Chapter 4
The Synthesis of Enantiomerically Pure γ-Butyrolactone Based Molecules Employing (2S,3S) and (2S,3R)-Tetrahydro-3-Hydroxy-5-Oxo-2, 3- Furan Dicarboxylic Acids

4.1 Introduction

The γ-butyrolactones, bislactones\textsuperscript{13,144} and α-methylene-γ-butyrolactone\textsuperscript{148} structural motifs are found in a vast array of synthetically challenging and biologically significant natural products. Many of these entities are useful as building blocks for alkaloids, macro cyclic antibiotics, lignan lactones, pheromones, antileukemicals and flavor components.\textsuperscript{13,145,154a,167} These molecules possess biological activities such as anticancer, antimalarial, antiviral, antibacterial, antifungal, anti-inflammatory etc. The favourable cis/trans orientation of adjacent C2 and C3 carboxyl groups, the matching absolute configurations and appropriate number of carbon atoms make 6 and 7, ideal precursors for the synthesis of γ-butyrolactone-based natural products. Few instances are natural products such as (-) funebrine\textsuperscript{13b,147i,j,150} (213), methylenolactocins\textsuperscript{148} (214 & 215), (+)-avenaciolide\textsuperscript{13a,156} (223), isoavenaciolide (224) ethisolide\textsuperscript{13a,156} (225), (-)-canadensolide\textsuperscript{13a,157} (226), cis -whisky lactones\textsuperscript{13b,155} (233), cinatrins\textsuperscript{147b,158} (234 & 235), funebral (237), anthecotulides (238-240) and lignan lactones\textsuperscript{10f,5a} (247 & 248) (Chapter 1, Table 1.9). Preparation of these compounds from tartaric acid, a four carbon skeleton with two chiral centres, is rather cumbersome. However, optically active 2-hydroxycitric acids 6 and 7 (a six carbon skeleton with two chiral centres, visualized as a derivative of tartaric acid), could be the most appropriate choice as a starting molecules for the synthesis of these class of molecules to minimize synthetic steps.

4.1.1 (+)-Avenaciolide and related bislactones

The (+)-avenaciolide (223), (+)-isoavenaciolide (224) and (+)/(−) ethisolide (225) constitute a trio of naturally occurring secondary metabolites, which exhibit diverse and potent biological activity. The tetrahydrofuro[3,4-b]furandione skeleton has been observed as a common structural motif in these antifungal mold metabolites. In 1963, Brookes, Tidd and Turner first isolated the bislactones 223-225 from cultures of \textit{Aspergillus avenaceus},\textsuperscript{156a} of these, 223 exhibits the most diverse and potent biological activity, including inhibition of fungal spore germination, antibacterial
properties. Furthermore it was found to inhibit glutamate transport in rat liver mitochondria\textsuperscript{156b} and irreversible inhibition of vaccinia H1 related (VHR) phosphotase activity.

The biological activity coupled with its interesting structure (bis-fused $\gamma$-lactone core with three contiguous chiral centres) has stimulated considerable synthetic efforts in these molecules resulting in numerous syntheses.\textsuperscript{156f, 147f} One particularly elegant total synthesis utilised an intramolecular alkoxy carbonylation of tungsten–$\pi$-allyl complexes in the key step\textsuperscript{156g}.

Almost all the known methods for the construction of the concave skeleton are tedious, time consuming and often result in racemic products.\textsuperscript{292} W.L. Parker and F. Johnson reported the first total synthesis of dl -avenaciolide in 1969 and R.C. Anderson and B. Fraser-Raid synthesized optically pure avenaciolide in 1975.\textsuperscript{293} A good account of various synthetic strategies considering the contemporary interest of these molecules has been reported.\textsuperscript{156} The approaches include Fittig condensation, carbohydrate modification, nucleophilic addition to butenolides, furan [4+2] cycloaddition, furan-aldehyde [2+2] cycloaddition, glycolate Claisen rearrangement, epoxyalcohol rearrangement, radical cyclisation and the carbonyl ene reaction \textsuperscript{147f} (Figure 4.1). Figure 4.2 depicts the stereoselective synthesis\textsuperscript{294} of bislactones 223-225.

![Figure 4.1](image-url)  
**Figure 4.1  Racemic syntheses of the bislactones 223-225**
4.1.2 (-)-Canadensolide and related bislactones

The (-)-canadensolide (226), xylobovide (227) and sporothriolide (228) (Figure 4.3) are naturally occurring α-methylene bis-γ-butyrolactones isolated from Xylaria obovata, Pencillium canadense and Sporothrix sp. respectively. They are closely related natural products which differ simply in the length of their side chain. Canadensolide, metabolite isolated from the culture filtrates of the fungus Pencillium canadense has been found to inhibit the germination of fungi Botrytis alli. The fungicidal activity of bislactone 226, the phytotoxic activity of 227 and the antibacterial, fungicidal, algicidal and herbicidal activities of 228 are noteworthy. Substituted furofurandiones were found to be useful in the treatment of duodenal ulcers. The unusual and unique α-methylene bis-γ-butyrolactone moiety, which may be responsible for the biological activity, is an added interest on these molecules. The concave bislactonic structure with all cis stereochemistry of the adjacent methine protons as well as the potent biological activity exhibited by these
molecules has attracted a great deal of attention and hence the syntheses of these structures are challenging and fascinating targets to synthetic chemists. Figure 4.4 shows the stereoselective synthesis of bislactone 226.

![Figure 4.3 Structure of (-)-canadensolide and related bislactones](image)

![Figure 4.4 Stereoselective synthesis of bislactone 226](image)

4.1.3 Lignans

The lignans are widely distributed plant natural products with diverse biological activity such as antitumor, antimitotic and antiviral properties. Enterolactone (431) was the first lignan isolated from a mammalian source. Enterolactone and enterodiol are considered to be products of colonic bacterial metabolism of the plant-derived precursor matairesinol (427) and secoisolariciresinol (428) respectively. Flaxseed was reported to be the richest source of precursors of mammalian lignans. The lignan composition of flaxseed meal was recently characterized, and the major lignan was identified as 428, whereas
matairesinol, pinoresinol (429) and isolariciresinol (430) were identified as minor lignan components.\textsuperscript{161} (Figure 4.5).

The plant derived precursors of enterodiol and enterolactone are classified as phytoestrogens because it can mimic some of the effects of estrogens. It has various biological activities, such as antitumour activity, platelet activating factor antagonists, sodium selective diuretic properties etc. (-) Enterolactone seems to be under endocrine control and it depresses estrogen stimulated RNA synthesis. The lignan 431, which is produced by intestinal microflora from dietary precursors, has been proposed to possess several biological activities including antioxidant activity and inhibition of several enzymes involved in steroid hormone metabolism, thus providing potential mechanisms for a preventive influence in hormone dependent cancers and cardiovascular diseases. Lignans have also been suggested to play a role in the prevention of prostate cancer, breast cancer and endometrial ovarian and thyroid cancers.\textsuperscript{161}

E. Jacobs and M. Metzler have synthesized the lignan 431 from 2 butene-4-olide by reaction with 3- benzyloxy benzaldehyde bis (phenylthio) acetal and 3-benzyloxy benzylbromide with high purity (Figure 4.6).
The butyrolactone (-)-trachelogenin or wikstromol (247) is obtained from the phytochemical investigation of *Glycydendron amazonirum* Ducke (*Euphorbiaceae*) leaves. The lignan 247 has been shown to be a Ca$^{2+}$ antagonist and possess potent antihypertensive activity. Also shown to be an antagonist of platelet activating factor (PAF) and possess antileukemic, anticancer and in vitro anti-HIV activities.$^{161}$

Y. Moritani *et al.* have synthesized racemic trachelogenin based on the electrophilic addition to the metal enolate of $\alpha$-benzyl-$\gamma$-butyrolactone derivatives as the key step$^{161}$ (Figure 4.7).

