Recent Advances in the Stereoselective Total Synthesis of Natural Pyranones Having Long Side Chains

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Abstract: Pyranone natural products have attracted great attention in recent years from chemists and biologists due to their fascinating stereoisomeric structural features and impressive bioactivities. A large number of stereoselective total syntheses of these compounds have been described in the literature. The natural pyranones with long side chains have recently received significant importance in the synthetic field. In the present article, we aim to review the modern progress of the stereoselective total syntheses of these natural pyranones containing long-chain substituents.

Keywords: pyranone; side chain; natural product; total synthesis; stereoselectivity

1. Introduction

Pyranones are an important class of natural products [1]. Several natural pyranones have been found to contain long side chains. The side chain is generally present at the C-6 portion of the pyranone ring. These naturally occurring pyranones with long-chain substituents have recently drawn considerable attention from the scientific community due to their impressive structural characteristics as well as interesting biological activities. Structurally, they contain a lactone ring, which is usually within the framework of a 5,6-dihydropyran-2-one (α,β-unsaturated δ-lactone). The H-6 in these molecules may be with the relative stereoposition of α or β. For example, in dodoneine [2] and rugulactone [3], the stereoposition of H-6 is the opposite (Figure 1).
The side chains of the pyranones may be of various lengths; they may even contain more than 20 carbons. Thus, the side chain of passifloricin A consists of 21 carbons [4]. These side chains possess several stereogenic centers with various functionalities. Generally hydroxyl, acetoxy, and carbonyl groups are located at different positions of the side chains. However, natural pyranones (such as rugulactone) having no chiral center in the side chains are also observed. Some compounds are found to possess a double bond [(E) or (Z) stereostructure] in their side chains. Rugulactone contains an (E)-double bond while spicigerolide has a (Z)-double bond in their respective side chains [3,5].

The bioactivity of this class of compounds is promising. They are found to exhibit manifold biological properties including anticancer [3,6], antiviral [7], antifungal [8], antituberculosis [9], and antimicrobial [10] activities. The α,β-unsaturated lactone moiety plays an important role in the bioactivity as it can act as a Michael acceptor in the presence of protein functional groups [11].

The interesting structural features and important bioactivities of these molecules have inspired synthetic chemists to explore their total syntheses [12–14] and biologists to discover novel therapeutics [15–17]. In several cases, the pyranones obtained from natural sources are insufficient to conduct further experiments. The total synthesis can generate the compounds in larger amounts required to explore their new medicinal values. Total syntheses are also useful to verify the established structures of the molecules.

Various modern synthetic approaches have now been applied to construct the natural pyranone molecules with proper stereostructures. Efficient diastereoselective and enantioselective synthetic protocols have been employed to introduce the required chirality in their side chains; ring-closing metathesis (RCM) and cross-metathesis (CM) reactions [18] have frequently been applied to construct the lactone rings and side chains, respectively. Various improved approaches have currently been utilized by different synthetic chemists to accomplish successfully stereoselective syntheses of natural pyranones. In this review, we have described the recent progress of the total syntheses of these compounds having long side chains. We have focused our discussion on the total syntheses of the molecules, which have repeatedly been constructed by applying various modern synthetic protocols.

2. Stereoselective Total Syntheses

In recent years, different research groups utilized various efficient procedures for the stereoselective syntheses of naturally occurring pyranones having long-chain substituents. The total syntheses of the following molecules will highlight the current advances in the field.
2.1. Dodoneine

Dodoneine (1), a naturally occurring 5,6-dihydropyran-2-one, was isolated from a medicinal parasitic plant, *Tapinunthus dodoneifolius* that grows on the sheanut tree in West Africa [2]. The structure of the compound was derived from its spectroscopic data and X-ray crystallographic analysis of its camphorsulfonate derivative. Dodoneine (1) was found to possess relaxation effects on preconstricted rat aortic rings. The compound was also evaluated as a hypotensive agent and as an inhibitor of human carbonic anhydrases [19,20].

Dodoneine (1) has recently been synthesized by several research groups [21–29]. The synthetic methods generally involve the asymmetric allylation of an aldehyde for introducing the stereogenic centers and the formation of the pyranone ring by ring-closing metathesis (RCM) or intramolecular transesterification. The first total synthesis of dodoneine (1) was reported independently by Falomir et al. [21] and Srihari et al. [22]. Falomir et al. used commercially available dihydro *p*-coumaric acid (2) as the starting material (Scheme 1). The acid was converted to silylated dihydro *p*-coumaraldehyde (3), which underwent asymmetric Keck allylation [30] to generate the homoallylic alcohol 4 (ee ca. 95%). The silylation of 4 and ozonolysis of the product afforded aldehyde 5. Asymmetric allylation of 5 using (+)-Ipc$_2$BCl/allylmagnesiumbromide (Ipc = isopinocamphenyl) yielded the homoallylic alcohol 6, which was obtained as a single diastereomer after purification. The subsequent acrylation of 6 with acryloyl chloride followed by ring-closing metathesis of the acrylate (7) applying a Grubbs first-generation catalyst provided the pyranone 8. Finally, the cleavage of the two silyl groups of 8 using aqueous HF in MeOH furnished dodoneine (1).

![Scheme 1](image-url)

*Scheme 1.* Reagents and conditions: (a) allyltriti-n-butyltin, (R)-BINOL, Ti(PrO)$_4$, (approximately 60% overall); (b) TBSOTf, CH$_2$Cl$_2$, 2,6-lutidine, r.t., 2 h, 85%; (c) O$_3$, −78 °C to r.t., PPh$_3$, 2 h; (d) (+)-Ipc$_2$BCl, Et$_2$O,allylMgBr, −90 °C, 2 h, (approximately 60% overall); (e) CH$_2$=CHCOCl, CH$_2$Cl$_2$, iPr$_2$Net, −78 °C, 62%; (f) 10% Grubbs first-generation catalyst, CH$_2$Cl$_2$, Δ, 4 h, 84%; (g) aq HF, MeCN, r.t., 16 h, 89%.
Srihari et al. applied the aldehyde 3 prepared from 4-hydrobenzaldehyde (9) (Scheme 2) [22]. The aldehyde 3 was reacted with (S)-1-(4-benzyl-2-thioxothiazolidin-3-yl) ethanone in the presence of TiCl₄ following the Crimmins protocol [31]. The major syn product 10 was converted to TBS ether 11, which upon treatment with DIBAL-H yielded the aldehyde 12. The aldehyde 12 underwent the Crimmins aldol reaction with (S)-1-(4-benzyl-2-thioxothiazolidin-3-yl) ethanone and TiCl₄ to produce the 1,3-syn compound 13 as the major product. The hydroxyl group of 13 was protected with MOMCl, and product was treated with DIBAL-H to form the aldehyde 14. The latter was treated with bis-(2,2,2-trifluoromethyl) (methoxycarbonylmethyl) phosphonate following the Horner–Wadsworth–Emmons olefination reaction [32] to produce the cis-olefinic ester 15. At the final stage, it was observed that 3 mol% HCl solution afforded the best result for the simultaneous deprotection and cyclization of the ester 15 to generate dodoneine 1.

