




Review

Medicinally Significant Enantiopure Compounds from Garcinia Acid Isolated from *Garcinia gummi-gutta*

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Abstract: *Garcinia gummi-gutta*, commonly known as *Garcinia cambogia* (syn.), is a popular traditional herbal medicine known for its role in treating obesity, and has been incorporated into several nutraceuticals globally for this purpose. The fruit rind is also used as a food preservative and a condiment because of its high content of hydroxycitric acid, which imparts a sharp, sour flavour. This review highlights the major bioactive compounds present in the tree *Garcinia gummi-gutta*, with particular emphasis on (2S, 3S)-tetrahydro-3-hydroxy-5-oxo-2,3-furan dicarboxylic acid, commonly referred to as garcinia acid. This acid can be isolated in large amounts through a simple procedure. Additionally, it explores the synthetic transformations of garcinia acid into biologically potent and functionally useful enantiopure compounds, a relatively under-documented area in the literature. This acid, with its six-carbon skeleton, a γ -butyrolactone moiety, and two chiral centres bearing chemically amenable functional groups, offers a versatile framework as a chiron for the construction of diverse molecules of both natural and synthetic origin. The synthesis of chiral 3-substituted and 3,4-disubstituted pyrrolidine-2,5-diones, analogues of the Quararibea metabolite—a chiral enolic- γ -lactone; the concave bislactone skeletons of fungal metabolites (+)-avenaciolide and (−)-canadensolide; the structural skeletons of the furo[2,3-*b*]furanol part of the anti-HIV drug Darunavir; (−)-tetrahydropyrrolo[2,1-*a*]isoquinolinones, an analogue of (−)-crispine A; (−)-hexahydroindolizino[8,7-*b*]indolones, an analogue of the naturally occurring (−)-harmicine; and furo[2,3-*b*]pyrroles are presented here.

Keywords: garcinia acid; chiral enolic lactone; furo[2,3-*b*]furanol; (−)-crispine A; (−)-harmicine; bislactone



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1. Introduction

Natural products comprise secondary metabolites produced by both terrestrial and marine organisms, including plants, animals, fungi, and bacteria [1–3]. From a medical perspective, the majority of these natural products provide a rich source of bioactive agents including anti-tumour, immunosuppressive, anti-insecticidal, anti-bacterial, as well as various clinically significant activities. This traditional knowledge about the biological and pharmacological activities of these compounds has significantly influenced modern scientific endeavours in both synthetic and semi-synthetic drug discovery and development efforts. Plant-derived molecules continue to be indispensable in healthcare; with their utilization across diverse cultures were extensively documented [4,5]. According to the World Health Organization (WHO), approximately 65% of the global population relies predominantly on plant-derived traditional medicines for primary healthcare. These plant products also play a significant, albeit more indirect, role in healthcare systems in developed countries [6]. These secondary metabolites can also serve as starting materials

for synthesizing structurally and stereochemically related molecules that are beneficial to humanity.

Garcinia gummi-gutta (synonym of *Garcinia cambogia* Desr.), is a member of the Clusiaceae family and is closely related to several other *Garcinia* species [7]. More commonly known as Malabar tamarind, it is an economically significant spice tree valued for its sun-dried, smoked rind, which imparts a tart flavour. This spice is widely used as a flavouring condiment in various dishes. The small fruit resembles a pumpkin and is heavily marketed as a weight loss supplement.

2. Traditional Uses of *Garcinia gummi-gutta* Extracts

Ancient Indian tribes utilized various parts of the *Garcinia gummi-gutta* plant for diverse medicinal purposes, as documented in Sanskrit texts foundational to Indian traditional medicine. *Charaka samhita*, a key text in Ayurveda, mentions the dried fruit of the tree combined with curd as a remedy for piles and haemorrhoids. Vagbhata's *Ashtanga Hridaya*, which frequently references the earlier classical work *Charakasamhitha*, further discusses the medicinal properties of the fruit, highlighting it as an excellent remedy for gastrointestinal problems. *Vaidyamanorama*, another classical text of Ayurveda also discusses the medicinal properties of the fruit as the remedy for gulma disease. The text presents an ayurvedic formulation in which the dried fruit is mixed with rock salt as a decoction to treat this condition. Traditional tribes from Kerala use the fruit extract as a remedy for uterus related issues. Typically, after 60 days of delivery, women in the tribe consume the fruit extract once a day as part of their traditional healing practices [6]. Additionally, the plant extract is considered an antidote for venomous bites, including cobra bites and scorpion stings, and is known for its wound-healing properties. It can also be included in the diet of patients undergoing treatment for skin conditions. In this respect, it contrasts with conventional tamarind, which is typically avoided in the dietary regimen of sick patients. Various formulations derived from the plant have been traditionally used in many Asian countries to treat a range of ailments, including constipation, rheumatism, oedema, irregular menstruation, and intestinal parasites. These remedies reflect the plant's long-standing role in traditional medicine across the region [8–11]. It was also used in veterinary medicine to address mouth diseases in cattle [7], and served as a tonic for heart-related issues [7,10].

The fruit of the tree is renowned for its acidic flavour and has been extensively used in preparing a wide range of dishes. The fruit is also used in curing fish, a practice famously known as Colombo fish curing. Extensive culinary research and experimentation have demonstrated that the fruit rind and its extracts play a significant role as a curry condiment in India, adding a tangy element to various traditional recipes.

3. Plant Constituents of *Garcinia gummi-gutta*

The sour taste of the fruit is attributed to the presence of high amount of (–)-hydroxycitric acid [(–)-HCA, **1a**]. Earlier reports suggested that the fruit contains additional organic acids such as tartaric and citric acids. However, modern analytical research established that **1a** and its lactone form garcinia acid (**1**) are the major organic acids present in the fruit [12].

The major chemical constituents isolated from different parts of the plant includes, the organic acids such as **1a**, the lactone **1**, benzophenones and polyisoprenylated benzophenones, such as garcinol (**2**), isogarcinol (**3**), and guttiferones (**4–6**), [7,8,10,11], as well as xanthone-type compounds like garbogirol (**7**), rheediaxanthone A (**8**), oxy-guttiferone I (**9**), oxy-guttiferone K (**10**), oxy-guttiferone M (**11**), and oxy-guttiferone K2 (**12**) [12–14]. The major compounds, **1** to **12**, isolated from different parts of the plant are presented in Table 1.

Table 1. Chemical compounds isolated from different parts of the plant *Garcinia gummi-gutta*.

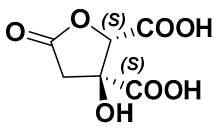
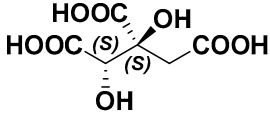
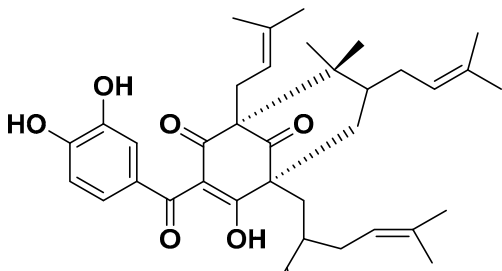
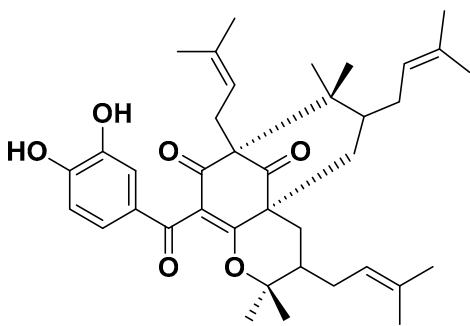
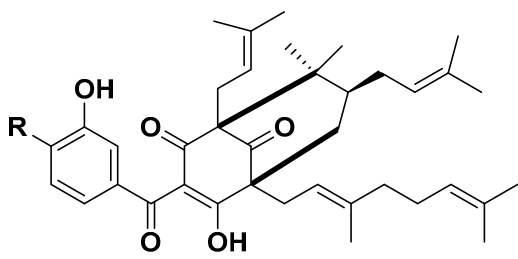
Structure & Name	Plant Part	Biological Activity
Major organic acids		
 1. Garcinia acid [(−)-Hydroxycitric acid lactone]	Isolated from the fruit [7,11]	Inhibit the enzyme ATP citrate lyase
 1a.(−)-Hydroxycitric acid		
Polyisoprenylated Benzophenones		
 2 Garcinol	Isolated from the peel [7,11]	Anti-inflammatory, antioxidant, anticancer, antiparasitic, action in nervous system
 3 Isogarcinol (Cambogin)	Isolated from the peel [7,11]	Anti-inflammatory, antioxidant, anticancer, antiparasitic, action in nervous system
 4 Guttiferone I, [R = OH] Guttiferone N, [R = H]	Isolated from the fruit [7,11]	Unknown

Table 1. Cont.

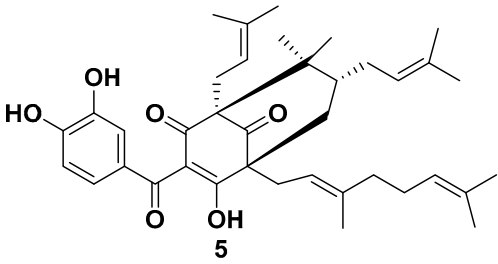
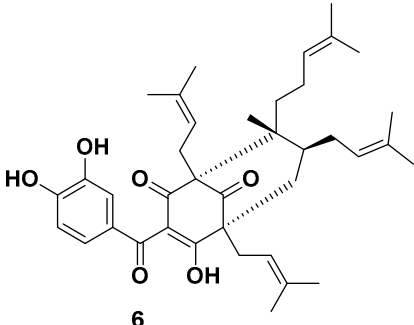
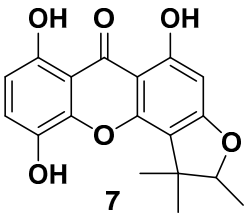
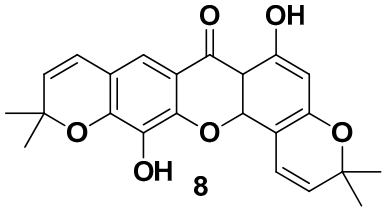
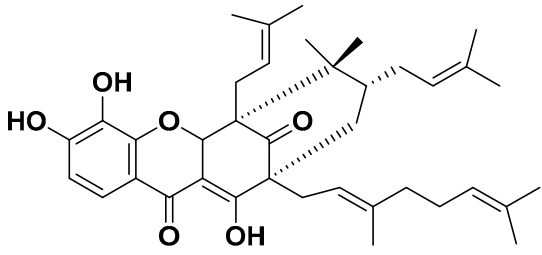
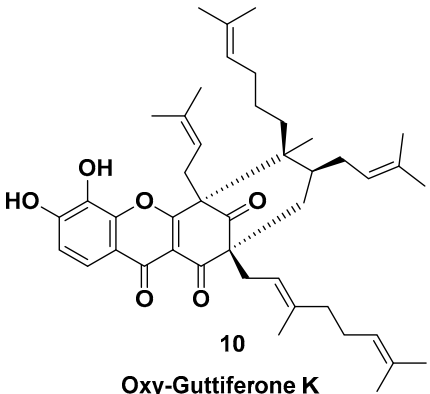
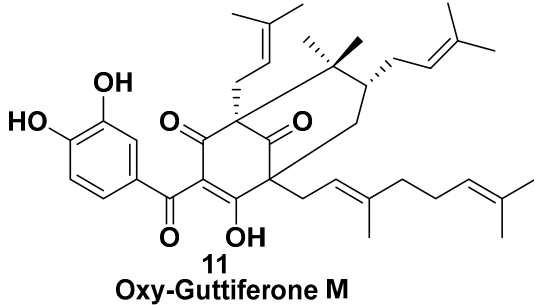
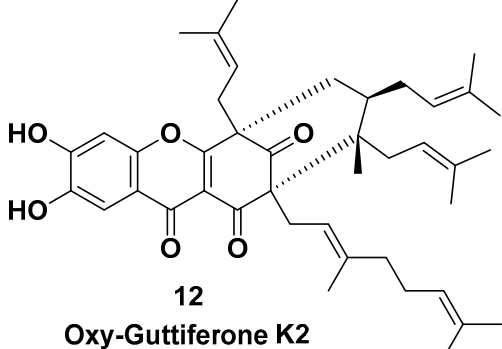
Structure & Name	Plant Part	Biological Activity
 <p>5 Guttiferone-M</p>	Isolated from the fruit [7,11]	Inhibitor of topoisomerase II
 <p>6 Guttiferone-K</p>	Isolated from the fruit [7,11]	Inhibitor of topoisomerase II
Xanthones		
 <p>7 Garbogiol</p>	Isolated from the root [7,11]	Inhibition of α -glucosidase
 <p>8 Rheedia xanthone A</p>	Isolated from the peel [7,11]	Unknown
 <p>9 Oxy-Guttiferone I</p>	Isolated from the fruit [7,11]	Unknown

Table 1. Cont.

