Stereoselective Synthesis of 1,2-Cyclopropanecarboxylated Furanoids: Applications towards the Preparation of Marine Natural Products and Unnatural Amino Acids

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Herrn Prof. Dr. O. Reiser möchte ich für die Überlassung des äußerst interessanten Themas, die anregenden Diskussionen und stete Unterstützung während der Durchführung dieser Arbeit danken.

Dedicated to Swamiji

For my mother,

Mangala

Ithaca

When you start your journey to Ithaca,
Then pray that the road is long,
Full of adventure, full of knowledge,
Do not fear the Lestrygonians
And the Cyclopes and the angry Poseidon.
You will never meet such as these on your path
If your thoughts remain lofty, if a fine

Emotion touches your body and your spirit.
You will never meet the Lestrygonians,
The Cyclopes and the fierce Poseidon,
If you do not carry them within your soul,
If your soul does not raise them up before you.

Then pray the road is long.
That the summer mornings are many,
That you will enter ports seen for the first time
With such pleasure, with such joy!
Stop at Phoenician markets,
And purchase fine merchandise,
Mother-of-pearl and corals, amber and ebony,
And pleasurable perfumes of all kinds,
Buy as many pleasurable perfumes as you can;
Visit hosts of Egyptian cities,
To learn and learn from those who have knowledge.
Always keep Ithaca fixed in your mind.
To arrive there is your ultimate goal.
But do not hurry the voyage at all.
It is better to let it last for long years;
And even to anchor at the isle when you are old,
Rich withal that you have gained on the way,
Not expecting that Ithaca will offer you riches.

Ithaca has given you the beautiful voyage.
Without her you would never have taken the road.
But she has nothing more to give you.

And if you find her poor, Ithaca has not defrauded you.
With the great Wisdom you have gained, with so much experience,
You must surely have understood by then what Ithaca means.

C. P. Cavafy

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Abbreviations

abs.	absolute
AIBN	azo-isobutyronitrile
B	base
Bn	benzyl
*t*Boc	*tert*-butoxycarbonyl
Bu	*n*-butyl
Bu_3P	tri-*n*-butyl phosphine
*n*BuLi	*n*-butyl lithium
Bz	benzyloxycarbonyl
CAN	ceric ammonium nitrate
cat.	catalytic
CSA	(+)-camphorsulfonic acid
m-CPBA	*m*-chloroperbenzoic acid
dr	diastereomeric ratio
DBU	1,8-Diazabicyclo[5.4.0]-undec-7-ene
DHF	dihydrofuran
Dibal-H	di-*iso*-butyl aluminium hydride
DMAP	N,N-dimethylamino pyridine
DMF	dimethyl formamide
DMP	Dess-Martin periodinane
DMS	dimethyl sulfide
DMSO	dimethylsulfoxide
ee	enantiomeric excess
equiv.	equivalents
E	electrophile
EI	electron impact (MS)
epi	epimer
EWG	electron withdrawing group
Et	ethyl
h	hours
HMPA	hexamethylphophoramide
HPLC	high pressure liquid chromatography
HRMS	high resolution mass spectrum
HWE	Horner-Wordswoth-Emmons
IR	infra red (spectrum)
L*	ligand
LAH	lithium alumiun hydride
LDA	lithiumdiisopropylamide
LiHMDS	lithium hexamethyldisilazide
M	metal
Me	methyl
MeCN	acetonitrile
Mes	mesyl
min.	minutes
MS	mass spectrum
NBS	N-bromosuccinimide
NIS	N-iodosuccinimide
NMO	4-methyl morpholine N-oxide
NMR	nuclear magnetic resonance
NOE	nuclear overhauser effect
Nu	nucleophile
ORTEP	Oak Ridge Thermal Ellipsoid Plot

PCC	pyridinium chlorochromate
PG	Protecting Group
Ph	Phenyl
PMB	*p*-methoxybenzyl
PMP	*p*-methoxyphenyl
PPh_3	tri-phenyl phosphine
PPTS	pyridinium-*p*-toluenesulfonate
Pyr	pyridine
Ra-Ni	Raney-Nickel
rt	room temperature
TBDMS	*t*-butyldimethylsilyl
TBAF	tetrabutyl ammonium fluoride
t/(*tert*)	tertiary
TES	triethylsilyl
THF	tetrahydrofuran
TFA	trifluoroacetic acid
TMS-	trimethylsilyl
Tr	trityl
Triflet (Tf)	trifluormethanesulfonate
Ts	tosyl
p-TsOH	*p*-Toluenesulfonic acid
TIPS	triisopropylsilyl
quant.	quantitative

1.1 Syntheses of Bicyclic Natural Products Having *cis*-Fused Furo[2,3-*b*]furan Structure: (Microreview):

1.1.1 Abstract: Bicyclic natural products containing a *cis*-fused furo[2,3-*b*]furan framework are attractive synthetic targets, many with significant biological activity. The bicyclic framework has a distinct convex and a concave face. The former being easily accessible compared to the latter. Introducing functional groups on these bicycles selectively, especially on the concave face, poses therefore a major synthetic challenge. The objective behind this microreview is to provide various strategies for stereoselective syntheses of such natural products or their analogues. A special focus is given to application of different synthetic methodologies for the construction of the constrained bicyclic core.

1.1.2 Introduction: The *cis*-fused dioxabicyclo[3.3.0]octane (Fig. 1) is an important structural component of a broad range of bicyclic natural products. Such compounds are extensively distributed in nature and have attracted much attention because of their unique structural properties and interesting biological activities. Generally, these natural products are highly functionalized, containing a number of asymmetric carbon centers. Therefore, from the viewpoint of synthetic organic chemistry, these natural products are challenging and interesting targets to test novel synthetic strategies in addition to exploring structure activity relationships within their biological profile.

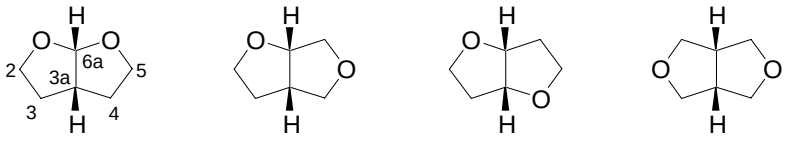
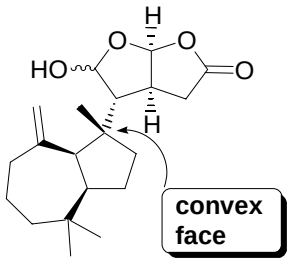


Figure 1 Basic structures of dioxabicyclo[3.3.0]octanes

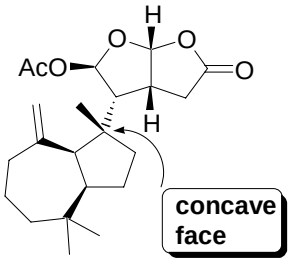
This microreview details the various routes employed for the syntheses of bicyclic natural products containing *cis*-fused furo[2,3-*b*]furan (**Type A**) framework in the literature up until the end of 2005.

1.1.3 Natural Products Having furo[2,3-*b*]furan Core (Type A): From the four possible isomeric core structures (Type **A-D**, Fig. 1), the furo[2,3-*b*]furans (Type **A**) are

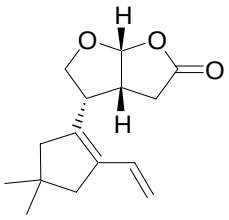
convincingly prominent in nature. Along with distinct structural features, they also display a wide range of biological significance.



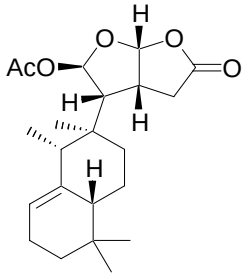
1 α-OH (**Cheloviolene A**)
2 β-OH (**Cheloviolene B**)



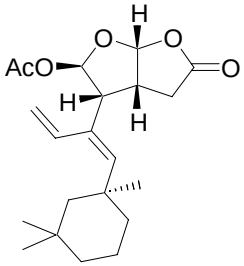
3 Dendrillolide A



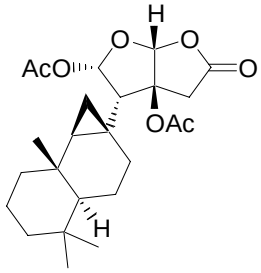
4 Dermatolactone



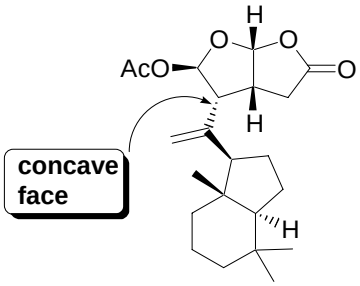
5 Macfarlandin C



6 Spongionellin



7 Omriolide B



8 Norrisolide

Figure 2 Structures of spongiane diterpenoids

Sponges are marine organisms expressing a large number of natural compounds, which display interesting biological properties such as antibacterial or cytotoxic activities. A scarcely explored sub-group of spongiane diterpenoids (Fig. 2) shares the structural motif of a *cis*-fused 5-oxofuro[2,3-*b*]furan unit (type **A**, Fig. 1), found in cheloviolene A (**1**) and B (**2**), dendrillolide A (**3**), dermatolactone (**4**), macfarlandin C (**5**), spongionellin (**6**), omriolide B (**7**) and norrisolide (**8**). A distinct structural feature

of all these natural products, with the exception of the cheloviolenes (**1** and **2**, Fig. 2) is the placement of a sterically bulky cyclic substituent on the concave face of the bicyclus.

The isolation and biological profile of these natural products is listed in the following table:

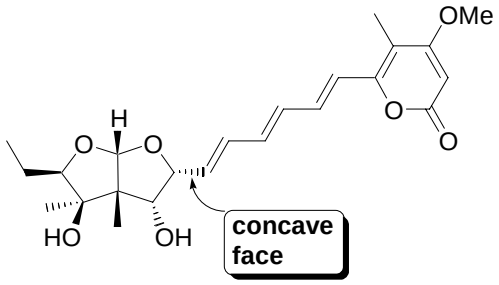
Entry	Natural Product	Natural Source	Year of Isolation	Biological Profile
1	Cheloviolene A[1], [2]	*C. violacea*	1993	unknown
2	Cheloviolene B[1]	*C. violacea*	1993	unknown
3	Dendrillolide A	*Chromodoris norrisi* [3]	1984	unknown
		Chromodoris gleneii[4]	1991	unknown
4	Dermatolactone[5]	Basidiomycete *Irpex lacteus*	1996	cytotoxic
5	Macfarlandin C[6]	*Chromodoris macfarlandi*	1986	unknown
6	Spongionellin[7]	*Spongionella gracilis*	1986	unknown
7	Omriolide B[8]	*Dictyodendrilla aff. Retiara*	2005	unknown
8	Norrisolide[9]	*Chromodoris norrisi*	1984	Golgi disrupting agent

Table 1 Isolation and biological profile of **1-8**

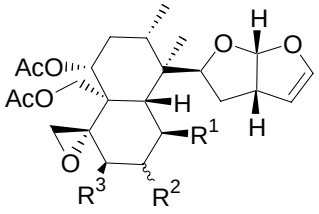
Despite of their abundance in nature, the synthesis as well as biological profile of these natural products is not much explored. Among these only norrisolide (**8**) has been recently synthesized having a unique property to irreversibly fragment the golgi apparatus in rat kidney cells.

The second class, having a comparable structural motif referred to as bis(tetrahydrofuran) belongs asteltoxin[10] (**9**, Fig. 3) and the clerodanes[11] (**10-17**, Fig. 3). Asteltoxin is a mytotoxin isolated from toxic maize cultures, showing inhibitory

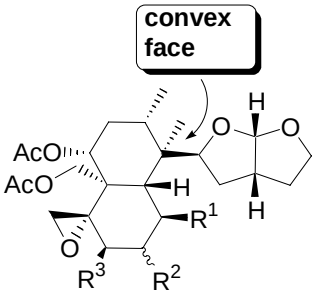
effect on oxidative phosphorylation on E.coli BF_1-ATPase. On the other hand, the clerodanes are natural diterpenoids possessing interesting antifeedant properties.



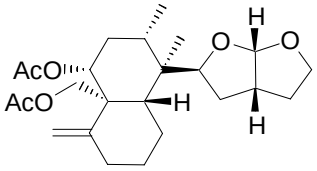
9 Asteltoxin



10 Clerodin:
R_1 = H; R_2 = H; R_3 = H



11-16



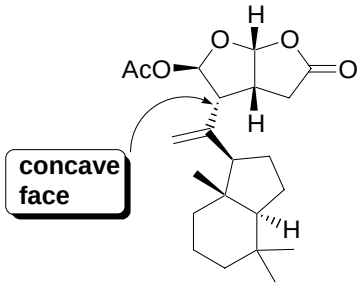
17 lupulin C

11 Dihydroclerodin: R^1 = H; R^2 = H; R^3 = H
12 Ajugatansin D1: R^1 = OTig; R^2 = b-OH; R^3 = OMeBu
13 Ajugavensin A: R^1 = OMeBu; R^2 = H; R^3 = H
14 Ajugavensin B: R^1 = OTig; R^2 = H; R^3 = H
15 Ajugareptansin: R^1 = OMeBu; R^2 = H; R^3 = OH
16 Areptin A: R^1 = OH; R^2 = a-OAc; R^3 = OMeBu
MeBu = (*S*)-2-Methylbutanoyl
Tig = (*E*)-2-Methyl-2-butenoyl (Tigloyl)

Figure 3 Structures of other natural products having core of Type A

For the synthesis of these natural products, the major challenge to meet is the development of a flexible strategy for the construction of *cis*-fused furo[2,3-*b*]furan core in enantiomerically pure form that allows introduction of bulky groups especially on the concave face and ii) assembly as well as introduction of side chains possessing differently sized and functionalized bulk at the appropriate stage of synthesis on the desired face of the bicycle.

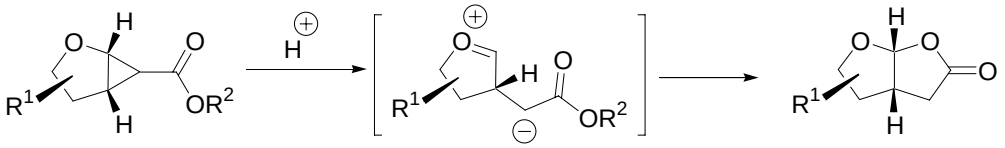
1.1.4 Norrisolide: Norrisolide (Fig. 4) was isolated in 1983 by Faulkner, Clardy and co-workers in a study of the chemical defense system of nudibranch molluscs. It is the first compound reported to vesiculate the golgi apparatus irreversibly.[12] Therefore norrisolide is of great use as a biological tool and could provide further information about dynamics and mechanism of Golgi apparatus.



8 Norrisolide

Figure 4 Structure of norrisolide

1.1.4a Model Studies Towards Norrisolide: In 1999, Theodorakis and co-workers reported the synthesis of the *cis*-fused furo[2,3-*b*]furan motif of norrisolide.[13] As a key step, the ring expansion of appropriately substituted cyclopropyl esters was developed (Fig. 5).



18 **19** **20**

Figure 5 General scheme for ring expansion of substituted cyclopropyl ester

The idea behind this strategy was to utilize the ability of the anomeric bond in **18** to undergo cleavage under mild acidic conditions. The transiently produced 1,3-dipolar synthon **19** could then cyclize at the anomeric center to produce desired bicyclus **20.**

The dihydrofuran **22** was chosen as the starting point for this method which was synthesized from D-mannose **21** in four steps by applying the method reported by Kartha (Fig. 6).[14] Rhodium-acetate catalyzed cyclopropanation of **22** produced the

cyclopropyl ester **23** as a mixture of diastereomers at C4 center (4:1 in favor of the *exo* adduct). The acid catalyzed cyclopropane ring opening of **23** yielded the compound **24**. The 1,2-diol in **24** which was opened under the effect of acid was converted to methyl ketone **25** in three steps. The formation of *cis*-fused furo[2,3-*b*]furan **26** was then achieved by subjecting **25** to methanesulfonic acid. The cyclization underwent with complete diastereoelectivity. Finally, the *O*-acetyl functionality was installed at C2 carbon of **26** to yield **27**.

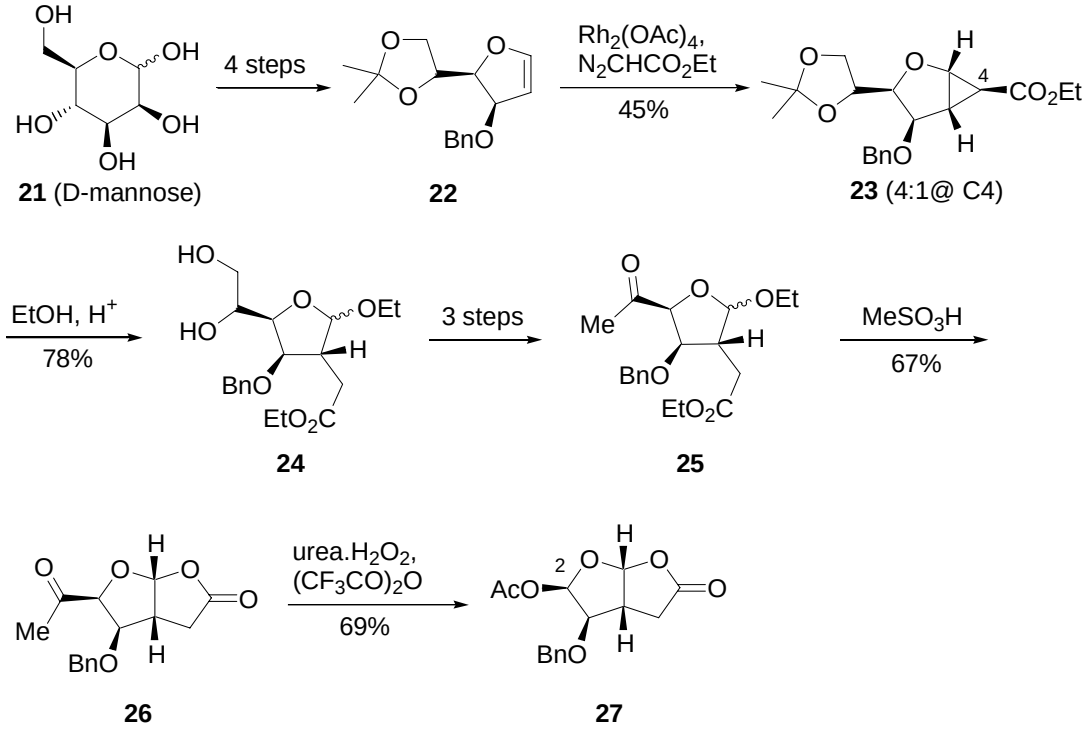
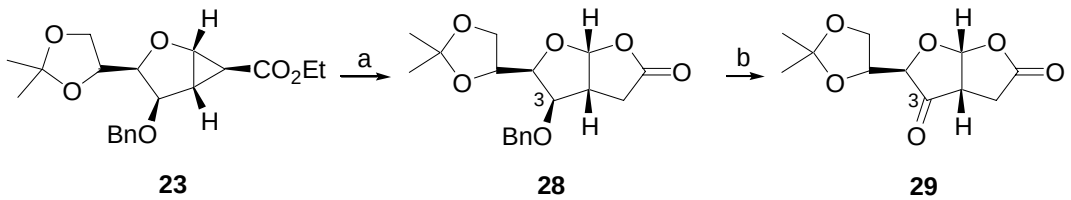


Figure 6 Synthesis of the side-chain motif of norrisolide by Theodorakis

The cyclopropyl ester **23** could also be directly converted to *cis*-fused furo[2,3-*b*]furan **28** in one pot using methanesulfonic acid/acetone combination (Fig. 7).[15]



a. $MeSO_3H$, acetone, 77%; b. i) H_2, $Pd(OH)_2$, ii) DMP, 76% over two stps

Figure 7 One pot ring expansion of cyclopropyl ring by Theodorakis

The benzyl ether functionality in **28** was easily converted to carbonyl group to yield **29** in two steps. However, attempts to further functionalize the C3 center in **28** or in **29** were unsatisfactory probably due to the steric hinderance imposed by the bicyclic system and also the reactivity of lactone.

Analogous to the aforementioned approach, Reiser and co-workers in 2005, reported a strategy for the enantioselective synthesis of *cis*-fused 5-oxofuro[2,3-*b*]furan derivatives (Fig. 8).[16] Inexpensive methyl-2-furoate **30** was used as a source for the 1,2-cyclopropanecarboxylated furan substrates, which were to be subjected to the acid mediated one pot ring expansion of cyclopropane.

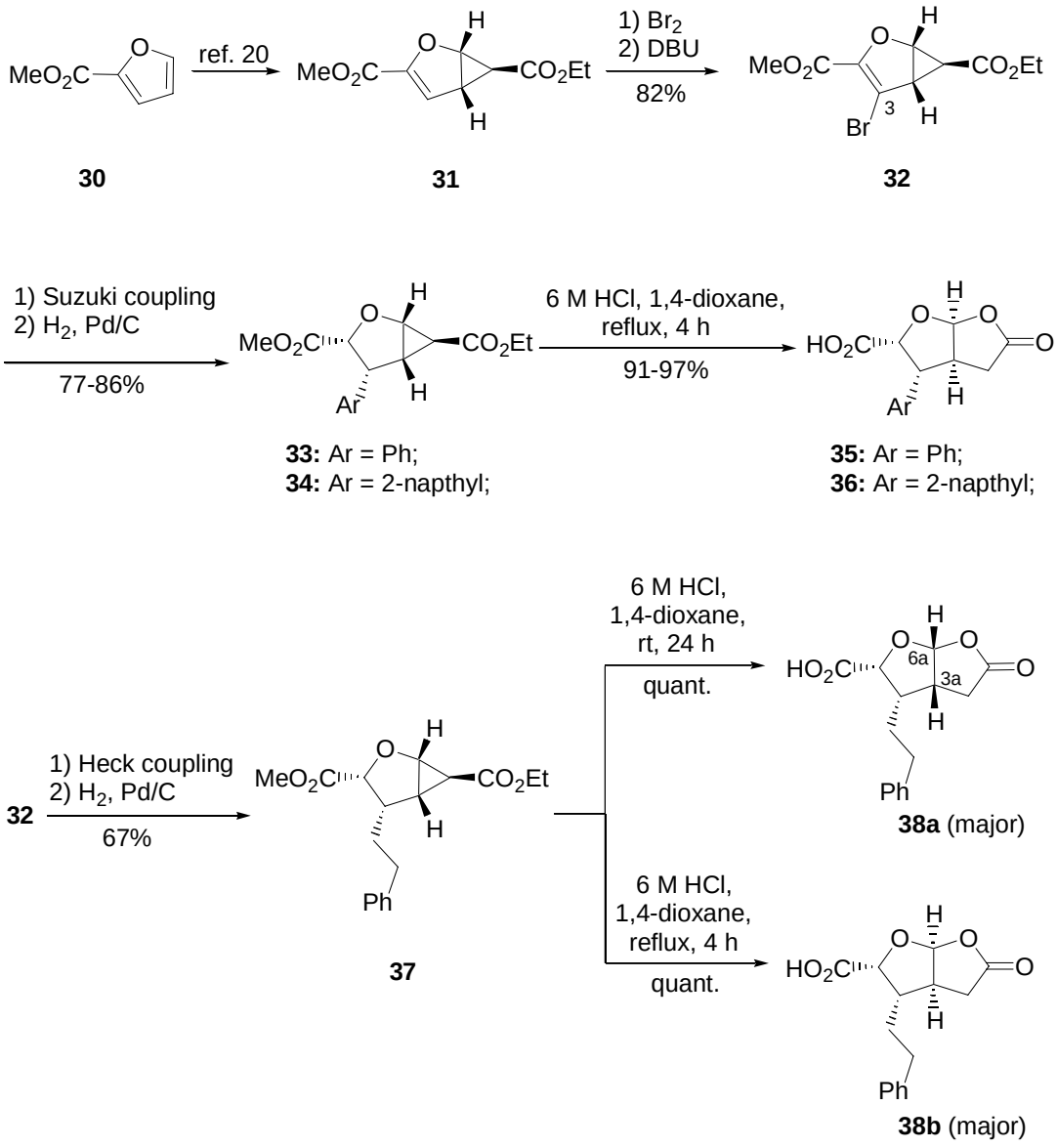


Figure 8 One pot ring expansion of cyclopropyl ring by Reiser

Methyl-2-furoate **30** was already reported to undergo an asymmetric cyclopropanation in the presence of copper (I) bis(oxazolines) to give rise to 2-oxo-bicyclo[3.1.0]octane **31** with excellent regio-, enantio-, and diastereoselectivities.[17] Unlike the approach disclosed by Theodorakis, the introduction of the side-chain at C3 center was achieved successfully by carrying out palladium catalyzed cross couplings on vinyl bromide **32,** which in turn was prepared from **31** in two steps. After the catalytic hydrogenation of the double bond in the cross coupling products, the 1,2-cyclopropanecarboxylated furan substrates **33**, **34** and **37** were obtained. In the hydrogenation the side-chain was selectively oriented on concave face of the bicyclic system attaining the correct stereochemistry as in norrisolide. Upon acid mediated one pot ring expansion, **33**, **34**, and **37** yielded *cis*-fused furo[2,3-*b*]furans **35**, **36** and **38** respectively. In case of **37**, the ring expansion yielded a diastereomeric mixture at the 3a,6a ring junction. The diastereomeric ratio varied according to the reaction temperature.

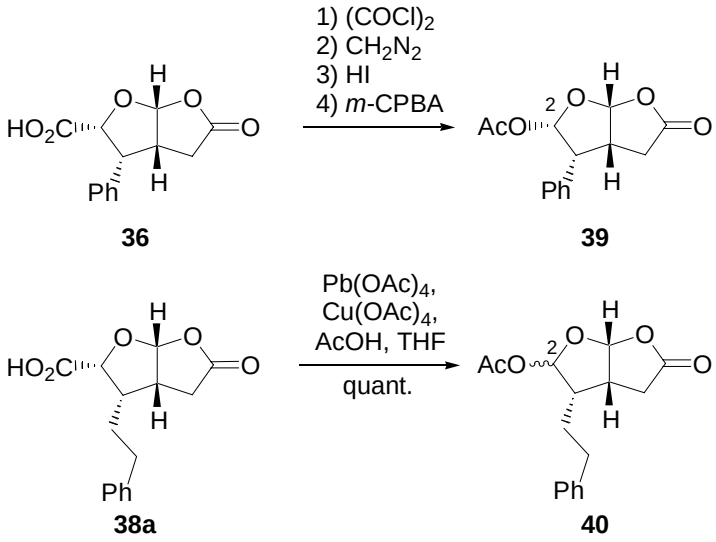


Figure 9 Methods for *O*-acetylation at C2 center

Conversion of the carboxylic acid in **36** *via* Baeyer-Villiger oxidation yielded the *O*-acetyl derivative **39** as a single diastereomer. On the other hand, one step oxidative decarboxylation of **38a** yielded the *O*-acetyl derivative **40** as a mixture of diastereomers, one of which was with the acetoxy group on convex face of the bicycle as in norrisolide, being the major diastereomer (Fig. 9).

The overall strategy was enantioselective and shorter than the one reported by Theodorakis. However, only aromatic side-chains were introduced at C3 center, while for the side-chain of norrisolide the perhydroindane core is required.

1.1.4b Total Synthesis of Norrisolide by Theodorakis: In 2004 Theodorakis and co-workers reported the first total synthesis of norrisolide (Fig. 10).[18, 19] The *cis*-fused furo[2,3-*b*]furan fragment **48** possessing the aldehyde functionality at C3 center was synthesized first using a Diels-Alder approach.

Initially, vinyl iodide **42** was synthesized from the enantiomerically enriched enone **41** in 13 steps.

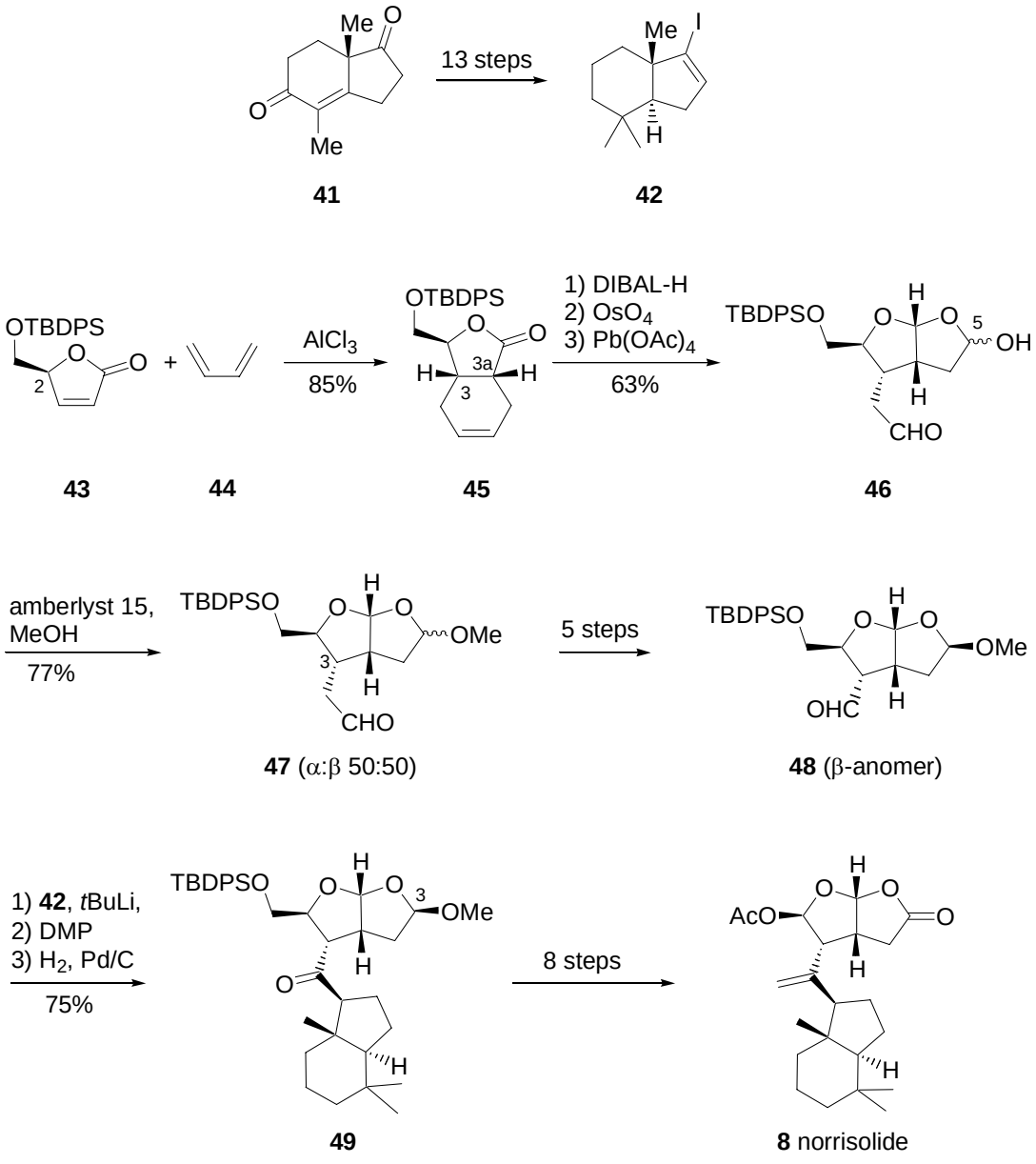
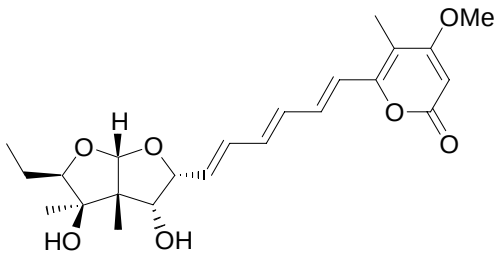


Figure 10 First total synthesis of norrisolide by Theodorakis

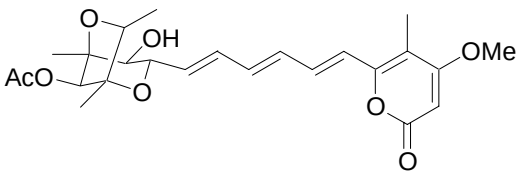
The synthesis of bicyclic motif **48** was started from butenolide **43** in which the desired stereochemistry at C2 center is already fixed. Diels–Alder reaction of **43** with butadiene **44**, catalyzed by $AlCl_3$ yielded **45** as a single diastereomer, in which the diene has approached the butenolide from the opposite side of the hydroxyl methyl group. Lactone reduction followed by oxidative cleavage of the double bond in **45** yielded the lactol **46** which was converted to the corresponding methyl ether **47** as a separable 1:1 mixture of epimers at C3 center. Both the epimers were carried on in the subsequent sequence. The one carbon degradation at C3 center was carried out in five steps to give **48**.

The aldehyde **48** was then efficiently coupled with vinyl iodide **42** after lithium halogen exchange to yield a mixture of diastereomeric alcohols which was oxidized to the corresponding ketone followed by the selective hydrogenation of the double bond to give rise to **49**. Further 8 steps, manipulating the TBDPS ether as well as the lactol functionality were required to furnish norrisolide **8** with complete retention of configuration.

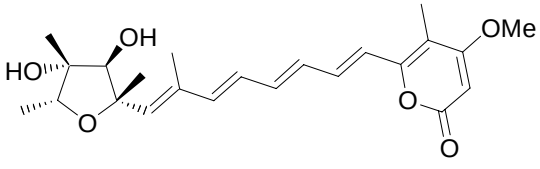
1.1.5 Asteltoxin: Asteltoxin (**9**, Fig. 11) was isolated in 1979 by Vleggaar and co-workers during the investigation of toxic maize cultures of *Aspergillus stellatus*.[20] This mytotoxin is structurally related to aurovartin **50**[21] and citreoviridin **51**[22], compounds which have been used as inhibitors of oxidative phosphorylation.[23]



9 Asteltoxin



50 aurovertin



51 Citreoviridin

Figure 11 Structures of asteltoxin, aurovertin and citreoviridin

Asteltoxin also happens to show similar inhibitory effect on the activity of E-coli BF_1-ATPase.[24] It is also suggested that the bis(tetrahydrofuran) moiety is responsible for the inhibition and binding properties of asteltoxin.

1.1.5a Schreiber`s Total Synthesis of Asteltoxin: In 1984, Schreiber and co-workers reported the first total synthesis of asteltoxin in a racemic form, using a convergent approach (Fig. 12).[25, 26]

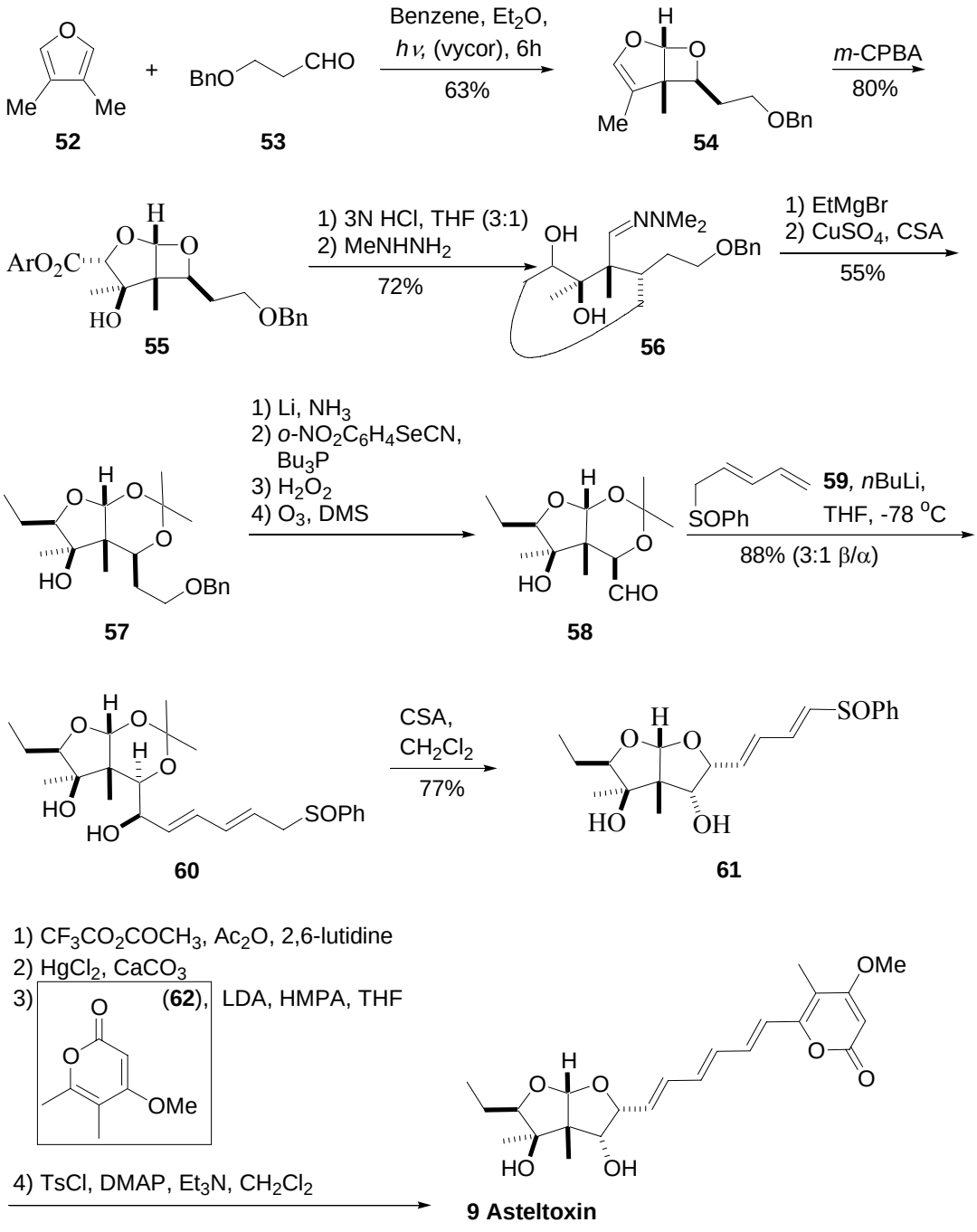


Figure 12 Schreiber`s total synthesis of racemic asteltoxin

The aldehyde **58** was chosen as a key synthon which was prepared starting from 3,4-dimethylfuran **52** in 10 steps. The Paterno-Büchi photocycloaddition of **52** and β-benzyloxypropanal **53** afforded **54** in good yield, which was further functionalized to accomplish the synthesis of **58**. Metalation of pentadienyl sulfoxide **59** with *n*BuLi and addition of aldehyde **58** followed by double [2, 3] sigmatropic rearrangement furnished an easily separable diastereomeric mixture of the diol **60**, the desired isomer being major. The desired isomer of **60** was then cyclized in good yield to *cis*-fued furo[2,3-*b*]furan **61** using camphorsulfonic acid.

The introduction of pyrone ring **62** by cross aldol condensation with **61** followed by the selective dehydration of the less hindered alcohol attaining the *trans* geometry of the double bonds were the finishing steps to arrive at asteltoxin.

**1.1.5b Tadano`s Total Synthesis of (+)-Asteltoxin:** Subsequent to Schreiber`s synthesis of racemic asteltoxin, Tadano and co-workers reported a total synthesis of (+)-asteltoxin using D-glucose as an enantiomerically pure starting material (Fig. 13).[27, 28]

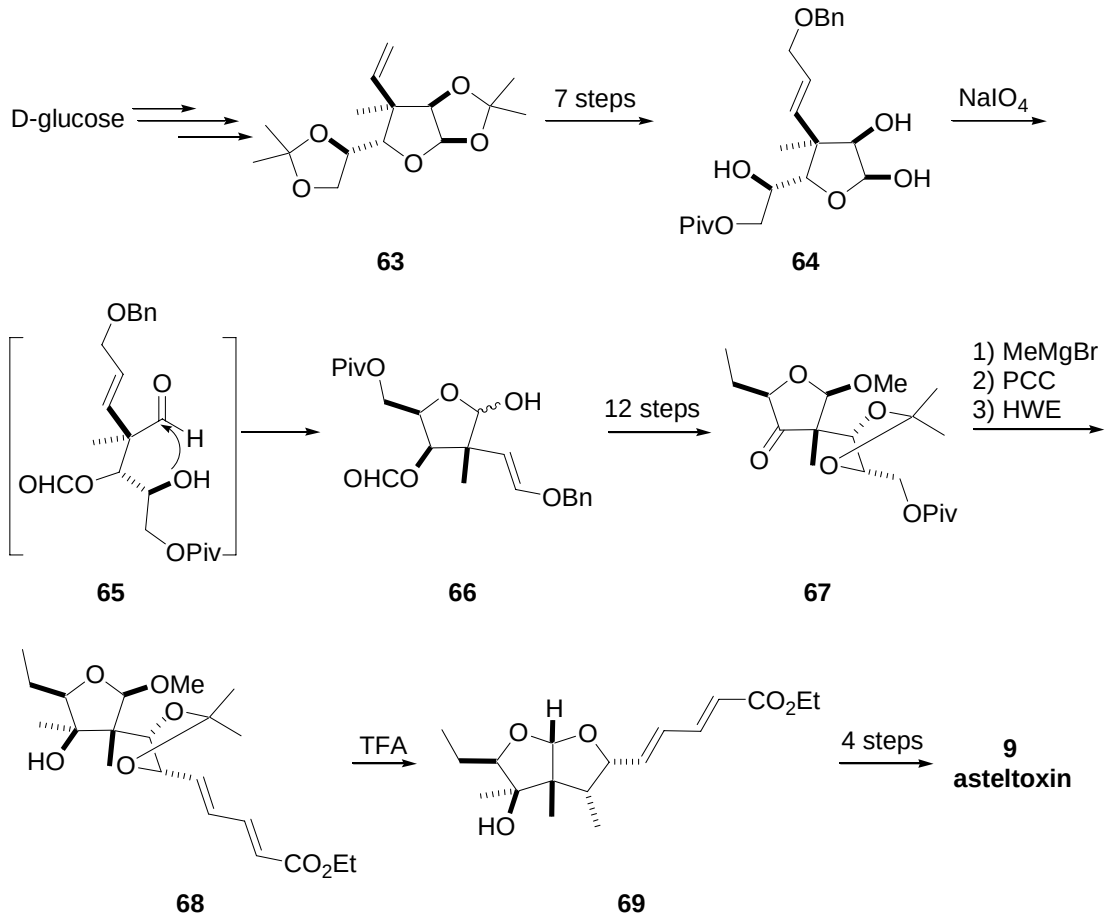


Figure 13 Tadano`s total synthesis of (+)-asteltoxin

Synthesis of compound **63** was already reported from D-glucose by employing ortho ester Claisen rearrangement as a key step.[29] It already includes a stereochemically defined C3 carbon center in asteltoxin. The modification of the vinyl group in **63** to benzyl protected allyl ether **64** was achieved in seven steps. $NaIO_4$ oxidation of **64** afforded a pentasubstituted tetrahydrofuran **66** *via* the intermediate **65**. The conversion of **66** into tetrahydrofuranone **67** was achieved in 12 steps. The sequential Grignard reaction, followed by the oxidation of the primary alcohol resulting due the deprotection of pivolyl ester during Grignard addition and Horner-Emmons reaction afforded unsaturated ester **68**. Acid hydrolysis of **68** smoothly resulted in the cyclization of the second tetrahydrofuran ring to yield the *cis*-fused furo[2,3-*b*]furan **69**. The total synthesis of (+)-asteltoxin was then completed in 4 steps from **69** using the aldol condensation strategy analogues to the one used by Schreiber and co-workers (**61** to asteltoxin **9**, Fig. 12).

Even though the synthesis of a single enantiomer of asteltoxin was accomplished, this strategy suffered from the lengthy synthesis of *cis*-fused furo[2,3-*b*]furan **69** possessing the correct stereochemistry at all the asymmetric centers.

1.1.5c Cha`s Total Synthesis of (+)-Asteltoxin: In 2003, Cha and co-workers, efficiently utilized a Lewis acid catalyzed pinacol type rearrangement of epoxy silyl ether **73** in order to synthesize (+)-asteltoxin (Fig. 14).[30],[31] This pivotal rearrangement strategy was analogous to the proposed biosynthetic pathway of asteltoxin.

The allylic alcohol **71** was synthesized from ester **70** in four steps. The Sharpless epoxidation of **71** furnished epoxy alcohol **72** in very good yield and with 94% diastereoselectivity. The epoxy silyl ether **73** was synthesized from **72** in three steps. The Pinacol type rearrangement of **73** was accomplished by the action of $TiCl_4$ providing aldehyde **74**. Both the epimers of **73** smoothly underwent this acid catalyzed rearrangement. The diol **75** was then synthesized in 3 steps starting from **74**. The treatment of **75** with methanolic hydrogen chloride followed by TIPS protection of the resulting alcohol gave fully protected acetal **76** as a single diastereomer.

Building up the left tetrahydrofuran ring was targeted in further sequence. The osmylation of **76** followed by oxidation of the primary alcohol in the resulting diol, and Grignard addition on the resulting aldehyde gave **77**. A Lewis acid catalyzed cyclization of **77** afforded *cis*-fused furo[2,3-*b*]furan, which was then converted to **78** after the deprotection of TIPS ether.

Finally, in order to achieve the total synthesis of (+)-asteltoxin, **78** was converted to aldehyde **79** in 8 steps. The union of α-pyrone phosphonate **80** with the aldehyde **79**, followed by deprotection of silyl ethers furnished (+)-asteltoxin **9**.

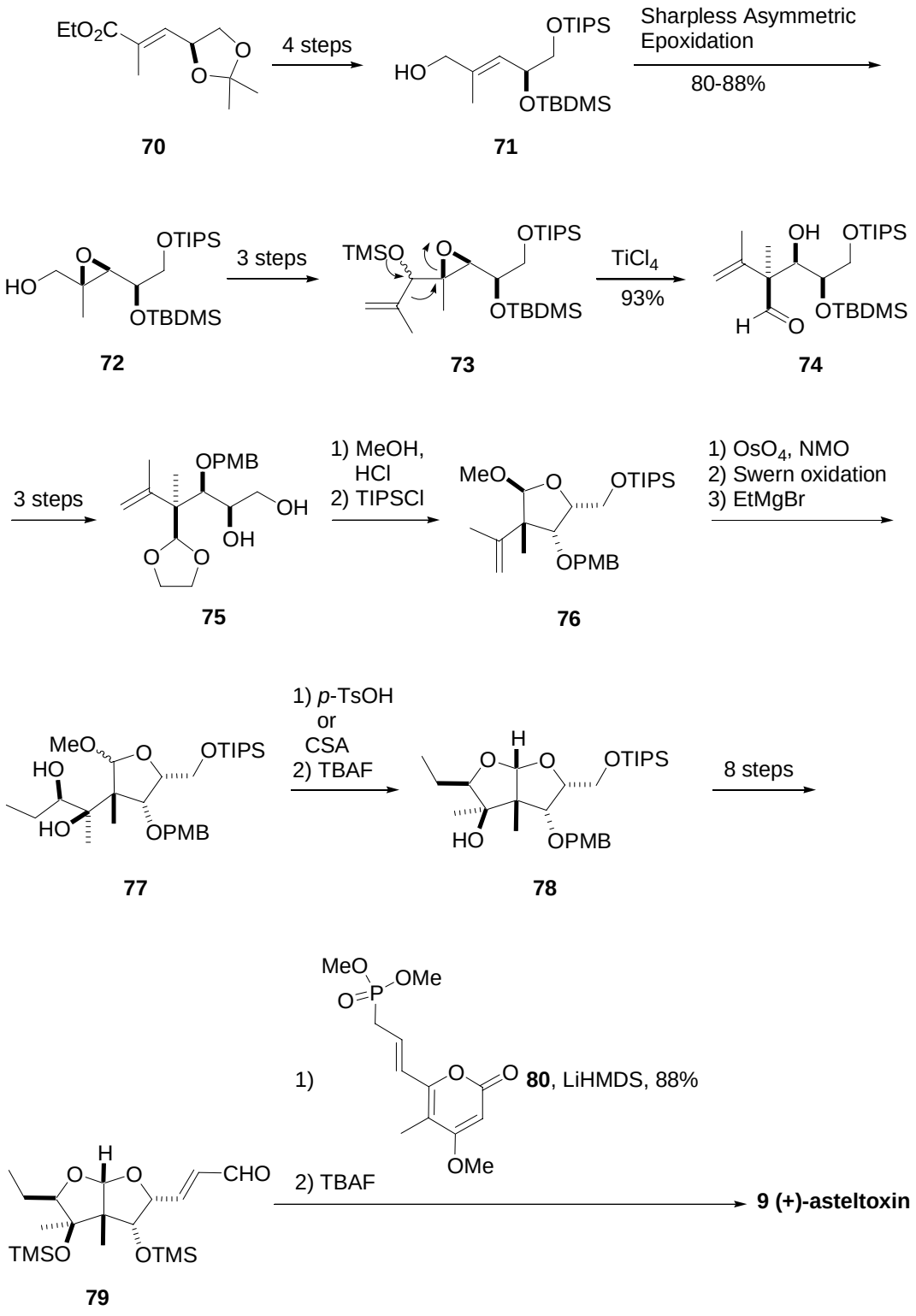


Figure 14 Cha`s total synthesis of (+)-asteltoxin

1.1.5d Synthesis of *cis*-Fused Furo[2,3-*b*]furan fragment of Asteltoxin: Meanwhile, Yamamura and co-workers (1990) as well as Mulzer and co-workers (1994) reported the synthesis of the *cis*-fused furo[2,3-*b*]furan fragment **91** of asteltoxin.

The strategy reported by Yamamura and co-workers was based on branched chain D-xylohexofuranose derivative as a starting point (Fig. 15).[32]

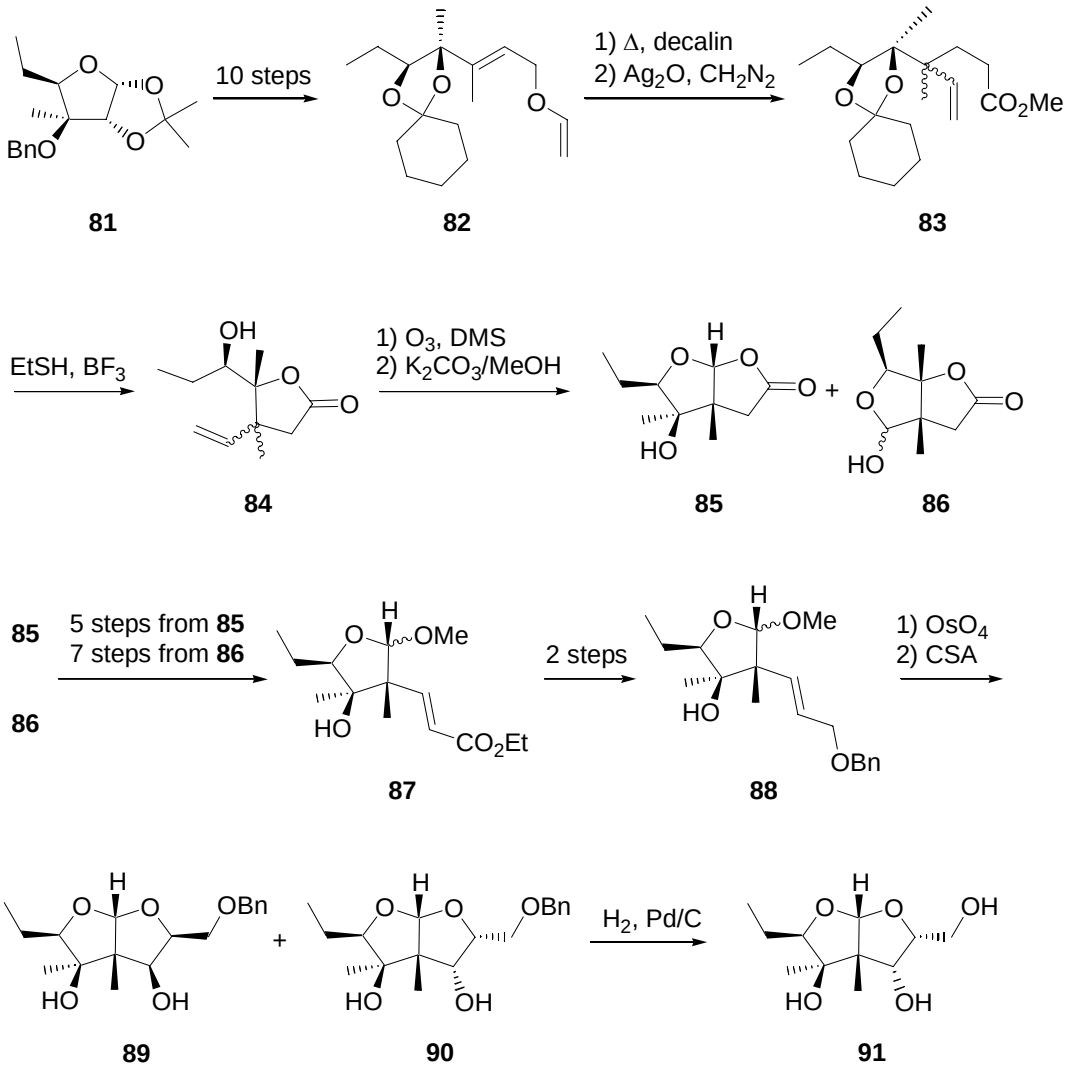


Figure 15 Yamamura`s synthesis of *cis*-fused furo[2,3-*b*]furan fragment of asteltoxin

Compound **81** was transformed to vinyl ether **82** in 10 steps. The Claisen rearrangement of **82** gave 1:1 inseparable mixture of the corresponding aldehydes which was converted to methyl esters **83** in two steps. Treatment of **83**, with EtSH-BF_3·Et_2O effected acetal deprotection and concomitant rearrangement to γ-lactone **84**. Conversion of **84** to a mixture of **85** and **86** was carried out with ozonolysis, followed by exposure to K_2CO_3 in MeOH. The mixture of **85** and **86** could be separated by acylation. Both **85**

and **86** were converted to **87** in 5 and 7 steps respectively in two different pathways. Compound **87** was then converted to the allyl benzyl ether **88** in two steps. Treatment of **88** with OsO_4 afforded a mixture of vicinal diols, which was subjected to acidic conditions to give chromatographically separable mixture of **89** and **90**. Finally catalytic hydrogenation of the desired **90** provided hexahydrofuro[2,3-*b*]furan **91**.

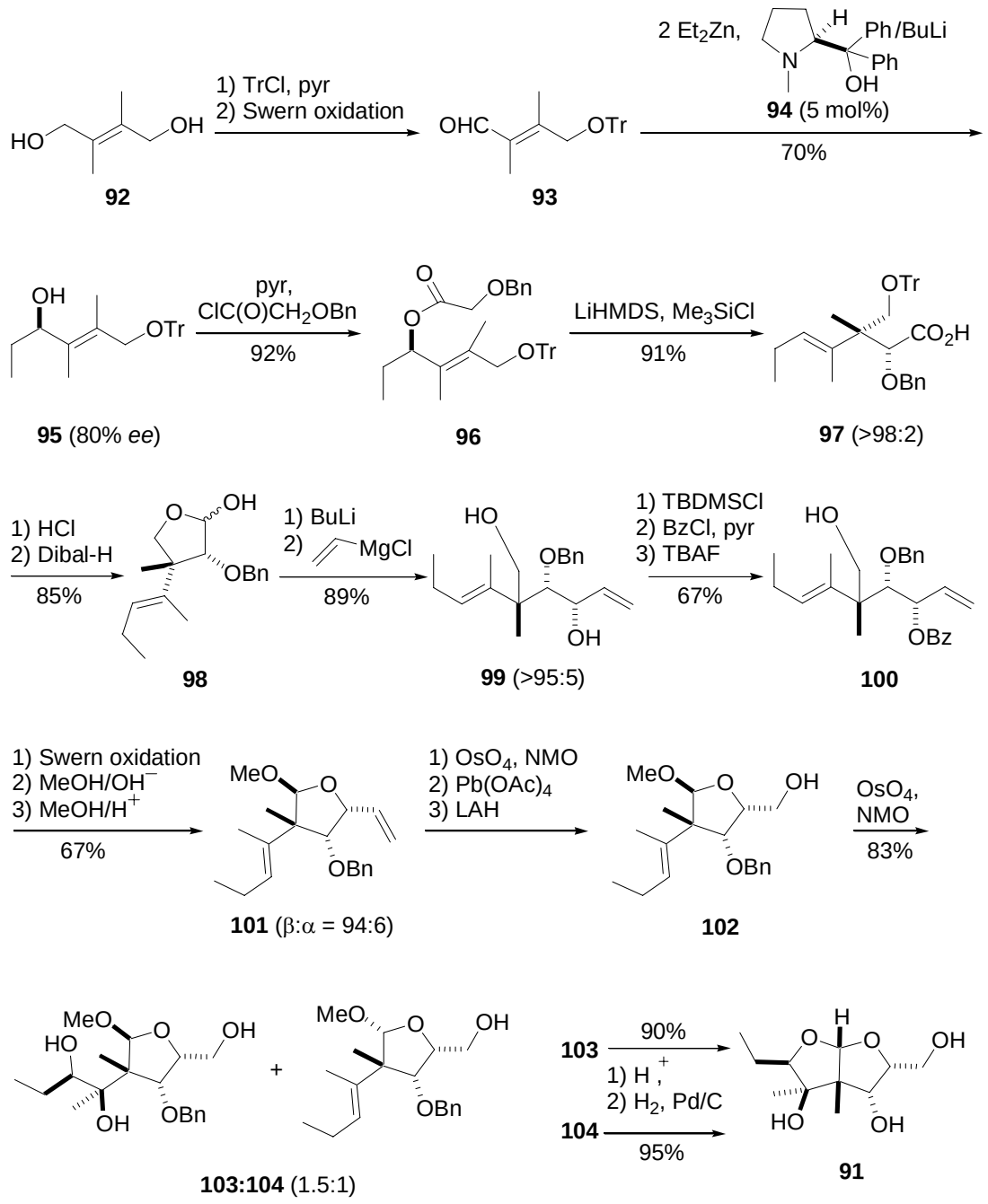


Figure 16 Mulzer`s synthesis of *cis*-fused furo[2,3-*b*]furan fragment of asteltoxin

The approach reported by Mulzer and co-workers started from **92** which is easily available from 2,3-dimethyl-1,3-butadiene (Fig. 16).[33]

Monoprotection of **92** as trityl ether and and Swern oxidation of the resulting alcohol yielded aldehyde **93**. Diethylzinc was added to **93** under the conditions described by Soai.[34] Catalyst **94** furnished secondary alcohol **95** in 80 %*ee*, which was determined *via* the Mosher ester. Acylation of **95** led to the ester **96** which was smoothly rearranged to **97** as single diastereomer, using Burke and Kallmerten version of a Claisen type rearrangement. By recrystallization the optical purity of **97** was raised to >98 %*ee*. The stereoselectivity of rearrangement is remarkably hinged on the trityl protecting group. The newly formed **97** was cyclized to lactone **98**. The lactone was then reduced to hemiketal **98** as an anomeric mixture. The deprotection of **98** with one equivalent of n-butyllithium followed by the addition of vinylmagnesium chloride yielded diol **99** as a single diastereomer *via* chelate Cram intermediate. Selective monobenzoylation of the secondary alcohol in **99** was accomplished in three steps to form **99**, which was then submitted to Swern oxidation of the primary hydroxyl group and debenzoylation of the secondary one. The hydroxy aldehyde spontaneously cyclized to the lactol which was ketalized to give **101** as a 94:6 mixture of the β as well as α anomer. The controlled osmylation of vinyl group and glycol cleavage in **101** followed by reduction of aldehyde with LAH furnished alcohol **102** with less then 5% epimerization at C5 center in the aldehyde stage. The osmylation of **102** yielded 1.3:1 mixture of anomeric diols **103** and **104** with >95:5 diastereoselectivity. Both anomers were treated separately with acid to close the second tetrahydrofuran ring by trans ketalization and finally debenzylation of the corresponding product furnished **91**.

1.1.6 Clerodanes (Dihydroclerodin and Lupulin C): Diterpenoids possessing the clerodane skeleton (**10**-**17**, Fig. 3) are widely distributed in nature and new members of this subclass of diterpenes continue to appear in the literature. Of the relatively few clerodanes that were tested for biological activity, many were found to possess interesting properties, which vary from antifeedant to antiviral, antitumour, antibiotic, antipeptic ulcer and piscicidal activity.

1.1.6a Kato`s Stereocontrolled Synthesis of Clerodin homologue: In 1980, Kato and co-workers reported the stereoselective synthesis of clerodin homologue **110** (Fig. 17).[35]

The epoxy acetonide **106** was synthesized starting from hydroquinone **105** in 20 steps. The reaction of **106** with lithium-di-(3-furyl)-cuprate·2-furyllithium-dimethyl complex yielded the desired furan alcohol **107** as a major product.

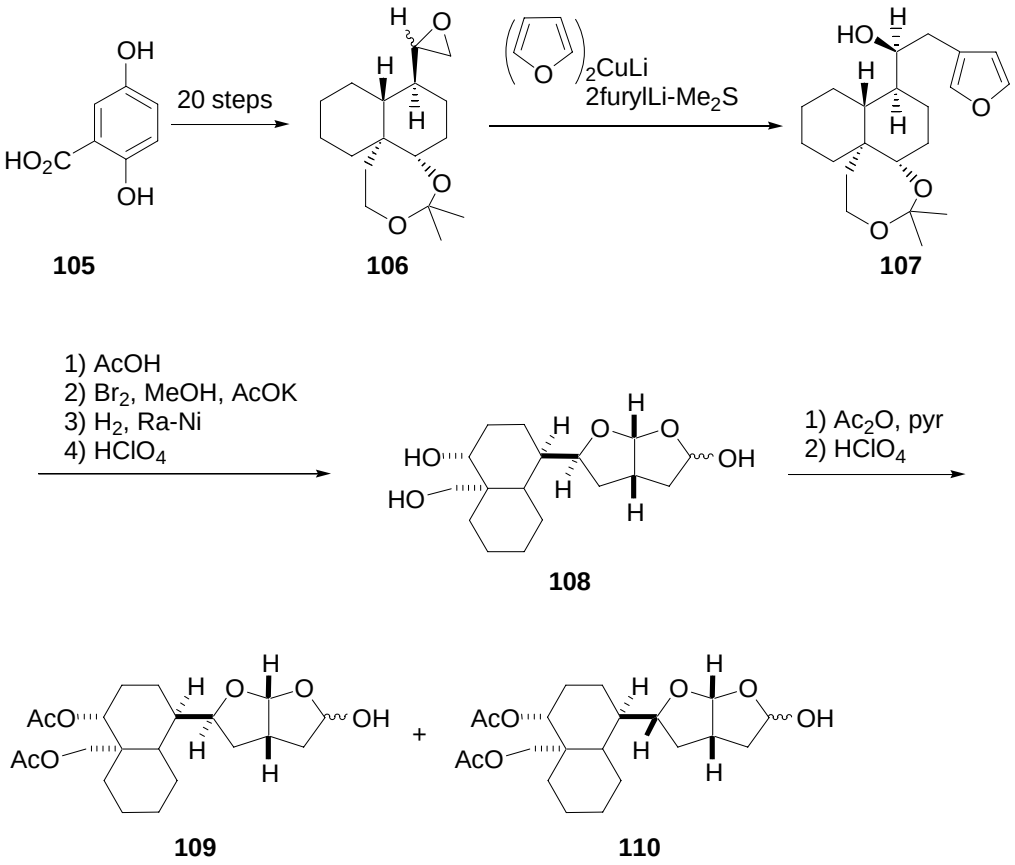


Figure 17 Kato`s stereoselective synthesis of clerodin homologue

The sequential deprotection of acetonide, bromination of the resulting triol, catalytic hydrogenation and demethylation using perchloric acid resulted in a perhydrofuro[2,3-*b*]furan derivative **108** in 77% yield, having the natural form. The acetylation followed by acidic hydrolysis furnished the mixture of **109** and **110**, former being a major diastereomer.

1.1.6b Lallemand`s Studies Towards Synthesis of Clerodin: Lallemand and co-workers reported the synthesis furofuranic model of clarodanes in 1989, using a single electron transfer cyclization as a key step (Fig. 18).[36]

Ketone **111** was prepared according to previously published procedures. The photochemical activation of **111** in presence of triethylamine afforded alcohol **112**. The hydoxyl group in **112** was protected as the acetate which was followed by ozonolysis to

yield **113**. Reduction of **113** followed by tosylation afforded diastereomeric mixture of **114** and **115**. Only **115** yielded the desired product **116** after heating with DBU. A better method to achieve the synthesis of **116** from **112** was based on Bamford-Stevens reaction.[37]

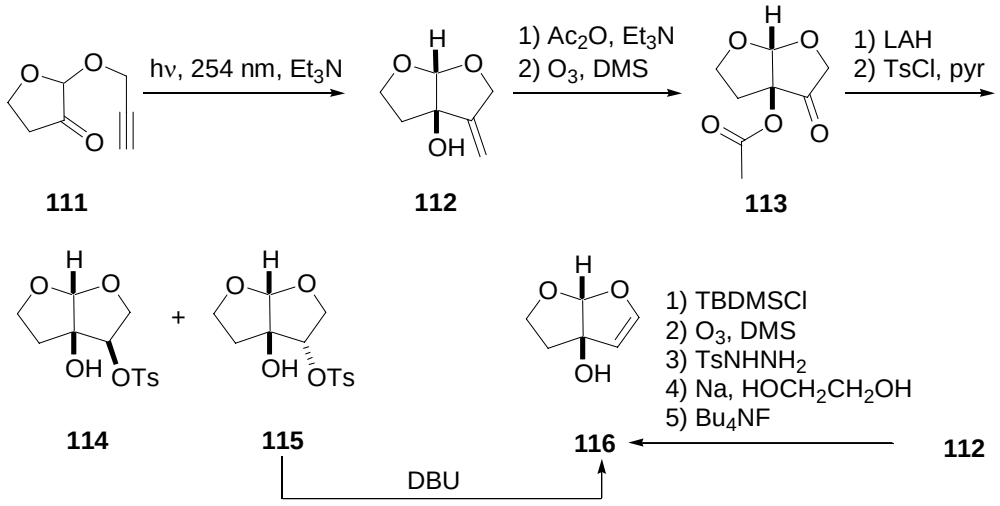


Figure 18 Lallemand`s synthesis furofuranic model of clarodanes

Later in 1983 Lallemand and co-workers reported a new preparation of furo[2,3-*b*]furan derivatives by iodocyclization of unsaturated lactols (Fig. 19).[38]

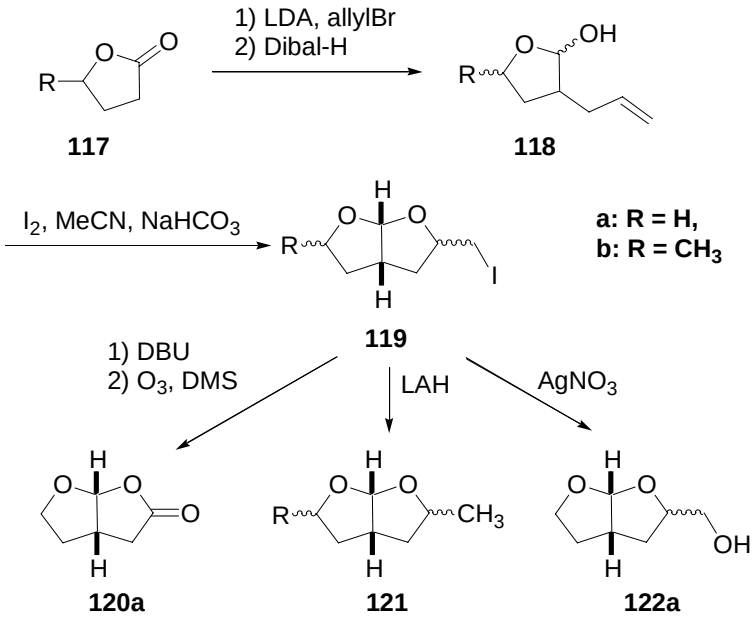


Figure 19 Synthesis furo[2,3-*b*]furan derivatives *via* iodocyclization of lactols

Lactols **118a** and **118b** were prepared from lactone **117** by using standard allylation protocol, followed by reduction using Dibal-H. The iodocyclization of **118** was then carried out using iodine and sodium bicarbonate in acetonitrile to afford **119** in good yield. In order to perform some model reactions, **119a** was transformed to **120a**, **121a**, **122a** respectively. **119b** could be easily converted to **121b** in a diastereomeric mixture of three possible isomers.

In 1991, Lallemand and co-workers also reported a model study aimed at the total synthesis of clerodin **10**. The tricyclic furo[2,3-*b*]furan moiety **133** was prepared. This approach was based on Claisen rearrangement between a cyclohexanol and a cyclic orthoester (Fig. 20).[39]

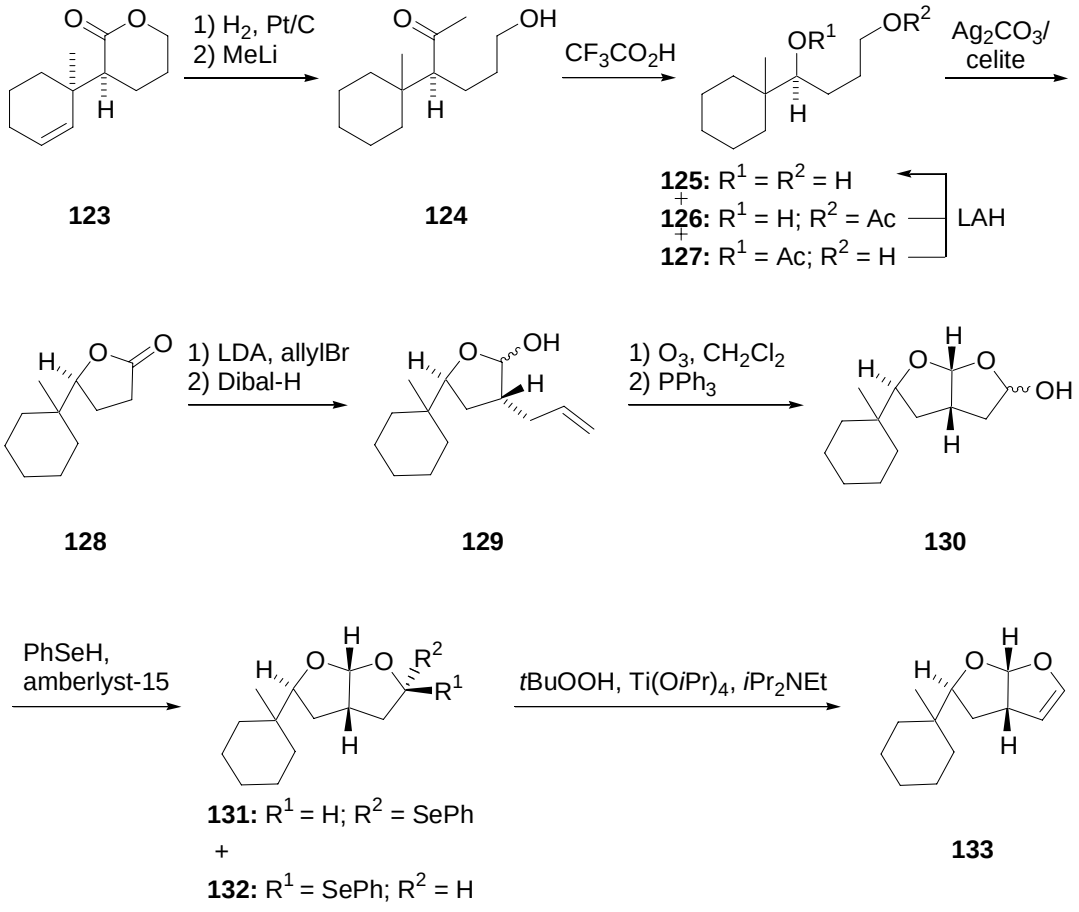


Figure 20 Lallemand`s model study aimed at the total synthesis of clerodin

The synthesis was started from the key intermediate **123**, which was previously reported.[40] The double bond was hydrogenated followed by the opening of lactone to provide methyl ketone **124**. The reaction of **124** with trifluoroperacetic acid gave a mixture of secondary acetate **127**, primary acetate **126** and diol **125**. Reduction of the

crude mixture gave diol **125** which was selectively converted to lactone **128** with Fetizon`s reagent. The sequential allylation and Dibal-H reduction afforded lactol **129**. Ozonolysis of terminal double bond in **129** and treatment with excess triphenylphosphine provided inseparable mixture of diastereomeric mixture of bicyclic lactol **130**. Phenyl selenylation of the lactol **130** led to the separable selenyl derivatives **131** and **132** in 2:1 ratio, which underwent an oxidation elimination step to afford model **133**.

1.1.6c Furstoss` Synthesis of Subunit of Clerodane Derivatives: In 1995, Furstoss and co-workers reported the seven step synthesis of (1*S*,5*R*)-2,8-dioxabicyclo[3.3.0]octane-3-one from its (1*R*,5*S*) antipode prepared by microbiologically mediated Baeyer-Villiger oxidation of the corresponding bicyclic precursor (Fig. 21).[41] This lactone could be a valuable building block for the synthesis of clerodane derivatives.

