(8)		
C(6)–C(1)–C(2)	118.9(6)	C(6)–C(1)–C(7)	119.2(6)
C(2)–C(1)–C(7)	121.8(6)	C(3)–C(2)–C(1)	120.2(6)
C(4)–C(3)–C(2)	119.7(6)	C(5)–C(4)–C(3)	120.0(6)
C(4)–C(5)–C(6)	120.9(6)	C(5)–C(6)–C(1)	120.4(6)
O(1)–C(7)–C(1)	112.1(5)	O(1)–C(7)–C(8)	108.1(4)
C(1)–C(7)–C(8)	112.0(5)	C(7')–C(8)–C(7)	110.0(8)
C(9)–O(1)–C(7)	113.1(5)		

Symmetry operations for equivalent atoms
' −x+1,−y,z

Table 4. Anisotropic displacement parameters ($Å^2$) for 369. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ...+ 2hka^*b^*U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	0.009(2)	0.033(3)	0.016(3)	0.003(3)	0.002(2)	0.007(2)
C(2)	0.033(3)	0.021(3)	0.020(3)	0.003(3)	0.011(3)	0.004(3)
C(3)	0.019(3)	0.047(4)	0.019(3)	−0.001(4)	0.002(3)	−0.011(3)
C(4)	0.017(3)	0.051(4)	0.017(3)	0.001(4)	0.003(3)	0.012(3)
C(5)	0.030(3)	0.028(3)	0.023(3)	0.002(3)	0.008(3)	0.003(3)

C(6)	0.017(3)	0.037(4)	0.026(3)	−0.002(3)	0.006(3)	−0.005(2)
C(7)	0.015(2)	0.018(3)	0.020(3)	−0.002(2)	0.002(2)	0.000(2)
C(8)	0.013(3)	0.029(4)	0.016(4)	0.000	0.000	0.001(3)
O(1)	0.018(2)	0.0183(19)	0.011(2)	−0.0024(17)	0.0038(19)	−0.0015(15)
C(9)	0.032(4)	0.032(4)	0.012(3)	−0.005(2)	0.011(3)	0.000(3)

Table 5. Hydrogen coordinates and isotropic displacement parameters (Å^2) for 369.

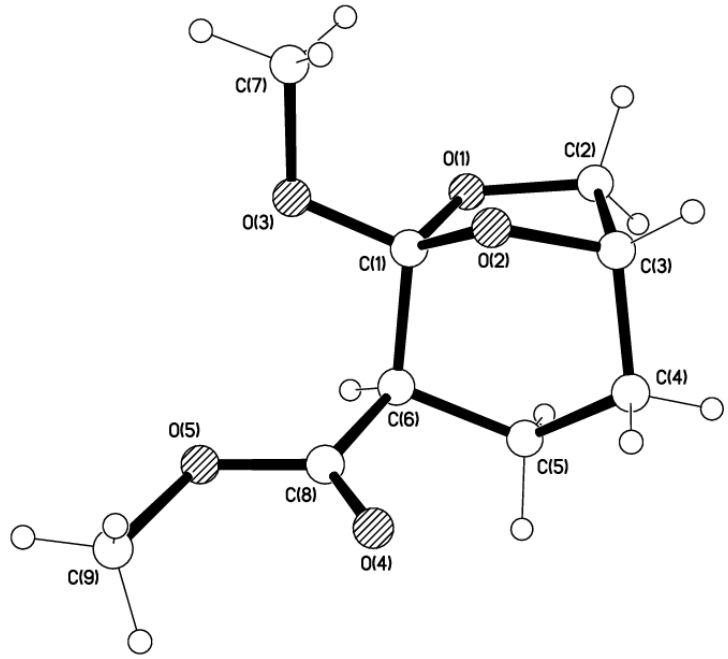
	x	y	z	U
H(2)	0.3524	−0.0836	0.4841	0.029
H(3)	0.2697	0.0041	0.2898	0.034
H(4)	0.2573	0.2352	0.2637	0.034
H(5)	0.3260	0.3760	0.4298	0.032
H(6)	0.4079	0.2910	0.6248	0.032
H(7)	0.4292	−0.0374	0.7749	0.021
H(8A)	0.4871	−0.0753	0.4781	0.023
H(8B)	0.5129	0.0753	0.4781	0.023
H(9A)	0.3883	0.1687	0.9959	0.038
H(9B)	0.4518	0.2004	1.1188	0.038
H(9C)	0.4311	0.0490	1.0794	0.038

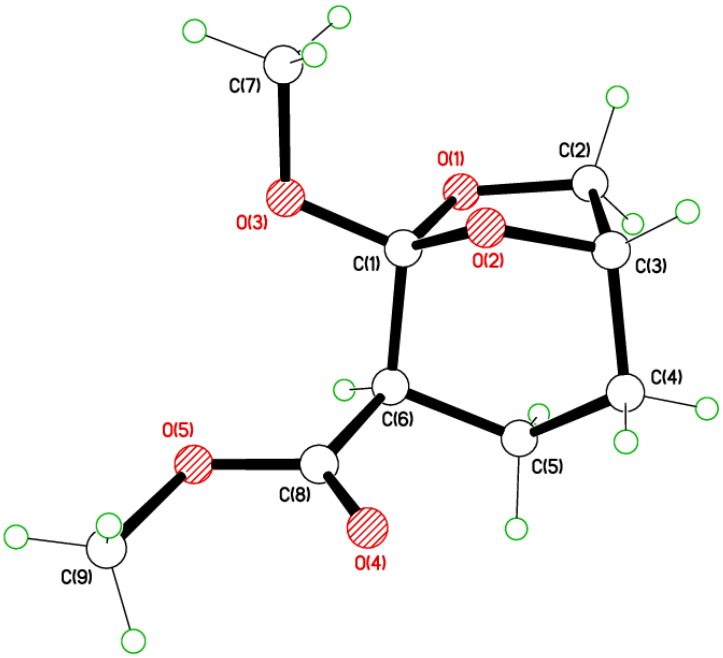
Table 6. Torsion angles [°] for 369.

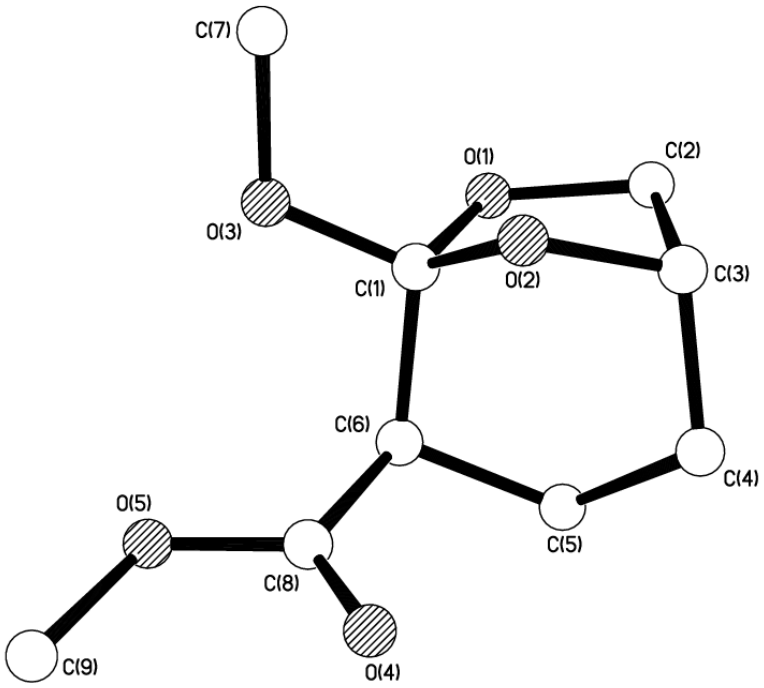
C(6)–C(1)–C(2)–C(3)	0.4(10)	C(7)–C(1)–C(2)–C(3)	−178.8(6)
C(1)–C(2)–C(3)–C(4)	0.0(11)	C(2)–C(3)–C(4)–C(5)	−0.2(10)
C(3)–C(4)–C(5)–C(6)	0.0(11)	C(4)–C(5)–C(6)–C(1)	0.4(11)
C(2)–C(1)–C(6)–C(5)	−0.6(10)	C(7)–C(1)–C(6)–C(5)	178.6(6)
C(6)–C(1)–C(7)–O(1)	21.2(8)	C(2)–C(1)–C(7)–O(1)	−159.6(6)
C(6)–C(1)–C(7)–C(8)	−100.6(6)	C(2)–C(1)–C(7)–C(8)	78.7(7)
O(1)–C(7)–C(8)–C(7')	51.9(4)	C(1)–C(7)–C(8)–C(7')	175.9(6)
C(1)–C(7)–O(1)–C(9)	84.4(6)	C(8)–C(7)–O(1)–C(9)	−151.6(5)

Symmetry operations for equivalent atoms
' −x+1,−y,z

Appendix II X-Ray crystallographic data for 434.






C(7)
O(1)
C(2)
O(3)
C(1)
O(2)
C(3)
C(6)
C(4)
O(5)
C(5)
C(8)
C(9)
O(4)

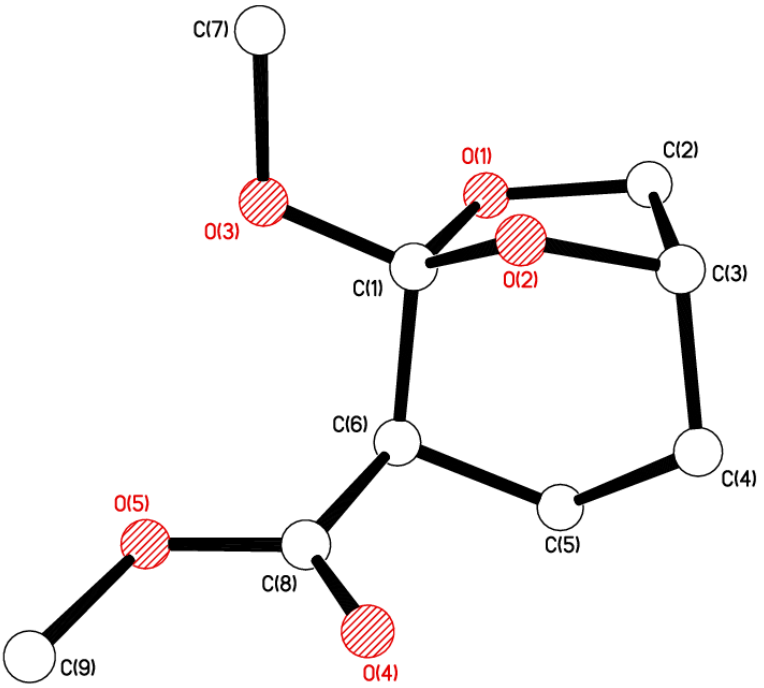

C(7)
O(1)
C(2)
O(3)
C(1)
O(2)
C(3)
C(6)
C(4)
O(5)
C(5)
C(8)
C(9)
O(4)

Table 1. Crystal data and structure refinement for 434.

Identification code	gp23	
Chemical formula	$C_9H_{14}O_5$	
Formula weight	202.20	
Temperature	150(2) K	
Radiation, wavelength	MoK, 0.71073 Å	
Crystal system, space group	monoclinic, I2/a	
Unit cell parameters	a = 11.960(3) Å	□ = 90°
	b = 10.526(2) Å	□ = 101.368(2)°
	c = 15.425(4) Å	□ = 90°
Cell volume	1903.8(8) $Å^3$	
Z	8	
Calculated density	1.411 g/cm^3	
Absorption coefficient □	0.115 mm^{-1}	
F(000)	864	
Crystal colour and size	colourless, 0.89 × 0.34 × 0.34 mm^3	
Reflections for cell refinement	4150 (□ range 2.36 to 30.49°)	
Data collection method	Bruker APEX 2 CCD diffractometer	
	□ rotation with narrow frames	
□ range for data collection	2.36 to 30.62°	
Index ranges	h −16 to 17, k −15 to 14, l −21 to 21	
Completeness to □ = 29.00°	99.9 %	
Intensity decay	0%	
Reflections collected	10496	
Independent reflections	2880 (R_{int} = 0.0491)	
Reflections with F^2>2□	2143	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.904 and 0.962	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting parameters a, b	0.0698, 0.4214	
Data / restraints / parameters	2880 / 0 / 129	
Final R indices [F^2>2□]	R1 = 0.0438, wR2 = 0.1214	
R indices (all data)	R1 = 0.0587, wR2 = 0.1321	
Goodness-of-fit on F^2	1.058	
Largest and mean shift/su	0.001 and 0.000	
Largest diff. peak and hole	0.284 and −0.271 e $Å^{-3}$	

Table 2. Atomic coordinates and equivalent isotropic displacement parameters ($Å^2$) for 434. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
C(1)	0.07409(9)	0.75444(10)	0.09086(8)	0.0230(2)
O(1)	0.19412(7)	0.75004(7)	0.12348(6)	0.0270(2)
C(2)	0.23686(10)	0.87787(11)	0.12049(9)	0.0282(3)
C(3)	0.12898(9)	0.95663(11)	0.08975(7)	0.0253(2)
O(2)	0.05516(7)	0.86361(7)	0.03817(5)	0.02311(19)
C(4)	0.07264(10)	0.99794(11)	0.16467(8)	0.0297(3)
C(5)	0.05700(11)	0.88439(12)	0.22352(8)	0.0312(3)
C(6)	0.01415(10)	0.76379(11)	0.17017(8)	0.0254(2)
O(3)	0.03734(7)	0.64769(7)	0.04262(6)	0.0275(2)
C(7)	0.07530(11)	0.63735(12)	−0.04022(9)	0.0315(3)
C(8)	−0.11395(10)	0.76334(12)	0.14111(8)	0.0290(3)
O(4)	−0.17237(9)	0.85569(10)	0.12557(10)	0.0597(4)
O(5)	−0.15661(7)	0.64583(9)	0.13722(7)	0.0348(2)
C(9)	−0.27874(12)	0.63515(15)	0.11569(11)	0.0436(4)

Table 3. Bond lengths [Å] and angles [°] for 434.

C(1)–O(3)	1.3713(13)	C(1)–O(2)	1.3999(13)
C(1)–O(1)	1.4253(14)	C(1)–C(6)	1.5381(17)
O(1)–C(2)	1.4434(13)	C(2)–C(3)	1.5284(16)
C(3)–O(2)	1.4471(13)	C(3)–C(4)	1.5118(16)
C(4)–C(5)	1.5345(18)	C(5)–C(6)	1.5444(17)
C(6)–C(8)	1.5091(16)	O(3)–C(7)	1.4421(15)
C(8)–O(4)	1.1935(16)	C(8)–O(5)	1.3348(15)
O(5)–C(9)	1.4371(16)		
O(3)–C(1)–O(2)	111.09(10)	O(3)–C(1)–O(1)	110.96(8)
O(2)–C(1)–O(1)	105.55(8)	O(3)–C(1)–C(6)	109.52(9)
O(2)–C(1)–C(6)	111.21(9)	O(1)–C(1)–C(6)	108.43(10)
C(1)–O(1)–C(2)	107.27(8)	O(1)–C(2)–C(3)	103.47(9)
O(2)–C(3)–C(4)	107.41(9)	O(2)–C(3)–C(2)	100.94(9)
C(4)–C(3)–C(2)	113.26(10)	C(1)–O(2)–C(3)	103.00(8)
C(3)–C(4)–C(5)	110.67(10)	C(4)–C(5)–C(6)	113.04(10)
C(8)–C(6)–C(1)	111.63(10)	C(8)–C(6)–C(5)	111.82(10)
C(1)–C(6)–C(5)	108.59(9)	C(1)–O(3)–C(7)	114.79(9)
O(4)–C(8)–O(5)	122.84(12)	O(4)–C(8)–C(6)	125.23(12)
O(5)–C(8)–C(6)	111.90(10)	C(8)–O(5)–C(9)	116.42(10)

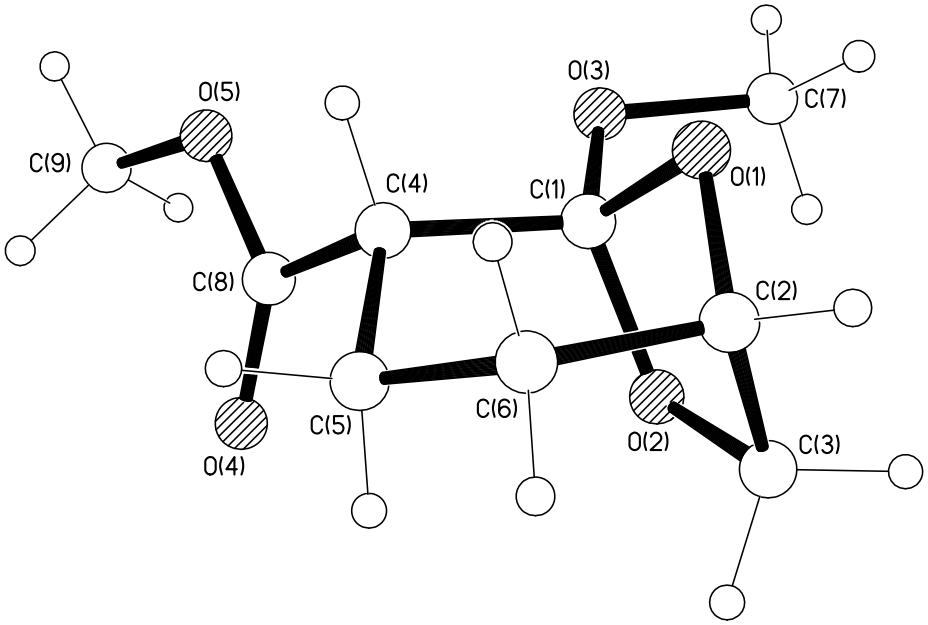
Table 4. Hydrogen coordinates and isotropic displacement parameters ($Å^2$) for 434.

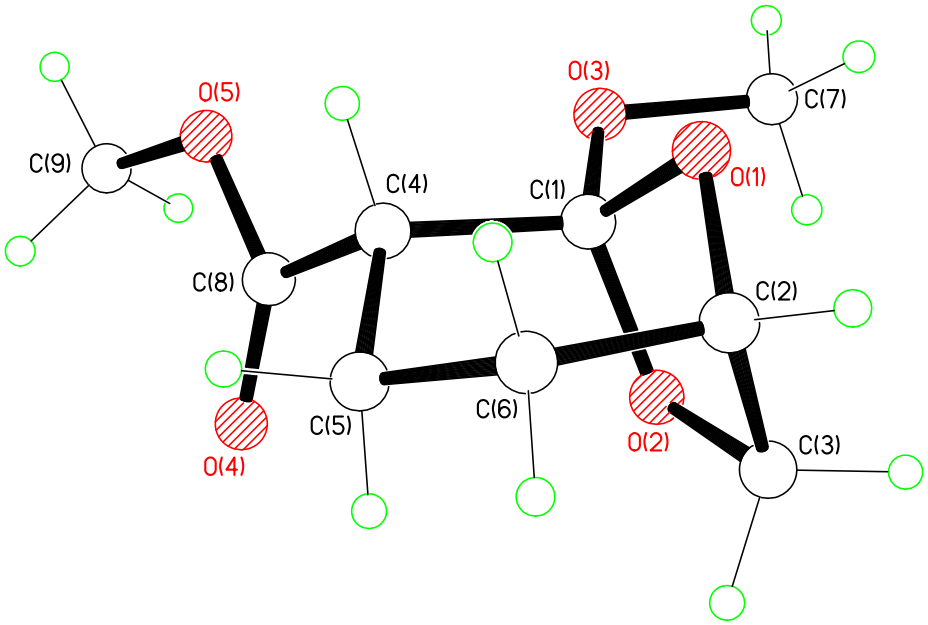
	x	y	z	U
H(2A)	0.2889	0.8845	0.0781	0.034
H(2B)	0.2778	0.9056	0.1796	0.034
H(3)	0.1435	1.0305	0.0527	0.030
H(4A)	−0.0026	1.0361	0.1402	0.036
H(4B)	0.1202	1.0633	0.2006	0.036
H(5A)	0.0018	0.9077	0.2610	0.037
H(5B)	0.1308	0.8654	0.2632	0.037
H(6)	0.0366	0.6882	0.2090	0.031
H(7A)	0.0385	0.7034	−0.0809	0.047
H(7B)	0.0549	0.5535	−0.0662	0.047
H(7C)	0.1583	0.6482	−0.0299	0.047
H(9A)	−0.3117	0.6767	0.1617	0.065
H(9B)	−0.3003	0.5452	0.1121	0.065
H(9C)	−0.3075	0.6762	0.0586	0.065

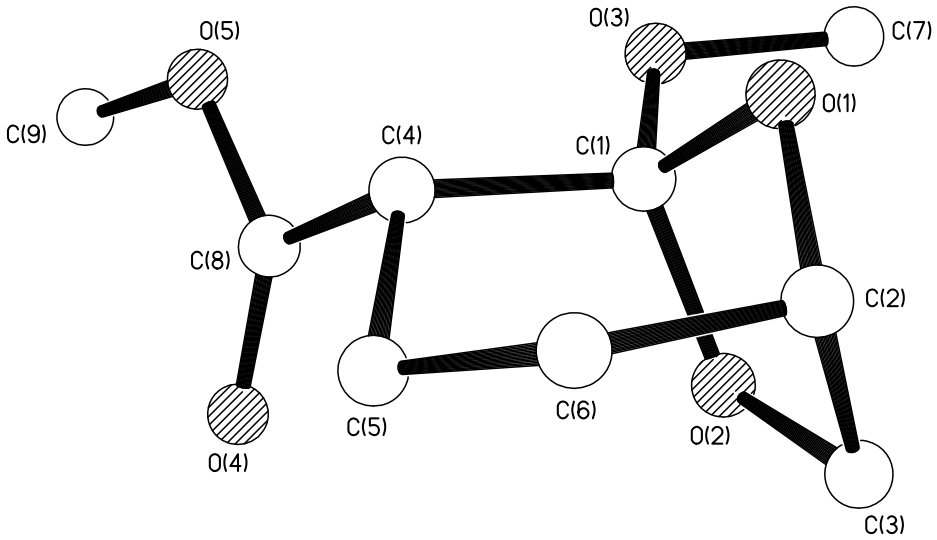
Table 5. Torsion angles [°] for 434.

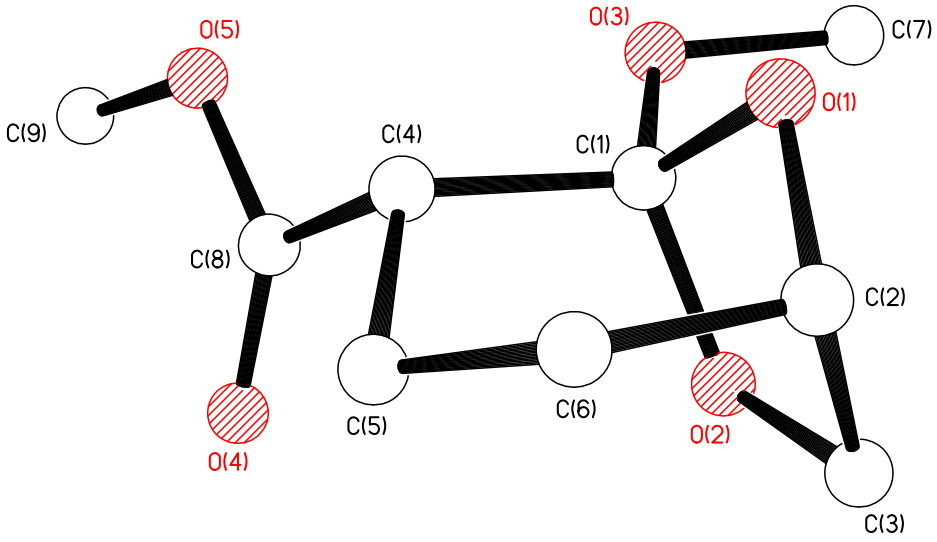
O(3)–C(1)–O(1)–C(2)	143.63(10)	O(2)–C(1)–O(1)–C(2)	23.20(11)
C(6)–C(1)–O(1)–C(2)	−96.04(10)	C(1)–O(1)–C(2)–C(3)	4.07(12)
O(1)–C(2)–C(3)–O(2)	−28.51(11)	O(1)–C(2)–C(3)–C(4)	86.00(11)
O(3)–C(1)–O(2)–C(3)	−162.56(9)	O(1)–C(1)–O(2)–C(3)	−42.21(10)
C(6)–C(1)–O(2)–C(3)	75.17(11)	C(4)–C(3)–O(2)–C(1)	−75.70(10)
C(2)–C(3)–O(2)–C(1)	43.13(10)	O(2)–C(3)–C(4)–C(5)	60.49(12)
C(2)–C(3)–C(4)–C(5)	−50.08(13)	C(3)–C(4)–C(5)–C(6)	−42.90(14)
O(3)–C(1)–C(6)–C(8)	−56.39(12)	O(2)–C(1)–C(6)–C(8)	66.78(12)
O(1)–C(1)–C(6)–C(8)	−177.60(9)	O(3)–C(1)–C(6)–C(5)	179.89(9)
O(2)–C(1)–C(6)–C(5)	−56.95(12)	O(1)–C(1)–C(6)–C(5)	58.67(11)
C(4)–C(5)–C(6)–C(8)	−84.38(12)	C(4)–C(5)–C(6)–C(1)	39.23(13)
O(2)–C(1)–O(3)–C(7)	48.60(13)	O(1)–C(1)–O(3)–C(7)	−68.49(12)
C(6)–C(1)–O(3)–C(7)	171.83(9)	C(1)–C(6)–C(8)–O(4)	−91.96(16)
C(5)–C(6)–C(8)–O(4)	29.92(18)	C(1)–C(6)–C(8)–O(5)	90.09(12)
C(5)–C(6)–C(8)–O(5)	−148.03(11)	O(4)–C(8)–O(5)–C(9)	−1.9(2)
C(6)–C(8)–O(5)–C(9)	176.13(11)		

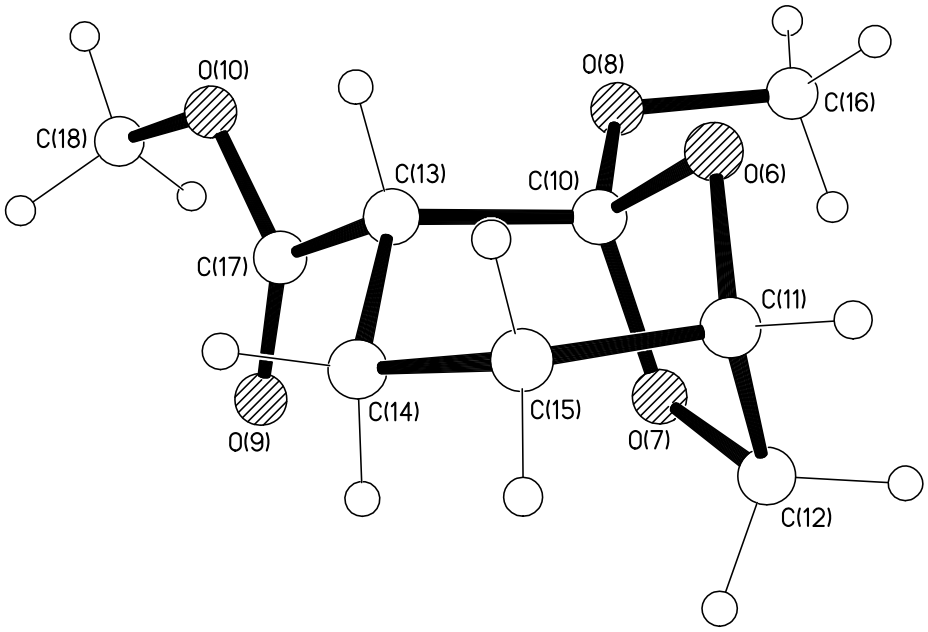
Appendix III X-Ray crystallographic data for 435.






O(5)
O(3)
C(7)
C(9)
O(1)
C(4)
C(1)
C(8)
C(2)
C(6)
C(5)
O(2)
O(4)
C(3)


O(5)
O(3)
C(7)
C(9)
O(1)
C(4)
C(1)
C(8)
C(2)
C(6)
C(5)
O(2)
O(4)
C(3)


O(10)
C(18)
C(13)
O(8)
C(16)
C(10)
O(6)
C(17)
C(11)
O(9)
C(14)
C(15)
O(7)
C(12)

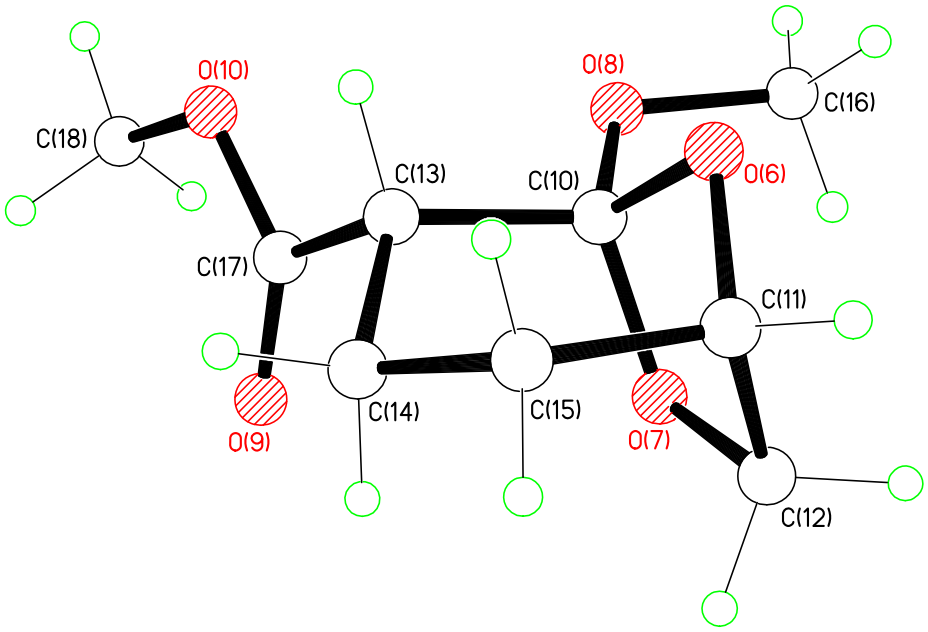

O(10)
C(18)
C(13)
O(8)
C(16)
C(10)
O(6)
C(17)
C(11)
O(9)
C(14)
C(15)
O(7)
C(12)

Table 1. Crystal data and structure refinement for 435.

Identification code	sdrc35	
Chemical formula	$C_9H_{14}O_5$	
Formula weight	202.20	
Temperature	150(2) K	
Radiation, wavelength	MoK, 0.71073 Å	
Crystal system, space group	monoclinic, $P2_1/n$	
Unit cell parameters	a = 13.8312(16) Å	□ = 90°
	b = 7.8846(9) Å	□ = 98.3668(18)°
	c = 17.820(2) Å	□ = 90°
Cell volume	1922.6(4) $Å^3$	
Z	8	
Calculated density	1.397 g/cm^3	
Absorption coefficient □	0.114 mm^{-1}	
F(000)	864	
Crystal colour and size	colourless, 0.75 × 0.30 × 0.20 mm^3	
Reflections for cell refinement	6096 (□ range 2.83 to 30.34°)	
Data collection method	Bruker APEX 2 CCD diffractometer	
	□ rotation with narrow frames	
□ range for data collection	1.75 to 30.61°	
Index ranges	h −19 to 19, k −11 to 11, l −25 to 25	
Completeness to □ = 29.00°	99.8 %	
Intensity decay	0%	
Reflections collected	21614	
Independent reflections	5794 (R_{int} = 0.0454)	
Reflections with F^2>2□	4526	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.919 and 0.978	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting parameters a, b	0.0582, 0.3180	
Data / restraints / parameters	5794 / 0 / 257	
Final R indices [F^2>2□]	R1 = 0.0418, wR2 = 0.1075	
R indices (all data)	R1 = 0.0564, wR2 = 0.1176	
Goodness-of-fit on F^2	1.030	
Largest and mean shift/su	0.000 and 0.000	
Largest diff. peak and hole	0.404 and −0.214 e $Å^{-3}$	

Table 2. Atomic coordinates and equivalent isotropic displacement parameters ($Å^2$) for 435. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
C(1)	0.78360(8)	0.15212(13)	0.06730(6)	0.0198(2)
O(1)	0.78773(6)	0.33098(10)	0.07137(5)	0.02358(18)
C(2)	0.86371(9)	0.37191(15)	0.02681(7)	0.0258(2)
C(3)	0.83624(10)	0.25598(16)	−0.04107(7)	0.0305(3)
O(2)	0.79433(6)	0.11039(10)	−0.00866(4)	0.02597(19)
C(4)	0.86895(8)	0.08135(14)	0.12346(6)	0.0205(2)
C(5)	0.96463(8)	0.13952(15)	0.09696(7)	0.0269(2)
C(6)	0.96134(9)	0.32736(16)	0.07385(8)	0.0291(3)
O(3)	0.69701(6)	0.09228(10)	0.08588(5)	0.02595(18)
C(7)	0.61118(9)	0.15069(17)	0.03639(9)	0.0358(3)
C(8)	0.86445(8)	−0.11031(14)	0.12990(6)	0.0231(2)
O(4)	0.89626(8)	−0.20977(12)	0.08837(6)	0.0378(2)
O(5)	0.82157(7)	−0.15595(11)	0.18968(5)	0.0292(2)
C(9)	0.81573(11)	−0.33665(16)	0.20309(8)	0.0373(3)
C(10)	0.38126(8)	0.33539(13)	0.11736(6)	0.0180(2)
O(6)	0.38686(6)	0.15615(9)	0.11641(4)	0.02083(17)
C(11)	0.31448(8)	0.10644(14)	0.16304(6)	0.0221(2)
C(12)	0.23048(8)	0.22381(15)	0.13198(7)	0.0246(2)
O(7)	0.28030(6)	0.37471(10)	0.11181(5)	0.02219(17)
C(13)	0.43751(8)	0.39673(13)	0.19352(6)	0.0191(2)
C(14)	0.38436(9)	0.32902(14)	0.25741(6)	0.0232(2)
C(15)	0.35592(9)	0.14165(14)	0.24568(6)	0.0236(2)
O(8)	0.42212(6)	0.40605(10)	0.05917(4)	0.02211(17)
C(16)	0.37871(10)	0.35221(15)	−0.01548(6)	0.0265(2)
C(17)	0.44545(8)	0.58889(14)	0.19520(6)	0.0206(2)
O(9)	0.38107(7)	0.68497(11)	0.20600(6)	0.0321(2)
O(10)	0.53466(6)	0.63992(10)	0.18368(5)	0.02326(17)
C(18)	0.54883(10)	0.82152(15)	0.18379(7)	0.0291(3)

Table 3. Bond lengths [Å] and angles [°] for 435.

