Chapter III

Chiral Functionalized Butenolides from

(2S, 3S)-Tetrahydro-3-hydroxy-5-oxo-2,3-furandicarboxylic acid

III.1 Introduction

Appropriately functionalized chiral butenolides are flexible synthetic species useful for the synthesis of a variety of biologically interesting molecules bearing 2(5H) furanone subunits\textsuperscript{135}. Such structural motifs are found in pheromones, the antibiotic strobilin, pencillanic acid, pulvinones, and several secondary metabolites of fungal and marine origin as well as sesquiterpenoid lactones\textsuperscript{136}. Thus use of butenolides as synthetic precursors, especially as Diels-Alder dienophiles or Michael acceptors are frequently encountered\textsuperscript{135,137-142}. Often these chiral butenolides have been obtained either from carbohydrates, \(\gamma\)-keto acids, glutamic acid or from acyclic systems like acetylnic compounds, pyruvic acid derivatives, cyanhydrins of conjugated aldehydes etc, mostly involving multi step procedures or complex retro Diels-Alder strategies\textsuperscript{143-146}. Alternatively chiral 5- alkoxy 2(5H)-furanones have been obtained by Fenna and co-workers only in moderate overall chemical and optical purity that too by resolution method\textsuperscript{141,142}. Hence there has been a continuing interest in practical, large-scale syntheses of enantiomerically pure low molecular weight butenolides as building blocks for incorporation into larger targets. Few instances are presented below.
Ranuncilin is a glucoside present in many plants of the family *Ranunculaceae* and contains α-hydroxymethyl-α,β-butenolide (237), in its S configuration as the aglycone136,143 (Scheme III.1).

![Scheme III.1](image)

Butenolide (238) is the key intermediate for the preparation of an antifungal antibiotic (+) Cerulenin which is isolated from the culture filtered of *Cephalosporium caerulens*147 (Scheme III.2).

![Scheme III.2](image)

Butenolide 239 is an important intermediate in the enantioselective synthesis of the sexual attracting insect pheromone (+)-grandisol146 (Scheme III.3).

![Scheme III.3](image)
Butyrolactone (240), another natural product isolated from Aspergillus terreus var. africans, which has been found to exhibit antiproliferative activity against colon and pancreatic carcinoma, human lung cancer and prostatic cancer cell lines also bears a butenolide moiety\(^1\) (Figure III.1).

![Butyrolactone](image)

**Figure III.1**

Eldanolide is a pheromone of the African sugar cane borer *Eldana saccharina*. Optically active butenolide (241) is a key intermediate in its synthesis (Scheme III.4).^8^

![Eldanolide and 241](image)

**Scheme III.4**

The flowers of the Mexican tree *Quararibea funebris* (Llave) Vischer have been shown to give rise to the enolic 3-lactone (242) along with the novel pyrrole alkaloid funebrine (52). Attention was drawn to the genus *Quararibea* by its equivocal taxonomic position and because of its ethnobotanical interest. Treatment of 242 with diazomethane yielded the methyl ether (243)\(^9\) (Scheme III.5).
Some of the existing methods for the synthesis of butenolides are presented in the ensuing discussion.

Conditions developed by Alper and co-workers for the cyclocarbonylation of allylic alcohols were applied to give butenolides from both terminal and internal alkynols. Although yields were excellent and a range of substitution pattern was produced, the reaction required very high gas pressures, which is a practical limitation (Scheme III.6).

The cyclocarbonylation of vinyl iodide occurred smoothly under mild conditions to give the butenolides. The vinyl iodide and analogues were readily prepared by tandem nucleophilic addition-aldol reactions of an electron deficient allene with iodide and aldehydes respectively (Scheme III.7).
Simple 4-aryl butenolides (251) and tetronates were assembled via the Heck reaction of 2,5 dihydrofuran (249) and subsequent oxidations\(^ {150} \) (Scheme III.8).

\[
\begin{align*}
\text{249} & \quad \rightarrow \quad \text{250} \quad \rightarrow \quad \text{251} \\
\end{align*}
\]

Scheme III.8

Simple 5-substituted butenolides (254) were reached in high enantiomeric excess starting with baker's yeast reduction of 3-chloro-4-oxoalkanoates (252)\(^ {122} \) (Scheme III.9).