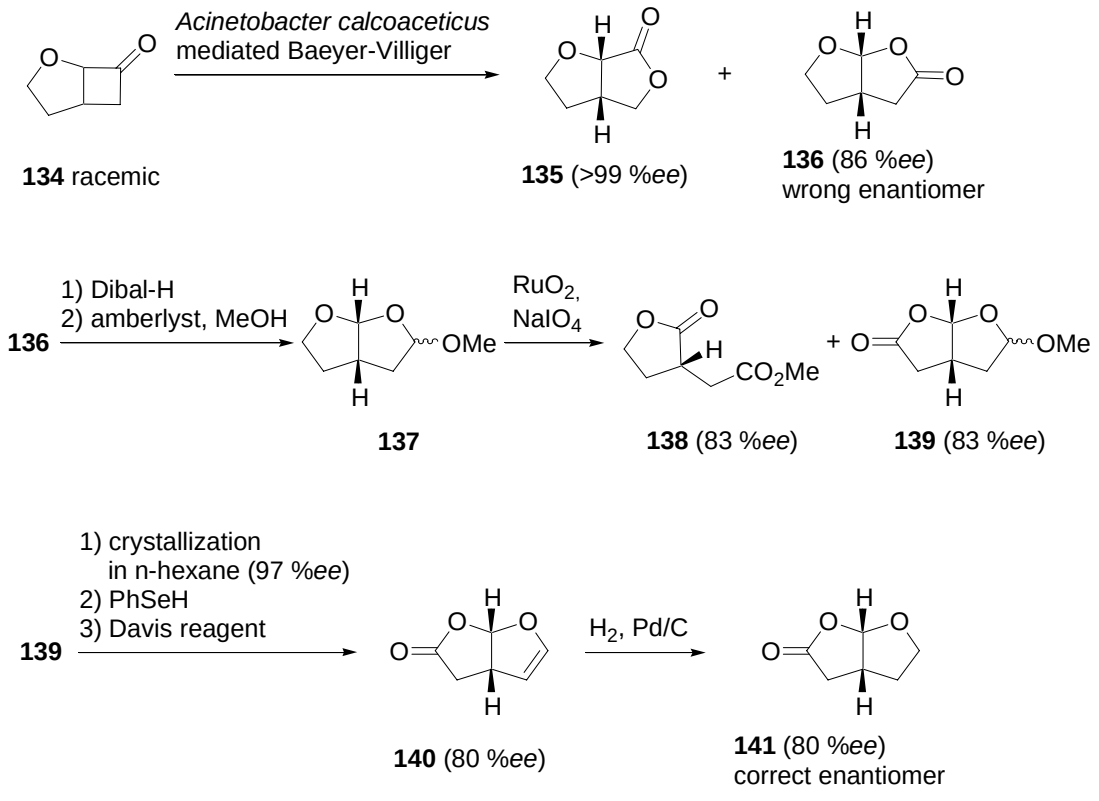


Figure 21 Furstoss` synthesis of a subunit of clerodane derivatives

The bioconversion of *rac*-**134** on gram scale was carried out using culture of *A. calcoaceticus* which lead to the separable mixture of **135** and **136** with enantiomeric

excess of 99% and 86% respectively. The lactone **136** was the wrong enantiomer as compared to the absolute configuration of the natural clerodane moeity.

In order to achieve the synthesis of the desired enantiomer, lactone **136** was reduced using Dibal-H to the corresponding separable epimeric ethers **137**. The successful oxidation of this ether to the corresponding lactone was achieved using ruthenium oxide and sodium periodate combination, delivering a mixture of monocyclic lactone **138** and the desired bicyclic lactone **139**. The enantiomeric excess of **139** was improved by crystallization in n-hexane to 97%. This bicyclic lactone **139** was further transformed into the corresponding phenylselenium derivative which underwent an oxidation/elimination sequence when reacted with Davis reagent to afford the olefinic lactone **140** in 80 %*ee*, which is the furofuran subunit of clerodane derivatives. This lactone **140** was then smoothly hydrogenated to afford **141**, the saturated (1*S*,5*R*) enantiomer of **136**.

1.1.6d Groot`s Total Synthesis of Dihydroclerodin and Lupulin C: In 1989 Groot and co-workers reported the first total synthesis of the natural enantiomer of dihydroclerodin and lupulin C starting from (*R*)-(−)-carvone (Fig. 22).[42]

For enantioselective synthesis of 2-methoxyhexahydrofuro[2,3-*b*]furan **144**, the *racemic* ester **142** was chosen as a starting point. Enzymatic trans esterification of **142** with butanol resulted in a mixture of (*R*)-methyl- and (*S*)-butylesters that could be separated by preparative gas chromatography. **142** was then converted to **143** in five steps, which could be then transformed into **144** by reduction and transacetalization in 62% yield.

In order to find a shorter route to obtain **144**, enol ether **145** was converted to lactone **146** in one step which was then transfromed to *racemic* **144** by reduction and transacetalization. This could be carried out in multigram scale and the other advantage of this method was, Mukiyama aldol of this compound with silylenol ether **146** proved to be remarkably diastereoselective. Mukiyama aldol was applied as a key step for introduction of bulky side chain on less hindered convex face of the bicycle. Silylenol ether **146** was prepared from (*R*)-(−)-carvone. It was then subjected to aldol reaction with **144** in presence of $TrClO_4$. **147** and **148** were the only two of possible eight diastereomers formed, which could be separated easily by crystallization of **148** by diisopropyl ether. The desired diastereomer **147** remained in solution. The diastereoselectivity of Mukiyama reaction could be explained by an approach of silylenol ether to the less hindered convex face of both enantiomers of the

hexahydrofuro[2,3-*b*]furan cation, which leads to the formation of **147** and **148**. Thus Mukiyama approach proved to be the best method to build up the correct configuration at C9, C11, C13 and C16 stereocenters.

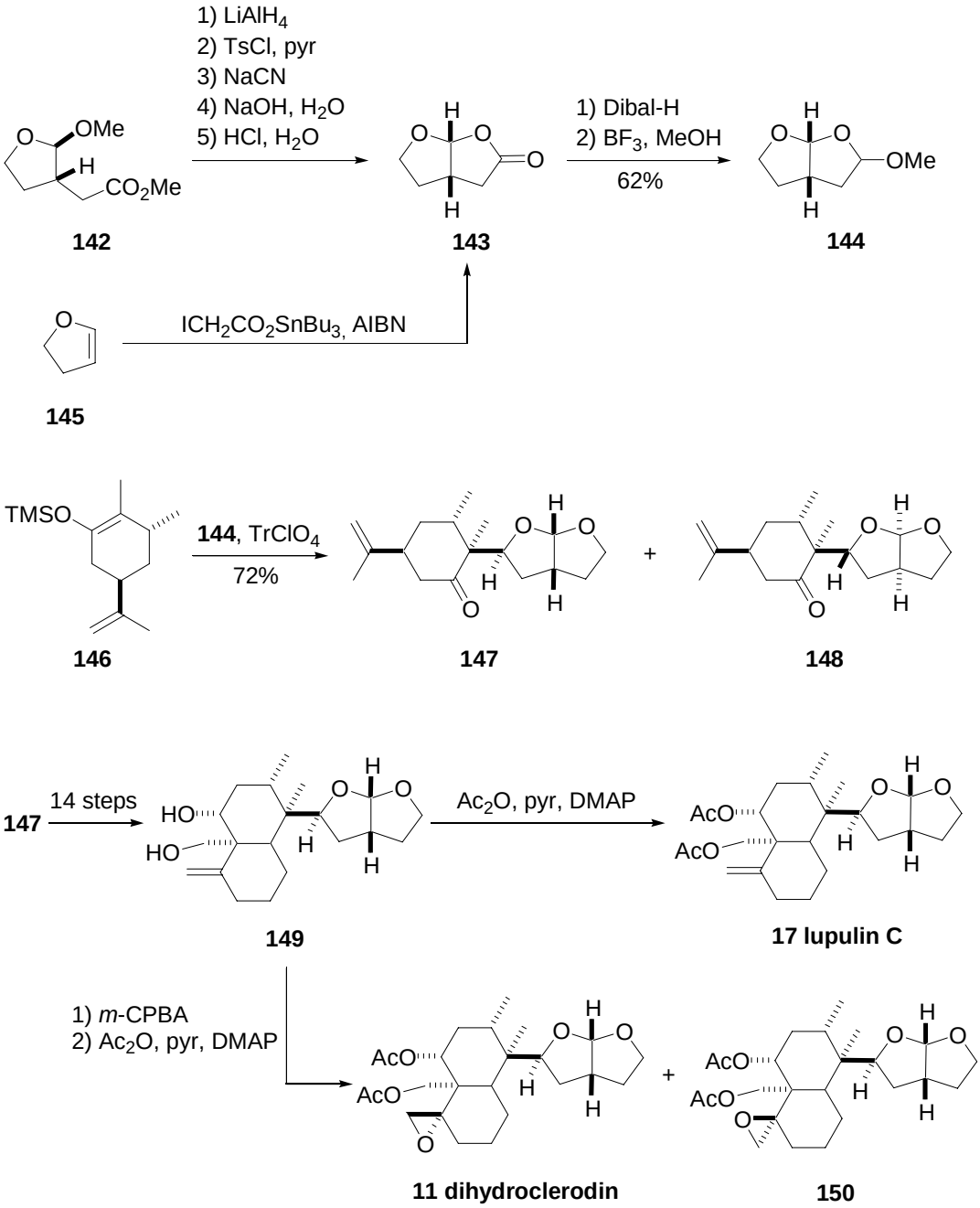


Figure 22 Groot`s total synthesis of dihydroclerodin and lupulin C

The diastereomer **147** was then carried further for next sequence of 14 steps to yield diol **149**, during which isopropenyl group was removed, ring A was annulated with the correct stereochemistry at C10 center and characteristic functionalities at C5,

C6 and C4 were introduced. The *m*-CPBA epoxidation of **149** gave 1:1 mixture of epoxides and acylation of this mixture yielded dihydroclerodin 11 (26%) and 4-*epi*-dihydroclerodin **150** (25%). Acylation of diol **149** yielded the natural clerodane lupulin C 17.

1.1.7 Conclusions: Several *de novo* strategies towards *cis*-fused furo[2,3-*b*]furan frameworks have been developed in recent years, making use of readily available starting materials that allow great functional diversity. Although most of these approaches are target driven aiming at a specific class of natural products containing this unique structural motif, many of the strategies reported clearly demonstrate their broad scope, which should make them attractive in the future for the rarely explored synthesis of biologically important natural products like clerodin (**10**, Fig. 3) and also scarcely explored sub-group of spongiane diterpenoids which shares the structural motif of a *cis*-fused 5-oxofuro[2,3-*b*]furan unit (**1-7**, Fig. 2).

In conclusion, this microreview has detailed several methods for the construction of uncommon *cis*-fused furo[2,3-*b*]furan frameworks as well as the total syntheses of natural products containing this core. It also highlights the stereoselective introduction of bulky side-chains on the concave or convex face of this bicycle at appropriate stages of the syntheses.

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1.2 Background: During the studies directed towards the mysterious molluscan chemical defences, Faulkner and co-workers in 1983 reported the structure of an architecturally novel diterpenoid norrisolide (**8**, Fig. 2, **1.1.3**), isolated from the skin extracts of the nudibranch *Chromodoris norrisi* (Fig. 23).[1] These mulluscs are popular called as Clown Nudibranch due to their brilliant coloration pattern and known to be ranging throughout the Gulf of California. They secrete norrisolide, which is probably the result of modification of chemicals obtained from their sponge prey.

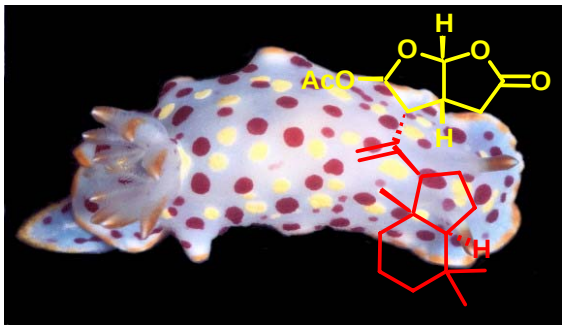
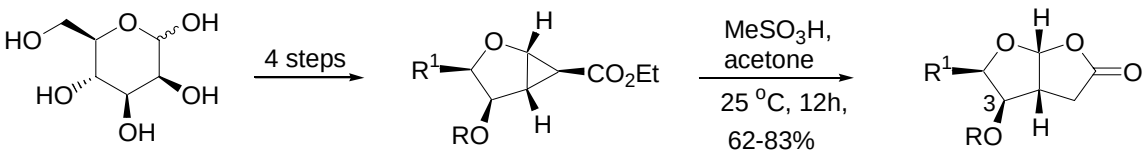


Figure 23 *Chromodoris norrisi* and norrisolide

Almost two decades after the structure elucidation, Theodorakis and co-workers reported the first total synthesis of norrisolide and also disclosed its effects on the vesiculation of the golgi apparatus.[2-4] Meanwhile, meticulous studies established that norrisolide belongs to a family of rearranged spongiane diterpenes also including cheloviolene A and B, dendrillolide A, dermatolactone, macfarlandin C, spongionellin and omriolide B **(1-8,** Fig. 2**, 1.1.3)**, which shares a common structural motif highlighted by a *cis*-fused furo[2,3-*b*]furan framework attached to a hydrophobic core. The combination of fascinating structural features and rather unexplored biological profile of these compounds continues to foster immense interest in their design and synthesis.



21: D-mannose **151** **152**

Figure 24 Theodorakis` approach for the synthesis of *cis*-fused furo[2,3-*b*]furans

Earlier, Theodorakis and co-workers developed a synthesis of such *cis*-fused furo[2,3-*b*]furans **152** based on ring expansion of a fused cyclopropyl ester **151** which was synthesized starting from a carbohydrate derivative D-mannose **21 (**Fig. 24**)**.[5] This methodology offers the advantage from inexpensive chiral starting material but suffers limited options for the control of stereochemistry and functional groups that can be introduced. Moreover, attempts to homologate the C3 center in **152** were unsatisfactory due to the difficulties stated before (section **1.1.4a**).

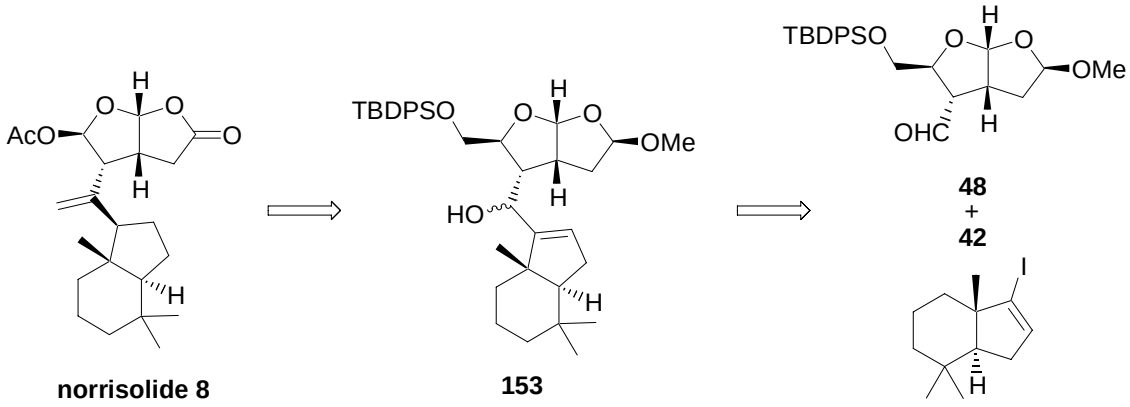


Figure 25 Retrosynthetic analysis of norrisolide by Theodorakis

Even so, Theodorakis et al. reported the first total synthesis of norrisolide using *t*BuLi mediated coupling of bis(tetrahydrofuran) fragment **48** and vinyl iodide **42** containing perhydroindane core in a key step (Fig. 25).[6]

1.3 Aim of This Work: Taking into consideration all the facts concerning synthesis and biological activity of this class of spongiane diterpenoids, this thesis is aimed especially at the stereoselective synthesis of a *cis*-fused furo[2,3-*b*]furan intermediates which can be broadly applied for the synthesis of spongiane diterpenoids such as norrisolide.

The synthesis of intermediate **162** is envisioned starting from furan derivative **154** which is commercially available and can also be prepared easily using methyl chloroacetate and acetylacetaldehyde-dimethylacetal in two steps. The retrosynthetic strategy is illustrated in Fig. 26. In the synthetic direction, the plan will entail the asymmetric cyclopropanation of **154** in the presence of copper-(I)-bisoxazolines to yield **155**, followed by introduction of an extensive range of functionalities at C3 position to get hold of the dihydrofuran derivatives **156**. 1,2-cyclopropanecarboxylated furanoids **157** are anticipated to be formed by the hydrogenation of the double bond, which is expected to orient the substituents at C3 center on the concave face of the bicycle as observed in the majority of the spongiane diterpenoids containing *cis*-fused furo[2,3-*b*]furan structure.

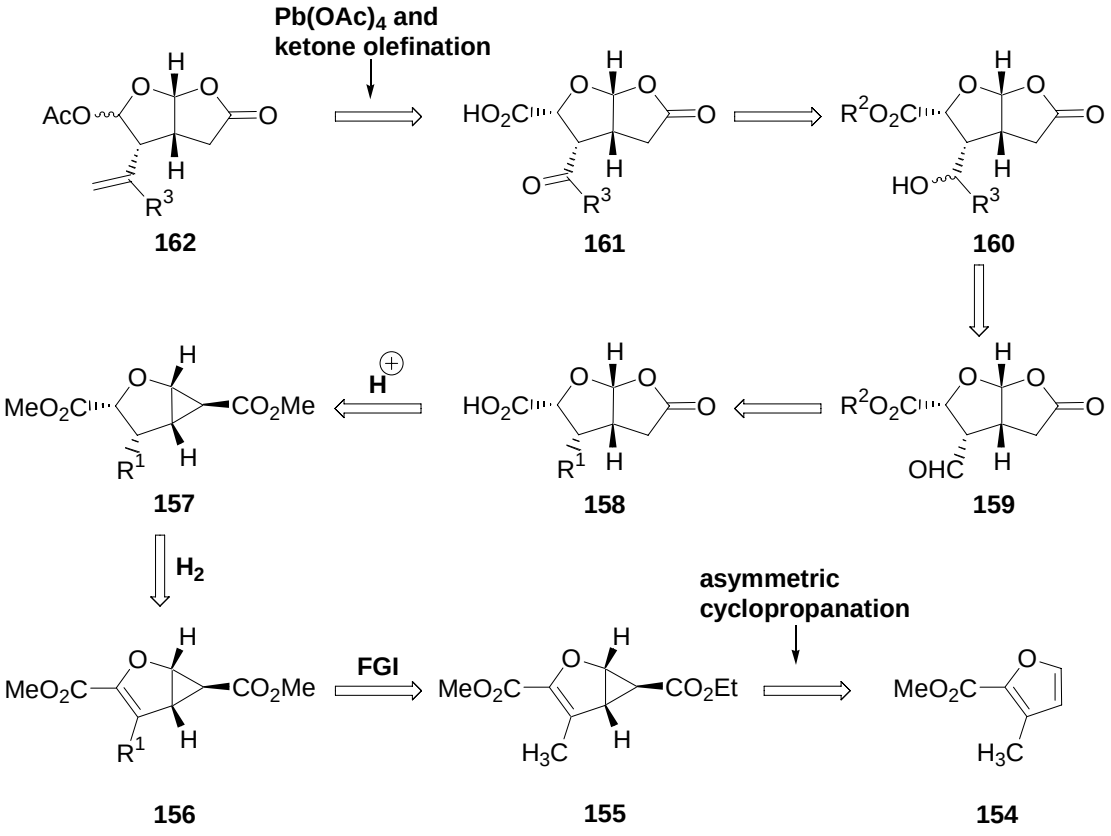


Figure 26 Retrosynthetic analysis of furo[2,3-*b*]furan intermediate **162**

A Lewis acid mediated rearrangement of these furanoids **157** is to be a key step in the construction of carboxylic acids **158** containing this unique bicyclic framework. The choice of appropriate protecting group for carboxylic acid functionality in **158** is crucial, as there might be a possibility of lactonization after nucleophilic addition on the aldehyde **159**. Therefore, *O*-benzyl which is not a very good leaving group will be the suitable choice. The later operations will be the nucleophilic additions on the aldehyde **159** followed by oxidation of the resulting alcohol **160** to obtain ketone **161**. The oxidative decarboxylation of carboxylic acid functionality in **161**, in order to achieve the *O*-acetylation at C2 center and ketone olefination to accomplish the synthesis of **162** will be the finishing point.

The implementation of this strategy, culminating in the stereoselective synthesis of a range of versatile building blocks for the synthesis of marine natural products such as norrisolide will be described in detail in the following chapter.

Furthermore, applications of 1,2-cyclopropanecarboxylated furanoids **157** in a variety of cyclopropane rearrangements are investigated as an additional part of this work in the subsequent chapters.

2 Towards the Total Synthesis of Norrisolide:

2.1 Asymmetric Cyclopropanation of Furan Derivatives:

2.1.1 Introduction: The first synthesis of a cyclopropane derivative was reported in 1884 by William Henry Perkin.[7] Nearly 123 years after, cyclopropane chemistry still offers for the chemists of 21st century significant challenges in this distinctive class of three membered ring compounds. Investigations on how far we can get a carbon atom and its homologues to bend their preferred bonding angles and accommodate unusual bonding situations are still on the way. In course of time, modern synthetic methodology has made it possible to deal with these extremely strained cycloalkanes in the perspective of their synthesis and applications. As a result cyclopropane derivatives are frequently employed as multipurpose building blocks in organic synthesis.[8]

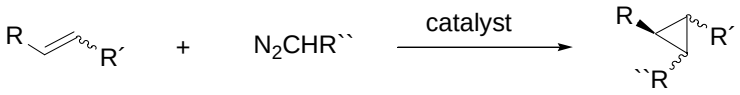


Figure 27 Cyclopropanation using metal-catalyzed decomposition of diazoalkanes

The cyclopropanation of olefins using the transition metal-catalyzed decomposition of diazoalkanes (Fig. 27) is one of the most extensively studied methods.[9] Both inter- and intramolecular versions of this reaction have been developed. The nature of the starting diazo reagent as well as the type of the reaction (inter- or intramolecular), plays a key role in the appropriate selection of the most efficient catalyst for a given transformation.

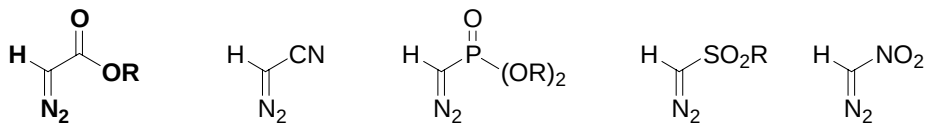


Figure 28 Structures of α-diazoesters

α-diazoesters are the most profoundly studied diazo reagents for intermolecular cyclopropanation. Many other reagents, all containing at least one electron withdrawing group have been used to prepare cyclopropanes (Fig. 28). The simple α-diazoesters can

be prepared on gram scale and reacted in the presence of the metal catalyst and alkenes.[10]

Among a wide range of metal catalysts, the ones derived from Cu, Rh, Ru and Os are known to react faster with electron-rich alkenes, whereas Pd metal carbenes are optimal for electron-deficient alkenes. In most of these cases, the mechanism of the transition metal-catalyzed decomposition of α-diazocarbonyl compounds is believed to proceed *via* formation of the illustrious metal carbene complex. [11]

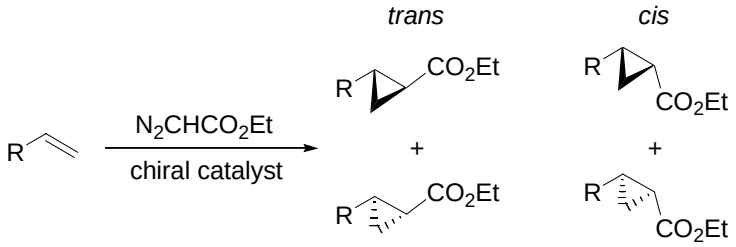


Figure 29 Decomposition of α-diazoesters by chiral transition metal complex

A pre-eminent approach practised for the asymmetric cyclopropanation is the decomposition of α-diazoesters by chiral transition metal complexes to cyclopropanate achiral alkenes in an intermolecular fashion (Fig 29).

The most effective catalysts for the preparation of the *trans* isomer with the widest reaction scope are copper-based catalysts. The catalysts based on other transition metals are also very effective, but they generally produce lower enantio- and diastereoselectivites and have a narrower scope.

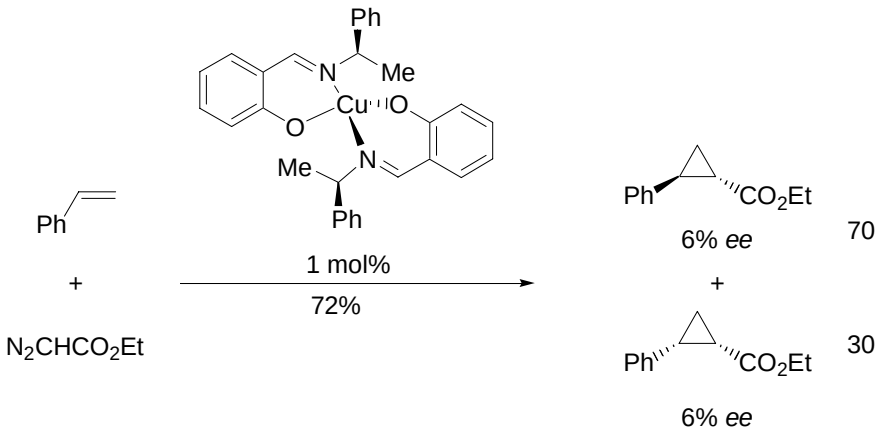


Figure 30 The first enantioselective cyclopropanation by Nozaki

The first example of an enantioselective copper-based intermolecular cyclopropanation was reported by Nozaki in 1966.[12] A copper-catalyzed decomposition of ethyl diazoacetate in the presence of an *N*-benzylethylamine-based chiral salicylaldimino complex gave about 6% enantiomeric excess of the corresponding *cis* and *trans* cyclopropanecarboxylates (Fig. 30).

Though the enantiomeric ratios were very low, this exercise led to a class of catalysts which further proved to be quite effective in the synthetic tasks then going on in Nozaki group.

As a consequence of this enantioselective transformation, several hundred chiral ligands have been synthesized and tested in copper catalyzed processes in the past four decades. Most of these ligands comprise the structural variations of the basic types including substituted salicylaldimines, semicorrins, bis(oxazolines), bipyridines and many others.

The copper (I) complex of bis(oxazoline) **163**, disclosed by Evans in the early 1990s,[13, 14] is still a standard to which new bis(oxazoline) ligands are compared. The catalyst **163** has been extensively used in cyclopropanation reactions of some cyclic as well as acyclic enol ethers[15] of protected allylic alcohols[16] and of vinyl fluorides[17].

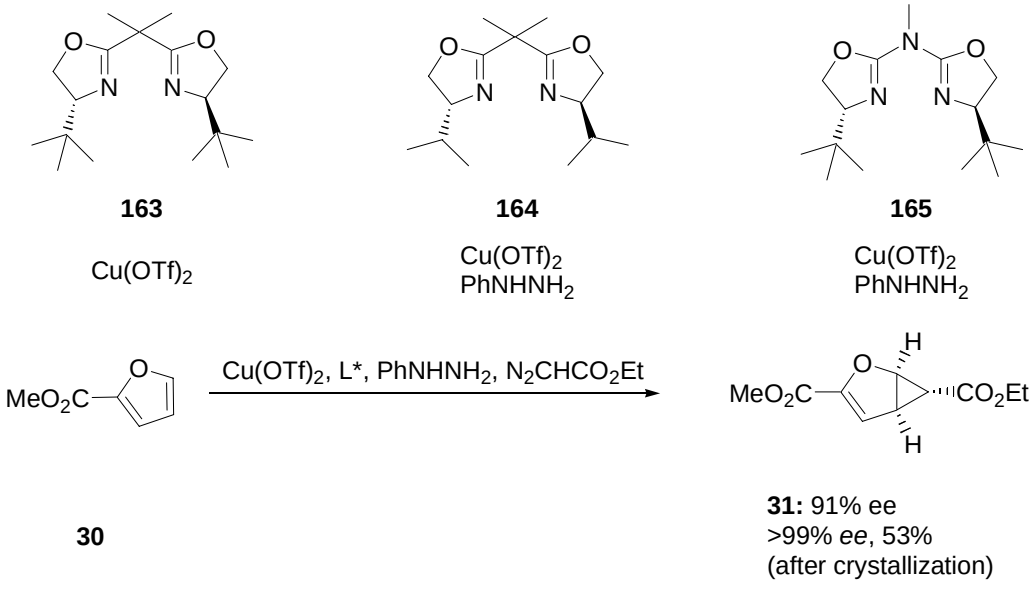


Figure 31 Structures of bis(oxazoline) ligands and cyclopropanation of **30**

The past research in our group has also focused on the development of a number of modified bis-(oxazoline) ligands[18] and their applications in various enantioselective synthetic transformations. In the course of these investigations, the enantioselective

cyclopropanation of furans using Cu (I) complex of these ligands has been reported.[19, 20]

The structures of Evans bis(oxazoline) **163**, the modified bis(oxazoline) ligands **164** and **165** synthesized in our group and their applications in enantioselective cyclopropanation of furan derivative **30** is shown in Fig 31.

The initial part of the present work was designed towards the improvements in the synthesis of bis(oxazoline) ligand **164** and its application to the enantioselective cyclopropanation of furan derivatives possessing substituents at different positions.

2.1.2 Synthesis of (*S*,*S*)-bis(4-isopropyloxazoline) 164: The commercially available *tert*-butyl-substituted bis(oxazoline) **163** often gives rise to the highest selectivities. A number of applications have been developed in which the bis(4-isopropyloxazoline) **164** gives similar or even superior results. Furthermore, for the synthesis of *tert*-butyl-substituted bis(oxazoline) **163,** the unnatural and therefore expensive amino acid *tert*-leucine is required. As an alternative, bis(4-isopropyloxazoline) **164**, available as either enantiomer prepared from inexpensive (*S*)- or (*R*)-valine **166**, is an attractive ligand for large scale applications if equally good enantioselectivity can be achieved.

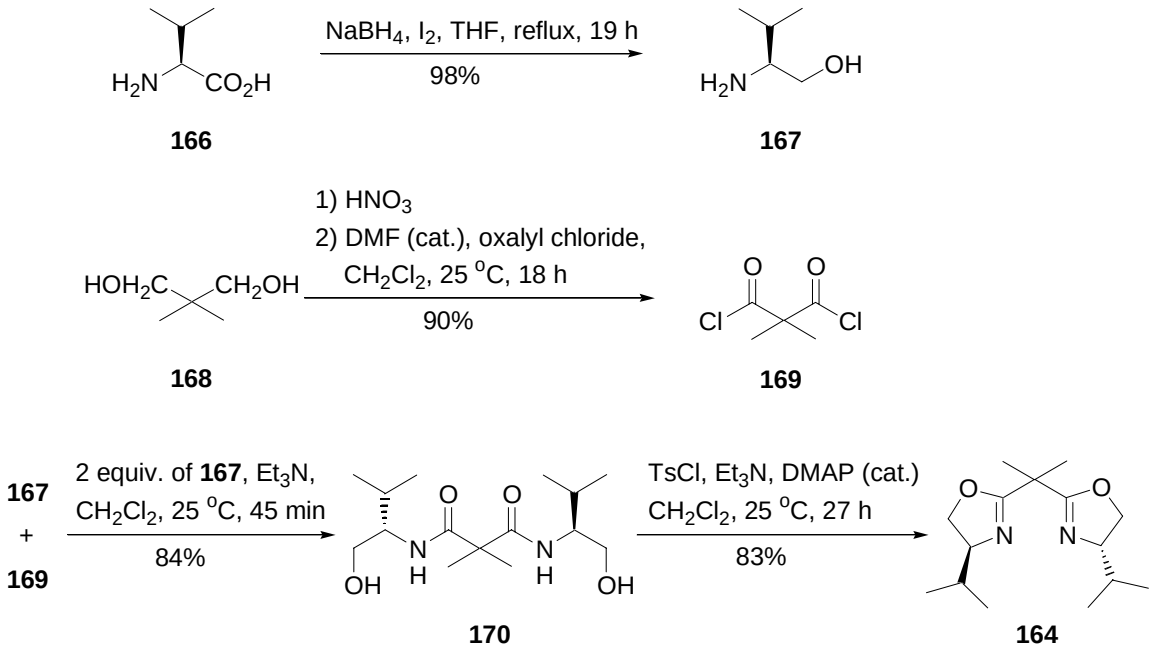


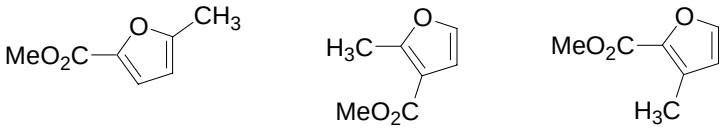
Figure 32 Synthesis of (*S*,*S*)-bis(4-isopropyloxazoline) **164**

Meyers` procedure[21] ($NaBH_4$, I_2, THF, reflux) was used to prepare (L)-valinol **167** from (L)-valine **166**. While dimethylmalonyl acid is commercially available, its synthesis *via* nitric acid oxidation of 2,2-dimethyl-1,3-propanediol **168** significantly

increases the cost effectiveness.[22] It was then converted to dimethylmalonyl dichloride **169** using oxalyl chloride in dichloromethane.

The subsequent acylation mediated by triethylamine yielded dihydroxy malonodiamide **170** in 84% yield after two crystallizations. The dihydroxy malonodiamide **170** was cyclized to bis(oxazoline) **164** *via* the bis(tosyl chloride) in 83% yield (Fig. 32).

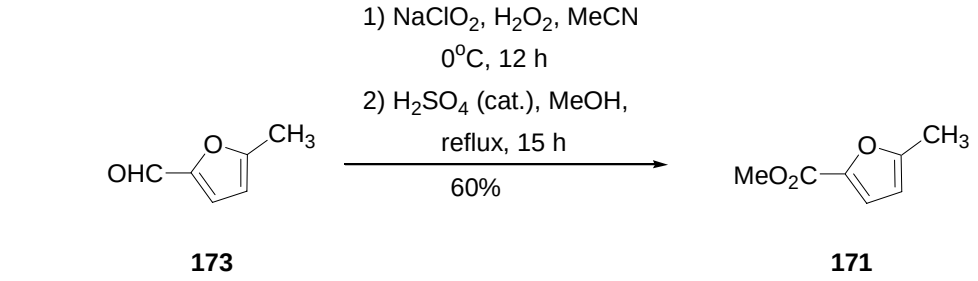
2.1.3 Synthesis of Furan Derivatives: As a simple selection of substrates for the asymmetric cyclopropanation, furan derivatives shown in Fig. 33 were chosen.



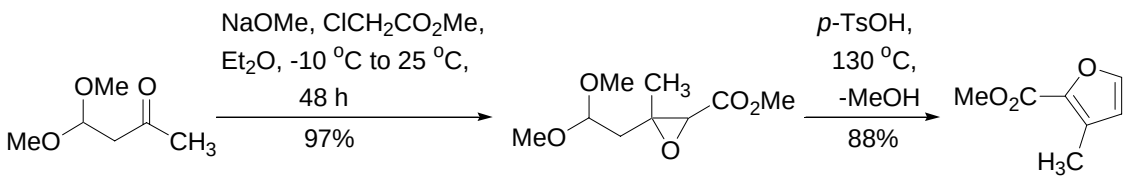
171 **172** **154**

Figure 33 Structures of furan derivatives

171 was synthesized from 3-methyl-furfural **173** in two simple steps (Fig. 34). $NaClO_2$ oxidation of **173** yielded the acid which was then converted to the corresponding methyl ester **171**. The derivative **172** was commercially available.



173 **171**



174 **175** **154**

Figure 34 Syntheses of furan derivatives **171** and **154**

To accomplish the synthesis of 3-methyl-2-furoic ester **154** proved to be an interesting task. The two step synthesis of **154** *via* the Darzens glycidic ester condensation reported by Burness was followed (Fig. 34).[23]

The Darzen reaction of **174** proceeded effectively, yielding the glycidic ester **175** quantitatively. The addition of catalytic amounts *p*-toluenesulfonic acid in the rearrangement of glycidic ester **175** helped to get the conversion to the product **154** at 130 ^{o}C instead of 160 ^{o}C as reported by Burness. Moreover, the yield was improved from 70% to 88%. It is also noteworthy that in the reported procedure the thermal rearrangement of **175** is carried out without the addition of acid. However, no formation of the product **154** was observed even at the higher temperature, when this protocol was followed.

2.1.4 Cyclopropanation: The furan derivative **171** did not react at all in copper catalyzed cyclopropanation reaction with ethyl diazoacetate. Also **172** gave extremely low conversion towards the cyclopropanated products. Further attempts to optimize the reaction conditions were not carried out.

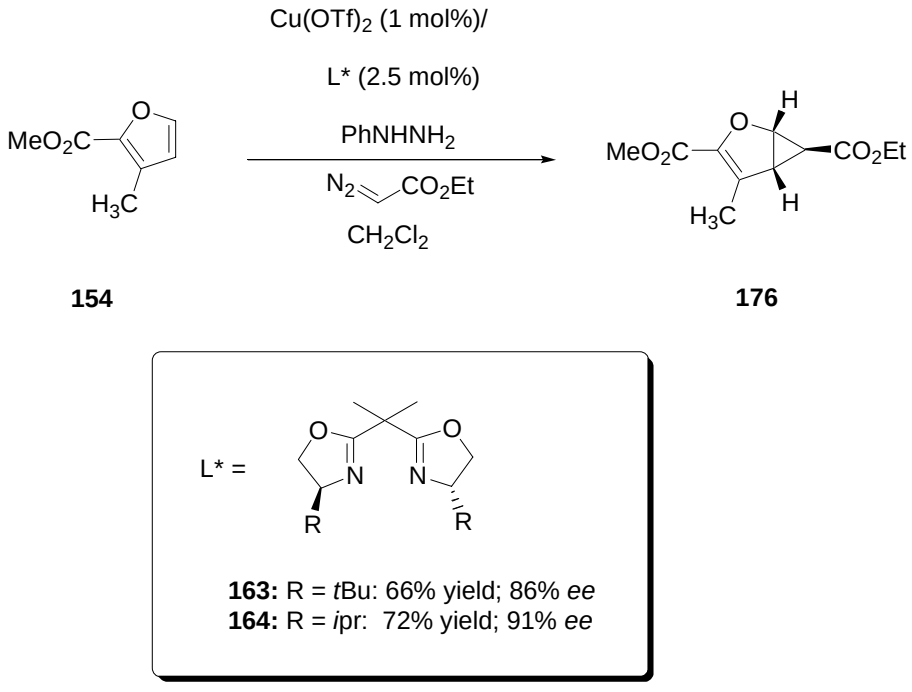


Figure 35 Cyclopropanation of 3-methyl-2-furoic ester

In contrast, the cyclopropanation of 3-methyl-2-furoic ester **154** was quite successful as compared to that of other substrates (Fig. 35). The reaction proceeded regioselectively, as only the less substituted double bond was cyclopropanated. The

complete diastereoselection was the other special feature of in course of this reaction, as the ester functionality was oriented exclusively on the convex face of the bicyclic framework. Not even a trace amount of the corresponding *endo* isomer was observed. The yield of the reaction was quite agreeable ranging from 60% to 72%, depending on the choice of reaction parameters. The equivalents of ethyl diazoacetate (4 equiv.) employed was probably the most important factor regarding the improved yields. Even though excess ethyl diazoacetate resulted in the formation of diethyl maleate, diethyl fumarate and a trimer[24] resulting from the [3+2] cycloddition reaction, it was well compensated by the improved yields of the desired cyclopropanated product **176**.

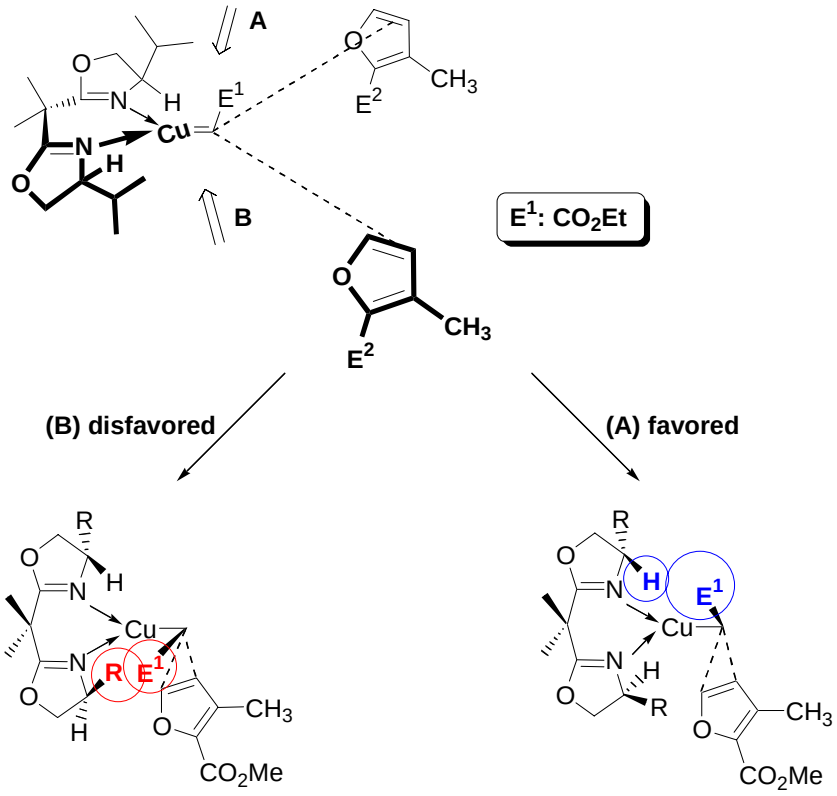


Figure 36 The stereochemical investigation of the cyclopropanation of 3-methyl-2-furoic ester **154**

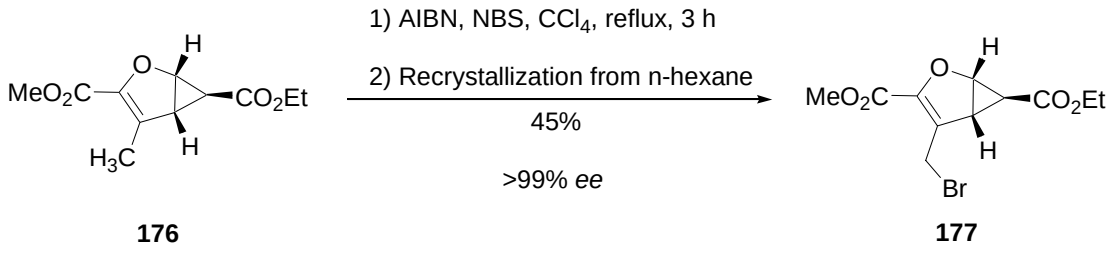
Lastly, the enantioselectivity of the reaction was also encouraging. With Evans` *tert*-butyl-substituted bis(oxazoline) **163**, the enantiomeric excess obtained was 86% and with bis(4-isopropyloxazoline) **164** it was 91%. As expected, the modified bis(oxazoline) **164** yielded comparable enantioselectivity as the Evans` standard system. The product **176**, being a low melting solid could not be crystallized in order to improve

the enantiomeric excess. The option to attain the pure enantiomeric form of **176** will be discussed in the next section **2.2**.

The stereoselectivity of the cyclopropanation can be explained by means of the model proposed by Pfaltz (Fig. 36).[25] Due to the C_2 symmetry in bis(oxazoline), two opposite quadrants are sterically blocked. The ligand forms a plane which is perpendicular to the plane formed by the trigonal carbenoid atom. The less substituted and electron-rich double bond of the furoic ester can attack either from *Re*-face (favored path) or from *Si*-face (disfavored path).

The interactions of olefin with the carbenoid atom change its hybridization to sp^3 arranging it in tetrahedral geometry. As shown in **B**, the path B results in repulsive interaction between the ester group at the formerly carbenoid center and on β-alkyl group at the stereocenter on the oxazoline ring. Moreover, the α-alkyl group blocks the attack of furan from *Si*-face as in path B. These types of interactions will not appear on attack from *Re*-face, forming the corresponding product as a major outcome. This is in accordance with the experimental results, principally based on the transition state **A**.

2.2 Allylic Bromination (Wohl-Ziegler Bromination): 2-oxobicyclo[3.1.0]hexene derivative **176** was envisioned as a suitable substrate for allylic bromination in order to have the versatile functionalities at C3 carbon center. Indeed, it yielded the corresponding allyl bromide **177** in a satisfactory yield, when subjected to AIBN and NBS in CCl_4 at reflux temperature. After the recrystallization from *n*-hexane, the enantiomeric excess was enhanced to more than 99% (Fig. 37).

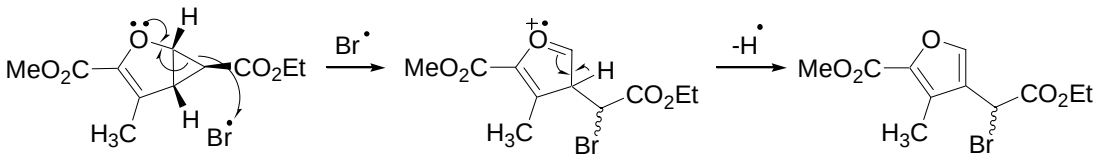


176 **177**

Figure 37 Allylic bromination and improvement in enantiomeric excess

On the other hand, attempts to improve the chemical yield were not successful, essentially due to formation of the furan derivative **178** as a result of cyclopropane opening and rearomatization under the radical reaction conditions. The yield of **178** was ranging from 20% to 50%. The structure and mechanism for the formation of **178** is

shown in Fig. 38. The mechanism clearly reveals the fact that it would not be viable to avoid the formation of this furan derivative during the allylic bromination.



178

Figure 38 Mechanism for the formation of furan derivative **178**

Another interesting fact observed during this reaction was that on larger scale (20 g.) even at reflux temperature, the reaction was not initiated. After careful literature search explaining a general survey of reaction conditions, water was employed as an additive. Disappointingly, the reaction yielded major amount of furan derivative **178** rather than the desired allyl bromide product **177**. Nevertheless, the employement of molecular bromine in catalytic amount accelerated the reaction considerably, also minimizing the formation of the side product to 20%.

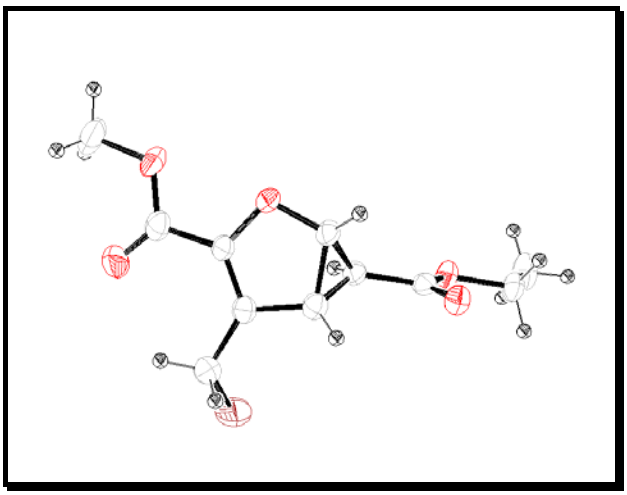


Figure 39 ORTEP drawing of **177**

Finally, the absolute configuration of **177** was unambiguously proven by X-ray structure analysis. The ORTEP diagram is shown in Fig. 39.

Upon catalytic hydrogenation, **177** underwent de-bromination to yield **176** back. Thus, allylic bromination proves as a practical method to obtain **176** in enantiopure form. What's more, enantiomerically pure allyl bromide **177** could prove as a versatile intermediate, as a number of constructive conversions of this moiety are well known.

2.3 Functionalization at C3 Carbon Center: Having enantiopure cyclopropyl derivatives **176** with methyl and **177** with bromomethyl functionality at C3 carbon in hand, the synthesis of the derivatives having a wide range of other functionalities was envisioned.

Initially, **177** was exposed to Mg in THF or diethyl ether in order to form the corresponding Grignard reagent. However, these experiments were not successful. The effort to form a Wittig salt by reacting **177** with triphenyl phosphine gave very low yields.

Moreover, the substitution of bromide in **177** with *O*-acetyl also proceeded only in very low yields.

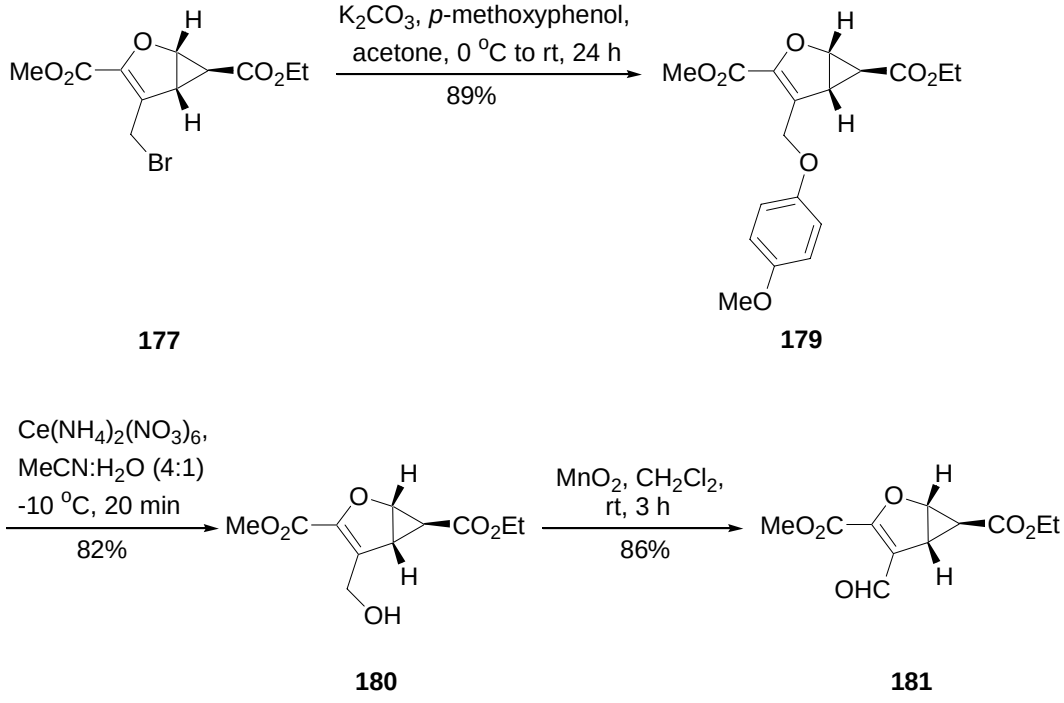


Figure 40 Functionalization at C3 carbon center

Subsequently, the attention was focused to introduce aldehyde functionality at C3 carbon, which was anticipated as a perfect intermediate for the introduction of side-chains. SeO_2 mediated allylic oxidation of **176** gave poor yield. Hence, the

bromomethyl derivative **177** was transformed into aldehyde **181** in three steps (Fig. 40). **177** was exposed to the mixture of K_2CO_3 and *p*-methoxy phenol in acetone to afford the *p*-methoxy phenyl ether **179** in very good yield. Ceric ammonium nitrate mediated oxidative cleavage of *p*-methoxy phenyl ether **179** yielded the allylic alcohol **180**. This was then oxidized to aldehyde **181** using activated MnO_2.

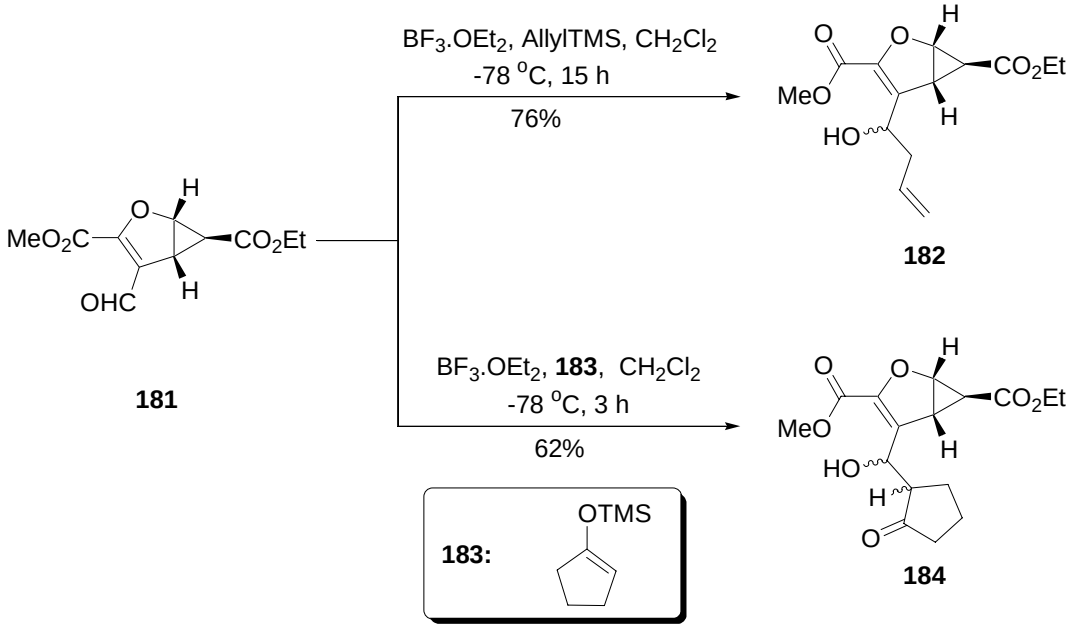


Figure 41 Side-chain introduction and oxidation sequence

The model reactions for side-chain introduction tried on aldehyde **181**, were Sakurai allylation with allyl silane and Mukiyama aldol reaction with cyclic enol ether **183** (Fig. 41). Both yielded the respective products **182** and **184** in good yield as a mixture of diastereomers. The diastereomeric ratios were not determined. Subsequent oxidation of the resulting alcohols failed entirely under various conditions, most likely caused by the steric hinderance of the cyclopropyl moiety plus the possible interactions between methyl ester and hydroxy functionality.

The aldehyde functionality in **181** was also protected effectively as cyclic (**185**) as well as acyclic (**186**) acetal. **181** was subjected to *p*-toluene sulfonic acid and ethylene glycol at reflux temperature, in Dean-Stark condenser to yield cyclic acetal **185** in very good yield. The synthesis of acyclic acetal **186** was achieved also in good yield by reacting **181** with triethyl orthoformate in the presence of the catalytic amount of (+)-camphorsulfonic acid (Fig 42).

Thus, a small library of cyclopropane derivatives was synthesized productively, the members of which possess different functionalities at C3 carbon center such as methyl, bromomethyl, alkoxymethyl, hydroxymethyl, aldehyde and acetal protected aldehyde.

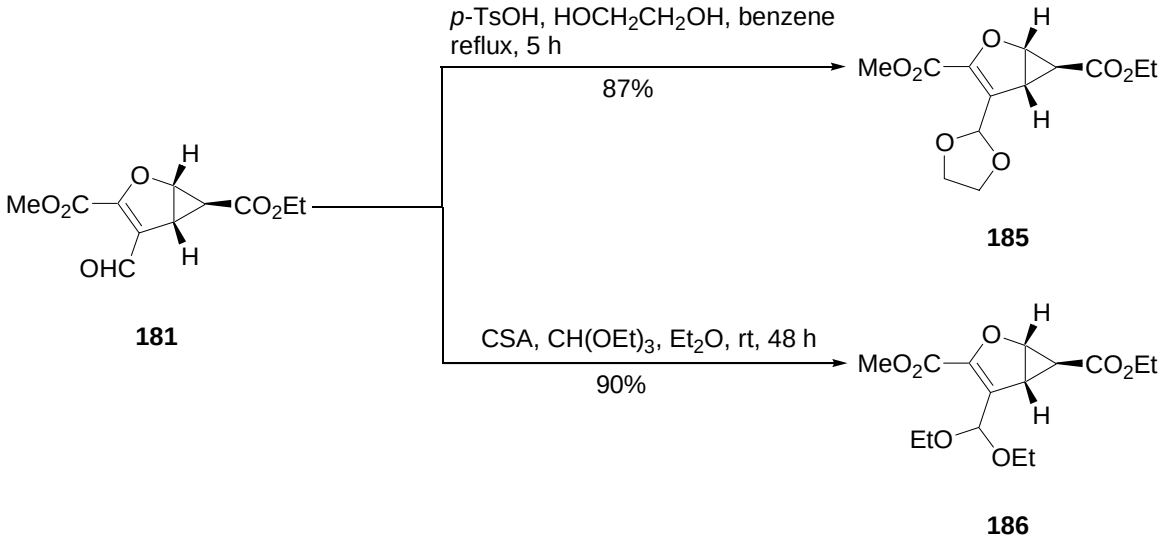
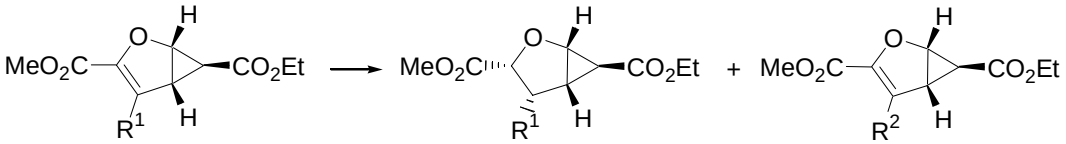


Figure 42 Protection of aldehyde as cyclic and acyclic acetal

2.4 Hydrogenation of Cyclopropanated Dihydrofurans: To prepare the 1,2-cyclopropanecarboxylated furanoid scaffolds for acid mediated rearrangement, hydrogenation of the tetrasubstituted double bond in all the cyclopropaned dihydrofuran derivatives was the next assignment to complete. However, this reaction proved to be quite substrate dependant.

The methyl derivative **176** upon catalytic hydrogenation unpredictably yielded a diastereomeric mixture of optically inactive diester **187**. The furan ring as well as cyclopropane ring underwent the hydrogenation to yield this completely saturated entity. The bromomethyl derivative **177** afforded the methyl derivative **176** under a range of hydrogenation conditions. This proved to be an easy way to get enantiomerically pure methyl derivative **176** as stated before. The hydroxymethyl derivative **180** underwent hydrogenolysis under various conditions also yielding the methyl derivative **176**. The formyl derivative **181** yielded hydroxymethyl derivative **180** under various hydrogenation conditions (Fig. 43).

These results proved to be a major restriction of the strategy, as they reduced the number of possible derivatives possessing diverse functionalities ready to be subjected to the acid mediated rearrangement in order to form *cis*-fused furo[2,3-*b*]furans.

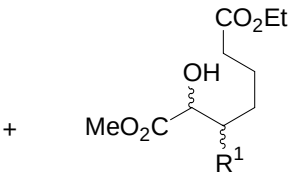


176: $R^1 = CH_3$,

177: $R^1 = CH_2Br$,

180: $R^1 = CH_2OH$,

181: $R^1 = CHO$



C (187)

Compound	Catalyst [(a)]	Time	A	B	C (187)
	a) Pd/C	3 h	-	-	65%
	b) Pt/C	3 h	-	-	63%
	c) $Pd/BaSO_4$	48 h	-	-	-
176	d) Wilkinson`s catalyst	48 h	-	-	-
	e) Pd/cyclohexadiene	48 h	-	-	-
	a) or b) or c)	30 min	-	$R^2 = CH_3$	-
177				Quantitative.	
	d) or e)	48 h	-	-	-
	a) or b) or c)	30 min	-	$R^2 = CH_3$	-
180				Quantitative.	
	d) or e)	48 h	-	-	-
	a) or b) or c)	30 min	-	$R^2 =$ CH_2OH Quantitative.	-
181					
	d) or e)	48 h	-	-	-

(a) All the reactions were carried out at 25 ^oC and balloon (atm.) pressure.

Figure 43 Substrate dependant hydrogenation

Nevertheless, the hydrogenation of **179** yielded less than 30% hydrogenation product **188** together with a number of other unidentified products. Conversely, acetals **185** and **186** underwent smooth hydrogenation when subjected to Palladium on charcoal under the hydrogen atmosphere yielding **189** and **190** respectively (Fig. 44).

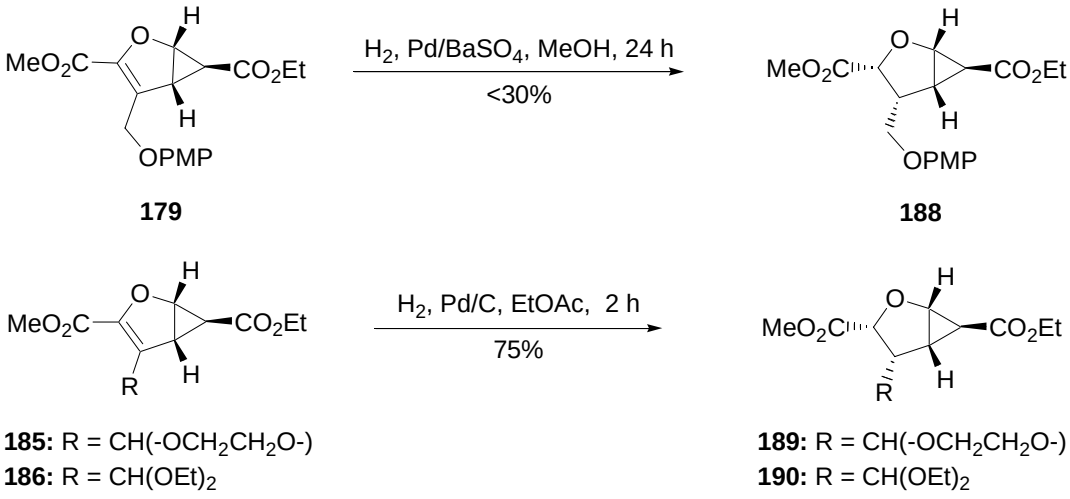


Figure 44 Synthesis of 1,2-cyclopropanecarboxylated furanoids

In all the successful cases, hydrogenation occured exclusively from the convex face of the bicyclus, resulting in highly congested derivatives in which the functional group at C3 carbon as well as methyl ester are forced on the concave face. The possible reason for this could be the steric hinderance created by cyclopropyl group which allowed the hydrogen addition only from the more accessible convex face.

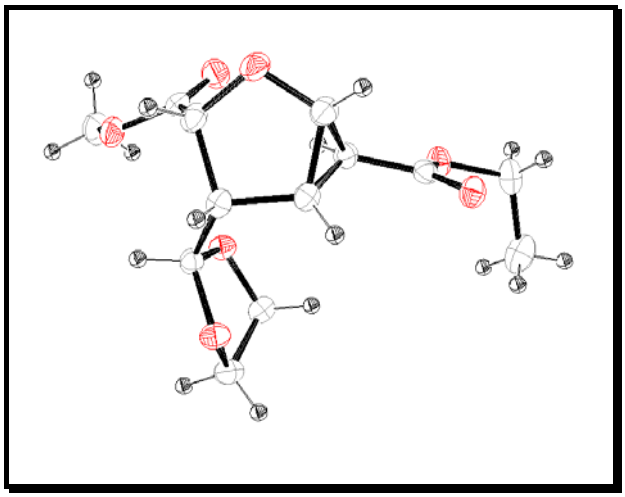
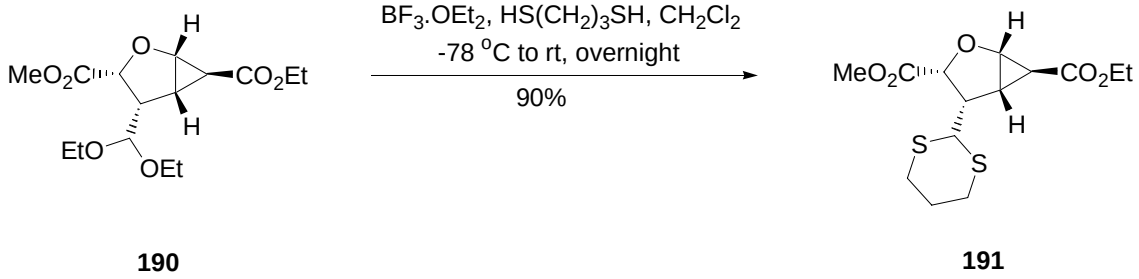


Figure 45 ORTEP drawing of **189**

X-ray analysis of **189** (Fig. 45) and NOE experiments explicitly proved these structural assignments.

2.5 Trans-thioacetalization: The cyclic as well as acyclic acetals are known to be acid senstitive. For that reason, considering the possibility of concomitant acetal deprotection during the acid mediated rearrangement of 1,2-cyclopropanecarboxylated furanoids **189** and **190**, the preparation of such a furanoid derivative possessing the acid-stable masking group of aldehyde was the next intention. The dithioacetal protecting group which was thought to be a better alternative is, in most cases, cleaved by reaction with Hg(II) salts or oxidation; acid hydrolysis is known to be inadequate.

As a first option to accomplish the synthesis of such a derivative, α,β-unsaturated aldehyde **181** was protected as a dithioacetal quantitatively. But, the catalytic hydrogenation of the double bond failed completely, most likely due to the potential poisoning of the catalyst by sulfur part present in the substrate. Trans-thioacetalization of **190** proved to be the perfect alternative to overcome this problem.



190 **191**

Figure 46 $BF_3 \cdot Et_2O$-mediated trans-thioacetalization

A combination of $BF_3 \cdot OEt_2$/1,3-propane dithiol proved to be the best, yielding the corresponding dithioacetal **191** as the exclusive product in an excellent yield (Fig. 46). Thus, along with *O*,*O*-acetals **189** and **190**, *S*,*S*-acetal **191** was also prepared as the potential substrate for the acid mediated rearrangement. The other benefit of this derivative could be that it also creates the prospect to form a quaternary center on the side-chain in later stages by performing the reactions involving an umpolung of reactivity, as many of the target spongiane diterpenoids hold such a quaternary center.

2.6 Synthesis of Furo[2,3-*b*]furan Motif *via* Acid-Mediated One-Pot Ring Expansion of Cyclopropane Rings: As expected, *O*,*O*-acetals **189** and **190** on treatment with acid yielded a series of anonymous products, most likely due to the simultaneous acetal deprotection, ester hydrolysis and cyclopropane rearrangement.

Nonetheless, *S,S*-acetal **191** on the treatment with 6 M (aq.) HCl in 1,4-dioxane yielded the straightforwardly separable mixture of *cis*-fused furo[2,3-*b*]furans **192** and **193** in reasonable yield. The complete conversion to acid **193** could not be observed even after stirring the reaction at room temperature for 96 hours, perhaps due to the steric hinderance produced by six-membered thioacetal ring. The slight increase in reaction temperature helped in hydrolyzing the methyl ester completely affording **193** as an exclusive product in 69% yield (Fig. 47).

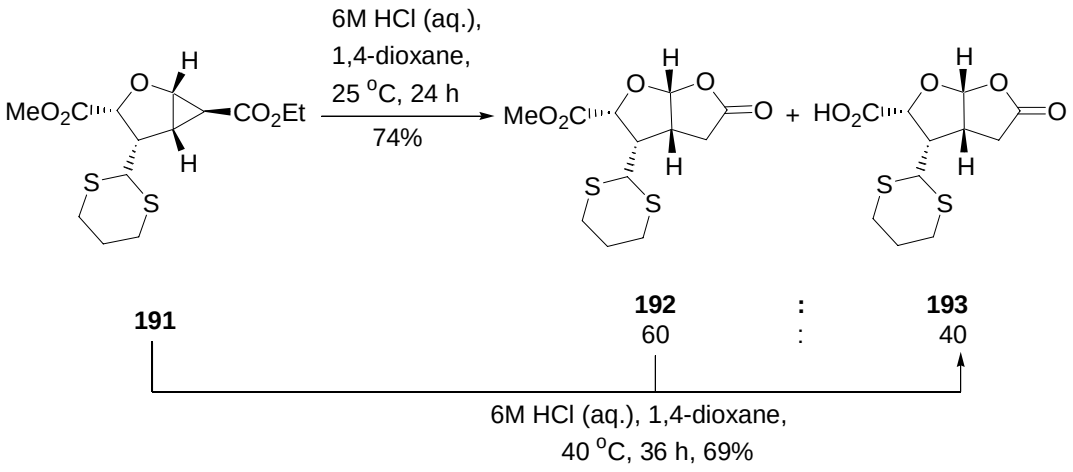


Figure 47 HCl-mediated rearrangements of **191**

As expected, the presence of both electron withdrawing and electron donating substituents at vicinal positions of the cyclopropyl ring of **191** allowed the cleavage of

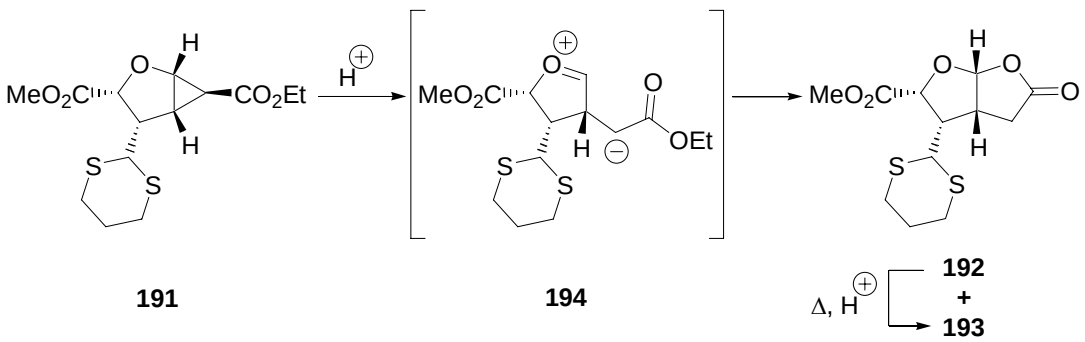


Figure 48 Mechanism of HCl-mediated rearrangement

anomeric bond to occur under acidic conditions. The transiently produced 1,3-dipolar synthon **194** could then cyclize *in situ* at the anomeric center to produce the desired

bicyclic ring system of methyl ester **192**, along with the acid **193**. The complete conversion to acid **193** was then achieved at elevated temperature under the effect of aq. HCl (Fig. 48).

An important advantage of this strategy was that only one diastereomer was obtained, retaining the stereochemistry at all the carbon centers producing the substantially strained system in which methyl ester as well as thioacetal ring are oriented on the concave face of the bicycle.

The structures of **192** and **193** were unequivocally proved by NOE experiments particularly performed on methyl ester **192** (Fig 49).

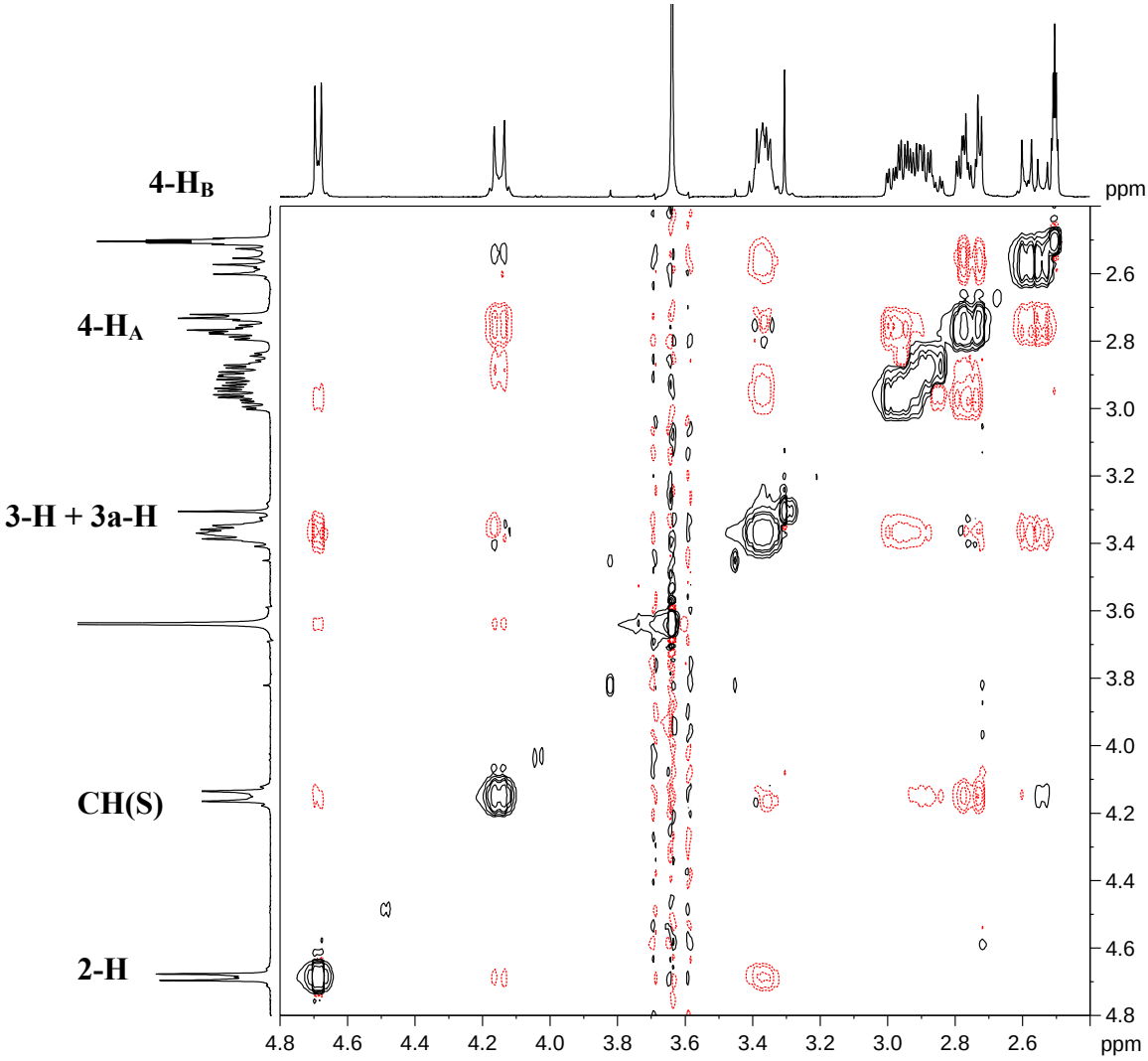


Figure 49 NOE spectrum of methyl ester **192**

The key NOE signals which establish the stereochemistry as exposed in Fig. 50 are, H-2 to H-3, H-3 to H-3a and H-3a to H_A-4.

