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Total synthesis of natural products containing benzofuran rings

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Research on natural products containing benzofuran has remarkably increased during the past few decades. Newly isolated natural products with complex structures are being studied, characterized and screened for possible biological activities. Several of such compounds have exhibited various biological activities, thus their total syntheses have attracted much attention from synthetic organic chemists. In this review, we aim to highlight the origins, structures, biological potencies, and synthetic approaches of those natural products bearing at least one benzofuran in their complex structures. Furthermore, we especially focus on the step in which this key heterocycle is installed during the total synthesis of a natural product as the desired target.

1 Introduction

Benzofuran and its derivatives are widely present as scaffolds in the complex molecules of natural products. These kinds of naturally occurring compounds have attracted much attention from synthetic organic chemists, due to their interesting biological and pharmacological activities.[1–3] Several natural products bearing benzofuran and its derivatives as a moiety,[4–6] exhibit diverse biological activities such as being potent anti-bacterial,[7] antimicrobial,[8] antitumor,[9] anticonvulsant anti-inflammatory,[10] antidiabetic[11] and antineophobic agents.[12] Furthermore, certain derivatives of benzofuran present in natural products show high cytotoxicity.[13] The exceptional structural features of benzofuran and its wide assortment of biological as well as pharmacological activities make it

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a privileged structure in the field of drug discovery. Nowadays, several benzofurans are being prescribed for treatment of Alzheimer's disease.[14] They have also been screened and found being acting as protein tyrosine phosphatase inhibitors (PTP-1B).[15] Indeed benzofuran is a versatile scaffold for its synthetic pathways and functionalization; moreover, it exhibits a medicinal chemistry interest due to its presence in several natural products.[16] Various benzofuran derivatives have been isolated from plants kingdom and marine sources.[17] Furthermore, they were also provided from bacterial or fungal metabolites.[18] Benzofurans occur in numerous natural products, as part of small molecule *i.e.* benzofury,[19] as well as more complex drug such as notorious morphine (as street drug) and macromolecule like rifamycin.[20] They also can be assembled in more complex architectures in a wide range of natural products such as fungi, bacteria, *etc.*

Naltrindole (NTI) and its benzofuran derivative (NTB) were proved being antagonist of different opioid receptor agonists in the tail-flick antinociceptive evaluation in mice.[21] Amiodarone, (2-{4-[(2-butyl-1-benzofuran-3-yl)carbonyl]-2,diiodophenoxy} ethyl)diethylamine, **1** is an antiarrhythmic agent which nowadays prescribed for treatment of different types of cardiac dysrhythmias, both ventricular and atrial.[22] Dronedarone, *N*-(2-butyl-3-(*p*-(3-(dibutylamino)propoxy)benzoyl)-5-benzofuranyl) methane sulfonamide, **2** is an efficient drug which stop atrial fibrillation and atrial flutter relapses, which is prescribe for low-risk patient (Fig. 1).[23]

Psoralen (also called psoralene) (7*H*-furo[3,2-*g*]chromen-7-one) **3** is the parent in a family of naturally occurring compounds known as furocoumarins. It is structurally related to coumarin and can be regarded as an umbelliferone derivative (Fig. 2).[24]

Machicendiol **4**, a benzofuran isolated from the extracts of *Machilus glaucescens*,[25] has been long used as traditional medicine in the treatment of asthma, rheumatism, and ulcers for a long period of time.[26] It has been found that 2,5-disubstituted benzofurans are particularly active in enhancement of insulin sensitivity.[27] The benzofuran-fused benzocarbazol has been found to inhibit the growth of malignant cells and they also showed antibiotic properties (Fig. 3).[28,29]

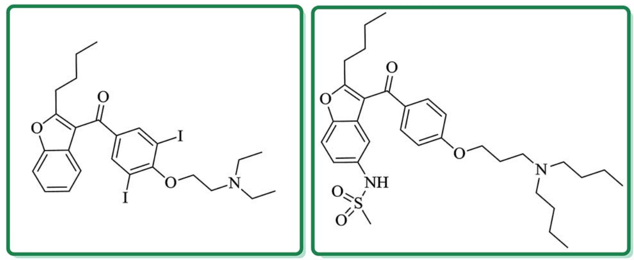
1: Amiodarone 2: Dronedarone

Fig. 1 The structure of amiodarone **1** and dronedarone **2**.

Ailanthoidol **5** (ref. 30) and XH-14 **6** were isolated from the chloroform-soluble fraction of stem woods of *Zanthoxylum ailanthoidos*.[31] Studies on the constituents of plants of *Zanthoxylum ailanthoidos*, they are used in Chinese traditional herbal medicine. These compounds exhibit different interesting pharmacological activities.[32,33] Ailanthoidol **5**, a neolignan derivative, demonstrated antiviral, antioxidant and antifungal potencies (Fig. 4).[34–39]

Significantly, the benzofuran derivatives containing the pyrazole nucleus were reported to be analgesic, anti-inflammatory, antipyretic, antiarrhythmic, muscle relaxant, psychoanaleptic, anticonvulsant and hypotensive.[40–53] Remarkably, a large number of synthetic approaches have been attempted and accomplished for the synthesis of fused benzofurans. The synthesis frequently starting from differently appropriate substituted benzene rings. Most synthetic approaches towards benzofurans are based on the generation of the O–C2 or the C2–C3 bonds, in the vital ring closing step. Nevertheless, those approaches manipulating C3–C3 bond generation, *via* intramolecular cyclization of an already appropriately functionalized precursor. These approaches are particularly striking and much anticipated. They include: (a) acid-catalyzed cyclization of compounds continuing carbonyl group by dehydration,[54,55] (b) palladium[56,57] or platinum[58]-

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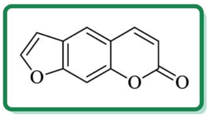
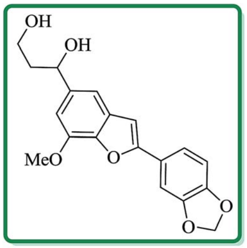


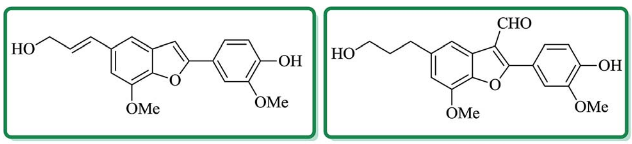
3: Psoralen

Fig. 2 The structure of psoralen **3**.



4: Machicendiol

Fig. 3 The structure of machicendiol **4**.



5: Ailanthoidol 6: XH14

Fig. 4 The structure of ailanthoidol **5** and XH-14 **6**.

catalyzed[59] ring closure by an intramolecular Wittig reaction[60–62] or *o*-(acyloxy)benzyl anions,[63] (c) condensation of activated methylene following Dieckmann reaction condtiions[64,65] or ketene intermediate involved cyclization,[66] (d) acid-catalyzed ring construction of α-aryloxycarbonyls[67] or (e) intramolecular Friedel–Crafts reaction,[68] (f) photolytic cyclization of α-phenylketones,[69] and (g) gold(III)-catalyzed tandem reaction of *O*-arylhydroxylamines with 1,3-dicarbonyl substrates.[70] Moreover, a one-pot reaction for the transformation of allyl aryl ethers to 2-methylbenzofurans *via* sequential reaction involving Claisen rearrangement/oxidative cyclization has been reported.[71] 3-Acyl-2-aminobenzofurans give 2-(cycanomethyl) phenyl esters using catalytic quantity of $Pd(OAc)_2$, PCy_3, and Zn.[72]

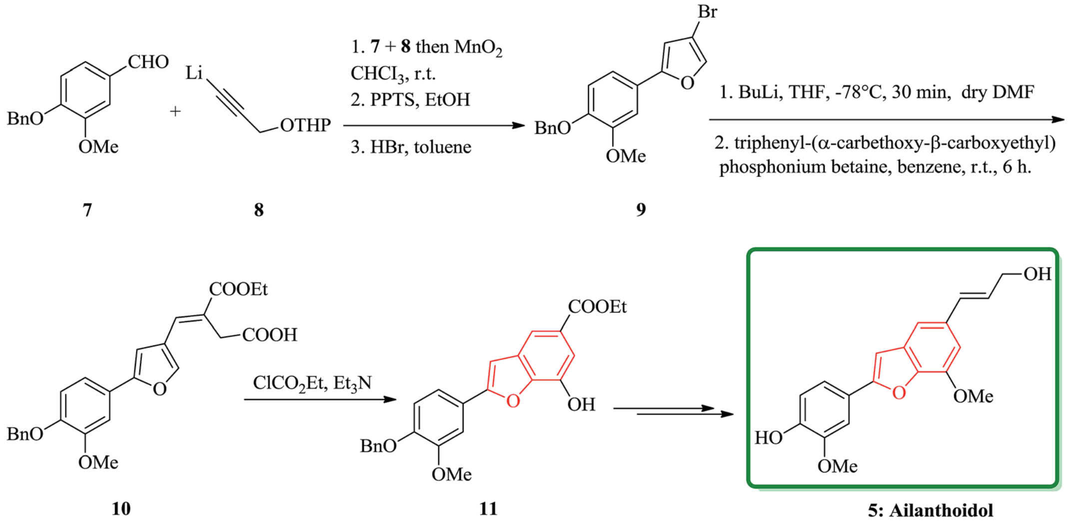
Recently, the role of benzofuran and its derivatives present in natural products as emerging framework for antimicrobial agents,[73] antibreast cancer agents[74] and in other natural lead molecules with diverse pharmacological properties have been comprehensively, revealed.[75,76] We are especially interested in heterocyclic chemistry[77–88] and heterocyclic compounds showing high biological activity.[89] In recent years, we have highlighted the applications of several name reactions in the total synthesis of biologically active natural products and applications of asymmetric synthesis in total synthesis of natural products.[90–95]

In this line very recently, we focused on chemistry of benzofurans and published a chapter in Advances in Heterocyclic Chemistry entitled the recent advances in the synthesis of benzo[*b*]furans.[78] Due to the massive number of pertinent references, coverage of the chemistry of this key heterocycle from different aspects, features and issues were surpassed by the limits in length and pages imposed by the editorial board of this book series. Thus, we had to divide the rest of this vast subject into three reviews. In our two recent reviews, we disclosed the full perspective of reactivity of benzofurans[96] and advances in the synthesis of biologically potent compounds bearing at least one benzo[*b*]furan moiety in their structures, respectively.[97] In the present review, we collated the published reports on the total synthesis of natural products containing at least one benzofuran moiety in their complex structures. Noticeably, in spite of brief introduction of the natural products, their sources and the methods used for their characterization, we focused on the key step of construction of benzofuran moiety during the total synthesis of such natural products.

2 Construction of benzofuran as a scaffold in the structures of natural products during their total synthesis

Lignans and neolignans are interesting goals for organic synthetic chemists. The members of this family containing benzofuran showing broad spectrum of biologically activity. Among these compounds, the total synthesis of benzofuran neolignans[98,99] have been considered following the biomimetic routes. In this approach, initially an appropriate 4-furyl-3-alkoxy-3-butenoic acid **10** was synthesized. As illustrated in Scheme 1, the aldehyde **7** (ref. 7) was reacted with the lithium salt of protected propynol **8** to afford the corresponding carbinol, which was then transformed into the 3-bromofuran **9** involving sequential reactions including oxidation of propargylic carbinol/selective deprotection of tetrahydropyranyl ether/acid-catalyzed cyclization to afford 3-bromofuran **9** in moderate overall yield. 3-Bromofuran **9** was then converted into the benzofuran **11** *via* the formation of 4-furyl-3-alkoxy-3-butenoic acid **10**. The desired benzofuran **11** converted to **5** in several steps, eventually, ailanthoidol **5** obtained in moderate overall yield.[34]

XH-14 **6** was initially isolated from the plant so called *Salvia miltiorrhiza*. Latter on it was found being a potent antagonist against the adenosine receptors.[100] Ailanthoidol **5** is also a structurally related compound to **6**. Although, there is no report on biological activity of this compound on the adenosine receptor, the extracts of the leaves and bark of this tree had been used as traditional medicine for long period. It has been reported several methods for the synthesis of XH-14 **6**.[100–102] Another method towards the synthesis of XH-14 involved an oxidative dimerization of methyl ferulate (methyl-3-methoxy-4-hydroxycinnamate) to form the benzofuran skeleton has also been reported.[103] This strategy gave only low overall yield (34%) and showed no flexibility for the synthesis of other analogs. An improved and efficient strategy for the total synthesis of ailanthoidol **5** has been reported by Lütjens and co-workers in 1998. This approach for the total synthesis found being attractive and practical. In this protocol, the total synthesis of ailanthoidol



Scheme 1 Total synthesis of ailanthoidol **5**.

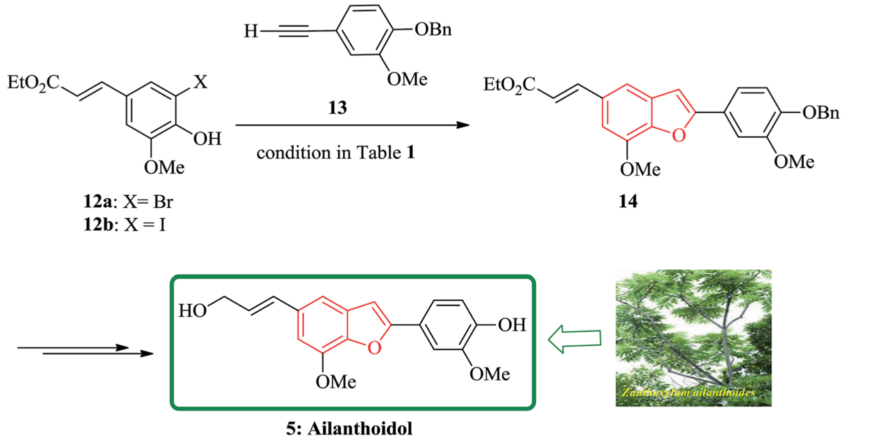
commenced with the building up of the benzofuran nucleus *via* coupling of the *ortho*-halophenol **12** and the alkyne **13** with simultaneous cyclization. The coupling of **12** and **13** was conducted under Sonogashira conditions.[104] It affords a better yield and also found being re-producible (Table 1). It was also found that $PdC1_2(PPh_3)_2$ is more efficient catalyst than $Pd(PPh_3)_4$ and also iodophenol **12b** was proved to react better than bromophenol **12a**. The resultant benzofuran **14** was then converted into ailanthoidol in two steps. The first step was involving the removal of the protecting group using $TiCl_4$ and the second step involved the reduction of the ester group using DIBAL to give the desired target **5** in 77% overall yield after crystallization from MeOH (Scheme 2).[105]

Notably, the synthesis of XH-14 **6** was accomplished using a similar protocol, employing the Sonogashira coupling reaction conditions. Nevertheless, in the case of the generation of the intermediate *ortho*-hydroxytolan, it was isolated preceding to cyclization and then subjected into Pd-catalyzed carbonylative cyclization reaction was to construct the benzofuran ring system with simultaneous acylation at the 3-position. Ethyl-3-methoxy-4-hydroxy-5-iodocinnamate **12b** was protected as MOM ether and then coupled with the various substituted alkyne to provide the corresponding MOM protected *ortho*-hydroxytolan in high yield (92%). For the removal of the MOM protecting group oxalic acid in aqueous methanol was used to afford virtually quantitative yield of the *ortho*-hydroxytolan **16**. Using a catalytic amount of $PdCl_2$ to solution of **16** and NaOAc/MeOH under atmosphere of CO imposed cyclization to a vinylpalladium(II) species in which after insertion of CO and reaction with methanol afforded the substituted benzofuran **17** in a satisfactory isolated yield. The resulting Pd(0) species were re-oxidized by copper(II)chloride permitting the utilization of a sub-stoichiometric amount of Pd. It was proved that the choice of base is crucial as **16,** since a noticeable inclination being subjected to un-catalyzed auto-cyclization under basic conditions were observed. Therefore, the un-functionalized benzofuran **18** was constructed solely when K_2CO_3 was employed instead of Na_2CO_3. Conversion of **17** into the desired product **6** was then achieved *via* straightforward strategy in which after three steps, XH-14 **6** was provided. This strategy provides a new gateway for the efficient synthesis of XH-14 **6** in which affords the formulated isomer, only. This synthesis is also high yielding and flexible to give a wide variety of differently 2-substituted analogs (Scheme 3).[105]

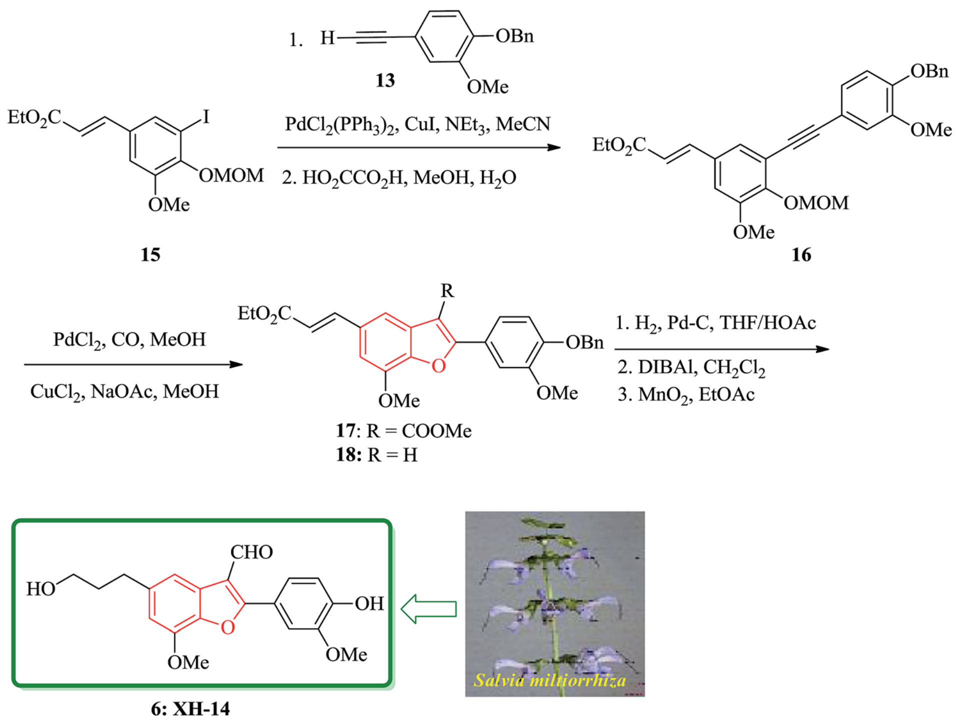
Table 1 Reaction conditions for the synthesis of benzofuran **14**

Entry	Substrate	Conditions	Yield (%)
1	**12a**	Cu-acetylide of **13**, Py, reflux	65
2	**12a**	Cu_2O, Py, reflux	62
3	**12a**	$PdCl_2(PPh_3)_2$, CuI, NEt_3, MeCN	69
4	**12a**	$Pd(PPh_3)_4$, CuI, NEt_3, MeCN	52
5	**12b**	$Pd(PPh_3)_2$, CuI, NEt_3, MeCN	88

In another attempt, the total synthesis of ailanthoidol was also accomplished in 12 steps manipulating different functional transformations in a 17% overall yield starting from vanillin **19**. A convenient method for the synthesis of ailanthoidol from vanillin is established, using trimethylsilyl diazomethane lithium salt to generate diphenyl acetylene which followed by oxymercuration cyclization of the resulting alkyne using mercury acetate in acetic acid as key steps. The mercurial intermediate **21** is found to be a very useful intermediate for the syntheses of analogs by the direct replacement of the mercurial moiety with a variety of functional groups. The desired intermediate **20** upon treatment with mercury acetate in acetic acid and then quenching with saturated sodium chloride solution afforded 2-(*p*-benzyloxy-*m*-methoxyphenyl)-3-chloromercurio-5-(5′,5′-dimethyl-1′,3′-dioxan-2′-yl)-7-methoxybenzofuran **21**. The chloromercurial intermediate **21** without further purification was isolated and reduced with $NaBH_4$ in THF to afford benzofuran **22** in high yields. After several steps the latter was converted into the desired natural product ailanthoidol **5** (Scheme 4).[106]



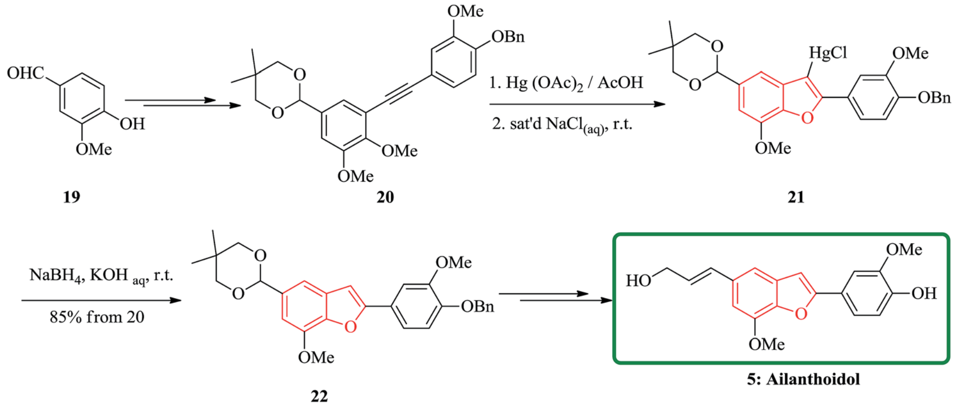
Scheme 2 Total synthesis of ailanthoidol 5.



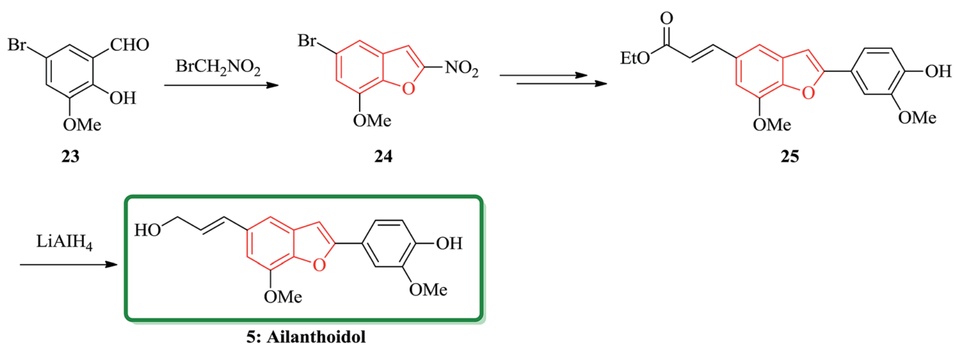
Scheme 3 Total synthesis of XH-14 6.

Furthermore, ailanthoidol **5**, was also synthesized *via* a route which is the longest linear sequence is only six steps in 48% overall yield. This pathway started from commercially available 5-bromo-2-hydroxy-3-methoxybenzaldehyde **23**. The key transformation in the synthesis is the Stille coupling reaction of benzofuranyl bromide with stannanyl compounds. This synthetic strategy can be modified to give access to a variety of different ailanthoidol analogues. With the aim of developing a successful route to ailanthoidol **5**, an alternative method of construction was examined. Accordingly, the removal of the benzyl protecting group with $TiCl_4$ followed by DIBAL or $LiAlH_4$ reduction of the ester to give **5** in the highest 95% yield (over two steps) (Scheme 5).[30]

In addition, some other natural products bearing 2-arylbenzofurans moiety in their structures such as, egonol **31a**, homoegonol **31b**, and demethoxyegonol **31c** were also isolated from *Styrax japonicum*, *Styrax officinalis* L., and *Styrax obassia*.[107–109] They were found exhibiting cytostatic activity towards human leukemic HL-60 cells.[110] The brief total synthesis of all three naturally occurring **31a**, **31b**, and **31c** was achieved only in five steps in overall yields of 40, 40, and 34%, respectively. The bromobenzofuran **28** present in these natural products were all also provided in two steps *via* selective cross MacMurry coupling in good yields. The introduction of 3-hydroxypropy moiety on the benzofuran rings was accomplished *via* Sonogashira cross coupling reaction with subsequent hydrogenation



Scheme 4 Total synthesis of ailanthoidol **5**.



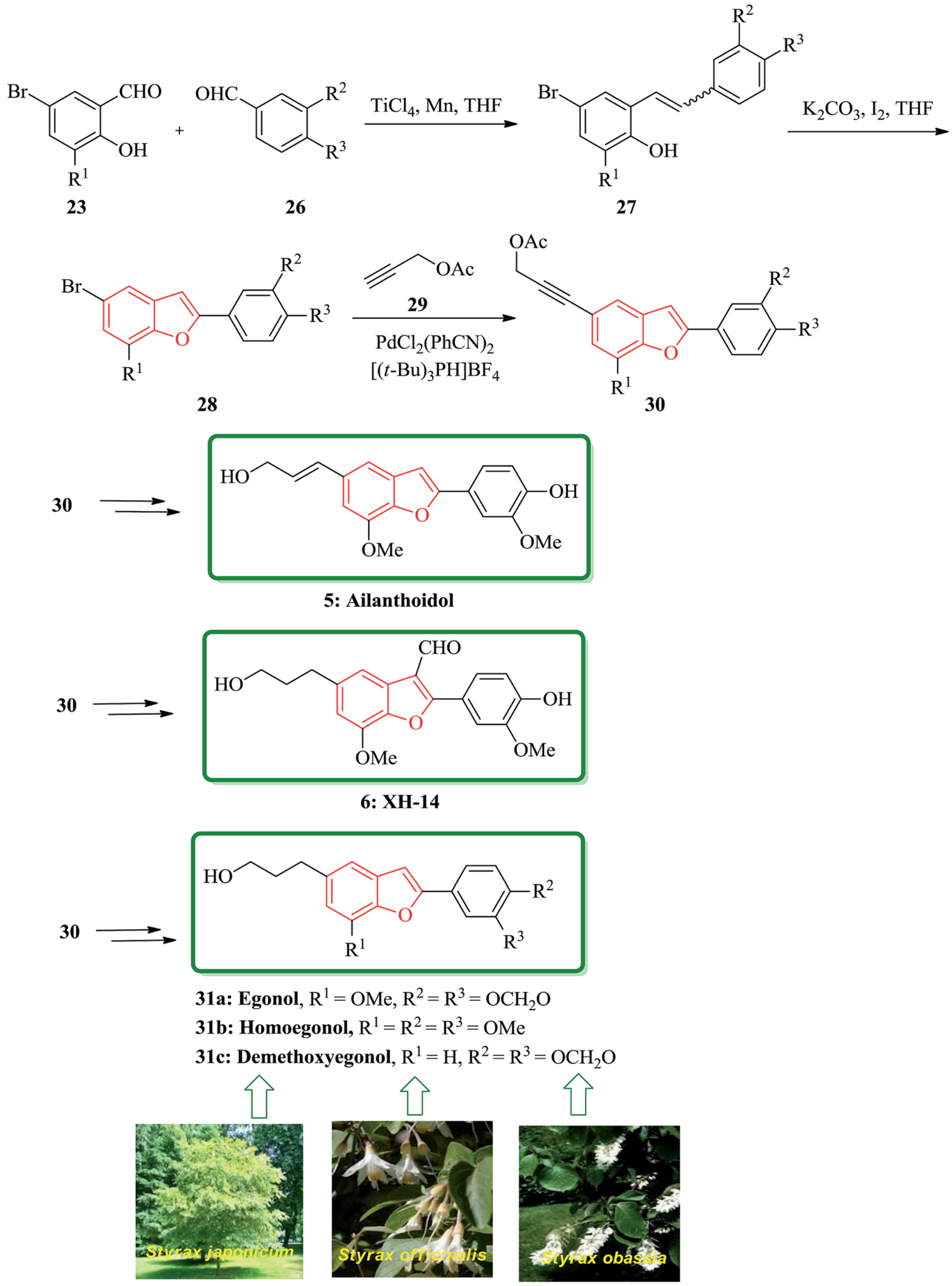
Scheme 5 Total synthesis of ailanthoidol **5**.

followed by hydrolysis. The total synthesis started from readily available **23** and **26** which are coupled by means of selective MacMurry cross coupling reaction[110] to afford intermediate **27**, which followed by oxidative cyclization to form compound **28**. The bromobenzofuran was coupled with propargyl acetate by a palladium-catalyzed Sonogashira reaction to generate **30** as a key intermediate to produce ailanthoidol **5**, XH-14 **6** and the other three natural products **31a–c** (Scheme 6).[111]

Yang and co-workers have carried out the total synthesis, which could also substantiate unambiguously the structure of XH-14 **6**. A key feature of this synthetic program was the conventional coupling reaction[112] between the copper acetylide **32** (ref. 113) and the aryl bromide **33**,[114] generating as anticipated the benzofuran **34** with the desired skeleton. Finally, after several steps, hydrolysis of **35** provided the target molecule **6**, which was identical in all aspects to the natural XH-14 **6** (Scheme 7).[115]

A brief, high yielding practical and highly efficient total synthesis of natural product XH-14 containing benzofuran moiety is achieved in nine steps by Jun and co-workers. In this approach, the key features are Sonogashira coupling, iodine-promoted cyclization, Wittig reaction, and formylation. The total synthesis started from another natural product vanillin **19**, which was transformed into diarylyne **36** in three steps. Then, it was subjected into iodine-induced cyclization to afford 3-iodo-benzofuranaldehyde **37** containing the benzofuran core. The latter in turn is converted into 2-(4-benzyloxy-3-methoxyphenyl)-3-iodo-5-(3-benzyloxypropyl)-7-methoxybenzofuran **38** in several steps. Upon formylation using *n*-BuLi/*N*-formylpiperidine the latter is transformed into 2-(4-benzyloxy-3-methoxyphenyl)-5-(3-benzyloxypropyl)-7-methoxybenzofuran-3-carbaldehyde **39** in 70% yield. Nevertheless, when BCl_3 is used for debenzylation of **39** the desired natural product XH-14 **6** is obtained in very high yield (90%) (Scheme 8).[116]

Vibsanol **42**, a benzofuran-type lignan isolated from the wood of *Viburnum awabuki* (*Caprifoliaceae*), was synthesized by the tandem cyclization of *o*-*tert*-butyldimethylsiloxy diaryl alkyne with tetrabutylammonium fluoride and excess para-formaldehyde as the key step. The leaves of *Viburnum awabuki* (*Caprifoliaceae*) are known to have been used as a fish poison for the purpose of catching fish around the Okinawa Islands. Vibsanine A, an unprecedented humulene-type diterpene, was isolated from these leaves as a piscicidal compound.[117] Recently, vibsanol **42**, a natural occurring benzofuran-type lignan showed moderate inhibitory activity toward lipid peroxidation in rat brain homogenates.[118] The structure of vibsanol **42** was mainly established on the basis of spectroscopic methods and composed of 2-aryl and 3-hydroxymethyl substituents. It is well known that 2-substituted benzofurans are readily prepared from the *o*-hydroxyarylalkynes under basic conditions.[119] Total synthesis of vibsanol **42** was started from vanillin that after several steps provided the benzofuran

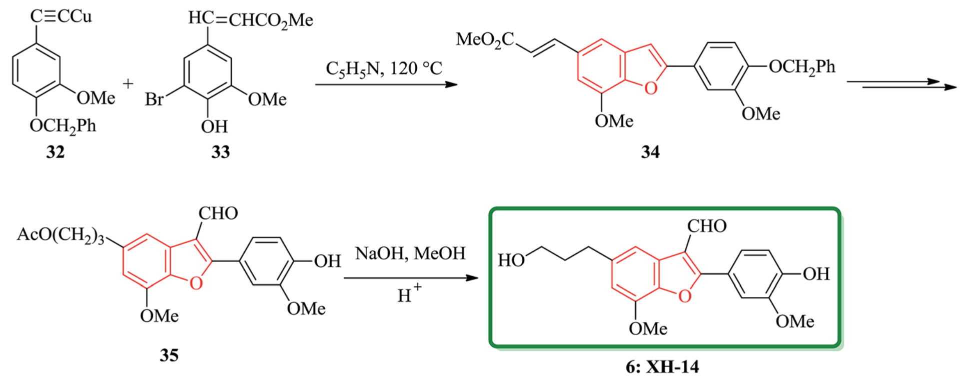


Scheme 6 Total synthesis of ailanthoidol **5**, XH-14 **6** egonol **31a**, homoegonol **31b**, and demethoxyegonol **31c**.