4.1.4 $\alpha$-Methylene-$\gamma$-butyrolactones: Anthecotulide, hydroxy anthecotulide and acetoxy anthecotulide

Since, the first isolation of $\alpha$-methylene-$\gamma$-butyrolactone pyrethrosin (432) in 1891, (Figure 4.8) there have been numerous reports covering the biosynthesis, biological properties and medical applications of these class of compounds. The $\alpha$-methylene-$\gamma$-butyrolactone structural motifs are found in a
range of natural products, especially irregular sesquiterpene lactones. For instance, hydroxy anthecotulide (238), acetoxy anthecotulide (239) and anthecotulide (240) are optically active irregular sesquiterpene lactone isolated from Anthemis cotula L. (stinking chamomile). Anthecotulide has attracted interest due to its contact allergen properties (contamination of chamomile preparations by A. cotula is to be avoided) and its unusual biosynthesis for a sesquiterpene, involving head-to-middle coupling of geranyl diphosphate and dimethylallyl diphosphate. More recently, the lactone 238 demonstrated antibacterial, antimalarial trypanocidal and leishmanicidal activity and has also been shown to inhibit the activation pathway of the transcription factor NF-kB which regulates pro-inflammatory mediators (cytokines, nitric oxide, prostaglandins).

![Figure 4.8 Structure of lactones α-methylene-γ-butyrolactone](image)

4.1.5 Hydroxy Pyrroolidine: Inhibitors of purine nucleoside phosphorylase and UDP-galactose transferase

The World Health Organization (WHO) has estimated that one third of the world’s population is infected with *Mycobacterium tuberculosis*, the causative agent of TB, and it has predicted that by 2020 one billion people will be newly infected if new anti-TB treatments are not developed. The cell wall is essential for cell growth in mycobacteria. The *D*-Galactans are the key components of the mycobacterial cell wall and since their main constituents (*D*-galactofuranose residues) are not found in mammalian metabolism; their biosynthesis constitutes a very attractive and accessible target for new anti-TB drugs without any deleterious side effects. The biosynthesis of these alternating β-1,5 and β-1,6 galactofuranosyl polymers involves two specific enzymes, UDP-galactopyranose mutase (UDPGalp mutase EC 5.4.99.9) and UDP-galactofuranosyl transferase (UDP-Galf transferase). It has recently been shown that UDP-Galf transferase is
a bifunctional enzyme capable of catalyzing both $\beta$-1,5 and $\beta$-1,6 linkages in \textit{M. tuberculosis} (gene product of \textit{Rv3808c}).$^{296b}$

The hydroxy pyrrolidines, also known as imino sugars, are known to have an inhibitory effect on certain enzymes such as UDP-Galf transferase and glial GABA uptake. The iminosugars, analogues of monosaccharides where the ring oxygen or anomeric carbon has been replaced by a nitrogen atom, are inhibitors of carbohydrate enzymes. In particular, they have been demonstrated to be potent inhibitor of glycosidases and glycosyl transferases. The use of these imino sugars as building blocks for the synthesis of some compounds having antibacterial activity is well documented.$^{296b}$ The very first aza $C$-nucleoside incorporating imino sugar was reported. Recently, some highly potent purine nucleoside phosphorylase (PNP) inhibitors have been reported based upon imino sugars. The clinical candidate, BCX-4208 (433), has evolved from the second generation of PNP inhibitors,$^{296b}$ where (3$R$,4$R$)-4-(hydroxymethyl)pyrrolidin-3-ol (434) is the precursor for its preparation (Figure 4.9). The pyrrolidine (435) was found to be a moderate inhibitor of purine nucleoside phosphorylases.

The first synthesis of 434 was reported by Jaeger and Biel from N-benzylglycinate and ethyl acrylate. This compound was obtained as a mixture of \textit{cis}/\textit{trans}-isomers. The synthesis of the \textit{trans}-racemic compound was first reported by Makino and Ichikawa starting from fumaric acid dimethylester. The pure enantiomer of the \textit{trans}-isomer 434 was prepared from glucose and xylose involving a 14–15 step synthesis. A shorter synthesis of this isomer was achieved via asymmetric 1,3-dipolar cycloaddition using camphor sultam as a chiral auxiliary. This synthesis was recently modified and adapted to a practical large-scale preparation of the desired \textit{trans}-isomer, which was used for the preparation of kilo quantities of clinical candidate 433.
4.2 Results and Discussion

In continuation to the above discussions, 6 and 7 are ideally suited as building blocks for the synthesis of several biologically active natural products such as the bislactones 223-225, sesquiterpene lactones 238-240, imino sugars 433-436. Simultaneous regio- and chemoselective reduction of the carboxyl groups of 6 and 7 or its esters is expected to afford suitable chiral precursors for cumulating the synthesis of many of the chiral γ-butyrolactones and related bislactones listed above (Figure 4.10). The precursors 204 and 406 obtained by the regio-selective reduction of C3 carboxylate of esters of 6, using BMS and catalytic amount of sodium borohydride, have been successfully employed for the syntheses of a few enantiomerically pure natural product intermediates namely concave bislactone skeleton (3aR, 6aS)-3a-hydroxytetrahydrofuro[3, 4-b] furan- 2,6-dione (208), methyl (2S)- hydroxyl [(3R)-3-hydroxy-5-oxotetrahydrofuran-3-yl]ethanoate (210), (2S)-N-benzyl-2-hydroxy-2-
[(3R)-3-hydroxy-5-oxotetrahydrofuran-3-yl]ethanamidie (387), methyl (2S,3R)-3-
hydroxy-3-([(4-methylphenyl)sulfonyl]oxy)methyl)-5-oxotetrahydrofuran-2-
carboxylate (446), (4R)-4-[(1R)-1,2-dihydroxyethyl]-4-hydroxydihydrofuran-2(3H)-
one (231), dimethyl (5S)-4-(2-methoxy-2-oxoethyl)-2-(trichloromethyl)-1,3-
dioxolane-4,5-dicarboxylate (449), (2R,3R)-3-(hydroxymethyl) pentane-1,2,3,5-
tetraol (386).
4.2.1 Enantiomerically pure synthesis of concave bislactone skeleton (3aR, 6aS)-3a-hydroxytetrahydrofuro[3, 4-b]furan-2,6-dione (208)

A retrosynthetic analysis of the bislactones 223-225 (Scheme 4.1) clearly indicates the involvement of the alcohol 204 which is turned out to be the key element in the most of the subsequent transformations. The Swern oxidation of 204 or partial reduction of 153 using BMS followed by the nucleophilic addition of alkyl donor synthons, subsequent deoxygenation followed by the introduction of a methylene group is expected to give 223-225 respectively. Alternatively, the aldehyde 440 could be obtained directly by the partial reduction of 153 or 155 using BMS and subsequent quenching of the reaction with methanol.
Scheme 4.1 Retrosynthetic scheme for the synthesis of bislactones 223-225 from 204

An examination of the structure of 204 reveals that the C2 carboxylate and the primary alcoholic group are in a favorable cis orientation for the lactonisation of the molecule. In presence of an acid catalyst, 204 can eliminate a molecule of methanol to give the desired bislactone 208. Either of trifluoroacetic acid or p-toluene sulphonic acid has been used as acid catalyst. However the lactonisation of 204 under a variety of the standard conditions failed to give the bislactone 204. There are instances of silica gel catalysing such cyclisations. The crude alcohol 204 obtained by the selective reduction of C3 carboxylate of 153, using BMS and catalytic NaBH₄, was loaded on a silica gel (60-120 mesh) column and up on chromatographic purification (dichloromethane-hexane mixture) (7:3) yielded the bislactone 208 in 81% as a sharp melting solid (mp, 136–138 °C) [α]$_D^{20}$ +20.64, (c 0.28, H₂O) (Scheme 4.2). The isolated bislactone, an analogue of 223, is having same carbon skeleton. The structure was confirmed on the basis of IR, $^1$H, $^{13}$C NMR and mass spectra. The single crystal X-ray analysis confirmed the concave nature and absolute configuration of 208.

