Phloroglucinol compounds of natural origin: Synthetic aspects

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This review covers the synthetic aspects of various naturally occurring phloroglucinols, describing syntheses of 42 compounds and citing 137 references.

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1 Introduction

Phloroglucinols include about 700 naturally occurring compounds with various biological activities. The enormous structural scope of this class ranges from 1,3,5-trihydroxybenzene to the complex phlorotannins with 31 phloroglucinol moieties. The parent molecule phloroglucinol itself has been isolated from natural sources and is used in medicine, cosmetics, pesticides, paints, cements and dyeing. Several syntheses of phloroglucinol have been reported, patented and commercialized; in particular, Li *et al.* have reviewed various synthetic procedures of phloroglucinol.[1] The occurrence, pharmacology and biosynthetic aspects of phloroglucinol derivatives have been reviewed previously,[2–4] and recently, we have reviewed various patents on therapeutically important phloroglucinols.[5] In addition, Ciochina and Grossman have reviewed synthetic aspects of naturally occurring polycyclic polyprenylated acylphloroglucinols.[6] However, to date, there has been no comprehensive review on the synthetic aspects of other phloroglucinols. The aim of the present review is therefore to provide an overview of the literature on the strategies used in the syntheses of various naturally occurring bioactive phloroglucinol compounds.† The emphasis is on total syntheses of molecules of contemporary interest. Fig. 1 provides an overview of syntheses of naturally occurring phloroglucinol compounds.

2 Monomeric phloroglucinols

2.1 Acyl phloroglucinols

Acyl phloroglucinols comprise the largest group of naturally occurring phloroglucinol compounds, and more than 100 simple acylated phlorolgucinols have been reported. These include phloroglucinol or its mono-, di- and tri-ethers acylated to varying degrees with linear or branched chains. Owing to the vast array

† The literature has been searched through the following sources: Chemical Abstracts (CA), Dictionary of Natural Products, PubMed, Scifinder and Google Scholar.

of biological activities shown by these compounds, numerous research groups have endeavoured to synthesize these compounds. A multitude of different strategies have been documented and many of these approaches are summarized here.

The three basic steps involved in the syntheses of acylphloroglucinols are outlined in Fig. 2. These include (i) acylation using acyl chlorides, anhydrides, alkyl nitriles and occasionally carboxylic acids, (ii) mono-, di- or tri-*O*-alkylation of phloroglucinol with diazomethane, dimethyl sulfate, methyl iodide, *etc.*, and (iii) mono- or di-*C*-alkylation (most often methylation) with dimethyl sulfate, alkyl iodide or bromide in the presence of an alkali. The general strategy for synthesis of this class of compounds includes Friedel–Crafts acylation using acyl chlorides/anhydrides or the Houben–Hoesch reaction using alkyl nitriles as acylating agents.

2.1.1 Synthesis of grandinol. Grandinol (**1**) is the most widely studied monomeric acyl phloroglucinol. The first synthesis of grandinol reported by Yuste *et al.* involved a three-step procedure starting from 2,4,6-trinitrotoluene (Scheme 1). 2,4,6-Trinitrotoluene (**2**) was reduced with Sn and HCl to afford 2,4,6-trihydroxytoluene (**3**), which upon Friedel–Crafts acylation with isovaleryl chloride and $TiCl_4$ in CH_2Cl_2–CS_2 at 25 °C resulted in the formation of compound **4**. The last step involved

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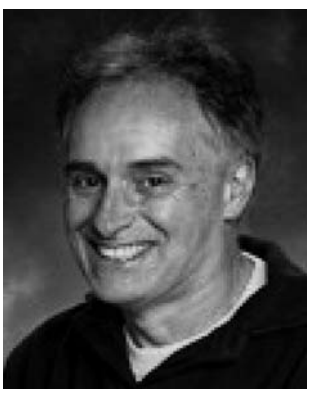

William J. Foley

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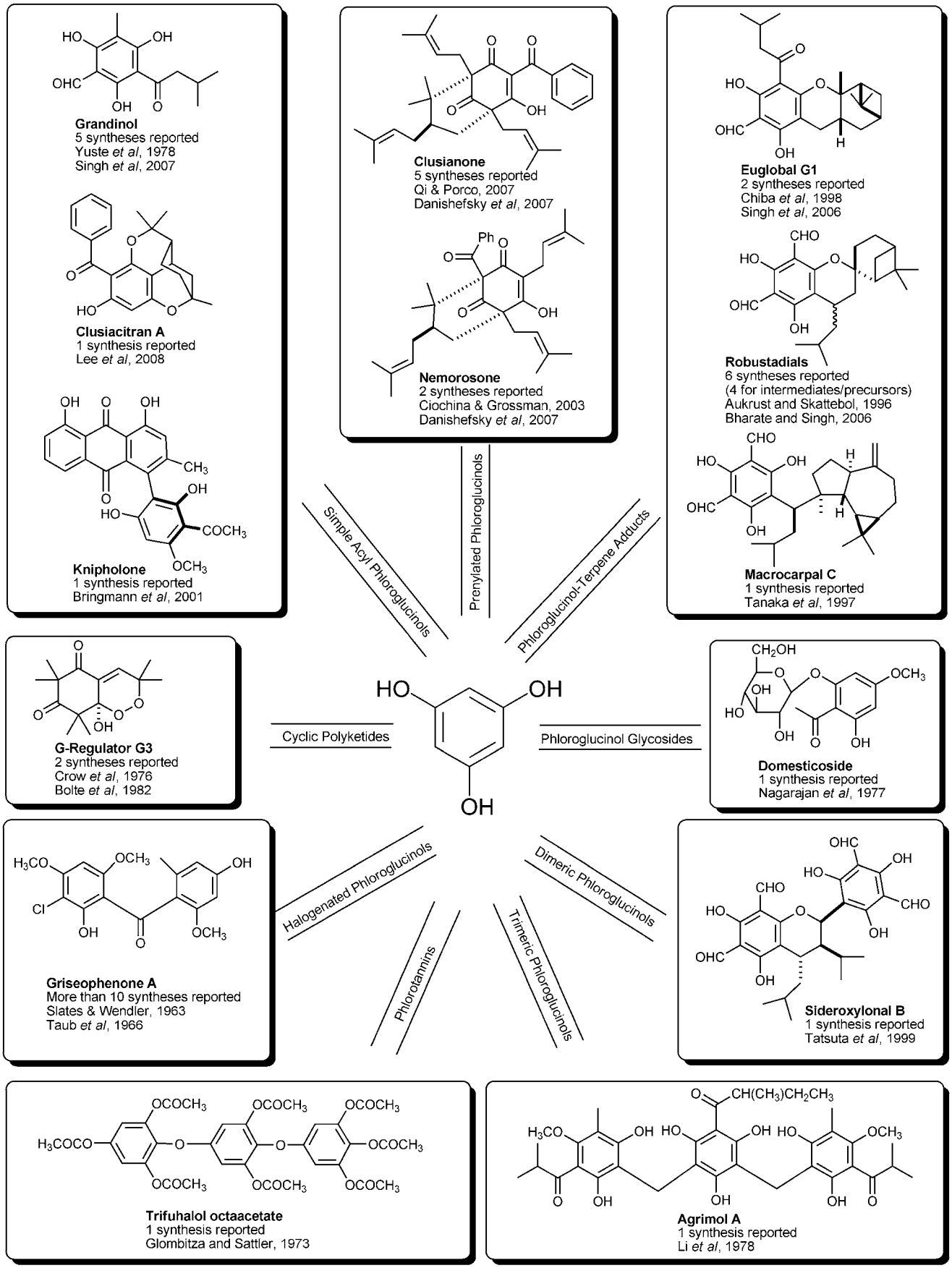


Fig. 1 Overview of syntheses of phloroglucinol compounds from the parent molecule.

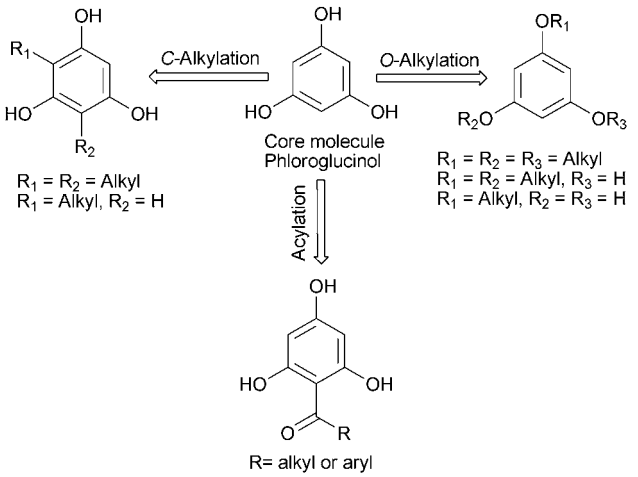


Fig. 2 The basic steps used in syntheses of acylphloroglucinols.

formylation of **4** using dichloromethyl methyl ether and $TiCl_4$ as catalyst in CH_2Cl_2 at 0 °C, affording grandinol (**1**) in 1.8% overall yield.[7] In 1985, Yoshida *et al.* reported the synthesis of grandinol starting from commercially available phloroglucinol (**5**) in three steps. Friedel–Crafts acylation of phloroglucinol using isovaleryl chloride gave phloroisovalerophenone (**6**) in 70% yield. Acylation was followed by formylation using triethyl orthoformate to give **7** and finally methylation using iodomethane and methanolic alkali.[8] To date, several groups have synthesized grandinol as a key intermediate by different routes for synthesis of euglobals. Table 1 summarizes the approaches taken towards the synthesis of grandinol.

2.1.2 Synthesis of torquatone. Torquatone (**8**) has been synthesized starting from 2,4,6-trinitro-*m*-xylene as depicted in Scheme 2. 2,4,6-Trinitro-*m*-xylene (**9**) was converted to dimethyl phloroglucinol (**10**) by treatment with Sn/HCl, which on reaction with isovaleric acid in the presence of BF_3 gave **11**. Treatment of **11** with an excess of dimethyl sulfate in the presence of potassium carbonate in acetone resulted in the formation of torquatone.[12]

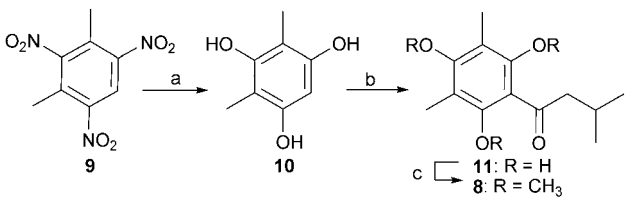
Similar strategies and reaction conditions have been used in syntheses of numerous natural and synthetic monomeric acylphloroglucinols. Friedel–Crafts acylation was the key step in the synthesis of homograndinol (**12**),[13] multifidol (**13**),[14,15] robustaol B (**14**),[16] conglomerone (**15**),[17] verticilone (**16**)[18] and vertinone (**17**).[18] In some of these syntheses, like that of xanthoxylin (**18**)[19] and flopropione (**19**)[20] (for structures see Fig. 3), acid anhydrides have been used as acylating agents.

2.1.3 Synthesis of jensenone. Jensenone (**20**), a diformylated acyl phloroglucinol, has been synthesized in two steps involving Friedel–Crafts acylation of phloroglucinol and then introduction of the diformyl functionality by a modified Duff reaction. Most of the reported formylation reactions involve electrophilic attack on aromatic rings to introduce a latent formyl group which is easily convertible to a formyl group during work-up – for example, formylation using $POCl_3$/DMF or triethyl orthoformate. However, diformylation onto an aromatic ring is difficult, as the introduction of one formyl group deactivates the system for a second formylation. Jensenone (**20**) was obtained exclusively in 28% yield when **6** was refluxed with 2 equivalents of hexamethylene tetraamine for 20 h at 70 °C.[21]

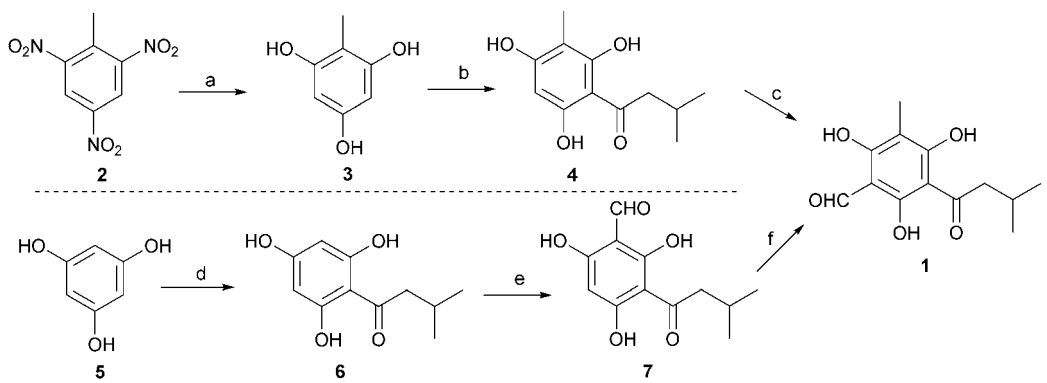
The Houben–Hoesch reaction, using alkyl nitriles, is another important approach for the synthesis of acylated

Table 1 Comparison of reported syntheses of grandinol (**1**)

Year	Starting material	Steps	Yield (%)	Ref.
1978	2,4,6-Trinitrotoluene	3	1.8	7
1985	Phloroglucinol	3	12	8
1985	Phloroglucinol	3	12.5	9
1996	Phloroglucinol diisopropyl ether	5	24	10
2007	Phloroglucinol	3	20	11



Scheme 2 Bowyer & Jefferies' synthesis of torquatone. *Reagents and conditions*: (a) Sn/HCl, NaOH; (b) isovaleric acid, BF_3; (c) Me_2SO_4, K_2CO_3, acetone.



Scheme 1 Yuste's (top) and Yoshida's (bottom) syntheses of grandinol. *Reagents and conditions*: (a) Sn/HCl, NaOH; (b) isovaleryl chloride, $TiCl_4$, CH_2Cl_2–CS_2, 25 °C; (c) dichloromethyl methyl ether, $TiCl_4$, CH_2Cl_2, 0 °C, 1 h; (d) isovaleryl chloride, $AlCl_3$, $PhNO_2$, H_2O, RT, 1 h; (e) $CH(OC_2H_5)_3$, $AlCl_3$, CH_2Cl_2, 30 min; (f) CH_3I, CH_3OH, KOH, 65 °C, 24 h.