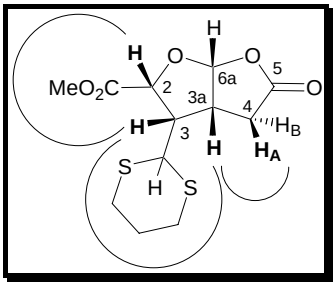


Figure 50 Key NOE signals of methyl ester **192**

As both methyl ester **192** and acid **193** could be isolated in good yields depending upon the reaction conditions, it broadened the choice for the next manipulations by exploiting the chemoselectivity of different reagents towards both the functional groups. However, reduction of the methyl ester in **192** as well as carboxylic acid in **193** selectively to the corresponding primary alcohol was not successful.

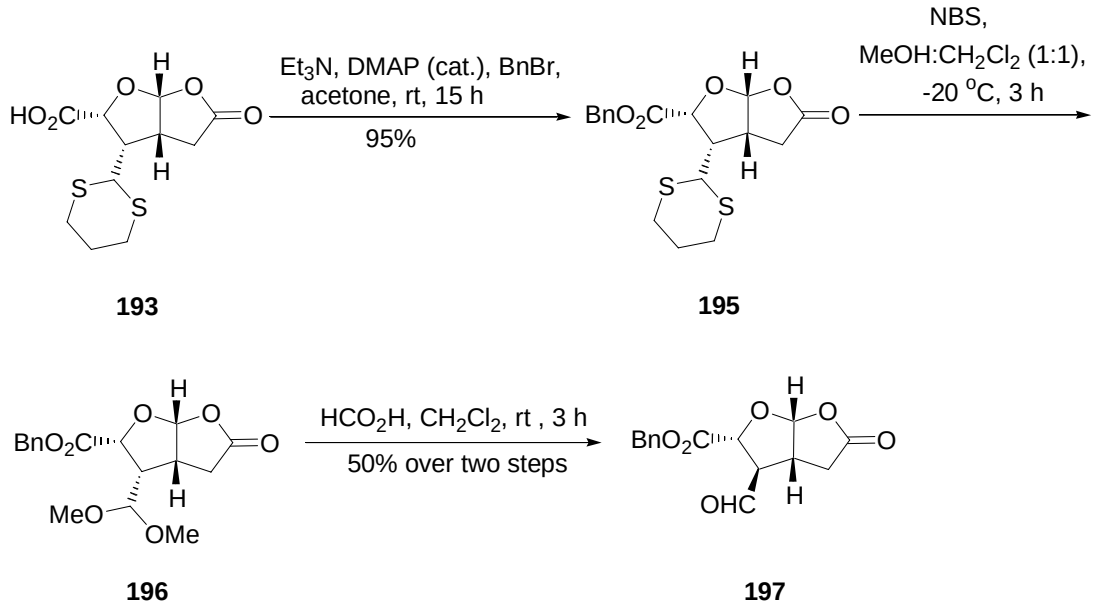


Figure 51 Benzyl protection and dithioacetal deprotection

Therefore, the benzyl protection of the carboxylic acid was anticipated as a better choice. This would avoid the possibility of cyclization (see Fig. 26) of the

secondary alcohol resulting from nucleophilic additions of the side-chains on demasked aldehyde at C3 carbon center, as *O*-benzyl is not as good leaving group as *O*-methyl.

193 was converted to benzyl ester **195** in excellent yield (Fig. 51). As a final point, the deprotection of dithioacetal was the critical objective. The early attempts running this reaction with some metals that are commonly used to catalyze the hydrolysis (oxidation) of dithioacetal, namely, $HgCl_2/CdCO_3$, $AgNO_3/AgO$, $FeCl_3/CuO$ or other reagents like NBS, BTI, DMP failed completely. For this reason, dithioacetal **195** was converted to the corresponding dimethyl acetal **196** using NBS in methanol. The hydrolysis of **196** was achieved using formic acid in dichloromethane affording the aldehyde **197** in 50% yield over two steps.

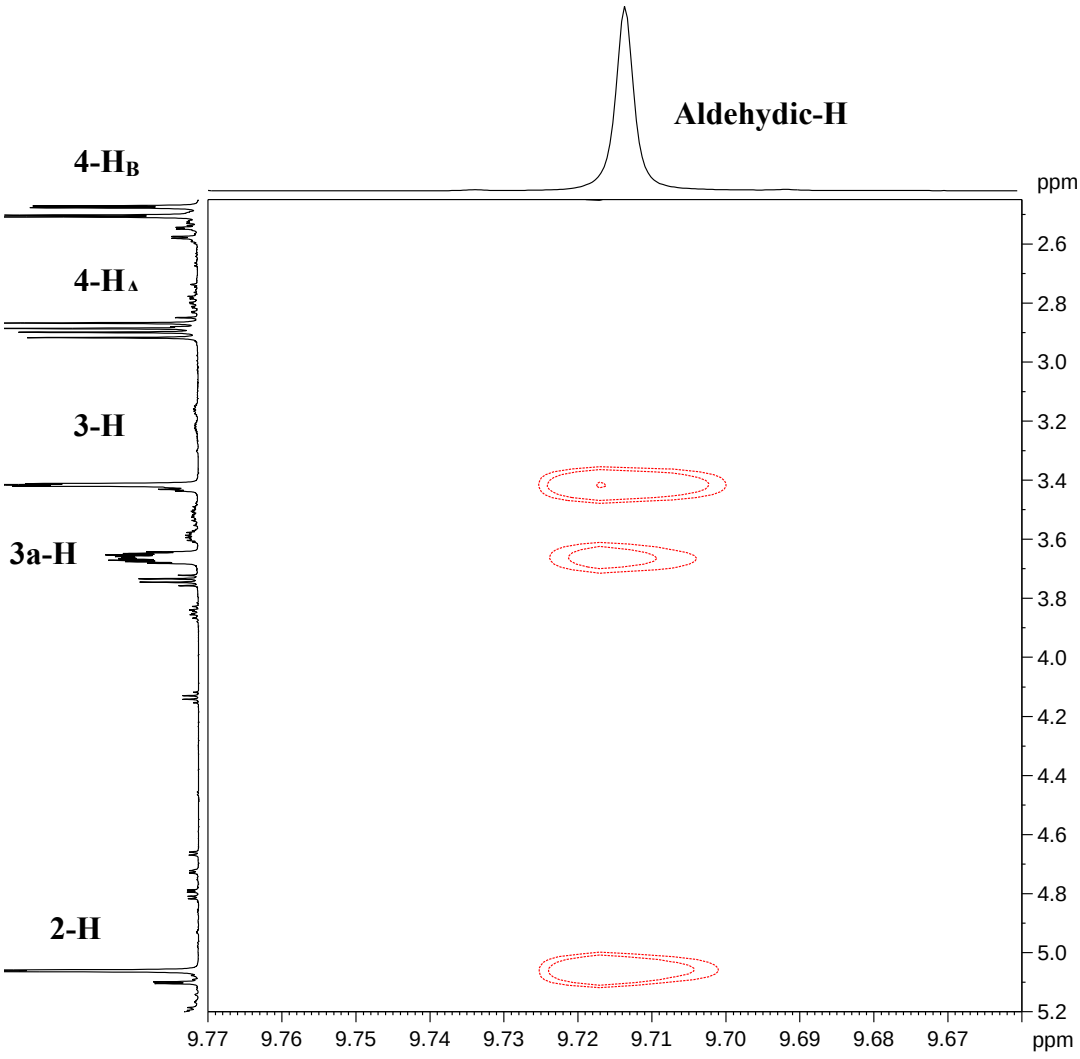


Figure 52 NOE spectrum of aldehyde **197**

However, after the NOE experiments it was revealed that the stereocenter bearing aldehyde functionality in **197** was epimerized possibly as a result of acidity of the reaction medium. The structure of **197** was unambiguously assigned by NOE experiments as shown in Fig. 53.

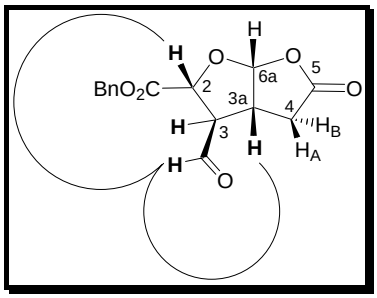


Figure 53 Key NOE signals of aldehyde **197**

The key NOE signals which prove the stereochemistry as given in Fig. 53 are, aldehyde-H to H-3a and aldehyde-H to H-2. These studies demonstrated that the aldehyde functionality was oriented on the convex face of the bicylic system.

2.7 Conclusions and Outlook: In summary, the stereoselective synthesis of *cis*-fused furo[2,3-*b*]furan intermediates was achieved, which can be broadly applied for the synthesis of norrisolide as well as various spongiane diterpenoids containing this distinctive bicyclic framework. The strategy described is predominantly based on acid-mediated one-pot ring expansion of the corresponding cyclopropanes and also allows the introduction of versatile functionalities on C3 carbon center such as dithioacetal, dimethyl acetal or aldehyde. These functionalities can be utilized with the intention of introducing the bulky side-chains on either concave or convex face of the bicyclus.

Moreover, the compact and sterically cumbersome structure of *cis*-fused furo[2,3-*b*]furans as well as cyclopropane precursors led to several ineffective reactions and numerous modifications of the overall strategy. Nonetheless, exploration of each strategy led to conclusions that were decisive in designing the successful strategy.

This strategy can also be utilized as groundwork for the synthesis of potential insect antifeedant clerodin (Fig. 3). Furoic ester **30** could be transformed into **198** in four steps (Fig. 54), which could be used as a substrate for Mukiyama aldol reaction with the silyl enol ether **146** derived from carvone. The addition of enol ether might take place from the convex face directed by steric hinderance caused by lactone ring

giving the intermediate **199**. After the lactone reduction and protection of resulting lactol, the intermediate **200** could be obtained.

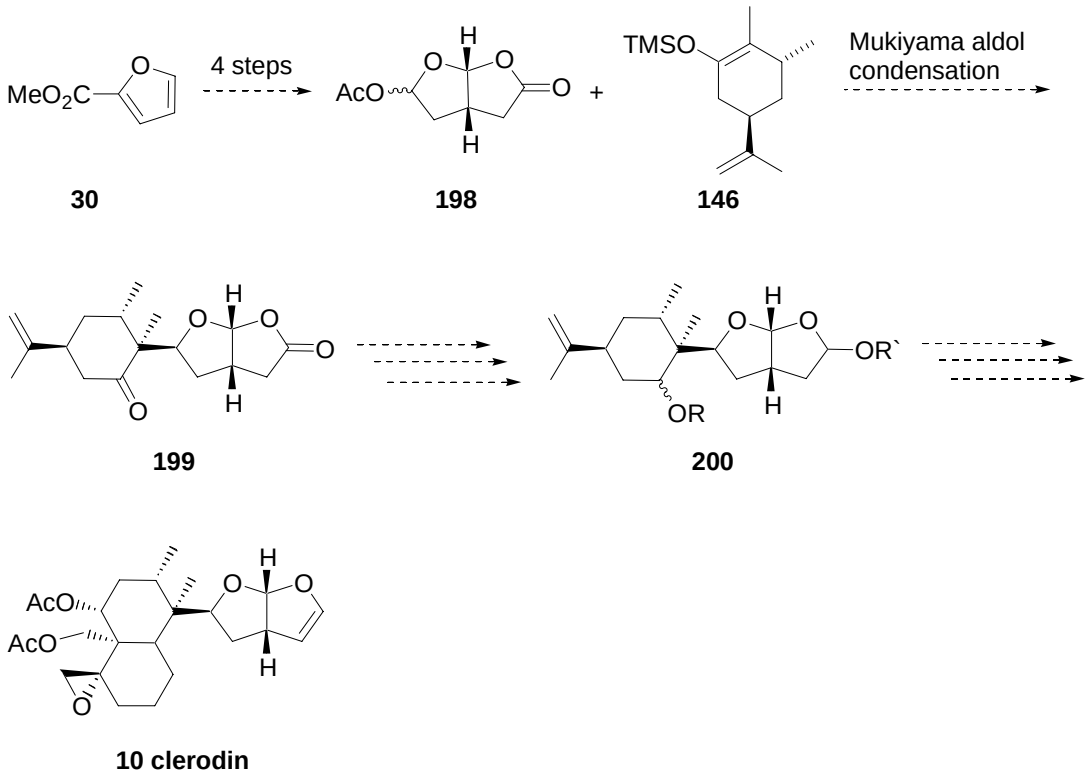


Figure 54 Proposed Synthesis of clerodin

The protocol followed by Groot and co-workers in the total synthesis of dihydroclerodin[26] could be used in order to achieve the annulation of the second ring and introducing the other structural features in order to accomplish the total synthesis of clerodin **10**.

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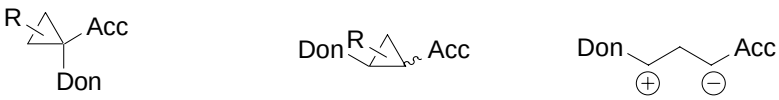
3.1 Donor-Acceptor Substituted Cyclopropanes: The diverse functionality and reactivity present in the cyclopropanes makes them attractive substrates for the chemical development in modern organic synthesis.[1, 2] While unactivated cyclopropanes have been directly employed for certain useful chemical transformations[3, 4], most of the cyclopropane based methodologies have relied on derivatives substituted by electron donor and acceptor groups. Since electronic relationship of these substituents effect the activation of the cyclopropanes and a high versatility of the products after ring cleavage, they are particularly suitable for synthetic applications. Following are the general structures of *geminally* and *vicinally* donor-acceptor (DA) substituted cyclopropanes.



201 **202** **203**

Figure 55 General structures of donor-acceptor (DA) cyclopropanes.

Only a few examples for the use of *geminally* DA-substituted cyclopropanes (**201**, Fig. 55) are known, since substituents do not act in a synergistic (push-pull) manner. However, *vicinally* DA-substituted cyclopropanes (**202**, Fig. 55) which serve as 1,3-dipolar synthons (**203**, Fig. 55) are used in many synthetically valuable transformations.[5, 6]

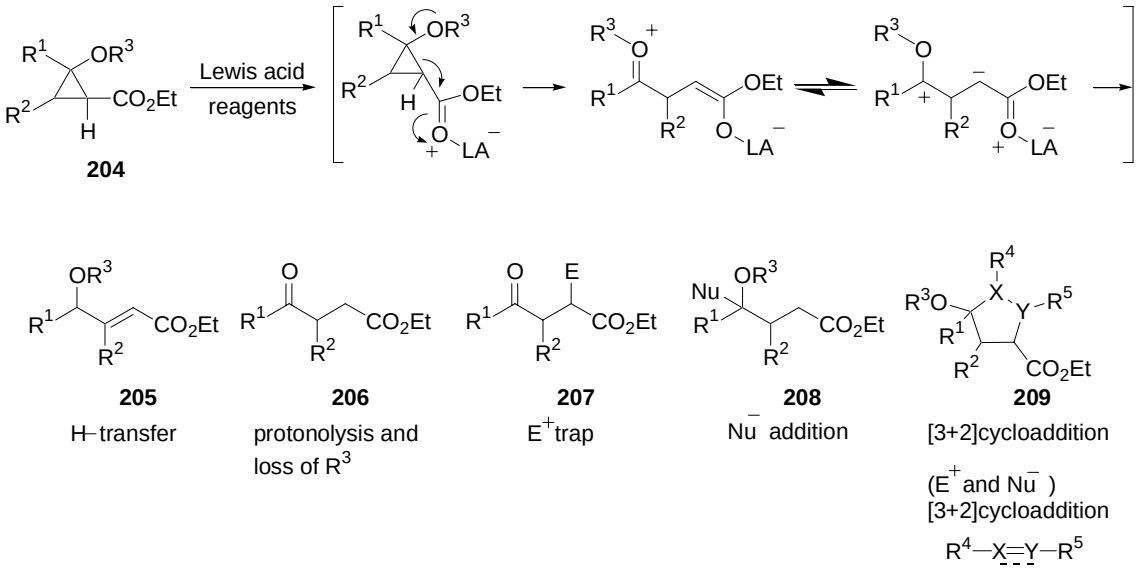


Figure 56 Reactions of *vicinally* substituted donor-acceptor (DA) cyclopropanes

Generally, the nature of reaction conditions directs the ultimate outcome of the 1,3-zwitterion and the intermediates react in an intramolecular fashion by hydride[7, 8] or proton transfers to give γ-alkoxy α,β-unsaturated esters **205** or saturated γ-oxoesters **206** (Fig. 56). Siloloxy substituted DA cyclopropanes are particularly susceptible to give simple protonolysis products **206**. Intermolecular reactions can occur at just one or both sites of the dipole. Examples of α-addition from electrophilic trapping of enolates to afford **207** and nucleophilic addition to the intermediate oxocarbenium ions to give **208** are both known. Combining the dual reactivity of the 1,3-dipole results in formal [3+2] cycloadditions furnishing highly functionalized carbon or heterocyclopentane derivatives **209**. These latter transformations involving DA substituted cyclopropanes are synthetically powerful methods for accessing products often not readily available through traditional routes.

The stereoselective cyclopropanation of furans reported in the preceding section affords unique bicyclic structures combining the high reactivity of cyclopropanes together with the extreme optical purity and functional diversity associated with them. The electron donating effect from the furan ring oxygen conveniently helps to drive a variety of rearrangement as well as ring enlargement reactions of these DA substituted cyclopropane derivatives.

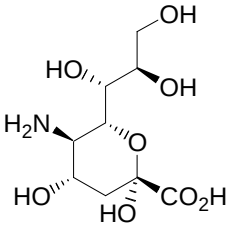
Therefore, the studies investigating the utilization of already synthesized 1,2-cyclopropanecarboxylated furanoids in such rearrangements and their applications towards the synthesis of unnatural amino acids, dihydro- and tetrahydrofurans as well as γ-butyrolactones are envisioned as an additional part of this work.

3.2 NBS-Promoted Ring Opening of 1,2-Cyclopropanecarboxylated Furanoids: Synthesis of Enantiomerically Pure Amino Acid Containing 2,3,4,5-Tetrasubstituted THF Ring in the Molecular Backbone:

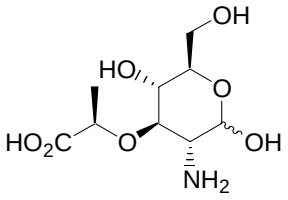
3.2.1 Introduction: In recent years the interest in a rational design of amino acid and peptide mimetics has steadily grown due to the pharmacological limitations of bioactive peptides. The biological relevance of unnatural amino acids continues to promote enormous attention to their design and synthesis.[9]

The cation-binding ability of ether subunits as well as the synthetic and conformational potential of amino acids are the foremost reasons which has caused the great interest in the synthesis of amino acids containing ether functionalities in the side-chain and/or the molecular backbone.[10]

Examples of naturally occurring ether amino acids are neuraminic acid (**210**, Fig. 57) found as subunits of oligosaccharides, muraminic acid (**211**, Fig. 57) found in cell-walls of bacteria.[11]



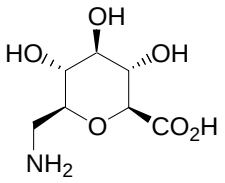
210 neuraminic acid



211 muraminic acid

Figure 57 Naturally occuring ether amino acids

Most contributions to the field of synthetic ether amino acids start from carbohydrates. Sugar amino acids (SAA) were developed by Kessler et al.[12] (**212, 213** Fig. 58), Lansbury et al.[13] (**214**, Fig. 58), Dondoni et al.[14, 15], Wessel et al.[16] and Ichikawa et al.[17] Sugar derived THF amino acids of type **215** (Fig. 58) have been synthesized by several groups.[18, 19] THF peptides made out of **215** show remarkable secondary structures.[20]



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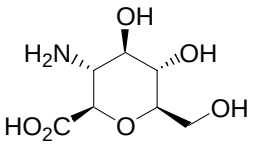

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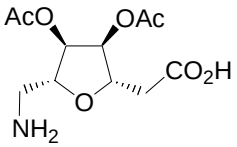

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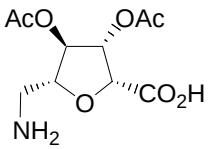


215

Figure 58 Sugar-derived synthetic THP and THF amino acids.

The approach to THF amino acids in the present work started with already synthesized 1,2-cyclopropanecarboxylated furanoid scaffolds as a chiral pool source.

The diastereoselective ring opening of cyclopropane sugar derivatives was already demonstrated by Danishefsky and co-workers[21] as well as by Chandrasekaran and co-workers.[22]

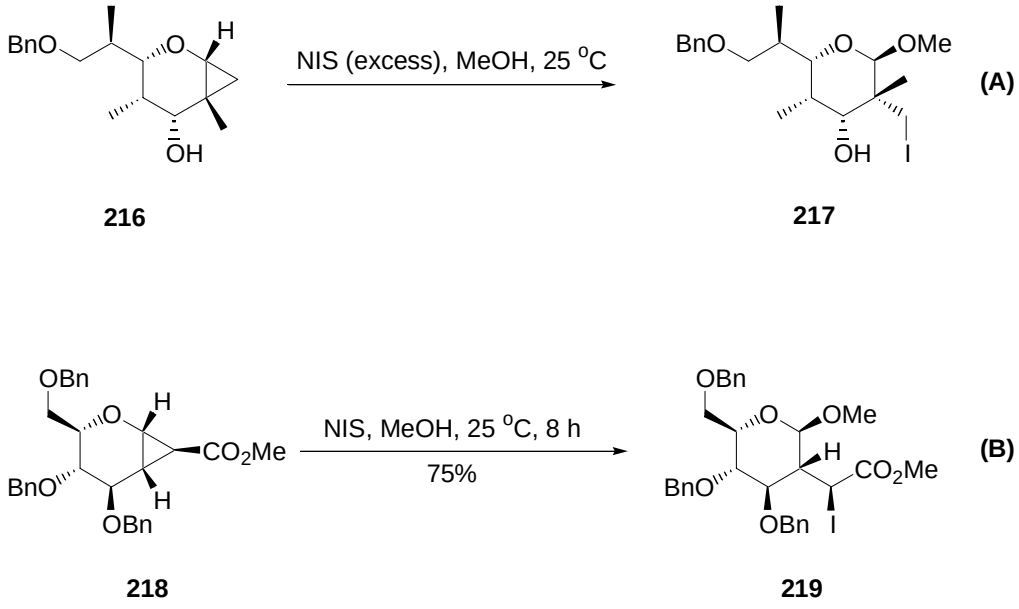


Figure 59 Diastereoselective ring opening of cyclopropane sugars

During the studies towards the synthesis of Epothilone A, Danishefsky and co-workers reported that **216**, when subjected to oxidative opening with *N*-iodosuccinimide (NIS) afforded **217** (**A**, Fig. 59). The idea behind this was to acquire the *geminal* dimethyl groups. Later Chandrasekaran and co-workers followed the same strategy, treating **218** with NIS/MeOH (28 °C, 8 h) yielding **219** in 75% yield as a single diastereomer (**B**, Fig. 59). **219** was then efficiently applied for the synthesis of 2-C-branched glyco-amino acid derivatives.

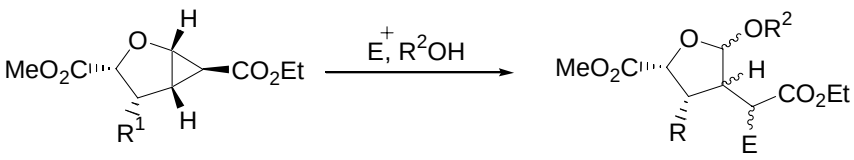
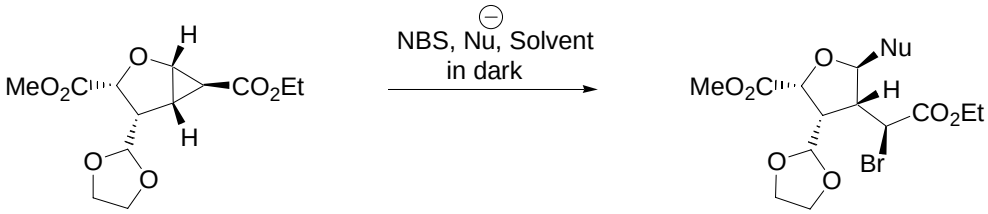


Figure 60 General scheme for the ring opening of cyclopropane

3.2.2 NBS-Promoted Cyclopropane Ring Opening: In accordance with the aforementioned results, 1,2-cyclopropanecarboxylated furanoid **189** was envisioned as a

suitable synthon for the diastereoselective ring opening of the cyclopropane, utilizing its ability to undergo, in the presence of a protic solvent, electrophilic ring opening assisted by adjacent oxygen (Fig. 60).

However, taking into consideration the low stability of iodo-derivatives, *N*-bromosuccinimide (NBS) was preferred as an electrophile. Acetic acid as well as methanol was chosen as the appropriate protic solvent. Additionally azide was also examined as a potential nucleophile with the intention of introducing the amine functionality at the anomeric center. The results obtained are summarized in Fig. 61.



189 **220**

Nucleophile	Solvent	Temp.	Time	Yield	Diastereomeric Ratio [a]
OMe	MeOH	25 °C	24 h	78%	90:10
OMe	MeOH	15 °C	36 h	86%	100:0
OAc	AcOH	25 °C	3 h	Decomposition	-
N_3	MeOH[b]	25 °C	48 h	No reaction	-
N_3	MeOH[b]	Reflux [c]	24 h	No reaction	-

(a) Diastereomeric ratio was determined according to the stereochemistry at the anomeric center.

(b) NBS was not used in this reaction.

(c) NaN_3 in MeOH: the trans-esterification was observed.

Figure 61 Results for the ring opening of cyclopropane in **189**

Initially, when the reaction was carried out in the presence of light, very low yields were obtained. Moreover, the formation of unidentified side-products was also

observed. Hence, the subsequent experiments were carried out under exclusion of light. In case of the acetic acid, decomposition of the substrate was observed probably due to the concomitant deprotection of the cyclic acetal. When sodium azide was used as a nucleophile at room temperature, there was no formation of the product. However, at higher temperature only trans-esterification was observed.

Nevertheless, the treatment of **189** with NBS in MeOH under exclusion of light for 24 hours furnished the desired product **220**. The temperature of the reaction played a significant role for the diastereomeric ratio with respect to the configuration at the anomeric center. While the reaction was carried out at 25 ^{o}C, the diastereomeric ratio obtained was 90:10, the one bearing the β-OMe group as a major diastereomer. However, at slightly lower temperature, complete β-diastereoselectivity could be attained. Even though the reaction time was longer (36 hours) in this case, it was well compensated by excellent diastereoselectivity as well as very good yield. Thus, two new stereocenters could be introduced in a single reaction, with complete diastereoselectivity.

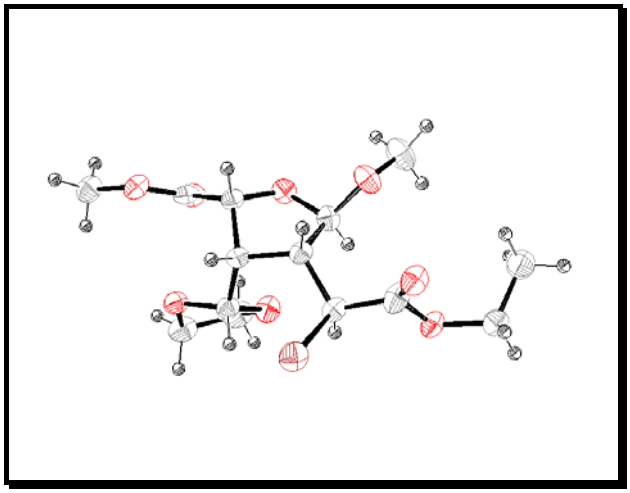


Figure 62 ORTEP diagram of **220**

The structure and the absolute configuration of the α-bromo ester derivative **220** was unambiguously established by NOE experiments and X-ray structure analysis. The ORTEP diagram is shown in Fig. 62. The crystal structure of **220** was in agreement with the stereochemical assignment for the ring opening products on the basis of NOE experiments.

On the basis of all these studies, it was confirmed that the anomeric bond in the strained cyclopropane ring in **189** underwent cleavage mediated by NBS under the effect of a protic solvent methanol (Fig. 63).

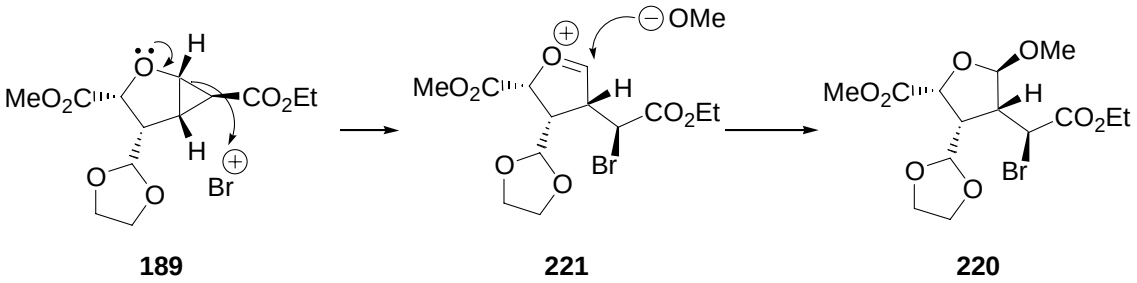


Figure 66 Mechanism of the ring opening of cyclopropane in **189**

The simultaneous cleavage of the cyclopropane ring and trapping of the electrophilic bromine clearly followed the SN_2 pathway. The resulting oxo-carbenium ion **221** is then attacked by methoxide acting as the nucleophile to yield the α-bromo ester **220**. The attack occured exclusively from the β-face, probably because of the steric hinderance created by acetal ring as well as methyl ester functionality.

3.2.3 Synthesis of Amino Acid Containing 2,3,4,5-Tetrasubstituted THF Ring in the Molecular Backbone: The conversion of α-bromo ester **220** into the amino acid scaffold was the next objective which was accomplished in three steps (Fig. 64).

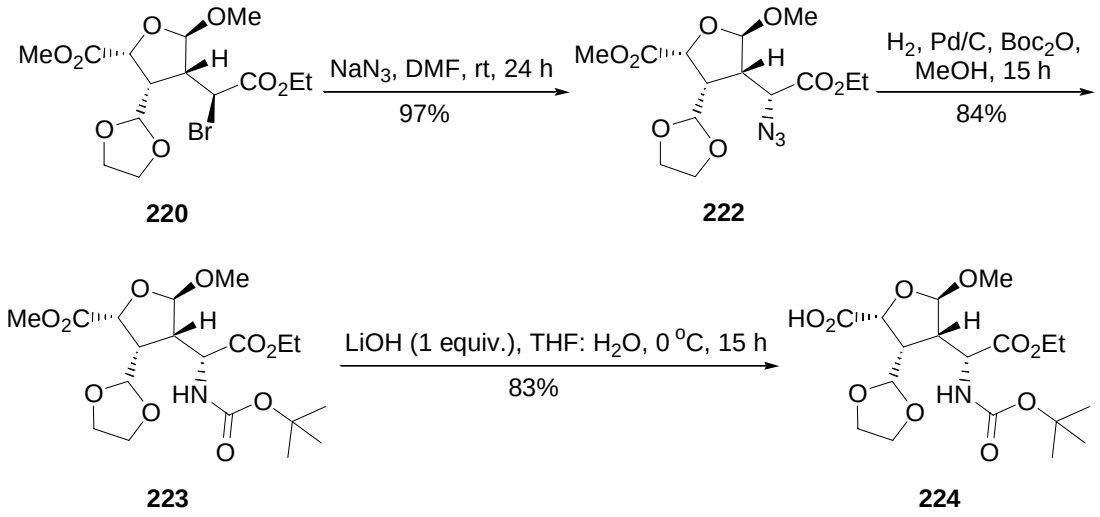
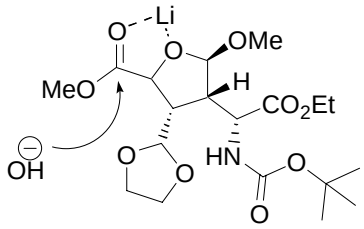


Figure 64 Conversion of **220** to amino acid scaffold

The SN_2 substitution of bromine in **220** was achieved in excellent yield using sodium azide. Catalytic hydrogenolysis of the resulting azido ester **222** in the presence of Boc_2O afforded the corresponding N-Boc-amino ester **223**. The *in situ* protection of the amine functionality was carried out to in order to avoid the possible cyclization of amine with methyl ester. Finally, the differentiation between the two esters was the decisive task to complete. In fact, the methyl ester in **223** could be selectively hydrolyzed to the corresponding acid **224**, when carefully subjected to 1 equivalent of lithium hydroxide at low temperature.



223

Figure 65 The probable chelation responsible for the selective ester hydrolysis

The selective hydrolysis of the methyl ester was achieved successfully probably assisted by the tetrahydrofuran ring oxygen by forming a five membered chelate ring with the Li^+ ion and the carbonyl oxygen of the methyl ester (Fig. 65).

3.2.4 Conclusions and Outlook: In conclusion, the NBS-promoted cyclopropane ring opening of 1,2-cyclopropanecarboxylated furanoid in presence of a protic solvent was achieved with complete diastereoselectivity. This method was applied efficiently for the synthesis of a enantiomerically pure amino acid containing 2,3,4,5-tetrasubstituted THF ring in the molecular backbone. This amino acid can be further functionalized (e.g. chemoselective ring opening of the cyclic acetal and exploiting the reactivity of the resulting aldehyde) in order to acquire a library of THF amino acids. Also, the THF amino acids are interesting candidates as peptidomimetics or for the assembly of artificial ion channels.

This strategy can also be utilized as groundwork for the synthesis of γ- and δ-lactone amino acids as shown in Fig. 66. Furan derivative **30** can be converted to **224** in 6 steps *via* NBS-promoted ring opening. The treatment of **224** with 1,3-propane dithiol in the presence of $BF_3{\cdot}OEt_2$ would result in the tetrahydrofuran ring opening yielding

the amino ester **225**. A Lewis acid catalyzed cyclization of **225** would afford the δ-lactone **226**.

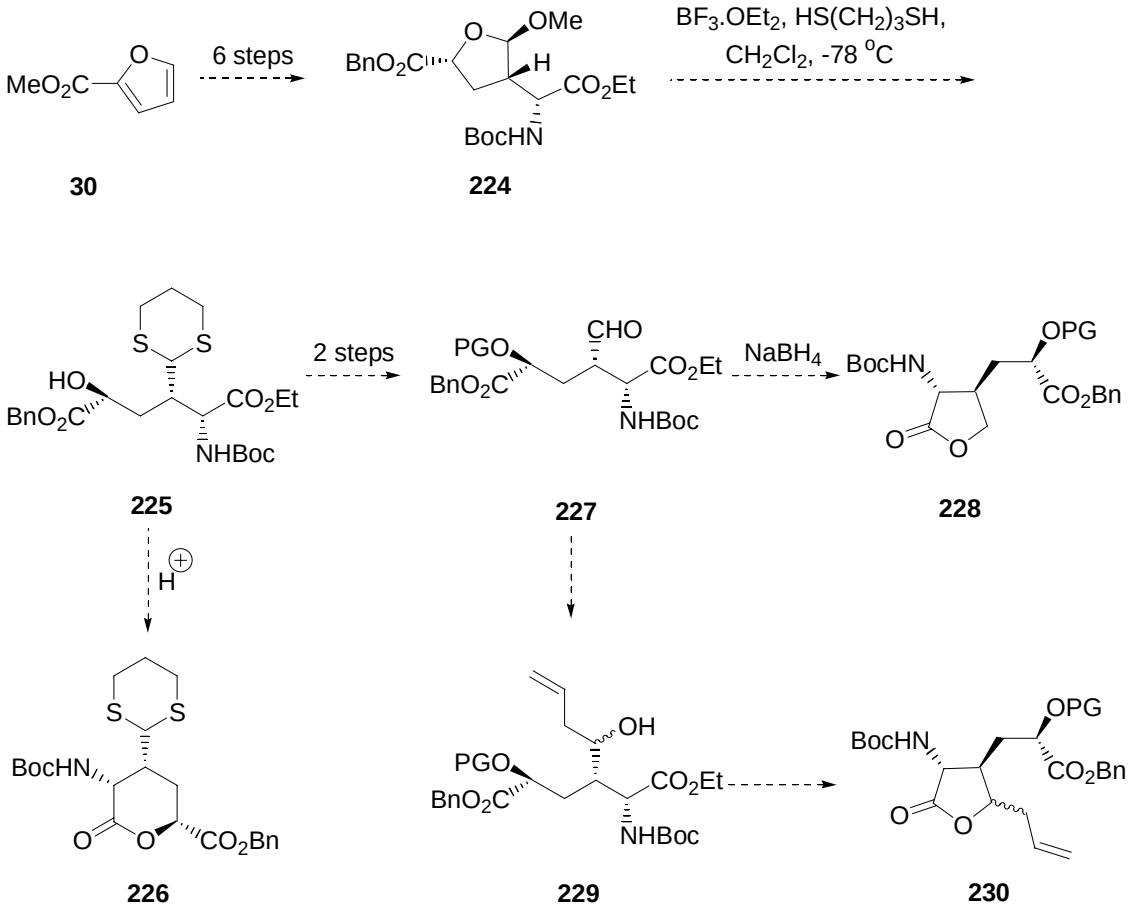


Figure 66 The proposed scheme for synthesis of γ- and δ-lactone amino acids

Alternatively, the benzyl protection of the secondary alcohol in **225** followed by the deprotection of dithio acetal would provide the aldehyde **227**. The $NaBH_4$ reduction of **227** should afford the primary alcohol which is anticipated to cyclize *in situ* furnishing the γ-lactone amino acid **228**. On the other hand, nucleophilic addition on **227** would provide **229** which would further cyclize to form **230**.

3.3 Silica Catalyzed Ring Opening of Cyclopropane Ring in 1,2-cyclopropanecarboxylated Furanoid: A New Entry to Functionalized 2,3,5-Trisubstituted 2,5-Dihydro- And Tetrahydrofuran Derivatives:

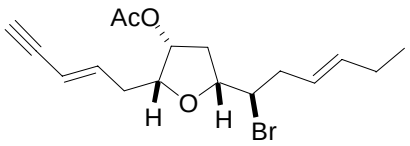
3.3.1 Introduction: The widespread occurrence of 2,5-dihydrofuran units in a number of natural products has led to increased interest in versatile and stereoselective methods for preparing such compounds.[23] 2,5-dihydrofurans represent pivotal structural

elements of a wide variety of different biologically active molecules. For instance, 2,5-dihydrofurans can be found in mycotoxins, polyether antibiotics, spiroketals and even amino acids.[24-28] Examples in nature include 2,5-dihydrofurans **231** and **232**, which are found in hops and similar spirans occur in the *Santalina* species (Fig 67).[29]

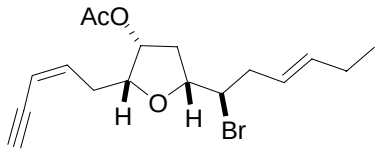
231 **232**

Figure 67 Structures of naturally occurring 2,5-dihydrofurans

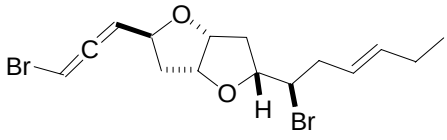
Similarly, saturated five membered ring heterocyclics such as tetrahydrofuran appear in a number of natural products. For example kumausynes (**233** and **234**)[30], kumausallene (**235**)[31] and laurefucin (**236**)[32, 33] (Fig. 68), found in the secondary metabolites of red algae of the genus *Laurencia*, growing in the costal waters around Japan.



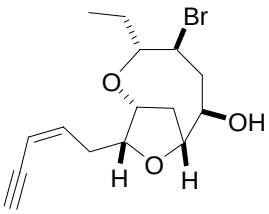
233 *trans*-kumausyne



234 *cis*-kumausyne



235 kumausallene



236 laurefucin

Figure 68 Structures of the natural products containing tetrahydrofuran

Despite the fact that dihydro- and especially tetrahydrofurans are found in the molecular backbone of many natural products, synthesis of this class of compounds with desired substituents in a stereoselective manner remains to be a significant challenge.

For the synthesis of tetrahydrofurans,[34] reduction (catalytic hydrogenation) of furans represents one approach, which has the advantage that a variety of substituents can be introduced in the precursor furans, often regioselectively, *via* electrophilic substitution. However, this approach generally lacks stereoselectivity. Starting from ribose or deoxy-ribose is another common approach, which offers the advantage of inexpensive chiral starting materials but suffers from limited option of stereochemistry and functional groups that can be introduced. A variety of methodologies have also been developed for forming the DHF or THF rings from the acyclic precursors. These include cyclodehydration of 1,4-diols under acid catalysis or Mitsunobu conditions, cycloetherification of 5-hydroxy-olefins (5-*exo* cyclization) or 4-hydroxy olefins (5-*endo*-cyclization) induced by halogens, mercury, selenium or transition metals and atom transfer radical cyclization of acyclic ethers.

3.3.2 Silica Catalyzed Cyclopropane Ring Opening: During the investigation directed towards synthesis of norrisolide, the synthesis of 2,3,5-trisubstituted 2,5-dihydrofuran intermediate **239** in enantiomerically and diastereomerically pure form was developed (Fig. 69).

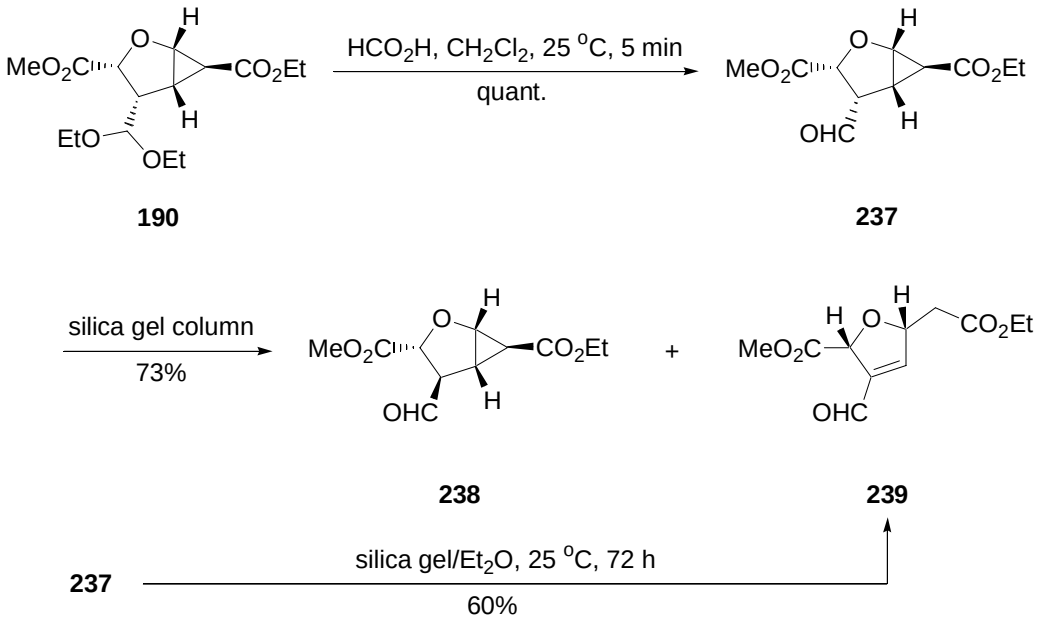


Figure 69 Synthesis of **239**

With the intention of exploring the reactivity of the acetals in **189** and **190**, as well as of the aldehyde **237** resulting after the deprotection of these acetals, attempts to deprotect **189** were carried out. Being sterically hindered and also comprising the

possibility of concomitant cyclopropane rearrangement, **189** did not respond satisfactorily to the various deprotection conditions tried e.g. *p*-TsOH, PPTS, HCl (1.5 M), CAN, amberlyst-15, Montmorillonite-K10, TFA and I_2. Nevertheless, the **190** was deprotected quantitatively when it was subjected to formic acid in dichloromethane for 5 minutes. The structure and absolute configuration of the resulting aldehyde **237** was explicitly established by NOE experiments.

During the purification of **237** by silica gel chromatography the rearrangement of **237** into the mixture of the epimerized aldehyde **238** and the rearranged **239** was observed. Slow and repeated purification gave the unsaturated aldehyde **239** as an exclusive product. Alternatively, the aldehyde **239** was obtained exclusively in good yield, when crude **237** was stirred with silica gel in diethyl ether for 72 hours at 25 ^{o}C.

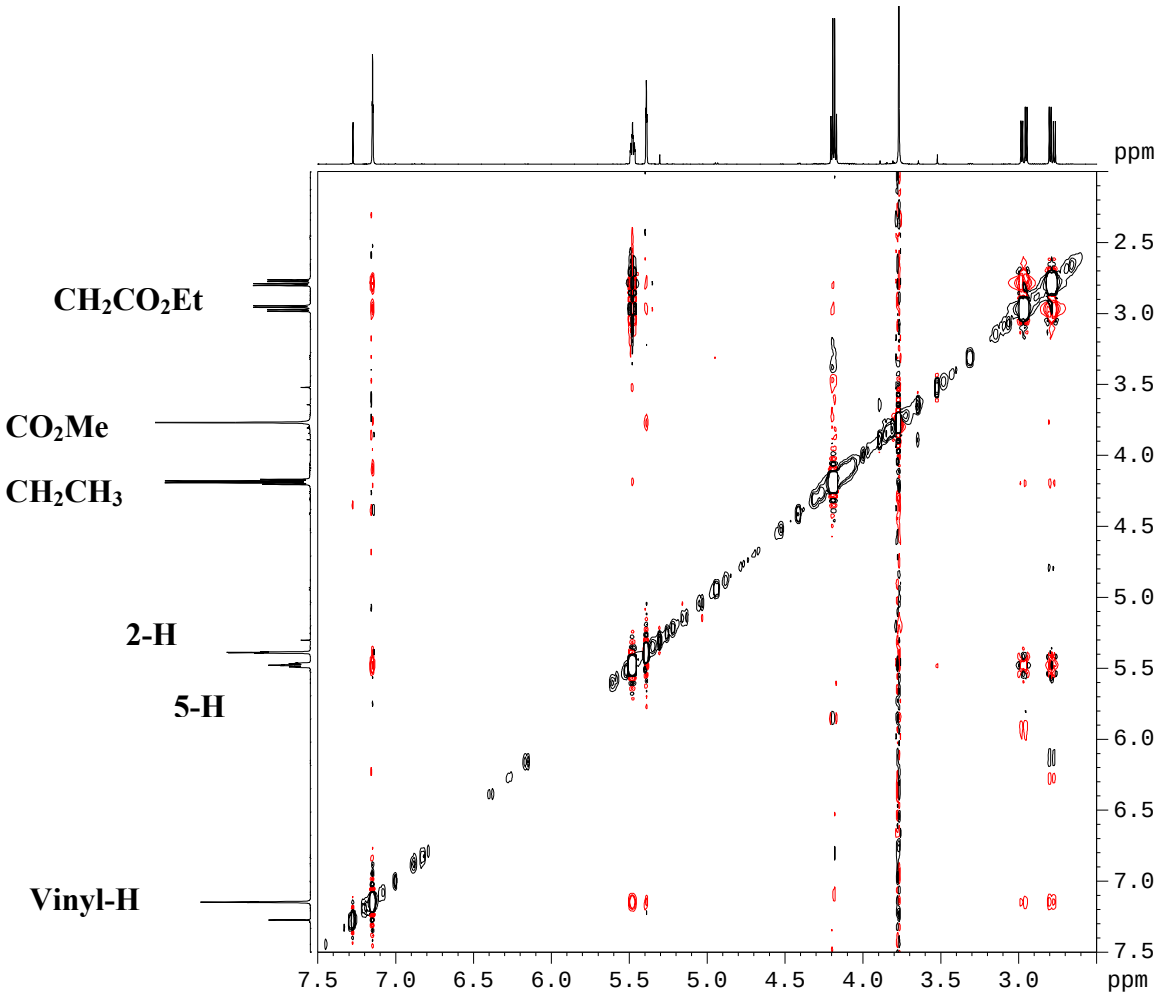


Figure 70 NOE spectrum of aldehyde **239**

In order to establish the structure and stereochemistry of **239**, NOE experiments were carried out (Fig 70). The key NOE signals observed were H-5 to CH_2CO_2Et, H-4 to CHO and CHO to H-2. But the interesting fact observed was that unlike other NOE signals, the protons H-2 and H-5 did not show any NOE signal (Fig 71). On the basis of this observation, one could assume that these protons are *trans* to each other.

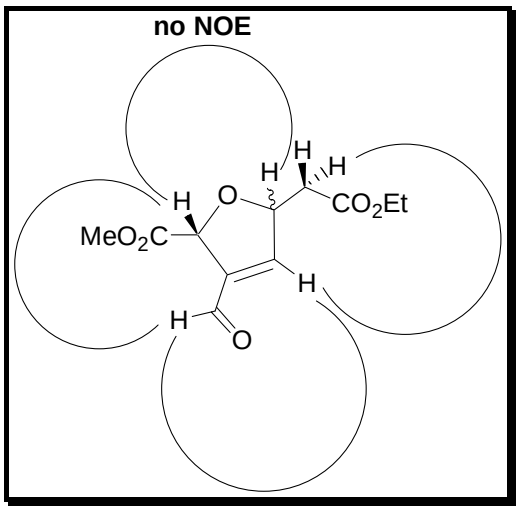


Figure 71 Key NOE signals of aldehyde **239**

The improved force field molecular mechanics calculations (MM2) of the structure were preformed in order to get an estimate for the distance between 2-H and 5-H (Fig. 72).

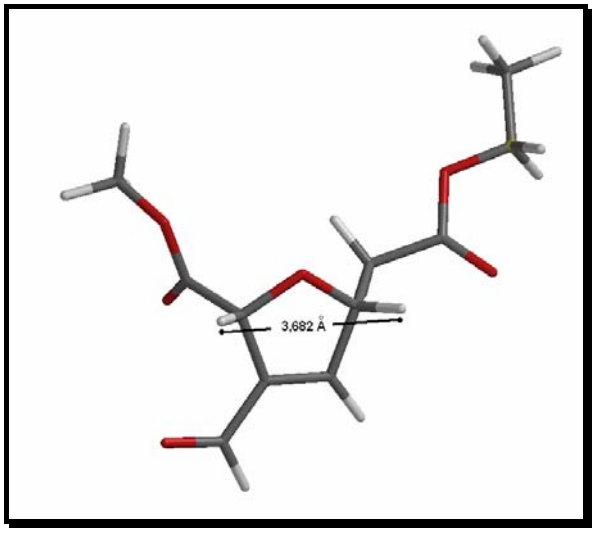
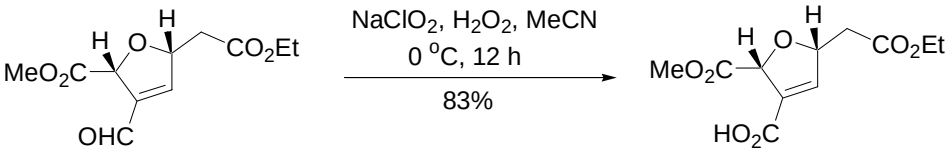


Figure 72 The minimum energy conformation of **239**

These calculations revealed that in case of the minimum energy conformation of **239**, the distance between 2-H and 5-H is 3.682 Å, where as the maximum distance between which the two protons exhibit the NOE signal is 3.2 Å. Due to this, the corresponding NOE signal is not seen.



239 **240**

Figure 73 Oxidation of **239**

To confirm the assignment of the structure in **239**, the aldehyde functionality was oxidized using $NaClO_2$ in a very good yield affording the acid **240** as a white crystalline solid (Fig. 73). After recrystallization of **240**, it was subjected to X-ray crystallography analysis. The ORTEP diagram of **240** is shown in Fig. 74, which confirms that both the hydrogens 2-H and 5-H are on the α-face. This proves that the C-5 center did not epimerize during the silica catalyzed rearrangement of **237**.

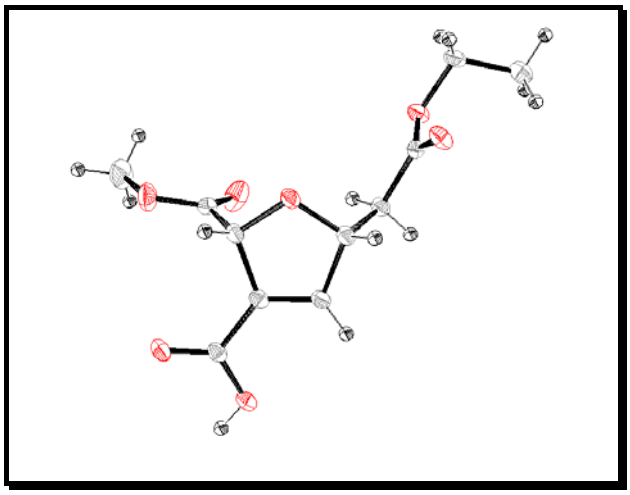


Figure 74 ORTEP diagram of the acid **240**

The combination of all the aforementioned studies helped to propose the mechanism for the silica catalyzed ring opening of cyclopropane ring in **237** (Fig. 75).

Due to the acidity of silica gel the aldehyde present at C3 center of **237** undergoes epimerization forming the β-aldehyde **238**. Under the effect of acid, **238** enolizes to form the intermediate **241**, which then undergoes ring opening *via* **242** to form **239**.

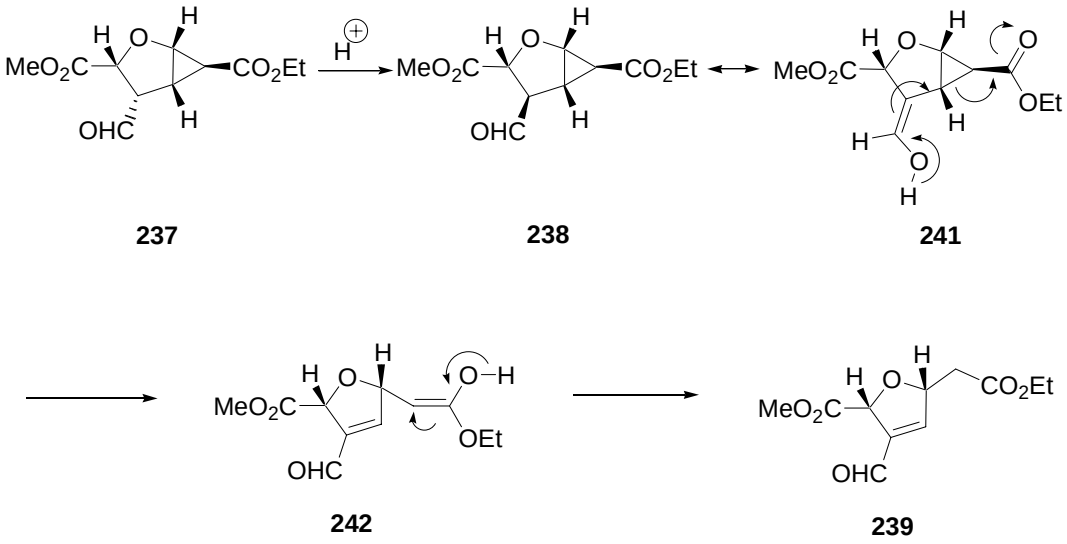


Figure 75 Mechanism of the silica catalyzed cyclopropane ring opening of **237**

The efforts to carry out this rearrangement in the presence of other Lewis acids e.g. *p*-TsOH, amberlyst-15, etc. were unsatisfactory.

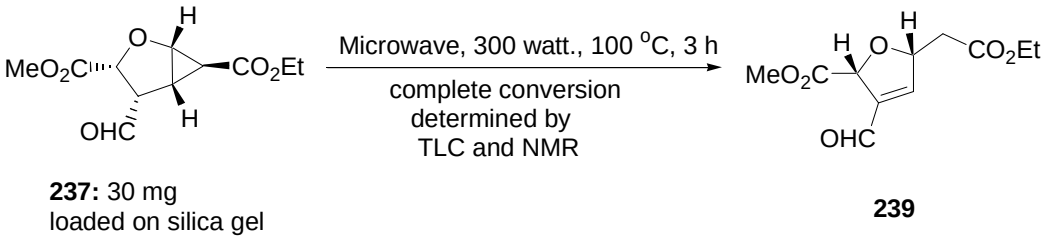


Figure 76 Microwave acceleration of the rearrangement of **237**

To accelerate the reaction rate, it was also carried out under microwave irradiations on silica support. Indeed, the complete conversion to the product was observed on TLC as well as on ^{1}H NMR in 3 hours in quantitative yield (Fig. 76).

3.3.3 Synthesis of Dihydro- And Tetrahydrofuran Derivatives: Attempts to carry out 1,4 addition of azide as well as alkyl nucleophile on the unsaturated aldehyde in **239** with the intention of forming tetrasubstituted tetrahydrofuran derivatives were not

satisfactory. In order to synthesize the corresponding trisubstituted tetrahydrofuran derivative, **239** was hydrogenated to afford **243** as a single diastereomer orienting the aldehyde on β-face (Fig. 77).

239 **243**

Figure 77 Derivatization of **239**

3.3.4 Conclusions and Outlook: In conclusion, a practical synthesis of 2,3,5-trisubstituted 2,5-dihydro and tetrahydrofuran derivatives was developed. This approach is principally based on the silica catalyzed rearrangement of 1,2-cyclopropanecarboxylated furanoid **237** being accessible in the enantiomerically pure form, which undergoes a completely diastereoselective cyclopropane rearrangement. It is conceivable that **239** can be a valuable intermediate for the synthesis of structurally more complex compounds.

3.4 Ozonolysis of 1,2-cyclopropanecarboxylated Dihydrofurans: A Synthetic Strategy Towards Structurally Diverse γ-butyrolactone Scaffolds:

3.4.1 Introduction: γ-Butyrolactones are a very common structural element in organic compounds present in about 10% of all natural products. A wide variety of naturally occurring mono-, di- and trisubstituted monocyclic γ-butyrolactones are known, but they are also found as part of more complex frameworks, especially in bicyclic and tricyclic ring systems. They display a broad biological profile including strong antibiotic, antihelmitic, antifungal, antitumor, antiviral, antiinflammatory and cytostatic properties, which makes them interesting lead structures for new drugs. Consequently, several methods for the stereoselective synthesis of γ-butyrolactone scaffold are continuously evolving.[35]

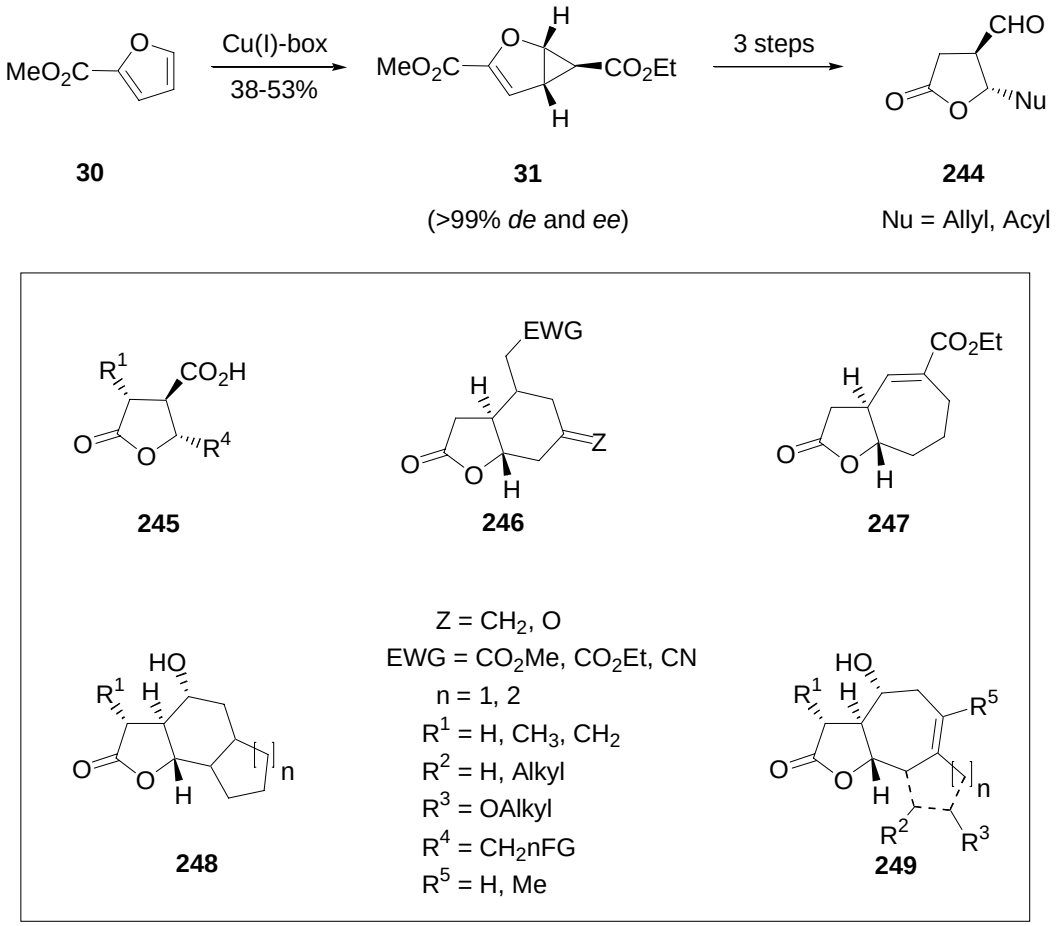


Figure 78 Stereoselective Synthesis of γ-butyrolactones by Reiser et. al.

Recently our group has reported the stereoselective synthesis of anti-disubstituted γ-butyrolactones **244** in either enantiomeric form using the 1,2-cyclopropanecarboxylated dihydrofuran **31** as a starting point. The strategy was predominantly based on the ozonolysis of **31** followed by the addition of allyl nucleophiles on the resulting aldehyde and subsequent lactonization.

In the resulting lactones **244**, the aldehyde functionality was readily transformed by alkenylation, allylation or amination reactions, while the allyl group was used in cross-metathesis (CM) and ring closing metathesis (RCM) or radical cyclization reactions. Thereby, paraconic acids or a variety of bi- (5.6 or 5.7) and tricyclic (5.6.5, 5.6.6, 5.7.5, or 5.7.6) scaffolds, being commonly found in elemanolides, eudesmanolides, xanthanolides or guaianolides, were accessible in only a few steps (Fig. 78).[36-40]

The 1,2-cyclopropanecarboxylated dihydrofurans synthesized in the preceding sections were envisioned as the suitable substrates for the abovementioned ozonolysis strategy. These substrates were expected to form the corresponding γ-butyrolactones with a quaternary center caused by the substituent at C3 center.

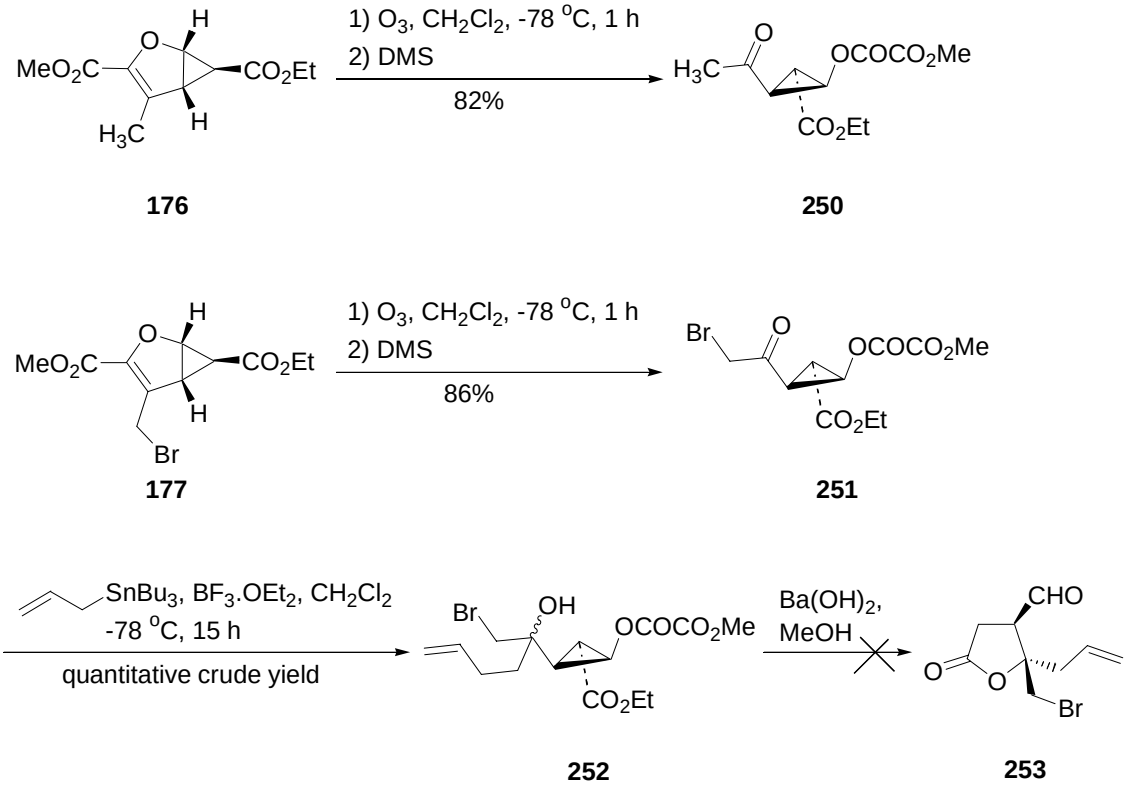


Figure 79 Attempted ozonolysis strategy

3.4.2 Ozonolysis and Lactonization: As expected, the ozonolysis of **176** was quite successful yielding **250** in good yield (Fig. 79). However, various attempts to add a nucleophile on the ketone functionality in **250** failed completely. The possible reason behind this could be the reduced electrophilicity of the ketone functionality because of which the oxalyl ester got cleaved before the nucleophile could add on the ketone in all the attempts.

Consequently, the bromomethyl derivative **251** was chosen as an alternative substrate, which was synthesized by cleaving the double bond in **177** oxidatively *via* ozonolysis. The carbonyl carbon in **251** was anticipated to be more electrophilic due to the –I effect exerted by the bromine atom. Indeed, the allyl nucleophile could be added without difficulty on the bromoketone **251** using allyl-tri-butyl tin in the presence of $BF_3.OEt_2$. The product was obtained as a diastereomeric mixture of the corresponding

alcohol **252**. However, lactonization of these alcohols under the effect of base was not successful probably due to the side reactions caused by the halohydrin functionality present in **252**.

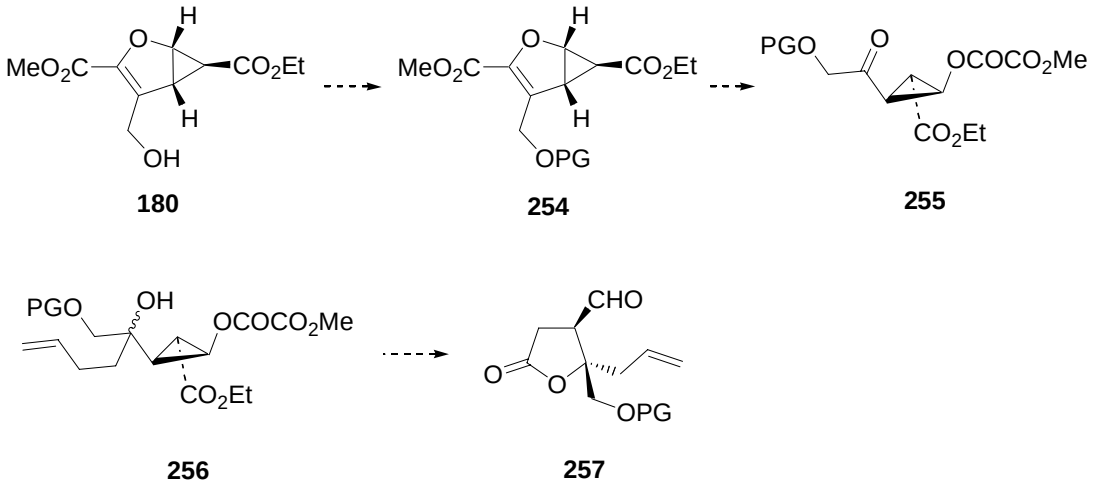


Figure 80 Plan for the synthesis of γ-butyrolactone with a quaternary center

3.4.3 Conclusions and Outlook: In conclusion, the attempt towards development of a new asymmetric strategy to γ-butyrolactones containing a quaternary center was carried out. The resulting lactones were envisioned as versatile building blocks for the natural product syntheses. However, due the reasons discussed above the result was not fairly satisfying.

Nevertheless, an alternative to achieve this synthesis could be as shown in Fig. 80. Protection of the primary alcohol in **180** with appropriate protecting group will result in the ether **254** which might serve as a better starting point for the ozonolysis, nucleophilic addition and lactonization sequence to yield the desired product **257**.

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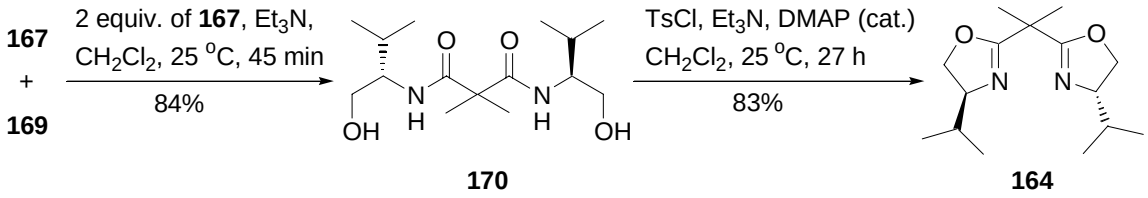
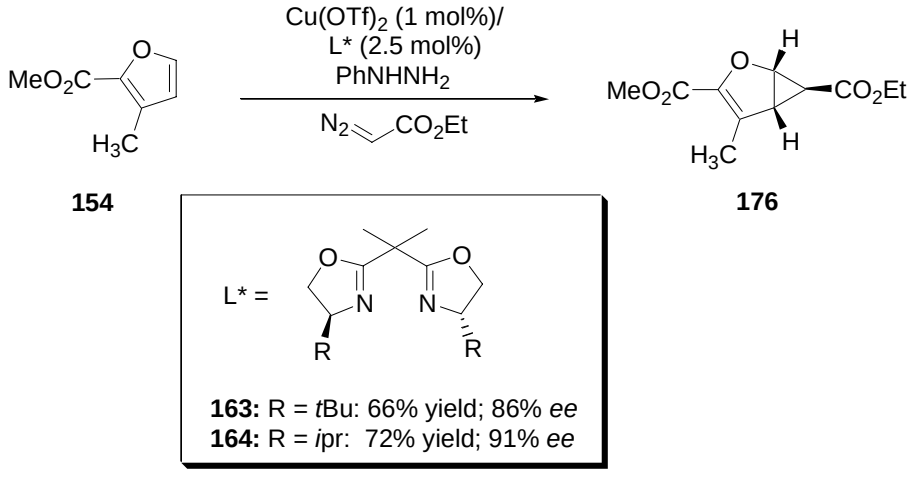
4 Summary:

The overall goal of the present thesis was the further development of copper-(I)-bisoxazoline catalyzed cyclopropanation of furans as a key step towards furanoids as found in a range of marine natural products.

In this context, an improved procedure for the synthesis of bis(4-isopropyloxazoline) **164** was developed. This procedure resembles the previously reported protocols for **163.** The main differences can be found in the workup conditions, which accommodate the quite different solubility and crystallization properties of intermediates and final ligand **164**.

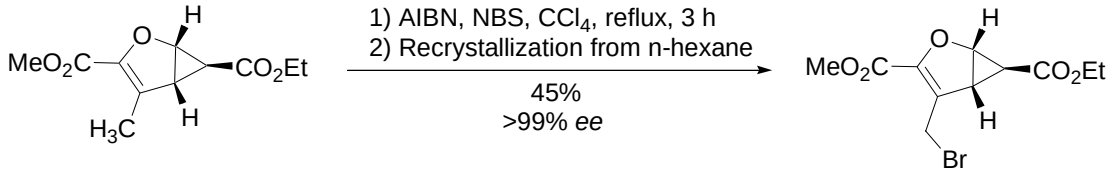


The asymmetric cyclopropanation of the substituted furan derivative **154** was developed with excellent regio-, diastereo- and enantioselectivity.