Structure & Name	Plant Part	Biological Activity
 <p>10 Oxy-Guttiferone K</p>	Isolated from the fruit [7,11]	Unknown
 <p>11 Oxy-Guttiferone M</p>	Isolated from the fruit [7,11]	Unknown
 <p>12 Oxy-Guttiferone K2</p>	Isolated from the fruit [7,11]	Unknown

4. Medicinal Properties

Various extracts and pure compounds isolated from the plant possess a wide range of biological activities, including anti-obesity, anti-inflammatory, anti-diabetic, anti-oxidant, anti-cancer, and others. Extensive studies are being conducted regarding the anti-obesity activity of the phytochemical constituents. Numerous nutraceuticals are being marketed as anti-obesity agents based on the various extracts of *Garcinia gummi-gutta* [6,7,9].

Acids **1a** and **1** are recognised for potential anti-obesity or weight-reducing properties due to their ability to inhibit the enzyme ATP citrate lyase. This enzyme is responsible for catalysing the extra-mitochondrial cleavage of citrate to oxaloacetate and acetyl coenzyme A (acetyl-CoA). Acetyl-CoA is the key precursor in the synthesis of fatty acids. Consequently, the energy that would be used for fatty acid synthesis is diverted to the production of muscle and liver glycogen [15–17].

While there have been promising findings regarding the effectiveness of the acid **1a**, concerns about its dosage and administration exist. It is generally advised that individuals diagnosed with diabetes mellitus, pregnant women, and lactating women should avoid taking the plant extract due to potential risks. This caution stems from the inhibition of

acetyl-CoA, which subsequently affects the production of malonyl-CoA. Malonyl-CoA plays a crucial role in insulin signalling, potentially impacting insulin sensitivity.

The derivatives of **1a** such as calcium, potassium, and sodium salts, along with other ingredients, have been incorporated into various pharmaceutical combinations aimed at enhancing weight loss and correcting lipid abnormalities. These formulations are designed to leverage the potential benefits of acid **1a** while addressing safety concerns and optimizing therapeutic outcomes.

5. Toxicity Studies

Although compounds isolated from *Garcinia gummi-gutta* and its extracts have found various applications in the medicinal and food additives industry, concerns about the safety of *Garcinia gummi-gutta* extracts have been raised in some reports [14,18–22].

The majority of these reports indicate that *Garcinia gummi-gutta* extracts or its active principle **1a** itself may not have significant toxic effects. However, a few clinical toxicity reports have raised concerns about formulations that include *Garcinia gummi-gutta* extracts or **1a** as active ingredients, showing potential toxicity toward spermatogenesis [23]. Despite these concerns, studies examining the effects of **1a** on human sex hormones have found no significant changes in serum hormone levels. Other reports have also indicated that both **1a** and **1**, are safe based on biochemical and histopathological analyses [22]. A majority of adverse reports have been associated with multi-ingredient formulations, making it challenging to attribute negative effects to a specific component. Some reports suggest a potential interaction between medications that increase serotonin levels, such as Selective Serotonin Reuptake Inhibitors, and **1a**, which is known to also elevate serotonin levels. This underscores the importance of pre-marketing safety assessments [23].

6. Hydroxycitric Acids

HCA, also known as 1,2-dihydroxypropane-1,2,3-tricarboxylic acid, is a six-carbon organic acid featuring two adjacent chiral centres. (–)-HCA is widely utilised as a significant component in pharmaceuticals and food additives, highlighting its versatile applications in both medicinal and culinary industries. However, the natural occurrence of these chiral organic acids is limited. In 1833, Lippmann first reported the natural existence of HCA [24]. Of the four isomers of HCA, **1**, **13**, **14**, and **15** (Figure 1), garcinia acid (**1**), or (2*S*,3*S*)-3-hydroxy-5-oxo-tetrahydrofuran-2,3-dicarboxylic acid, and hibiscus acid (**13**), or (2*S*,3*R*)-3-hydroxy-5-oxo-tetrahydrofuran-2,3-dicarboxylic acid, are naturally available. The natural existence of the other two stereoisomers has not yet been reported. However, all these isomers have been synthesised from *trans*-aconitic acid by Martius [25]. The presence of hydroxycitric acid in the fruit of *Garcinia gummi-gutta* was first reported by Lewis and Neelakantan in 1965 [26]. Since then, various attempts have been made to isolate **1** in its enantiopure form.

In 1969, Boll et al. determined the absolute configurations of the two asymmetric centres of the acid. The same group also reported the pK_a values of both carboxylic acids as 1.82 and 3.75 from a potentiometric titration method [27]. In 1971, Gluskar et al. published the X-ray crystal structure of the dicalcium salt of **1** and determined its absolute configuration [28]. Additionally, Jayaprakash and coworkers reported the HPLC profile of organic acids present in the fruit extract and estimated the (–)-HCA content to be between 16% and 30% in the fruit [29].

Various attempts have been made to determine whether (–)-HCA exists in the fruit as an open chain or in a lactone form. This is due to the presence of a hydroxyl group at the gamma position, which is prone to lactonization and forms a cyclic γ -butyrolactone moiety (Figure 2). The systematic study conducted by Ibnusaud et al. using capillary electrophoresis confirmed the presence of both open-chain and lactonized forms of the acid in the plant [30].

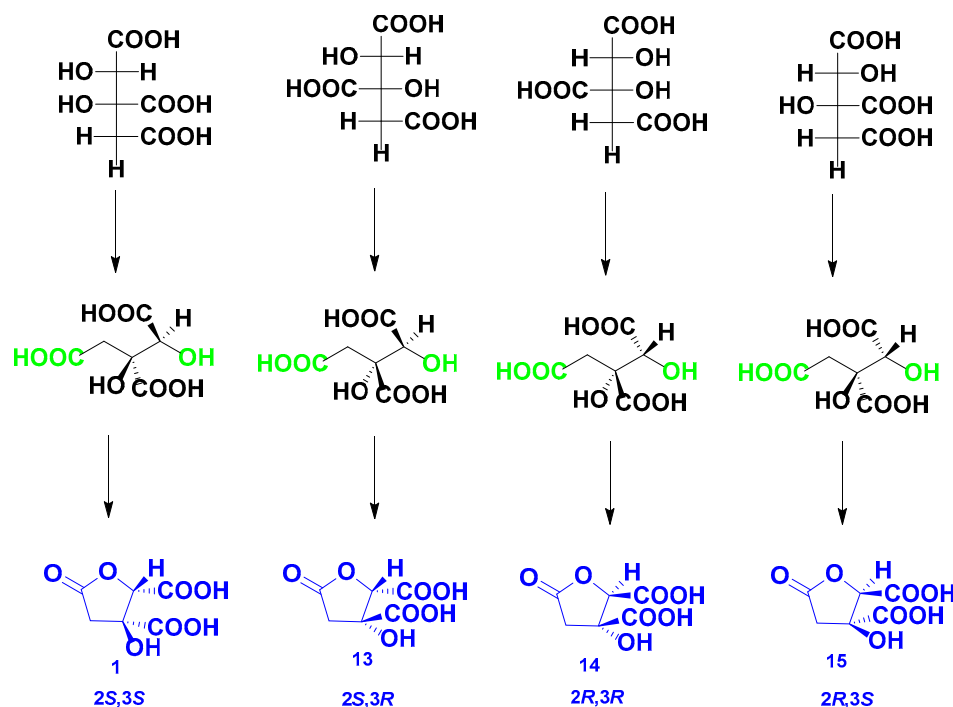


Figure 1. Optical isomers of HCA.

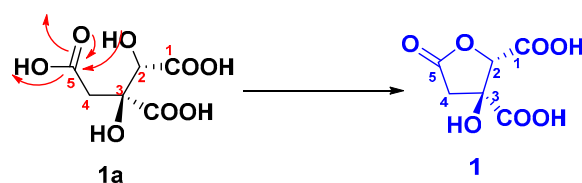


Figure 2. The lactonisation of (–)-HCA.

7. Garcinia Acid as Chiral Building Block: A Value Addition to India's Natural Resources

It is interesting to note that mineral and biological resources of India, including its flora and fauna, have not been extensively explored for value addition. According to a report by the Department of Science and Technology, Government of India, Indian researchers have not yet fully tapped into the potential of the country's rich biodiversity. Only a small fraction, around 5%, of India's plant materials have undergone systematic investigation. This highlights a significant opportunity for further research and development to unlock the potential benefits and applications of these resources.

There is a growing interest in identifying, isolating, and utilising natural products for semi-synthetic approaches to produce desired chiral compounds. This approach not only aims to streamline synthetic processes but also leverages natural resources more sustainably, aligning with global trends towards eco-friendly and efficient chemical synthetic methods. Hence, considerable effort and creativity have focused on using enantiopure and inexpensive compounds, such as terpenes, carbohydrates, hydroxy acids, and amino acids obtained directly from the chiral pool for target-oriented syntheses [31,32].

Among these compounds, naturally occurring α -hydroxy acids, **1**, **13**, **16** to **27** (Figure 3) have been extensively used as a renewable source of enantiomerically pure compounds for various aspects of chirality. However, there has been little exploration into the synthetic potential of the closely related but lesser-known acid **1**, which is abundantly distributed in nature.

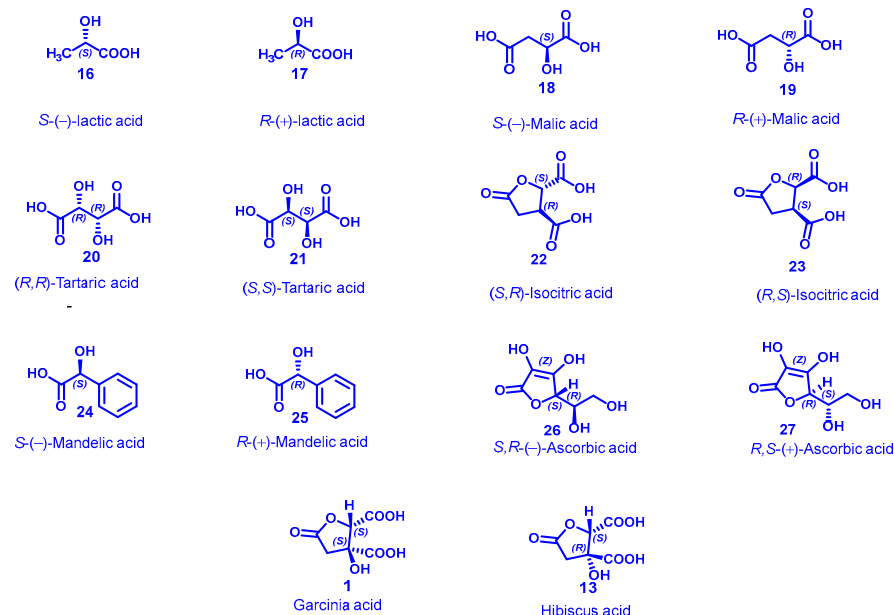


Figure 3. Important chiral hydroxy acids.

The research group led by Ibnusaoud et al. identified the potential of **1** as a chiron to synthesise both natural and unnatural organic compounds in an enantiomerically pure form. They also developed a procedure for the large-scale isolation of **1** from the dried fruit rinds of *Garcinia gummi-gutta* [33–39].