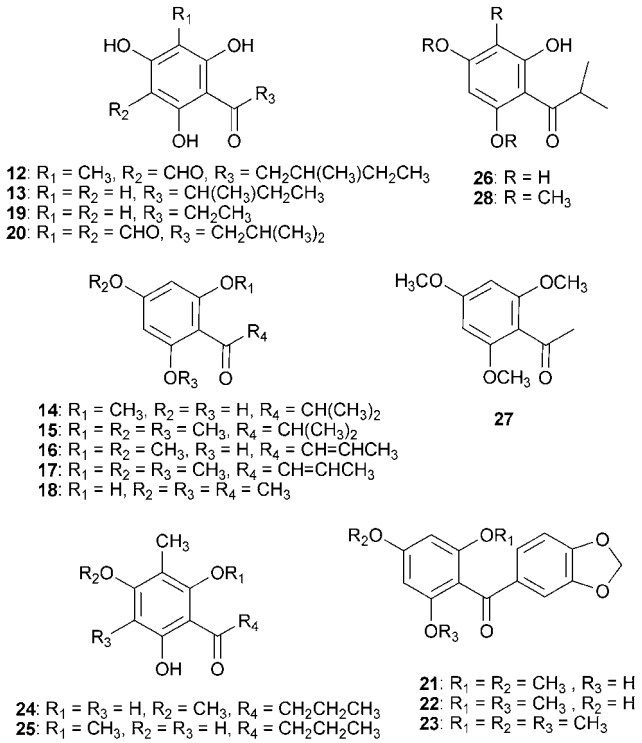
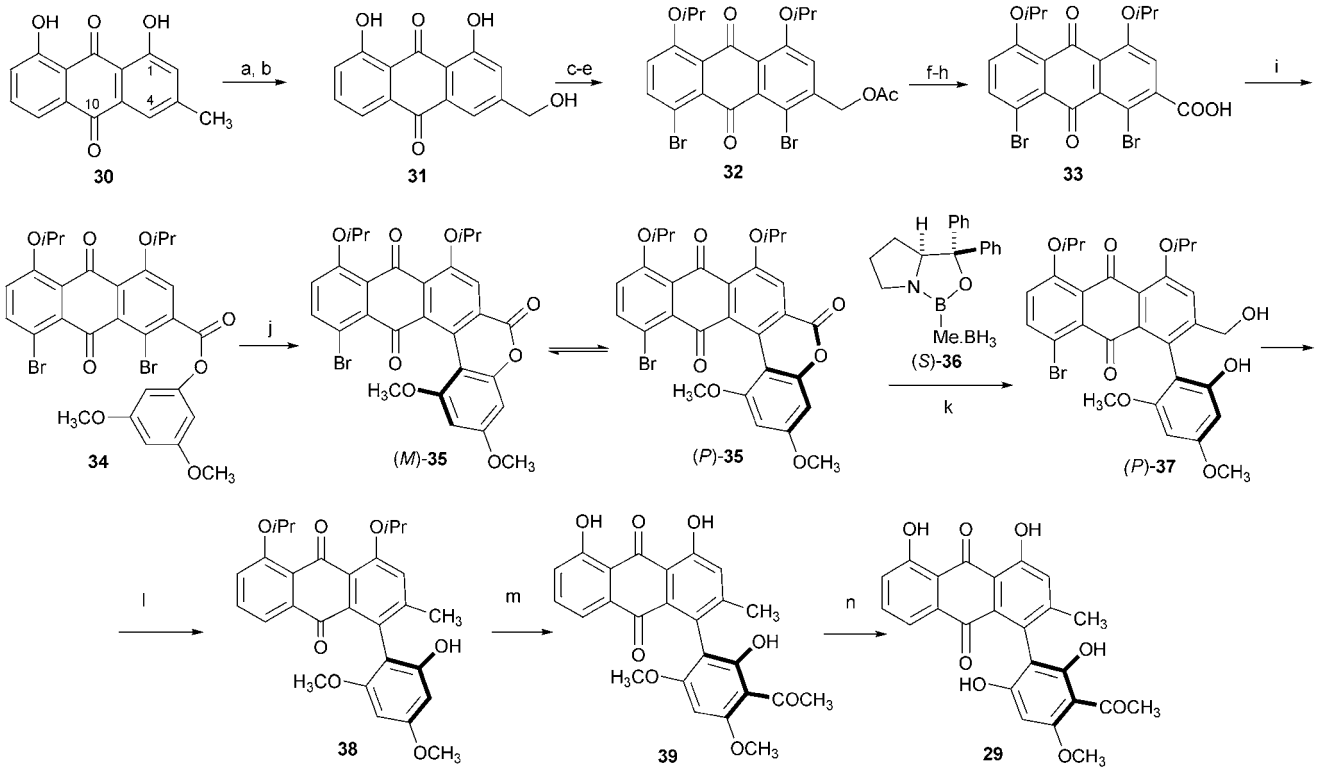


Fig. 3 Structures of some naturally occurring acylphloroglucinols.

phloroglucinols. Zinc chloride is the most widely used Lewis acid in this reaction, although aluminium chloride is also used. The various natural phloroglucinols synthesized using this reaction include protocotoin (**21**),[22,23] isoprotocotoin (**22**),[22] methyl protocotoin (**23**),[22,23] aspidinol (**24**),[24] pseudoaspidinol (**25**)[25] and flopropione (**19**).[26] The modified Houben–Hoesch reaction, in which aliphatic nitriles react with phenols in the presence of triflic acid, has been applied for the synthesis of (**26**)[27] and acetyl phloroglucinol trimethyl ether (**27**) (for structures see Fig. 3).[28]

Other less commonly employed methods for the synthesis of acylphloroglucinols include Fries migration of esters (phloroglucinol triacetate gives 2,4,6-triacetylphlorolgucinol)[29] and nuclear acylation in the presence of polyphosphoric acid (phloroglucinol reacts with glacial acetic acid to give triacetyl and/or diacetyl phloroglucinol).[30]

2.1.4 Synthesis of baeckeol. The first synthesis of a methylated acylphloroglucinol, baeckeol (**28**), was reported by Ramage and Stowe. Methyl phloroisobutyrophenone was synthesized from methyl phloroglucinol with isobutyronitrile in the presence of zinc chloride, and the final *O*-methylation was carried out using diazomethane.[31] Schiemenz *et al.* used boron trifluoride for selective demethylation of the trimethoxy intermediate for the synthesis of **28**.[32]



Scheme 3 Bringmann's enantioselective synthesis of knipholone. *Reagents and conditions*: (a) *N*-bromosuccinimide, $(PhCO_2)_2$, CCl_4, reflux 6 h; (b) $CaCO_3$, dioxane–H_2O, 120 °C, 7 h; (c) *i*PrI, Cs_2CO_3, acetone, reflux, 4 days; (d) Ac_2O, pyridine, 50 °C, 3 h; (e) Br_2, NaOAc, $CHCl_3$–CCl_4, 70 °C, 3 h; (f) KOH, MeOH, 70 °C, 2 h; (g) MnO_2, CH_2Cl_2, RT, 6 h; (h) $NaClO_2$, amidosulfuric acid, NaOAc, dioxane–H_2O–HOAc, RT; (i) phloroglucinol dimethyl ether, DCC, DMAP, CH_2Cl_2, DMF, 0 °C to RT, 1 h; (j) $Pd(OAc)_2$, PPh_3, sodium pivalate, *N*,*N*′-dimethylacetamide, 4.5 h; (k) (*S*)-**36**, BH_3, THF, 0 °C, 1 h; (l) $(CBrCl_2)_2$, polymer-bound PPh_3, CH_2Cl_2, RT, 10 min then Pd/C, H_2, MeOH; (m) $TiCl_4$, CH_2Cl_2, 0 °C to RT, 2 h then Ac_2O, $TiCl_4$, −20 °C to RT, 1 h; (n) $AlBr_3$, chlorobenzene, 80 °C, 2 h.

2.1.5 Synthesis of knipholone. Bringman *et al.* reported an enantioselective synthesis of the unsymmetric anthraquinone knipholone (**29**). The key steps involved were the biaryl coupling (C–C bond formation between C4 of chrysophanol and C1 of phloroglucinol) and lactonization of **34** to give the enantiomeric biaryls **35*P*** and **35*M***. The key anthraquinone (**33**) was synthesized in 8 steps from commercially available chrysophanol (**30**). Bromination of **30** followed by Br/OH exchange gave the aloe emodin (**31**). The hydroxyl groups at C1 and C8 of compound **31** were protected by isopropylation and the side-chain hydroxyl was protected by acetylation. This was followed by bromination at C4 and C5 to give compound **32**. Although bromine at C5 was not required functionally, it did not interfere in any of the reaction steps. The brominated product **32** was subjected to hydrolysis and subsequent oxidation to yield acid **33**, which was esterified using phloroglucinol dimethyl ether to give ester **34**. In the next key step, ester **34** was subjected to Pd-catalyzed intramolecular biaryl coupling to give the configurationally unstable lactones **35*P*** and **35*M***. The lactone moiety of **35*M*/*P*** can be selectively cleaved using a chiral-H nucleophile such as oxazaborolidine **36** (*S* or *R*). Compound **37*P*** was obtained by an enantioselective reductive cleavage of **35*P*** using **36*S***. Reductive elimination of the benzylic oxygen of **37*P*** followed by hydrogenolytic removal of bromine resulted in **38**. Removal of the *O*-isopropyl protective groups and regioselective introduction of an acetyl group at C3′ gave *O*-methylknipholone (**39**). Finally, demethylation of **39** yielded knipholone **29** (Scheme 3).[33,34]

2.1.6 Synthesis of clusiacitran A. Clusiacitrans A and B constitute a regioisomeric pair of phlorobenzophenones bearing a tricyclic ring skeleton. Synthesis of clusiacitran A (**40**) has been accomplished in two steps from phloroglucinol. Friedel–Crafts acylation of phloroglucinol was carried out as usual with benzoyl chloride to yield 2,4,6-trihydroxybenzophenone (**41**). The key step involved tandem electrocyclization of **41** and citral (**42**). Treatment of **41** with 2.0 equivalents of citral (**42**) in the presence of 20 mol% of ethylenediamine diacetate (EDDA) at 100 °C for 10 h in DMF afforded the desired product (Scheme 4).[35]

2.2 Phloroglucinol–terpene adducts with a chroman ring (euglobals)

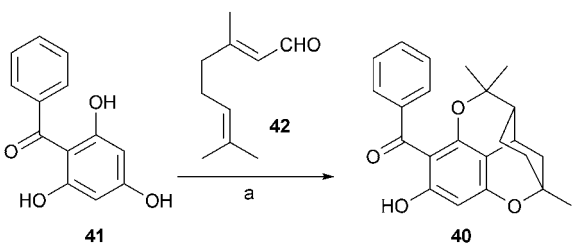
Most phloroglucinol–terpene adducts have been isolated from different species of *Eucalyptus*.[3] Depending on their structural features, these compounds can be divided into two categories. Adducts containing a chroman ring are called *euglobals*, and those which do not are called *macrocarpals*.

The unique and multifarious structures and diverse biological activities of euglobals have provoked considerable synthetic efforts, including approaches towards related compounds like ficifolidione.

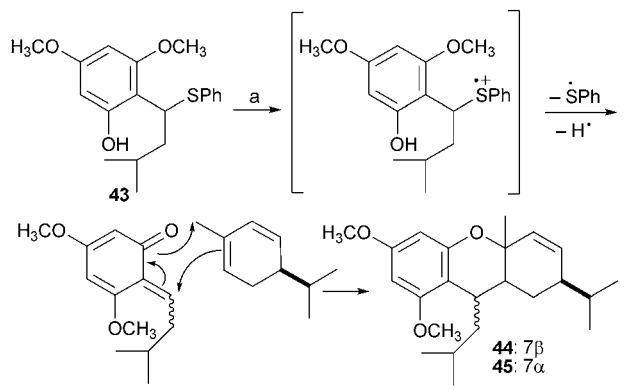
2.2.1 Syntheses of euglobal skeletons/precursors. Synthesis of the euglobal skeleton was first achieved by Chiba *et al.* in 1995 by employing an electrochemical method that involved initial conversion of *o*-[1-(propylthio)alkyl]phenol (**43**) to the corresponding *O*-quinone methides by electrochemical oxidation in a lithium perchlorate–nitroalkane system. The quinone methides were then trapped *in situ* by unactivated terpenes to form chroman skeletons.[36] The synthetic procedure to obtain the skeletons of euglobal $1a_1$ (**44**) and $1a_2$ (**45**) is depicted in Scheme 5. The same group also synthesized euglobals G1–G4 and the skeletons of euglobal T1 and IIc using the same methodology.[37,38]

Raggelin *et al.* developed an alternative approach to the tetracyclic precursor of euglobals G1 and G2 (**46–47**) *via* metallated 2-alkenyl sulfoximines. Retrosynthetic analysis of euglobals G1 and G2 *via* sulfoximines following the 4-hydroxyalkylation reaction and retro-Michael-like addition envisaged grandinol-related aldehydes and myrtenol-derived sulfoximines as the building blocks (Scheme 6).[39]

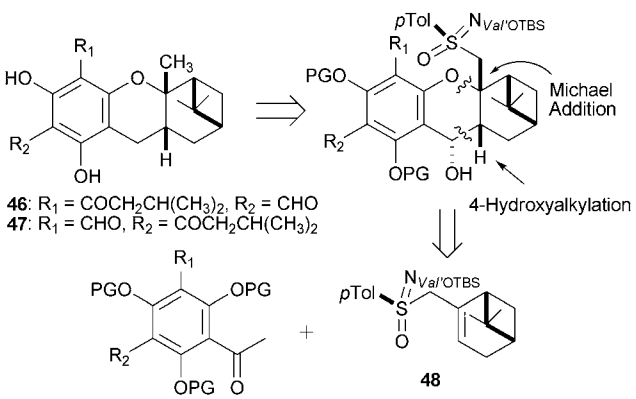
The sulfoximine (**48**) was synthesized in an overall yield of 61% from (1*R*)-myrtenol (**49**) *via* the selenide **50**. The sulfoximine, on reaction with silylated trihydroxybenzaldehyde (**51**), resulted in formation of the tetracyclic compound **52** having the euglobal skeleton (Scheme 7).



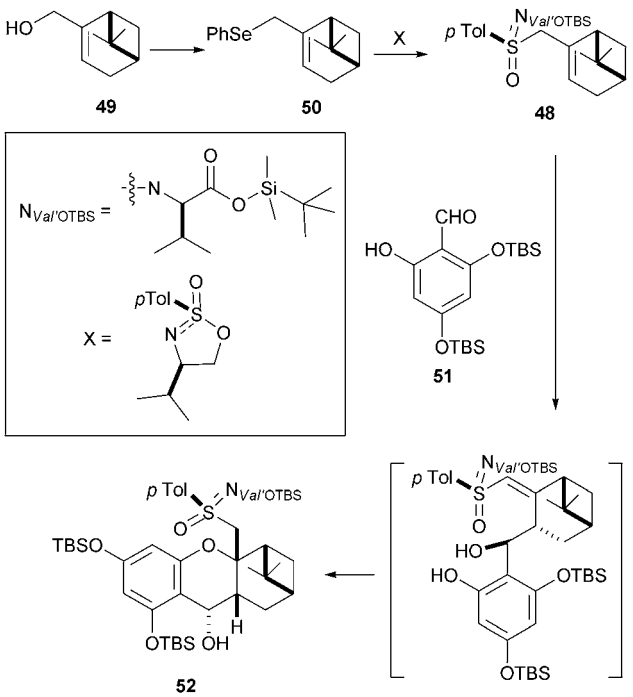
Scheme 4 *Reagents and conditions*: (a) EDDA, DMF, 100 °C, 10 h.



Scheme 5 Chiba's electrochemical synthesis of euglobal skeletons. *Reagents and conditions*: (a) $LiCl_4$, $EtNO_2$, electrolysis.



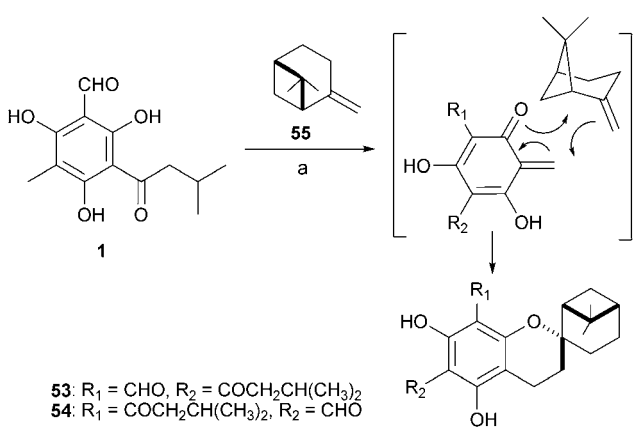
Scheme 6 Retrosynthetic analysis of euglobals G1 and G2.



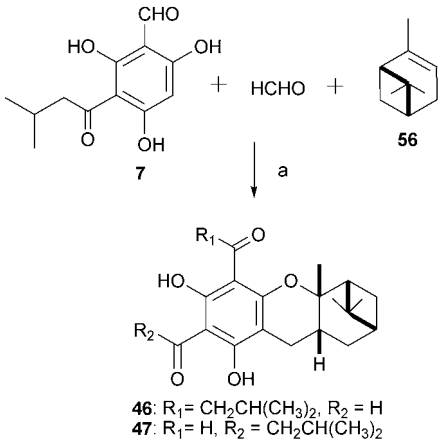
Scheme 7 Raggelin's synthetic strategy for the tetracyclic euglobal precursor.

2.2.2 Biomimetic syntheses of euglobals. A methodology based on biogenetic considerations to synthesize euglobals G3 (**53**) and G4 (**54**) was subsequently developed by Chiba's group. This involved generation of the *O*-quinone methide by oxidative activation of the benzylic site of grandinol (**1**) followed by [4 + 2] cycloaddition with a terpene moiety (**55**). Although the intermolecular cycloaddition of *O*-quinone methides has been shown to be difficult, the DDQ-mediated oxidation of **1** in the presence of β-pinene (**55**) in nitromethane gave the desired cycloadducts **53** and **54** in a yield of 60% (**53**:**54** = 6:5) (Scheme 8).[10] The choice of solvent was crucial in this reaction, as the desired products were obtained only in nitromethane and not in solvents such as methanol, benzene, ether or acetonitrile.

An alternative strategy for synthesis of non-natural euglobals was reported in 2008. Singh and co-workers initiated efforts for preparing euglobals using monoterpenes that are not normally



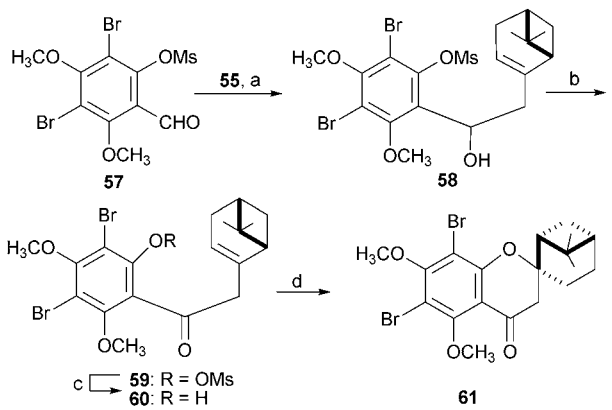
Scheme 8 Chiba's biomimetic approach for synthesis of euglobals. *Reagents and conditions*: (a) DDQ, $MeNO_2$.