Scheme 2. Reagents and conditions: (a) TiCl₄, DIPEA, CH₂Cl₂, −78 °C, 85%; (b) TiCl₄, DIPEA, CH₂Cl₂, −78 °C, 81%; (c) (CF₃CH₂O)₂P(O)CH₂COOCH₃, NaH, THF, −78 °C, 82%; (d) PTSA or PPTS or 3 mol% HCl.

A short and efficient synthesis of dodoneine (1) was reported by Cosy et al. [23]. They prepared the aldehyde 3 from the ester 16 (Scheme 3). This aldehyde (3) was treated with allyl titanium complex (S,S)-Ti-I to produce the homoallylic alcohol 4 (ee 96%). A cross-metathesis reaction [33] of 4 with ethyl acrylate in the presence of a Grubbs–Hoveyda second-generation catalyst afforded the unsaturated ester 17. On treatment with benzaldehyde using tert-BuOK, the ester 17 furnished the protected 1,3-diol 18 (syn:anti; 98:2). Reduction of the compound 18 with DIBAL-H afforded the aldehyde 19, which was subjected to Horner–Wadsworth–Emmons reaction [34] using bis (2,2,2-trifluoromethyl) (methoxycarbonylmethyl) phosphonate to produce the unsaturated ester 20 (Z:E = 90:10). Finally, the treatment of 20 with 80% aq. AcOH afforded dodoneine (1).
Scheme 3. Reagents and conditions: (a) (S,S)-Ti-I, Et₂O, −78 °C, 3 h, 97%; (b) GH-II (5 mol%), CH₂Cl₂, r.t., 2 d, 80%; (c) PhCHO, t-BuOK, THF, 0 °C, 2 h, 68%; (d) DIBAL-H, toluene, −78 °C, 94%; (e) (CF₃CH₂O)₂P(O)CH₂COOEt, KHMDS, 18-C-6, THF, −78 °C, 2 h, 70%; (f) aq AcOH, 60 °C, 24 h, 70%.

Das et al. utilized 4-hydroxy benzaldehyde as the starting material and applied Sharpless asymmetric epoxidation, 1,3-syn diastereoselective reduction, and Grubbs ring-closing metathesis in their synthetic sequence for the stereoselective construction of dodoneine (1) (Scheme 4) [24].
Scheme 4. Reagents and conditions: (a) Ti(iPrO)₄, (1.0 equiv), (+)-DIPT (1.1 equiv), TBHP (2.5 equiv), CH₂Cl₂, −20 °C, 12 h, 92%; (b) Red-Al (3.0 equiv), THF, 0 °C, 0.5 h, 82%; (c) CH₂=CHCH₂MgBr, Et₂O, 0 °C, 1 h, 74%; (d) DMP, NaHCO₃, CH₂Cl₂, 0 °C to r.t., 1 h, 88%; (e) LiAlH₄-LiI, Et₂O, −100 °C, 30 min, 94%; (f) acryloyl chloride, Et₃N, 0 °C to rt, 30 min, 96%; (g). Grubbs first-generation catalyst, CH₂Cl₂, 50 °C, 24 h, 85%; (h) TiCl₄, DCM, 0 °C, 89%.

Sharpless asymmetric epoxidation [35] of 22 was carried out with (+)-DIPT and the diastereoselective reduction of the ketone 27 with LiAlH₄-LiI at −100 °C (syn:anti = 94:6). The intramolecular metathesis reaction of 29 was conducted using a Grubbs catalyst of the first generation.

In another synthesis, Sharpless asymmetric dihydroxylation [36] and the regioselective nucleophile opening of cyclic sulfate formed from the resulting diol were used to generate the required chiral center (Scheme 5).
Sabitha et al. completed the synthesis of dodoneine (1) starting from the known chiral alcohol 35 (Scheme 6) [26]. The latter was oxidized with IBX to the corresponding aldehyde, which was treated with trimethylsulfoxoniumiodide using NaH in DMSO-THF to afford a racemic epoxide. Jacobson’s hydrolytic kinetic resolution (HKR) of this epoxide by applying (S,S)-Salen-Co-OAc catalyst yielded the chiral 36 (ee 95%) [37]. The epoxide 36 was converted into the homoallylic alcohol 37 by treatment with vinyl magnesium bromide and CuI. The compound is structurally related to 6. It was subsequently transformed into dodoneine (1) following a similar reaction sequence as shown earlier in Scheme 1.

Rauniyar and Hall prepared the chiral alcohol 4 (ee 97%) from the aldehyde 3 by using p-F-Vivol.SnCl4 catalyzed allylboration with allylboron pinacolate (Scheme 7) [27]. In a similar manner, the chiral diol 6 (dr 99:1) was produced from the aldehyde 5. Compound 6 was subsequently converted to dodoneine (1) following a sequence similar to that of Macro et al. [21] (Scheme 1).
Compound by Rauniyar and Hall (Scheme 9) [27]. This alcohol to dodoneine (43:57). The desired iodocarbonate
converted to dodoneine (Scheme 8). Compound Keck’s asymmetric allylation, iodine
induced electrophilic cyclization, and ring-closing metathesis (Scheme 8).