The acid **1**, with a six-carbon skeleton, has been explored for developing molecules possessing chiral centres in a six-carbon framework. These include several biologically/ functionally important enantiopure molecules such as potential chiral pyrrolidinediones, analogues of the Quararibea metabolite—a chiral enolic- γ -lactone, concave bislactone skeletons of fungal metabolites like (+)-avenaciolide and (–)-canadensolide, as well as the structural skeletons of furo[2,3-*b*]furanol (part of the anti-HIV drug Darunavir), (–)-tetrahydropyrrolo[2,1-*a*]isoquinolinone, (–)-hexahydroindolizino[8,7-*b*]indole, and furo[2,3-*b*]pyrrole (Table 2).

Table 2. Select significant compounds prepared from **1** and their relevant applications.

Structure of the Compound	Applications (Relevant Properties of the Derived Compounds)
<p>28</p>	Chiral synthon, building block used for the synthesis of pharmacologically important natural products like substituted indolizines and other heterocyclic scaffolds
<p>29</p>	Chiral synthon, building block used for the synthesis of pharmacologically important natural products like substituted indolizines and other heterocyclic scaffolds
<p>30</p>	Chiral intermediate for the synthesis of trisammonium salt for asymmetric catalysis

Table 2. Cont.

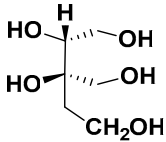
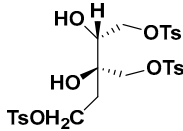
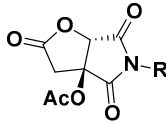
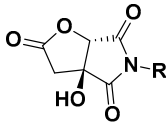
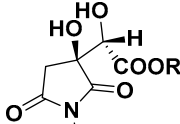
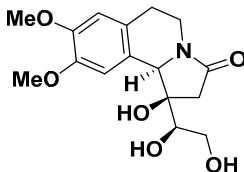
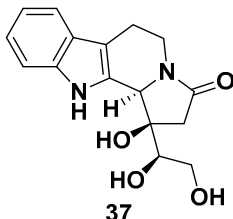
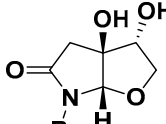
Structure of the Compound	Applications (Relevant Properties of the Derived Compounds)
 <p>31</p>	Chiral intermediate for the synthesis of iminosugars
 <p>32 unpublished work</p>	Chiral intermediate for the synthesis of chiral catalysts
 <p>33</p>	Chiral pyrrolidine diones, a common structural subunit found in a variety of natural and unnatural bioactive compounds
 <p>34</p>	Chiral pyrrolidine diones, a common structural subunit found in a variety of natural and unnatural bioactive compounds
 <p>35</p>	Chiral building blocks used for the syntheses of compounds having potent inhibitory activities against purine nucleoside phosphorylases, aldose reductase inhibitors, antibacterial activity etc.
 <p>36</p>	Pyrrolo[2,1- <i>a</i>]isoquinoline alkaloid, an analogue of naturally occurring anti-tumor agent (–)-crispine A
 <p>37</p>	Indolizino[8,7- <i>b</i>]indole alkaloid, an analogue of naturally occurring (–)-harmicine, known for its antileishmanial and antinociceptive activities
 <p>38</p>	Furo[2,3- <i>b</i>]pyrrolo skeleton, a rare class of concave <i>cis</i> -fused bicyclic nitrogen and oxygen heterocycles, subunit in complex natural products like millingtonine A, madindoline, as well as in several synthetic drugs

Table 2. Cont.

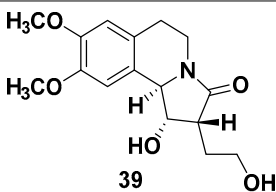
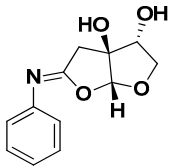
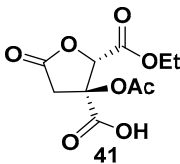
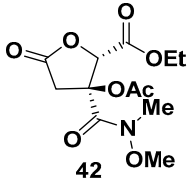
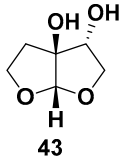
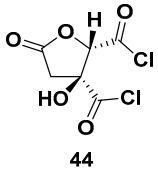
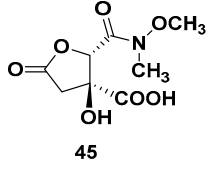
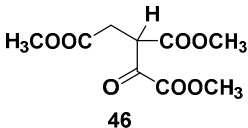
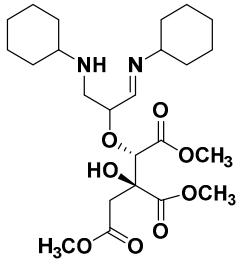
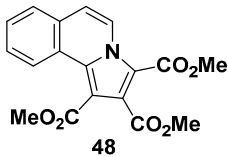
Structure of the Compound	Applications (Relevant Properties of the Derived Compounds)
 <p>39</p>	Pyrrolo[2,1- <i>a</i>]isoquinoline alkaloid, fundamental structural component of many synthetic and biologically active compounds
 <p>40</p> <p>(Unpublished work)</p>	Chiral intermediate
 <p>41</p>	Chiral intermediate for the synthesis of bis-tetrahydrofuran (bis-THF) alcohol moiety found in the structure of HIV protease inhibitors (PIs) like Darunavir, Breacanavir, GS-9005, and SPI-256
 <p>42</p>	Weinreb amide derivative, Chiral intermediate for the synthesis of bis-tetrahydrofuran (bis-THF) alcohol moiety found in the structure of HIV protease inhibitors (PIs) like Darunavir, Breacanavir, GS-9005, and SPI-256
 <p>43</p>	Furo[2,3- <i>b</i>]furanol, part of anti-HIV drug Darunavir, Breacanavir, GS-9005, and SPI-256
 <p>44</p>	Chiral synthon
 <p>45</p> <p>(Unpublished work)</p>	Weinreb amide derivative, chiral intermediate
 <p>46</p>	Chiral intermediate

Table 2. Cont.

Structure of the Compound	Applications (Relevant Properties of the Derived Compounds)
 <p style="text-align: center;">47</p>	Chiral intermediate
 <p style="text-align: center;">48</p>	Biologically and functionally important substituted indolizine

All of the reported compounds have found wide implementations in pharmaceutical industries. Table 2 lists some of the significant compounds (28 to 48), prepared from **1**, and Table 3 presents a collection of significant synthons and natural products (49 to 72), which have matching structure and stereochemistry with that of **1** and can be synthesised from **1**. The enantio-purity of the target molecules is guaranteed during the synthesis as the chirality is transferred from the enantiomerically pure starting molecules to target molecules.

Table 3. Significant synthons and natural products that can be synthesised from **1**.

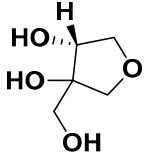
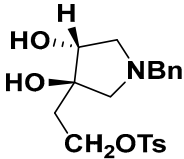
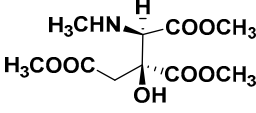
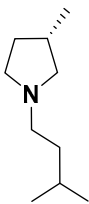
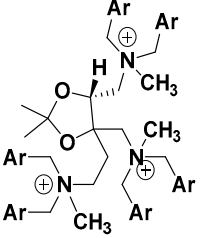
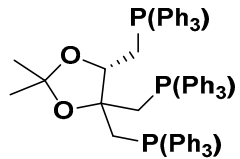
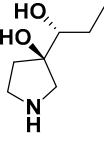
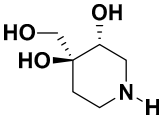
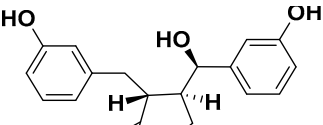
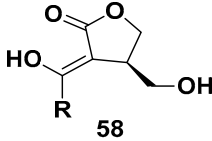
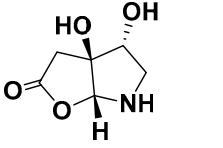
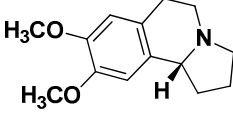
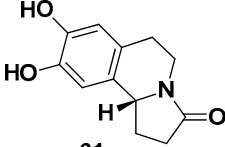
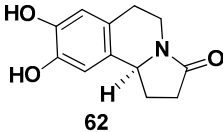
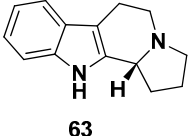
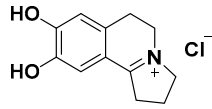
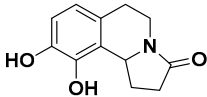
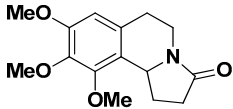
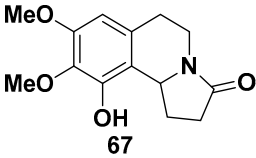
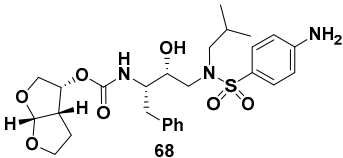
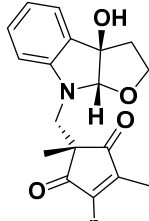
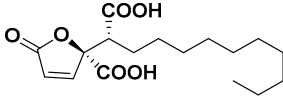
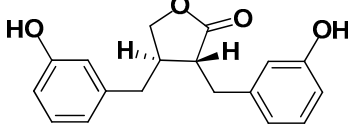
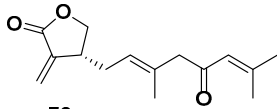
 <p style="text-align: center;">49 [40]</p>	 <p style="text-align: center;">50 Iminosugar [40,41]</p>	 <p style="text-align: center;">51 Unnatural amino acid [42]</p>
 <p style="text-align: center;">52 Antvenom alkaloid [43]</p>	 <p style="text-align: center;">53 Tris ammonium salt for asymmetric catalysis [44]</p>	 <p style="text-align: center;">54 Chiral catalyst for asymmetric catalysis [45–47]</p>

Table 3. Cont.

 <p>55 pyrrolidin A core substructure in many biologically active natural products. [48]</p>	 <p>56 Iminosugar [49,50]</p>	 <p>57 (7'<i>R</i>)-7'-Hydroxyenterolactone [51]</p>
 <p>58 3<i>S</i>(+)-A- factor [51]</p>	 <p>59 furo[2,3-<i>b</i>]pyrrole skeleton [52]</p>	 <p>60 (<i>R</i>)-(+)-crispine A [53]</p>
 <p>61 (<i>R</i>)-(+)-oleracine E [53]</p>	 <p>62 (<i>S</i>)-(-)-trolline [53]</p>	 <p>63 (<i>R</i>)-(+)-harmicine [53]</p>
 <p>64 Crispine B [53]</p>	 <p>65 Salsoline B [53]</p>	 <p>66 Mescalotam [54]</p>
 <p>67 Peyoglutam [54]</p>	 <p>68 Darunavir Non-peptide HIV protease inhibitor [53,55]</p>	 <p>69 (+)-madindoline A [53]</p>
 <p>70 5-epi-spiculispic acid [51]</p>	 <p>71 (-)-Enterolactone [51]</p>	 <p>72 Anthecotulide [51,56,57]</p>

7.1. Synthesis of Bislactones

Several enantiomerically pure lactones and related bislactones have been the focus of recent research to develop a variety of compounds with biological significance. Compounds like paraconic acids, mescaline isocitrimide lactone, avenaciolide, whisky lactones, cinatrins, methylenolactocins etc. have distinct structural frameworks that do not align with tartaric acid. Additionally, the known methods for synthesising certain concave bislactones such as (+)-avenaciolide (73), (+)-isoavenaciolide (74), ethisolide (75), (–)-canadensolide (76), xylobovide (77), sporothriolide (78), and dihydrocandensolide (79) are often described as tedious and time-consuming [58–68]. Interestingly, **1** appears to be the most suitable chiron for minimising synthetic steps and maximising the synthetic efficiency of these lactones/bislactones (Figure 4) [35].