\[
\begin{align*}
\text{252} & \quad \rightarrow \quad \text{253} \quad \rightarrow \quad \text{254} \\
\end{align*}
\]

Scheme III.9

Brukner and co-workers have proposed a general route to \(\gamma\)-(hydroxyalkyl) butenolides (256) by Lewis acid catalysed aldol reactions of 2-(trialkylsilyloxy) furans (255)\(^ {151} \) (Scheme III.10).

\[
\begin{align*}
\text{255} & \quad \rightarrow \quad \text{256} \\
\end{align*}
\]

Scheme III.10
The isoxazolidines (257) were transformed to simple racemic butenolides (273) by N-methylation, reductive ring opening and Cope elimination. Similarly, 3-acylteronic acids were made from the isoxazole (259) by the reductive cleavage of the N-O bond using hydrogen bromide in acetic acid\textsuperscript{151} (Scheme III.11).

![Chemical structures](image)

**Scheme III.11**

### III.2 Results and Discussion

It is clear that chiral butenolides represent an important class of synthetic targets which are often prepared by methods involving several steps and most of them end up with racemic mixtures, that too in low overall yield. In this direction, facile and effective methods for the enantioselective synthesis of diversely functionalized butenolides are worthwhile. The syntheses of chiral butenolides by the dehydration of the appropriate functional groups are rare. In this section the ideal suitability of Garcinia acid [(2S, 3S)-tetrahydro-3-hydroxy-5-oxo-2,3-furandicarboxylic acid, 1], for the synthesis of chiral butenolides adopting dehydration reaction have been explored (Scheme III.12).
Since the \( \text{–OH} \) group at C3 position of 1 is tertiary, usual methods for the transformation of the \( \text{–OH} \) group to another functional group is difficult. In this context, a convenient and simple strategy has been developed for the preparation of chiral butenolides employing dialkyl esters (10-13) of 1.

III.2.1 Preparation of Dialkyl (2S, 3S)-tetrahydro-3-hydroxy-5-oxo-2, 3-furandicarboxylates (11-13)

Preparation of 10 is already described in chapter II. The other diesters were prepared by first converting the lactone to its disodium salt (6) using aqueous sodium bicarbonate solution (Figure III.2a-b). The disodium salt (6) on treating with thionyl chloride yielded the diacid chloride, which upon treatment with the alcohol gave the corresponding diester exclusively. 6 can be stored as white crystalline solid. It was suspended in dry ethanol and two equivalents of thionyl chloride were added drop wise under ice-cold conditions with stirring. Stirring was continued for two hours and the reaction mixture was neutralized using aqueous sodium bicarbonate solution and the diethyl ester (11) was isolated as colourless oil. The experiment was repeated using dry isopropyl alcohol to yield the diisopropyl ester (12) as yellow oil. Both the products were characterized using IR, \(^1\)H, \(^{13}\)C and mass spectra\(^{10}\) (Scheme III.13) (Figure III.3a-d & Figure III.4a-d).

![Scheme III.12](image)

![Scheme III.13](image)
Attempts to prepare the dibenzyl ester from the diacid chloride failed to give the desired products since the reactivity of benzyl ester differ from other alkyl esters. However following a reported procedure, the dibenzyl ester was prepared in good yield and purity. A suspension of 1 in toluene was treated with dry benzyl alcohol and p-toluene sulphone acid for 13 hours. Subsequent work up and recrystallisation with chloroform - hexane resulted in the formation of white crystals of dibenzyl ester (13)\(^{10}\) (Scheme III.14) (Figure III.5a-d).

![Scheme III.14](image_url)
III.2.2 Preparation of Chiral Butenolides from Dialkyl (2S, 3S)-tetrahydro-3-hydroxy-5-oxo-2,3-furandicarboxylates (265-267)

With the objective of preparing chiral butenolides from dialkyl esters of 1, the halogenation of tertiary hydroxyl group was tried first. Bromination of the tertiary alcoholic group was attempted using several reagents\(^{152}\). The reagents are:

1. Hydrobromic acid
2. HBr in acetic acid
3. N-bromo succinimide / triphenyl phosphine
4. Hydrobromic acid / sulphuric acid

However, all the attempts were failed to isolate the expected product 263 (Scheme III.15).