Scheme 9 Singh's biomimetic approach to euglobals. *Reagents and conditions*: (a) HCHO, AcOH, NaOAc, 60 °C, 2 h.

encountered in natural euglobals. Their synthetic strategy relied on a biomimetic three-component reaction involving Knoevenagel condensation between formyl isovalerylphloroglucinol (**7**) followed by a [4 + 2] Diels–Alder cycloaddition with the monoterpene α-pinene (**56**). Euglobals G1 and G2 (**46**–**47**)[40] and several S-euglobals[41] were synthesized by this biomimetic approach in 50–70% yield, as depicted in Scheme 9.

2.2.3 Syntheses of robustadials/robustadial precursors. These compounds continue to attract much attention from synthetic groups. There have been several reports on the total synthesis of robustadials by different routes involving varying numbers of steps. Most of the syntheses were for dimethyl ether derivatives of robustadials, and some were of key precursors required for robustadial synthesis. Majewski *et al.* reported a stereoselective synthesis of one of the key intermediates involved in the synthesis of robustadials by the Prins reaction (Scheme 10). The synthesis started from (1*S*)-(−)-β-pinene (**55**), which was coupled to a substituted benzaldehyde (**57**) by the Prins reaction, and incorporated a diastereoselective Michael-type intramolecular addition. Swern oxidation of alcohol (**58**) produced the ketone (**59**), which on treatment with NaOH in aqueous ethanol or with sodium carbonate in 95% ethanol yielded ketone **60** in 80% yield.

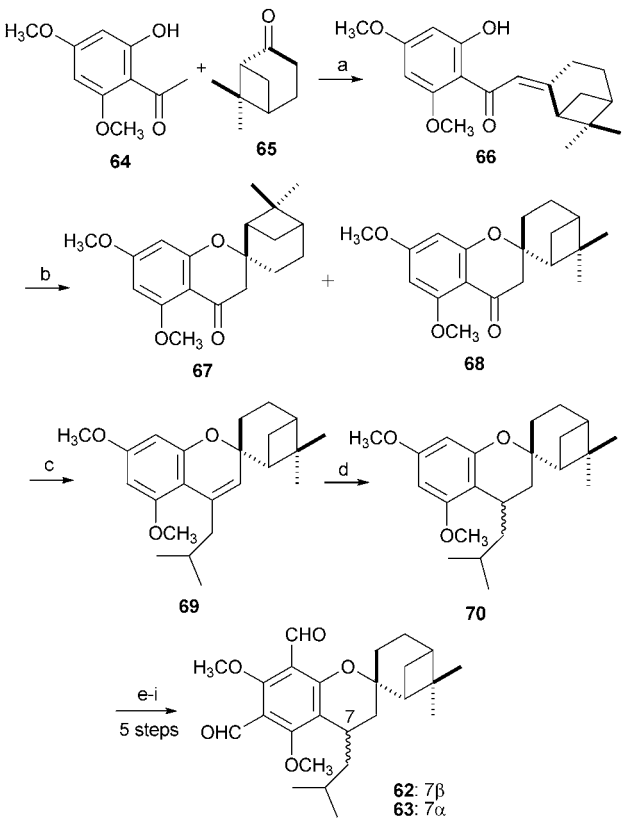


Scheme 10 Majewski's approach to robustadial precursors. *Reagents and conditions*: (a) (−)-β-pinene, Me_2AlCl, then H_3O^+; (b) DMSO–$(COCl)_2$; (c) OH^-, EtOH–H_2O; (d) Et_3N, EtOH.

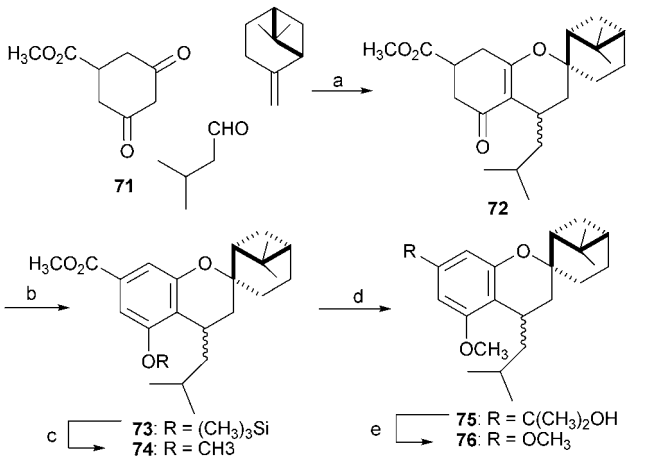
Ring closure was attempted using several reagents. These included various bases *viz.* Na_2CO_3–EtOH, CS_2CO_3–EtOH, NaOH–EtOH, $NaHCO_3$–Na_2CO_3–EtOH, PhONa–EtOH, Et_3N–DMSO, Et_3N–EtOH, piperidine–EtOH, morpholine–EtOH, DMAP–EtOH and proton-sponge–EtOH. As a result of these investigations, the amine-catalyzed cyclization of enone was achieved successfully to construct a chromone skeleton (**61**).[42,43]

Salomon *et al.* synthesized robustadial dimethyl ethers (**62** and **63**) from 2,4-dimethoxy-6-hydroxyacetophenone (**64**) by condensation with (+)-nopinone (**65**), followed by cyclization and introduction of an isobutyl functionality. The robustadial ring system was assembled in one step by a pyrrolidine-catalyzed condensation of **64** and **65**. A mixture of chromanones **67** and **68** was obtained in a 20% yield and in a ratio of 2:5 together with an α,β-unsaturated ketone **66**, which was obtained as the major product (41%). Base-catalyzed cyclization of **66** gave **67** and **68** in the same ratio. The isobutyl functionality was introduced followed by dehydration of the resulting tertiary benzylic alcohol, which gave the desired carbon skeleton (**69**). Catalytic hydrogenation of alkene **69** yielded epimers **70**. Finally, the diformyl functionality was introduced through a five-step procedure involving bromination with Br_2 in CH_2Cl_2 in the presence of pyridine, lithiation with butyllithium, introduction of the methyl ester, reduction with DIBAL, and oxidation with PDC (Scheme 11).[44,45]

Koser and Hoffman synthesized the dimethyl robustadial skeleton (which lacks the diformyl functionality) *via* a five-step



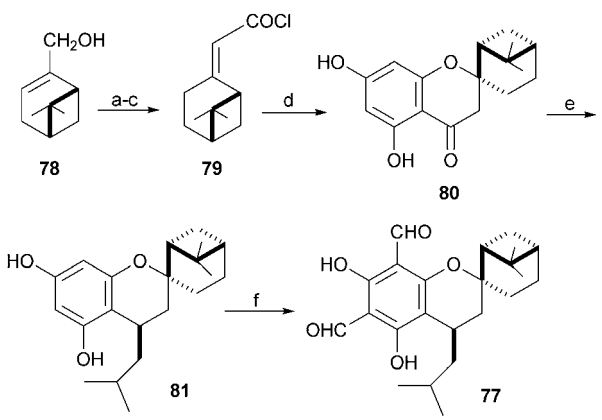
Scheme 11 Salomon's synthesis of robustadial dimethyl ethers. *Reagents and conditions*: (a) pyrrolidine, benzene–H_2O; (b) K_2CO_3, 90% EtOH, boil; (c) Me_2CHCH_2MgCl, then aq. HCl; (d) H_2, Pd/C; (e) pyridine, Br_2/CH_2Cl_2; (f) *n*BuLi, THF, then CO_2, then HCl; (g) CH_2N_2/Et_2O; (h) DIBAL-H/toluene; (i) PDC.



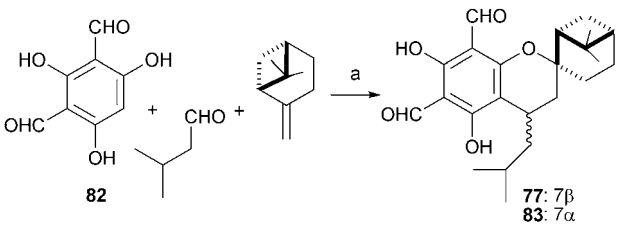
Scheme 12 Koser & Hoffman's synthesis of robustadial precursors. *Reagents and conditions*: (a) HOAc, KOAc, hydroquinone, 3 Å MS, 100 °C, 20 h; (b) BSA, DDQ, degassed dioxane, 110 °C, 1 h; (c) DMF, KF, aq. HBr, RT, 30 min; acetone, $(MeO)_2SO_2$, K_2CO_3, 50 °C, 1.5 h; (d) Et_2O, MeMgI, reflux, 3 h; (e) i) Et_2O, H_2O_2; *p*-TsOH, RT, 6.5 h; ii) CH_2Cl_2, py, $(CF_3CO)_2$, 0 °C, 5 min; iii) CH_2Cl_2–H_2O, CF_3COOH, 0 °C, 3 h; iv) acetone, $(MeO)_2SO_2$, K_2CO_3, RT, 17 h.

procedure starting from 3,5-dioxocyclohexanecarboxylic acid methyl ester (**71**) and involving condensation with β-pinene followed by a Diels–Alder cycloaddition to yield tetracycle **72** (α/β diastereomers). Aromatization of **72** to **73** gave the chroman skeleton. Subsequent steps involved conversion of the silyl ether to the methyl ether **74** followed by the formation of tertiary alcohol **75**, which was finally transformed to **76** (mixture of diastereomers) (Scheme 12).[46]

Aukrust and Skattebol reported a synthesis of robustadial A (**77**) starting from commercially available (−)-nopol (**78**). The acid chloride (**79**) was prepared from nopol in three steps involving a Swern oxidation to the aldehyde with double-bond migration followed by further oxidation to the corresponding acid. Acid chloride **79** was prepared for a condensation reaction with phloroglucinol, as the reaction of the acid with phloroglucinol led to rearrangements in the terpene framework. The chromanone (**80**) formed after reaction of **79** with phloroglucinol



Scheme 13 Aukrust & Skattebol's synthesis of robustadial A. *Reagents and conditions*: (a) oxalyl chloride, TEA; (b) $AgNO_3$, EtOH, NaOH; (c) oxalyl chloride, benzene; (d) phloroglucinol, $ZnCl_2$; (e) methallyl bromide, activated Zn; (f) dichloromethyl methyl ether, $TiCl_4$.



Scheme 14 Bharate & Singh's synthesis of robustadials. *Reagents and conditions*: (a) NaOAc, AcOH, MW, 1000 W, 4 min.

yielded the chromone **81** on the introduction of an isobutyl moiety. The last step of the synthesis involved diformylation of the skeleton **81**. Monoaldehydes were formed when the Rieche reaction was used and a prolonged reaction time (for the second formylation) led to rearrangements in the pinene skeleton. Finally, diformylation was carried out using the dichloromethyl methyl ether reagent to yield robustadial A (**77**) (Scheme 13).[47]

A simple and efficient two-step synthesis of robustadials A and B from commercially available phloroglucinol was achieved by Bharate and Singh with an overall yield of 27%, involving a Knoevenagel condensation followed by Diels–Alder cycloaddition as the key biomimetic step (Scheme 14). Phloroglucinol (**5**) was diformylated by the Duff reagent to give **82** which in the presence of isovaleraldehyde and β-pinene (**55**) gave the pair of desired stereoisomers **77** and **83**.[48] An earlier synthesis of ficifolidione, an insecticidal compound, had been achieved by Khambey *et al.* using a similar strategy.[49]

2.3 Phloroglucinol–terpene adducts without a chroman ring (macrocarpals)

Phloroglucinol–terpene adducts that do not involve formation of a chroman ring are called macrocarpals. Since the first isolation of macrocarpal A in 1990, a number of similar compounds have been isolated. To date, only the synthesis of macrocarpal C has been achieved, by Tanaka *et al.* in 1997. Biosynthetically, (−)-macrocarpal C (**84**) is proposed to be derived from the benzyl cation (**85**) and bicyclogermacrene (**86**). The benzyl cation equivalent **85** can replace a proton as a cationic initiator in the cyclization of sesquiterpene **86**. The resulting tricyclic carbocation **87** gives macrocarpal C after deprotonation (Scheme 15a).

Based on the above hypothesis, the aromatic unit and terpene moiety of macrocarpal C were synthesized. For preparation of the aromatic unit, commercially available 1,3,5-trimethoxybenzene (**88**) was used as the starting material. Scheme 15b outlines the synthesis of a chiral chromium complex as an optically active benzyl cation equivalent used as a key intermediate in the synthesis of macrocarpal C.

1,3,5-Trimethoxybenzene (**88**) was acylated by the usual methods to give ketone **89**, which was subjected to $LiAlH_4$ reduction to yield the racemic alcohol **90**. The resulting alcohol **90** was complexed with $Cr(CO)_6$ followed by double direct lithiation with *n*BuLi and LDA respectively. The complexed diester **91** was a mixture of (*R*)- and (*S*)-isomers. Diasteromeric carbamates **92** prepared from **91** with (*R*)-(−)-1-(1-naphthyl)ethyl isocyanate were separated by silica gel chromatography. Treatment of each carbamate with boron trifluoride diethyl etherate gave $Cr(CO)_6$-stabilized benzyl cations which were trapped by water without rotation about the benzylic carbon–arene bond, giving optically pure complexed alcohols **93**. (*R*)- and (*S*)-**93** were converted to the chloroacetates (**94**) to increase the reactivity of the system towards the next crucial coupling reaction. (Only reactions of the (*S*)-isomer are shown in this scheme for clarity). In the next stage of macrocarpal synthesis, silyldienol ether **95** (prepared from the sesquiterpene moiety **96**) was coupled with (*S*)-**94** to give **97**. The last fragment of this synthesis involved conversion of the precursor **97** to macrocarpal C. Catalytic hydrogenation of enone **97** afforded a desilylated saturated ketone **98**. Stereoselective reduction and acetylation of **98** gave the hydroxyacetate **99** that, under modified Grieco conditions (excess of 2-nitrophenyl selenocyanate and $n Bu_3P$ at 75 °C in a sealed tube), gave **100**. This dehydration reaction is thought to occur *via* E2 elimination of an oxo-phosphonium salt intermediate. After a series of steps including deacetylation, hydrogenation, dehydration, reduction and oxidation, **100** gave the trimethyl ether of macrocarpal C (**101**) which was then subjected to tris-*O*-demethylation in the presence of lithium *p*-thiocresolate to give the final product (**84**) (Scheme 15c).[50,51]

2.4 Phloroglucinol glycosides

More than 50 glycosides of phloroglucinol and its derivatives have been reported from natural sources. These include non-acylated, mono- and di-acylated glycosides wherein the sugar moiety is attached to the aglycone through an *O*- or *C*-glycosidic linkage. Phloroglucinol β-D-glucoside, phlorin (**102**), is the simplest phloroglucinol glycoside, and has been isolated from *Cannabis sativa*, *Cornus capitata* and some citrus fruits. Phlorin can be synthesized from phloroglucinol (**5**) and tetra-*O*-acetyl-D-glucopyranosyl bromide (**103**) in alkaline media (Scheme 16).[52]

Similarly, picraquassioside D (**104**) and taxicatin (**105**) have been synthesized from mono- and dimethyl ethers of phloroglucinol respectively.[52,53] [^{14}C]-Labeled phlorin was also synthesized in leaf disks of *Pelargonium* by feeding the tissues with phloroglucinol and labelled glucose.[54,55]