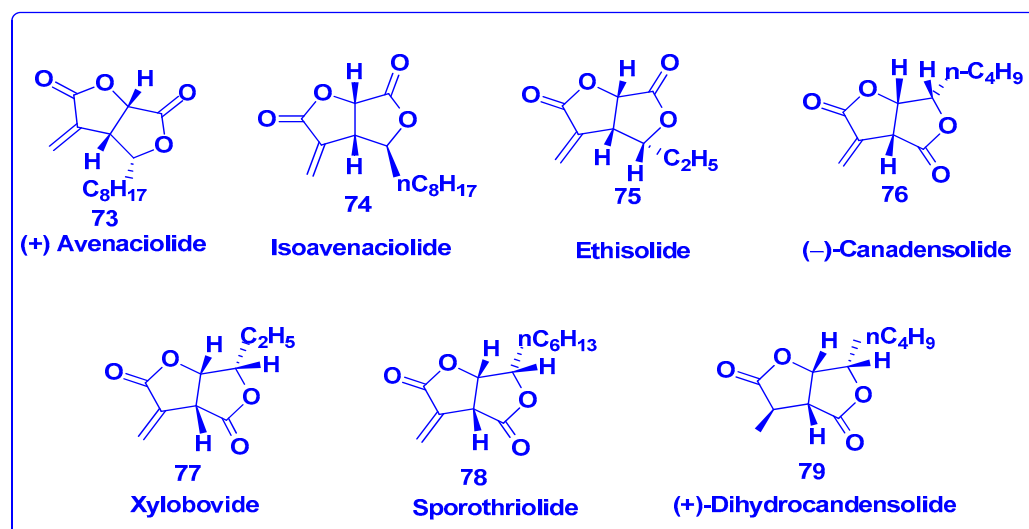
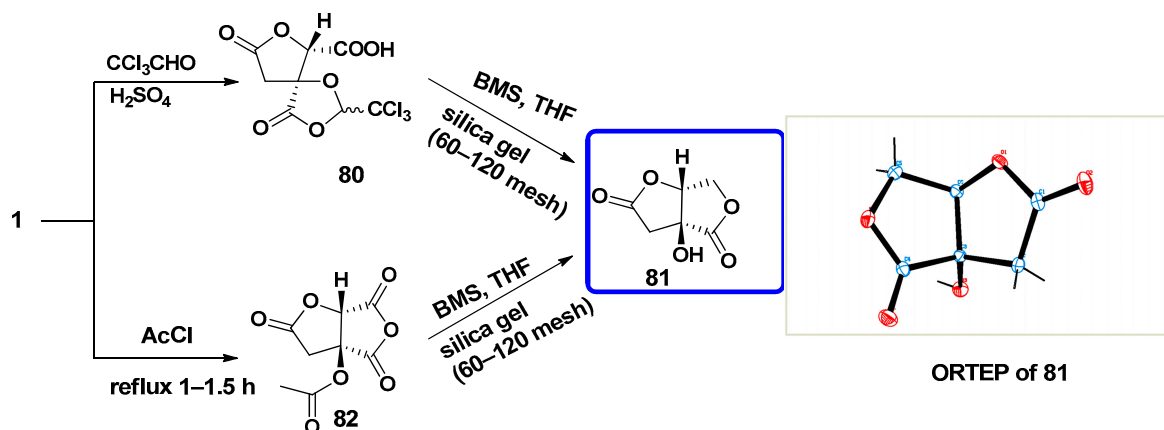


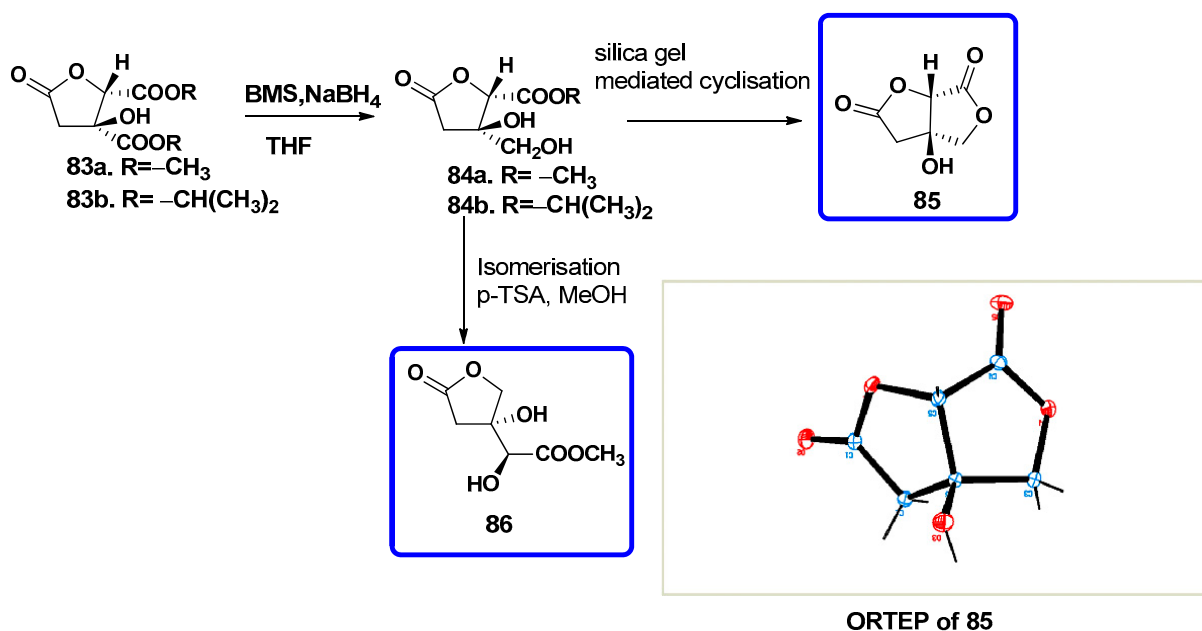
Figure 4. Naturally occurring compounds having bislactone moiety.

In this respect, a quick semi-synthetic method for constructing these challenging and fascinating bislactones (**81** and **85**) has been developed by Ibnusaud et al. from readily available acid **1** [35]. This method can be further tuned for a variety of natural molecules. After protecting the geminal hydroxyl and carboxylic acid group at the C-3 position of acid **1** with trichloroacetaldehyde (Scheme 1), the selective reduction of the carboxylic group at the C-2 position was conducted using borane dimethyl sulphide in tetrahydrofuran (BMS/THF) [69]. The chromatographic purification over silica gel furnished the bis-lactone **81**, a derivative of the fungal metabolite (–)-candensolide. The structure of **81** was confirmed based on IR, ^1H and ^{13}C NMR spectroscopy, X-ray diffraction studies (CCDC 667543), and mass spectrum. Additionally, an alternative route was reported for the synthesis of bislactone **81** by employing borane dimethyl sulphide in tetrahydrofuran (BMS/THF) for the selective reduction of anhydride **82** (Scheme 1).



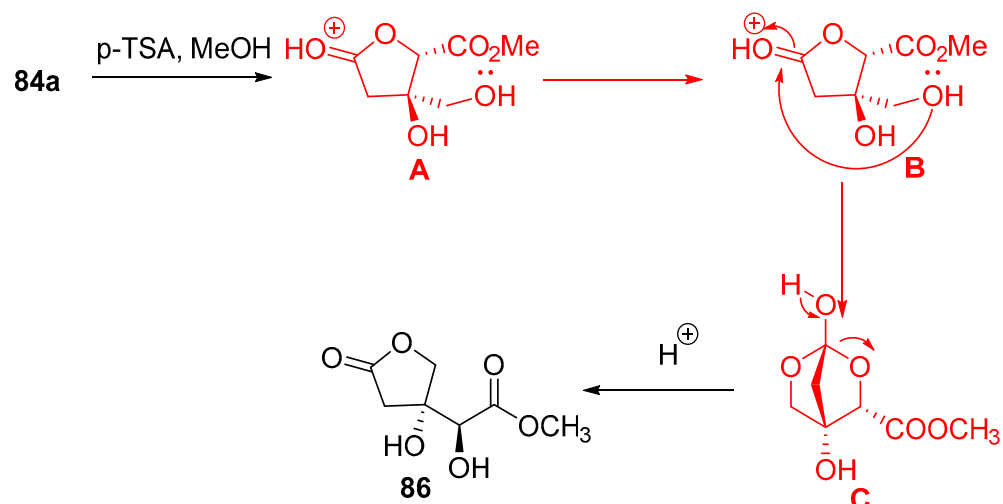
Scheme 1. Synthesis of chiral bislactone **81**, an analogue of (–)-candensolide [35].

The tertiary hydroxyl group at C-3 position of **83a**, the dimethyl ester of **1**, was utilised to facilitate a regio-selective reduction using borane dimethyl sulfide (BMS) in tetrahydrofuran and catalytic NaBH_4 [70]. This reduction furnished the bislactone **85**, the core skeleton of the fungal metabolite (+)-avenaciolide, as a sharp melting solid upon chromatographic purification over silica gel (Scheme 2) [35,71]. The structure of **85** was confirmed based on IR, ^1H and ^{13}C NMR spectroscopy, X-ray diffraction studies (CCDC 667542), and mass spectrum.



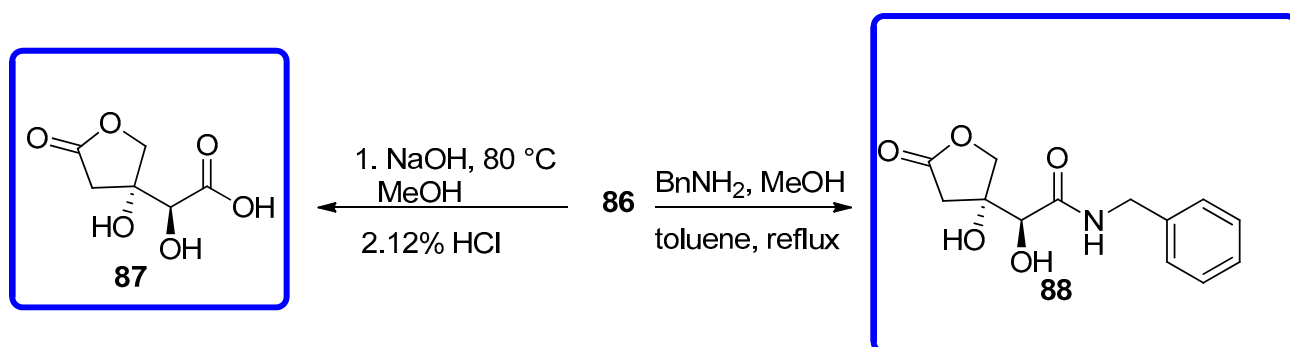
Scheme 2. Synthesis of chiral bislactone **85**, an analogue of (+)-avenaciolide [35].

Vicinal diol **84a** was isomerised to hydroxy ester **86**, a lactone motif present in many natural products [56,57] via acid-catalysed trans-lactonization. A plausible mechanism for the transformation is depicted in Scheme 3 [72].



Scheme 3. A plausible mechanism for the formation of **86**.

The subsequent hydrolysis of **86** in an alkaline medium furnished the acid **87** (Scheme 4). Treatment of **86** with benzylamine in methanol under reflux resulted in the formation of amide **88** [72], a valuable intermediate for the synthesis of iminosugars [73].



Scheme 4. Conversion of diol **86** to iminosugar intermediate **88**.

7.2. Synthesis of Analogues of the Quararibea Metabolite Chiral Enolic- γ -Lactones

Chiral butenolide sub-structures are estimated to serve as building blocks for the synthesis of approximately 13,000 natural products, including molecules like (–) funebrisin (**89**) and angelica lactone (**90**), with 2(5H)-furanone subunits (Figure 5). These structural motifs are found in various compounds such as pheromones, the antibiotic strobilin, penicillanic acid, pulvinones, and several secondary metabolites of fungal and marine origin, as well as sesquiterpenoid lactones. Often, chiral butenolides are obtained from sources like carbohydrates, α -keto acids, glutamic acid, or acyclic systems such as acetylenic compounds, pyruvic acid derivatives, and cyanohydrins of conjugated aldehydes, typically involving multi-step procedures [51,74,75].