C(1)–O(3)	1.3719(13)	C(1)–O(1)	1.4128(12)
C(1)–O(2)	1.4215(13)	C(1)–C(4)	1.5370(15)
O(1)–C(2)	1.4430(14)	C(2)–C(3)	1.5197(18)
C(2)–C(6)	1.5231(17)	C(3)–O(2)	1.4439(15)
C(4)–C(8)	1.5175(15)	C(4)–C(5)	1.5384(16)
C(5)–C(6)	1.5361(16)	O(3)–C(7)	1.4472(15)
C(8)–O(4)	1.2046(14)	C(8)–O(5)	1.3416(14)
O(5)–C(9)	1.4488(15)	C(10)–O(8)	1.3695(12)
C(10)–O(6)	1.4156(12)	C(10)–O(7)	1.4197(13)
C(10)–C(13)	1.5408(15)	O(6)–C(11)	1.4452(13)
C(11)–C(12)	1.5250(16)	C(11)–C(15)	1.5260(16)
C(12)–O(7)	1.4463(14)	C(13)–C(17)	1.5191(15)
C(13)–C(14)	1.5380(15)	C(14)–C(15)	1.5353(15)
O(8)–C(16)	1.4415(14)	C(17)–O(9)	1.2058(14)

C(17)–O(10)	1.3417(13)	O(10)–C(18)	1.4452(13)
O(3)–C(1)–O(1)	111.16(9)	O(3)–C(1)–O(2)	111.47(9)
O(1)–C(1)–O(2)	105.72(8)	O(3)–C(1)–C(4)	109.44(9)
O(1)–C(1)–C(4)	107.90(9)	O(2)–C(1)–C(4)	111.05(9)
C(1)–O(1)–C(2)	102.84(8)	O(1)–C(2)–C(3)	100.71(9)
O(1)–C(2)–C(6)	107.69(9)	C(3)–C(2)–C(6)	113.47(10)
O(2)–C(3)–C(2)	103.19(9)	C(1)–O(2)–C(3)	107.49(8)
C(8)–C(4)–C(1)	112.01(9)	C(8)–C(4)–C(5)	111.51(9)
C(1)–C(4)–C(5)	107.78(9)	C(6)–C(5)–C(4)	112.11(10)
C(2)–C(6)–C(5)	111.05(10)	C(1)–O(3)–C(7)	114.27(9)
O(4)–C(8)–O(5)	123.81(11)	O(4)–C(8)–C(4)	125.39(11)
O(5)–C(8)–C(4)	110.79(10)	C(8)–O(5)–C(9)	115.88(10)
O(8)–C(10)–O(6)	111.58(8)	O(8)–C(10)–O(7)	111.62(8)
O(6)–C(10)–O(7)	105.80(8)	O(8)–C(10)–C(13)	109.15(8)
O(6)–C(10)–C(13)	107.60(8)	O(7)–C(10)–C(13)	111.00(8)
C(10)–O(6)–C(11)	102.72(8)	O(6)–C(11)–C(12)	100.46(8)
O(6)–C(11)–C(15)	108.13(9)	C(12)–C(11)–C(15)	113.53(9)
O(7)–C(12)–C(11)	102.95(8)	C(10)–O(7)–C(12)	107.60(8)
C(17)–C(13)–C(14)	111.88(9)	C(17)–C(13)–C(10)	110.87(9)
C(14)–C(13)–C(10)	107.97(9)	C(15)–C(14)–C(13)	111.95(9)
C(11)–C(15)–C(14)	111.05(9)	C(10)–O(8)–C(16)	114.62(8)
O(9)–C(17)–O(10)	123.58(10)	O(9)–C(17)–C(13)	125.23(10)
O(10)–C(17)–C(13)	111.19(9)	C(17)–O(10)–C(18)	115.11(9)

Table 4. Hydrogen coordinates and isotropic displacement parameters ($Å^2$) for 435.

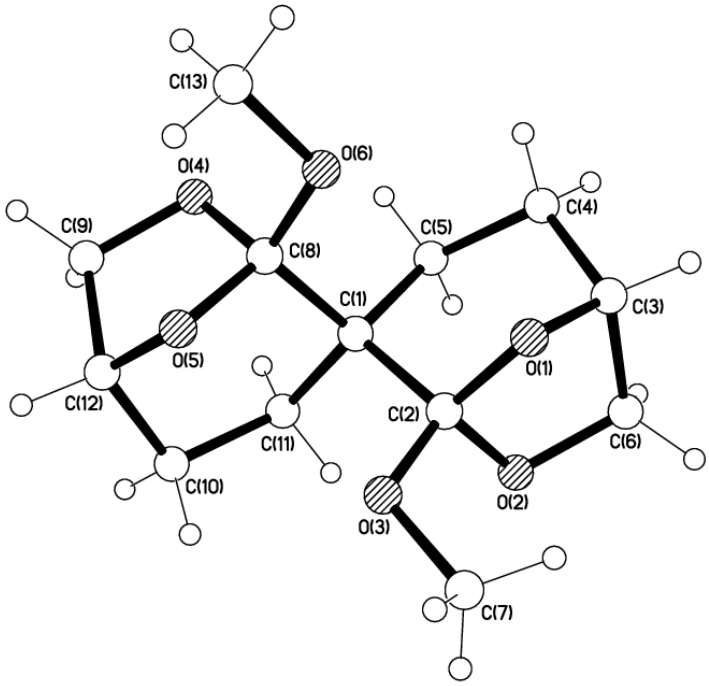
	x	y	z	U
H(2)	0.8611	0.4940	0.0114	0.031
H(3A)	0.7881	0.3109	−0.0801	0.037
H(3B)	0.8945	0.2237	−0.0641	0.037
H(4)	0.8657	0.1315	0.1746	0.025
H(5A)	1.0195	0.1214	0.1384	0.032
H(5B)	0.9769	0.0695	0.0532	0.032
H(6A)	0.9715	0.3990	0.1199	0.035
H(6B)	1.0148	0.3513	0.0440	0.035
H(7A)	0.6115	0.2749	0.0342	0.054
H(7B)	0.5524	0.1121	0.0561	0.054
H(7C)	0.6115	0.1046	−0.0147	0.054
H(9A)	0.7682	−0.3878	0.1634	0.056
H(9B)	0.7950	−0.3561	0.2527	0.056
H(9C)	0.8800	−0.3883	0.2023	0.056
H(11)	0.2958	−0.0155	0.1551	0.026
H(12A)	0.1901	0.1736	0.0870	0.030
H(12B)	0.1883	0.2488	0.1710	0.030
H(13)	0.5049	0.3476	0.1998	0.023
H(14A)	0.4273	0.3421	0.3066	0.028
H(14B)	0.3247	0.3972	0.2594	0.028
H(15A)	0.4142	0.0697	0.2607	0.028

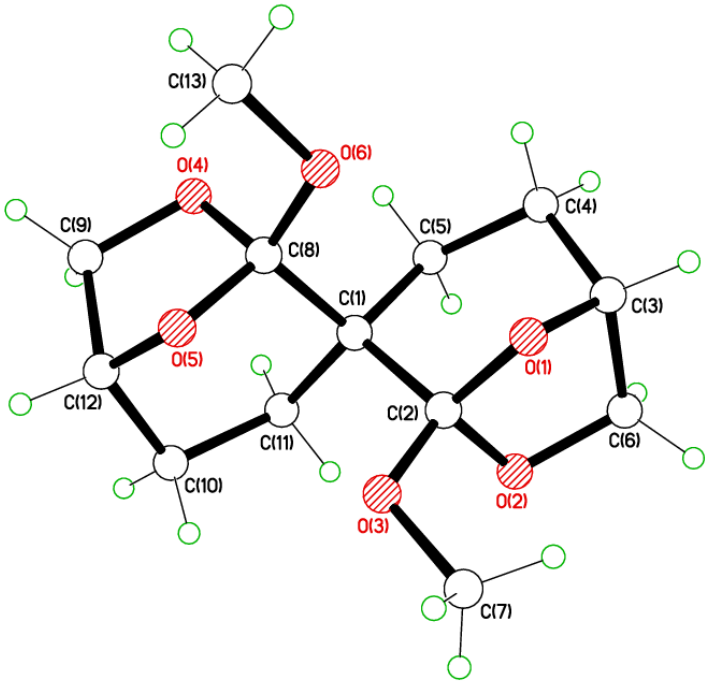
H(15B)	0.3065	0.1119	0.2785	0.028
H(16A)	0.3843	0.2288	−0.0195	0.040
H(16B)	0.4127	0.4067	−0.0536	0.040
H(16C)	0.3096	0.3846	−0.0241	0.040
H(18A)	0.4995	0.8736	0.1457	0.044
H(18B)	0.6142	0.8472	0.1718	0.044
H(18C)	0.5424	0.8670	0.2340	0.044

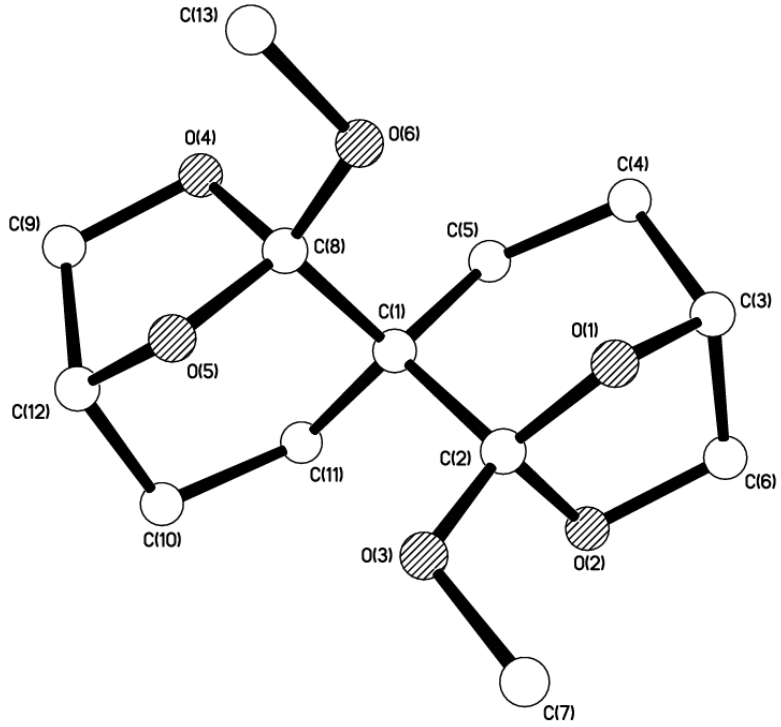
Table 5. Torsion angles [°] for 435.

O(3)–C(1)–O(1)–C(2)	−161.23(9)	O(2)–C(1)–O(1)–C(2)	−40.12(10)
C(4)–C(1)–O(1)–C(2)	78.77(10)	C(1)–O(1)–C(2)–C(3)	44.26(10)
C(1)–O(1)–C(2)–C(6)	−74.81(11)	O(1)–C(2)–C(3)–O(2)	−32.45(11)
C(6)–C(2)–C(3)–O(2)	82.34(12)	O(3)–C(1)–O(2)–C(3)	139.54(9)
O(1)–C(1)–O(2)–C(3)	18.63(11)	C(4)–C(1)–O(2)–C(3)	−98.15(10)
C(2)–C(3)–O(2)–C(1)	9.05(12)	O(3)–C(1)–C(4)–C(8)	52.50(12)
O(1)–C(1)–C(4)–C(8)	173.58(9)	O(2)–C(1)–C(4)–C(8)	−70.98(11)
O(3)–C(1)–C(4)–C(5)	175.53(9)	O(1)–C(1)–C(4)–C(5)	−63.39(11)
O(2)–C(1)–C(4)–C(5)	52.04(12)	C(8)–C(4)–C(5)–C(6)	167.80(10)
C(1)–C(4)–C(5)–C(6)	44.47(13)	O(1)–C(2)–C(6)–C(5)	57.57(13)
C(3)–C(2)–C(6)–C(5)	−52.99(13)	C(4)–C(5)–C(6)–C(2)	−43.14(14)
O(1)–C(1)–O(3)–C(7)	61.07(13)	O(2)–C(1)–O(3)–C(7)	−56.60(12)
C(4)–C(1)–O(3)–C(7)	−179.84(10)	C(1)–C(4)–C(8)–O(4)	84.98(14)
C(5)–C(4)–C(8)–O(4)	−35.91(16)	C(1)–C(4)–C(8)–O(5)	−96.29(11)
C(5)–C(4)–C(8)–O(5)	142.82(10)	O(4)–C(8)–O(5)–C(9)	0.57(17)
C(4)–C(8)–O(5)–C(9)	−178.18(10)	O(8)–C(10)–O(6)–C(11)	−161.75(8)
O(7)–C(10)–O(6)–C(11)	−40.17(10)	C(13)–C(10)–O(6)–C(11)	78.55(9)
C(10)–O(6)–C(11)–C(12)	44.72(10)	C(10)–O(6)–C(11)–C(15)	−74.47(10)
O(6)–C(11)–C(12)–O(7)	−33.23(10)	C(15)–C(11)–C(12)–O(7)	81.96(11)
O(8)–C(10)–O(7)–C(12)	139.66(9)	O(6)–C(10)–O(7)–C(12)	18.11(11)
C(13)–C(10)–O(7)–C(12)	−98.33(10)	C(11)–C(12)–O(7)–C(10)	9.86(11)
O(8)–C(10)–C(13)–C(17)	51.93(11)	O(6)–C(10)–C(13)–C(17)	173.16(8)
O(7)–C(10)–C(13)–C(17)	−71.52(11)	O(8)–C(10)–C(13)–C(14)	174.81(8)
O(6)–C(10)–C(13)–C(14)	−63.95(10)	O(7)–C(10)–C(13)–C(14)	51.37(11)
C(17)–C(13)–C(14)–C(15)	167.26(9)	C(10)–C(13)–C(14)–C(15)	45.00(12)
O(6)–C(11)–C(15)–C(14)	57.26(12)	C(12)–C(11)–C(15)–C(14)	−53.29(13)
C(13)–C(14)–C(15)–C(11)	−43.04(13)	O(6)–C(10)–O(8)–C(16)	58.48(12)
O(7)–C(10)–O(8)–C(16)	−59.66(11)	C(13)–C(10)–O(8)–C(16)	177.27(9)
C(14)–C(13)–C(17)–O(9)	−42.51(15)	C(10)–C(13)–C(17)–O(9)	78.08(14)
C(14)–C(13)–C(17)–O(10)	136.92(9)	C(10)–C(13)–C(17)–O(10)	−102.48(10)
O(9)–C(17)–O(10)–C(18)	−0.97(16)	C(13)–C(17)–O(10)–C(18)	179.59(9)

Appendix IV X-Ray crystallographic data for 455.






C(13)
O(6)
O(4)
C(4)
C(9)
C(8)
C(5)
C(3)
C(1)
O(1)
O(5)
C(12)
C(11)
C(2)
C(6)
C(10)
O(3)
O(2)
C(7)

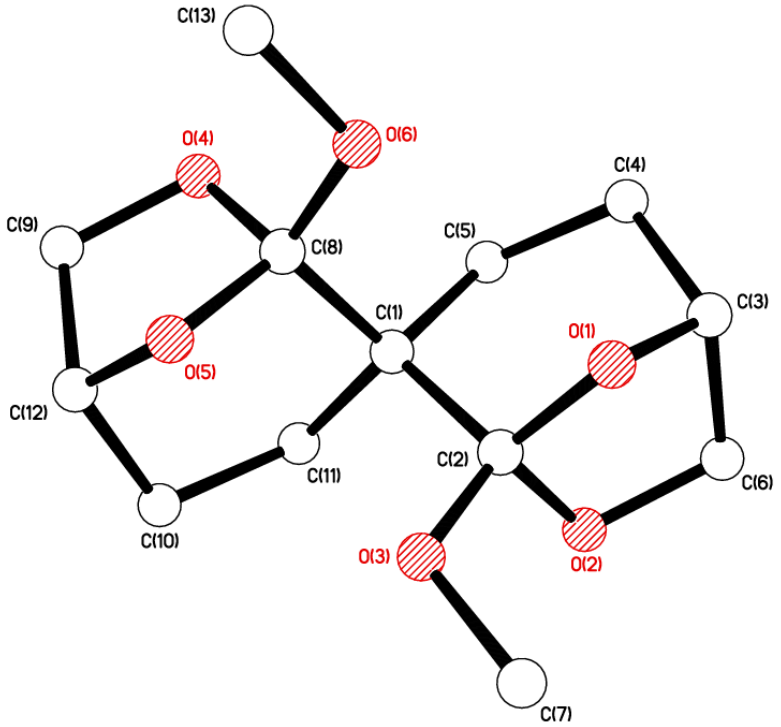

C(13)
O(6)
O(4)
C(4)
C(9)
C(8)
C(5)
C(3)
C(1)
O(1)
O(5)
C(12)
C(11)
C(2)
C(6)
C(10)
O(3)
O(2)
C(7)

Table 1. Crystal data and structure refinement for 455.

Identification code	gp25	
Chemical formula	$C_{13}H_{20}O_6$	
Formula weight	272.29	
Temperature	150(2) K	
Radiation, wavelength	MoK, 0.71073 Å	
Crystal system, space group	monoclinic, $P2_1$	
Unit cell parameters	a = 8.8470(9) Å	□ = 90°
	b = 7.3471(7) Å	□ = 93.7110(15)°
	c = 9.7536(10) Å	□ = 90°
Cell volume	632.65(11) $Å^3$	
Z	2	
Calculated density	1.429 g/cm^3	
Absorption coefficient □	0.113 mm^{-1}	
F(000)	292	
Crystal colour and size	colourless, 0.98 × 0.26 × 0.09 mm^3	
Reflections for cell refinement	5331 (□ range 2.31 to 30.47°)	
Data collection method	Bruker APEX 2 CCD diffractometer	
	□ rotation with narrow frames	
□ range for data collection	2.09 to 30.58°	
Index ranges	h −12 to 12, k −10 to 10, l −13 to 13	
Completeness to □ = 30.58°	98.3 %	
Intensity decay	0%	
Reflections collected	11159	
Independent reflections	6585 (R_{int} = 0.0225)	
Reflections with F^2>2□	6393	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.897 and 0.990	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting parameters a, b	0.0509, 0.0936	
Data / restraints / parameters	6585 / 1 / 175	
Final R indices [F^2>2□]	R1 = 0.0319, wR2 = 0.0821	
R indices (all data)	R1 = 0.0331, wR2 = 0.0831	
Goodness-of-fit on F^2	1.038	
Absolute structure parameter	0.5(5)	
Largest and mean shift/su	0.000 and 0.000	
Largest diff. peak and hole	0.270 and −0.205 e $Å^{-3}$	

Table 2. Atomic coordinates and equivalent isotropic displacement parameters ($Å^2$) for 455. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
C(1)	0.21347(11)	0.06659(14)	0.25422(10)	0.01485(17)
C(2)	0.24035(11)	0.10656(14)	0.41017(10)	0.01542(17)
O(1)	0.37865(8)	0.03350(10)	0.46438(7)	0.01734(15)
C(3)	0.34716(12)	−0.15863(15)	0.47562(10)	0.02003(19)
C(4)	0.33965(13)	−0.23979(16)	0.33201(11)	0.0222(2)
C(5)	0.21789(12)	−0.14357(14)	0.23943(10)	0.01912(19)
O(2)	0.12577(8)	0.01190(11)	0.48018(8)	0.01960(15)
C(6)	0.19279(13)	−0.15177(17)	0.53807(11)	0.0235(2)
O(3)	0.23342(9)	0.28937(10)	0.43558(7)	0.01951(15)
C(7)	0.24226(13)	0.33777(17)	0.57894(10)	0.0241(2)
C(8)	0.32743(12)	0.15932(14)	0.16299(10)	0.01645(18)
O(4)	0.28534(9)	0.11045(11)	0.02159(7)	0.02132(16)
C(9)	0.20486(14)	0.26119(17)	−0.04119(11)	0.0246(2)
C(10)	0.04449(12)	0.33456(16)	0.16038(10)	0.0204(2)
C(11)	0.05374(11)	0.13288(15)	0.20021(11)	0.01826(19)
O(5)	0.31467(8)	0.35034(10)	0.16591(7)	0.01777(14)
C(12)	0.18010(12)	0.38691(14)	0.08047(10)	0.0195(2)
O(6)	0.47372(8)	0.10732(11)	0.19722(8)	0.02048(16)
C(13)	0.58425(13)	0.1918(2)	0.11545(14)	0.0319(3)

Table 3. Hydrogen coordinates and isotropic displacement parameters ($Å^2$) for 455.

	x	y	z	U
H(3)	0.4248	−0.2213	0.5380	0.024
H(4A)	0.3159	−0.3712	0.3369	0.027
H(4B)	0.4393	−0.2267	0.2924	0.027
H(5A)	0.1177	−0.1929	0.2599	0.023
H(5B)	0.2345	−0.1736	0.1426	0.023
H(6A)	0.1310	−0.2599	0.5114	0.028
H(6B)	0.2045	−0.1445	0.6396	0.028
H(7A)	0.1406	0.3656	0.6074	0.036
H(7B)	0.3074	0.4448	0.5935	0.036
H(7C)	0.2848	0.2358	0.6335	0.036
H(9A)	0.1071	0.2216	−0.0868	0.030
H(9B)	0.2656	0.3221	−0.1095	0.030
H(10A)	−0.0503	0.3575	0.1033	0.025
H(10B)	0.0428	0.4101	0.2443	0.025
H(11A)	0.0203	0.0591	0.1189	0.022

H(11B)	−0.0181	0.1099	0.2720	0.022
H(12)	0.1750	0.5174	0.0514	0.023
H(13A)	0.5631	0.1592	0.0187	0.048
H(13B)	0.6858	0.1494	0.1464	0.048
H(13C)	0.5790	0.3243	0.1256	0.048

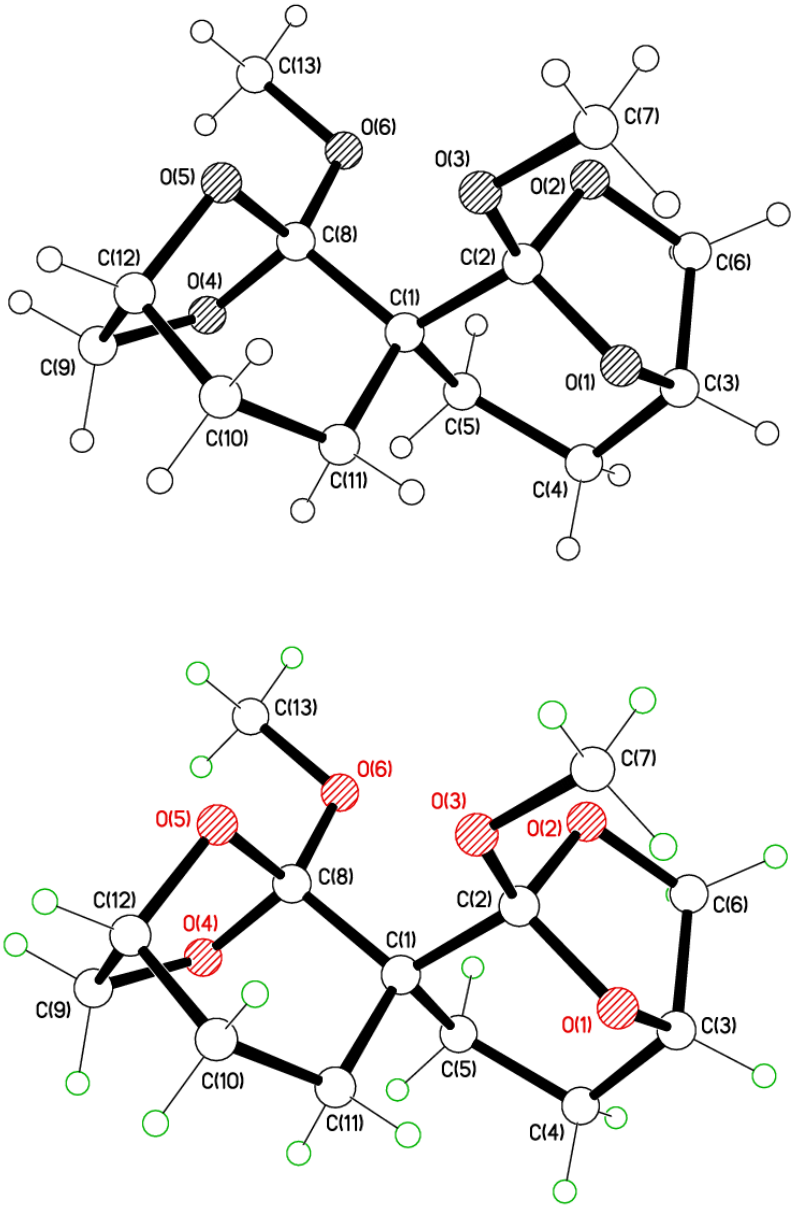
Table 4. Bond lengths [Å] and angles [°] for 455.

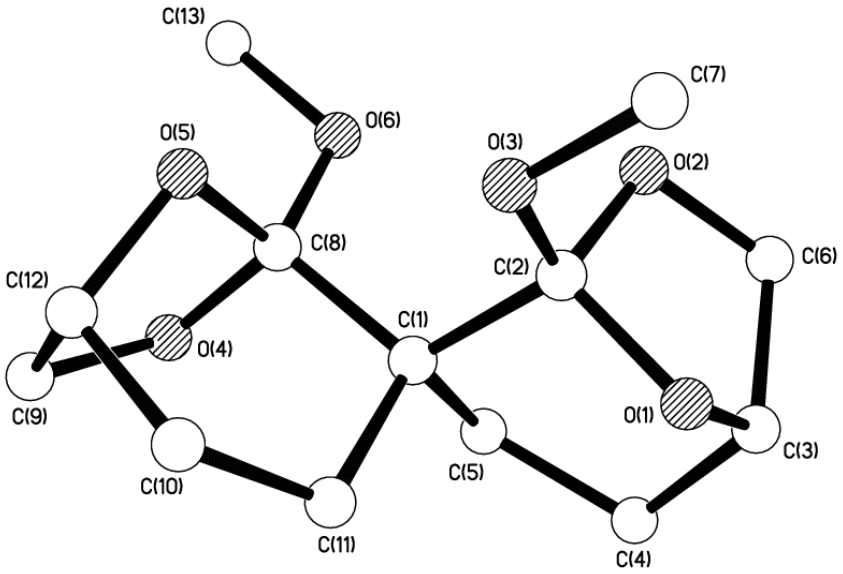
C(1)–C(8)	1.5455(13)	C(1)–C(5)	1.5515(15)
C(1)–C(2)	1.5522(13)	C(1)–C(11)	1.5542(14)
C(2)–O(3)	1.3679(12)	C(2)–O(1)	1.4075(11)
C(2)–O(2)	1.4378(12)	O(1)–C(3)	1.4444(13)
C(3)–C(4)	1.5198(15)	C(3)–C(6)	1.5318(15)
C(4)–C(5)	1.5328(15)	O(2)–C(6)	1.4398(13)
O(3)–C(7)	1.4399(12)	C(8)–O(6)	1.3699(12)
C(8)–O(5)	1.4084(12)	C(8)–O(4)	1.4502(12)
O(4)–C(9)	1.4325(14)	C(9)–C(12)	1.5307(15)
C(10)–C(12)	1.5217(15)	C(10)–C(11)	1.5327(16)
O(5)–C(12)	1.4337(12)	O(6)–C(13)	1.4417(13)
C(8)–C(1)–C(5)	111.34(8)	C(8)–C(1)–C(2)	114.61(8)
C(5)–C(1)–C(2)	106.04(8)	C(8)–C(1)–C(11)	106.22(8)
C(5)–C(1)–C(11)	107.95(8)	C(2)–C(1)–C(11)	110.56(8)
O(3)–C(2)–O(1)	110.76(8)	O(3)–C(2)–O(2)	110.34(8)
O(1)–C(2)–O(2)	105.04(8)	O(3)–C(2)–C(1)	110.95(8)
O(1)–C(2)–C(1)	111.73(8)	O(2)–C(2)–C(1)	107.81(8)
C(2)–O(1)–C(3)	103.53(8)	O(1)–C(3)–C(4)	108.10(8)
O(1)–C(3)–C(6)	100.33(8)	C(4)–C(3)–C(6)	113.11(9)
C(3)–C(4)–C(5)	110.44(9)	C(4)–C(5)–C(1)	115.16(9)
C(2)–O(2)–C(6)	107.77(8)	O(2)–C(6)–C(3)	103.10(8)
C(2)–O(3)–C(7)	114.72(8)	O(6)–C(8)–O(5)	110.41(8)
O(6)–C(8)–O(4)	110.06(8)	O(5)–C(8)–O(4)	104.48(8)
O(6)–C(8)–C(1)	112.21(8)	O(5)–C(8)–C(1)	111.81(8)
O(4)–C(8)–C(1)	107.55(8)	C(9)–O(4)–C(8)	107.76(8)
O(4)–C(9)–C(12)	103.14(8)	C(12)–C(10)–C(11)	110.08(9)
C(10)–C(11)–C(1)	114.92(9)	C(8)–O(5)–C(12)	103.86(8)
O(5)–C(12)–C(10)	107.91(8)	O(5)–C(12)–C(9)	100.51(8)
C(10)–C(12)–C(9)	113.68(9)	C(8)–O(6)–C(13)	114.14(9)

Table 5. Torsion angles [°] for 455.