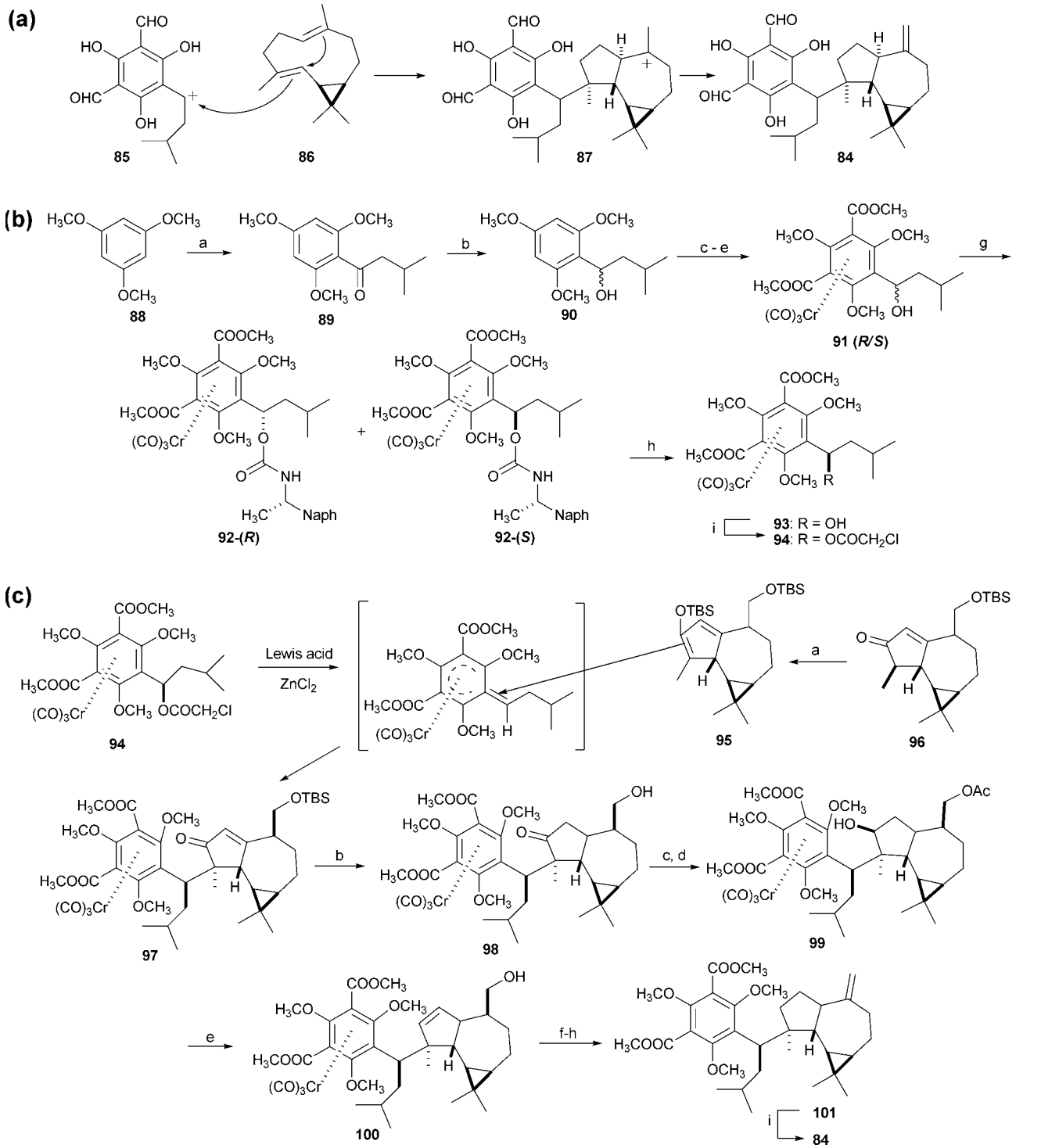
Direct condensation of phloroglucinol with unprotected sugars has also been investigated. Phloroglucinol-*C*-β-D-glucoside (**106**) was formed when D-glucose was used as a glycosylating agent at temperatures below 80 °C. Glucosylation of phloroacetophenone was also carried out in a similar way but at elevated temperatures.[56] The condensation reaction of phloroglucinol with D-xylose and L-arabinose gave the corresponding *C*-β-D-xylopyranoside and *C*-α-L-arabinopyranoside.

Domesticoside (**107**) was prepared by direct condensation of tetraacetylglucosyl bromide and phloroacetophenone 4-methyl ether in the presence of silver carbonate and anhydrous calcium sulfate followed by deacetylation.[57] Similarly, rodiolinozide (**108**) was prepared from phloroacetophenone 2-methyl ether.[58]

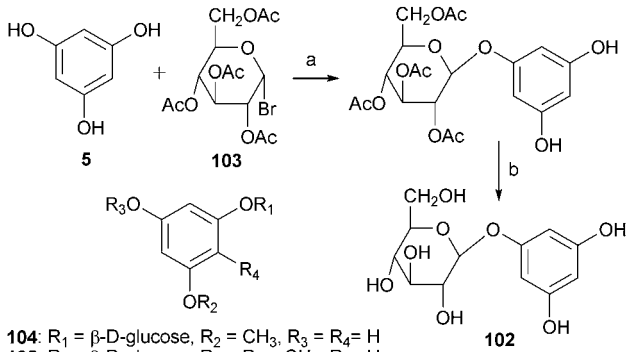
2.5 Halogenated phloroglucinols

About 15 halogenated phloroglucinol compounds have been identified from natural sources. These compounds are largely mono-halogenated derivatives of substituted phloroglucinols. The halogens encountered are mostly chlorine and bromine.

Reports on synthesis of this class of compounds are very few. The general strategy followed in the syntheses was halogenation



Scheme 15 **(a)** A proposed biosynthetic pathway to macrocarpal C. **(b)** Synthetic strategy for the generation of $Cr(CO)_6$-complexed aromatic side-chain unit. *Reagents and conditions*: (a) isovaleryl chloride, $AlCl_3$, CH_2Cl_2, 0 °C, 3.5 h; (b) $LiAlH_4$, Et_2O, 0 °C, 4 h, (c) $Cr(CO)_6$, nBu_2O–1,4-dioxane–*n*-heptane (5:5:1), 120 °C, 34 h; (d) *n*BuLi, TMEDA, THF, −78 °C, 2 h, then CO_2, −78 °C, 30 min; (e) $TMSCHN_2$, benzene–MeOH (4:1); (f) LDA, TMEDA, THF, −50 °C, 3 h then CO_2, −78 °C, 30 min; (g) (*R*)-(−)-1-(1-naphthyl)ethyl isocyanate, CuCl, DMF, RT, 3 h, then separation; (h) $BF_3 \cdot Et_2O$, wet MeCN, 0 °C, 2–4 h; (i) $(ClCH_2CO)_2O$, py, CH_2Cl_2, 0 °C, 2–3 h. **(c)** Mechanism of stereoselective coupling of aromatic unit (**94**) and silyldienol ether of the terpene moiety (**95**), and conversion of precursor **101** to macrocarpal C. *Reagents and conditions*: (a) TBSOTf, Et_3N, Et_2O–CH_2Cl_2 (1:1); (b) H_2 (5 atm), 10% Pd/C, MeOH, RT, 27 h; (c) $NaBH_4$, MeOH, RT, 1 h; (d) Ac_2O, DMAP, CH_2Cl_2, RT, 1 h; (e) 2-$NO_2C_6H_4SeCN$, nBu_3P, THF, 75 °C, sealed tube, 20 h, then 30% H_2O_2, RT, 3 h, and NaOMe, MeOH, RT, 6.5 h; (f) 2-$NO_2C_6H_4SeCN$, nBu_3P, THF, 50 °C, sealed tube, 12 h, then 30% H_2O_2, RT, 30 min; (g) DIBAL-H, toluene, −78 °C, 1 h; (h) TPAP, NMO, 4 Å MS, MeCN, RT, 1 h; (i) lithium *p*-thiocresolate, HMPA, toluene, reflux.



Scheme 16 Synthesis of phlorin and structures of naturally occurring phloroglucinol glycosides. *Reagents and conditions*: (a) i) KOH (aq.), acetone, pH = 10–11.5 then refrigeration for 12 h; ii) pH adjusted to 1.5; (b) sodium methoxide, chloroform, −10 °C, 1.5 h.

of substituted phloroglucinols. A summary of the syntheses of halogenated phloroglucinols is given in Table 2.

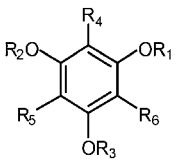
2.6 Prenylated phloroglucinols

More than 50 prenylated and/or geranylated phlorolgucinols have been reported from plant sources. These include mono-, di-, and poly-prenylated/geranylated phloroglucinols.

2.6.1 Syntheses of vismiaphenones and related compounds. Three prenylated phlorobenzophenones, vismiaphenone A (**120**), vismiaphenone B (**121**) and isovismiaphenone B (**122**), have been synthesized from phlorobenzophenone (**43**). The key steps involved in the syntheses were prenylation followed by protection of the hydroxyl groups and then DDQ-mediated cyclization to yield the final products (Scheme 17).[59] Several other methods of synthesis of vismiaphenones have been reported. Vismiaphenone A has also been synthesized from isocotoin by prenylation with 2-methyl-3-buten-2-ol.[60] Vismiaphenone B and isovismiaphenone B were simultaneously synthesized from 2,4,6-trihydroxybenzophenone (**41**) in two steps. The monoprenylated product was obtained in a 42% yield when **41** was prenylated in the presence of DBU. Treatment of this monoprenylated compound with 3-methyl-2-butenal in the presence of EDDA gave a mixture of **121** and **122** in 31% and 51% yields respectively.[35] Vismiaphenone C (**123**), a structural analogue of vismiaphenone A, was synthesized from 2,6-dihydroxy-4-methoxybenzophenone by the same methodology.[61] The antimicrobial caespitin (**124**) and its derivatives were synthesized using similar reagents and reaction conditions.[62] Another prenylated phloroglucinol, myrtiaphenone (**125**), was synthesized in 75% yield from isovismiaphenone by methylation with dimethyl sulfate. The dimethyl derivative was obtained as a minor side product.[35]

Two structurally related prenylated phloroglucinols, namely preremirol (**126**) and acronylin (**127**), were synthesized from 2-*O*-methyl-phloroacetophenone. The 5-*C*-prenyl derivative

Table 2 Reactants and reagents used in syntheses of naturally occurring halogenated phloroglucinols **109–119**



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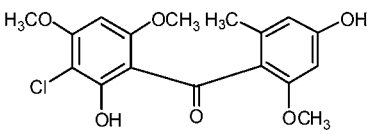
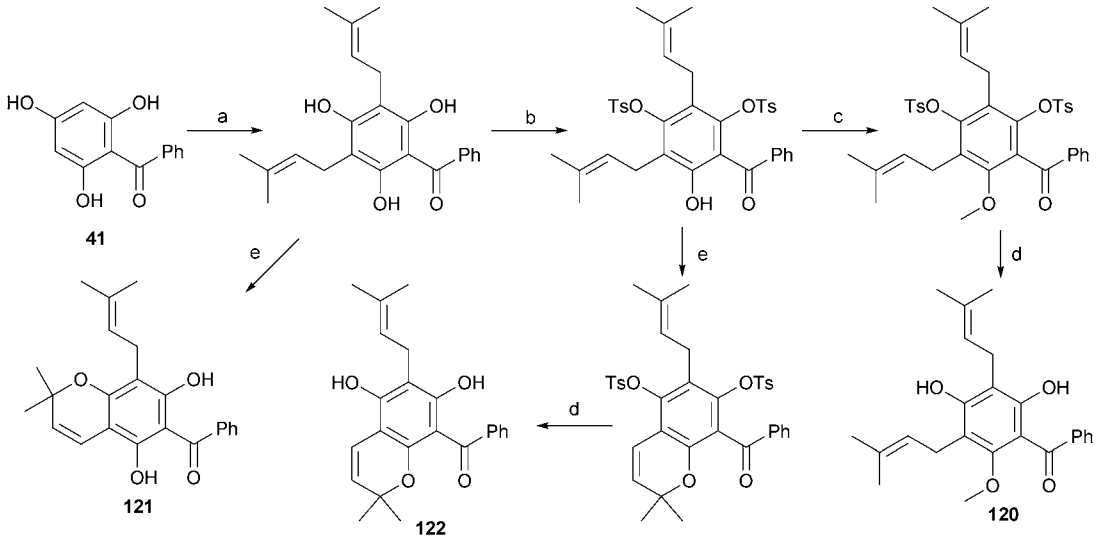


119

Cpd	R-groups						Reactant	Reagent(s)/solvent(s)	Ref.
	R_1	R_2	R_3	R_4	R_5	R_6			
109	H	H	H	H	H	Br	Phloroglucinol	KBr/MeCN or H_2O	67
							Phloroglucinolic acid	Br_2/CS_2	68
							Tribromophloroglucinol	$NaHCO_3$, Na_2SO_3/H_2O or MeOH	68
110	H	H	H	H	Br	Br	Phloroglucinol	KBr/MeCN or H_2O	68
							Phloroglucinolic acid	Br_2/CS_2	68
111	H	H	H	Br	Br	Br	Phloroglucinol	Benzyltrimethylammonium bromide	68
							Phloroglucinolic acid	Br_2/CS_2	68
112	H	H	H	H	H	Cl	2-Chlorophloroglucinolic acid	Cu_2O	69
113	H	H	H	H	H	I	Phloroglucinol	I_2, $NaHCO_3$	70
114	$COCH_3$	$COCH_3$	$COCH_3$	H	H	Br	Phloroglucinolic acid	Br_2/CS_2 then Ac_2O/py	68
							1-Bromophloroglucinolic acid	Ac_2O in py	68
115	CH_3	CH_3	CH_3	H	Br	Br	1,3,5-Trimethoxy-benzaldehyde	Pyridinium hydrobromide perbromide	67,68
							Trimethoxybenzene	(KBr, $HClO_4$, H_2O_2) or Br_2	71,72
							Phloroglucinolic acid	Br_2/CS_2 then H_2O then CH_2N_2/Et_2O	71,72
							3,5-Dibromophloroglucinolic acid	H_2O then CH_2N_2/Et_2O	71,72
							1,3,5-Trimethoxy(trimethylsilyl)benzene	Br_2/CS_2	71,72
116	H	CH_3	H	Cl	Cl	$CO(CH_2)_4CH_3$	Phloroglucinol monomethyl ether	Caproyl chloride, $AlCl_3$, CH_2Cl_2 then H_2O then $SOCl_2$, EtOH, $CHCl_3$	73
117	H	CH_3	H	Cl	H	$CO(CH_2)_4CH_3$	Phlorocaprophenone 4-methyl ether	$SOCl_2$, EtOH, $CHCl_3$	73
118	H	CH_3	H	Cl	Cl	$CO(CH_2)_3CH_3$	Phlorovalerophenone 4-methyl ether	$SOCl_2$, EtOH, $CHCl_3$	73
119	Griseophenone A						2-Methoxy-4-methoxycarbonyl-6-methylbenzoyl choride	2-Chloro-3,5-dimethoxyphenol	74,75



Scheme 17 Synthesis of prenylated phloroglucinols. *Reagents and conditions*: (a) 2-methyl-3-buten-2-ol, dioxane, $BF_3 \cdot Et_2O$, 6 h, 25–30 °C; (b) *p*-toluenesulfonyl chloride, dry acetone, K_2CO_3, reflux, 6 h; (c) Me_2SO_4, K_2CO_3, reflux, 12 h; (d) 10% ethanolic KOH, 2 h, 50–55 °C; (e) DDQ, benzene, reflux, 3 h.

(preremirol) and the 2-*C*-prenyl derivative (acronylin) were prepared by reaction of the phloroacetophenone derivative with prenyl bromide and 2-methyl-but-3-en-2-ol, respectively.[63,64] Other routes to syntheses of preremirol include methylation of 2,4,6-trihydroxy-3-(3-methyl-2-butenyl)acetophenone with diazomethane[65] and acetylation of 4-methoxy-2,6-dihydroxy-prenylbenzene by the usual methods (for structures see Fig. 4).[66]

2.6.2 Syntheses of humulones. The hop plant is known to contain phloroglucinol compounds such as humulones, lupulones, isohumulones, reduced isohumulones, tetrahydroisohumulones and deoxyhumulones. Collins *et al.* reported a convenient synthesis of humulones (**128**)/cohumulones (**129**) and adhumulones (**130**) by direct alkenylation of acylated phloroglucinols. The process of alkenylation was aided by Lewis acid catalysts like $ZnCl_2$, acid zeolites like KSF, or $BF_3 \cdot Et_2O$. The deoxy-intermediates were then oxidized with *tert*-butylhydroperoxide in a basic medium to give the corresponding products (Scheme 18).[76–78]

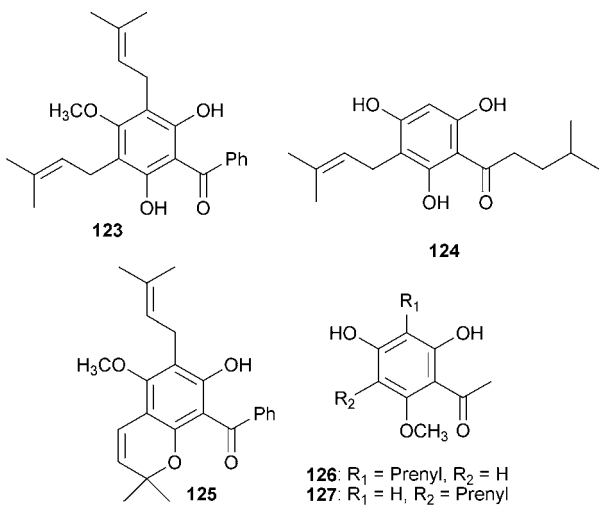


Fig. 4 Structures of some prenylated phloroglucinols.