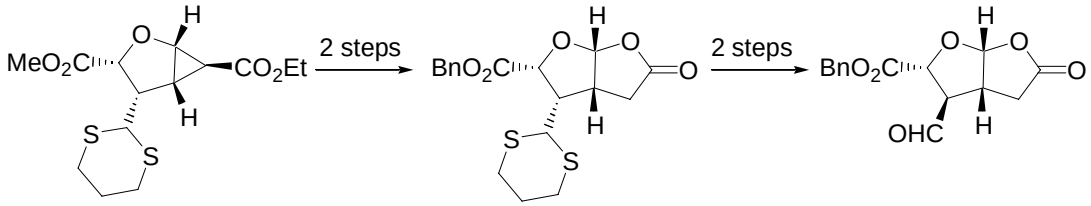
Conversion of the 1,2-cyclopropanecarboxylated dihydrofuran **176** to **177** allowed to enhance the enantiomeric excess to >99% *ee*. Moreover, the allylic bromide

is a versatile functionality, which could be further manipulated towards the synthesis of various 1,2-cyclopropanecarboxylated dihydrofurans (e.g. **191**).

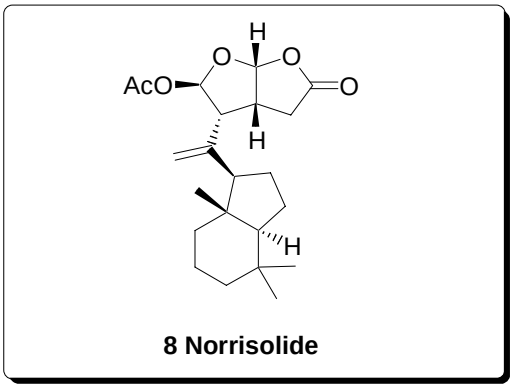


176 **177**

The stereoselective synthesis of *cis*-fused furo[2,3-*b*]furans was achieved as an application of these derivatives, which gave intermediates **193**-**197**, relevant for the synthesis of norrisolide **8** as well as various spongiane diterpenoids containing distinctive furo[2,3-*b*]furan framework.



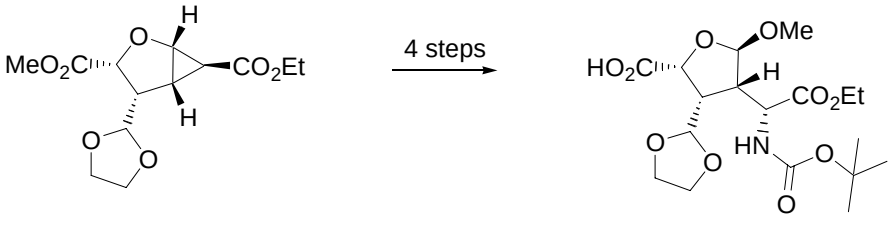
191 **193** **197**



8 Norrisolide

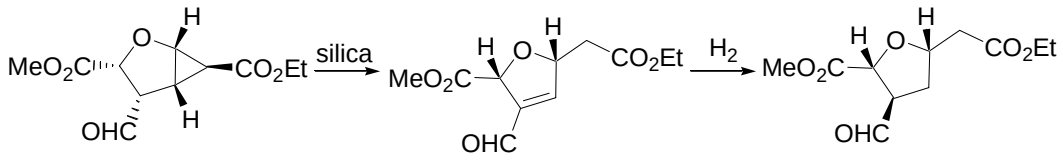
The strategy followed is predominantly based on acid-mediated one-pot ring expansion of the corresponding cyclopropanes. The main advantage of the strategy is the orientation of the functional group in such a way that the side-chains could be introduced on concave as well as convex face of the bicycle.

NBS-promoted ring opening of 1, 2 cyclopropanecarboxylated furanoid **189** was another application which provided the stereocontrolled 4 steps access to unnatural THF-containing α-amino acid **224** with multiple stereocenters.



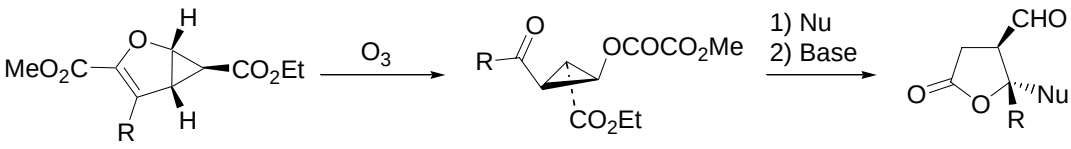
189 **224**

Silica catalyzed ring opening of 1,2-cyclopropanecarboxylated furanoid **237** yielding the enantiomerically pure dihydrofuran derivative **239** was further studied in the course of these investigations. This intermediate can be used in the synthesis of substituted tetrahydrofurans (e.g. **243**), being found in many natural products.



237 **239** **243**

The ozonolysis, nucleophilic addition and base catalyzed lactonization sequence in order to build up γ-butyrolactones of the type **258** containing quaternary center was not successful due to various reasons as stated before.



176: R = CH_3,
177: R = CH_2Br **251** **258**

In conclusion, the stereoselective synthesis of 1,2-cyclopropanecarboxylated furanoids and their applications in the preparation of marine natural products and unnatural amino acids was carried out.

5 Experimental part

5.1 Instruments and general techniques:

^{1}H NMR: Bruker ARX 400 (400 MHz), Bruker Avance 300 (300 MHz). The chemical shifts are reported in δ (ppm) relative to chloroform ($CDCl_3$, 7.26 ppm), dimethylsulfoxide (DMSO-d6, 2.50 ppm), methanol (CD_3OD, 3.31 ppm) and tetramethylsilane (TMS, 0 ppm). The spectra were analyzed by first order, the coupling constants are reported in Hertz (Hz). Characterization of signals: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet, dd = double of a doublet, dt = double of a triplet, dq = double of a quartet, ddd = double of a doublet of a doublet, dddd = doublet of a doublet of a doublet of a doublet, Integration is determined as the relative number of atoms. Diastereomeric ratios were determined by comparing the integrals of corresponding protons in the ^{1}H NMR spectra.

^{13}C NMR: Bruker ARX 400 (100.6 MHz), Bruker Avance 300 (75.5 MHz). The chemical shifts are reported in δ (ppm) relative to chloroform ($CDCl_3$, 77.16 ppm), dimethylsulfoxide (DMSO-d6, 36.52 ppm), methanol (CD_3OD, 49.0 ppm) and tetramethylsilane (TMS, 0 ppm). ^{13}C NMR resonance assignment were aided by the use of the DEPT 135 (DEPT = distortionless enhancement by polarization transfer) technique to determine the number of hydrogens attached to each carbon atom and is declared as: + = primary or tertiary (positive DEPT signal intensity), – = secondary (negative DEPT signal) and $_{quat}$ = quaternary (no DEPT signal intensity) carbon atoms. In some cases DEPT 90 spectra were recorded to distinguish between primary and tertiary carbon atoms. This is marked with the CH or CH_3 notation at the corresponding signal.

2D-NMR: Bruker DRX-500 spectrometer operating at a basic ^{1}H frequency of 500 MHz at 298 ^{o}K. The spectra were recorded at 280 ^{o}K, using the solvent line (CD_3OH, 1 H δ 3.31) for referencing. DQF-COSY, 80 ms-TOCSY and 500 ms-ROESY standard experiments were performed with suppression of the methanol OH line by low-power presaturation.

IR-spectra: were recorded with an ATI Mattson Genesis Series FT-IR or a Bio-Rad Excalibur series FT-IR.

MS-spectra: masspectroscopy department of the University of Regensburg, Varian Mat 311 A.

Elemental analysis: microanalytical department of the University of Regensburg.

Melting points: (**m.p.**) were determined with a Buchi SMP 20 and are uncorrected.

Thin layer chromatography: (TLC) was performed on alumina plates coated with silica gel (Merck silica gel 60 F 254, layer thickness 0.2 mm). Visualization was accomplished by UV light (wavelenght λ = 254 nm) and a vanillin/sulphuric acid solution or Mostain.

Optical rotations: were measured on a Perkin-Elmer-Polarimeter 241 with sodium lamp at 589 nm in the specified solvent. The optical rotation was calculated with the following formula:

$$[\alpha]_D^{20} = ([\alpha]_{exp} \text{ x } 100)/ (c \text{ x } d)$$

20̥ = temperature (°C)

$[\alpha]_{exp}$ = measured value

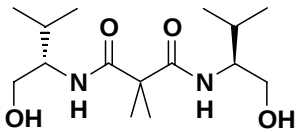
c = concentration (g/100 ml)

d = length of the cuvette

Column chromatography: was performed on silica gel Geduran SI 60 (70-230 mesh) purchased from Merck and flash chromatography on flash-silica gel 60 (230-400 mesh ASTM) purchased from Merck. Solvents were purified according to standard laboratory methods. THF, diethyl ether and toluene were distilled over sodium/benzophenone before use. Dichloromethane, DMSO and DMF were distilled over calcium hydride and acetonitrile over P_2O_5. Methanol was refluxed 2 h over magnesia, distilled and stored under nitrogen over 4 Å molecular sieves. The hexanes used had a boiling point of 40-60 °C. All solvents were distilled before use. Other chemicals were purchased from commercial suppliers and used as received.

All reactions with oxygen or moisture sensitive reactants were performed under nitrogen atmosphere.

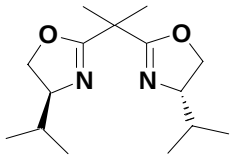
5.2 Synthesis of compounds



(–)-(*S*,*S*)-N,N'-Bis(1-hydroxymethyl-2-methylpropyl)-2,2-dimethyl-malonamide (**170**): An oven-dried 250 mL, 3-necked round-bottom flask equipped with a stirring bar and two 50 mL pressure-equalizing addition funnels connected to a mineral oil bubbler was purged with nitrogen and charged with (*L*)-valinol **167** (5.13 g, 0.050 moles). The flask was immersed in an ice bath at 0 °C and triethylamine (17.4 mL, 0.124 moles) was added dropwise *via* the first addition funnel. 2,2-Dimethylpropanedioyl dichloride **169** (3.3 mL, 0.25 moles) in abs. dichloromethane (25 mL) was then added dropwise over 25 minutes *via* the second addition funnel. The internal temperature increased from 0 °C to 10 °C during the addition. Subsequently, the ice bath was removed and the reaction mixture was allowed to warm to room temperature. Stirring was continued for 45 min, resulting in a colorless precipitate that was dissolved by addition of abs. dichloromethane (120 mL). After addition of aqueous HCl (1N, 30 mL), the aqueous layer was separated and extracted with dichloromethane (3 x 15 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (30 mL) and brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford crude **170** as a pale yellow solid. Recrystallization of the crude product from ethyl acetate (40 mL) yielded **170** (4.30 g, 14.2 mmol, 57%) as white crystals. The mother liquor was concentrated and the residue recrystallized from ethyl acetate (10 mL) to yield a second crop of **170** (1.60 g, 5.27 mmol, 21%); the process was repeated to yield a third crop of **170** (0.440 g, 1.45 mmol, 6%, total yield: 6.40 g, 21.1 mmol, 84%).

$\mathbf{R_f}$ = 0.25 (SiO_2, EtOAc/MeOH, 95:5); **m.p.** = 98−99 °C; $[\alpha]_D^{20}$ = −6.0 (c = 0.50, CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 0.92 (d, *J* = 6.8 Hz, 6 H), 0.96 (d, *J* = 6.8 Hz, 6 H), 1.50 (s, 6 H), 1.82 (oct, *J* = 6.8 Hz, 2 H), 2.66 (bs, 2 H), 3.52 (m, 2 H), 3.69−3.86 (m, 4 H), 6.41 (d, *J* = 8.6 Hz, 2 H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 18.8, 19.6, 23.7, 29.1, 50.2, 57.1, 63.5, 174.5; **IR (KBr)**: $\tilde{\nu}$ = 3349, 3380, 2962, 2886, 1658, 1530, 1049, 1033 cm^{-1}; **MS (ES)** *m/z* (%) = 405.2 (20), 325.2 ($[M+Na]^+$, 100), 285.2 (10); **HRMS (ES)** calcd. for $C_{15}H_{30}N_2O_4Na$ 325.2103, found 325.2084; **elemental**

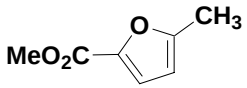
analysis calcd (%) for $C_{15}H_{30}N_2O_4$ (302.41): C 59.57, H 10.00, N 9.26; found: C 59.01, H 10.12, N 9.11.



(–)-(*S*,*S*)-Bis(4-isopropyloxazoline) (164): An oven-dried 500 mL, 2-necked round-bottom flask equipped with a stirring bar and a 50 mL, pressure-equalizing addition funnel connected to a mineral oil bubbler was purged with nitrogen and charged with (–)-(*S*,*S*)-N,N'-bis-(1-hydroxymethyl-2-methylpropyl)-2,2-dimethylmalonamide **170** (5.5 g, 18.4 mmol), 4-dimethylaminopyridine (0.204 g, 1.67 mmol) and abs. dichloromethane (130 mL). The flask was immersed in a water bath at room temperature and triethylamine (10.25 mL, 73.4 mmol) was added slowly *via* syringe. Subsequently, tosyl chloride (7.10 g, 37 mmol, 2.0 equiv.), dissolved in abs. dichloromethane (15 mL), was added dropwise over 30 minutes *via* the addition funnel. After completion of the addition, the funnel was rinsed with abs. dichloromethane (2.5 mL) and the reaction mixture was stirred for an additional 27 hours at room temperature. The reaction mixture was treated with saturated NH_4Cl solution (70 mL) followed by water (40 mL). The aqueous layer was separated and extracted with dichloromethane (3 x 55 mL), and the combined organic layers were dried over $MgSO_4$. The organic solution was filtered and concentrated under vacuum. The oily residue was treated with hot pentane (40 mL), stirred for 5 min and the supernatant liquid was decanted. This procedure was repeated three times and the collected pentane layers were combined and concentrated under vacuum to yield **164** (4.05 g, 15.2 mmol, 83%) as colorless oil.

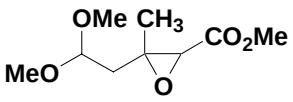
$\mathbf{R_f}$ = 0.25 (SiO_2, CH_2Cl_2/MeOH, 19:1); $[\alpha]_D^{20}$ = −107.5 (c 1.0, CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 0.85 (d, *J* = 6.8 Hz, 6 H), 0.91 (d, *J* = 6.8 Hz, 6 H), 1.51 (s, 6 H), 1.88−1.73 (m, 2 H), 4.06−3.93 (m, 4 H), 4.26−4.15 (m, 2 H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 17.3, 18.5, 24.4, 32.2, 38.5, 69.9, 71.5, 168.7; **IR (film)** $\tilde{\nu}$ = 3308, 2960, 2874, 1746, 1525, 1353, 1303, 1037, 1017, 895, 815, 714 cm^{-1}; **MS (EI)** *m/z (%)* 266 (M^+, 15), 265 (30), 223 (100), 195 (30), 155 (65), 137 (97), 110 (50); **HRMS (EI)** calcd

for $C_{15}H_{26}N_2O_2$ 266.1994, found 266.1987; **elemental analysis calcd (%)** for $C_{15}H_{26}N_2O_2$ (266.38): C 67.63, H 9.84, N 10.52; found C 66.65, H 9.81, N 10.08.



5-Methyl-furan-2-carboxylic acid methyl ester (171): A solution of $NaClO_2$ (2.715 g, 30 mmol, 3 equiv.) in water (1 mL) was added dropwise to a stirred mixture of 5-methyl-furfural **173** (1.1 g, 10 mmol, 1 equiv.) in acetonitrile (20 mL), KH_2PO_4 (1.293 g, 9.5 mmol, 0.95 equiv.) in water (10 mL) and of 30% H_2O_2 (1.54 mL, 15 mmol, 1.5 equiv.), keeping the temperature at 0 ^oC. Oxygen evolved from the solution until the end of the reaction (12 hours) with a bubbler connected to the apparatus. A small amount of Na_2SO_3 (1.89 g, 15 mmol, 1.5 equiv.) was added to destroy the unreacted HOCl and H_2O_2. After acidification with 6N HCl, the mixture was extracted with dichloromethane (3 × 30 mL). The combined organic layers were washed with water (1 × 10 mL), dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The crude acid was dissolved in methanol (10 mL) and then Conc. H_2SO_4 (0.2 mL) was added to it. The solution was refluxed for 24 hours. Methanol was removed under *vacuo* and the residue was taken into dichloromethane (10 mL). This was washed with saturated $NaHCO_3$ (1 × 5 mL), brine (1 × 5 mL) and dried over anhydrous $MgSO_4$ and filtered. The dichloromethane was removed under *vacuo*. The residue was purified by column chromatography on silica (hexanes/ethyl acetate 9:1) to provide **171** as colorless oil (0.84 g, 60%).

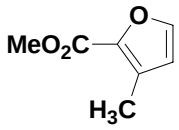
$\mathbf{R_f}$ = 0.25 (SiO_2, hexanes/ethyl acetate, 9:1); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 2.37 (s, 3 H, CH_3), 3.86 (s, 3 H, CO_2Me), 6.10 (dd, *J* = 0.89, 3.36 Hz, 1 H, 4-H), 7.08 (dd, *J* = 3.36 Hz, 1 H, 3-H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 14.1 (+, CH_3), 51.9 (+, CO_2Me), 108.6 (+, C-4) 119.6 (+, C-3), 143.1 (C_{quat}, C-2) 157.3 (C_{quat}, C-5), 159.3 (C_{quat}, CO_2Me).



3-(2,2-dimethoxy-ethyl)-3-methyl-oxirane-2-carboxylic acid methyl ester (175): A 2-L. three-necked flask was equipped with a sealed centrifugal stirrer, a thermometer

inserted through an adapter with a side arm connected to a source of dry nitrogen, and a 250-mL Erlenmeyer addition flask. The apparatus was dried with a free flame in a slow stream of nitrogen; from this point the reaction was conducted in an atmosphere of nitrogen. A mixture of 4,4-dimethoxy-2-butanone **174** (94.373 g, 0.714 moles, 1 equiv.), methyl chloroacetate (124 g, 1.143 moles, 1.6 equiv.), and 570 mL of abs. ether was placed in the reaction flask, then sodium methoxide (61.719 g, 1.143 moles, 1.6 equiv.) was placed in the addition flask. The solution was cooled in an ice-salt bath to –10 ^{o}C, and then sodium methoxide was added gradually at a rate such that a temperature below –5 ^{o}C could be maintained (about 2 hours). The mixture was stirred for an additional 2 hours and then allowed to warm to room temperature. It was then stirred at the same temperature for 48 hours. It was cooled again to 0 ^{o}C and made slightly acidic by the addition of 8 mL of glacial acetic acid in 120 mL of water. The ether was decanted and the residual slurry was extracted with ether (3 × 100 mL). The combined ether solutions were washed with 50 mL of sat. NaCl solution to which was added 1 g portions of $NaHCO_3$ until the washings were no longer acidic. Finally ether layer was washed with sat. NaCl solution and then dried over anhydrous $MgSO_4$. The ether was removed in *vacuo*. The residual glycidic ester was distilled through a 15-cm vigreux column to yield (148.85 g, 97%) of colorless oil as the product **175**.

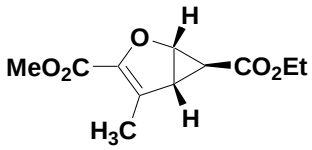
b.p. = 113-122 ^{o}C/8 mm; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.36 (d, *J* = 15.4 Hz, 3 H), 1.95 (m, 2 H), 3.24 (d, *J* = 8.5Hz, 3 H), 3.27(d, *J* = 7.96 Hz, 3 H), 3.72 (d, *J* = 4.39 Hz, 3 H), 3.39 (s, 1 H), 4.45 (m, 1 H).



3-Methyl-furan-2-carboxylic acid methyl ester (154): **175** (148.85 g, 0.73 moles, 1 equiv.) was taken in a flask which was connected to a distillation condenser. Toluene-4-sulfonic acid monohydrate (2.773 g, 0.015 moles, 2.0 mol%) was added to it. The mixture was then heated. When the liquid temperature reached 130 ^{o}C, MeOH began to distill. The heating was continued until the distillation of MeOH essentially ceased. After the heating bath had been allowed to cool, the product was distilled at reduced

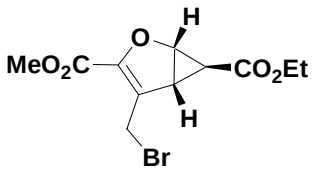
pressure (**b.p.** = 72-78 °C/8mm). The crude product **154** was recrystallized in EtOH to yield a white crystalline solid (85.1 g., 88%).

m.p. = 36.5-37 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 2.35 (s, 3 H, CH_3), 3.89 (s, 3 H, CO_2Me), 6.35 (d, *J* = 1.65 Hz, 1 H, 4-H), 7.43 (d, *J* = 1.65 Hz, 1 H, 5-H); **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ = 11.6 (+, CH_3), 51.7 (+, CO_2Me), 115.2 (+, C-4), 131.3 (C_{quat}, C-3), 140.3 (C_{quat}, C-2), 145.0 (+, C-5), 160.1 (C_{quat}, CO_2Me); **MS (EI, 70 eV)**: *m*/*z* (%) = 140.0 (65) [M^+], 125.0 (11) [$M^+ - CH_3$], 109.0 (100) [$M^+ - OCH_3$].



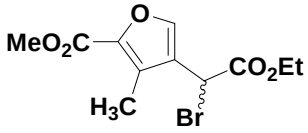
(**1*S*,5*R*,6*S*)-(–)-4-Methyl-2-oxa-bicyclo[3.1.0]hex-3-ene-3,6-dicarboxylic acid 6-ethyl ester 3-methyl ester (176):** Phenylhydrazine (0.34 mL, 3.25 mmol, 1.2 mol%) was added under nitrogen at 0 °C to a solution of **154** (40.00 g, 0.285 moles, 1.0 equiv.), $Cu(OTf)_2$ (1.032 g, 2.85 mmol, 1 mol%) and (–)-**164** (1.901 g, 7.14 mmol, 2.5 mol%) in CH_2Cl_2 (20 mL). After 20 min, a solution of ethyl diazoacetate (132.30 g, 1.142 moles, 4 equiv.) in CH_2Cl_2 (800 mL) was added through a dropping funnel over 10 days. The reaction mixture was filtered through a short pad of basic alumina and solvent was removed in *vacuo*. The residue was purified by column chromatography on silica (hexanes/ethyl acetate 19:1) to provide **176** as colorless oil (46.79 g, 72%, 91% *ee*).

R_f = (SiO_2, hexanes/ethyl acetate 4:1) = 0.24; $[\alpha]_D^{20}$ = –215.2 (c 1.0, CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.18 (dd, *J* = 2.64, 1.06 Hz, 1 H, 6-H), 1.27 (t, *J* = 7.15 Hz, 3 H, CH_2CH_3), 2.21 (d, *J* = 0.58 Hz, 3 H, 4-CH_3), 2.79 (ddq, *J* = 0.58, 5.32, 2.64 Hz, 1 H, 5-H), 3.81 (s, 3 H, CO_2Me), 4.15 (m, 2 H, CH_2CH_3), 4.82 (dd, *J* = 5.32, 1.06 Hz, 1 H, 1-H); **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ = 12.8 (+, 4-CH_3), 14.4 (+, CH_2CH_3), 21.8 (+, C-6), 37.2 (+, C-5), 52.0 (+, CO_2Me), 61.2 (–, CH_2CH_3), 65.4 (+, C-1), 130.0 (C_{quat}, C-4), 141.5 (C_{quat}, C-3), 160.7 (C_{quat}, CO_2Me), 172.1 (C_{quat}, CO_2Et); **IR (film)**: $\tilde{\nu}$ = 2955, 1715, 1639, 1441, 1284, 1162, 1047, 998, 833, 776 cm^{-1}; **MS (EI, 70 eV)**: *m*/*z* (%) = 226.0 (13) [M^+], 181.0 (7) [$M^+ - OCH_2CH_3$], 153 (100) [$M^+ - CO_2CH_2CH_3$], 139 (26), 111 (21), 93 (7); **MS (HR-EI, 70 eV)**: 226.0840 ($C_{11}H_{14}O_5$: calc. 226.0841 [M^+]).



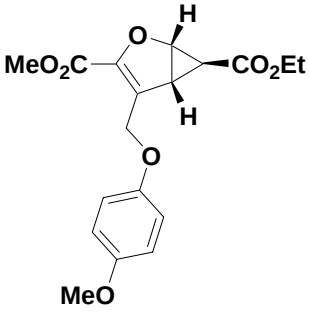
(1*S*,5*R*,6*S*)-(–)-4-Bromomethyl-2-oxa-bicyclo[3.1.0]hex-3-ene-3,6-dicarboxylic acid 6-ethyl ester 3-methyl ester (177): 176 (20.00 g, 88.4 mmol, 1 equiv.), AIBN (1.452 g, 8.8 mmol, 10 mol%) and NBS (16.52 g, 92.8 mmol, 1.05 equiv.) were refluxed in CCl_4 (400 mL) for 3 hours (TLC control). The drop of molecular bromine was used to initiate the reaction. The solution was cooled to 0 °C overnight and filtered. The organic layer was then washed with water (3 × 100 mL), dried over anhydrous $MgSO_4$ and filtered. The CCl_4 was removed in *vacuo*. The residue was purified by column chromatography on silica (hexanes/ethyl acetate 19:1) to provide **177** as colorless oil (16.60 g, 62%). The product was then recrystallized in n-hexane to obtain a white crystalline solid (12.14 g, 45%, >99% *ee*).

R_f = (SiO_2, hexanes/ethyl acetate 4:1) = 0.22; **m.p.** = 42 °C; $[\alpha]_D^{20}$ = –75.1 (c 1.0, CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.28 (dd, *J* = 2.73, 1.08 Hz, 1 H, 6-H), 1.28 (t, *J* = 7.13 Hz, 3 H, CH_2CH_3), 2.99 (dd, *J* = 5.44, 2.73 Hz, 1 H, 5-H), 3.86 (s, 3 H, CO_2Me), 4.17 (dq, *J* = 7.13, 1.53 Hz, 2 H, CH_2CH_3), 4.55 (d, *J* = 10.36 Hz, 1 H, CH_2Br), 4.68 (d, *J* = 10.36 Hz, 1 H, CH_2Br), 4.89 (dd, *J* = 5.44, 1.08 Hz, 1 H, 1-H); **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ = 14.3 (+, CH_2CH_3), 21.9 (+, C-6), 25.0 (–, CH_2Br), 34.5 (+, C-5), 53.0 (+, CO_2Me), 61.4 (–, CH_2CH_3), 65.8 (+, C-1), 128.1 (C_{quat}, C-4), 143.4 (C_{quat}, C-3), 159.8 (C_{quat}, CO_2Me), 171.5 (C_{quat}, CO_2Et); **IR (KBr)**: $\tilde{\nu}$ = 2989, 2360, 1712, 1628, 1439, 1385, 1358,1300, 1210, 1186, 1124, 1070, 1029, 995,927, 899, 826,784, 742 cm^{-1}; **MS (CI, NH_3)**: *m*/*z* (%) = 323.9 (100)) [$M^+ + NH_4^+$], 322 (96) [$M^+ + NH_4^+$], 306.9 (8) [MH^+], 305.0 (7) [MH^+], 244.1 (4) [$M^+ – CO_2Me$], 242.1 (4) [$M^+ – CO_2Me$], 225.1 (10) [M^+ – Br]; **elemental analysis** calcd (%) for $C_{11}H_{13}BrO_5$ (305.12): C 43.30, H 4.29, Br 26.19, O 26.22; found C 43.31, H 4.32.



4-(Bromo-ethoxy-carbonyl-methyl)-3-methyl-furan-2-carboxylic acid methyl ester (178): After the column chromatography, of the residue of the reaction for **177**, the white crystalline solid was obtained as a side product (5.395 g, 20%).

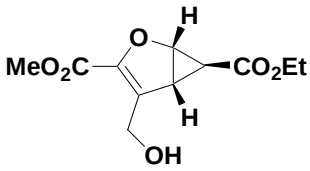
R_f = (SiO_2, hexanes/ethyl acetate 4:1) = 0.23; **m.p.** = 42 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.32 (t, *J* = 7.14 Hz, 3 H, CH_2CH_3), 2.33 (s, 3 H, 3-CH_3), 3.89 (s, 3 H, CO_2Me), 4.30 (dq, *J* = 7.14, 2.42 Hz, 2 H, CH_2CH_3), 5.41 (s, 1 H, $CHBrCO_2Et$), 6.65 (s, 1 H, Ar-H); **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ = 11.7 (+, $C(CH_3)$), 14.0 (+, CH_2CH_3), 36.8 (+, $CHBrCO_2Et$), 51.9 (+, CO_2Me), 63.1 (–, CH_2CH_3), 116.0 (+, C-5), 132.4 (C_{quat}, C-4), 140.8 (C_{quat}, C-3), 150.2 (C_{quat}, C-2), 159.7 (C_{quat}, CO_2Me), 166.1 ($C_{quat,}$ CO_2Et); **IR (KBr)**: $\tilde{\nu}$ = 3470, 3400, 2959, 2579, 2509, 2241, 1895, 1749, 1611, 1539, 1440, 1380, 1096, 949, 733 cm^{-1}; **MS (EI, 70 eV)**: *m*/*z* (%) = 304.1 (3) [M^+], 225.0 (100), 179.9 (12), 153.0 (35), 93.0 (14), 64.9 (11), **MS (HR-EI, 70 eV)**: 303.9947 ($C_{11}H_{13}BrO_5$: calc. 303.9946 [M^+]). **elemental analysis** calcd (%) for $C_{11}H_{13}BrO_5$ (305.12): C 43.30, H 4.29, Br 26.19, O 26.22; found C 43.31, H 4.32.



(1*S*,5*R*,6*S*)-(−)-4-(4-Methoxy-phenoxymethyl)-2-oxa-bicyclo[3.1.0]hex-3-ene-3,6-dicarboxylic acid 6-ethyl ester 3-methyl ester (179): A mixture of 4-Methoxyphenol (3.753 g, 30.2 mmol, 1.025 equiv.) and anhydrous K_2CO_3 (5.096 g, 36.9 mmol, 1.25 equiv.) in acetone (100 mL) was stirred at 0 °C for 15 min. To this mixture was added a solution of **177** (9.0 g, 29.5 mmol, 1 equiv.) in acetone (50 mL) dropwise over a period of 30 min., reaction mixture being maintained at 0 °C during the addition. After the

addition reaction mixture was slowly allowed to come to room temperature, stirred for 24 hours. The inorgainc salts were then filtered off and acetone was distilled off. The residue was taken up in ether (80 mL). The ether extract was washed with 2N NaOH (2 × 30 mL), water (2 × 30 mL), dried over anhydrous $MgSO_4$ and filtered. The ether was removed in *vacuo*. The residue was purified by column chromatography on silica (hexanes/ethyl acetate 4:1) to provide **179** as colorless oil (9.15 g, 89%).

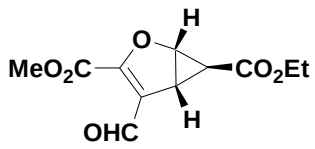
R_f = (SiO_2, hexanes/ethyl acetate 4:1) = 0.21; $[\alpha]_D^{20}$ = –116.6 (c 1.0, CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.11 (dd, *J* = 2.69, 1.11 Hz, 1 H, 6-H), 1.26 (t, *J* = 7.14 Hz, 3 H, CH_2CH_3), 3.06 (dd, *J* = 5.35, 2.69 Hz, 1 H, 5-H), 3.77 (s, 3 H, OCH_3), 3.85 (s, 3 H, CO_2Me), 4.13 (dq, *J* = 7.14, 4.91 Hz, 2 H, CH_2CH_3), 4.88 (dd, *J* = 5.33, 1.11 Hz, 1 H, 1-H), 5.04 (d, *J* = 13.69 Hz, 1 H, CH_2Ar), 5.15 (d, *J* =13.69 Hz, 1 H, CH_2Ar), 6.85 (m, 4 H, Ar); **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ = 14.3 (+, CH_2CH_3), 21.5 (+, C-6), 34.0 (+, C-5), 52.5 (+, CO_2Me), 55.8 (+, C-1), 61.2 (–, CH_2CH_3), 62.9 (–, CH_2Ar), 66.1 (+, OMe), 114.8 (+, Ar), 116.1 (+, Ar), 130.0 (C_{quat}, C-4), 143.0 (C_{quat}, C-3), 152.2 (C_{quat}, Ar), 154.4 (C_{quat}, Ar), 160.1 (C_{quat}, CO_2Me), 171.7 (C_{quat}, CO_2Et); **IR (film)**: $\tilde{\nu}$ = 3419, 2985, 2838, 1726, 1636, 1589, 1506, 1462, 1440, 1377, 1355, 1300, 1227, 1167, 1137, 1088, 1039, 1016, 924, 896, 829, 771 cm^{-1}; **MS (CI, NH_3)**: *m*/*z* (%) = 366.2 (100) [M + NH_4^+], 349.2 (7) [MH^+], 331.2 (31) [$MH^+ - H_2O$], 242.1 (35), 225.1 (19); **MS (HR-EI, 70 eV)**: 348.1205 ($C_{18}H_{20}O_7$: calc. 348.1209 [M^+]).



(1*S*,5*R*,6*S*)-(−)-4-Hydroxymethyl-2-oxa-bicyclo[3.1.0]hex-3-ene-3,6-dicarboxylic acid 6-ethyl ester 3-methyl ester (180): Ceric ammonium nitrate (43.20 g, 78.8 mmol, 3 equiv.) was added in a single portion to the **179** (9.15 g, 26.3 mmol, 1 equiv) in acetonitrile : water (300 : 75 mL) at –5 °C under an atmosphere of nitrogen. The reaction mixture was stirred for an additional *ca*. 20 minutes (TLC control) and partitioned between ethyl acetate and water. The combined organic phases were washed with saturated $NaHCO_3$ (3 × 75 mL), water (3 × 75 mL), dried over anhydrous $MgSO_4$

and filtered. The solvent was removed in *vacuo*. The residue was purified by flash column chromatography on silica (hexanes/ethyl acetate 4:1) to provide **180** as colorless oil (5.22 g, 82%).

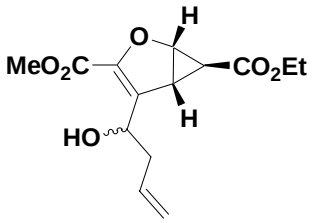
R_f = (SiO_2, hexanes/ethyl acetate 1:1) = 0.18; $[\alpha]_D^{20}$ = –184.7 (c 1.0, CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.22 (dd, *J* = 2.69, 1.05 Hz, 1 H, 6-H), 1.27 (t, *J* = 7.14 Hz, 3 H, CH_2CH_3), 3.00 (dd, *J* = 5.33, 2.69 Hz, 1 H, 5-H), 3.03 (bs, 1 H, -OH), 3.85 (s, 3 H, CO_2Me), 4.13 (q, *J* = 7.14 Hz, 2 H, CH_2CH_3), 4.63 (s, 2 H, -CH_2OH), 4.89 (dd, *J* = 5.33, 1.05 Hz, 1 H, 1-H); **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ = 14.3 (+, CH_2CH_3), 21.6 (+, C-6), 34.6 (+, C-5), 52.6 (+, CO_2Me), 57.4 (–, CH_2OH), 61.3 (–, CH_2CH_3), 65.8 (+, C-1), 133.5 (C_{quat}, C-4), 142.6 (C_{quat}, C-3), 160.9 (C_{quat}, CO_2Me), 171.8 (C_{quat}, CO_2Et); **IR (film)**: $\tilde{\nu}$ = 3457, 3444, 3069, 2984, 2957, 2199, 2089, 2013, 1890, 1712, 1633, 1440, 1402, 1354, 1301, 1134, 1085, 1044, 1014, 953, 923, 893, 837, 813, 755 cm^{-1}; **MS (CI, NH_3)**: *m*/*z* (%) = 260.1 (100) [M + NH_4^+], 242.1 (32) [MH^+], 225.1 (69); **MS (HR-EI, 70 eV)**: 242.0792 ($C_{11}H_{14}O_6$): calc. 242.0790 [$M^{+\bullet}$]).



(1*S*,5*R*,6*S*)-(–)-4-Formyl-2-oxa-bicyclo[3.1.0]hex-3-ene-3,6-dicarboxylic acid 6-ethyl ester 3-methyl ester (181): To a solution of **180** (4.91 g, 20.3 mmol, 1 equiv.) in CH_2Cl_2 (250 mL) was added manganese dioxide (26.43 g, 30.4 mmol, 15 equiv.) at room temperature and the mixture was stirred for 3 hours. The reaction mixture was then filtered through a short celite pad. The solvent was removed in *vacuo.* The residue obtained was crystallized in n-pentane to provide **181** as a white crystalline solid (4.2 g, 86%).

R_f = (SiO_2, hexanes/ethyl acetate 4:1) = 0.23; **m.p.** = 71°C; $[\alpha]_D^{20}$ = –221.6 (c 1.0, CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.24 (dd, *J* = 2.92, 1.01 Hz, 1 H, 6-H), 1.28 (t, *J* = 7.15 Hz, 3 H, CH_2CH_3), 3.27 (ddq, *J* = 0.46, 5.39, 2.92 Hz, 1 H, 5-H), 3.94 (s, 3 H, CO_2Me), 4.17 (q, *J* = 7.15 Hz, 2 H, CH_2CH_3), 5.05 (dd, *J* = 5.39, 1.01 Hz, 1 H, 1-H), 10.33 (s, 1 H, CHO); **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ = 14.3 (+, CH_2CH_3), 21.2 (+, C-

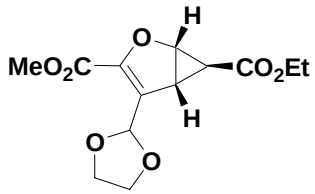
5), 29.5 (+, C-6), 53.4 (+, CO_2Me), 61.6 (–, CH_2CH_3), 67.4 (+, C-1), 129.9 (C_{quat}, C-4), 155.2 (C_{quat}, C-3), 158.4 (C_{quat}, CO_2Me), 170.6 (C_{quat}, CO_2Et), 186.5 (+, CHO); **IR (KBr)**: $\tilde{\nu}$ = 3064, 3009, 2960, 2886, 2729, 1703, 1654, 1610, 1466, 1134, 1078, 1045, 1005, 930, 874, 821, 769 cm^{-1}; **MS (CI, NH_3)**: *m/z* (%) = 258.1 (100.0) [M + NH_4^+], 241.1 (76.8) [MH^+], 167.0 (2.1); **elemental analysis** calcd (%) for $C_{11}H_{12}O_6$ (240.21): C 55.00, H 5.04; found C 54.94, H 5.05.



(1*S*,5*R*,6*S*)-4-(1`-Hydroxy-but-3`-enyl)-2-oxa-bicyclo[3.1.0]hex-3-ene-3,6-dicarboxylic acid 6-ethyl ester 3-methyl ester (182): A solution of **181** (100 mg, 0.4 mmol, 1 equiv.) in abs. CH_2Cl_2 (5 mL) was treated with $BF_3{\cdot}OEt_2$ (57 µL, 0.45 mmol, 1.1 equiv.) at –78 °C. After 10 minutes, allyltrimethylsilane (72 µL, 0.45 mmol, 1.1 equiv.) was added and stirring was continued for 24 hours. The reaction was quenched with saturated $NaHCO_3$ (2 mL). The layers were separated and organic layer was washed with brine (1 × 2 mL) and dried over anhydrous $MgSO_4$ and filtered. The solvent was removed in *vacuo*. The residue was purified by column chromatography on silica (hexanes/ethyl acetate 4:1) to provide **182** as colorless oil (89 mg, 76%).

R_f = (SiO_2, hexanes/ethyl acetate 4:1) = 0.13; **^{1}H NMR** (300 MHz, $CDCl_3$): δ (**minor diastereomer**) = 1.14 (dd, *J* = 1.03, 2.71 Hz, 1 H, 6-H), 1.24 (t, *J* = 7.14 Hz, 3 H, CH_2CH_3), 2.39-2.58 (m, 2 H, 2`-H), 2.92 (dd, *J* = 5.32, 2.71 Hz, 1-H, 5-H), 3.80 (s, 3 H, $CO_2Me$), 4.04-4.17 (m, 2 H, $CH_2CH_3$), 4.82 (dd, *J* = 1.03, 5.32 Hz, 1 H, 1-H), 4.95-4.99 (m, 1 H, 1`-H), 5.10-5.13 (m, 2 H, 4`-H); 5.72-5.89 (m, 1 H, 3`-H); δ (**major diastereomer**) = 1.18 (dd, *J* = 1.03, 2.71 Hz, 1 H, 6-H), 1.25 (t, *J* = 7.14 Hz, 3 H, CH_2CH_3), 2.39-2.58 (m, 2 H, 2`-H), 3.07 (dd, *J* = 5.32, 2.71 Hz, 1-H, 5-H), 3.81 (s, 3 H, $CO_2Me$), 4.04-4.17 (m, 2 H, $CH_2CH_3$), 4.85 (dd, *J* = 1.03, 5.32 Hz, 1 H, 1-H), 4.95-4.99 (m, 1 H, 1`-H), 5.10-5.13 (m, 2 H, 4`-H); 5.72-5.89 (m, 1 H, 3`-H); **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ (**minor diastereomer**) = 14.3 (+, CH_2CH_3), 21.7 (+, C-5), 32.6 (+, C-6), 40.8 (–, C-2`), 52.5 (+, $CO_2Me$), 61.3 (–, $CH_2CH_3$), 65.6 (+, C-1), 66.0 (+,C-1`),

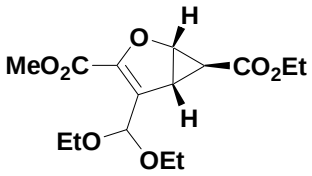
118.7 (–, C-4`), 133.5 (+, C-3`), 135.4 (C_{quat}, C-4) 141.7 (C_{quat}, C-3), 160.5 (C_{quat}, CO_2Me), 171.8 (C_{quat}, CO_2Et); δ (**major diastereomer**) = 14.3 (+, CH_2CH_3), 21.8 (+, C-5), 33.7 (+, C-6), 41.1 (–, C-2´), 52.7 (+, CO_2Me), 61.3 (–, CH_2CH_3), 65.7 (+, C-1), 67.1 (+,C-1`), 118.8 (–, C-4`), 133.6 (+, C-3`), 136.6 (C_{quat}, C-4) 142.1 (C_{quat}, C-3), 161.0 (C_{quat}, CO_2Me), 171.8 (C_{quat}, CO_2Et); **IR (film)**: $\tilde{\nu}$ = 3496, 3077, 2955, 2909, 1734, 1629, 1441, 1175, 1032, 921, 894, 838, 757, 736 cm^{-1}.



(1*S*,5*R*,6*S*)-(–)-4-[1´,3´]Dioxolan-2´-yl-2-oxa-bicyclo[3.1.0]hex-3-ene-3,6-dicarboxylic acid 6-ethyl ester 3-methyl ester (185): 181 (1.20 g, 5 mmol, 1 equiv.) in benzene (70 mL) was treated with *p*-toluene sulfonic acid hydrate (0.048 g, 0.25 mmol, 5 mol%) and ethylene glycol (0.56 mL, 10 mmol, 2 equiv.) and then heated at reflux in a Dean-Stark condenser, under nitrogen up to 5 hours (with TLC monitoring). It was then cooled to room temperature. After addition of water (10 mL), the mixture was extracted with CH_2Cl_2 (3 × 30 mL) which was washed with saturated $NaHCO_3$ (3 × 30 mL) and then water (3 × 30 mL). The organic phase was then dried over anhydrous $MgSO_4$ and filtered. The solvent was removed in *vacuo*. The residue was purified by column chromatography on silica (hexanes/ethyl acetate 4:1) to provide **185** as colorless oil (1.24 g, 87%).

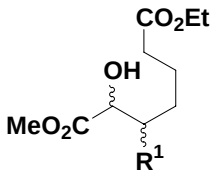
R_f (SiO_2, hexanes/ethyl acetate 4:1) = 0.21; $[\alpha]_D^{20}$ = –107.5 (c 1.0, CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.26 (m, 1 H, 6-H), 1.27 (t, *J* = 7.15 Hz, 3 H, CH_2CH_3), 3.04 (dd, *J* = 5,49, 2.74 Hz, 1 H, 5-H), 3.84 (s, 3 H, CO_2Me), 3.94 – 4.23 (m, 6 H, CH_2CH_3 and –OCH_2CH_2O-), 4.88 (dd, *J* = 5.49, 0.93 Hz, 1 H, 1-H), 6.19 (s, 1 H, 2`-H); **$^{13}$C NMR** (75.5 MHz, $CDCl_3$): δ = 14.3 (+, $CH_2CH_3$), 21.1 (+, C-5), 31.4 (+, C-6), 52.6 (+, $CO_2Me$), 61.2 (–, $CH_2CH_3$), 65.7 (–, -$OCH_2CH_2O$-), 65.8 (–, -$OCH_2CH_2O$-), 66.2 (+, C-1), 97.3 (+, C-2`), 128.6 (C_{quat}, C-4), 145.7 (C_{quat}, C-3), 159.5 (C_{quat}, CO_2Me), 171.8 ($C_{quat,}$ CO_2Et); **IR (film)**: $\tilde{\nu}$ = 3066, 2983, 2957, 2894, 1737, 1642, 1553, 1440, 1396, 1358, 1304, 1290, 1174, 1142, 1084, 1036, 999, 948, 897, 846, 818, 778, 735, 703 cm^{-1};

MS (CI, NH_3): *m*/*z* (%) = 302.3 (21) [M + NH_4^+], 285.2 (100) [MH^+], 240.2 (7); **MS (HR-EI, 70 eV)**: 284.0898 ($C_{13}H_{16}O_7$: calc. 284.0896 [M^+]).



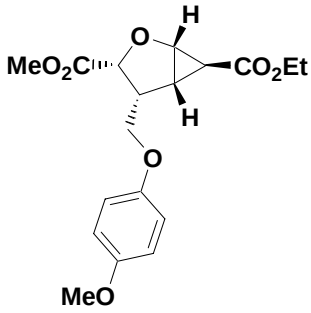
(1*S*,5*R*,6*S*)-(−)-4-Diethoxymethyl-2-oxa-bicyclo[3.1.0]hex-3-ene-3,6-dicarboxylic acid 6-ethyl ester 3-methyl ester (186): 181 (8.0 g, 33 mmol, 1 equiv.) in Et_2O (180 mL) was treated with (+)-Camphor-10-sulfonic acid (0.8 g, 10% wt/wt) and triethyl orthoformate (16.5 mL, 100 mmol, 3 equiv.) and then stirred at room temperature for 48 hours. Then the mixture was poured into 5% aq. ammonium hydroxide solution (40 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with brine (3 × 30 mL). The organic phase was then dried over $MgSO_4$ and filtered. The solvent was removed in *vacuo*. The residue was purified by column chromatography on silica (hexanes/ethyl acetate 9:1) to provide **186** as colorless oil (9.239 g, 89%).

R_f (SiO_2, hexanes/ethyl acetate 4:1) = 0.25; $[\alpha]_D^{20}$ = –148.4 (c 1.0, CH_2Cl_2); **^{1}H NMR** (300 MHz, DMSO-d6): δ = 1.1-1.21 (m, 9 H, 1 -$CO_2CH_2CH_3$ and 2 -OCH_2CH_3), 1.22 (dd, *J* = 2.61, 1.10 Hz, 1 H, 6-H), 2.89 (dd, *J* = 5.49, 2.61 Hz, 1 H, 5-H), 3.42-3.70 (m, 4 H, 2 -OCH_2CH_3), 3.75 (s, 3 H, CO_2Me), 4.09 (d, *J* = 7.14 Hz, 2 H, -$CO_2CH_2CH_3$), 5.04 (dd, *J* = 5.49, 1.10 Hz, 1 H, 1-H), 5.70 (s, 1 H, $CH(OEt)_2$); **^{13}C NMR** (75.5 MHz, DMSO-d6): δ = 14.1 (+, CH_2CH_3), 15.0 (+, -OCH_2CH_3), 15.1 (+, -OCH_2CH_3), 20.4 (+, C-5), 31.4 (+, C-6), 52.2 (+, CO_2Me), 60.7 (–, -OCH_2CH_3), 61.8 (–, -OCH_2CH_3), 62.5 (–, -$CO_2CH_2CH_3$), 65.1 (+, C-1), 95.5 (+, $CH(OEt)_2$), 129.1 (C_{quat}, C-4), 143.0 (C_{quat}, C-3), 159.2 (C_{quat}, CO_2Me), 171.0 (C_{quat}, CO_2Et); **IR (film)**: $\tilde{\nu}$ = 3427, 2979, 1722, 1641, 1553, 1440, 1398, 1352, 1288, 1164, 1141, 1062, 994, 930, 893, 843, 820, 776, 733 cm^{-1}; **MS (EI, 70 eV)**: *m*/*z* (%) = 314.2 (5) [$M^{+\bullet}$], 269.2 (85), 241.1 (73), 197.1 (84), 181.1 (100); **MS (HR-EI, 70 eV)**: 314.1368 ($C_{15}H_{22}O_7$: calc. 314.1366 [$M^{+\bullet}$]).



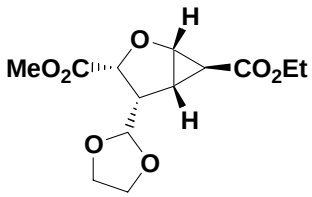
2-Hydroxy-3-methyl-heptanedioic acid 7-ethyl ester 1-methyl ester (187): A solution of **176** (1.00 g, 4.4 mmol, 1 equiv.) in EtOAc (80 mL) was treated with 10 % Pd/C (100 mg) and purged with hydrogen for 10 minutes followed by vigorous stirring in an atmosphere of hydrogen (*via* balloon) for 2 h (TLC control). The reaction mixture was filtered through a pad of celite. The solvent was removed in *vacuo*. The residue was purified by column chromatography on silica (hexanes/ethyl acetate 4:1) to provide **187** as a white crystalline solid (0.667 g, 65%).

R_f (SiO_2, hexanes/ethyl acetate 4:1) = 0.10; **^{1}H NMR** (300 MHz, $CDCl_3$): δ (**minor diastereomer**) = 0.98 (d, *J* = 6.93 Hz, 3 H, 3-CH_3), 1.22 (t, *J* = 7.15 Hz, 3 H, -CH_2CH_3), 1.27-1.94 (m, 5 H, 3-H, 4-CH_2 and 5-CH_2), 2.22-2.31 (m, 2 H, 6-CH_2), 2.80 (d, *J* = 5.57 Hz, 1 H, -OH, exchanged in D_2O), 3.76 (s, 3 H, CO_2Me),4.04-4.15 (m, 2 H, -CH_2CH_3), 4.16 (dd, *J* = 5.57, 2.83 Hz, 1 H, 2-H); δ (**major diastereomer**) = 0.80 (d, *J* = 6.86 Hz, 3 H, 3-CH_3), 1.22 (t, *J* = 7.15 Hz, 3 H, -CH_2CH_3), 1.27-1.94 (m, 5 H, 3-H, 4-CH_2 and 5-CH_2), 2.22-2.31 (m, 2 H, 6-CH_2), 2.75 (d, *J* = 5.66 Hz, 1 H, -OH, exchanged in D_2O), 3.76 (s, 3 H, CO_2Me),4.04-4.15 (m, 2 H, -CH_2CH_3), 4.16 (dd, *J* = 5.57, 2.83 Hz, 1 H, 2-H); **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ (**minor diastereomer**) = 14.3 (+, CH_2CH_3), 15.9 (+, 3-CH_3), 22.7 (–, C-5), 30.5 (–, C-4), 34.5 (–, C-6), 37.1 (+, C-3), 52.5 (+, CO_2Me), 60.4 (–, CH_2CH_3), 74.9 (+. C-2), 173.6 (C_{quat}, CO_2Me), 175.3 (C_{quat}, CO_2Et); δ (**major diastereomer**) = 14.3 (+, CH_2CH_3), 13.5 (+, 3-CH_3), 22.8 (–, C-5), 32.6 (–, C-4), 34.5 (–, C-6), 36.6 (+, C-3), 52.6 (+, CO_2Me), 60.4 (–, CH_2CH_3), 73.2 (+. C-2), 173.7 (C_{quat}, CO_2Me), 175.6 (C_{quat}, CO_2Et); **MS (CI, NH_3)**: *m*/*z* (%) = 250.1 (100) [M + NH_4^+], 233.2 (41) [MH^+], 204.1 (8).



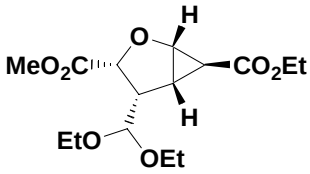
(1*S*,3*R*,4*R*,5*R*,6*S*)-(–)4-(4`-Methoxy-phenoxymethyl)-2-oxa-bicyclo[3.1.0]hexane-3,6-dicarboxylic acid 6-ethyl ester 3-methyl ester (188): A solution of **179** (1.00 g, 2.9 mmol, 1 equiv.) in MeOH (80 mL) was treated with 10% $Pd/BaSO_4$ (0.100 g) and purged with hydrogen for 10 minutes followed by vigorous stirring in an atmosphere of hydrogen (*via* balloon) for 24 h (TLC control). The reaction mixture was filtered through a pad of celite. The solvent was removed in *vacuo*. The residue was purified by column chromatography on silica (hexanes/ethyl acetate 4:1) to provide **188** as colorless oil (0.281 g, 28%).

R_f (SiO_2, hexanes/ethyl acetate 4:1) = 0.19; $[\alpha]_D^{20}$ = –12.1 (c 1.0, CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.24 (t, *J* = 7.14 Hz, 3 H, CH_2CH_3), 2.35 (ddd, *J* = 5.66, 5.51, 4.20 Hz, 1 H, 5-H), 2.58-2.59 (m, 1 H, 6-H), 3.43-3.53 (m, 1 H, 4-H), 3.59 (s, 3 H, CO_2Me), 3.76 (s, 3 H, OCH_3), 3.97-4.18 (m, 4 H, CH_2CH_3 and 1`-$CH_2$), 4.33 (dd, *J* = 0.79, 5.66 Hz, 1-H), 4.88 (d, *J* = 10.43 Hz, 1 H, 3-H), 6.77-6.86 (m, 4 H, Ar); **$^{13}$C NMR** (75.5 MHz, $CDCl_3$): δ = 14.3 (+, $CH_2CH_3$), 25.7 (+, C-6), 28.5 (+, C-5), 43.1 (+, C-4), 52.4 (+, $CO_2Me$), 55.8 (+, $OCH_3$), 60.7 (–, $CH_2CH_3$), 66.3 (–, 1`-CH_2), 66.4 (+, C-1), 80.1 (+, C-3), 114.7 (+, Ar), 115.5 (+, Ar), 152.5 (C_{quat}, Ar), 154.3 (C_{quat}, Ar), 170.6 (C_{quat}, CO_2Me), 171.8 (C_{quat}, CO_2Et); **IR (film)**: $\tilde{\nu}$ = 3453, 3449, 2954, 2836, 1717, 1638, 1508, 1467, 1413, 1369, 1301, 1233, 114, 1068, 1039, 930, 826, 755 cm^{-1}; **MS (CI, NH_3)**: *m*/*z* (%) = 368.2 (100) [M + NH_4^+], 351.1 (27) [MH^+], 227.1 (11).; **MS (HR-EI, 70 eV)**: 350.1363 ($C_{18}H_{22}O_7$: calc. 350.1366 [$M^{+\bullet}$]).



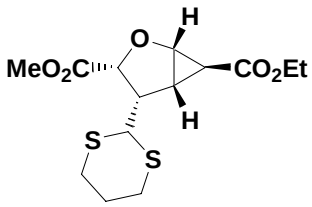
(1*S*,3*R*,4*S*,5*S*,6*S*)-(+)-4-[1´´,3´´]Dioxolan-2´-yl-2-oxa-bicyclo[3.1.0]hexane-3,6-dicarboxylic acid 6-ethyl ester 3-methyl ester (189): A solution of **185** (1.24 g, 4.4 mmol, 1 equiv.) in EtOAc (80 mL) was treated with 10% Pd/C (0.186 g) and purged with hydrogen for 10 minutes followed by vigorous stirring in an atmosphere of hydrogen (*via* balloon) for 2 h (TLC control). The reaction mixture was filtered through a pad of celite. The solvent was removed in *vacuo*. The residue was purified by column chromatography on silica (hexanes/ethyl acetate 4:1) to provide **189** as a white crystalline solid (0.937 g, 75%).

R_f (SiO_2, hexanes/ethyl acetate 4:1) = 0.20; **m.p.** = 52 °C; $[\alpha]_D^{20}$ = +16.4 (c 1.0, CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 7.14 Hz, 3 H, CH_2CH_3), 2.27 (ddd, *J* = 5.56, 5.66, 4.15 Hz, 1 H, 5-H), 2.70 (ddd, *J* = 4.15, 1.06, 0.55 Hz, 1 H, 6-H), 3.23 (dddd, *J* = 10.63, 5.56, 5.28, 0.55 Hz, 1 H, 4-H), 4.07 (dq, *J* = 10.78, 7.14 Hz, 1 H, CH_2CO_2Et), 4.13 (dq, *J* = 10.78, 7.14 Hz, 1 H, CH_2CO_2Et), 3.82-4.16 (m, 4 H, -OCH_2CH_2O-), 4.29 (dd, *J* = 5.66, 1.06 Hz, 1 H, 1-H), 4.83 (d, *J* = 10.63 Hz, 1 H, 3-H), 5.09 (d, *J* = 5.28 Hz, 1 H, 4`-H); **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ = 14.2 (+, CH_2CH_3), 25.3 (+, C-5), 26.7 (+, C-6), 47.4 (+, C-4), 52.3 (+, CO_2Me), 60.5 (–, CH_2CH_3), 65.3 (–, -OCH_2CH_2O-), 65.6 (–, -OCH_2CH_2O-), 66.0 (+, C-1), 79.2 (+, C-3), 102.5 (+, C-4´), 170.5 (C_{quat}, CO_2Me), 171.7 (C_{quat}, CO_2Et); **IR (KBr)**: $\tilde{\nu}$ = 3073, 2982, 2955, 2894, 2772, 2255, 2053, 2200, 1747, 1720, 1603, 1414, 1367, 1302, 1211, 1179, 1117, 1059, 979, 939, 879, 854, 814, 733 cm^{-1}; **MS (CI, NH_3)**: *m*/*z* (%) = 304.3 (100) [M + NH_4^+], 287.2 (17) [MH^+]; **elemental analysis** calcd (%) for $C_{13}H_{18}O_7$ (286.28): C 54.54, H 6.34, O 39.12; found C 54.26, H 6.22.



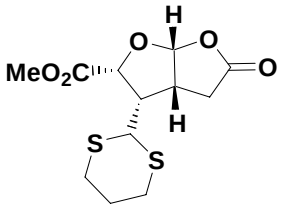
(1*S*,3*R*,4*S*,5*S*,6*S*)-(+)-4-Diethoxymethyl-2-oxa-bicyclo[3.1.0]hexane-3,6-dicarboxylic acid 6-ethyl ester 3-methyl ester (190): A solution of **186** (1.00 g, 3.18 mmol, 1 equiv.) in EtOAc (80 mL) was treated with 10% Pd/C (0.100 g) and purged with hydrogen for 10 minutes followed by vigorous stirring in an atmosphere of hydrogen (*via* balloon) for 2 h (TLC control). The reaction mixture was filtered through a pad of celite. The solvent was removed in *vacuo*. The residue was purified by column chromatography on silica (hexanes/ethyl acetate 4:1) to provide **190** as a low melting solid (0.755 g, 75%).

R_f (SiO_2, hexanes/ethyl acetate 4:1) = 0.24; $[\alpha]_D^{20}$ = +4.1 (c 1.0, CH_2Cl_2); **^{1}H NMR** (300 MHz, DMSO-d6): δ = 1.02-1.12 (m, 7 H, 5-H and 2 -OCH_2CH_3), 1.17 (t, *J* = 7.10 Hz, 3 H, CH_2CH_3), 2.11 (ddd, *J* = 5.70, 5.65, 4.21 Hz, 1 H, 6-H), 2.60 (m, 1 H, 4-H), 3.27-3.70 (m, 4 H, 2 -OCH_2CH_3), 3.63 (s, 3 H, CO_2Me), 4.04 (q, *J* = 7.10 Hz, 2 H, CH_2CH_3), 4.27 (dd, *J* = 0.82, 5.65, 1 H, 1-H), 4.48 (d, *J* = 10.43 Hz, 1 H, 3-H) , 4.72 (d, *J* = 8.23 Hz, 1 H, 1`-H); **$^{13}$C NMR** (75.5 MHz, DMSO-d6): δ = 14.1 (+, $CH_2CH_3$), 14.9 (+, -$OCH_2CH_3$), 15.3 (+, -$OCH_2CH_3$), 25.2 (+, C-5), 27.3 (+, C-6), 46.4 (+, C-4), 52.0 (+, $CO_2Me$), 60.1 (–, -$CO_2CH_2CH_3$), 61.7 (–, -$OCH_2CH_3$), 62.0 (–, -$OCH_2CH_3$), 65.8 (+, C-1), 79.5 (+, C-3), 101.6 (+, C-1`), 169.6 (C_{quat}, CO_2Me), 171.4 (C_{quat}, CO_2Et); **IR (KBr)**: $\tilde{\nu}$ = 3059, 2981, 1713, 1371, 1307, 1209, 1173, 1114, 1001, 922, 854, 705 cm^{-1}; **MS (EI, 70 eV)**: *m*/*z* (%) = 271.2 (16) [M-$^{\bullet}$OEt], 210.2 (48), 196.1 (51), 157.1 (100), 143.1 (55); **elemental analysis** calcd (%) for $C_{15}H_{24}O_7$ (316.35): C 56.95, H 7.65, O 35.40; found C 56.68, H 7.36.



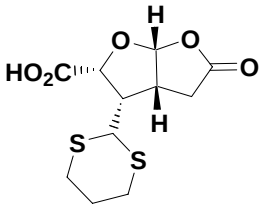
(1*S*,3*R*,4*S*,5*S*,6*S*)-(–)4-[1`,3`]Dithian-2-yl-2-oxa-bicyclo[3.1.0]hexane-3,6-dicarboxylic acid 6-ethyl ester 3-methyl ester (191): To a solution of **190** (1.00 g, 3.16 mmol, 1 equiv.) and 1,3-propanedithiol (0.42, 3.49 mmol, 1.2 equiv.) in dichloromethane (50 mL) under nitrogen atmosphere at −78 °C was added boron trifluoride diethyl etherate (0.9 mL, 6.25 mmol, 2.2 equiv.) over 10 min. The mixture was stirred for 4 hours, allowed to warm to room temperature over 15 hours, poured into cold saturated aqueous sodium bicarbonate (10 mL), and extracted with diethyl ether (2 x 20 mL). The combined organic phase was successively washed with saturated sodium bicarbonate (2 x 20 mL) and brine (2 x 20 mL). The organic phase was then dried over anhydrous $MgSO_4$ and filtered. The solvent was removed in *vacuo*. The residue was purified by column chromatography on silica (hexanes/ethyl acetate 4:1) to provide **191** as a white crystalline solid (1.00 g, 95%).

R_f (SiO_2, hexanes/ethyl acetate 4:1) = 0.24; **m.p.** = 86-87 °C; $[\alpha]_D^{20}$ = –19.7 (c 1.0, CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 7.20 Hz, 3 H, CH_2CH_3), 1.83-2.12 (m, 2 H, 5`-$CH_2$); 2.42 (ddd, *J* = 5.50, 4.23, 5.50 Hz, 1 H, 5-H), 2.80-2.90 (m, 5 H, 6-H and 4` and 6`-$CH_2$), 3.44 (ddd, *J* = 10.09, 10.09, 5.50, 1 H 4-H), 3.70 (s, 3 H, $CO_2Me$), 4.04-4.16 (m, 2 H, $CH_2CH_3$), 4.25-4.28 (m, 2 H, 1-H and 3-H), 4.76 (d, *J* = 10.09 Hz, 1 H, 4`-H); **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ = 14.3 (+, CH_2CH_3), 25.42 (+, C-6), 25.44 (–, C-5`), 28.9 (+, C-5), 29.4 (–, C-4` or C-6`), 29.6 (–, C-4` or C-6`), 45.7 (+, C-4), 48.4 (+, C-2`), 52.6 (+, CO_2Me), 60.8 (–, CH_2CH_3), 66.9 (+, C-1), 80.5 (+, C-3), 170.4 (C_{quat}, CO_2Me), 171.2 (C_{quat}, CO_2Et); **IR (KBr)**: $\tilde{\nu}$ = 3436, 3078, 2986, 1721, 1413, 1374, 1317, 1281, 1248, 1209, 1109, 1009, 954, 876, 760 cm^{-1}; **MS (EI, 70 eV)**: *m*/*z* (%) = 332.1(2) [$M^{+\bullet}$], 204.1 (33), 203.1 (60), 115.0 (100); **MS (HR-EI, 70 eV)**: 332.0749 ($C_{14}H_{20}O_5S_2$: calc. 332.0752 [$M^{+\bullet}$]); **elemental analysis** calcd (%) for $C_{14}H_{20}O_5S_2$ (332.44): C 50.58, H 6.06, O 24.06, S 19.29; found C 50.39, H 5.92, S 19.43.



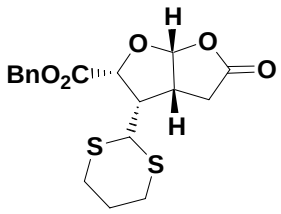
(2*R*,3*S*,3a*R*,6a*R*)-(–)-3-[1`,3`]Dithian-2-yl-5-oxo-hexahydro-furo[2,3-*b*]furan-2-carboxylic acid methyl ester (192): To a solution of **191** (1.16 g., 3.49 mmol, 1 equiv.) in 1,4-dioxane (40 mL), 6M aq. HCl (40 mL) was added and was stirred at room temperature for 24 hours. The reaction mixture was then extracted with dichloromethane (3 × 30 mL). The combined organic layers were washed with saturated sodium bicarbonate (3 × 30 mL) and dried over anhydrous $MgSO_4$ and filtered. The solvent was removed in *vacuo*. The residue was purified by column chromatography on silica (hexanes/ethyl acetate 1:1) to provide **192** as a white crystalline solid (0.467 g, 44%).

R_f (SiO_2, hexanes/ethyl acetate 1:1) = 0.24; **m.p.** = 159 °C; $[\alpha]_D^{20}$ = –25.5 (c 1.0, CH_2Cl_2); **^{1}H NMR** (300 MHz, DMSO-d6): δ = 1.77-1.99 (m, 2 H, 5`-$CH_2$), 2.52-2.80 (m, 2 H, 4-$CH_2$), 2.82-3.0 (m, 4 H, 4` and 6`-$CH_2$), 3.30-3.42 (m, 2 H, 3-H and 3a-H), 3.63 (s, 3 H, $CO_2Me$), 4.15 (d, *J* = 12.04 Hz, 1 H, 2`-H), 4.68 (d, *J* = 7.12 Hz, 1 H, 2-H), 6.11 (d, *J* = 5.56 Hz, 1 H, 6a-H); **^{13}C NMR** (75.5 MHz, DMSO-d6): δ = 25.2 (–, C-4), 26.4 (–, C-4` or C-6`), 26.7 (–, C-4` or C-6`), 29.2 (–, C-5`), 40.0 (+, C-3a) 41.2 (+, C-3), 46.9 (+,C-2`), 52.2 (+, CO_2Me), 79.7 (+,C-2), 108.4 (+,C-6a), 170.3 (C_{quat}, CO_2Me), 176.0 (C_{quat}, C-5); **IR (KBr)**: $\tilde{\nu}$ = 3445, 2955, 1788, 1734, 1421, 1381, 1279, 1164, 1082, 947, 883, 772 cm^{-1}; **MS (EI, 70 eV)**: *m*/*z* (%) = 304.0 (25) [$M^{+\bullet}$], 203.0 (100), 160.9 (67), 118.9 (34); **MS (HR-EI, 70 eV)**: 304.0434 ($C_{12}H_{16}O_5S_2$: calc. 304.0439 [$M^{+\bullet}$]); **elemental analysis** calcd (%) for $C_{12}H_{20}O_5S_2$ (304.38): C 47.35, H 5.30, O 26.28, S 21.07; found C 47.16, H 5.26, S 20.98.



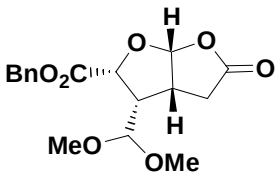
(2*R*,3*S*,3a*R*,6a*R*)-(–)-3-[1`,3`]Dithian-2-yl-5-oxo-hexahydro-furo[2,3-*b*]furan-2-carboxylic acid (193): To a solution of **191** (1.16 g., 3.49 mmol, 1 equiv.) in 1,4-dioxane (40 mL), 6M aq. HCl (40 mL) was added and was stirred at 40 ^{o}C for 36 hours. The reaction mixture was then extracted with dichloromethane (3 × 30 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and filtered. The solvent was removed in *vacuo*. The crude acid was washed with chloroform (20 mL) to obtain purified **193** as a white crystalline solid (0.699 g, 69%), which was used without further purification for the next reaction.

R_f (SiO_2, CH_2Cl_2/MeOH 5:1) = 0.24; **m.p.** = 227 ^{o}C; $[\alpha]_D^{20}$ = –8.0 (c 1.0, CH_2Cl_2); **^{1}H NMR** (300 MHz, DMSO-d6): δ = 1.83-1-94 (m, 2 H, 5`-$CH_2$), 2.5-3.0 (m, 6 H, 4, 4` and 6`-$CH_2$), 3.19-3.39 (m, 2 H, 3-H and 3a-H), 4.23 (d, *J* = 12.04 Hz, 1 H, 2`-H), 4.56 (d, *J* = 7.44 Hz, 1 H, 2-H), 6.10 (d, *J* = 5.90 Hz, 1 H, 6a-H), 13.09 (s, 1 H, CO_2H); **^{13}C NMR** (75.5 MHz, DMSO-d6): δ = 25.2 (–, C-4), 26.6 (–, C-4` or C-6`), 27.0 (–, C-4` or C-6`), 29.4 (–, C-5`), 40.0 (+, C-3a), 41.6 (+, C-3), 46.5 (+, C-2`), 79.9 (+,C-2), 108.3 (+,C-6a), 171.2 (C_{quat}, CO_2H), 175.9 (C_{quat}, C-5); **IR (KBr)**: $\tilde{\nu}$ = 3316, 2905, 1751, 1730, 1403, 1334, 1267, 1201, 1114, 1079, 967, 867, 760 cm^{-1}; **MS (EI, 70 eV)**: *m*/*z* (%) = 289.9 (36) [$M^{+\bullet}$], 188.9 (100), 161.0 (78), 118.9 (74); **MS (HR-EI, 70 eV)**: 290.0289 ($C_{11}H_{14}O_5S_2$: calc. 290.0283 [$M^{+\bullet}$]); **elemental analysis** calcd (%) for $C_{11}H_{14}O_5S_2$ (290.36): C 45.50, H 4.86, O 27.55, S 22.09; found C 45.36, H 4.88, S 21.84.



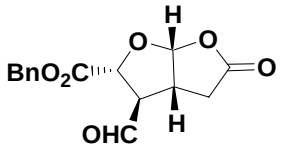
(2*R*,3*S*,3a*R*,6a*R*)-(+)-3-[1`,3`]Dithian-2-yl-5-oxo-hexahydro-furo[2,3-*b*]furan-2-carboxylic acid benzyl ester (195): BnBr (0.46 mL, 3.90 mmol, 1.1 equiv.) in acetone (20 mL) was added to a cooled solution of **193** (1.030 g, 3.55 mmol, 1 equiv.), Et_3N (0.54 mL, 3.55 mmol, 1.1 equiv.), and DMAP (22 mg, 0.18 mmol, 0.05 equiv.) in acetone (40 mL). After being stirred at room temperature overnight, the acetone was removed in *vacuo* and the residue was taken in CH_2Cl_2. The CH_2Cl_2 phase was washed with H_2O (3 × 30 mL), brine (3 × 30 mL) and dried over anhydrous $MgSO_4$. After removal of the solvent in *vacuo*, the resulting residue was purified by silica gel chromatography (hexane/ethyl acetate, 4:1) to give **195** as a white crystalline solid (1.282 g, 95%).

R_f (SiO_2, hexanes/ethyl acetate 4:1) = 0.5; **m.p.** = 138 °C; $[\alpha]_D^{20}$ = +3.7 (c 1.0, CH_2Cl_2); **^{1}H NMR** (300 MHz, DMSO-d6): δ = 1.74-1-95 (m, 2 H, 5`-$CH_2$), 2.5-2.95 (m, 6 H, 4, 4` and 6`-$CH_2$), 3.29-3.42 (m, 2 H, 3-H and 3a-H), 4.09 (d, *J* = 12.01 Hz, 1 H, 2`-H), 4.73 (d, *J* = 7.55 Hz, 1 H, 2-H), 5.12 (d, *J* = 12.18 Hz, 1 H, CH_2Ph), 5.19 (d, *J* = 12.32 Hz, 1 H, CH_2Ph), 6.12 (d, *J* = 5.69 Hz, 1 H, 6a-H), 7.30-7.41 (m, 5 H, Ar); **NMR** (75.5 MHz, DMSO-d6): δ = 25.1 (–, C-4), 26.8 (–, C-4` or C-6`), 27.0 (–, C-4` or C-6`), 29.3 (–, C-5`), 40.1 (+, C-3a), 41.5 (+, C-3), 47.1 (+, C-2`), 66.5 (–, CH_2Ph), 79.8 (+,C-2), 108.4 (+,C-6a), 128.3 (+, Ar), 128.4 (+, Ar), 128.5 (+, Ar), 135.4 (C_{quat}, Ar), 169.8 (C_{quat}, CO_2Bn), 176.0 (C_{quat}, C-5); **IR (KBr)**: $\tilde{\nu}$ = 3551, 3449, 2905, 2361, 1786, 1736, 1495, 1359, 1296, 1179, 1084, 914, 855, 752 cm^{-1}; **MS (EI, 70 eV)**: *m*/*z* (%) = 380.1 (5) [$M^{+\bullet}$], 289.0 (100), 91.1 (79); **MS (HR-EI, 70 eV)**: 380.0749 ($C_{18}H_{20}O_5S_2$: calc. 380.0752 [$M^{+\bullet}$]); **elemental analysis** calcd (%) for $C_{18}H_{20}O_5S_2$ (380.48): C 56.82, H 5.30, O 21.03, S 16.86; found C 56.15, H 5.28, S 16.73.