C(8)–C(1)–C(2)–O(3)	58.87(11)	C(5)–C(1)–C(2)–O(3)	−177.89(8)
C(11)–C(1)–C(2)–O(3)	−61.13(11)	C(8)–C(1)–C(2)–O(1)	−65.26(11)
C(5)–C(1)–C(2)–O(1)	57.97(11)	C(11)–C(1)–C(2)–O(1)	174.73(8)
C(8)–C(1)–C(2)–O(2)	179.81(8)	C(5)–C(1)–C(2)–O(2)	−56.96(10)
C(11)–C(1)–C(2)–O(2)	59.81(10)	O(3)–C(2)–O(1)–C(3)	159.54(8)
O(2)–C(2)–O(1)–C(3)	40.41(9)	C(1)–C(2)–O(1)–C(3)	−76.21(9)
C(2)–O(1)–C(3)–C(4)	74.02(9)	C(2)–O(1)–C(3)–C(6)	−44.62(9)
O(1)–C(3)–C(4)–C(5)	−57.98(11)	C(6)–C(3)–C(4)–C(5)	52.17(12)
C(3)–C(4)–C(5)–C(1)	42.56(12)	C(8)–C(1)–C(5)–C(4)	85.11(10)
C(2)–C(1)–C(5)–C(4)	−40.17(11)	C(11)–C(1)–C(5)–C(4)	−158.67(9)
O(3)–C(2)–O(2)–C(6)	−138.14(9)	O(1)–C(2)–O(2)–C(6)	−18.73(10)
C(1)–C(2)–O(2)–C(6)	100.55(9)	C(2)–O(2)–C(6)–C(3)	−8.94(11)
O(1)–C(3)–C(6)–O(2)	32.28(10)	C(4)–C(3)–C(6)–O(2)	−82.62(11)
O(1)–C(2)–O(3)–C(7)	−61.13(11)	O(2)–C(2)–O(3)–C(7)	54.75(11)
C(1)–C(2)–O(3)–C(7)	174.18(8)	C(5)–C(1)–C(8)–O(6)	−60.74(11)
C(2)–C(1)–C(8)–O(6)	59.61(11)	C(11)–C(1)–C(8)–O(6)	−178.01(8)
C(5)–C(1)–C(8)–O(5)	174.58(8)	C(2)–C(1)–C(8)–O(5)	−65.07(11)
C(11)–C(1)–C(8)–O(5)	57.31(10)	C(5)–C(1)–C(8)–O(4)	60.44(10)
C(2)–C(1)–C(8)–O(4)	−179.21(8)	C(11)–C(1)–C(8)–O(4)	−56.83(9)
O(6)–C(8)–O(4)–C(9)	−136.68(9)	O(5)–C(8)–O(4)–C(9)	−18.15(10)
C(1)–C(8)–O(4)–C(9)	100.81(9)	C(8)–O(4)–C(9)–C(12)	−9.33(11)
C(12)–C(10)–C(11)–C(1)	43.14(12)	C(8)–C(1)–C(11)–C(10)	−40.34(11)
C(5)–C(1)–C(11)–C(10)	−159.85(8)	C(2)–C(1)–C(11)–C(10)	84.58(10)
O(6)–C(8)–O(5)–C(12)	158.44(7)	O(4)–C(8)–O(5)–C(12)	40.14(9)
C(1)–C(8)–O(5)–C(12)	−75.88(9)	C(8)–O(5)–C(12)–C(10)	74.41(9)
C(8)–O(5)–C(12)–C(9)	−44.88(9)	C(11)–C(10)–C(12)–O(5)	−58.82(10)
C(11)–C(10)–C(12)–C(9)	51.73(12)	O(4)–C(9)–C(12)–O(5)	32.69(10)
O(4)–C(9)–C(12)–C(10)	−82.33(11)	O(5)–C(8)–O(6)–C(13)	−54.03(12)
O(4)–C(8)–O(6)–C(13)	60.80(12)	C(1)–C(8)–O(6)–C(13)	−179.48(9)

Appendix V X-Ray crystallographic data for 456.

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O(6)
C(7)
O(5)
O(3)
O(2)
C(8)
C(6)
C(12)
C(2)
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O(4)
C(9)
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C(3)
C(10)
C(5)
C(11)
C(4)

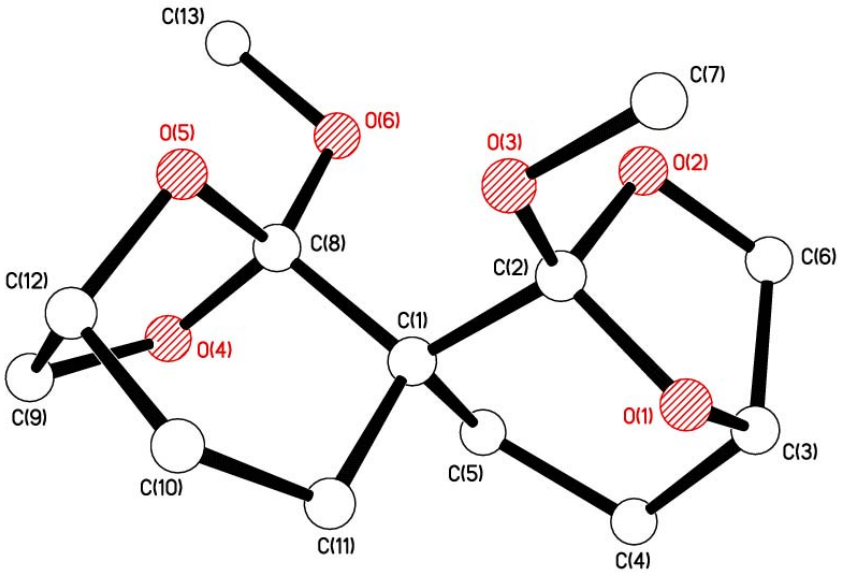

C(13)
O(6)
C(7)
O(5)
O(3)
O(2)
C(8)
C(6)
C(12)
C(2)
C(1)
O(4)
C(9)
O(1)
C(3)
C(10)
C(5)
C(11)
C(4)

Table 1. Crystal data and structure refinement for 456.

Identification code	gp24	
Chemical formula	$C_{13}H_{20}O_6$	
Formula weight	272.29	
Temperature	150(2) K	
Radiation, wavelength	MoK, 0.71073 Å	
Crystal system, space group	orthorhombic, $P2_12_12_1$	
Unit cell parameters	a = 8.4355(13) Å	□ = 90°
	b = 10.4726(17) Å	□ = 90°
	c = 14.540(2) Å	□ = 90°
Cell volume	1284.5(3) $Å^3$	
Z	4	
Calculated density	1.408 g/cm^3	
Absorption coefficient □	0.111 mm^{-1}	
F(000)	584	
Crystal colour and size	colourless, 0.97 × 0.64 × 0.47 mm^3	
Reflections for cell refinement	7616 (□ range 2.40 to 30.42°)	
Data collection method	Bruker APEX 2 CCD diffractometer	
	□ rotation with narrow frames	
□ range for data collection	2.40 to 30.59°	
Index ranges	h −11 to 12, k −14 to 14, l −20 to 20	
Completeness to □ = 29.00°	99.9 %	
Intensity decay	0%	
Reflections collected	13970	
Independent reflections	2230 (R_{int} = 0.0513)	
Reflections with F^2>2□	1999	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.900 and 0.950	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting parameters a, b	0.0376, 0.3652	
Data / restraints / parameters	2230 / 0 / 174	
Final R indices [F^2>2□]	R1 = 0.0361, wR2 = 0.0940	
R indices (all data)	R1 = 0.0423, wR2 = 0.0968	
Goodness-of-fit on F^2	1.075	
Largest and mean shift/su	0.000 and 0.000	
Largest diff. peak and hole	0.342 and −0.185 e $Å^{-3}$	

Friedel pairs merged, no indication of which enantiomer from the data.

Table 2. Atomic coordinates and equivalent isotropic displacement parameters ($Å^2$) for 456. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
C(1)	0.6926(2)	0.42540(17)	0.58004(12)	0.0213(3)
C(2)	0.5346(2)	0.39950(17)	0.63182(12)	0.0222(3)
O(1)	0.47813(17)	0.27679(13)	0.60549(10)	0.0264(3)
C(3)	0.5753(3)	0.19047(19)	0.65887(14)	0.0317(4)
C(4)	0.7395(3)	0.18670(19)	0.61399(16)	0.0322(4)
C(5)	0.8103(2)	0.32036(18)	0.61206(15)	0.0274(4)
O(2)	0.55675(17)	0.39011(12)	0.72867(9)	0.0241(3)
C(6)	0.5759(3)	0.25739(18)	0.75125(14)	0.0298(4)
O(3)	0.42353(15)	0.49070(13)	0.61064(10)	0.0260(3)
C(7)	0.2677(2)	0.4682(2)	0.64706(16)	0.0316(4)
C(8)	0.7679(2)	0.55717(17)	0.59874(12)	0.0206(3)
O(4)	0.91333(16)	0.56591(14)	0.54796(9)	0.0259(3)
C(9)	0.8795(3)	0.6347(2)	0.46407(13)	0.0293(4)
C(10)	0.6101(3)	0.5397(2)	0.42869(13)	0.0295(4)
C(11)	0.6662(3)	0.41599(19)	0.47449(13)	0.0268(4)
O(5)	0.67435(16)	0.65821(12)	0.56515(9)	0.0230(3)
C(12)	0.7009(2)	0.6526(2)	0.46698(13)	0.0275(4)
O(6)	0.79653(17)	0.57402(13)	0.69130(9)	0.0251(3)
C(13)	0.8764(3)	0.6903(2)	0.71464(15)	0.0327(4)

Table 3. Hydrogen coordinates and isotropic displacement parameters ($Å^2$) for 456.

	x	y	z	U
H(3)	0.5270	0.1035	0.6629	0.038
H(4A)	0.8098	0.1289	0.6492	0.039
H(4B)	0.7305	0.1534	0.5505	0.039
H(5A)	0.9031	0.3204	0.5704	0.033
H(5B)	0.8486	0.3420	0.6745	0.033
H(6A)	0.4875	0.2270	0.7903	0.036
H(6B)	0.6772	0.2427	0.7840	0.036
H(7A)	0.2285	0.3856	0.6251	0.047
H(7B)	0.1960	0.5361	0.6265	0.047
H(7C)	0.2722	0.4676	0.7144	0.047
H(9A)	0.9117	0.5847	0.4094	0.035
H(9B)	0.9349	0.7181	0.4631	0.035
H(10A)	0.6269	0.5342	0.3614	0.035
H(10B)	0.4953	0.5515	0.4400	0.035
H(11A)	0.7668	0.3892	0.4453	0.032
H(11B)	0.5868	0.3484	0.4624	0.032
H(12)	0.6685	0.7340	0.4363	0.033
H(13A)	0.9826	0.6903	0.6873	0.049

H(13B)	0.8853	0.6971	0.7817	0.049
H(13C)	0.8160	0.7631	0.6909	0.049

Table 4. Bond lengths [Å] and angles [°] for 456.

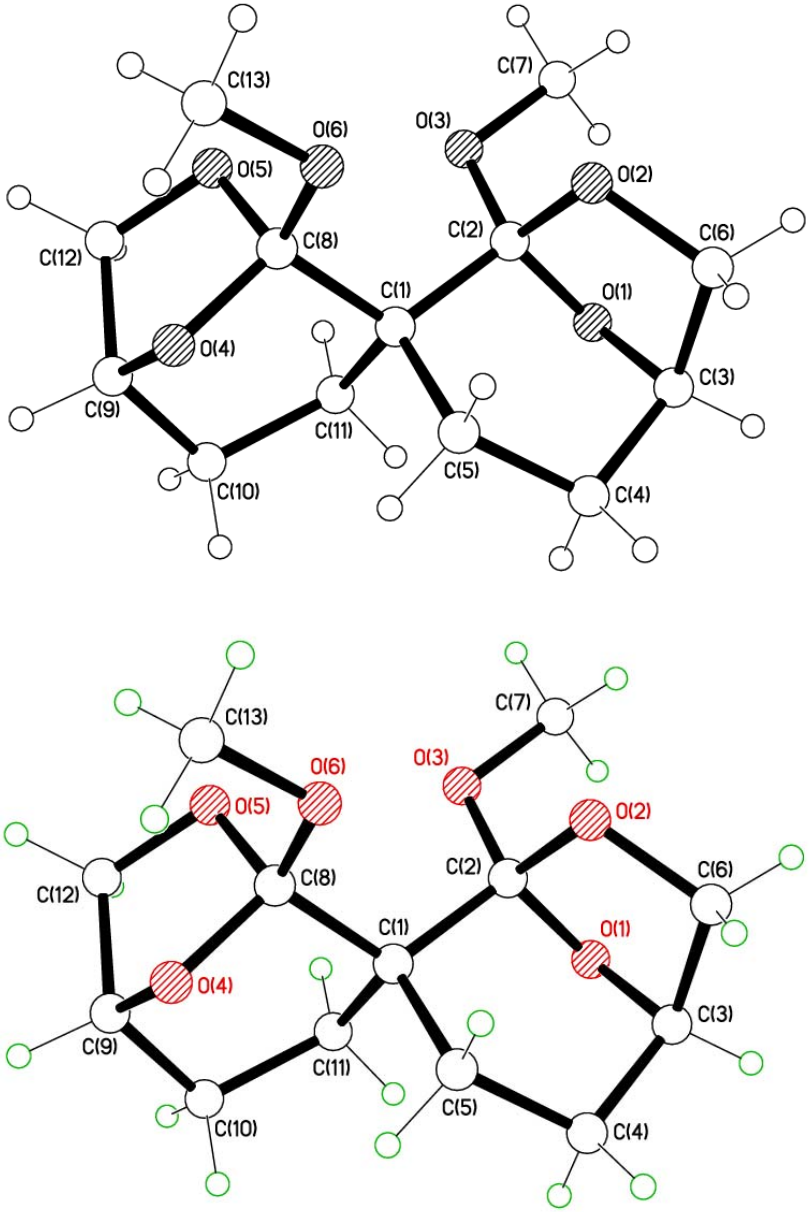
C(1)–C(8)	1.543(2)	C(1)–C(5)	1.553(3)
C(1)–C(11)	1.554(3)	C(1)–C(2)	1.555(3)
C(2)–O(3)	1.373(2)	C(2)–O(1)	1.423(2)
C(2)–O(2)	1.424(2)	O(1)–C(3)	1.446(2)
C(3)–C(6)	1.515(3)	C(3)–C(4)	1.532(3)
C(4)–C(5)	1.522(3)	O(2)–C(6)	1.437(2)
O(3)–C(7)	1.437(2)	C(8)–O(6)	1.379(2)
C(8)–O(5)	1.408(2)	C(8)–O(4)	1.435(2)
O(4)–C(9)	1.445(2)	C(9)–C(12)	1.520(3)
C(10)–C(12)	1.515(3)	C(10)–C(11)	1.532(3)
O(5)–C(12)	1.446(2)	O(6)–C(13)	1.433(2)
C(8)–C(1)–C(5)	108.50(14)	C(8)–C(1)–C(11)	106.85(14)
C(5)–C(1)–C(11)	110.05(15)	C(8)–C(1)–C(2)	115.06(14)
C(5)–C(1)–C(2)	106.21(15)	C(11)–C(1)–C(2)	110.13(15)
O(3)–C(2)–O(1)	109.84(15)	O(3)–C(2)–O(2)	111.06(15)
O(1)–C(2)–O(2)	104.33(14)	O(3)–C(2)–C(1)	110.80(14)
O(1)–C(2)–C(1)	108.32(15)	O(2)–C(2)–C(1)	112.24(15)
C(2)–O(1)–C(3)	103.32(14)	O(1)–C(3)–C(6)	100.87(16)
O(1)–C(3)–C(4)	107.46(16)	C(6)–C(3)–C(4)	112.73(19)
C(5)–C(4)–C(3)	109.82(16)	C(4)–C(5)–C(1)	113.96(16)
C(2)–O(2)–C(6)	107.91(14)	O(2)–C(6)–C(3)	104.15(15)
C(2)–O(3)–C(7)	115.33(15)	O(6)–C(8)–O(5)	109.91(15)
O(6)–C(8)–O(4)	110.16(14)	O(5)–C(8)–O(4)	104.65(14)
O(6)–C(8)–C(1)	111.01(14)	O(5)–C(8)–C(1)	112.34(14)
O(4)–C(8)–C(1)	108.56(14)	C(8)–O(4)–C(9)	107.32(14)
O(4)–C(9)–C(12)	103.51(16)	C(12)–C(10)–C(11)	110.15(16)
C(10)–C(11)–C(1)	114.84(15)	C(8)–O(5)–C(12)	103.03(14)
O(5)–C(12)–C(10)	108.43(16)	O(5)–C(12)–C(9)	100.71(16)
C(10)–C(12)–C(9)	113.25(18)	C(8)–O(6)–C(13)	114.98(15)

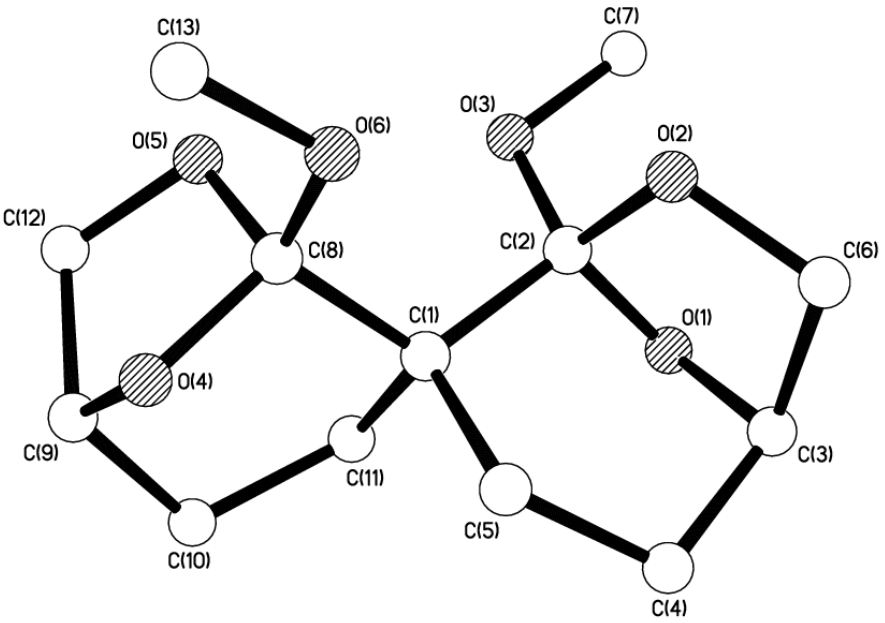
Table 5. Torsion angles [°] for 456.

C(8)–C(1)–C(2)–O(3)	57.74(19)	C(5)–C(1)–C(2)–O(3)	177.80(14)
C(11)–C(1)–C(2)–O(3)	−63.07(19)	C(8)–C(1)–C(2)–O(1)	178.29(14)
C(5)–C(1)–C(2)–O(1)	−61.66(18)	C(11)–C(1)–C(2)–O(1)	57.48(18)
C(8)–C(1)–C(2)–O(2)	−67.06(19)	C(5)–C(1)–C(2)–O(2)	53.00(19)
C(11)–C(1)–C(2)–O(2)	172.13(14)	O(3)–C(2)–O(1)–C(3)	−160.68(15)
O(2)–C(2)–O(1)–C(3)	−41.58(18)	C(1)–C(2)–O(1)–C(3)	78.17(17)
C(2)–O(1)–C(3)–C(6)	42.83(19)	C(2)–O(1)–C(3)–C(4)	−75.39(18)
O(1)–C(3)–C(4)–C(5)	58.8(2)	C(6)–C(3)–C(4)–C(5)	−51.4(2)
C(3)–C(4)–C(5)–C(1)	−45.2(2)	C(8)–C(1)–C(5)–C(4)	169.35(16)

C(11)–C(1)–C(5)–C(4)	−74.1(2)	C(2)–C(1)–C(5)–C(4)	45.1(2)
O(3)–C(2)–O(2)–C(6)	141.01(16)	O(1)–C(2)–O(2)–C(6)	22.7(2)
C(1)–C(2)–O(2)–C(6)	−94.34(18)	C(2)–O(2)–C(6)–C(3)	4.0(2)
O(1)–C(3)–C(6)–O(2)	−28.5(2)	C(4)–C(3)–C(6)–O(2)	85.8(2)
O(1)–C(2)–O(3)–C(7)	53.9(2)	O(2)–C(2)–O(3)–C(7)	−61.0(2)
C(1)–C(2)–O(3)–C(7)	173.58(15)	C(5)–C(1)–C(8)–O(6)	−61.12(18)
C(11)–C(1)–C(8)–O(6)	−179.75(15)	C(2)–C(1)–C(8)–O(6)	57.67(19)
C(5)–C(1)–C(8)–O(5)	175.36(15)	C(11)–C(1)–C(8)–O(5)	56.72(18)
C(2)–C(1)–C(8)–O(5)	−65.86(19)	C(5)–C(1)–C(8)–O(4)	60.11(18)
C(11)–C(1)–C(8)–O(4)	−58.52(18)	C(2)–C(1)–C(8)–O(4)	178.90(14)
O(6)–C(8)–O(4)–C(9)	−140.55(16)	O(5)–C(8)–O(4)–C(9)	−22.45(18)
C(1)–C(8)–O(4)–C(9)	97.70(17)	C(8)–O(4)–C(9)–C(12)	−5.4(2)
C(12)–C(10)–C(11)–C(1)	42.3(2)	C(8)–C(1)–C(11)–C(10)	−39.1(2)
C(5)–C(1)–C(11)–C(10)	−156.68(16)	C(2)–C(1)–C(11)–C(10)	86.55(19)
O(6)–C(8)–O(5)–C(12)	160.79(15)	O(4)–C(8)–O(5)–C(12)	42.52(17)
C(1)–C(8)–O(5)–C(12)	−75.07(17)	C(8)–O(5)–C(12)–C(10)	74.48(18)
C(8)–O(5)–C(12)–C(9)	−44.63(18)	C(11)–C(10)–C(12)–O(5)	−59.2(2)
C(11)–C(10)–C(12)–C(9)	51.7(2)	O(4)–C(9)–C(12)–O(5)	30.17(19)
O(4)–C(9)–C(12)–C(10)	−85.39(19)	O(5)–C(8)–O(6)–C(13)	−59.2(2)
O(4)–C(8)–O(6)–C(13)	55.7(2)	C(1)–C(8)–O(6)–C(13)	175.94(16)

Appendix VI X-Ray crystallographic data for 457.

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O(6)
O(5)
O(2)
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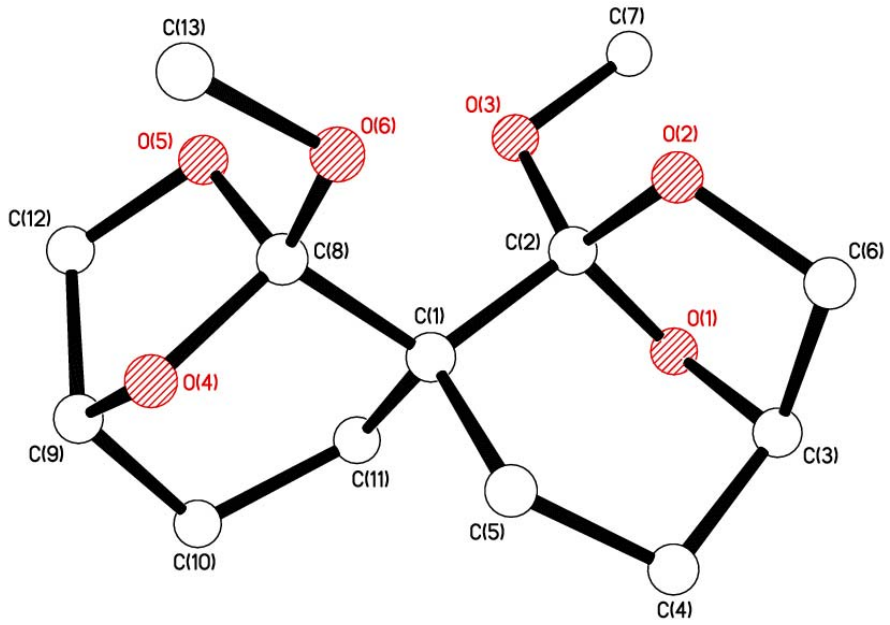
C(8)
C(2)
C(6)
C(1)
O(1)
O(4)
C(9)
C(11)
C(3)
C(5)
C(10)
C(4)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O(5)
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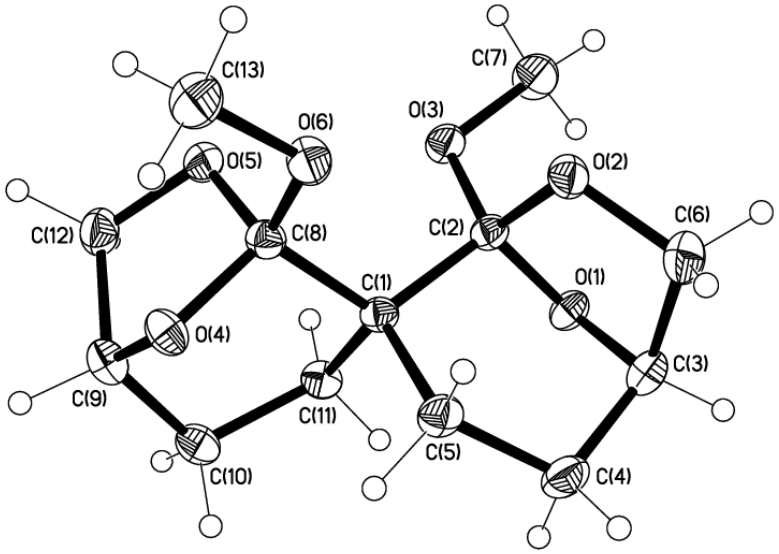
O(1)
O(4)
C(9)
C(11)
C(3)
C(5)
C(10)
C(4)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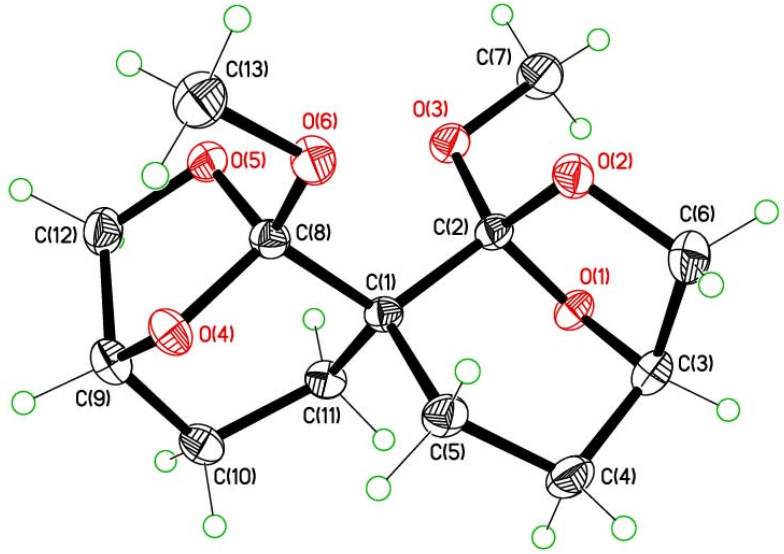
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C(5)
C(4)

Table 1. Crystal data and structure refinement for 457.

Identification code	gp18	
Chemical formula	$C_{13}H_{20}O_6$	
Formula weight	272.29	
Temperature	150(2) K	
Radiation, wavelength	MoK, 0.71073 Å	
Crystal system, space group	monoclinic, $P2_1/n$	
Unit cell parameters	a = 8.5623(3) Å	□ = 90°
	b = 13.3514(5) Å	□ = 100.6704(6)°
	c = 11.5109(4) Å	□ = 90°
Cell volume	1293.16(8) $Å^3$	
Z	4	
Calculated density	1.399 g/cm^3	
Absorption coefficient □	0.110 mm^{-1}	
F(000)	584	
Crystal colour and size	colourless, 0.57 × 0.49 × 0.24 mm^3	
Reflections for cell refinement	6796 (□ range 2.36 to 30.51°)	
Data collection method	Bruker APEX 2 CCD diffractometer	
	□ rotation with narrow frames	
□ range for data collection	2.36 to 30.54°	
Index ranges	h −12 to 12, k −18 to 18, l −16 to 16	
Completeness to □ = 30.00°	99.7 %	
Intensity decay	0%	
Reflections collected	14640	
Independent reflections	3903 (R_{int} = 0.0197)	
Reflections with F^2>2□	3337	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.940 and 0.974	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting parameters a, b	0.0584, 0.2728	
Data / restraints / parameters	3903 / 0 / 174	
Final R indices [F^2>2□]	R1 = 0.0367, wR2 = 0.1003	
R indices (all data)	R1 = 0.0431, wR2 = 0.1050	
Goodness-of-fit on F^2	1.046	
Largest and mean shift/su	0.000 and 0.000	
Largest diff. peak and hole	0.442 and −0.218 e $Å^{-3}$	

Table 2. Atomic coordinates and equivalent isotropic displacement parameters ($Å^2$) for 457. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
C(1)	0.50701(10)	0.11863(6)	0.23164(7)	0.01514(16)
C(2)	0.44366(10)	0.21549(7)	0.28076(7)	0.01615(17)
O(1)	0.28133(7)	0.22727(5)	0.22656(6)	0.01857(14)
C(3)	0.29145(11)	0.26743(8)	0.11154(8)	0.02177(19)
C(4)	0.33955(12)	0.18286(8)	0.03726(8)	0.0244(2)
C(5)	0.49856(11)	0.13705(7)	0.09779(8)	0.02019(18)
O(2)	0.52114(8)	0.30238(5)	0.24783(6)	0.02066(15)
C(6)	0.42042(12)	0.34611(8)	0.14661(9)	0.0246(2)
O(3)	0.45708(8)	0.21057(5)	0.40184(6)	0.02086(15)
C(7)	0.39028(14)	0.29412(9)	0.45369(9)	0.0308(2)
C(8)	0.68001(10)	0.08916(7)	0.28801(8)	0.01692(17)
O(4)	0.72314(8)	0.00241(5)	0.23039(6)	0.01959(15)
C(9)	0.64642(12)	−0.07735(7)	0.28266(9)	0.02122(18)
C(10)	0.47034(11)	−0.07283(7)	0.22960(9)	0.02128(18)
C(11)	0.40037(11)	0.02943(7)	0.25396(8)	0.01829(17)
O(5)	0.69217(8)	0.06025(5)	0.40895(6)	0.02060(15)
C(12)	0.68121(12)	−0.04705(7)	0.41293(9)	0.0240(2)
O(6)	0.78420(7)	0.16572(5)	0.27778(6)	0.02169(15)
C(13)	0.94906(11)	0.13766(8)	0.30440(10)	0.0273(2)

Table 3. Hydrogen coordinates and isotropic displacement parameters ($Å^2$) for 457.

	x	y	z	U
H(3)	0.1887	0.2986	0.0728	0.026
H(4A)	0.3496	0.2088	−0.0416	0.029
H(4B)	0.2562	0.1305	0.0261	0.029
H(5A)	0.5860	0.1826	0.0869	0.024
H(5B)	0.5145	0.0726	0.0590	0.024
H(6A)	0.4799	0.3580	0.0819	0.030
H(6B)	0.3745	0.4102	0.1675	0.030
H(7A)	0.4336	0.3565	0.4279	0.046
H(7B)	0.4171	0.2892	0.5400	0.046
H(7C)	0.2745	0.2938	0.4286	0.046
H(9)	0.6932	−0.1441	0.2698	0.025
H(10A)	0.4136	−0.1266	0.2641	0.026
H(10B)	0.4551	−0.0840	0.1432	0.026
H(11A)	0.3853	0.0315	0.3372	0.022
H(11B)	0.2946	0.0369	0.2027	0.022
H(12A)	0.5942	−0.0682	0.4534	0.029
H(12B)	0.7822	−0.0768	0.4542	0.029
H(13A)	0.9692	0.0981	0.3774	0.041
H(13B)	1.0151	0.1981	0.3147	0.041
H(13C)	0.9752	0.0976	0.2392	0.041

Table 4. Bond lengths [Å] and angles [°] for 457.