Scheme 4.2 Synthesis of 208

The IR spectrum of 208 displayed absorption frequencies at $\nu_{max}$ 3452.34 (due to –OH group), at 2954.7 (due to –CH stretchings) and at 1778. 25 cm$^{-1}$ (due to the carbonyl groups). The $^1$H NMR spectrum showed signals at $\delta$ 5.03 (singlet; due to
methine proton), at δ 4.367 - 4.244 (AB quartet; shows the presence of methylene protons) and at δ 3.214 – 2.732 (AB quartet; indicates the presence of -CH₂CO protons). In the ¹³C NMR spectrum, six different signals appeared at δ 174.2, 170.7, 81.2, 77.5, 74.5 and 40.3 also confirmed the number of carbon atoms of the molecule 208 (Figure 4.12a-d). HRMS (ES+) Exact mass calculated for C₆H₇O₅ (M+H)⁺ is 159.0293 value experimentally found is 159.0290 (Figure 4.11)

**Elemental Composition Report**

**Single Mass Analysis**

Tolerance = 200.0 mDa / DBE: min = -1.5, max = 50.0
Isotope cluster parameters: Separation = 1.0  Abundance = 1.0%

Multanucleic Mass, Odd and Even Electron ions
5 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)

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Figure 4.11  Single mass analysis of 208

IR (KBr pellet)

Figure 4.12a
$^1$H NMR: 300 MHz, Solvent: DMSO-d$_6$

Figure 4.12b

$^{13}$C NMR: 75 MHz, Solvent: DMSO-d$_6$

Figure 4.12c
A single crystal XRD analysis confirmed the concave nature and absolute configuration of 208. A colourless block shaped crystal of 208 with approximate dimensions 10 x 15 x 30 mm was mounted for data collection. The X-ray intensity data were measured at room temperature on Bruker X8 Apex-II Kappa CCD area detector diffractometer with graphite monochromated Mo Kα radiation (50kV, 30mA). The detector was placed at a distance of 35 cm from the crystal. The spatial arrangement of 208 is confirmed from the ORTEP diagram (Figure 4.13)
4.2.2 Synthesis of methyl (2S)-hydroxyl [(3R)-3-hydroxy-5-oxotetrahydrofuran-3-yl] ethanoate (210)

The alcohol 204, obtained by the selective reduction of BMS and catalytic amount of sodium borohydride, was equilibrated using p-TSA and methanol to get the more stable isomer 210.\textsuperscript{160b} The γ-butyrolactone moieties bearing this type of substitution pattern is found in many natural products such as irregular sesquiterpene lactones 238-240, lignans 247-248 and the non-natural amino-lactone 222. A retrosynthetic strategy to sesquiterpene lactones 238-240 shows the involvement of 210 as the key intermediate (Scheme 4.3).

Further reduction of 210 using BMS and catalytic NaBH\textsubscript{4} furnished the alcohol 231. Following the known strategy,\textsuperscript{160a,b} the sesquiterpene lactones 238-240 could be achieved with minimum steps (Scheme 4.3).

The equilibration of 204 to 210 was carried out using p-TSA in methanol. After the aqueous work up, the reaction mixture was extracted with dichloromethane and concentrated under vacuum. Chromatographic purification of the residue over silica gel column (CH\textsubscript{2}Cl\textsubscript{2}:Hexane, 8:2) afforded 210 as an oil in 70% yield (Scheme 4.4). The structure was confirmed on the basis of IR, \textsuperscript{1}H, \textsuperscript{13}C NMR and mass spectra. It was observed that the DCC also does the equilibration process.

The IR spectrum of 210 showed absorption frequencies at \(\nu_{\text{max}}\) 3440.77 (due to –OH), at 1743.53 and 1743.54 cm\(^{-1}\) (due to the carbonyl groups). The \textsuperscript{1}H NMR spectrum displayed signals at \(\delta\) 4.2929 (singlet; presence of methine proton), at \(\delta\) 4.41595- 4.28925 (AB quartet; presence of –CH\textsubscript{2}O protons), at \(\delta\) 2.8905 - 2.63185 (AB quartet; indicates the lactone ring methylene protons) and at \(\delta\) 3.872 (singlet; due to –OCH\textsubscript{3} protons). The \textsuperscript{13}C spectrum displayed seven different signals at \(\delta\) 175.208, 171.751, 78.115, 77.427, 77, 53.338 and 39.083 which confirmed the
structure of 210. Mass spectrum (FAB+) indicated (M+H)⁺ at m/e 191 (Figures 4.16a-d).

![Scheme 4.4 Synthesis of 210](image)

Similar attempts were made for equilibrating the alcohol 406 to the isomer 443 with p-TSA in methanol (Scheme 4.5). However, the alcohol 406 was recovered unchanged. In this context a computational study has been carried out to understand the anomaly. Density functional calculations with B3LYP exchange–correlation functional was used to explore the conformers of both isomers of 210 and 406 with 6-311G(d) basis set. It was found from the gas phase calculations that the isomer 210 is slightly preferred over 204 by an energy difference of 0.81 Kcal/mol, which is sufficient to convert 204 into 210 quantitatively during solvent extraction (Le Chatelier’s principles). Since both isomers have similar number of hydrogen bonds, and the difference in energy is quiet low, the contributing factor could be the R-group (-COOCH₃), which is absent in the lactone ring of 210 (Figure 4.14). In the case of 406 and 443, the energy differences between two isomers turn out to be negligible (0.04 kcal/Mol). An examination of structures indicates that the lowest conformation 443 (more hindered i-Pr-substituted) is different from 210 (less hindered Me-substituted), a clear case of steric effect of isopropyl group present in 443 (Figure 4.15). The lack of formation of 443 may lie in kinetic reasons, besides, the weakening of thermodynamic drive for the formation of 443 in comparison to 210.

![Scheme 4.5 Attempted conversion of 406 to 443 using p-TSA in methanol](image)
Figure 4.14 3D structures of the isomers 204 and 210

Figure 4.15 3D structures of the isomers 406 and 443
IR (liquid film)

Figure 4.16a

$^1$H NMR, 300 MHz, Solvent: CDCl$_3$

Figure 4.16b
4.2.3 Synthesis of (2S)-N-benzyl-2-hydroxy-2-[(3R)-3-hydroxy-5-oxotetrahydrofuran-3-yl]ethanamide (387)

The iminosugar (3R,4R)-3-(2-hydroxyethyl)pyrrolidine-3,4-diol (388), is emerging as a high profile biologically active molecule due to its application in the designing of drug resistance stain and a precursor for preparing the inhibitors of PNP and UDP-galβf transferase enzymes.296 A retrosynthetic strategy for the synthesis of the iminosugar 388 indicates the involvement of the intermediate, (2S)-N-benzyl-2-hydroxy-2-[(3R)-3-hydroxy-5-oxotetrahydrofuran-3-yl]ethanamide (387). This intermediate can be obtained from 208. The debenzylation followed by tandem reduction of 387 using Lithium Aluminium Hydride (LAH) and subsequent cyclisation would be expected to give 388 (Scheme 4.6)
Hence the bislactone 208 has been used as starting molecule for the synthesis of 387. The bislactone 208 was refluxed with one equivalent of benzyl amine in methanol and toluene using Dean-Stark equipment for 4 h (Scheme 4.7). The reaction mixture was concentrated under vacuum and chromatographic purification over silica gel (CH₂Cl₂: Hexane, 8:2) afforded 387 as a white crystalline solid in 87% yield.