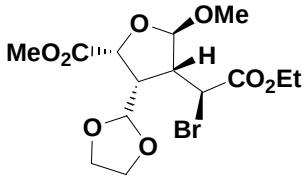
(2*R*,3*S*,3a*R*,6a*R*)-(–)-3-Dimethoxymethyl-5-oxo-hexahydro-furo[2,3-*b*]furan-2-carboxylic acid benzyl ester (196): To a solution of **195** (0.200 g, 0.52 mmol, 1.0 equiv.) in MeOH (20 mL) NBS (0.280 g, 1.57 mmol, 3.0 equiv.) was added at 0 °C and stirred at the same temperature for 3 hours. Then saturated solution of Na_2SO_3 was added to this mixture. The resulting white slurry was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (3 × 10 mL), dried over anhydrous $MgSO_4$ and filtered. The CH_2Cl_2 was removed in *vacuo*. The residue was purified by column chromatography on silica (hexanes/ethyl acetate 1:1) to provide **196** as colorless oil (0.117 g, 66%).

R_f (SiO_2, hexanes/ethyl acetate 1:1) = 0.5; $[\alpha]_D^{20}$ = –4.1 (c 1.0, CH_2Cl_2); **^{1}H NMR** (300 MHz, DMSO-d6): δ = 2.54-2.70 (m, 2 H, 4-CH_2), 3.0-3.38 (m, 2 H, 3-H and 3a-H), 3.11 (s, 3 H, -OMe), 3.28 (s, 3 H, -OMe), 4.45 (d, *J* = 8.61, 1 H, 2-H), 4.61 (d, *J* = 8.61 Hz, 1 H, $CH(OMe)_2$, 5.15 (s, 2 H, CH_2Ph), 6.11 (d, *J* = 5.93 Hz, 1 H, 6a-H), 7.32-7.42 (m, 5 H, Ar); **NMR** (75.5 MHz, DMSO-d6): δ = 29.1 (–, C-4), 38.7 (+, C-3a) 45.9 (+, C-3), 52.4 (+, OMe), 54.2 (+, OMe), 66.6 (–, CH_2Ph), 79.8 (+,C-2), 101.7 (+, $CH(OMe)_2$), 108.7 (+,C-6a), 128.4 (+, Ar), 128.5 (+, Ar), 128.7 (+, Ar), 135.4 (C_{quat}, Ar), 170.5 (C_{quat}, CO_2Bn), 176.1 (C_{quat}, C-5); **IR (film)**: $\tilde{\nu}$ = 3536, 3348, 3244, 2835, 1787, 1382, 1349, 1291, 1177, 1000, 945, 825, 750 cm^{-1}; **MS (EI, 70 eV)**: *m*/*z* (%) = 336.0 (1) [$M^{+\bullet}$], 202.0 (14), 168.9 (43), 140.9 (41); **MS (HR-EI, 70 eV)**: 336.1203 ($C_{17}H_{20}O_7$: calc. 336.1209 [$M^{+\bullet}$]).



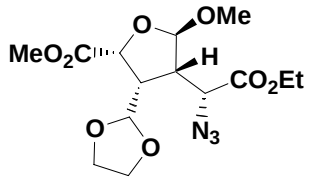
(2*R*,3*R*,3a*R*,6a*R*)-(–)-3-Formyl-5-oxo-hexahydro-furo[2,3-b]furan-2-carboxylic acid benzyl ester (197): To a solution of **196** (100 mg, 0.30 mmol, equiv.) in CH_2Cl_2 (2 mL) was added at room temperature formic acid (1.1 mL, 29.7 mmol, 100 equiv.). After being stirred for 3 hours, the mixture was neutralized with solid Na_2CO_3 (mg.) and diluted with saturated Na_2CO_3 solution. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and filtered. The solvent was removed in vacuo. The residue was purified by column chromatography on silica (hexanes/ethyl acetate 1:1) to provide **197** as colorless oil (29 mg, 34%).

R_f (SiO_2, hexanes/ethyl acetate 1:1) = 0.3; $[\alpha]_D^{20}$ = –50.8 (c 1.0, CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 2.46 (dd, *J* = 18.76, 3.70 Hz, 1 H, 4-CH_2), 2.88, (dd, *J* = 18.76, 10.87 Hz, 1 H, 4-CH_2), 3.40 (dd, *J* = 2.57, 2.37 Hz, 1 H, 3-H), 3.65 (dddd, *J* = 10.87, 5.80, 3.70, 2.57 Hz, 1 H, 3a-H), 5.05 (d, *J* = 2.37 Hz, 1 H, 2-H), 5.19 (d, *J* = 11.94 Hz, 1 H, CH_2Ph), 5.27 (d, *J* = 11.94 Hz, 1 H, CH_2Ph), 6.10 (d, *J* = 5.80 Hz, 1 H, 6a-H), 9.70 (s, 1 H, CHO); **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ = 34.2 (–, C-4), 38.1 (+, C-3a), 60.1 (+, C-3), 68.5 (–, CH_2Ph), 78.2 (+, C-2), 108.4 (+, C-6a), 128.9 (+, Ar), 129.0 (+, Ar), 134.6 (+, Ar), 134.8 (C_{quat}, Ar), 170.1 (C_{quat}, CO_2Bn), 173.7 (C_{quat}, C-5), 195.7 (+; CHO); **IR (film)**: $\tilde{\nu}$ = 3358, 2890, 1800, 1732, 1348, 1256, 1176, 1126, 1001, 946, 826, 752 cm^{-1}; **MS (EI, 70 eV)**: *m*/*z* (%) = 289.9 (1) [$M^{+\bullet}$], 183.9 (11), 108.9 (15),91.0 (100); **MS (HR-EI, 70 eV)**: 290.0787 ($C_{15}H_{14}O_6$: calc. 290.0790 [$M^{+\bullet}$]).



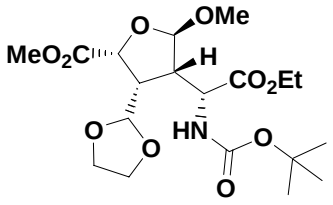
(1`*S*,2R,3*S*,4*R*,,5*R*)-(–)-4-(Bromo-ethoxycarbonyl-methyl)-3-[1´´,3´´]dioxolan-2´´-yl-5-methoxy-tetrahydro-furan-2-carboxylic acid methyl ester (220): A mixture of **189** (0.600 g, 2.10 mmol, 1.0 equiv.) and NBS (1.119 g, 6.28 mmol, 3.0 equiv.) in MeOH (30 mL) was stirred at 15 °C for 36 hours, in the dark. Then saturated solution of Na_2SO_3 was added to this mixture. The resulting white slurry was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with brine (3 × 15 mL), dried over anhydrous $MgSO_4$ and filtered. The CH_2Cl_2 was removed in *vacuo*. The residue was purified by column chromatography on silica (hexanes/ethyl acetate 7:3) to provide **220** as a white crystalline solid (0.713 g, 86%).

R_f (SiO_2, hexanes/ethyl acetate 1:1) = 0.39; **m.p.** = 78 °C; $[\alpha]_D^{20}$ = –69.8 (c 1.0, CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.31 (t, *J* = 7.15 Hz, 3 H, CH_2CH_3), 3.05 (ddd, *J* = 11.32, 6.82, 5.65 Hz, 1 H, 4-H), 3.10 (ddd, *J* = 6.83, 4.53, 3.48 Hz, 1 H, 3-H), 3.36 (s, 3 H, -OMe), 3.73 (s, 3 H, -CO_2Me), 3.78-4.11 (m, 4 H, -OCH_2CH_2O-), 4.20 (dq, *J* = 10.76, 7.15 Hz, 1 H, CH_2CO_2Et), 4.25 (dq, *J* = 10.76, 7.15 Hz, 1 H, CH_2CO_2Et), 4.56 (d, *J* = 11.32 Hz, 1 H, 1´-H), 4.68 (d, *J* = 4.53 Hz, 1 H, 2-H), 5.09 (d, *J* = 5.64 Hz, 1 H, 5-H), 5.18 (d, *J* = 3.48 Hz, 1 H, 2´´-H); **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ = 13.9 (+, CH_2CH_3), 43.5 (+, C-3), 47.4 (+, C-4), 51.9 (+, OMe), 53.4 (+, C-1´), 56.7 (+, CO_2Me), 62.4 (–, CH_2CH_3), 64.9 (–, -OCH_2CH_2O-), 65.3 (–, -OCH_2CH_2O-), 75.8 (+, C-2), 100.9 (+, C-5), 106.6 (+, C-2´´), 168.37 (C_{quat}, CO_2Me), 169.70 (C_{quat}, CO_2Et); **IR (KBr)**: $\tilde{\nu}$ = 3073, 2982, 2955, 2894, 2772, 2255, 2053, 2200, 1747, 1720, 1603, 1414, 1367, 1302, 1211, 1179, 1117, 1059, 979, 939, 879, 854, 814, 733 cm^{-1}; **MS (EI, NH_3)**: *m*/*z* (%) = 396.9 $[M - H^{\cdot}]^+$, 395.0 $[M - H^{\cdot}]^+$, 73.0 (100.0); **MS (HR-EI, 70 eV)**: 395.0341 ($C_{14}H_{20}BrO_8$: calc. 394.0342 $[M^+]$); **elemental analysis calcd** (%) for $C_{14}H_{21}BrO_8$ (397.22): C 42.33, H 5.33, Br 20.12, O 32.22; found C 42.32, H 5.25.



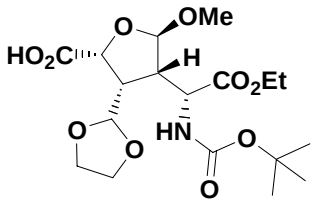
(1´*R*,2*R*,3*S*,4*S*,5*R*)-(+)-4-(Azido-ethoxycarbonyl-methyl)-3-[1´´,3´´]dioxolan-2´´-yl-5-methoxy-tetrahydro-furan-2-carboxylic acid methyl ester (222): To a solution of **220** (0.315 g, 0.79 mmol, 1 equiv.) in DMF (10 mL) was added sodium azide (0.093 g, 1.43 mmol, 1.8 equiv.). The mixture was stirred at room temperature for 24 h and the reaction was quenched with water (10 mL). After extraction with EtOAc (3 × 15 mL), the organic layers were dried over anhydrous $MgSO_4$ and filtered. The EtOAc was removed in *vacuo*. The residue was purified by column chromatography on silica (hexanes/ethyl acetate 7:3) to provide **222** as colorless oil (0.278 g, 97%).

R_f (SiO_2, hexanes/ethyl acetate 1:1) = 0.34; $[\alpha]_D^{20}$ = +17.2 (c 1.0, CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.33 (t, *J* = 7.10 Hz, 3 H, CH_2CH_3), 3.05 (ddd, *J* = 10.29, 7.15, 4.53 Hz, 1 H, 4-H), 3.10 (ddd, *J* = 7.15, 5.21, 4.53 Hz, 1 H, 3-H), 3.46 (s, 3 H, OMe), 3.77 (s, 3 H, CO_2Me), 3.78-3.92 (m, 4 H, -OCH_2CH_2O-), 4.19 (d, *J* = 10.29 Hz, 1 H, 1´-H), 4.27 (q, *J* = 7.10 Hz, 2 H, CH_2CH_3), 4.73 (d, *J* = 5.21 Hz, 1 H, 2´´-H), 4.90 (d, *J* = 5.21 Hz, 1 H, 2-H), 5.16 (d, *J* = 4.53 Hz, 1 H, 5-H); **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ = 14.2 (+, CH_2CH_3), 46.9 (+, C-4), 48.7 (+, C-3), 52.1 (+, OMe), 56.5 (+, C-1´), 60.5 (+, CO_2Me), 61.9 (–, CH_2CH_3), 64.2 (–, -OCH_2CH_2O-), 65.0 (–, -OCH_2CH_2O-), 76.7 (+, C-2), 101.4 (+, C-5), 106.9 (+, C-2´´), 168.6 (C_{quat}, CO_2Me), 169.6 (C_{quat}, CO_2Et); **IR (film)**: $\tilde{\nu}$ = 2901, 2498, 2109, 2200, 1739, 1628, 1441, 1372, 1259, 1215, 1102, 1055, 1027, 943, 861, 732 cm^{-1}; **MS (EI, NH_3)**: *m/z* (%) = 358.2 $[M - H^{\cdot}]^+$, 73.0 (100.0); **MS (HR-EI, 70 eV)**: 358.1251 ($C_{14}H_{20}N_3O_8$: calc. 358.1250 $[M^+]$).



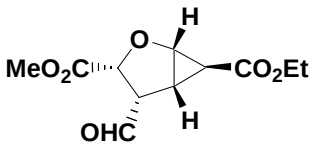
(1´*R*,2*R*,3*S*,4*S*,5*R*)-(–)-4-(*tert*-Butoxycarbonylamino-ethoxycarbonyl-methyl)-3-[1´´,3´´]dioxolan-2´´-yl-5-methoxy-tetrahydro-furan-2-carboxylic acid methyl ester (223): A solution of the **222** (0.111 g, 0.31 mmol, 1 equiv.) and Boc_2O (.074 g, 0.34 mmol, 1.1 equiv.) in MeOH (6 mL) was treated with 10% Pd/C (0.016 g) and purged with hydrogen for 10 minutes followed by vigorous stirring in an atmosphere of hydrogen (*via* balloon) for 15 h. The reaction mixture was filtered through a pad of celite. The solvent was removed in *vacuo*. The residue was purified by column chromatography on silica (hexanes/ethyl acetate 1:1) to provide **223** as colorless oil (0.113 g, 84%).

R_f (SiO_2, hexanes/ethyl acetate 1:1) = 0.24; $[\alpha]_D^{20}$ = –7.1 (c 1.0, CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.27 (t, *J* = 7.15 Hz, 3 H, CH_2CH_3), 1.44 (s, 9 H, -$C(CH_3)_3$), 2.72 (ddd, *J* = 8.74, 7.62, 4.37, 1 H, 4-H), 2.96-3.01 (m, 1 H, 3-H), 3.39 (s, 3 H, OMe), 3.75 (s, 3 H, CO_2Me), 3.77-4.26 (m, 6 H, -OCH_2CH_2O and CH_2CH_3), 4.59-4.65 (m, 1 H, 1´-H), 4.69 (d, *J* = 6.21 Hz, 1 H, 2-H), 5.01 (d, *J* = 4.94 Hz, 1 H, 2´´-H), 5.12 (d, *J* = 4.37 Hz, 1 H, 5-H), 5.30-5.31 (d, *J* = 7.68 Hz, 1 H, NHBoc); **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ = 14.2 (+, CH_2CH_3), 28.3 (+, $C(\underline{C}H_3)_3$), 46.5 (+, C-3), 48.9 (+, C-4), 51.8 (+, C-1´), 52.1 (+, OMe), 56.2 (+, CO_2Me), 61.4 (–,CH_2CH_3), 64.7 (–,-$O\underline{C}H_2CH_2O$-), 65.1 (–,-$OCH_2\underline{C}H_2O$-), 76.5 (+, C-2), 79.9 (C_{quat}, -$\underline{C}(CH_3)_3$), 101.5 (+, C-5), 106.9 (+, C-2´´), 155.3 (C_{quat}, CO^tBu), 169.7 (C_{quat}, CO_2Me) , 171.5 (C_{quat}, CO_2Et); **IR (film)**: $\tilde{\nu}$ = 3371, 2978, 2425, 2199, 1738, 1721, 1512, 1443, 1368, 1284, 1219, 1165, 1105, 1060, 1027, 943, 863, 755, 663 cm^{-1}; **MS (EI, NH_3)**: *m*/*z* (%) = 433.3 $[M]^+$, 360.1 (12.4) [M^+ – $CO_2CH2CH3$], 200.0 (100.0) ; MS **(HR-EI, 70 eV)**: 433.1949 ($C_{19}H_{31}NO_{10}$: calc. 433.1949 [$M^{+\bullet}$]).



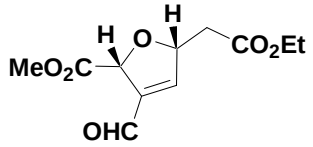
(1´*R*,2*R*,3*S*,4*S*,5*R*)-(+)-4-(*tert*-Butoxycarbonylamino-ethoxycarbonyl-methyl)-3-[1´´,3´´]dioxolan-2´´-yl-5-methoxy-tetrahydro-furan-2-carboxylic acid (224): To a solution of **223** (0.100 g, 0.23 mmol, 1 equiv.) in THF (3 mL) cooled to 0 °C was added a solution of LiOH (0.055 g, 0.23 mmol, 1 equiv.) in water (1 mL) slowly. The solution was then warmed to room temperature overnight (15 h) and quenched with HOAc (1 mL). After extracting with EtOAc (4 × 3 mL), the organic layer was dried over anhydrous $MgSO_4$ and filtered. The EtOAc was removed in *vacuo*. The residue was dried on high vaccum pump for 48 h to afford **224** as low melting amorphous white solid (0.080 g, 83%).

R_f (SiO_2, dichloromethane/Methanol 5:1) = 0.30; $[\alpha]_D^{20}$ = + 15.6 (c 1.0, CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.21 (t, *J* = 7.15 Hz, 3 H, CH_2CH_3), 1.38 (s, 9 H, -$C(CH_3)_3$), 2.67 (m, 1 H, 4-H), 2.98-3.04 (m, 1 H, 3-H), 3.35 (s, 3 H, OMe), 3.69-4.19, m, 6 H, -OCH_2CH_2O and CH_2CH_3), 4.54-4.60 (m, 1 H,1´-H), 4.66 (d, *J* = 5.83 Hz, 1 H, 2-H), 4.98 (d, *J* = 3.60 Hz, 1 H, 2´´-H), 5.07 (d, *J* = 4.84 Hz, 1 H, 5-H), 5.18 (d, *J* = 8.23 Hz, 1 H, N<u>H</u>Boc); 7.53 (bs, 1 H, CO_2H); **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ = 13.1 (+, CH_2CH_3), 27.3 (+, C(<u>C</u>$H_3)_3$), 44.9 (+, C-3), 48.2 (+, C-1´), 50.6 (+, C-4), 55.5 (+, OMe), 60.5 (–,CH_2CH_3), 63.5 (–,-OCH_2CH_2O-), 64.0 (–,-OCH_2CH_2O-), 75.4 (+, C-2), 79.9 (C_{quat}, -<u>C</u>$(CH_3)_3$), 100.4 (+, C-5), 106.3 (+, C-2´´), 154.3 (C_{quat}, CO^tBu), 170.2 (C_{quat}, CO_2Et), 171.8 (C_{quat}, CO_2H); **IR (KBr)**: $\tilde{\nu}$ = 3558, 2978, 2199, 1730, 1700, 1255, 1164, 1101, 1052, 862, 802, 755 cm^{-1}; **MS (EI, NH_3)**: *m*/*z* (%) = 420.0 $[MH]^+$, 404.1 (12) [M – •CH3], 346.0 (12.2), 230.0 (24.6), 186.0 (76.4), 73.0 (100.0) ; **MS (HR-EI, 70 eV)**: 419.1790 ($C_{18}H_{29}NO_{10}$: calc. 419.1791 [$M^{+\bullet}$]).



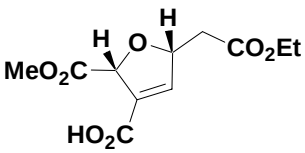
(1*S*,3*R*,4*S*,5*S*,6*S*)-4-Formyl-2-oxa-bicyclo[3.1.0]hexane-3,6-dicarboxylic acid 6-ethyl ester 3-methyl ester (237): To a solution of **190** (3.0 g, 9.48 mmol, 1 equiv.) in CH_2Cl_2 (60 mL) was added at room temperature formic acid (72 mL, 1.89 mol, 200 equiv.). After being stirred for 5 minutes, the mixture was neutralized with solid Na_2CO_3 and diluted with saturated Na_2CO_3 solution. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 30 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and filtered. The solvent was removed in *vacuo* to provide crude **237** as colorless oil (2.29 g., quant.). The crude **237** was further carried for the next reaction without purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 7.15 Hz, 3 H, CH_2CH_3), 2.40-2.46 (m, 2 H, 5-H and 6-H), 3.75 (s, 3 H, CO_2Me), 3.84 (ddd, *J* = 10.21, 5.57, 2.21 Hz, 1 H, 4-H), 4.05-4.17 (m, 2 H, CH_2CH_3), 4.40-4.43 (m, 1 H, 1-H), 4.98 (d, *J* = 10.21 Hz, 1 H, 3-H), 9.63 (d, *J* = 2.21 Hz, CHO); **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ = 14.3 (+, CH_2CH_3), 26.2 (+, C-6), 26.6 (+, C-5), 52.8 (+, CO_2Me), 53.9 (+, C-4), 61.1 (–, CH_2CH_3), 66.7 (+, C-1), 79.7 (+, C-3), 169.7 (C_{quat}, CO_2Me), 170.9 (C_{quat}, CO_2Et), 196.5 (C_{quat}, CHO).



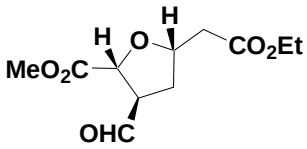
(2*R*,5*R*)-(+)-5-Ethoxycarbonylmethyl-3-formyl-2,5-dihydro-furan-2-carboxylic acid methyl ester (239): To a solution of **237** (1.0 g., 4.12 mmol, 1 equiv.) in diethyl ether (50 mL) was added silica gel (20 g, Merck 60–230 mesh) and the heterogeneous mixture was stirred at room temperature for 72 h, after which time TLC indicated disappearance of the substrate. The silica gel was filtered off and washed with diethyl ether (2 × 20 mL). The solvent was removed in *vacuo*. The residue was purified by column chromatography on silica (hexanes/ethyl acetate 1:1) to provide **239** as colorless oil (0.600 g., 60%).

R_f (SiO_2, hexanes/ethyl acetate 1:1) = 0.40; $[\alpha]_D^{20}$ = +12.8 (c 1.0, CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 7.14 Hz, 3 H, CH_2CH_3), 2.78 (dd, *J* = 16.40, 7.31 Hz, 1 H, CH_2CO_2Et), 2.97 (dd, *J* = 16.40, 6.83 Hz, 1 H, CH_2CO_2Et), 3.77 (s, 3 H, CO_2Me), 4.19 (q, *J* = 7.14 Hz, 2 H, CH_2CH_3), 5.39 (ddd, *J* = 2.64, 1.85, 0.48 Hz, 1 H, 2-H), 5.48 (dddd, *J* = 2.64, 1.81, 7.30, 6.83 Hz, 1 H, 5-H), 7.15 (dd, *J* = 1.85, 1.81 Hz, 1 H, 4-H), 9.81 (d, *J* = 0.48 Hz, 1 H, CHO); **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ = 14.3 (+, CH_2CH_3), 40.3 (–, CH_2CO_2Et), 52.8 (+, CO_2Me), 61.1 (–, CH_2CH_3), 82.4 (+, C-5), 84.0 (+, C-2), 141.1 (C_{quat}, C-3), 148.4 (+, C-4), 170.2 (C_{quat}, CO_2Me), 170.4 (C_{quat}, CO_2Et), 185.9 (+, CHO); **IR (film)**: $\tilde{\nu}$ = 2957, 2848, 2733, 1746, 1683, 1629, 1437, 1376, 1285, 1180, 1082, 926, 852, 765 cm^{-1}; **MS (EI, 70 eV)**: *m*/*z* (%) = 242.0 (4) [$M^{+\bullet}$], 183.0 (100), 155.0 (60), 109.0.0 (54); **MS (HR-EI, 70 eV)**: 242.0789 ($C_{11}H_{14}O_6$: calc. 242.0790 [$M^{+\bullet}$]).



(2*R*,5*R*)-(+)-5-Ethoxycarbonylmethyl-2,5-dihydro-furan-2,3-dicarboxylic acid 2-methyl ester (240): A solution of $NaClO_2$ (0.225 g, 2.49 mmol, 3 equiv.) in water (1 mL) was added dropwise to a stirred mixture of 5-methyl-furfural **239** (0.100 g, 0.83 mmol, 1 equiv.) in acetonitrile (2 mL), KH_2PO_4 (0.107 g, 0.79 mmol, 0.95 equiv.) in water (2 mL) and of 30% H_2O_2 (0.13 mL, 1.25 mmol, 1.5 equiv.), keeping the temperature at 0 °C. Oxygen evolved from the solution until the end of the reaction (12 hours) with a bubbler connected to the apparatus. A small amount of Na_2SO_3 (0.157 g, 1.25 mmol, 1.5 equiv.) was added to destroy the unreacted HOCl and H_2O_2. After acidification with HCl 6 N, the mixture was extracted with dichloromethane (3 × 30 mL). The combined organic layers were washed with water (1 × 10 mL), dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The residue was purified by column chromatography on silica (hexanes/ethyl acetate 9:1) to provide **240** as a white crystalline solid (0.088 g, 83%).

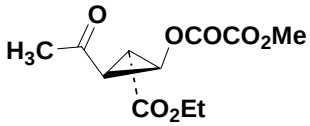
R_f (SiO_2, hexanes/ethyl acetate 1:1) = 0.1; **m.p.** = 79 °C; $[\alpha]_D^{20}$ = +30.8 (c 1.0, CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.27 (t, *J* = 7.14 Hz, 3 H, CH_2CH_3), 2.73 (dd, *J* = 16.33, 6.72 Hz, 1 H, CH_2CO_2Et), 2.90 (dd, *J* = 16.33, 7.27 Hz, 1 H, CH_2CO_2Et), 3.77 (s, 3 H, CO_2Me), 4.17 (q, *J* = 7.14 Hz, 2 H, CH_2CH_3), 5.33 (dd, *J* = 2.74, 2.20 Hz, 1 H, 2-H), 5.45 (dddd, *J* = 2.74, 1.78, 7.00, 7.00 Hz, 1 H, 5-H), 7.15 (dd, *J* = 1.78, 1.781 Hz, 1 H, 4-H), 8.69-9.49 (bs, 1 H, CO_2H); **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ = 14.3 (+, CH_2CH_3), 40.3 (–, CH_2CO_2Et), 52.9 (+, CO_2Me), 61.1 (–, CH_2CH_3), 83.3 (+, C-5), 84.3 (+, C-2), 131.7 (C_{quat}, C-3), 145.5 (+, C-4), 166.4 (C_{quat}, CO_2H), 170.2 (C_{quat}, CO_2Me), 170.5(C_{quat}, CO_2Et); **IR (KBr)**: $\tilde{\nu}$ = 2987, 1745, 1703, 1405, 1278, 1181, 1115, 1081, 1021, 749 cm^{-1}; **MS (PI-LSIMS, Glycerin/MeOH)**: *m*/*z* (%) = 351.2 [MH^++glyc.], 259.1 [MH^+]; **MS (HR- PI-LSIMS, Glycerin/MeOH)**: 259.0815 ($C_{11}H_{15}O_7$: calc. 259.0818 [M^+]); **elemental analysis calcd** (%) for $C_{11}H_{14}rO_7$ (258.22): C 51.16, H 5.46, O 43.37; found C 50.92, H 4.95.



(2*R*,3*R*,5*S*)-(+)-5-Ethoxycarbonylmethyl-3-formyl-tetrahydro-furan-2-carboxylic acid methyl ester (243): A solution of **239** (0.100 g, 0.41 mmol, 1 equiv.) in MeOH (5 mL) was treated with 10% Pd/C (0.010 g) and purged with hydrogen for 10 minutes followed by vigorous stirring in an atmosphere of hydrogen (*via* balloon) for 2 h (tlc control). The reaction mixture was filtered through a pad of celite. The solvent was removed in *vacuo*. The residue was purified by column chromatography on silica (hexanes/ethyl acetate 1:1) to provide **243** as colorless oil (0.070 g., 69%).

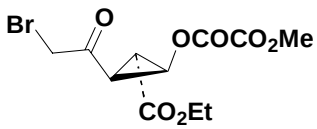
R_f (SiO_2, hexanes/ethyl acetate 1:1) = 0.30; $[\alpha]_D^{20}$ = +5.5 (c 1.0, CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.20 (t, *J* = 7.17 Hz, 1 H, CH_2CH_3), 1.86 (ddd, *J* = 12.97, 9.09, 8.78 Hz, 1 H, 4-CH_2), 2.48 (ddd, *J* = 12.96, 6.18, 3.40 Hz, 1 H, 4-CH_2), 2.52 (dd, *J* = 15.92, 6.72 Hz, 1 H, CH_2CO_2Et), 2.78 (dd, *J* = 15.98, 6.52 Hz, 1 H, CH_2CO_2Et), 3.25 (ddd, *J* = 9.09, 4.19, 3.40 Hz, 1 H, 3-H), 3.71 (s, 3 H, CO_2Me), 4.09 (q, *J* = 7.17 Hz, 2 H, CH_2CH_3), 4.33 (dddd, *J* = 8.78, 6.72, 6.52, 6.17 Hz, 1 H, 5-H), 4.75 (d, *J* = 4.19 Hz, 1 H, 2-H), 9.69 (d, *J* = 0.89 Hz, 1 H, CHO); **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ = 14.2 (+,

CH_2CH_3), 31.3 (–, C-4), 40.3 (–, CH_2CO_2Et), 52.6 (+, C-3), 55.3 (+, CO_2Me), 60.8 (–, CH_2CH_3), 76.3 (+, C-5), 76.7 (+, C-2), 170.6 (C_{quat}, CO_2Me), 172.0 (C_{quat}, CO_2Et), 198.4 (C_{quat}, CHO); **IR (KBr)**: $\tilde{\nu}$ = 3463, 2981, 2740, 2199, 2092, 1734, 1439, 1394, 1370, 1206, 1096, 846, 702 cm^{-1}; **MS (EI, 70 eV)**: *m*/*z* (%) = 245.2 (4) [MH^+], 226.1 (10), 185.1 (100).



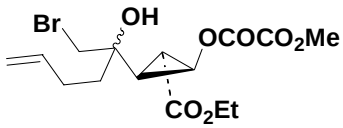
(1*S*,2*R*,3*S*)-Oxalic acid 2-acetyl-3-ethoxycarbonyl-cyclopropyl ester methyl ester (250): A solution of **176** (0.500 g, 2.2 mmol) in dry CH_2Cl_2 (25 mL) was cooled to –78 °C and treated with ozone until the mixture turned blue. Excess ozone was expelled by passing oxygen through the solution, followed by addition of dimethyl sulfide (0.3 mL, 4.42 mmol, 5.0 equiv.). The reaction mixture was allowed to warm to room temperature and stirring was continued for 24 hours. Saturated $NaHCO_3$ (10 mL) was added and layers were separated. The organic layer was washed with water (2 x 10 mL), dried, filtered and evaporated to yield **250** as the colorless oil (0.468 g, 82%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (t, *J* = 7.14 Hz, 3 H, CH_2CH_3), 2.34 (s, 3 H, $C(O)CH_3$), 2.86-2.94 (m, 2 H, 2-H and 3-H), 3.88 (s, 3 H, CO_2Me), 4.17 (dq, *J* = 7.14, 1.23 Hz, 2 H, CH_2CH_3), 4.54 (dd, *J* = 7.27, 3.98 Hz, 1 H, 1-H); **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ = 14.2 (+, CH_2CH_3), 26.6 (+, $C(O)CH_3$), 31.6 (+, C-3), 34.8 (+, C-2), 53.9 (+, CO_2Me),58.9 (+, C-1), 61.7 (–, CH_2CH_3), 156.8 (C_{quat}, -OC(O)C(O)OMe), 157.2 (C_{quat}, -OC(O)C(O)OMe), 169.1 (C_{quat}, CO_2Et), 198.6 (C_{quat}, C(O)Me); **MS (CI, NH_3)**: *m*/*z* (%) = 276.3 (100) [$M+NH_4^+$].



(1*S*,2*R*,3*S*)-Oxalic acid-2-(2-bromo-acetyl)-3-ethoxycarbonyl-cyclopropyl ester methyl ester (251): 251 was synthesized from **177** using the similar procedure and scale as in the synthesis of **250**. The product obtained was the colorless oil in 86% yield.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 7.27 Hz, 3 H, CH_2CH_3), 2.92 (dd, *J* = 6.31, 3.84 Hz, 1 H, 2-H), 3.19 (dd, *J* = 7.55, 6.31 Hz, 1 H, 3-H), 3.19 (s, 3 H, CO_2Me), 3.99 (d, *J* = 12.35, 1 H, CH_2Br), 4.08 (d, *J* = 12.35, 1 H, CH_2Br), 4.17 (dq, *J* = 7.27, 1.23 Hz, 2 H, CH_2CH_3), 4.61 (dd, *J* = 7.55, 3.84 Hz, 1 H, 1-H); **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ = 14.2 (+, CH_2CH_3), 27.3 (+, C-2), 32.2 (+, C-3), 34.6 (–, CH_2Br), 54.1 (+, CO_2Me), 59.5 (+, C-1), 62.1 (–, CH_2CH_3), 156.7 (C_{quat}, -OC(O)C(O)OMe), 157.2 (C_{quat}, -OC(O)C(O)OMe), 168.7 (C_{quat}, CO_2Et), 192.5 (C_{quat}, C(O)Me); **MS (CI, NH_3)**: *m*/*z* (%) = 354.0 (94) [M+NH_4^+], 355.9 (100) [M+NH_4^+].



(1*S*,2*R*,3*S*)-Oxalic acid 2-(1`-bromomethyl-1`-hydroxy-pent-4-enyl)-3-ethoxycarbonyl-cyclopropyl ester methyl ester (252): A solution of **251** (200 mg, 0.59 mmol, 1 equiv.) in dichloromethane (10 mL) was added dropwise to a stirred solution of boron trifluoride diethyl etherate (0.11 mL, 0.89 mmol, 1.5 equiv.) in dichloromethane (4 mL) at 0 °C. After 5 min, allyltributyltin (0.22 mL, 0.71 mmol, 1.2 equiv.) was added, and the mixture was stirred for 24 h at 0 °C. Saturated aqueous $NaHCO_3$ (10 mL) was added, and the mixture was allowed to warm to room temperature before being partitioned between dichloromethane and water. The organic extract was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield **252** as the colorless oil (0.225 g., quant.). The crude product was carried for the next reaction without chromatography, as it is not stable on silica.

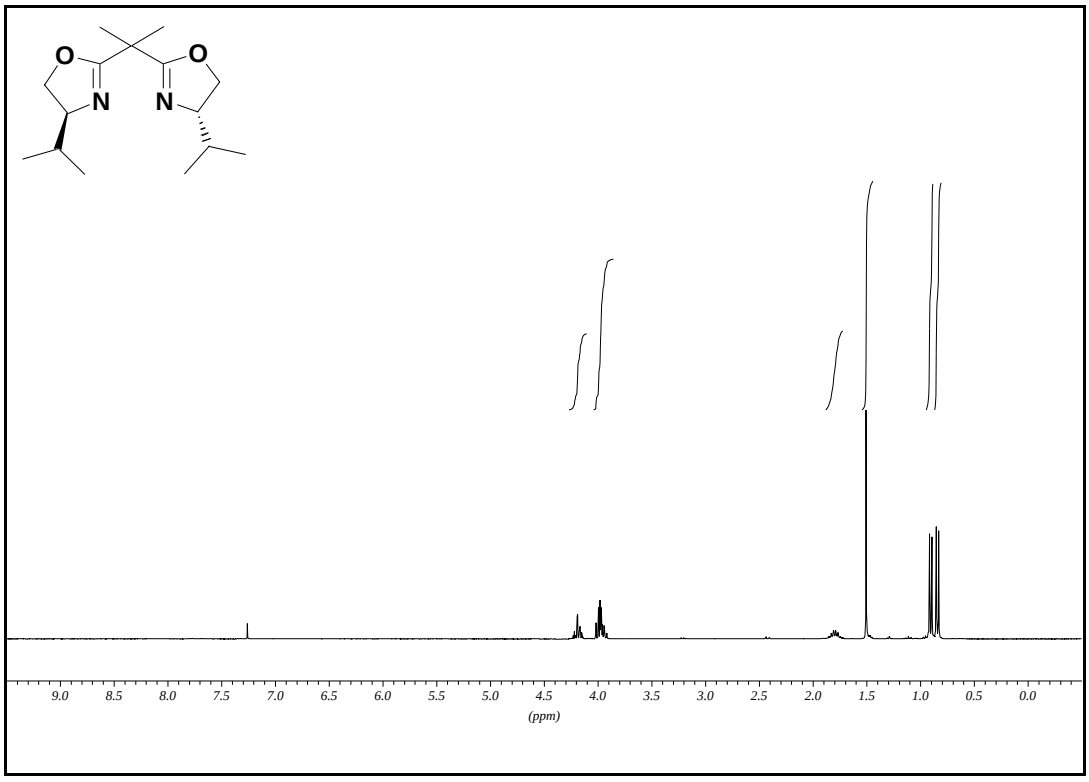
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 7.14 Hz, 3 H, CH_2CH_3), 2.33 (bs, 1 H, OH), 2.36 (dd, *J* = 7.14, 3.02 Hz, 1 H; 2-H), 2.46 (dd, *J* = 6.72, 2.88 Hz, 1 H, 3-H), 2.50-2.67 (m, 2 H, 2`-$CH_2$), 3.49-3.54 (m, 2 H, $CH_2Br$), 3.90 (s, 3 H, $CO_2Me$), 4.16 (dq, *J* = 7.14, 1.10 Hz, 2 H, $CH_2CH_3$), 4.76-4.82 (m, 1 H, 1-H), 5.11-5.27 (m, 2 H, 4`-CH_2), 5.76-5.91 (m, 1 H, 3`-H); **MS (CI, NH_3)**: *m*/*z* (%) = 396.1 (100) [M+NH_4^+], 398.0 (99) [M+NH_4^+]. Note: As tri-butyl tin hydride impurities were also present in the crude product, it was cumbersome to analyze ^{13}C NMR spectrum. Hence, after confirming the structure on the basis of 1H NMR and mass, the product was carried further for the next reaction.

6.0 Appendix

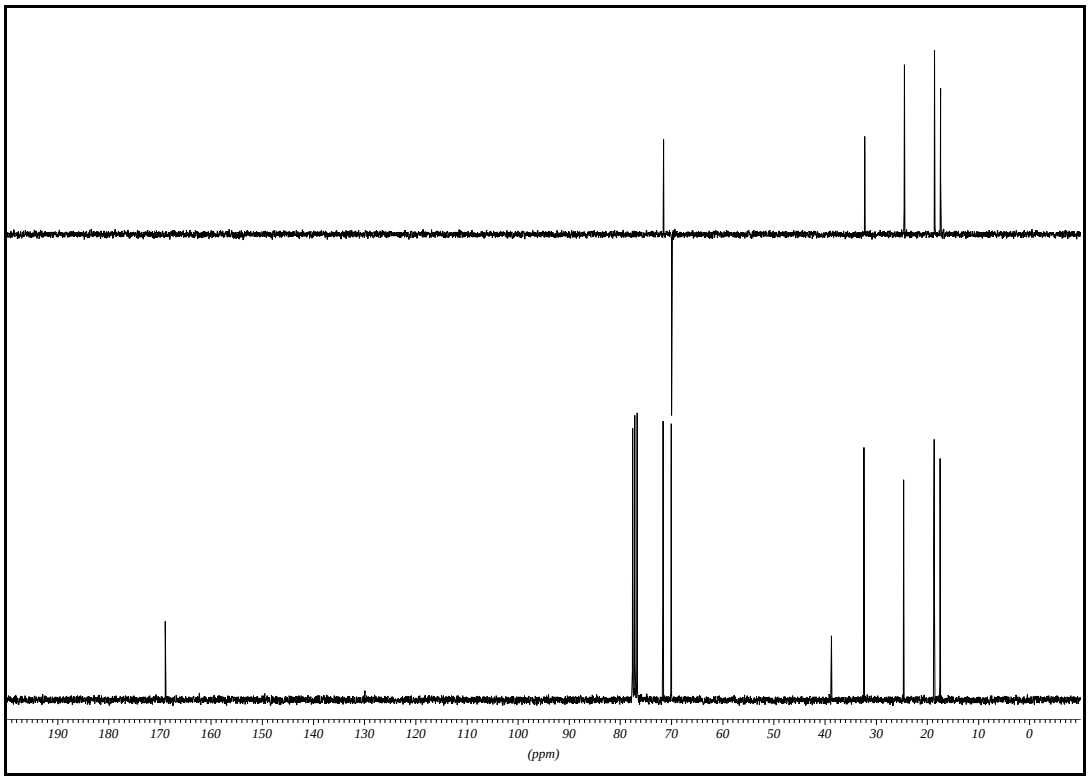
6.1 NMR Spectra

(–)-(*S*,*S*)-Bis(4-isopropyloxazoline) (164):

^{1}H NMR (300 MHz, $CDCl_3$)

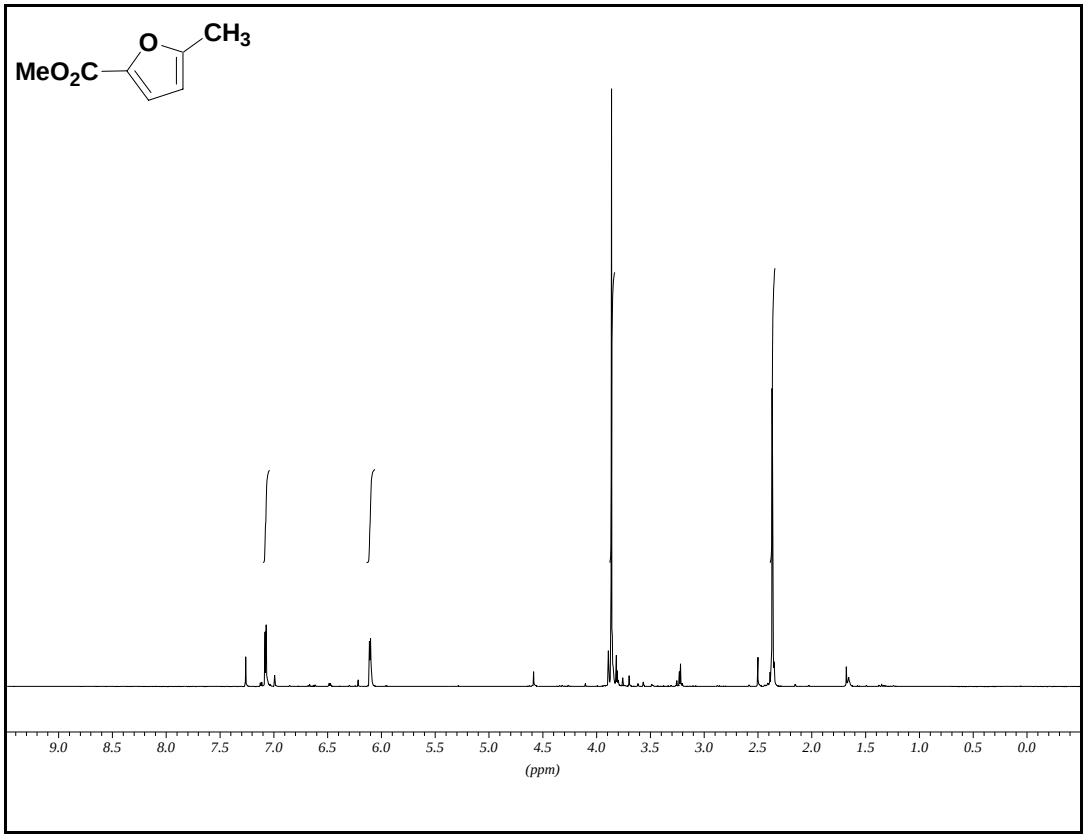


^{13}C NMR (75.5 MHz, $CDCl_3$)

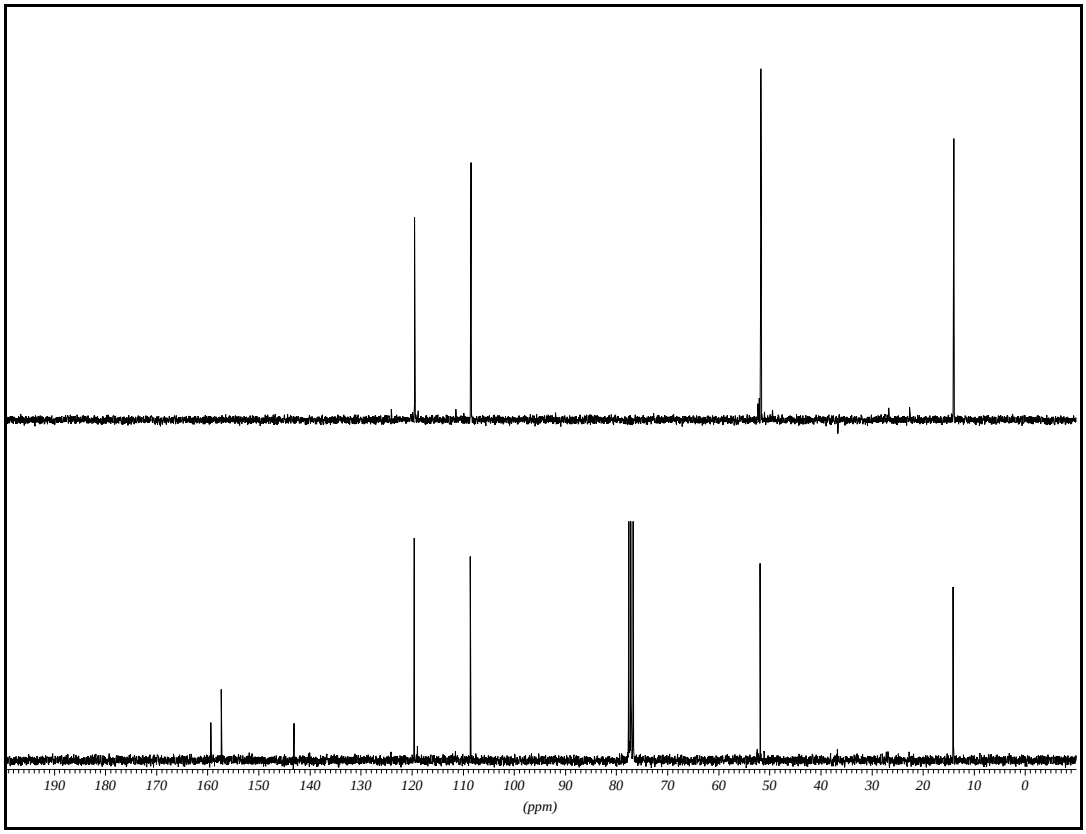


5-Methyl-furan-2-carboxylic acid methyl ester (171):

^{1}H NMR (300 MHz, $CDCl_3$)

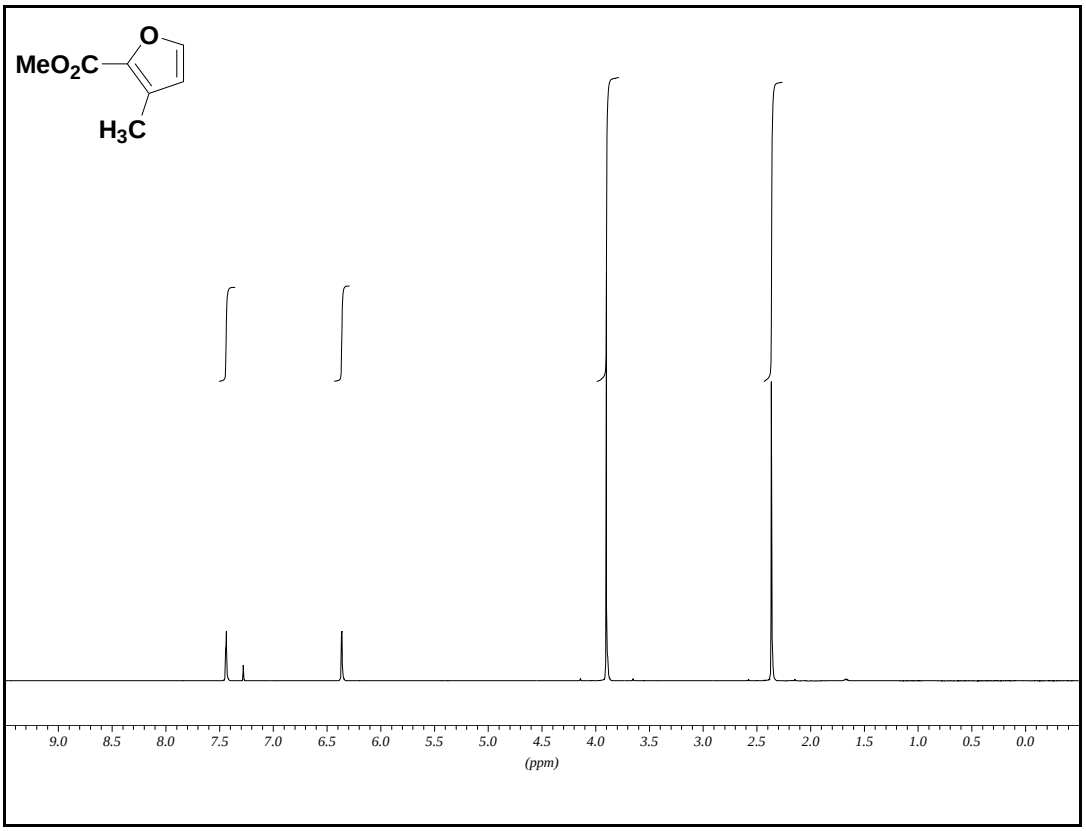


^{13}C NMR (75.5 MHz, $CDCl_3$)

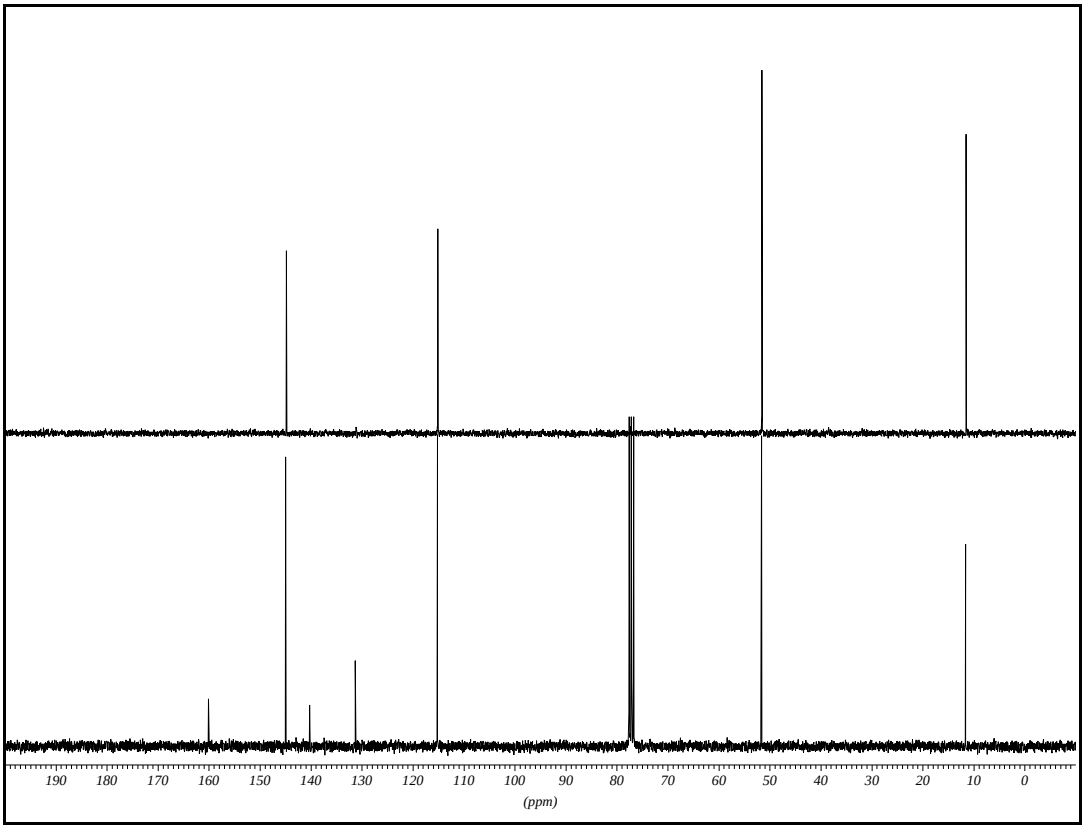


3-Methyl-furan-2-carboxylic acid methyl ester (154):

^{1}H NMR (300 MHz, $CDCl_3$)

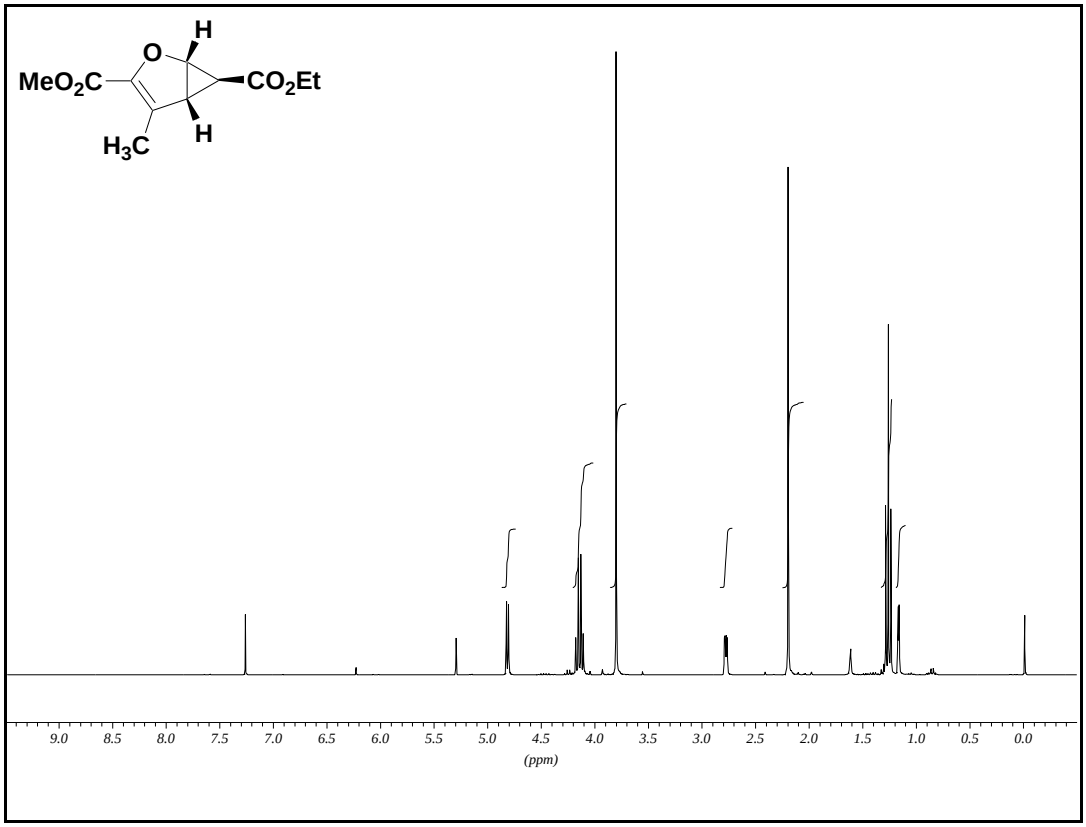


^{13}C NMR (75.5 MHz, $CDCl_3$)

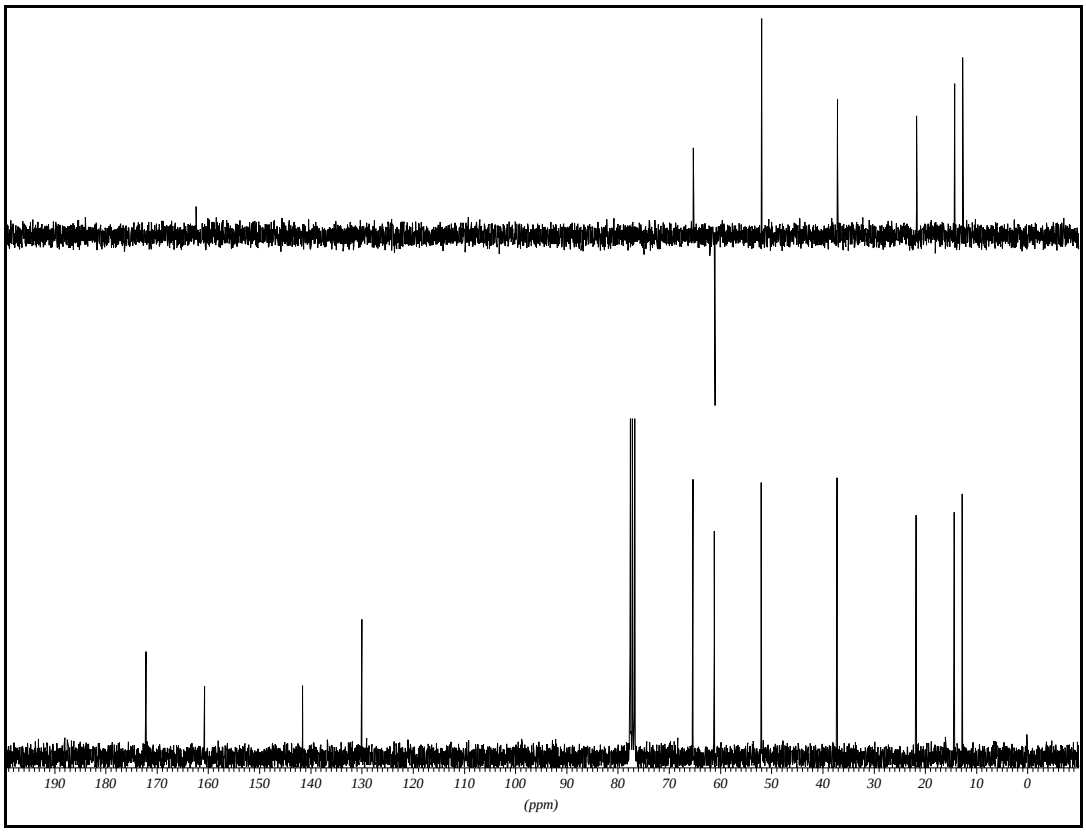


(1*S*,5*R*,6*S*)-(−)-4-Methyl-2-oxa-bicyclo[3.1.0]hex-3-ene-3,6-dicarboxylic acid 6-ethyl ester 3-methyl ester (176):

^{1}H NMR (300 MHz, $CDCl_3$)

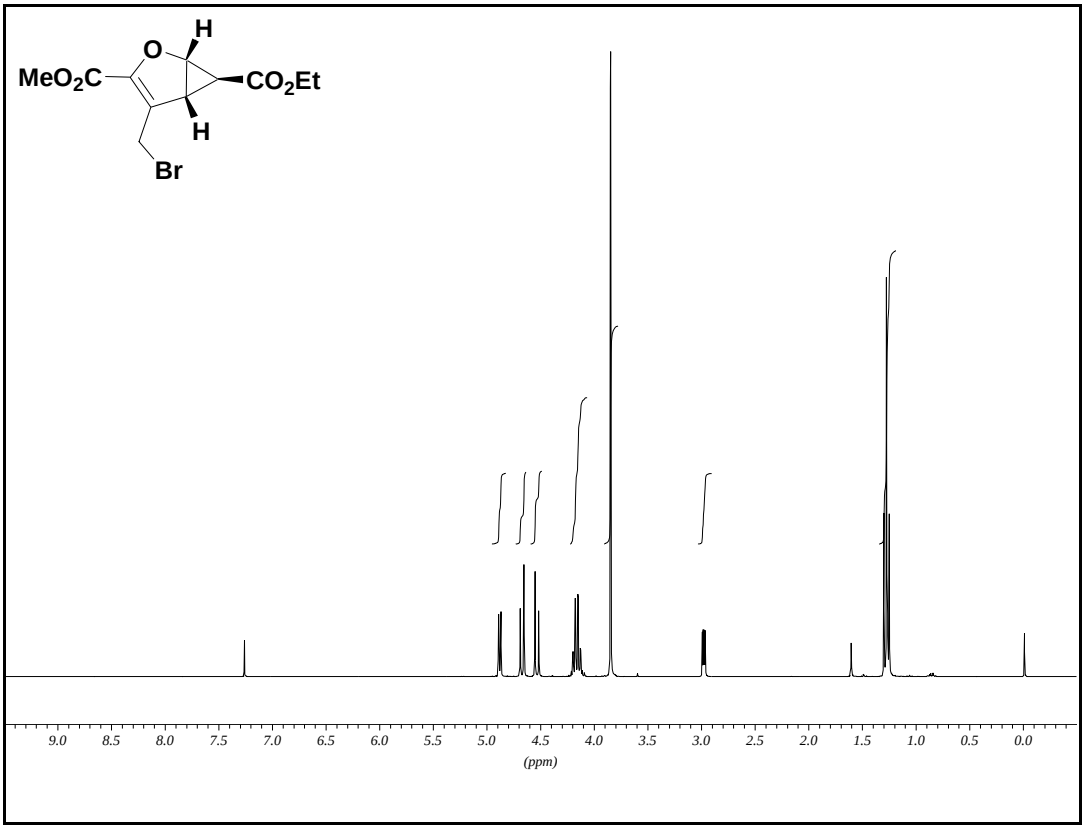


^{13}C NMR (75.5 MHz, $CDCl_3$)

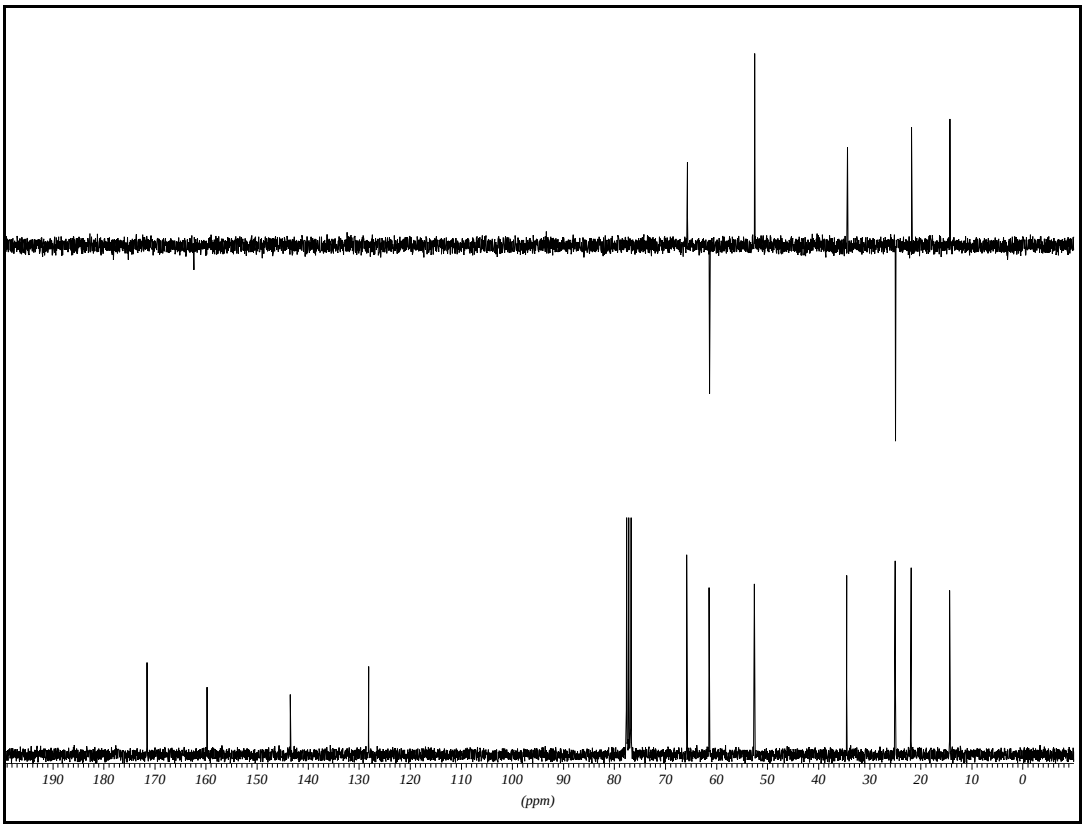


(1*S*,5*R*,6*S*)-(−)-4-Bromomethyl-2-oxa-bicyclo[3.1.0]hex-3-ene-3,6-dicarboxylic acid 6-ethyl ester 3-methyl ester (177):

^{1}H NMR (300 MHz, $CDCl_3$)

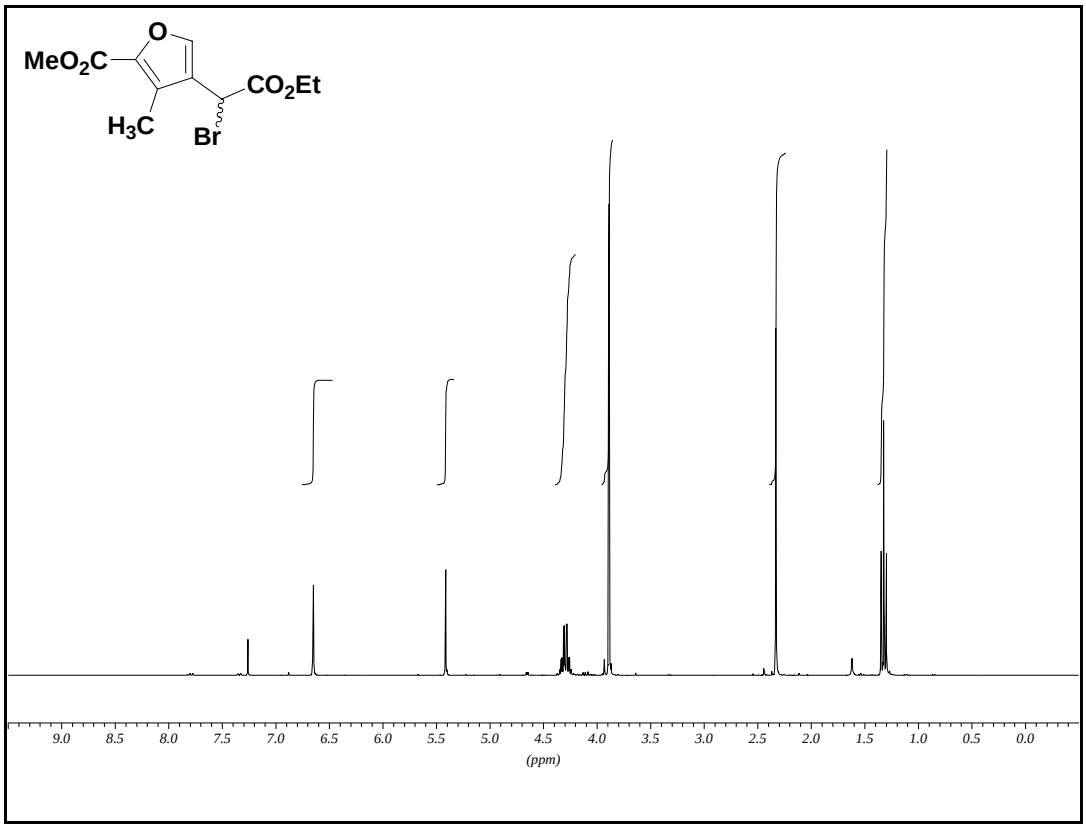


^{13}C NMR (75.5 MHz, $CDCl_3$)

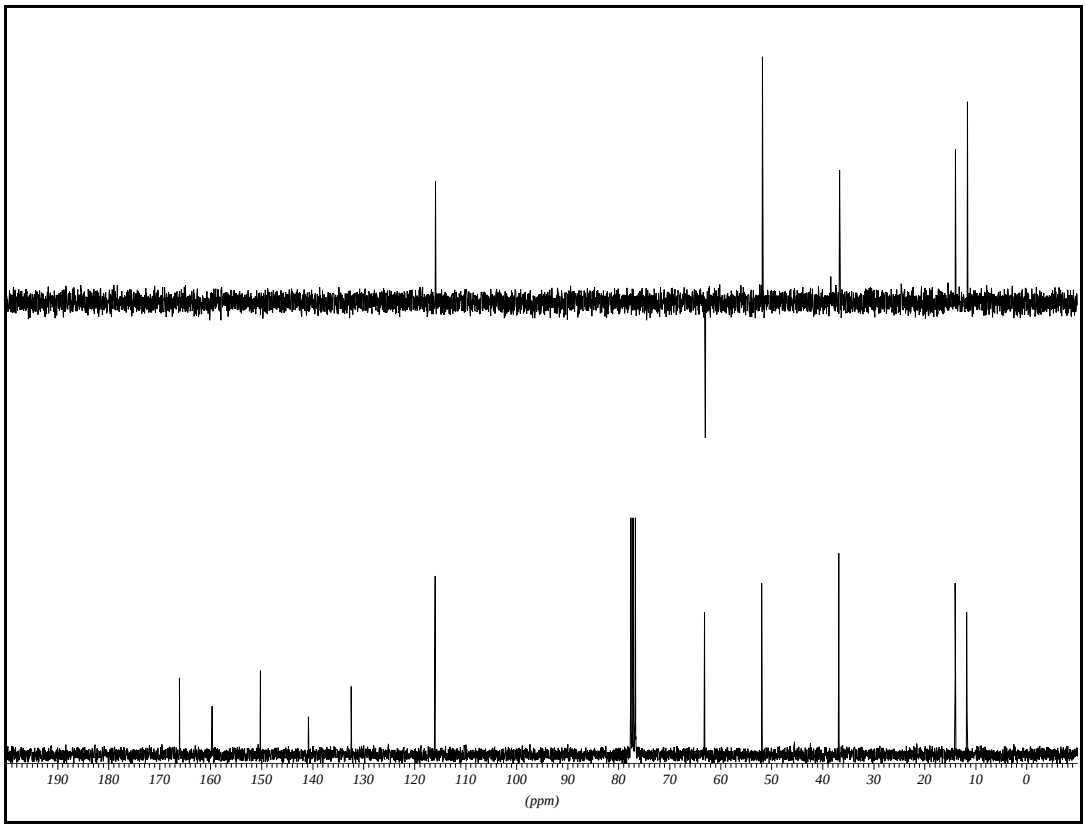


4-(Bromo-ethoxy-carbonyl-methyl)-3-methyl-furan-2-carboxylic acid methyl ester (178):

^{1}H NMR (300 MHz, $CDCl_3$)

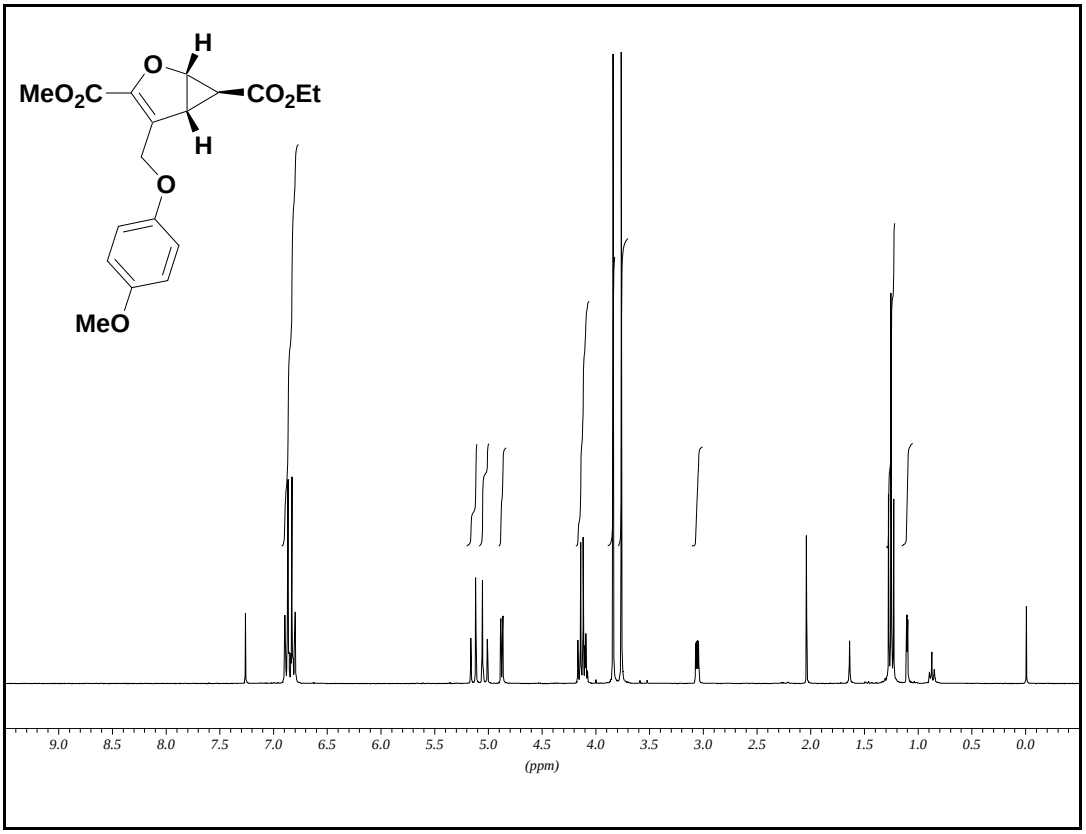


^{13}C NMR (75.5 MHz, $CDCl_3$)