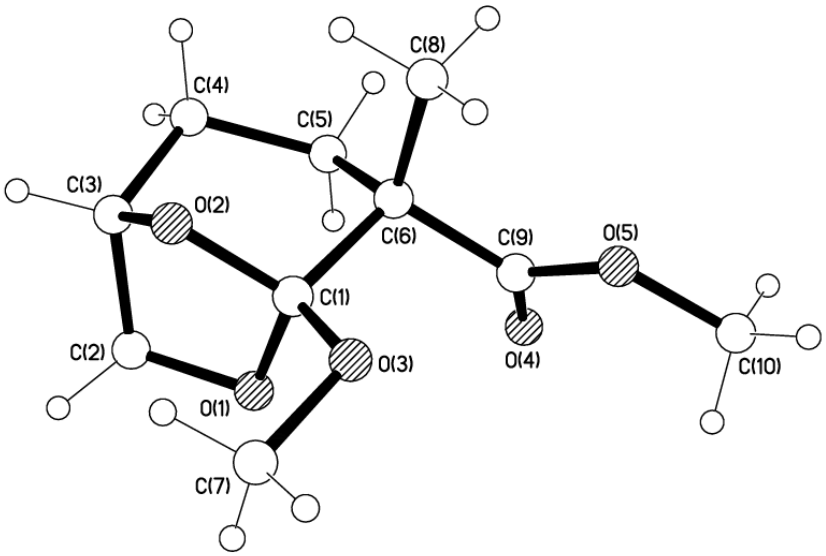
C(1)–C(5)	1.5487(12)	C(1)–C(2)	1.5492(12)
C(1)–C(11)	1.5508(12)	C(1)–C(8)	1.5537(12)
C(2)–O(3)	1.3787(10)	C(2)–O(2)	1.4222(11)
C(2)–O(1)	1.4229(10)	O(1)–C(3)	1.4459(11)
C(3)–C(4)	1.5186(14)	C(3)–C(6)	1.5235(14)
C(4)–C(5)	1.5368(13)	O(2)–C(6)	1.4387(12)
O(3)–C(7)	1.4332(12)	C(8)–O(6)	1.3760(11)
C(8)–O(4)	1.4172(10)	C(8)–O(5)	1.4297(11)
O(4)–C(9)	1.4401(11)	C(9)–C(10)	1.5195(13)
C(9)–C(12)	1.5281(14)	C(10)–C(11)	1.5376(13)
O(5)–C(12)	1.4370(12)	O(6)–C(13)	1.4376(11)
C(5)–C(1)–C(2)	105.99(7)	C(5)–C(1)–C(11)	111.49(7)
C(2)–C(1)–C(11)	108.90(7)	C(5)–C(1)–C(8)	108.72(7)
C(2)–C(1)–C(8)	115.48(7)	C(11)–C(1)–C(8)	106.34(7)
O(3)–C(2)–O(2)	110.65(7)	O(3)–C(2)–O(1)	109.90(7)
O(2)–C(2)–O(1)	105.01(7)	O(3)–C(2)–C(1)	111.09(7)
O(2)–C(2)–C(1)	111.81(7)	O(1)–C(2)–C(1)	108.17(7)
C(2)–O(1)–C(3)	102.90(6)	O(1)–C(3)–C(4)	107.95(8)
O(1)–C(3)–C(6)	100.16(7)	C(4)–C(3)–C(6)	113.77(8)
C(3)–C(4)–C(5)	110.52(8)	C(4)–C(5)–C(1)	112.86(7)
C(2)–O(2)–C(6)	107.92(7)	O(2)–C(6)–C(3)	103.36(7)
C(2)–O(3)–C(7)	114.76(7)	O(6)–C(8)–O(4)	109.74(7)
O(6)–C(8)–O(5)	110.63(7)	O(4)–C(8)–O(5)	104.88(7)
O(6)–C(8)–C(1)	111.05(7)	O(4)–C(8)–C(1)	108.81(7)
O(5)–C(8)–C(1)	111.53(7)	C(8)–O(4)–C(9)	103.31(6)
O(4)–C(9)–C(10)	107.34(8)	O(4)–C(9)–C(12)	101.13(7)
C(10)–C(9)–C(12)	112.49(8)	C(9)–C(10)–C(11)	110.68(7)
C(10)–C(11)–C(1)	112.99(7)	C(8)–O(5)–C(12)	107.86(7)
O(5)–C(12)–C(9)	103.57(7)	C(8)–O(6)–C(13)	114.51(7)

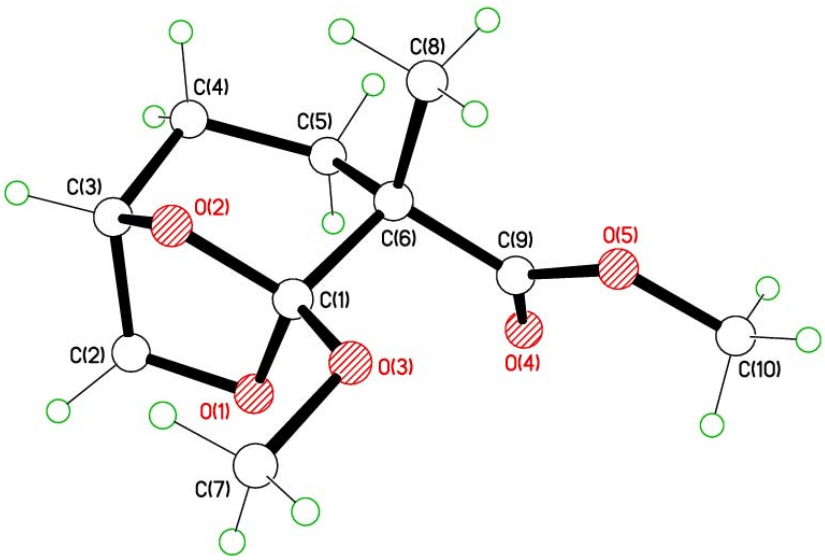
Table 5. Torsion angles [°] for 457.

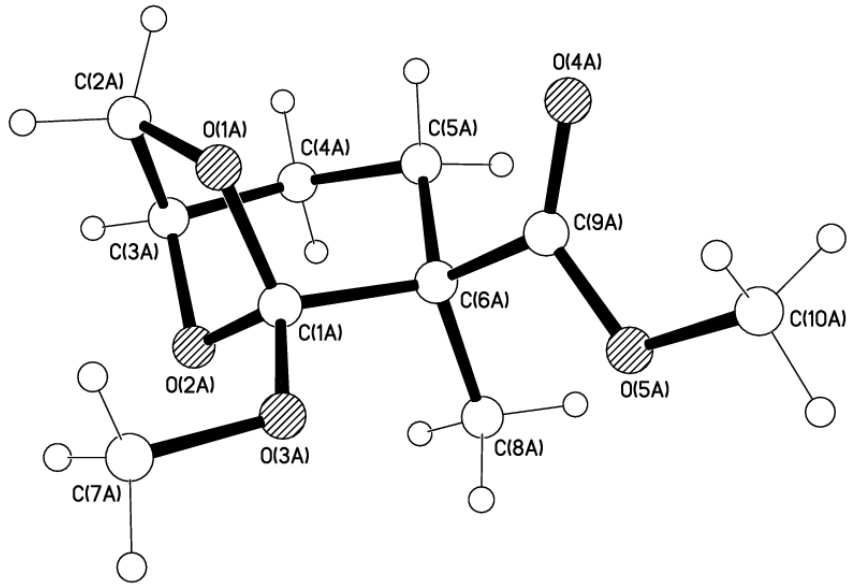
C(5)–C(1)–C(2)–O(3)	−175.39(7)	C(11)–C(1)–C(2)–O(3)	64.56(9)
C(8)–C(1)–C(2)–O(3)	−54.96(10)	C(5)–C(1)–C(2)–O(2)	−51.23(9)
C(11)–C(1)–C(2)–O(2)	−171.28(7)	C(8)–C(1)–C(2)–O(2)	69.20(9)
C(5)–C(1)–C(2)–O(1)	63.92(8)	C(11)–C(1)–C(2)–O(1)	−56.14(9)
C(8)–C(1)–C(2)–O(1)	−175.65(7)	O(3)–C(2)–O(1)–C(3)	159.68(7)
O(2)–C(2)–O(1)–C(3)	40.65(8)	C(1)–C(2)–O(1)–C(3)	−78.88(8)
C(2)–O(1)–C(3)–C(4)	74.43(8)	C(2)–O(1)–C(3)–C(6)	−44.82(8)
O(1)–C(3)–C(4)–C(5)	−57.97(10)	C(6)–C(3)–C(4)–C(5)	52.23(11)
C(3)–C(4)–C(5)–C(1)	44.96(11)	C(2)–C(1)–C(5)–C(4)	−46.08(10)
C(11)–C(1)–C(5)–C(4)	72.28(10)	C(8)–C(1)–C(5)–C(4)	−170.81(8)
O(3)–C(2)–O(2)–C(6)	−137.34(8)	O(1)–C(2)–O(2)–C(6)	−18.81(9)
C(1)–C(2)–O(2)–C(6)	98.25(8)	C(2)–O(2)–C(6)–C(3)	−9.16(9)
O(1)–C(3)–C(6)–O(2)	32.88(9)	C(4)–C(3)–C(6)–O(2)	−82.03(9)
O(2)–C(2)–O(3)–C(7)	59.61(10)	O(1)–C(2)–O(3)–C(7)	−55.90(10)
C(1)–C(2)–O(3)–C(7)	−175.57(8)	C(5)–C(1)–C(8)–O(6)	62.60(9)
C(2)–C(1)–C(8)–O(6)	−56.33(10)	C(11)–C(1)–C(8)–O(6)	−177.24(7)

C(5)–C(1)–C(8)–O(4)	−58.30(9)	C(2)–C(1)–C(8)–O(4)	−177.23(7)
C(11)–C(1)–C(8)–O(4)	61.86(8)	C(5)–C(1)–C(8)–O(5)	−173.51(7)
C(2)–C(1)–C(8)–O(5)	67.56(9)	C(11)–C(1)–C(8)–O(5)	−53.35(9)
O(6)–C(8)–O(4)–C(9)	159.94(7)	O(5)–C(8)–O(4)–C(9)	41.08(8)
C(1)–C(8)–O(4)–C(9)	−78.36(8)	C(8)–O(4)–C(9)–C(10)	75.15(8)
C(8)–O(4)–C(9)–C(12)	−42.88(8)	O(4)–C(9)–C(10)–C(11)	−58.81(9)
C(12)–C(9)–C(10)–C(11)	51.57(10)	C(9)–C(10)–C(11)–C(1)	44.75(10)
C(5)–C(1)–C(11)–C(10)	74.05(9)	C(2)–C(1)–C(11)–C(10)	−169.35(7)
C(8)–C(1)–C(11)–C(10)	−44.30(9)	O(6)–C(8)–O(5)–C(12)	−140.01(7)
O(4)–C(8)–O(5)–C(12)	−21.75(9)	C(1)–C(8)–O(5)–C(12)	95.86(8)
C(8)–O(5)–C(12)–C(9)	−4.97(9)	O(4)–C(9)–C(12)–O(5)	29.10(9)
C(10)–C(9)–C(12)–O(5)	−85.13(9)	O(4)–C(8)–O(6)–C(13)	−47.01(10)
O(5)–C(8)–O(6)–C(13)	68.24(10)	C(1)–C(8)–O(6)–C(13)	−167.35(8)

Appendix VII X-Ray crystallographic data for 469.



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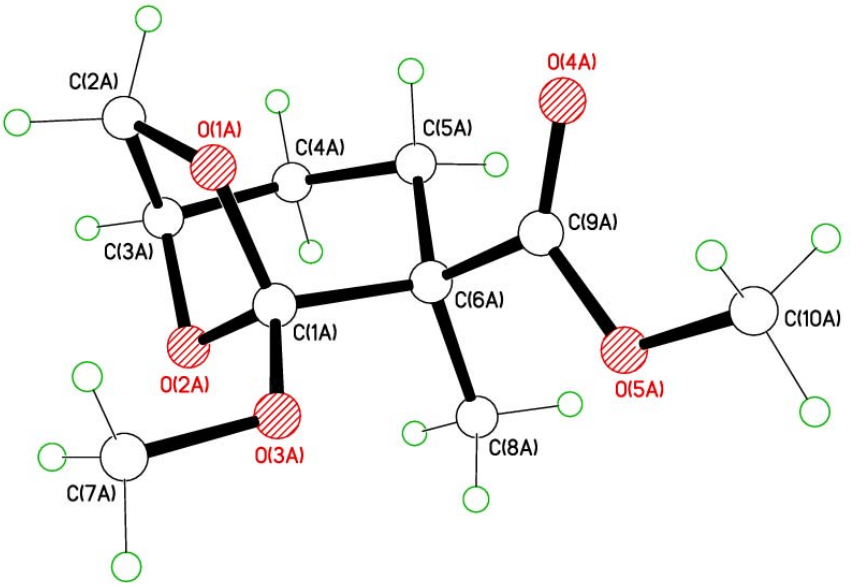
C(4A)
C(5A)
O(4A)
C(3A)
C(9A)
C(6A)
C(10A)
C(1A)
O(2A)
O(5A)
O(3A)
C(8A)
C(7A)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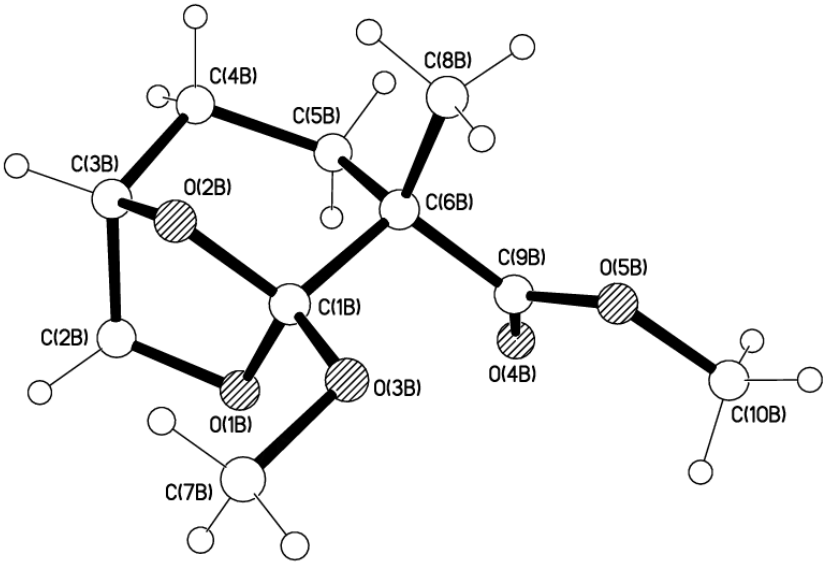
O(1A)
C(4A)
C(5A)
O(4A)
C(3A)
C(9A)
C(6A)
C(10A)
C(1A)
O(2A)
O(5A)
O(3A)
C(8A)
C(7A)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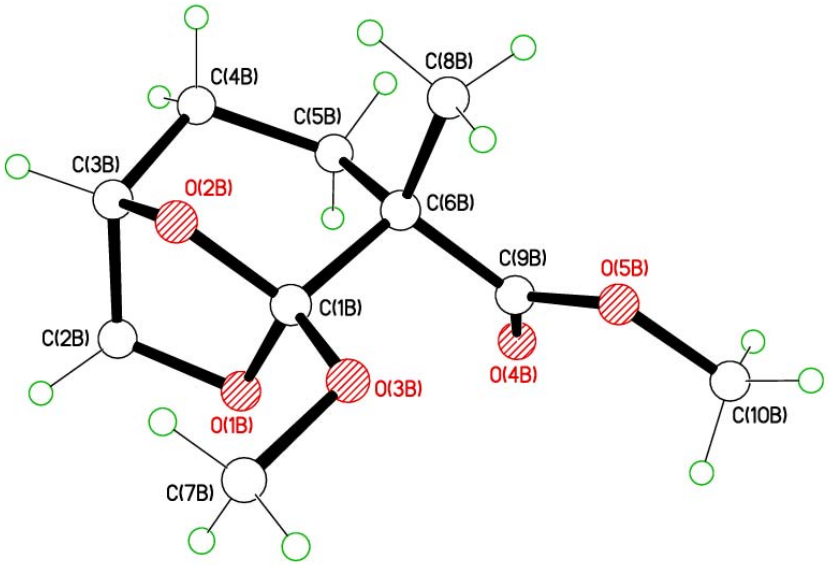
C(5B)
C(3B)
O(2B)
C(6B)
C(9B)
O(5B)
C(1B)
C(2B)
O(4B)
O(3B)
O(1B)
C(10B)
C(7B)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C(8B)
C(5B)
C(3B)
O(2B)
C(6B)
C(9B)
O(5B)
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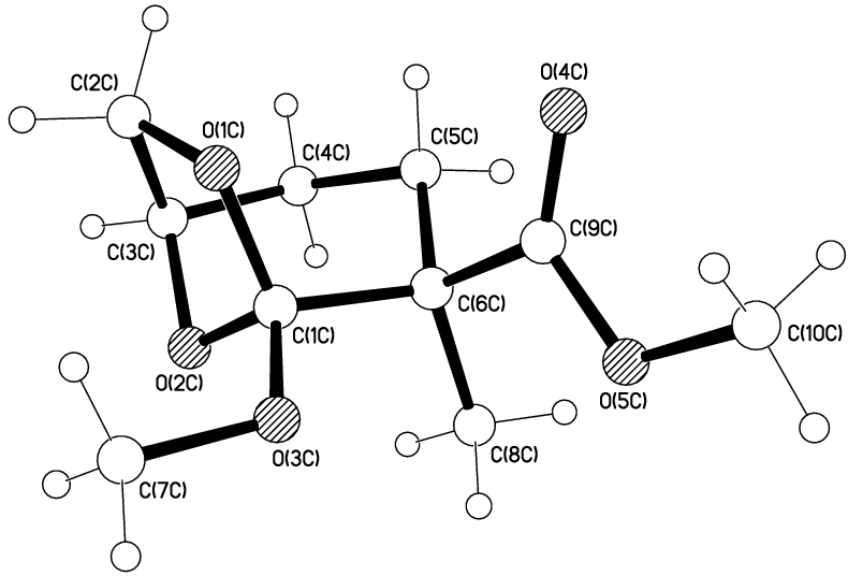
C(2B)
O(4B)
O(3B)
O(1B)
C(10B)
C(7B)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O(4C)
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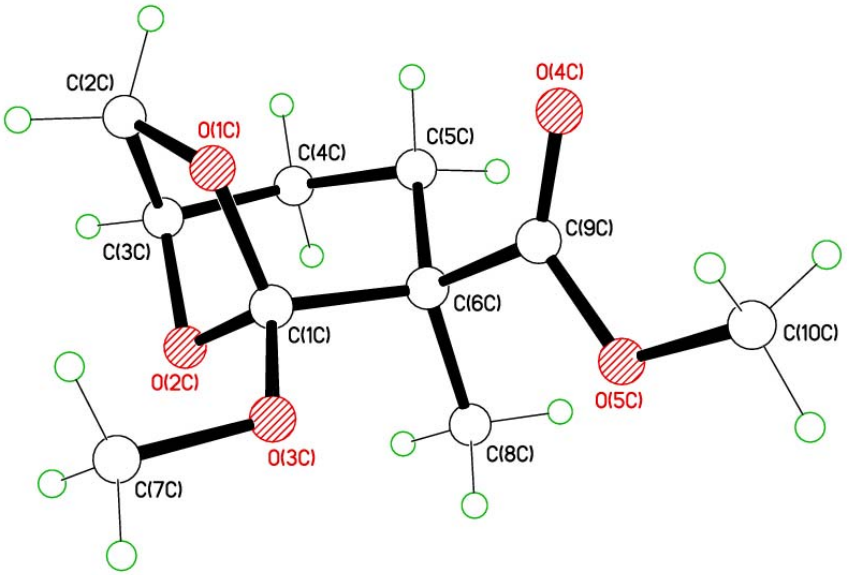
O(5C)
O(3C)
C(8C)
C(7C)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O(1C)
C(4C)
C(5C)
O(4C)
C(3C)
C(9C)
C(6C)
C(1C)
C(10C)
O(2C)
O(5C)
O(3C)
C(8C)
C(7C)

Identification code	gp16
Chemical formula	$C_{10}H_{16}O_5$
Formula weight	216.23
Temperature	150(2) K
Radiation, wavelength	MoK, 0.71073 Å
Crystal system, space group	orthorhombic, $Pna2_1$
Unit cell parameters	a = 22.8417(15) Å □ = 90°
	b = 7.8571(5) Å □ = 90°
	c = 23.4504(16) Å □ = 90°
Cell volume	4208.6(5) $Å^3$
Z	16
Calculated density	1.365 g/cm^3
Absorption coefficient □	0.109 mm^{-1}
F(000)	1856
Crystal colour and size	colourless, 1.12 × 0.33 × 0.23 mm^3
Reflections for cell refinement	15902 (□ range 2.49 to 28.31°)
Data collection method	Bruker Apex 2 CCD diffractometer
	□-scans
□ range for data collection	1.78 to 28.54°
Index ranges	h 0 to 30, k 0 to 10, l 0 to 31
Completeness to □ = 28.54°	99.3 %
Intensity decay	0%
Reflections collected	67584
Independent reflections	5448 (R_{int} = 0.0722)
Reflections with F^2>2□	4691
Absorption correction	semi-empirical from equivalents
Min. and max. transmission	0.887 and 0.975
Structure solution	direct methods
Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.1407, 0.3227
Data / restraints / parameters	5448 / 1 / 553
Final R indices [F^2>2□]	R1 = 0.0673, wR2 = 0.1686
R indices (all data)	R1 = 0.0752, wR2 = 0.1789
Goodness-of-fit on F^2	1.063
Largest and mean shift/su	0.000 and 0.000
Largest diff. peak and hole	1.109 and –0.274 e $Å^{-3}$
De-twinned data; Friedels merged.	

Table 2. Atomic coordinates and equivalent isotropic displacement parameters ($Å^2$) for 469. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
C(1)	0.07635(13)	0.8538(4)	0.50337(12)	0.0142(6)
O(1)	0.10498(10)	0.9094(3)	0.45253(10)	0.0217(5)
C(2)	0.10775(16)	0.7647(5)	0.41402(16)	0.0250(7)
O(2)	0.07872(10)	0.6743(3)	0.50195(10)	0.0178(5)
C(3)	0.06815(16)	0.6369(4)	0.44264(14)	0.0241(7)
C(4)	0.00299(17)	0.6644(4)	0.43114(16)	0.0269(7)
C(5)	−0.01492(15)	0.8467(4)	0.44581(15)	0.0236(7)
C(6)	0.01123(13)	0.9095(4)	0.50339(13)	0.0162(5)
O(3)	0.10387(9)	0.9155(3)	0.55104(9)	0.0184(4)
C(7)	0.16414(13)	0.8662(4)	0.55698(15)	0.0213(6)
C(8)	−0.01980(13)	0.8304(4)	0.55505(14)	0.0206(6)
C(9)	0.00794(13)	1.1039(4)	0.50519(13)	0.0184(6)
O(4)	0.00912(14)	1.1955(3)	0.46350(11)	0.0374(7)
O(5)	0.00210(11)	1.1648(3)	0.55812(11)	0.0195(5)
C(10)	−0.00215(16)	1.3463(4)	0.56255(17)	0.0229(7)
C(1A)	0.24151(13)	0.3597(4)	0.49956(13)	0.0150(6)
O(1A)	0.20331(10)	0.4172(3)	0.45568(10)	0.0253(5)
C(2A)	0.19596(19)	0.2764(6)	0.41647(17)	0.0336(9)
O(2A)	0.24093(10)	0.1816(3)	0.49662(10)	0.0195(5)
C(3A)	0.24137(17)	0.1483(4)	0.43585(14)	0.0274(7)
C(4A)	0.30311(17)	0.1843(5)	0.41413(16)	0.0317(8)
C(5A)	0.32122(16)	0.3692(4)	0.42730(16)	0.0273(7)
C(6A)	0.30516(12)	0.4241(4)	0.48881(13)	0.0162(5)
O(3A)	0.22304(9)	0.4158(3)	0.55187(10)	0.0209(5)
C(7A)	0.16532(15)	0.3625(4)	0.56764(17)	0.0279(7)
C(8A)	0.34592(14)	0.3433(4)	0.53283(17)	0.0265(7)
C(9A)	0.30625(13)	0.6179(4)	0.49224(14)	0.0188(6)
O(4A)	0.29559(14)	0.7134(4)	0.45294(12)	0.0386(6)
O(5A)	0.32221(10)	0.6745(3)	0.54355(11)	0.0230(5)
C(10A)	0.32692(16)	0.8556(4)	0.54863(18)	0.0268(8)
C(1B)	0.32816(13)	0.6490(4)	0.23287(14)	0.0154(6)
O(1B)	0.35804(11)	0.5932(3)	0.28268(10)	0.0236(5)
C(2B)	0.36382(19)	0.7389(5)	0.31972(16)	0.0308(9)
O(2B)	0.33064(10)	0.8282(3)	0.23362(10)	0.0191(5)
C(3B)	0.32201(17)	0.8682(5)	0.29309(15)	0.0272(7)
C(4B)	0.25784(18)	0.8396(5)	0.30713(19)	0.0343(9)
C(5B)	0.23868(16)	0.6574(5)	0.29258(17)	0.0271(8)
C(6B)	0.26243(13)	0.5942(4)	0.23427(14)	0.0186(6)
O(3B)	0.35370(9)	0.5856(3)	0.18434(9)	0.0184(4)
C(7B)	0.41394(13)	0.6354(4)	0.17699(15)	0.0231(6)
C(8B)	0.22983(14)	0.6733(4)	0.18398(15)	0.0220(6)
C(9B)	0.25895(13)	0.3988(4)	0.23342(14)	0.0195(6)

O(4B)	0.25951(14)	0.3087(3)	0.27455(11)	0.0377(7)
O(5B)	0.25282(11)	0.3397(3)	0.18042(10)	0.0187(5)
C(10B)	0.24829(16)	0.1560(4)	0.17589(16)	0.0213(7)
C(1C)	0.49232(12)	0.1519(4)	0.24059(13)	0.0137(6)
O(1C)	0.45591(10)	0.0952(3)	0.28603(10)	0.0232(5)
C(2C)	0.45025(19)	0.2370(5)	0.32524(17)	0.0283(8)
O(2C)	0.49231(9)	0.3306(3)	0.24286(10)	0.0168(5)
C(3C)	0.49525(15)	0.3638(4)	0.30347(14)	0.0234(6)
C(4C)	0.55811(16)	0.3268(4)	0.32228(16)	0.0286(8)
C(5C)	0.57473(15)	0.1415(4)	0.30881(15)	0.0249(7)
C(6C)	0.55594(13)	0.0872(4)	0.24824(13)	0.0173(6)
O(3C)	0.47222(9)	0.0950(3)	0.18850(10)	0.0207(5)
C(7C)	0.41360(14)	0.1508(4)	0.17440(16)	0.0256(7)
C(8C)	0.59454(14)	0.1677(4)	0.20208(16)	0.0250(7)
C(9C)	0.55675(13)	−0.1080(4)	0.24532(13)	0.0187(6)
O(4C)	0.54571(14)	−0.2024(3)	0.28415(12)	0.0382(7)
O(5C)	0.57210(11)	−0.1643(3)	0.19308(11)	0.0223(5)
C(10C)	0.57613(16)	−0.3469(4)	0.18807(17)	0.0240(7)

Table 3. Bond lengths [Å] and angles [°] for 469.

C(1)–O(3)	1.371(4)	C(1)–O(2)	1.412(4)
C(1)–O(1)	1.428(4)	C(1)–C(6)	1.550(4)
O(1)–C(2)	1.453(4)	C(2)–C(3)	1.509(5)
O(2)–C(3)	1.442(4)	C(3)–C(4)	1.528(5)
C(4)–C(5)	1.529(5)	C(5)–C(6)	1.557(4)
C(6)–C(9)	1.530(4)	C(6)–C(8)	1.535(4)
O(3)–C(7)	1.437(3)	C(9)–O(4)	1.214(4)
C(9)–O(5)	1.337(4)	O(5)–C(10)	1.433(4)
C(1A)–O(3A)	1.370(4)	C(1A)–O(2A)	1.402(3)
C(1A)–O(1A)	1.423(4)	C(1A)–C(6A)	1.560(4)
O(1A)–C(2A)	1.448(5)	C(2A)–C(3A)	1.515(6)
O(2A)–C(3A)	1.449(4)	C(3A)–C(4A)	1.526(5)
C(4A)–C(5A)	1.542(5)	C(5A)–C(6A)	1.550(5)
C(6A)–C(9A)	1.525(4)	C(6A)–C(8A)	1.528(4)
O(3A)–C(7A)	1.432(4)	C(9A)–O(4A)	1.213(4)
C(9A)–O(5A)	1.334(4)	O(5A)–C(10A)	1.431(4)
C(1B)–O(3B)	1.373(4)	C(1B)–O(2B)	1.409(4)
C(1B)–O(1B)	1.422(4)	C(1B)–C(6B)	1.562(4)
O(1B)–C(2B)	1.443(4)	C(2B)–C(3B)	1.528(6)
O(2B)–C(3B)	1.443(4)	C(3B)–C(4B)	1.519(5)
C(4B)–C(5B)	1.536(5)	C(5B)–C(6B)	1.552(5)
C(6B)–C(8B)	1.527(4)	C(6B)–C(9B)	1.538(4)
O(3B)–C(7B)	1.441(4)	C(9B)–O(4B)	1.196(4)
C(9B)–O(5B)	1.334(4)	O(5B)–C(10B)	1.451(4)
C(1C)–O(3C)	1.379(4)	C(1C)–O(2C)	1.405(4)
C(1C)–O(1C)	1.423(4)	C(1C)–C(6C)	1.550(4)

O(1C)–C(2C)	1.450(4)	C(2C)–C(3C)	1.520(5)
O(2C)–C(3C)	1.447(4)	C(3C)–C(4C)	1.530(5)
C(4C)–C(5C)	1.538(5)	C(5C)–C(6C)	1.544(4)
C(6C)–C(8C)	1.533(4)	C(6C)–C(9C)	1.535(4)
O(3C)–C(7C)	1.447(4)	C(9C)–O(4C)	1.201(4)
C(9C)–O(5C)	1.349(4)	O(5C)–C(10C)	1.443(4)
O(3)–C(1)–O(2)	110.8(2)	O(3)–C(1)–O(1)	111.3(2)
O(2)–C(1)–O(1)	105.5(2)	O(3)–C(1)–C(6)	109.9(2)
O(2)–C(1)–C(6)	108.6(2)	O(1)–C(1)–C(6)	110.7(2)
C(1)–O(1)–C(2)	107.4(2)	O(1)–C(2)–C(3)	102.6(3)
C(1)–O(2)–C(3)	102.7(2)	O(2)–C(3)–C(2)	101.1(3)
O(2)–C(3)–C(4)	107.7(3)	C(2)–C(3)–C(4)	114.3(3)
C(3)–C(4)–C(5)	110.7(3)	C(4)–C(5)–C(6)	112.9(2)
C(9)–C(6)–C(8)	111.1(2)	C(9)–C(6)–C(1)	109.2(2)
C(8)–C(6)–C(1)	109.2(2)	C(9)–C(6)–C(5)	108.7(2)
C(8)–C(6)–C(5)	112.3(3)	C(1)–C(6)–C(5)	106.2(2)
C(1)–O(3)–C(7)	115.0(2)	O(4)–C(9)–O(5)	122.5(3)
O(4)–C(9)–C(6)	124.7(3)	O(5)–C(9)–C(6)	112.8(3)
C(9)–O(5)–C(10)	115.5(2)	O(3A)–C(1A)–O(2A)	111.2(2)
O(3A)–C(1A)–O(1A)	110.9(2)	O(2A)–C(1A)–O(1A)	106.0(2)
O(3A)–C(1A)–C(6A)	109.1(2)	O(2A)–C(1A)–C(6A)	109.0(2)
O(1A)–C(1A)–C(6A)	110.6(2)	C(1A)–O(1A)–C(2A)	106.7(3)
O(1A)–C(2A)–C(3A)	103.7(3)	C(1A)–O(2A)–C(3A)	103.2(2)
O(2A)–C(3A)–C(2A)	99.8(3)	O(2A)–C(3A)–C(4A)	107.5(3)
C(2A)–C(3A)–C(4A)	114.2(3)	C(3A)–C(4A)–C(5A)	110.8(3)
C(4A)–C(5A)–C(6A)	112.7(3)	C(9A)–C(6A)–C(8A)	111.7(3)
C(9A)–C(6A)–C(5A)	108.9(3)	C(8A)–C(6A)–C(5A)	111.6(3)
C(9A)–C(6A)–C(1A)	109.3(2)	C(8A)–C(6A)–C(1A)	108.9(3)
C(5A)–C(6A)–C(1A)	106.3(3)	C(1A)–O(3A)–C(7A)	114.9(3)
O(4A)–C(9A)–O(5A)	122.3(3)	O(4A)–C(9A)–C(6A)	125.0(3)
O(5A)–C(9A)–C(6A)	112.7(3)	C(9A)–O(5A)–C(10A)	115.3(3)
O(3B)–C(1B)–O(2B)	110.9(2)	O(3B)–C(1B)–O(1B)	111.4(2)
O(2B)–C(1B)–O(1B)	106.2(2)	O(3B)–C(1B)–C(6B)	109.0(3)
O(2B)–C(1B)–C(6B)	108.3(2)	O(1B)–C(1B)–C(6B)	111.0(2)
C(1B)–O(1B)–C(2B)	107.1(2)	O(1B)–C(2B)–C(3B)	103.0(3)
C(1B)–O(2B)–C(3B)	103.0(2)	O(2B)–C(3B)–C(4B)	108.0(3)
O(2B)–C(3B)–C(2B)	99.5(3)	C(4B)–C(3B)–C(2B)	114.6(3)
C(3B)–C(4B)–C(5B)	111.4(3)	C(4B)–C(5B)–C(6B)	113.2(3)
C(8B)–C(6B)–C(9B)	111.8(3)	C(8B)–C(6B)–C(5B)	112.3(3)
C(9B)–C(6B)–C(5B)	108.2(3)	C(8B)–C(6B)–C(1B)	109.9(2)
C(9B)–C(6B)–C(1B)	108.9(2)	C(5B)–C(6B)–C(1B)	105.4(3)
C(1B)–O(3B)–C(7B)	114.0(2)	O(4B)–C(9B)–O(5B)	123.1(3)
O(4B)–C(9B)–C(6B)	125.4(3)	O(5B)–C(9B)–C(6B)	111.4(3)
C(9B)–O(5B)–C(10B)	114.9(2)	O(3C)–C(1C)–O(2C)	110.9(2)
O(3C)–C(1C)–O(1C)	111.5(2)	O(2C)–C(1C)–O(1C)	106.5(2)
O(3C)–C(1C)–C(6C)	108.0(2)	O(2C)–C(1C)–C(6C)	108.9(2)
O(1C)–C(1C)–C(6C)	111.0(2)	C(1C)–O(1C)–C(2C)	106.6(2)