In an alternative approach [28], the total synthesis of dodoneine (1) was achieved by applying
Keck’s asymmetric allylation, iodine-induced electrophilic cyclization, and ring-closing metathesis
(Scheme 8). Compound 40 underwent diastereoselective iodolactoxization with I2 to form the cyclic
iodocarbonate 41 as a single diastereoisomer. This iodocarbonate (41) when kept in basic MeOH
solution afforded syn-epoxy alcohol 42. The free hydroxyl group of 42 was protected to form TBS-ether 43,
which was treated with allylmagnesiumbromide to furnish a diastereoisomeric mixture (syn:anti = 43:57).
The desired syn-epoxy alcohol 44 was purified by column chromatography and was converted
to dodoneine (1).

Allais and Ducrot prepared the chiral homoallylic alcohol 4 [29] following the method developed
by Rauniyar and Hall (Scheme 9) [27]. This alcohol 4 was treated with OsO4 and NaIO4 to form the
corresponding β-hydroxyaldehyde, which was reacted with trimethylallylsilane and SnCl₄ to produce the diol 45 (dr > 97:3) favoring the syn-product. The diol 45 was converted to a ketal 46. The latter underwent an oxidative cleavage with OsO₄, NaIO₄ and the resulting aldehyde was subjected to Horner–Wardsworth–Emmons olefination to furnish the unsaturated ester 47, (Z:E = 90:10). At the final step, the treatment of 47 with 80% aq. AcOH afforded dodoneine (1).

![Scheme 9](image)

**Scheme 9.** Reagents and conditions: (a) OsO₄, 2,6-lutidine, NaIO₄, dioxane-H₂O (3:1), r.t.; (b) allylsiMe₃, SnCl₄, CH₂Cl₂, –78 °C, 12 h, 80%; (c) 2,3-DMP, PPTS, CH₂Cl₂, r.t., 2 h, 96%; (d) OsO₄, 2,6-lutidine, NaIO₄, dioxane-H₂O (3:1); (e) 2-[bis(2,2,2-trifluoroethoxy)phosphoryl]acetate, KHCl, 18-crown-6, THF, –78 °C, 4 h, 51%; (f) 80% aq AcOH, 60 °C, 1 d, 68%.

2.2. Rugulactone

![Rugulactone](image)

Rugulactone (48) was isolated from *Cryptocarya rugulosa* [3]. It contains only one chiral center at C-6 with R-stereoconfiguration and an α, β-unsaturated γ-lactone along with an α, β-unsaturated ketone. The compound was found to inhibit constitutive NF-kB activity in human lymphoma cell lines. Several syntheses of rugulactone (48) have recently been reported [38–48]. In these syntheses, the chirality has been introduced by applying different methodologies such as Jacobsen’s hydrolytic kinetic resolution of epoxides, Keck/Marukawa asymmetric allylation, chemoenzymatic process, the chiral pool approach, and allylation with chiral boronic esters.

The first stereoselective total synthesis of rugulactone (48) was reported by Venkateshwarlu et al. [38] as well as by Yadav et al. [39]. The first group used 1,3-propane diol (49) as the starting material (Scheme 10). It was converted to monobenzylether (50), which was oxidized with IBX and the resulting aldehyde underwent Keck allylation to form the homoallylic alcohol 51 (ee 97.5%). Protection of the hydroxyl group and removal of the benzyl group compound 51 yielded the alcohol 52. The latter was oxidized with IBX, and the corresponding aldehyde was converted to the unsaturated ester 53 (Z:E = 95:5) by Still-Gennari modification of the Horner–Emmons olefination reaction. Treatment with 3% HCl in MeOH 53 yielded the pyranone 54.
unsaturated ester 53 (Z:E = 95:5) by Still–Gennari modification of the Horner–Emmons olefination reaction. Treatment with 3% HCl in MeOH yielded the pyranone 54.

Scheme 10. Reagents and conditions: (a) BnBr, NaH, TBAI, THF, 0 °C to r.t., 2 h, 85%; (b) (i) IBX, dry DMSO, CH₂Cl₂, 5 h, 88%; (ii) (R)-BINOL, 4 Å MS, Ti(iPrO)₄, allyltributylstannane, CH₂Cl₂, –78 °C to –20 °C, 80%; (c) TBDPSCl, imidazole, CH₂Cl₂, 4 h, 95%; (d) Li in naphthalene, −20 °C, 3 h, 81%; (e) (i) IBX, dry DMSO, CH₂Cl₂, 5 h, 85%; (ii) MeO₂CCH₂P(O)(OCH₂CF₃)₂, NaH, THF, −78 °C, 2 h, 76%; (f) 3% HCl in MeOH 30 min, 78%; (g) Grubbs second-generation catalyst (5 mol %), CH₂Cl₂, 40 °C, 12 h, 74%.

The ether part of rugulactone, fragment 56 was prepared from phenyl propanol (55) by treatment with vinyl magnesium bromide followed by oxidation of the generated alcohol with IBX. Finally, the cross-metathesis reaction of 54 and 56 using a second-generation Grubbs catalyst produced the natural rugulactone (48).

Venkateshwarlu et al. in a later publication [41] showed the introduction of chirality through D-proline catalyzed α-aminoxylation of the aldehyde 57 (Scheme 11).
From the known corresponding racemic compound by Jacobsen’s hydrolytic kinetic resolution using (R,R)-(Salen) Co^{III} (OAc) catalyst. Epoxide 61 was reacted with vinyl magnesium bromide and CuI to form the homoallyl alcohol 62 (ee > 98%). The esterification of 62 with acryloyl chloride, removal of the hydroxyl protection, and subsequently oxidation with DMP yielded the aldehyde 63. This aldehyde 63 was subjected to Horner–Wadsworth–Emmons homologation using dimethyl (2-oxo-4-phenylbutyl) phosphonate to furnish the unsaturated ketone 64. Finally, by treatment of this ketone (64) with Grubb’s first-generation catalyst, rugulactone (48) was formed.

In a chemoenzymatic synthetic approach, both (R)- and (S)-rugulactone were prepared by applying the Candida rugosa lipase to hydrolyze the butyrate ester of the protected 3-hydroxy homoallylic alcohol 65 (Scheme 13) [42]. The key intermediates (R)-66 (ee > 99%) and (S)-67 (ee > 98%) were obtained with high enantiomeric purity. The ester 66 was hydrolyzed and deprotected to form (R)-68. Both the alcohols (R)-68 and (S)-67 were converted to (R)-48 and (S)-48 respectively following the earlier established method (Scheme 10). (R)-48 is the naturally occurring rugulactone.
α,β-unsaturated ketone using Grubbs II catalyst to furnish the α,β-unsaturated ketone (Scheme 15) [44].

