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L-Ascorbic acid in Organic Synthesis: An Overview

Rama Pati Tripathi*, Biswajit Singh, Surendra Singh Bisht and Jyoti Pandey

Medicinal and Process Chemistry Division, Central Drug Research Institute, Lucknow-226001(India).
Email: rpt.cdri@gmail.com; Fax: 091-(522)-2623405 / 2623938 / 2629504;

Abstract: L-Ascorbic acid, commonly known as vitamin C is well-known in chemistry since long back. It has tremendous medical applications in several diseases. However, application of this chiral molecule in organic synthesis has been neglected earlier. In the later part of twentieth century application of ascorbic acid has gained momentum in organic synthesis of different molecules of biological importance and of chemotherapeutic significance. We have given an account of the history, chemistry, biochemistry and biosynthesis of ascorbic acid and application of this small molecule in organic synthesis. The application of ascorbic acid in accessing chiral synthons has also been described.

1.1 Introduction

L-Ascorbic acid (Figure **1**) is a ubiquitous carbohydrate of vital importance in the living beings. This vitamin is present in various foods, particularly of plant origin, in quantities, that are several orders of magnitude higher than those of other vitamins [1].

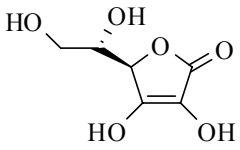


Fig. (**1**)**.** L-Ascorbic acid

Structurally, it is unique and one of the rare compounds containing an acidic hydroxyl group which is completely dissociated at neutral pH (C-3 hydroxyl, p*K*a = 4.2). The presence of electron rich C2, C3-ene-diol moiety in the molecule makes it a member of redox system having both electron donating and electron accepting properties [8]. At the submolecular level the living process is nothing but a stepwise transfer of electrons, therefore, ascorbic acid in coherent with other oxidative-reductive system, aids in maintaining electron transfer process effectively in living organism [2]. It is one of the most important biomolecules, which acts as antioxidant and radical scavenger [3]. The antioxidant behavior of L-ascorbic acid is due to its ability to terminate the radical chain reactions and after reaction it is transformed into non-toxic oxidized product like semidehydro-L-ascorbic acid radical (SDA) and dehydro-L-ascorbic acid (DA). Semidehydro-L-ascorbic acid radical, disproportionates back to L-ascorbic acid and dehydro-L-ascorbic acid (Figure **2**).

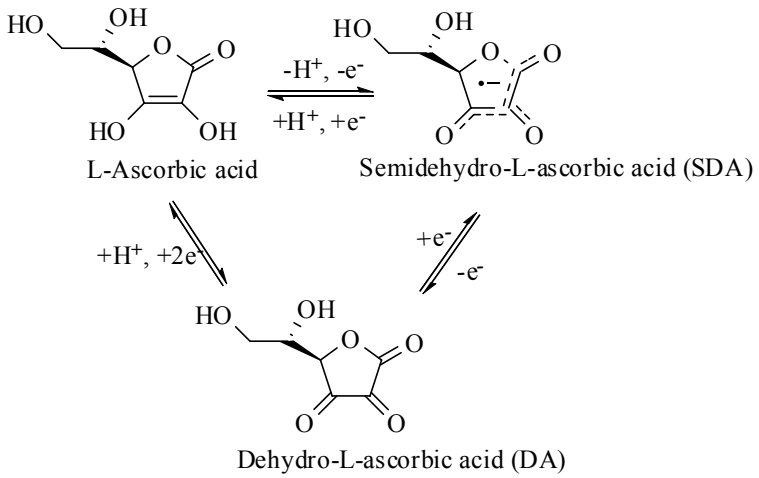


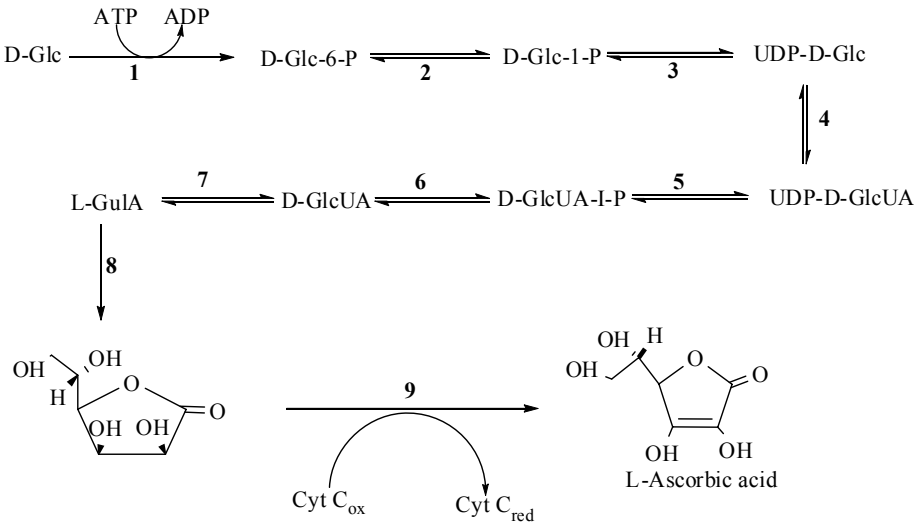
Fig. (2). Disproportionation of L-ascorbic acid

It is widely distributed in aerobic organisms where, it play a crucial role in the protection of cellular components against oxidative damage by free radicals and oxidants that are involved in the development and exacerbation of a multitude of chronic diseases such as cancer, heart disease, brain malfunction, aging, rheumatism, inflammation, stroke emphysema and AIDS [4-20]. It also plays crucial role as a physiological reductant for key enzymatic transformations in catecholamine neurotransmitter, amidated peptide hormone, and collagen biosynthetic pathways. Several of its derivatives are associated with numerous biological activities; 5,6-*O*- modified ascorbic acid derivatives have been found to be effective anti-tumor agents in various human cancers and induce apoptosis in tumor cells [21-28]; C-2 alkyl derivatives possess immuno-stimulant activity [29-34]; while C2-*O*- and C3-*O*- alkylated derivatives act as protecting reagents against peroxidation of lipids of the biomembranes [35-36]. Recently, the chemistry of ascorbic acid has also been exploited in developing strategies for central nervous system drug delivery [37].

1.2 Biosynthesis of L-ascorbic Acid

Ascorbic acid is synthesized by many vertebrates. The biosynthetic capacity has, however, subsequently been lost in a number of species, such as teleost fishes, passeriform birds, bats, guinea pigs and primates including humans, for whom ascorbic acid has thus become a vitamin [38]. Fish, amphibians and reptiles synthesize ascorbic acid in the kidney, whereas mammals produce it in the liver [39, 40]. Vitamin C is also formed by all the plant species studied so far [41]. Interestingly, different pathways have evolved for vitamin C biosynthesis in animals, plants and fungi.

The biosynthesis of L-ascorbic acid in animals followed the glucuronic acid metabolic pathway which is crucial in the metabolism of sugars under both normal and disease states. The glucuronic acid pathway is regulated by other physiological functions of the body. It is an important mechanism during detoxification processes in the body and varies from species to species [42-44]. In animals, D-glucuronate, derived from UDP-glucuronate, is reduced to L-gulonate. The latter is converted to its lactone which in turn, oxidized to L-ascorbic acid, catalyzed by L-gulono-1,4-lactone oxidase (GLO). The complete biosynthetic pathways [44-46] are shown in (Figure **3**).

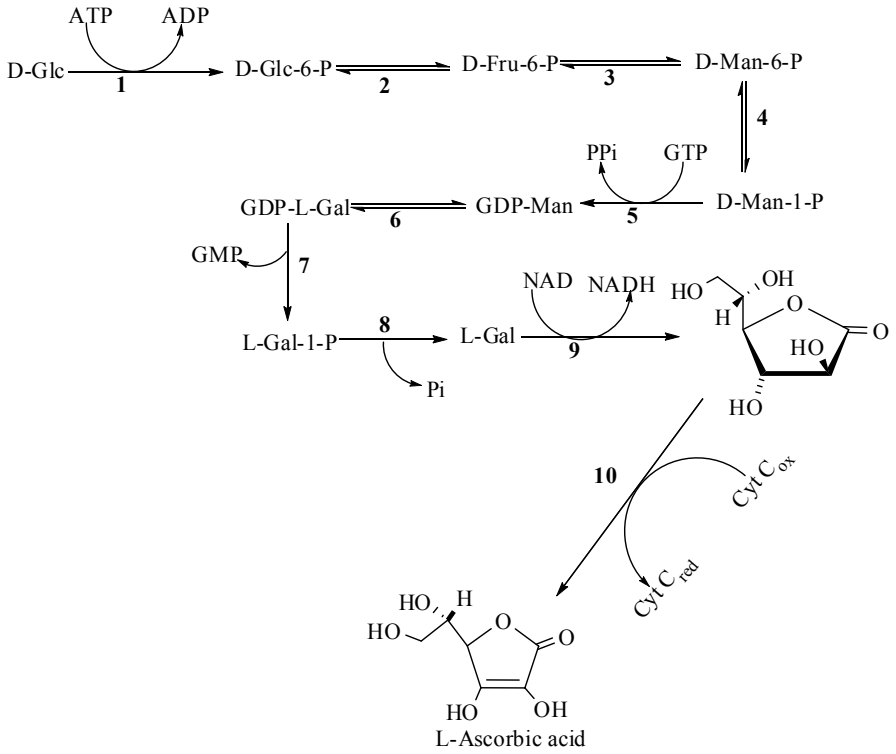


Catalytic Step	Enzyme	Substrate
1	Hexokinase	D-Glucose
2	Phosphoglucomutase	D-Glucose-6-phosphate
3	UDP-D-Glucose pyrophosphorylase	D-Glucose-1-phosphate
4	UDP-D-Glucose dehydrogenase	UDP-D-Glucose
5	D-Glucuronate-1-phosphate	UDP-D-Glucuronic acid
6	D-Glucurono kinase	UDP-D-Glucuronic acid-1-phosphate
7	D-Glucuronate reductase	D-Glucuronic acid
8	Aldonolactonase	L-Galacturonic acid
9	L-Gulono-1,4-lactone dehydrogenase	L-Gulono-1,4-lactone

Fig. (3). Biosynthetic Pathway of L-ascorbic acid in animals

The deficiency of L-ascorbic acid biosynthesis in certain animals and humans is due to the lack of the terminal flavor-enzyme, L-gulono-1,4-lactone oxidase (GLO), which completely blocks the production of L-ascorbic acid in the liver of human beings [42-44]. This oxidizing enzyme is required in the last step of the conversion of L-gulono-γ-lactone to 2-oxo-L-gulono-γ-lactone, which is a tautomer of L-ascorbic acid that is spontaneously transformed into vitamin C.

The biosynthesis of L-ascorbic acid in plants is not clearly understood as compared to that in animals. But recent advances helped to understand its biosynthesis in plants and resolved the several past contradictions. Biosynthetic pathways generally proceed *via* GDP-D-mannose and GDP-L-galactose [42-47], which was proposed by the Smirnoff group [47]. The Smirnoff-Wheeler-L-ascorbic acid biosynthetic pathway represents the major route of L-ascorbic acid biosynthesis in plants (Figure **4**). The initial step of L-ascorbic acid biosynthesis in plants is also utilized for the synthesis of cell wall polysaccharide precursors, while later steps following GDP-L-galactose are solely dedicated to plant biosynthesis of L-ascorbic acid.



Catalytic Step	Enzyme	Substrate
1	Hexokinase	D-Glucose
2	Phosphoglucose isomerase	D-Glucose-6-phosphate
3	Phophomannose isomerase	D- Fructose -6-phosphate
4	Phophomannose mutase	D- Mannose -6-phosphate
5	GDP-Mannose pyrophoshorylase	D- Mannose -1-phosphate
6	GDP-Mannose-3,5-epimerase	GDP-D-Mannose
7	GDP-L-Galactose	GDP-L-Galactose
8	L-Galactose-1-phosphate phosphatase	L-Galactose-1-phosphate
9	L-Galactose dehydrogenase	L-Galactose
10	L-Galactono-1,4-lactone dehydrogenase	L-Galactono-1,4-lactone

Fig. (4). Biosynthetic Pathway of L-Ascorbic acid in plants

1.3 Discovery and history of L-ascorbic Acid

All living organisms either make ascorbic acid or get it in their food stuffs. The enzyme systems for the production of vitamin C is of ancient origin and were formed very early in the development of life process on this planet, probably the most developed forms were still primitive unicellular forms. The deficiency syndrome of vitamin C in animals is scurvy. Symptoms of scurvy include anorexia, anaemia, arthralgia, bleeding gums, coiled hair, depression, dry eyes and mouth (Sjogren's Syndrome), eccymosis, follicular hyperkeratosis, fatigue, frequent infections, impaired wound healing, inflamed gums, joint effusions, myalgia, muscle weakness, perifollicular hemorrhages, and petechiae. The later stage conditions include patients exhibiting extreme exhaustion, kidney and pulmonary problems, as well as diarrhea, eventually leading to death. The necessity to take fresh animal flesh or plant food in the diet to prevent scurvy disease was known since ancient times. Eber's Papyrus, an ancient Egyptian medical treatise in 1,500 B.C., described scurvy as a disease characterized by spongy and bleeding gums and bleeding under the skin. Around 400 BC, Hippocrates, a Greek physician known as the founder of medicine, preached against one sided nutrition and described how good a daily and healthy diet rich in foods that are known today to contain great amount of vitamin C could help to prevent diseases such as scurvy. In 1200 AD, the Crusaders were plagued with scurvy. From 1492 to1600, world exploration was

threatened by scurvy. Ferdinand Magellan, a Portuguese sea captain around 1520, lost 80% of his crew to scurvy. Also Vasco de Gama a Portuguese conquistador was the first to sail across the African coast on his way to India in 1492 and lost 100 of his 160 crew to scurvy. Scurvy was severe threat to thousands of soldiers and sailors alike and many died of the disease during military campaign and lengthy ocean voyages, respectively, until in 1720, when physician J.G.H. Kramer found that fresh herbs and lemons cured the disease [48-77].