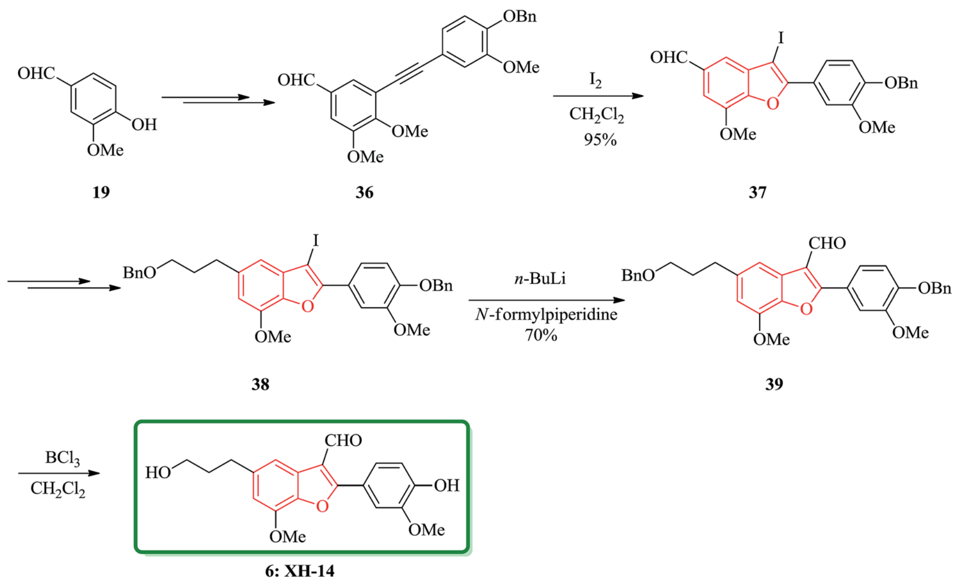
precursor **40.** The tandem cyclization of **40** gave the desired benzofuran **41** in 67% yields. Finally, the deprotection of **41** smoothly occurred using a catalytic amount of PPTS in MeOH to give vibsanol **42** in 99% yield (Scheme 9).[120]

The first total synthesis of a norneolignan isolated from Ratanhia, 5-(3-hydroxypropyl)-2-(2′-methoxy-4′-hydroxyphenyl) benzofuran **46,** is described in 2002. The key steps contain the one-pot reaction for a 2-arylbenzofuran from methyl 3-(4-hydroxyphenyl)propionate **43** with 2-chloro-2-methylthio-(2′-methoxy-4′-acetoxy)acetophenone **44** in the presence of $ZnCl_2$, and reductive desulfurization of the resulting product **45.** Significantly, the total synthesis of a norneolignan **46** was accomplished by a one-pot reaction of methyl 3-(4-hydroxyphenyl)propionate and chloride **44** under Friedel–Crafts reaction conditions and reductive desulfurization of the resultant benzofuran **45,** as the key steps (Scheme 10).[121]

Among the natural products bearing benzofuran as scaffold, the eupomatenoids form an expanded class of neolignans,[122] are worthy being considered. These compounds initially were isolated from two plant species, which were placed in the archaic angiosperm family eupomatiaceae. Structurally, the eupomatenoids **50** are identified by a 2,3,5-substitution pattern. In this pattern an aryl group is placed as a substituent at the 2-position, a methyl group positioned at 3 and a C3-substituent R stands at position 5. Different eupomatenoids **50a–c, 50f–h** were synthesized starting from 2,3,5-tribromobenzofuran **48** *via*

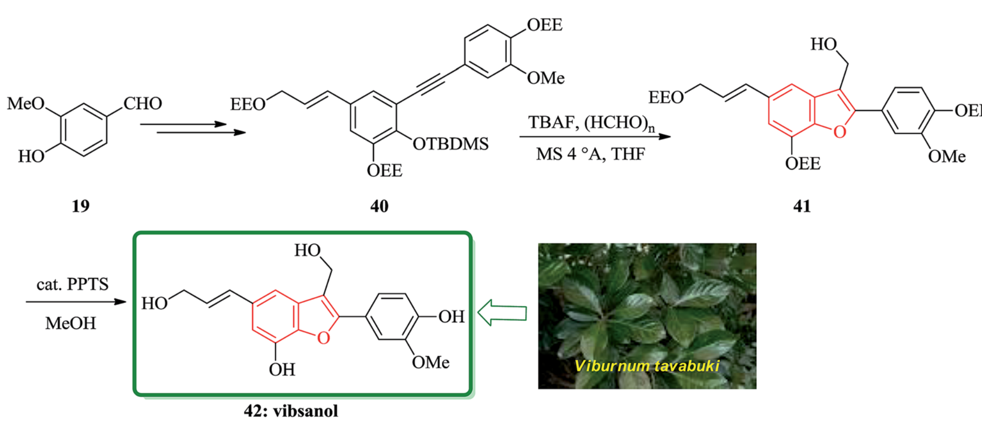


Scheme 7 Total synthesis of XH-14 **6**.

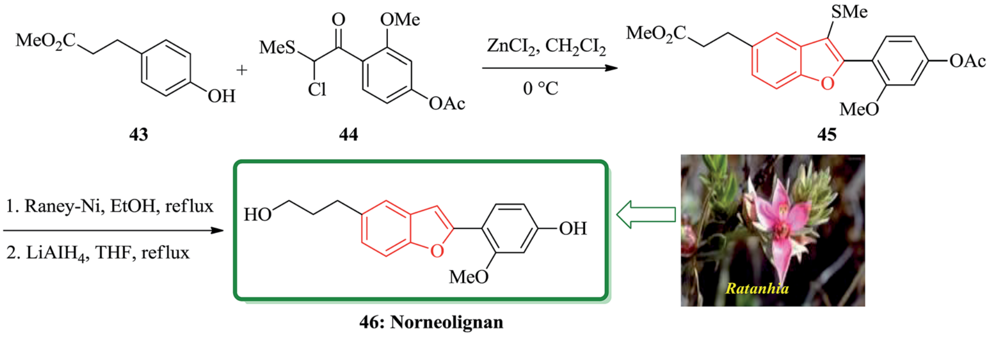


Scheme 8 Total synthesis of XH-14 **6**.

a short and high-yielding synthetic strategy. The total synthesis commenced from tribromobenzofuran **48** and commercially purchasable bromide **47a**. The overall yields diverge between 29 and 60% over four to six steps. Remarkably the important and key step of this strategy is to achieve the high regioselectivity from three Pd(0)- and Ni(0)-catalyzed cross-coupling reactions which are performed, sequentially. The order of substitution at the benzofuran nucleus is C-2, C-5 and C-3. In this way, the



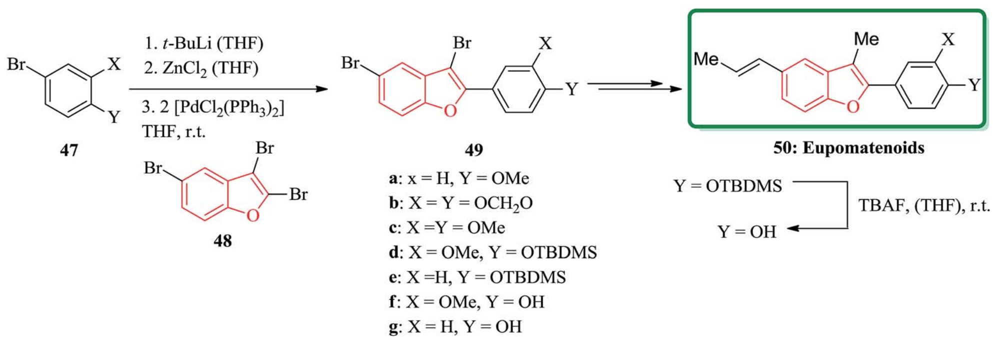
Scheme 9 Total synthesis of vibsanol **42**.



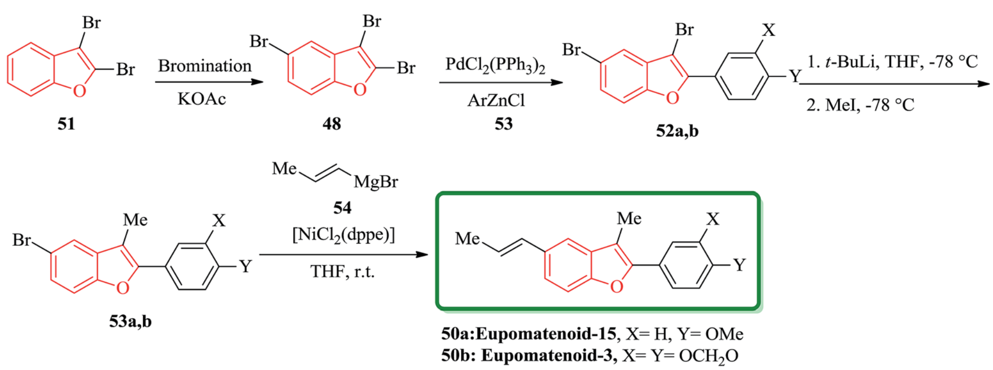
Scheme 10 Total synthesis of a norneolignan **46**.

introduction of the third substituent onto the benzofuran nucleus was possible. Upon double bond equilibration *via* treatment with iodine,[123] (*E*)-configured eupomatenoid-15 was obtained **50a** in 46% overall yield. In a similar manner, eupomatenoids-3 **50b** and -4 **50c** were synthesized from the respective aryl bromides **47b**[124] and **47c.** In this way a concise and effective synthesis of 2,3,5-trisubstituted benzofurans *via* three successive cross-coupling reactions were accomplished. The applicability of this strategy was successfully attempted for the synthesis of a variety of naturally occurring compounds continuing benzofuran moiety such as eupomatenoids but it is also anticipated to be also functional for the synthesis of some other benzofurans (Scheme 11).[125]

Eupomatenoids, neolignans isolated from *Eupomatia laurina* and *Eupomatia bennettii*[126] represent naturally occurring 2,3,5-trisubstituted benzofurans **50a** and **50b** which are interesting targets for total synthesis. Initially, the required precursor **51** was synthesized by a direct bromination of benzofuran in the presence of a base (*e.g.* KOAc).[127] Compound **52** is the product of regioselective cross-coupling reaction between 2,3,5-tribromobenzofuran **48** and the corresponding arylzinc, under optimized conditions. Compound **52** was converted *via* selective bromine–lithium exchange/methylation to the 2,3-disubstituted 5-bromobenzofurans **53.** Ni-catalyzed reaction of compound **53** with alyl magnesium bromide **54** led to the synthesis of desired natural product, eupomatenoids **50** in overall yields of up to 60% (Scheme 12).[128]



Scheme 11 Total synthesis of eupomatenoids **50**.



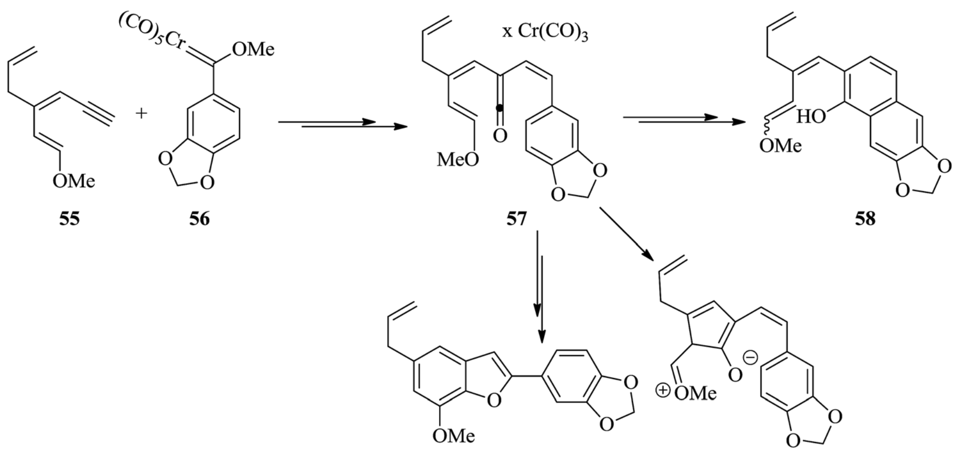
Scheme 12 Total synthesis of eupomatenoids **50**.

Egonol **31a** is a natural benzofuran glycoside occurring widely in *Styrax officinalis*.[129] Primarily, nor-neolignan egonol was isolated by Okada from the seed-oil of *Styrax japonicum*.[130] It has attracted enormous attention due to its versatile biological activities.[131] The synthesis of nor-neolignan egonol **59** has been achieved in five steps starting from easily accessible staring materials.[132] The total synthesis of nor-neolignan natural product egonol has been anticipated. The benzofuran derivative **59** is actually a known egonol precursor,[132] that is itself a natural product. Noticeably, compound **59** was initially isolated from the wood of *Anaxagorea clavata*.[133]

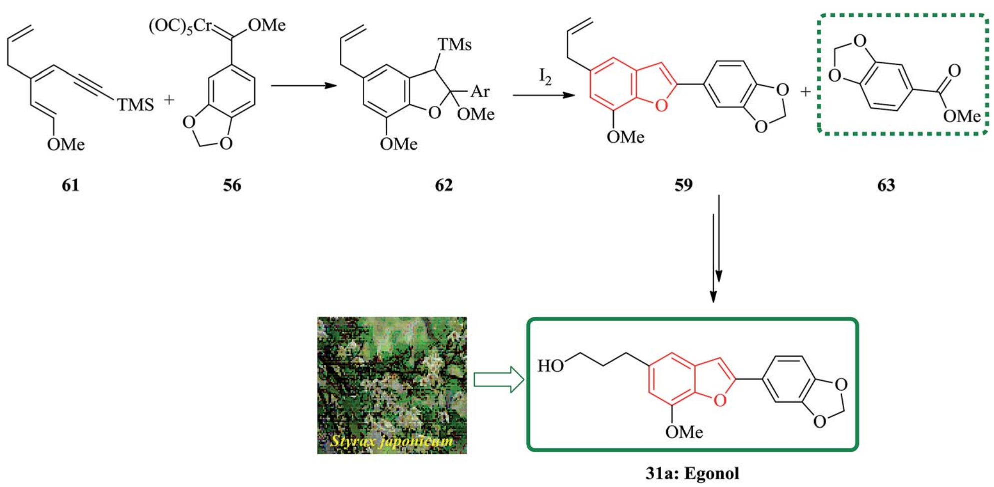
The suggested synthetic pathway has three main problems: (a) highly conjugated enol ether derivative **55** is not stable, (b) the Dötz reaction[134,135] is competitive due to the formation of naphthol **58** (Scheme 13) with the desired benzofuran-formation[135] and finally (c) the enol ether can be subjected to cyclization at the ketene carbon present in intermediate **57** leading to the formation of compound **60**. This phenomenon has previously been observed in related enamine intermediates.[136] Nevertheless, in some related systems the completion of Dötz reaction has not been reported. Thus, the selective cyclization is considered being done due to the strong complexation followed by annulation at the non-oxygenated vinylketene ligand. For the total synthesis of **59**, both dienyne **55** and an enediyne **56** can be used as starting materials.[137,138]

The use of silylated methoxydienyne **61** produces egonol precursor **59** in 47% yields along with compound **63** in 15% yields, which is considered as the result of carbene oxidation. After several steps, intermediate **59** is converted into the desired natural product egonol **31a**. Noticeably, higher temperatures or/and longer reaction times resulted in the formation of the conjugated alkene moiety. Worthy to mention that the hydroboration of **63** has been reported to give egonol **31a** (Scheme 14).[132,138]

Salvia miltiorrhiza bunge (dan-shen) was extensively utilized as a Chinese customary medicine for the cure of atherosclerosis.[139] Hydrosoluble salvianolic acids, which have initially been isolated from water-soluble part of dan-shen are found being the showed several biological activities. They showed antitumor, antithrombotic, anti-oxidative, anticoagulant and anti-



Scheme 13 Proposed pathway for the synthesis of compound **59**.

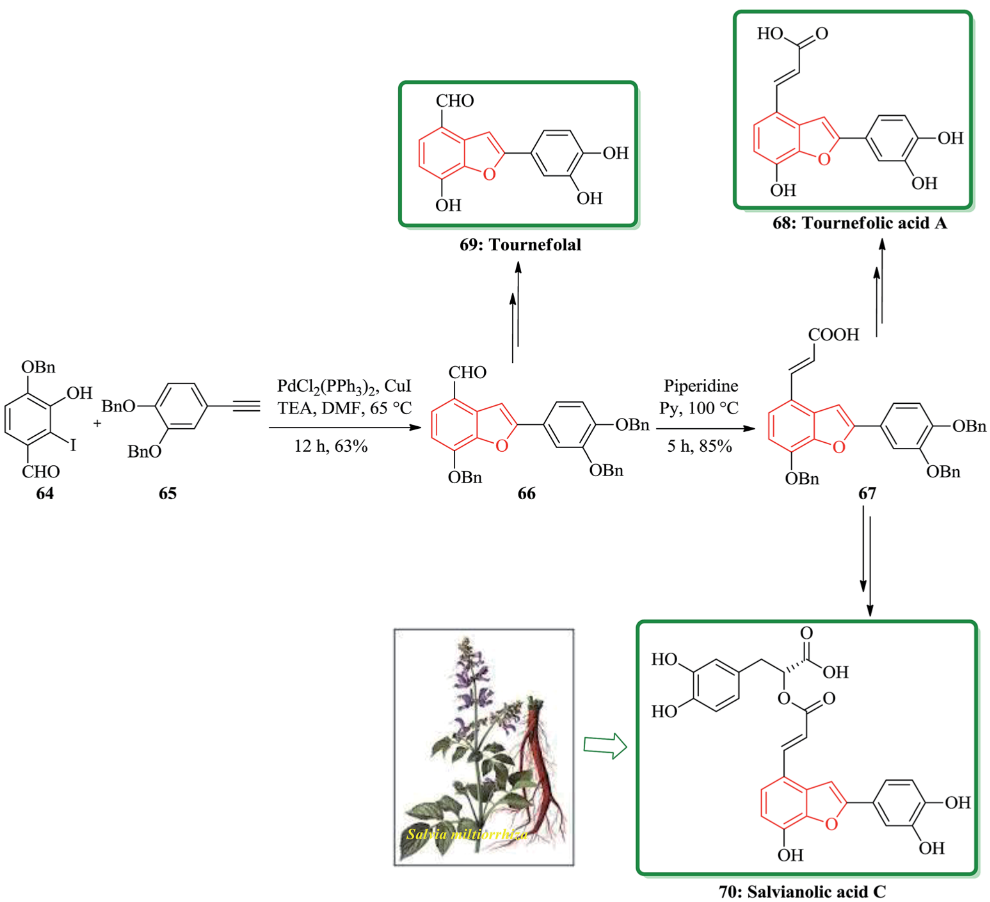


Scheme 14 Total synthesis of egonol **31a**.

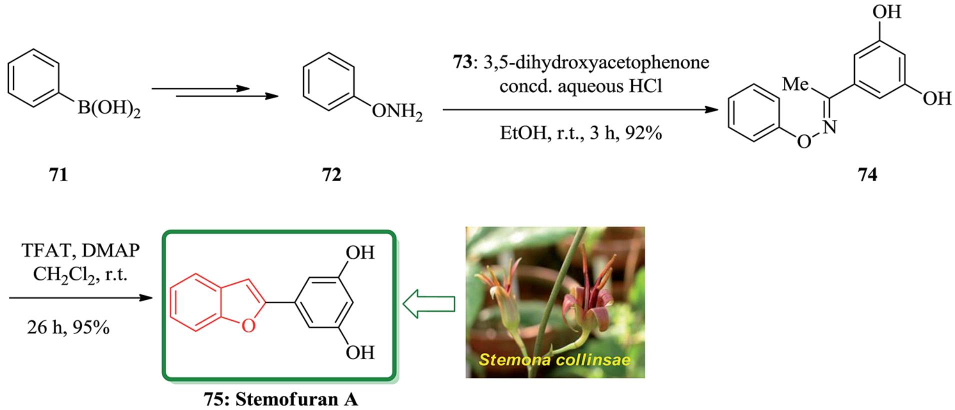
HIV activities.[140] Salvianolic acid C **70**, is actually one of the salvianolic acids, which are present in the structure of 2-phenylbenzofuran neolignan tournefolic acid A **68**.[141] The total synthesis of the naturally occurring compounds salvianolic acid C **70**, tournefolal **69** and tournefolic acid A **68** have been achieved and reported in 2012. Noticeably, the key benzofuran framework were synthesized *via* selective iodination to obtain **64** followed by Sonogashira coupling[142] in which 3-hydroxy-2-iodobenzaldehyde **64** was coupled to the ethynylbenzene analogues **65** in a catalyzed-Pd$(Ph_3P)_2Cl_2$ and co-catalyzed-CuI reaction to give benzofuran aldehyde **66** in satisfactory yield. The latter can be converted to (*E*)-3-(7-(benzyloxy)-2-(3,4-bis(benzyloxy)phenyl)benzo[*b*]furan-4-yl) acrylic acid **67** by Knoevenagel condensation, and then the benzofuran aldehyde **66**, which can be transformed into the desired natural product **70** in several steps in overall yields of 40%. On the other hand, upon the debenzylation of **67** and **66**, are converted into tournefolic acid A **68** and tournefolal **69** respectively (Scheme 15).[143]

A novel and efficient synthetic approach for the synthesis of biologically potent natural benzofurans is reported in 2007 by Naito and co-workers.[144] The important step of this protocol is the well-known [3,3]-sigmatropic rearrangement. TFAA has been established as the best reagent to promote [3,3]-sigmatropic rearrangement for the preparation of cyclic or acyclic dihydrobenzofurans. Alternatively, the TFAT-DMAP system was proved as the most efficient system for the synthesis of different benzofurans. This method is particularly practical since the protection of the phenolic hydroxy groups in the synthesis of hydroxylated 2-arylbenzofurans is non-required.

In accordance with Naito and co-workers protocol[144] the synthesis of naturally occurring compounds containing benzofuran moiety such as stemofuran A **75** (ref. 145) eupomatenoid 6 **50g**,[146] and coumestan **83** were achieved.[147] These compounds showed various biological activities. For the synthesis of compounds **75**, **50g** and **83** with no hydroxy group, this synthetic approach was especially remarkable since they can be accomplished without any protection of the phenolic hydroxy groups (Scheme 16). Initially, the synthesis of stemofuran A **75**, which had been isolated from *Stemona collinsae*,[145] was attempted. The synthesis of stemofuran A was achieved through condensation of ketones with aryloxyamine followed by reaction with TFAT-DMAP in sequential reactions involving four steps giving the desired products in 72% yield. This reported synthesis of stemofuran A by Pasturel and co-workers[148] involved several steps including the required protection/deprotection of the hydroxy group. In the new synthetic route, *O*-phenylhydroxylamine **72**, easily synthesized from phenylboronic acid **71**, which was subsequently condensed with dihydroxyacetophenone to furnish the oxime ether **74** in good



Scheme 15 Total synthesis of tournefolic acid A **68**, tournefolal **69** and salvianolic acid C **70**.



Scheme 16 Total synthesis of stemofuran A **75**.

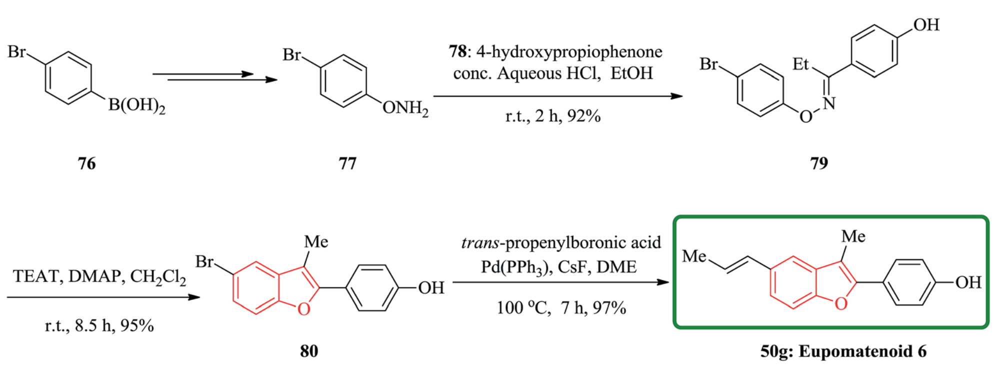
yield. The oxime ether **74** upon treatment with TFAT mediated by DMAP at ambient temperature gave the desired benzofuran **75** in excellent yield. It was found being identical with stemofuran A **75** by comparison of their spectroscopic and physical data with those of the natural product reported in the literature, previously.[145]

In a similar way, eupomatenoid 6 **50g** were also synthesized *via* the treatment of oxime ether with TFAT-DMAP. Condensation of *O*-phenylhydroxylamine **77** bearing the *p*-bromo group with *p*-hydroxypropiophenone afforded the oxime ether **79**, which upon reaction with TFAT-DMAP in dicloromethane at room temperature gave the 5-bromobenzofuran **80** in 95% yields. Finally, the latter underwent Suzuki coupling reaction with (*E*)-propenyl boronic acid to furnish eupomatenoid 6 **50g** in excellent yield. Thus, the total synthesis of eupomatenoid 6 **50g** in 52% overall yield from (4-bromophenyl)boronic acid **76** in five steps was accomplished and found to be identical with natural eupomatenoid 6 by comparison of its spectroscopic data reported in the literature for the naturally occurring compound (Scheme 17).[146]

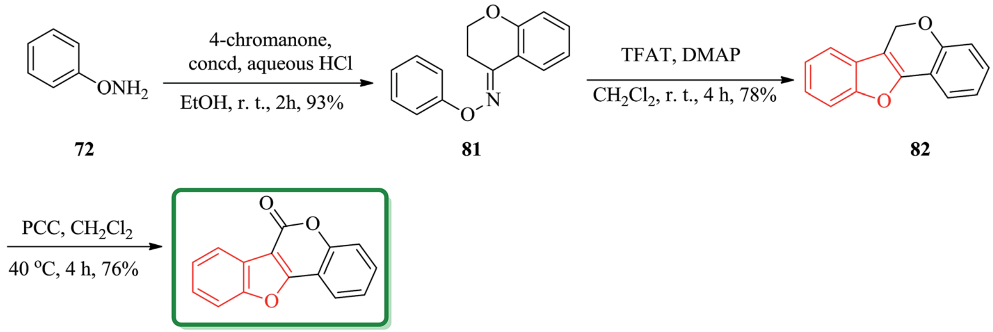
The third desired target was coumestan **83**.[147] That is a basic pharmacophore having coumestanes such as coumestrol,[149] which exhibits estrogenic potency. Due to its unique and remarkable structure, coumestan **83** has attracted the attention of several organic chemists who were attempting independently different approaches.[150,151] One of successful reported synthetic strategies involved the synthesis of the benzofuran moiety in the second step. Initial condensation of readily available *O*-phenylhydroxylamine **72** with 4-chromanone *via* sequential acylation/rearrangement of the resulting oxime ether **81** gave the desired tricyclic benzofuran **82** in 73% yield in only two steps. Finally, the carbonyl group was introduced upon the treatment of tricyclic benzofuran **82** with PCC to furnish coumestan **83** in good yield (Scheme 18).[143]

(−)-Machaeriols A, B, C, and D bearing the cannabinoid structure were recently isolated from the bark of the *Machaerium multiflorum* spruce located in Loreto and Peru.[152] They have been reported to have potential *in vitro* antimicrobial activity against *Staphylococcus aureus* and methicillin-resistant *S. aureus*.[152] They showed potent *in vitro* antimalarial activity against *Plasmodium falciparum* D6 and W2 clones.[152] These important biological activities have led to the development of a variety of synthetic approaches to these natural products. An efficient and concise synthesis of the biologically interesting (+)-machaeriol B **89** and its enantiomer **90** was accomplished from *O*-phenylhydroxylamine **72** in four steps. The key strategies in the synthesis of **89** and **90** involved benzofuran formation through a [3,3]-sigmatropic rearrangement and *trans*-hexahydrodibenzopyran formation by a domino aldol-type/hetero-Diels–Alder reaction.