Finally, a practical entry into the unsaturated ring system was achieved using phosphorous oxy chloride and pyridine. 10 was dissolved in pyridine and POCl\(_3\) was added drop wise at \(-10\) - \(0^\circ C\) and the reaction mixture was stirred at that temperature for two hours. The reaction was quenched using dil. HCl and the TLC shows the presence of a highly polar species. Under the assumption that the ester groups may hydrolyze under work-up conditions the reaction mixture was treated with diazomethane. The product formed (265) was isolated using column chromatography and the reaction sequence was outlined in the following scheme\(^{153}\) (Scheme III.16).
IR spectrum of 265 shows the absence of hydroxyl group and absorbances at 1750 and 1780 cm⁻¹ confirms the lactone ring carbonyl as well as the ester carbonyl. ¹H NMR clearly shows the presence of three –OCH₃ groups at δ 3.95, 3.89, 3.88 ppm. The absence of a double doublet, characteristic of the C4 hydrogens is clear indication of the structure of the product. In ¹³C spectra signals δ 162.7, 161.9 & 157.7 ppm confirms the three carbonyl groups and signals at δ 133.48 & 126.72 ppm confirms the two unsaturated carbons (Figure III.10a-d). The structures of 266 and 267 are also confirmed by IR, ¹H, ¹³C and mass spectra (Figure III.11a-d & Figure III.12a-d). The structure of the product expected by a normal dehydration reaction is as follows (268) (Figure III.6).

Though all the spectroscopic data established the structure as 265 mechanistically formation of 265 is unusual. To further confirm the structure of the product DEPT (Distortionless Enhancement of Polarised Transfer) spectrum was recorded which showed the presence of CH₃ and CH protons and the absence of CH₂ protons. The signal at δ 84.3 indicates the presence of C2 carbon, signal at δ 58.1 shows the presence of OCH₃ carbon, and signals at δ 52.4 and 55.2 represent methoxy carbons of the two ester groups (Figure III.7).
Exact assignments of the carbonyl carbon shifts were made on the basis of the $^1$H-$^{13}$C long range correlations observed in the 2D HMBC (Heteronuclear Multiple Bond Connectivity) spectrum (Figure III.8a-c) which again confirms the structure of the product. The $^1$H-$^{13}$C long range correlations observed are shown in figure (Figure III.11).
To understand clearly the reaction pathway, attempts were made to isolate the intermediate of the reaction. However all the attempts failed to isolate the highly polar species.
III.2.3 Preparation of Chiral Butenolide from Diisopropyl (2S, 3S)-tetrahydro-3-hydroxy-5-oxo-2,3-furandicarboxylates (269)

It is interesting to note that when the reaction was performed using 12 following the above conditions, no meaningful reaction was observed. Repeated experiments were conducted by changing the reaction conditions. When the reaction was carried out at room temperature the reaction proceeded smoothly furnishing 269 as yellow oil (Scheme III.17).

![Scheme III.17](image)

IR, $^1$H and $^{13}$C and mass spectra confirms the structure of the product. A signal at $\delta$ 6.9 indicates the presence of $\text{-C}=$C-H, multiplet at $\delta$ 4.9 - 5.0 and at 5.1-5.2 are due to the presence of $\text{-CH}$ protons of the isopropyl ester group and multiplet at $\delta$1.2 -1.4 stands for methyl protons of isopropyl ester groups. Signal at $\delta$ 4.0 is due to hydrogen on C2 carbon atom. In the $^{13}$C spectrum signals at $\delta$169.3, 165.5 and 164.9 are due to the three carbonyl carbons. Signals at $\delta$140 and 129.1 indicate the presence of two unsaturated carbons (Figure III.13a-d).