In 1746, James Lind, a British naval surgeon on H.M.S. Salisbury conducted a controlled test on 12 of his seamen suffering from the debilitating effects of scurvy and became the first person to give a scientific basis for the cause of scurvy. In 1753, James Lind published the results of his famous finding in his 400-page book, *Treatise of the scurvy*, where for the first time he established the benefit of citrus fruits in combating scurvy and by 1795, royal navy had mandated the use of lime juice or other citrus fruits as a scurvy preventative. In 1912, for the first time, the vitamin hypothesis was suggested by polish American chemist Funk, part of which stated that scurvy was a deficiency disease caused by the lack of unknown water soluble substance called the anti-scorbutic factor. In 1920, Sir Jack Cecil Drummond, the first professor of biochemistry in the University of London, suggested calling this substance as Vitamin C, because man, guinea pigs, and certain monkeys unlike other mammals cannot make their own ascorbic acid. This unknown water soluble anti-scorbutic substance was isolated from Ox adrenal cortex (and various plants) in 1928 by Hungarian biochemist research team of Joseph L. Svirbely and Albert Von Szent Gyorgyi. In autumn of 1931, this reducing substance with molecular formula $C_6H_8O_6$, which he named hexuronic acid, was unequivocally proven in experimentation as the powerful anti-scorbutic substance, and that the anti-scorbutic activity of plant juices corresponded to their hexuronic acid content. About the same time, the Americans Glen King and William A. Waugh also reported crystals from lemon juice, which were actively anti-scorbutic and resembled hexuronic acid. In 1932, Albert Von Szent Gyorgyi and British chemist Sir Walter Norman Haworth subsequently renamed hexuronic acid as ascorbic acid. In 1933 main features of the constitution of ascorbic acid and its formula as a lactone of 2-keto-L-gulonic acid, capable of reacting in various tautomeric forms, was first announced from the University of Birmingham. Almost at the same time, the Polish Tadeous Reichstein, in Switzerland, as well as Haworth's group independently achieved the synthesis of vitamin C. The synthetic form of vitamin was identical to the natural form and this made possible the cheap production of vitamin C on mass scale. Three patent applications were filed in 1935 and patents were granted in 1935 and 1940. Thus American biochemist and chemical engineer Dr. Irwin Stone obtained the first patent on an industrial application of ascorbic acid. Sir Walter Norman Haworth and Paul Karrer shared the Nobel Prize for Chemistry in 1937 partly due to their work in determining the structure and synthesis of vitamin C. Also in 1937, Albert Von Szent-Gyorgyi was awarded the Nobel Prize for his studies of the biological functions of vitamin C [48-77].

1.4 Sources of L-ascorbic Acid

The main sources of L-ascorbic acid are plant and animals derived products. The ubiquitous nature of L-ascorbic acid throughout the human body emphasizes its daily requirement and vitality as nutrients for healthy maintenance [78-80]. Its half life in humans is 14-40 days after normal intake and a vitamin C free diet in humans develops scurvy in about 3-4 months [81].

The vast majority of plants and animals such as amphibians, reptiles, birds, and mammals are known to synthesize their own vitamin C. All algal classes can synthesize vitamin C from glucose or other sugars. All higher plant species can also synthesize vitamin C and thus make it prevalent in surrounding food sources [82]. For example, large concentrations of vitamin C are found in fruits such as oranges, grapefruits, tangerines, lemons, limes, papaya, strawberries and cantaloupe. Also many vegetables are known to pack in vitamin C and these include tomatoes, broccoli, green and red bell peppers, raw lettuce and other leafy greens. A complete listing of every food containing vitamin C according to USFDA food database is available through the Vitamin C Foundation [82].

1.5 Physico-chemical properties of L-ascorbic Acid

The physiological activity of L-ascorbic acid stems from its basic functional structure. It is a five-membered lactone sugar acid and its C3 and C2- enolic hydroxyl groups may dissociate to form a dibasic acid. The 2, 3-enediol moiety conjugated with the lactone carbonyl group, results the C3 hydroxyl proton significantly acidic (pK1= 4.25) as compared to the C2 hydroxyl proton (pK2 = 11.79) [83]. The 2,3-enediol moiety of L-ascorbic acid enables it to donate one or two electrons (reducing equivalents) and

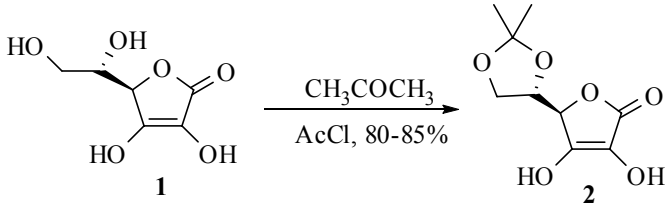
form a comparatively stable oxidized intermediate (semidehydro-L-ascorbic acid) and the finally oxidized product (dehydro-L-ascorbic acid). This phenomenon of electron donation is responsible for most, but not all the chemical and biological functions of L-ascorbic acid. The other two -OH at C5 and C6 behave as alcoholic groups. They react with aldehydes and ketones to give cyclic acetals and ketals, respectively. Due to the presence of two asymmetric centers at C4 and C5 it possesses a positive value of optical rotation. The optical rotation is not significantly affected by the acidity of the solution, but in contrast it varies greatly with alkalinity, increasing over +160° in 2N NaOH solution [84]. A number of physical properties of L-ascorbic acid are listed in Table 1 [85, 86].

Insert table 1 here.

Chemical reactions of L-ascorbic Acid

1.6 Chemoselective alkylations of L-ascorbic Acid

Taking into account of the acidity of four hydroxyl groups (p*K*a value) and their steric environments in L-ascorbic acid, alkylation studies have been carried out under different experimental conditions. The four hydroxyl groups show different reactivity toward electrophiles under basic reaction conditions. These hydroxyl groups impart highly hydrophilic character to it and therefore, insoluble in organic solvents. Because of its hydrophilic character it has been modified to synthetically useful intermediates which are soluble in organic solvents. One of such derivative, 5,6-*O*-ketal or 5,6-*O*-acetal, are soluble in organic solvents. The protection of 5 and 6 -OH groups also limits their interference during reaction, involving the C-2 and C-3 enol hydroxyls. These derivatives 5,6-*O*-isopropylidene-L-ascorbic acid (**2**) has been prepared, using different methods [87], but the simplest method was to dissolve L-ascorbic acid (**1**) in excess acetone containing a catalytic amount of acetyl chloride [88] (Scheme **1**).

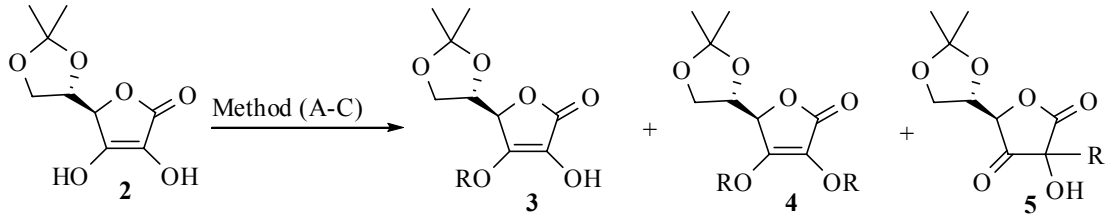


Scheme 1.

1.6.1. 3-O-Alkylation of 5,6-*O*-isopropylidene-L-ascorbic Acid

During reactions of 5,6-*O*-isopropylidene-L-ascorbic acid (**2**) with various electrophilic reagents under mild basic condition should predominantly occur at the C3-OH position in comparison to C2-OH. This is primarily due to the preferential deprotonation of C3-OH over C2-OH to produce monoanion. Further, the electron density distribution pattern of the negatively charged monoanion, between C3-O^- and C1-carbonyl of the lactone ring with little density on C2-OH [89]. Therefore, the reactions of 5,6-OH protected ascorbic acid with electrophilic reagents under mild basic conditions preferably occur at the C3-OH position as experimentally observed [90, 91]. However, the electron density at the C-2 carbon of monoanion is significantly higher than that of the C2-OH, which renders the C-2 position of the monoanion susceptible to electrophilic reagents. Therefore, its C-2 alkylated products were also observed as minor products during alkylation of (**2**) under mild alkaline conditions [89, 90].

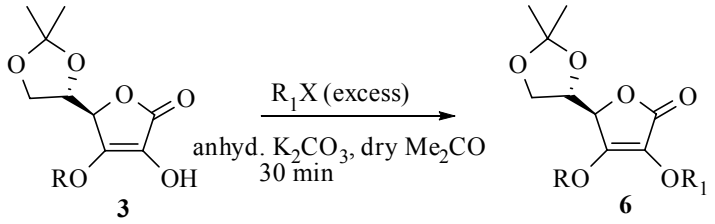
The 3-*O*-alkylation of 5,6-*O*-isopropylidene ascorbic acid has been studied in detail by Kulkarni and Thorpate [90]. During alkylation of 5,6-*O*-isopropylidene ascorbic acid with alkyl halides under basic condition 3-*O*-alkyl derivative is major product while small amount of C-2 alkyl and 2,3-di-*O*-alkyl products were also observed (Scheme **2**). The effects of solvent and temperature on the formation of alkylated products have also been elucidated.



Method A: 2, Et_3N, RBr, Dry Methanol, 3-6 hrs,
Method B: 2, anhyd. K_2CO_3, RBr, THF:DMSO (1:1), 1-3 hrs,
Method C: 2, anhyd.K_2CO_3, RBr, acetone, 1h, Method D: 2, anhyd. K_2CO_3, RBr, dry acetone, 1h, reflux.

Scheme 2.

The alkylation of 5,6-*O*-isopropylidene-L-ascorbic acid (**2**) in dry acetone shows better selectivity for 3-*O*-alkylation as compared to reaction in THF:DMSO (1:1) at ambient temperature or under triethylamine-methanol. Refluxing **3** in acetone with excess of various alkylating agents in presence of K_2CO_3 furnished corresponding 2,3-di-*O*-alkyl product **6** (Scheme **3**).

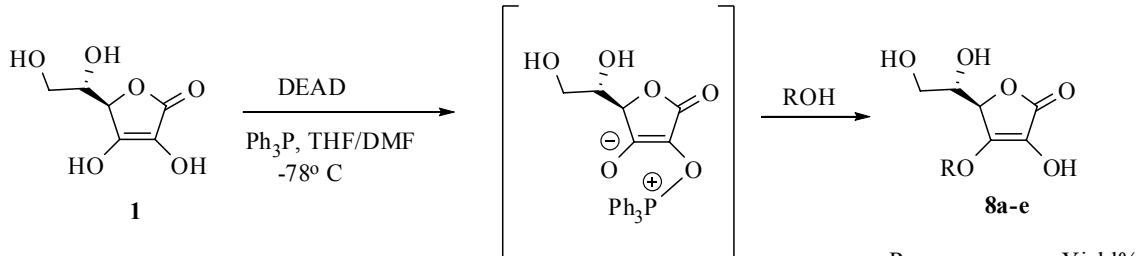


Scheme 3.

Wimalasena et.al. [91] also carried out 3-*O*-alkylation in THF: DMSO (9:8) in the presence of K_2CO_3 to get the alkylated products **3** and **5** respectively.

1.6.2 Direct 3-*O*-alkylation of L-ascorbic acid under Mitsunobu condition

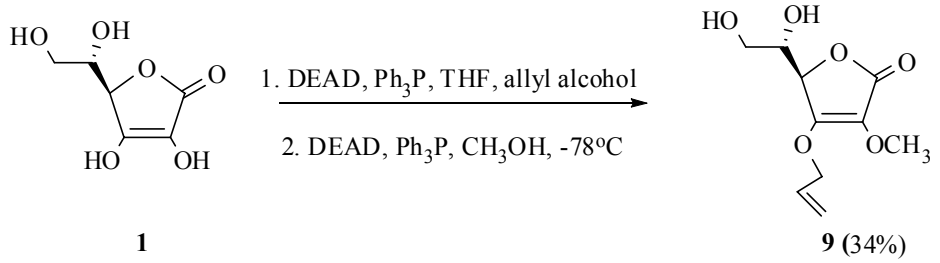
3-*O*-Alkylation of L-ascorbic acid under Mitsunobu reaction condition [92] with different alkyl and allyl alcohols is shown below (Scheme **4**).



R	Yield%
Me (8a)	77
Propyl (8b)	63
Octyl (8c)	72
Allyl (8d)	72
Benzyl (8e)	64

Scheme 4.

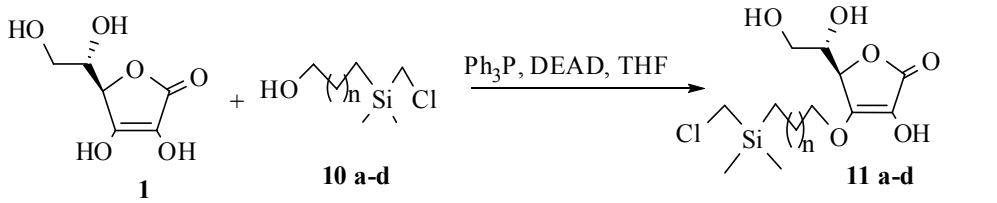
Application of Mitsunobu reaction condition [92] to prepare 3-*O*-allyl-2-*O*-methyl-L-ascorbic acid in one pot from L- ascorbic acid and allyl alcohol has also been elucidated as shown in Scheme **5**.



1 **9** (34%)

Scheme 5.

Further, a number of 3-*O*-silane derivatives of L-ascorbic acid (**11a-d**) have also been prepared, by the reaction of L-ascorbic acid (**1**) with *O*-silyl chlorides [93, 94] as shown in Scheme **6**. In this synthesis, the versatility of the Mitsunobu reaction allowed the intermolecular dehydration to take place under mild conditions, resulting in the ether linkage in compounds **11a-d**. The beauty of this synthesis is the absence of any protecting group on the other hydroxyls. Further, the yield of the products obtained is independent of the alkyl chain length of the above *O*-silyl chlorides.



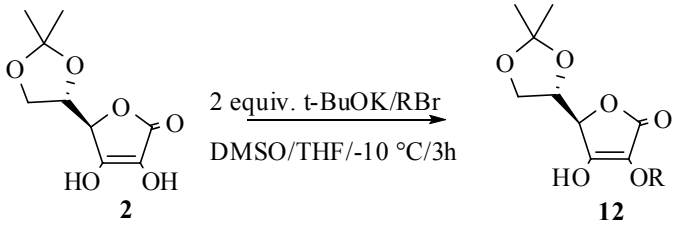
1 **10 a-d** **11 a-d**

11a n=1 (51%)
11b n=2 (31%)
11c n=3 (42%)
11d n=4 (40%)

Scheme 6.

1.6.3 Direct 2-*O*-alkylation of 5,6-*O*-isopropylidene-L-ascorbic Acid

Direct alkylation of C2-OH in 5,6- *O* -isopropylidene-L-ascorbic acid is difficult due to much less electron density at C2-OH as compared to C3-OH. Wimalasena et.al. [89] have prepared exclusively the derivative of L-ascorbic acid and 2-*O*-alkyl derivative (**12**) of 5,6-*O*-isopropylidene-L-ascorbic acid by the reaction of 5,6-*O*-isopropylidene-L-ascorbic acid (**2**) with alkyl halides in the presence of 2 eq. of potassium *tert*-butoxide (*t*-BuOK) in DMSO/THF (3:2) at -10 °C (Scheme **7**).