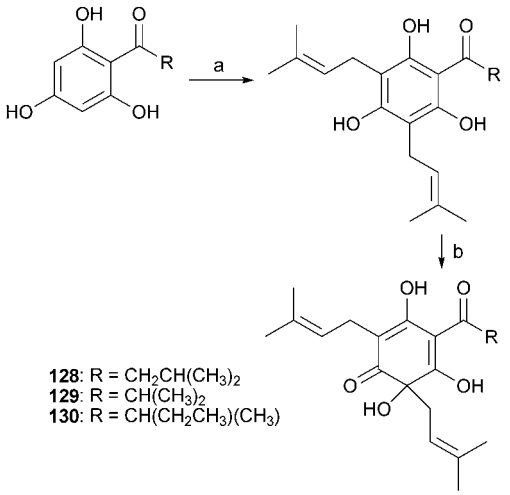
Humulone (**128**) was also synthesized by the prenylation of 2,3,4,6-tetrahydroxyisovalerophenone with 1-bromo-3-methyl-2-butene.[79] Several other literature reports for the syntheses of humulones, their derivatives and analogues cite similar acylation and prenylation strategies.[80–85]

2.6.3 Syntheses of polyprenylated phloroglucinols. Several polycyclic polyprenylated acylphloroglucinols (PPAPs) have been reported from natural sources. Recently, Ciochina and Grossmann reviewed polyprenylated acylphloroglucinols.[6] (Compounds covered therein are not included here.) Owing to their interesting biological activities, PPAPs have stimulated considerable synthetic efforts in recent years.

Raikar *et al.* devised a regioselective tri-*C*-prenylation of phloroglucinol resulting in a *gem*-disubstituted derivative amenable to biomimetic cyclization to give polyprenylated acylphloroglucinols. Grandone (**131**), kolanone (**132**) and an isomer of weddellinone (**133**) were synthesized in a two-step procedure involving prenylation in alkaline aqueous medium followed by *C*-benzoylation of the resulting 1,3-cyclohexanediones in the presence of benzoyl cyanide.[86] Sulfonium salts have also been used for the introduction of prenyl, geranyl and isolavandulyl groups onto the phloroglucinolic core. These reagents are considered as synthetic equivalents of pyrophosphates in natural systems.[87] Raikar's synthesis of prenylated phloroglucinols is depicted in Scheme 19.

Raikar *et al.* also reported the biomimetic electrophilic cyclization of triprenylated phloroglucinols. A bicyclo[3.3.1]nonane-2,4,9-trione skeleton (present in polycyclic polyprenylated acyl phloroglucinols) was constructed, but yields were low.[86]

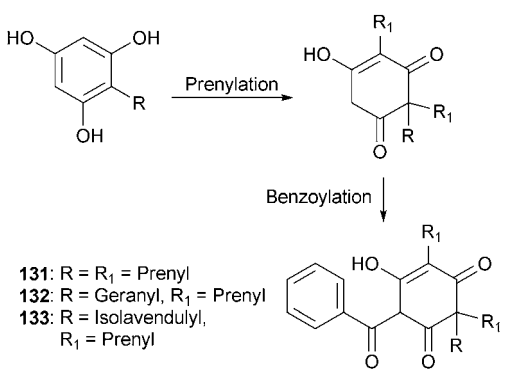
Mehta and Bera developed a concise synthetic strategy for construction of the bicyclo[3.3.1]nonan-9-one core present in various natural products. The synthone **134** was generated from commercially available citral (**42**) in four steps. One-pot tandem Michael addition to methyl acrylate and prenylation of the



Scheme 18 Synthesis of humulones. *Reagents and conditions*: (a) 2-methyl-3-butene-2-ol, $ZnCl_2$, dioxane, reflux, 1 h or prenyl bromide, $ZnCl_2$, Et_2O–CH_2Cl_2 (1:1), 1 h; (b) NaOH, *tert*-butylhydroperoxide, MeOH, 2 h.

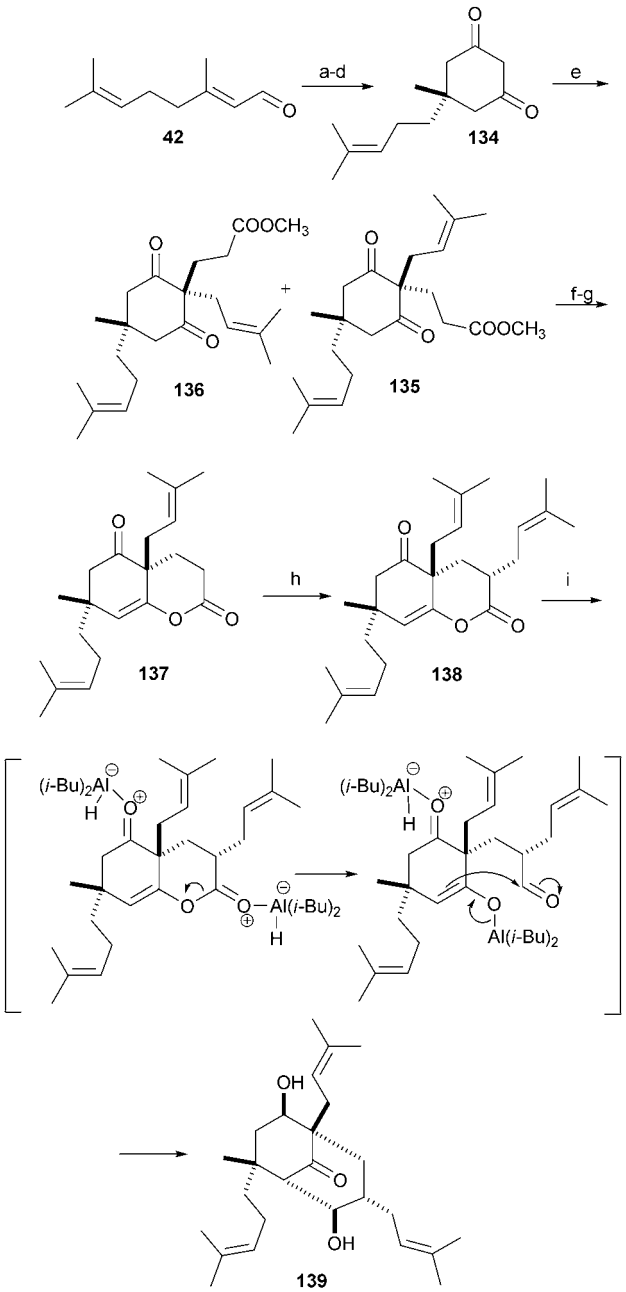
1,3-diketone **134** in the presence of DBU yielded a mixture of diastereomers **135** and **136**. The prenylated compound **135**, upon hydrolysis and subsequent cyclisation, gave the enol-lactone **137**. Kinetic deprotonation of **137** followed by prenylation with prenyl bromide gave **138**. Reduction of the lactone moiety of **138** by DIBAL-H was accompanied by retro-aldol reaction and re-aldolization to furnish the desired scaffold **139** (Scheme 20).[88]

2.6.4 Syntheses of clusianone. Clusianone (**140**), a potent anti-HIV and cancer chemopreventive compound, has attracted much attention recently. Qi and Porco used α-acetoxy-enal **142** to provide a prenyl handle in the structure of the starting material clusiaphenone (**141**). Clusiaphenone undergoes alkylative dearomatization–annulation after treatment with **142** in the presence of KHMDS. Addition of vinyl magnesium bromide to the aldehyde (**143**), followed by acetylation of the resultant secondary alcohol, afforded allylic acetate (**144**). Palladium-catalyzed formate reduction of **144** followed by conversion of the allyl functionality to a prenyl group by Grubbs' metathesis gave clusianone methyl ether (**145**). Finally, nucleophilic demethylation in the presence of lithium chloride or lithium hydroxide generated the desired product in racemic form (Scheme 21).[89]

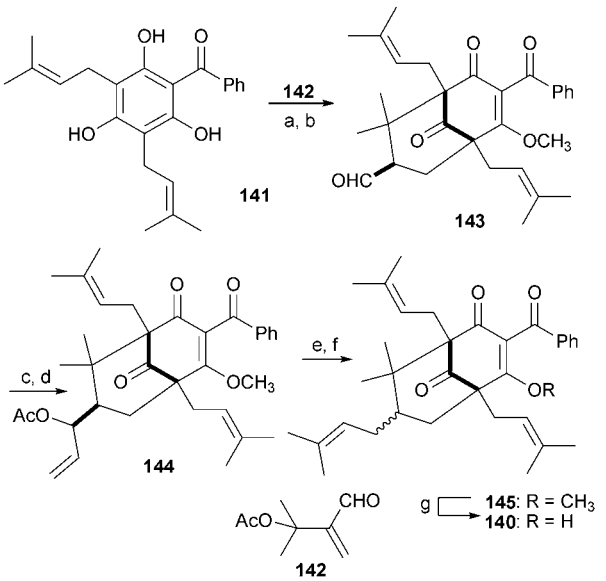


Scheme 19 Raikar's approach to the synthesis of prenylated phloroglucinols.

Another route to clusianone has been reported by Danishefsky and coworkers. Beginning from commercially available 3,5-dimethoxyphenol (**146**), the synthesis was accomplished in 12 steps. Two-fold allylation of **146** was carried out to yield **147** with the aid of of π-allylpalladium chemistry. In the presence of Grubbs' 2nd-generation catalyst, both of the allyl functionalities of **147** were converted to prenyl functions by two-fold cross-metathesis. One of the methoxy groups of **148** was cleaved in the presence of lithium iodide–collidine. An iodinium-induced



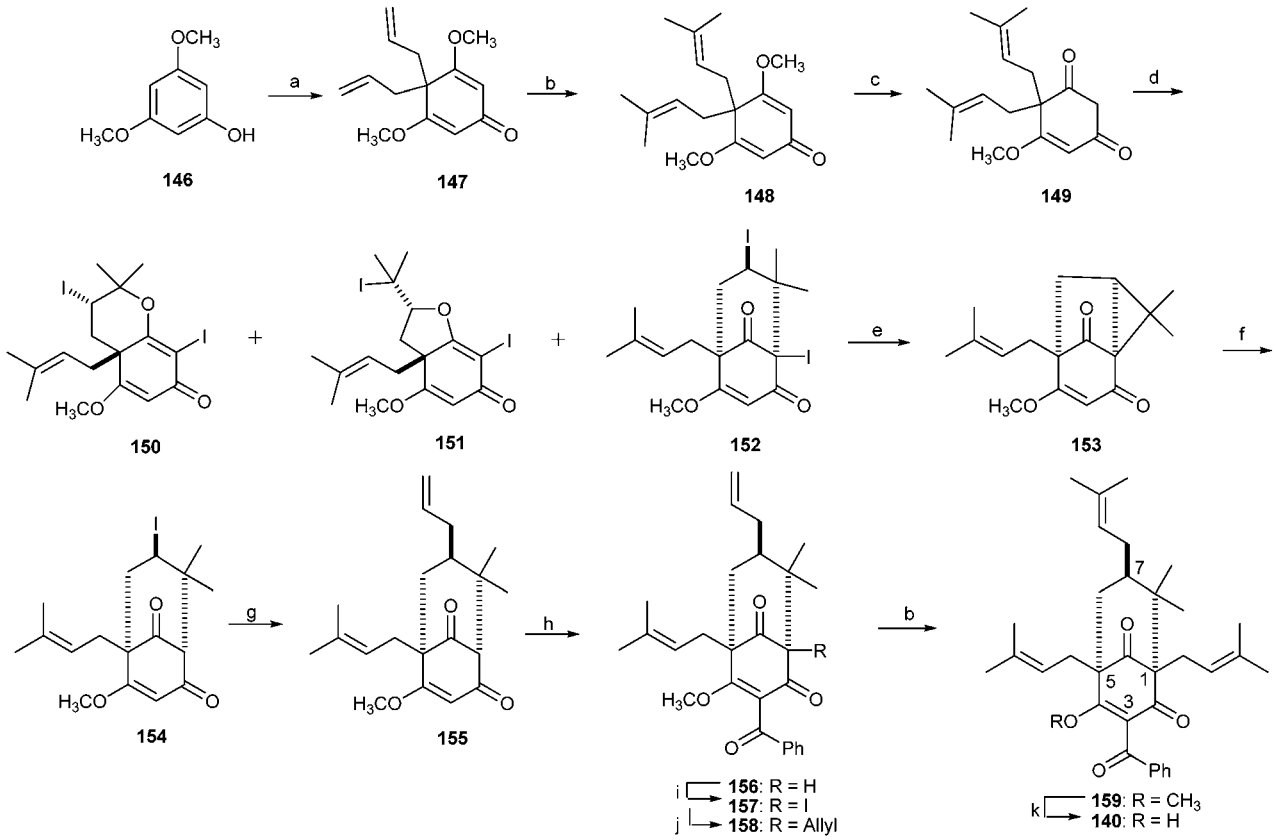
Scheme 20 Mehta & Bera's synthesis of the bicyclo[3.3.1]nonan-9-one core. *Reagents and conditions*: (a) MeLi, Et_2O, 0 °C, 3 h; (b) MnO_2, hexane, RT, 12 h; (c) $CH_2(COOEt)_2$, NaOEt, EtOH, 60 °C, 12 h; (d) KOH, EtOH, 60 °C, 72 h; (e) i) methyl acrylate, DBU, THF, RT, 3 h; ii) $Me_2C{=}CHCH_2Br$, DBU, THF, RT, 3 h; (f) conc. HCl, acetone, H_2O, 50 °C, 12 h; (g) NaOAc, Ac_2O, 140 °C, 1 h; (h) LDA, $Me_2C{=}CHCH_2Br$, −78 °C, 1 h; (i) DIBAL-H, CH_2Cl_2, 0 °C, 2 h.



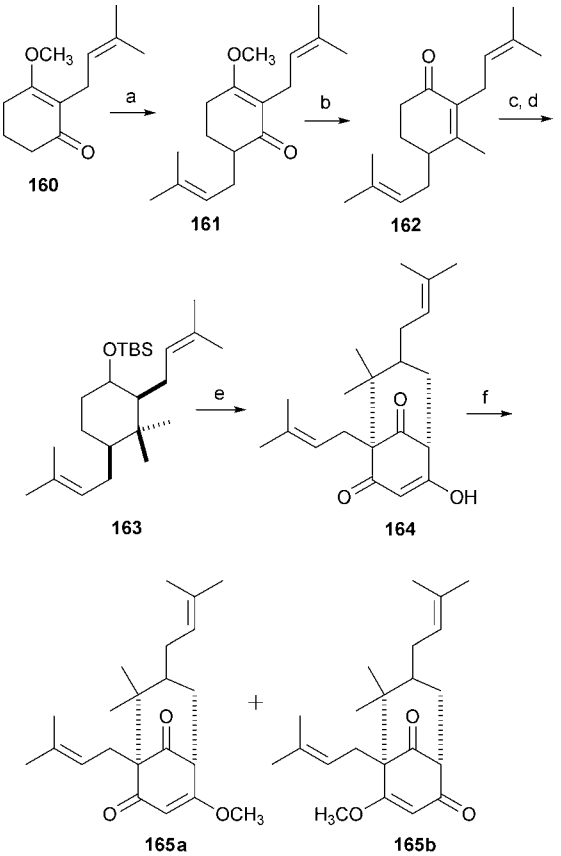
Scheme 21 Qi & Porco's synthesis of clusianone. *Reagents and conditions*: (a) KHMDS, THF, 65 °C; (b) $TMSCHN_2$, iPr_2EtN, MeCN; (c) CH_2=CHMgBr, THF, −78 °C; (d) Ac_2O, iPr_2EtN, DMAP, CH_2Cl_2, 0 °C; (e) $Pd(PPh_3)_4$, $HCOONH_4$, toluene, 105 °C; (f) Grubbs' 2nd-generation catalyst, 2-methyl-2-butene; (g) LiOH, dioxane, reflux.

carbocyclization reaction on substrate **149** gave a mixture of three products (**150–152**). Of these, **152**, the compound of interest, was obtained in 32% yield. **150** and **151** were converted back to **149** in high yields by the action of zinc in the presence of aqueous THF. **152** was then subjected to reductive elimination to give bridgehead-fused cyclopropane **153**. Ring expansion of **153** with TMSI afforded **154**, which on allylation gave **155**, a key intermediate for the synthesis of clusianone and nemorosone. Treatment of **155** with LDA and benzaldehyde followed by oxidation introduced a benzoyl group at the C3 position. The resulting **156** was converted to the C1-iodo derivative (**157**), which gave **158** by transformation of the iodo group to an allyl functionality. Simultaneous cross-olefin metathesis of **158** at C1 and C7 gave **159**, which was then subjected to *O*-demethylation to give clusianone (**140**) (Scheme 22).[90]

Another strategy for synthesis of clusianone has been described by Simpkins *et al.* Vinylogous ester **160** was chosen as the starting material because a correctly placed vinyl group would become C1 in the cyclized product. Prenylation of **160** gave **161**, which was hydrolyzed to give the enone **162**. Conjugate addition of a methyl group to this tetra-substituted system followed by conversion of the *cis* (major) isomer to the enol silane yielded **163**. Compound **164** was obtained after the reaction of **163** with malonyl dichloride, and *O*-methylation then furnished



Scheme 22 Danishefsky's synthesis of clusianone. *Reagents and conditions*: (a) CH_2=$CHCH_2OH$, $Pd(OAc)_2$, PPh_3, $Ti(OiPr)_4$, 4 Å MS, 50 °C; (b) Grubbs' 2nd-generation catalyst, 2-methyl-2-butene, CH_2Cl_2, 40 °C; (c) LiI, 2,4,6-collidine, 140 °C; (d) I_2, KI, $KHCO_3$, THF–H_2O, RT; (e) *i*PrMgCl, Et_2O–THF, −78 °C; (f) TMSI, CH_2Cl_2, 0 °C; (g) allyl$SnBu_3$, AIBN, benzene, 80 °C; (h) LDA, THF, −78 °C then PhCHO then Dess–Martin periodinane, CH_2Cl_2, RT; (i) LDA, TMSCl, THF, −78 °C to 0 °C then I_2; (j) allyl$SnBu_3$, Et_3B, air, benzene, RT; (k) 10% aq. NaOH, 1,4-dioxane, 90 °C.