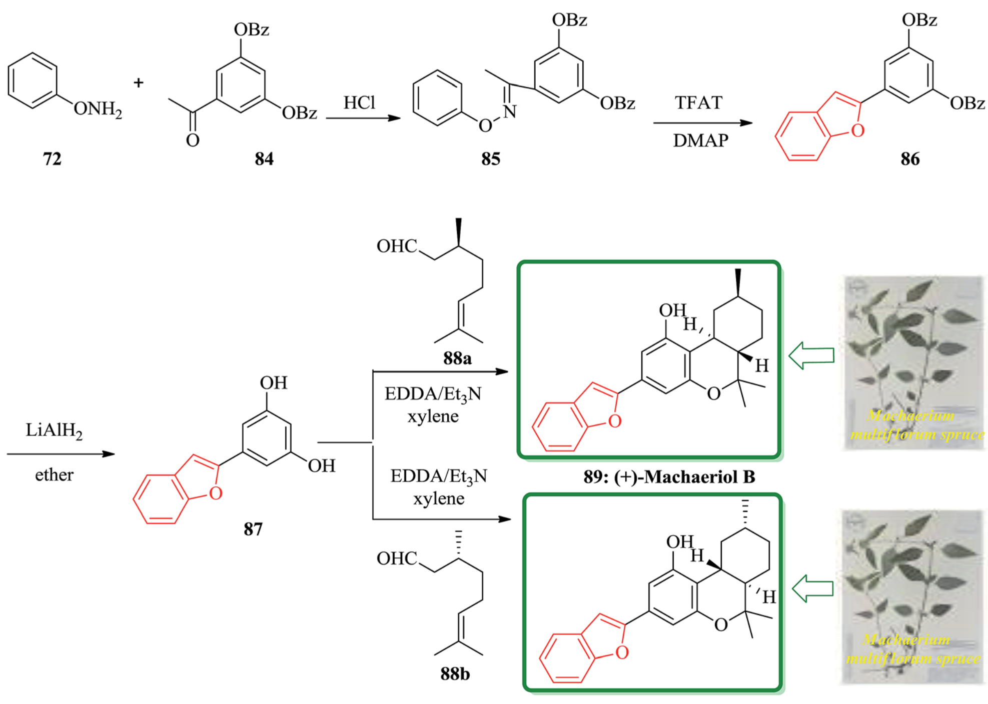
Scheme 19 shows a concise synthetic approach to natural (−)-machaeriol B **89** and its unnatural enantiomer **90**. The



Scheme 17 Total synthesis of eupomatenoid 6 **50g**.



Scheme 18 Total synthesis of coumestan **83**.

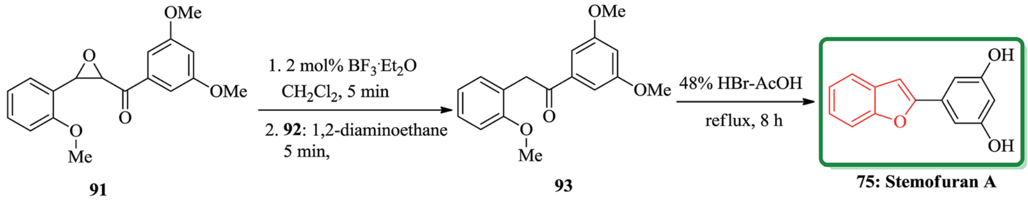


Scheme 19 Total synthesis of (+)-machaeriol B **89** and its enantiomer **90**.

precursor **87** for the total synthesis of **89** and **90** was obtained by a known method.[153] Thus, the condensation of *O*-phenylhydroxylamine **73** with 3,5-bis(dibenzoyloxy)acetophenone **84** in the presence of conc. HCl in EtOH gave the oxime ether **85** in 93% yield. The latter was treated with trifluoroacetyl triflate and *N*,*N*-dimethylpyridin-4-amine (DMAP) in CH_2Cl_2 at room temperature to afford the desired cycloadduct **86** in 95% yield as the sole product *via* a [3,3]-sigmatropic rearrangement which is the well-known oxa-variant of Fischer's indole synthesis. Removal of the two benzoyl groups from 5-(benzofuran-2-yl)benzene-1,3-diol 1,3-dibenzoate **86** with $LiAlH_4$ in ether at room temperature afforded stemofuran **87** in 90% yield.[145] Treatment of benzofuranylbenzenediol **87** with (−)-(*S*)-citronellal **88a** in the presence of EDDA/Et_3N in refluxing xylene gave (−)-machaeriol B **89** in 65% yield. The spectroscopic data of the synthetic **89** are in good agreement with the reported data. Conversely, the corresponding treatment of **87** with (−)-(*R*)-citronellal **88b** gave (−)-machaeriol B **90** in 63% yield.[154]

Also, stemofuran A **75** exhibited a wide range of biological potencies.[155,156] A highly effective and facile strategy for the construction of 2-arylbenzo[*b*]furans has been reported by Ruan and co-workers in 2014.[157] As depicted in Scheme 20, stemofuran A **75** was synthesized by a method starting from 2-methoxychalcone epoxide **91** which upon treatment with $BF_3\cdot Et_2O$ (2 mol%) with subsequent deformylation gave the intermediate **93** in 76% overall yield. Compound **93** underwent demethylation and cyclodehydration reactions in the presence of 48% HBr in acetic acid to give stemofuran A **75** in excellent yield (94%).[157]

The total synthesis of the naturally occurring demethoxyegonol **31c** [5-(3-hydroxypropyl)-2-(3′,4′-methylenedioxyphenyl)benzofuran], a congener of which is used in the treatment of

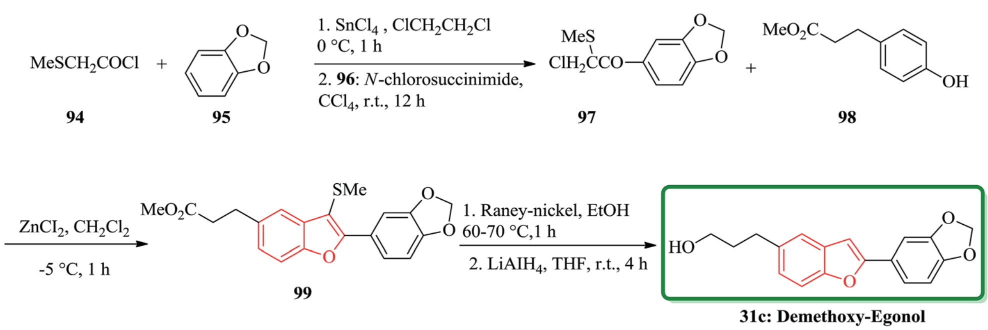


Scheme 20 Total synthesis of stemofuran A **75**.

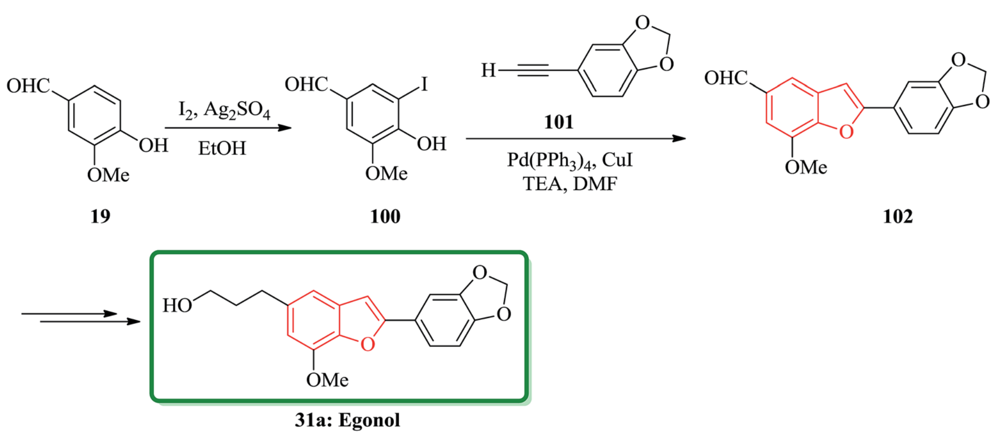
asthma and rheumatism. The key steps involve the construction of a 2-arylbenzofuran skeleton **99** from methyl 3-(4-hydroxyphenyl)propionate with 2-chloro-2-methylthio-(3′,4′-methylenedioxy)acetophenone **97** in the presence of $ZnCl_2$ and successive desulfurization of the resulting product **99** (Scheme 21).[158]

Benzo[*b*]furan natural product **31a** was initially isolated from the Styracaceae family such as *Styrax japonicum*,[159] *S. formosanus*,[160] *S. obassia*,[108] *S. macranthus*[161] and *S. officinalis*,[107] which showed a variety of biological activities including insecticidal, fungicidal, antimicrobial, antiproliferative, cytotoxic and antioxidant properties.[131] Egonol, 5-(3-hydroxypropyl)-7-methoxy-2-(3,4-methylenedioxyphenyl) benzofuran was first isolated in 1915 from the seed oil of *Styrax japonicum*[159] and first total synthesized by Kawai[162] condensing an *o*-hydroxybenzaldehyde with an α-chlorophenylacetic acid, which known to be an effective pyrethrum synergist.[163] It was reported the most effective total synthesis of egonol **31a** in 5 steps with 74% overall yield from vanillin by using Sonogashira coupling reaction. Vanillin **19** reacted with I_2/Ag_2SO_4 in EtOH at room temperature to give iodovanillin **100** in 80% yields. Sonogashira coupling of **100** with 3,4-methylenedioxyphenylacetylene **101** which was easily prepared from piperonal *via* Colvin rearrangement,[164] by using $Pd(PPh_3)_4/CuI/Et_3N$ in DMF yielded benzofuran **102** in 95% yield through successive coupling and cyclization in one-step. Noticeably the latter was very sensitive to the haloaryl substituents as shown in Scheme 22.

The highly efficient total synthesis of homoegonol **31b** was achieved and reported in 2005.[165] For the construction of benzofuran moiety present in **31b** a facile two-step synthesis of 2-arylbenzofurans was implemented, proceeding *via* a selective cross-pinacol sort coupling between a salicylaldehyde and an



Scheme 21 Total synthesis of demethoxy-egonol **31c**.



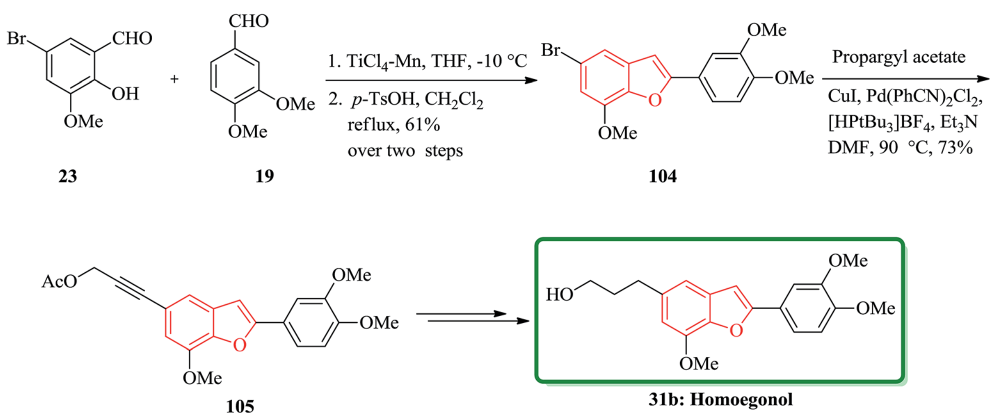
Scheme 22 Total synthesis of egonol **31a**.

aromatic aldehyde, with subsequent acid-induced cyclization. Therefore, bromobenzofuran **104** was synthesized from salicylaldehyde **23** and aromatic aldehyde **19** in two steps overall yield 61%. Subsequently, bromobenzofuran **104** was subjected into Sonogashira coupling with propargyl acetate to yield alkyne **105**, which was subsequently hydrogenated and hydrolyzed to generate homoegonol **31b** in satisfactory overall yield (38%) (Scheme 23).[166]

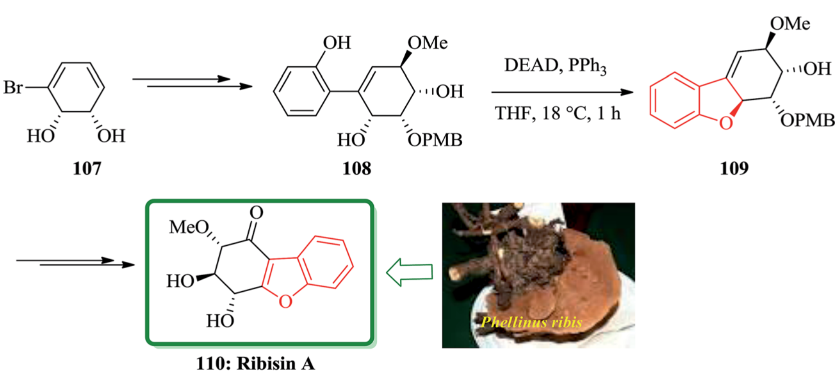
Recently, Fukuyama and co-workers disclosed[167] the results of their study on biological activity related to *Phellinus ribis* (Schmach) a fungus grown in East Asia which has been used as folk medicines for keeping immunity and for the treatment of gastrointestinal cancer.[168] Ribisins A–D were recognized to increase neurite outgrowth in nerve growth factor (NGF). Total synthesis of the desired products **110**, **113** and **118**, which were found being the biologically potent part of naturally occurring compounds, ribisins A, B and D, have been accomplished. The total synthesis started from optically active pure *cis*-1,2-dihydrocatechol **107**. The key features involve Suzuki–Miyaura cross-coupling reaction, intramolecular Mitsunobu and tandem epoxidation/rearrangement reactions. For the synthesis of ribisins A **110**, initially, *cis*-1,2-dihydrocatechol **107** is transformed into the expected product **108** in several steps. Upon treatment of the latter with diethyl azodicarboxylate (DEAD) mediated by triphenylphosphine, an intramolecular Mitsunobu reaction occurs with the phenolic OH group acting as the internal nucleophile. In this way, the corresponding benzofuran **109** is obtained in high yield, resulted in construction of the tricyclic scaffold of the natural product **110** (Scheme 24).[169]

For the synthesis of ribisins B **113**, diol **107** can also be transformed into the expected product **111** in several steps. The latter then can be subjected into a sequential reaction involving an intramolecular Mitsunobu reaction, which resulted in the formation of tricycle **112** in 89% yields. The latter has benzofuran moiety in its structure. Finally, compound **112** can be converted in several steps to the desired ribisins **113** in high yield (Scheme 25).[169]

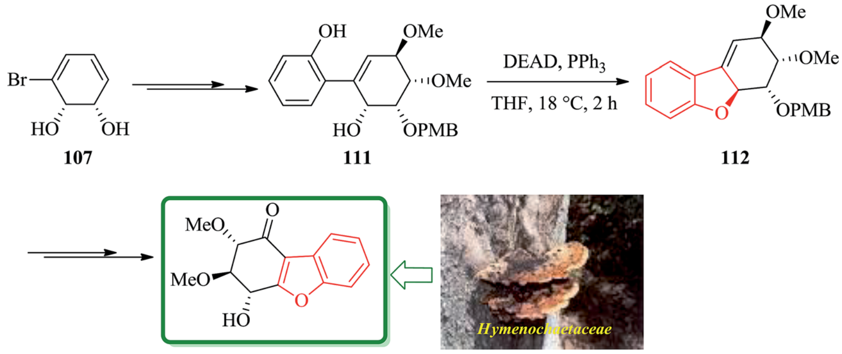
In continuation of developing a synthetic strategy to obtain **118**, Fukuyama and co-workers designed a convenient strategy for the total synthesis of natural product ribisin D. For the purpose, the boronate ester **114** was recognized being capable to cleave aryl isopropyl ethers under mild reaction conditions.[170] It was also found that a phenolic hydroxyl group is also needed being present at C6 in the target **118**. The reaction of compounds **114** and **115** gave the arylated cyclohexene **116**, which was easily subjected into an intramolecular Mitsunobu reaction to afford the cyclodehydration product **117** in excellent yield (94%). The latter that bears the benzofuran moiety was converted into the desired natural product ribisin D **118** in several steps (Scheme 26).[169]



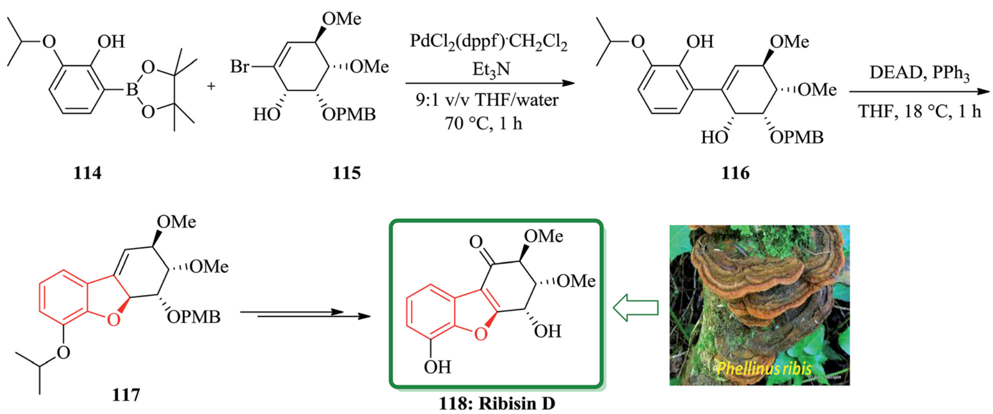
Scheme 23 Total synthesis of homoegonol **31b**.



Scheme 24 Total synthesis of ribisin A **110**.



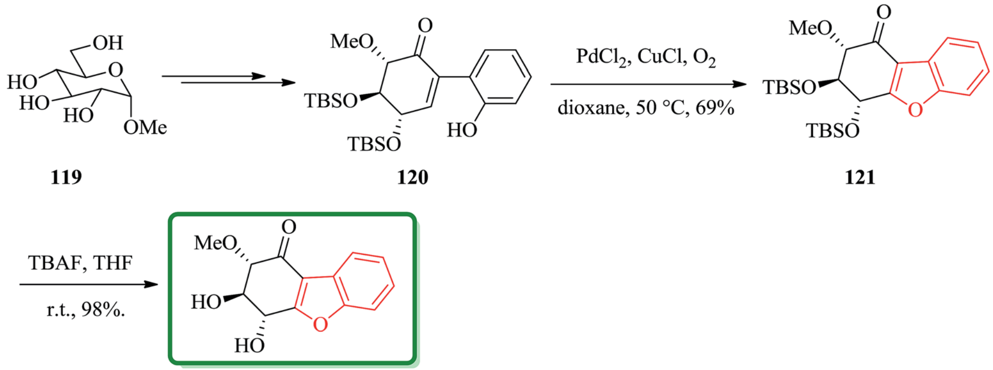
Scheme 25 Total synthesis of ribisin B **113**.



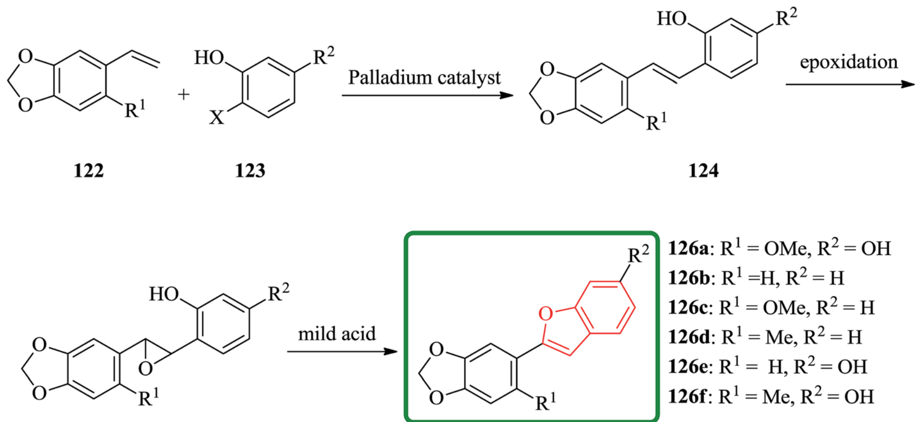
Scheme 26 Total synthesis of ribisin D **118**.

In 2014, the isolation of four novel naturally occurring compounds as ribisin A–D was achieved and reported. They were isolated from the methanol extraction of the fruiting bodies of *P. ribis*.[167] A concise total synthesis of natural product ribisin A has been accomplished in 11 steps.[171] This approach started from market purchasable methyl α-D-glucopyranoside. Ribisin A has a highly oxygenated benzofuran scaffold, thus for its total synthesis, it was taken advantages of the intrinsic chirality of D-glucose. The important features of this total synthesis are applying some name reactions. It involved the Ferrier carbocyclization, Johnson iodination, Suzuki cross-coupling reaction, and Wacker oxidative cyclization. In this total synthesis, initially the commercially available methyl α-D-glucopyranoside **119** was converted to benzofuran precursor **120** in several steps. For the synthesis of the core benzofuran structure, the authors designed a route involving conversion of benzofuran precursor **120** to **121**. To oxidize **120**, *m*-CPBA and H_2O_2 were used which resulted in generation of a complex mixture containing, some unidentified products. Pd(II)-catalyzed Wacker reaction is an efficient protocol for olefin conversation and heterocyclic synthesis *via* anti-oxypalladation.[172] It was successfully applied to oxidative cyclization of **120** by using $PdCl_2/CuCl/O_2$. This oxidation proceeds smoothly at 50 °C in dioxane to give the expected product **121** in satisfactory yield. Upon conventional deprotection of **121** by using TBAF in THF gave the desired compound ribisin A **110**. The spectroscopic data for this synthetic product was found being identical to those obtained from the product isolated from natural source (Scheme 27).[171]

Cicerfuran **126a**, with antifungal potency was isolated from roots of wild chickpea.[173] It has been synthesized from sesamol (3,4-methylenedioxyphenol) **122** in seven steps and 37% overall yield. Benzofurans **126a–f** and the respective stilbene intermediates were synthesized. They exhibited antifungal and antibacterial potencies. Novak and co-workers accomplished and reported the synthesis of cicerfuran **126a**.[174] It involves palladium-catalyzed coupling of a styrene and 2-hydroxyaryl halide to form a stilbene, followed by epoxidation, subsequent cyclization and dehydration. Two analogues **126c**, **126d** of cicerfuran **126a** were also synthesized effectively *via* this method, however the palladium coupling step did not occur with the dioxygenated aryl halides which are required for preparation of cicerfuran itself (Scheme 28, R_2 = OH). Palladium-catalyzed coupling of the more reactive aryl acetylenes[175–177] with 2-iodophenol afforded two analogues **126b** and **126c** of cicerfuran, albeit in low yields. In the original synthetic plan, the required stilbene was synthesized by using a Wittig reaction between 2-methoxy-4,5-methylenedioxybenzyltriphenylphosphonium bromide and 2,4-di-*tert*-butyldimethylsiloxy-benzaldehyde. An alternative pathway to cicerfuran **126a** involves epoxidation and



Scheme 27 Total synthesis of ribisin A **110**.



Scheme 28 Total synthesis of cicerfuran **126**.

cyclization, which affords quantities sufficient for further biological studies. Two other analogues **126e**, **126f** of cicerfuran were synthesized by this route but were only characterized partially due to decomposition during their purification (Scheme 28).[178]

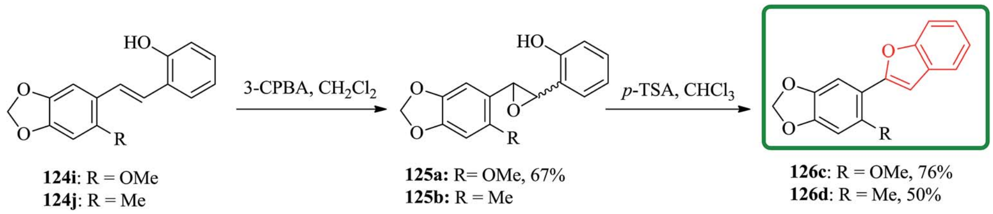
Stilbenes **124i** and **124j** were epoxidized with MCPBA. Stilbene **124j** were subjected to sequential epoxidation and cyclization under these conditions to yield 2-(2-methyl-4,5-methylenedioxyphenyl)benzofuran **126d** in moderate yield and relatively long reaction time. Notably, when the same process applied to **124i** complete decomposition occurred thus, the isolated epoxide **125a** underwent acid-catalyzed ring-opening, cyclization and dehydration in the presence of *p*-toluenesulphonic acid in chloroform to provide 2-(2-methoxy-4,5-methylenedioxyphenyl) benzofuran **126c**. The 2-methoxy group in **126c** makes the benzofuran moiety much less stable in the presence of acid than that of in **126d**, which bears methyl group (Scheme 29).[178]

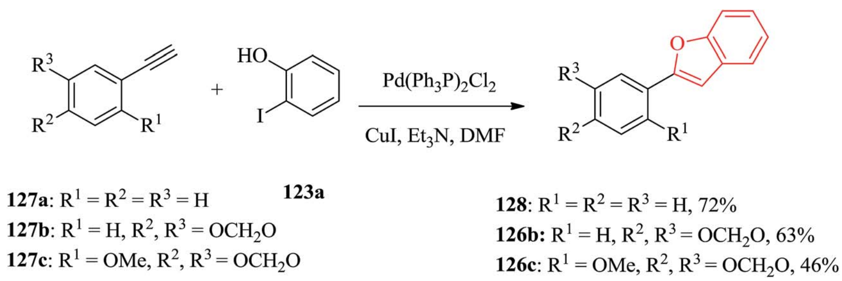
Palladium catalyzed coupling of terminal acetylenes with *o*-hydroxy aryl halides gave corresponding benzofurans in a single step reaction. Aryl acetylenes, which are usually more reactive in palladium-catalyzed coupling reaction were reacted with multioxygenated aryl halides for the synthesis of cicerfuran and its analogues. Three arylbenzofurans, **128**, **126b** and **126c** were prepared *via* palladium-catalyzed coupling of acetylenes **127a–c** with 2-iodophenol **123a** as illustrated in Scheme 30.[178]

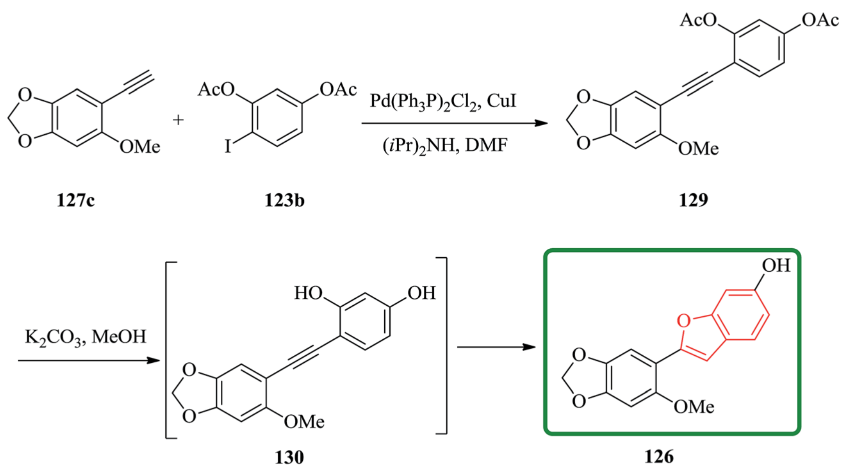
Remarkably, acetylation of the hydroxyl groups usually makes the aryl halide more reactive to nucleophilic attack. Therefore, the synthesis of cicerfuran was studied *via* palladium-catalyzed coupling[179] of acetylene **127c** with the diacetate of iodoresorcinol **123b**, as depicted in Scheme 31.[178]

In another route, the desired stilbenes **131a–c** (prepared *via* Wittig reactions of phosphonium bromides and benzaldehyde) which obtained approximately as 1 : 1 mixtures of the *E* and *Z* isomers were epoxidized by using MCPBA. Yields were relatively low apparently because the instability of the OTBDMS protected epoxides **132a–c**. These epoxides can be easily converted to the desired compound by using a few crystals of *p*-toluenesulphonic acid in chloroform (Scheme 32).[178]

Sonogashira coupling/cyclization reaction of aryl iodide **134** with 2-methyl-3-butyn-2-ol **135** was achieved in the presence of $Pd(PPh_3)_2Cl_2$ and CuI. Deprotection of the acetylene moiety in the same pot using a strong base and the second Sonogashira coupling/cyclization of substituted *o*-iodophenols led to the formation of the appropriate benzo[*b*]furans. This protocol was


Scheme 29 Total synthesis of cicerfuran **126c**, **d**.

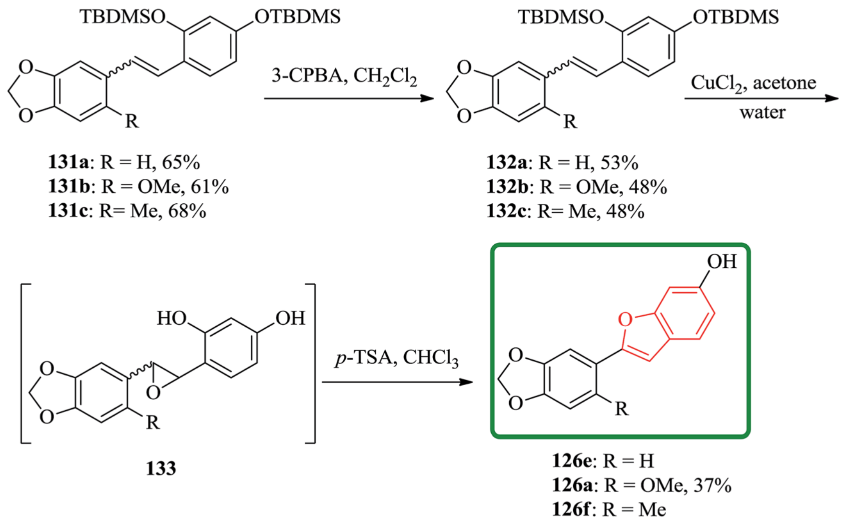

Scheme 30 Synthesis of arylbenzofurans **128**, **126b** and **126c**.