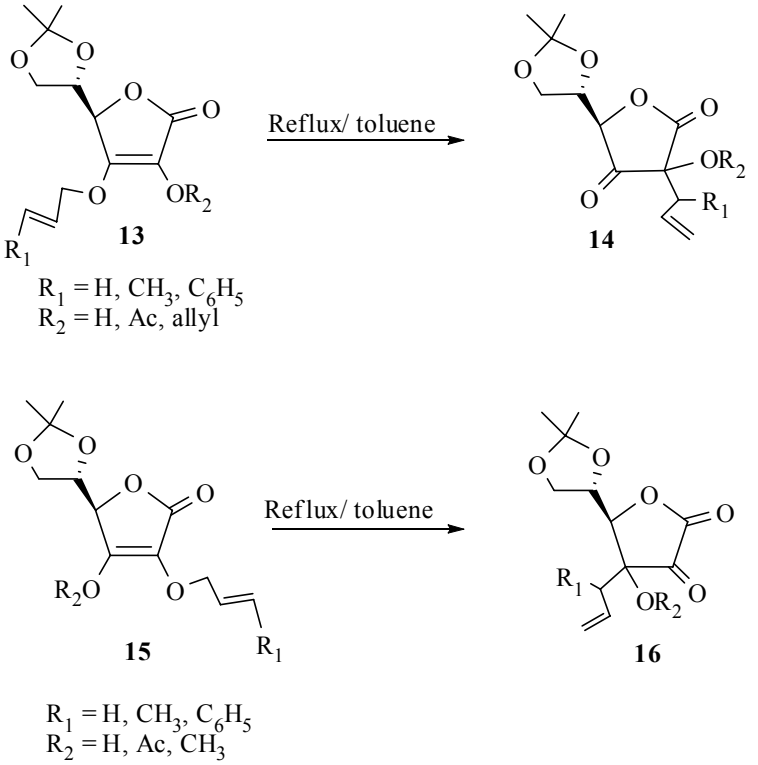
2 **12**

Scheme 7.

Taking the advantage of electron density at *C* and *O* atoms of the L-ascorbic acid, the dianion of L-ascorbic acid was generated by reacting 2 eq. of potassium *tert*-butoxide (*t*-BuOK) in DMSO/THF (3:2) at -10°C. The reaction of dianion, so generated, with 1 eq. of activated or unactivated electrophilic alkylating agents gave the respective 2-*O*- alkyl ascorbic acid derivatives in good yields.

1.7 2-*C* and 3-*C* Allylation of 5,6-*O*-isopropylidene-L-ascorbic acid: thermal Claisen rearrangement [91,95]

A convenient synthesis of 5,6-*O*-isopropylidene-2-allyl-3-keto-L-galactono-γ-lactones (**14**) and 5,6-*O*-isopropylidene-3-allyl-2-keto-L-galactono-γ-lactones (**16**) involve thermal claisen rearrangement of the corresponding 3-*O*- and 2-*O*-allyl derivatives of 5,6-*O*-isopropylidene-L-ascorbic acid (**13**) and (**15**) respectively.

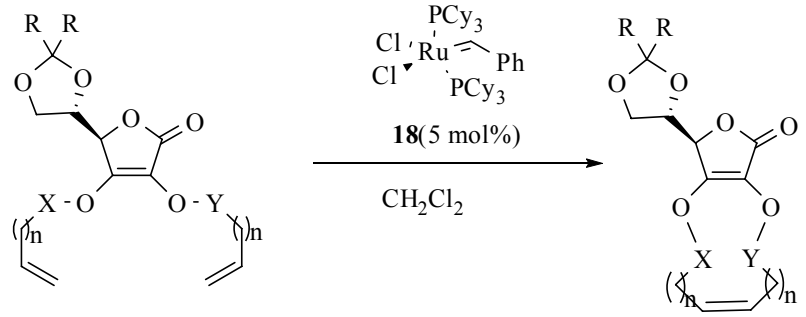


Scheme 8.

In contrast to the smooth rearrangement of C3-*O*-allyl ascorbic acid derivatives under relatively mild conditions whereas, the rearrangement of their C2-*O*-allyl counterparts (Scheme **8**) is much slower and requires much drastic reaction conditions. The relative difficulty for the rearrangement of C2-*O*-allyl in comparison to C3-*O*-allyl derivatives could be due to a combination of steric and electronic effects. Firstly, the steric constraints on the transition state for the C2-*O* to C-3 allyl migration are more pronounced relative to that of the C3-*O* to C-2 allyl migration, due to the presence of a bulky 1,2-*O*-isopropylidene-1,2-ethanediol moiety at the C-4 in the substrate. Secondly, the relatively high lability of C3-*O*- allylic ether linkage compared to that of the C2-*O*-allylic ether linkage is due to the direct interaction of the C3-*O* with the conjugated enone moiety which also facilitates the rearrangement to produce the thermodynamically more stable C2- allylated products.

1.8 Diastereoselective transannular [2+2] photocycloaddition

Sebastein Redon and Oliver Piva [96] reported the synthesis of 2-, 3-*O*-alkenyl derivatives of 5,6-*O*-isopropylidene-L-ascorbic acid (**19a-c**) via diastereoselective transannular [2+2] photocycloaddition. Thus compounds (**17a-c**) were respectively converted into cyclic bisethers (**19a-c**) in the presence of catalytic amounts of first generation Grubbs' catalyst (**18**). The results are shown in Scheme **9**.



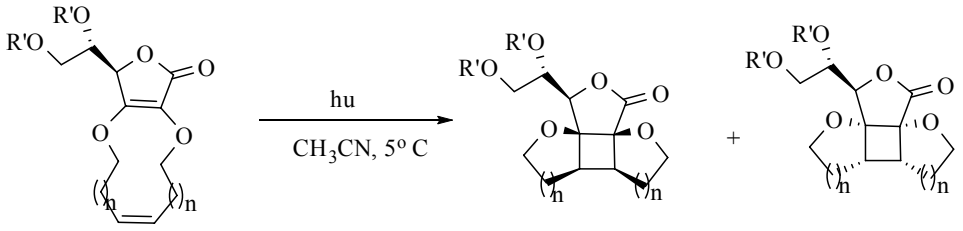
17a,b (R, R = CH_3, CH_3)
17c (R, R) = - $(CH_2)_5$-

19a-c

Substrate	X, Y	n	Product	% yield
17a	CH_2/CH_2	0	**19a**	50
17b	CH_2/CH_2	1	**19b**	66
17c	CH_2/CH_2	1	**19c**	55

Scheme 9.

Further, a transannular cycloaddtion of the above metathesis product (**19a**) by its irradiation at 254 nm at 5°C, in dichloromethane or in acetonitrile at low concentration (10^{-2}M) resulted into a tricyclo[2.2.0]octane (**20a**), a highly unfavorable product. Similarly, irradiation of **19b** afforded two diastereoisomers **20b** and **21b** while irradiation of **19c** gave the diastereoisomers **20c** and **21c** respectively**.** The results are shown in Scheme **10**.



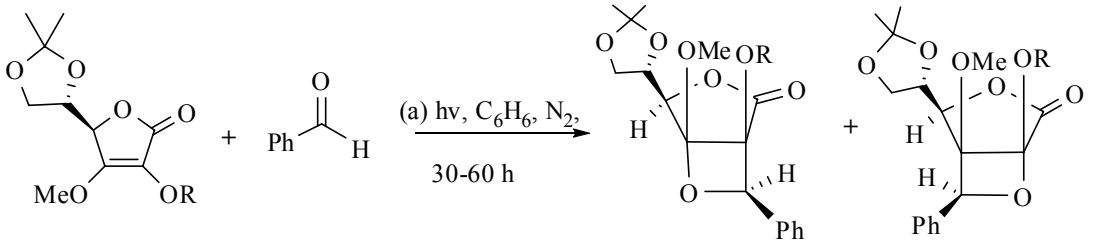
19a-c **20a-c** **21a-c**

Substrate	R'	n	Product 20/21 (ratio)	Overall Yield (%)
19a	Isopropylidene	0	20a	50
19b	Isopropylidene	1	20b/21b(47/53)	66
19c	Cyclohexylidene	1	20c/21c(59/41)	55

Scheme 10.

1.9 The Paterno-Buchi Reaction of L-ascorbic Acid

The irradiation of a solution of 5,6-*O*-isopropylidene-2,3-di-*O*-alkyl ascorbic acid derivatives (**22**) and benzaldehyde in benzene under UV light through a pyrex filter resulted in the oxetanes **23a** and **23b** in moderate to good yields [98]. The results are shown in Scheme **11**.



22 R = Me
24 R = Benzyl

23a R = Me (60%)
25a R = Bn (57%)

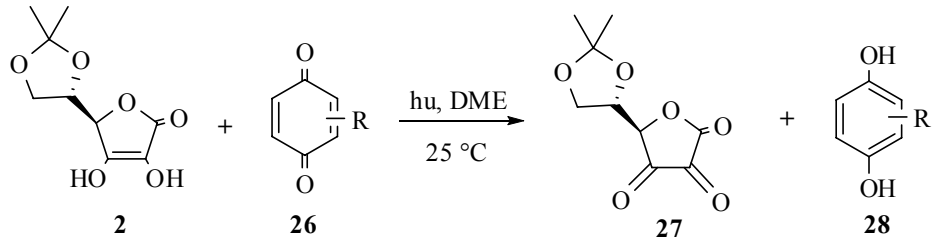
23b R = Me (25%)
25b R = Bn (28%)

Scheme 11.

The preferred mode of attack for the photoexcited carbonyl group of benzaldehyde on enediols **22** and **24** would presumably be from the less hindered α face, with aldehyde proton oriented in *endo* fashion. Therefore, the phenyl residue and alkoxy groups on the oxetane ring are in *cis* orientation in the products **23a, 23b, 25a** and **25b.**

1.10 Photoreduction of quinones with 5,6-*O*-isopropylidene-L-ascorbic Acid

L-Ascorbic acid is known to reduce different systems [99], including inorganic compounds [100] under photolytic condition. It is also reported [101] to reduce quinones in a ground state reaction. Irradiation of a mixture of 5,6-*O*-isopropylidene-L-ascorbic acid (**2**) and quinones (**26**) in 1,2-dimethoxy ethane (DME), resulted in their respective hydroquinones (**28**) [102] (Scheme **12**).



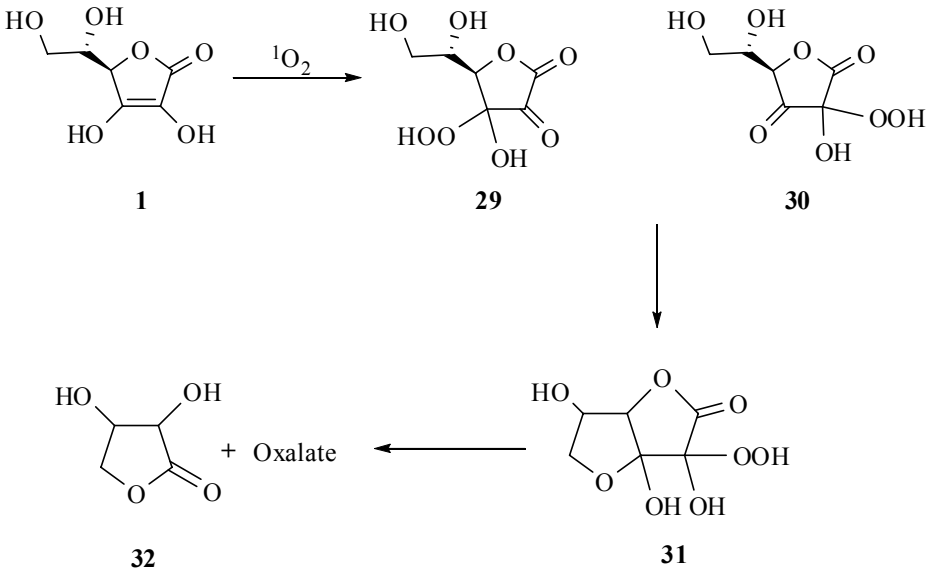
2 **26** **27** **28**

Scheme 12.

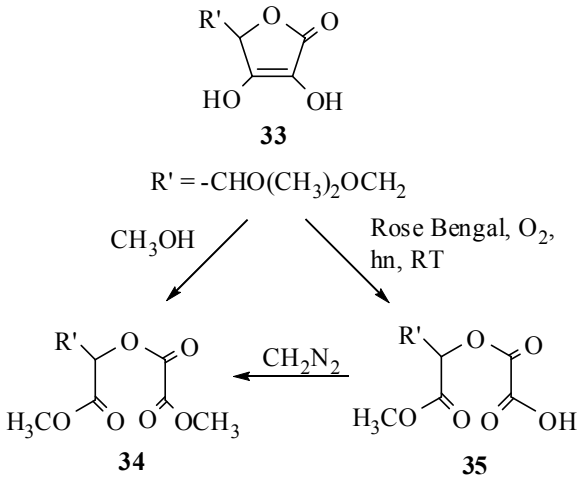
1.11 Photooxygenation of L-ascorbic acid derivatives

The singlet oxygen reacts with L-ascorbic acid (**1**) at low temperature in an ene-type reaction [103] to give two unstable hydroperoxy ketones (**29**) and (**30**). The latter rearranges to hydroperoxydehydroascorbic acid (**31**) by intramolecular cyclisation [104]. Hydroperoxide (**31**), in turn, is converted to the oxalic acid and L-threonolactone (**32**) on warming and hydrolysis (Scheme **13**).

Kwon et al. [105] have shown that photooxygenation of 3-*O*-methyl-5,6-*O*-isopropylidene-L-ascorbic acid (**33**) at ambient temperature in methanol using rose bengal as a sensitizer resulted in 80% of the oxalate methyl ester (**34**) and 20% of the corresponding acid (**35**) (Scheme **14**). The oxalic acid monoester was easily converted to methyl ester (**34**) by reaction with CH_2N_2 in methyl alcohol.



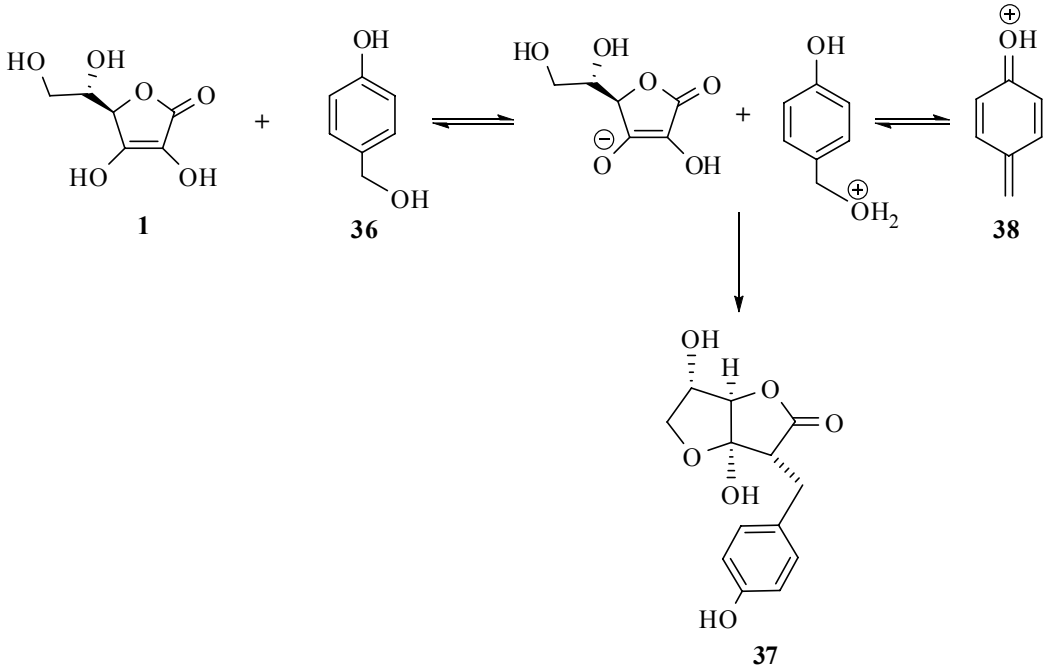
Scheme 13.