The IR spectrum of 387 displayed absorption frequencies at 3375 cm⁻¹ (due to −OH group), at 1774, 1654 and at 1542 cm⁻¹ (due to the lactone and amide carbonyl groups respectively). The ¹H NMR spectrum displayed signals at δ 7.3 (due to the aromatic protons), at δ 5.2 (singlet due to methine proton), at δ 4.36-4.09 (AB quartet; indicates the presence of methylene proton), at δ 3.0-2.4 (AB quartet; indicates the methylene protons in the lactone ring) and at 4.3 (doublet; represents the benzylic −CH₂ protons). The ¹³C NMR spectrum showed 13 different signals at δ 175.724, 172.782, 139.971, 129.237, 128.393, 127.886, 79.311, 76.332, 73.382, 43.292 and 39.695 which confirmed the structure of 387 (Figure 4.18a-d). HRMS (ES+) Exact mass calculated for C₁₃H₁₆NO₅ (M+H)⁺ is 266.1028 and value experimentally found is 266.1021 (Figure 4.17).
Elemental Composition Report

Single Mass Analysis

Tolerance = 200.0 mDa / DBE: min = -1.5, max = 50.0
Isotope cluster parameters: Separation = 1.0 Abundance = 1.0%

Monoisotopic Mass, Odd and Even Electron Ions
10 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)

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Figure 4.17 Single mass analysis of 387

IR (KBr pellet)
$^1\text{H NMR, 400 MHz, Solvent: Acetone-d}_6$

Figure 4.18b
A single crystal XRD analysis confirmed the absolute configuration of 387. The X-ray intensity data were measured at room temperature on Bruker X8 Apex-II Kappa CCD area detector diffractometer with graphite monochromator MoKα radiation (50kV, 30mA). The spatial arrangement of 387 was confirmed from the ORTEP diagram (Figure 4.19)
4.2.4 The attempted conversion of methyl (2S, 3R)-3-hydroxy-3-hydroxymethyl-5-oxo-tetrahydro furan-2-carboxylate (204) to methyl (2S,3R)-3-hydroxy-3-([(4-methylphenyl)sulfonyl]oxy)methyl)-5-oxotetrahydrofuran-2-carboxylate (446)

Deoxygenation of alcohols is a key functional group transformation in organic synthesis. Suitable modification of the functional groups of 204 can lead to methyl (2S,3R)-3-hydroxy-3-([(4-methylphenyl)sulfonyl]oxy)methyl)-5-oxotetrahydrofuran-2-carboxylate (446) using which the synthesis of (−)-cis whisky and cognac lactones243,254 can be formulated.

The C3 hydroxymethyl group of 204 was tosylated,268 using p-Toluene sulphonyl chloride and pyridine at 0 °C, to obtain 446 (Scheme 4.8). After the aqueous work up, the residue was extracted with dichloromethane. The combined dichloromethane extracts were dried over anhydrous sodium sulfate and concentrated under vacuum. However the chromatographic purification (silica gel 60-120 mesh, hexane-dichloromethane, 7:3) of the residue yielded an intractable mixture.
The compound 446 showed IR absorption bands at 3058.8, 1600 and 1438 cm\(^{-1}\) (indicative of the presence of aromatic region), at 833.1 and 736.76 cm\(^{-1}\) (the presence of a \(p\)-substituted benzene ring), at 1787 and 1743 cm\(^{-1}\) (indicate the presence of lactone and the ester carbonyl groups respectively) (Figure 4.20a-b). The \(^1\)H NMR displayed signals at \(\delta\) 7-8 (due to aromatic protons) and at \(\delta\) 2.7-3.2 (AB quartet; due to methyl protons). Thus it may be assumed that tosylation had taken place successfully. However, the chromatographic purification of the reaction mixture failed to furnish 446 due to decomposition. Hence the subsequent reduction of 446 to 447, using NaBH\(_3\)CN and HMPA, seems to be an unsuccessful effort.
4.2.5 Conversion of methyl (2S)-hydroxyl [(3R)-3-hydroxy-5-oxotetrahydrofuran-3-yl] ethanoate (210) to (4R)-4-[(1R)-1,2-dihydroxyethyl]-4-hydroxydihydrofuran-2(3H)-one (231)

With the objective of preparing (4R)-4-[(1R)-1,2-dihydroxyethyl]-4-hydroxydihydrofuran-2(3H)-one (231), a key intermediate for the irregular sesquiterpene lactones 238-240 and (4R)-4-hydroxy-4-methylidihydrofuran-2(3H)-one (447), reduction of the alcohol 210 with BMS and catalytic amount of NaBH₄ has been carried out. Work up of the reaction mixture yielded 231 (Scheme 4.9), as an oil (25%). The ¹H NMR spectrum displayed signals at δ 4.337 and 2.8 ppm (AB quartet; due to methylene protons) and at 5.197 (singlet; shows the presence of methine proton in the lactone ring). The ¹³C NMR showed the presence of only one carbonyl peaks δ 173.84 and hence confirmed the formation of 231 (Figure 4.21a-d)

\[ 210 \xrightarrow{\text{BMS/Cat.NaBH}_4, \text{THF, 0 °C}} 231 \]

Scheme 4.9 Synthesis of 231
IR (Liquid film)

Figure 4.21a

$^1$H NMR, 400 MHz, Solvent: Acetone-d$_6$

Figure 4.21b

$^{13}$C NMR: 100 MHz, Solvent: Acetoned$_6$

Figure 4.21c
4.2.6 The attempted α-alkylation of dimethyl (2S,3S)-3-hydroxy-5-oxotetrahydrofuran-2,3-dicarboxylate (153) to dimethyl (2S,3S)-3-hydroxy-4-ethyl-5-oxotetrahydrofuran-2,3-dicarboxylate (448)

With the objective of preparing the cinatrin class of compounds (234 and 235) (Figure 4.22) α-alkylation of the anions derived from the lactone 153, using ethyl iodide and LDA in HMPA at -78 °C, has been planned. The attempted C-alkylation of 153 using ethyl iodide and LDA in HMPA at -78 °C was unsuccessful (Scheme 4.10). It may be noted that α-alkylation of the ester 153 underwent significant decomposition during the reaction conditions. TLC of the reaction mixture after work up indicated the absence of starting molecule. The IR spectrum of the reaction mixture did not show any signal attributable to carbonyl groups (Figure 4.23).
4.2.7 Preparation of trialkyl (1S, 2S)-and (1S, 2R)-1,2-dihydroxy-1,2,3-propanetricarboxylates (168 and 172)

Having two centers of chirality and vicinal diol moiety, trialkyl esters of 6 and 7 are expected to find application in the designing of chiral phosphorous ligands and TADDOL-type compounds for enantioselective catalysis.

Difficulties are encountered in the esterification of 6 and 7 following usual procedures involving the treatment of carboxylic acids with appropriate alcohol in
acidic medium. The product obtained was a mixture of cyclic dialkyl \((2S,3S)\)- or \((2S,3R)\)-tetrahydro-3-hydroxy-5-oxo-2,3-furan dicarboxylate and trialkyl \((1S,2S)\)- and \((1S,2R)\)-1,2-dihydroxy-1,2,3-propane tricarboxylates in almost equal ratios. This could be due to the fact that the esterification conditions are suitable for lactonisation also.\(^{14}\)

To overcome this difficulty, efforts were made to prepare trisodium salt \((167\) and \(171)\) from 6 and 7 by carrying out the reaction with thionyl chloride and appropriate alcohol to get the desired triesters. Refluxion of 6 and 7 with sodium hydroxide furnished trisodium salt \(167\) and \(171\). The molecules \(167\) and \(171\) are found to be highly hygroscopic solids. The structure of the compounds was characterized by \(\textsuperscript{1}H\) and \(\textsuperscript{13}C\) NMR spectra (Figure 4.24a-b and Figure 4.26a-b). Refluxing thionyl chloride with a suspension of \(167\) or \(171\) in alcohol readily furnishes the corresponding triester in high yield and purity (Scheme 4.11). The structure of the compounds was characterized by IR, \(\textsuperscript{1}H\) and \(\textsuperscript{13}C\) NMR and mass spectra (Figure 4.25a-d and Figure 4.27a-d).