The thioacetal group of the starting material and applying Maruoka allylation and ring-closing metathesis as the key steps (Scheme 15) [44].

In another chemoenzymatic synthesis of rugulactone (48), chirality was induced by a stereoselective enzymatic reduction of a ketoester employing NADPH-dependent ketoreductase [40].

A chiral-pool method [43] was developed by Allais et al. for the asymmetric synthesis of rugulactone (48) (Scheme 14). The starting material was commercially available (2S)-glycidyl tosylate (69), which was converted to the olefin 70. The olefin 70 was subjected to a cross-metathesis reaction with 5-phenyl-pent-1-en-3-one using Grubb’s II catalyst to furnish the α,β-unsaturated ketone 71. The thioacetal group of 71 was removed, and the generated aldehyde 72 underwent a Still–Gennari olefination with methyl P,P-bis (2,2,2-trifluoromethyl) phosphonium acetate to form the unsaturated ester 73. The latter on treatment with AcOH yielded natural rugulactone (48).

Das et al. achieved the total synthesis of rugulactone (48) using 3-phenyl propanol (74) as the starting material and applying Maruoka allylation and ring-closing metathesis as the key steps (Scheme 15) [44].
Compound 75 was prepared from 74 by oxidation of the latter under Swern conditions and treatment of the corresponding aldehyde with THP protected homopropargyl alcohol. The alkenol 76 was obtained by reduction of 75 with LiAlH₄ and subsequently, it was converted to 77. This alcohol (77) was oxidized with IBX, and the resulting aldehyde was subjected to Maruoka allylation [49] to form the homoallylic alcohol 78 (ee 97%). The latter was esterified with acryloyl chloride and the ester 79 was then converted to rugulactone (48).

Das et al. also synthesized rugulactone (48) through an alternative route (Scheme 16) [47]. They prepared the chiral aldehyde 81 from propane 1,3-diol applying Maruoka allylation and ring-closing metathesis. This aldehyde 81 underwent Wittig olefination with the phosphorane, PhCH₂CH₂COCH=PPh₃ to yield rugulactone (48).

The intermediate 81 was prepared by Barua et al. [45] from the chiral epoxide 82 (Scheme 17) and by Pietruszka et al. [46] from the allylic boronic ester 85 (Scheme 18).
Synaptoglutaric acid was synthesized by Sabitha et al. [51] with the known (-)-benzyl glycidyl ether (88a) synthesized the structure on the basis of spectroscopic studies, Mosher ester analysis, and acetonide formation [51]. Macro et al. observed that the synthetic compound was not identical to natural products [3,6]. The structure of the compound was originally proposed as 88a on the basis of spectroscopic studies, Mosher ester analysis, and acetonide formation [51]. Macro et al. synthesized the structure 88a and observed that the synthetic compound was not identical to natural product [52]. Sabitha et al. also synthesized 88a and its one stereoisomer 88b (Scheme 19) [53]. Their synthesis was initiated with the known (R)-benzyl glycidyl ether 89, which was converted to allyl alcohol 90. The latter was subjected to Sharpless asymmetric epoxidation to form the single isomer 91.
This epoxide (91) was transformed to the alcohol 93, which on epoxidation generated the epoxide 94. Later, this epoxide (94) was converted to acetonides 95a and 95b.

Next, these acetonides 95a and 95b furnished separately the triacetates 96a and 96b respectively by deprotection, acetylation, and partial reduction. Finally, the cross-metathesis reaction between 95a/95b and vinyl lactone (97) using Grubbs second-generation catalyst produced 88a/88b. After inspection of the NMR spectra of 88a and 88b, the authors revised the structure of synargentolide A as 88b.

Several other syntheses of 88b have recently been reported [54–59]. Das et al. developed an efficient synthesis of both 88a and 88b starting from D-tartaric acid (Scheme 20) [56]. The compound was converted to the alcohol 98, which was subjected to Swern oxidation, and the corresponding aldehyde was treated with methyl magnesium bromide to produce the second alcohol 99. The deprotection and acetylation of this compound (99) yields 96a and 96b, which were then converted to 88a and 88b, respectively (following the method shown earlier in Scheme 19).
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Scheme 20. Reagents and conditions: (a) i) (COCl)$_2$, DMSO, Et$_3$N, CH$_2$Cl$_2$, 1 h, 89%; ii) MeMgBr, Et$_2$O, $-50\,^\circ$C, 2 h, 62%; (b) i) MeOH, 2N HCl, r.t., 1 h, ii) Ac$_2$O, Et$_3$N, DMAP, CH$_2$Cl$_2$, 0 °C to r.t., 1 h, 92% (2 steps); (c) Grubbs second-generation catalyst, refluxing CH$_2$Cl$_2$, 2 h, 67% for 88a and 66% for 88b.

It is interesting to mention here that the calculation of density functional theory (DFT) NMR parameters has recently suggested that both the structures 88a and 88b are incorrect and 88c is the correct structure of the natural synargentolide A [60].

2.4. Synargentolide B

Synargentolide B was isolated from the South Africa species Syncolostemon argenteus [51]. Its structure was tentatively proposed as 100a. Prasad and Gutala [61] carried out the total synthesis of possible diastereoisomers of the compound (Scheme 21) and derived the structure of the natural product as 100b, which was earlier reported for a constituent of Hyptis oblongifolia [62].

Compound 100b was synthesized [61] from the aldehyde 101, which was converted to the major allyl alcohol 102. This allyl alcohol 102 was elaborated to the ester 103. On the reduction of 103 with NaBH$_4$/CeCl$_3$, two diastereoisomeric compounds 104 and 105 were obtained. Compound 104 was transformed to 105 by Mitsunobu inversion. Subsequently, 105 was converted to synargentolide B (100b) by reaction sequences involving deprotection, acetylation, and cross-metathesis.
Scheme 21. Reagents and conditions: (a) allylmagnesiumbromide, THF, 0 °C, 1 h, 40%; (b) NaBH$_4$/CeCl$_3$, MeOH, $-78^\circ$C, 1 h, 94%.