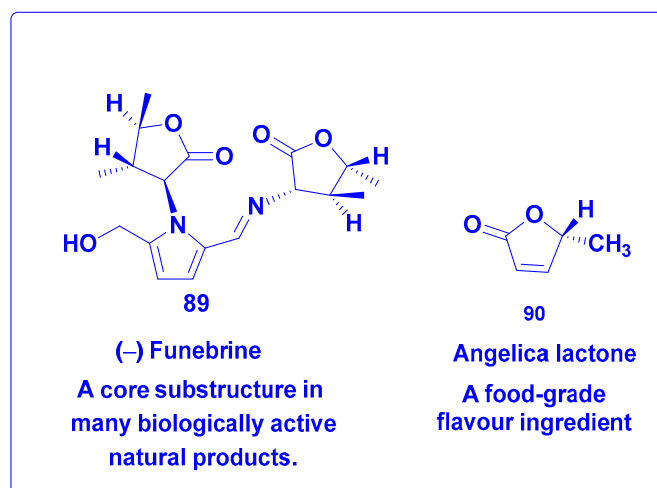
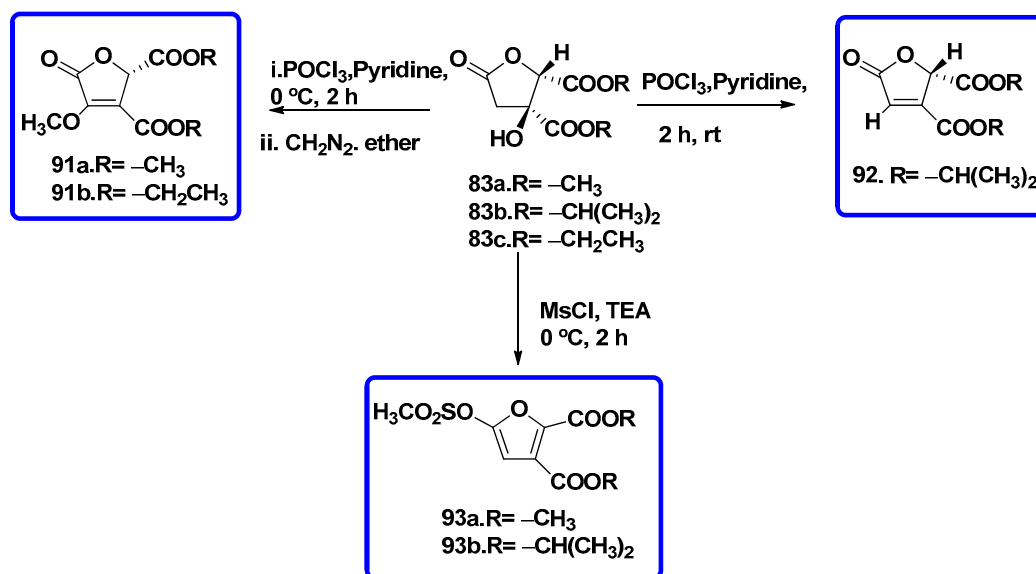


Figure 5. Naturally occurring Quararibea metabolite chiral enolic- γ -lactones.

It was reported that minor functional group modification on the acid **1** yields the chiral enolic lactone [36]. The dialkylesters of acid **1** were used to synthesize analogues of the Quararibea metabolite chiral enolic- γ -lactones. Methyl ethers of chiral enolic- γ -lactone (**91**) were isolated by reacting dimethyl or diethyl esters of **1** with POCl_3 in pyridine and then reacting the mixture with diazomethane (Scheme 5). However, when the reaction was conducted using **83b**, the diisopropyl ester of **1**, a simple dehydration product (**92**), was obtained. Irrespective of the substitution, when methane sulfonyl chloride in triethyl amine reacted with the dialkylesters of acid **1**, aromatic dialkyl-5-[(methyl-sulfonyl)oxy]-2,3-furandicarboxylates **93a** and **93b** were isolated.



Scheme 5. Synthesis of chiral enolic- γ -lactones [36].

A plausible mechanism for the formation of compounds **91a–b** and **93a–b** is proposed (Figures 6 and 7).

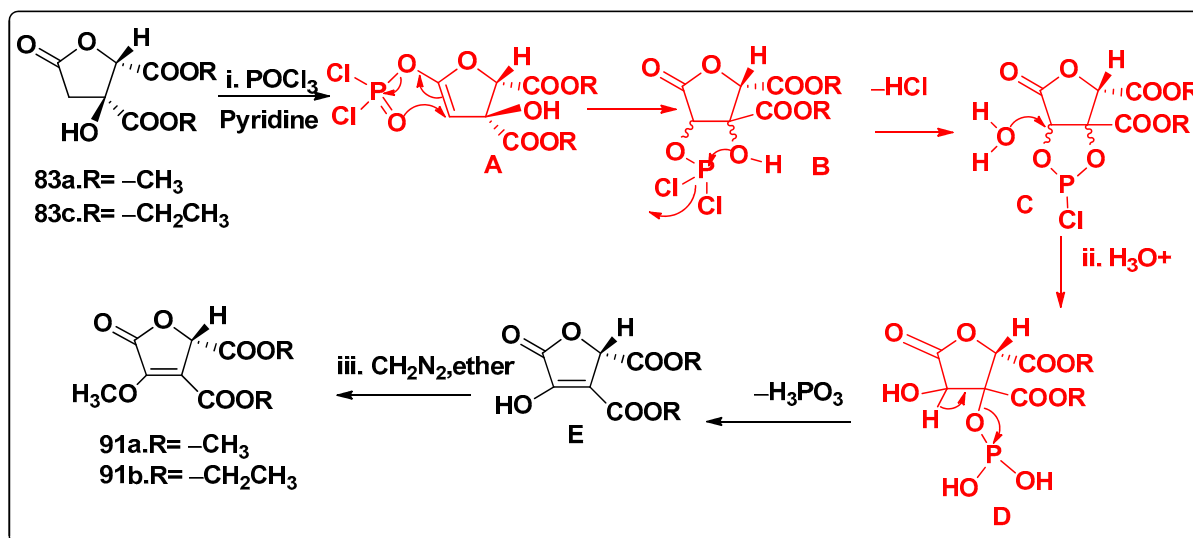


Figure 6. Plausible mechanism for the formation of 91a–b [36].

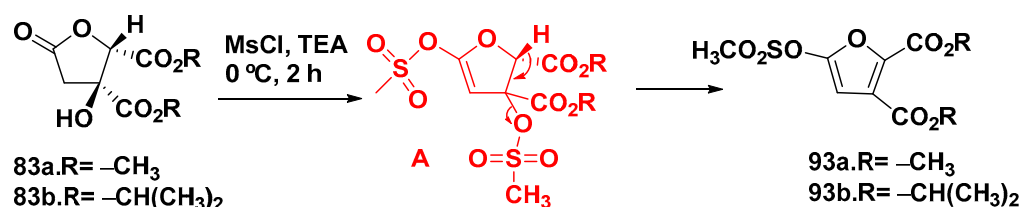


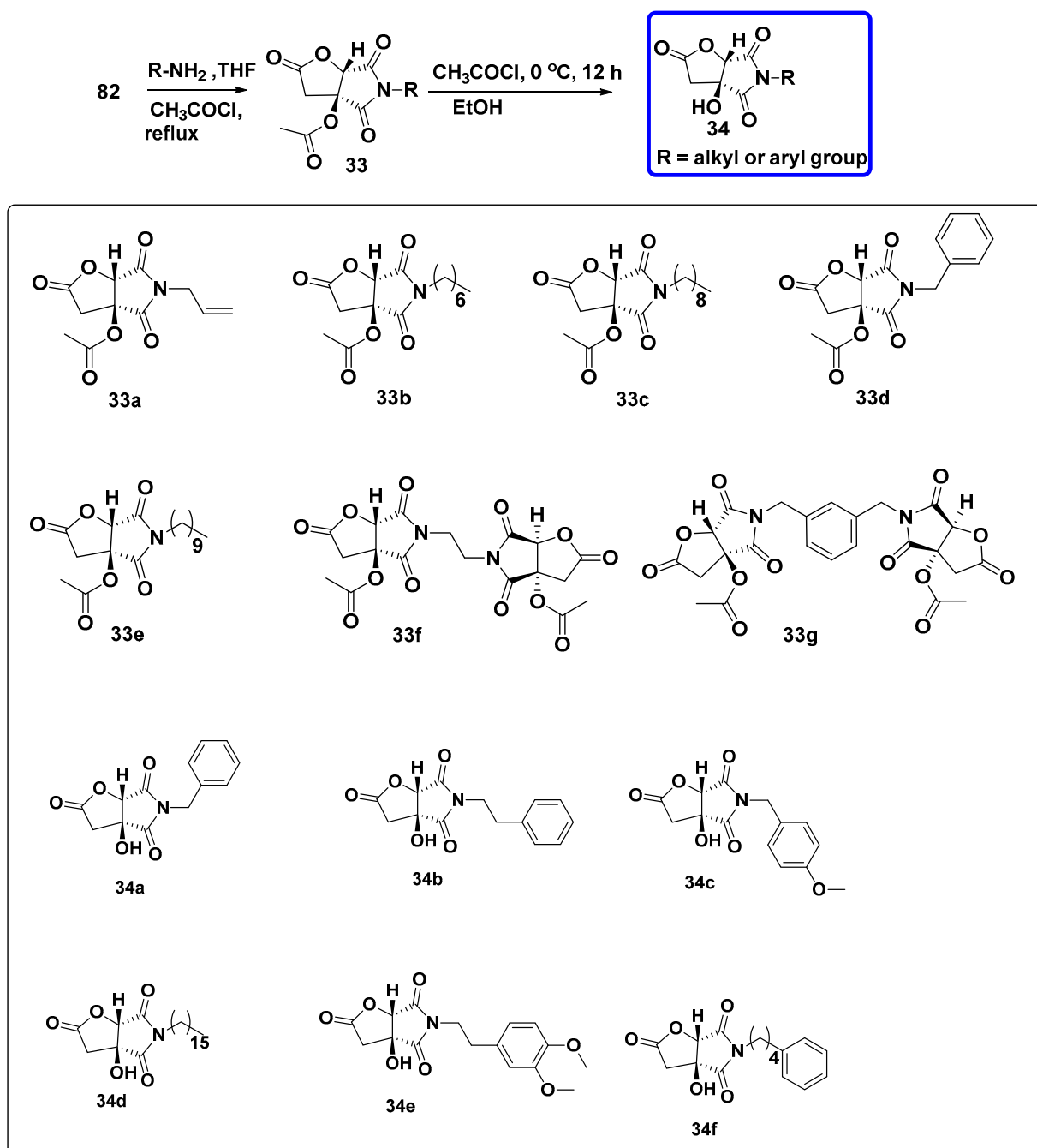
Figure 7. Plausible mechanism for the formation of 93a–b [36].

7.3. Synthesis of 3-Substituted and 3,4-Disubstituted Pyrrolidine-2,5-Diones

Syntheses of pyrrolidines, pyrrolizidine alkaloids, amino acids, and other compounds have been achieved starting from hydroxy acids such as tartaric or malic acids, which involve intermediates like pyrrolidine-2,5-diones. Hence, a great deal of research has been focused on the synthesis of 2,5-disubstituted pyrrolidines [32]. Ibnusaoud et al. have reported the synthesis of 3 and 3,4-disubstituted chiral pyrrolidines by the judicious conversion of **1** since various natural compounds include pyrrolidine skeletons with 3 and 3,4-disubstitution.

They have developed two distinct strategies to synthesize chiral pyrrolidine-2,5-diones. By using acetyl chloride, the acid **1** is converted to the corresponding anhydride **82** in the first approach. Several primary amines were refluxed with the resulting acetylated anhydride to produce the appropriate bicyclic pyrrolidine-2,5-diones (**33a–g**). Subsequently, the acetylated anhydride was deacetylated to obtain the final compounds (**34a–f**) (Scheme 6) [34,38,39,53,76].