Scheme 23 Simpkins' synthesis of clusianone. *Reagents and conditions*: (a) LDA, prenyl bromide, THF, −78 °C; (b) MeLi, THF, −78 °C then HCl; (c) MeMgBr, TMSCl, HMPA, CuBr–SMe_2, THF, −78 °C to −30 °C; (d) *t*BuOK, DMSO then Me_2SO_4 or LDA TBSOTf, THF, −78 °C to 0 °C; (e) malonyl dichloride, Et_2O, −20 °C, 24 h then $BnEt_3NCl$, KOH, H_2O, RT, 24 h; (f) Me_2SO_4, K_2CO_3, acetone, reflux.

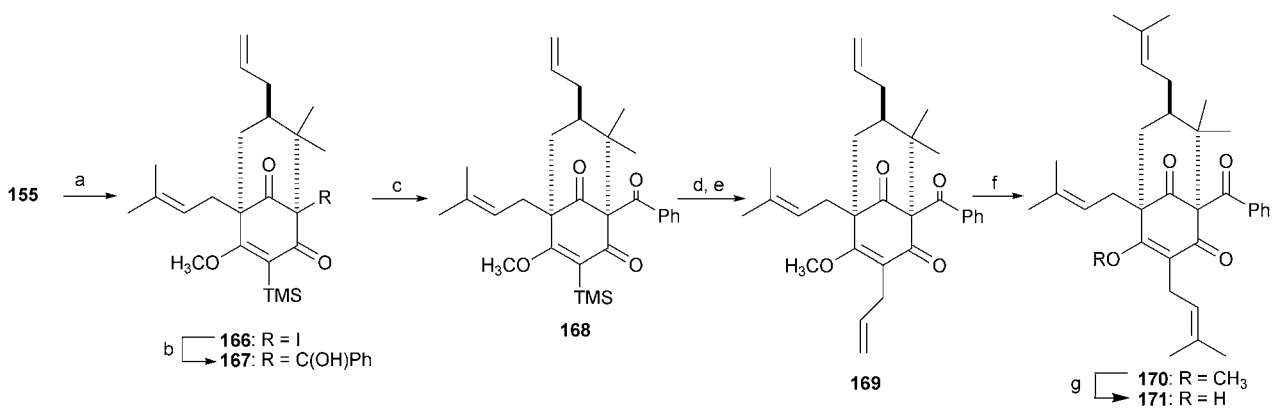
a mixture of regioisomeric vinylogous esters **165a** and **165b**, which were easily separable by chromatography. Synthesis of clusianone was completed by appending a third prenyl group onto **165a/b** followed by acylation at C3 and, finally, hydrolysis of the vinylogous ester to yield the desired product in an overall yield of 12% (Scheme 23).[91]

A similar strategy was used by Nuhant *et al.* for the synthesis of clusianone. An Effenberger annulation of 3,3′-dimethyl-2,4,6-triphenylcyclohexanone silyl enol ether with malonyl chloride gave bicyclo[3.3.1]nonane trione in 35% yield.[92]

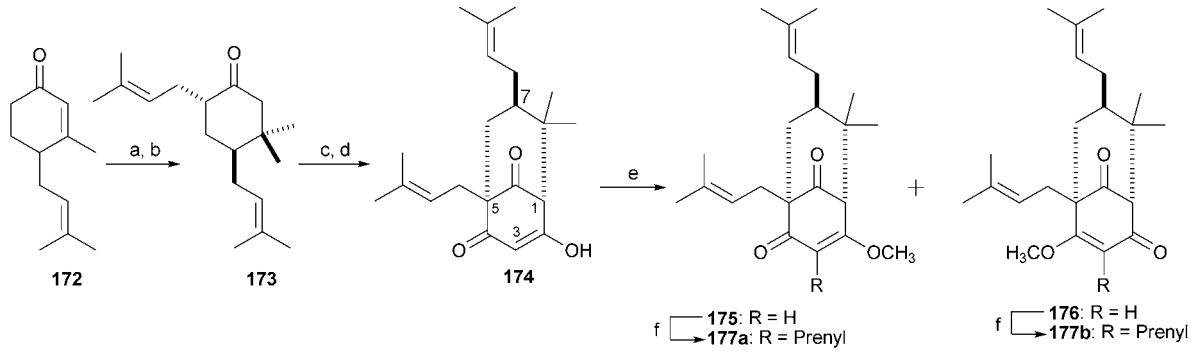
2.6.5 Syntheses of nemorosone. Another PAPP, nemorosone, was synthesized from **155** in seven steps. Compound **155** was treated with excess LDA in the presence of excess TMSCl followed by oxidative quenching with iodine to yield **166**. Reductive de-iodination of **166** followed by treatment with benzaldehyde gave the benzaldehyde adduct (**167**), which upon oxidation gave an intermediate (**168**) with a C1-anchored benzoyl group. Further cleavage of the C3 vinylsilane **168** followed by allylation gave the bis-allyl compound (**169**). Concurrent cross-olefin metathesis (as in clusianone) followed by cleavage of the methyl ether (**170**) gave nemorosone (**171**) (Scheme 24).[90]

The Simpkins group probed their strategy of synthesis of clusianone by applying it to synthesize nemorosone, starting from enone **172**. Prenylation of **172** followed by copper-catalyzed methyl conjugate addition gave **173**. Conversion of **173** to the enol silane and cyclization with malonyl dichloride afforded trione **174**, protection of which gave a mixture of regioisomers, **175/176** (as in the case of clusianone). After deprotonation with LTMP, copper-mediated vinylic alkylation was carried out to obtain **177a/b** (Scheme 25). However, despite several trials, bridgehead substitution at C1 could not be achieved, and so this route to nemorosone was unsuccessful.[91]

2.6.6 Synthesis of garsubellin A. A formal synthesis of racemic garsubellin A (**178**) was reported by Ahmad *et al.* The bicyclo[3.3.1]nonane derivative **180** was prepared from enone **179** in four steps. Bridgehead prenylation of **180** gave **181**, which on epoxidation with DMDO yielded a 1:1 mixture of isomers (**182/183**). The tertiary hydroxyl group of **182** was protected by silylation, and the product was then subjected to C3 lithiation and allylation followed by deprotection with Et_3N–HF to produce the key intermediate **184** (Scheme 26).[91] The same intermediate had been exploited earlier by Danishefsky's group for the synthesis of garsubellin in an 18-step sequence starting from 3,5-dimethoxyphenol. In this sequence, the allyl group in intermediate **184** was converted to a prenyl group using Grubbs'



Scheme 24 Danishefsky's synthesis of nemorosone. *Reagents and conditions*: (a) LDA, TMSCl then I_2; (b) *i*PrMgCl, −78 °C, THF then PhCHO, −78 °C to 0 °C; (c) Dess–Martin periodinane, CH_2Cl_2, RT; (d) TBAF, THF, RT; (e) LDA, THF, −78 °C, then lithium 2-thienylcyanocuprate, then allyl bromide; (f) Grubbs' 2nd-generation catalyst, 2-methyl-2-butene, CH_2Cl_2, 40 °C; (g) LiI, 2,4,6-collidine, 140 °C.



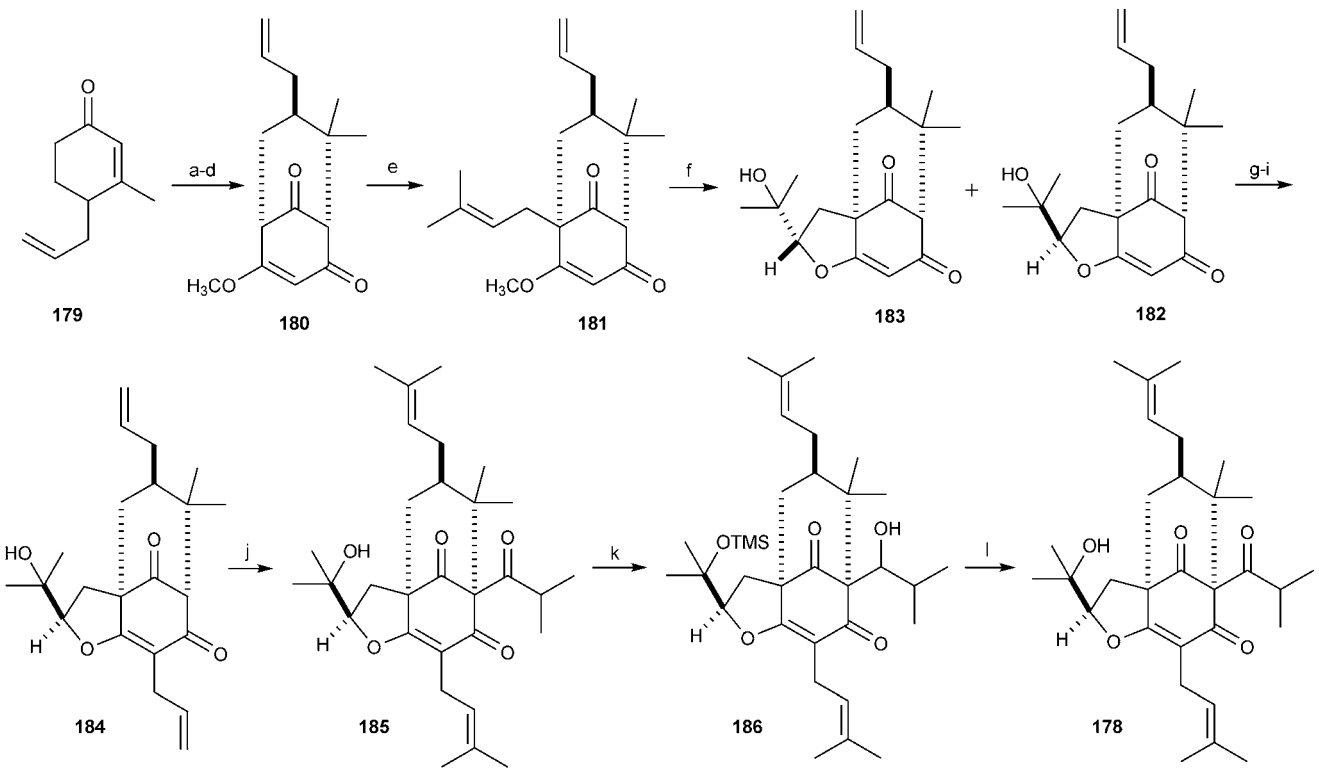
Scheme 25 Simpkins' attempted synthesis of nemorosone. *Reagents and conditions*: (a) LDA, prenyl bromide, −78 °C; (b) MeMgBr, CuI, THF, Me_2S, 0 °C; (c) TBSCl, Et_3N, NaI, MeCN, reflux; (d) malonyl dichloride, Et_2O, −20 °C, 24 h then $BnEt_3NCl$, KOH, H_2O, RT, 6 h; (e) Me_2SO_4, K_2CO_3, acetone, reflux, 1 h; (f) LTMP, −78 °C, 20 min then 2-thienyl(cyano)copper lithium, −40 °C, 30 min, then prenyl bromide, −78 °C to −40 °C, 1.5 h.

2nd-generation metathesis catalyst to give **185**. This was followed by bridgehead iodination, iodine–magnesium exchange and electrophilic quenching with isobutyraldehyde to afford **186**. Oxidation and deprotection of tertiary alcohol **186** gave garsubellin A (**178**) (Scheme 26).[93]

2.7 Cyclic polyketides

Synthesis of several cyclic polyketides such as leptospermone (**187**),[94] isoleptospermone (**188**),[95] agglomerone (**189**),[96] flavesone (**190**)[97] and papuanone (**191**)[95] has been reported in the literature (for structures see Fig. 5). In most of the syntheses, polymethylation was carried out using alkyl halides in the presence of NaOMe/MeOH or aqueous KOH.

2.7.1 Syntheses of leptospermone. Scheme 27 illustrates the synthesis by Briggs *et al.* of leptospermone (**187**). This was a single-step procedure involving *C*-methylation of phloroisovalerophenone (**6**) in alkaline media with methyl iodide as the methylating agent.[94] Jain and Sheshadri used sodium methoxide as the base in place of potassium hydroxide.[98] Leptospermone has also been synthesized by acylation of syncarpic acid[99] or tetra-*C*-methylphloroglucinol[100] with isopentanoyl chloride. Similarly, agglomerone was synthesized from



Scheme 26 Ahmad's synthesis of intermediate **184**, and Danishefsky's synthesis of garsubellin A from intermediate **184**. *Reagents and conditions*: (a) MeMgBr, CuI, THF, 0 °C; (b) TBSCl, Et_3N, NaI, MeCN, reflux; (c) malonyl dichloride, Et_2O, −20 °C, 24 h then $BnEt_3NCl$, KOH, H_2O, RT, 6 h; (d) PTSA, MeOH, reflux; (e) LDA, THF, prenyl bromide; (f) DMDO, CH_2Cl_2, 0 °C then TMSCl, CH_2Cl_2; (g) TMSCl, DMAP, DMF; (h) LTMP, THF, 2-thienyl(cyano)copper lithium, then allyl bromide; (i) Et_3N–HF, THF; (j) Grubbs' 2nd-generation catalyst, 2-methyl-2-butene, CH_2Cl_2, 40 °C; (k) i) LDA, TMSCl then I_2, THF, −78 to 0 °C; ii) *i*PrMgCl, THF, then *i*PrCHO, −78 to 0 °C; (l) i) DMP, CH_2Cl_2, 23 °C; ii) $Et_3N{\cdot}(HF)_3$, THF, 23 °C.

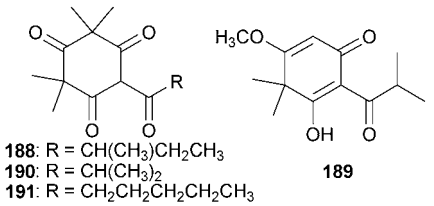
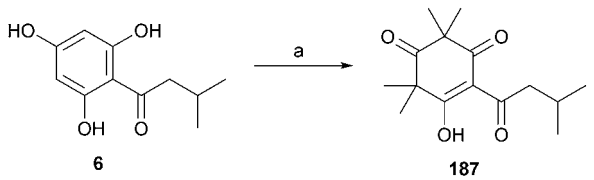
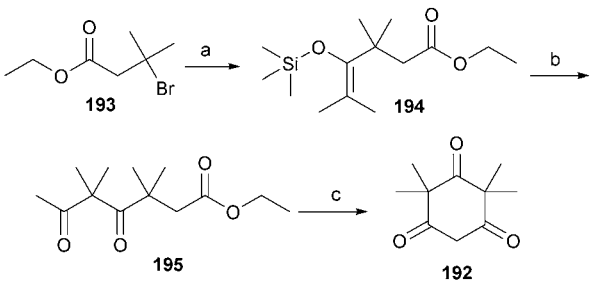


Fig. 5 Structures of some naturally occurring cyclic polyketides.



Scheme 27 Briggs' synthesis of leptospermone. *Reagents and conditions*: (a) KOH, CH_3I, 70 °C, 3 days.