In a tandem ring-closing/cross-metathesis approach for the synthesis of synargentolide B (100b), D-(-)-diethyl tartarate and D-ribose were used as starting materials (Scheme 22) [63].

Scheme 22. Reagents and conditions: (a) Grubbs second-generation catalyst, benzene, r.t. to reflux, 1.5 h, 83%; (b) TFA, CH$_2$Cl$_2$, 12 h, 87%.

Akkewar et al. obtained the diacetyl compound 107 from l-ascorbic acid, and they prepared the other part of 100b from D-ribose employing the Bestmann–Ohira reaction, zinc allylation, and ring-closing metathesis (Scheme 23) [64].
Liu et al. prepared the intermediates 107 and 110 from L-ethyl lactate and D-mannitol respectively [65]. They also synthesized the enantiomer of natural synargentolide B [66]. A diastereoselective synthesis of 5'-epi-synargentolide B has also been reported [67].

Suresh Babu et al. followed a different strategy for the stereoselective synthesis of synargentolide B (Scheme 24) [68]. They started their synthesis with ethyl (S)-2-hydroxypropanoate (111), which was protected to form 112. The latter on reduction with DIBAL-H followed by treatment with ethyl propiolate and LiHMDS furnished the hydroxyl ester 113. This ester (113) was subsequently converted to the protected allyl alcohol 114 following a reaction sequence involving protection, reduction, and Wittig olefination. Compound 114 underwent Sharpless asymmetric dihydroxylation using an AD-mix-β to form the diol 115 (dr 97.5:2.5). Next, this diol (115) was used to produce the allyl alcohol 116, which was converted to two isomeric acryloylesters, and the major isomer was subsequently transformed to natural synargentolide B (100b).

Scheme 23. Reagents and conditions: (a) Bestmann–Ohira reaction, reflux, 8 h, 65%; (b) i) Grubbs second-generation catalyst, CH2Cl2, reflux, 6 h, 67%; ii) PTSA, MeOH, reflux, 12 h, 78%.

Scheme 24. Reagents and conditions: (a) TBSCI, CH2Cl2, imidazole, r.t., 8 h, 93%; (b) (i) DIBAL-H, CH2Cl2, −78 °C, 0.5 h, 84%; (ii) ethyl propiolate, LiHMDS, THF, −78 °C to r.t., 3 h, 76%.
2.5. Synrotolide

Synrotolide (117) was isolated from the leaves of *Syncalostemon ratundifolius* [69]. Its structure was determined from spectroscopic analysis and X-ray crystallographic studies. The structure of synrotolide (117) is interesting, as it contains a five-chiral center and a cis-double bond. Initially, the synthesis of its diacetate was reported [70,71], and later, the total synthesis of the natural product was published [72,73].

The total synthesis of synrotolide (117) was started from (S)-ethyl lactate, which was converted to the allyl alcohol 118 (Scheme 25) [72]. The Sharpless epoxidation of this allyl alcohol (118) using L-(-)-DIPT and TBHP yielded the epoxy alcohol 119 (*dr* 97:3). The ring opening of the epoxide 119 with 0.5 N NaOH in *t*-BuOH:H₂O (1:5) afforded the alcohol 120, which was converted to aldehyde 121. Treatment of 121 with the protected hydroxyl propyne generated the compound 122 (*dr* 97:3), which by following protection/deprotection methodologies produced the alcohol 123. Oxidation of the alcohol 123 with IBX and stereoselective allylation of the aldehyde with (+)-(IPC)₂ Ballyl furnished the homoallyl alcohol 124 (*dr* 97:3). This homoallyl alcohol with different protecting groups was also prepared from (S)-ethyl lactate through an alternative route. Next, the alcohol 124 was converted to the pyranone derivative 125, which on partial hydrogenation with Lindlar’s catalyst followed by treatment with H₂SiF₆ provided the natural synrotolide (117).

**Scheme 25.** Reagents and conditions: (a) Ti(PrO)₄, (+)-DIPT, TBHP, CH₂Cl₂, −20 °C, 24 h, 91%; (b) 0.5 N NaOH, *t*-BuOH:H₂O (1:5), 75 °C, 15 h, 72%; (c) n-BuLi, THF, −78 °C, 2 h, 91%; (d) i) IBX, DMSO, CH₂Cl₂, 0 °C to r.t., 2 h; ii) (+)-(IPC)₂ Ballyl, Et₂O, −100 °C, 81%, over two steps.
In another approach of the synthesis of synrotolide (117), the intermediates 128 (related to 124 with different protecting groups) was prepared from d-(−)-ribose (Scheme 26) [73]. This intermediate (128) was subsequently transformed to synrotolide (117).

Scheme 26. Reagents and conditions: (a) EtMgBr, THF, 0 °C to r.t., 3 h, 92%.

The synthesis synrotolide (117) prepared by this method (Scheme 26) was evaluated for cyclotoxic activity. The compound was found to inhibit the growth of PANC1 cell lines [73].

2.6. Lippialactone

Lippialactone (129) was isolated from the acrial parts of Lippia javanica [74]. The compound is structurally related to synargentolide A (88c), but its stereoconfiguration is different. Lippialactone (129) was found to be active against the chloroquine-sensitive D10 strain of Plasmodium falciparum. The total synthesis of 129 was initiated from l. (−)-threonine, which was converted to the alcohol 130 (Scheme 27) [75]. This alcohol (130) was oxidized, and the corresponding aldehyde was subjected to Keck allylation to produce the allyl alcohol 131 (dr = 84:16). Then, this allyl alcohol (131) was transformed to the required triacetate 132. Finally, the cross-metathesis reaction between the triacetate 132 and vinyl lactone (97) using Grubbs second-generation catalyst furnished lippialactone (129).
Scheme 27. Reagents and conditions: (a) i) DMP, CH$_2$Cl$_2$, 0 °C to r.t., 1 h; ii) CH$_2$=CHCH$_2$SnBu$_3$, MgBr$_2$·OEt$_2$, CH$_2$Cl$_2$, −78 °C, 2 h, 66% (over two steps); (b) Grubbs second-generation catalyst, CH$_2$Cl$_2$, reflux, 4 h, 68%.