Scheme 14.

1.12 Reaction of *p*-hydroxy benzylalcohol derivatives with L-Ascorbic Acid

L-Ascorbic acid (**1**) on reaction with p-hydroxy benzyl alcohol (**36**) yields 2-(p-hydroxybenzyl)-3-ketohexulosonic acid lactone (**37**) [106]. The reaction proceeds via protonation of the benzylic alcohol moiety with ascorbic acid followed by elimination of water which is triggered by phenol. The resulting protonated quinine methide (**38**) adds to the conjugate base of ascorbic acid (**1**) to yield a bicyclic product (**37**) (scheme **15**).



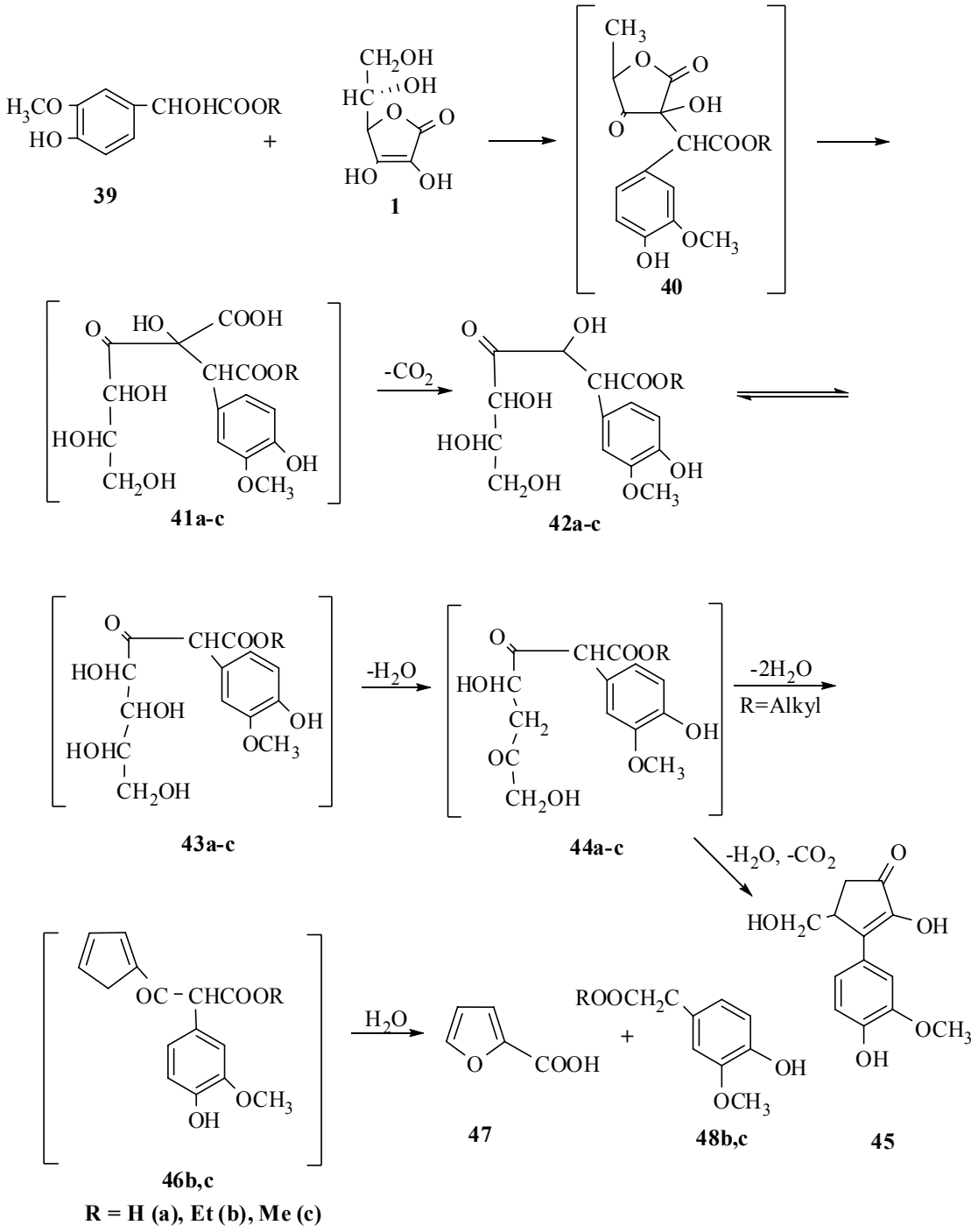
Scheme 15.

The alkylation occurs from the less hindered α-face of (**1**) as dictated by C-5,6 side chain. The total syntheses of delesserine, methyl rhodomelol and rhodomelol have also been accomplished using this methodology [106].

1.13 Reaction of Vanilmandelic Acid derivatives with L-Ascorbic Acid

Preobrazhenskaya and co-workers [107] have reported that the incubation of vanilmandelic acid (**39a**) and L-ascorbic acid **1** at pH 1 and 50-60 °C for 5-days resulted in the formation of 2-hydroxy-3-(4-hydroxy-3-methoxyphenyl)-4-hydroxymethylcyclopent-2-en-one (**45**) in 10% yield, about 20% of vanillin and traces of 2-furancarboxylic acid (**47**) are also obtained (Scheme **16**). The same reagents in 75% aqueous ethanol at pH 1 gave 41% of ethyl vanillylmandelate (**39b**) and about 58% of (**47**). Under the same conditions methyl vanilmandelate (**39c**) and ascorbic acid gave (**47**) as the main product along with the traces of (**47**) and vanillin as shown in Scheme **16**.

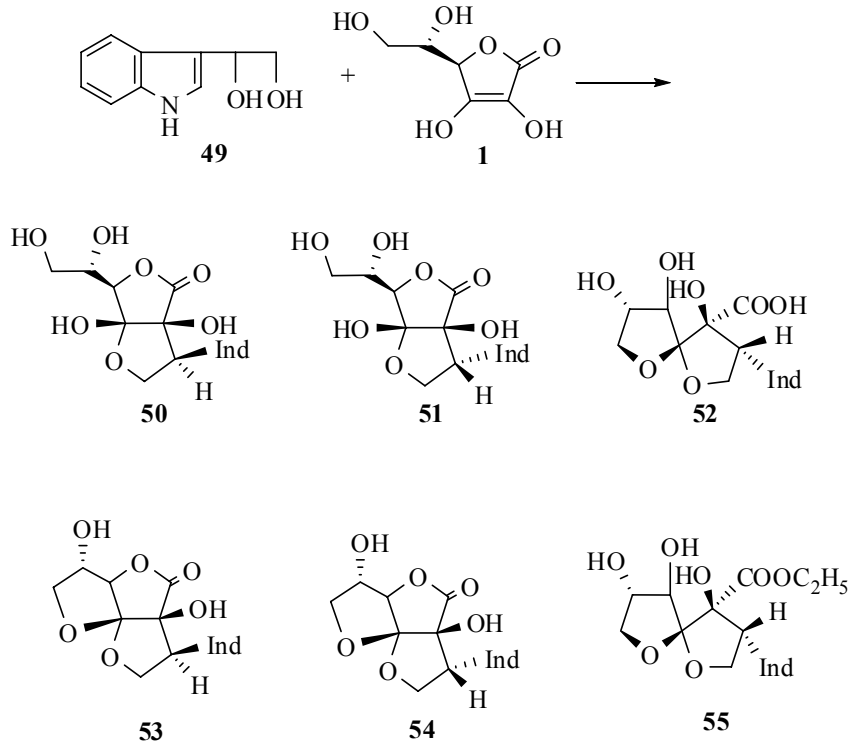
The retrosynthetic analysis suggests that 2-*C*-(carboxy)(4-hydroxy-3-methoxyphenyl)methylation of the L-ascorbic acid moiety in the presence of an acid give the desired framework (**40a**) in the same way as the interaction of L-ascorbic acid with 4-hydroxyphenyl alcohol described earlier [106]. The intermediate (**40a**) appears to be unstable as its lactone ring is opened to give β-keto acid (**41a**), which easily decarboxylates to a ketone intermediate (**43a**) and the latter, on dehydration gives the intermediate γ-diketone (**44a**). The γ-diketone, on further reactions viz. dehydration, decarboxylation and cyclization produces 2-hydroxy-3-(4-hydroxy-3-methoxyphenyl)-4-hydroxymethylcyclopent-2-en-one (**45**). The above β-keto ester (**44b** or **c**) on reaction with L-ascorbic acid resulted in esters (**39b** or **c**) respectively. Further, dehydrative cyclization *via* β-keto ester (**46**) results in 2-furancarboxylic acid (**47**) and alkyl 4-hydroxy-3-methoxyphenyl acetate (**48**) in good yields (Scheme **16**).



Scheme 16.

1.14 Reaction of (indol-3-yl) ethanediol with L-ascorbic acid

Reaction of (indol-3-yl)ethanediol (**49**) [109] and L- ascorbic acid (**1**) in aqueous ethanol under ambient condition led to formation of a mixture of compounds **50**, **51**

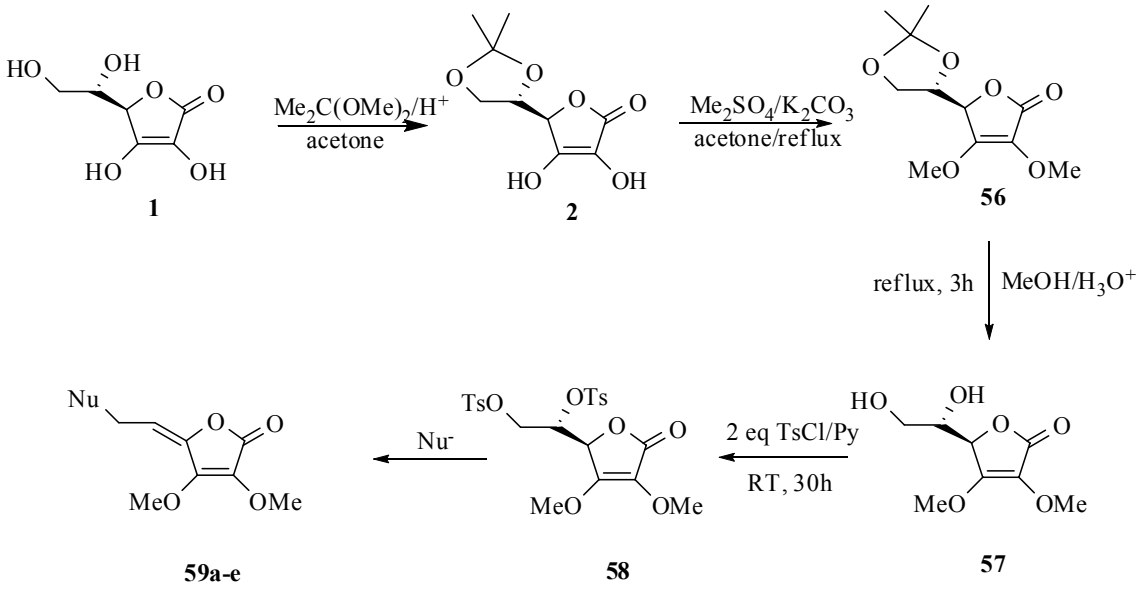


Scheme 17.

and **52**. The latter on further incubation with 2% ethanolic HCl at ambient temperature led to a mixture of ketal derivatives **53**, **54** and **55** respectively as shown in Scheme **17**.

1.15 Synthesis of (*Z*)-alkylidene-2, 3-dimethoxy butenolides and their reactions:

A simple and efficient synthesis of (*Z*)-alkylidene-2,3-dimethoxy butenolide from L-ascorbic acid has been reported by Khan et al [110]. It involves deketalization of 2,3-*O*-dimethyl-5,6-*O*-isopropylidene-L-ascorbic acid **(56)** with an acid to give the respective diol **(57)**. The latter on reaction with *p*-toluene sulphonyl chloride led to the formation of an intermediate ditosyl derivative **(58)** which on reaction with different nucleophiles yielded the respective γ-(Z)-alkylidene-2,3-dimethoxy butenolides (**59)** (Scheme **18**).



Nu = $(EtO_2C)_2HC^-$, $(EtO_2C)(SO_2Ph)HC^-$
$(EtO_2C)(COMe)HC^-$, N_3^-, AcO-

Scheme 18.

Mechanistically, the formation of (**59)** from (**58)** is believed to involve a two-step reaction pathway in which the first step is an elimination (E2) process that produces an exocyclic allylic tosylate which on the subsequent reaction undergoes S_N2 reaction with the nucleophile.

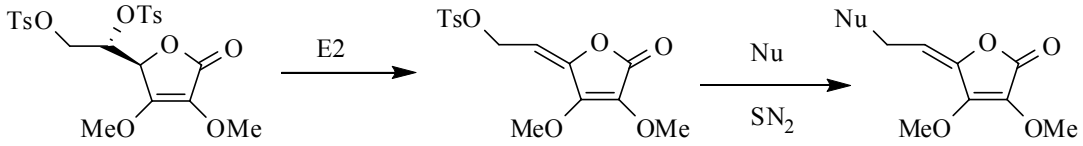
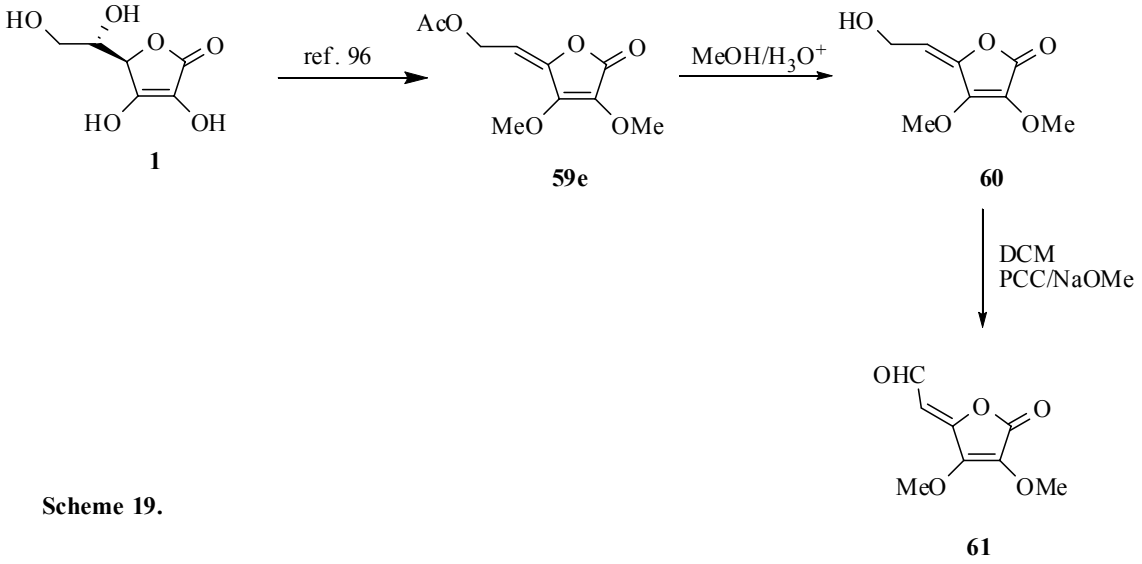


Fig. (5).