Scheme 4.11 Preparation of trialkylesters of 6 and 7

![Scheme 4.11 Preparation of trialkylesters of 6 and 7](image-url)
Figure 4.24b

IR (liquid film)

Figure 4.25a

Figure 4.25b
Figure 4.25c

Figure 4.25d
Figure 4.26a

Figure 4.26b
Figure 4.27a

Figure 4.27b

Figure 4.27c
4.2.8 Conversion of trimethyl (1S, 2S)-1,2-dihydroxy-1,2,3-propanetricarboxylate (168) to dimethyl (5S)-4-(2-methoxy-2-oxoethyl)-2-(trichloromethyl)-1,3-dioxolane-4,5-dicarboxylate (449)

Asymmetric catalysis is one of the most cost-effective and environmentally responsible methods for the production of a truly vast array of structurally diverse, enantiomerically pure compounds of pharmaceutical, flavor and fragrance, agrochemical, animal health, polymer and liquid crystal interests.

Over the past decades several historically important ligands have been developed (Figure 4.28). In 1971, Kagan reported a breakthrough in catalytic enantioselectivity by the introduction of enantiomerically pure chelating biphosphine ligand DIOP (9) derived from tartaric acid and showed the importance of “backbone” chirality (Figure 4.28). Kagan’s work had a strong influence on the course of research in the field of asymmetric catalysis, leading to the development of a variety of C2-symmetric ligands and stimulating the study of several important reactions, such as asymmetric hydrogenation, hydroformylation, hydrosilylation and allylic alkylation.

Figure 4.28 Chiral phosphorous ligands
With the objective of preparing chiral phosphine ligand (453) from 168 (Scheme 4.12), the tandem reduction of the ester group of 168 was carried out after protecting the vicinal hydroxyl groups. Since the molecule 168 was a 1,2 diol, the possibility for the formation of chloral derivative (dioxolane) is highly expected. Treatment of 168 with anhydrous trichloroacetaldehyde in presence of con.H₂SO₄ gave the corresponding chloral derivative dimethyl (S)-4-(2-methoxy-2-oxoethyl)-2-(trichloromethyl)-1,3-dioxolane-4,5-dicarboxylate as a diasteromeric mixture. After work up, the residue obtained was recrystallised (CHCl₃-Hexane) which yielded 449 as a solid in 87%, [α]²⁰D+28.64, (c 0.28, CHCl₃). Structure of the compound 449 was confirmed on the basis of IR, ¹H, ¹³C NMR (Figure 4.29a-c).

The IR spectrum of 449 showed absorption frequencies at 1895, 1767 cm⁻¹ (due to the lactone carbonyl groups). The ¹H NMR spectrum displayed signals at δ 6.07 (singlet; due to the proton in the dioxolane ring, -OCHCCl group), at 5.353 (singlet; due to -CHCO proton) and at 3.27-2.93 (AB quartet; shows the presence of methylene protons). The ¹³C NMR displayed signals at δ 176.70, 170.22, 169.49, 103.95, 96.87, 83.39, 81.85, 53.64 and 38.48 which confirmed the number of carbon atoms of the molecule.

\[
\begin{align*}
  & \text{H}_3\text{COOC} \quad \text{H} \quad \text{CCl}_3\text{CHO, Con. H}_2\text{SO}_4 \\
  & \text{OH} \quad \text{HO COOCH}_3 \\
  & \text{168} \\
  \text{H}_3\text{COOC} \quad \text{H} \quad \text{CCl}_3\text{CHO, Con. H}_2\text{SO}_4 \\
  & \text{OH} \quad \text{HO COOCH}_3 \\
  & \text{449}
\end{align*}
\]

Scheme 4.12 Conversion of 168 to 449
IR (KBr pellet)

Figure 4.29a

$^1$H NMR, 400 MHz, Solvent: CDCl$_3$

Figure 4.29b

$^{13}$C NMR, 100 MHz, Solvent: CDCl$_3$

Figure 4.29c
4.2.9 Tandem reduction of dimethyl (5S)-4-(2-methoxy-2-oxoethyl)-2-(trichloromethyl)-1,3-dioxolane-4,5-dicarboxylate (449) to (2R,3R)-3-(hydroxymethyl)pentane-1,2,3,5-tetraol (386)

The tandem reduction of 449 was carried out with excess of Lithium Aluminium Hydride (LAH) in dry THF (Scheme 4.13). After work up with successive dropwise addition of water and NaOH solution, the reaction mixture afforded a granular precipitate which was filtered off. The crude mass obtained was concentrated under vacuum. Chromatographic purification over silica gel was unsuccessful. Extraction with Soxhlet apparatus was hampered by its poor solubility in most of the organic solvents. The impure mass was washed with organic solvents and extracted with dry MeOH. The residue obtained was characterized spectroscopically and observed that the compound 449 has been deprotected during the course of the reaction and work up gave the polyol 386 as oil in 75% yield. The IR, $^1$H, $^{13}$C, mass and DEPT spectra confirmed the structure of the product (Figure 4.30a-e).

Alternatively sodium borohydride in methanol reduced tandemly the lactone and ester carbonyls of both garcinia and hibiscus esters at 0 °C. The tandem reduction of 153 using sodium borohydride in methanol at 0 °C yielded 386. The tandem reduction of ester and lactone carbonyls using NaBH$_4$-MeOH at 0 °C could be an alternative to LAH.

![Scheme 4.13 Tandem reduction of 449 using LAH](image-url)
**Figure 4.30a**

$^1$H NMR: 400 MHz, Solvent: Methanol-d$_4$

![NMR Spectrum](image)

**Figure 4.30b**

$^{13}$C NMR: 100 MHz, Solvent: Methanol-d$_4$

![NMR Spectrum](image)
4.3 Conclusion

In conclusion, chapter 4 concerns with the efficient use of the title acids for the synthesis of few natural product intermediates. The intermediates synthesized are, the concave bislactone skeleton \((3aR, 6aS)-3a\text{-hydroxytetrahydrofuro}[3, 4-b]\) furan-2,6-dione, an analogue of antifungal (+)-avenaciolide; methyl \((2S)-\text{hydroxyl}\)
[(3R)-3-hydroxy-5-oxotetrahydrofuran-3-yl] ethanoate, a key intermediate for sesquiterpene lactones; (2S)-N-benzyl-2-hydroxy-2-[(3R)-3-hydroxy-5-oxotetrahydrofuran-3-yl]ethanamide, a precursor for preparing the inhibitors of PNP and UDP-galf transferase enzymes; (4R)-4-[(1R)-1,2-dihydroxyethyl]-4-hydroxydihydrofuran-2(3H)-one, intermediate suited for the synthesis of sesquiterpene lactones and non-natural amino lactones; methyl (2S,3R)-3-hydroxy-3-([(4-methylphenyl)sulfonyl]oxy)methyl)-5-oxotetrahydrofuran-2-carboxylate, an intermediate for the synthesis of funebrin; and (2R,3R)-3-hydroxymethyl-pentane-1,2,3,5-tetraol, a precursor for chiral trisphosphine ligand. Attempts towards the α-alkylation of dimethyl (2S,3S)-3-hydroxytetrahydro-5-oxo-2,3-furandicarboxylate to dimethyl (2S,3S)-3-hydroxy-4-ethyl-5-oxotetrahydrofuran-2,3-dicarboxylate, for cumulating the synthesis of phospholipase inhibitors (PLA₂) Cinatrin C₂ and C₃ are also discussed.