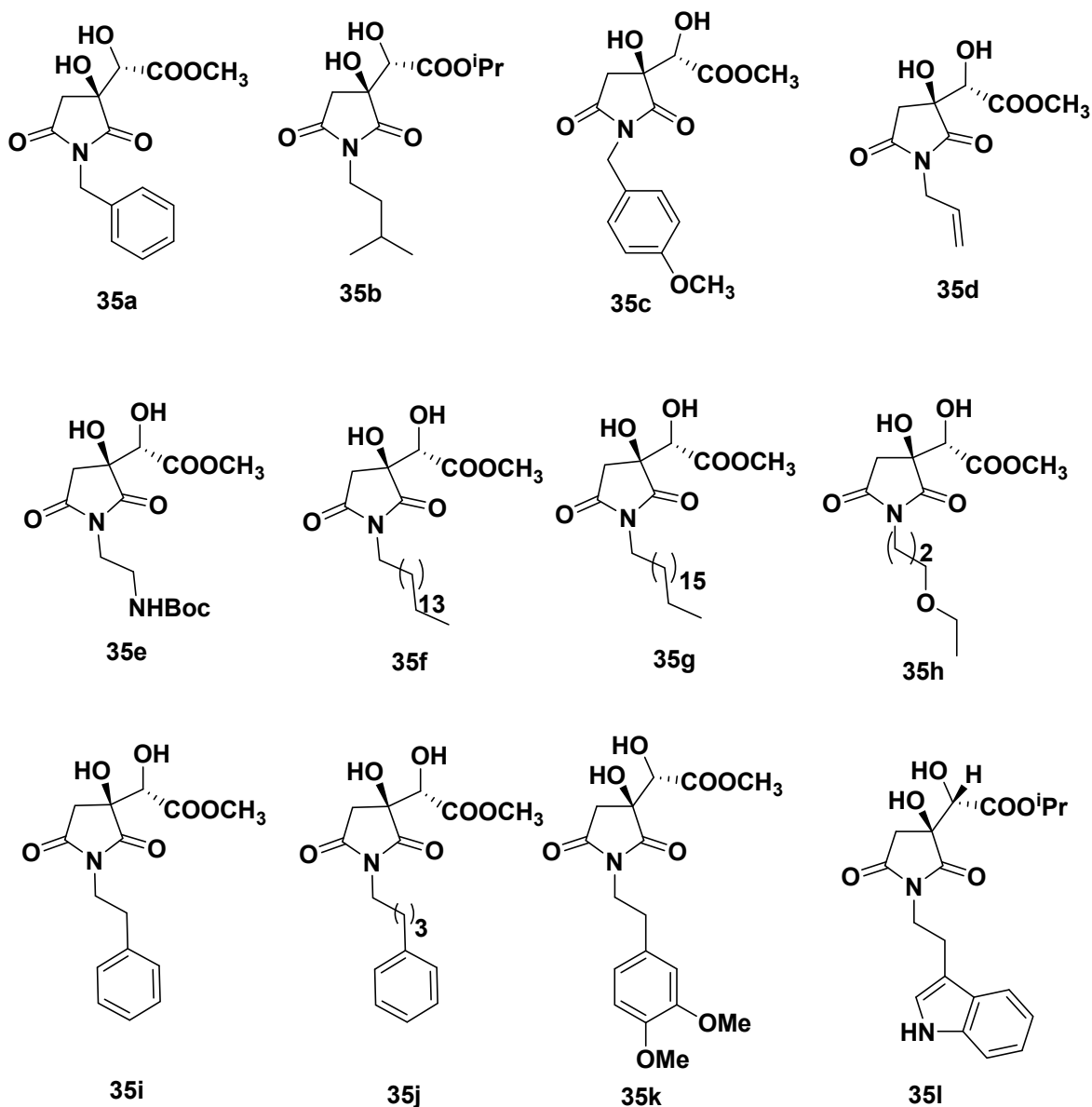
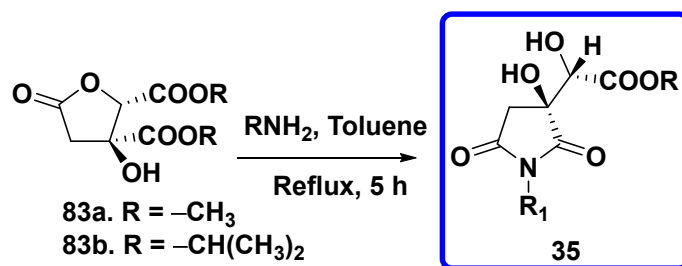
The anhydride-based pyrrolidine-2,5-diones are limited to the HCA variants (2*S*,3*S*) and (2*R*,3*R*) because the *cis* orientation of carboxylic acid groups is necessary to achieve five-membered ring fusion. However, pyrrolidine-2,5-diones derived from the (2*S*,3*S*) isomer of HCA are the only compounds known, as the (2*R*,3*R*) isomer of HCA has not yet been reported in natural sources.



Scheme 6. Synthesis of 3,4-disubstituted pyrrolidine-2,5-diones from bicyclic anhydride 82 [53].

In the second strategy, diesters of **1** were employed as starting compounds. These diesters were refluxed with one equivalent of a primary amine in toluene leading to the formation of cyclic imides for the subsequent conversion of pyrrolidine-2,5-diones (Scheme 7). Thus, a novel class of 3-substituted pyrrolidine-2,5-diones (**35a–l**) with yields varying from 71% to 90% was obtained by utilizing a variety of primary amines. The diversity in substituents bonded to the imide nitrogen contributed to the inherent diversity of this library of 3-substituted pyrrolidine-2,5-diones.

Furthermore, these pyrrolidine-2,5-diones possess an improved coupling motif that enables the one-pot generation of a wide range of skeletally diverse and bio-relevant compounds [53]. By considering the imide carbonyl as a shared coupling point in the pairing phase, it has been reported that monocyclic precursors can be folded to form two distinct types of polycyclic ring systems.



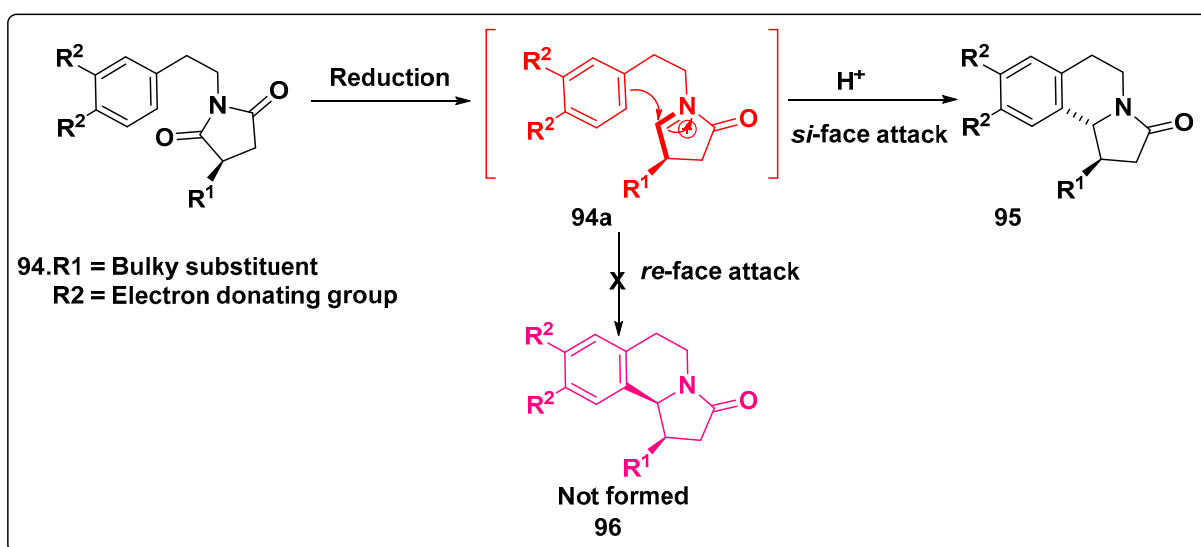
Scheme 7. Synthesis of 3-substituted pyrrolidine-2,5-diones from ester derivatives of **1** [53].

7.4. Synthesis of Tetrahydropyrrolo[2,1-*a*] Isoquinolinone, Hexahydroindolizino[8,7-*b*] Indolones and Furo[2,3-*b*]pyrroles

N-heterocyclic scaffolds based on pyrrolo[2,1-*a*]isoquinoline are the fundamental structural component of many synthetic and biologically active compounds. It is well known that there are several natural compounds containing a pyrrolo[2,1-*a*]isoquinoline

structure (Table 3, Nos. 60–67). Although naturally occurring simple, tricyclic, non-annulated pyrrolo[2,1-*a*]isoquinolines have existed since 1963, their significance has recently increased. There is ample documentation on the synthesis and characteristics of pyrrolo[2,1-*a*] isoquinolines [37,76].

Many compounds with the ring structures of pyrroloisoquinolin [53,77–79] and indolizinoindolone [77,80–82] are commonly found in tropical and sub-tropical folk medicines [76,81]. The most promising technique for synthesizing these fused heterocyclic complexes is *N*-acyliminium ion cyclization [80,83,84]. This synthetic strategy involves the reduction of chiral unsymmetrical pyrrolidine-2,5-diones (94). These intermediates then undergo diastereoselective *N*-acyliminium cyclization leading to the formation of tetrahydropyrrolo[2,1-*a*]isoquinoline (95), and hexahydroindolizino[8,7-*b*]indolone ring systems. The reduction of chiral pyrrolidine-2,5-diones exhibits regioselectivity at the more substituted carbonyl group [85]. The nucleophilic aryl ring on the least hindered side of the acyliminium ion is known to be attacked in a diastereospecific manner during the *N*-acyliminium cyclization process, yielding only one diastereomer and therefore 96 is not formed (Scheme 8) [79].



Scheme 8. *N*-acyliminium cyclization involving unsymmetrical pyrrolidine-2,5-dione [53].

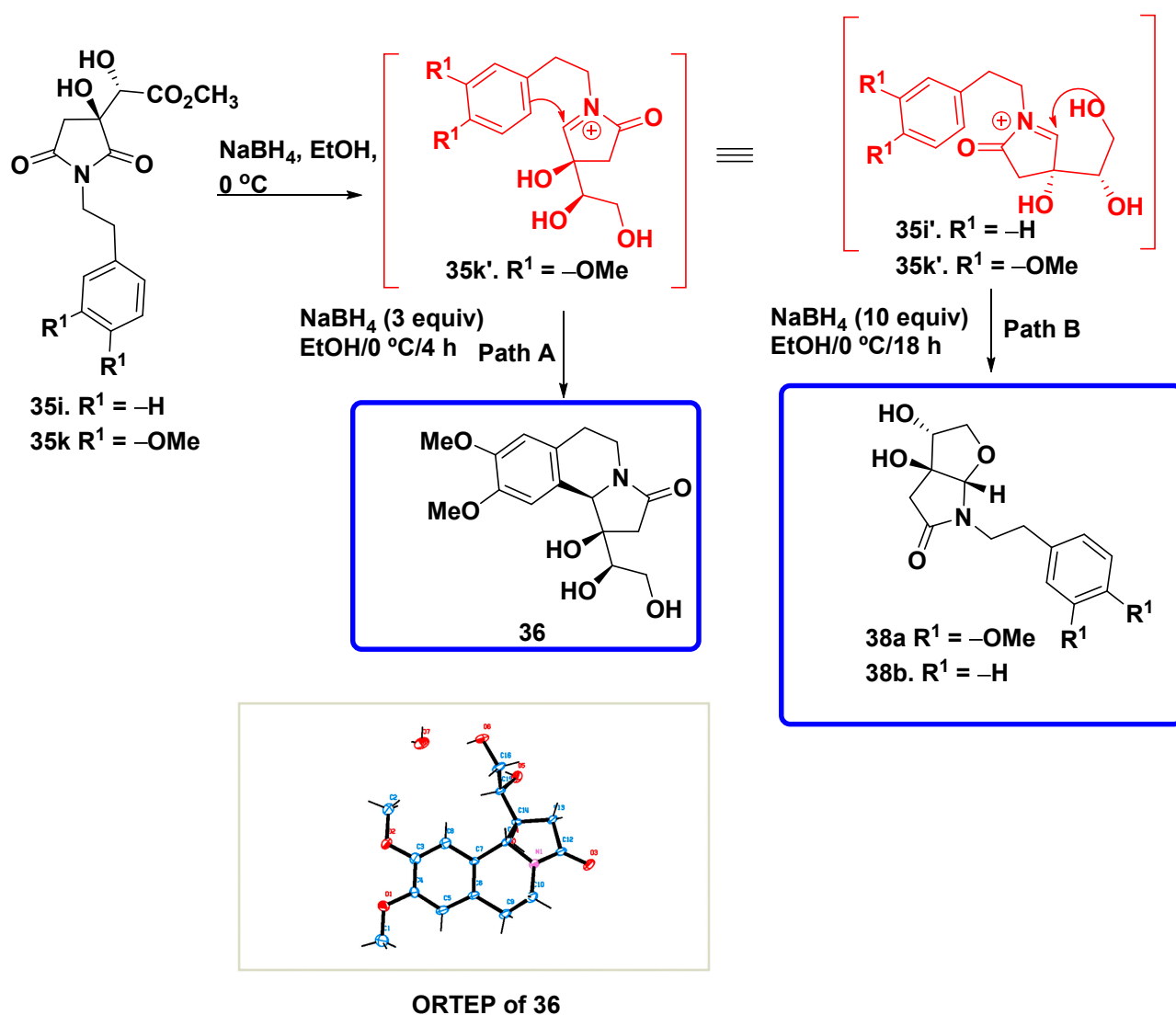
In this background, tetrahydropyrrolo[2,1-*a*]isoquinone derivatives (36) were prepared in an enantiomerically pure form from chiral 3-substituted pyrrolidine-2,5-diones (35), in good yield (Scheme 9). The proximal hydroxy groups facilitated the regioselective reductions. The reduction products from 35 could be folded to obtain either five- or six-membered polycyclic ring systems, depending on the workup conditions and electronic status of the aromatic ring (Schemes 9 and 10). The scope of this work has been extended to include pyrrolidine-2,5-diones with different electronic characteristics.