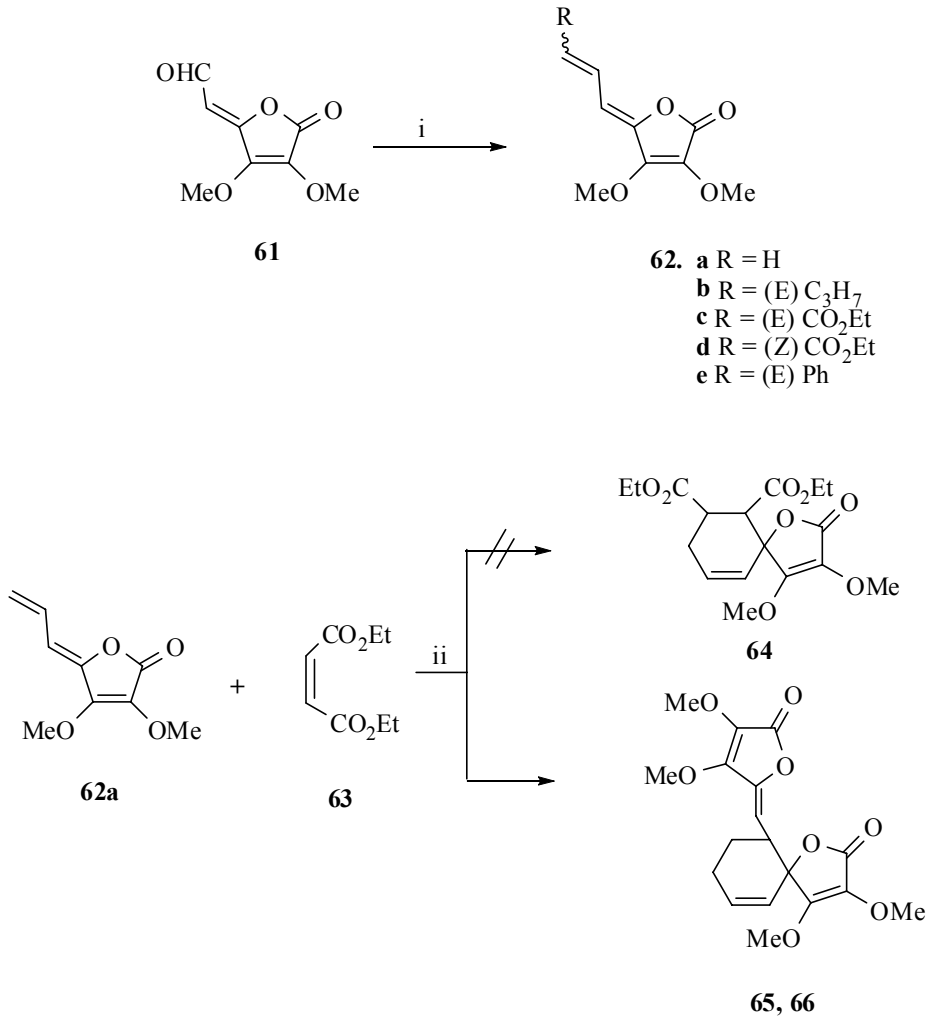
1.16 Synthesis of triene systems from L-ascorbic acid and their application: oxaspiro [4, 5] decanenones

L-Ascorbic acid (**1)** has been transformed into the (*Z*)-butenolide acetate (**59e) [**110] via a multistep process. The intermediate **59e** on acid catalyzed deacetylation results in an allylic alcohol (**60)**, which on oxidation with pyridinium chlorochromate (PCC) yielded the (*Z*)-butenolide aldehyde (**61)** in good yield (Scheme **19**) [111].



Scheme 19.

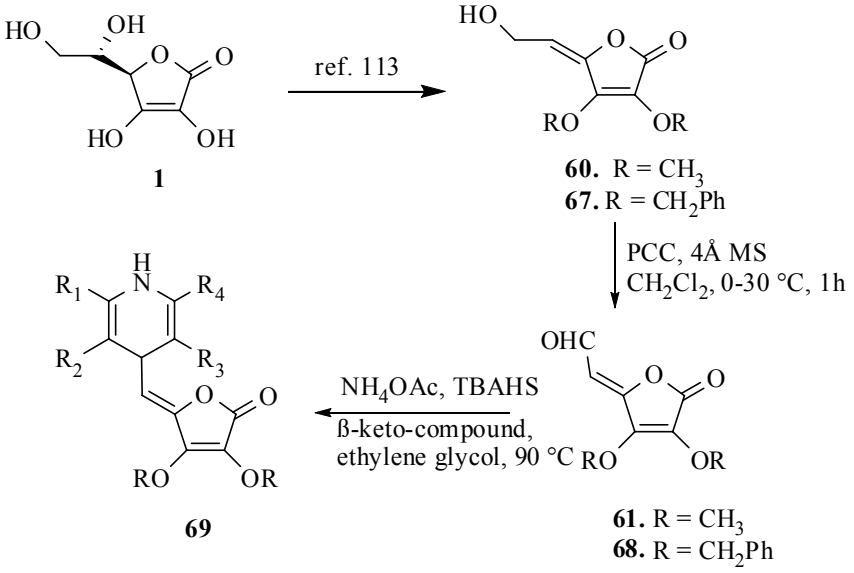
The (*Z*)-butenolidyl aldehyde (**61)** has been reacted smoothly with a variety of ylides in THF at -78 °C to give the trienes (**62a-e)** shown in Scheme **20**. The trienes in the above reactions either have the (*E*)-geometry exclusively (**62b** and **63c**) or the compounds with (*E*)-geometry were the major product. Diels Alder cycloaddition reaction **(62a)** with one equivalent of diethyl maleate **(63)** in 1,1,2,2-tetrachloroethane in an autoclave at 140 °C and 30 atm pressure for 33 h, did not give the cycloaddition product instead of two molecules of (**62a)** itself undergo Diels Alder reaction to give two oxaspiro [4,5] decanones (±) (**65)** and (±) (**66)** (Scheme **20**)**.**



Scheme 20. (i) $RCH_2PPH_3Br/BuLi/THF/ -78\ ^{\circ}C$ (ii)$Cl_2CHCHCl_2/140\ ^{\circ}C/33h$

1.17 Synthesis of 4-(butenolide-5-methylidenyl)-1,4-dihydropyridines

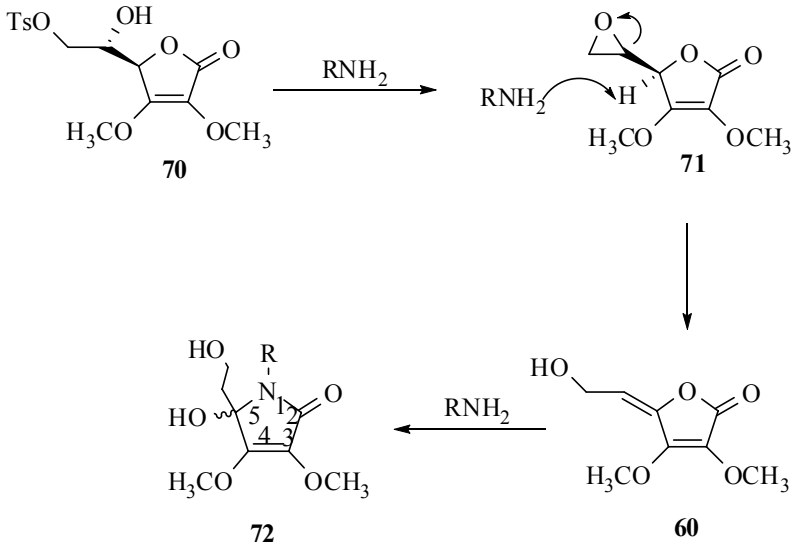
Very recently [112] few 4-(butenolide-5-methylidenyl)-1,4-dihydropyridines (**69)** were synthesized as possible antitubercular agents in our group starting from the the allylic aldehyde. L-ascorbic acid was at first converted into the allyl alcohols (**60), (67)** [113] by our modified procedure [112] which on PCC oxidation gave the respective butenolidyl aldehydes **(61**) and (**68**) respectively. These butenolidyl aldehydes on treatment with β-keto esters or ketones and ammonium acetate in the presence of tetrabutyl ammonium hydrogen sulphate in ethylene glycol yielded the respective butenolidedyl 1, 4-dihydropyridine (**69)** in good yield (Scheme **21**). The compounds have shown mild antitubercular activity against M. tuberculosis H37Rv.



Scheme 21.

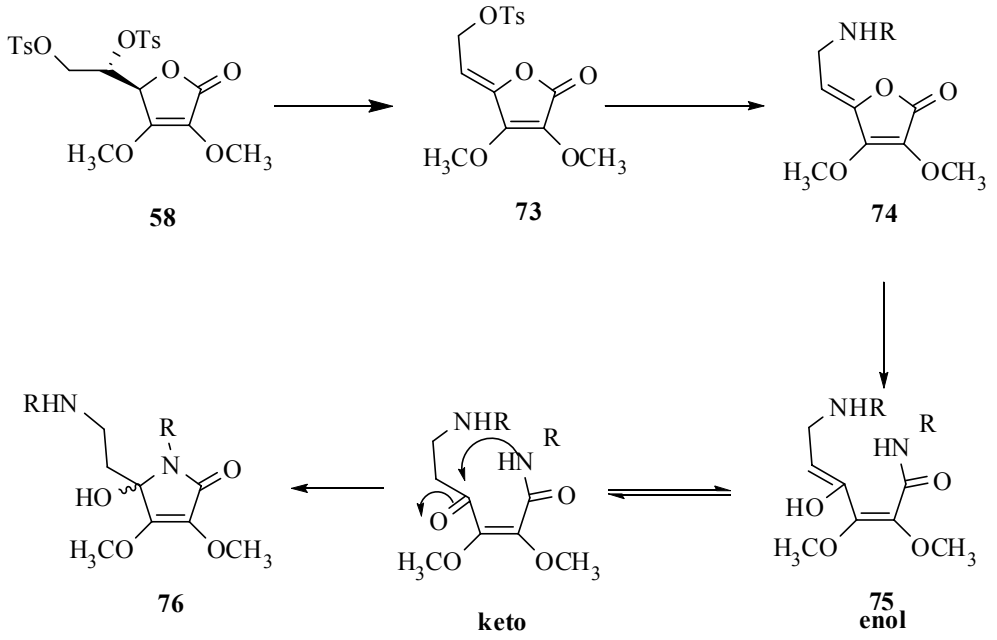
1.18 Formation of Lactams

2, 3-*bis*- *O*-methyl-6-*O*-*p*-toluenesulphonyl-L-ascorbic acid (**70)** reacted with the primary amines at room temperature to give the 1-alkyl-2,3-dimethoxy-4-hydroxy-4-(hydroxyethyl) but-3-enimide (**72)** (Scheme **22**) [114].



Scheme 22.

However, 2, 3-*O*-dimethyl-5,6-di-*O*-*p*-toluenesulphonyl-L-ascorbic acid (**58)** reacted with the primary amines to give the 1-alkyl-2,3-dimethoxy-4-hydroxy-4-[1'-(2'-aminoalkyl)ethyl]but-3-enimide (**76)** (Scheme **23**). Compounds (**58)** and (**70)** were prepared by a sequence of reactions from L-ascorbic acid [114].



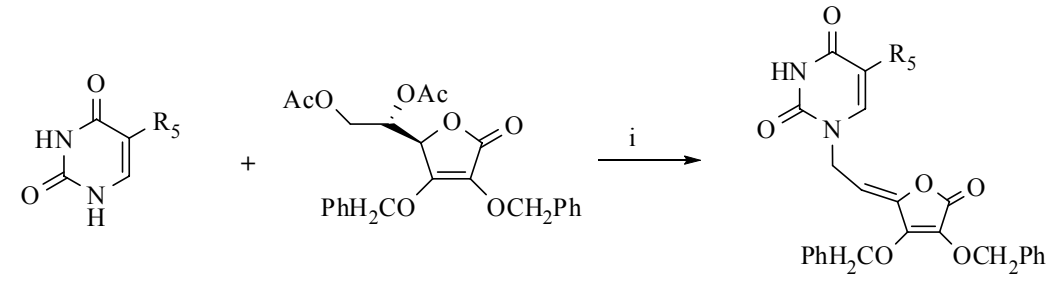
Scheme 23.

1.19 Nucleoside analogs from L-ascorbic acid

There are several reports on the synthesis and biological activities of L-ascorbic acid based nucleosides. These compounds show pronounced antitumour, antiviral and anticancer activities.

1.19.1 Novel pyrimidine and purine derivatives of L-ascorbic Acid

Raic´-Malic´ et al [115] have developed the synthesis of few novel pyrimidine derivatives (**78-83)** of 2,3-di-*O*-benzyl-4,5-didehydro-5,6-dideoxy-L-ascorbic acid by the condensation of pyrimidine bases with 5,6-diacetyl-2,3-dibenzyl-L-ascorbic acid (**77)** (Scheme 24). Similar condensation of 6-chloropurine bases with 5-acetyl-6-bromo-2,3-dibenzyl-L-ascorbic acid (ABDA **84)** resulted in both the N-9 (**85**) and N-7 (**86**) regioisomers, while the reaction of 6-(*N*-pyrrolyl)purine with ABDA afforded exclusively the N-9 isomer (**87)** (Scheme **25**).