Scheme 31 Synthesis of the natural product **126**.

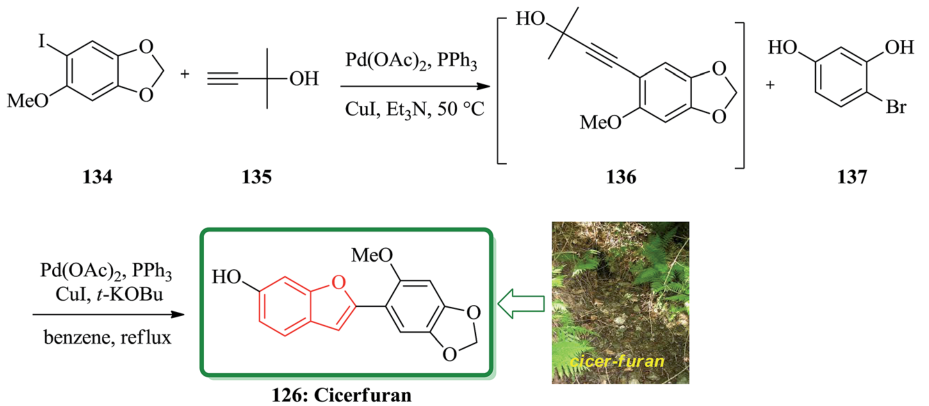
used in the synthesis of natural product cicerfuran **126** (Scheme 33).[180]

A concise total synthesis of eupomatenoid 6 **50g** was reported by Stevenson research group in seven steps.[181] After that, two other five-step synthesis were reported by Bach and co-workers (25% overall yield).[182] Eidamshaus and Burch in 2008 accomplished a four-step total synthesis of **50g**, in a three-pot approach. Initially, 2-bromo-4-chlorophenol **138** was coupled with 4′-methoxypropiophenone **139**, which was followed by concurrent cyclization under optimized reaction conditions to afford compound **140** containing a benzofuran moiety in 45% yield. The latter was then transformed to the desired natural product **50g** *via* a cascade reaction involving Stille reaction and demethylation with ethanethiolate in one-pot fashion (Scheme 34).[183]

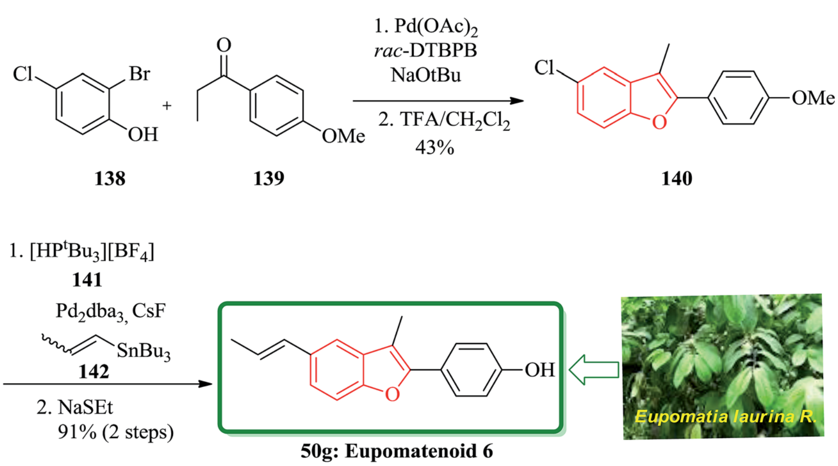
The aglyconic part, which is also called eupomatenoid-6 **50g**, is a naturally occurring compound. It was initially isolated from extract of the leaves of *Piper fulvescens*. Compound **146** can be subjected into glycodiversification,[184–186] thus can create a set of diverse modulators of Hsp90 activity.[187–189] For glycol diversification, eupomatenoid-2 of the 2-(4′-hydroxyphenyl)benzofuran aglycon (a.k.a. eupomatenoid-6) was subjected into glycosylation. Glycosylation of the phenol by glycosylbromides under basic conditions afforded the desired products in the gluco-, galacto- and fuco- series. This procedure failed in the manno- and rhamno-series. However, mannosylation and rhamnosylation of eupomatenoid-6 could be obtained under carefully controlled acidic conditions using *O*-benzoxazolyl imidate (OBox) donors. Eupomatenoid-6 **50g** was provided following the previously reported procedure, which is depicted in Scheme 35. This protocol began from 2-bromo-4-chlorophenol **144**, which reacted with 1-(4-methoxyphenyl)propan-1-one **143** to afford the intermediate 5-chlorobenzofuran **145**. Finally, the latter was transformed to the desired natural product **146** in several steps.[190]



Scheme 32 Synthesis of the natural products **126**.

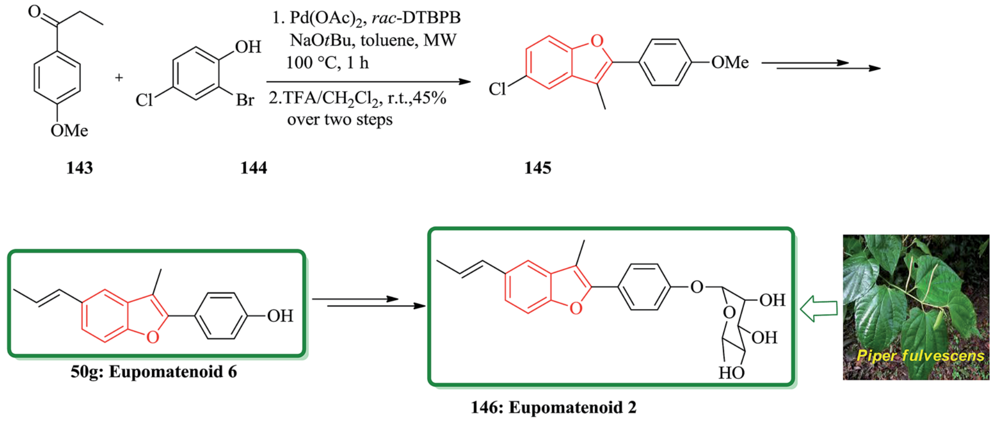


Scheme 33 Total synthesis of cicerfuran **126**.



Scheme 34 Total synthesis of eupomatenoid 6 **50g**.

Kendomycin [**151**, (−)-TAN2162], an ansamycin isolated from different *Streptomyces* species has been frequently studied over the last decade. It was found being a potent endothel in receptor antagonist and antiosteoperotic with remarkable antibacterial and cytostatic activity.[191] The synthesis of the benzofuran fragment **150** started from the known aldehyde

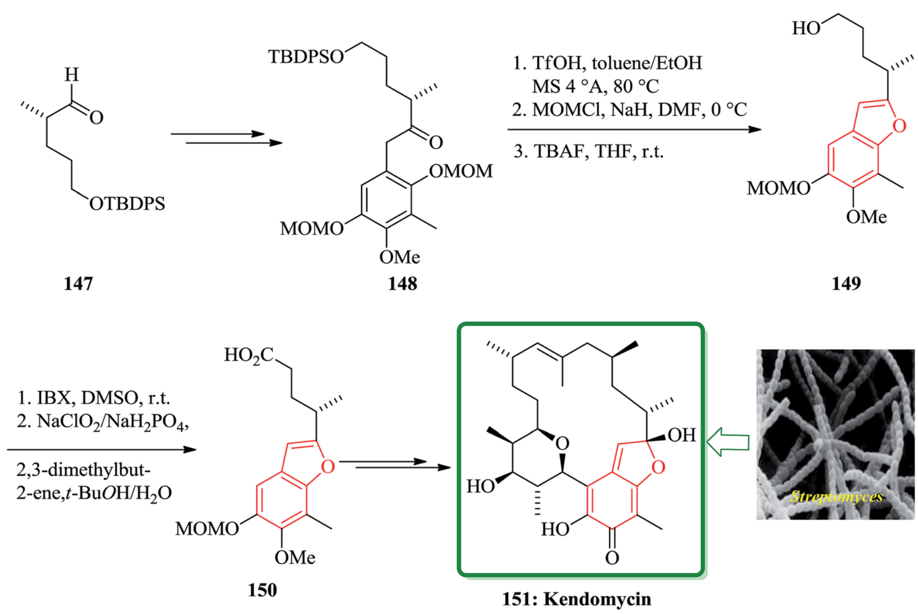


Scheme 35 Total synthesis of eupomatenoid 6 **50g** and eupomatenoid 2 **146**.

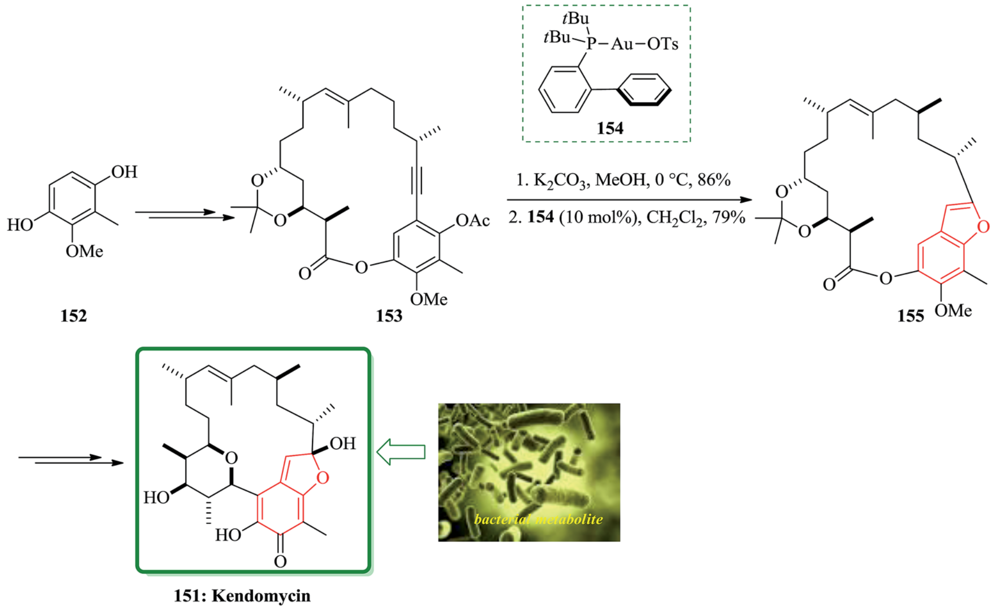
147,[192] which is easily available from citronellene. Compound **147** is transformed into ketone **148** in several steps including palladium(0)-mediated rearrangement. The latter was then subjected to acid-catalyzed formation of the furan ring which concomitantly removes the 3-OMOM group to give **149** which was oxidized to carboxylic acid **150** (Scheme 36). After several steps, involving functional groups transformations compound **50g** was converted into the desired natural product **151**.[193]

A pathway for the total synthesis of the bacterial metabolite kendomycin **151** was reported in 2014. Furthermore, an efficient strategy for the total synthesis of **151** was achieved starting from readily available 2-methoxy-3-methylbenzene-1,4-diol **152**, which was initially transformed into cycloalkyne **153**. The latter was then underwent to a gold-catalyzed hydroalkoxylation resulting in benzofuran **155**, which contains benzofuran moiety in its structure. Worthy to mention that benzofuran **155** had been utilized as an intermediate en route to **151**. In this strategy, cycloalkyne **153** was submitted to saponification of the remaining acetate. Noticeably, upon treatment of cycloalkyne **153** with $PtCl_2$ the cyclization was not achieved. However, in the presence of electrophilic cationic gold complexes **154**, the cyclization of **153** was smoothly proceeded to give the benzofuran derivative **155**. The latter was then transformed in several steps to the desired natural product kendomycin **151**. The total synthesis was interrupted through the route reported by Mulzer and co-workers.[194] However, the subsequent ring contraction reported by these authors *via* a photo-Fries rearrangement[195] could be also occurred (Scheme 37).[196]

Liphagal **160** was isolated from the sponge *Aka coralliphaga*, collected from reefs in Prince Rupert Bay, Portsmouth, Dominica.[197] Liphagal **160** showed significant biological activity involving inhibitory activity against PI3K α (phosphoinositide-3-kinase α).[197] Due to its importance, three approaches have been reported for its total synthesis including (A) a relatively short synthesis (nine linear steps) that follows a biomimetic route to the bioactive marine natural product liphagal, from



Scheme 36 Total synthesis of kendomycin **151**.

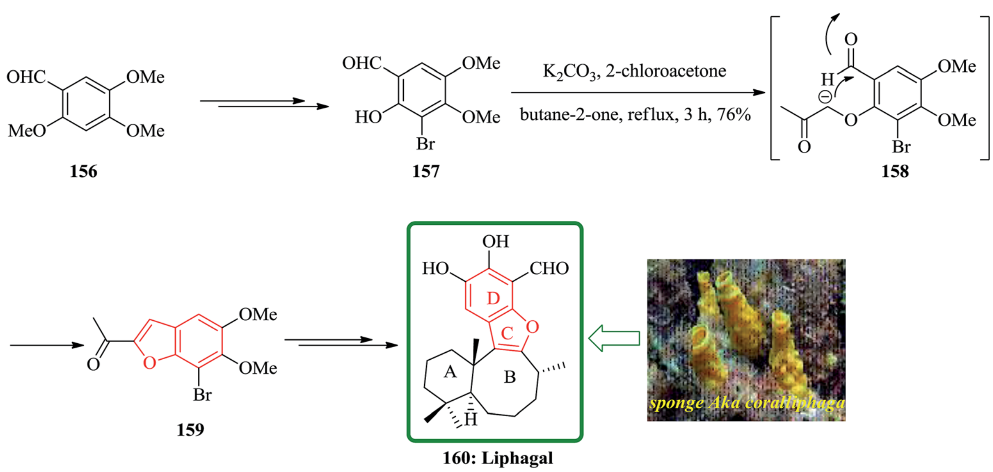


Scheme 37 Total synthesis of kendomycin **151**.

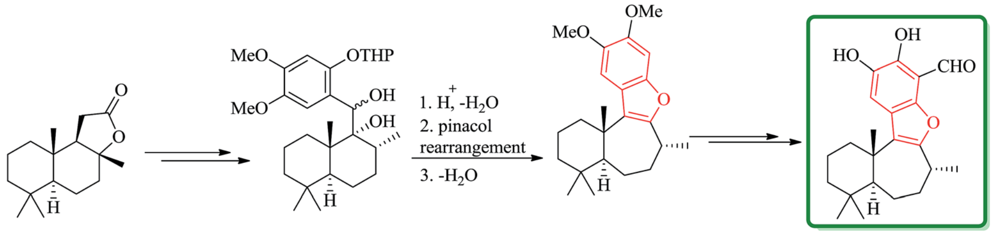
a commercially available starting materials, was described by Mehta and co-workers. Liphagal **160** is the first member of a new 'liphagane' type of meroterpenoid carbon skeleton. A mixed biogenetic route for liphagal **160** was suggested[197] in which forms the AB rings of this natural product showing a typical sesquiterpene-like structure. For the synthesis of liphagal **160**, the key furan precursor was synthesized from an easily available aromatic starting materials. Regioselective mono demethylation of commercially accessible aldehyde **156** after several steps provided **157**. One-pot furan annulation[198] of **157** went smoothly and furnished the required bromobenzofuran **159** in moderate yield. At the end bromobenzofuran **159** was converted into liphagal **160** after several steps (Scheme 38).[199]

(B) The total synthesis of (+)-liphagal[200] has also been accomplished in 13 steps with 9% overall yield and reported. The total synthesis was started from a natural product (+)-sclareolide **161**. In this approach, the key step is a ring expansion involving the generation of a highly stabilized benzylic carbocation, which is converted into the seven-membered ring and the benzofuran moiety of the natural product in a single cascade reaction. Compound **161** was converted into **162** in several steps. Having **162** available, the biomimetic step involving ring-expansion reaction was examined. Upon treatment of compound **162** with TFA/CH_2Cl_2 at −78 °C and then gradual warming to ambient temperature the ring-expanded product **163** was obtained in two steps *via* pinacol rearmament in 74% overall yield. Then, the synthesis of (+)-liphagal, the desired natural product **160** was accomplished after two steps (Scheme 39).[201]

(C) The total synthesis of liphagal[202] was started from market purchasable (+)-sclareolide **161**. Compound **160** as a structurally



Scheme 38 Total synthesis of liphagal **160**.



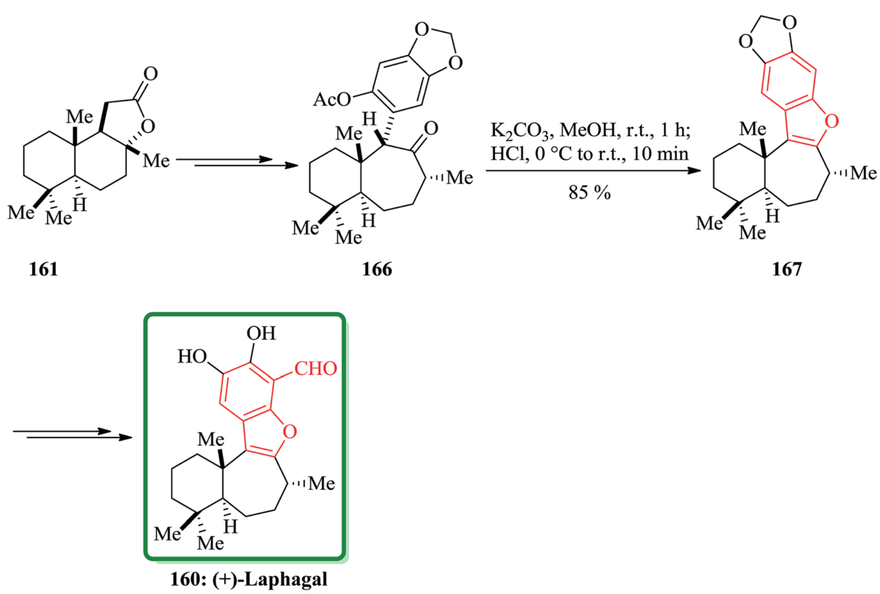
Scheme 39 Total synthesis of liphagal **160**.

outstanding marine natural product, with characteristic tetracyclic core structure was prepared in 29% overall yield in 13 steps modeled biosynthesis. In this total synthesis, starting from **161** and after several steps, the intermediate **166** was provided and transformed into the intermediate **167**, which bears the benzofuran moiety, *via* conventional conditions. Then the latter was converted into the desired natural product (+)-liphagal **160** in several steps (Scheme 40).[203]

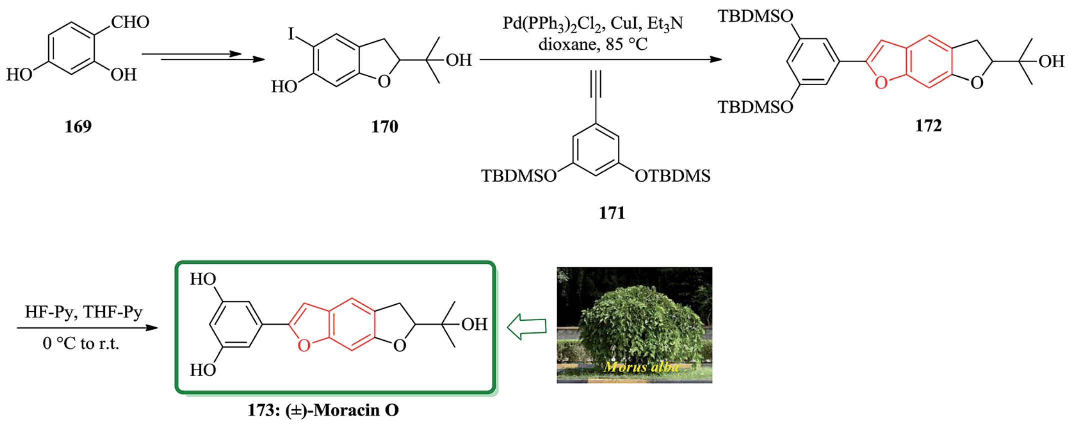
Moracins O and P were first isolated in 1998 from an acetone extract of cortex and phloem tissues of *Morus alba* shoots infected with *Fusarium solani* f. sp. Mori. Their structures were determined by their IR, ^{1}H-NMR and ^{13}C-NMR spectral data.[204] The first total synthesis of the naturally occurring benzofurans, moracins O and P was achieved using a Sonogashira cross coupling reaction followed by *in situ* cyclization. In this route, the total synthesis of **173** was started from 2,4-dihydroxybenzaldehyde **169**. The reaction of benzohydrofuran nucleus **170** with the substituted acetylene, 1,3-bis-(*tert*-butyldimethylsilanyloxy)-5-ethynylbenzene **171** employing Sonogashira cross coupling under basic conditions and *in situ* cyclization afforded **172** which upon final deprotection with HF-pyridine provided (−)-moracin O **173** in a 75% yield. The NMR spectra of synthetic (−)-**173** were identical to the spectra of the corresponding natural products (Scheme 41).[204]

Then, the synthesis of (−)-**176** was started from 2,4-dihydroxybenzaldehyde **169** is converted into dihydrochomarine. **174** The latter was reacted with alkyne **171** under Sonogashira cross coupling conditions followed by *in situ* cyclization in dioxane to afford benzo[*b*]furan intermediate **175** in a 36% yield. Early attempts to remove the TBDMS groups from benzofuran derivative **175** using TBAF yielded a mixture of products, possibly due to the strong basic conditions and/or the long reaction time which either permitted group migration[205] or opening of the pyran ring. The same deprotection reaction with HF–pyridine complex afforded clean removal of the TBDMS protective groups and provided the desired racemic moracin P **176** in a 75% yield (Scheme 42).[206]

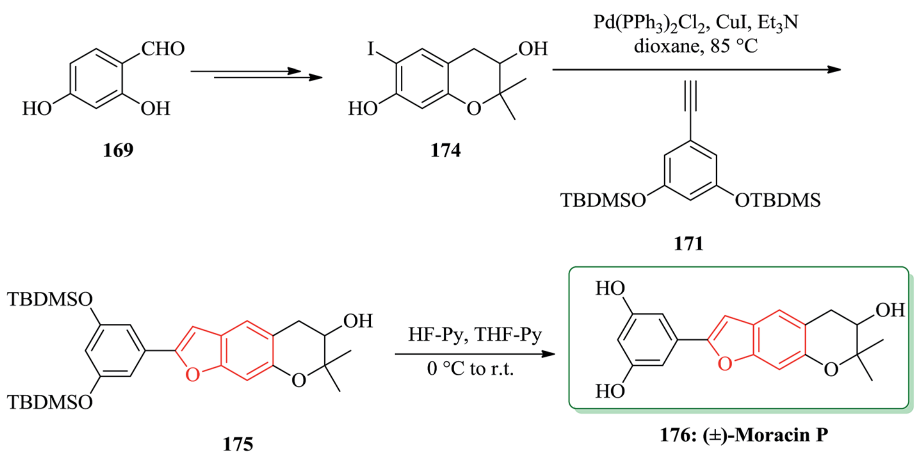
The natural products moracins O and P showed being active *in vitro* inhibitory against hypoxiainducible factor (HIF-1), a mediator, which is a key important during adaptation of cancer cells to tumor hypoxia. Systematic studies revealed the significance of presence of the 2-arylbenzofuran ring and particularly the core framework should have (*R*)-configuration. The 2-arylbenzofuran is a common unit, consisting of B, C, and D rings. All the benzofuran derivatives **179–191** were



Scheme 40 Total synthesis of liphagal **160**.



Scheme 41 Total synthesis of (−)-moracin O **173**.

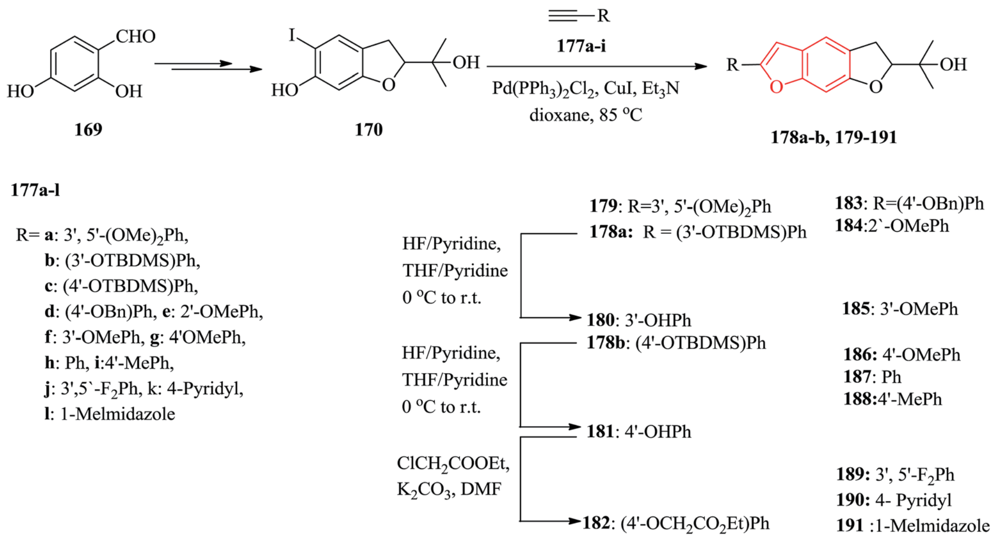


Scheme 42 Total synthesis of (−)-moracin P **176**.

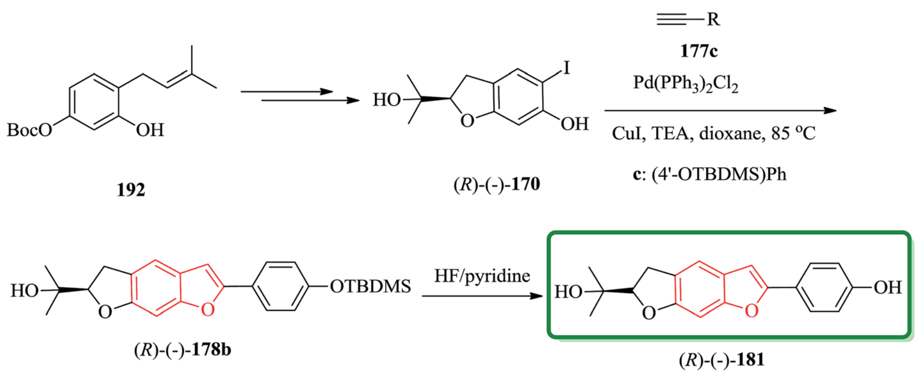
synthesized as outlined in Scheme 43. The key and important intermediates for the synthesis of moracin O or P derivatives as shown in Scheme 43 is dihydrobenzofuran **170** which can be synthesized from 2,4-dihydroxybenzaldehyde in several steps. The terminal acetynyl derivatives either were purchased from commercial sources **177e–l** or synthesized **177a–d**. The acetynyl compounds can be provided *via* a procedure developed by Ramirez–Corey–Fuchs, in which compounds **177a–d** were synthesize in three steps.[207] The Sonogashira catalyzed coupling of terminal acetylenes **177a–l** with substituted *o*-iodophenol **170** afforded the moracin O analogues **178a, b** and **179–191**. Compounds **178a, b** were deprotected using HF/pyridine to yield the corresponding phenol analogues **180** and **181** in satisfactory yields. Treatment of compound **181** with ethyl chloroacetate gave the alkylated product **182**.[208]

It has been reported that the (*R*)-isomer of moracin O was more active than its (*S*)-isomer. Unpleasantly, the stereogenic center of the synthesized analogues was generated in a non-stereospecific fashion. Thus, it was desirable to synthesize the corresponding (*R*)-stereoisomer of the analogues **181** asymmetrically in optically pure form for further biological screening. The asymmetric synthetic approach was outlined in Scheme 44. In this pathway, the key intermediate is an optically pure iodobenzofuran derivative (*R*)-(−)-**170** which can be obtained from the prenylated derivative **192** in five steps including a stereoselective synthesis. (*R*)-(−)-**170** reacted with the protected ethynyl benzene compound **177c** *via* Sonogashira reaction to provide (*R*)-(−)-**178** with subsequent deprotection with HF/pyridine, which gave the desired target (*R*)-(−)-**181**.[208]

Furoventalene **200** is an irregular isoprenoid benzofuran, which has initially been isolated from the sea fan *Gorgonia ventalina*.[209] Natural product **200** was first synthesized by Weinheimer and Washecheck in a non-regioselective fashion.[209] The scaffold of furoventalene **200** was regioselectively build up from methyl 2-fomy1-6-methyl-heptenoate **194** and 2,5-dihydro-3-methyl-4-vinyl-2-furanone **195** *via* successive 1,6-conjugate addition/aldol-type cyclization to provide a diastereomeric mixture of bicyclic butenolide **196a** and **196b**. Both of the annulated species can be converted into **200** by a sequential reactions involving, reduction/hydrolysis/dehydrative decarboxylation and dehydrogenation through intermediates **197–199**.[209] In the total synthesis of **200** dicarbonyl compound **194** is a key compound, which was readily synthesized and provided as the enol form by formylation of the methyl ester of 6-methyl-5-



Scheme 43 Total synthesis of compounds **179–191**.