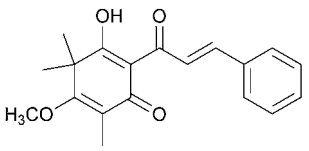


Scheme 28 Synthesis of syncarpic acid. *Reagents and conditions*: (a) Mg, Br_2, THF, then Me_3SiCl; (b) Ac_2O, $AlCl_3$, $ClCH_2CH_2Cl$, Et_2O, 0–5 °C, 2 h then 12 h, RT; (c) NaOH, DMSO.

phloroisobutyrophenone in two steps. *O*-Methylation of the reactant followed by *C*-methylation afforded the product in a 31% yield.[96]

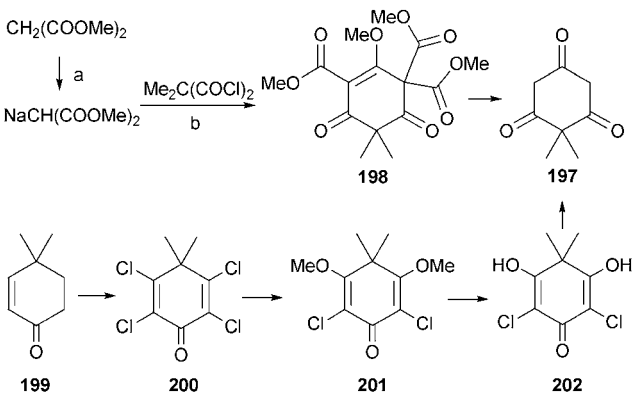
2.7.2 Syntheses of syncarpic acid. Syncarpic acid (**192**) was synthesized from ethyl 2-bromo-2-methylpropanecarboxylate (**193**) in three steps. The reactant was gently refluxed in the presence of a metallic reagent such as Mg/Li or organolithium and then silylated to give ethyl 2,2,4-trimethyl-3-trimethylsilyloxypent-3-enecarboxylate (**194**), which was acetylated in the presence of a Lewis acid such as aluminium chloride to yield ethyl 2,2,4,4-tetramethyl-3,5-dioxohexanecarboxylate (**195**). Finally, treatment with base gave the desired product in 95% yield (Scheme 28).[101] The intermediate **195** can also be obtained by silylation of 2,2,4,4-tetramethyl-1,3-cyclobutanedione.[102] Syncarpic acid was also synthesized in two steps by *C*-acylation of the trimethylsilyl enolate of ethyl 1,1,3-trimethyl-2-oxo-butanecarboxylate followed by intramolecular cyclization.[103]

Another phloroglucinol derivative, desmosdumotin C (**196**), was synthesized from 2,4,6-trihydroxyacetophenone by methylation and aldol condensation with benzaldehyde.[104]

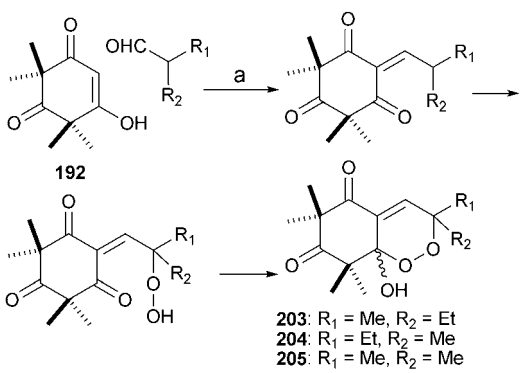


2.7.3 Syntheses of filicinic acid. Filicinic acid (**197**) was synthesized from malonic ester in three steps. 1,1-Dimethyl-3,5,5-tricarbomethoxy-4-methoxy-3-cyclohexene-2,6-dione (**198**) was the key intermediate formed by the condensation of dimethylmalonyl chloride and $NaCH(COOMe)_2$.[105] Another strategy for synthesis of filicinic acid involved conversion of the cyclohexanone derivative **199** to the tetrachloro derivative **200**, which then underwent facile substitution by methoxide to afford the bis-enol ether **201**, which was converted into **202** by hot sulfuric acid. Filicinic acid was obtained by palladium-catalyzed low-pressure hydrogenation of **202** (Scheme 29).[106] Another method of preparation of filicinic acid involved methylation of 2,4-diacetylphloroglucinol to yield diacetylfilicinic acid, which could be deacetylated to give filicinic acid.[107] Filicinic acid has also been prepared by deacetylation of 3-acetylfilicinic acid obtained by *C*-methylation of phloroacetophenone.[108] Several other syntheses of filicinic acid and related compounds and analogues have also been reported.[109–112]

2.7.4 Syntheses of G-regulators. G-inhibitors or G-regulators are derivatives of 2,3-dioxabicyclo[4.4.0]decane that inhibit root development in cuttings of mature *Eucalyptus*. Biomimetic



Scheme 29 Synthetic approaches to filicinic acid. *Reagents and conditions*: (a) Na, benzene; (b) benzene, reflux, 1 h; (c) 1% NaOH, MeOH, 5 days, RT.



Scheme 30 Biomimetic synthesis of G-regulators. *Reagents and conditions*: (a) MeOH, KOH, 7 h, reflux (for G1 and G2) or EtOH, piperidine, 20 °C, 5 min (for G3).

synthesis of G-regulators G1–G3 (**203–205**) involved Knoevenagel condensation of the appropriate aldehyde with syncarpic acid (**192**) in the presence of a catalytic amount of piperidine, followed by incorporation of a peroxide functionality by autooxidation over silica gel and closure of the heterocyclic ring (Scheme 30).[113]

An alternative approach for the synthesis of G-regulators/analogues involved a Lewis acid-catalyzed Prins reaction between aldehydes and alkenes (*e.g.* dimedone, **206**) forming the 1,3-dioxan (**207**). This, when adsorbed over silica gel, resulted in an analogue (**208**) of the G-regulators; however, G-regulators could not be synthesized by this method (Scheme 31).[114] The same authors presented another strategy involving formation of a Mannich base for the synthesis of G-regulator analogues.[115,116]

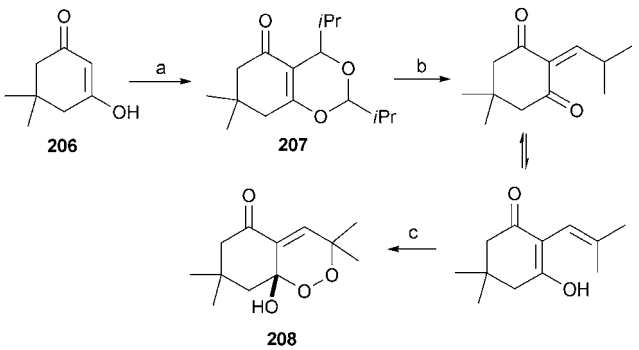
3 Dimeric phloroglucinols

This class encompasses compounds having two phloroglucinol units joined either through a methylene linkage or by a chroman ring.

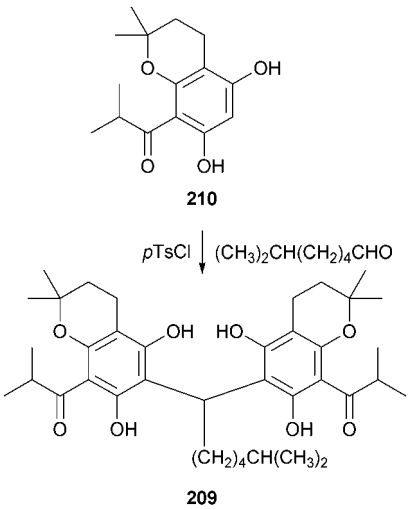
3.1 Dimers formed *via* a methylene linkage

Extensive research has been undertaken on this class of compounds in the laboratories of Pentilla & Sundman and Riedl, with many dimeric and higher phloroglucinols being successfully isolated and synthesised. A number of dimeric phloroglucinols have been isolated from *Dryopteris* species. Syntheses of many of these derivatives have been accomplished using monomeric phloroglucinols as starting material and an aliphatic aldehyde as the linker molecule. In all cases, a methylene bridge links one monomer with another that is not capable of condensing further. Kuhnke and Bohlmann synthesized a naturally occurring dimeric phloroglucinol with a benzopyran skeleton (**209**) starting from **210** in a single step. The key dimerization step was accomplished with *p*TsCl in chloroform (Scheme 32).[117]

Meikle and Stevens synthesized antibacterial albaspidins and uliginosins starting from phloroglucinol. Albaspidin iBiB (**211**) was synthesized by condensation of two acylfilicinic acid (**212**) moieties using formaldehyde in aqueous alkali. Rottlerone exchange between albaspidin iBiB and 2′,4′,6′-trihydroxy-3′-(3-methylbut-2-enyl)isobutyrophenone (**213**) in the presence of sodium hydride resulted in the formation of uliginosin A (**214**)



Scheme 31 Bolte's synthetic strategy for G-regulators/analogues. *Reagents and conditions*: (a) 2-methylpropanal, CH_2Cl_2, $BF_3 \cdot Et_2O$, RT, 12 h; (b) SiO_2, (c) O_2.



Scheme 32 Kuhnke & Bohlmann's synthesis of dimeric phloroglucinols.

(Scheme 33).[118] Synthesis of uliginosin B-iBiB (**215**) and B-iBiV (**216**) was also reported by same group (for structures see Fig. 6).[119]

Sato *et al.* used sodium methoxide in dry methanol for the dimerization step during the synthesis of one of the key intermediates involved in the synthesis of carthamin, a dimeric pigment of safflower petals. An analogue (**218**) of the carthamin precursor was synthesized from **217** in 99% yield by a coupling reaction in the presence of glyoxylic acid in an alkaline medium (Scheme 34).[120]

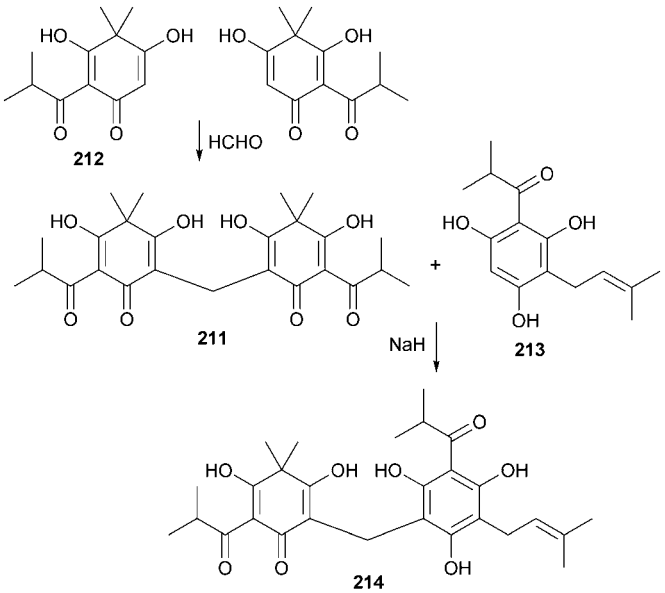
Condensation of *C*-methylphloroacetophenone (**219**) with 6,7-dihydroxy-8-β-phenylpropionyl-2,2-dimethylchroman (**220**) in the presence of formaldehyde as the linker gave tetrahydrorottlerin (**221**). Homodimers of phloroacetophenone and chroman subunits, namely hexahydroxydiphenylmethane (**222**) and octahydrorottlerone (**223**), were formed as side-products. Similarly, tetrahydroallorottlerin (**224**) was formed from **219** and 5,7-dihydroxy-6-β-phenylpropionyl-2,2-dimethylchroman (**225**); **222** and octahydroallorottlerone (**226**) were formed as side-products (Scheme 35).[121]

Aspidin (**227**),[122] Ψ-aspidin (**228**),[122] flavaspidic acid (**229**),[123,124] phloraspin (**230**),[125] phloraspyron (**231**),[126] phloraspidinol (**232**),[126] kosin (**233**)[127] and other homologues of albaspidin (**234**),[124] flavaspidic acid (**229**) and desaspidin (**235**) have also been synthesized by similar strategies (for structures see Fig. 6).[128]

3.2 Dimers involving a chroman ring

Two diformyl phloroglucinol derivatives, namely sideroxylonal B (**236**) and grandinal (**237**), have been synthesized by considering biosynthetic pathways.

3.2.1 Synthesis of sideroxylonal B. The fully functionalized 2-phenyl-1-benzopyran framework present in sideroxylonal B was first constructed by Tatsuta *et al.* in 1999. The synthesis required developing a new method to synthesize the 2-phenyl-1-benzopyran skeleton with four appropriately placed formyl functionalities. Biosynthetically, sideroxylonals are thought to be formed by a Diels–Alder cycloaddition of the *O*-quinone methide (**238**) and an isopentenyl intermediate (**239**) (Scheme 36a).



Scheme 33 Meikle & Steven's synthesis of albaspidin iBiB and uliginosin A.

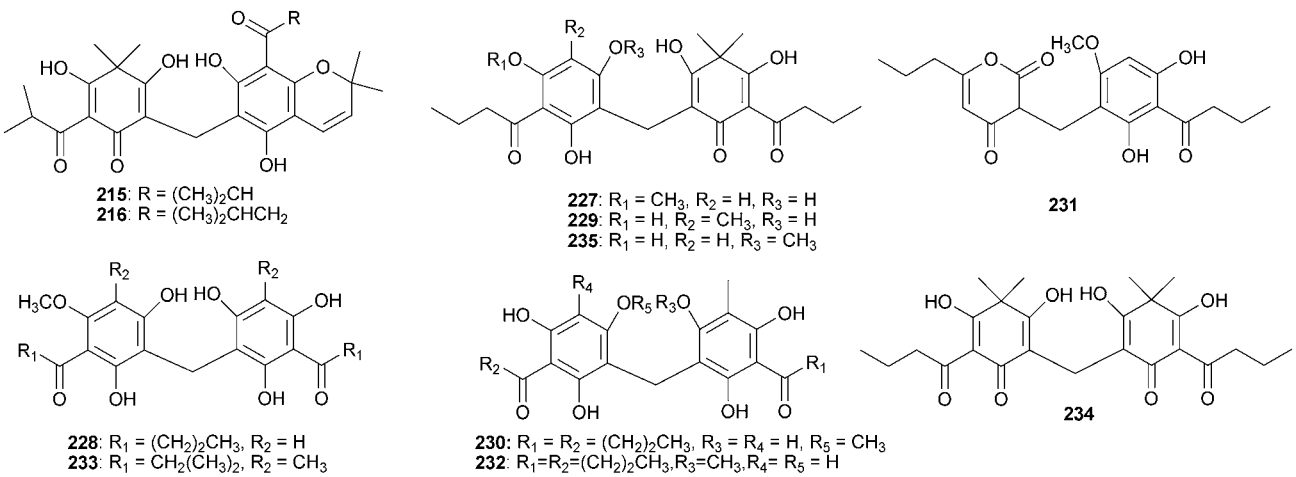
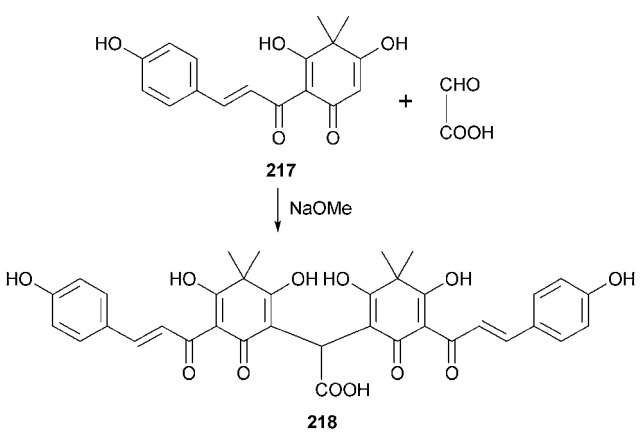
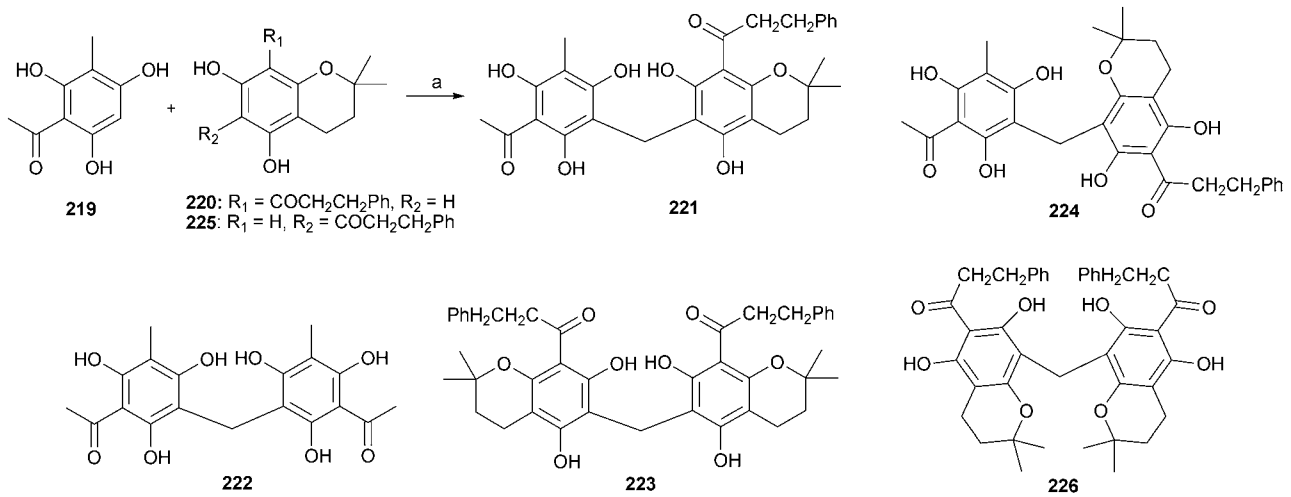


Fig. 6 Structures of some naturally occurring dimeric phloroglucinols.