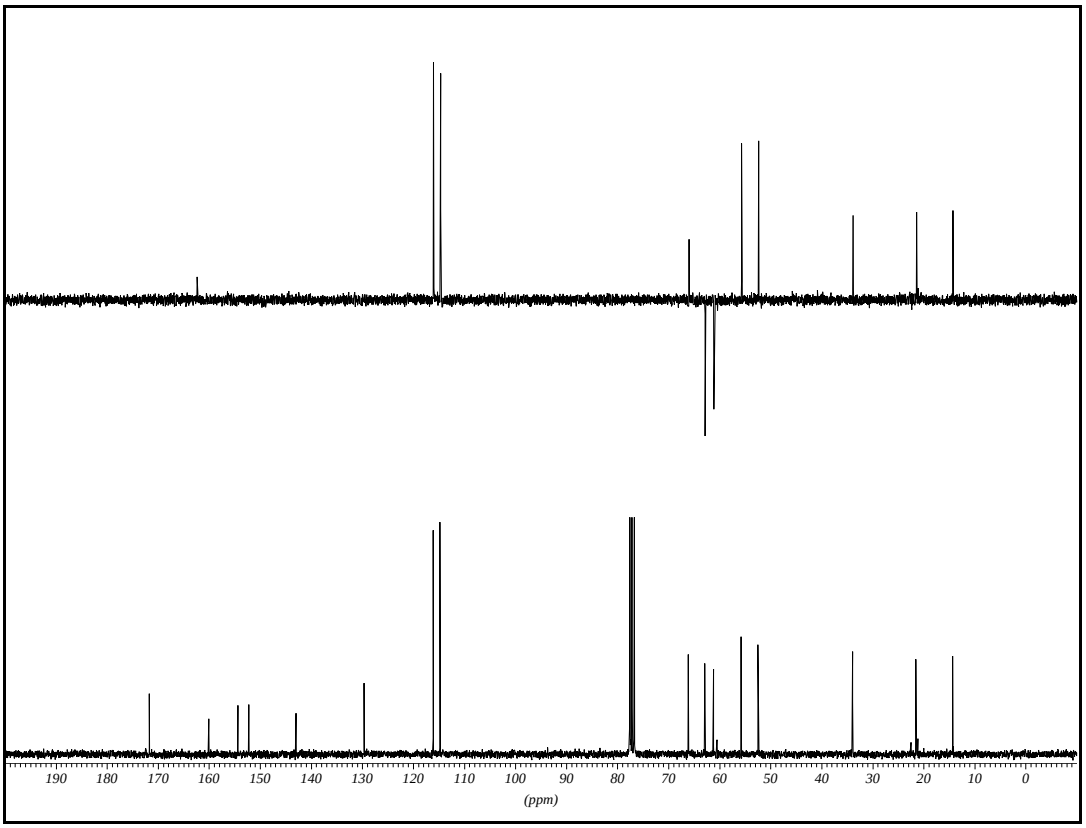


(1*S*,5*R*,6*S*)-(–)-4-(4-Methoxy-phenoxymethyl)-2-oxa-bicyclo[3.1.0]hex-3-ene-3,6-dicarboxylic acid 6-ethyl ester 3-methyl ester (179):

^{1}H NMR (300 MHz, $CDCl_3$)

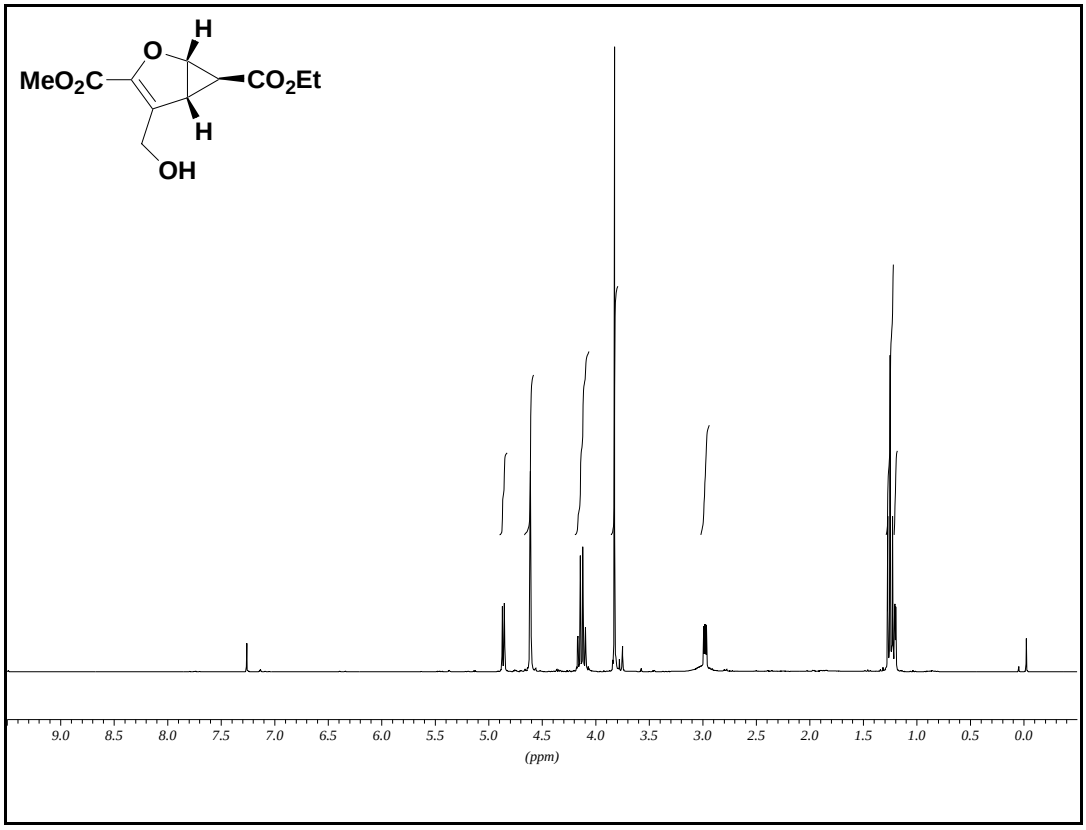


^{13}C NMR (75.5 MHz, $CDCl_3$)

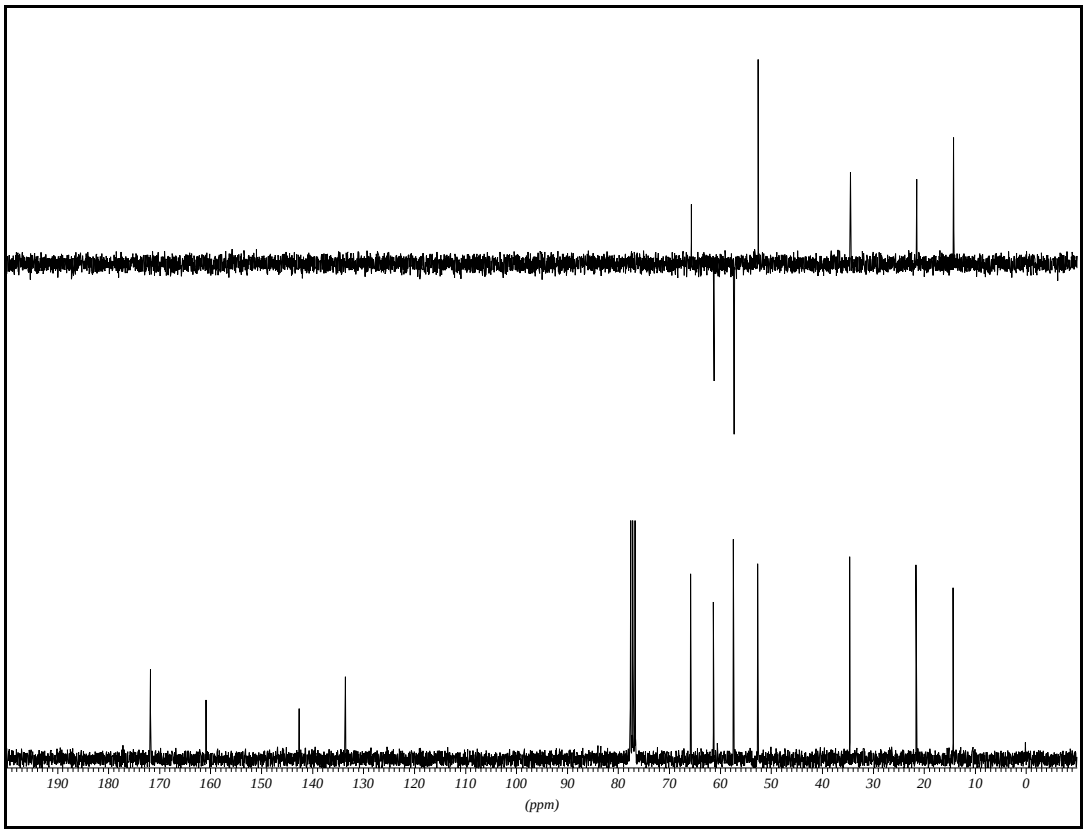


(1*S*,5*R*,6*S*)-(−)-4-Hydroxymethyl-2-oxa-bicyclo[3.1.0]hex-3-ene-3,6-dicarboxylic acid 6-ethyl ester 3-methyl ester (180):

^{1}H NMR (300 MHz, $CDCl_3$)

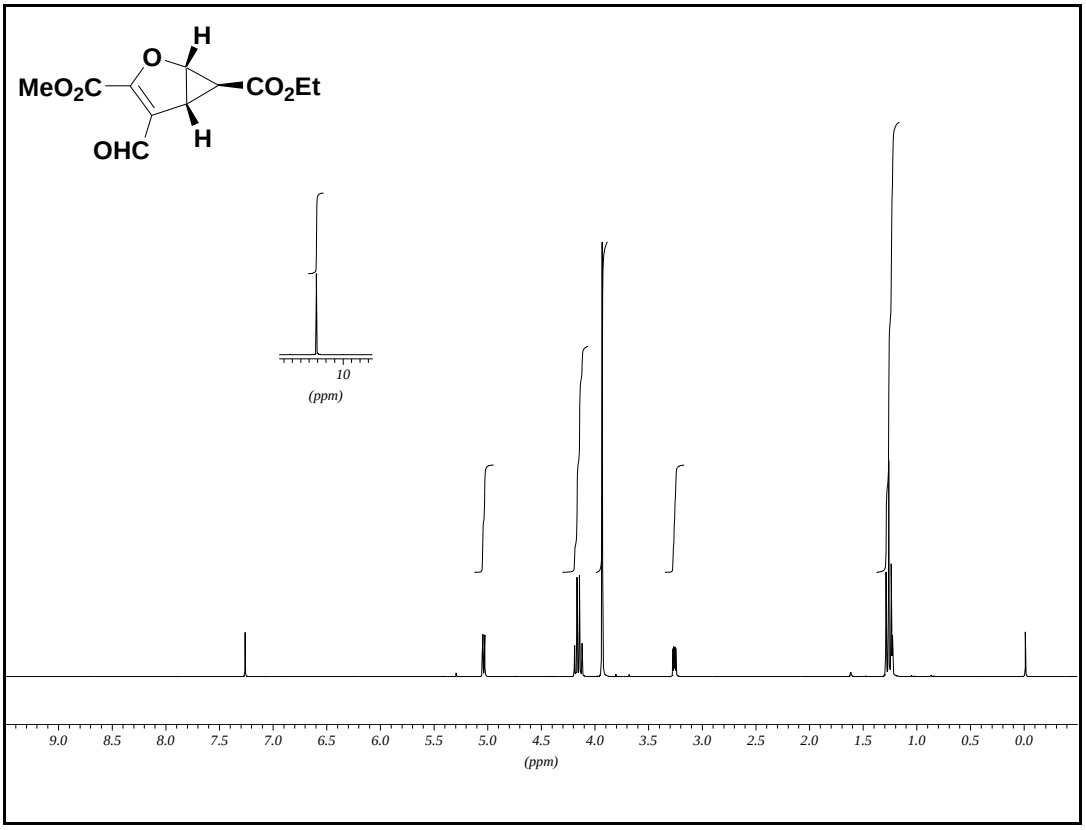


^{13}C NMR (75.5 MHz, $CDCl_3$)

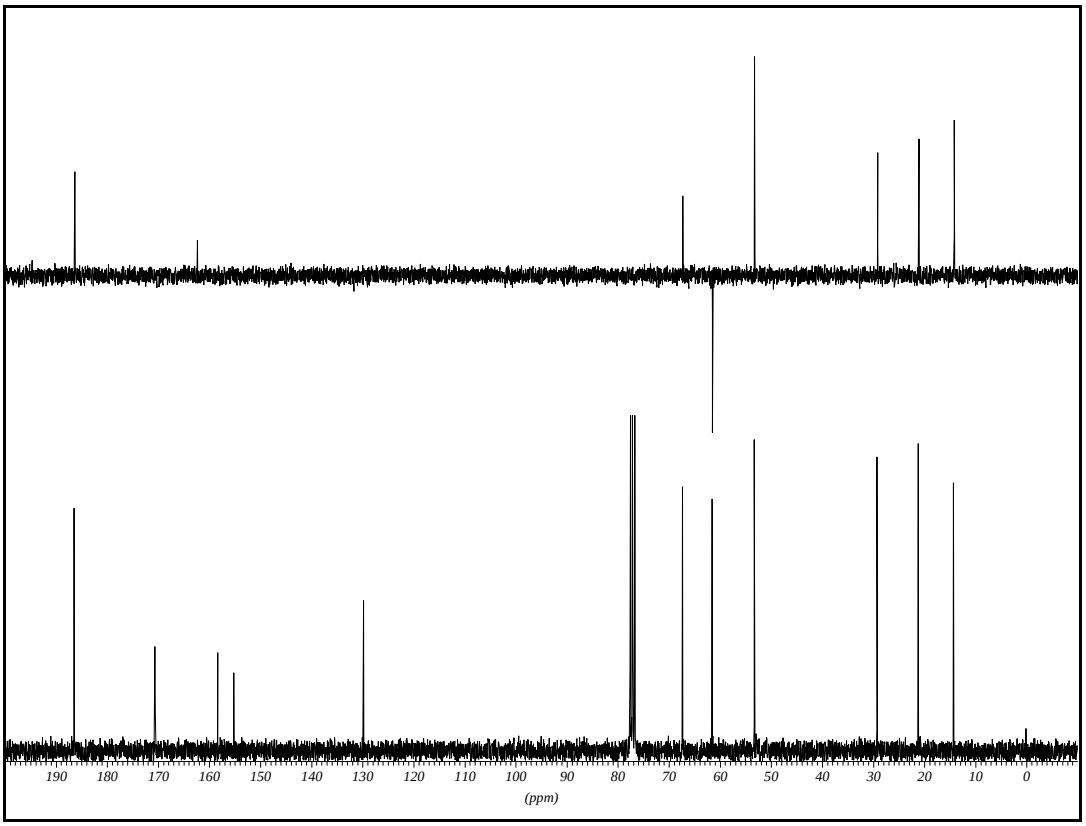


(1*S*,5*R*,6*S*)-(–)-4-Formyl-2-oxa-bicyclo[3.1.0]hex-3-ene-3,6-dicarboxylic acid 6-ethyl ester 3-methyl ester (181):

^{1}H NMR (300 MHz, $CDCl_3$)

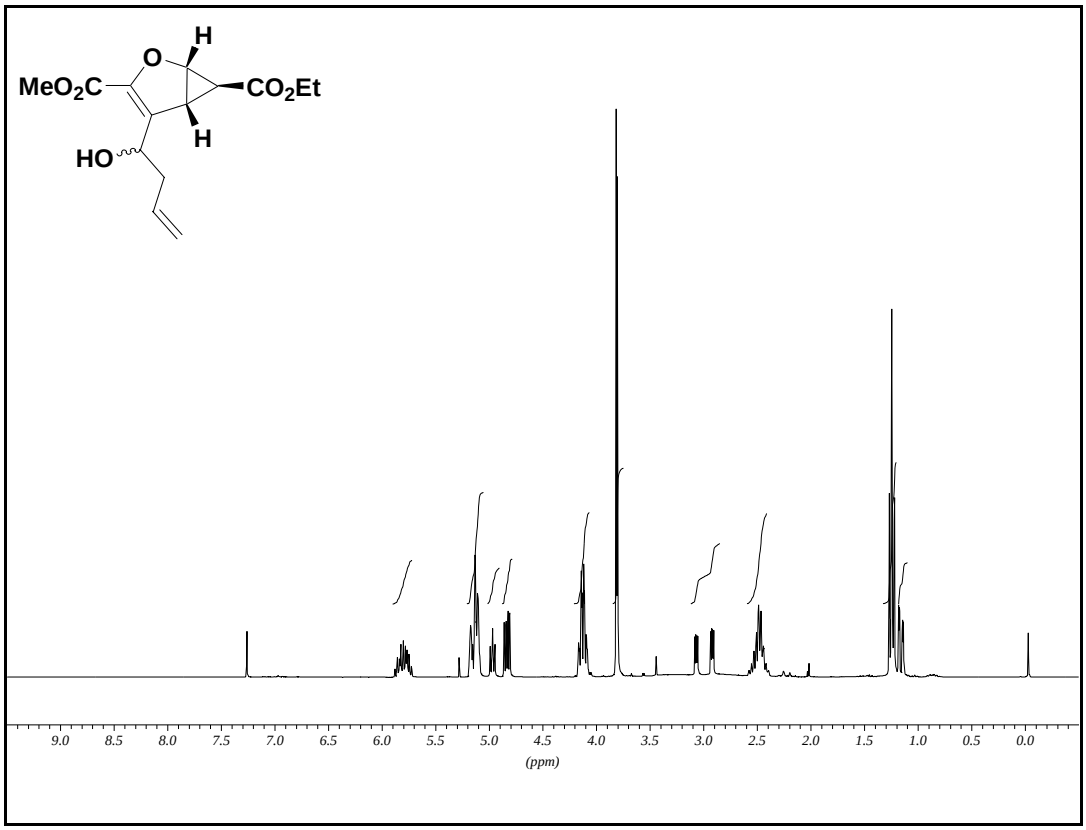


^{13}C NMR (75.5 MHz, $CDCl_3$)

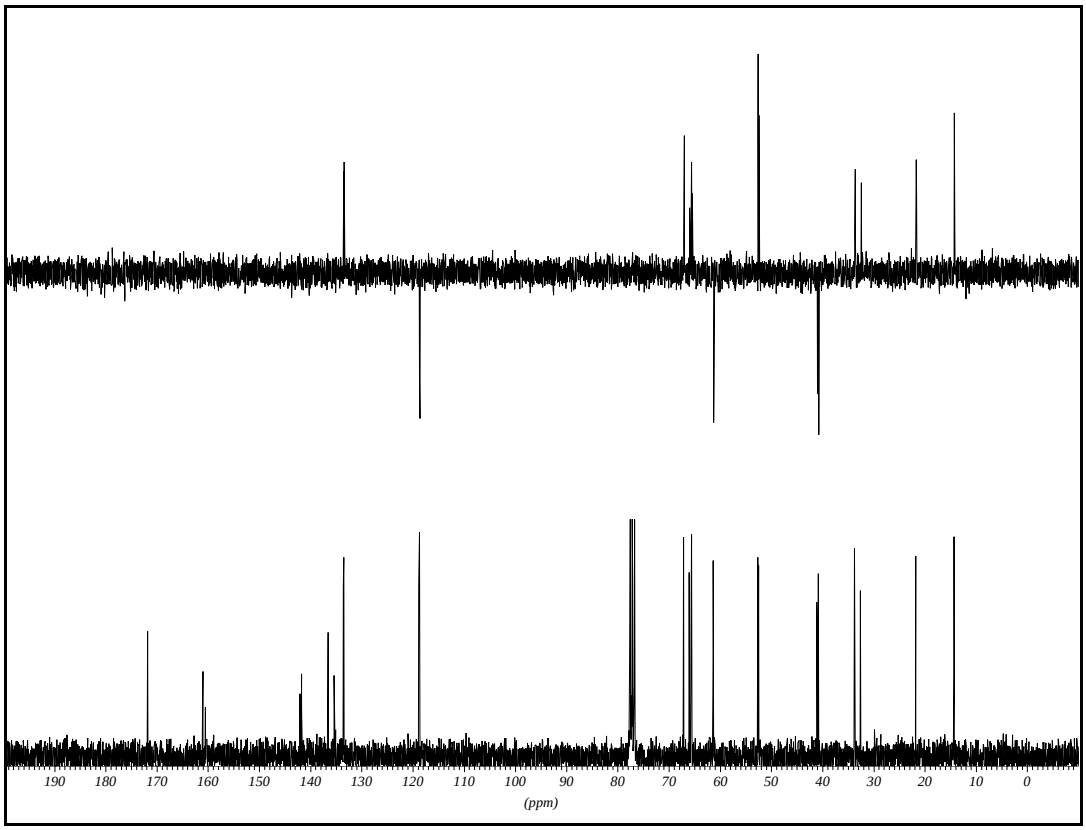


(1*S*,5*R*,6*S*)-4-(1`-Hydroxy-but-3`-enyl)-2-oxa-bicyclo[3.1.0]hex-3-ene-3,6-dicarboxylic acid 6-ethyl ester 3-methyl ester (182):

^{1}H NMR (300 MHz, $CDCl_3$)

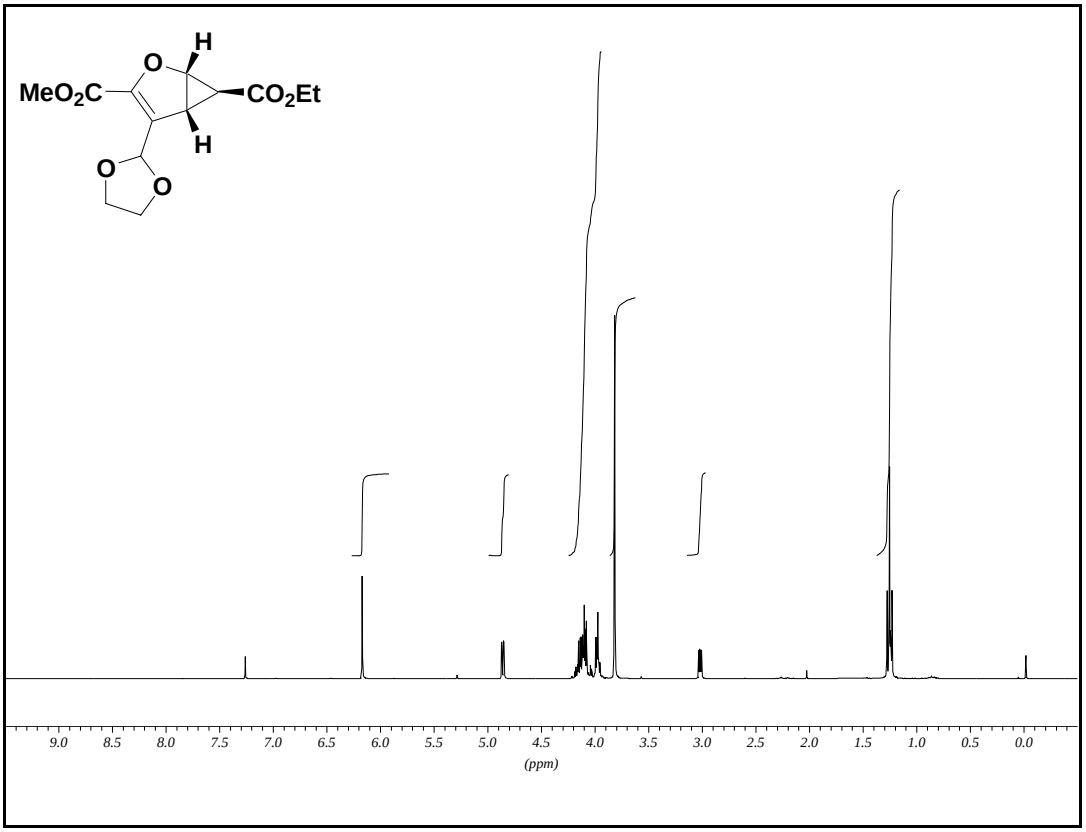


^{13}C NMR (75.5 MHz, $CDCl_3$)

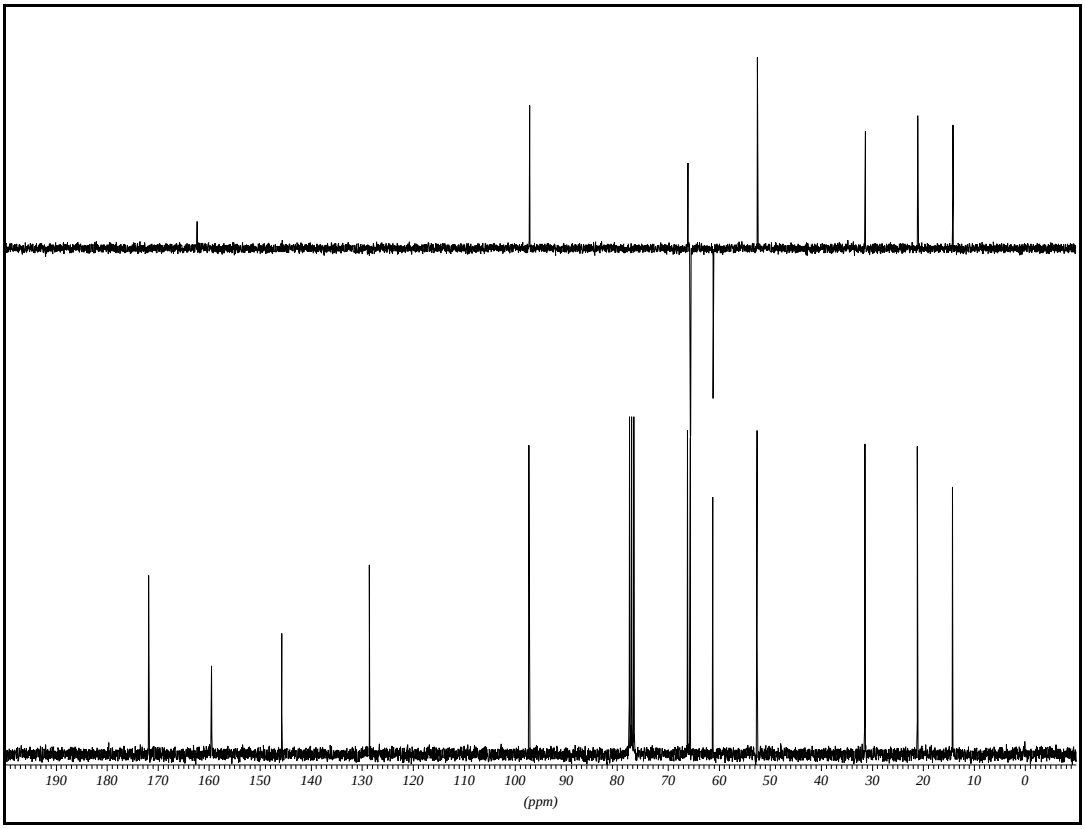


(1*S*,5*R*,6*S*)-(–)-4-[1′,3′]Dioxolan-2′-yl-2-oxa-bicyclo[3.1.0]hex-3-ene-3,6-dicarboxylic acid 6-ethyl ester 3-methyl ester (185):

^{1}H NMR (300 MHz, $CDCl_3$)

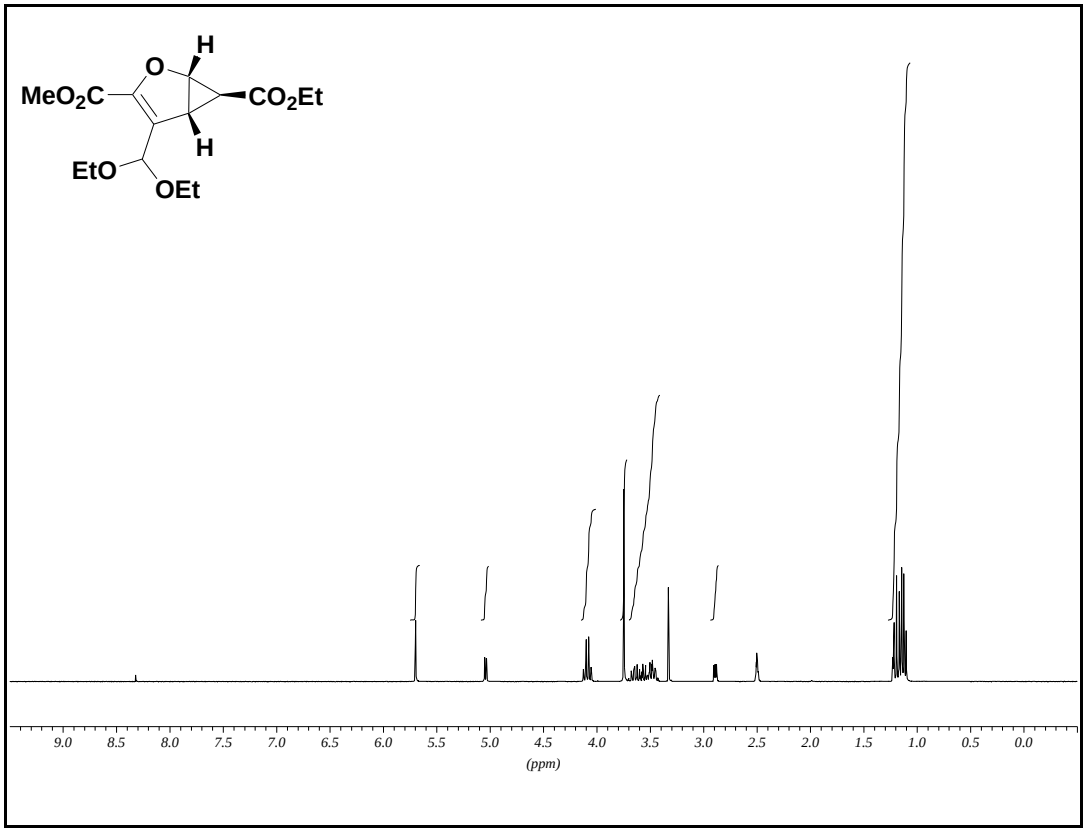


^{13}C NMR (75.5 MHz, $CDCl_3$)

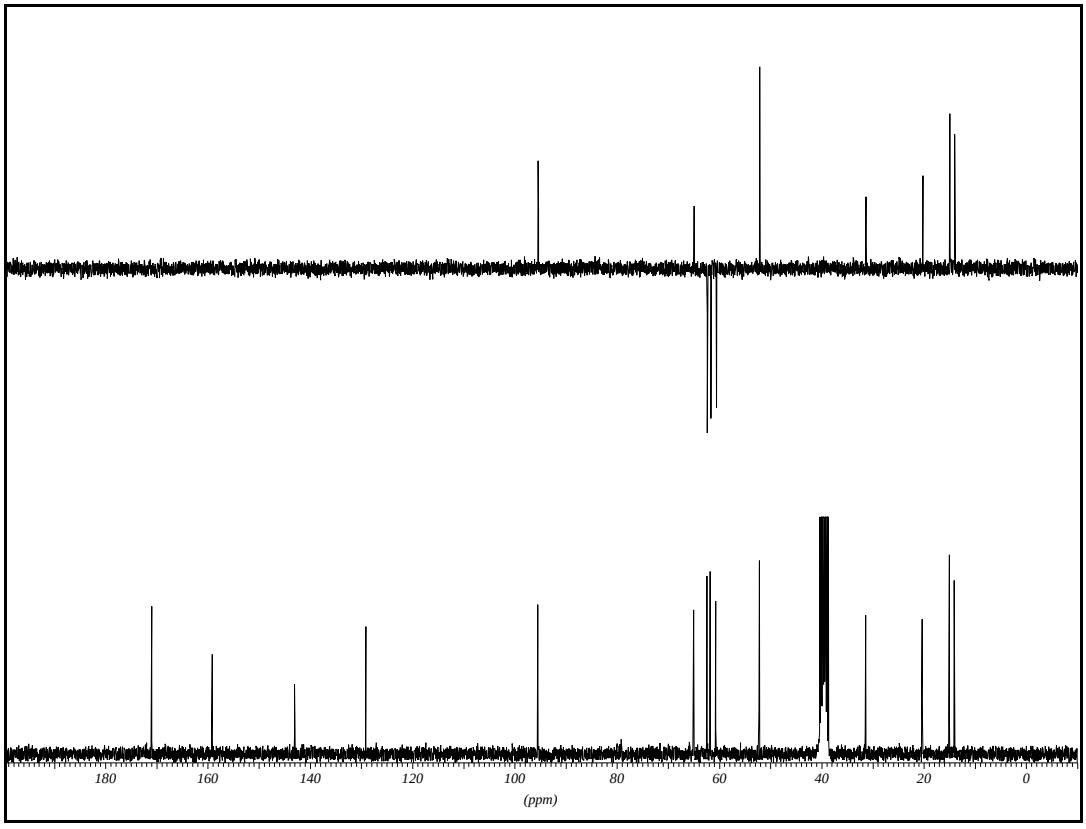


(1*S*,5*R*,6*S*)-(−)-4-Diethoxymethyl-2-oxa-bicyclo[3.1.0]hex-3-ene-3,6-dicarboxylic acid 6-ethyl ester 3-methyl ester (186):

^{1}H NMR (300 MHz, DMSO-d6)

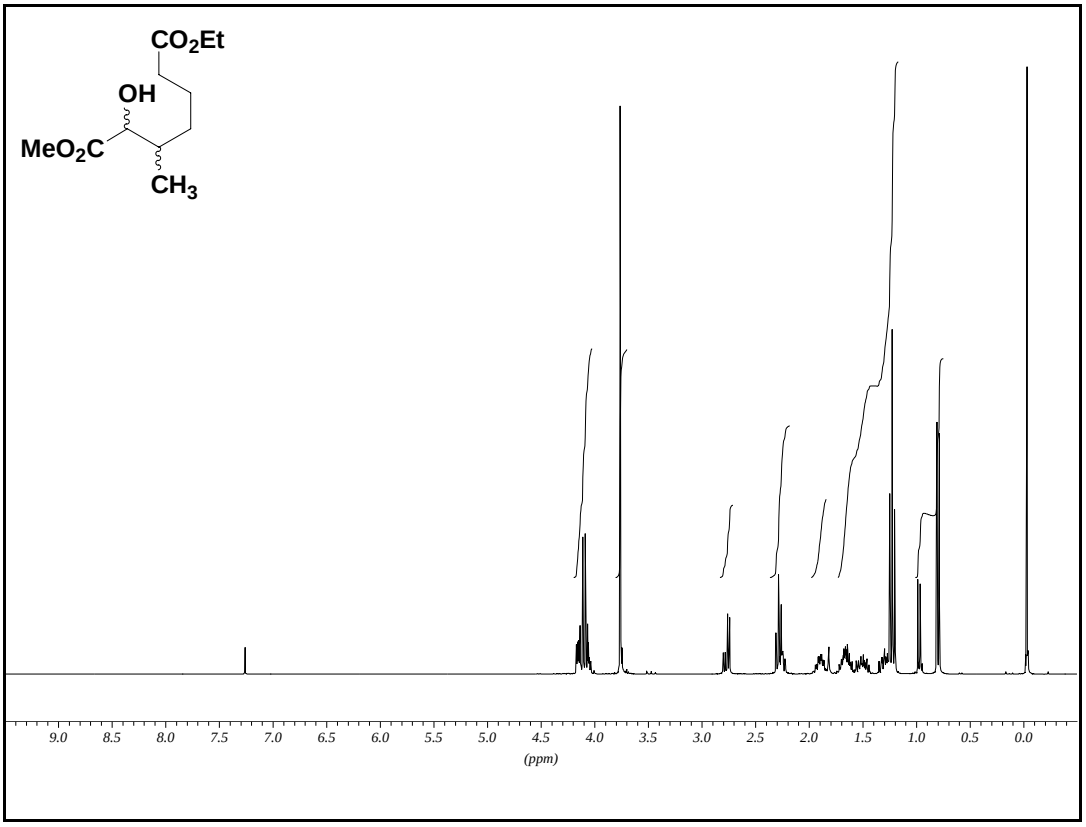


^{13}C NMR (75.5 MHz, DMSO-d6)

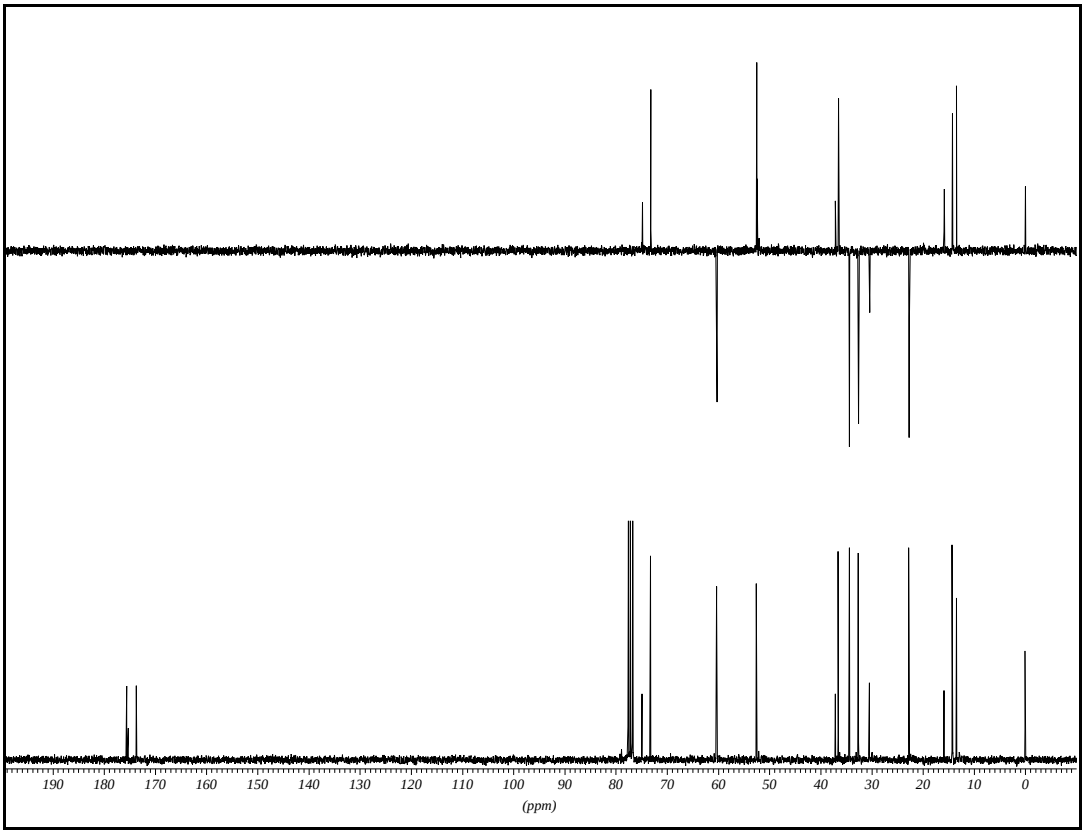


2-Hydroxy-3-methyl-heptanedioic acid 7-ethyl ester 1-methyl ester (187):

^{1}H NMR (300 MHz, $CDCl_3$)

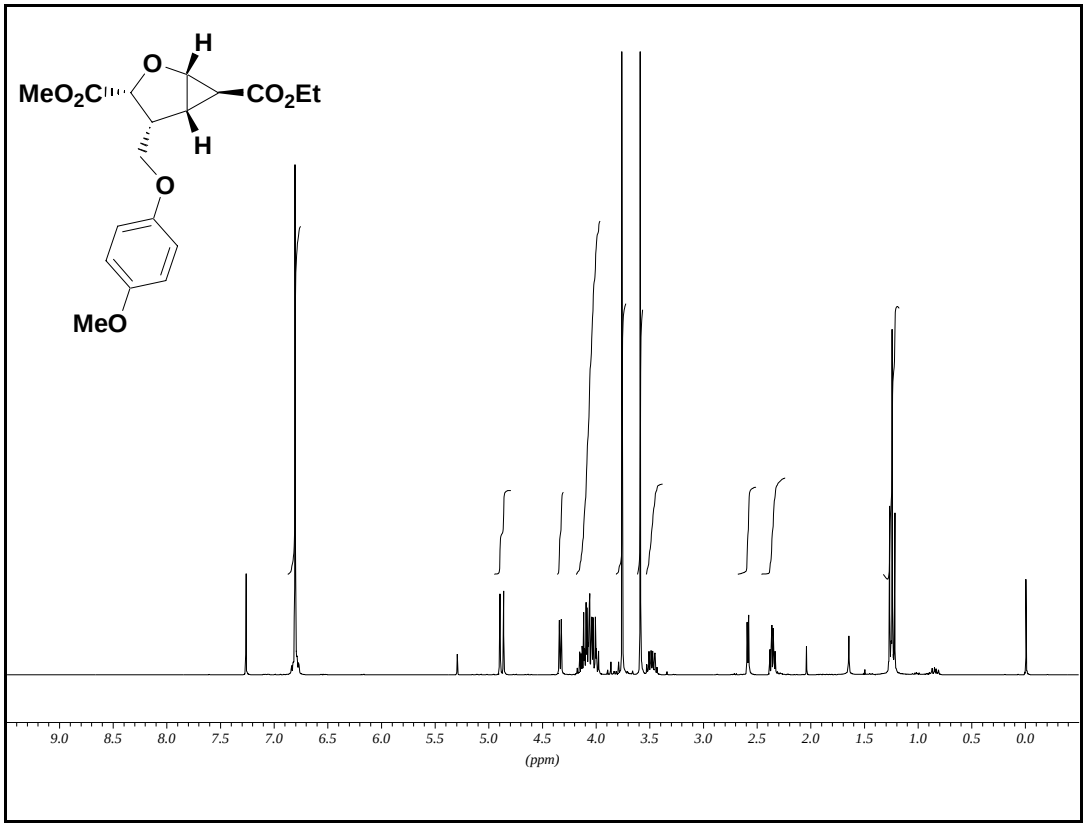


^{13}C NMR (75.5 MHz, $CDCl_3$)

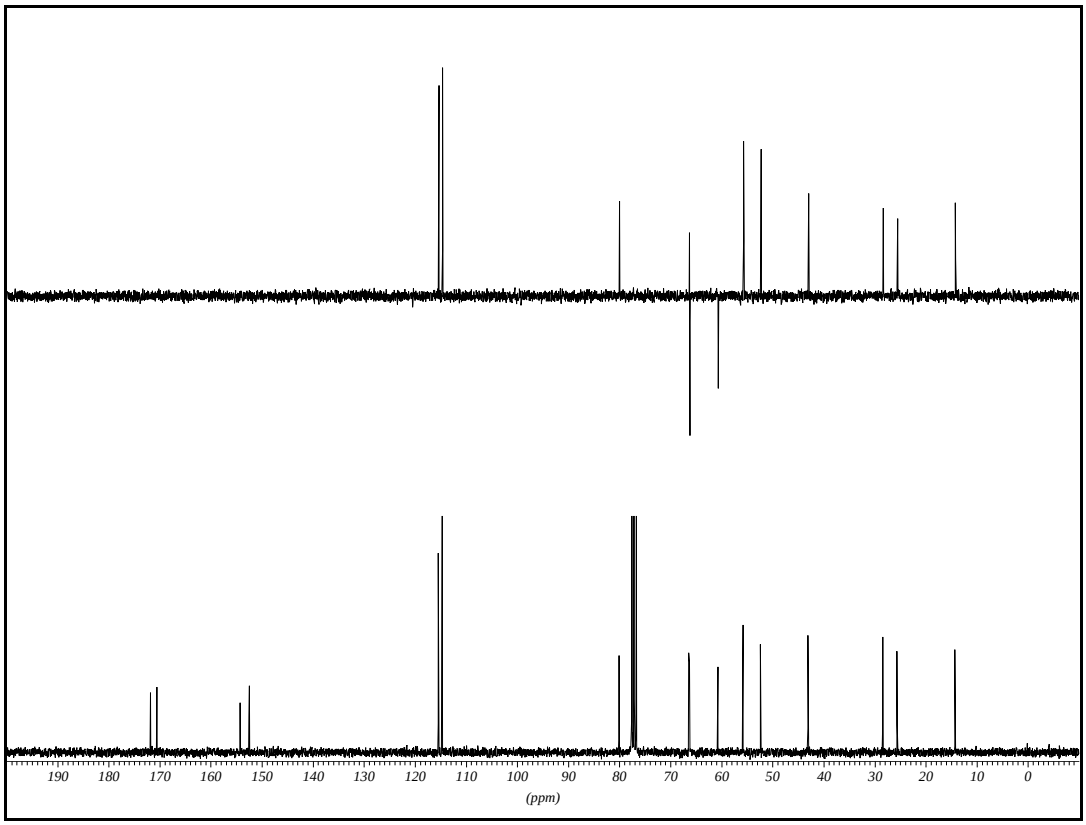


(1*S*,3*R*,4*R*,5*R*,6*S*)-(–)4-(4`-Methoxy-phenoxymethyl)-2-oxa-bicyclo[3.1.0]hexane-3,6-dicarboxylic acid 6-ethyl ester 3-methyl ester (188):

^{1}H NMR (300 MHz, $CDCl_3$)

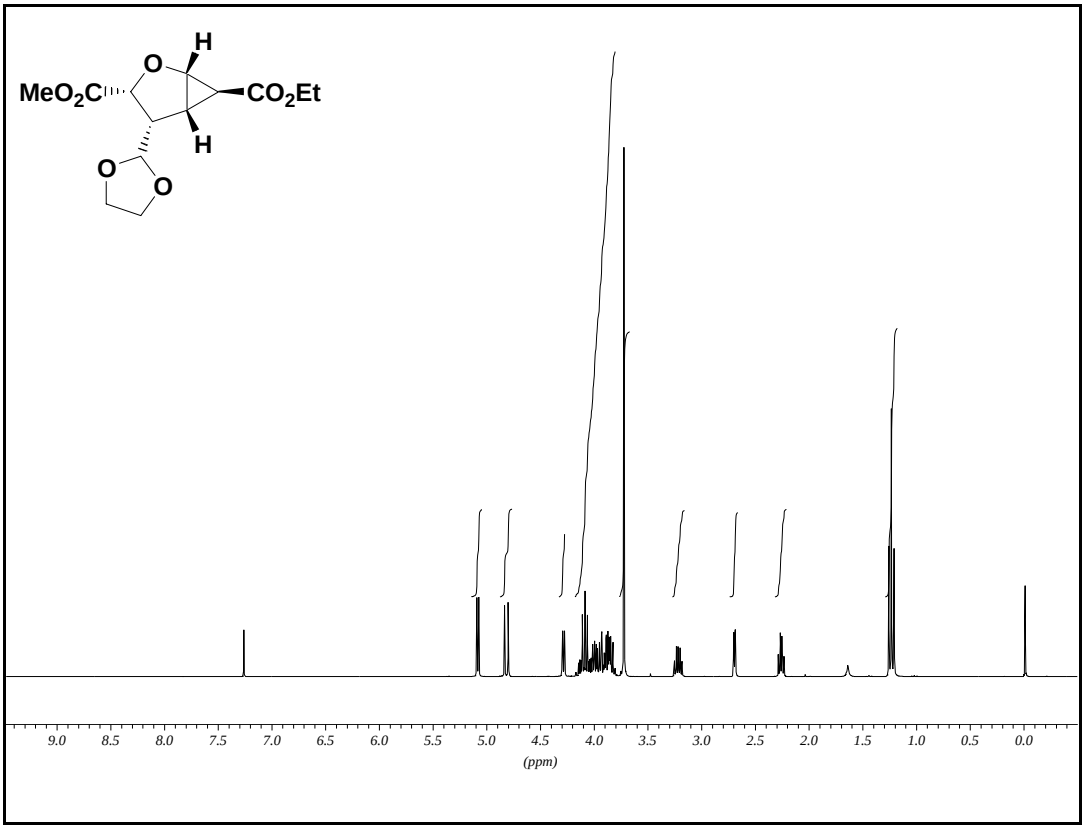


^{13}C NMR (75.5 MHz, $CDCl_3$)

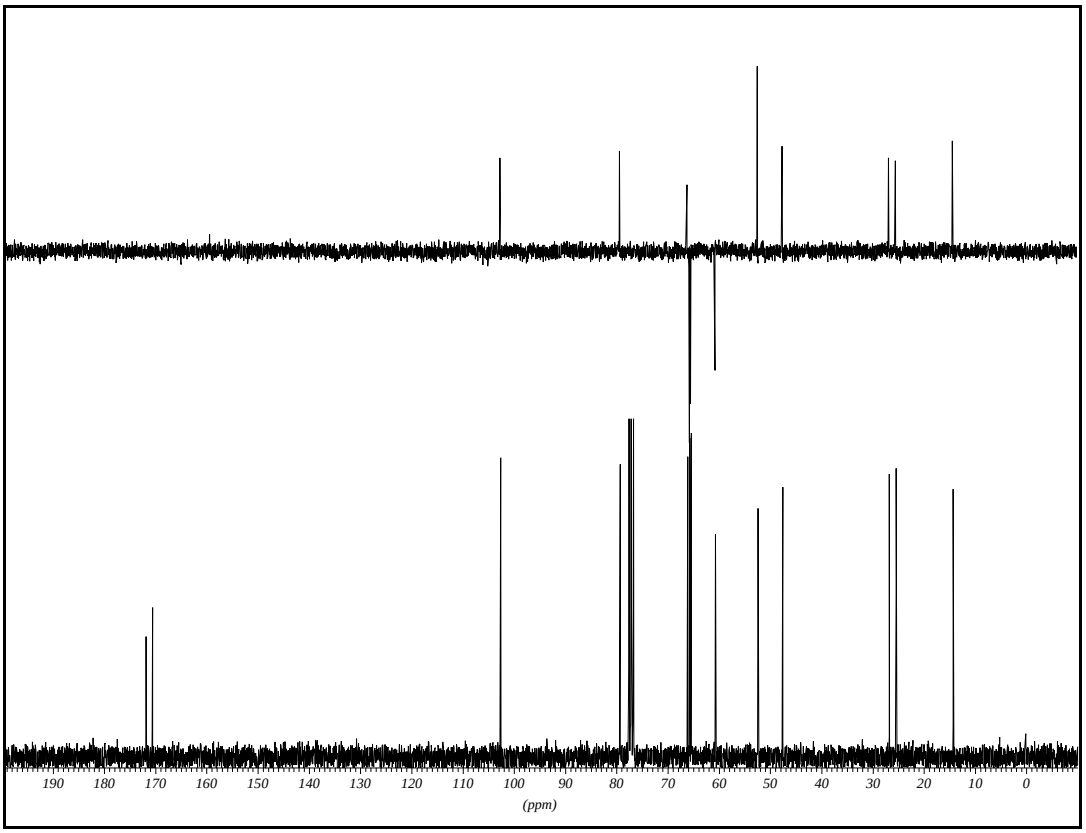


(1*S*,3*R*,4*S*,5*S*,6*S*)-(+)-4-[1´´,3´´]Dioxolan-2´-yl-2-oxa-bicyclo[3.1.0]hexane-3,6-dicarboxylic acid 6-ethyl ester 3-methyl ester (189):

^{1}H NMR (300 MHz, $CDCl_3$)

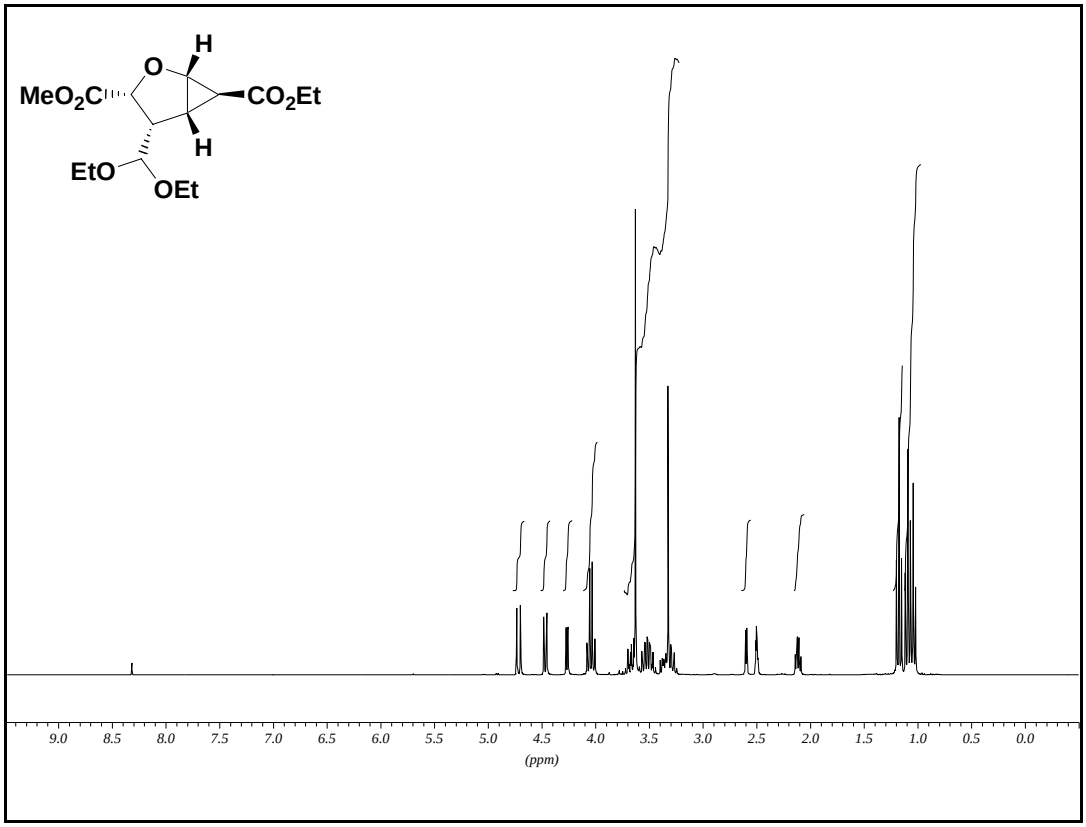


^{13}C NMR (75.5 MHz, $CDCl_3$)

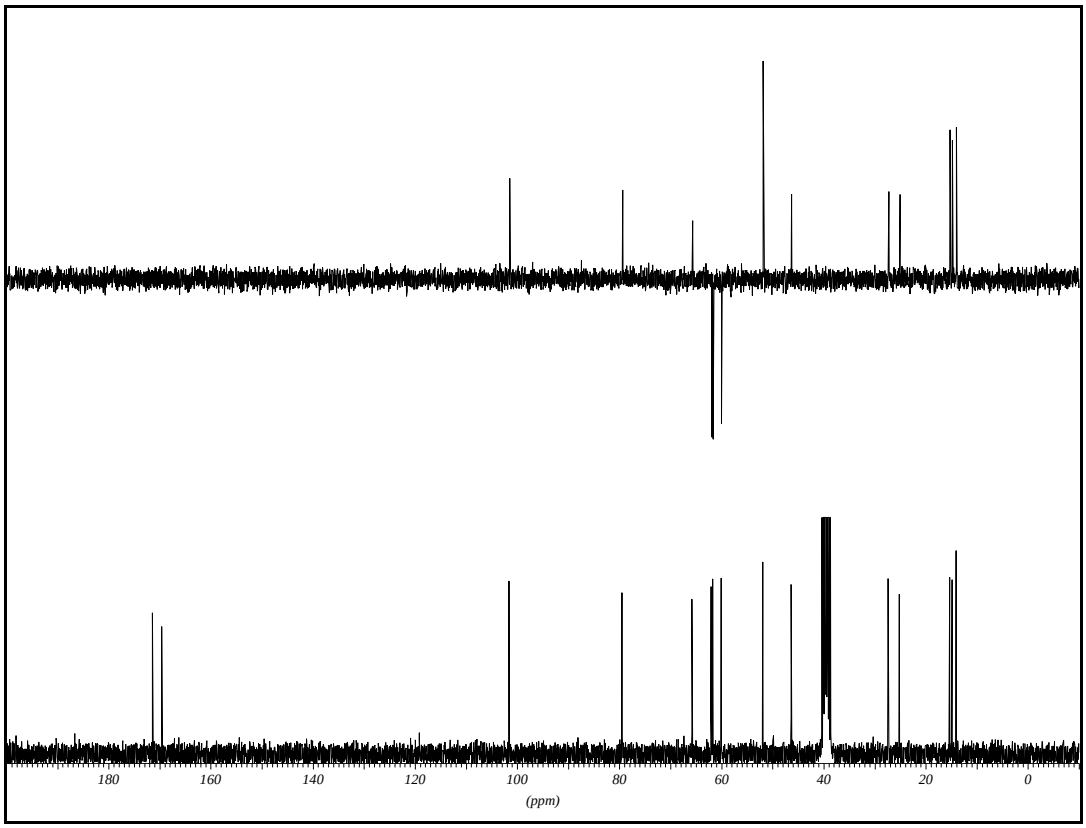


(1*S*,3*R*,4*S*,5*S*,6*S*)-(+)-4-Diethoxymethyl-2-oxa-bicyclo[3.1.0]hexane-3,6-dicarboxylic acid 6-ethyl ester 3-methyl ester (190):

^{1}H NMR (300 MHz, DMSO-d6)

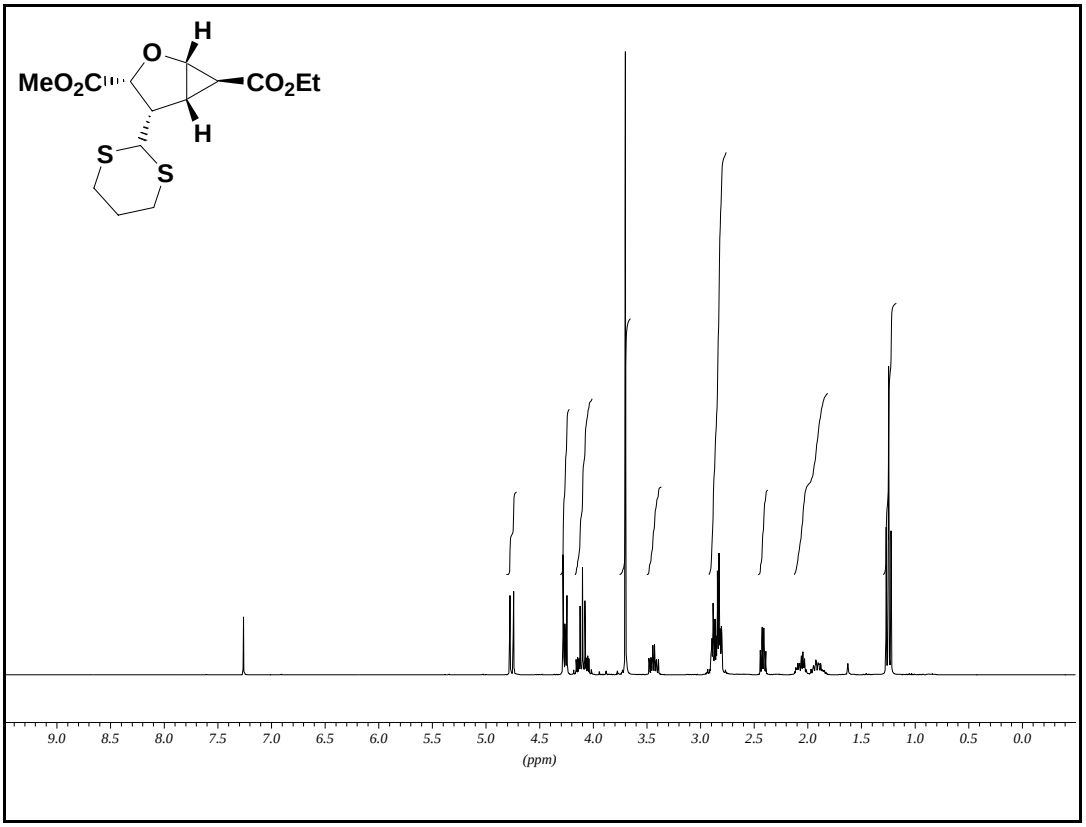


^{13}C NMR (75.5 MHz, DMSO-d6)

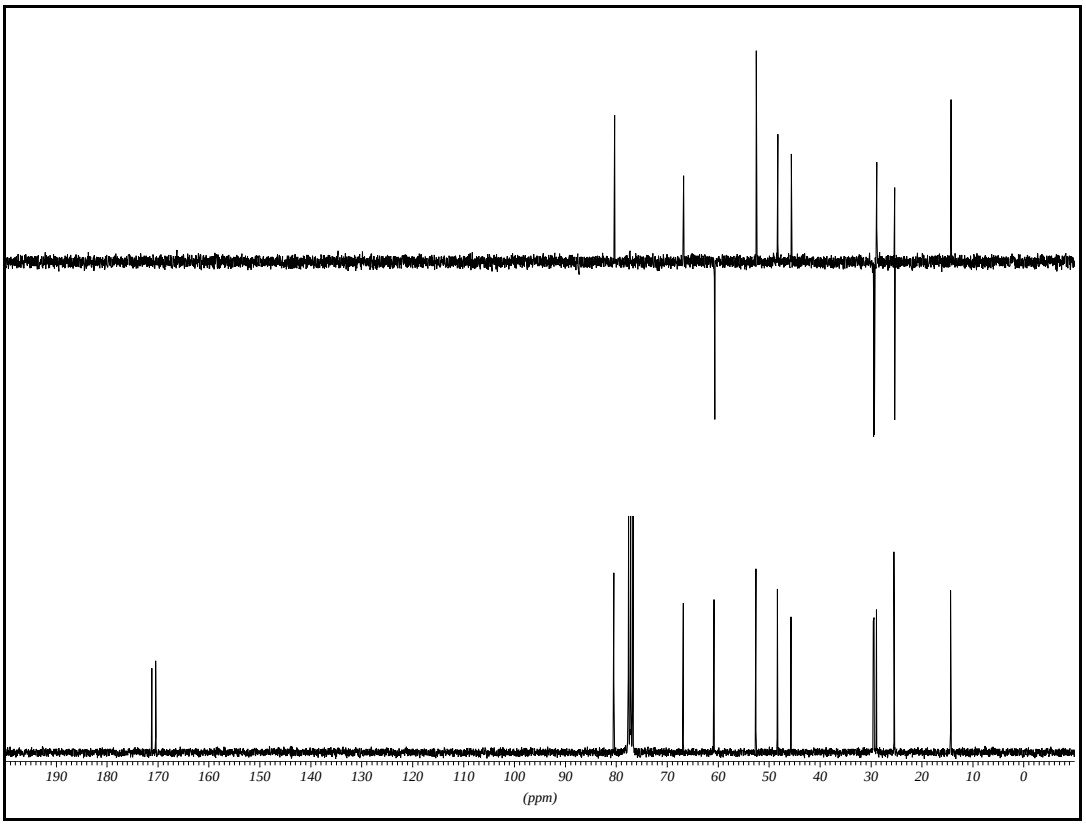


(1*S*,3*R*,4*S*,5*S*,6*S*)-(–)4-[1`,3`]Dithian-2-yl-2-oxa-bicyclo[3.1.0]hexane-3,6-dicarboxylic acid 6-ethyl ester 3-methyl ester (191):

^{1}H NMR (300 MHz, $CDCl_3$)

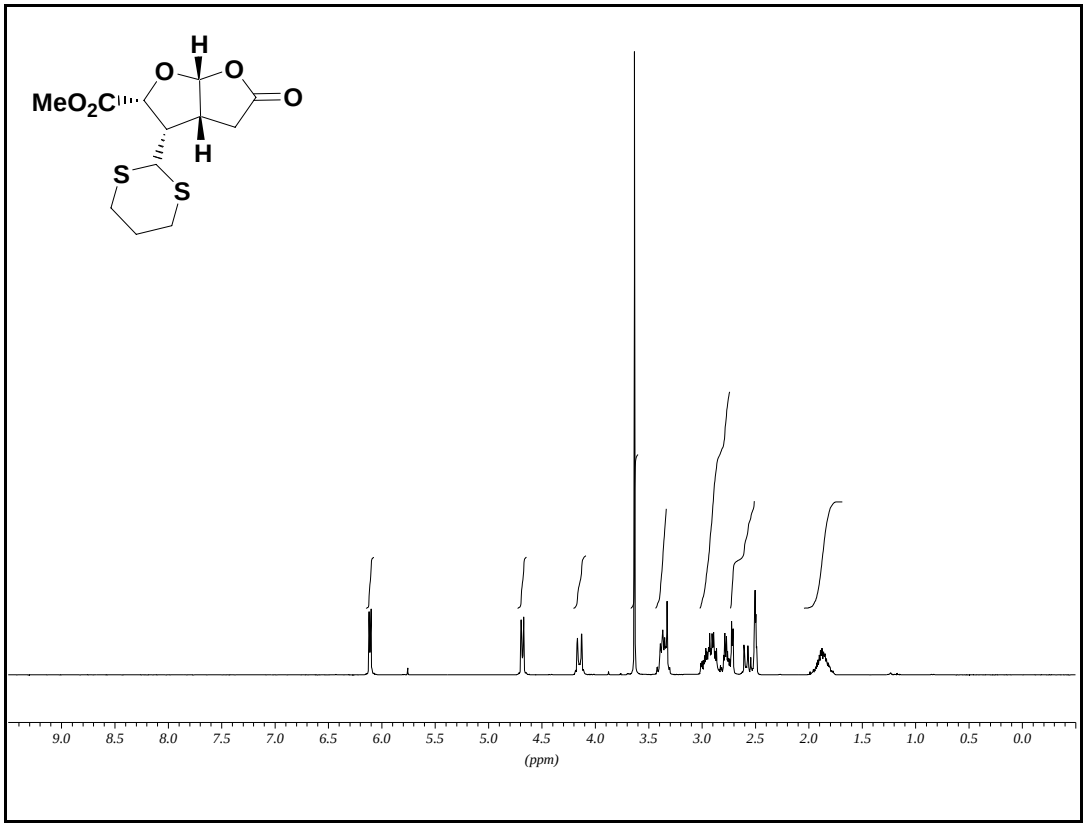


^{13}C NMR (75.5 MHz, $CDCl_3$)

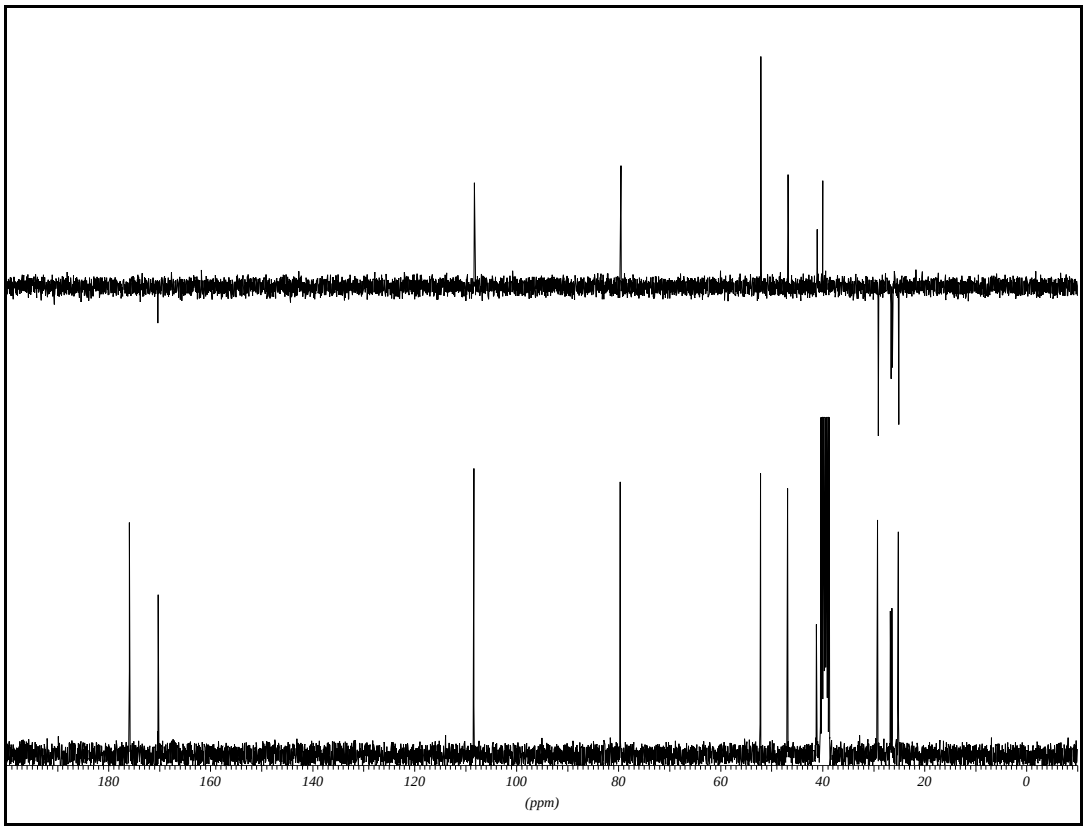


(2*R*,3*S*,3a*R*,6a*R*)-(–)-3-[1`,3`]Dithian-2-yl-5-oxo-hexahydro-furo[2,3-*b*]furan-2-carboxylic acid methyl ester (192):

^{1}H NMR (300 MHz, DMSO-d6)

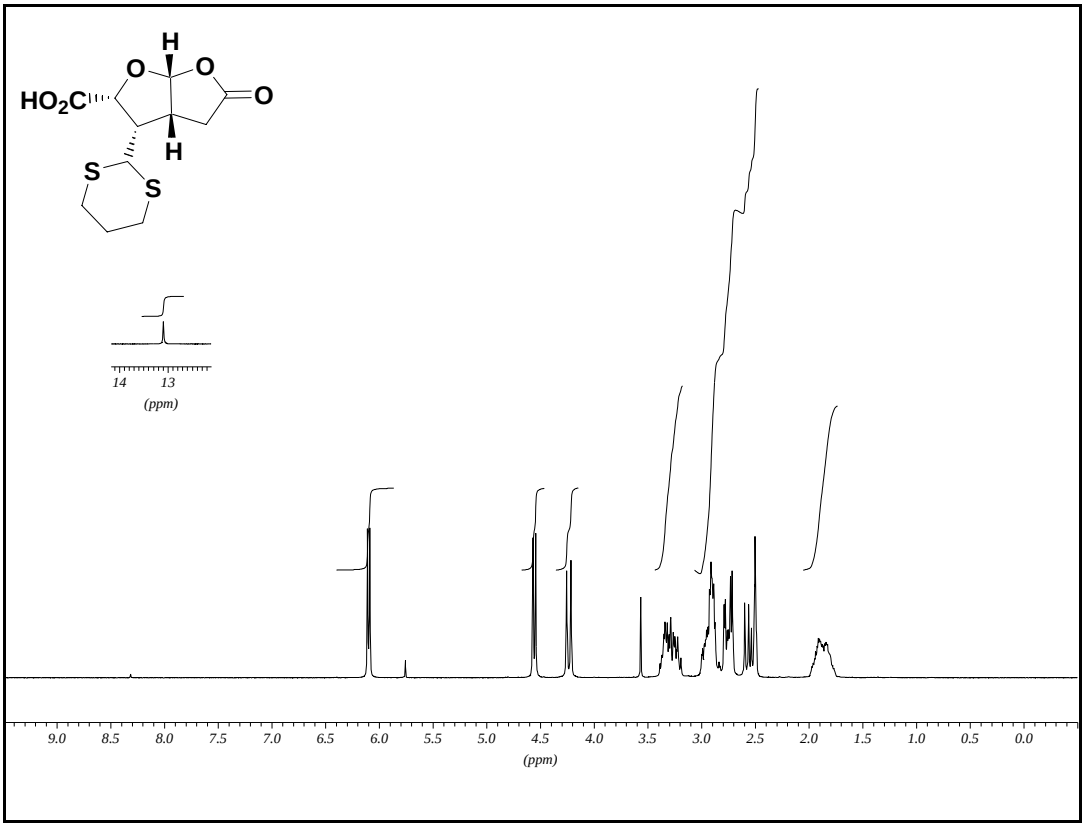


^{13}C NMR (75.5 MHz, DMSO-d6)