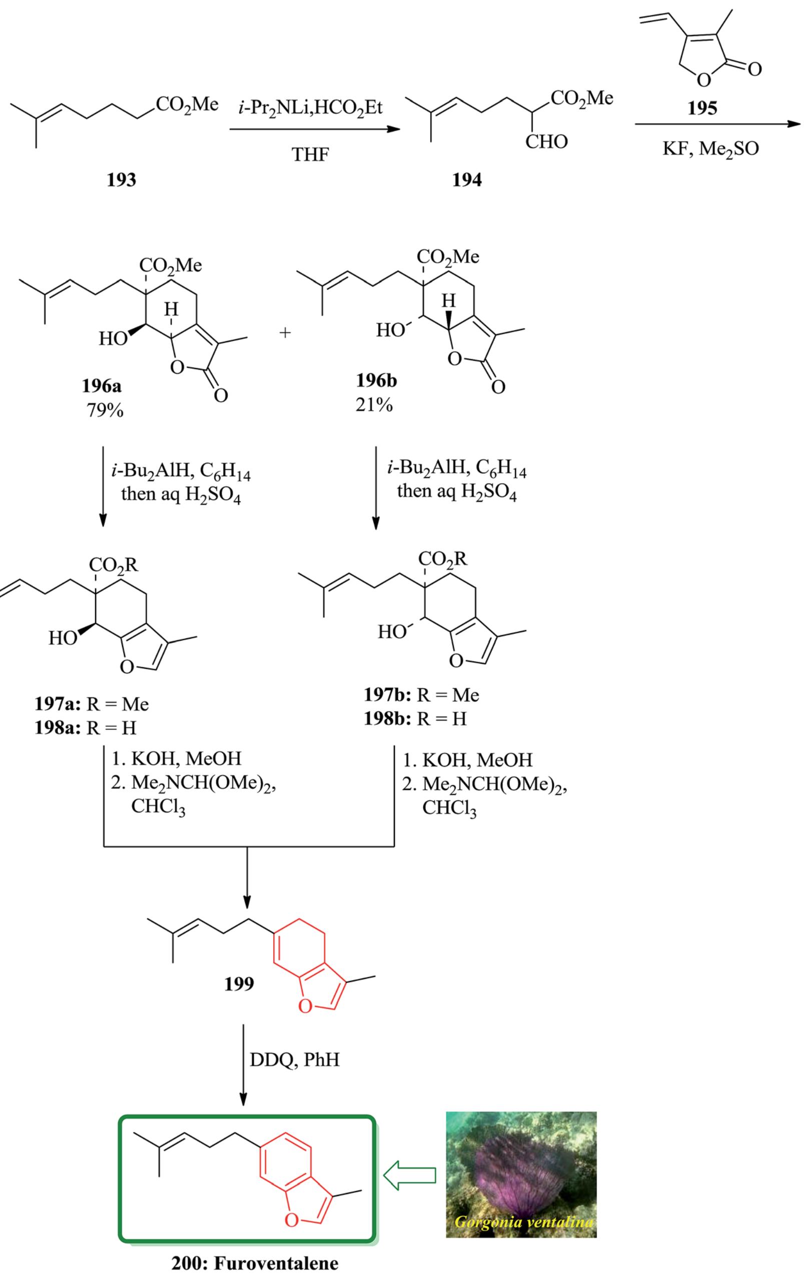


Scheme 44 Total synthesis of (*R*)-(−)-**181**.

heptenoic acid **193** with ethyl formate in the presence of LDA in THF. The formyl ester **194** upon treatment with the butenolide **195** in Me_2SO and KF at ambient temperature annulation product gives a mixture of diastereomer in excellent yield. This mixture can be cleanly separated by column chromatography to afford **196a** and **196b** (79 : 21) as crystalline products. Compound **199** was dehydrogenated at ambient temperature using DDQ. The latter was then transformed in several steps to compound, which was identified as furoventalene **200** by comparison of its spectroscopic data with those obtained from the original natural product (Scheme 45).[210]

Khellin **207** is one of several furochromones that was isolated from *Ammi visnaga* L., a perennial herbaceous plant that cultivates desolate in several Eastern Mediterranean countries.[211,212] The total synthesis of **207** was started from 3-furoic acid **201**. Regiospecific introduction of the (dimethylamino)-methylene unit adjacent to the ketone was achieved *via* reaction of a neat mixture of **202** and *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) (1 : 1.1) in the presence of TsOH at ambient temperature in couple of days. The desired acyclic precursor **203** (80%) as yellow oil was obtained after chromatography. The latter was subjected to Dieckmann cyclization (potassium *tert*-butoxide/THF/-78 °C) followed by acid treatment (HCl/THF/4 h) to give the fully substituted benzofuran **204** in 75% yield. Methylation (CH_3I/K_2CO_3/18-crown-6/PhH/A) of **204** yielded the highly versatile benzofuran intermediate **205** (90%). The latter was converted to compound **206** in two steps. Compound **206** is an intermediate which, is converted to the desired natural product khellin **207** (Scheme 46).[213]

Pongamol has been isolated from *Pongamia glabra*,[214] *Tephrosiapurpurea*.[215] *T. IanceolotaPongamia glabra*[216] and *T. hamiltonii*.[217] The structure of pongamol was established as the enol by X-ray crystallography.[218] Lanceolatin B was isolated from *P. pinnata*[219] and *T. purpurea*.[220] A new method for dipolar cycloaddition of diazocyclohexane-1,3-diones, leading to benzofuran derivatives has been applied to the tota1 synthesis of natural products from *Tephrosia* and *Pongamia*. Total synthesis of pongamol **211** and lanceolatin B **212** started from 6,7-dihydrobenzofuran-4(5*H*)-one **208**, which initially reacted with acetone, DME in the presence of NaH or KH to give compound **209** upon carboxylation and then subjected to dehydrogenation to be converted into methoxy derivative **210.** The latter was

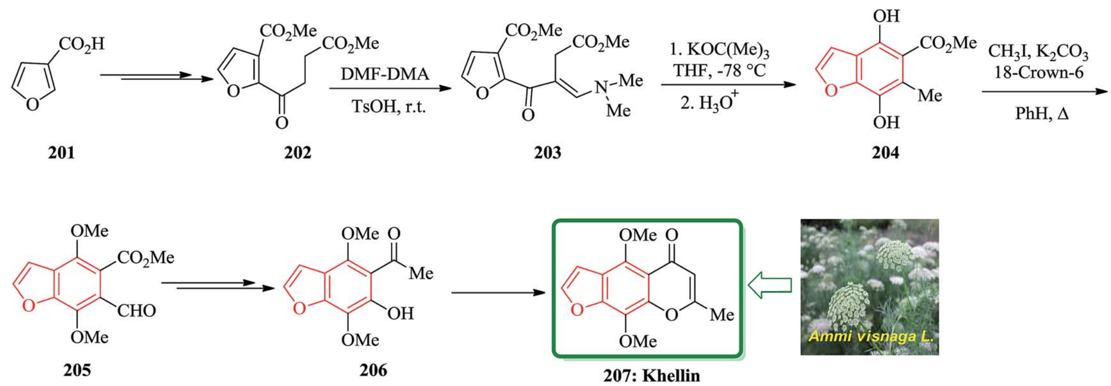


Scheme 45 Total synthesis of furoventalene **200**.

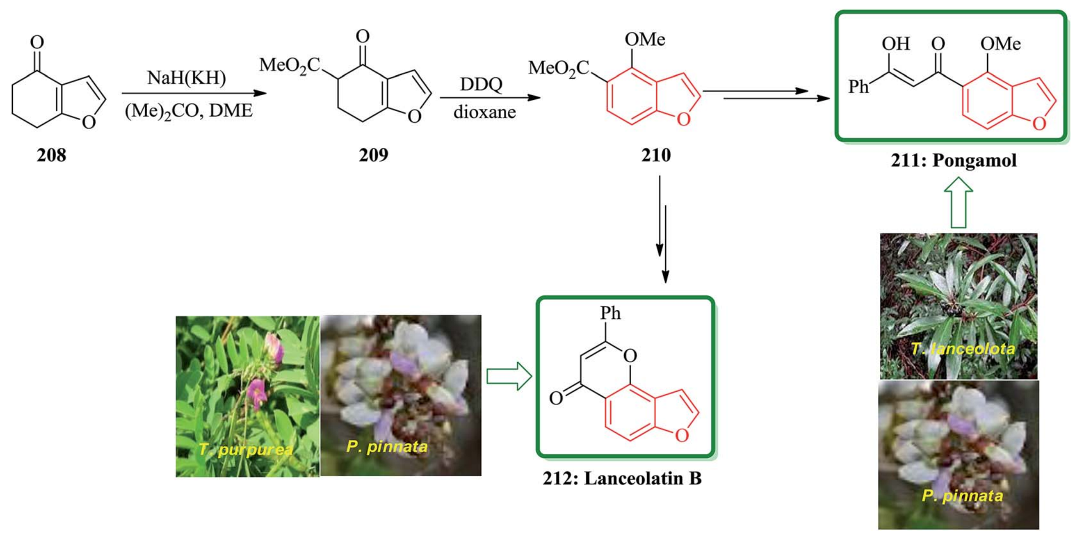
converted into the desired natural products **211** and **212** *via* two different reaction routes. The spectroscopic properties of this synthetic materials agreed well with those obtained from natural products reported in the literature (Scheme 47).[221]

Total synthesis of garcifuran B **217**, which is the constituents of plants of the *Garcinia* genus (Guttiferae) was achieved and reported. This plant has been used in traditional herbal-medicines in areas of southeastern Asia, shown later to contain a number of toxic components.[222] Garcifurans A (also known as garcinol) and B were isolated from the roots of *Garcinia kola* Heckel collected in Nigeria by Niwa and co-workers in 1994.[223] The total synthesis of garcifuran B **217** started with 5-bromo-2-hydroxybenzaldehyde **213** which was reacted with $BrCH(CO_2Et)_2$ in the presence of K_2CO_3 to provide benzofuran **214** and after 2 steps is converted into 5-bromobenzofuran **216.** The reactive trimethylstannyl **215** reacted smoothly with 5-bromobenzofuran **216** to give the desired benzofuran in 44% yield, which was then deprotected by heating under reflux in AcOH/H_2O to afford the natural product, garcifuran B **217** (Scheme 48).[224]

Benzofuran derivative **220** was isolated from various yeasts as an antioxidant[225] and its structure was determined by degradation studies.[226,227] Total synthesis of an antioxidant **220** having a benzofuran skeleton was achieved in four steps *via* the palladium(0)-catalyzed cross-coupling reaction. Some derivatives of **220** demonstrate antioxidative activity. Scheme 49



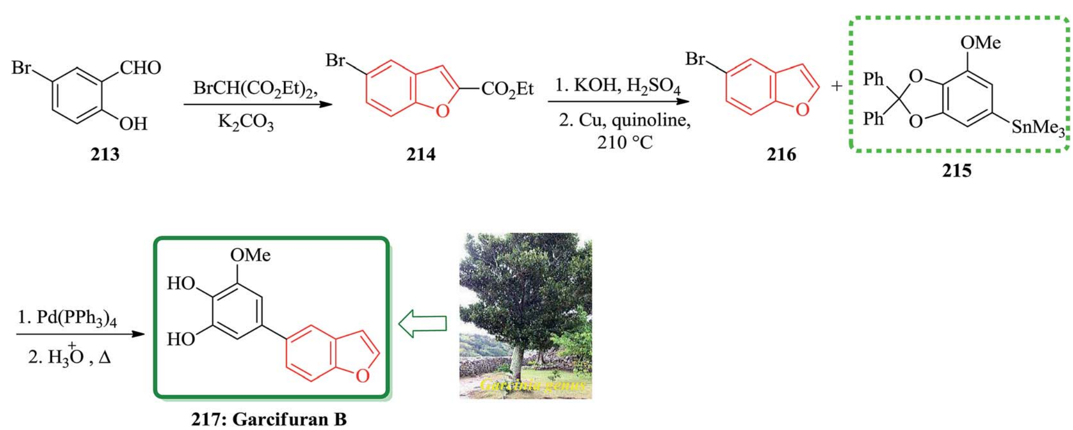
Scheme 46 Total synthesis of khellin **207**.



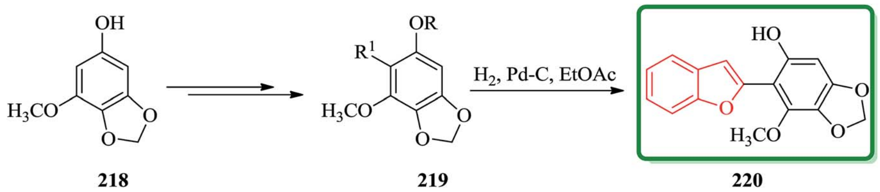
Scheme 47 Total synthesis of pongamol **211** and lanceolatin B **212**.

illustrates the synthetic route for the synthesis of **220**. Regioselective bromination of the known benzodioxole derivative **218** (ref. 228) along with several other steps afforded arylbenzofuran **219** in an excellent yield. The latter is hydrogenated and upon deprotection under the normal conditions gave the desired benzofuran **220** in a 62% overall yield. Remarkably, physicochemical data of the synthetic product were in good agreement with those reported values (Scheme 49).[229]

Novel antibacterial substance, AB0022A, was isolated from the cellular slime mold *Dictyostelium purpureum* K1001, that it inhibited the growth of Gram-positive bacteria. Because AB0022A was a highly substituted aromatic compound, its structure could



Scheme 48 Total synthesis of garcifuran B **217**.



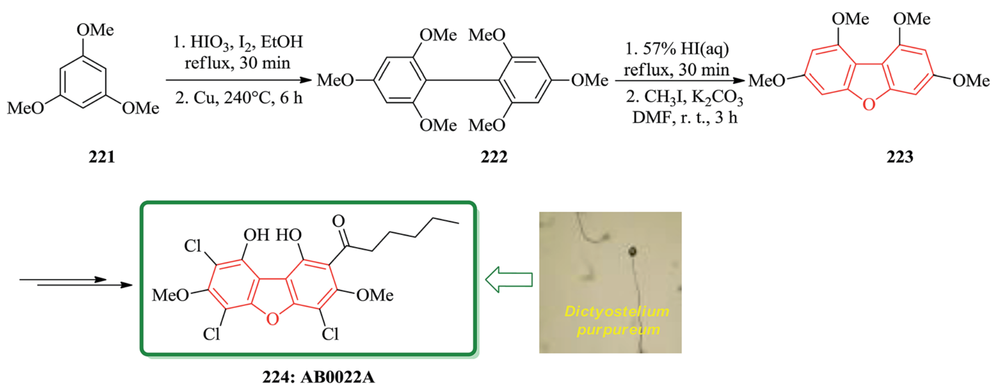
Scheme 49 Total synthesis of benzofuran derivative **220**.

not be determined based on only physicochemical and spectral data. Therefore, a dehalogenated derivative from AB0022A was prepared and deduced that its structure is actually l,9-dihydroxy-3,7-dimethoxy-2-hexanoyl-4,6,8-trichlorodibenzofuran. The synthetic product was identical to naturally occurring AB0022A. The strategy for synthesizing AB0022A **224** was as follows. It was selected 1,3,7,9-tetramethoxydibenzofuran **223**, which is known to be synthesized from 1,3,5-trimethoxybenzene **221** in three steps.[230] At first, they tried to synthesize 1,3,7,9-tetramethoxydibenzofuran **223**. Iodination of 1,3,5-trimethoxybenzene **221** and Ullmann coupling gave 2,2′,4,4′,6,6′-hexamethoxybiphenyl **222**. Cyclization of this biphenyl under the reported reaction conditions (57% HI aq., reflux) gave a complex mixture, which was methylated with iodomethane to give 1,3,7,9-tetramethoxydibenzofuran **223** in low yield. Finally, the latter was converted after several steps to natural product AB0022A **224** (Scheme 50).[231]

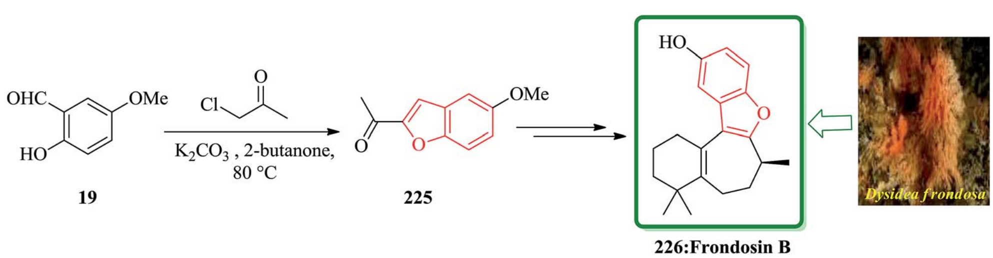
Frondosins A–E were recently isolated from the sponge *Dysidea frondosa*. These derivatives, which bear a causal relationship to one another, inhibit the binding of IL-8 to its receptor in the low micromolar range.[232] IL-8 promotes the accumulation and activation of neutrophils and has been implicated in a wide range of acute and chronic inflammatory disorders.[233] Commercially available 5-methoxysalicylaldehyde **19** was converted into **225**. After several steps and under basic conditions frondosin B **226** was produced in pure form and free of double bond isomers (Scheme 51).[234]

Chemical examination of the diethyl ether extract from the liverwort *Corsinia coriandrina* led to the isolation and characterization of a new 2-arylbenzofuran product so-called corsifuran A. Cycloaddition between 4-methoxystyrene **227** and *p*-quinone **228** catalyzed by ferric(III)chloride hexahydrate in acetonitrile gave 5-hydroxy-2-(4-methoxyphenyl)-2,3-dihydrobenzofuran **229** in moderate yield, which was proved being identical to corsifuran B. Methylation of **229** afforded corsifuran A **230**, which showed MS and ^{1}H-NMR data as same as to the natural product isolated from *C. coriandrina*. Upon to dehydrogenation of **230** using 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) in dioxane corsifuran C **231** was obtained (Scheme 52).[235]

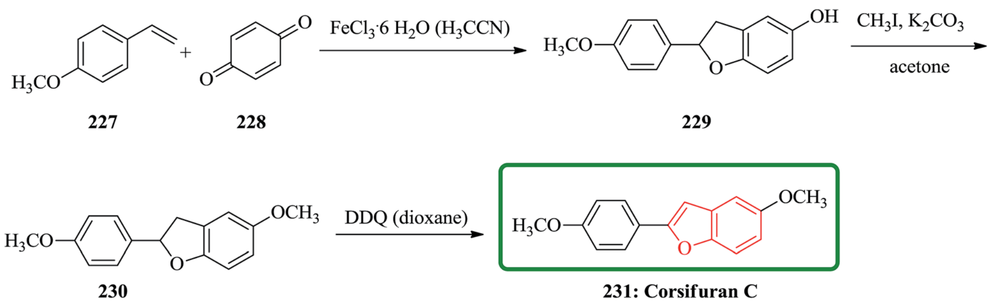
Natural 2-acetylbenzofurans calebertin **235a**, caleprunin A **235b**, and caleprunin B **235c** have been isolated from *Calea* species.[236] Caleprunin B **235c** had been previously isolated from



Scheme 50 Total synthesis of AB0022A **224**.



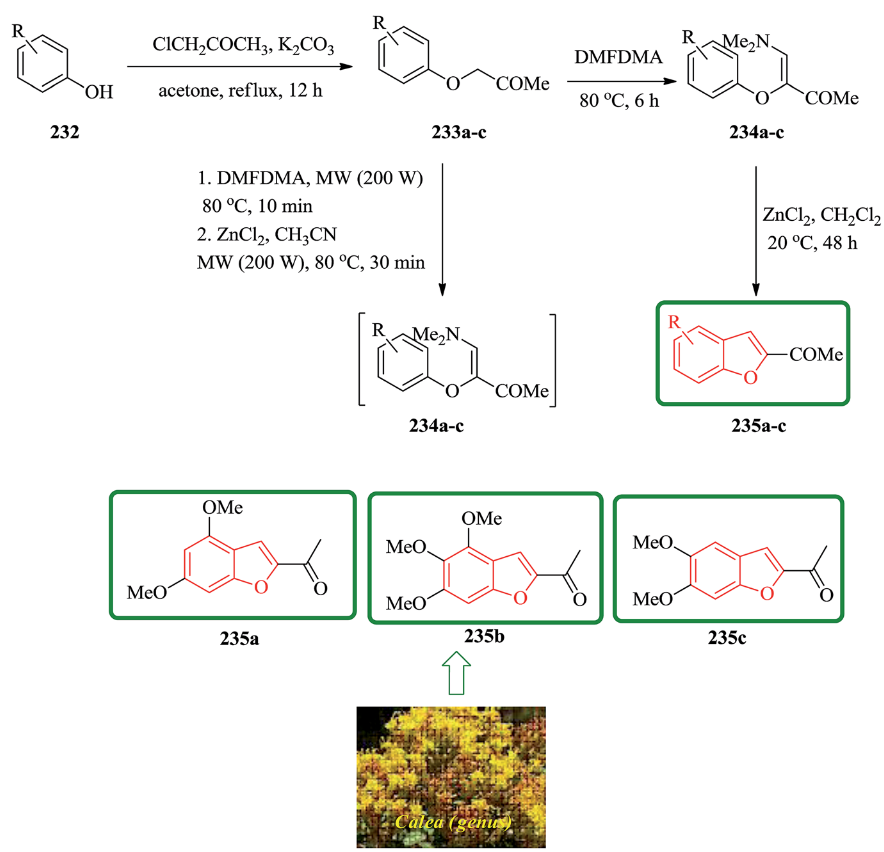
Scheme 51 Total synthesis of frondosin B **226**.



Scheme 52 Total synthesis of corsifuran C **231**.

Eupatorium sternbergianum and called eupatarone.[237] These naturally occurring compounds **235a–c** were synthesized in an acceptable overall yields. These benzofurans were also provided by direct treatment under MW irradiation of the precursor 1-aryloxypropan-2-ones **233a–c** with DMFDMA, with subsequent addition of the catalyst, providing a route that was literally one-step shorter. For the synthesis of 2-acetylbenzofurans **235**, first the corresponding 1-aryloxypropan-2-ones **233** were prepared *via* a base promoting Williamson reaction between the substituted phenols **232**, and chloroacetone in refluxing acetone. Then, a series of compounds **234a–f** was synthesized in high yields by the reaction of the corresponding 1-aryloxypropan-2-ones **233a–f** with DMFDMA. The intramolecular cyclization of 3-aryloxy-4-dimethylamino-3-buten-2-ones **234** gave compound **235a–c**. In this way, natural benzofurans **235a–c** were provided in good overall yields using phenols **232a–c** in a three-step syntheses in which calebertin **235a** was obtained in 35%, caleprunin A **235b** in 37%, and caleprunin B **235c** in 48% yield (Scheme 53).[238]

Furocoumarins **240a** are natural tricyclic compounds exhibiting a wide range of biological properties.[239] Linear furocoumarins are well-known photosensitizing drugs for the treatment of a number of skin diseases such as psoriasis, vitiligo, mycosis, and eczema,[240,241] as well as fungal, viral, and bacterial infections.[242,243] Recently, it was reported that some linear furocoumarins were applied to the treatment of cutaneous T-cell lymphoma.[244] More notably, they were found to have potential utility in the treatment of human

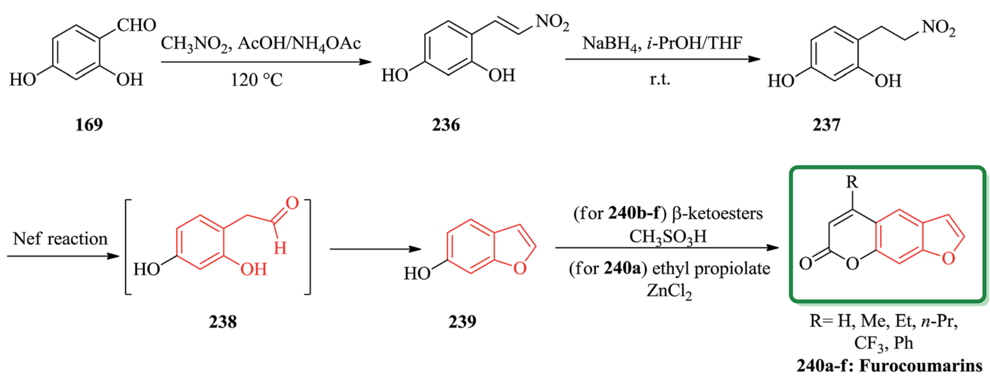


Scheme 53 Total synthesis of calebertin **235a**, caleprunin A **235b**, and caleprunin B **235c**.

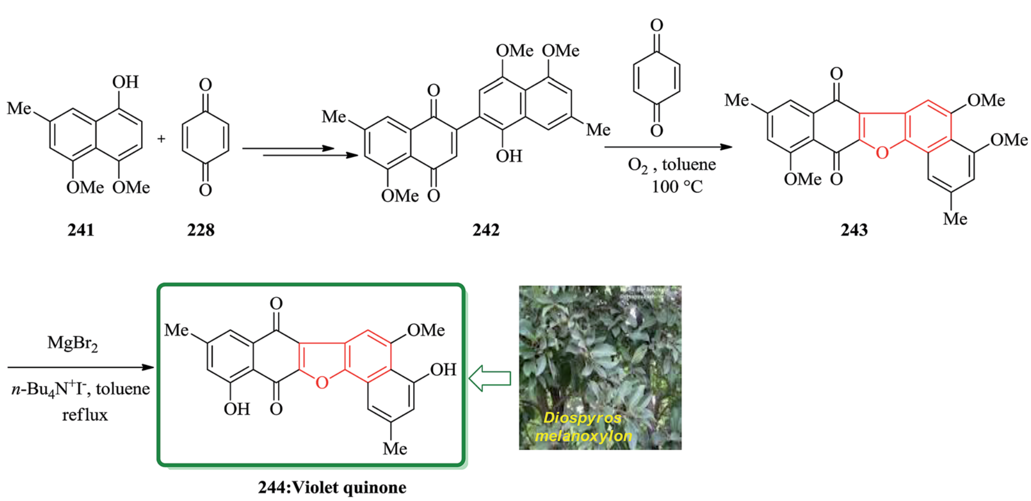
immunodeficiency disease[245] and in the prevention of organ transplant rejection.[246] A new and efficient method for the synthesis of linear furocoumarins was reported by the Nef reaction.[247] This strategy has also been applied to the preparation of four additional benzofuran derivatives. A mixture of 2,4-dihydroxybenzaldehyde and nitromethane was stirred in AcOH in the presence of NH_4OAc to give 5-hydroxy-2-(2-nitroethenyl)phenol **236** (ref. 248) in 84% yield. The unsaturated compound **236** was then converted into the desired product **237** (ref. 248) in 87% yields by treatment with $NaBH_4$ in i-PrOH-THF (1 : 4) at room temperature. It is well known that a nitro group can be easily converted to a carbonyl by the Nef reaction. 4-(2-Nitroethyl)benzene-1,3-diol **237** was thus subjected to the Nef reaction. Interestingly, the predicted aldehyde **238** was not obtained, while the required benzofuran-6-ol **239**,[249] was produced directly in a one-pot reaction under the reaction conditions. It is visualized that benzofuran-6-ol **239** could produce the intermediate **238** *via* an intramolecular cyclocondensation under Nef conditions. Based on this finding, a major attempt was there after made to modify the Nef reaction conditions aiming to improve the yield of benzofuran-6-ol **239**, which is the key intermediate for the synthesis of diversified furocoumarins **240a** (Scheme 54).[250]

The dibenzofuran-1,4-dione core is found being present in many naturally occurring compounds, some showing interesting biological activities. Some of them are cytotoxic popolohuanone E,[251] antipruritic balsaminone A[252] and violet-quinone.[253] An oxidative cyclization of quinone-arenols **242** resulted in the construction of benzofuran derivatives **243** containing 1,4-dibenzofuran core. The oxidative cyclization was employed as a part of the total synthesis of violet-quinone **244**. The quinonearenol **242** was easily synthesized from 4,5-dimethoxy-7-methylnaphthalen-1-ol **241** *via* a two-step sequential reaction. Relied on, these back grounds, the oxidative cyclization of quinone-arenols **242** was conducted by using benzoquinone **228** as an efficient oxidant in the presence of molecular oxygen, giving raise in **243** in satisfactory yield. Ultimately, $MgBr_2$-iodide-catalyzed selective demethylation of the C4– and C11–OMe motives of **243** gave the desired target violet-quinone **244** in high yield (Scheme 55).[254]

Erypoegin H **251** is the most active of lavonoid isolated from the roots of this ornamental plant. It is not only exhibits a broad spectrum of activity against Gram positive bacteria in general, but also exhibits a significant and uniform activity against a panel of **249** different MRSA strains and vancomycin-resistant enterococci.[255] The synthetic venture commenced with the di-



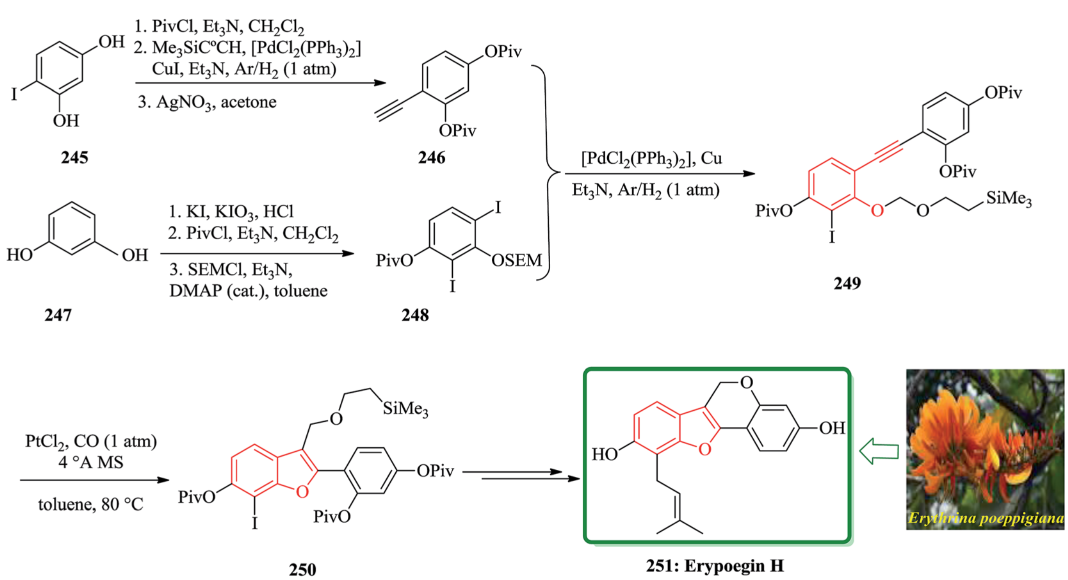
Scheme 54 Total synthesis of diversified furocoumarins **240**.