4.4 General experimental details

All operations were carried out under nitrogen atmosphere. All glassware, syringes, and needles were oven-dried and cooled under nitrogen gas before use. THF was freshly distilled from sodium benzophenone ketyl. Anhydrous MeOH was freshly distilled from calcium hydride. Toluene was distilled from sodium wire. The ¹H and ¹³C NMR spectrum were recorded on Brucker AMX 400 MHz, WM 300 MHz, or Brucker AV 400 MHz NMR spectrometer. Chemical shifts are expressed in parts per million (ppm) relative to TMS (δ = 0) and coupling constants are reported as Hertz (Hz). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, br = broad, m = multiplet), coupling constant, and integration. Melting points were determined on “Sunbim” make electrically heated melting point apparatus and were uncorrected. The IR spectra were recorded using a Shimadzu IR 470 spectrophotometer as KBr pellets (solids) or thin films (liquids) and ThermoFisher Is 10 FTIR spectrometer with diamond plate ATR and reported as wave number (cm⁻¹). Electron impact mass spectra were recorded on a Finnigan MAT MS 8230 or jeol D-300, HRMS were recorded on Micromass UK, Q-TOF. Optical rotations were measured on a Rudolph IV Autopol polarimeter operating at the sodium D line with a 100 mm path length cell, and are reported as follows: [α]¹D (concentration (g/100 mL), solvent).
Column chromatography was carried out with Merck product silica (silica gel 60-120 mesh) and thin layer chromatography was performed using glass-backed silica gel plates (Merck silica gel G for TLC).

4.5 Experimental procedures for single crystal X-ray analysis for 208

A colourless block shaped crystal of 208 with approximate dimensions 10mm x 15mm x 30mm was mounted for data collection. The X-ray intensity data were measured at room temperature on Bruker X8 Apex-II Kappa CCD area detector diffractometer with graphite monochromated Mo K radiation (50kV, 30mA). The detector was placed at a distance of 35 cm from the crystal.

The frames were integrated with the Bruker SAINT software package using narrow-frame integration algorithm. The integration of the data has been carried out using an orthorhombic unit cell. The final cell constants of a=6.2489, b=9.2529, c=10.949, α=90.00, β=90.00, γ=90.00. Data reduction was carried out using the program SAINT+ (Bruker, 1999).

The crystal was solved by direct methods using Bruker SHELXS (Sheldrick, 1997). The Structure was refined using the Bruker SHELXTL (Version 6.12) software package, in the space group Orthorhombic P2(1)2(1)2(1) for the formula unit C₆H₆O₅. Non-hydrogen atoms were first refined isotropically followed by anisotropic refinement by full matrix least-squares calculation based on F2 using SHELXL (Sheldrick,1997). Hydrogen atoms were first located in the fourier difference map then positioned geometrically and allowed to ride on their respective parent atoms. The final anisotropic full-matrix least-squares refinement of F2 converged at R1=0.0282, wR2=0.0291 and the goodness-of-fit of 1.061. Diagrams and publication material were generated using CIFTAB (Sheldrick,1997) and PLATON (Spek, 2003).

4.6 Experimental procedures for single crystal X-ray analysis for 387

A colourless block shaped crystal of 387 with approximate dimensions 0.22 x 0.16 x 0.13 mm was mounted for data collection. The X-ray intensity data were measured at room temperature on Bruker X8 Apex-II Kappa CCD area detector diffractometer with graphite monochromated Mo K radiation (50kV, 30mA). The detector was placed at a distance of 35 cm from the crystal.
The frames were integrated with the Bruker SAINT software package using narrow-frame integration algorithm. The integration of the data has been carried out using an orthorhombic unit cell. The final cell constants of \( a = 9.1374(8) \) Å, \( b = 10.4053(9) \) Å, \( c = 13.2424(9) \) Å, \( \alpha = 90.00 \), \( \beta = 90.00 \), \( \gamma = 90.00 \). Data reduction was carried out using the program SAINT+ (Bruker, 1999).

The crystal was solved by direct methods using Bruker SHELXS (Sheldrick, 1997). The Structure was refined using the Bruker SHELXTL (Version 6.12) software package, in the space group Orthorhombic \( P2(1)2(1)2(1) \) for the formula unit \( \text{C}_{13}\text{H}_{15}\text{NO}_{5} \). Non-hydrogen atoms were first refined isotropically followed by anisotropic refinement by full matrix least-squares calculation based on \( F^2 \) using SHELXL (Sheldrick, 1997). Hydrogen atoms were first located in the fourier difference map then positioned geometrically and allowed to ride on their respective parent atoms. The final anisotropic full-matrix least-squares refinement of \( F^2 \) converged at \( R_1 = 0.0443, wR_2 = 0.0707 \) and the goodness-of-fit of 0.958. Diagrams and publication material were generated using CIFTAB (Sheldrick, 1997) and PLATON (Spek, 2003).

4.7 Experimental Section

4.7.1 Synthesis of \((3aR,6aS)-3a\text{-hydroxytetrahydrofuro}[3,4-b]\text{furan}-2,6\text{-dione} \) (208)

A 100 mL two-necked round-bottom flask equipped with a magnetic stir bar and fitted with a rubber septum was filled with a solution of dimethyl \((2S,3S)\)-tetrahydro-3-hydroxy-5-oxo-furandicarboxylate, \( \text{153} \) (1.0 gm, 4.6 mmol) in dry tetrahydrofuran (10mL). Through the septum one equivalent of Borane dimethyl sulphide, 10 M (0.8 mL, 4.6 mmol) was added dropwise via syringe over a period of 10 min at 0 °C with constant stirring. Hydrogen evolution was rapid and essentially completed at 30 min at 25 °C. The reaction mixture was cooled to 0 °C and powdered NaBH\(_4\) (catalytic) was added in one portion under vigorous stirring. After 20 min of stirring, the reaction mixture was warmed to 25 °C. The reaction mixture was left aside for an additional 2.5 h to ensure the complete reaction. The reaction mixture was quenched with dry methanol (3 mL) (Caution! Hydrogen evolution) and stirred for further 30 min at room temperature. Upon concentration under reduced pressure gave a clear transparent gum. The gum was dissolved in dry MeOH (5 mL) and again concentrated under reduced
pressure. The operation was repeated to eliminate B (OMe)$_3$ as thoroughly as possible. The crude alcohol methyl (2S, 3R)-terahydro-3-hydroxy-3-hydroxymethyl-5-oxo-furan-2-carboxylate (204) obtained was purified through silica (60-120 mesh, dichloromethane-hexane 7:3) column to get 208 as a colourless crystalline solid.

**Yield** : 81%

**Mp** : 136-138 °C

[α]$^D_{20}$ : +20.64°, (c 0.28%, H$_2$O)

**IR** (KBr pellet) : $\nu_{max}$ 3452.34, 1778.25, 1207.36, 1168.78, 1053.06, 1026.06 cm$^{-1}$

**$^1$H-NMR** (DMSO-d$_6$, 300 MHz) : δ 5.03 (s, 1H), 4.367 (d, $J$ = 9.3 Hz, 1H), 4.24 (d, $J$ = 9.3 Hz, 1H), 3.21 (d, $J$ = 18.6 Hz, 1H), 2.73 (d, $J$ = 18.6 Hz, 1H)

**$^{13}$C NMR** (DMSO-d$_6$, 75 MHz) : δ 174.2, 170.7, 81.2, 77.5, 74.5, 40.3

**Molecular formula** : C$_6$H$_7$O$_5$

**Molecular weight** : 158.11

HRMS calculated for C$_6$H$_7$O$_5$ (M+H): 159.0293; Found:159.0290

**4.7.2 Preparation of methyl (2S)-hydroxyl [(3R)-3-hydroxy-5-oxotetrahydrofuran-3-yl] ethanoate (210)**

To a solution of crude alcohol 204 (500 mg, 2.6 mmol) in dichloromethane (DCM, 50 mL) at room temperature was added p-toluene sulphonic acid (1 equ.) After the mixture was stirred for 24 h, distilled water (20 mL) was added. The aqueous solution was extracted with diethyl ether (3x50 mL). The combined organic layers (~150 mL) were dried and evaporated. The crude mass was then purified by column chromatography (60-120 mesh silica gel, dichloromethane–hexane, 8:2) to afford 210 as an oil.