In another total synthesis of lippialactone (129), D-mannitol was used as the starting material (Scheme 28) [76]. It was converted to the diol (133), which was esterified with PivCl to form the ester 134. Mesylation of the ester 134 and then treatment with anhydrous K$_2$CO$_3$ yielded the epoxide 135. Ring opening of the epoxide (135) with vinyl magnesium bromide and Cul furnished a homoallyl alcohol, which on acetylation afforded the monoacetate 136. The latter was converted to lippialactone (129) by a cross-metathesis reaction with vinyl lactone (97) followed by deprotection and acetylation.

![Chemical structure](image)

Scheme 28. Reagents and conditions: (a) PivCl, Et$_3$N, DMAP, CH$_2$Cl$_2$, 0 °C to r.t., 4 h, 87%; (b) i) MsCl, Et$_3$N, DMAP, CH$_2$Cl$_2$, −80 °C to −20 °C, 12 h, ii) K$_2$CO$_3$, MeOH, rt, 2 h, 85% for two steps.

2.7. Spicigerolide

![Chemical structure](image)
Spicigerolide (137) was isolated from the Mexican traditional medicinal plant, *Hyptis spicigera* [5]. The compound showed cytotoxic activity in some cell tumoral lines. The first synthesis of the compound [77,78] was described by Marco et al. [12]. Later, some other total syntheses of 137 were reported [79,80].

Garcia et al. used protected (S)-lactaldehyde as the starting material (Scheme 29) [79]. This was treated with (R)-1-phenylprop-2-ynyl acetate (137) under Carreira’s condition [81] to form the anti-syn alcohol 138, which was converted to the olefin 139. This olefin (139) was subjected to a Pd-catalyzed [3,3]-sigmatropic rearrangement to form the triacetate 140. The latter was transformed to the aldehyde 141, which on treatment with 2-tert-butyldiphenylsilyloxy-1-propyne followed by acetylation afforded the tetraacetyl compound 142 as a single diastereoisomer. The partial hydrogenation of 142 using Lindlar’s catalyst and removal of the silicon-protecting group furnished the allyl alcohol 143. Next, the latter was oxidized to the aldehyde 143 under Swern condition, and this aldehyde (144) was allylated using Duthaler’s Ti-TADDOL-mediated allylation [82] to form the alcohol 145 (dr 87:13). Compound 145 with proper stereoconfiguration was subsequently converted to spicigerolide (137).

![Scheme 29](image)

**Scheme 29.** Reagents and conditions: (a) Zn(OTf)$_2$, Et$_3$N, (-)-NME, toluene, 4 h, 95%; (b) PdCl$_2$(NCPh)$_2$, CH$_2$Cl$_2$, r.t., 24 h, 70%; (c) Swern oxidation conditions; (d) CpTiCl-(S,S)-TADDOL, Et$_2$O, CH$_2$=CHCH$_2$MgBr, –78 °C, 2.5 h, 84%.

In a recent synthetic approach, spicigerolide (137) was prepared from 1-(-)-DET, which was transformed to the aldehyde (146) (Scheme 30) [80]. The Grignard reagent prepared from this aldehyde and ethyl bromide and Mg was treated with the alkyne 147 to produce the alcohol 148 (1:1 mixture of diastereoisomers). The alcohol (148) was oxidized, and the corresponding ketone was reduced using (S)-CBS catalyst [83] to furnish the chiral propargyl alcohol 149 (dr 9:1). Next, the aldehyde 150 generated from this alcohol (149) was used for chain elongation using a Still–Gennari reagent to form the ester 151, which was subsequently converted to spicigerolide (137).
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A stereoselective reaction of L (+) DET, \( \text{EtOOC} - \text{COOEt} \), with borane–dimethyl sulfide adduct using (S)-CBS catalyst yielded the chiral alcohol \( \text{O} - \text{CHO} \) (Scheme 30) [88]. This epoxide (153) was treated with acyl anion equivalent 154, and the product was converted to the ketone 155. A diastereoselective reaction of 155 with borane–dimethyl sulfide adduct using (S)-CBS catalyst yielded the chiral alcohol \( \text{O} - \text{CHO} \) (de > 95%). The removal of the MOM protecting group of the latter afforded the required diol-intermediate, which was transformed to the ketone 155. A diastereoselective reaction of 155 with borane–dimethyl sulfide adduct using (S)-CBS catalyst yielded the chiral alcohol \( \text{O} - \text{CHO} \) (de > 95%). The removal of the MOM protecting group of the latter afforded the required diol-intermediate, which was transformed to the ketone 155. A diastereoselective reaction of 155 with borane–dimethyl sulfide adduct using (S)-CBS catalyst yielded the chiral alcohol \( \text{O} - \text{CHO} \) (de > 95%). The removal of the MOM protecting group of the latter afforded the required diol-intermediate, which was transformed to the ketone 155. A diastereoselective reaction of 155 with borane–dimethyl sulfide adduct using (S)-CBS catalyst yielded the chiral alcohol \( \text{O} - \text{CHO} \) (de > 95%). The removal of the MOM protecting group of the latter afforded the required diol-intermediate, which was transformed to the ketone 155. A diastereoselective reaction of 155 with borane–dimethyl sulfide adduct using (S)-CBS catalyst yielded the chiral alcohol \( \text{O} - \text{CHO} \) (de > 95%).

Recently, a total synthesis of an epimer of spicigerolide has also been reported. \( \text{O} - \text{CHO} \) was employed as a chiral source to generate the four stereogenic centers in the side chain [84].