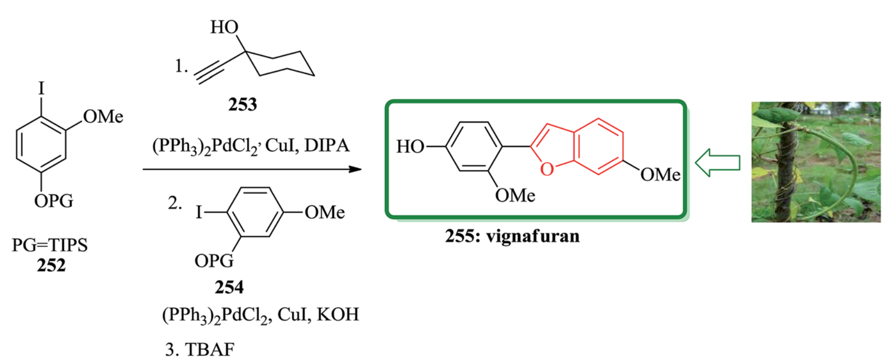
Scheme 55 Total synthesis of violet-quinone **244**.

iodination of resorcinol **247** (ref. 256) followed by consecutive attachment of a pivaloyl and a trimethylsilylethoxymethyl group. The resulting crude product from **250** was subjected to an intramolecular etherification under standard conditions to complete the construction of tetracyclic framework of erypoegin H **251**, which was obtained in a respectable 28% yield over the nine steps of the longest linear sequence. The resulting compound **249**, upon exposure to catalytic amounts of $PtCl_2$ in toluene under a CO atmosphere,[257,258] underwent a clean cycloisomerization with the formation of the desired benzofuran derivative **250.** This reaction was best performed in the presence of powdered molecular sieves to sequester traces of water that might protonate the putative organo platinum intermediate of type C and/or D and hence reduce the efficiency of the O → C shift. Under these optimized conditions, the cycloisomerization of **249** proceeded exceedingly well and afforded **250** in 84% yield on a multi-gram scale (Scheme 56).[259]

The study on the phytoalexins of cowpea, *Vigna unguiculata* (L.) Walp, showed that a natural product antifungal so called vignafuran **255** which has benzofuran moiety in its structure.[260] Interestingly, the total synthesis of this naturally occurring compound was accomplished *via* an efficient one-pot manner. In this sequential approach for the formation of the benzofuran moiety, aryl halides protected iodophenols and carbinol-based acetylene sources were employed. The sequence involved alternating palladium-catalyzed Sonogashira couplings/deprotection and ring closing step. Initially, a suitable *O*-methyl-iodoresorcinol was silylated to prepare the required corresponding aryl halides **252.**[261] In a suitable vessel **252,** reacted with 1-ethynyl-cyclohexanol **253** and catalytic amounts of suitable Pd catalyst under optimized reaction conditions. The progress of this reaction was monitored which upon its completion, potassium hydroxide, compound **254** and small amount of catalyst were added to the reaction mixture. It is presumed that the reaction gives the intermediate diarylacetylene, which was transformed to vignafuran **255** upon treatment with tetrabutylammonium fluoride. This achievement is a unique example of total synthesis of natural products *via* one pot manner, attractively showing the value of the 'one-pot' cascade Sonogashira coupling based strategy (Scheme 57).[262]



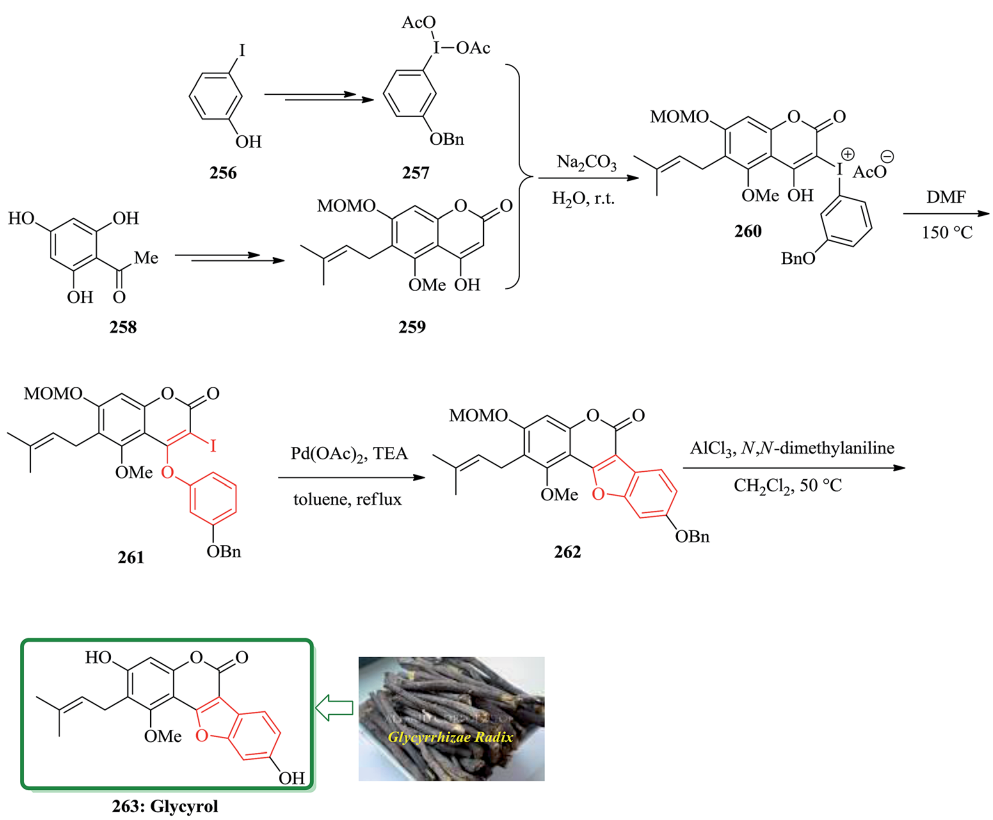
Scheme 56 Total synthesis of erypoegin H **251**.



Scheme 57 Total synthesis of vignafuran **255**.

The first total synthesis of glycyrol, isolated from glycyrrhizae radix, with a unique skeleton of a benzofuran coumarin was reported in 2008. Glycyrrhizae radix is a traditional medicine in the East Asia, and contains biologically active natural products such as glycyrrhizin, glycyrol, glycycoumarin, and liquoric acid.[263] Glycyrol has antibacterial activity against upper airway respiratory tract pathogens.[264] The key steps are Smiles rearrangement and selective introduction of prenyl and *O*-methyl groups. Preparation of *O*-benzyl-(diacetoxyiodo)arene **257** as a Smiles rearrangement precursor for the construction of benzofuran coumarin had unexpected difficulties. Benzylation of commercially available 2-iodophenol was achieved and after several steps, a crude 1-benzyloxy-3-(diacetoxyiodo)benzene **257** was provided. However, 1-benzyloxy-3-(diacetoxyiodo)benzene **257** was more unstable than commercially available 3-methoxy-1-(diacetoxyiodo)benzene and decomposed within one day, even with refrigeration. It was guessed that the (diacetoxyiodo)benzene is likely to be an oxidizing agent and the benzylic position could be susceptible to this reagent, although the reactivity of (diacetoxyiodo)benzene is not so powerful as common oxidizing agents. Fortunately, a base-catalyzed condensation of 4-hydroxycoumarin **259** with freshly prepared 1-benzyloxy-3-(diacetoxyiodo)benzene **257** successfully yielded an iodiumacetate salt **260**, which was directly converted to 2-iodo-4-phenoxycoumarin **261** in 87% yield by refluxing in DMF *via* Smiles rearrangement. The palladium-mediated intramolecular coupling reaction of vinyl iodide with the phenyl group in **261** was readily achieved by using palladium(II) acetate and triethylamine in refluxing toluene to provide the crude benzofuran **262**. Finally, simultaneous deprotection of the MOM and benzyl groups with *N*,*N*-dimethylaniline and aluminum chloride in refluxing methylene chloride, followed by careful purification on a silica gel, furnished the desired target material glycyrol **263** in 68% yield in two steps (Scheme 58).[265]

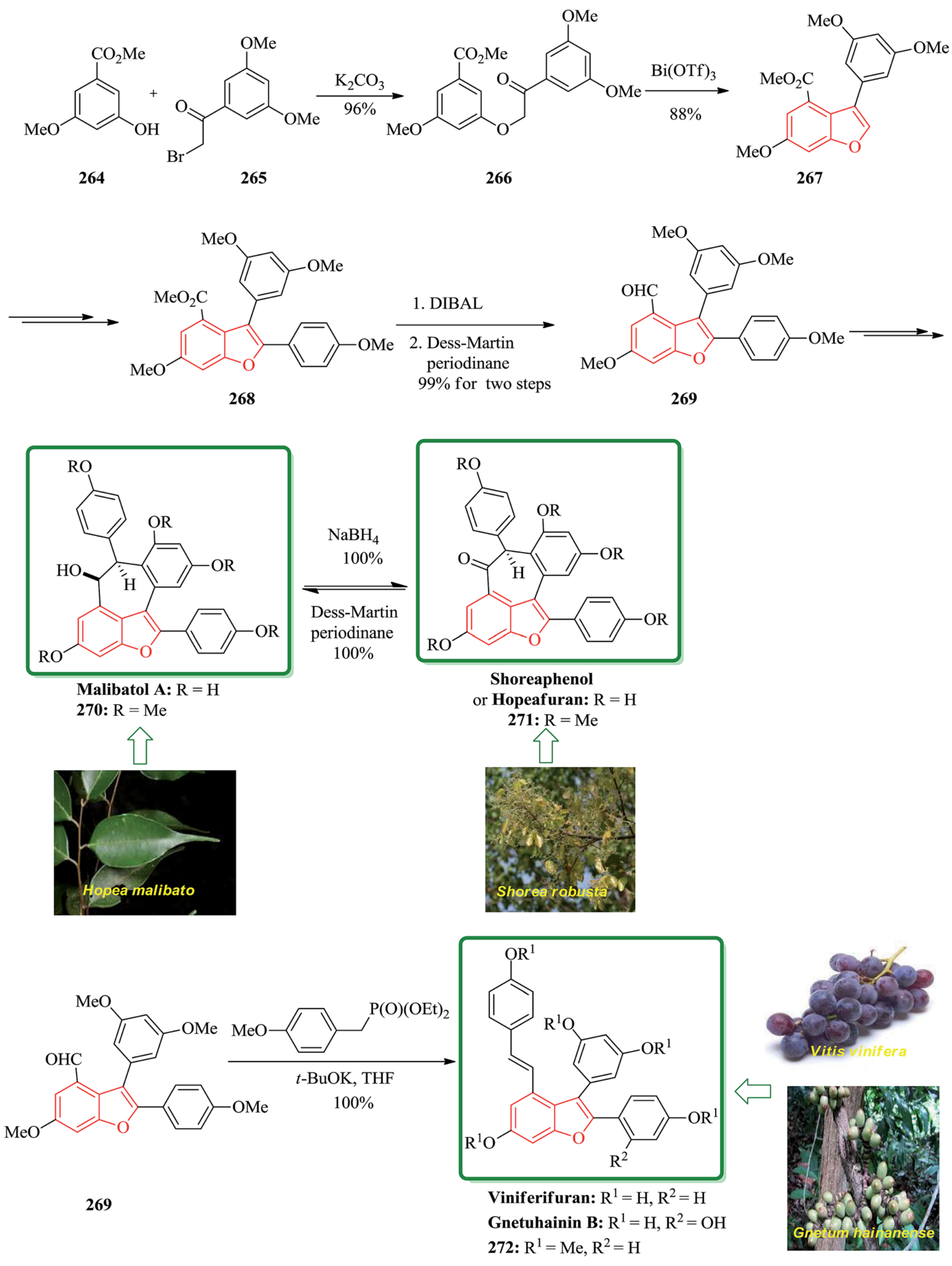
Gnetuhainin B **272** was initially isolated from the lianas of *Gnetum hainanense* by Lin and co-workers.[266] The structure of viniferifuran as the congerer of gnetuhainin, extracted from *Vitis vinifera* 'Kyohou' was fully characterized based on the widespread ^{1}H-NMR and ^{13}C-NMR data and elemental analysis and reported by Niwa.[267] On the other hand, in 1998, Boyd research group based on extensive spectroscopic data revealed the structures of two novel oligostilbenes, malibatols A and B, which were long ago isolated from the extract of the leaves of *Hopea malibato*.[268] Malibatols A and B were found showing cytotoxicity to the host cells (CEM SS) in an extensively antiviral test. Significantly, an oxidized analogue of malibatol A, has an oxidized analogue so-called shoreaphenol or hopeafuran. It was initially isolated from the bark of *Shorea robusta* and the stem wood of *Hopea utilis*.[269] Oligostilbenes[270] are a typical of highly oxygenated naturally occurring compounds, which bear more than two stilbene units. In the total synthesis of these compounds a region selectively Bi(OTf)$_3$-catalyzed cyclodehydration was performed for the facile access to 3-arylbenzofuran moiety. Consequently, for the introduction of aryl group at the C-2 position of benzofuran a Pd-catalyzed direct C–H activation of benzofuran followed by cross-coupling with



Scheme 58 Total synthesis of glycyrol **263**.

aryl halide is a key reaction. In an approach towards the total synthesis of these analogues, Chakraborty and co-workers synthesized aryloxyketone **266**, which was in turn can be readily synthesized from the treatment of phenol **264** (ref. 271) with α-bromoketone **265** (ref. 272) mediated by K_2CO_3. Upon the treatment of ketone **266** with BCl_3 the desired benzofuran **267** was obtained in satisfactory yield. On the other hand, the ester group in **268** was transformed into formyl group through a two-step sequential reaction including DIBAL reduction/Dess–Martin oxidation[273] in excellent overall yield. Upon Horner–Wadsworth–Emmons type olefination of **269** using diethyl 4-methoxybenzylphosphonate gave **272** in virtually quantitative yield. For the construction of the seven-membered ring implanted in malibatol A **270** and shoreaphenol or hopeafuran **271**, the epoxide ring opening by nucleophilic attack of the neighboring aromatic moiety was successfully conducted (Scheme 59).[274]

The total synthesis of kynapcin-24, **279** was achieved in 12% overall yield from commercially available 3,4-dihydroxybenzaldehyde by a route in which the longest linear sequence is only 14 steps. Compound **279** was initially isolated from the Korean mushroom *Polyozellus multiflex* Murr Prolyl endopeptidase (PEP), a serine protease, is known to cleave a peptide substrate on the C-terminal side of a proline residue.[275]



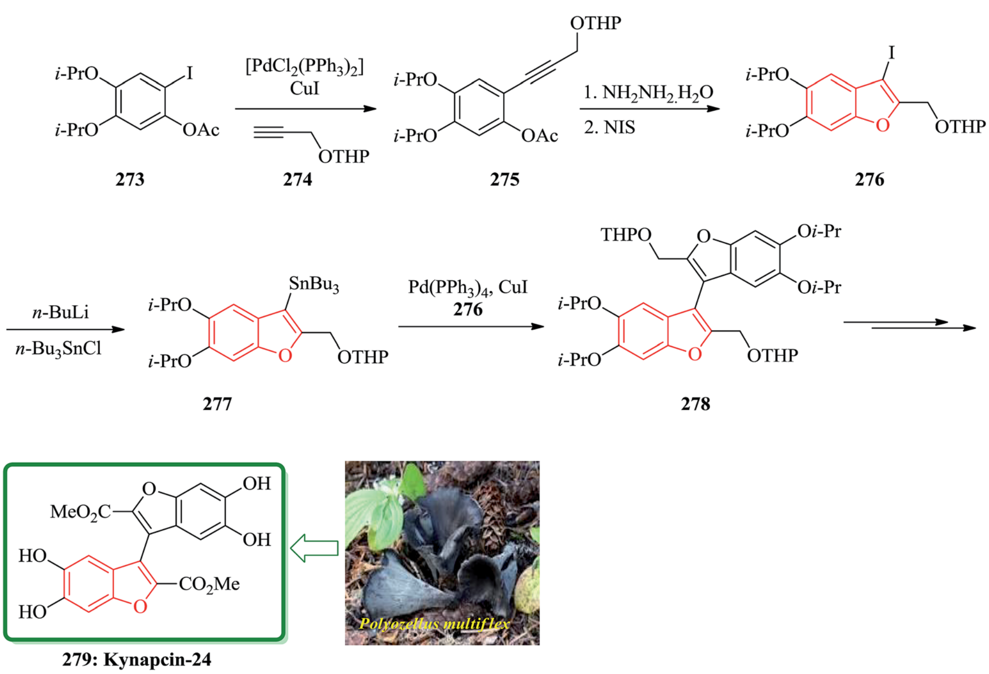
Scheme 59 Total synthesis of natural products **270–272**.

Additionally, the PEP activity of Alzheimer's patients has been found to be significantly higher than that of the normal person.[276] Recently Song and co-workers reported the synthesis of two novel PEP inhibitors, one of them is the benzofuran dimer kynapcin-24 **279**. Propeptin has inhibition similar to **279** that is a hydrophilic and large-molecular weight peptide, which may make it difficult to penetrate into the blood–brain barrier.

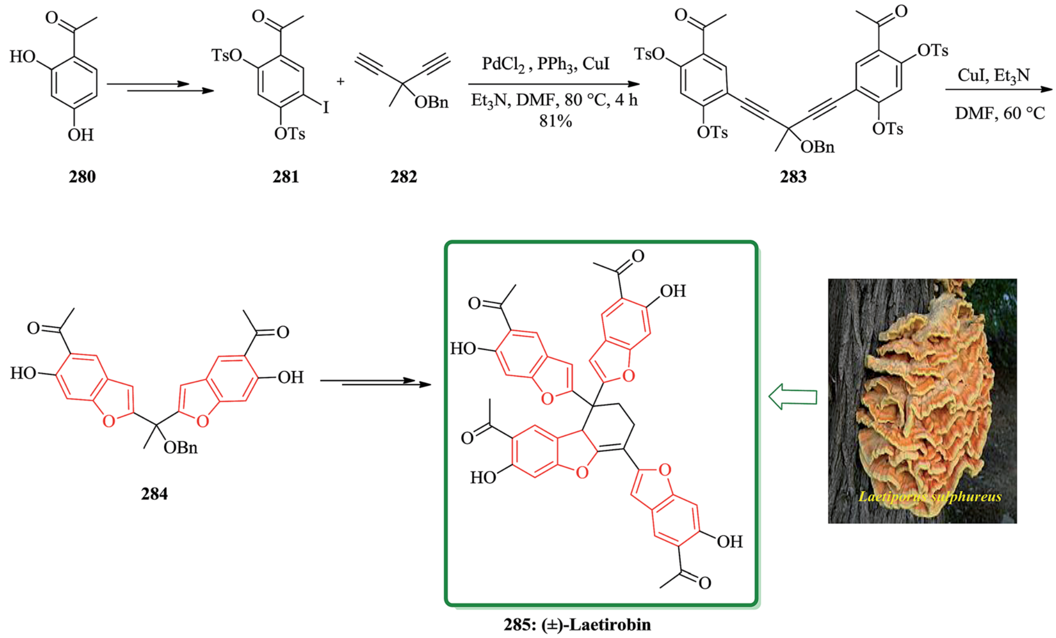
The key transformations in the total synthesis are copper-mediated and palladium-catalyzed coupling reactions of the iodide 3-iodo-5,6-diisopropoxy-2-[(tetrahydropyran-2-yloxy)methyl] benzofuran with the corresponding stannane 5,6-diisopropoxy-2-[(tetrahydropyran-2-yloxy)methyl]-3-(tributylstannyl)benzofuran, and a 5-*endo*-dig iodocyclization of a (hydroxyphenyl)propargyl ether. For the total synthesis of kynapcin-24 **279**, coupling of phenyl iodide **273** with protected propargyl alcohol **274** instead of methyl propynoate proceeded smoothly in dioxane under the copper-mediated palladium catalysis to give the desired **275** in excellent 96% yield. The latter is reacted with NIS in the presence of hydrazine hydrate to give benzofuran **276**. The latter upon lithiation and quenching with tributylstannyl chloride provided stannane benzofuran **277** in 73% yields. Then **277** reacted with iodide **276** reacted under the copper-mediated palladium-catalyzed coupling to give dibenzofuran **278** in 72% yield. The latter was subjected to sequential deprotection, oxidation, and oxidation-esterification using pyridinium *p*-toluene-sulfonate, 2-iodoxybenzoic acid, and silver(I)oxide-thionyl chloride, providing the desired target **279** in 98% yield (Scheme 60).[277]

(±)-Laetirobin **285** as a new cytostatic agent was isolated from the fruiting bodies of the fungus *Laetiporus sulphureus* and its structure was fully characterized.[278] It was found, laetirobin has the potency to prevent tumor cell division (mitosis) and appealing automatic cell death (apoptosis). A brief and efficient total synthesis of laetirobin was achieved in 12% overall yield in six steps. In this approach, the total synthesis started from market purchasable 2,4-dihydroxyacetophenone **280**. The latter was converted to **281** in several steps compound **281** was the reacted with protected dipropargyl alcohol to give the tosylate **283** sequential reactions involving (a) the double Sonogashira reaction of a bis(alkyne), (b) a highly efficient copper(I)-catalyzed construction of a bis(benzo[*b*]furan), and (c) the biomimetic [4 + 2] dimerization. The phenol **284** was synthesized by treatment of tosylate **283** with newly activated Mg in MeOH.[279] The optimal conditions for such conversion is using of 25 mol% of copper(I) iodide under the conditions of a modified Stephens–Castro reaction. After several steps, phenol **284**, was transformed into the desired natural product (±)-**285** (Scheme 61).[280]

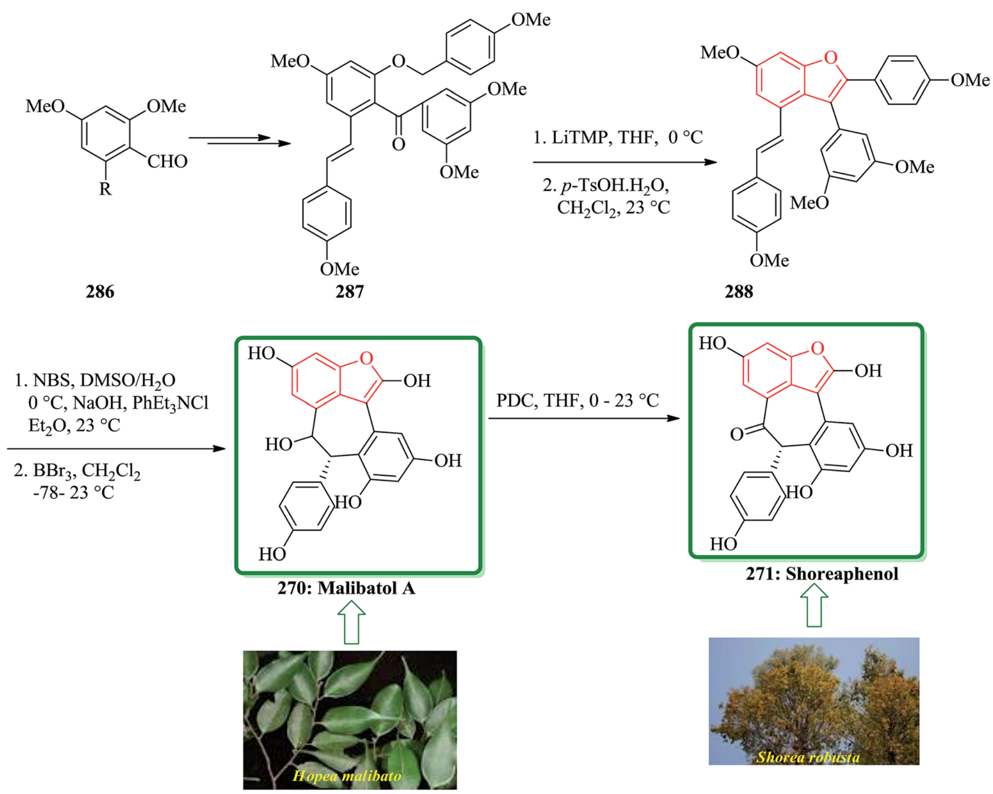
Malibatol A **270** and shoreaphenol **271**, are two dimeric resveratrol polyphenolic benzofurans which isolated initially from *Hopea malibato* and *Shorea robusta*, respectively.[268,269] A flexible protocol for the synthesis of hexacyclic dimeric resveratrol polyphenolic benzofurans has been achieved and revealed in 2010. In this approach, firstly benzyl ethers **287** were synthesized from appropriate **286** in high yield. Then, benzofuran formed from keto benzyl ethers **287** was converted into a compound bearing benzofuran moiety **288** *via* a two-step reaction, which in general gives a satisfactory yields of the products (71–85% yield). In this procedure, when pentacyclic benzofuran **288** is used, the oxygen-substituted, seven-membered ring in the malibatol A **270** and shoreaphenol **271** are constructed. Therefore, in a one pot reaction, upon epoxidation of stilbene **288** using bromohydrin (NBS, NaOH), and subsequent treatment of the epoxide with BBr_3 led to cyclization and inclusive demethylation gave racemic malibatol A **270** as a sole diastereoisomer in acceptable yield. Upon oxidation of



Scheme 60 Total synthesis of kynapcin-24 **279**.



Scheme 61 Total synthesis of (±)-laetirobin **285**.



Scheme 62 Total synthesis of malibatol A **270** and shoreaphenol **271**.

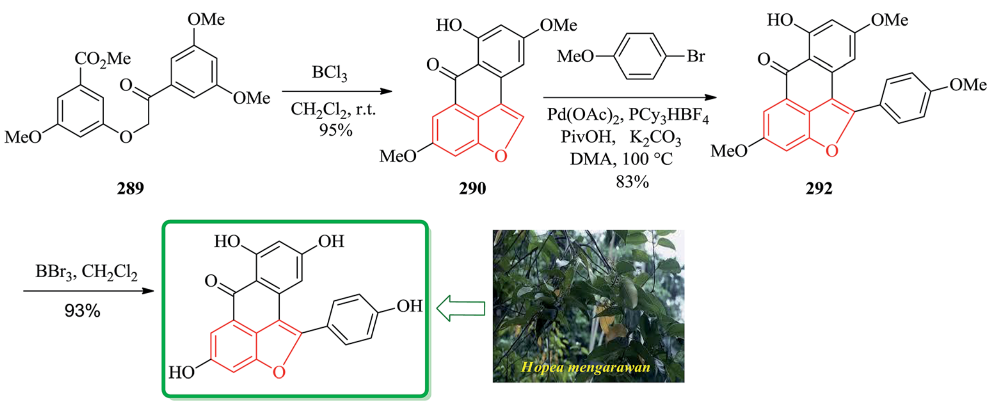
malibatol A **270** in the presence of PDC shoreaphenol **271**, is obtained, albeit in the moderate yield (Scheme 62).[281]

Syah and co-workers reported the isolation and characterization of a novel oligostilbenoid from the tree bark of *Hopea mengarawan*.[282] This natural product exhibited potent immunosuppressive activity.[283] As a matter of fact, several of oligomeric stilbenes have been isolated and recognized having divergent means of connectivity of their basic 1,2-diphenylethylene scaffold. Several remarkable biological functions of this family have been acknowledged comprising antibacterial antifungal, anti-inflammatory, and anticancer activities.[284] A total synthesis of diptoindonesin G starts from readily available aryloxyketone **289** including one pot sequential cyclization/intramolecular Friedel–Crafts acylation reaction of aryloxyketone in cascade manner which gives compound **290** and **292** bearing benzofuran framework respectively. The latter upon treatment with BCl_3 in CH_2Cl_2 undergoes regioselective demethylation to give the tetracyclic 6*H*-anthra[1,9-*bc*]furan-6-one G. In fact, treatment of **289** with BCl_3, resulted in benzofuran **290** in excellent yield. The latter was subjected to Pd-catalyzed direct arylation[285] to assemble an aryl group at the C2 position of the benzofuran[286] unit of **290**. Reaction of **290** under the conditions, previously reported for the synthesis of oligostilbenoids gave diptoindonesin G **293** in 18–22% yield (Scheme 63).[287]

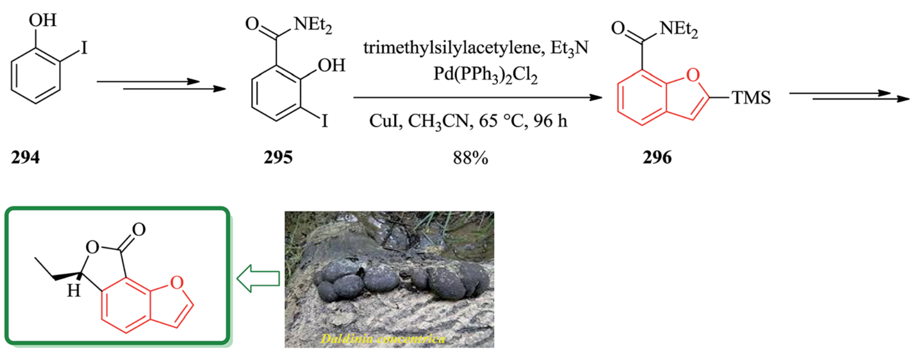
(+)-(*R*)-Concentricolide (+)-**297**, is the enantiomer of an anti-HIV-1 agent which was initially isolated from *Daldinia concentrica*. The concise total synthesis of (+)-**297** was achieved in 7 steps starting from 2-iodophenol. This total synthesis disclosed the (*S*)-configuration for the naturally occurring form of the furanophthalide. The key steps in this strategy are an anionic *ortho*-Fries rearrangement to give 3-iodosalicylamide, easy formation of the benzofuran system using the Sonogashira coupling/cyclization *via* tandem manner as well as orthometalation to attach a propanoyl group, and CBS reduction, creating the stereogenic center, enantioselectively. This brief total synthesis started with market purchasable 2-iodophenol **294**, which after 2 steps provided 3-iodosalicylamide **295**. The latter upon treatment with trimethylsilylacetylene mediated by bis-(triphenylphosphine)-palladium(II) chloride and in the presence of cuprous iodide under optimized conditions gave benzofuran **296** in high yield. Interestingly, it was found that the elevated temperature decreases the effectiveness of the catalyst system required for the cyclization of Sonogashira intermediate to the corresponding benzofuran **296**, thus, much higher catalyst loading as well as portion wise addition is needed for the completion of the reaction *via* tandem fashion (Scheme 64).[288]

Synthesis of new iboga-analogues, replacing the indole ring with a benzofuran moieties has been reported in 2011. The 3-benzofuranethanol **299** was obtained *via* Larock's hetero-annulation reaction[289] between 2-iodophenol and internal alkyne **298**, which subsequently treated with tetrabutyl ammonium fluoride in 55% yield in two steps, finally, compounds **300a** and **300b** were provided. Pd(II)–Ag(I) mixed metal mediated cyclization strategy was first developed by Trost in the synthesis of ibogamine.[290] This protocol was applied to **300a** and **300b** to afford **301a** and **301b** in 42% and 22% yields, respectively (Scheme 65).[291]

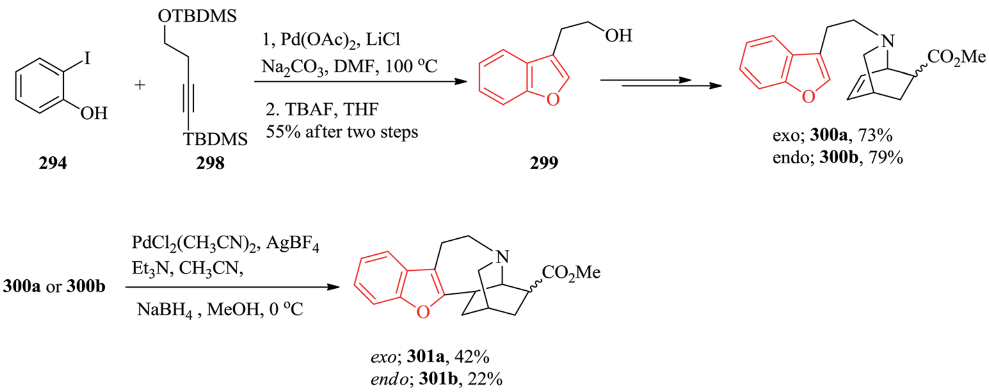
To synthesize of iboga analogues **304**, the requisite benzofuran alcohol **302** was obtained in one-pot from 2-iodophenol *via* Sonogashira coupling with 3-butyn-1-ol at ambient



Scheme 63 Total synthesis of diptoindonesin G **293**.