**Yield** : 70%

[α]$^D_{20}$ : +27.47° (c 1.02, CHCl$_3$)
IR (liquid film) : \( \nu_{\text{max}} 3440.77, 1743.53, 1639.38, 1442.66, 1238.65 \text{ cm}^{-1} \)

\(^1^H\) NMR (CDCl\(_3\), 300 MHz) : \( \delta 4.292 \ (s, 1H), 4.415 \ (d, J = 10.47 \text{ Hz}, 1H), 4.289 \ (d, J = 10.29 \text{ Hz}, 1H), 3.876 \ (s, 3H), 2.890 \ (d, J = 17.91 \text{ Hz}, 1H), 2.631 \ (d, J = 17.91 \text{ Hz}, 1H) \)

\(^{13}\)C NMR (CDCl\(_3\), 75 MHz) : \( \delta 175.208, 171.751, 78.115, 75.578, 53.338, 39.083 \)

Molecular formula : C\(_7\)H\(_{10}\)O\(_6\)

Molecular mass : 190.1497

Mass spectrum (FAB+) indicated (M+H)\(^+\) at m/e 191.

Elemental analysis : Calculated: C: 44.215, H: 5.301

Found : C: 45.265, H: 5.802

4.7.3 Preparation of (2S)-N-benzyl-2-hydroxy-2-[(3R)-3-hydroxy-5-oxotetrahydrofuran-3-yl]ethanamide (387)

To a refluxing solution of 208 (500 mg, 2.6 mmol) in MeOH (10 mL) and toluene (20 mL) was added benzyl amine (279 mg, 2.6 mmol) drop wise and the reaction mixture was refluxed for an additional 4 hours using Dean-stark water separator. The mixture was cooled to room temperature and concentrated under vacuum. The crude mass was then purified by column chromatography (60-120 mesh silica gel, dichloromethane–hexane, 8:2) to afford 387 as a crystalline solid.

Yield : 87%

Melting point : 160-162 °C

\([\alpha]_D^{20}\) : +34.25 ° (c = 1.0, CH\(_2\)Cl\(_2\))

IR (KBr pellet) : \( \nu_{\text{max}} 3417.63, 2997.18, 1645.17, 1485, 1461 \text{ cm}^{-1} \)

\(^1^H\) NMR (Acetone-d\(_6\), 400 MHz) : \( \delta 7.3 \ (m, 5H), 5.2 \ (s, 1H), 4.3 \ (d, J = 8 \text{ MHz}, 2H) 4.36 \ (d, J = 12 \text{ Hz}, 1H), 4.09 \)
4.7.4 Methyl(2S,3R)-3-hydroxy-3-{{[(4-methylphenyl)sulfonyl]oxy}methyl}-5-oxotetrahydrofuran-2-carboxylate (446)

To an ice-cold solution of 204 (1 g, 5.3 mmol) in dry pyridine (1.4 mL, 17.2 mmol), finely powdered tosyl chloride (1.51 g, 7.95 mmol) was added in one portion. The mixture was stirred for 12 h at 0 °C. Ether (30 mL) and water (7 mL) were added, the organic layer was washed successively with 2 N HCl, 5% NaHCO₃, and water, dried over anhydrous sodium sulphate and concentrated under reduced pressure to obtain 446 as an oil.

IR (film)  
ν<sub>max</sub> 3433, 3409, 2954, 1743, 1712, 1438, 1265, 1222, 1002, 991, 833 cm<sup>-1</sup>

4.7.5 (4R)-4-[(1R)-1,2-dihydroxyethyl]-4-hydroxydihydrofuran-2(3H)-one (231)

Followed the same procedure as in the preparation of 204 using methyl (2R)- hydroxyl [(3S)-3-hydroxy-5-oxotetrahydrofuran-3-yl] ethanoate (210).

Yield  
25%

IR (liquid film)  
ν<sub>max</sub> 3423.41, 3263.33, 1762.1, 1747.38, 1442.65 cm<sup>-1</sup>

<sup>1</sup>H NMR (Acetone-d₆, 400 MHz)  
δ 5.197 (s, 1H) 4.583 (d, J = 11.2 Hz, 1H), 4.091 (d, J = 12 Hz, 1H), 3.739 (d, J = 12 Hz, 1H), 3.0665 (d, J = 17.2 Hz, 1H), 2.533 (d, J = 17.2 Hz, 1H), 3.64 (d, J = 17.2 Hz, 1H)

<sup>13</sup>C NMR (Acetone-d₆, 100 MHz)  
δ 173.84, 85.28, 78.38, 76.70, 60.15, 42.92

Molecular formula  
C₆H₁₀O₅

Molecular mass  
162.14
4.7.6 Dimethyl (2S,3S)-3-hydroxy-4-ethyl-5-oxotetrahydrofuran-2,3-dicarboxylate (448)

To a solution of diisopropylamine (DIPA, 1.4 mL, 9.81 mmol) in THF (13.3 mL) was added n-BuLi at -20 °C to 0 °C. After stirring for 15 min the reaction was cooled to -78 °C and a solution of 153 (1 g, 4.5 mmol) in THF (4.5 mL) was added. This mixture was stirred for an additional 40 min and a solution of ethyl iodide (0.66 mL, 4.6 mmol) in HMPA (3.78 mL) was added at the same temperature via a cannula. The reaction mixture was warmed to -40 °C after stirring for 20 min and further stirred for 5 h at the same temperature. The reaction was quenched with 10% HCl and ethyl acetate (50 mL) and the organic phase was separated. The aqueous phase was extracted three times with EtOAc. The combined organic phases were then washed with brine, dried with anhydrous Na₂SO₄, filtered, and the solvent was removed in vacuum. The crude mass obtained was attempted to purify by column chromatography eluting with ethyl acetate/hexane.

IR (film) : $\nu_{\text{max}}$ 3398.34, 2974.03, 2912.31, 2488, 1475 cm⁻¹

4.7.7 Trisodium (1S,2S)-1,2-dihydroxy-1,2,3-propanetricarboxylate (167)

To an aqueous solution of 6 (1.0 g, 5.25 mmol, in 5 mL water), 2N of sodium hydroxide solution was added at about 80 °C, till reaction mixture is alkaline (~ pH = 9.0). The residue obtained after evaporation under reduced pressure, was triturated with dry methanol (5 x 25 mL). The solid 167 obtained was finally dried under vacuum.

Yield : 1.1 g (76.5%)

$^1$H NMR (D₂O, 300 MHz) : δ 4.08 (s, 1H), 3.36 (s, 1H), 2.82 (d, $J = 15.9$ Hz, 1H), 2.71 (d, $J = 15.9$ Hz, 1H)

$^{13}$C NMR (D₂O, 75 MHz) : δ 181.5, 180.6, 179.3, 79.7, 77.9, 44.3

4.7.8 Trimethyl (1S,2S)-1,2-dihydroxy-1,2,3-propanetricarboxylate (168)

To a suspension of 167 (1.0 g, 3.65 mmol) in dry methanol (10 mL), thionyl chloride (1.5 mL, 20 mmol) was added at 0 °C. After refluxing for 2 h, the reaction mixture was cooled and neutralised with saturated aqueous solution of sodium bicarbonate. The residue obtained upon concentration under reduced
pressure was extracted with chloroform (3 x 20 mL). The combined extract was 
dried and concentrated to furnish 168 as yellow oil.