The reduction of the double bond of the molecule (270) can lead to the formation of chiral functionalized isocitric acid (271). Isocitric acid, in recent years, attracted much interest as one of the organic acids concerned in reactions catalysed by the enzymes of various animal and plant tissues$^{154}$. R. Fittig first prepared racemic isocitric acid in 1889 and was first isolated from blackberry leaves ($Rubus fruticosus$)$^{155}$. d-isocitric acid is one of the components of the series of enzymatic reactions generally referred to as the tricarboxylic acid cycle of Krebs, a mechanism that is advanced as the explanation of respiration
in living cells. As a member of the Krebs cycle, it is also presumably present, although in only trace amounts, in all living cells in which this biochemical mechanism for respiration occurs. It is produced from citric acid by aconitase and is converted into α-ketoglutaric acid by isocitric acid dehydrogenase\textsuperscript{156} (Scheme III.18).

\[\text{Scheme III.18}\]
Figure III.13a

Figure III.13b
III.3 Experimental

III.3.1 Disodium (2S, 3S)-tetrahydro-3-hydroxy-5-oxo-2,3-furandicarboxylate (6)

To an aqueous solution of 1 (2.0 g, 10.5 mmol, in 10 ml of water), saturated aqueous sodium bicarbonate was added till the pH of the reaction mixture became neutral (ca 15 ml). The residue obtained after evaporation of the reaction mixture under reduced pressure, was triturated and washed with dry methanol followed by acetone (5 X 20 ml). The product (6) was finally dried under vacuum to give a colourless solid.

Yield : 2.0 g (82%)

$[\alpha]_D^{25}$ : +81.8° (c 1.63, H$_2$O)

IR (KBr) : $v_{\text{max}}$ 3400, 1800, 1600 cm$^{-1}$

$^1$H NMR (D$_2$O) : 4.84(s, 1H); 3.19(d, 1H), 2.83(d, 1H), 2.27 (s, 1H)

$^{13}$C NMR (D$_2$O) : 179.4, 177.4, 174.69, 89.1, 81.5, 42.7 ppm;

Mass spectrum (E.I) : 257(M+ 23, 100), 240(58), 195(35.5), 155(20.9)

Molecular formula : C$_6$H$_4$O$_7$Na$_2$

Elemental analysis

Found : C, 30.68, H, 1.70

Calculated : C, 30.76, H, 1.71

III.3.2 Diethyl (2S,3S)-tetrahydro-3-hydroxy-5-oxo-2,3-furandicarboxylate (11)

To a precooled (-5-0°C) suspension of 6 (1.0 g, 4.4 mmol) in dry ethanol (10 ml), thionyl chloride (0.7 ml, 10 mmol) was added. The mixture was then stirred for 48 h at room temperature. After filtration of the reaction mixture, pH of the filtrate was adjusted to 7.0, by adding saturated aqueous sodium bicarbonate
and was extracted with chloroform (3X10ml). The combined extract upon drying and evaporation gave the compound (no) as a pale yellow liquid.

Yield : 0.9 g (77%)

$\alpha_{D}^{25}$ : -81.0° (c 1.0, CHCl$_3$)

IR (liquid film) : $\nu_{max}$ 3500, 2990, 1800, 1740 cm$^{-1}$

$^1$H NMR (D$_2$O) : 4.90(s, 1H), 4.30(m, 4H), 3.10(d, 1H), 2.8(d, 1H), 1.18-1.32 (m, 6H)

$^{13}$C NMR (CHCl$_3$) : 172.0, 170.5, 170.0, 84.0, 75.0, 62.5, 62.0, 40.0, 15.2, 15.0 ppm;

Mass spectrum (E.I) : 246(M+ 1, 5.5), 218(29.8), 200(5.96), 188(41.7), 172(99.8), 156(17.9), 144(87.9), 127(5.9), 114(67.05), 104(90.9), 99(95.4), 88(20.8), 76(70), 59(5.9), 42(65.6%)

Molecular formula : C$_{10}$H$_{14}$O$_7$

Elemental analysis

Found : C, 48.74, H, 5.69

Calculated : C, 48.98, H, 5.71

III.3.3 Diisopropyl (2S, 3S)-tetrahydro-3-hydroxy-5-oxo-2,3-furandicarboxylate (12)

The procedure adopted for (11) was followed with (6) (1.0 g, 4.4 mmol), isopropyl alcohol (10 ml) and thionyl chloride (0.7 ml, 10 mmol). After work-up, gave 12 as yellow oil.