2.8. Cryptofolione

Cryptofolione (152) was isolated from Cryptocarya myrtrifolia and C. moschata, which are indigenous to South Africa and Brazil, respectively [85,86]. The compound was evaluated to be active against the trypomastigots of Trypanosoma cruzi, reducing their number by 77% at 250 µg/mL. The first synthesis of 152 [87] was mentioned by Macro et al. [12]. In recent years, several other syntheses of the molecule have been reported [88–92]. In a recent synthetic approach, the required intermediate was prepared from a chiral allyl epoxide (153) (Scheme 31) [88]. This epoxide (153) was treated with acyl anion equivalent 154, and the product was converted to the ketone 155. A diastereoselective reaction of 155 with borane–dimethyl sulfide adduct using (S)-CBS catalyst yielded the chiral alcohol 156 (de > 95%). The removal of the MOM protecting group of the latter afforded the required diol-intermediate, which was transformed to the acetonide 157. The same intermediate was also prepared by Prins cyclization of a chiral homoallylic alcohol with trans-cinnamaldehyde. Finally, the cross-metathesis reaction between 157 and the vinyl
lactone (97) in the presence of Grubbs second-generation catalyst followed by treatment of the product with aq 4% HCl furnished the natural cryptofolione (152).

\[
\text{Scheme 31. Reagents and conditions: (a) S-CBS catalyst, toluene, BH}_3\text{-DMS, 0 }^\circ\text{C, 0.5 h, 78%, 98% de.}
\]

Das et al. initiated the synthesis of cryptofolione (152) starting from propane-1,3-diol, which was transformed to the alcohol 158 (Scheme 32) [89]. Oxidation of this alcohol (158) with IBX followed by reduction with BH₃-Me₂S using the catalyst (R)-2-methyl-CBS-oxazaborolidine furnished the chiral alcohol 159 (ee 97%). Acetylation of the free –OH group, removal of the PMB group, and oxidation of the generated alcohol with IBX formed an aldehyde. This aldehyde underwent Maruoka allylation to produce the allyl alcohol 160, which was subsequently converted to cryptofolione (152).

\[
\text{Scheme 32. Reagents and conditions: (a) IBX, DMSO, CH}_3\text{Cl}_2, 0 ^\circ\text{C to r.t., 4 h, 88%; (b) (R)-(Me)-CBS (1.0 M in toluene), THF, BH}_3\text{-Me}_2\text{S, }-20 ^\circ\text{C, 2 h, 70%; (c) (S,S)-I, allyl tributyl stannane, CH}_3\text{Cl}_2, 0 ^\circ\text{C, 18 h, 74%}.}
\]

In some current synthesis of natural cryptofolione, an asymmetric aldol reaction has been applied to generate the required chirality of the molecule [90–92]. Das et al. also completed the stereoselective synthesis of the non-lactonic portion of (Z)- cryptofolione [93].
2.9. Passifloricin A

Passifloricin A was isolated from *Passiflora foctida var. hispida* [4]. Its structure was originally proposed to be 161a from its spectroscopic data, and its correct structure was settled as 161b on the basis of the syntheses of its different isomers [94–97]. The compound was found to inhibit impressive leishmanicidal and antiprotozoal properties [4].

In recent years, several new syntheses of passifloricin (161b) have been reported. Chandrasekar et al. prepared the compound starting from the olefin (162) (Scheme 33) [98]. This was converted to the chiral epoxide 163 by epoxidation followed by resolution of the racemic form using Jacobson’s catalyst. The epoxide 163 was transformed to the allyl alcohol 164 following a series of known reactions. This allyl alcohol 164 was subjected to Sharpless asymmetric epoxidation using (+)-DET to produce the chiral epoxy alcohol 165. The latter was converted to the α,β-unsaturated ester 166, which was treated with benzaldehyde and potassium tert-butoxide to form the acetal 167. The ester group of 167 was reduced to aldehyde, and the product underwent Maruoka allylation to furnish the major syn-isomer 168. This allyl alcohol (168) was subjected to its conversions to passifloricin A (161b) with proper stereo configuration.

![Diagram](image)

Scheme 33. Reagents and conditions: (a) Ti(PrO)₄, (+)-DET, tBuOOH, CH₂Cl₂, 4 Å MS, −20 °C, 8 h, 85%; (b) PhCHO, KO²Bu, THF, 0 °C, 45 min, 72%.

A similar intermediate as 168 with different protecting groups was also prepared by a different research group [99]. They employed Prins cyclization [100] as the key step.

Das et al. accomplished the total synthesis of passifloricin A (161b) starting from protected glyceraldehyde and employing Maruoka allylation, iodo-carbonate cyclization, and olefin metathesis as the key reactions in their synthesis sequence (Scheme 34) [101].
Protected glyceraldehyde was treated with 1-bromotetradecane and the major product, anti-isomer \textit{169}, was purified by chromatography. This compound \textit{169} was converted to the ester \textit{170}, which was reduced with DIBAL-H, and the resulting aldehyde was subjected to Maruoka allylation to give the allyl alcohol \textit{171} (ee 97%). The free hydroxyl group of \textit{171} was protected with Boc\textsubscript{2}O, and the product underwent iodo-carbonate cyclization with NIS to furnish the major syn-isomer \textit{173} (>95%). The purified \textit{173} was reacted with K\textsubscript{2}CO\textsubscript{3} in MeOH, and the resulting epoxide was treated with vinyl Grignard reagent and CuI to produce the allyl 1,3-diol \textit{174}. The protection of two hydroxyl groups of \textit{174}, conversion of the olefin moiety to aldehyde, and again Maruoka allylation produced the required intermediate \textit{175}, which generated passifloricin A in a stereoselective manner.

2.10. \textit{Strictifolione}

\textit{Strictifolione} \textit{176} was isolated from the stem bark of \textit{Cryptocarya strictifolia} that grows in Indonesia \cite{102}. Its structure was deduced from spectroscopic analysis. The compound was found to display antifungal property. Its earlier syntheses were mentioned by Macro et al. \cite{12}. Recently, a large number of new syntheses of \textit{strictifolione} \textit{176} have been reported \cite{92,103–109}.

In a recent synthesis, known chiral allyl alcohol \textit{177} was used as a starting material (Scheme 35) \cite{103}. The Prins reaction between \textit{177} and benzaldehyde followed by hydrolysis of the generated trifluoroacetate and protection of the hydroxyl group afforded \textit{178}. The tetrahydropyran ring of \textit{178} was opened with Li in liquid NH\textsubscript{3} to form the open chain compound \textit{179}. The protection of the primary
hydroxyl group of 179 as a tosyl derivative and treatment of the product with NaH yielded the epoxide 180. The opening of this epoxide (180) with Li acetylide afforded the homopropargyl alcohol 181. The partial reduction of 181 with Lindlar’s catalyst and deprotection of the MOM group furnished the required intermediate 182. Finally, the cross-metathesis reaction between 182 and vinyl lactone 97 using Grubbs second-generation catalyst afforded natural strictifolione (176).