After reducing the pyrrolidine-2,5-diones 35i or 35k with three equivalents of NaBH₄, followed by workup under acidic conditions (5M HCl) (Path A), tetrahydropyrrolo[2,1-*a*]isoquinone (36) were obtained, through a 6-*endo-trig* cyclization process that involved the aromatic ring as the nucleophilic entity (Scheme 9) [53]. Similarly, reduction of pyrrolidine-2,5-dione 35l led to the formation of hexahydroindolizino[8,7-*b*]indolone (37) (Scheme 10).

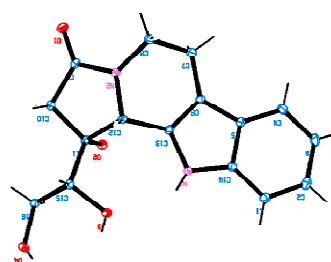
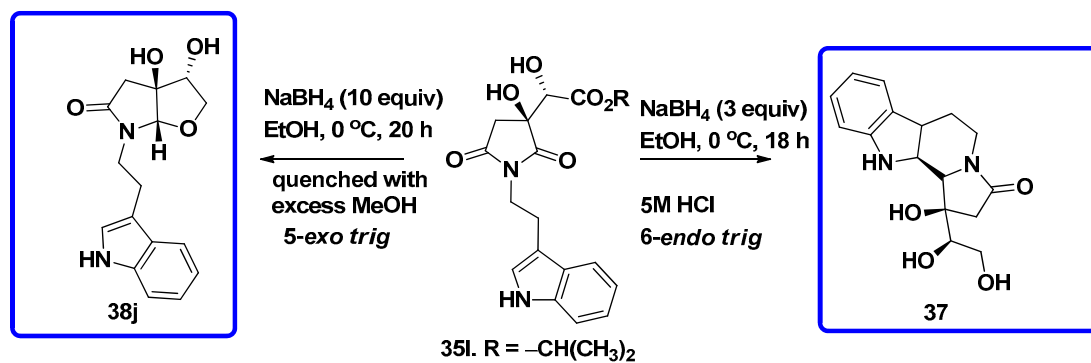
When the reduction of 35i, or 35k and 35l was performed with an excess of NaBH₄ (ten equivalents) followed by quenching with excess methanol (Path B), the furo[2,3-*b*]pyrroles (38a,b,j) were obtained diastereospecifically. This transformation proceeded via a 5-*exo-trig* cyclization involving the hydroxyl group of the reduced ester as the nucleophilic entity. The alkaline reaction mixture generated by the excess NaBH₄ allowed the isolation of furo[2,3-*b*]pyrroles as *O*-*N* acetals, which were stable under the isolation conditions (Schemes 9 and 10).

Accordingly, compounds **36**, an analogue of naturally occurring (–)-crispine A (Scheme 9) and **37**, an analogue of naturally occurring (–)-harmicine (Scheme 10), were synthesized from **35k** and **35l** respectively as single diastereomers. The structure and stereochemistry of these molecules were established with all spectroscopic data including the single crystal XRD (for **36**, CCDC 1852021, and for **37**, CCDC 1852024) as well as chiroptical spectroscopy. The absolute configurations of the final molecules were determined by relating them to the known absolute configurations of the starting compound. The diastereoselective outcome can be explained based on the favoured conformation of the intermediate so that intramolecular cyclisation of **35k'** leads to **36** via a *re*-face attack of the aryl group. Further, the diastereoselective attack of the nucleophilic aryl ring occurs at the least hindered side of the acyliminium ion [53].

When the pyrrolidine-2,5-dione **35i** or **35k** was used, a 5-*exo-trig* cyclisation was triggered in the acyliminium ion, using ten equivalent NaBH_4 in ethanol, followed by quenching with excess methanol, resulting in the exclusive formation of furo[2,3-*b*]pyrrole **38** [29,52]. However, when the aryl ring bears electron-donating groups, it competes with the hydroxyl group acting as the nucleophile for the acyliminium cyclisation. Thus, the pyrrolidine-2,5-dione **35** furnished tetrahydropyrrolo[2,1-*a*]isoquinolinones (**36**) via a 6-*endo-trig* Pictet-Spengler cyclisation with excellent yield. By judiciously tuning the electron density on aryl ring of the pyrrolidinediones, cyclisation can be switched to either furopyrroles or pyrroloisoquinolines [53].



Scheme 9. Synthesis of tetrahydropyrrolo[2,1-*a*]isoquinolinones and furo[2,3-*b*]pyrroles [53].



Scheme 10. Synthesis of hexahydroindolizino[8,7-*b*]indolone and furo[2,3-*b*]pyrroles [53].

7.4.1. Synthesis of Furopyrroles

Enantiopure furo[2,3-*b*]pyrroles, a rare class of concave *cis*-fused bicyclic nitrogen and oxygen heterocycles, are found as subunits in complex natural products like millingtonine A (Figure 8), madindoline (Table 3, No. 69), as well as in several synthetic drugs [86]. A practical approach to the synthesis of this rare class of nitrogen–oxygen heterocycles was disclosed by Ibnusaud et al. (Scheme 11) [52,53].

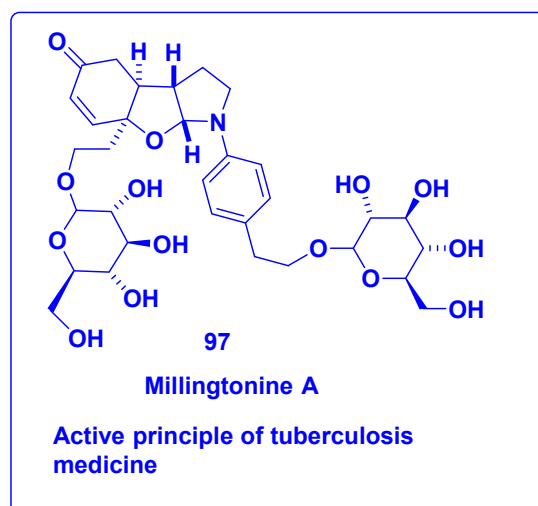
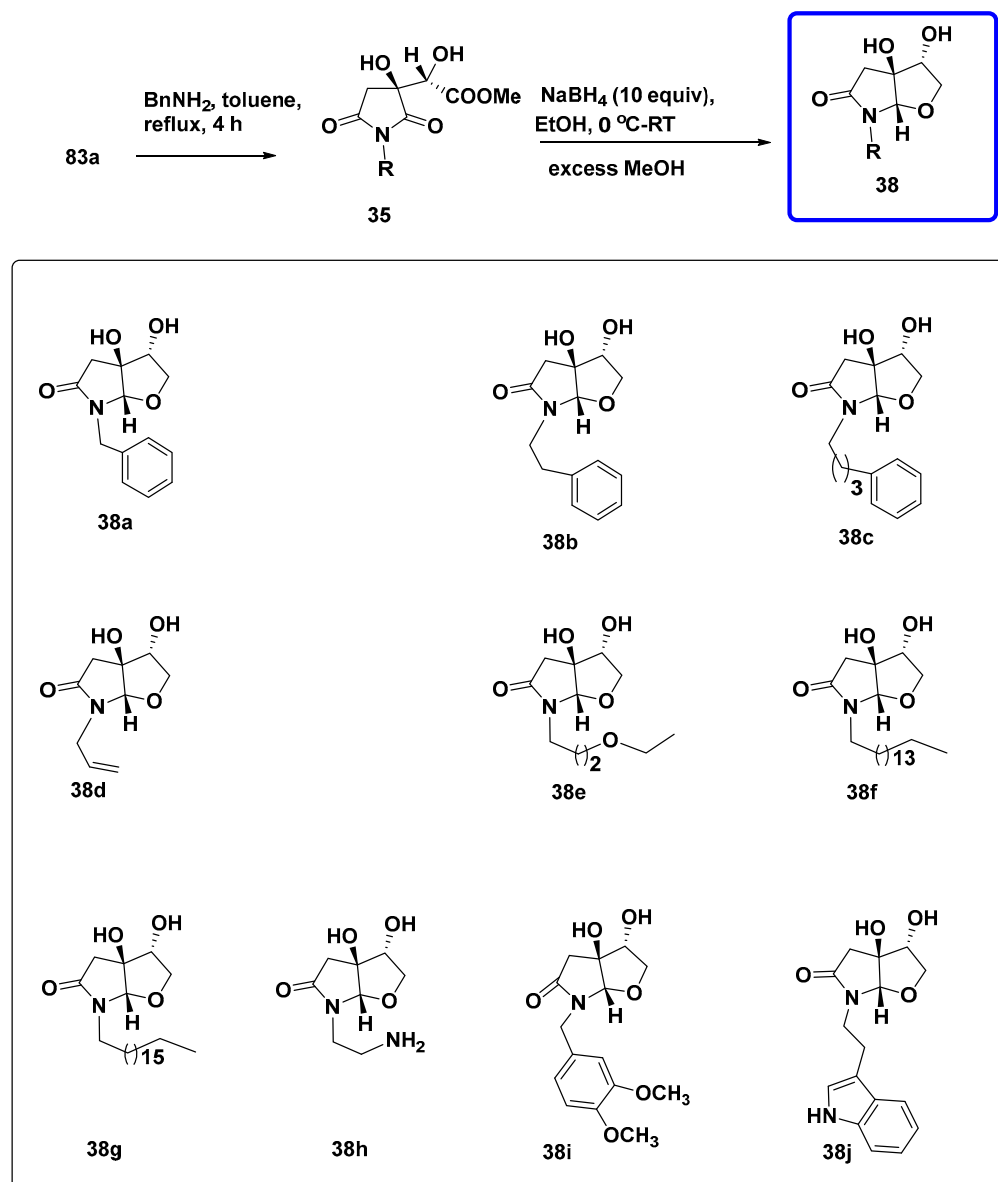