Scheme 64 Total synthesis of (+)-(*R*)-concentricolide (+)-**297**.

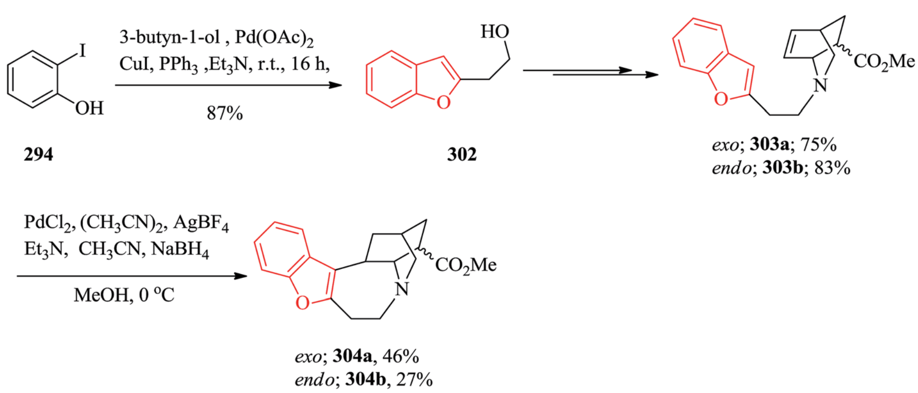


Scheme 65 Synthesis of **301a**, **b**.

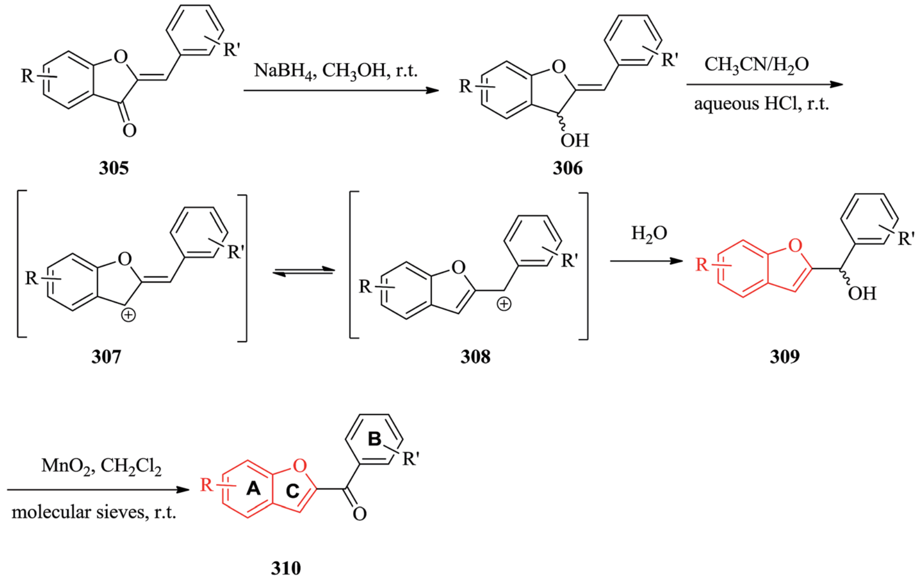
temperature. After two steps, **302** afforded **303a** and **303b** in high yields. Compound **303a** underwent the mixed-metal-mediated cyclization. This reaction proceeded smoothly and nicely to afford the desired product **304a** in moderate yield. A similar cyclization of compound **303b** also occurred to give the product **304b**, although in lower yield (Scheme 66). Unexpectedly, the *endo*-isomers **300b** and **303b** found to be more polar than their *exo*-isomers.[291]

2-Benzoylbenzo[*b*]furans and aurones (2-benzylidene-3-(2*H*)-benzofuran-3-ones) are occurring in nature and bearing the same carbon unit scaffold (C6–C3–C6). 2-Benzoylbenzo[*b*] furans were initially isolated from different plants, used traditionally as medicine by native inhabitants.[292] Both compounds were screened, showing interesting biological activities.[293] In some cases, they were employed as intermediates for the total synthesis of biological active compounds, *i.e.*, aromatase inhibitors.[294] The naturally occurring aurones (2-benzylidene-3(2*H*)-benzofuran-3-ones) can be cleanly transformed to another class of natural products 2-benzoylbenzo[*b*]furans by an efficient reduction, acid-mediated rearrangement, and oxidation cascade. This facile transform was performed with no purification of intermediates. This simple conversion may be considered as a possible biosynthesis route of 2-benzoylbenzo [*b*]furans in plants. The aurones were prepared following a previously reported method[295] and provided as solely *Z*-isomers, in respective to the configuration of naturally occurring aurones. The reduction of aurones was conducted with sodium borohydride in methanol at ambient temperature to afford the corresponding allylic alcohols (2,3-dihydrobenzofuran-3-ols) **306**. These alcohols are sensitive to high temperature and acidic conditions. The isomerization was taken place at room temperature in a mixture of water and acetonitrile mediated by aqueous HCl to give **309**. The plausible mechanism involves a carbocation generation **307** followed by rearrangement of the later to the extracyclic methine carbon **308**, stabilized by the B-aryl group. The organic solution of the rearranged alcohol was directly used in the oxidation step using MnO_2 as an oxidant in dry conditions. These three steps conversion were applied for the synthesis of a series of aurones **305** in high to excellent yields. The benzoylbenzo[*b*]furans analogs **310** were obtained with excellent yields (76–86%) (Scheme 67).[296]

In 2005, the naturally occurring compound (+)-fulicineroside was isolated from the slime mold *Fuligo cinerea*, the plant was found and collected in the Czech republic.[297] The total synthesis of (+)-fulicineroside **315** was accomplished and reported in 2013. The total synthesis was started with the Ullman-type coupling[298] commercially available resorcin **312** with readily accessible 1-bromo-3,5-dimethoxybenzene **311** to obtain the corresponding biarylether phenol as an intermediate which without isolation is transformed into the dimethyl carbamate **313** *via* a one-pot fashion. The dimethyl carbamate **313** under



Scheme 66 Synthesis of iboga analogues **304**.

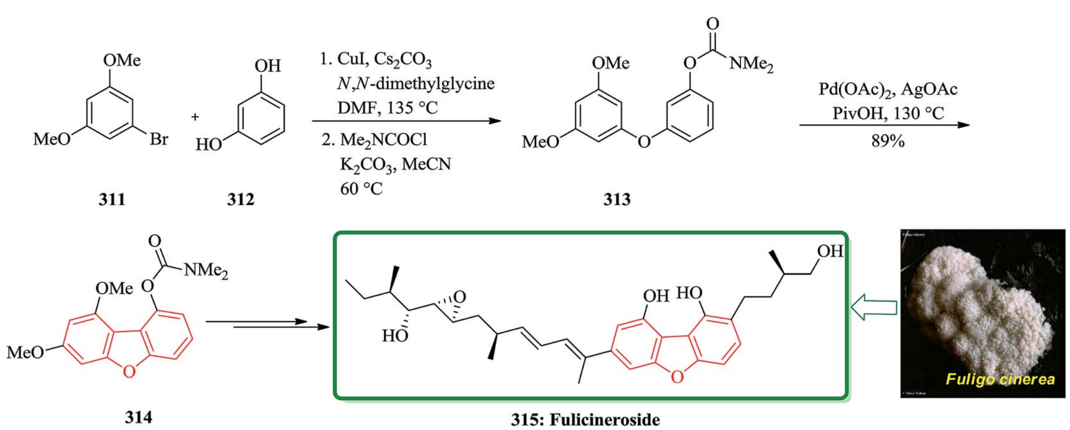


Scheme 67 Synthesis of the benzoylbenzo[*b*]furans analogs **310**.

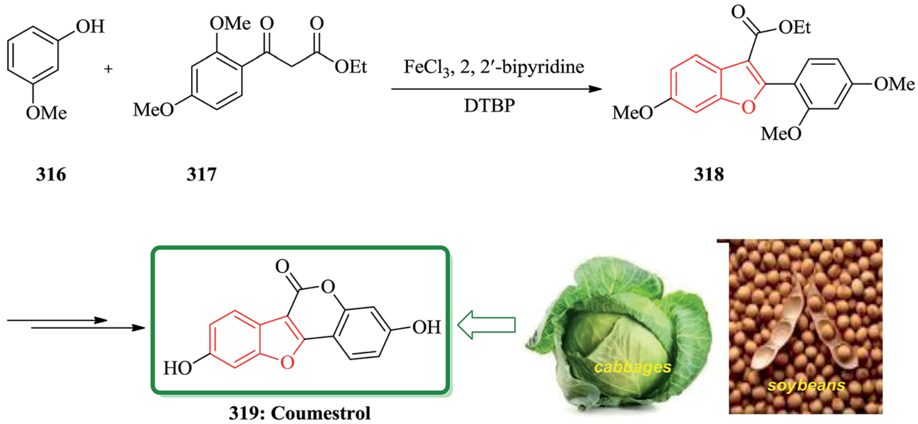
Fagnou's C–H activation conditions[299] and Pd-mediated C–H activation provided compound **314** containing the dibenzofuran ring moiety present in the structure of the desired natural product **315**.[300] Worthy to mention that in this treatment the reaction times were remarkably decreased and the best yields were obtained when AgOAc was used as an oxidant instead of molecular oxygen present in air under ambient conditions. Compound **314** was transformed into (+)-fulicineroside **315** as the desired target *via* multi-steps reaction through different functional group transformations (Scheme 68).[301]

Coumestrol **319** is an essential dietary ingredient found in forage plants, cabbages and soybeans.[302] Due to its importance in human nutrition, it has been extensively studied.[303,304] The total synthesis of **319** based on the iron-catalyzed cross-dehydrogenative coupling (CDC) was achieved and revealed in 2013. In this approach, a modified aerobic oxidative cross-coupling applied for the construction of benzofuran, a moiety present in coumestrol **319**. Ethyl 2-(2,4-dimethoxybenzoyl) acetate **317** and 3-methoxy phenol **316**, were reacted in DCE as solvent at 70 °C in the presence of $FeCl_3$ as the catalyst and 2,2′-bipyridine as additives to give compound **318**. The latter was then submitted to sequential deprotection/lactonization giving the desired natural product in good (59%) overall yield (Scheme 69).[305]

The dried root of *Salvia miltiorrhiza* bunge so called danshen, in the Lamiacea family is one of the mostly common used Chinese folk medicines (CFM). This medicine has a history of at least 2000 years in China and has been also used globally, since 1970s. It helps circulation and develop blood thus to provide therapeutic relief from stroke and angina pectoris. Moreover, it shows antiviral, antioxidant and antitumor potencies.[306–309] In 2013, the total synthesis of a methylated analogue of (+)-salvianolic acid C has been accomplished and reported. Key features in this synthetic approach are using readily available and inexpensive Cu(I) acetylide, significant carboxyl activation under microwave irradiation (MW), and using kinetic resolution of a racemic mixture of secondary



Scheme 68 Total synthesis of fulicineroside **315**.

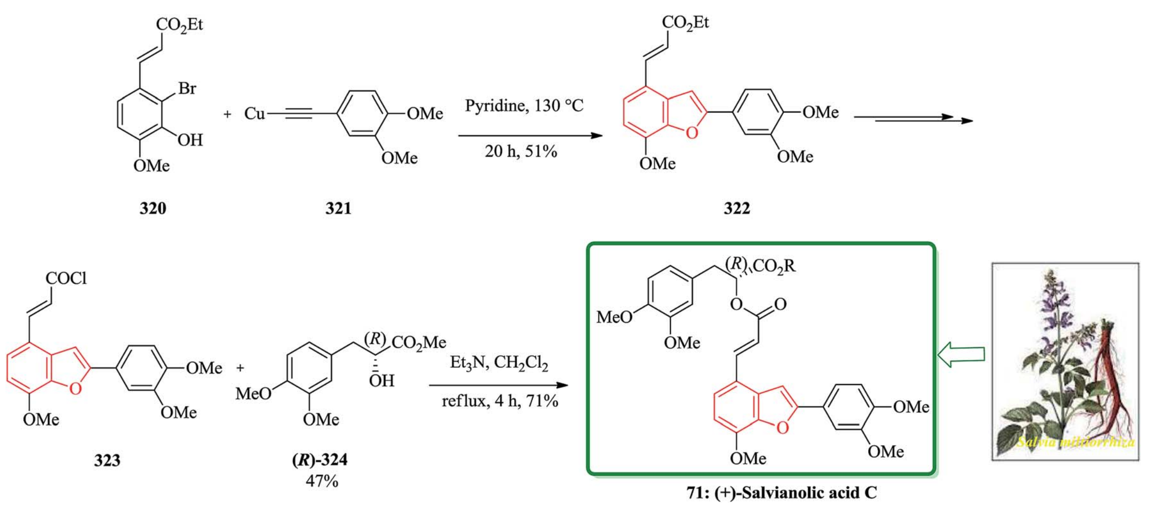


Scheme 69 Total synthesis of coumestrol **319**.

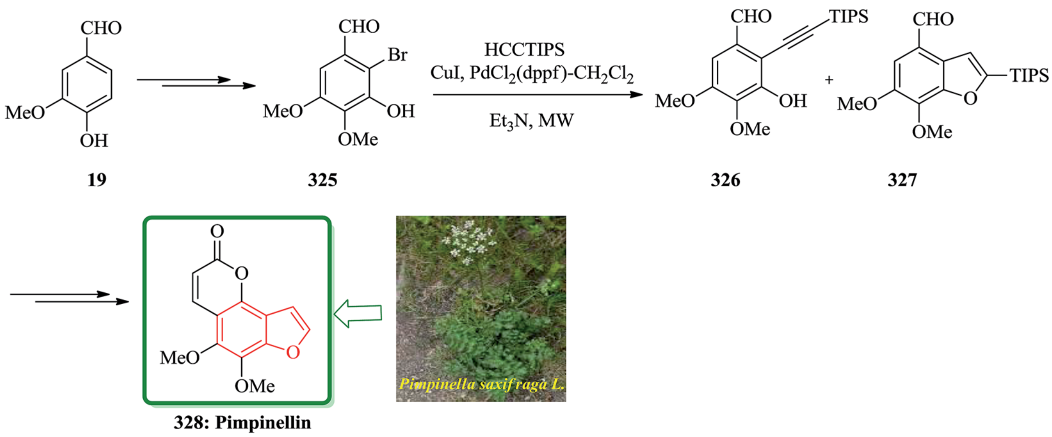
alcohol *via* lipase catalyzed danshensu. The total synthesis starts from coupling of readily accessible **321** with **320** under the optimal reaction conditions reported by Scammells and co-workers[102] to give the 2-arylbenzo[*b*]furan core **322** (51% yield). Finally, reaction of **323** and **324**, in the presence of Et_3N gave carboxylic acid **71** in satisfactory yield (Scheme 70).[310]

Pimpinellin **328** acts as a phytoalexin in parsley and celery. It was found to serve as an inhibitor of trichothecene toxin biosynthesis. It has been isolated from a variety of plant cradles,[311] such as *Pimpinella saxifraga* L.[312] The total synthesis of pimpinellin **328** involves the Au(I)-catalyzed intramolecular hydroarylation (IMHA) of the appropriate aryl propiolate esters, which were themselves provided by the reaction of the respective phenols with either 3-(trimethylsilyl)propiolic acid or propiolic acid and *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride or dicyclohexylcarbodiimide. The total synthesis of pimpinellin **328** started from vanillin **19**, which was transformed to substituted arene **325** in 84% yield. The latter was then submitted to a Sonogashira cross-coupling[313] reaction with triisopropylsilylacetylene to afford a 1 : 8 mixture of acetylene **326** (5%) and the isomeric benzofuran **327** (39%). Delightfully, they could be separated by column chromatographically. The rather moderate yields linked with the transformed **325** → **326** + **327** can be ascribed to possible competitive oxidative coupling of the triisopropylsilylacetylene. It is worthy to mention that such process is expected to generate likely volatile compounds, which actually were not detected in the obtained crude product mixture. Compound **327** is transformed into the desired natural product **328** in several steps including a step required for the assembly of the lactone ring, present in the species isolated from natural products (Scheme 71).[314]

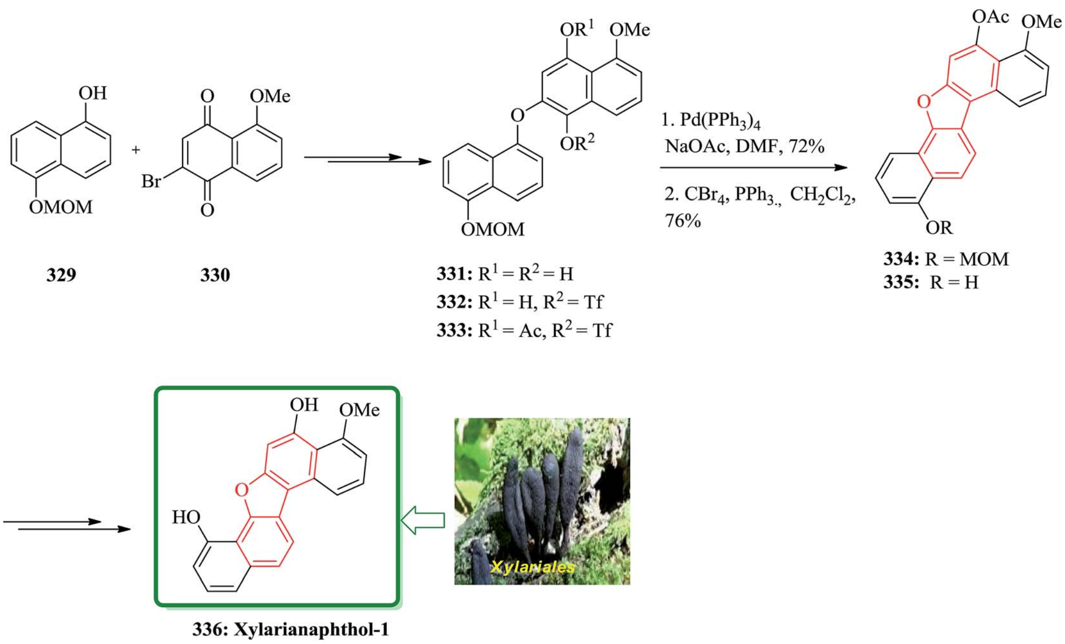
Xylarianaphthol-1 **336**, a dinaphthofuran derivative showing divers biological activities was originally isolated from a marine sponge-derived fungus of order *Xylariales* on the control of a bioassay employing the transfected human osteosarcoma MG63 cells.[315,316] The total synthesis of **336** was achieved as illustrated in Scheme 72. The total synthesis started from coupling of 1,5-naphthalenediol mono-methoxymethyl (MOM) ether **329** with bromobenzoquinone **330** mediated by K_2CO_3 in DMSO[317] to afford a C–O coupling product. Upon reduction of the quinone moiety, present in acetonitrile using aqueous $Na_2S_2O_4$, the mono-triflation was regioselectively proceeded



Scheme 70 Total synthesis of (+)-salvianolic acid C **71**.



Scheme 71 Total synthesis of pimpinellin **328**.



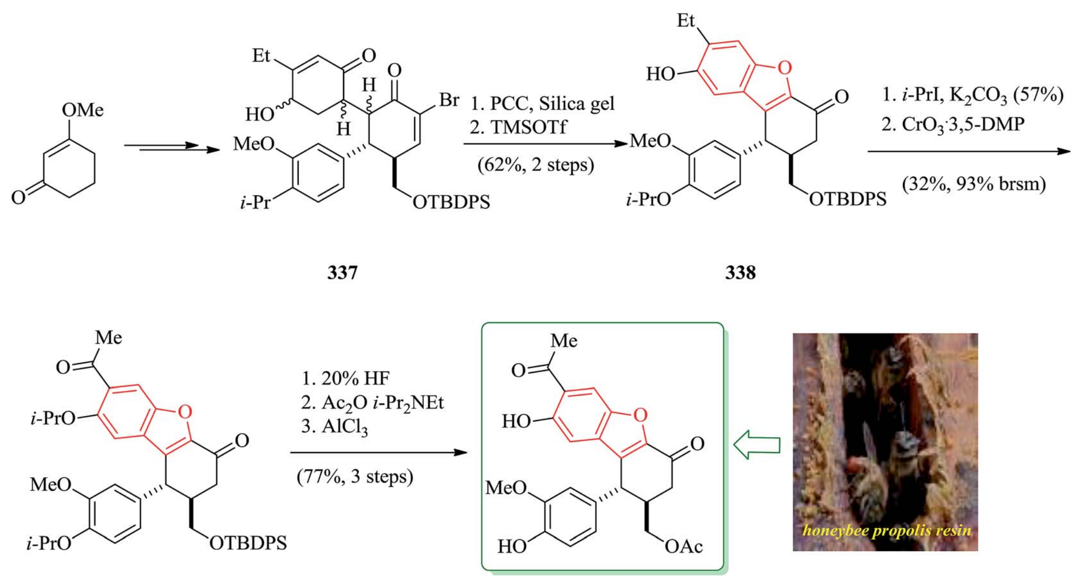
Scheme 72 Total synthesis of xylarianaphthol-1 **336**.

resulting in the formation of compound **332**. The latter was further treated with sodium acetate to produce acetate **333**, which can be used as the precursor of the key intramolecular arylation. Among several efforts to find optimal conditions the combination of $Pd(PPh_3)_4$ and NaOAc was found most operative to promote Mizoroki–Heck-type intramolecular arylation, which is leading into the formation of the desired pentacyclic product **334** in satisfactory yield.[318]

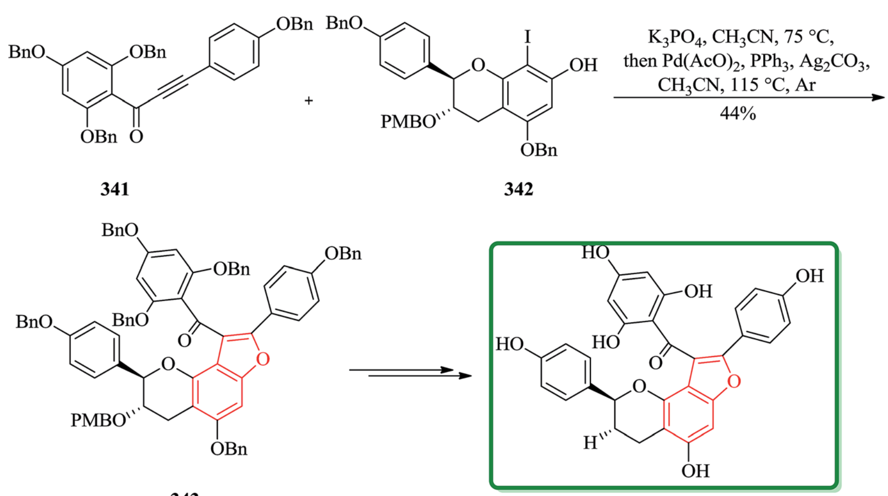
Propolisbenzofuran B **340**, is a biologically active naturally occurring compound, which was initially isolated from honeybee propolis resin. The total synthesis of **340** includes a silicon-tether controlled oxidative ketone–ketone cross coupling and a benzofuran construction *via* cascade manner to provide the core structure of the target. The total synthesis commenced with easily accessible 3-methoxycyclohex-2-enone which in several steps is converted into 1,4-diketone **337** in accordance with a pathway reported by Clift and co-workers previously.[319] This 1,4-diketone **337** was then converted into dihydroquinone **338** using PCC on silica in excellent yield. Worthy to mention that initially the Ley oxidation was used but found being unsuccessful since remarkable unchanged starting material was recovered. Even increases in catalyst loading in this case did not work, it could be attributed to the presence of the adjacent ethyl group, which apparently hinders initial formation of the required ruthenate ester. Delightfully, the ethyl substituent could not prevent the construction and aromatization of benzofuran *via* cascade reaction. Compound **338** was converted into ethyl substituted benzofuran **339** in satisfactory yield. Completion of the synthesis from this point was direct and classical. Upon removal of the silylether using 20% HF followed by acetylation of the resulting primary alcohol, which proceeded clean and smoothly caused to selective deprotection of the isopropyl ethers which were performed in the presence of $AlCl_3$. These three sequential steps gave the desired natural product, propolisbenzofuran B **340** in 77% overall yield. This synthetic product showed identical spectral data with those of obtained and reported for the species isolated from natural sources (Scheme 73).[320]

Daphnodorin A **344**, is a member of the daphnodorins. The total synthesis of **344** was achieved and reported in 2014. Key aspects of the synthetic protocol involve the assembly of 2-substituted-3-functionalized benzofuran through intramolecular Heck reaction[321] and a mild Barton–McCombie deoxygenation process catalyzed by triethylborane. This strategy provided daphnodorin A in 7 steps with overall yield of 19.7% or 15 steps with overall yield of 5.6%. Initially, compound **341** and the desired *o*-iodophenol **342** were synthesized. Then the corresponding *o*-iodophenol **342** reacted, subjected into conjugate addition followed by intramolecular Heck reaction with ynone **341** to form an entirely protected daphnodorin B **343**. Finally, upon deprotection of the latter daphnodorin A **344** was provided (Scheme 74).[322]

Two new flavones (±)-anastatins A and B, isolated from *Anastatica hierochuntica* have a benzofuran moiety as scaffold in their structures and their total synthesis was reported very recently. The key features for their synthesis are bromination, Suzuki coupling reaction,[323] and an oxidation/oxa-Michael reaction.[324] The concise total synthesis of (±)-anastatins A and B were accomplished in eight steps starting from the market purchasable phloroglucinol with acceptable overall yield of 9%



Scheme 73 Total synthesis of propolisbenzofuran B **340**.