![Scheme 35](image)

Scheme 35. Reagents and conditions: (a) i) PhCHO, TFA, CH₂Cl₂, K₂CO₃, MeOH, r.t., 0.5 h, 59%; ii) MOMCl, Hunig’s base, 0 °C to r.t., 2 h, 90%; (b) Li-liq NH₃, dry THF, −78 °C, 60%; (c) LiC≡CH, DMSO, 0 °C to r.t., 4 h, 80%.

During the studies [104,110–114] on the syntheses of natural pyranones, Das et al. accomplished the stereoselective total synthesis of strictifolione (Scheme 36) [104]. The starting material, phenyl propanal, was subjected to 2C-Wittig homologation with (carboethylmethylene) triphenylphosphorane to produce the α,β-unsaturated ester 183. Reduction of the ester 183 with Dibal-H and allylation of the resulting aldehyde afforded the racemic alcohol 184. The Sharpless kinetic resolution of 184 by applying (+)-DIPT yielded the chiral epoxy alcohol 185 (ee 97%). The epoxide ring of 185 was opened with Red-Al to give the intermediate 182, which was transformed to strictifolione (176).

![Scheme 36](image)

Scheme 36. Reagents and conditions: (a) Ph₃PCHCOOEt, CH₂Cl₂, r.t., 8 h, 84%; (b) Ti(PrO)₄, (+)-DIPT, TBHP, CH₂Cl₂, 4 Å MS, −20 °C, 5 h, 45%; (c) Red-Al, THF, 0 °C to r.t., 3 h, 77%.

The same intermediate 182 or its protected form was also prepared by different other research groups by utilizing various synthetic methodologies, such as hydrolytic kinetic resolution [105,106], chemoenzymatic means [107], and asymmetric aldol reaction [92]. In addition, one modular approach that utilized phosphate tether mediate protocol was also developed for the synthesis of 182 [108].

An efficient synthesis of strictifolione (176) was achieved by She et al. by employing one-pot double allyl boration and ring-closing metathesis (Scheme 37) [109]. The required intermediate 188 was prepared by the treatment of 3-butenal with boryl-substituted allylborane 186 and then with the
known aldehyde 187 utilizing a double allylboration methodology. Compound 188 was obtained with high diastereoselectivity and enantioselectivity (dr ≥ 20:1, ee 92%). The esterification of this compound with acryloyl chloride and ring-closing metathesis of the resulting diester followed by deprotection of the product 189 furnished the ketone 190. Finally, the reduction of this ketone (190) with Me₄NBH (OAc)₃ yielded strictifolione (176).

![Scheme 37. Reagents and conditions: (a) 186, Et₂O, −78 °C, 2 h, then 187, r.t., 24 h, 55%, 92% ee; (b) Me₄NBH(OAc)₃, AcOH/CH₃CN (1:1), −20 °C, 10 h, 91%.](image)

3. Conclusions

In the present article, we have described briefly the recent progress in the stereoselective total syntheses of natural pyranones having long-chain substituents. A large number of molecules have currently been synthesized by different workers following various synthetic approaches. As for examples, nine syntheses of dodoneine (from 2008) and 12 syntheses of rugulactone (from 2009) have been reported. The interesting structural features as well as promising biological activities of natural pyranones stimulated the research groups to develop new methodologies for their total syntheses. We have considered some important bioactive natural pyranones having long side chains and discussed the different modern approaches for their stereoselective syntheses. From this review, it is apparent that the rapid achievement in the diastereoselective and enantioselective synthetic protocols have made it possible to introduce proper chirality in the pyranone molecules. The ring-closing metathesis and cross-metathesis reactions have been largely utilized for the construction of their lactone rings and side chains, respectively. It is expected that the knowledge generated from the modern synthetic endeavors of the described natural pyranones in this article will enable the further development of more concise, efficient, and practical syntheses of this class of compounds.

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### Abbreviations

| Abbreviation | Full Form |
|--------------|-----------|
| HF           | Hydrofluoric acid |
| TBS          | tert-Butylmethylsilyl |
| DIBAL-H      | Disobutylaluminium hydride |
| DIPEA        | N,N-Diisopropylethylamine |
| PTSA         | para-toluensulfonic acid |
| PPTS         | Pyridinium p-toluenesulfonate |
| DIPT         | Disopropyltartrate |
| TBHP         | tert-Butylhydroperoxide |
| DMP          | 2,2-Dimethoxypropane |
| TBSCI        | tert-Butylmethylsilyl chloride |
| BINOL        | 1,1′-Bi-2-naphthol |
| Ti(OPr)₄     | Titanium isopropoxide |
| PMB          | 4-Methoxybenzyl |
| KHMD          | Potassium hexamethyldisilazide |
| NF-kB        | Nuclear factor kappa-light-chain-enhancer of activated B cells |
| TBAI         | tert-Butylammonium iodide |
| TBDPSCI      | tert-Butyldiphenylsilyl chloride |
| NaHMDS       | Sodium bis (trimethylsilyl) amide |
| NADPH        | Nicotinamide adenine dinucleotide phosphate |
| THP          | Tetrahydropyran |
| TEMPO        | (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl |
| TPP          | Thiamine pyrophosphate |
| TsCl         | Para-toluene sulfonic chloride |
| TESCl        | Triethylsilyl Chloride |
| DET          | N,N-Diethyldiamine |
| (S)-CBS      | (S)-5,5-Diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborolidine |
| NIS          | N-Bromo succinimide |
| TBSOTf       | Trimethylsilyl trifluoromethanesulfonate |
| t-BuOK       | Potassium tert-butoxide |
| AcOH         | Acetic acid |
| LiAlH₄       | Lithium aluminium hydride |
| Et₃N         | Triethyl amine |
| t-BuOH       | tert-Butyl alcohol |
| NaH          | Sodium hydride |
| CHCl₃        | Chloroform |
| DMAP         | 4-Dimethylaminopyridine |
| NaH          | Sodium hydride |
| NH₄Cl        | Ammonium chloride |
| NaLO₄        | Sodium periodate |
| Ac           | Acetyl |
| TFA          | Trifluoroacetic acid |
| MOMCl        | Methoxymethyl chloride |

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