O(1C)–C(2C)–C(3C)	103.3(3)	C(1C)–O(2C)–C(3C)	102.6(2)
O(2C)–C(3C)–C(2C)	100.4(3)	O(2C)–C(3C)–C(4C)	107.0(3)
C(2C)–C(3C)–C(4C)	114.4(3)	C(3C)–C(4C)–C(5C)	110.6(3)
C(4C)–C(5C)–C(6C)	112.4(3)	C(8C)–C(6C)–C(9C)	112.0(3)
C(8C)–C(6C)–C(5C)	112.1(3)	C(9C)–C(6C)–C(5C)	108.3(2)
C(8C)–C(6C)–C(1C)	108.8(2)	C(9C)–C(6C)–C(1C)	109.5(2)
C(5C)–C(6C)–C(1C)	106.1(2)	C(1C)–O(3C)–C(7C)	114.4(2)
O(4C)–C(9C)–O(5C)	122.7(3)	O(4C)–C(9C)–C(6C)	125.5(3)
O(5C)–C(9C)–C(6C)	111.8(3)	C(9C)–O(5C)–C(10C)	114.6(3)

Table 4. Hydrogen coordinates and isotropic displacement parameters ($Å^2$) for 469.

	x	y	z	U
H(2A)	0.1482	0.7207	0.4107	0.030
H(2B)	0.0931	0.7950	0.3756	0.030
H(3)	0.0801	0.5179	0.4331	0.029
H(4A)	−0.0202	0.5836	0.4544	0.032
H(4B)	−0.0054	0.6417	0.3904	0.032
H(5A)	−0.0582	0.8532	0.4478	0.028
H(5B)	−0.0018	0.9235	0.4149	0.028
H(7A)	0.1670	0.7418	0.5568	0.032
H(7B)	0.1796	0.9105	0.5930	0.032
H(7C)	0.1869	0.9128	0.5252	0.032
H(8A)	−0.0017	0.8723	0.5902	0.031
H(8B)	−0.0162	0.7062	0.5534	0.031
H(8C)	−0.0613	0.8622	0.5545	0.031
H(10A)	0.0302	1.3990	0.5415	0.034
H(10B)	−0.0001	1.3797	0.6028	0.034
H(10C)	−0.0395	1.3842	0.5464	0.034
H(2C)	0.2033	0.3128	0.3767	0.040
H(2D)	0.1560	0.2283	0.4191	0.040
H(3A)	0.2290	0.0290	0.4272	0.033
H(4C)	0.3046	0.1649	0.3724	0.038
H(4D)	0.3310	0.1050	0.4325	0.038
H(5C)	0.3017	0.4464	0.3999	0.033
H(5D)	0.3640	0.3809	0.4219	0.033
H(7D)	0.1364	0.4342	0.5483	0.042
H(7E)	0.1605	0.3733	0.6090	0.042
H(7F)	0.1596	0.2435	0.5564	0.042
H(8D)	0.3855	0.3892	0.5281	0.040
H(8E)	0.3467	0.2197	0.5273	0.040
H(8F)	0.3317	0.3692	0.5713	0.040
H(10D)	0.3567	0.8975	0.5220	0.040
H(10E)	0.3382	0.8851	0.5877	0.040
H(10F)	0.2891	0.9079	0.5397	0.040

H(2E)	0.4045	0.7821	0.3199	0.037
H(2F)	0.3520	0.7107	0.3592	0.037
H(3B)	0.3343	0.9876	0.3019	0.033
H(4E)	0.2336	0.9214	0.2853	0.041
H(4F)	0.2513	0.8610	0.3482	0.041
H(5E)	0.1954	0.6524	0.2920	0.032
H(5F)	0.2525	0.5797	0.3229	0.032
H(7G)	0.4161	0.7590	0.1717	0.035
H(7H)	0.4302	0.5782	0.1434	0.035
H(7I)	0.4364	0.6030	0.2109	0.035
H(8G)	0.2502	0.6452	0.1484	0.033
H(8H)	0.2285	0.7972	0.1886	0.033
H(8I)	0.1899	0.6282	0.1826	0.033
H(10G)	0.2847	0.1036	0.1892	0.032
H(10H)	0.2415	0.1244	0.1360	0.032
H(10I)	0.2156	0.1158	0.1994	0.032
H(2G)	0.4592	0.2016	0.3648	0.034
H(2H)	0.4103	0.2857	0.3240	0.034
H(3C)	0.4837	0.4835	0.3125	0.028
H(4G)	0.5619	0.3473	0.3638	0.034
H(4H)	0.5853	0.4048	0.3023	0.034
H(5G)	0.5559	0.0654	0.3370	0.030
H(5H)	0.6177	0.1280	0.3126	0.030
H(7J)	0.3857	0.1019	0.2016	0.038
H(7K)	0.4037	0.1129	0.1358	0.038
H(7L)	0.4117	0.2752	0.1762	0.038
H(8J)	0.6351	0.1294	0.2070	0.038
H(8K)	0.5929	0.2920	0.2054	0.038
H(8L)	0.5804	0.1333	0.1644	0.038
H(10J)	0.6072	−0.3891	0.2132	0.036
H(10K)	0.5852	−0.3774	0.1485	0.036
H(10L)	0.5387	−0.3984	0.1991	0.036

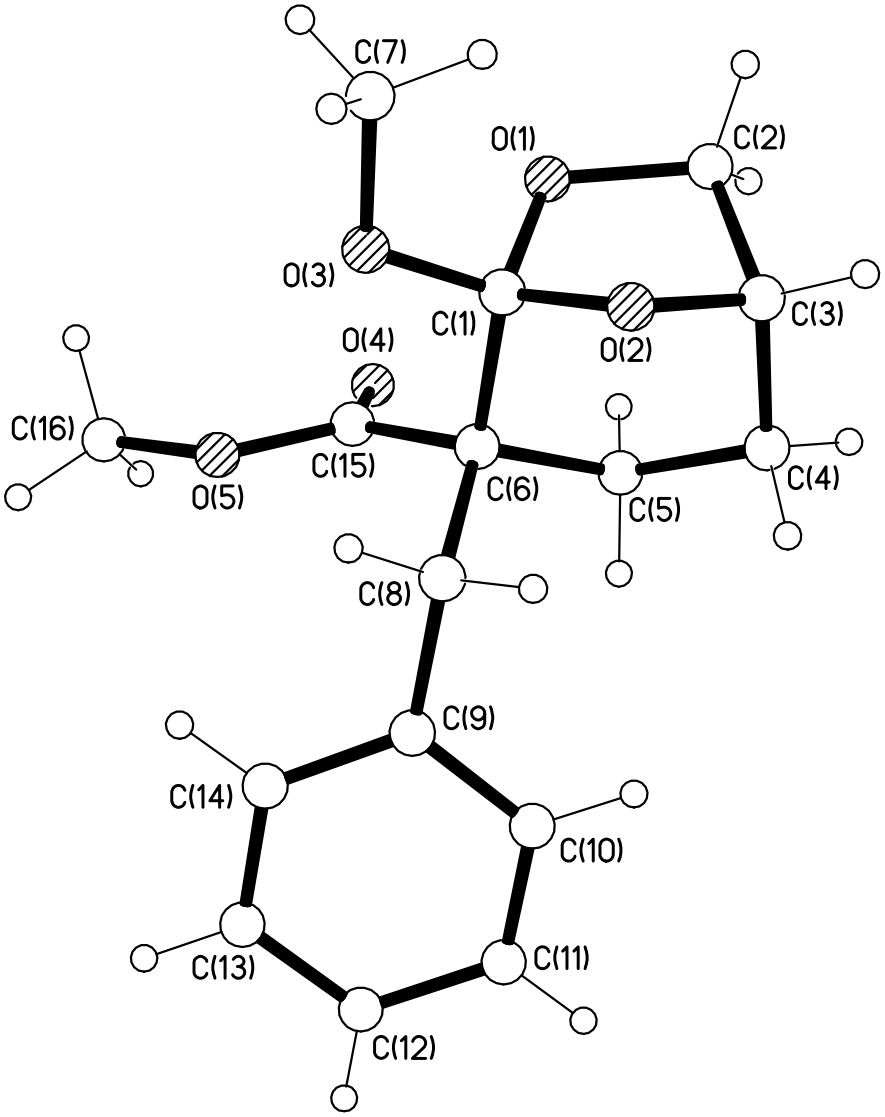
Table 5. Torsion angles [°] for 469.

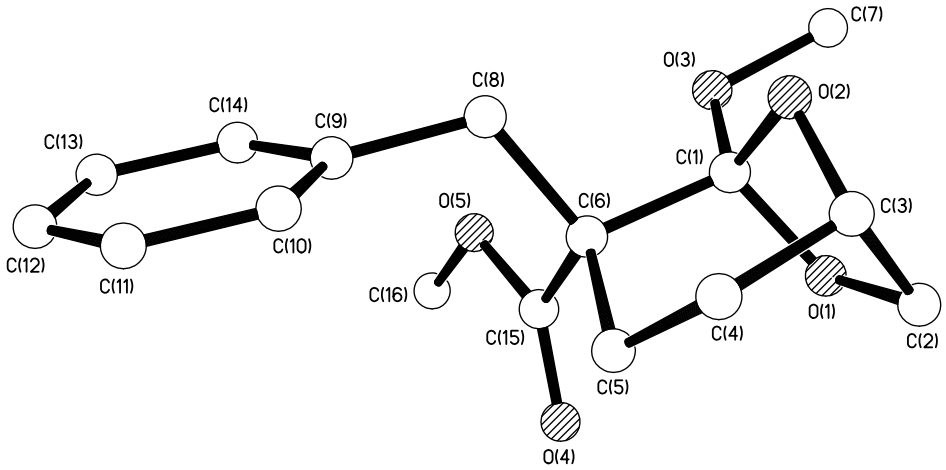
O(3)–C(1)–O(1)–C(2)	137.4(3)	O(2)–C(1)–O(1)–C(2)	17.2(3)
C(6)–C(1)–O(1)–C(2)	−100.1(3)	C(1)–O(1)–C(2)–C(3)	10.8(3)
O(3)–C(1)–O(2)–C(3)	−160.0(3)	O(1)–C(1)–O(2)–C(3)	−39.5(3)
C(6)–C(1)–O(2)–C(3)	79.2(3)	C(1)–O(2)–C(3)–C(2)	45.3(3)
C(1)–O(2)–C(3)–C(4)	−75.0(3)	O(1)–C(2)–C(3)–O(2)	−34.0(3)
O(1)–C(2)–C(3)–C(4)	81.4(3)	O(2)–C(3)–C(4)–C(5)	58.1(4)
C(2)–C(3)–C(4)–C(5)	−53.4(4)	C(3)–C(4)–C(5)–C(6)	−44.0(4)
O(3)–C(1)–C(6)–C(9)	58.4(3)	O(2)–C(1)–C(6)–C(9)	179.8(2)
O(1)–C(1)–C(6)–C(9)	−64.8(3)	O(3)–C(1)–C(6)–C(8)	−63.2(3)
O(2)–C(1)–C(6)–C(8)	58.1(3)	O(1)–C(1)–C(6)–C(8)	173.5(2)
O(3)–C(1)–C(6)–C(5)	175.5(2)	O(2)–C(1)–C(6)–C(5)	−63.1(3)
O(1)–C(1)–C(6)–C(5)	52.3(3)	C(4)–C(5)–C(6)–C(9)	162.0(3)

C(4)–C(5)–C(6)–C(8)	−74.6(4)	C(4)–C(5)–C(6)–C(1)	44.6(4)
O(2)–C(1)–O(3)–C(7)	57.6(3)	O(1)–C(1)–O(3)–C(7)	−59.5(3)
C(6)–C(1)–O(3)–C(7)	177.6(2)	C(8)–C(6)–C(9)–O(4)	−152.5(3)
C(1)–C(6)–C(9)–O(4)	87.0(4)	C(5)–C(6)–C(9)–O(4)	−28.5(4)
C(8)–C(6)–C(9)–O(5)	25.9(4)	C(1)–C(6)–C(9)–O(5)	−94.6(3)
C(5)–C(6)–C(9)–O(5)	150.0(3)	O(4)–C(9)–O(5)–C(10)	−0.5(4)
C(6)–C(9)–O(5)–C(10)	−179.1(2)	O(3A)–C(1A)–O(1A)–C(2A)	−139.0(3)
O(2A)–C(1A)–O(1A)–C(2A)	−18.2(3)	C(6A)–C(1A)–O(1A)–C(2A)	99.8(3)
C(1A)–O(1A)–C(2A)–C(3A)	−10.0(4)	O(3A)–C(1A)–O(2A)–C(3A)	161.0(3)
O(1A)–C(1A)–O(2A)–C(3A)	40.4(3)	C(6A)–C(1A)–O(2A)–C(3A)	−78.7(3)
C(1A)–O(2A)–C(3A)–C(2A)	−44.8(3)	C(1A)–O(2A)–C(3A)–C(4A)	74.6(3)
O(1A)–C(2A)–C(3A)–O(2A)	33.1(3)	O(1A)–C(2A)–C(3A)–C(4A)	−81.3(4)
O(2A)–C(3A)–C(4A)–C(5A)	−58.0(4)	C(2A)–C(3A)–C(4A)–C(5A)	51.7(4)
C(3A)–C(4A)–C(5A)–C(6A)	44.5(4)	C(4A)–C(5A)–C(6A)–C(9A)	−162.2(3)
C(4A)–C(5A)–C(6A)–C(8A)	74.1(4)	C(4A)–C(5A)–C(6A)–C(1A)	−44.5(4)
O(3A)–C(1A)–C(6A)–C(9A)	−58.1(3)	O(2A)–C(1A)–C(6A)–C(9A)	−179.7(2)
O(1A)–C(1A)–C(6A)–C(9A)	64.2(3)	O(3A)–C(1A)–C(6A)–C(8A)	64.2(3)
O(2A)–C(1A)–C(6A)–C(8A)	−57.5(3)	O(1A)–C(1A)–C(6A)–C(8A)	−173.6(2)
O(3A)–C(1A)–C(6A)–C(5A)	−175.4(2)	O(2A)–C(1A)–C(6A)–C(5A)	63.0(3)
O(1A)–C(1A)–C(6A)–C(5A)	−53.2(3)	O(2A)–C(1A)–O(3A)–C(7A)	−58.6(3)
O(1A)–C(1A)–O(3A)–C(7A)	59.1(3)	C(6A)–C(1A)–O(3A)–C(7A)	−178.8(2)
C(8A)–C(6A)–C(9A)–O(4A)	153.4(3)	C(5A)–C(6A)–C(9A)–O(4A)	29.7(4)
C(1A)–C(6A)–C(9A)–O(4A)	−86.0(4)	C(8A)–C(6A)–C(9A)–O(5A)	−24.6(4)
C(5A)–C(6A)–C(9A)–O(5A)	−148.4(3)	C(1A)–C(6A)–C(9A)–O(5A)	95.9(3)
O(4A)–C(9A)–O(5A)–C(10A)	−1.1(4)	C(6A)–C(9A)–O(5A)–C(10A)	177.0(3)
O(3B)–C(1B)–O(1B)–C(2B)	136.1(3)	O(2B)–C(1B)–O(1B)–C(2B)	15.3(3)
C(6B)–C(1B)–O(1B)–C(2B)	−102.2(3)	C(1B)–O(1B)–C(2B)–C(3B)	13.3(3)
O(3B)–C(1B)–O(2B)–C(3B)	−160.5(3)	O(1B)–C(1B)–O(2B)–C(3B)	−39.4(3)
C(6B)–C(1B)–O(2B)–C(3B)	79.9(3)	C(1B)–O(2B)–C(3B)–C(4B)	−74.2(3)
C(1B)–O(2B)–C(3B)–C(2B)	45.7(3)	O(1B)–C(2B)–C(3B)–O(2B)	−35.9(3)
O(1B)–C(2B)–C(3B)–C(4B)	79.0(4)	O(2B)–C(3B)–C(4B)–C(5B)	56.3(4)
C(2B)–C(3B)–C(4B)–C(5B)	−53.6(5)	C(3B)–C(4B)–C(5B)–C(6B)	−43.1(5)
C(4B)–C(5B)–C(6B)–C(8B)	−75.1(4)	C(4B)–C(5B)–C(6B)–C(9B)	161.0(3)
C(4B)–C(5B)–C(6B)–C(1B)	44.6(4)	O(3B)–C(1B)–C(6B)–C(8B)	−63.5(3)
O(2B)–C(1B)–C(6B)–C(8B)	57.2(3)	O(1B)–C(1B)–C(6B)–C(8B)	173.4(2)
O(3B)–C(1B)–C(6B)–C(9B)	59.3(3)	O(2B)–C(1B)–C(6B)–C(9B)	180.0(2)
O(1B)–C(1B)–C(6B)–C(9B)	−63.9(3)	O(3B)–C(1B)–C(6B)–C(5B)	175.2(2)
O(2B)–C(1B)–C(6B)–C(5B)	−64.1(3)	O(1B)–C(1B)–C(6B)–C(5B)	52.1(3)
O(2B)–C(1B)–O(3B)–C(7B)	57.9(3)	O(1B)–C(1B)–O(3B)–C(7B)	−60.1(3)
C(6B)–C(1B)–O(3B)–C(7B)	177.0(2)	C(8B)–C(6B)–C(9B)–O(4B)	−149.7(3)
C(5B)–C(6B)–C(9B)–O(4B)	−25.5(4)	C(1B)–C(6B)–C(9B)–O(4B)	88.6(4)
C(8B)–C(6B)–C(9B)–O(5B)	27.8(4)	C(5B)–C(6B)–C(9B)–O(5B)	152.0(3)
C(1B)–C(6B)–C(9B)–O(5B)	−93.8(3)	O(4B)–C(9B)–O(5B)–C(10B)	−1.5(4)
C(6B)–C(9B)–O(5B)–C(10B)	−179.1(2)	O(3C)–C(1C)–O(1C)–C(2C)	−139.3(3)
O(2C)–C(1C)–O(1C)–C(2C)	−18.1(3)	C(6C)–C(1C)–O(1C)–C(2C)	100.3(3)

C(1C)–O(1C)–C(2C)–C(3C)	−10.1(4)	O(3C)–C(1C)–O(2C)–C(3C)	161.8(3)
O(1C)–C(1C)–O(2C)–C(3C)	40.3(3)	C(6C)–C(1C)–O(2C)–C(3C)	−79.5(3)
C(1C)–O(2C)–C(3C)–C(2C)	−44.8(3)	C(1C)–O(2C)–C(3C)–C(4C)	74.9(3)
O(1C)–C(2C)–C(3C)–O(2C)	33.4(3)	O(1C)–C(2C)–C(3C)–C(4C)	−80.8(4)
O(2C)–C(3C)–C(4C)–C(5C)	−58.8(4)	C(2C)–C(3C)–C(4C)–C(5C)	51.5(4)
C(3C)–C(4C)–C(5C)–C(6C)	45.3(4)	C(4C)–C(5C)–C(6C)–C(8C)	73.2(4)
C(4C)–C(5C)–C(6C)–C(9C)	−162.8(3)	C(4C)–C(5C)–C(6C)–C(1C)	−45.4(4)
O(3C)–C(1C)–C(6C)–C(8C)	63.6(3)	O(2C)–C(1C)–C(6C)–C(8C)	−56.9(3)
O(1C)–C(1C)–C(6C)–C(8C)	−173.8(2)	O(3C)–C(1C)–C(6C)–C(9C)	−59.0(3)
O(2C)–C(1C)–C(6C)–C(9C)	−179.5(2)	O(1C)–C(1C)–C(6C)–C(9C)	63.6(3)
O(3C)–C(1C)–C(6C)–C(5C)	−175.6(2)	O(2C)–C(1C)–C(6C)–C(5C)	63.9(3)
O(1C)–C(1C)–C(6C)–C(5C)	−53.1(3)	O(2C)–C(1C)–O(3C)–C(7C)	−58.8(3)
O(1C)–C(1C)–O(3C)–C(7C)	59.8(3)	C(6C)–C(1C)–O(3C)–C(7C)	−178.0(2)
C(8C)–C(6C)–C(9C)–O(4C)	156.8(3)	C(5C)–C(6C)–C(9C)–O(4C)	32.7(4)
C(1C)–C(6C)–C(9C)–O(4C)	−82.5(4)	C(8C)–C(6C)–C(9C)–O(5C)	−22.7(4)
C(5C)–C(6C)–C(9C)–O(5C)	−146.8(3)	C(1C)–C(6C)–C(9C)–O(5C)	98.0(3)
O(4C)–C(9C)–O(5C)–C(10C)	−2.0(4)	C(6C)–C(9C)–O(5C)–C(10C)	177.5(2)

Appendix VIII X-Ray crystallographic data for 472.




C(7)
O(3)
O(2)
C(8)
C(14)
C(9)
C(13)
C(1)
O(5)
C(6)
C(3)
C(10)
C(12)
C(11)
C(16)
O(1)
C(15)
C(4)
C(2)
C(5)
O(4)

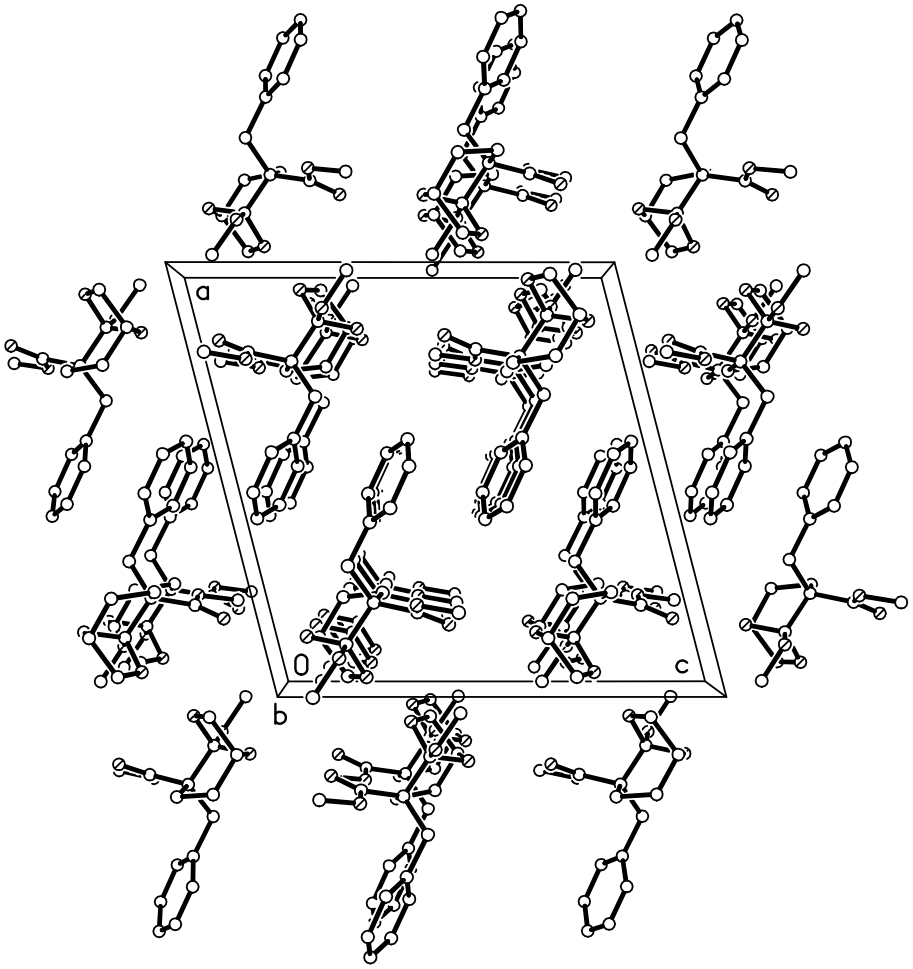

a
0
c
b

Table 1. Crystal data and structure refinement for 472.

Identification code	gp15	
Chemical formula	$C_{16}H_{20}O_5$	
Formula weight	292.32	
Temperature	150(2) K	
Radiation, wavelength	MoK, 0.71073 Å	
Crystal system, space group	monoclinic, $P2_1/c$	
Unit cell parameters	a = 14.5069(7) Å	□ = 90°
	b = 6.9902(4) Å	□ = 104.4428(8)°
	c = 14.5145(7) Å	□ = 90°
Cell volume	1425.34(13) $Å^3$	
Z	4	
Calculated density	1.362 g/cm^3	
Absorption coefficient □	0.101 mm^{-1}	
F(000)	624	
Crystal colour and size	colourless, 0.61 × 0.49 × 0.16 mm^3	
Reflections for cell refinement	4762 (□ range 2.90 to 30.29°)	
Data collection method	Bruker APEX 2 CCD diffractometer	
	□ rotation with narrow frames	
□ range for data collection	2.90 to 30.55°	
Index ranges	h –20 to 20, k –9 to 9, l –20 to 20	
Completeness to □ = 30.00°	99.8 %	
Intensity decay	0%	
Reflections collected	15975	
Independent reflections	4312 (R_{int} = 0.0248)	
Reflections with F^2>2□	3500	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.941 and 0.984	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting parameters a, b	0.0637, 0.3475	
Data / restraints / parameters	4312 / 0 / 192	
Final R indices [F^2>2□]	R1 = 0.0429, wR2 = 0.1140	
R indices (all data)	R1 = 0.0539, wR2 = 0.1221	
Goodness-of-fit on F^2	1.048	
Largest and mean shift/su	0.000 and 0.000	
Largest diff. peak and hole	0.413 and –0.284 e $Å^{-3}$	

Table 2. Atomic coordinates and equivalent isotropic displacement parameters ($Å^2$) for 472. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
C(1)	0.13587(7)	0.51342(14)	0.19421(7)	0.01743(19)
O(1)	0.06045(5)	0.40996(11)	0.21785(5)	0.02104(17)
C(2)	0.05572(8)	0.22421(16)	0.17372(8)	0.0241(2)
C(3)	0.14353(8)	0.22194(15)	0.13344(8)	0.0233(2)
O(2)	0.15107(5)	0.42249(10)	0.11236(5)	0.01995(16)
C(4)	0.23337(9)	0.16410(16)	0.20722(8)	0.0260(2)
C(5)	0.24562(8)	0.28506(15)	0.29761(8)	0.0217(2)
C(6)	0.22829(7)	0.50057(14)	0.27635(7)	0.01695(19)
O(3)	0.11148(5)	0.70203(11)	0.17615(5)	0.02180(17)
C(7)	0.02748(8)	0.73508(17)	0.10073(8)	0.0254(2)
C(8)	0.31039(7)	0.59794(15)	0.24263(7)	0.0198(2)
C(9)	0.40680(8)	0.60419(17)	0.31330(8)	0.0230(2)
C(10)	0.46852(9)	0.4478(2)	0.32363(9)	0.0310(3)
C(11)	0.55836(9)	0.4559(3)	0.38648(10)	0.0408(3)
C(12)	0.58821(9)	0.6195(3)	0.43859(9)	0.0441(4)
C(13)	0.52910(10)	0.7759(3)	0.42777(10)	0.0421(3)
C(14)	0.43859(9)	0.7691(2)	0.36559(9)	0.0311(3)
C(15)	0.20945(7)	0.59601(15)	0.36498(7)	0.0186(2)
O(4)	0.18043(6)	0.51265(12)	0.42506(6)	0.0298(2)
O(5)	0.22860(6)	0.78321(11)	0.36953(6)	0.02458(18)
C(16)	0.21488(9)	0.88138(18)	0.45281(8)	0.0288(2)

Table 3. Bond lengths [Å] and angles [°] for 472.

C(1)–O(3)	1.3732(12)	C(1)–O(2)	1.4122(12)
C(1)–O(1)	1.4231(12)	C(1)–C(6)	1.5588(14)
O(1)–C(2)	1.4418(13)	C(2)–C(3)	1.5284(16)
C(3)–O(2)	1.4448(13)	C(3)–C(4)	1.5207(17)
C(4)–C(5)	1.5335(16)	C(5)–C(6)	1.5457(14)
C(6)–C(15)	1.5329(14)	C(6)–C(8)	1.5531(14)
O(3)–C(7)	1.4392(13)	C(8)–C(9)	1.5148(15)
C(9)–C(14)	1.3937(17)	C(9)–C(10)	1.3972(17)
C(10)–C(11)	1.3932(18)	C(11)–C(12)	1.380(2)
C(12)–C(13)	1.374(2)	C(13)–C(14)	1.3963(18)
C(15)–O(4)	1.2085(12)	C(15)–O(5)	1.3359(13)
O(5)–C(16)	1.4462(13)		
O(3)–C(1)–O(2)	111.00(8)	O(3)–C(1)–O(1)	110.91(8)
O(2)–C(1)–O(1)	105.36(8)	O(3)–C(1)–C(6)	109.44(8)
O(2)–C(1)–C(6)	109.42(8)	O(1)–C(1)–C(6)	110.65(8)
C(1)–O(1)–C(2)	107.74(8)	O(1)–C(2)–C(3)	103.15(8)
O(2)–C(3)–C(4)	108.08(9)	O(2)–C(3)–C(2)	100.67(8)
C(4)–C(3)–C(2)	112.52(9)	C(1)–O(2)–C(3)	102.87(7)

C(3)–C(4)–C(5)	110.61(9)	C(4)–C(5)–C(6)	112.84(9)
C(15)–C(6)–C(5)	108.11(8)	C(15)–C(6)–C(8)	112.65(8)
C(5)–C(6)–C(8)	113.00(8)	C(15)–C(6)–C(1)	108.50(8)
C(5)–C(6)–C(1)	105.95(8)	C(8)–C(6)–C(1)	108.34(8)
C(1)–O(3)–C(7)	115.36(8)	C(9)–C(8)–C(6)	116.76(8)
C(14)–C(9)–C(10)	118.19(11)	C(14)–C(9)–C(8)	121.12(10)
C(10)–C(9)–C(8)	120.58(11)	C(11)–C(10)–C(9)	120.55(13)
C(12)–C(11)–C(10)	120.47(14)	C(13)–C(12)–C(11)	119.67(12)
C(12)–C(13)–C(14)	120.41(14)	C(9)–C(14)–C(13)	120.68(13)
O(4)–C(15)–O(5)	122.83(10)	O(4)–C(15)–C(6)	124.25(9)
O(5)–C(15)–C(6)	112.92(8)	C(15)–O(5)–C(16)	115.84(9)

Table 4. Hydrogen coordinates and isotropic displacement parameters ($Å^2$) for 472.