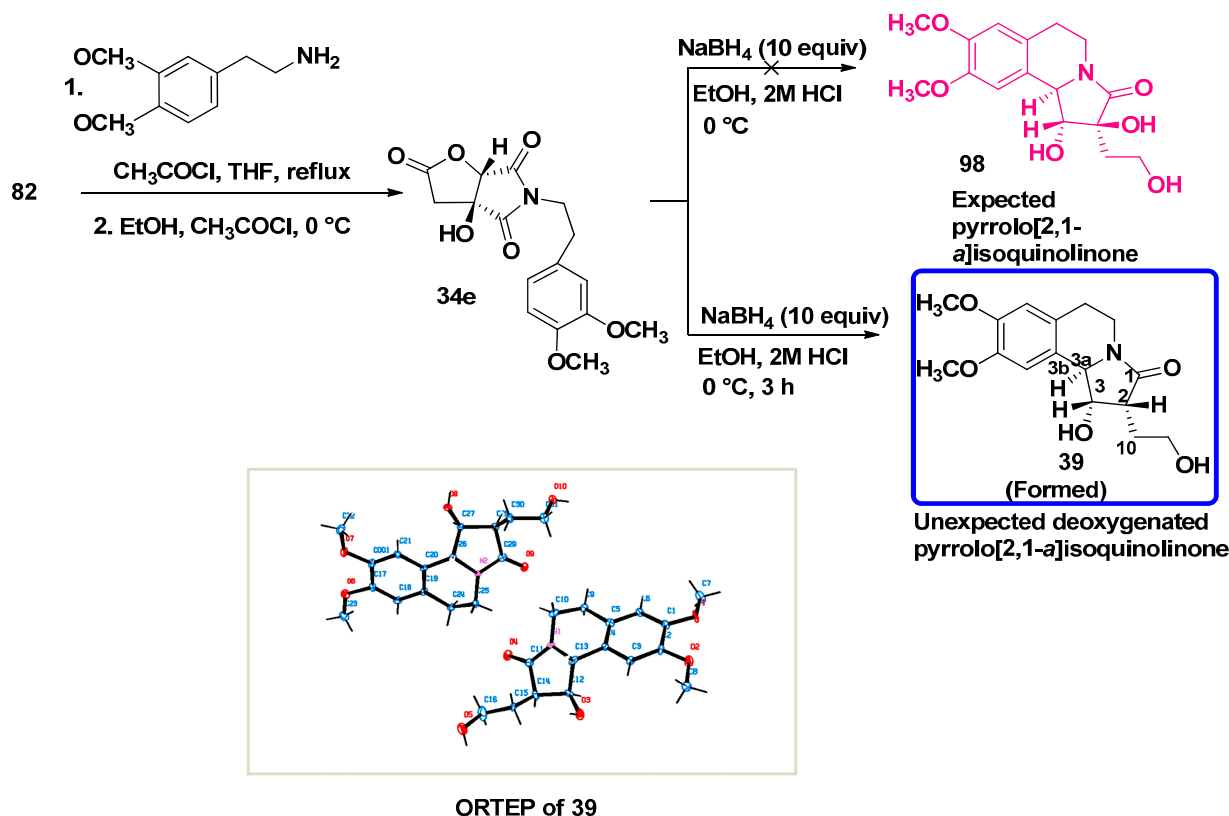
Figure 8. Natural product associated with furopyrrole structure.



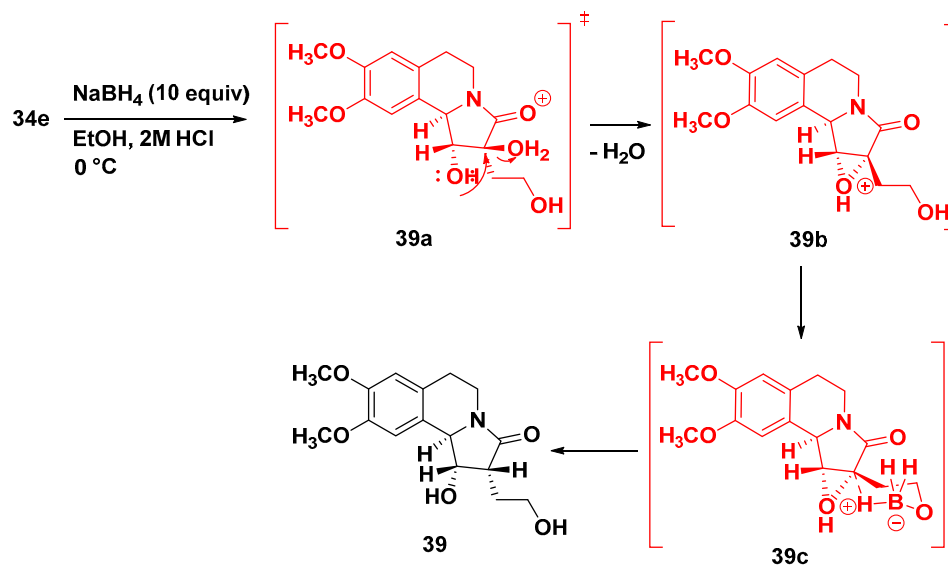
Scheme 11. List of furopyrroles synthesized from 1 [52].

7.4.2. Synthesis of Pyrroloisoquinolinone from Bicyclic Anhydride

The reaction of compound 34e with excess NaBH_4 (ten equivalents), followed by acidic workup, led to the formation of 2,3-disubstituted pyrrolo[2,1-a]isoquinolinone 39 (Scheme 12). Similar to the case with pyrrolidine-2,5-diones, the proximal hydroxy group of 34e directs the reducing agent to selectively reduce the C-2 carbonyl group. The resulting *N*-acyliminium ion undergoes Pictet-Spengler cyclisation to furnish compound 39 instead of the anticipated 98. A plausible mechanistic pathway for the formation of 39 involves the formation of epoxide 39b via an intra-molecular substitution of the tertiary hydroxyl group of 39a, followed by an intramolecular hydride transfer in an $\text{S}_{\text{N}}2$ fashion through a six-membered borohydride intermediate 39c (Scheme 13). The structure and configuration of 39 were established with spectroscopic data and X-ray crystallography (CCDC 1852026).



Scheme 12. Synthesis of pyrroloisoquinolinone 39 from bicyclic anhydride 82 [53].

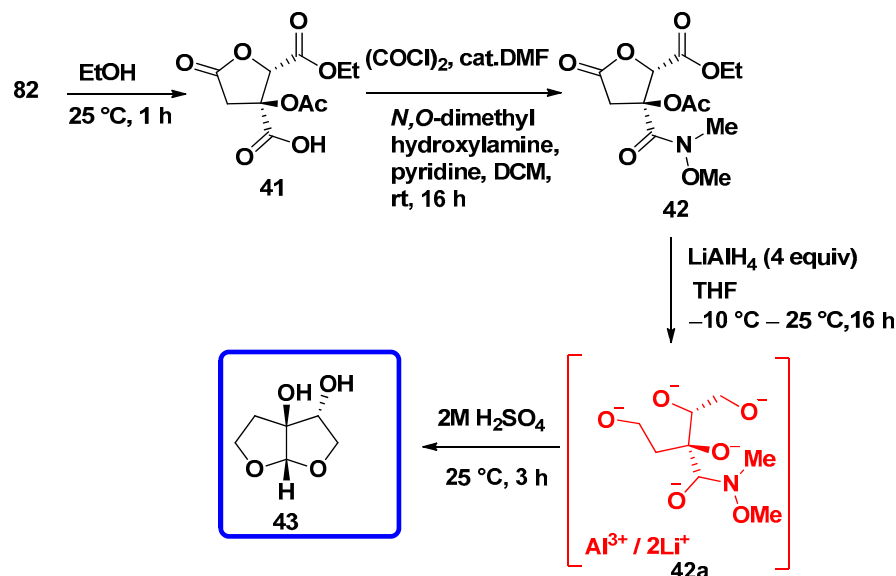


Scheme 13. Proposed mechanism for stereospecific deoxygenation [53].

7.4.3. Synthesis of Furo[2,3-b]furanol Skeletons

The bis-tetrahydrofuran (bis-THF) alcohol moiety plays a crucial role in the structure of HIV protease inhibitors (PIs) like Darunavir, Brexanavir, GS-9005, and SPI-256 [55,87–90]. This moiety constitutes a substantial portion of the manufacturing cost of the active pharmaceutical ingredient. Various synthetic routes for preparing the bis-THF moiety, particularly for compounds like Darunavir, often start with the synthesis of the racemic form of bis-THF. This racemic mixture is then subjected to enzymatic resolution methods to obtain the desired enantiomerically pure form [91].

The strategic conversion of anhydride **82** into the monoester (**41**) through a regioselective ring-opening reaction with ethanol followed by condensation with *N,O*-dimethylhydroxylamine yields monoamide **42** in one pot. Subsequent reduction of the monoamide **42** with LiAlH_4 (four equivalent), followed by the cyclisation of the hemiaminal (**42a**) using 2M sulfuric acid, results in the formation of the bis-THF diol **43** as a single stereoisomer, which was isolated as a viscous liquid (Scheme 14). The absolute configuration of **43** was assigned relatively, with the chiral integrity of the tertiary carbon atom bearing hydroxyl group maintained throughout the reaction process. The formation of the concave bis-furan structure is achieved only in the *cis* fashion, highlighting the stereochemical constraints and preferences in the synthesis of such ring systems.



Scheme 14. Synthesis of furo[2,3-*b*]furanol **43** [87].

8. Conclusions

This review highlights the traditional uses and medicinally important chemical compounds isolated from *Garcinia gummi-gutta*, a valuable spice tree known for its sun-dried, smoked fruit rind that imparts a distinctive tart flavour. The biological properties of extracts from various parts of the plant are mediated by several phytochemicals, with the majority of the effects attributed to its hydroxycitric acid content. Despite being synthetically underutilized, this naturally occurring acid, or its lactone form, has demonstrated the ability to facilitate the construction of a wide range of enantiomerically pure molecules with promising biological and functional applications. This includes the synthesis of concave bislactone skeletons present in naturally occurring secondary metabolites, such as (+)-avenaciolide and (−)-canadensolide, both recognized for their potent biological activities, including antifungal properties. Additionally, the synthesis of analogues of the quararibea metabolite—a chiral enolic- γ -lactone, serve as key building blocks for the synthesis of natural products including pheromones, the antibiotic strobilin, pencillianic acid, pulvinones, are described. Furthermore, the structure and stereochemistry of garcinia acid make it an ideal precursor for preparing chiral 3-substituted and 3,4-disubstituted pyrrolidine-2,5-diones, which are common structural subunits found in a variety of natural and synthetic bioactive products. The acid also enables the synthesis of the structural skeletons of the furo[2,3-*b*]furanol moiety, found in the anti-HIV drug Darunavir, as well as (−)-tetrahydropyrrolo[2,1-*a*]isoquinolinones, an analogue of the anti-tumour alkaloid (−)-crispine A, and (−)-hexahydroindolizino[8,7-*b*]indolones, an analogue of the naturally occurring (−)-harmicine, known for its antileishmanial and antinociceptive activities. Moreover, the syntheses of furo[2,3-*b*]pyrroles are also demonstrated. These syntheses are promising and pave the way for utilizing garcinia acid as a chiral building block

for synthesising biologically significant compounds, with the potential to develop new drugs. This approach also encourages more sustainable and environmentally friendly synthetic methods.

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Abbreviations

Acetyl-CoA	Acetyl coenzyme A
BnNH ₂	Benzyl amine
bis-THF	bis-tetrahydrofuran
BMS	Borane dimethyl sulphide
CH ₃ COCl	Acetyl chloride
CH ₂ N ₂	Diazomethane
(COCl) ₂	Oxalyl chloride
DCM	Dichloromethane
DMF	N,N-Dimethylformamide
EtOH	Ethanol
HCA	Hydroxycitric acid
HCl	Hydrochloric acid
HIV	Human immunodeficiency virus
HPLC	High-performance liquid chromatography
H ₃ PO ₃	Orthophosphorous acid
H ₂ SO ₄	Sulphuric acid
LiAlH ₄	Lithium aluminum hydride
MeOH	Methanol
MsCl	Methane sulfonyl chloride
NaBH ₄	Sodium borohydride
NaOH	Sodium hydroxide
ORTEP	Oak Ridge Thermal-Ellipsoid Plot Program
POCl ₃	Phosphorus oxychloride
THF	Tetrahydrofuran
TEA	Triethyl amine
p-TSA	p-Toluene sulfonic acid

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