R_5 = H, F, Cl, Br, I, CF_3

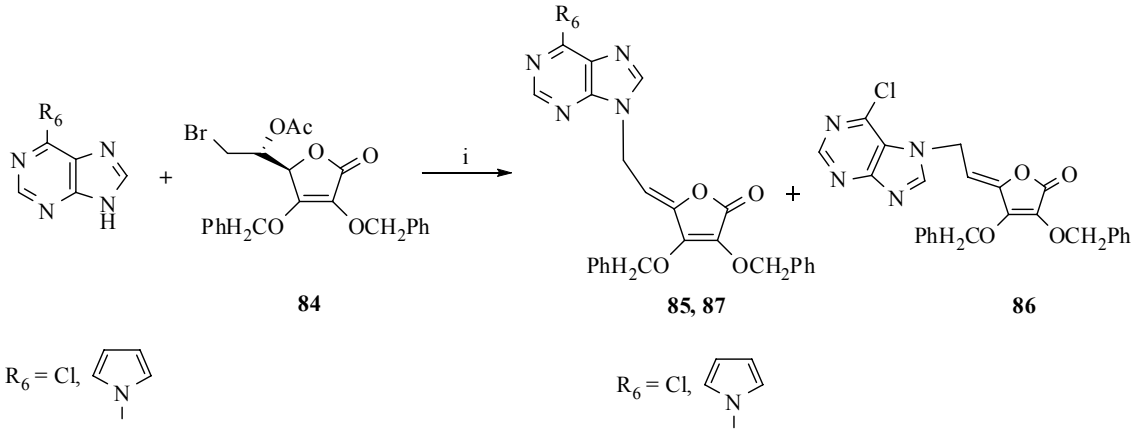
77

78-83

Scheme 24. Reagents and conditions: (i) HMDS, $(NH_4)_2SO_4$/argon atmosphere/reflux/3h; then trimethyl silyl triflate/dry acetonitrile/55-70 °C/12 h

Compounds (**78-83)** and (**85-87)** exhibited cytostatic activities against malignant cell lines: pancreatic carcinoma (MiaPaCa2), breast carcinoma (MCF7), cervical carcinoma (HeLa), laryngeal carcinoma (Hep2), murine leukemia (L1210/0), murine mammary carcinoma (FM3A), and human T-lymphocytes

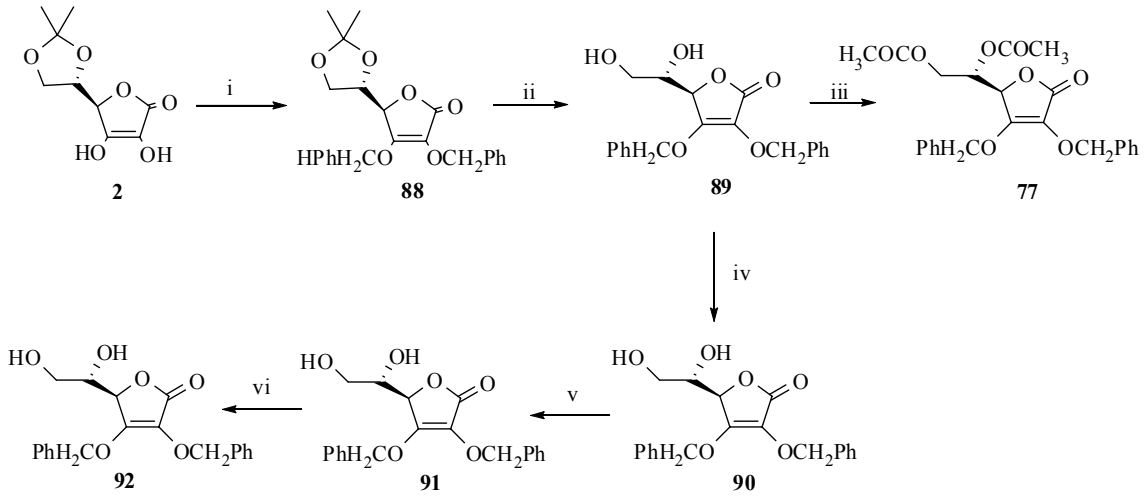
(Molt4/C8 and CEM/0), these compounds also displayed antiviral activities against varicellazoster virus (TK+VZV and TK-VZV) and cytomegalovirus (CMV). Out of the above compound (**83),** containing a trifluoromethyl-substituted uracil ring exhibited potent antitumor activity. It has been established that N-7- purine regioisomer (**86)** had greater inhibitory effects on the murine L1210/0 and human CEM/0 cell lines than the N-9 regio isomer (**85)**. Compound (**87)** with a 6- pyrroyl substituent had a selective cytostatic activity against human (Molt4/C8 and CEM/0) cell lines than murine (L1210/0, FM3A/0), human (MiaPaCa2, MCF7, HeLa, and Hep2) tumor cell lines and normal fibroblasts (Hef522). The compound (**83)** exhibited the most potent antiviral activities against TK+VZV, TK-VZV, and CMV, albeit at concentrations those were only slightly lower than the cytotoxic concentrations.



Reagents and conditions: (i) triethyl amine/dry DMF/70 °C/11 h

Scheme 25.

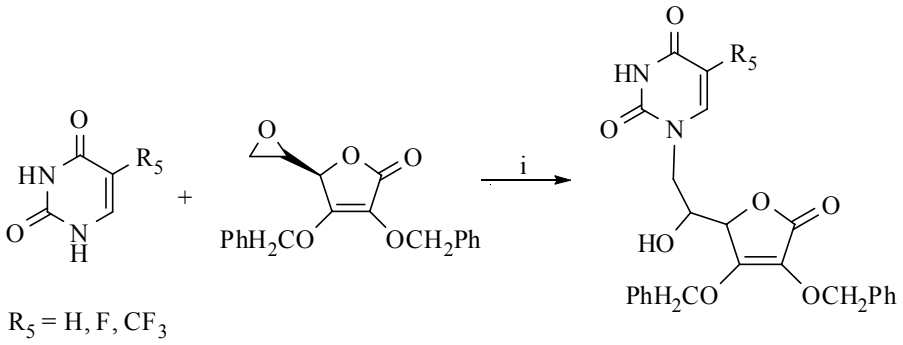
Several 2, 3-di-*O*-benzyl-6-deoxy-L-ascorbic acid derivatives of pyrimidine bases (**93-95**) were also prepared by the condensation of uracil and its 5-trifluromethyl substituted derivatives with 4-(5,6-epoxypropyl)-2, 3-*O, O*-dibenzyl-L-ascorbic acid (**92)** [116]. The key intermediate 5,6-di-*O*-acetyl-2,3-*O*,*O*-dibenzyl-L-ascorbic acid (**77)** and 4-(5,6-epoxypropyl)-2,3-di-*O*-dibenzyl-L-ascorbic acid (**92)**, were prepared from 5,6-*O*-isopropylidene-L-ascorbic acid (**2) [**117]. The benzylation of C-2 and C-3 hydroxyl groups of ascorbic acid with benzyl chloride in DMF provides an intermediate (**88)** [117,118]. Deblocking of the 5,6-*O*,*O*-protected derivative of L-ascorbic acid (**88)** with acetic acid in methanol gave 2,3-*O*,*O*-dibenzyl-L-ascorbic acid (**89) [**117]. The latter on subsequent acetylation with acetic anhydride in pyridine and CH_2Cl_2 gave **87,** in an analogous procedure for the preparation of 5-*O*-acetyl-6-bromo-6-deoxy-2,3-*O*,*O*-dibenzyl-L-ascorbic acid [118]. 2,3-*O*,*O*-Dibenzyl-6-*O*-tosyl-L-ascorbic acid (**90)** was obtained by tosylation of the 6-hydroxy group in **89** using toluene-4-sulfonyl chloride in pyridine [117]. Bromination of **90** with sodium bromide in acetone gave 6-bromo-2,3-*O*,*O*-dibenzyl-L-ascorbic acid (**91)** [118]. The later on reaction with sodium carbonate in acetonitrile gave 4-(5,6-epoxypropyl)-2,3-*O*,*O*-dibenzyl-L-ascorbic acid (**92)**.



Reagents and conditions: (i) benzyl chloride, K_2CO_3/dry DMF; (ii) 50% acetic acid/MeOH/100 °C/5 h; (iii) acetic anhydride/pyridine/CH_2Cl_2/-10-24°C/2h;(iv)toluene-4-sulfonyl chloride/CH_2Cl_2/ pyridine/0-24 °C; (v) NaBr/acetone/130 °C/7 h; (vi) Na_2CO_3/acetonitrile/rt/1 h.

Scheme 26.

Pyrimidine derivatives of 2,3-*O*,-dibenzyl-6-deoxy-L-ascorbic acid (**93-95)** were prepared by silylation of the uracil and its 5-substituted derivatives with 1,1,1,3,3,3-hexamethyldisilazane and subsequent condensation of the intermediates, thus obtained, with ascorbic acid derivative (**92)** (Scheme **27**).

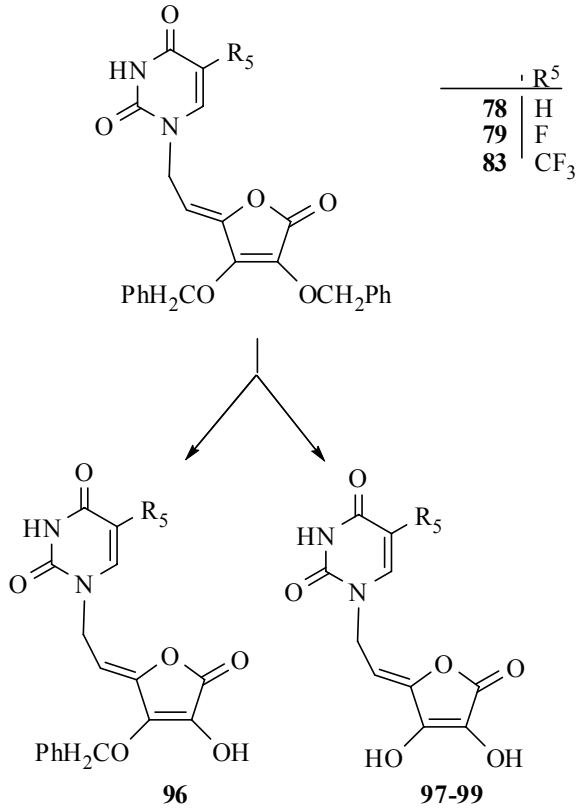


Reagents and conditions: (i) HMDS, $(NH4)_2SO_4$/argon atmosphere/reflux/3h, then trimethyl silyl triflate/dry acetonitrile/55-70 °C/12 h.

Scheme 27.

Coupling of (**77)** with uracil and its 5-substituted derivatives gave pyrimidine derivatives of 2,3-*O*,*O*-dibenzyl-4,5-didehydro-5,6-dideoxy-L-ascorbic acid (**78-79), (83)**; (Scheme **24**) [115]. Debenzylation of compounds (**78-79)** and **(83)** with boron trichloride in CH_2Cl_2 led to the formation of nucleoside analogues (**96-94)** (Scheme **28**) [119, 120]. Of all the compounds in the series, compound (**98)** containing

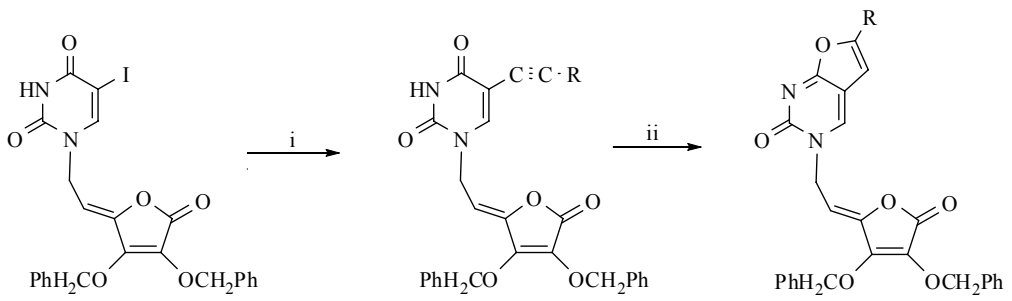
a 5-fluorosubstituted uracil ring showed the most significant antitumor activities against murine leukemia L1210/0 (IC_{50} = 1.4 μg/mL), murine mammary carcinoma FM3A/0 (IC_{50} = 0.78 μg /mL), and, to a lesser extent, human T-lymphocyte cells Molt4/C8 (IC_{50} = 31.8 μg /mL) and CEM/0 cell lines (IC_{50} = 20.9 μg /mL).



Reagents and conditions: (i) BCl_3, CH_2Cl_2/-78 °C/2h.

Scheme 28.

Very recently Gazivoda et al [121] synthesized a series of novel C-5 alkynyl substituted pyrimidines (**100-110**) and furo[2,3-d]pyrimidine derivatives (**111-121**) of L-ascorbic acid by coupling of 5-iodouracil-4',5'-didehydro-5',6'-dideoxy-L-ascorbic acid with terminal alkynes under the Sonogashira cross-coupling conditions. A number of alkynyl-2',3'-di-*O*-benzyl-4',5'-didehydro-5',6'-dideoxy-L-ascorbic acids (IUAA) were prepared by Pd (0) catalyzed reaction condition [122-127]. The 6-alkyl furo[2, 3-d]pyrimidine-2-one L-ascorbic acid derivatives (**111-121**) could be prepared by copper (I)-promoted in *situ* cyclization of alkynyl uracil derivatives of ascorbic acid (**100-110**) (Scheme **29**) [124, 128].



82 **100-110** **111-121**

Reagents and conditions: (i) R-C≡CH, *i*Pr$_2$EtN, (PPh$_3$)$_4$Pd, CuI, DMF, rt; (ii) Et$_3$N, CuI, 60 °C

R	100, 111	101, 112	102, 113	103, 114	104, 115	105, 116
	-(CH$_2$)$_3$CH$_3$	-(CH$_2$)$_4$CH$_3$	-(CH$_2$)$_5$CH$_3$	-(CH$_2$)$_7$CH$_3$	—CH(OH)(CH$_2$)$_4$CH$_3$	—(H$_2$C)$_3$C≡CH

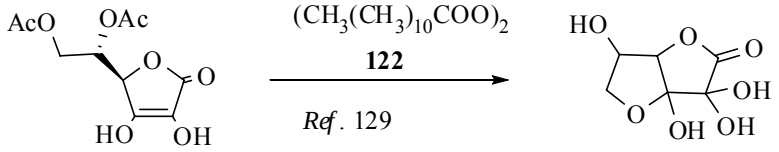
R	106, 117	107, 118	108, 119	109, 120	110, 121
	—(CH$_2$)$_2$—	—Br	—CH$_3$	—(CH$_2$)$_3$CH$_3$	—(CH$_2$)$_4$CH$_3$

Scheme 29.

The synthesized compounds were evaluated for their cytostatic and antiviral activities. The octynyl-substituted uracil derivative of L-ascorbic acid (**102**) exhibited the most pronounced cytostatic activities against all the experimental tumor cell lines (IC_{50} = 2-12 μM). Pyrimidine derivatives of L-ascorbic acid containing *p*-substituted phenylacetylene groups (**107-110**) possess (IC_{50} = 3-37 μM) towards all the experimental tumor cell lines. Among the bicyclic series of compounds, 6-butyl furo[2, 3-*d*]pyrimidine derivative (**111**) and 6-*p*-bromophenyl furo[2,3-*d*]pyrimidine derivative (**118**) showed the best cytostatic activity (IC_{50} = 4.5-20 μM), particularly against malignant leukemia (L1210) and T-lymphocyte (Molt4/C8 and CEM) cells. Compounds (**102)** and (**108)** showed specific albeit moderate activity against cytomegalovirus (CMV, Davis strain), with EC_{50} = 1.8 and 3.8 μM, respectively, for compounds (**102** and **108**) at a ~5-fold lower to cytotoxic concentration. Another synthesis for novel C-5 aryl, alkenyl, and alkynyl substituted uracil derivatives of L-ascorbic acid was developed by Gozivoda et al. [129]. The compounds were evaluated for their cytostatic and antiviral activity.

1.20. Redox reaction of organic peroxide with L-ascorbic acid

L-ascorbic acid (**1)** reacts spontaneously with dilauroyl peroxide (**122)** to produce dehydro ascorbic acid (**123)**, CO_2, lauric acid and undecane [129] (Scheme **30**).