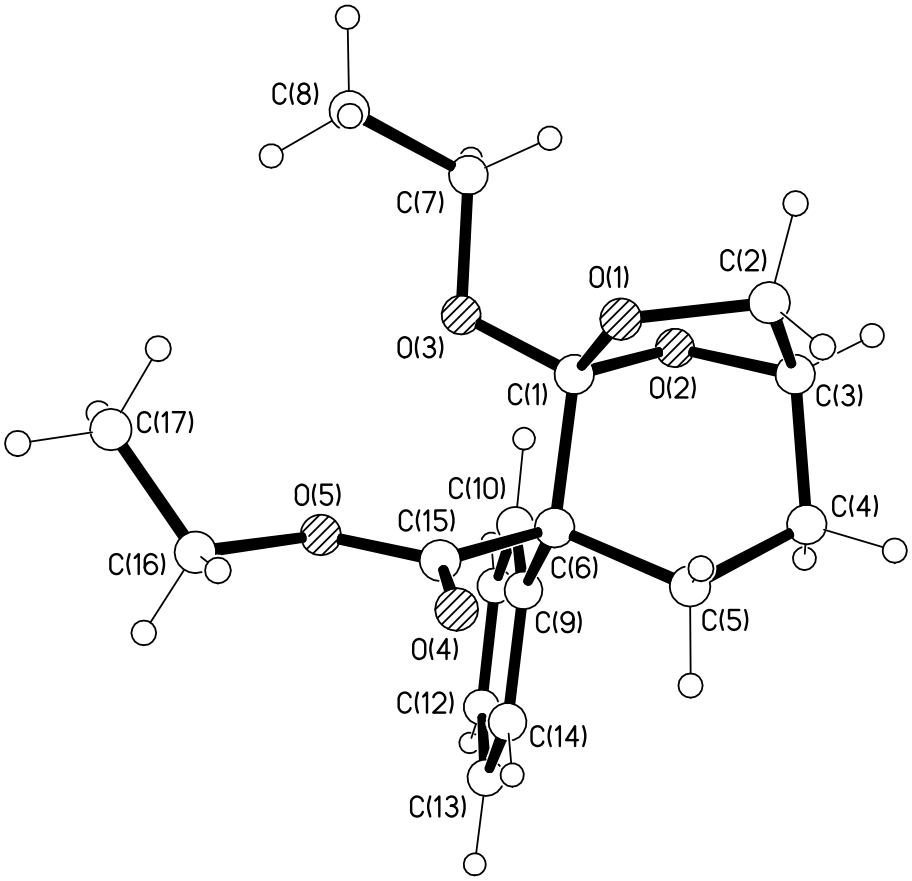
	x	y	z	U
H(2A)	−0.0034	0.2099	0.1225	0.029
H(2B)	0.0587	0.1208	0.2210	0.029
H(3)	0.1332	0.1414	0.0748	0.028
H(4A)	0.2893	0.1817	0.1806	0.031
H(4B)	0.2296	0.0271	0.2232	0.031
H(5A)	0.3109	0.2671	0.3380	0.026
H(5B)	0.2005	0.2392	0.3339	0.026
H(7A)	0.0049	0.6134	0.0697	0.038
H(7B)	0.0426	0.8230	0.0540	0.038
H(7C)	−0.0223	0.7913	0.1271	0.038
H(8A)	0.3177	0.5305	0.1849	0.024
H(8B)	0.2910	0.7310	0.2238	0.024
H(10)	0.4491	0.3350	0.2875	0.037
H(11)	0.5994	0.3480	0.3935	0.049
H(12)	0.6493	0.6240	0.4817	0.053
H(13)	0.5499	0.8893	0.4628	0.051
H(14)	0.3983	0.8780	0.3588	0.037
H(16A)	0.1472	0.9114	0.4439	0.043
H(16B)	0.2519	1.0002	0.4622	0.043
H(16C)	0.2362	0.7991	0.5088	0.043

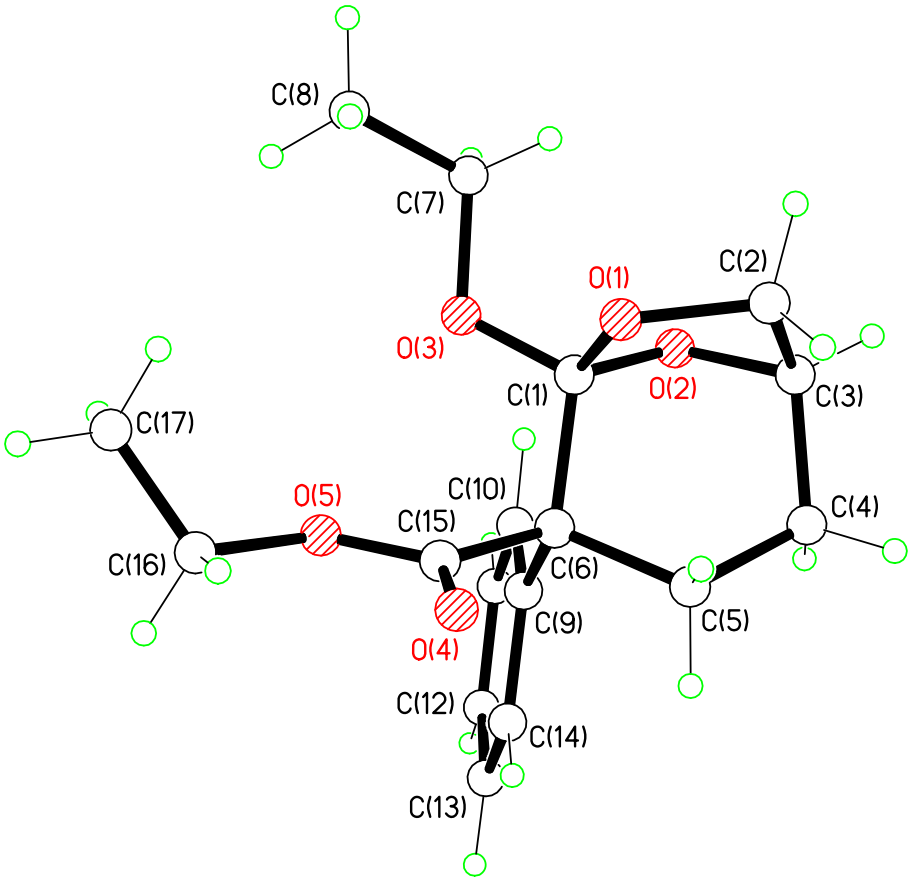
Table 5. Torsion angles [°] for 472.

O(3)–C(1)–O(1)–C(2)	140.81(9)	O(2)–C(1)–O(1)–C(2)	20.62(10)
C(6)–C(1)–O(1)–C(2)	−97.54(9)	C(1)–O(1)–C(2)–C(3)	7.03(11)
O(1)–C(2)–C(3)–O(2)	−31.08(10)	O(1)–C(2)–C(3)–C(4)	83.75(10)
O(3)–C(1)–O(2)–C(3)	−161.41(8)	O(1)–C(1)–O(2)–C(3)	−41.28(10)
C(6)–C(1)–O(2)–C(3)	77.70(9)	C(4)–C(3)–O(2)–C(1)	−73.99(10)
C(2)–C(3)–O(2)–C(1)	44.14(10)	O(2)–C(3)–C(4)–C(5)	58.74(11)
C(2)–C(3)–C(4)–C(5)	−51.52(12)	C(3)–C(4)–C(5)–C(6)	−45.51(12)

C(4)–C(5)–C(6)–C(15)	161.44(9)	C(4)–C(5)–C(6)–C(8)	−73.19(11)
C(4)–C(5)–C(6)–C(1)	45.29(11)	O(3)–C(1)–C(6)–C(15)	59.44(10)
O(2)–C(1)–C(6)–C(15)	−178.73(8)	O(1)–C(1)–C(6)–C(15)	−63.07(10)
O(3)–C(1)–C(6)–C(5)	175.32(8)	O(2)–C(1)–C(6)–C(5)	−62.85(10)
O(1)–C(1)–C(6)–C(5)	52.81(10)	O(3)–C(1)–C(6)–C(8)	−63.15(10)
O(2)–C(1)–C(6)–C(8)	58.68(10)	O(1)–C(1)–C(6)–C(8)	174.33(8)
O(2)–C(1)–O(3)–C(7)	58.50(11)	O(1)–C(1)–O(3)–C(7)	−58.27(11)
C(6)–C(1)–O(3)–C(7)	179.37(8)	C(15)–C(6)–C(8)–C(9)	58.84(12)
C(5)–C(6)–C(8)–C(9)	−64.05(12)	C(1)–C(6)–C(8)–C(9)	178.87(9)
C(6)–C(8)–C(9)–C(14)	−100.07(12)	C(6)–C(8)–C(9)–C(10)	83.69(12)
C(14)–C(9)–C(10)–C(11)	1.62(17)	C(8)–C(9)–C(10)–C(11)	177.97(11)
C(9)–C(10)–C(11)–C(12)	−0.83(19)	C(10)–C(11)–C(12)–C(13)	−0.5(2)
C(11)–C(12)–C(13)–C(14)	1.0(2)	C(10)–C(9)–C(14)–C(13)	−1.11(18)
C(8)–C(9)–C(14)–C(13)	−177.44(11)	C(12)–C(13)–C(14)–C(9)	−0.2(2)
C(5)–C(6)–C(15)–O(4)	−23.52(14)	C(8)–C(6)–C(15)–O(4)	−149.10(10)
C(1)–C(6)–C(15)–O(4)	90.96(12)	C(5)–C(6)–C(15)–O(5)	156.41(9)
C(8)–C(6)–C(15)–O(5)	30.83(12)	C(1)–C(6)–C(15)–O(5)	−89.11(10)
O(4)–C(15)–O(5)–C(16)	1.57(15)	C(6)–C(15)–O(5)–C(16)	−178.36(9)

Appendix IX X-Ray crystallographic data for 475.

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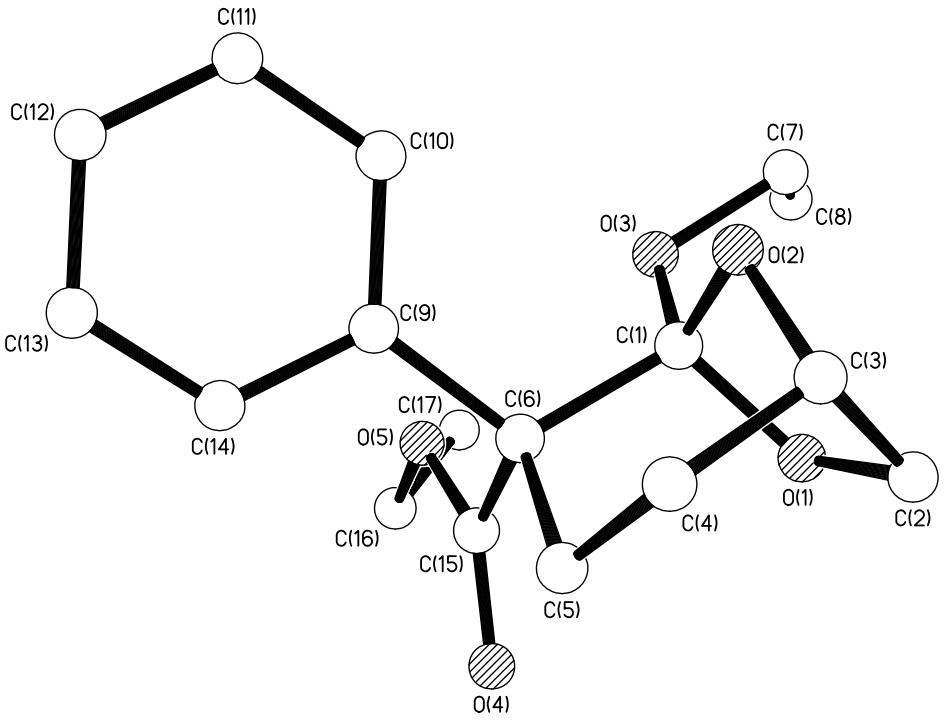
O(3)
O(2)
C(1)
C(3)
C(17)
O(5)
C(10)
C(15)
C(4)
C(16)
C(6)
C(9)
C(5)
O(4)
C(12)
C(14)
C(13)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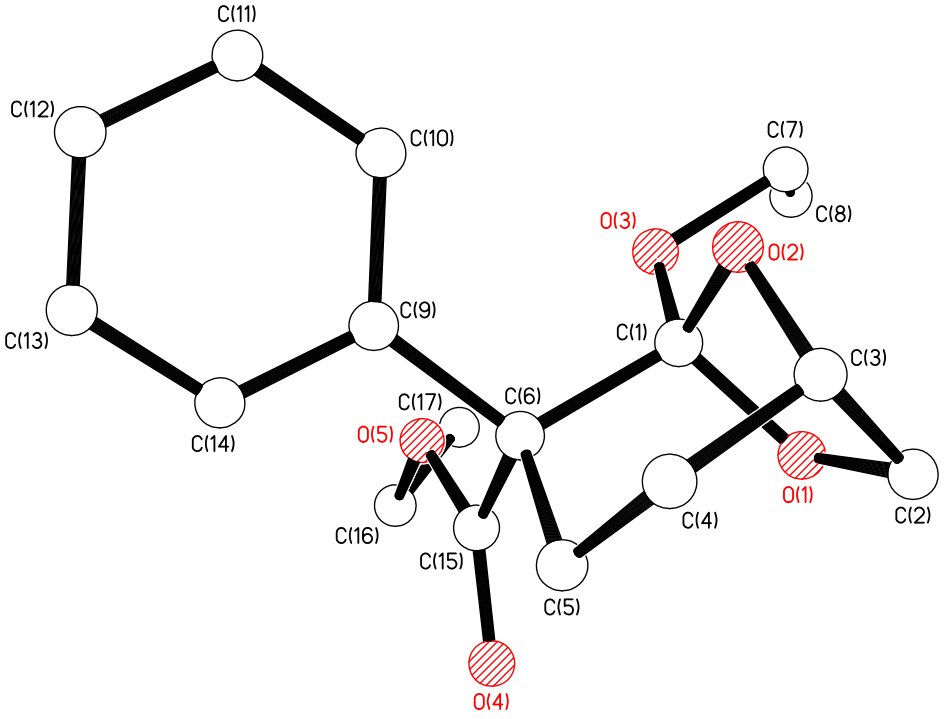
C(10)
C(7)
C(8)
O(3)
O(2)
C(9)
C(13)
C(1)
C(3)
C(17)
C(6)
O(5)
C(14)
O(1)
C(2)
C(16)
C(4)
C(15)
C(5)
O(4)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C(10)
C(7)
C(8)
O(3)
O(2)
C(9)
C(13)
C(1)
C(3)
C(17)
C(6)
O(5)
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O(1)
C(2)
C(16)
C(4)
C(15)
C(5)
O(4)

Table 1. Crystal data and structure refinement for 475.

Identification code	gp17	
Chemical formula	$C_{17}H_{22}O_5$	
Formula weight	306.35	
Temperature	150(2) K	
Radiation, wavelength	MoK, 0.71073 Å	
Crystal system, space group	tetragonal, P $\bar{4}2_1c$	
Unit cell parameters	a = 19.6095(10) Å	□ = 90°
	b = 19.6095(10) Å	□ = 90°
	c = 8.1865(4) Å	□ = 90°
Cell volume	3148.0(3) $Å^3$	
Z	8	
Calculated density	1.293 g/cm^3	
Absorption coefficient □	0.094 mm^{-1}	
F(000)	1312	
Crystal colour and size	colourless, 0.71 × 0.22 × 0.17 mm^3	
Reflections for cell refinement	9788 (□ range 2.32 to 27.09°)	
Data collection method	Bruker APEX 2 CCD diffractometer	
	□ rotation with narrow frames	
□ range for data collection	2.08 to 28.30°	
Index ranges	h −25 to 26, k −26 to 26, l −10 to 10	
Completeness to □ = 28.30°	100.0 %	
Intensity decay	0%	
Reflections collected	30908	
Independent reflections	2199 (R_{int} = 0.0429)	
Reflections with F^2>2□	1912	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.936 and 0.984	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting parameters a, b	0.0428, 0.8910	
Data / restraints / parameters	2199 / 0 / 201	
Final R indices [F^2>2□]	R1 = 0.0349, wR2 = 0.0836	
R indices (all data)	R1 = 0.0439, wR2 = 0.0903	
Goodness-of-fit on F^2	1.035	
Largest and mean shift/su	0.000 and 0.000	
Largest diff. peak and hole	0.209 and −0.214 e $Å^{-3}$	

Table 2. Atomic coordinates and equivalent isotropic displacement parameters ($Å^2$) for 475. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
O(2)	0.49824(7)	0.26670(7)	0.39922(16)	0.0279(3)
C(1)	0.49656(10)	0.25956(10)	0.2276(2)	0.0241(4)
O(1)	0.56424(6)	0.27520(7)	0.17464(18)	0.0306(3)
C(2)	0.59743(10)	0.31282(12)	0.3038(3)	0.0363(5)
C(3)	0.53936(10)	0.32695(11)	0.4223(3)	0.0342(5)
C(4)	0.49546(12)	0.38772(11)	0.3750(3)	0.0386(5)
C(5)	0.47520(10)	0.38377(10)	0.1953(3)	0.0319(4)
C(6)	0.44620(9)	0.31225(9)	0.1514(2)	0.0227(4)
O(3)	0.47939(7)	0.19443(7)	0.18480(19)	0.0290(3)
C(7)	0.52347(12)	0.14147(12)	0.2476(3)	0.0376(5)
C(8)	0.54072(18)	0.09436(15)	0.1119(4)	0.0709(10)
C(9)	0.37237(9)	0.30616(9)	0.2131(2)	0.0223(4)
C(10)	0.35026(9)	0.25887(10)	0.3288(2)	0.0266(4)
C(11)	0.28287(10)	0.25885(11)	0.3831(3)	0.0343(5)
C(12)	0.23651(10)	0.30539(12)	0.3226(3)	0.0370(5)
C(13)	0.25735(10)	0.35205(11)	0.2054(3)	0.0336(5)
C(14)	0.32473(10)	0.35239(10)	0.1525(2)	0.0277(4)
C(15)	0.44731(9)	0.30489(10)	−0.0354(2)	0.0265(4)
O(4)	0.47512(9)	0.34441(10)	−0.1256(2)	0.0504(5)
O(5)	0.41313(10)	0.25096(8)	−0.08587(18)	0.0449(4)
C(16)	0.4147(2)	0.23540(14)	−0.2595(3)	0.0604(9)
C(17)	0.43358(19)	0.16517(15)	−0.2841(4)	0.0664(9)

Table 3. Bond lengths [Å] and angles [°] for 475.

O(2)–C(1)	1.412(2)	O(2)–C(3)	1.443(2)
C(1)–O(3)	1.367(2)	C(1)–O(1)	1.430(2)
C(1)–C(6)	1.559(3)	O(1)–C(2)	1.444(3)
C(2)–C(3)	1.522(3)	C(3)–C(4)	1.520(3)
C(4)–C(5)	1.526(3)	C(5)–C(6)	1.555(3)
C(6)–C(15)	1.536(3)	C(6)–C(9)	1.538(2)
O(3)–C(7)	1.446(2)	C(7)–C(8)	1.484(4)
C(9)–C(14)	1.393(3)	C(9)–C(10)	1.395(3)
C(10)–C(11)	1.394(3)	C(11)–C(12)	1.380(3)
C(12)–C(13)	1.387(3)	C(13)–C(14)	1.391(3)
C(15)–O(4)	1.201(2)	C(15)–O(5)	1.318(2)
O(5)–C(16)	1.454(3)	C(16)–C(17)	1.440(4)
C(1)–O(2)–C(3)	102.98(16)	O(3)–C(1)–O(2)	110.70(16)
O(3)–C(1)–O(1)	110.58(15)	O(2)–C(1)–O(1)	105.00(16)
O(3)–C(1)–C(6)	111.14(15)	O(2)–C(1)–C(6)	110.30(15)
O(1)–C(1)–C(6)	108.94(15)	C(1)–O(1)–C(2)	107.81(15)

O(1)–C(2)–C(3)	102.88(15)	O(2)–C(3)–C(4)	106.98(16)
O(2)–C(3)–C(2)	100.68(16)	C(4)–C(3)–C(2)	113.8(2)
C(3)–C(4)–C(5)	110.69(18)	C(4)–C(5)–C(6)	111.32(18)
C(15)–C(6)–C(9)	109.43(15)	C(15)–C(6)–C(5)	108.02(17)
C(9)–C(6)–C(5)	109.77(15)	C(15)–C(6)–C(1)	109.09(15)
C(9)–C(6)–C(1)	114.43(15)	C(5)–C(6)–C(1)	105.87(15)
C(1)–O(3)–C(7)	115.64(16)	O(3)–C(7)–C(8)	108.48(19)
C(14)–C(9)–C(10)	117.78(17)	C(14)–C(9)–C(6)	117.64(17)
C(10)–C(9)–C(6)	124.55(16)	C(11)–C(10)–C(9)	120.75(19)
C(12)–C(11)–C(10)	120.7(2)	C(11)–C(12)–C(13)	119.35(18)
C(12)–C(13)–C(14)	119.92(19)	C(13)–C(14)–C(9)	121.53(19)
O(4)–C(15)–O(5)	123.76(19)	O(4)–C(15)–C(6)	123.88(19)
O(5)–C(15)–C(6)	112.34(17)	C(15)–O(5)–C(16)	117.6(2)
C(17)–C(16)–O(5)	110.1(2)		

Table 4. Hydrogen coordinates and isotropic displacement parameters ($Å^2$) for 475.

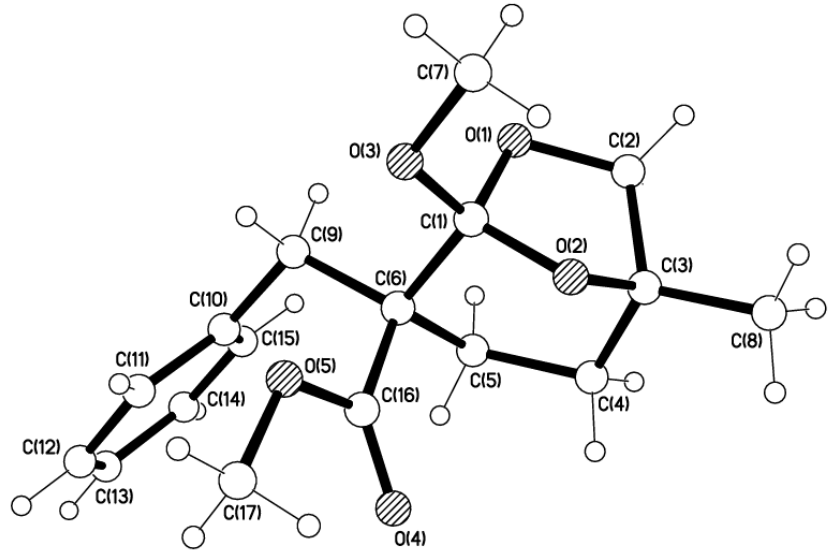
	x	y	z	U
H(2A)	0.6175	0.3558	0.2622	0.044
H(2B)	0.6337	0.2853	0.3560	0.044
H(3)	0.5561	0.3307	0.5373	0.041
H(4A)	0.5211	0.4304	0.3950	0.046
H(4B)	0.4539	0.3885	0.4437	0.046
H(5A)	0.5156	0.3933	0.1264	0.038
H(5B)	0.4404	0.4190	0.1718	0.038
H(7A)	0.5000	0.1162	0.3361	0.045
H(7B)	0.5656	0.1619	0.2930	0.045
H(8A)	0.4987	0.0788	0.0589	0.106
H(8B)	0.5656	0.0550	0.1552	0.106
H(8C)	0.5693	0.1182	0.0320	0.106
H(10)	0.3815	0.2263	0.3711	0.032
H(11)	0.2687	0.2265	0.4625	0.041
H(12)	0.1908	0.3055	0.3608	0.044
H(13)	0.2256	0.3837	0.1615	0.040
H(14)	0.3386	0.3849	0.0731	0.033
H(16A)	0.3692	0.2439	−0.3079	0.072
H(16B)	0.4481	0.2655	−0.3148	0.072
H(17A)	0.4804	0.1580	−0.2459	0.100
H(17B)	0.4307	0.1541	−0.4007	0.100
H(17C)	0.4025	0.1356	−0.2226	0.100

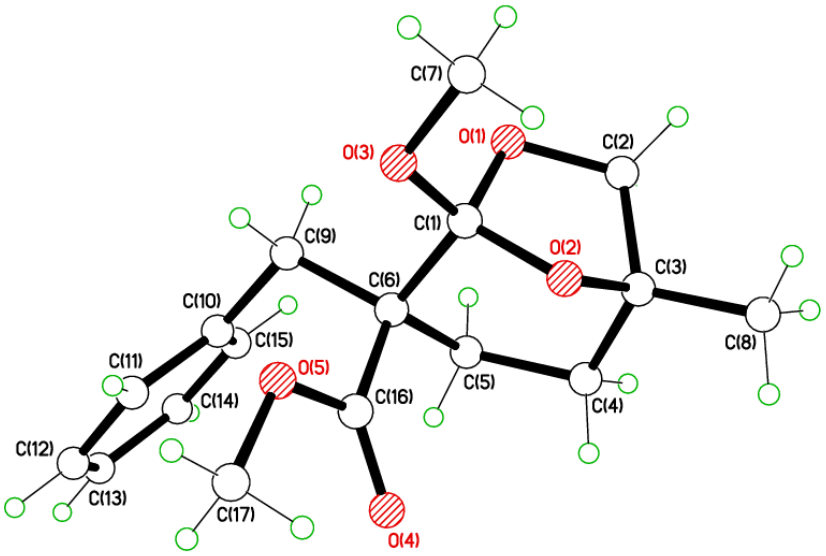
Table 5. Torsion angles [°] for 475.

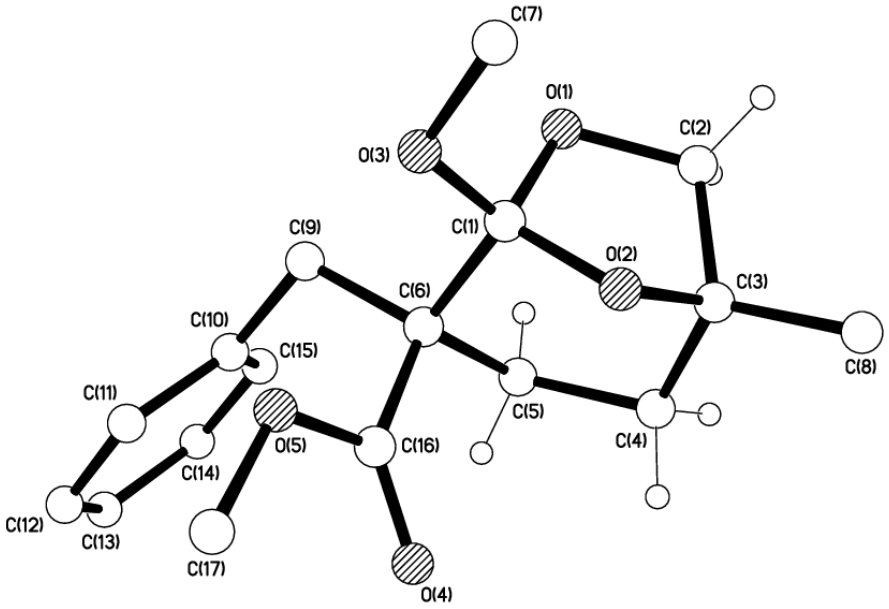
C(3)–O(2)–C(1)–O(3)	160.13(15)	C(3)–O(2)–C(1)–O(1)	40.76(18)
C(3)–O(2)–C(1)–C(6)	−76.45(19)	O(3)–C(1)–O(1)–C(2)	−138.61(16)
O(2)–C(1)–O(1)–C(2)	−19.2(2)	C(6)–C(1)–O(1)–C(2)	98.98(17)

C(1)–O(1)–C(2)–C(3)	−8.8(2)	C(1)–O(2)–C(3)–C(4)	74.2(2)
C(1)–O(2)–C(3)–C(2)	−45.02(19)	O(1)–C(2)–C(3)–O(2)	32.6(2)
O(1)–C(2)–C(3)–C(4)	−81.5(2)	O(2)–C(3)–C(4)–C(5)	−62.2(2)
C(2)–C(3)–C(4)–C(5)	48.0(2)	C(3)–C(4)–C(5)–C(6)	49.2(2)
C(4)–C(5)–C(6)–C(15)	−163.28(17)	C(4)–C(5)–C(6)–C(9)	77.5(2)
C(4)–C(5)–C(6)–C(1)	−46.5(2)	O(3)–C(1)–C(6)–C(15)	−58.7(2)
O(2)–C(1)–C(6)–C(15)	178.10(16)	O(1)–C(1)–C(6)–C(15)	63.35(19)
O(3)–C(1)–C(6)–C(9)	64.2(2)	O(2)–C(1)–C(6)–C(9)	−59.0(2)
O(1)–C(1)–C(6)–C(9)	−173.71(15)	O(3)–C(1)–C(6)–C(5)	−174.76(16)
O(2)–C(1)–C(6)–C(5)	62.1(2)	O(1)–C(1)–C(6)–C(5)	−52.68(19)
O(2)–C(1)–O(3)–C(7)	−57.8(2)	O(1)–C(1)–O(3)–C(7)	58.2(2)
C(6)–C(1)–O(3)–C(7)	179.29(16)	C(1)–O(3)–C(7)–C(8)	−132.8(2)
C(15)–C(6)–C(9)–C(14)	−58.3(2)	C(5)–C(6)–C(9)–C(14)	60.0(2)
C(1)–C(6)–C(9)–C(14)	178.90(16)	C(15)–C(6)–C(9)–C(10)	123.55(19)
C(5)–C(6)–C(9)–C(10)	−118.1(2)	C(1)–C(6)–C(9)–C(10)	0.8(3)
C(14)–C(9)–C(10)–C(11)	−0.9(3)	C(6)–C(9)–C(10)–C(11)	177.18(18)
C(9)–C(10)–C(11)–C(12)	0.4(3)	C(10)–C(11)–C(12)–C(13)	0.6(3)
C(11)–C(12)–C(13)–C(14)	−1.2(3)	C(12)–C(13)–C(14)–C(9)	0.7(3)
C(10)–C(9)–C(14)–C(13)	0.4(3)	C(6)–C(9)–C(14)–C(13)	−177.88(17)
C(9)–C(6)–C(15)–O(4)	129.1(2)	C(5)–C(6)–C(15)–O(4)	9.6(3)
C(1)–C(6)–C(15)–O(4)	−105.0(2)	C(9)–C(6)–C(15)–O(5)	−49.7(2)
C(5)–C(6)–C(15)–O(5)	−169.16(16)	C(1)–C(6)–C(15)–O(5)	76.2(2)
O(4)–C(15)–O(5)–C(16)	5.8(3)	C(6)–C(15)–O(5)–C(16)	−175.4(2)
C(15)–O(5)–C(16)–C(17)	128.8(3)		

Appendix X X-Ray crystallographic data for 488.






C(7)
O(1)
O(3)
C(2)
C(9)
C(1)
O(2)
C(3)
C(6)
C(10)
C(15)
C(8)
C(11)
C(5)
O(5)
C(16)
C(4)
C(14)
C(12)
C(13)
C(17)
O(4)

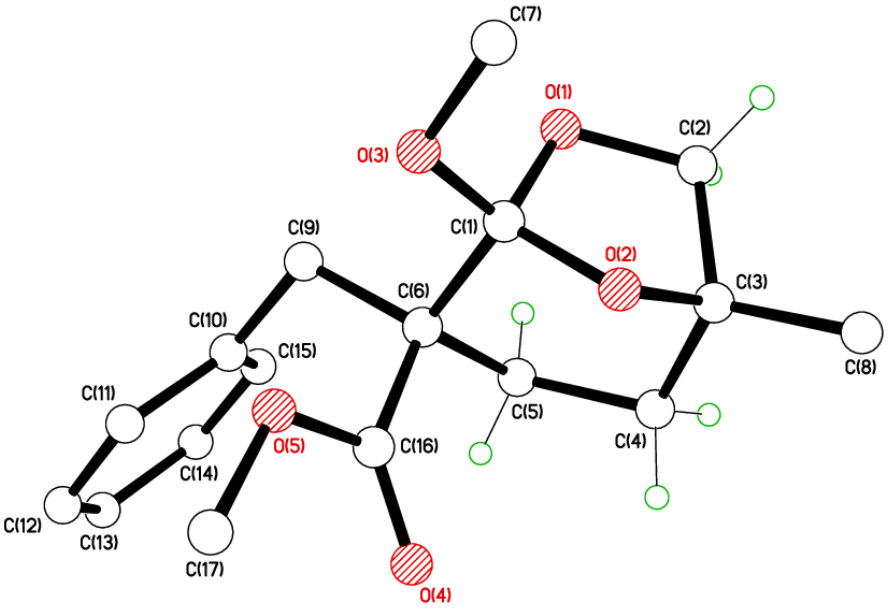

C(7)
O(1)
O(3)
C(2)
C(9)
C(1)
O(2)
C(3)
C(6)
C(10)
C(15)
C(8)
C(11)
C(5)
O(5)
C(16)
C(4)
C(14)
C(12)
C(13)
C(17)
O(4)

Table 1. Crystal data and structure refinement for 488.