Yield : 0.5 g (41%)

$\alpha_{D}^{25}$ : +32.0° (c 0.0, CHCl$_3$)
**IR (liquid film)**  
$\nu_{\text{max}}$ 3500, 2980, 1800, 1740 cm$^{-1}$

**$^1$H NMR (D$_2$O)**  
5.10-5.18 (m, 1H), 3.96 (s, 1H), 2.98 (d, 1H), 2.93 (d, 1H), 1.18-1.32 (m, 6H)

**$^{13}$C NMR (CHCl$_3$)**  
171.5, 170.1, 169.2, 83.9, 74.6, 71.7, 69.8, 40.0, 21.6, 21.5 ppm

**Mass spectrum (E.I.)**  
274(M+, 7.4), 246(60.3), 232(34.2), 216(21.8), 204(37.1), 190(15.8), 174(23), 162(52.3), 144(58.7), 132(43.6), 117(12), 98(15), 76(52), 42(100%)

**Molecular formula**  
$\text{C}_{12}\text{H}_{18}\text{O}_7$

**Elemental analysis**

**Found**  
$\text{C}$, 52.32, $\text{H}$, 6.59

**Calculated**  
$\text{C}$, 52.55, $\text{H}$, 6.57

**III.3.4 Dibenzyl (2S, 3S)-tetrahydro-3-hydroxy-5-oxo-2,3-furandicarboxylate (13)**

To a suspension of 1 (4.0 g, 20.8 mmol) in dry benzyl alcohol (6.4 ml), p-toluene sulphonie acid monohydrate (50.0 g, 0.26 mmol) and toluene (42.4 ml) were added. The mixture was then refluxed for 13 h at about 130°C. The mixture was allowed to cool, diluted with chloroform and poured into saturated aqueous sodium bicarbonate. The organic layer was separated and the aqueous layer was extracted with chloroform. The combined organic phase upon drying, evaporation and recrystallisation from chloroform-hexane gave 13 as colourless crystals.

**Yield**  
7.0 g (90%)

**Mp**  
81-83°C

**$[\alpha]_D^{15}$**  
+34.7° (c 1.0, CHCl$_3$)
IR (KBr) : \( \nu_{\text{max}} 3500, 3100, 1820, 1700 \text{ cm}^{-1} \)

\(^1\text{H} \text{NMR} \ (\text{D}_2\text{O}) : 7.25-7.34 (\text{m, 10H}), 5.09-4.92 (\text{m, 4H}), 4.87 (\text{s, 1H}), 3.07 (\text{d, 1H}), 2.80 (\text{d, 1H})

\(^{13}\text{C} \text{NMR} \ (\text{CHCl}_3) : 171.8, 170.0, 166.2, 134.3, 133.8, 129.1, 128.8, 128.7, 128.6, 84.1, 78.9, 69.0, 67.9, 39.7 \text{ ppm};

Mass spectrum (E.I) : 370 (M+ 7.0), 280 (6.6), 251 (3.9), 180 (9.4), 107 (86.4), 91 (100), 65 (20.9), 43 (4.4%)

Molecular formula : C\(_{20}\)H\(_{18}\)O\(_7\)

Elemental analysis

Found : C, 64.55, H, 4.87
Calculated : C, 64.86, H, 4.89

III.3.5  Dimethyl 3-methoxy 2(5H) furanone 4, 5 dicarboxylate (265)

To a solution of 10 (1g, 4 mmol), in pyridine, POC\(_3\) (4 mmol) was added at 0°C and stirred for two hours. The reaction mixture was quenched with 2N hydrochloric acid, extracted with CHCl\(_3\) and concentrated. The oil residue obtained was dissolved in methanol, followed by the addition of diazomethane in ether. After completion of the reaction (monitored by TLC), excess diazomethane was removed and concentrated. The residue obtained was purified by column chromatography (silica gel, hexane – chloroform 8:2).

Yield : 0.4gm (4C %),

Melting point : 71°C

\([\alpha]_D^5\) : -31° (c 1.0, CHCl\(_3\))

IR (KBr) : \( \nu_{\text{max}} 2970, 1750, 1730, 1420 \text{ cm}^{-1} \)

\(^1\text{H} \text{NMR} \ (\text{CDCl}_3) : \delta \text{ ppm 5.6} (\text{s, 1H}); 3.95 (\text{s, 3H}), 3.89 (\text{s, 3H}), 3.88 (\text{s, 3H}) \)
\[^{13}C\ NMR\ (CDCl_3)\quad \delta\ 162.7,\ 161.9,\ 157.7,\ 133.4,\ 126.7,\ 84.4,\ 58.9,\ 52.4,\ 52\ \text{ppm}\]

**Mass spectrum (E.I)**

- m/z 230(M\(^{+}\), 7.1), 217(2.5), 216(13.6), 215(100), 185(3.4), 184(26), 172(21.7), 156(15.1), 141(4.1), 127(8.7%).