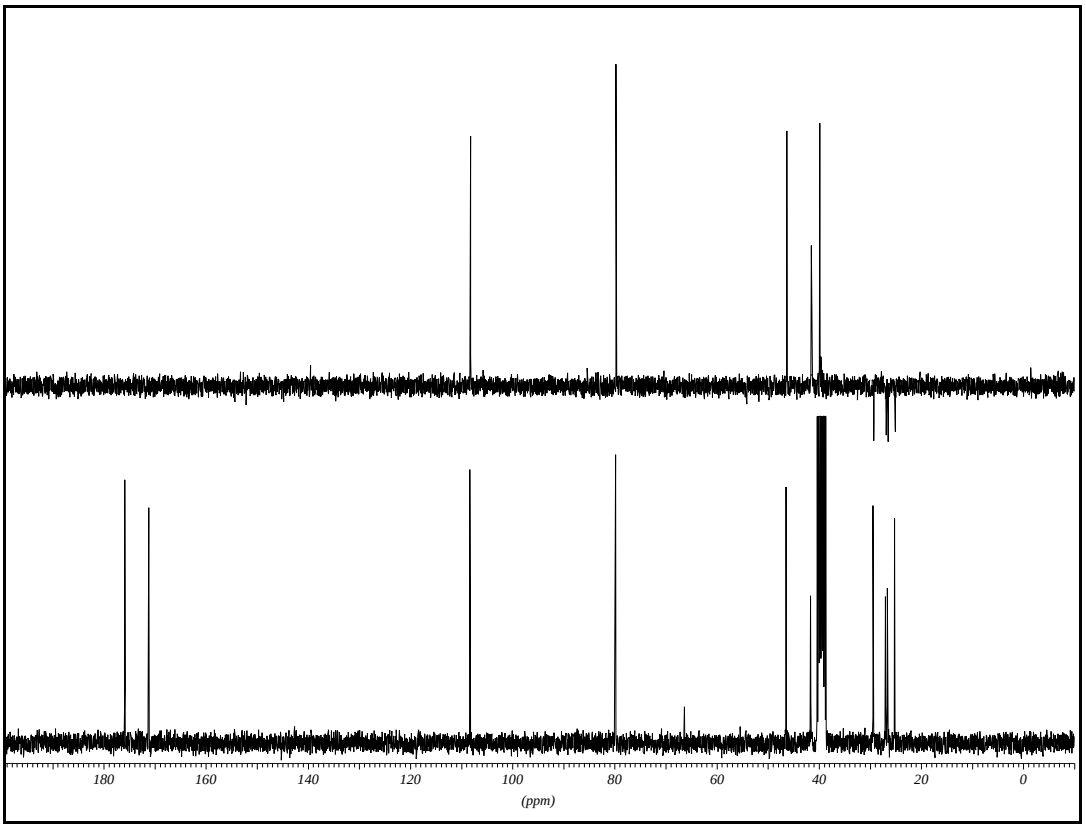


(2*R*,3*S*,3a*R*,6a*R*)-(–)-3-[1`,3`]Dithian-2-yl-5-oxo-hexahydro-furo[2,3-*b*]furan-2-carboxylic acid (193):

^{1}H NMR (300 MHz, DMSO-d6)

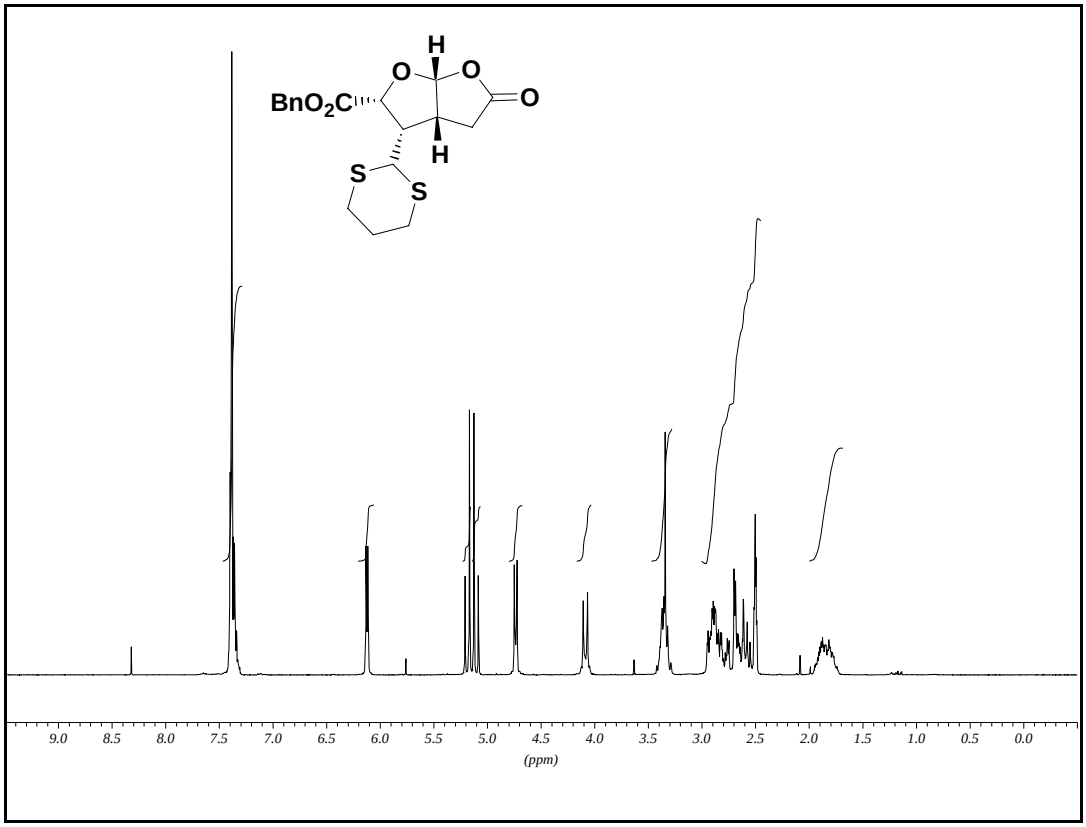


^{13}C NMR (75.5 MHz, DMSO-d6)

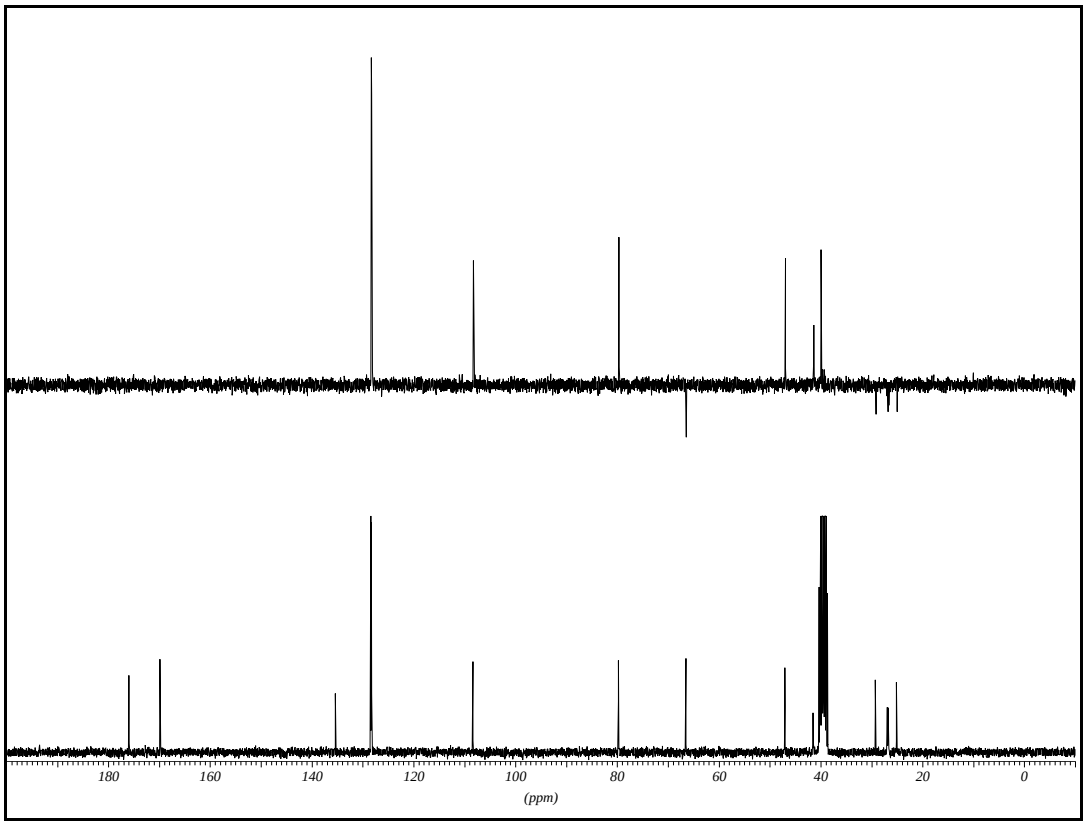


(2*R*,3*S*,3a*R*,6a*R*)-(+)-3-[1`,3`]Dithian-2-yl-5-oxo-hexahydro-furo[2,3-*b*]furan-2-carboxylic acid benzyl ester (195):

^{1}H NMR (300 MHz, DMSO-d6)

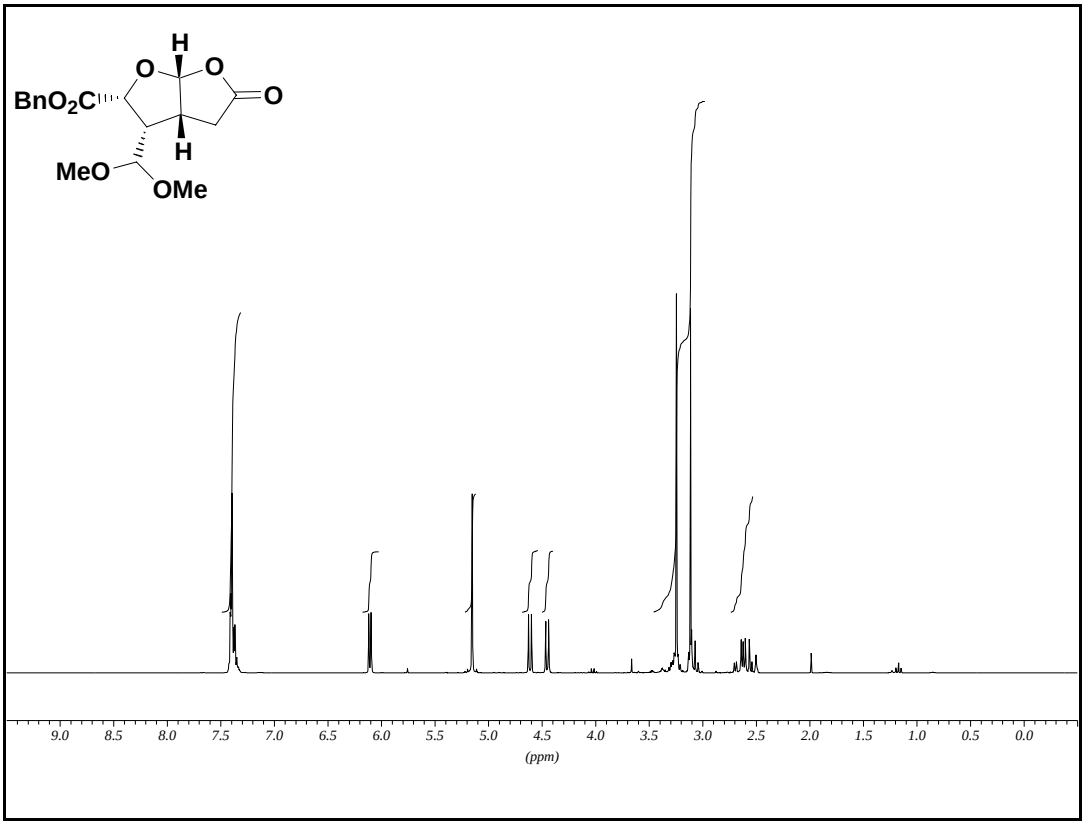


^{13}C NMR (75.5 MHz, DMSO-d6)

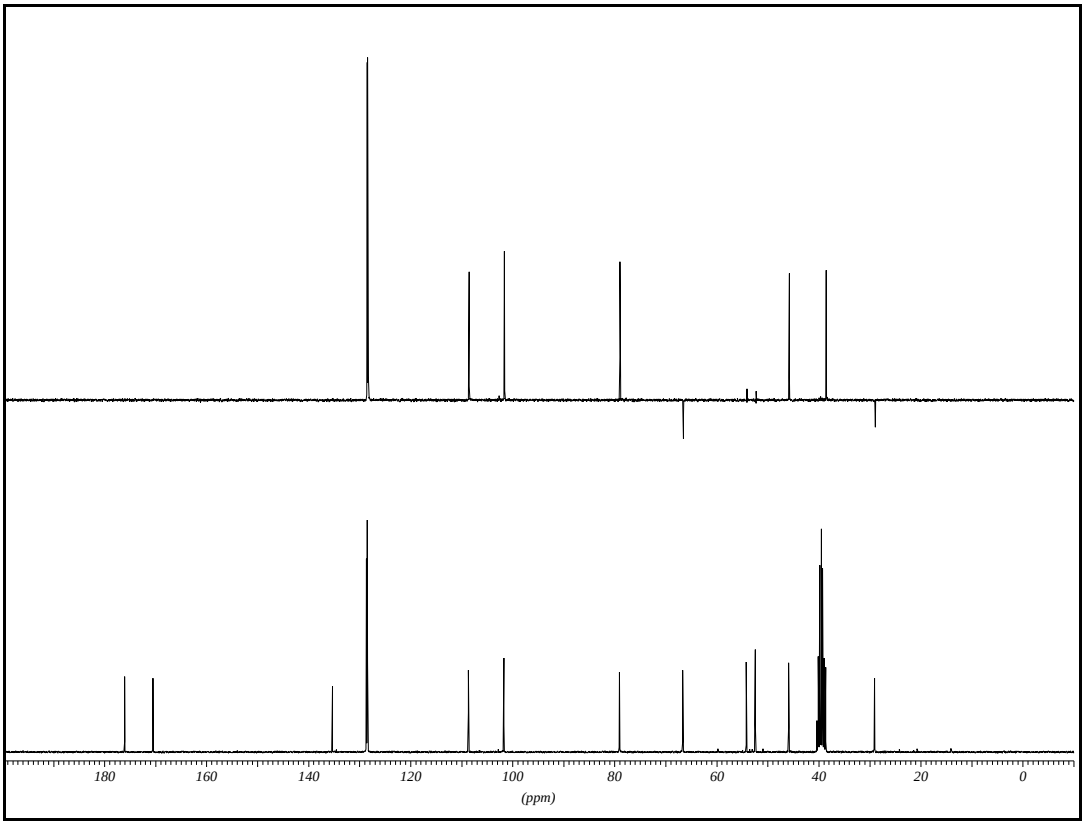


(2*R*,3*S*,3a*R*,6a*R*)-(–)-3-Dimethoxymethyl-5-oxo-hexahydro-furo[2,3-*b*]furan-2-carboxylic acid benzyl ester (196):

^{1}H NMR (300 MHz, DMSO-d6)

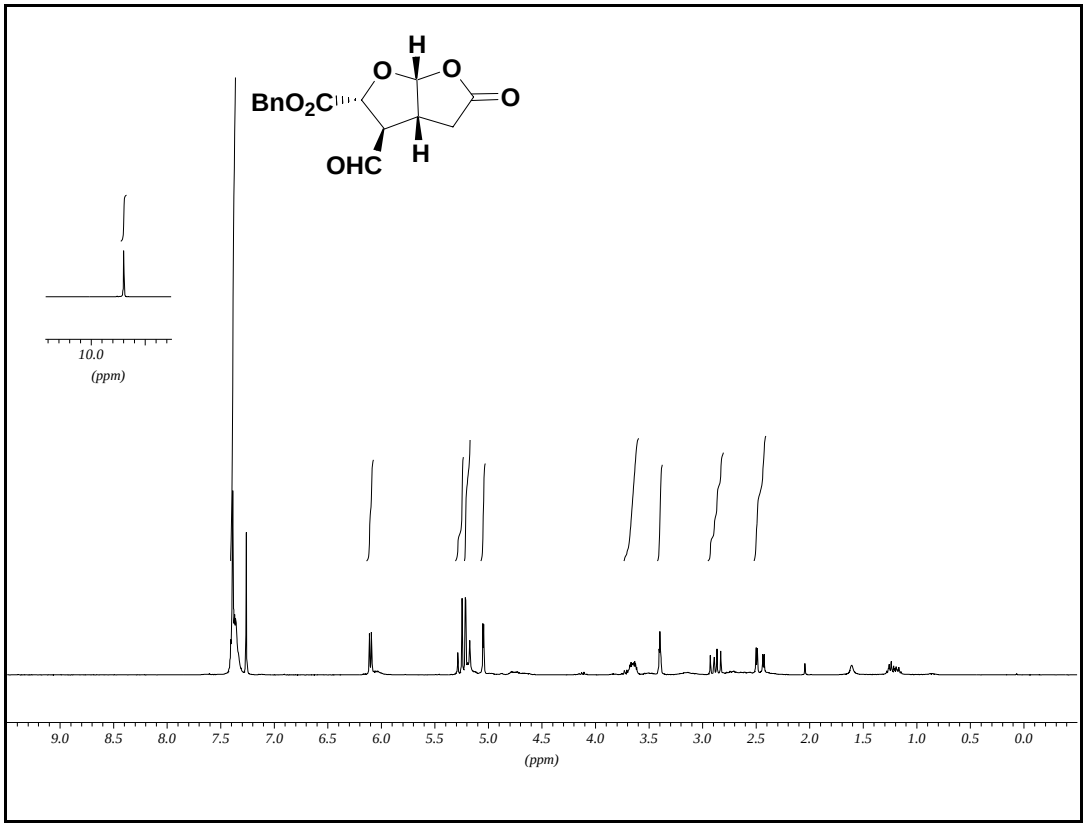


^{13}C NMR (75.5 MHz, DMSO-d6)

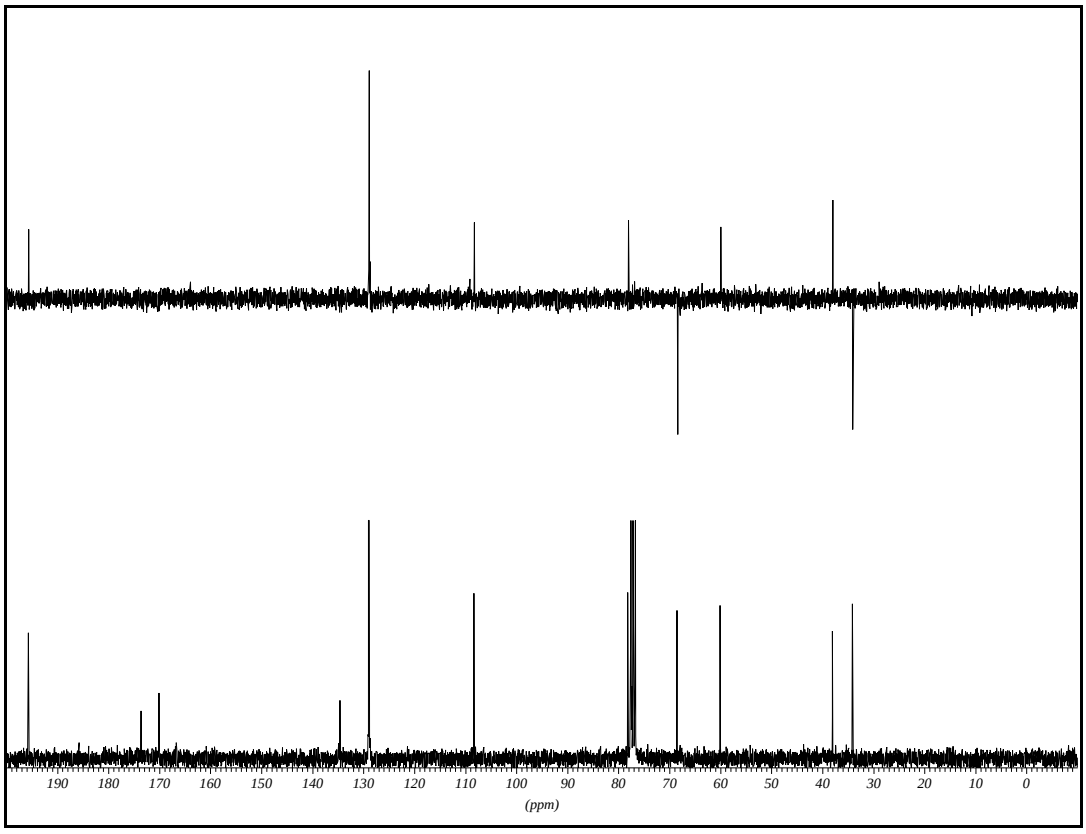


(2*R*,3*R*,3a*R*,6a*R*)-(−)-3-Formyl-5-oxo-hexahydro-furo[2,3-*b*]furan-2-carboxylic acid benzyl ester (197):

^{1}H NMR (300 MHz, $CDCl_3$)

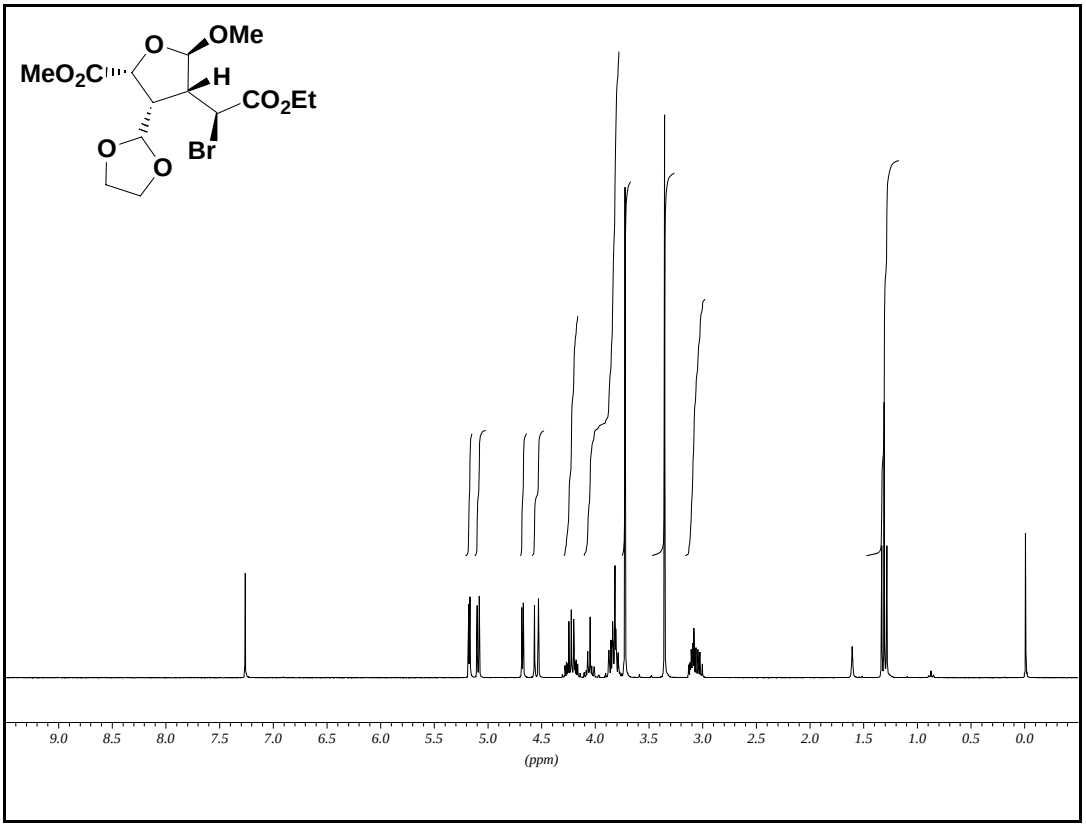


^{13}C NMR (75.5 MHz, $CDCl_3$)

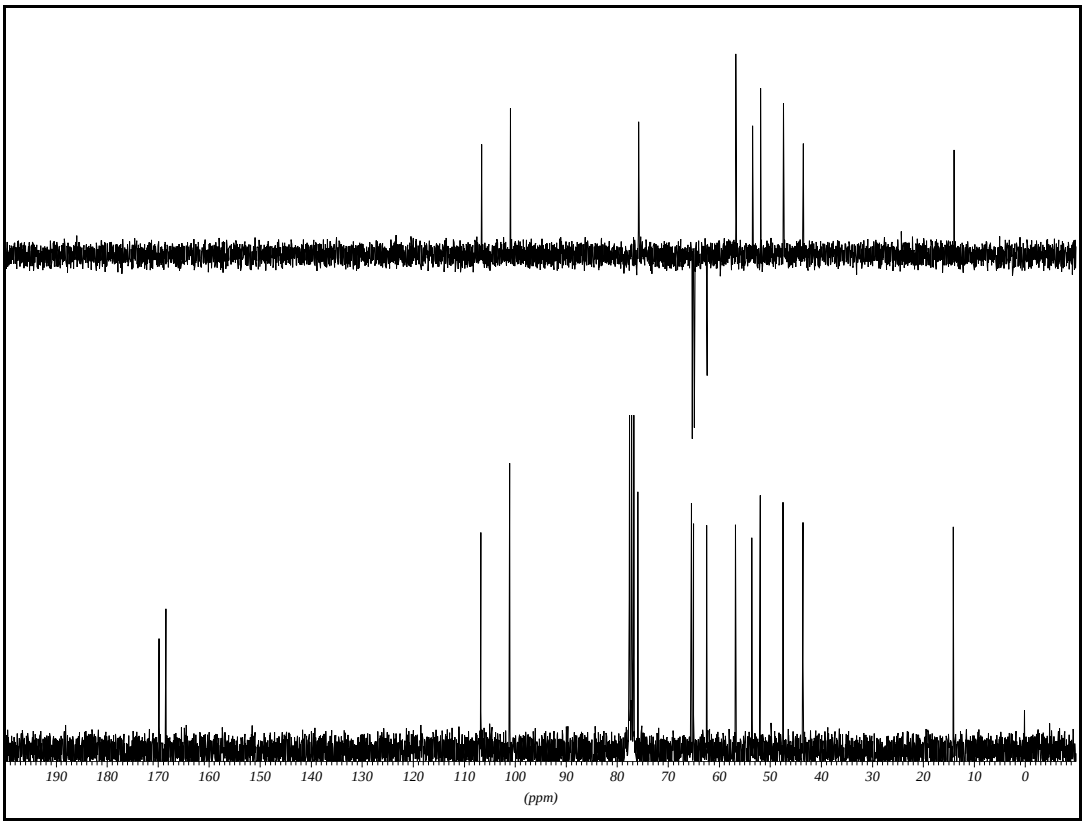


(1`*S*,2R,3*S*,4*R*,,5*R*)-(–)-4-(Bromo-ethoxycarbonyl-methyl)-3-[1´´,3´´]dioxolan-2´´-yl-5-methoxy-tetrahydro-furan-2-carboxylic acid methyl ester (220):

^{1}H NMR (300 MHz, $CDCl_3$)

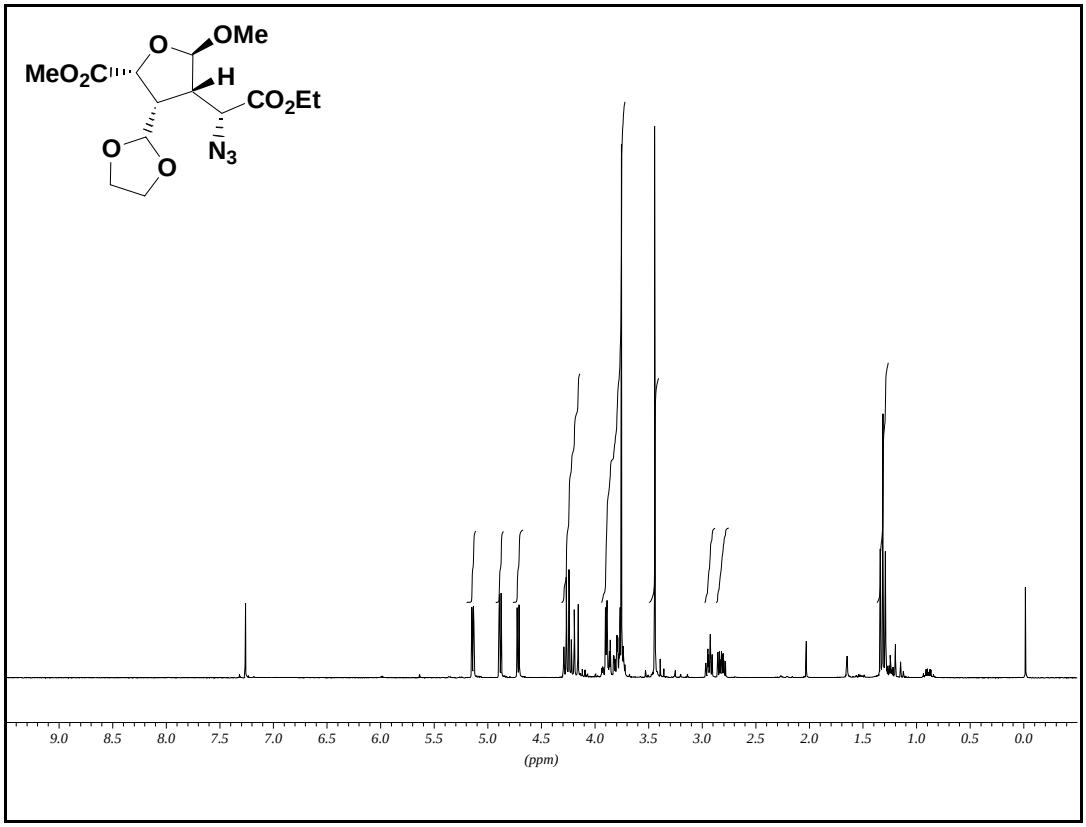


^{13}C NMR (75.5 MHz, $CDCl_3$)

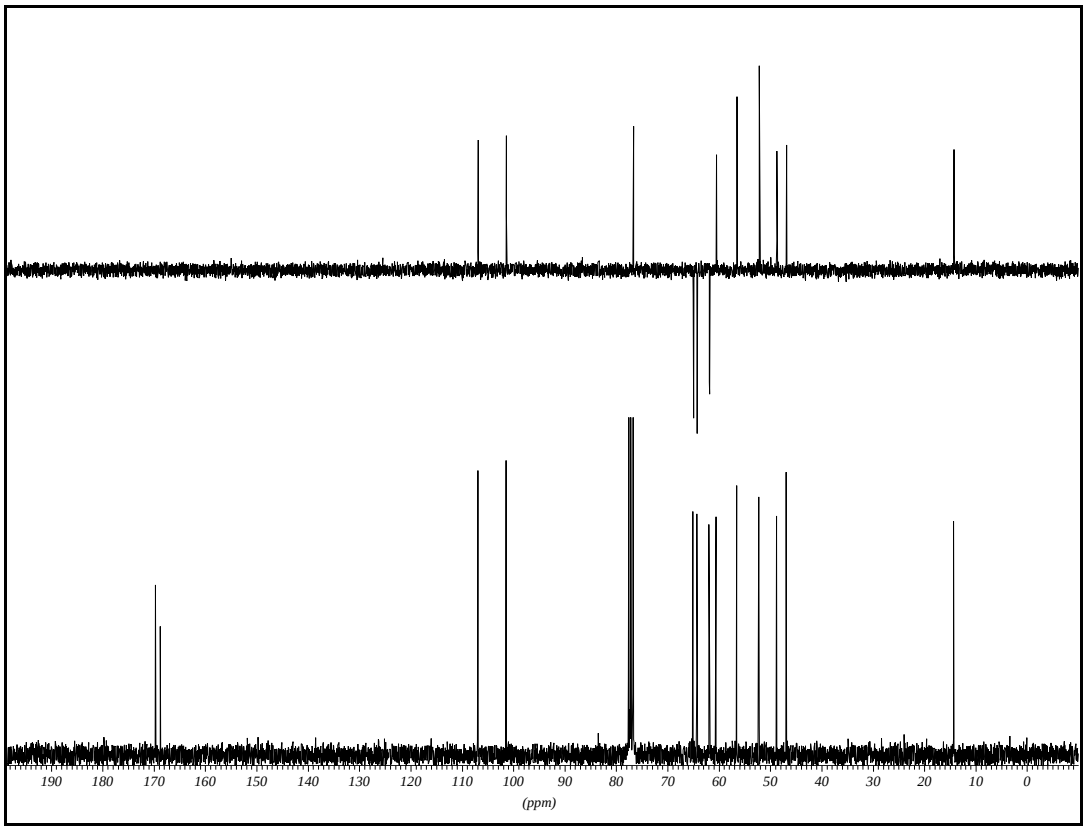


(1´*R*,2*R*,3*S*,4*S*,5*R*)-(+)-4-(Azido-ethoxycarbonyl-methyl)-3-[1´´,3´´]dioxolan-2´´-yl-5-methoxy-tetrahydro-furan-2-carboxylic acid methyl ester (222):

^{1}H NMR (300 MHz, $CDCl_3$)

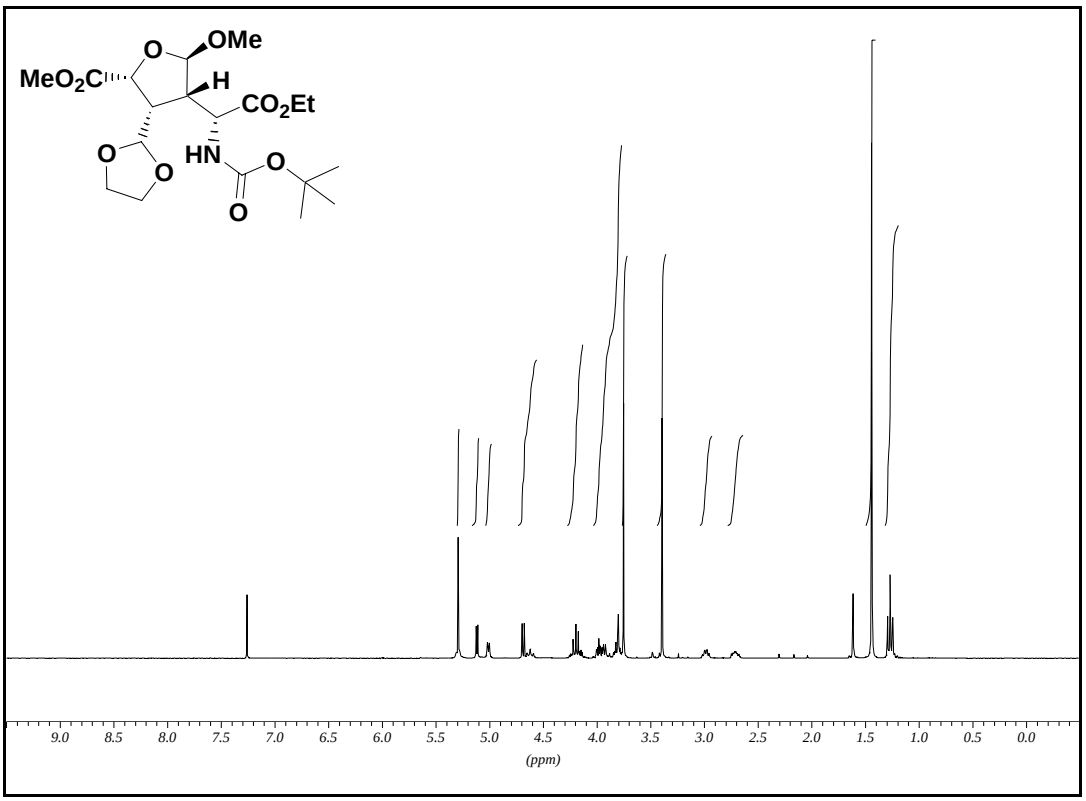


^{13}C NMR (75.5 MHz, $CDCl_3$)

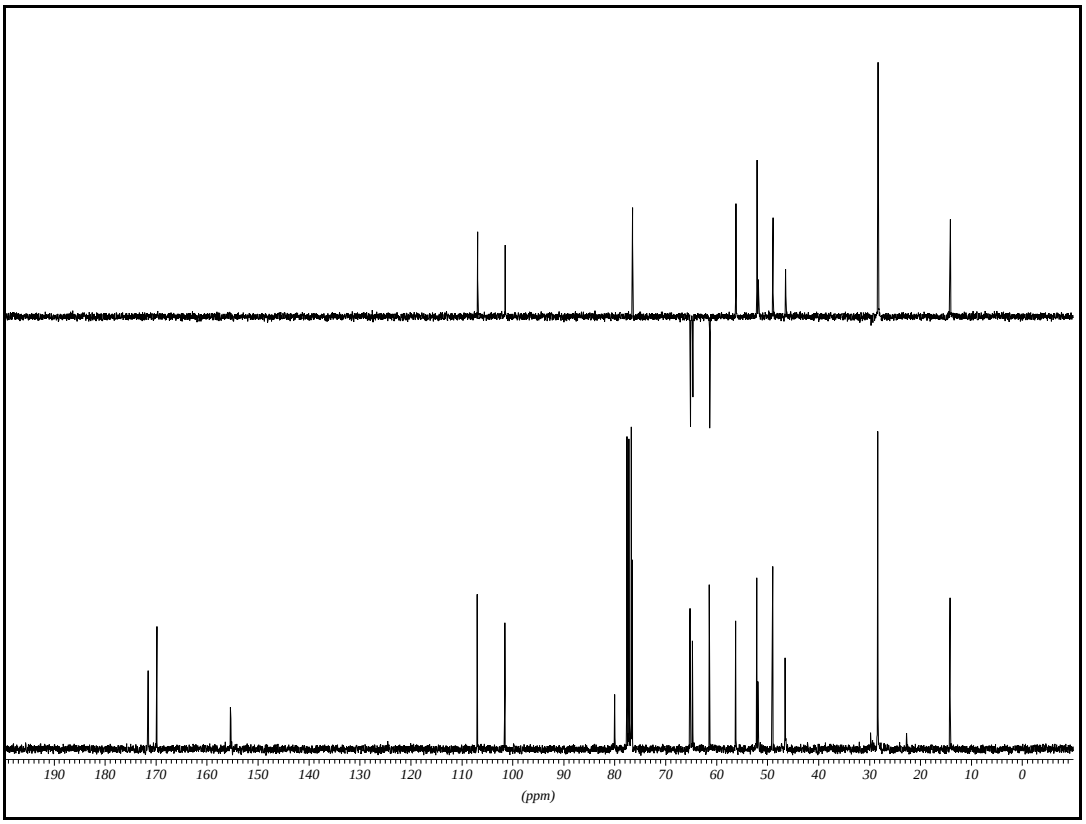


(1´*R*,2*R*,3*S*,4*S*,5*R*)-(–)-4-(*tert*-Butoxycarbonylamino-ethoxycarbonyl-methyl)-3-[1´´,3´´]dioxolan-2´´-yl-5-methoxy-tetrahydro-furan-2-carboxylic acid methyl ester (223):

^{1}H NMR (300 MHz, $CDCl_3$)

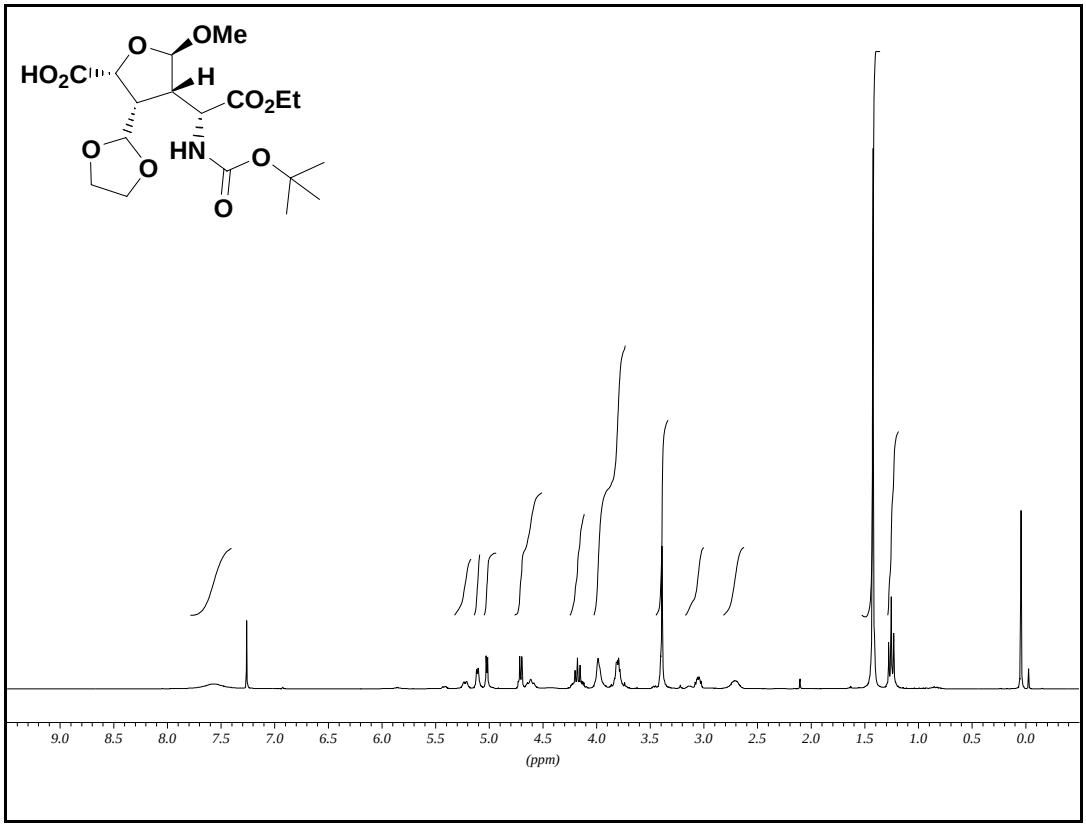


^{13}C NMR (75.5 MHz, $CDCl_3$)

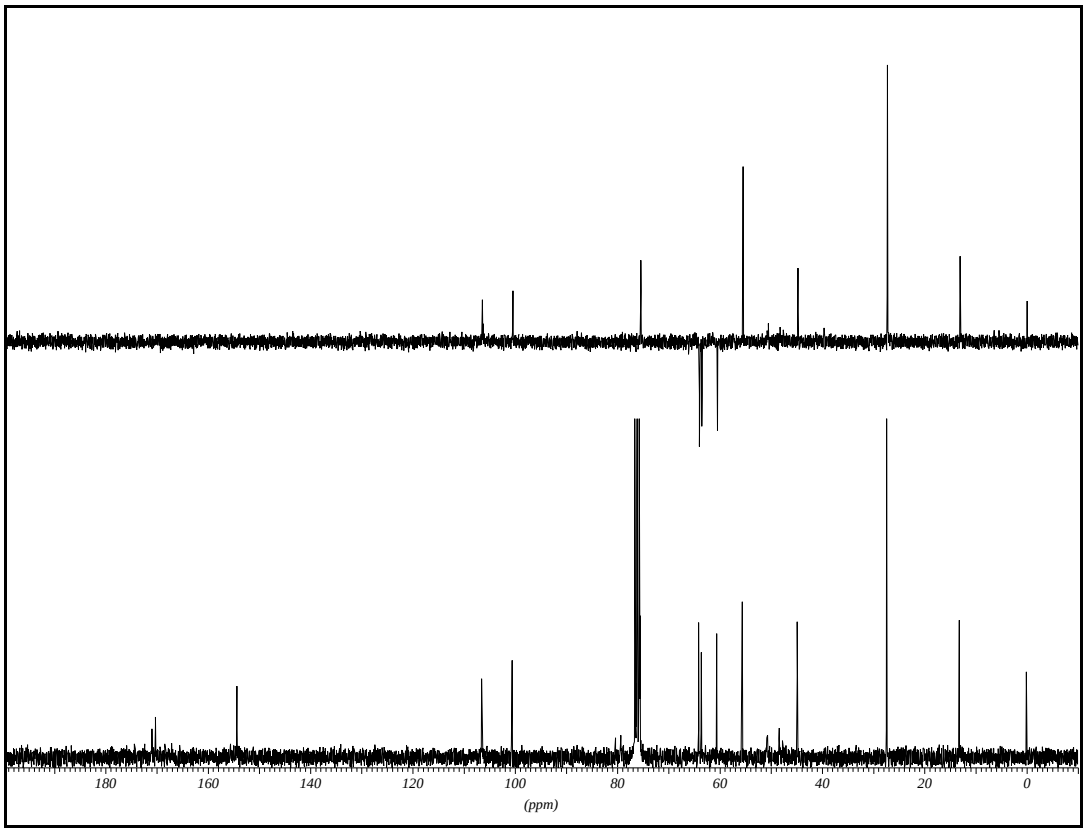


(1´*R*,2*R*,3*S*,4*S*,5*R*)-(+)-4-(*tert*-Butoxycarbonylamino-ethoxycarbonyl-methyl)-3-[1´´,3´´]dioxolan-2´´-yl-5-methoxy-tetrahydro-furan-2-carboxylic acid (224):

^{1}H NMR (300 MHz, $CDCl_3$)

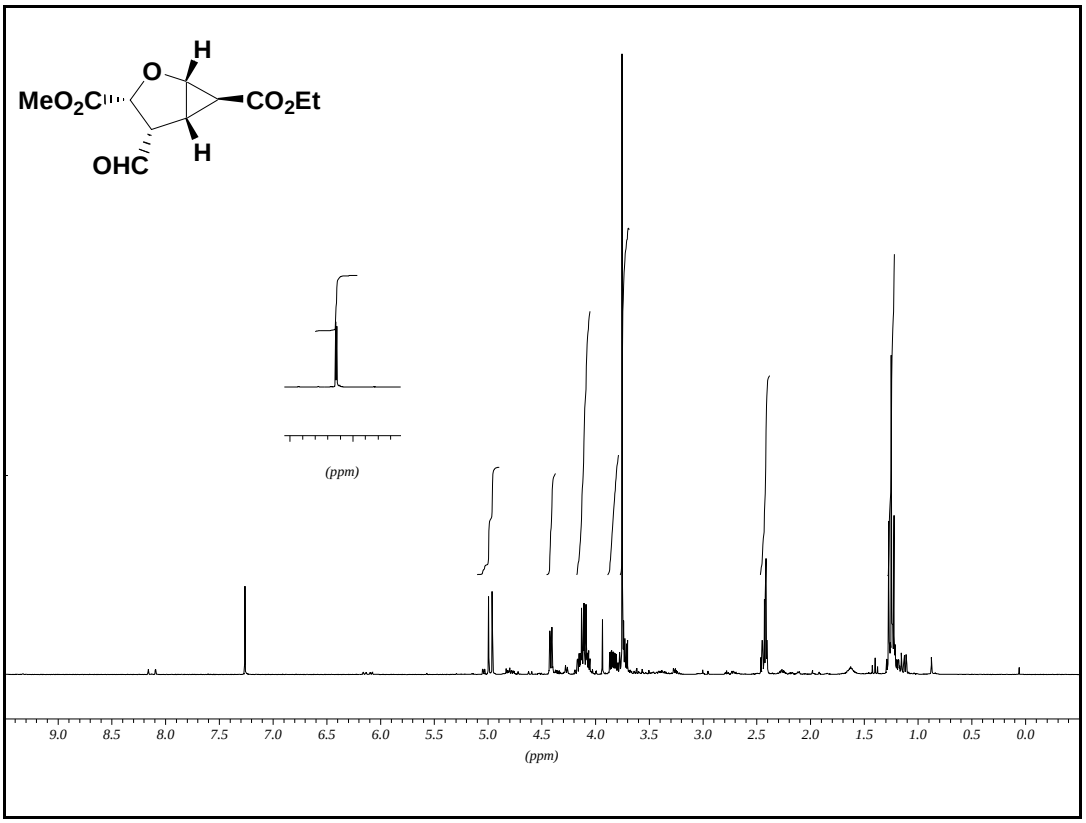


^{13}C NMR (75.5 MHz, $CDCl_3$)

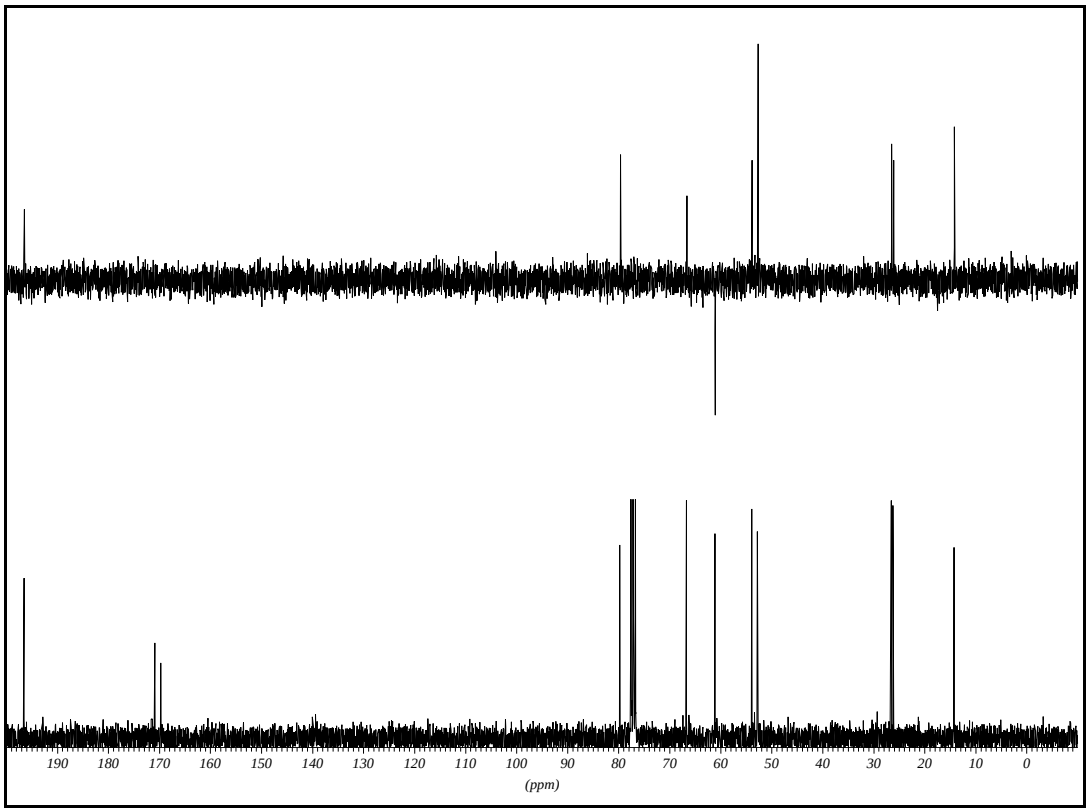


(1*S*,3*R*,4*S*,5*S*,6*S*)-4-Formyl-2-oxa-bicyclo[3.1.0]hexane-3,6-dicarboxylic acid 6-ethyl ester 3-methyl ester (237):

^{1}H NMR (300 MHz, $CDCl_3$)

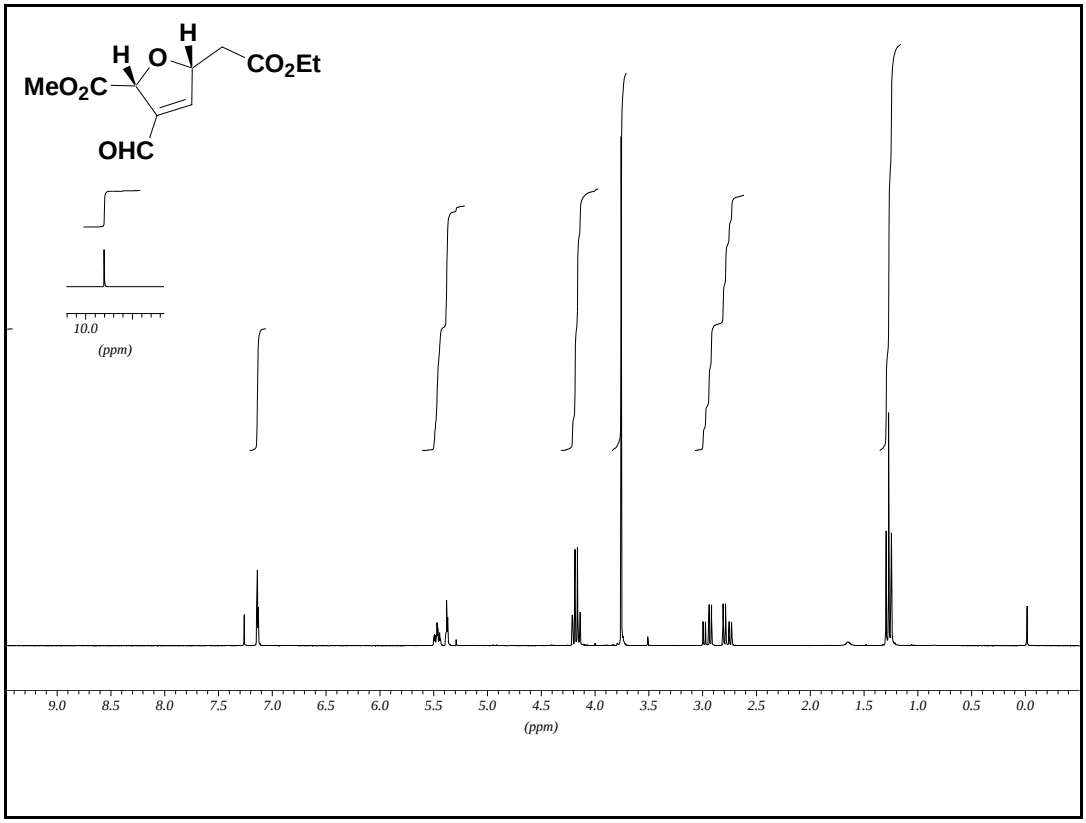


^{13}C NMR (75.5 MHz, $CDCl_3$)

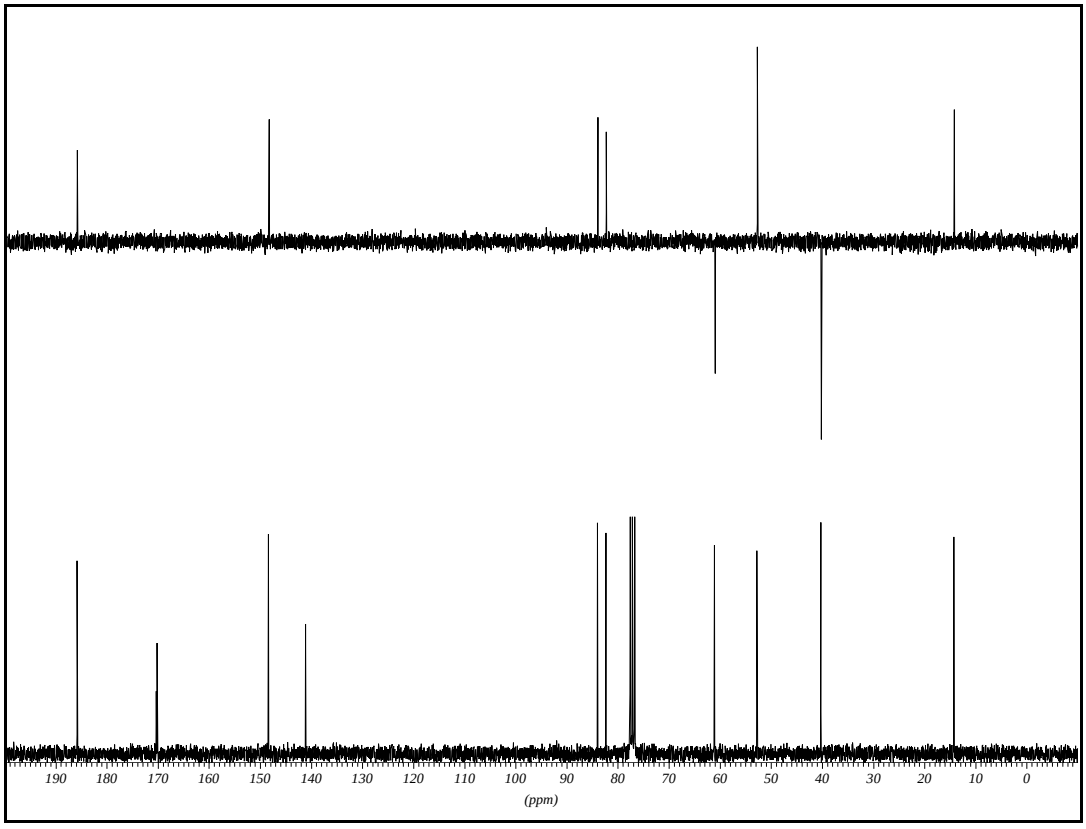


(2*R*,5*R*)-(+)-5-Ethoxycarbonylmethyl-3-formyl-2,5-dihydro-furan-2-carboxylic acid methyl ester (239):

^{1}H NMR (300 MHz, $CDCl_3$)

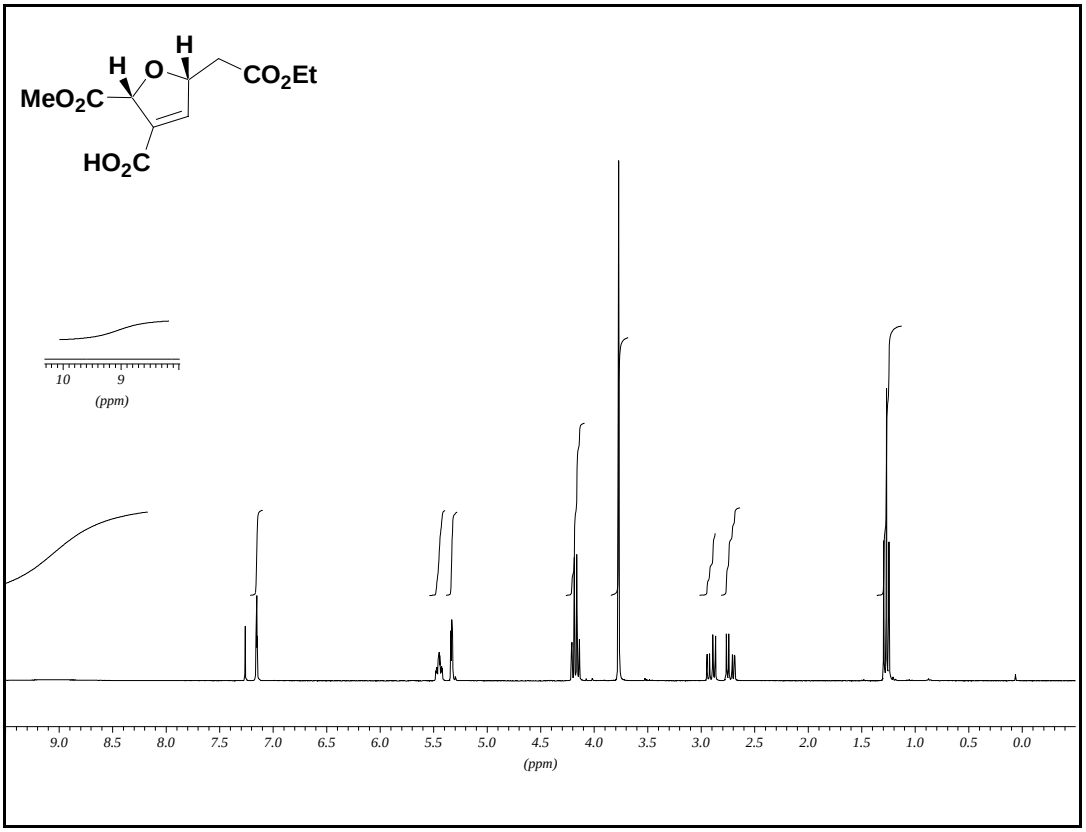


^{13}C NMR (75.5 MHz, $CDCl_3$)

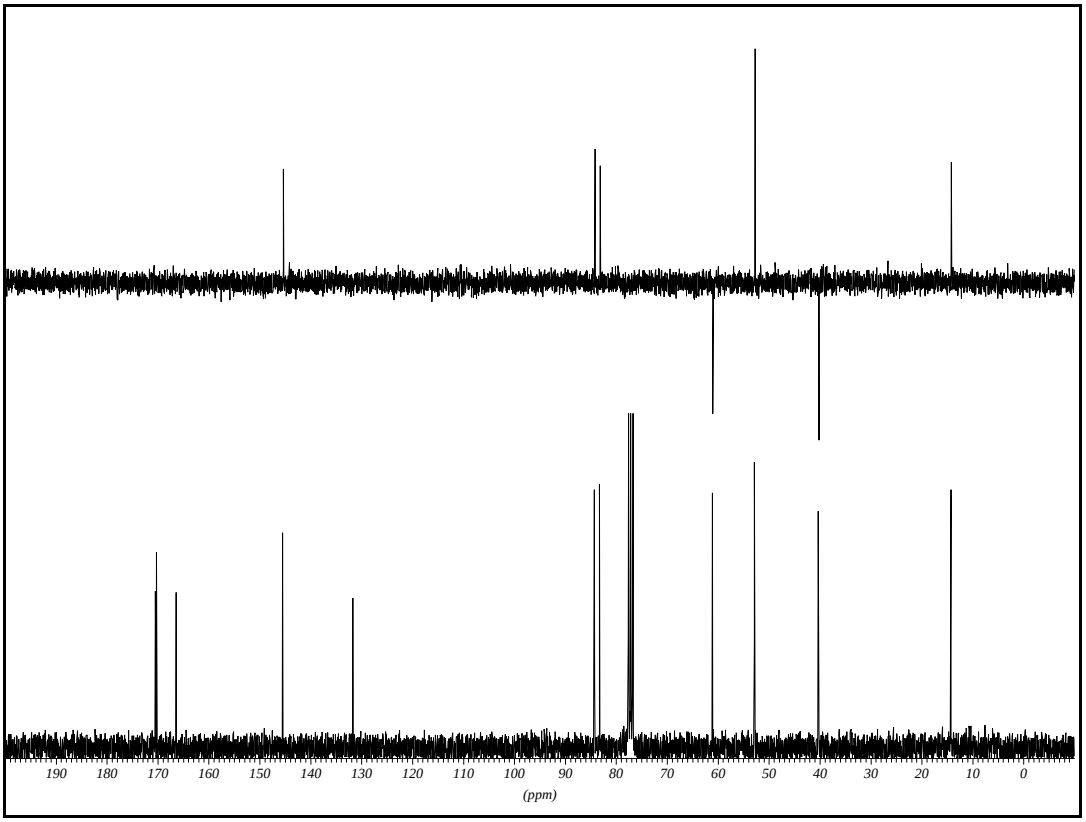


(2*R*,5*R*)-(+)-5-Ethoxycarbonylmethyl-2,5-dihydro-furan-2,3-dicarboxylic acid 2-methyl ester (240):

^{1}H NMR (300 MHz, $CDCl_3$)

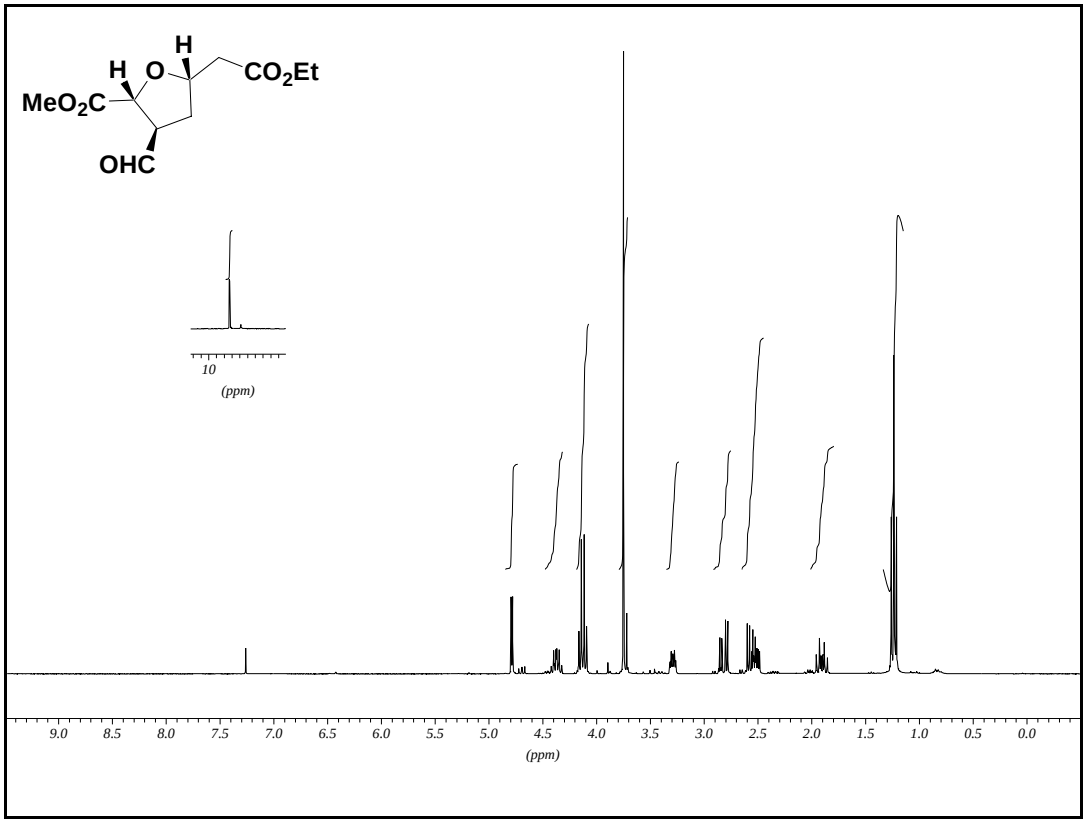


^{13}C NMR (75.5 MHz, $CDCl_3$)

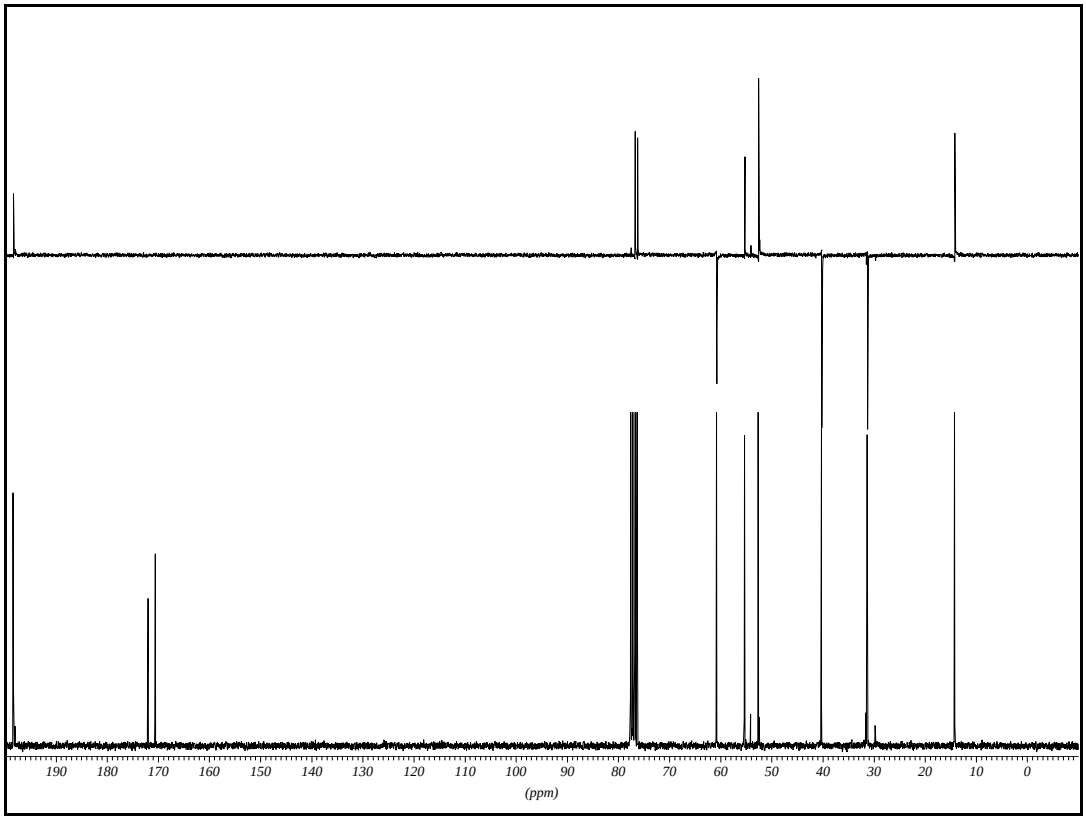


(2*R*,5*R*)-(+)-5-Ethoxycarbonylmethyl-3-formyl-tetrahydro-furan-2-carboxylic acid methyl ester (243):

^{1}H NMR (300 MHz, $CDCl_3$)

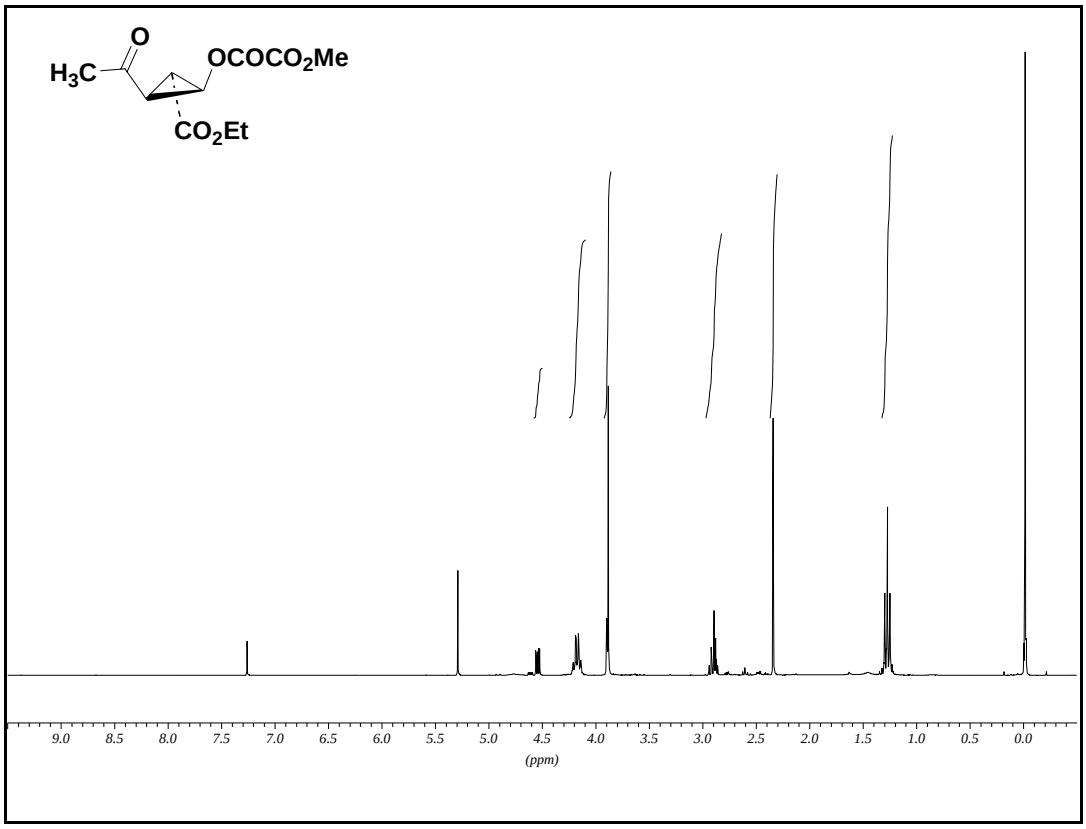


^{13}C NMR (75.5 MHz, $CDCl_3$)

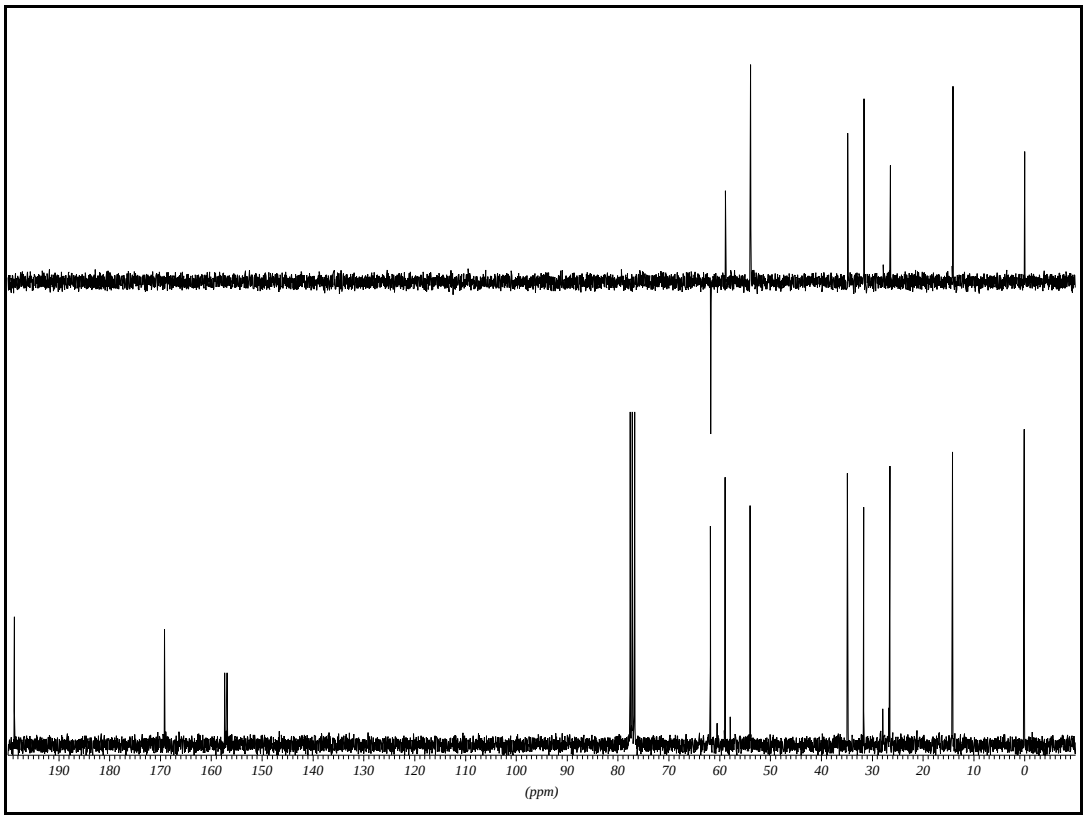


(1*S*,2*R*,3*S*)-Oxalic acid 2-acetyl-3-ethoxycarbonyl-cyclopropyl ester methyl ester (250):

^{1}H NMR (300 MHz, $CDCl_3$)