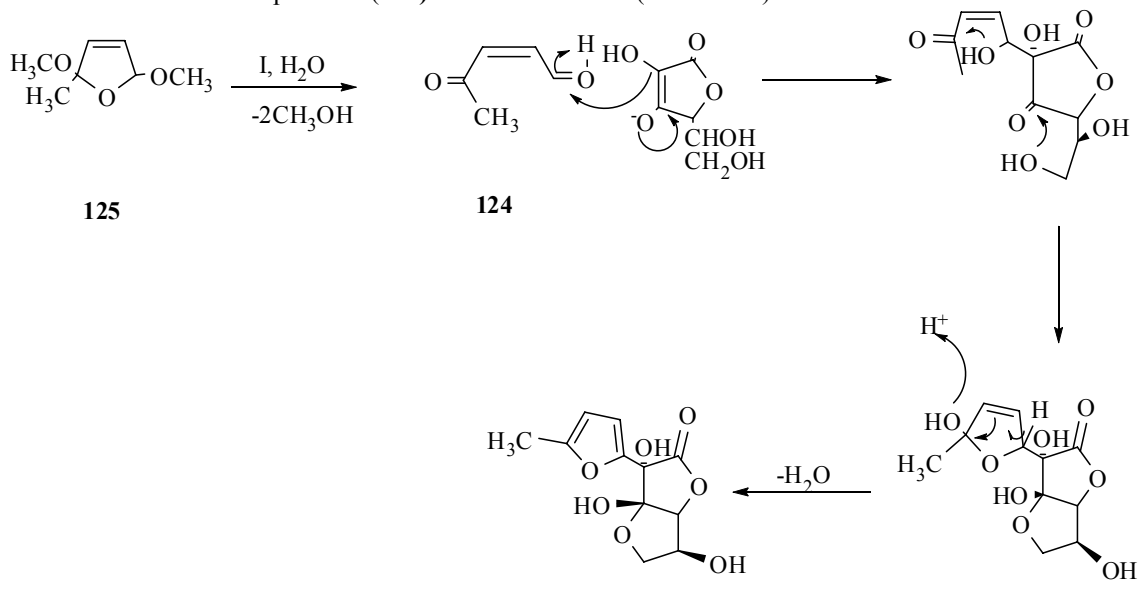
1 **123**

Scheme 30.

The reaction between (**1)** and (**122)** was conveniently performed in 85/15 (V/V) isopropyl alcohol under a nitrogen atmosphere. A constant pH was maintained by a phosphate buffer. The stoichiometry of the reactants were determined by iodometry. The products were dehydroascorbic acid (**123)**, CO_2, and undecane.

1.21 Unusual molecular complexes from L-ascorbic acid

Certain unusual molecular complexes have been prepared using L-ascorbic acid as starting material. 2-Methyl-2,5-dimethoxy-2,5-dihydrofuran (**125) ,** an acyclic acetal *cis*-3-acetyl acrolein (**124)** reacts with L-ascorbic acid (**1)** in aqueous solution to give amorphous 2-(5-methyl-2-furyl)-3-keto-L-gulonolactone-3,6-hemiketal (**126)** [131]. The reaction mechanism most likely involves *cis*-3-acetyl acrolein *i.e.* 4-keto-*cis*-2-pentenal (**124)** as an intermediate (Scheme **30**).

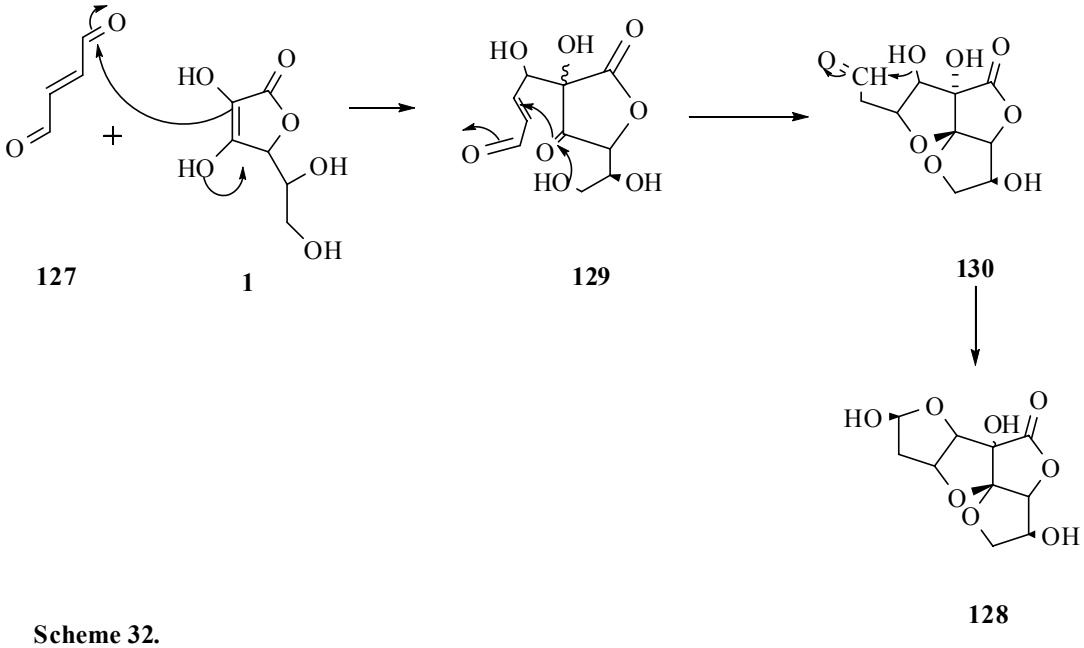


125 **124** **126**

Scheme 31.

1.22 Reaction of L-ascorbic acid with *cis* and *trans* olefinic 1,4-dicarbonyl compounds

L-ascorbic acid (**1)** reacts with fumaraldehyde (**127)** to give 2-(1', 2'-dihydroxy-4'-oxobutyl)-3-keto-2',3-anhydro-L-gulonolactone-1',4'-cyclohemiacetal-3,6-cycloheketal (**128)** [132]. The reaction mechanism (Scheme 32) involves an acid-catalyzed addition of the ascorbic acid (**1)** to the carbonyl carbon of fumaraldehyde to give an intermediate (**129)**. This is followed by a Michael addition of the C-3 oxygen at the β-carbon of the α,β-unsaturated hydroxybutenal moiety, attached to C-2 in the compound (**129)**. Synchronous hemiketal ring closure between C-6 hydroxyl and C-3 of the ascorbate skeleton leads to an intermediate (**130)** (Scheme **31**). Finally, hemiacetal formation between the two, originally terminal, carbons of the fumaraldehyde moiety concludes the process to give compound **128**.



127 **1** **129** **130** **128**

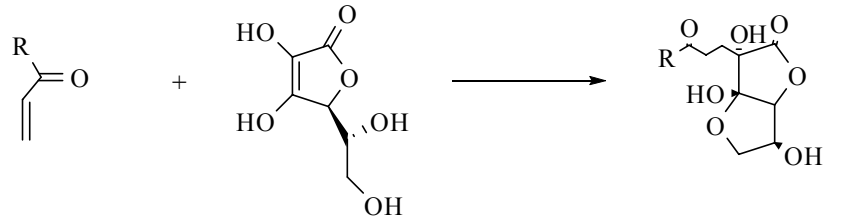
Scheme 32.

1.23 L-Ascorbic Acid as a Michael Donor

L-ascorbic acid undergoes Michael reaction with α,β-unsaturated aldehydes, ketones, nitriles and alicyclic enones to give a variety of organic compounds of great biological significance. Selected reactions are described in the succeeding sections.

1.23.1 Michael reaction with α,β-unsaturated aldehydes and ketones

L-ascorbic acid (**1**) undergoes Michael reaction with acrolein (**131a**) and methyl vinyl ketone (**131b**) to give C-2 alkylated derivatives of L-ascorbic acid (**132a**) and (**132b**) (Scheme **33**) [132(a-b)].



131a, R = H
131b, R = CH_3

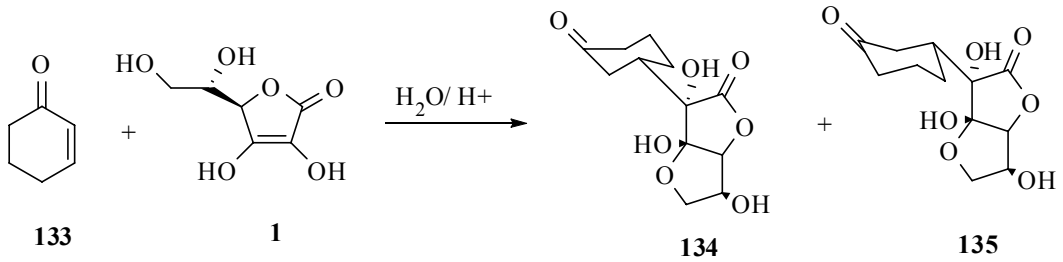
1

132a, R = H
132b, R = CH_3

Scheme 33.

1.23.2 Michael reaction with alicyclic enones

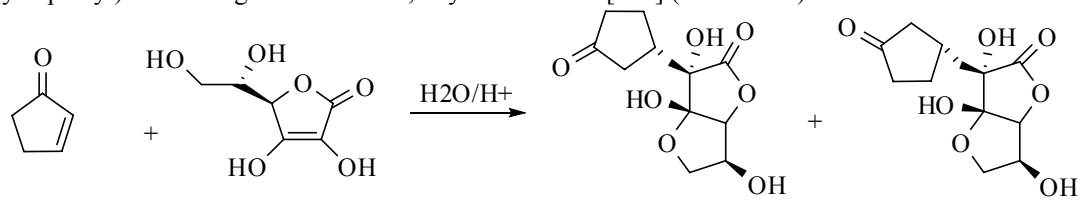
Michael addition of L-ascorbic acid and 2-cyclohexen-1-one **133** leads to the formation of two C-3' epimers (**134**) and (**135**) of 2-(1'-keto-3'-cyclohexyl)-3-keto-L-gulonolactone-3,6-cyclohemiketal [133] (Scheme **34**).



133 **1** **134** **135**

Scheme 34.

Similarly reaction of (**1**) and 2-cyclopentene-1-one (**136**) gives two epimers (**137**) and (**138**) of 2-(1'-keto-3'-cyclopentyl)-3-keto-L-gulonolactone-3,6-cyclohemiketal [133] (Scheme **35**).

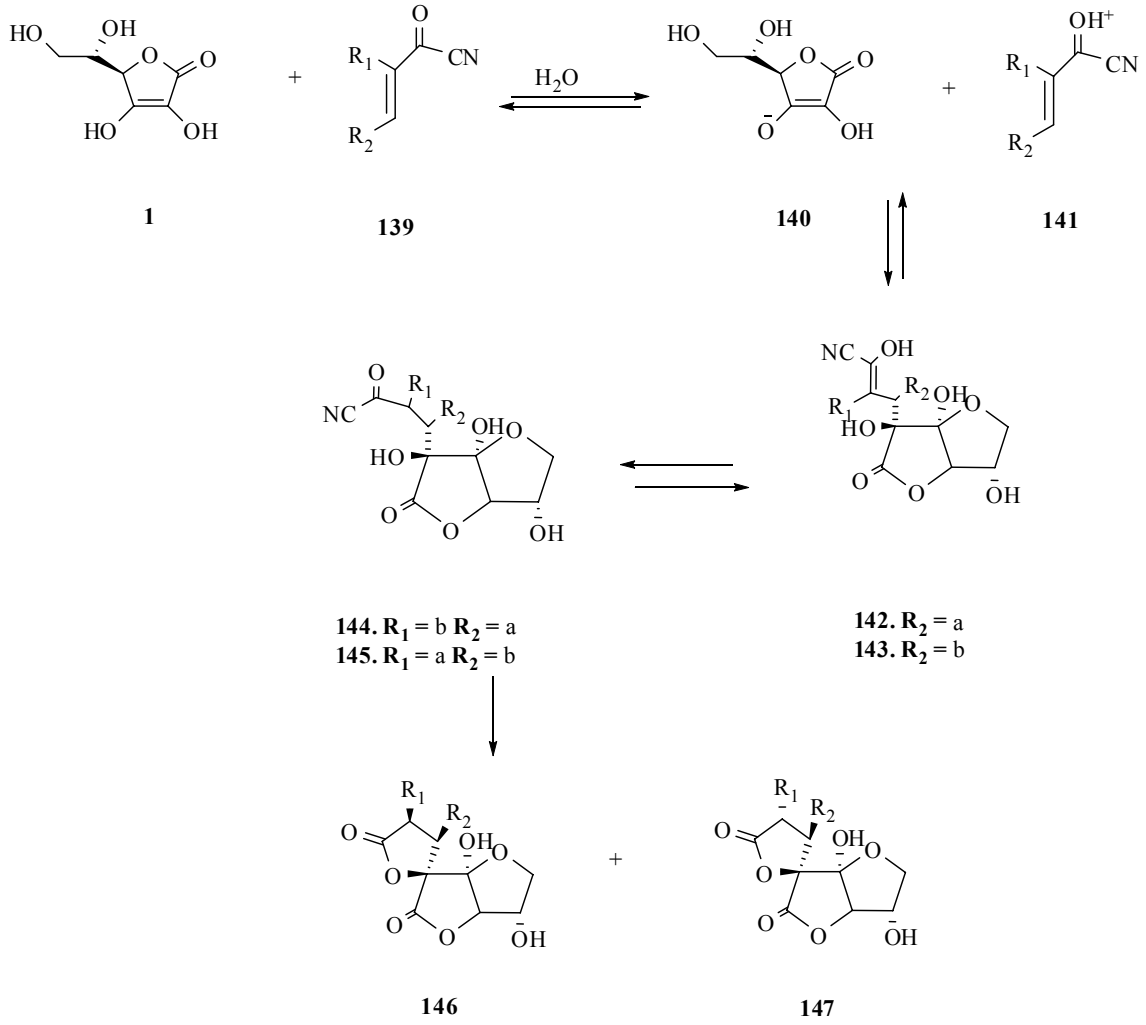


136 **1** **137** **138**

Scheme 35.

1.23.3 Michael reaction with tigolyl cyanide

The Michael addition of tigolyl cyanide (**139**) [134] is initiated by ascorbic acid involving protonation of tigolyl cyanide followed by conjugate addition of ascorbate anion to give α, and β- enols (**142** and **143**), which tautomerize to the respective acyl cyanides (**144** and **145**) respectively. The latter on ring closure leads to tricyclic products **146** and **147.** During ring closure the major product, piptosidin (**146**) is formed due to steric encumberment of C-3 methyl and C-5 hydroxyl in (**143**) (Scheme **36**).



Scheme 36.

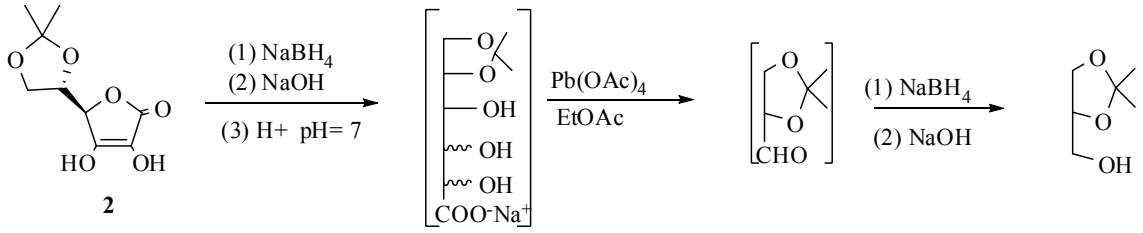
.

1.24 L-Ascorbic acid as a Chiral Synthon

Since L-ascorbic acid possesses two chiral and several pro-chiral centers, significant work has been done on its chiral chemistry involving its application in various asymmetric synthesis leading to access several commercially unavailable and highly functionalized chiral synthons. Several of such chiral synthons including bicyclic alkylidene-dimethoxy butenolides, glycerol acetonides, threitols, erythreitol and a series of hydroxyl lactone have been prepared starting with L-ascorbic acid [135-152]. A few of them are described briefly below.