**Molecular formula**: C\(_9\)H\(_{10}\)O\(_7\)

**Elemental analysis**

**Found**: C, 47.01, H, 4.37

**Calculated**: C, 46.99, H, 4.38

III.3.6 **Diethyl 3-methoxy 2(5H) furanone 4, 5 dicarboxylate (266)**

The procedure adopted for 265 was followed with 11. After work-up the product was isolated as pale yellow oil.

**Yield**: 0.5g (59%)

\[^{1}H\ NMR\ (CDCl_3)\quad 5.6\,(s,\ 1\ H);\ 4.3\,(m,\ 4\ H),\ 3.9\,(s,\ 3\ H),\ 1.5\,(m,6\ H)\]

**\[^{12}C\ NMR\ (CDCl_3)\quad 170,\ 162,\ 158,\ 135,\ 126,\ 84,\ 62,\ 61.2,\ 59,\ 42,\ 25,15\ \text{ppm};\]

**Mass spectrum (E.I)**

- 258(M\(^{+}\), 10.6), 244(20.7), 243(69.6), 214(14.4), 200(23.4), 198(43.5), 186(25), 172(27), 171(100), 169(73.9), 158(34), 144(49.9), 127(32.3), 126(52%).

**Molecular formula**: C\(_9\)H\(_{10}\)O\(_7\)
Elemental analysis

**Found**  :  C, 47.01, H, 4.37

**Calculated**  :  C, 46.99, H, 4.38

III.3.7 Dibenzyl 3-methoxy 2-(5H) furanone 4, 5-dicarboxylate (267)

The procedure adopted for (265) was followed with (13). After work-up the product was isolated as pale yellow oil.

**Yield**  :  0.4g(38.5%)

**[α]D^25**  :  -11(0.1% CHCl_3):  

**IR (liquid film )**  :  ν_max 2970,1740,1718,1558,1123, 752, 697 cm⁻¹

**^1H NMR (CDCl_3)**  :  δ 7.3(m, 5H), 5.6(s, 1H), 5.3(q, 2H), 3.9(s, 3H) ppm

**^13C NMR (CDCl_3)**  :  δ 162.2, 162, 157, 135, 128,126, 84.5, 67 2, 66.6, 58.2 ppm

**Mass spectrum (EI)**  :  m/z 382 (M⁺, 3), 366(72.8), 260(12.8), 232(31.5), 214(12.5), 169(49.5), 91(100), 65(20.5%).

**Molecular formula**  :  C_{29}H_{10}O_{7}

Elemental analysis

**Found**  :  C, 47.01, H, 4.37

**Calculated**  :  C, 46.99, H, 4.38

III.3.8 Diisopropyl 3-methoxy- 2-(5H) furanone 4, 5- dicarboxylate (269)

To a solution of 12 (4 mmol), in pyridine, POCl_3 (4 mmol) was added at 25° C and stirred for two hours. The reaction mixture was quenched with 2N hydrochloric acid, extracted with CHCl_3 and concentrated. The residue obtained was purified by column chromatography (silica gel, hexane – chloroform 8:2).
Yield : 0.45g (53%)

$[\alpha]_D^{25}$ : -14° (c 1.0, CHCl$_3$)

IR (liquid film) : $\nu_{\text{max}}$ 2990, 1750, 1420 cm$^{-1}$

$^1$H NMR (CDCl$_3$) : 6.9 (s, 1 H), 5.1 (m, 1 H), 5.0 (m, 1 H), 3.9 (s, 1 H), 1.5 (m, 12 H)

$^{13}$C NMR (CDCl$_3$) : 169.3, 165.5, 164.9, 140, 129.7, 69.4, 68.3, 33, 21.6 ppm;

Mass spectrum (E.I) : 256(M$^+$, 10.6), 244(20.7), 243(69.6), 214(14.4),

200(23.4), 198(43.5), 186(25), 172(27), 171(100),

169(73.9), 158(34), 144(49.9), 127(32.3), 126(52%).

Molecular formula : C$_{12}$H$_{19}$O$_6$