Identification code	gp20	
Chemical formula	$C_{17}H_{22}O_5$	
Formula weight	306.35	
Temperature	150(2) K	
Radiation, wavelength	MoK, 0.71073 Å	
Crystal system, space group	orthorhombic, Pbca	
Unit cell parameters	a = 8.3499(4) Å	□ = 90°
	b = 14.2473(7) Å	□ = 90°
	c = 26.4628(13) Å	□ = 90°
Cell volume	3148.1(3) $Å^3$	
Z	8	
Calculated density	1.293 g/cm^3	
Absorption coefficient □	0.094 mm^{-1}	
F(000)	1312	
Crystal colour and size	colourless, 0.67 × 0.62 × 0.20 mm^3	
Reflections for cell refinement	8495 (□ range 2.86 to 29.58°)	
Data collection method	Bruker APEX 2 CCD diffractometer	
	□ rotation with narrow frames	
□ range for data collection	2.86 to 29.62°	
Index ranges	h −11 to 11, k −19 to 19, l −36 to 36	
Completeness to □ = 29.62°	99.9 %	
Intensity decay	0%	
Reflections collected	33031	
Independent reflections	4439 (R_{int} = 0.0307)	
Reflections with F^2>2□	3581	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.939 and 0.981	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting parameters a, b	0.0551, 0.7320	
Data / restraints / parameters	4439 / 0 / 202	
Final R indices [F^2>2□]	R1 = 0.0395, wR2 = 0.1009	
R indices (all data)	R1 = 0.0513, wR2 = 0.1094	
Goodness-of-fit on F^2	1.037	
Largest and mean shift/su	0.001 and 0.000	
Largest diff. peak and hole	0.376 and −0.184 e $Å^{-3}$	

Table 2. Atomic coordinates and equivalent isotropic displacement parameters ($Å^2$) for 488. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
C(1)	−0.12012(12)	0.55575(7)	0.39328(4)	0.0229(2)
O(1)	−0.17138(9)	0.49625(5)	0.35318(3)	0.02890(18)
C(2)	−0.34359(14)	0.49091(8)	0.35502(4)	0.0312(2)
C(3)	−0.38972(13)	0.56653(7)	0.39329(4)	0.0260(2)
O(2)	−0.25152(8)	0.56284(5)	0.42667(3)	0.02357(16)
C(4)	−0.39021(13)	0.66450(8)	0.36969(4)	0.0273(2)
C(5)	−0.23245(13)	0.68594(8)	0.34211(4)	0.0257(2)
C(6)	−0.08211(12)	0.65478(7)	0.37169(4)	0.02124(19)
O(3)	0.01095(9)	0.51857(5)	0.41716(3)	0.02811(18)
C(7)	−0.01719(16)	0.42949(8)	0.44130(5)	0.0367(3)
C(8)	−0.53824(14)	0.54369(9)	0.42359(5)	0.0346(3)
C(9)	0.06740(13)	0.65110(7)	0.33685(4)	0.0257(2)
C(10)	0.11514(12)	0.74587(7)	0.31577(4)	0.0243(2)
C(11)	0.21750(13)	0.80484(8)	0.34293(4)	0.0284(2)
C(12)	0.25900(14)	0.89308(9)	0.32493(5)	0.0341(3)
C(13)	0.20115(15)	0.92318(9)	0.27853(5)	0.0364(3)
C(14)	0.10249(14)	0.86516(9)	0.25058(5)	0.0368(3)
C(15)	0.05870(14)	0.77736(9)	0.26921(4)	0.0310(2)
C(16)	−0.05180(12)	0.72299(7)	0.41529(4)	0.0219(2)
O(4)	−0.13430(10)	0.79006(5)	0.42495(3)	0.03044(18)
O(5)	0.08055(10)	0.70166(5)	0.44135(3)	0.02901(18)
C(17)	0.11850(17)	0.76445(9)	0.48239(5)	0.0379(3)

Table 3. Bond lengths [Å] and angles [°] for 488.

O(2)–C(1)	1.4123(12)	O(2)–C(3)	1.4542(12)
C(1)–O(3)	1.3702(12)	C(1)–O(1)	1.4242(12)
C(1)–C(6)	1.5549(14)	O(1)–C(2)	1.4408(14)
C(2)–C(3)	1.5280(15)	C(3)–C(8)	1.5122(16)
C(3)–C(4)	1.5292(15)	C(4)–C(5)	1.5366(15)
C(5)–C(6)	1.5447(14)	C(6)–C(16)	1.5295(14)
C(6)–C(9)	1.5528(14)	O(3)–C(7)	1.4403(13)
C(9)–C(10)	1.5144(15)	C(10)–C(15)	1.3933(15)
C(10)–C(11)	1.3976(15)	C(11)–C(12)	1.3884(16)
C(12)–C(13)	1.3873(18)	C(13)–C(14)	1.3817(19)
C(14)–C(15)	1.3934(17)	C(16)–O(4)	1.2054(12)
C(16)–O(5)	1.3376(13)	O(5)–C(17)	1.4423(13)
C(1)–O(2)–C(3)	103.83(7)	O(3)–C(1)–O(2)	111.08(8)
O(3)–C(1)–O(1)	110.70(8)	O(2)–C(1)–O(1)	105.98(8)
O(3)–C(1)–C(6)	110.93(8)	O(2)–C(1)–C(6)	108.88(8)
O(1)–C(1)–C(6)	109.12(8)	C(1)–O(1)–C(2)	107.83(8)
O(1)–C(2)–C(3)	103.70(8)	O(2)–C(3)–C(8)	108.72(9)

O(2)–C(3)–C(2)	100.20(8)	C(8)–C(3)–C(2)	113.98(9)
O(2)–C(3)–C(4)	106.46(8)	C(8)–C(3)–C(4)	114.25(9)
C(2)–C(3)–C(4)	111.93(9)	C(3)–C(4)–C(5)	111.91(9)
C(4)–C(5)–C(6)	113.50(8)	C(16)–C(6)–C(5)	109.52(8)
C(16)–C(6)–C(9)	109.65(8)	C(5)–C(6)–C(9)	111.23(8)
C(16)–C(6)–C(1)	109.46(8)	C(5)–C(6)–C(1)	106.33(8)
C(9)–C(6)–C(1)	110.59(8)	C(1)–O(3)–C(7)	114.52(9)
C(10)–C(9)–C(6)	113.60(8)	C(15)–C(10)–C(11)	117.91(10)
C(15)–C(10)–C(9)	121.59(10)	C(11)–C(10)–C(9)	120.49(9)
C(12)–C(11)–C(10)	121.36(10)	C(13)–C(12)–C(11)	119.78(12)
C(14)–C(13)–C(12)	119.77(11)	C(13)–C(14)–C(15)	120.27(11)
C(10)–C(15)–C(14)	120.88(11)	O(4)–C(16)–O(5)	122.88(9)
O(4)–C(16)–C(6)	124.69(9)	O(5)–C(16)–C(6)	112.41(8)
C(16)–O(5)–C(17)	115.39(9)		

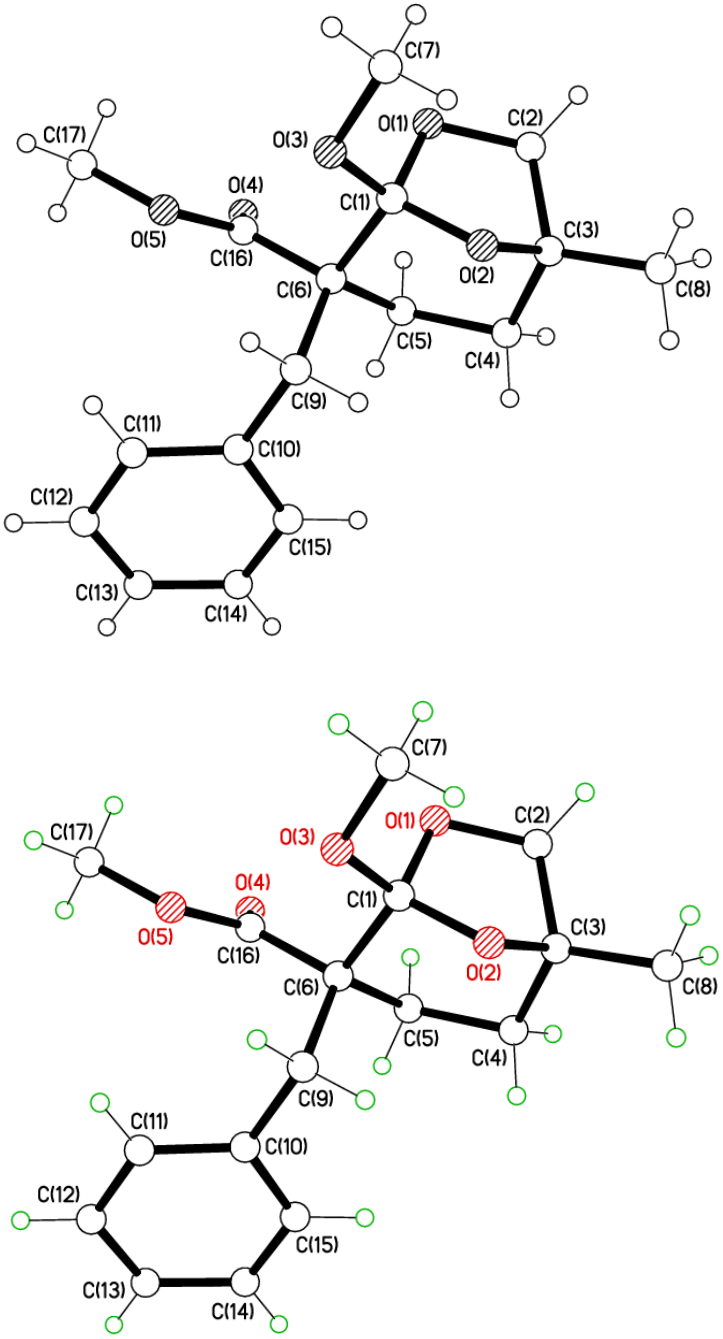
Table 4. Hydrogen coordinates and isotropic displacement parameters ($Å^2$) for 488.

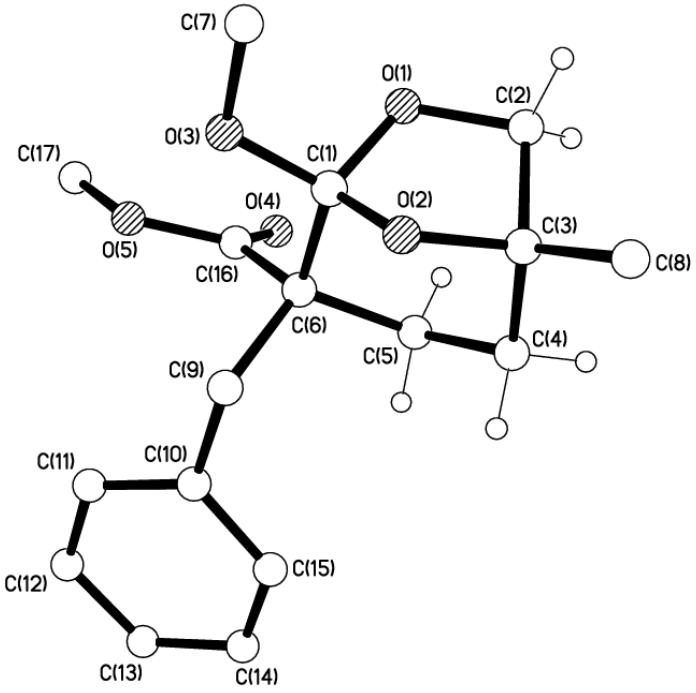
	x	y	z	U
H(2A)	−0.3793	0.4281	0.3664	0.037
H(2B)	−0.3910	0.5042	0.3215	0.037
H(4A)	−0.4074	0.7119	0.3965	0.033
H(4B)	−0.4802	0.6693	0.3455	0.033
H(5A)	−0.2259	0.7543	0.3358	0.031
H(5B)	−0.2334	0.6539	0.3089	0.031
H(7A)	−0.0965	0.4373	0.4683	0.055
H(7B)	0.0833	0.4060	0.4557	0.055
H(7C)	−0.0575	0.3845	0.4163	0.055
H(8A)	−0.5219	0.4847	0.4419	0.052
H(8B)	−0.6299	0.5372	0.4007	0.052
H(8C)	−0.5592	0.5944	0.4477	0.052
H(9A)	0.1585	0.6250	0.3562	0.031
H(9B)	0.0453	0.6079	0.3084	0.031
H(11)	0.2596	0.7841	0.3744	0.034
H(12)	0.3268	0.9327	0.3443	0.041
H(13)	0.2293	0.9835	0.2660	0.044
H(14)	0.0644	0.8852	0.2185	0.044
H(15)	−0.0106	0.7385	0.2499	0.037
H(17A)	0.1404	0.8272	0.4689	0.057
H(17B)	0.2132	0.7413	0.5004	0.057
H(17C)	0.0276	0.7675	0.5058	0.057

Table 5. Torsion angles [°] for 488.

C(3)–O(2)–C(1)–O(3)	−158.32(8)	C(3)–O(2)–C(1)–O(1)	−38.02(9)
C(3)–O(2)–C(1)–C(6)	79.25(9)	O(3)–C(1)–O(1)–C(2)	137.16(9)
O(2)–C(1)–O(1)–C(2)	16.61(10)	C(6)–C(1)–O(1)–C(2)	−100.49(9)
C(1)–O(1)–C(2)–C(3)	10.17(11)	C(1)–O(2)–C(3)–C(8)	162.42(9)
C(1)–O(2)–C(3)–C(2)	42.62(9)	C(1)–O(2)–C(3)–C(4)	−74.05(9)
O(1)–C(2)–C(3)–O(2)	−31.94(10)	O(1)–C(2)–C(3)–C(8)	−147.85(9)
O(1)–C(2)–C(3)–C(4)	80.56(10)	O(2)–C(3)–C(4)–C(5)	56.57(11)
C(8)–C(3)–C(4)–C(5)	176.58(9)	C(2)–C(3)–C(4)–C(5)	−51.97(12)
C(3)–C(4)–C(5)–C(6)	−43.19(12)	C(4)–C(5)–C(6)–C(16)	−75.02(11)
C(4)–C(5)–C(6)–C(9)	163.62(9)	C(4)–C(5)–C(6)–C(1)	43.15(11)
O(3)–C(1)–C(6)–C(16)	−66.36(10)	O(2)–C(1)–C(6)–C(16)	56.18(10)
O(1)–C(1)–C(6)–C(16)	171.43(8)	O(3)–C(1)–C(6)–C(5)	175.43(8)
O(2)–C(1)–C(6)–C(5)	−62.03(10)	O(1)–C(1)–C(6)–C(5)	53.21(10)
O(3)–C(1)–C(6)–C(9)	54.56(11)	O(2)–C(1)–C(6)–C(9)	177.09(8)
O(1)–C(1)–C(6)–C(9)	−67.66(10)	O(2)–C(1)–O(3)–C(7)	54.70(11)
O(1)–C(1)–O(3)–C(7)	−62.75(12)	C(6)–C(1)–O(3)–C(7)	175.95(9)
C(16)–C(6)–C(9)–C(10)	−57.26(11)	C(5)–C(6)–C(9)–C(10)	64.03(11)
C(1)–C(6)–C(9)–C(10)	−178.05(8)	C(6)–C(9)–C(10)–C(15)	−92.39(12)
C(6)–C(9)–C(10)–C(11)	87.30(12)	C(15)–C(10)–C(11)–C(12)	1.58(16)
C(9)–C(10)–C(11)–C(12)	−178.12(10)	C(10)–C(11)–C(12)–C(13)	−1.45(17)
C(11)–C(12)–C(13)–C(14)	0.06(18)	C(12)–C(13)–C(14)–C(15)	1.14(18)
C(11)–C(10)–C(15)–C(14)	−0.36(16)	C(9)–C(10)–C(15)–C(14)	179.34(10)
C(13)–C(14)–C(15)–C(10)	−1.00(18)	C(5)–C(6)–C(16)–O(4)	0.60(14)
C(9)–C(6)–C(16)–O(4)	122.91(11)	C(1)–C(6)–C(16)–O(4)	−115.61(11)
C(5)–C(6)–C(16)–O(5)	−177.75(8)	C(9)–C(6)–C(16)–O(5)	−55.43(11)
C(1)–C(6)–C(16)–O(5)	66.05(10)	O(4)–C(16)–O(5)–C(17)	0.27(15)
C(6)–C(16)–O(5)–C(17)	178.65(9)		

Appendix XI X-Ray crystallographic data for 489.

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O(1)
C(2)
O(3)
C(1)
C(17)
O(4)
O(2)
C(3)
O(5)
C(8)
C(16)
C(6)
C(4)
C(5)
C(9)
C(11)
C(10)
C(15)
C(12)
C(13)
C(14)

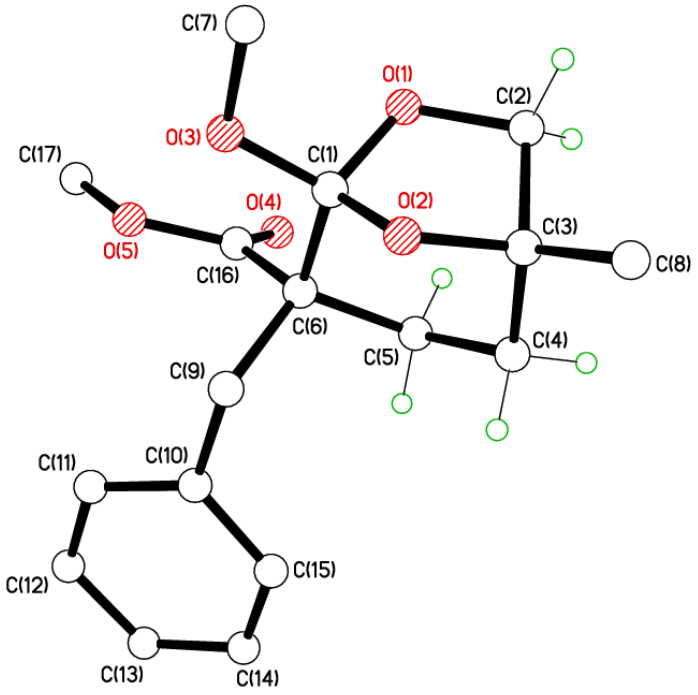

C(7)
O(1)
C(2)
O(3)
C(1)
C(17)
O(4)
O(2)
C(3)
O(5)
C(8)
C(16)
C(6)
C(4)
C(5)
C(9)
C(11)
C(10)
C(15)
C(12)
C(13)
C(14)

Table 1. Crystal data and structure refinement for 489.

Identification code	gp19	
Chemical formula	$C_{17}H_{22}O_5$	
Formula weight	306.35	
Temperature	150(2) K	
Radiation, wavelength	MoK, 0.71073 Å	
Crystal system, space group	monoclinic, $P2_1/c$	
Unit cell parameters	a = 14.7068(17) Å	□ = 90°
	b = 10.9177(13) Å	□ = 108.2485(19)°
	c = 10.3372(12) Å	□ = 90°
Cell volume	1576.3(3) $Å^3$	
Z	4	
Calculated density	1.291 g/cm^3	
Absorption coefficient □	0.094 mm^{-1}	
F(000)	656	
Crystal colour and size	colourless, 0.55 × 0.16 × 0.14 mm^3	
Reflections for cell refinement	4337 (□ range 2.79 to 25.92°)	
Data collection method	Bruker APEX 2 CCD diffractometer	
	□ rotation with narrow frames	
□ range for data collection	2.37 to 27.17°	
Index ranges	h −18 to 17, k 0 to 14, l 0 to 13	
Completeness to □ = 27.17°	99.8 %	
Intensity decay	0%	
Reflections collected	21561	
Independent reflections	3490 (R_{int} = 0.0360)	
Reflections with F^2>2□	2903	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.950 and 0.987	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting parameters a, b	0.0412, 0.2612	
Data / restraints / parameters	3490 / 0 / 203	
Final R indices [F^2>2□]	R1 = 0.0357, wR2 = 0.0832	
R indices (all data)	R1 = 0.0472, wR2 = 0.0883	
Goodness-of-fit on F^2	1.041	
Largest and mean shift/su	0.001 and 0.000	
Largest diff. peak and hole	0.270 and −0.193 e $Å^{-3}$	

Table 2. Atomic coordinates and equivalent isotropic displacement parameters ($Å^2$) for 489. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
C(1)	0.66762(10)	0.55989(13)	0.29267(15)	0.0269(3)
O(1)	0.59210(7)	0.49419(9)	0.19648(10)	0.0298(2)
C(2)	0.62186(11)	0.47151(16)	0.07867(16)	0.0350(4)
C(3)	0.72722(10)	0.50981(15)	0.12369(15)	0.0335(3)
O(2)	0.72488(7)	0.60741(9)	0.21820(10)	0.0296(2)
C(4)	0.79358(11)	0.41117(16)	0.20753(16)	0.0364(4)
C(5)	0.75747(11)	0.36506(14)	0.32235(16)	0.0332(3)
C(6)	0.72743(10)	0.46868(13)	0.40245(14)	0.0267(3)
O(3)	0.63163(7)	0.65275(9)	0.35131(10)	0.0299(2)
C(7)	0.57497(12)	0.74009(15)	0.25508(18)	0.0400(4)
C(8)	0.75939(12)	0.56083(19)	0.00948(17)	0.0468(4)
C(9)	0.81404(10)	0.53883(13)	0.50064(14)	0.0268(3)
C(10)	0.87919(10)	0.46123(14)	0.61330(15)	0.0280(3)
C(11)	0.87118(11)	0.46300(15)	0.74394(15)	0.0343(4)
C(12)	0.92976(12)	0.39008(17)	0.84705(17)	0.0414(4)
C(13)	0.99731(11)	0.31495(17)	0.82054(18)	0.0417(4)
C(14)	1.00797(11)	0.31376(16)	0.69254(18)	0.0399(4)
C(15)	0.94967(11)	0.38735(15)	0.59013(16)	0.0335(4)
C(16)	0.66546(10)	0.41188(13)	0.48091(15)	0.0291(3)
O(4)	0.63689(10)	0.30793(10)	0.46571(12)	0.0480(3)
O(5)	0.64701(8)	0.48759(9)	0.57059(11)	0.0346(3)
C(17)	0.58825(12)	0.43576(16)	0.64643(18)	0.0399(4)

Table 3. Hydrogen coordinates and isotropic displacement parameters ($Å^2$) for 489.

	x	y	z	U
H(2A)	0.5839	0.5211	0.0001	0.042
H(2B)	0.6148	0.3838	0.0532	0.042
H(4A)	0.8588	0.4452	0.2468	0.044
H(4B)	0.7971	0.3418	0.1476	0.044
H(5A)	0.8086	0.3159	0.3865	0.040
H(5B)	0.7019	0.3105	0.2831	0.040
H(7A)	0.6158	0.7834	0.2113	0.060
H(7B)	0.5466	0.7991	0.3027	0.060
H(7C)	0.5239	0.6971	0.1857	0.060
H(8A)	0.7224	0.6347	−0.0271	0.070
H(8B)	0.7490	0.4995	−0.0629	0.070
H(8C)	0.8276	0.5814	0.0443	0.070
H(9A)	0.8524	0.5744	0.4465	0.032
H(9B)	0.7893	0.6075	0.5424	0.032

H(11)	0.8250	0.5148	0.7630	0.041
H(12)	0.9233	0.3920	0.9356	0.050
H(13)	1.0365	0.2640	0.8904	0.050
H(14)	1.0550	0.2628	0.6745	0.048
H(15)	0.9581	0.3872	0.5027	0.040
H(17A)	0.5297	0.4014	0.5828	0.060
H(17B)	0.5714	0.5000	0.7011	0.060
H(17C)	0.6240	0.3709	0.7066	0.060

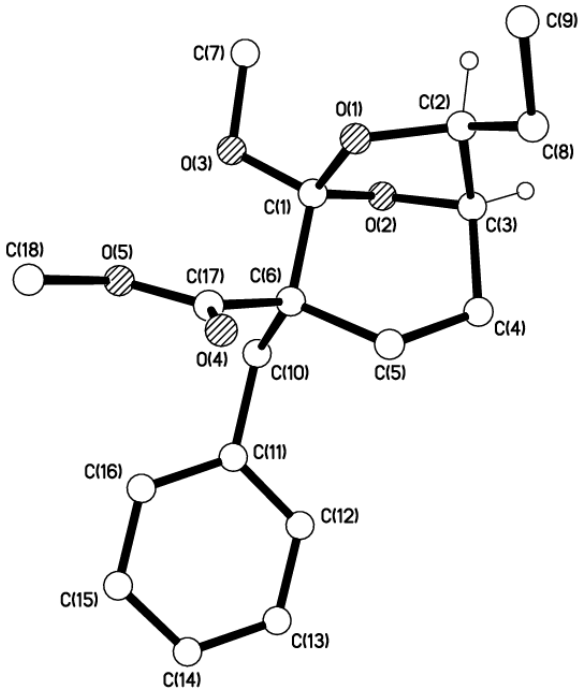
Table 4. Bond lengths [Å] and angles [°] for 489.

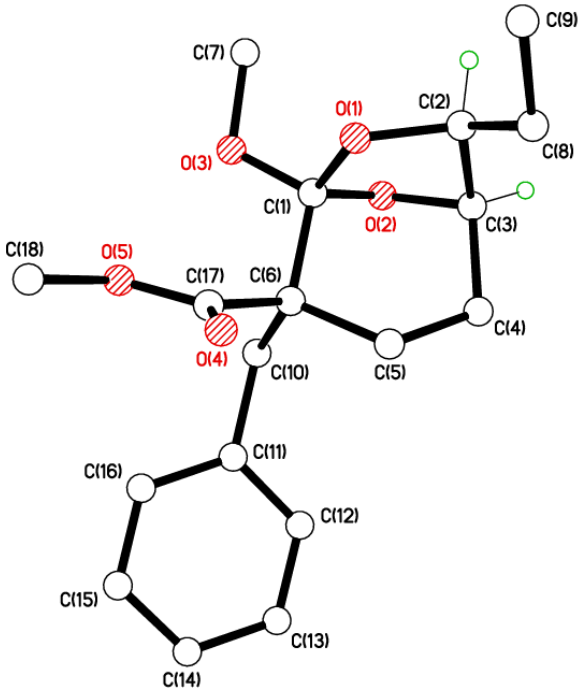
C(1)–O(3)	1.3698(18)	C(1)–O(2)	1.4061(18)
C(1)–O(1)	1.4301(17)	C(1)–C(6)	1.5582(19)
O(1)–C(2)	1.4387(19)	C(2)–C(3)	1.530(2)
C(3)–O(2)	1.4534(18)	C(3)–C(8)	1.509(2)
C(3)–C(4)	1.528(2)	C(4)–C(5)	1.529(2)
C(5)–C(6)	1.546(2)	C(6)–C(16)	1.528(2)
C(6)–C(9)	1.5587(18)	O(3)–C(7)	1.4401(18)
C(9)–C(10)	1.5143(19)	C(10)–C(11)	1.392(2)
C(10)–C(15)	1.392(2)	C(11)–C(12)	1.392(2)
C(12)–C(13)	1.380(3)	C(13)–C(14)	1.380(2)
C(14)–C(15)	1.390(2)	C(16)–O(4)	1.2032(18)
C(16)–O(5)	1.3318(18)	O(5)–C(17)	1.4511(19)
O(3)–C(1)–O(2)	110.48(12)	O(3)–C(1)–O(1)	110.81(11)
O(2)–C(1)–O(1)	105.80(11)	O(3)–C(1)–C(6)	111.04(12)
O(2)–C(1)–C(6)	109.65(11)	O(1)–C(1)–C(6)	108.92(11)
C(1)–O(1)–C(2)	107.40(11)	O(1)–C(2)–C(3)	104.07(11)
O(2)–C(3)–C(8)	109.53(13)	O(2)–C(3)–C(4)	106.31(11)
C(8)–C(3)–C(4)	113.76(14)	O(2)–C(3)–C(2)	99.79(12)
C(8)–C(3)–C(2)	113.50(13)	C(4)–C(3)–C(2)	112.72(14)
C(1)–O(2)–C(3)	103.99(11)	C(3)–C(4)–C(5)	110.91(13)
C(4)–C(5)–C(6)	113.68(13)	C(16)–C(6)–C(5)	107.77(12)
C(16)–C(6)–C(1)	110.56(11)	C(5)–C(6)–C(1)	105.57(11)
C(16)–C(6)–C(9)	110.81(12)	C(5)–C(6)–C(9)	113.34(12)
C(1)–C(6)–C(9)	108.67(11)	C(1)–O(3)–C(7)	113.86(12)
C(10)–C(9)–C(6)	114.65(11)	C(11)–C(10)–C(15)	117.95(14)
C(11)–C(10)–C(9)	120.86(14)	C(15)–C(10)–C(9)	121.18(13)
C(12)–C(11)–C(10)	120.99(16)	C(13)–C(12)–C(11)	119.95(16)
C(12)–C(13)–C(14)	120.05(16)	C(13)–C(14)–C(15)	119.75(17)
C(14)–C(15)–C(10)	121.25(15)	O(4)–C(16)–O(5)	122.51(15)
O(4)–C(16)–C(6)	123.73(15)	O(5)–C(16)–C(6)	113.75(12)
C(16)–O(5)–C(17)	114.81(12)		

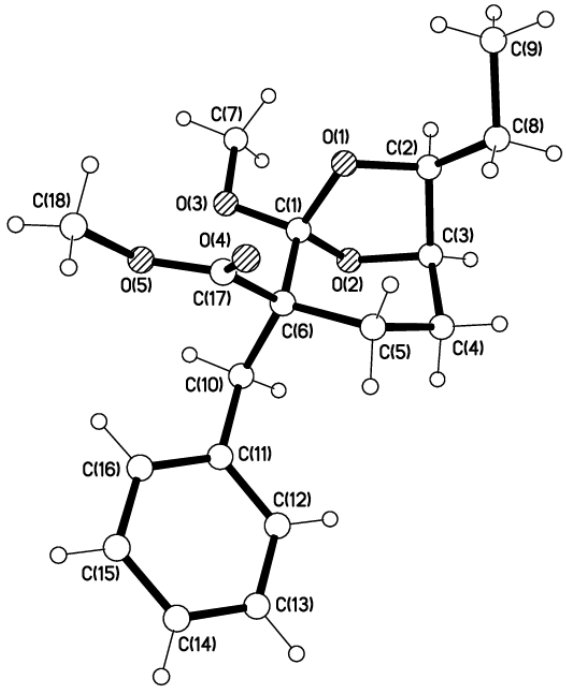
Table 5. Torsion angles [°] for 489.

O(3)–C(1)–O(1)–C(2)	137.52(12)	O(2)–C(1)–O(1)–C(2)	17.75(14)
C(6)–C(1)–O(1)–C(2)	−100.05(13)	C(1)–O(1)–C(2)–C(3)	9.35(15)
O(1)–C(2)–C(3)–O(2)	−31.62(14)	O(1)–C(2)–C(3)–C(8)	−148.04(14)
O(1)–C(2)–C(3)–C(4)	80.80(15)	O(3)–C(1)–O(2)–C(3)	−159.12(11)
O(1)–C(1)–O(2)–C(3)	−39.13(13)	C(6)–C(1)–O(2)–C(3)	78.19(13)
C(8)–C(3)–O(2)–C(1)	162.44(12)	C(4)–C(3)–O(2)–C(1)	−74.24(13)
C(2)–C(3)–O(2)–C(1)	43.07(13)	O(2)–C(3)–C(4)–C(5)	58.56(16)
C(8)–C(3)–C(4)–C(5)	179.19(13)	C(2)–C(3)–C(4)–C(5)	−49.77(17)
C(3)–C(4)–C(5)–C(6)	−45.99(17)	C(4)–C(5)–C(6)–C(16)	162.67(12)
C(4)–C(5)–C(6)–C(1)	44.49(15)	C(4)–C(5)–C(6)–C(9)	−74.34(15)
O(3)–C(1)–C(6)–C(16)	59.93(15)	O(2)–C(1)–C(6)–C(16)	−177.71(11)
O(1)–C(1)–C(6)–C(16)	−62.37(15)	O(3)–C(1)–C(6)–C(5)	176.22(11)
O(2)–C(1)–C(6)–C(5)	−61.42(14)	O(1)–C(1)–C(6)–C(5)	53.92(15)
O(3)–C(1)–C(6)–C(9)	−61.90(15)	O(2)–C(1)–C(6)–C(9)	60.47(15)
O(1)–C(1)–C(6)–C(9)	175.81(12)	O(2)–C(1)–O(3)–C(7)	58.48(15)
O(1)–C(1)–O(3)–C(7)	−58.45(16)	C(6)–C(1)–O(3)–C(7)	−179.64(12)
C(16)–C(6)–C(9)–C(10)	58.46(16)	C(5)–C(6)–C(9)–C(10)	−62.85(17)
C(1)–C(6)–C(9)–C(10)	−179.87(12)	C(6)–C(9)–C(10)–C(11)	−99.18(17)
C(6)–C(9)–C(10)–C(15)	81.71(17)	C(15)–C(10)–C(11)–C(12)	−2.1(2)
C(9)–C(10)–C(11)–C(12)	178.80(14)	C(10)–C(11)–C(12)–C(13)	0.3(2)
C(11)–C(12)–C(13)–C(14)	1.2(3)	C(12)–C(13)–C(14)–C(15)	−0.8(3)
C(13)–C(14)–C(15)–C(10)	−1.1(2)	C(11)–C(10)–C(15)–C(14)	2.5(2)
C(9)–C(10)–C(15)–C(14)	−178.39(14)	C(5)–C(6)–C(16)–O(4)	−8.64(19)
C(1)–C(6)–C(16)–O(4)	106.28(16)	C(9)–C(6)–C(16)–O(4)	−133.17(15)
C(5)–C(6)–C(16)–O(5)	170.15(11)	C(1)–C(6)–C(16)–O(5)	−74.93(14)
C(9)–C(6)–C(16)–O(5)	45.62(15)	O(4)–C(16)–O(5)–C(17)	−1.2(2)
C(6)–C(16)–O(5)–C(17)	180.00(11)		

Appendix XII X-Ray crystallographic data for 511.