**Yield** : 0.5 g (50%)

**$[\alpha]_{D}^{20}$** : +22.14 (c 0.52, CHCl$_3$)

**IR (film)** : $\nu_{\text{max}}$ 3455.85, 2985.18, 1802, 1754, 1375, 1215 cm$^{-1}$

**$^1$H NMR (CDCl$_3$, 300 MHz)**

- $\delta$ 4.98 (s, 1H), 3.84 (s, 6H), 3.68 (s, 3H), 3.2 (d, $J = 18.0$ Hz, 1H), 2.80 (d, $J = 18.0$ Hz, 1H)

**$^{13}$C NMR (CDCl$_3$, 75 MHz)**

- $\delta$ 172.3, 170.7, 166.9, 77.3, 74.6, 53.07 52.9, 51.7, 39.25

**Mass spectrum**

- m/z 251 (M+1) (100), 219 (23), 191 (32), 159 (50), 143 (3), 131 (4.5), 99 (10.5), 90 (15), 59 (6), 43 (15)

### 4.7.9 Trisodium (1S,2R)-1,2-dihydroxy-1, 2, 3-propanetricarboxylate (171)

The procedure adopted for 167 was followed with 7 (2.0 g, 10.5 mmol)
and gave the title compound 171 (1.1g, 78.2 %) as a colourless solid.

**Yield** : 1.1 g (78.2%).

**$^1$H NMR (D$_2$O, 300 MHz)**

- $\delta$ 4.82(1H, s), 4.12 (s, 1H), 2.74 (d, $J = 15.9$ Hz, 1H), 2.65 (d, $J = 15.9$ Hz, 1H)

**$^{13}$C NMR (D$_2$O, 75 MHz)**

- $\delta$ 181.18, 178.99, 179.3, 80.15, 78.30, 44.4

### 4.7.10 Trimethyl (1S,2R)-1,2-dihydroxy-1, 2, 3-propanetricarboxylate (172)

The procedure adopted for 168 was followed with 171 (1.0 g, 3.65 mmol).

After work-up 172 (1.2 g, 65.8%) was obtained as yellow oil.

**Yield** : 0.6 g (65.8%).

**$[\alpha]_{D}^{20}$** : +35.187(c 2.02, CHCl$_3$)

**IR (liquid film)**

- $\nu_{\text{max}}$ 3448, 3010, 2958, 2520, 1803, 1753, 1629, 1265 cm$^{-1}$
H NMR (CDCl$_3$, 300 MHz) : $\delta$ 4.36 (s, 1H), 3.84 (s, 3H), 3.77 (s, 3H), 3.69 (s, 3H), 3.16 (d, $J = 14.71$ Hz, 1H), 2.98 (d, $J = 14.71$ Hz, 1H)

$^{13}$C NMR (CDCl$_3$, 75 MHz) : $\delta$ 172.6, 170.8, 170.7, 81.9, 76.6, 53.1, 52.7, 51.9, 40.2

Mass Spectrum (EIMS) : 250 (15, M+), 218 (13.7), 190 (23.1), 158 (85.4), 142 (12), 130 (29.8), 98 (73.0), 90 (100), 69 (16.4), 59 (68.5), 44 (80.5%)

Anal. found : C, 43.31%; H, 5.68%

Calculated for C$_9$H$_{14}$O$_8$ : C, 43.24%; H, 5.64%.

4.7.11 Dimethyl (5S)-4-(2-methoxy-2-oxoethyl)-2-(trichloromethyl)-1,3-dioxolane-4,5-dicarboxylate (449)

To an ice-cold two-necked round-bottom flask fitted with a CaCl$_2$ guard tube containing 168 (1.0 g, 3.99 mmol) was added anhydrous chloral (0.4 mL, 4 mmol) dropwise under stirring followed by 1.25 mL of conc. H$_2$SO$_4$. The reaction mixture was stirred overnight in dark at room temperature. Crushed ice (50 g) was added to the reaction mixture, followed by diethyl ether (50 mL). After stirring for 10 min, the ether layer was separated and the process was repeated thrice (3x20 mL). The combined ether extract were dried with Na$_2$SO$_4$ and concentrated. The crude solid obtained was a diastereomeric mixture and was recrystallized from chloroform–hexane (7:3).

Yield : 87%

$[\alpha]^{20}_D$ : +28.64 (c 0.28, CHCl$_3$)

Mp : 178-185 °C

IR (liquid film) : $\nu_{\text{max}}$ 1805, 1767, 1636, 1439, 1359, 1247, 1157 cm$^{-1}$

H NMR (CDCl$_3$, 400 MHz) : $\delta$ 6.070 (s, 1H), 5.353 (s, 1H), 3.868 (s, 3H), 3.833 (s, 3H), 3.710 (s, 3H), 3.276 (d, $J = 18.8$ Hz, 1H), 2.9315 (d, $J = 18$ Hz, 1H)
\[ ^{13}\text{C NMR (CDCl}_3, 100 \text{ MHz)} : \delta 176.70, 170.22, 169.49, 103.95, 96.87, 83.39, 81.85, 53.64, 38.48 \]

Molecular formula : \( \text{C}_{11}\text{H}_{13}\text{Cl}_3\text{O}_8 \)
Molecular mass : 379.58

4.7.12 \((2R,3R)-3-(\text{hydroxymethyl})\text{pentane-1,2,3,5-tetraol (386)}\)

An oven-dried, 100 mL, three-necked flask equipped with a magnetic stirrer, a water condenser, and a nitrogen-inlet tube was flushed with nitrogen, and then charged with a suspension of lithium aluminum hydride (0.395 g, 10.6 mmol, 4 equiv.) in 20 mL of tetrahydrofuran (THF). The mixture was cooled (10°C, ice bath) and a solution of 449 (1 g, 2.66 mmol) in THF (5 mL) was added in portions over a 30 min period from a 100 mL addition flask connected to the reaction flask. After the addition is complete, the ice bath was removed, and the reaction mixture was warmed to room temperature and then refluxed for 16 hr. The reaction mixture was then cooled again (10°C, ice bath) and diluted with diethyl ether (50 mL). The reaction was quenched over a 30 min period with water (1 mL) (\text{Caution! Hydrogen evolution}) aqueous 15% sodium hydroxide (1 mL, over 20 min), and water (3 mL, over 30 min). The solution was stirred for another 30 min and the precipitate was filtered. The filter cake was washed with diethyl ether (3 × 20 mL) and the organic filtrates were combined, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. Distillation of the residue under vacuum affords 386 as a clear liquid.

Yield : 70%
IR (liquid film) : \( \nu_{\text{max}} 3325, 2976, 2901, 1607, 1372, 1270, 1044 \text{ cm}^{-1} \)
\[ ^1\text{H NMR (MeOH-d}_4, 400 \text{ MHz)} : \delta 3.772 (m, 7H), 2.159 (m, 2H) \]
\[ ^{13}\text{C NMR (MeOH-d}_4, 100 \text{ MHz)} : \delta 76.44, 76.24, 65.92, 64.29, 63.53, 37.17 \]
Molecular formula : \( \text{C}_6\text{H}_{14}\text{O}_5 \)
Molecular mass : 166.08

HRMS (ES+) calculated for \( \text{C}_6\text{H}_{14}\text{O}_5\text{Na} \): 189.0739, Found: 189.0735