1.24.1 Synthesis of (*R*)-Glycerol acetonide

Jung et al. [135] have synthesized (*R*)-glyceroyl acetonide [153-155] from L-ascorbic acid as shown in (Scheme **37**). Treatment of 5,6-*O*-isopropylidene ascorbic acid (**2**) with 1 eq. of sodium borohydride presumably reduces ene-diol functionality followed by the cleavage of the borate esters and the lactone with excess of sodium hydroxide. The neutralization of reaction mixture to pH 7 produces acetonide carboxylate (**148**). The latter on oxidation with 3.5 eq. of $Pb(OAc)_4$ led to the cleavage of all the glycol bonds and produces (*S*)-glyceraldehyde acetonide (**149**) in solution. Due to its instability **149** was immediately reduced with excess of sodium borohydride to give (*R*)-glycerol acetonide (**150**) in good yield.

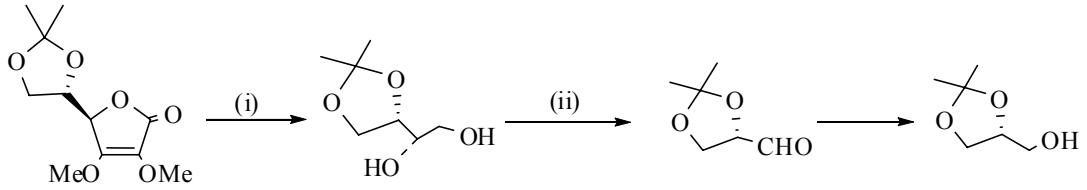


2 **148** **149** **150**

Scheme 37.

Marco et al. [146] have described the synthesis of the most useful 1,2-*O*-isopropylidene-L-threitol (**149a**) [156], L-(*S*)-glyceraldehyde (**149**) and L-(*R*)-glycerol acetonides (**150**) [157] starting from L-ascorbic acid successfully as shown in Scheme **38**.

Ozonolysis of 5,6- *O*-isopropylidene ascorbic acid **1** followed by reduction with $LiAlH_4$ led to formation of a chiral diol. The latter on lead tetraacetate oxidation gives the intermediate aldehyde (**149**), which on reduction with $NaBH_4$ gives the required product (**150**).

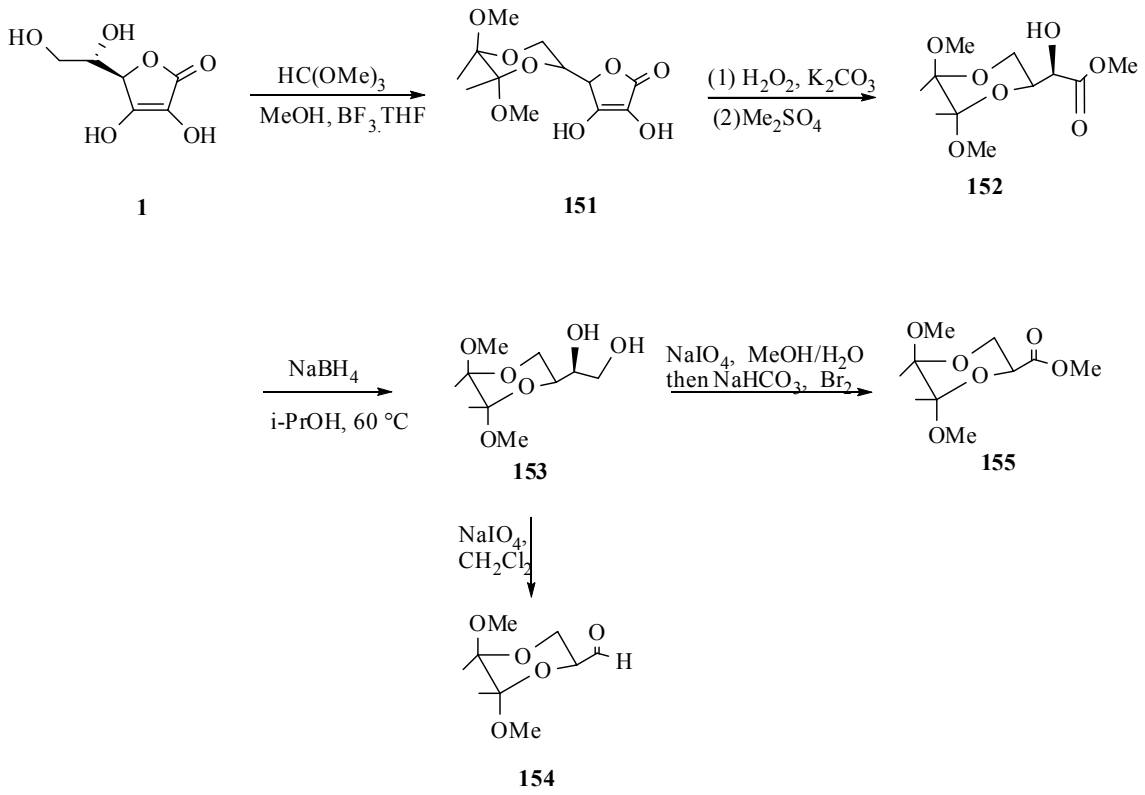


57 **149 a** **149** **150**

Reagents and conditios: (i) O_3, CH_2Cl_2, -78 °C, 15 min; then evaporation, LAH, THF, 0 °C - r.t, overnight (ii) $Pb(OAc)_4$, CH_2Cl_2, K_2CO_3 (iii) $NaBH_4$, EtOH

Scheme 38.

1.24.2 Synthesis of butane-1,2-diacetal protected glyceraldehyde: Butane-1,2-diacetal glyceralehyde has been prepared from L-ascorbic acid as shown below in scheme **39**.

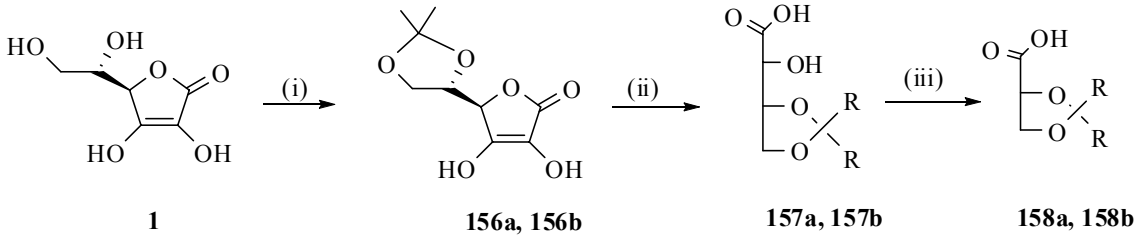


Scheme 39.

Ascorbic acid on reaction of butan 2,3-dione and trimethyl orthoformate in BF_3.THF led to formation of 5,6-*O*-protected ascorbic acid derivative (**151)** which on oxidation with hydrogen peroxide in presence of K_2CO_3 followed by esterification with dimethyl sulphate led to the formation of an intermediate (**152)** [158,137,140]. The later on reduction with sodium borohydride resulted in a diol (**153**), which was oxidized with $NaIO_4$ to afford butane-1,2-diacetal protected glyceraldehyde (**154)** [159]. Alternatively, oxidative cleavage of the crude diol (**153)** with sodium metaperiodate in methanol-water followed by bromine oxidation of the methyl hemiacetal [160] gave the ester (**155)** (Scheme **39**).

1.24.3 Synthesis of L-glyceric acid

Emmons et al. [145] described a facile route towards the synthesis of optically pure L-glyceric acids starting from L-ascorbic acid (**1**). The key step is a ruthenium catalyzed oxidative cleavage of the α-hydroxy acid (**157a** and **157b**) as shown in scheme **40**.



1 **156a, 156b** **157a, 157b** **158a, 158b**

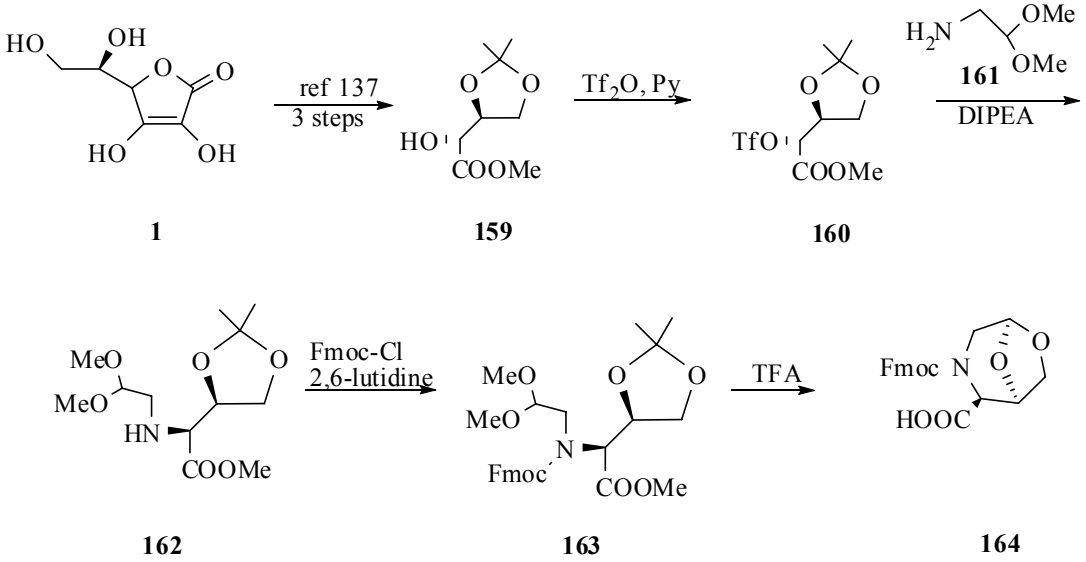
a : R = CH_3
b : R = -$(CH_2)_5$-

Reagents and condition: (i) (a) 2,2-dimethoxy propane, acetone, $SnCl_2$ (cat.), reflux, 5 min.
(b) 1,1-dimethoxycyclohexane, EtOAc, $SnCl_2$ (cat.), reflux, 30 min.
(ii) H_2O_2, $CaCO_3$; (iii)NaOCl, $RuCl_3$ (cat.), pH = 8, RT, 30-60 min.

Scheme 40.

1.24.4 Synthesis of a Bicyclic Proline Analogue

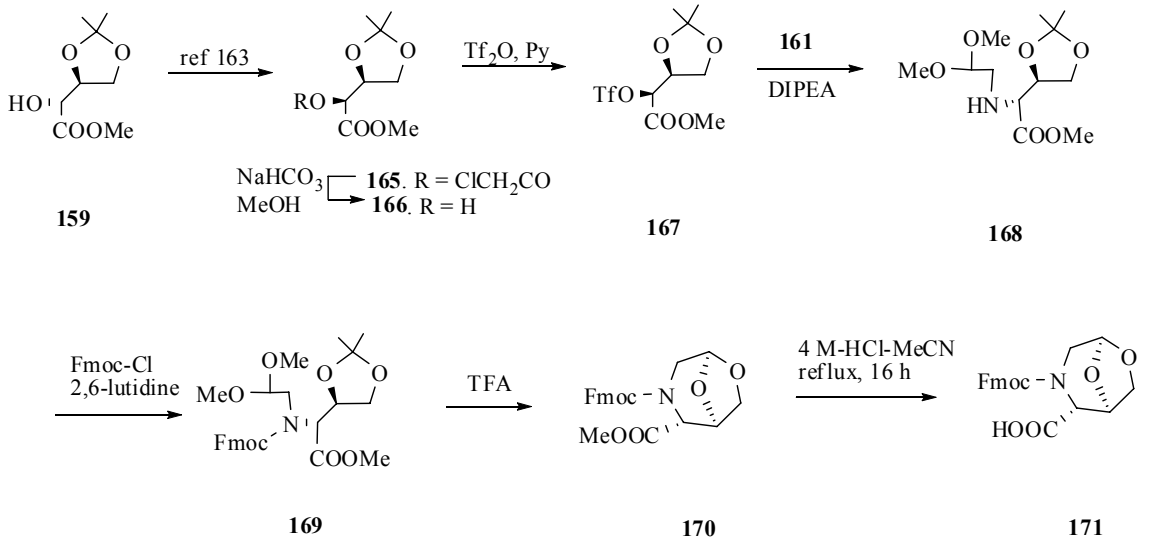
Trabocchi et al. [161] synthesized a bicyclic α-amino acid with endo carboxyl (**164)** and exo carboxyl groups (**171)** starting from L-ascorbic acid. The latter was sequentially converted to the triflate (**160)**, which on reaction with amino acetaldehyde dimethyl acetal (**161)** gave the intermediate (**162)** (Scheme **40**). The latter on F-moc protection of -(NH)- group gave an urethane derivative (**163)** which on acid catalyzed cyclization [162] afforded the bicyclic α-amino acid with an endo carboxyl group (**164)**.



162 **163** **164**

Scheme 41.

Formal inversion of the configuration at the C-2 stereocenter in the compound (**159)** gives (**171)**, the corresponding diastereomer of (**164)** carrying the carboxyl group at 2-exo position as shown in (scheme **42**).



Scheme 42.

Conclusion: L-ascorbic acid, commonly known as vitamin-C occurs in many natural flora and fauna. Its biosynthesis in plants has been studied in great detail to give different possible pathways. This small molecule apart from being used as vitamin exhibit potent antioxidant activity against several oxidants, the antioxidant activity of the molecule has been exploited in developing several ailments for human beings. Further, its application in the synthesis of large number of chemotherapeutic agents such as antileukemic, anticancer, immunomodulatory, antiviral and antibacterial agents has also been elucidated. Importance of chiral synthons in organic and medicinal chemistry is of vital importance. This review illustrates the application of L-ascorbic acid to access chiral auxiliaries of tremendous importance in bioorganic chemistry. The scope of this polyhydroxylated tetranolactone in bioorganic and biochemistry is wide and posses tremendous potential. The scope of this small organic molecule in development of new chemistry, potent chemotherapeutics and important materials is very wide and the studies carried out so far is only small fraction of the scope left.

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Table 1. Physical properties of L-ascorbic acid

Property	Comments
Appearance	White, odorless, crystalline solid with sharp acidic state
Formula/ molar mass	$C_6H_8O_6$/ 176.13 g/mol
Melting point	190-192 °C
Density	1.65 g/cm^3
pH	~3 (5 mg/ml); ~2 (50 mg/ml)
pK1	4.17
pK2	11.57
Redox Potential	First stage: E1O + 0.166 V(pH 4)
Spectral properties UV pH2	Emax (1%. 1cm), 695 at 245 nm (undissociated form)
Spectral properties UV pH6.4	Emax (1%. 1cm), 940 at 265 nm (monodissociated form)
Optical rotation	$[\alpha]_D$ at 25 °C = +20.5° to 21.5° (C = 1 in water)

	$[\alpha]_D$ at 23 °C = +48° (C = 1 in methanol)
Solubility (g/ml)	
Water	0.33
95% Ethanol	0.033
Propylene glycol	0.05
Glycerol	0.01
Fats and oil Solvents: ether, chloroform, benzene, petroleum ether etc.	insoluble