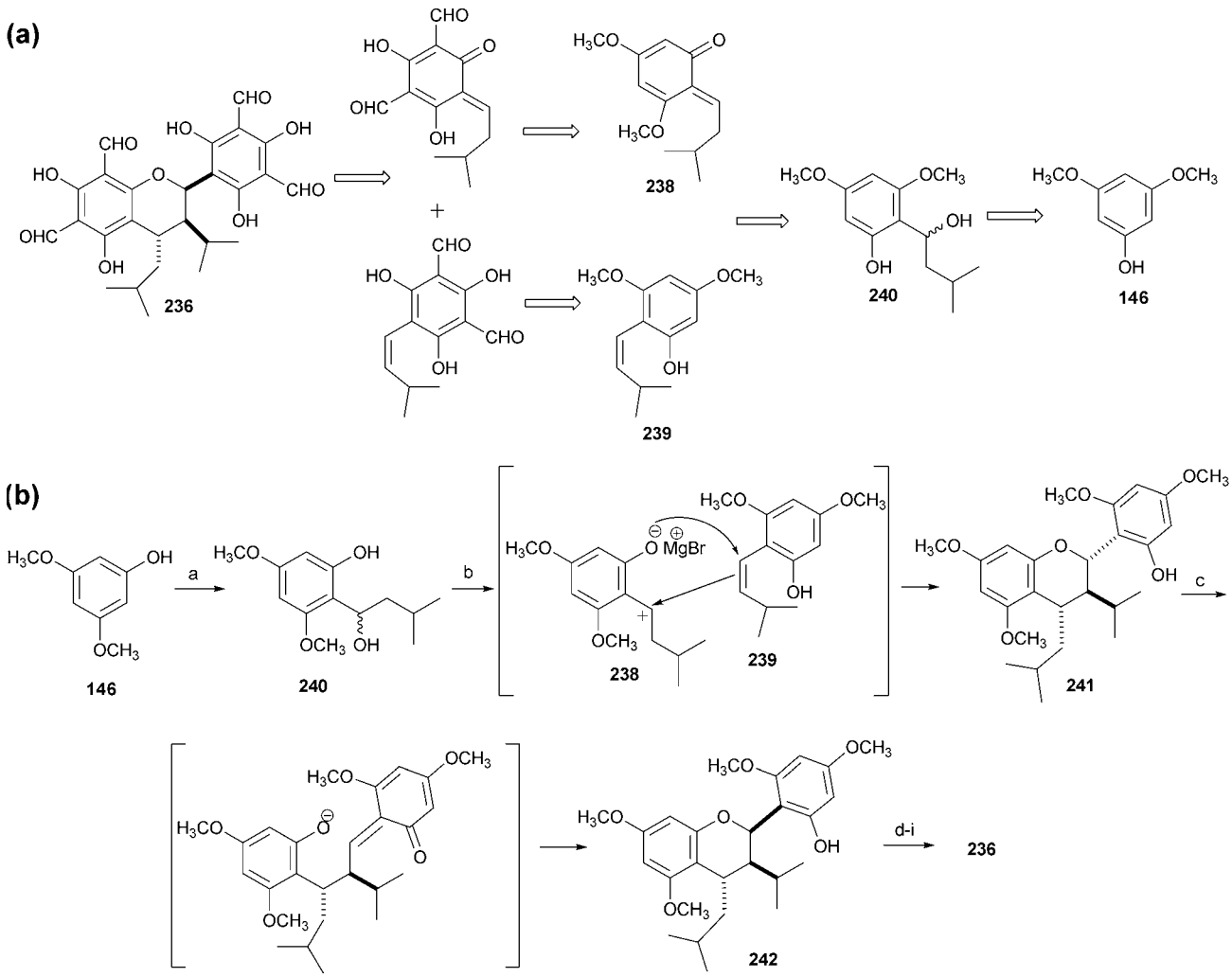


Scheme 34 Sato's synthesis of analogues of the dimeric pigments of safflower petals.

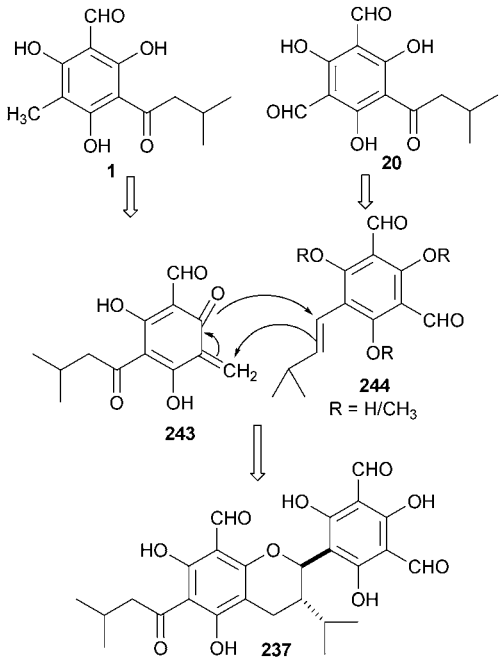
Therefore, a biomimetic strategy was considered and synthesis commenced with commercially available 3,5-dimethoxyphenol (**146**). The key intermediate **240** was prepared from **146** by reaction with isovaleric acid in the presence of boron trifluoride diethyl etherate followed by reduction of the resulting ketone. It was proposed that concurrent *in situ* formation of the *O*-quinone methide (**238**) and the isopentenyl derivative (**239**) occurs in the presence of the Grignard reagent. Cycloaddition of **238** and **239** gave a *trans* product **241**, which was thermodynamically changed to the *cis* isomer (**242**) through a pyran ring-opening and ring-closing process. An alternative mechanism, as shown in Scheme 36b, may also be possible. Opening of the pyran ring was followed by attack of hydroxyl on the *si*-face of the quinomethane intermediate to reform the pyran ring. The *cis*-isomer **242** was finally converted to sideroxylonal B (**236**) after a series of reactions involving bromination with benzyltrimethylammonium tribromide, lithiation with butyllithium, introduction of a methyl



Scheme 35 Synthesis of tetrahydrorottlerin and tetrahydroallorottlerin. *Reagents and conditions*: (a) 40% aq. HCHO, ethanol, H_2SO_4, RT, 24 h.



Scheme 36 **(a)** Retrosynthetic sequence for sideroxylonal B. **(b)** Synthesis of sideroxylonal B. *Reagents and conditions*: (a) i) isovaleric acid, $BF_3 \cdot Et_2O$, 80 °C; ii) 1 M $LiAlH_4$/THF, Et_2O, 0 °C; (b) i) EtMgBr/THF, Et_2O; ii) benzene, reflux, 30 min; (c) benzene, reflux, 29 h; (d) MeI, $Ba(OH)_2 \cdot 8H_2O$, BaO, DMF, RT; (e) $BnMe_3N^+ Br_3^-$, $NaHCO_3$, CH_2Cl_2, MeOH. RT; (f) $BnMe_3N^+ Br_3^-$, $ZnCl_2$, AcOH. 70 °C; (g) *t*BuLi/THF, −78 °C, then $ClCO_2Me$; (h) i) DIBAL/toluene, −78 °C; ii) PDC, CH_2Cl_2; (i) $BBr_3 \cdot SMe_2$, $ClCH_2CH_2Cl$, 70 °C.



Scheme 37 Proposed biogenetic pathway for grandinal.

ester with methyl chloroformate, reduction with DIBAL and oxidation using PDC (Scheme 36b).[129]

3.2.2 Synthesis of grandinal. Grandinal (**237**) has been synthesized along similar lines to sideroxylonal B. Biosynthetically, it is proposed to be derived from the *O*-quinone methide (**243**) generated from grandinol (**1**) and a jensenone derivative **244** (Scheme 37).

The jensenone derivative **244** (the OH was protected as a methyl ether in the synthesis) was synthesized from 1,3,5-trimethoxybenzene in nine steps in an overall yield of 13%. The *O*-quinone methide was generated *in situ* from grandinol (**1**). DDQ-mediated cyclization of both these building blocks yielded the desired product.[130]

4 Trimeric and higher phloroglucinols

Trimeric and tetrameric phloroglucinols have been synthesized using approaches similar to those for dimeric compounds. Agrimols A–E (**245–249**) were synthesized from three phloroglucinol units linked through a methylene bridge.[131,132] Similarly, filixic acid ABA (**250**) was synthesized from acetyl filicinic acid and phlorobutyrophenone,[133] methylene bisnorflavaspidic acid (**251**) from two molecules of norflavaspidic acid,[132,134] and dryocrassin (**252**) from methylene bis-phlorobutyrophenone and acetyl filicinic acid (for structures see Fig. 7).[135]

5 Phlorotannins

Phlorotannins have the highest molecular weight amongst the phloroglucinol class of compounds. Their enormous structural complexity and poorly explored biological activities have probably led to reduced attention to their synthesis. Syntheses of a few derivatives of natural molecules have been attempted. These include synthesis of an octaacetate derivative of trifuhalol by

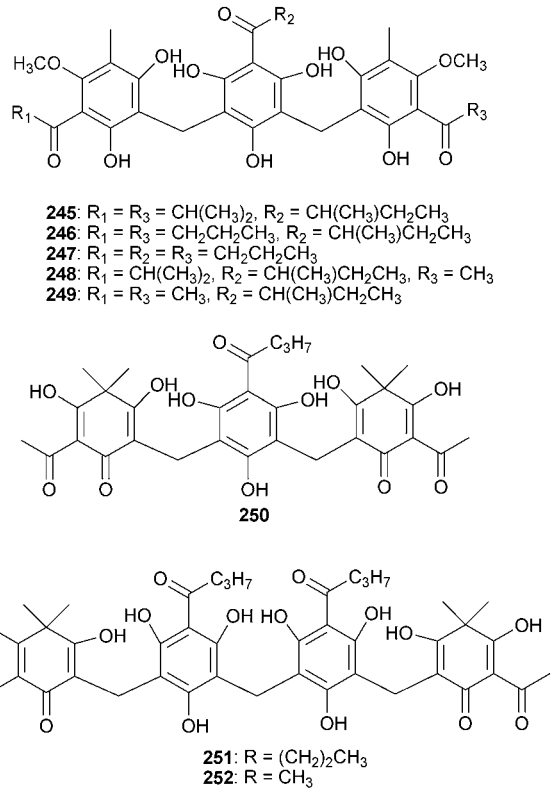


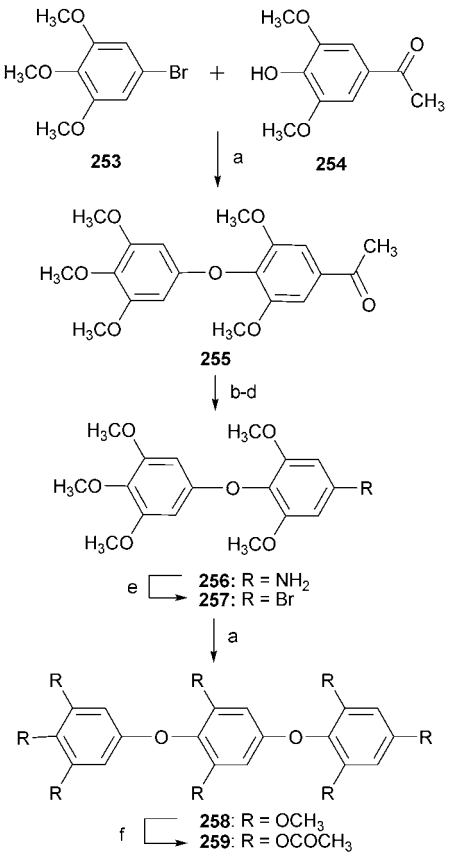
Fig. 7 Structures of some naturally occurring trimeric and tetrameric phloroglucinols.

Glombitza and Sattler. This was accomplished in seven steps using Cu_2O and collidine for linking the subunits 3,4,5-(trimethoxy)bromobenzene (**253**) and 4-hydroxy-3,5-(dimethoxy)-acetophenone (**254**). The acetyl group of the product (**255**) obtained was converted to an amino function in a three-step sequence to yield **256**. The amino functionality was again converted to a bromo group to obtain **257** for a condensation reaction with **254**. The subsequent coupling reaction gave **258**, which, in the presence of boron tribromide and acetic anhydride in pyridine, gave the octaacetate of trifuhalol (**259**) (Scheme 38).[136]

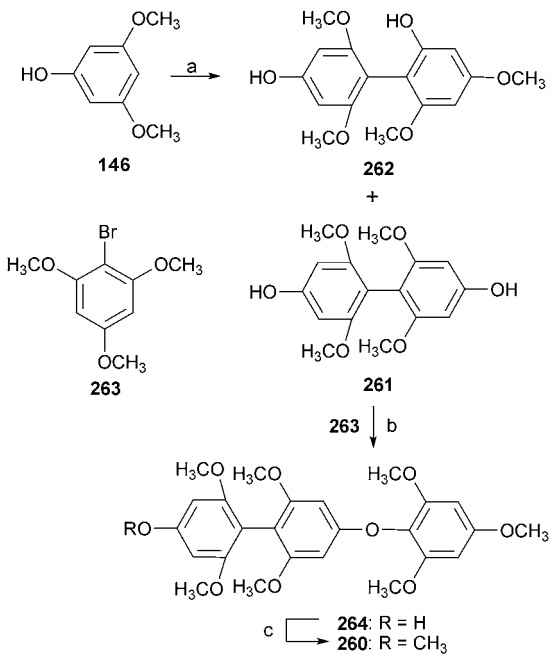
Another derivative of fucophlorethol (**260**) was synthesised from 3,5-dimethoxyphenol (**146**) using vanadium tetrachloride. 2,2′,6,6′-Tetramethoxy-4,4′-dihydroxybiphenyl (**261**), the key intermediate for the synthesis (which was obtained in large quantity in preference to its regioisomer 2,2′,4,6′-tetramethoxy-4′,6-dihydroxybiphenyl (**262**)), was subjected to Ullmann condensation with 2,4,6-(trimethoxy)bromobenzene (**263**) to yield **264**. The last step of the synthesis involved a Hakomori methylation of **264** to yield **260**, the octamethyl ether derivative of the naturally occurring brown algal metabolite fucophlorethol (Scheme 39).[137]

6 Conclusions

Although not exhaustive, this review serves to highlight the key strategies followed in the syntheses of variety of natural phloroglucinols. Synthesis of simple acyl phloroglucinols is unexceptional, but some of the compounds such as knipholone still present challenges to synthetic chemists because of chirality



Scheme 38 Glombitza & Sattler's synthesis of a trifuhalol derivative. *Reagents and conditions*: (a) Cu_2O, collidine; (b) $H_2NOH \cdot HCl$; (c) PCl_5, benzol; (d) HCl; (e) HNO_2 then HBr/CuBr; (f) BBr_3, Ac_2O, pyridine.



Scheme 39 Ragan's synthesis of a fucophlorethol A derivative. *Reagents and conditions*: (a) VCl_4, CCl_4; (b) Cu_2O, collidine; (c) $CH_3S(O)CH_2$, DMSO.

arising from their hindered biphenyl structure. Polycyclic polyprenylated acyl phloroglucinols have been a focus of numerous synthetic efforts. Their interesting biological activities (such as antidepressant, antianxiety, anti-Alzheimer, antiseptic, bactericidal and anti-inflammatory activities) mean that they will continue to attract the attention of synthetic chemists. Only one synthesis of macrocarpal C has been reported. Due to their anti-HIV activity and activity against periodontopathic bacteria, the synthesis of other macrocarpals should continue to be of considerable interest. Six different syntheses have been reported for the antimalarial robustadials, with the latest in 2006 from our laboratory. Few syntheses of higher phloroglucinols have been attempted, in part because their biological activities have not been well-explored. Considering the range of biological activities shown by various phloroglucinol molecules, we expect significant attention will be paid to syntheses of this group in the future.

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