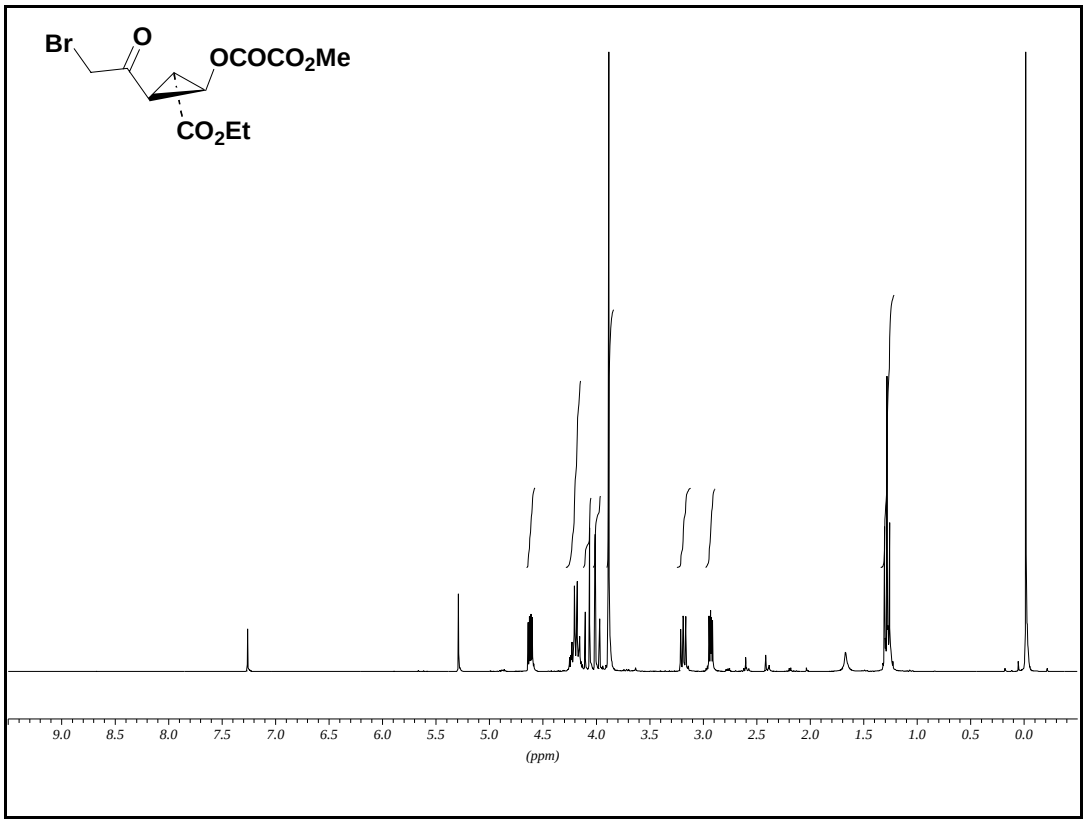


^{13}C NMR (75.5 MHz, $CDCl_3$)

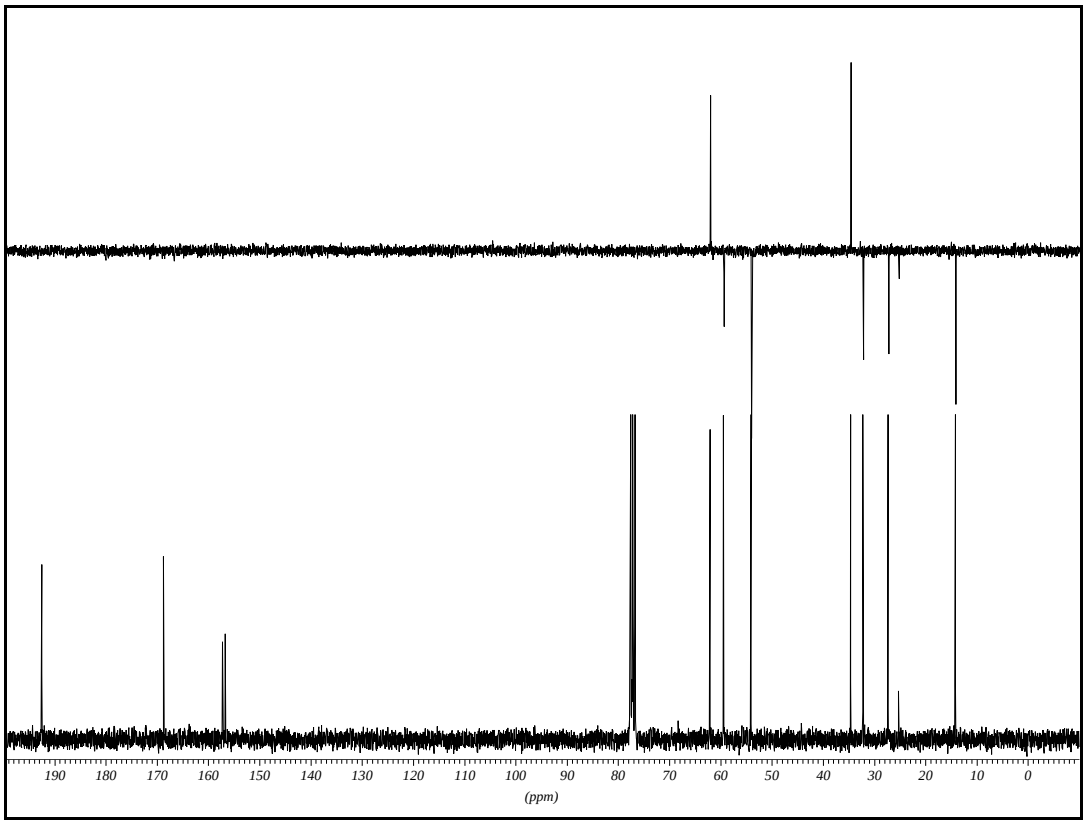


(1*S*,2*R*,3*S*)-Oxalic acid 2-(2-bromo-acetyl)-3-ethoxycarbonyl-cyclopropyl ester methyl ester (251):

^{1}H NMR (300 MHz, $CDCl_3$)

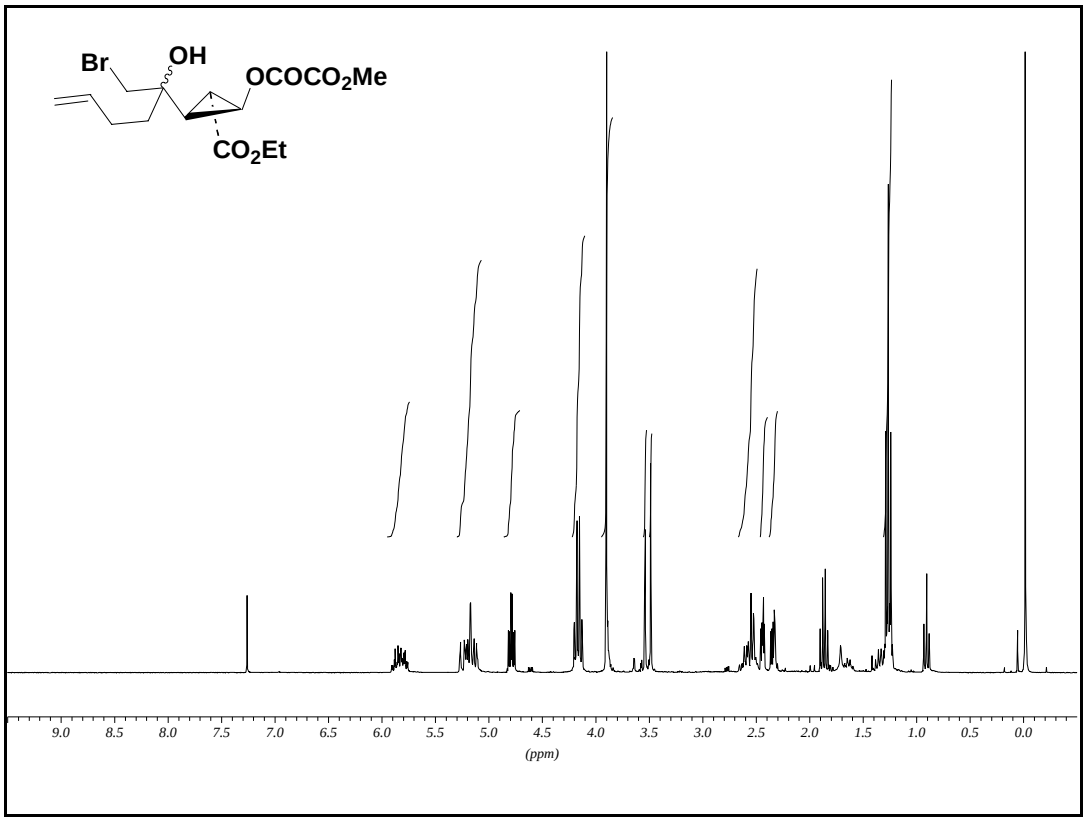


^{13}C NMR (75.5 MHz, $CDCl_3$)

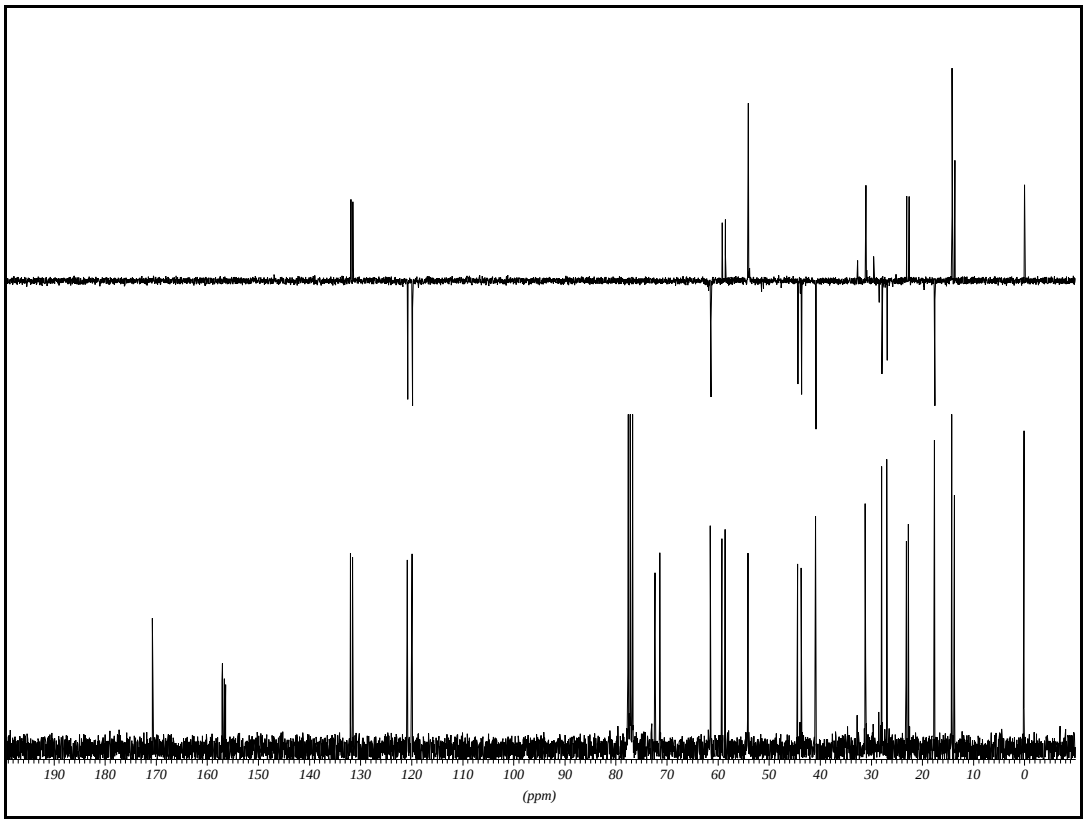


(1*S*,2*R*,3*S*)-Oxalic acid 2-(1-bromomethyl-1-hydroxy-pent-4-enyl)-3-ethoxycarbonyl-cyclopropyl ester methyl ester (252):

^{1}H NMR (300 MHz, $CDCl_3$)

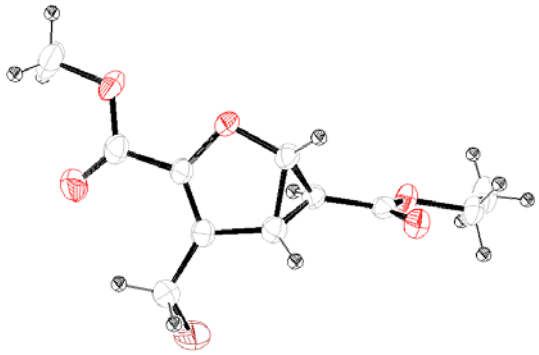


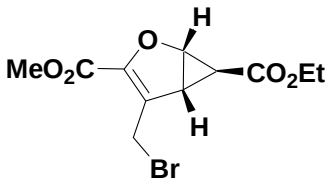
^{13}C NMR (75.5 MHz, $CDCl_3$)



6.2 X-ray Data:

6.2.1 (1*S*,5*R*,6*S*)-(−)-4-Bromomethyl-2-oxa-bicyclo[3.1.0]hex-3-ene-3,6-dicarboxylic acid 6-ethyl ester 3-methyl ester (177):





6.2.1a Crystal data and structure refinement for 177:

Crystal Data:		
Empirical formula	C11 H13 Br O5	
Formula weight	305.11	
Crystal size	0.40 x 0.12 x 0.04 mm	
Crystal description	stick	
Crystal colour	colorless	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 8.7496(12) Å	α = 90 deg.
	b = 8.4611(9) Å	β = 116.659(16) deg.
	c = 9.5715(16) Å	γ = 90 deg.
Volume	633.26(18) $Å^3$	
Z, Calculated density	2, 1.600 Mg/m^3	
Absorption coefficient	3.252 mm^{-1}	
F(000)	308	
Data Collection:		
Measurement device type	STOE-IPDS diffractometer	
Measurement method	rotation	
Temperature	173(1) K	
Wavelength	0.71073 Å	
Monochromator	graphite	
Theta range for data collection	2.38 to 25.64 deg.	
Index ranges	-10<=h<=10, -10<=k<=10, -11<=l<=11	
Reflections collected / unique	4681 / 2211 [R(int) = 0.0378]	
Reflections greater I>2\\s(I)	1865	
Absorption correction	Numerical	
Max. and min. transmission	0.7462 and 0.3977	
Refinement:		
Refinement method	Full-matrix least-squares on F^2	
Hydrogen treatment	:	
Data / restraints / parameters	2211 / 1 / 154	
Goodness-of-fit on F^2	0.969	
Final R indices [I>2sigma(I)]	R1 = 0.0346, wR2 = 0.0750	

R indices (all data)	R1 = 0.0438, wR2 = 0.0772
Absolute structure parameter	-0.013(10)
Largest diff. peak and hole	0.413 and -0.312 e.Å^{-3}

6.2.1b Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for 177. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor:

	x	y	z	U(eq)
Br(1)	6047(1)	8164(1)	3103(1)	59(1)
O(1)	1326(3)	4774(3)	2667(3)	32(1)
O(2)	673(3)	9191(3)	4687(3)	34(1)
O(3)	-330(4)	9982(3)	2180(3)	35(1)
O(4)	4731(4)	3473(4)	1903(4)	56(1)
O(5)	2093(4)	2549(3)	1218(4)	43(1)
C(1)	2937(5)	4812(4)	2775(4)	30(1)
C(2)	3951(5)	5969(4)	3696(5)	31(1)
C(3)	2899(5)	6921(4)	4243(4)	31(1)
C(4)	1202(5)	6094(4)	3535(4)	30(1)
C(5)	1339(5)	7717(3)	2907(4)	28(1)
C(6)	538(5)	9015(4)	3380(4)	28(1)
C(7)	-1148(5)	11352(4)	2524(5)	34(1)
C(8)	-2139(7)	12193(5)	1017(6)	52(2)
C(9)	5763(5)	6261(5)	4150(5)	40(1)
C(10)	3368(6)	3556(4)	1920(5)	35(1)
C(11)	2400(7)	1270(5)	380(6)	54(2)

6.2.1c Bond lengths [Å] and angles [deg] for 177:

Br(1)-C(9)	1.970(4)	C(7)-H(7B)	0.9901
O(1)-C(1)	1.367(6)	C(8)-H(8A)	0.9798
O(1)-C(4)	1.425(4)	C(8)-H(8B)	0.9811
O(2)-C(6)	1.212(4)	C(8)-H(8C)	0.9796
O(3)-C(6)	1.335(4)	C(9)-H(9A)	0.9895
O(3)-C(7)	1.475(5)	C(9)-H(9B)	0.9897
O(4)-C(10)	1.202(7)	C(11)-H(11A)	0.9800
O(5)-C(10)	1.323(6)	C(11)-H(11B)	0.9800
O(5)-C(11)	1.442(6)	C(11)-H(11C)	0.9800
C(1)-C(2)	1.349(5)		
C(1)-C(10)	1.489(6)	C(1)-O(1)-C(4)	106.5(3)
C(2)-C(3)	1.484(6)	C(6)-O(3)-C(7)	115.8(3)
C(2)-C(9)	1.465(7)	C(10)-O(5)-C(11)	116.2(4)
C(3)-C(4)	1.500(6)	O(1)-C(1)-C(2)	114.8(4)
C(3)-C(5)	1.545(5)	O(1)-C(1)-C(10)	116.6(3)
C(4)-C(5)	1.525(5)	C(2)-C(1)-C(10)	128.5(4)
C(5)-C(6)	1.479(5)	C(1)-C(2)-C(3)	107.1(4)
C(7)-C(8)	1.489(6)	C(1)-C(2)-C(9)	128.5(4)
C(3)-H(3)	1.0001	C(3)-C(2)-C(9)	124.3(3)
C(4)-H(4)	1.0000	C(2)-C(3)-C(4)	103.4(3)
C(5)-H(5)	1.0001	C(2)-C(3)-C(5)	113.7(3)
C(7)-H(7A)	0.9903	C(4)-C(3)-C(5)	60.1(2)

O(1)-C(4)-C(3)	108.1(3)	C(8)-C(7)-H(7B)	110.34
O(1)-C(4)-C(5)	115.8(3)	H(7A)-C(7)-H(7B)	108.51
C(3)-C(4)-C(5)	61.4(3)	C(7)-C(8)-H(8A)	109.48
C(3)-C(5)-C(4)	58.5(2)	C(7)-C(8)-H(8B)	109.45
C(3)-C(5)-C(6)	115.8(3)	C(7)-C(8)-H(8C)	109.50
C(4)-C(5)-C(6)	114.6(4)	H(8A)-C(8)-H(8B)	109.44
O(2)-C(6)-O(3)	124.5(4)	H(8A)-C(8)-H(8C)	109.51
O(2)-C(6)-C(5)	124.6(3)	H(8B)-C(8)-H(8C)	109.44
O(3)-C(6)-C(5)	110.9(3)	Br(1)-C(9)-H(9A)	109.55
O(3)-C(7)-C(8)	106.8(4)	Br(1)-C(9)-H(9B)	109.50
Br(1)-C(9)-C(2)	110.7(3)	C(2)-C(9)-H(9A)	109.49
O(4)-C(10)-O(5)	124.8(4)	C(2)-C(9)-H(9B)	109.48
O(4)-C(10)-C(1)	123.1(4)	H(9A)-C(9)-H(9B)	108.05
O(5)-C(10)-C(1)	112.0(4)	O(5)-C(11)-H(11A)	109.46
C(2)-C(3)-H(3)	121.02	O(5)-C(11)-H(11B)	109.45
C(4)-C(3)-H(3)	121.09	O(5)-C(11)-H(11C)	109.49
C(5)-C(3)-H(3)	121.11	H(11A)-C(11)-H(11B)	109.48
O(1)-C(4)-H(4)	119.27	H(11A)-C(11)-H(11C)	109.46
C(3)-C(4)-H(4)	119.22	H(11B)-C(11)-H(11C)	109.49
C(5)-C(4)-H(4)	119.18		
C(3)-C(5)-H(5)	118.12		
C(4)-C(5)-H(5)	118.11		
C(6)-C(5)-H(5)	118.12		
O(3)-C(7)-H(7A)	110.40		
O(3)-C(7)-H(7B)	110.41		
C(8)-C(7)-H(7A)	110.37		

6.2.1d Anisotropic displacement parameters (A^2 x 10^3) for 177. The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a^{*2} U11 + + 2 h k a* b* U12]:

	U11	U22	U33	U23	U13	U12
Br(1)	50(1)	50(1)	79(1)	-3(1)	31(1)	-15(1)
O(1)	33(2)	21(1)	43(2)	-4(1)	19(1)	-3(1)
O(2)	37(2)	31(1)	33(2)	0(1)	16(1)	4(1)
O(3)	47(2)	25(1)	39(2)	2(1)	24(1)	7(1)
O(4)	39(2)	63(2)	66(2)	-26(2)	25(2)	3(2)
O(5)	49(2)	26(1)	53(2)	-11(1)	20(2)	2(1)
C(1)	29(2)	21(2)	38(2)	3(2)	15(2)	3(1)
C(2)	31(2)	26(2)	35(2)	3(2)	13(2)	5(2)
C(3)	33(2)	28(2)	31(2)	0(1)	14(2)	2(2)
C(4)	34(2)	22(2)	39(2)	-1(1)	22(2)	-1(1)
C(5)	30(2)	22(2)	35(2)	0(1)	17(2)	-1(1)
C(6)	26(2)	21(2)	36(2)	0(2)	12(2)	-2(1)
C(7)	41(2)	24(2)	41(2)	1(2)	22(2)	8(2)
C(8)	65(3)	44(2)	56(3)	8(2)	35(3)	20(2)
C(9)	32(2)	36(2)	45(2)	-4(2)	12(2)	2(2)
C(10)	40(2)	28(2)	35(2)	3(1)	14(2)	7(2)
C(11)	64(3)	35(2)	52(3)	-13(2)	16(3)	11(2)

6.2.1e Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for 177:

	x	y	z	U(eq)
H(3)	3395	7344	5334	37
H(4)	550	5983	4161	35
H(5)	1308	7775	1851	33
H(7A)	-271	12061	3289	41
H(7B)	-1918	10997	2967	41
H(8A)	-2970	11466	259	62
H(8B)	-1355	12575	613	62
H(8C)	-2742	13092	1186	62
H(9A)	6257	5337	3864	47
H(9B)	6386	6401	5297	47
H(11A)	3375	642	1105	65
H(11B)	2652	1702	-444	65
H(11C)	1382	597	-90	65

6.2.1f Torsion angles [deg] for 177:

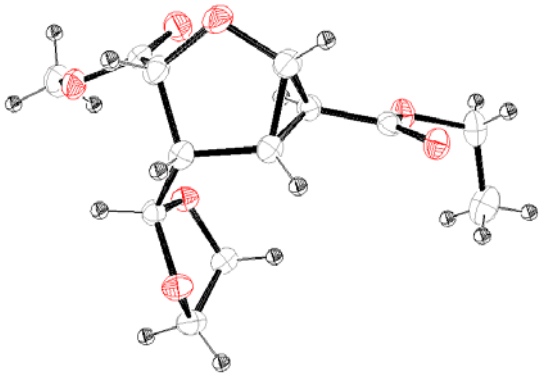
C(4)-O(1)-C(1)-C(2)	3.5(4)	O(4)	
C(4)-O(1)-C(1)-C(10)	-178.6(3)	C(2)-C(1)-C(10)-O(4)	-3.5(7)
C(1)-O(1)-C(4)-C(5)	64.2(4)	C(9)-C(2)-C(3)-C(5)	120.4(4)
C(1)-O(1)-C(4)-C(3)	-2.1(3)	C(1)-C(2)-C(3)-C(4)	1.7(4)
C(7)-O(3)-C(6)-C(5)	-178.4(3)	C(9)-C(2)-C(3)-C(4)	-176.7(4)
C(6)-O(3)-C(7)-C(8)	-175.9(4)	C(1)-C(2)-C(3)-C(5)	-61.3(4)
C(7)-O(3)-C(6)-O(2)	0.6(6)	C(3)-C(2)-C(9)-Br(1)	-73.1(4)
C(11)-O(5)-C(10)-C(1)	-178.9(3)	C(1)-C(2)-C(9)-Br(1)	108.8(4)
C(11)-O(5)-C(10)-O(4)	0.0(6)	C(2)-C(3)-C(5)-C(6)	-163.4(3)
O(1)-C(1)-C(2)-C(9)	175.0(4)	C(2)-C(3)-C(4)-O(1)	0.3(4)
C(10)-C(1)-C(2)-C(3)	179.1(3)	C(2)-C(3)-C(5)-C(4)	92.3(3)
C(10)-C(1)-C(2)-C(9)	-2.7(7)	C(2)-C(3)-C(4)-C(5)	-109.9(3)
O(1)-C(1)-C(2)-C(3)	-3.3(4)	C(5)-C(3)-C(4)-O(1)	110.1(3)
O(1)-C(1)-C(10)-O(5)	-2.2(5)	C(4)-C(3)-C(5)-C(6)	104.3(4)
C(2)-C(1)-C(10)-O(5)	175.4(4)	C(3)-C(4)-C(5)-C(6)	-106.3(4)
O(1)-C(1)-C(10)-	178.9(4)	O(1)-C(4)-C(5)-C(3)	-97.4(4)

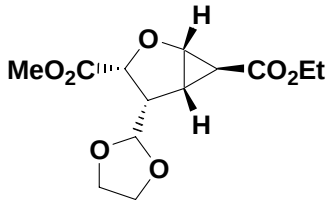
O(1)-C(4)-C(5)-C(6)	156.4(3)	O(3)	
C(4)-C(5)-C(6)-O(3)	-137.6(4)	C(3)-C(5)-C(6)-O(2)	-21.9(6)
C(3)-C(5)-C(6)-O(2)	157.0(3)	C(4)-C(5)-C(6)-O(2)	43.4(6)

6.2.1g Hydrogen-bonds for 177 [Å and deg.]:

D-H A	d(D-H)	d(H A)	d(D A)	(DHA)
C(3)-H(3) O(4) 1	1.0000	2.5900	3.573(5)	168.00
C(4)-H(4) O(2) 2	1.0000	2.3900	3.269(5)	146.00
C(9)-H(9A) O(4)	0.9900	2.3500	3.044(5)	126.00
C(9)-H(9A) O(2) 3	0.9900	2.6000	3.304(5)	129.00

6.2.2 (1*S*,3*R*,4*S*,5*S*,6*S*)-(+)-4-[1´´,3´´]Dioxolan-2´-yl-2-oxa-bicyclo[3.1.0]hexane-3,6-dicarboxylic acid 6-ethyl ester 3-methyl ester (189):





6.2.2a Crystal data and structure refinement for 189:

Crystal Data:

Empirical formula	C13 H18 O7	
Formula weight	286.27	
Crystal size	0.480 x 0.200 x 0.060 mm	
Crystal description	rod	
Crystal colour	colourless	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 8.6307(9) Å	α = 90 deg.
	b = 7.9396(6) Å	β = 108.157(12) deg.
	c = 10.5006(11) Å	γ = 90 deg.
Volume	683.72(12) A^3	
Z, Calculated density	2, 1.391 Mg/m^3	
Absorption coefficient	0.114 mm^{-1}	
F(000)	304	

Data Collection:

Measurement device type	STOE-IPDS diffractometer
Measurement method	rotation
Temperature	123(1) K
Wavelength	0.71073 Å
Monochromator	graphite
Theta range for data collection	3.57 to 26.91 deg.
Index ranges	-10<=h<=10, -10<=k<=10, -13<=l<=13
Reflections collected / unique	8682 / 2923 [R(int) = 0.0249]
Reflections greater I>2\s(I)	2760
Absorption correction	None
Max. and min. transmission	0.993 and 0.947
Refinement:	
Refinement method	Full-matrix least-squares on F^2
Hydrogen treatment	:
Data / restraints / parameters	2923 / 1 / 253
Goodness-of-fit on F^2	1.069
Final R indices [I>2sigma(I)]	R1 = 0.0292, wR2 = 0.0708
R indices (all data)	R1 = 0.0310, wR2 = 0.0714
Absolute structure parameter	-0.1(6)
Largest diff. peak and hole	0.252 and -0.138 e.A^{-3}

6.2.2b Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for 189. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor:

	x	y	z	U(eq)
O(1)	1568(1)	2829(1)	2124(1)	31(1)
O(2)	5785(1)	1715(1)	3322(1)	28(1)
O(3)	3913(1)	1585(2)	4415(1)	33(1)
O(4)	-375(1)	-1978(1)	3582(1)	26(1)
O(5)	-1929(1)	-1357(1)	1461(1)	26(1)
O(6)	4114(1)	-1547(1)	2507(1)	22(1)
O(7)	3415(1)	-1900(1)	224(1)	26(1)
C(1)	361(2)	1564(2)	1676(1)	26(1)
C(2)	729(1)	-144(2)	2375(1)	22(1)
C(3)	959(1)	183(2)	1001(1)	22(1)
C(4)	2663(1)	707(2)	1003(1)	22(1)
C(5)	3081(2)	2212(2)	2013(1)	25(1)
C(6)	4264(1)	1787(2)	3404(1)	25(1)
C(7)	7022(2)	1170(2)	4537(2)	36(1)
C(8)	-675(1)	-1206(2)	2390(1)	22(1)
C(9)	-1642(2)	-3098(2)	3749(1)	33(1)
C(10)	-1510(2)	-4829(2)	3201(2)	41(1)
C(11)	3936(1)	-688(2)	1269(1)	21(1)
C(12)	3714(2)	-3288(2)	2202(1)	26(1)
C(13)	3984(2)	-3489(2)	847(1)	28(1)

6.2.2c Bond lengths [Å] and angles [deg] for 189:

O(1)-C(1)	1.4174(17)	O(2)-C(6)	1.3437(16)
O(1)-C(5)	1.4330(17)	O(2)-C(7)	1.4513(18)

O(3)-C(6)	1.2022(15)	C(3)-C(4)-C(5)	103.13(10)
O(4)-C(8)	1.3436(15)	C(3)-C(4)-C(11)	116.17(11)
O(4)-C(9)	1.4622(17)	C(5)-C(4)-C(11)	115.49(10)
O(5)-C(8)	1.2161(14)	O(1)-C(5)-C(4)	107.04(10)
O(6)-C(11)	1.4330(14)	O(1)-C(5)-C(6)	110.54(11)
O(6)-C(12)	1.4361(17)	C(4)-C(5)-C(6)	114.93(11)
O(7)-C(11)	1.4232(15)	O(2)-C(6)-O(3)	124.81(12)
O(7)-C(13)	1.4356(17)	O(2)-C(6)-C(5)	108.80(10)
C(1)-C(2)	1.5275(18)	O(3)-C(6)-C(5)	126.37(12)
C(1)-C(3)	1.4828(18)	O(4)-C(8)-O(5)	124.55(11)
C(2)-C(3)	1.5386(17)	O(4)-C(8)-C(2)	110.39(10)
C(2)-C(8)	1.4807(17)	O(5)-C(8)-C(2)	125.06(11)
C(3)-C(4)	1.5273(18)	O(4)-C(9)-C(10)	111.14(12)
C(4)-C(5)	1.5641(18)	O(6)-C(11)-O(7)	107.28(10)
C(4)-C(11)	1.5235(18)	O(6)-C(11)-C(4)	112.35(10)
C(5)-C(6)	1.5358(18)	O(7)-C(11)-C(4)	108.24(9)
C(9)-C(10)	1.508(2)	O(6)-C(12)-C(13)	102.32(10)
C(12)-C(13)	1.5204(18)	O(7)-C(13)-C(12)	101.76(10)
C(1)-H(1)	0.926(18)	O(1)-C(1)-H(1)	113.0(10)
C(2)-H(2)	0.946(17)	C(2)-C(1)-H(1)	120.4(10)
C(3)-H(3)	0.925(15)	C(3)-C(1)-H(1)	125.5(10)
C(4)-H(4)	0.941(16)	C(1)-C(2)-H(2)	116.6(10)
C(5)-H(5)	0.942(17)	C(3)-C(2)-H(2)	119.2(10)
C(7)-H(7A)	0.966(18)	C(8)-C(2)-H(2)	116.2(10)
C(7)-H(7B)	0.97(2)	C(1)-C(3)-H(3)	121.9(10)
C(7)-H(7C)	1.00(2)	C(2)-C(3)-H(3)	118.3(10)
C(9)-H(9A)	0.936(16)	C(4)-C(3)-H(3)	119.2(10)
C(9)-H(9B)	0.923(18)	C(3)-C(4)-H(4)	109.5(10)
C(10)-H(10A)	0.93(3)	C(5)-C(4)-H(4)	107.7(10)
C(10)-H(10B)	0.98(3)	C(11)-C(4)-H(4)	104.7(10)
C(10)-H(10C)	0.91(2)	O(1)-C(5)-H(5)	109.9(10)
C(11)-H(11)	0.974(17)	C(4)-C(5)-H(5)	107.2(10)
C(12)-H(12A)	0.960(18)	C(6)-C(5)-H(5)	107.2(11)
C(12)-H(12B)	0.948(17)	O(2)-C(7)-H(7A)	105.3(10)
C(13)-H(13A)	0.955(18)	O(2)-C(7)-H(7B)	108.3(12)
C(13)-H(13B)	0.92(2)	O(2)-C(7)-H(7C)	112.3(11)
		H(7A)-C(7)-H(7B)	110.5(15)
C(1)-O(1)-C(5)	108.94(10)		
C(6)-O(2)-C(7)	114.94(10)	H(7A)-C(7)-H(7C)	109.8(15)
C(8)-O(4)-C(9)	117.06(10)		
C(11)-O(6)-C(12)	107.77(9)	H(7B)-C(7)-H(7C)	110.5(17)
C(11)-O(7)-C(13)	105.13(9)		
O(1)-C(1)-C(2)	116.64(10)	O(4)-C(9)-H(9A)	102.5(10)
O(1)-C(1)-C(3)	110.70(11)	O(4)-C(9)-H(9B)	108.1(11)
C(2)-C(1)-C(3)	61.45(8)	C(10)-C(9)-H(9A)	112.0(10)
C(1)-C(2)-C(3)	57.84(8)		
C(1)-C(2)-C(8)	117.52(11)	C(10)-C(9)-H(9B)	112.7(10)
C(3)-C(2)-C(8)	116.84(10)		
C(1)-C(3)-C(2)	60.70(8)	H(9A)-C(9)-H(9B)	110.0(15)
C(1)-C(3)-C(4)	106.05(10)		
C(2)-C(3)-C(4)	116.77(10)	C(9)-C(10)-	109.7(15)

H(10A)		H(12B)	
C(9)-C(10)-H(10B)	108.8(14)	C(13)-C(12)-H(12A)	109.2(10)
C(9)-C(10)-H(10C)	114.0(15)	C(13)-C(12)-H(12B)	118.3(11)
H(10A)-C(10)-H(10B)	112(2)	H(12A)-C(12)-H(12B)	108.9(16)
H(10A)-C(10)-H(10C)	105.3(18)	O(7)-C(13)-H(13A)	109.2(10)
H(10B)-C(10)-H(10C)	106.9(17)	O(7)-C(13)-H(13B)	109.6(13)
O(6)-C(11)-H(11)	107.3(9)	C(12)-C(13)-H(13A)	110.4(10)
O(7)-C(11)-H(11)	111.1(9)	C(12)-C(13)-H(13B)	114.7(12)
C(4)-C(11)-H(11)	110.6(9)	H(13A)-C(13)-H(13B)	110.7(15)
O(6)-C(12)-H(12A)	111.4(14)		
O(6)-C(12)-	106.6(10)		

6.2.2d Anisotropic displacement parameters (A^2 x 10^3) for 189. The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a^{*2} U11 ++ 2 h k a* b* U12]:

	U11	U22	U33	U23	U13	U12
O(1)	26(1)	20(1)	46(1)	-4(1)	8(1)	1(1)
O(2)	22(1)	32(1)	30(1)	-4(1)	7(1)	-6(1)
O(3)	27(1)	45(1)	28(1)	-12(1)	9(1)	-6(1)
O(4)	21(1)	35(1)	23(1)	4(1)	5(1)	-2(1)
O(5)	20(1)	29(1)	26(1)	2(1)	2(1)	-1(1)
O(6)	26(1)	21(1)	18(1)	0(1)	5(1)	1(1)
O(7)	29(1)	27(1)	19(1)	-3(1)	5(1)	0(1)
C(1)	22(1)	22(1)	32(1)	0(1)	4(1)	2(1)
C(2)	19(1)	23(1)	23(1)	0(1)	4(1)	0(1)
C(3)	20(1)	23(1)	21(1)	2(1)	2(1)	0(1)
C(4)	24(1)	22(1)	20(1)	3(1)	5(1)	-2(1)
C(5)	24(1)	19(1)	32(1)	2(1)	8(1)	-2(1)
C(6)	23(1)	21(1)	30(1)	-8(1)	8(1)	-6(1)
C(7)	25(1)	47(1)	32(1)	-5(1)	4(1)	-5(1)
C(8)	20(1)	22(1)	23(1)	-1(1)	6(1)	3(1)
C(9)	22(1)	47(1)	29(1)	8(1)	8(1)	-4(1)
C(10)	38(1)	37(1)	41(1)	11(1)	2(1)	-7(1)
C(11)	21(1)	23(1)	19(1)	-1(1)	6(1)	-3(1)
C(12)	27(1)	23(1)	25(1)	0(1)	5(1)	-1(1)
C(13)	27(1)	26(1)	27(1)	-5(1)	4(1)	3(1)

6.2.2e Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for 189:

	x	y	z	U(eq)
H(1)	-690(20)	1990(20)	1411(16)	26(4)
H(2)	1657(19)	-200(20)	3146(16)	24(4)
H(3)	280(17)	-369(19)	262(15)	16(3)

H(4)	2609(18)	1130(20)	153(16)	19(3)
H(5)	3580(20)	3050(20)	1639(17)	30(4)
H(7A)	8020(20)	1110(20)	4308(17)	29(4)
H(7B)	7110(20)	2010(30)	5220(20)	44(5)
H(7C)	6770(20)	40(30)	4850(20)	42(5)
H(9A)	-1421(18)	-3110(20)	4680(16)	20(3)
H(9B)	-2640(20)	-2600(20)	3345(18)	31(4)
H(10A)	-2310(30)	-5530(30)	3340(20)	50(5)
H(10B)	-410(30)	-5260(30)	3630(20)	51(6)
H(10C)	-1680(20)	-4850(30)	2300(20)	43(5)
H(11)	4999(19)	-230(20)	1318(15)	21(4)
H(12A)	2590(20)	-3510(30)	2108(17)	32(4)
H(12B)	4380(20)	-3920(20)	2935(17)	25(4)
H(13A)	5120(20)	-3600(20)	956(16)	29(4)
H(13B)	3400(20)	-4350(30)	326(19)	36(4)

6.2.2f Torsion angles [deg] for 189:

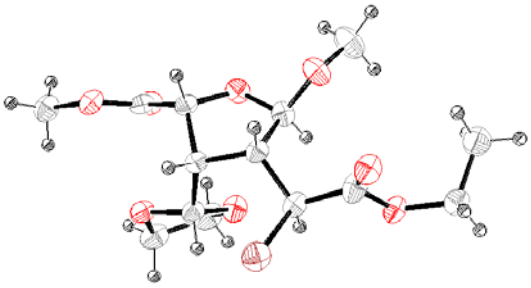
C(5)-O(1)-C(1)-C(2)	56.38(14)	C(4)	
C(5)-O(1)-C(1)-C(3)	-11.17(14)	C(2)-C(1)-C(3)-C(4)	-112.08(11)
C(1)-O(1)-C(5)-C(4)	19.57(13)	O(1)-C(1)-C(2)-C(3)	-100.22(12)
C(1)-O(1)-C(5)-C(6)	-106.27(12)	O(1)-C(1)-C(2)-C(8)	153.90(11)
C(7)-O(2)-C(6)-O(3)	6.9(2)	C(3)-C(1)-C(2)-C(8)	-105.89(12)
C(7)-O(2)-C(6)-C(5)	-174.58(11)	C(8)-C(2)-C(3)-C(1)	107.08(12)
C(9)-O(4)-C(8)-O(5)	1.22(18)	C(1)-C(2)-C(3)-C(4)	94.14(12)
C(8)-O(4)-C(9)-C(10)	83.93(15)	C(8)-C(2)-C(3)-C(4)	-158.79(11)
C(9)-O(4)-C(8)-C(2)	-179.08(11)	C(1)-C(2)-C(8)-O(5)	39.11(18)
C(12)-O(6)-C(11)-C(4)	119.44(11)	C(3)-C(2)-C(8)-O(5)	-26.75(18)
C(12)-O(6)-C(11)-O(7)	0.61(12)	C(1)-C(2)-C(8)-O(4)	-140.59(11)
C(11)-O(6)-C(12)-C(13)	22.49(12)	C(3)-C(2)-C(8)-O(4)	153.55(11)
C(13)-O(7)-C(11)-O(6)	-25.21(12)	C(2)-C(3)-C(4)-C(5)	-51.63(13)
C(13)-O(7)-C(11)-C(4)	-146.67(10)	C(1)-C(3)-C(4)-C(11)	140.58(10)
C(11)-O(7)-C(13)-C(12)	38.22(12)	C(1)-C(3)-C(4)-C(5)	13.21(12)
O(1)-C(1)-C(3)-C(2)	109.88(11)	C(2)-C(3)-C(4)-C(11)	75.74(14)
O(1)-C(1)-C(3)-	-2.20(13)	C(5)-C(4)-C(11)-O(7)	-176.68(10)

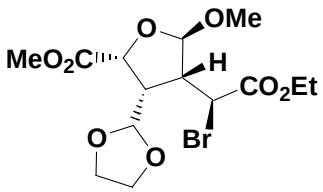
C(3)-C(4)-C(11)-O(7)	62.34(13)	C(3)-C(4)-C(5)-C(6)	103.11(12)
C(5)-C(4)-C(11)-O(6)	65.04(14)	C(4)-C(5)-C(6)-O(3)	-104.18(16)
C(3)-C(4)-C(11)-O(6)	-55.93(14)	O(1)-C(5)-C(6)-O(3)	17.10(19)
C(3)-C(4)-C(5)-O(1)	-20.05(12)	O(1)-C(5)-C(6)-O(2)	-161.44(11)
C(11)-C(4)-C(5)-O(1)	-147.86(11)	C(4)-C(5)-C(6)-O(2)	77.29(14)
C(11)-C(4)-C(5)-C(6)	-24.69(16)	O(6)-C(12)-C(13)-O(7)	-37.10(12)

6.2.2g Hydrogen-bonds for 189 [Å and deg.]:

D-H A	d(D-H)	d(H A)	d(D A)	(DHA)
C(1)-H(1) O(7) 1	0.926(18)	2.596(17)	3.4692(16)	157.5(14)
C(2)-H(2) O(3)	0.946(17)	2.441(16)	3.2178(16)	139.3(13)
C(4)-H(4) O(5) 1	0.941(16)	2.565(16)	3.3928(16)	146.9(13)
C(11)-H(11) O(2)	0.974(17)	2.526(15)	2.9474(16)	106.1(11)
C(13)-H(13B) O(5) 2	0.92(2)	2.49(2)	3.3951(16)	168.3(17)

6.2.3 (1`*S*,2R,3*S*,4*R*,,5*R*)-(−)-4-(Bromo-ethoxycarbonyl-methyl)-3-[1´´,3´´]dioxolan-2´´-yl-5-methoxy-tetrahydro-furan-2-carboxylic acid methyl ester (220):





6.2.3a Crystal data and structure refinement for 220:

Crystal Data:

Empirical formula	C14 H21 Br O8
Formula weight	397.25
Crystal size	0.47 x 0.31 x 0.19 mm
Crystal description	prism
Crystal colour	colourless
Crystal system	Monoclinic

Space group	P 21	
Unit cell dimensions	a = 8.8944(14) Å	α = 90 deg.
	b = 8.1736(9) Å	β = 96.977(18) deg.
	c = 11.6433(18) Å	γ = 90 deg.
Volume	840.2(2) A^3	
Z, Calculated density	2, 1.570 Mg/m^3	
Absorption coefficient	2.484 mm^{-1}	
F(000)	408	
Data Collection:		
Measurement device type	STOE-IPDS diffractometer	
Measurement method	rotation	
Temperature	173(1) K	
Wavelength	0.71073 Å	
Monochromator	graphite	
Theta range for data collection	2.73 to 25.76 deg.	
Index ranges	-10<=h<=10, -9<=k<=9, -14<=l<=14	
Reflections collected / unique	10361 / 3176 [R(int) = 0.0654]	
Reflections greater I>2\s(I)	2981	
Absorption correction	Analytical	
Max. and min. transmission	0.6629 and 0.4726	
Refinement:		
Refinement method	Full-matrix least-squares on F^2	
Hydrogen treatment	:	
Data / restraints / parameters	3176 / 1 / 218	
Goodness-of-fit on F^2	1.032	
Final R indices [I>2sigma(I)]	R1 = 0.0333, wR2 = 0.0812	
R indices (all data)	R1 = 0.0353, wR2 = 0.0823	
Absolute structure parameter	-0.011(8)	
Largest diff. peak and hole	0.546 and -0.322 $e.A^{-3}$	

6.2.3b Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for 220. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor:

	x	y	z	U(eq)
Br(1)	8659(1)	10600(1)	-55(1)	42(1)
O(1)	8856(2)	6553(3)	3376(2)	35(1)
O(2)	5168(2)	7048(3)	1428(2)	34(1)
O(3)	6342(3)	8895(3)	2721(2)	38(1)
O(4)	11738(3)	11094(3)	1544(2)	38(1)
O(5)	10329(5)	12345(6)	2759(4)	34(1)
O(7)	11154(2)	7966(3)	3474(2)	38(1)
O(8)	6282(3)	4658(3)	3314(2)	37(1)
O(9)	6631(3)	3772(3)	1526(2)	35(1)
C(1)	9122(3)	10271(3)	1623(2)	31(1)
C(2)	9253(3)	8425(4)	1874(2)	28(1)
C(3)	9579(3)	8068(4)	3183(2)	32(1)
C(4)	8244(3)	5867(4)	2287(2)	29(1)
C(5)	7865(3)	7352(4)	1474(2)	26(1)
C(6)	6356(4)	8195(4)	1595(3)	31(1)
C(7)	4962(4)	8370(4)	3146(3)	44(1)

C(8)	4032(4)	7672(5)	2101(3)	44(1)
C(9)	10599(4)	11143(4)	2015(3)	41(1)
C(10)	11613(8)	13426(9)	3144(6)	38(2)
C(11)	12718(9)	12627(10)	4057(7)	46(2)
C(14)	11592(4)	7934(6)	4704(3)	51(1)
C(15)	6925(3)	4741(4)	2464(3)	31(1)
C(16)	5277(4)	2772(4)	1495(3)	42(1)
C(12)	12017(10)	12179(10)	3807(6)	38(2)
C(13)	12181(10)	13962(11)	3602(8)	46(2)
O(6)	10591(6)	11547(6)	3193(4)	34(1)

6.2.3c Bond lengths [Å] and angles [deg] for 220:

Br(1)-C(1)	1.966(2)	C(10)-H(10B)	0.9899
O(1)-C(3)	1.426(4)	C(11)-H(11A)	0.9793
O(1)-C(4)	1.432(3)	C(11)-H(11B)	0.9795
O(2)-C(6)	1.408(4)	C(11)-H(11C)	0.9798
O(2)-C(8)	1.445(4)	C(14)-H(14A)	0.9795
O(3)-C(6)	1.432(4)	C(14)-H(14B)	0.9798
O(3)-C(7)	1.443(4)	C(14)-H(14C)	0.9806
O(4)-C(9)	1.210(4)	C(16)-H(16A)	0.9802
O(5)-C(9)	1.351(6)	C(16)-H(16B)	0.9801
O(5)-C(10)	1.470(9)	C(16)-H(16C)	0.9796
O(6)-C(12)	1.472(10)		
O(6)-C(9)	1.412(6)	C(3)-O(1)-C(4)	109.3(2)
O(7)-C(3)	1.403(3)	C(6)-O(2)-C(8)	104.6(3)
O(7)-C(14)	1.438(4)	C(6)-O(3)-C(7)	107.3(3)
O(8)-C(15)	1.204(4)	C(9)-O(5)-C(10)	116.2(4)
O(9)-C(15)	1.349(4)	C(9)-O(6)-C(12)	116.6(5)
O(9)-C(16)	1.452(4)	C(3)-O(7)-C(14)	112.5(2)
C(1)-C(9)	1.515(4)	C(15)-O(9)-C(16)	115.4(2)
C(1)-C(2)	1.539(4)	Br(1)-C(1)-C(9)	107.71(19)
C(2)-C(5)	1.540(4)	C(2)-C(1)-C(9)	111.2(2)
C(2)-C(3)	1.544(3)	Br(1)-C(1)-C(2)	108.94(16)
C(4)-C(15)	1.525(4)	C(1)-C(2)-C(3)	111.9(2)
C(4)-C(5)	1.551(4)	C(3)-C(2)-C(5)	103.8(2)
C(5)-C(6)	1.530(5)	C(1)-C(2)-C(5)	117.5(2)
C(7)-C(8)	1.499(5)	O(1)-C(3)-O(7)	111.5(2)
C(10)-C(11)	1.506(11)	O(7)-C(3)-C(2)	108.2(2)
C(12)-C(13)	1.487(12)	O(1)-C(3)-C(2)	106.6(2)
C(1)-H(1)	1.0000	O(1)-C(4)-C(5)	105.4(2)
C(2)-H(2)	1.0004	O(1)-C(4)-C(15)	109.4(2)
C(3)-H(3)	1.0002	C(5)-C(4)-C(15)	116.2(2)
C(4)-H(4)	1.0002	C(2)-C(5)-C(4)	98.9(2)
C(5)-H(5)	0.9999	C(2)-C(5)-C(6)	113.3(3)
C(6)-H(6)	1.0000	C(4)-C(5)-C(6)	115.1(2)
C(7)-H(7A)	0.9902	O(2)-C(6)-C(5)	109.8(3)
C(7)-H(7B)	0.9895	O(3)-C(6)-C(5)	111.7(3)
C(8)-H(8A)	0.9906	O(2)-C(6)-O(3)	107.6(3)
C(8)-H(8B)	0.9902	O(3)-C(7)-C(8)	104.1(3)
C(10)-H(10A)	0.9903	O(2)-C(8)-C(7)	102.8(3)

O(4)-C(9)-O(5)	122.6(4)	C(11)-C(10)-H(10A)	109.24
O(4)-C(9)-C(1)	126.2(3)	C(11)-C(10)-H(10B)	109.29
O(5)-C(9)-C(1)	108.7(3)	H(10A)-C(10)-H(10B)	107.91
O(6)-C(9)-C(1)	107.2(3)	C(10)-C(11)-H(11A)	109.46
O(4)-C(9)-O(6)	123.5(4)	C(10)-C(11)-H(11B)	109.44
O(5)-C(10)-C(11)	111.8(6)	C(10)-C(11)-H(11C)	109.42
O(6)-C(12)-C(13)	111.2(7)	H(11A)-C(11)-H(11B)	109.55
O(9)-C(15)-C(4)	108.8(3)	H(11A)-C(11)-H(11C)	109.47
O(8)-C(15)-O(9)	124.6(3)	H(11B)-C(11)-H(11C)	109.49
O(8)-C(15)-C(4)	126.5(3)	O(7)-C(14)-H(14A)	109.47
Br(1)-C(1)-H(1)	109.63	O(7)-C(14)-H(14B)	109.50
C(2)-C(1)-H(1)	109.66	O(7)-C(14)-H(14C)	109.43
C(9)-C(1)-H(1)	109.69	H(14A)-C(14)-H(14B)	109.48
C(1)-C(2)-H(2)	107.73	H(14A)-C(14)-H(14C)	109.51
C(3)-C(2)-H(2)	107.71	H(14B)-C(14)-H(14C)	109.44
C(5)-C(2)-H(2)	107.74	O(9)-C(16)-H(16A)	109.43
O(1)-C(3)-H(3)	110.11	O(9)-C(16)-H(16B)	109.45
O(7)-C(3)-H(3)	110.20	O(9)-C(16)-H(16C)	109.44
C(2)-C(3)-H(3)	110.19	H(16A)-C(16)-H(16B)	109.52
O(1)-C(4)-H(4)	108.56	H(16A)-C(16)-H(16C)	109.53
C(5)-C(4)-H(4)	108.58	H(16B)-C(16)-H(16C)	109.46
C(15)-C(4)-H(4)	108.49		
C(2)-C(5)-H(5)	109.68		
C(4)-C(5)-H(5)	109.71		
C(6)-C(5)-H(5)	109.69		
O(2)-C(6)-H(6)	109.26		
O(3)-C(6)-H(6)	109.20		
C(5)-C(6)-H(6)	109.21		
O(3)-C(7)-H(7A)	110.90		
O(3)-C(7)-H(7B)	110.96		
C(8)-C(7)-H(7A)	110.92		
C(8)-C(7)-H(7B)	110.96		
H(7A)-C(7)-H(7B)	108.97		
O(2)-C(8)-H(8A)	111.16		
O(2)-C(8)-H(8B)	111.20		
C(7)-C(8)-H(8A)	111.18		
C(7)-C(8)-H(8B)	111.25		
H(8A)-C(8)-H(8B)	109.17		
O(5)-C(10)-H(10A)	109.29		
O(5)-C(10)-H(10B)	109.27		

6.2.3d Anisotropic displacement parameters (A^2 x 10^3) for 220. The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a^{*2} U11 ++ 2 h k a* b* U12]:

	U11	U22	U33	U23	U13	U12
Br(1)	47(1)	41(1)	39(1)	9(1)	11(1)	-8(1)

O(1)	35(1)	38(1)	31(1)	5(1)	6(1)	-2(1)
O(2)	26(1)	31(1)	44(1)	3(1)	8(1)	0(1)
O(3)	31(1)	40(1)	45(1)	-8(1)	16(1)	-1(1)
O(4)	35(1)	37(1)	46(1)	-3(1)	18(1)	-4(1)
O(5)	37(2)	28(2)	39(2)	-6(1)	12(2)	-4(2)
O(7)	27(1)	57(2)	31(1)	0(1)	7(1)	0(1)
O(8)	39(1)	37(1)	36(1)	6(1)	11(1)	1(1)
O(9)	39(1)	28(1)	41(1)	-2(1)	13(1)	-1(1)
C(1)	36(2)	27(2)	33(1)	-2(1)	12(1)	-1(1)
C(2)	27(1)	27(2)	31(1)	-4(1)	11(1)	2(1)
C(3)	28(2)	38(2)	31(1)	-3(1)	8(1)	-2(1)
C(4)	29(1)	26(2)	32(1)	1(1)	7(1)	3(1)
C(5)	29(2)	25(2)	26(1)	1(1)	8(1)	2(1)
C(6)	31(2)	28(2)	35(2)	1(1)	6(1)	0(1)
C(7)	40(2)	39(2)	59(2)	-1(2)	28(2)	4(2)
C(8)	29(2)	40(2)	67(2)	3(2)	20(2)	4(1)
C(9)	42(2)	36(2)	48(2)	-10(1)	20(1)	-6(1)
C(10)	41(3)	35(3)	37(3)	-1(2)	6(2)	-1(2)
C(11)	44(3)	43(3)	50(3)	-2(2)	8(3)	-1(3)
C(14)	38(2)	79(3)	35(2)	1(2)	4(1)	-4(2)
C(15)	32(2)	26(2)	36(2)	5(1)	9(1)	7(1)
C(16)	44(2)	34(2)	49(2)	-1(2)	11(2)	-6(2)
C(12)	41(3)	35(3)	37(3)	-1(2)	6(2)	-1(2)
C(13)	44(3)	43(3)	50(3)	-2(2)	8(3)	-1(3)
O(6)	37(2)	28(2)	39(2)	-6(1)	12(2)	-4(2)

6.2.3e Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for 220:

	x	y	z	U(eq)
H(3)	9155	8960	3636	38
H(5)	7892	7011	652	32
H(6)	6176	9077	999	37
H(4)	9050	5202	1979	34
H(1)	8293	10748	2026	38
H(2)	10126	7997	1497	34
H(8B)	3407	8527	1671	53
H(10A)	11229	14449	3459	45
H(10B)	12142	13718	2472	45
H(11A)	12181	12258	4696	54
H(11B)	13502	13417	4346	54
H(11C)	13189	11686	3721	54
H(14A)	11279	8955	5046	61
H(14B)	12694	7817	4863	61
H(14C)	11101	7006	5041	61
H(16A)	5322	2129	2209	50
H(16B)	5215	2033	828	50
H(16C)	4382	3480	1427	50
H(7A)	4437	9306	3462	53
H(7B)	5173	7531	3757	53
H(8A)	3363	6784	2318	53

H(12A)	12881	11589	3539	45
H(12B)	12036	11977	4647	45
H(13A)	12144	14166	2770	54
H(13B)	13154	14341	3998	54
H(13C)	11355	14553	3904	54

6.2.3f Torsion angles [deg] for 220:

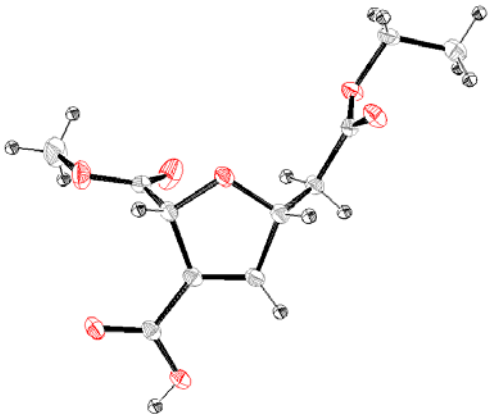
C(3)-O(1)-C(4)-C(15)	-154.7(2)	O(4)	
C(4)-O(1)-C(3)-O(7)	-112.1(2)	C(2)-C(1)-C(9)-O(4)	74.0(4)
C(4)-O(1)-C(3)-C(2)	5.8(3)	Br(1)-C(1)-C(9)-O(5)	116.9(3)
C(3)-O(1)-C(4)-C(5)	-29.1(3)	C(9)-C(1)-C(2)-C(5)	-177.2(2)
C(8)-O(2)-C(6)-O(3)	30.0(3)	C(1)-C(2)-C(3)-O(7)	-92.5(3)
C(8)-O(2)-C(6)-C(5)	151.8(3)	C(3)-C(2)-C(5)-C(4)	-34.8(3)
C(6)-O(2)-C(8)-C(7)	-37.1(3)	C(1)-C(2)-C(5)-C(4)	-159.0(2)
C(7)-O(3)-C(6)-C(5)	-130.8(3)	C(5)-C(2)-C(3)-O(7)	139.8(2)
C(6)-O(3)-C(7)-C(8)	-12.9(3)	C(3)-C(2)-C(5)-C(6)	87.5(3)
C(7)-O(3)-C(6)-O(2)	-10.2(3)	C(1)-C(2)-C(3)-O(1)	147.5(2)
C(10)-O(5)-C(9)-C(1)	-174.3(4)	C(5)-C(2)-C(3)-O(1)	19.8(3)
C(9)-O(5)-C(10)-C(11)	-77.7(7)	C(1)-C(2)-C(5)-C(6)	-36.6(3)
C(10)-O(5)-C(9)-O(4)	-11.3(7)	C(15)-C(4)-C(5)-C(6)	39.7(3)
C(14)-O(7)-C(3)-O(1)	-73.7(3)	C(15)-C(4)-C(5)-C(2)	160.7(2)
C(14)-O(7)-C(3)-C(2)	169.4(3)	O(1)-C(4)-C(5)-C(6)	-81.6(3)
C(16)-O(9)-C(15)-C(4)	-172.4(2)	O(1)-C(4)-C(15)-O(9)	-163.3(2)
C(16)-O(9)-C(15)-O(8)	10.7(5)	O(1)-C(4)-C(15)-O(8)	13.5(4)
C(2)-C(1)-C(9)-O(5)	-123.8(3)	O(1)-C(4)-C(5)-C(2)	39.4(2)
Br(1)-C(1)-C(2)-C(3)	-178.65(17)	C(5)-C(4)-C(15)-O(9)	77.6(3)
Br(1)-C(1)-C(2)-C(5)	-58.7(2)	C(5)-C(4)-C(15)-O(8)	-105.6(4)
C(9)-C(1)-C(2)-C(3)	62.8(3)	C(4)-C(5)-C(6)-O(2)	-56.0(3)
Br(1)-C(1)-C(9)-	-45.3(4)	C(2)-C(5)-C(6)-O(3)	-49.4(3)

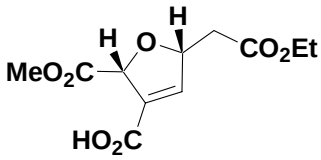
C(2)-C(5)-C(6)-O(2)	-168.8(2)	O(3)	
C(4)-C(5)-C(6)-O(3)	63.4(3)	O(3)-C(7)-C(8)-O(2)	30.5(3)

6.2.3g Hydrogen-bonds for 220 [Å and deg.]:

D-H A	d(D-H)	d(H A)	d(D A)	(DHA)
C(1)-H(1) O(3)	1.0000	2.5100	3.127(4)	120.00
C(2)-H(2) Br(1) 1	1.0000	2.8700	3.771(3)	149.00
C(3)-H(3) O(3)	1.0000	2.6000	2.943(4)	100.00
C(8)-H(8B) O(4) 2	0.9900	2.5600	3.476(5)	153.00
C(11)-H(11A) O(1) 3	0.9800	2.5900	3.561(8)	170.00

6.2.4 2*R*,5*R*-(+)-5-Ethoxycarbonylmethyl-2,5-dihydro-furan-2,3-dicarboxylic acid 2-methyl ester (240):





6.2.4a Crystal data and structure refinement for 240:

Crystal Data:

Empirical formula	C11 H14 O7	
Formula weight	258.22	
Crystal size	0.30 x 0.12 x 0.08 mm	
Crystal description	rod	
Crystal colour	colourless	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 8.9228(6) Å	α = 90 deg.
	b = 4.5629(3) Å	β = 97.005(8) deg.
	c = 14.7692(11) Å	γ = 90 deg.
Volume	596.82(7) A^3	
Z, Calculated density	2, 1.437 Mg/m^3	
Absorption coefficient	0.122 mm^{-1}	
F(000)	272	

Data Collection:

Measurement device type	STOE-IPDS diffractometer
Measurement method	rotation

Temperature	123(1) K
Wavelength	0.71073 Å
Monochromator	graphite
Theta range for data collection	2.30 to 26.83 deg.
Index ranges	-11<=h<=11, -5<=k<=5, -18<=l<=18
Reflections collected / unique	5209 / 2543 [R(int) = 0.0162]
Reflections greater	I>2\s(I);2404
Absorption correction	:
Refinement:	
Refinement method	Full-matrix least-squares on F^2
Hydrogen treatment	:
Data / restraints / parameters	2543 / 1 / 184
Goodness-of-fit on F^2	1.065
Final R indices [I>2sigma(I)]	R1 = 0.0262, wR2 = 0.0675
R indices (all data)	R1 = 0.0280, wR2 = 0.0684
Absolute structure parameter	-0.5(6)
Largest diff. peak and hole	0.234 and -0.139 e.A^{-3}

6.2.4b Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for 240. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor:

	x	y	z	U(eq)
O(1)	7335(1)	4146(2)	6918(1)	22(1)
O(2)	6223(1)	6373(2)	9579(1)	26(1)
O(3)	4662(1)	9686(2)	8822(1)	28(1)
O(4)	6768(1)	4600(2)	4590(1)	24(1)
O(5)	8606(1)	8024(2)	4702(1)	22(1)
O(6)	9715(1)	5124(2)	8909(1)	32(1)
O(7)	9389(1)	8413(2)	7774(1)	38(1)
C(1)	7458(1)	4734(3)	7872(1)	18(1)
C(2)	6131(1)	6734(3)	7975(1)	17(1)
C(3)	5452(1)	7494(3)	7157(1)	19(1)
C(4)	6200(1)	6023(3)	6422(1)	19(1)
C(5)	6927(1)	8152(3)	5810(1)	19(1)
C(6)	7410(1)	6673(3)	4977(1)	18(1)
C(7)	9108(1)	6962(3)	3854(1)	23(1)
C(8)	8146(1)	8220(3)	3032(1)	27(1)
C(9)	8965(1)	6327(3)	8168(1)	20(1)
C(10)	11135(2)	6548(4)	9240(1)	41(1)
C(11)	5681(1)	7567(3)	8871(1)	19(1)

6.2.4c Bond lengths [Å] and angles [deg] for 240:

O(1)-C(1)	1.4266(13)	O(6)-C(9)	1.3295(15)
O(1)-C(4)	1.4540(14)	O(6)-C(10)	1.4538(17)
O(2)-C(11)	1.2251(14)	O(7)-C(9)	1.2010(16)
O(3)-C(11)	1.3233(15)	O(3)-H(3O)	0.841(18)
O(4)-C(6)	1.2125(15)	C(1)-C(2)	1.5176(17)
O(5)-C(6)	1.3376(14)	C(1)-C(9)	1.5437(16)
O(5)-C(7)	1.4634(14)	C(2)-C(11)	1.4786(15)

C(2)-C(3)	1.3294(15)
C(3)-C(4)	1.4994(16)
C(4)-C(5)	1.5253(17)
C(5)-C(6)	1.5116(16)
C(7)-C(8)	1.5117(17)
C(1)-H(1)	0.950(17)
C(3)-H(3)	0.935(16)
C(4)-H(4)	1.0003
C(5)-H(5A)	0.949(15)
C(5)-H(5B)	0.944(16)
C(7)-H(7A)	0.947(18)
C(7)-H(7B)	0.933(17)
C(8)-H(8A)	0.9803
C(8)-H(8B)	0.9801
C(8)-H(8C)	0.9799
C(10)-H(10A)	0.9797
C(10)-H(10B)	0.9803
C(10)-H(10C)	0.9800
C(1)-O(1)-C(4)	110.58(8)
C(6)-O(5)-C(7)	116.48(9)
C(9)-O(6)-C(10)	114.99(10)
C(11)-O(3)-H(3O)	109.8(12)
O(1)-C(1)-C(9)	109.16(9)
C(2)-C(1)-C(9)	110.62(11)
O(1)-C(1)-C(2)	104.15(8)
C(1)-C(2)-C(11)	122.94(9)
C(3)-C(2)-C(11)	127.11(11)
C(1)-C(2)-C(3)	109.92(10)
C(2)-C(3)-C(4)	110.33(10)
O(1)-C(4)-C(5)	110.65(9)
C(3)-C(4)-C(5)	113.76(11)
O(1)-C(4)-C(3)	104.11(8)
C(4)-C(5)-C(6)	112.50(11)
O(4)-C(6)-C(5)	124.52(10)
O(5)-C(6)-C(5)	111.01(10)
O(4)-C(6)-O(5)	124.43(10)
O(5)-C(7)-C(8)	110.99(10)
O(6)-C(9)-C(1)	111.86(10)
O(7)-C(9)-C(1)	123.40(11)
O(6)-C(9)-O(7)	124.74(11)
O(2)-C(11)-C(2)	121.89(11)
O(3)-C(11)-C(2)	113.47(10)

O(2)-C(11)-O(3)	124.63(10)
O(1)-C(1)-H(1)	109.4(10)
C(2)-C(1)-H(1)	113.2(9)
C(9)-C(1)-H(1)	110.1(9)
C(2)-C(3)-H(3)	126.3(9)
C(4)-C(3)-H(3)	123.3(9)
O(1)-C(4)-H(4)	109.39
C(3)-C(4)-H(4)	109.40
C(5)-C(4)-H(4)	109.37
C(4)-C(5)-H(5A)	109.0(9)
C(4)-C(5)-H(5B)	109.1(9)
C(6)-C(5)-H(5A)	110.3(9)
C(6)-C(5)-H(5B)	105.0(9)
H(5A)-C(5)-H(5B)	110.9(13)
O(5)-C(7)-H(7A)	108.3(10)
O(5)-C(7)-H(7B)	102.8(10)
C(8)-C(7)-H(7A)	110.2(10)
C(8)-C(7)-H(7B)	110.2(10)
H(7A)-C(7)-H(7B)	114.2(14)
C(7)-C(8)-H(8A)	109.49
C(7)-C(8)-H(8B)	109.45
C(7)-C(8)-H(8C)	109.46
H(8A)-C(8)-H(8B)	109.48
H(8A)-C(8)-H(8C)	109.48
H(8B)-C(8)-H(8C)	109.48
O(6)-C(10)-H(10A)	109.48
O(6)-C(10)-H(10B)	109.47
O(6)-C(10)-H(10C)	109.45
H(10A)-C(10)-H(10B)	109.47
H(10A)-C(10)-H(10C)	109.45
H(10B)-C(10)-H(10C)	109.50

6.2.4d Anisotropic displacement parameters (A^2 x 10^3) for 240. The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a^{*2} U11 ++ 2 h k a* b* U12]:

	U11	U22	U33	U23	U13	U12
O(1)	29(1)	21(1)	15(1)	-2(1)	4(1)	6(1)

O(2)	27(1)	36(1)	15(1)	3(1)	6(1)	0(1)
O(3)	31(1)	38(1)	15(1)	-3(1)	7(1)	9(1)
O(4)	29(1)	26(1)	18(1)	-6(1)	6(1)	-6(1)
O(5)	21(1)	27(1)	20(1)	-5(1)	7(1)	-4(1)
O(6)	28(1)	46(1)	20(1)	5(1)	-5(1)	-4(1)
O(7)	26(1)	37(1)	48(1)	16(1)	-4(1)	-8(1)
C(1)	23(1)	17(1)	14(1)	0(1)	3(1)	1(1)
C(2)	17(1)	19(1)	17(1)	-2(1)	4(1)	-3(1)
C(3)	18(1)	23(1)	16(1)	-2(1)	5(1)	0(1)
C(4)	19(1)	21(1)	15(1)	-2(1)	2(1)	0(1)
C(5)	22(1)	18(1)	16(1)	-1(1)	3(1)	1(1)
C(6)	19(1)	19(1)	15(1)	2(1)	2(1)	2(1)
C(7)	22(1)	29(1)	21(1)	-4(1)	9(1)	0(1)
C(8)	32(1)	27(1)	22(1)	1(1)	9(1)	-2(1)
C(9)	20(1)	22(1)	19(1)	-1(1)	5(1)	5(1)
C(10)	30(1)	62(1)	28(1)	-3(1)	-8(1)	-6(1)
C(11)	17(1)	23(1)	16(1)	-1(1)	4(1)	-6(1)

6.2.4e Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for 240:

	x	y	z	U(eq)
H(1)	7424(16)	2940(40)	8196(10)	22
H(3)	4597(17)	8680(40)	7038(10)	22
H(3O)	4475(18)	10130(40)	9349(12)	33
H(4)	5443	4785	6040	22
H(5A)	7767(17)	9060(30)	6155(10)	22
H(5B)	6205(16)	9560(40)	5578(10)	22
H(7A)	9046(17)	4890(40)	3849(11)	28
H(7B)	10090(18)	7690(40)	3887(10)	28
H(8A)	7087	7686	3055	32
H(8B)	8483	7430	2474	32
H(8C)	8244	10359	3035	32
H(10A)	11819	6445	8770	49
H(10B)	11596	5554	9793	49
H(10C)	10945	8605	9379	49

6.2.3f Torsion angles [deg] for 240:

C(4)-O(1)-C(1)-C(2)	9.78(12)	C(7)-O(5)-C(6)-C(5)	-174.91(9)
C(4)-O(1)-C(1)-C(9)	-108.38(11)	C(10)-O(6)-C(9)-C(1)	-178.82(10)
C(1)-O(1)-C(4)-C(3)	-8.67(12)	C(10)-O(6)-C(9)-O(7)	0.70(18)
C(1)-O(1)-C(4)-C(5)	113.92(10)	C(2)-C(1)-C(9)-O(6)	114.21(11)
C(7)-O(5)-C(6)-O(4)	2.72(17)	C(9)-C(1)-C(2)-C(3)	109.84(12)
C(6)-O(5)-C(7)-C(8)	80.54(13)	O(1)-C(1)-C(2)-C(11)	170.97(11)

O(1)-C(1)-C(9)-O(7)	48.71(16)	C(4)	
C(2)-C(1)-C(9)-O(7)	-65.31(15)	C(1)-C(2)-C(3)-C(4)	2.11(15)
C(9)-C(1)-C(2)-C(11)	-71.88(14)	C(3)-C(2)-C(11)-O(2)	167.63(13)
O(1)-C(1)-C(9)-O(6)	-131.77(10)	C(2)-C(3)-C(4)-C(5)	-116.69(12)
O(1)-C(1)-C(2)-C(3)	-7.32(14)	C(2)-C(3)-C(4)-O(1)	3.83(14)
C(1)-C(2)-C(11)-O(3)	169.55(11)	C(3)-C(4)-C(5)-C(6)	-169.26(9)
C(3)-C(2)-C(11)-O(3)	-12.47(19)	O(1)-C(4)-C(5)-C(6)	73.97(11)
C(1)-C(2)-C(11)-O(2)	-10.35(19)	C(4)-C(5)-C(6)-O(5)	-150.31(10)
C(11)-C(2)-C(3)-	-176.08(12)	C(4)-C(5)-C(6)-O(4)	32.06(16)

6.2.3g Hydrogen-bonds for 240 [Å and deg.]:

D-H A	d(D-H)	d(H A)	d(D A)	(DHA)
O(3)-H(3O) O(2)#1	0.841(18)	1.859(17)	2.6921(12)	170.8(16)
C(3)-H(3) O(4) 2	0.935(16)	2.593(15)	3.2023(14)	123.2(12)

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