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C(7)
O(1)
C(2)
C(18)
O(3)
C(1)
C(3)
O(4)
O(5)
C(17)
O(2)
C(6)
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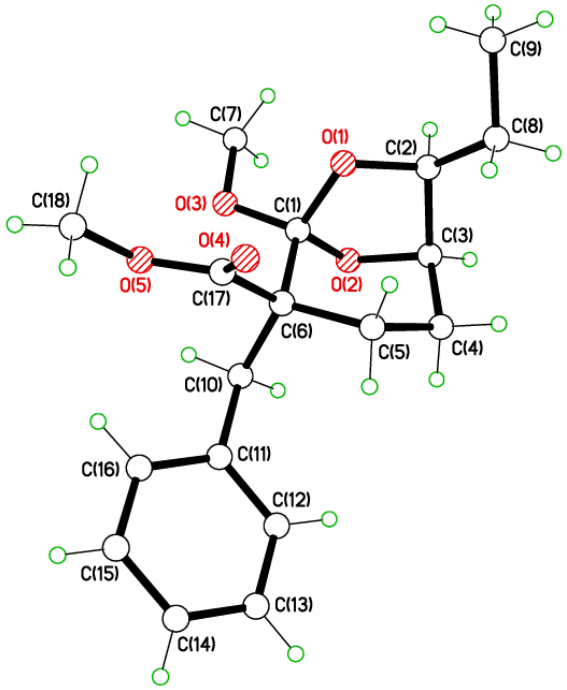
C(4)
C(10)
C(11)
C(16)
C(12)
C(15)
C(13)
C(14)


C(9)
C(8)
C(7)
O(1)
C(2)
C(18)
O(3)
C(1)
C(3)
O(4)
O(5)
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C(12)
C(15)
C(13)
C(14)

Table 1. Crystal data and structure refinement for 511.

Identification code	gp21	
Chemical formula	$C_{18}H_{24}O_5$	
Formula weight	320.37	
Temperature	150(2) K	
Radiation, wavelength	MoK, 0.71073 Å	
Crystal system, space group	orthorhombic, $Pca2_1$	
Unit cell parameters	a = 8.6092(10) Å	□ = 90°
	b = 13.7840(15) Å	□ = 90°
	c = 13.9589(15) Å	□ = 90°
Cell volume	1656.5(3) $Å^3$	
Z	4	
Calculated density	1.285 g/cm^3	
Absorption coefficient □	0.093 mm^{-1}	
F(000)	688	
Crystal colour and size	colourless, 0.63 × 0.44 × 0.16 mm^3	
Reflections for cell refinement	5660 (□ range 2.79 to 26.22°)	
Data collection method	Bruker APEX 2 CCD diffractometer	
	□ rotation with narrow frames	
□ range for data collection	2.79 to 28.40°	
Index ranges	h −11 to 11, k −18 to 18, l −18 to 18	
Completeness to □ = 28.40°	99.7 %	
Intensity decay	0%	
Reflections collected	15977	
Independent reflections	2162 (R_{int} = 0.0279)	
Reflections with F^2>2□	1949	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.944 and 0.985	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting parameters a, b	0.0410, 0.1658	
Data / restraints / parameters	2162 / 1 / 211	
Final R indices [F^2>2□]	R1 = 0.0278, wR2 = 0.0698	
R indices (all data)	R1 = 0.0334, wR2 = 0.0738	
Goodness-of-fit on F^2	1.058	
Largest and mean shift/su	0.000 and 0.000	
Largest diff. peak and hole	0.191 and −0.138 e $Å^{-3}$	

Table 2. Atomic coordinates and equivalent isotropic displacement parameters ($Å^2$) for 511. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
C(1)	0.12677(18)	0.27722(11)	0.13847(11)	0.0247(3)
O(1)	0.25804(14)	0.33961(8)	0.13833(8)	0.0265(2)
C(2)	0.38921(19)	0.28414(13)	0.10224(12)	0.0306(4)
C(3)	0.3312(2)	0.18038(13)	0.11519(14)	0.0339(4)
O(2)	0.17109(14)	0.19308(8)	0.08716(9)	0.0306(3)
C(4)	0.3314(2)	0.14126(13)	0.21703(15)	0.0363(4)
C(5)	0.2407(2)	0.20654(12)	0.28629(12)	0.0297(3)
C(6)	0.08803(18)	0.24750(11)	0.24356(11)	0.0251(3)
O(3)	0.00040(13)	0.31967(9)	0.09548(8)	0.0284(2)
C(7)	0.0279(2)	0.35241(15)	−0.00113(12)	0.0364(4)
C(8)	0.5386(2)	0.31474(15)	0.15111(15)	0.0388(4)
C(9)	0.5894(2)	0.41552(18)	0.11965(16)	0.0491(5)
C(10)	−0.0459(2)	0.17206(12)	0.24181(12)	0.0287(3)
C(11)	−0.09789(19)	0.13484(12)	0.33881(13)	0.0281(3)
C(12)	−0.03732(19)	0.04892(11)	0.37708(14)	0.0318(4)
C(13)	−0.0895(2)	0.01333(14)	0.46468(14)	0.0366(4)
C(14)	−0.1988(2)	0.06377(14)	0.51671(14)	0.0376(4)
C(15)	−0.2596(2)	0.14927(14)	0.48051(15)	0.0381(4)
C(16)	−0.2104(2)	0.18364(12)	0.39215(14)	0.0339(4)
C(17)	0.0411(2)	0.33703(12)	0.30166(11)	0.0263(3)
O(4)	0.11936(15)	0.37409(9)	0.36295(10)	0.0379(3)
O(5)	−0.09904(15)	0.37029(9)	0.27683(9)	0.0354(3)
C(18)	−0.1524(3)	0.45622(15)	0.32650(15)	0.0452(5)

Table 3. Bond lengths [Å] and angles [°] for 511.

C(1)–O(3)	1.3734(19)	C(1)–O(2)	1.4155(18)
C(1)–O(1)	1.4201(19)	C(1)–C(6)	1.559(2)
O(1)–C(2)	1.454(2)	C(2)–C(8)	1.515(3)
C(2)–C(3)	1.526(3)	C(3)–O(2)	1.444(2)
C(3)–C(4)	1.520(3)	C(4)–C(5)	1.534(3)
C(5)–C(6)	1.550(2)	C(6)–C(17)	1.531(2)
C(6)–C(10)	1.553(2)	O(3)–C(7)	1.442(2)
C(8)–C(9)	1.521(3)	C(10)–C(11)	1.515(2)
C(11)–C(16)	1.395(3)	C(11)–C(12)	1.400(2)
C(12)–C(13)	1.392(3)	C(13)–C(14)	1.377(3)
C(14)–C(15)	1.385(3)	C(15)–C(16)	1.387(3)
C(17)–O(4)	1.203(2)	C(17)–O(5)	1.337(2)
O(5)–C(18)	1.447(2)		
O(3)–C(1)–O(2)	109.97(13)	O(3)–C(1)–O(1)	111.83(12)
O(2)–C(1)–O(1)	106.32(12)	O(3)–C(1)–C(6)	110.70(13)
O(2)–C(1)–C(6)	108.57(12)	O(1)–C(1)–C(6)	109.31(12)

C(1)–O(1)–C(2)	107.47(11)	O(1)–C(2)–C(8)	110.91(14)
O(1)–C(2)–C(3)	101.41(13)	C(8)–C(2)–C(3)	119.03(15)
O(2)–C(3)–C(4)	107.31(15)	O(2)–C(3)–C(2)	99.60(14)
C(4)–C(3)–C(2)	116.28(15)	C(1)–O(2)–C(3)	102.69(12)
C(3)–C(4)–C(5)	112.36(14)	C(4)–C(5)–C(6)	113.76(14)
C(17)–C(6)–C(5)	108.27(13)	C(17)–C(6)–C(10)	110.63(13)
C(5)–C(6)–C(10)	113.07(13)	C(17)–C(6)–C(1)	110.06(13)
C(5)–C(6)–C(1)	106.04(13)	C(10)–C(6)–C(1)	108.66(12)
C(1)–O(3)–C(7)	114.31(14)	C(2)–C(8)–C(9)	111.60(16)
C(11)–C(10)–C(6)	115.59(13)	C(16)–C(11)–C(12)	117.58(16)
C(16)–C(11)–C(10)	121.25(15)	C(12)–C(11)–C(10)	121.15(16)
C(13)–C(12)–C(11)	120.87(17)	C(14)–C(13)–C(12)	120.39(17)
C(13)–C(14)–C(15)	119.69(18)	C(14)–C(15)–C(16)	119.97(18)
C(15)–C(16)–C(11)	121.46(16)	O(4)–C(17)–O(5)	122.99(16)
O(4)–C(17)–C(6)	124.85(16)	O(5)–C(17)–C(6)	112.16(14)
C(17)–O(5)–C(18)	116.31(14)		

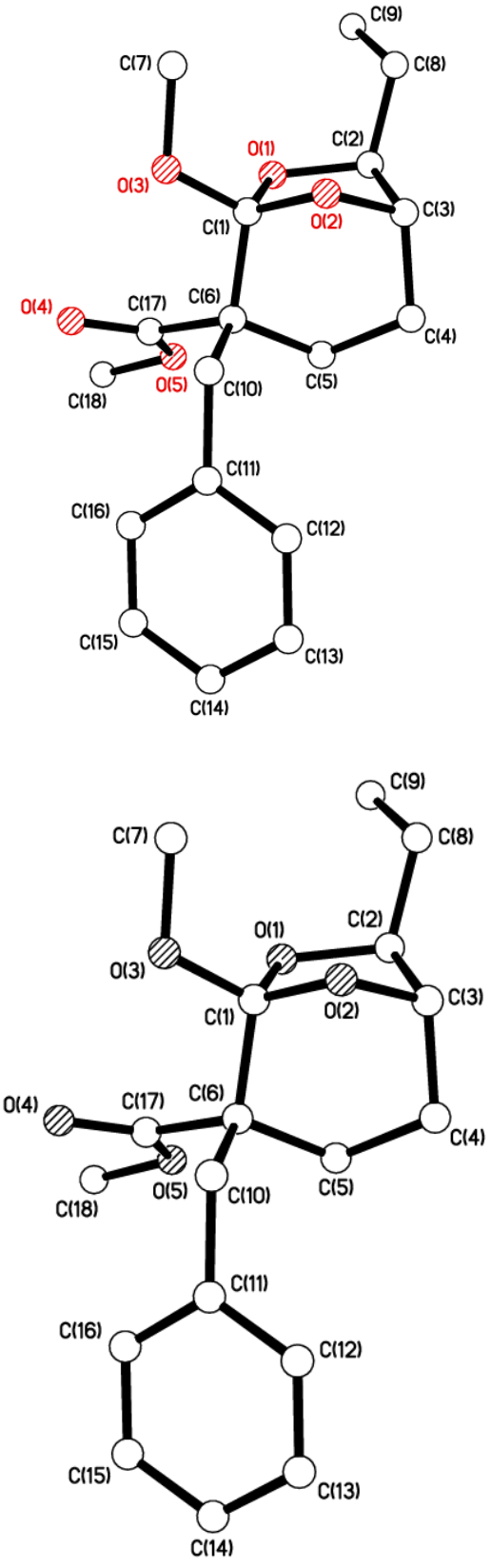
Table 4. Hydrogen coordinates and isotropic displacement parameters ($Å^2$) for 511.

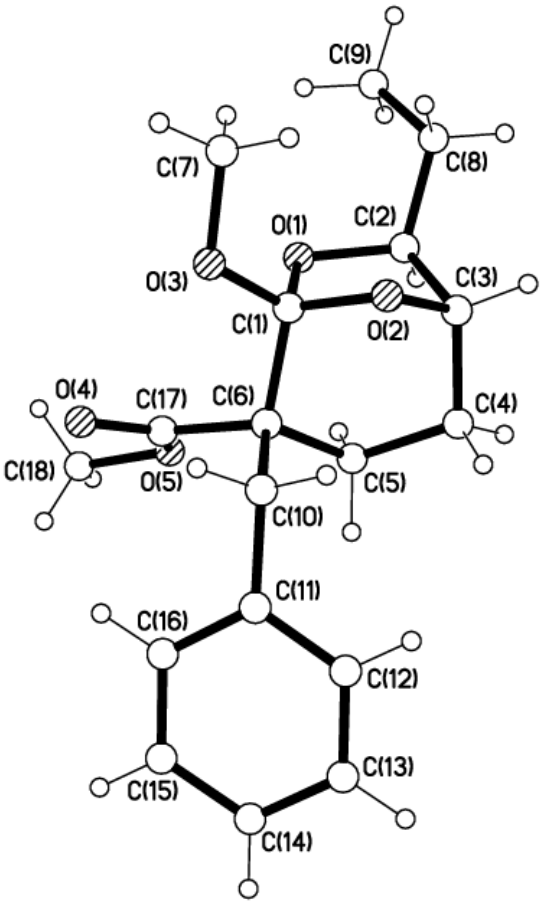
	x	y	z	U
H(2)	0.3997	0.2972	0.0321	0.037
H(3)	0.3861	0.1350	0.0707	0.041
H(4A)	0.4400	0.1354	0.2396	0.044
H(4B)	0.2849	0.0756	0.2173	0.044
H(5A)	0.3079	0.2614	0.3056	0.036
H(5B)	0.2156	0.1689	0.3447	0.036
H(7A)	0.1231	0.3914	−0.0029	0.055
H(7B)	−0.0600	0.3919	−0.0226	0.055
H(7C)	0.0395	0.2962	−0.0435	0.055
H(8A)	0.6215	0.2675	0.1356	0.047
H(8B)	0.5232	0.3143	0.2214	0.047
H(9A)	0.5937	0.4182	0.0495	0.074
H(9B)	0.6924	0.4297	0.1460	0.074
H(9C)	0.5147	0.4637	0.1431	0.074
H(10A)	−0.1365	0.2017	0.2094	0.034
H(10B)	−0.0124	0.1160	0.2026	0.034
H(12)	0.0404	0.0144	0.3428	0.038
H(13)	−0.0494	−0.0461	0.4887	0.044
H(14)	−0.2324	0.0400	0.5772	0.045
H(15)	−0.3350	0.1844	0.5162	0.046
H(16)	−0.2544	0.2417	0.3674	0.041
H(18A)	−0.1510	0.4445	0.3957	0.068
H(18B)	−0.2586	0.4715	0.3061	0.068
H(18C)	−0.0839	0.5108	0.3112	0.068

Table 5. Torsion angles [°] for 511.

O(3)–C(1)–O(1)–C(2)	−130.62(13)	O(2)–C(1)–O(1)–C(2)	−10.57(16)
C(6)–C(1)–O(1)–C(2)	106.44(14)	C(1)–O(1)–C(2)–C(8)	−145.69(14)
C(1)–O(1)–C(2)–C(3)	−18.32(16)	O(1)–C(2)–C(3)–O(2)	39.61(15)
C(8)–C(2)–C(3)–O(2)	161.50(15)	O(1)–C(2)–C(3)–C(4)	−75.23(17)
C(8)–C(2)–C(3)–C(4)	46.7(2)	O(3)–C(1)–O(2)–C(3)	158.23(13)
O(1)–C(1)–O(2)–C(3)	36.99(16)	C(6)–C(1)–O(2)–C(3)	−80.51(15)
C(4)–C(3)–O(2)–C(1)	74.59(16)	C(2)–C(3)–O(2)–C(1)	−46.95(15)
O(2)–C(3)–C(4)–C(5)	−55.5(2)	C(2)–C(3)–C(4)–C(5)	54.9(2)
C(3)–C(4)–C(5)–C(6)	40.5(2)	C(4)–C(5)–C(6)–C(17)	−159.57(14)
C(4)–C(5)–C(6)–C(10)	77.49(18)	C(4)–C(5)–C(6)–C(1)	−41.48(17)
O(3)–C(1)–C(6)–C(17)	−59.78(17)	O(2)–C(1)–C(6)–C(17)	179.41(13)
O(1)–C(1)–C(6)–C(17)	63.83(16)	O(3)–C(1)–C(6)–C(5)	−176.67(12)
O(2)–C(1)–C(6)–C(5)	62.52(15)	O(1)–C(1)–C(6)–C(5)	−53.06(16)
O(3)–C(1)–C(6)–C(10)	61.50(16)	O(2)–C(1)–C(6)–C(10)	−59.31(16)
O(1)–C(1)–C(6)–C(10)	−174.89(12)	O(2)–C(1)–O(3)–C(7)	−62.02(17)
O(1)–C(1)–O(3)–C(7)	55.86(17)	C(6)–C(1)–O(3)–C(7)	178.01(14)
O(1)–C(2)–C(8)–C(9)	−70.6(2)	C(3)–C(2)–C(8)–C(9)	172.38(17)
C(17)–C(6)–C(10)–C(11)	−59.34(19)	C(5)–C(6)–C(10)–C(11)	62.29(19)
C(1)–C(6)–C(10)–C(11)	179.73(14)	C(6)–C(10)–C(11)–C(16)	87.1(2)
C(6)–C(10)–C(11)–C(12)	−94.49(19)	C(16)–C(11)–C(12)–C(13)	0.8(2)
C(10)–C(11)–C(12)–C(13)	−177.74(15)	C(11)–C(12)–C(13)–C(14)	−1.9(3)
C(12)–C(13)–C(14)–C(15)	1.5(3)	C(13)–C(14)–C(15)–C(16)	0.1(3)
C(14)–C(15)–C(16)–C(11)	−1.2(3)	C(12)–C(11)–C(16)–C(15)	0.8(3)
C(10)–C(11)–C(16)–C(15)	179.29(16)	C(5)–C(6)–C(17)–O(4)	7.2(2)
C(10)–C(6)–C(17)–O(4)	131.62(17)	C(1)–C(6)–C(17)–O(4)	−108.28(18)
C(5)–C(6)–C(17)–O(5)	−172.62(13)	C(10)–C(6)–C(17)–O(5)	−48.20(18)
C(1)–C(6)–C(17)–O(5)	71.89(17)	O(4)–C(17)–O(5)–C(18)	1.4(2)
C(6)–C(17)–O(5)–C(18)	−178.76(14)		

Appendix XIII X-Ray crystallographic data for 517.




C(9)
C(7)
C(8)
O(1)
C(2)
O(3)
C(3)
C(1)
O(2)
O(4)
C(17)
C(6)
C(4)
C(18)
O(5)
C(5)
C(10)
C(11)
C(16)
C(12)
C(13)
C(15)
C(14)

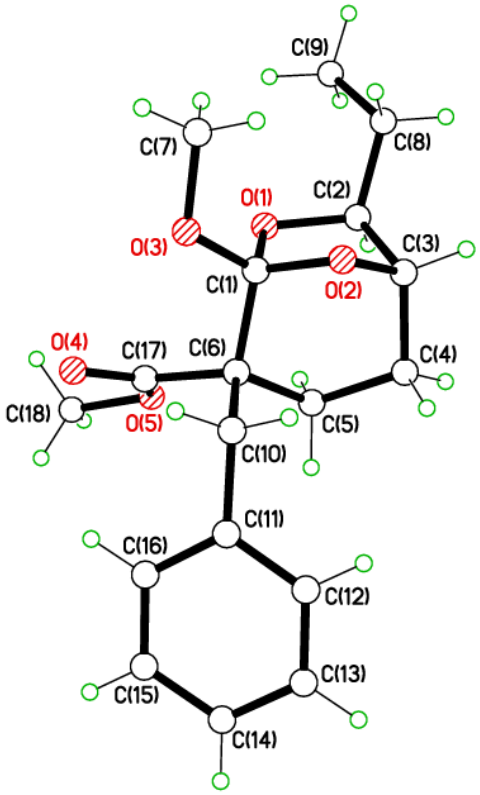

C(9)
C(7)
C(8)
O(1)
C(2)
O(3)
C(3)
C(1)
O(2)
O(4)
C(17)
C(6)
C(4)
C(18)
O(5)
C(5)
C(10)
C(11)
C(16)
C(12)
C(13)
C(15)
C(14)

Table 1. Crystal data and structure refinement for 517.

Identification code	gp22	
Chemical formula	$C_{18}H_{24}O_5$	
Formula weight	320.37	
Temperature	150(2) K	
Radiation, wavelength	MoK, 0.71073 Å	
Crystal system, space group	monoclinic, $P2_1/n$	
Unit cell parameters	a = 13.2706(9) Å	□ = 90°
	b = 7.5565(5) Å	□ = 109.8974(10)°
	c = 17.6919(13) Å	□ = 90°
Cell volume	1668.2(2) $Å^3$	
Z	4	
Calculated density	1.276 g/cm^3	
Absorption coefficient □	0.092 mm^{-1}	
F(000)	688	
Crystal colour and size	colourless, 1.06 × 0.33 × 0.10 mm^3	
Reflections for cell refinement	6260 (□ range 2.35 to 27.13°)	
Data collection method	Bruker APEX 2 CCD diffractometer	
	□ rotation with narrow frames	
□ range for data collection	1.67 to 27.16°	
Index ranges	h –17 to 16, k –9 to 9, l –22 to 22	
Completeness to □ = 27.16°	99.8 %	
Intensity decay	0%	
Reflections collected	15033	
Independent reflections	3697 (R_{int} = 0.0242)	
Reflections with F^2>2□	3177	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.909 and 0.991	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting parameters a, b	0.0440, 0.5093	
Data / restraints / parameters	3697 / 0 / 211	
Final R indices [F^2>2□]	R1 = 0.0359, wR2 = 0.0906	
R indices (all data)	R1 = 0.0424, wR2 = 0.0946	
Goodness-of-fit on F^2	1.052	
Largest and mean shift/su	0.000 and 0.000	
Largest diff. peak and hole	0.312 and –0.207 e $Å^{-3}$	

Table 2. Atomic coordinates and equivalent isotropic displacement parameters ($Å^2$) for 517. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
C(1)	0.29598(8)	0.41782(14)	0.13466(6)	0.0187(2)
O(1)	0.29019(6)	0.55683(10)	0.07922(4)	0.02029(18)
C(2)	0.29736(9)	0.72390(15)	0.12125(7)	0.0217(2)
C(3)	0.32504(9)	0.66377(15)	0.20891(7)	0.0221(2)
O(2)	0.27018(6)	0.49603(10)	0.19821(4)	0.02098(18)
C(4)	0.44338(9)	0.62656(16)	0.25155(7)	0.0232(2)
C(5)	0.48660(8)	0.50549(15)	0.19988(7)	0.0203(2)
C(6)	0.41278(8)	0.34444(14)	0.16643(6)	0.0183(2)
O(3)	0.22483(6)	0.28496(10)	0.10028(5)	0.02247(18)
C(7)	0.11454(9)	0.33940(17)	0.06843(8)	0.0291(3)
C(8)	0.19299(10)	0.82525(16)	0.08711(7)	0.0268(3)
C(9)	0.16479(10)	0.86472(18)	−0.00212(8)	0.0333(3)
C(10)	0.42356(9)	0.20149(15)	0.23164(7)	0.0216(2)
C(11)	0.53813(9)	0.14228(15)	0.27379(7)	0.0239(2)
C(12)	0.59553(10)	0.2063(2)	0.35006(7)	0.0337(3)
C(13)	0.70181(11)	0.1596(2)	0.38927(9)	0.0431(4)
C(14)	0.75244(11)	0.0466(2)	0.35227(9)	0.0435(4)
C(15)	0.69683(11)	−0.0202(2)	0.27696(9)	0.0399(3)
C(16)	0.59040(10)	0.02696(17)	0.23769(8)	0.0305(3)
C(17)	0.43602(8)	0.25278(15)	0.09671(6)	0.0195(2)
O(4)	0.39954(7)	0.11175(11)	0.06939(5)	0.0291(2)
O(5)	0.50390(7)	0.34258(11)	0.07000(5)	0.0275(2)
C(18)	0.53490(12)	0.25230(18)	0.00890(8)	0.0352(3)

Table 3. Bond lengths [Å] and angles [°] for 517.

C(1)–O(3)	1.3706(13)	C(1)–O(2)	1.4116(13)
C(1)–O(1)	1.4213(13)	C(1)–C(6)	1.5598(14)
O(1)–C(2)	1.4518(13)	C(2)–C(8)	1.5166(16)
C(2)–C(3)	1.5359(16)	C(3)–O(2)	1.4418(13)
C(3)–C(4)	1.5193(16)	C(4)–C(5)	1.5356(15)
C(5)–C(6)	1.5480(15)	C(6)–C(17)	1.5345(14)
C(6)–C(10)	1.5512(15)	O(3)–C(7)	1.4379(13)
C(8)–C(9)	1.5229(18)	C(10)–C(11)	1.5153(15)
C(11)–C(12)	1.3913(18)	C(11)–C(16)	1.3964(17)
C(12)–C(13)	1.3888(19)	C(13)–C(14)	1.382(2)
C(14)–C(15)	1.380(2)	C(15)–C(16)	1.3916(18)
C(17)–O(4)	1.2018(14)	C(17)–O(5)	1.3361(13)
O(5)–C(18)	1.4512(14)		
O(3)–C(1)–O(2)	110.06(8)	O(3)–C(1)–O(1)	111.58(9)
O(2)–C(1)–O(1)	105.63(8)	O(3)–C(1)–C(6)	110.46(9)
O(2)–C(1)–C(6)	110.03(8)	O(1)–C(1)–C(6)	108.97(8)

C(1)–O(1)–C(2)	108.09(8)	O(1)–C(2)–C(8)	110.08(9)
O(1)–C(2)–C(3)	102.20(8)	C(8)–C(2)–C(3)	115.06(9)
O(2)–C(3)–C(4)	107.03(9)	O(2)–C(3)–C(2)	101.01(8)
C(4)–C(3)–C(2)	114.06(9)	C(1)–O(2)–C(3)	102.95(8)
C(3)–C(4)–C(5)	110.31(9)	C(4)–C(5)–C(6)	112.33(9)
C(17)–C(6)–C(5)	112.83(8)	C(17)–C(6)–C(10)	106.90(9)
C(5)–C(6)–C(10)	112.14(9)	C(17)–C(6)–C(1)	108.53(8)
C(5)–C(6)–C(1)	106.27(8)	C(10)–C(6)–C(1)	110.14(8)
C(1)–O(3)–C(7)	114.83(9)	C(2)–C(8)–C(9)	112.37(10)
C(11)–C(10)–C(6)	113.25(9)	C(12)–C(11)–C(16)	117.86(11)
C(12)–C(11)–C(10)	120.07(11)	C(16)–C(11)–C(10)	122.05(11)
C(13)–C(12)–C(11)	121.59(13)	C(14)–C(13)–C(12)	119.69(13)
C(15)–C(14)–C(13)	119.80(13)	C(14)–C(15)–C(16)	120.44(13)
C(15)–C(16)–C(11)	120.61(13)	O(4)–C(17)–O(5)	122.40(10)
O(4)–C(17)–C(6)	124.05(10)	O(5)–C(17)–C(6)	113.53(9)
C(17)–O(5)–C(18)	114.89(9)		

Table 4. Hydrogen coordinates and isotropic displacement parameters ($Å^2$) for 517.

	x	y	z	U
H(2)	0.3576	0.7960	0.1156	0.026
H(3)	0.2966	0.7483	0.2402	0.026
H(4A)	0.4536	0.5690	0.3039	0.028
H(4B)	0.4837	0.7394	0.2619	0.028
H(5A)	0.5588	0.4628	0.2327	0.024
H(5B)	0.4938	0.5746	0.1545	0.024
H(7A)	0.0928	0.3885	0.1118	0.044
H(7B)	0.0695	0.2371	0.0448	0.044
H(7C)	0.1062	0.4297	0.0270	0.044
H(8A)	0.1988	0.9381	0.1167	0.032
H(8B)	0.1345	0.7553	0.0953	0.032
H(9A)	0.2216	0.9366	−0.0104	0.050
H(9B)	0.0969	0.9296	−0.0215	0.050
H(9C)	0.1577	0.7533	−0.0319	0.050
H(10A)	0.3945	0.2492	0.2721	0.026
H(10B)	0.3798	0.0974	0.2063	0.026
H(12)	0.5612	0.2839	0.3759	0.040
H(13)	0.7395	0.2052	0.4413	0.052
H(14)	0.8253	0.0150	0.3786	0.052
H(15)	0.7314	−0.0989	0.2518	0.048
H(16)	0.5530	−0.0197	0.1858	0.037
H(18A)	0.5702	0.1403	0.0306	0.053
H(18B)	0.5844	0.3272	−0.0072	0.053
H(18C)	0.4710	0.2284	−0.0380	0.053

Table 5. Torsion angles [°] for 517.

O(3)–C(1)–O(1)–C(2)	138.82(9)	O(2)–C(1)–O(1)–C(2)	19.23(10)
C(6)–C(1)–O(1)–C(2)	−98.95(9)	C(1)–O(1)–C(2)–C(8)	−114.41(9)
C(1)–O(1)–C(2)–C(3)	8.31(10)	O(1)–C(2)–C(3)–O(2)	−31.92(10)
C(8)–C(2)–C(3)–O(2)	87.35(10)	O(1)–C(2)–C(3)–C(4)	82.51(11)
C(8)–C(2)–C(3)–C(4)	−158.22(10)	O(3)–C(1)–O(2)–C(3)	−161.12(8)
O(1)–C(1)–O(2)–C(3)	−40.53(10)	C(6)–C(1)–O(2)–C(3)	76.93(10)
C(4)–C(3)–O(2)–C(1)	−75.22(10)	C(2)–C(3)–O(2)–C(1)	44.37(10)
O(2)–C(3)–C(4)–C(5)	61.39(11)	C(2)–C(3)–C(4)–C(5)	−49.43(12)
C(3)–C(4)–C(5)–C(6)	−47.24(12)	C(4)–C(5)–C(6)–C(17)	163.58(9)
C(4)–C(5)–C(6)–C(10)	−75.63(11)	C(4)–C(5)–C(6)–C(1)	44.76(11)
O(3)–C(1)–C(6)–C(17)	55.60(11)	O(2)–C(1)–C(6)–C(17)	177.31(8)
O(1)–C(1)–C(6)–C(17)	−67.31(10)	O(3)–C(1)–C(6)–C(5)	177.21(8)
O(2)–C(1)–C(6)–C(5)	−61.08(10)	O(1)–C(1)–C(6)–C(5)	54.30(10)
O(3)–C(1)–C(6)–C(10)	−61.10(11)	O(2)–C(1)–C(6)–C(10)	60.61(11)
O(1)–C(1)–C(6)–C(10)	175.99(8)	O(2)–C(1)–O(3)–C(7)	58.77(12)
O(1)–C(1)–O(3)–C(7)	−58.16(12)	C(6)–C(1)–O(3)–C(7)	−179.54(9)
O(1)–C(2)–C(8)–C(9)	−59.45(12)	C(3)–C(2)–C(8)–C(9)	−174.25(10)
C(17)–C(6)–C(10)–C(11)	70.40(11)	C(5)–C(6)–C(10)–C(11)	−53.75(12)
C(1)–C(6)–C(10)–C(11)	−171.88(9)	C(6)–C(10)–C(11)–C(12)	101.82(12)
C(6)–C(10)–C(11)–C(16)	−76.59(14)	C(16)–C(11)–C(12)–C(13)	0.72(19)
C(10)–C(11)–C(12)–C(13)	−177.75(12)	C(11)–C(12)–C(13)–C(14)	−0.2(2)
C(12)–C(13)–C(14)–C(15)	−0.5(2)	C(13)–C(14)–C(15)–C(16)	0.7(2)
C(14)–C(15)–C(16)–C(11)	−0.1(2)	C(12)–C(11)–C(16)–C(15)	−0.60(18)
C(10)–C(11)–C(16)–C(15)	177.83(11)	C(5)–C(6)–C(17)–O(4)	168.95(10)
C(10)–C(6)–C(17)–O(4)	45.21(14)	C(1)–C(6)–C(17)–O(4)	−73.56(13)
C(5)–C(6)–C(17)–O(5)	−9.25(13)	C(10)–C(6)–C(17)–O(5)	−132.99(10)
C(1)–C(6)–C(17)–O(5)	108.25(10)	O(4)–C(17)–O(5)–C(18)	−3.39(16)
C(6)–C(17)–O(5)–C(18)	174.84(10)		