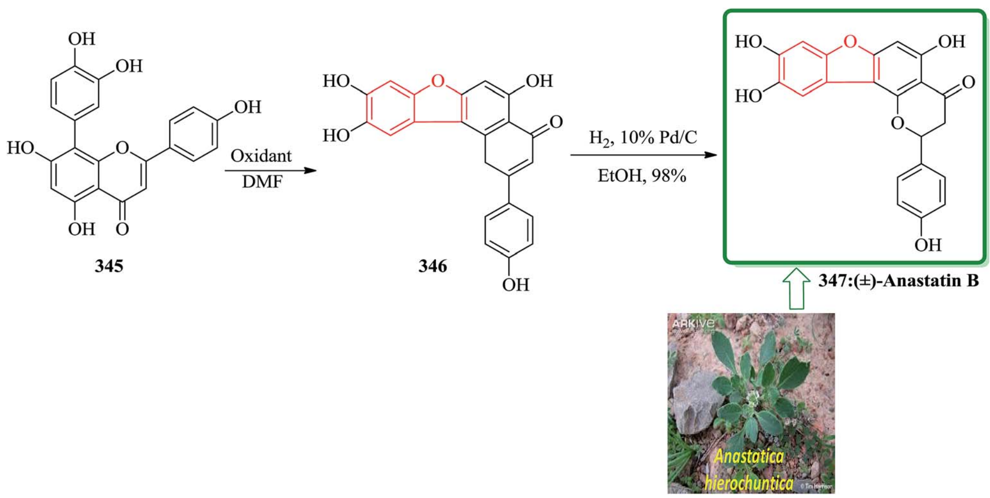
Scheme 74 Total synthesis of daphnodorin A **344**.

and 10%, respectively. The key intermediate **345** was synthesized in accordance with the procedure reported, previously.[325] Then, the stage was fixed for the assembly of the benzofuran moiety which was achieved through a one pot oxidation/oxa-Michael reaction using Ag_2O in DMF *via* cascade manner to afford compound **346** in 75% yield. Noticeably, the relatively low yield was probably due to decomposition of product **346** under influence of Ag_2O, which is used as oxidant with long reaction time. Upon hydrogenation of **346** in the presence of Pd/C, the total synthesis of (±)-anastatin B was completed. This hydrogenation step provided the natural product virtually in quantitative yield (Scheme 75).[326]

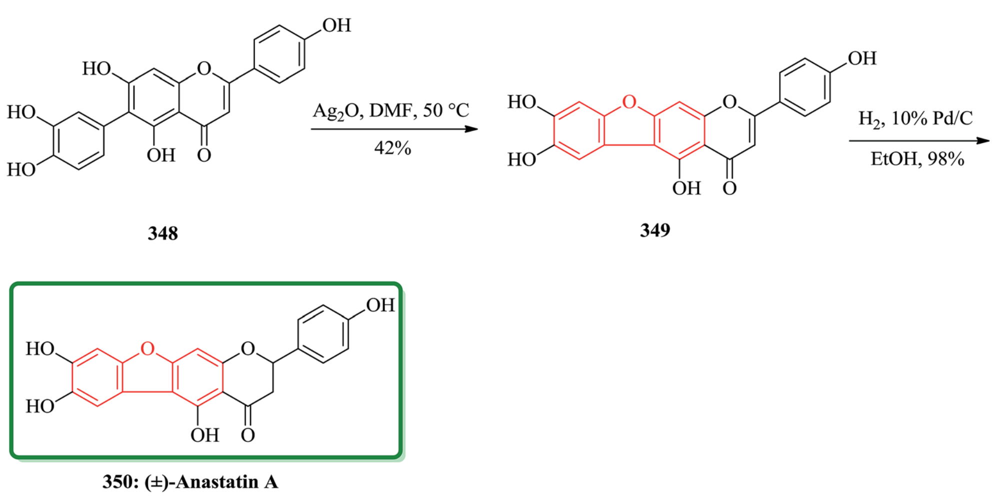
Moreover, the synthesis of (±)-anastatin A **350** was achieved in similar way. Intermediate **348** under the same conditions afforded compound **349** in 41% yields, starting from intermediate **348**. However, in this case the regioselectivity of the intramolecular Michael addition for the construction of the cyclized product **349** is significant. The possible regioisomer causing from cyclization of the 5-OH group onto the *ortho* quinone intermediate was not constructed and even detected. Compound **349**, upon hydrogenation on 10% Pd/C in ethanol gave the desired (±)-anastatin A **350** (Scheme 76).[326]

Vialinin C **355** was initially isolated from dry fruiting bodies of non-poisonous and eatable Chinese mushroom, *Thelephora vialis*. Ganbajunin B **356** has the same origin as C **355**. The structures of **355** and ganbajunin B **356** were established unambiguously, only after they were synthesized. The total synthesis of compounds **355** and **356** has been achieved and revealed very recently.[327] Compound **354**, which contains benzofuran moiety was synthesized from the reaction of sequential Suzuki–Miyaura coupling.[328] The reaction of **351**, **352** and **353** gave **354** which after several steps gave the desired natural product **355** in satisfactory overall yield. In another route, the benzofuran derivative **354** was also used as a precursor for the synthesis of ganbajunin B **356** in 30% overall yield (Scheme 77).[329]

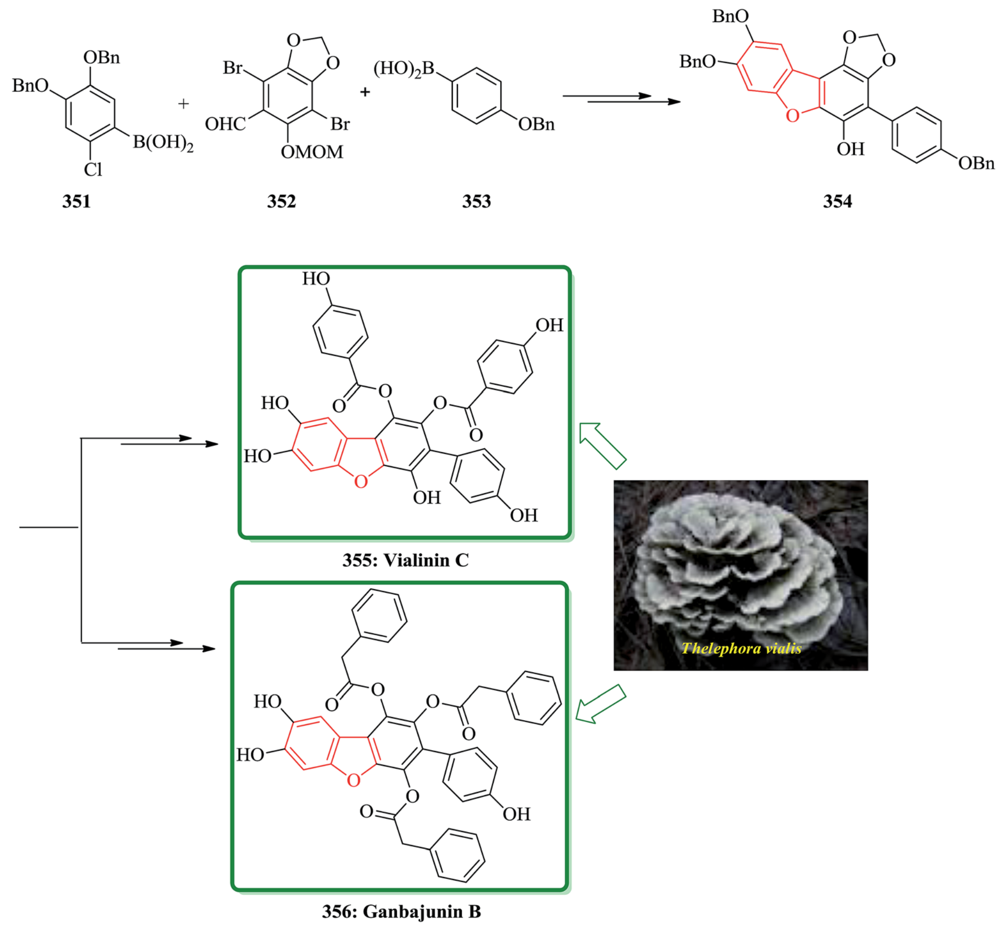
The naturally occurring compound diptoindonesin (Dip) G **293** was initially isolated from tree barks of *Hopea mengarawan* in Indonesia[282] and from *Hopea chinensis* stem barks in China.[283] Dip G has a tetracyclic core with A–D rings bearing



Scheme 75 Total synthesis of (±)-anastatins B **347**.



Scheme 76 Total synthesis of flavones (±)-anastatins A **350**.

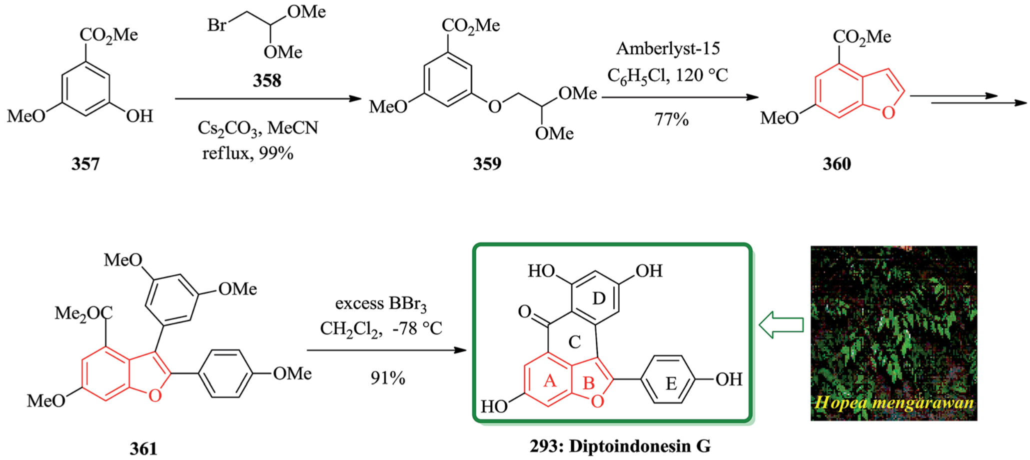


Scheme 77 Total synthesis of vialinin C **355** and ganbajunin B **356**.

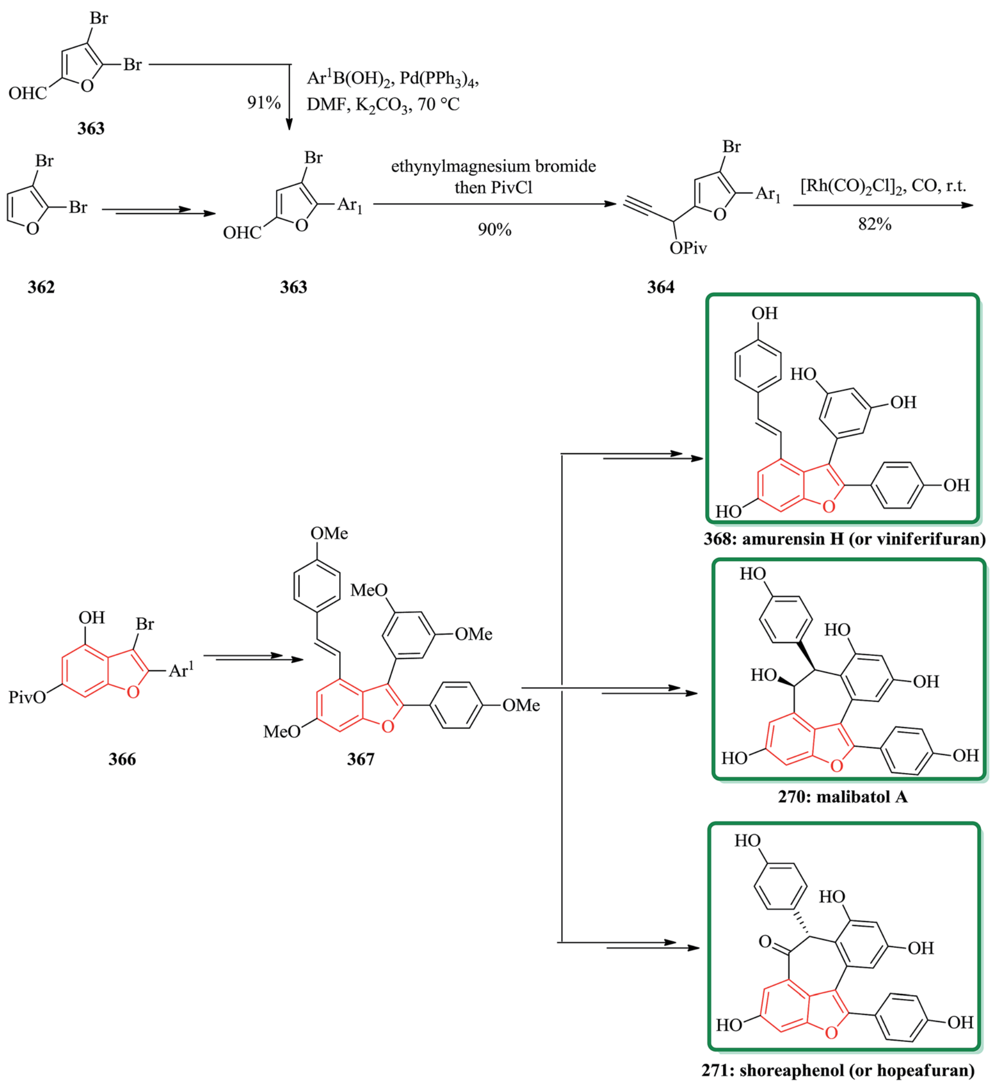
a ketone and three phenolic OH groups and also involves an additional E-ring bearing one more phenolic OH group. Dip G **293** exhibited anti-proliferation effect in murine leukemia P-388 cells.[282] A convergent synthetic approach for the total synthesis of diptoindonesin G **293** has been achieved and reported by Tang and co-workers in 2009.[330] The protocol comprises a regioselective dehydrative cyclization of arylacetals, a regioselective bromination of benzofurans, a sequential cross-coupling of bromo-benzofurans with aryl boronicacids and a BBr_3-mediated tandem cyclization and demethylation. This approach started with commercially available mono-protected resorcinol derivative **357**. The latter can be converted into the benzofuran core **360** by the sequence of alkylation with bromodimethylacetal and cyclodehydration *via* an intermediate **359** using Amberlyst-15.[331] Notably the cyclization was taken place regioselectively, which is consistent with similar reactions reported previously.[331] Compound **360** was transformed into penultimate intermediate **361** in several steps including cross-coupling with 3,5-dimethoxyphenyl boronic acid, which occurred at high temperature. The desired target Dip G **293** was synthesized from **361** *via* BBr_3 mediated tandem cyclization and demethylation in accordance with the procedure reported, previously (Scheme 78).[287]

A diverse total synthetic approach for the total synthesis of several natural products containing highly substituted benzofuran starting from furan derivatives has been achieved and reported by Tang and co-workers.[332] The key step in their strategy was Rh-catalyzed carbonylative benzannulation methodology, which led to the formation of various highly substituted benzofurans present in natural products. This protocol started with market purchasable or readily accessible 2,3-dibromofuran **362**. In this line, Tang and their research group accomplished and reported the first formal total synthesis of natural products amurensin H (or viniferifuran) **368**, malibatol A **270** and shoreaphenol (or hopeafuran) **271** containing benzofuran scaffold *via* Rh-catalyzed benzannulation. Initially, dibromofuran **362** or dibromofurfural **363** was converted to **365** (Scheme 79). This group tried to find that the key benzannulation reaction worked smoothly for substrate **365**, which bears a smaller bromine substituent. Then substrate **365** provided the highly substituted benzofuran core **366**. After several steps, permethylated precursor **367** was produced, which was then converted to natural products *via* different routs[333,334] to **368**, **270** and **271**.[332]

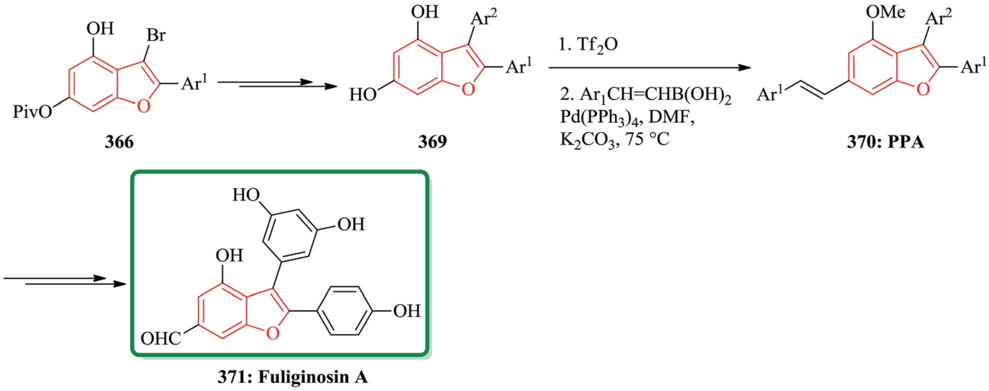
Alternatively, compound **366** was converted into intermediate **369**, the latter was subjected to methylation with subsequent cross-coupling with $Ar_2B(OH)_2$ followed by removal of



Scheme 78 Total synthesis of diptoindonesin (Dip) G **293**.



Scheme 79 Formal synthesis of benzofuran-containing natural products amurensin H (or viniferifuran) **368**, malibatol A **270**, shoreaphenol (or hopeafuran) **271** *via* Rh-catalyzed benzannulation.



Scheme 80 Synthesis of PPA **370** and fuliginosin A **371**.

pivalate gave the desired benzofuran, which could be transformed to anti-proliferation compound PAA **370** and natural product fuliginosin A **371** in two and four steps, respectively, *via* different functional group transformations. This is the first strategy for the total synthesis of fuliginosin A. It is also an example of the confirmation of structure of a natural product by its total synthesis. The overall yields for **370** and **371** are 24.3% and 3.6%, respectively, starting form **363** (Scheme 80).[332]

3 Conclusion

Benzofurans are significant moiety in a wide range of biologically potent naturally occurring compounds as well as synthetic products. Investigation on natural products including benzofuran has extraordinarily improved during the past few decades. New discovered naturally occurring compounds having complex structures have been extracted, well characterized, demonstrated important biological activities, therefore synthesized from commercially accessible or easily available starting precursors. Because of this extensive scope of biological properties, from long time ago, benzofurans have attracted the attentions and stirred up the interests of several research groups. Several of them display antimicrobial, anticancer, antioxidant, immune modulatory and anti-inflammatory activities. Benzo[*b*]furans have also attracted massive interest because of their existence in natural products, biologically active compounds, and other molecules of medicinal interest. In this review, we tried to highlight the total synthesis of natural product containing benzofuran moiety, since they have been found being a foremost source of drug discovery and drug development for a wide variety of diseases. The benzofuran framework can be labeled a 'skeleton key' as it is an unprecedented core in diverse compounds acting at different targets to inspire variety of pharmacological activities having various substitution patterns.

Abbreviations

(PTP-1B)	Protein tyrosine phosphatase inhibitors
(NTI)	Naltrindole
(DMAP)	*N*,*N*-dimethylpyridin-4-amine
(DEAD)	Diethyl azodicarboxylate
(DMF-DMA)	*N*,*N*-Dimethylformamide dimethyl acetal
(DDQ)	2,3-Dichloro-5,6-dicyano-*p*-benzoquinone
(PEP)	Prolyl endopeptidase
(CDC)	Cross-dehydrogenative coupling
(MW)	Microwave irradiation
(IMHA)	Intramolecular hydroarylation
(Dip)	Diptoindonesin

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References

1 P. Cagniant and D. Cagniant, *Adv. Heterocycl. Chem.*, 1975, **18**, 337–482.
2 C. W. Bird and G. W. H. Cheeseman, in *Compr. Heterocycl. Chem.*, ed. Katritzky, A. R., Pergamon, New York, 1984, vol. 4, pp. 89–153.
3 D. M. X. Donelly and M. J. Meegan, in *Compr. Heterocycl. Chem.*, ed. Katritzky, A. R., Pergamon, New York, 1984, vol. 4, pp. 657–712.
4 P. C. Stevenson, M. S. J. Simmonds, M. A. Yule, N. C. Veitch, G. C. Kite, D. Irwin and M. Legg, *Phytochemistry*, 2003, **63**, 41–46.
5 H. Tanaka, T. Oh-Uchi, H. Etoh, M. Sako, M. Sato, T. Fukai and Y. Teteishi, *Phytochemistry*, 2003, **63**, 597–602.
6 Z. Ali, T. Tanaka, I. Iliya, M. Iinuma, M. Furusawa, T. Ito, K.-I. Nakaya, J. Murata and D. Darnaedi, *J. Nat. Prod.*, 2003, **66**, 558–560.
7 G. K. Rao, K. N. Venugopala and P. N. S. Pai, *J. Pharmacol. Toxicol.*, 2007, **2**, 481–488.

8 M. Koca, S. Servi, C. Kirilmis, M. Ahmedzade, C. Kazaz, B. Özbek and G. Ötük, *Eur. J. Med. Chem.*, 2005, **40**, 1351–1358.
9 L. Pieters, S. V. Dyck, M. Gao, R. Bai, E. Hamel, A. Vlietinck and G. Lemiére, *J. Med. Chem.*, 1999, **42**, 5475–5481.
10 K. M. Dawood, H. Abdel-Gawad, E. A. Rageb, M. Ellithey and H. A. Mohamed, *Bioorg. Med. Chem.*, 2006, **14**, 3672–3680.
11 K. Tsujihara, M. Hongu, K. Saito, H. Kawanishi, K. Kuriyama, M. Matsumoto, A. Oku, K. Ueta, M. Tsuda and A. Saito, *J. Med. Chem.*, 1999, **42**, 5311–5324.
12 Y. Liao, A. P. Kozikowski, A. Guidotti and E. Costa, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 2099–2102.
13 A. H. Banskota, Y. Tezuka, K. Midorikawa, K. Matsushige and S. Kadota, *J. Nat. Prod.*, 2000, **63**, 1277–1279.
14 M. Ono, H. Kawashima, A. Nonaka, T. Kawai, M. Haratake, H. Mori, M. Kung, H. F. Kung, H. Saji and M. Nakayama, *J. Med. Chem.*, 2006, **49**, 2725–2730.
15 D. Manish, B. K. Tripathi, A. K. Tamrakar, A. K. Srivastava, B. Kumar and A. Goel, *Bioorg. Med. Chem.*, 2007, **15**, 727–734.
16 D. H. Choi, J. W. Hwang, H. S. Lee, D. M. Yang and J. G. Jun, *Bull. Korean Chem. Soc.*, 2008, **29**, 1594–1596.
17 Z. Liu, G. Xia, S. Chen, Y. Liu, H. Li and Z. She, *Mar. Drugs*, 2014, **12**, 3669–3680.
18 F. Xu, Y. Zhang, J. Wang, J. Pang, C. Huang, X. Wu, Z. She, L. L. P. Vrijmoed, E. B. Gareth Jones and Y. Lin, *J. Nat. Prod.*, 2008, **71**, 1251–1253.
19 P. Dawson, J. Opacka-Juffry, J. D. Moffatt, Y. Daniju, N. Dutta, J. Ramsey and C. Davidson, *Biol. Psychiatry*, 2014, **48**, 57–63.
20 N. Maggi, C. R. Pasqualucci, R. Ballotta and P. Sensi, *Chemotherapy*, 1966, **11**, 285–292.
21 M. Sofuoglu, P. S. Portoghese and A. E. Takemori, *J. Pharmacol. Exp. Ther.*, 1991, **257**, 676–680.
22 G. V. Naccarelli, D. L. Wolbrette, H. M. Patel and J. C. Luck, *Current Opinion in Cardiology*, 2000, **15**, 64–72.
23 S. Kathofer, D. Thomas and C. A. Karle, *Cardiovasc. Drug Rev.*, 2005, **23**, 217–230.
24 Q. Wu, L. A. Christensen, R. J. Legerski and K. M. Vasquez, *EMBO Rep.*, 2005, **6**, 551–557.
25 E. G. Schneiders and R. Stevensonm, *J. Org. Chem.*, 1979, **44**, 4710–4711.
26 F. G. Schreiber and R. Stevenson, *J. Chem. Soc., Perkin Trans. 1*, 1976, **1**, 1514–1518.
27 R. L. Shriner and P. McCutchan, *J. Am. Chem. Soc.*, 1929, **81**, 2193–2195.
28 M. W. Rathke, *J. Am. Chem. Soc.*, 1970, **92**, 3222–3223.
29 M. W. Rathke and D. F. Sullivan, *J. Am. Chem. Soc.*, 1973, **95**, 3050–3051.
30 S. Y. Lin, C.-L. Chen and Y.-J. Lee, *J. Org. Chem.*, 2003, **68**, 2968–2971.
31 W. S. Sheen, I. L. Tsai, C. M. Teng and I. S. Chen, *Phytochemistry*, 1994, **36**, 213–215.
32 C. L. Kao and J. W. Chern, *Tetrahedron Lett.*, 2001, **42**, 1111–1113.
33 C. L. Kao and J. W. Chern, *J. Org. Chem.*, 2002, **67**, 6772–6787.
34 C. Fuganti and S. A. Serra, *Tetrahedron Lett.*, 1998, **39**, 5609–5610.
35 R. Basawaraj, B. Yadav and S. S. Sangapure, *Indian J. Heterocycl. Chem.*, 2001, **11**, 31–34.
36 S. M. Rida, S. A. M. El-Hawash, H. T. Y. Fahmy, A. A. Hazzaa and M. M. M. El-Meligy, *Arch. Pharmacal Res.*, 2006, **29**, 826–833.
37 R. K. Ujjinamatada, R. S. Appala and Y. S. Agasimundin, *J. Heterocycl. Chem.*, 2006, **43**, 437–441.
38 S. Wachi, K. Takagi, G. Menichi and M. Hubert-Habart, *Bull. Soc. Chem.*, 1978, **56**, 230–233.
39 D. V. Singh, A. R. Mishra, R. M. Mishra, A. K. Pandey, C. R. Singh and A. K. Dwivedi, *Indian J. Heterocycl. Chem.*, 2005, **14**, 319–322.
40 A. M. Farag, A. S. Mayhoub, S. E. Barakat and A. H. Bayomi, *Bioorg. Med. Chem.*, 2008, **16**, 4569–4578.
41 B. Insuasty, A. Tigreros, F. Orozco, J. Quiroga, R. Abonia, M. Nogueras, A. Sanchez and J. Cobo, *Bioorg. Med. Chem.*, 2010, **18**, 4965–4974.
42 A. M. Farag, A. S. Mayhoub, S. E. Barakat and A. H. Bayomi, *Bioorg. Med. Chem.*, 2008, **16**, 881–889.
43 I. M. El-Deeb and S. H. Lee, *Bioorg. Med. Chem.*, 2010, **18**, 3961–3973.
44 B. S. Holla, P. M. Akberali and M. K. Shivananda, *Il Farmaco*, 2000, **55**, 256–263.
45 A. Mustafa, C. A. Hismat and M. M. J. Yannis, *J. Prakt. Chem.*, 1970, **312**, 1011–1019.
46 M. H. Elnagdi, M. R. H. Elmoghayor, E. A. A. Hafez and H. H. Alnima, *J. Org. Chem.*, 1975, **40**, 2604–2607.
47 H. G. Garg, *J. Med. Chem.*, 1972, **15**, 446–447.
48 F. Manna, F. Chementi, R. Fioravanti and A. Bolasco, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 4632–4635.
49 J. H. Ahn, H. M. Kim, S. H. Jung, S. K. Kang, K. R. Kim, S. D. Rhea, S. D. Yong, H. G. Cheon and S. S. Kim, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 4461–4465.
50 R. V. Ragavan, V. Vijayakumar and N. S. Kumari, *Eur. J. Med. Chem.*, 2010, **45**, 1173–1180.
51 Y. R. Prasad, A. L. Rao, L. Prasoona, K. Murali and K. P. Ravi, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 5030–5034.
52 J. C. Jung, E. B. Watkins and M. A. Avery, *Heterocycles*, 2005, **65**, 77–94.
53 A. E. Rashad, M. I. Hegab, R. E. Abdel-Megeid, J. A. Micky and F. M. E. Abdel-Megeid, *Bioorg. Med. Chem.*, 2008, **16**, 7102–7106.
54 P. D. Seemuth and H. Zimmer, *J. Org. Chem.*, 1978, **43**, 3063–3065.
55 B. Ledoussal, A. Gorgues and A. Le Coq, *J. Chem. Soc., Chem. Commun.*, 1986, 171–172.
56 L. Abmann and W. Friedrichsen, *Heterocycles*, 1989, **29**, 1003–1004.
57 A. Arcadi, S. Cacchi, M. Del Rosario, G. Fabrizi and F. Marinelli, *J. Org. Chem.*, 1996, **61**, 9280–9288.
58 I. Nakamura, Y. Mizushima and Y. Yamamoto, *J. Am. Chem. Soc.*, 2005, **127**, 15022–15023.
59 X. Z. Jiang, W. L. Liu, W. Zhang, F. Q. Jiang, Z. Gao, H. Zhuang and L. Fu, *Eur. J. Med. Chem.*, 2011, **46**, 3526–3530.
60 A. Hercouet and M. Le Corre, *Tetrahedron*, 1981, **37**, 2867–2873.

61 L. Capuano, S. Drescher, V. Hammerer and M. Hanisch, *Chem. Ber.*, 1988, **121**, 2259–2261.
62 (*a*) S. Ghosh and J. Das, *Tetrahedron Lett.*, 2011, **52**, 1112–1116; (*b*) S.-E. Syu, Y.-T. Lee, Y.-J. Jang and W. Lin, *Org. Lett.*, 2011, **13**, 2970–2973.
63 Y. Liu, H. K. Jacobs and A. S. Gopalan, *Tetrahedron Lett.*, 2011, **52**, 2935–2939.
64 D. C. Schroeder, P. O. Corcoran, C. A. Holden and M. C. Mulligan, *J. Org. Chem.*, 1962, **27**, 586–591.
65 G. Lamotte, P. Demerseman and R. Royer, *Synthesis*, 1984, 1068–1070.
66 W. T. Brady and Y. F. Giang, *J. Org. Chem.*, 1986, **51**, 2145–2147.
67 J. K. MacLeod and B. R. Worth, *Tetrahedron Lett.*, 1972, **13**, 237–240.
68 J. Einhorn, P. Demerseman and R. Royer, *J. Heterocycl. Chem.*, 1985, **22**, 1243–1247.
69 G. Pandey, A. Krishna and U. T. Bhalerao, *Tetrahedron Lett.*, 1989, **30**, 1867–1870.
70 Y. Liu, J. Qian, S. Lou and Z. Xu, *J. Org. Chem.*, 2010, **75**, 6300–6303.
71 S. W. Youn and J. I. Eom, *Org. Lett.*, 2005, **7**, 3355–3358.
72 M. Murai, K. Miki and K. Ohe, *Chem. Commun.*, 2009, 3466–3468.
73 A. Hiremathad, M. R. Patil, K. R. Chethana, K. Chand, M. A. Santos and R. S. Keri, *RSC Adv.*, 2015, **5**, 96809–96828.
74 G. Khodarahmi, P. Asadi, F. Hassanzadeh and E. Khodarahmi, *J. Res. Med. Sci.*, 2015, **20**, 1094–1104.
75 C. Selvam, B. C. Jordan, S. Prakash, D. Mutisya and R. Thilagavathi, *Eur. J. Med. Chem.*, 2017, **128**, 219–236.
76 K. C. Rajeshwari, A. Hiremathad, M. Singh, M. A. Santos and R. S. Keri, *Pharmacol. Rep.*, 2017, **69**, 281–295.
77 (*a*) M. M. Heravi and B. Talaei, *Adv. Heterocycl. Chem.*, 2016, **118**, 195–291; (*b*) M. M. Heravi and B. Talaei, *Adv. Heterocycl. Chem.*, 2015, **114**, 147–225; (*c*) M. M. Heravi and V. Fathi Vavsari, *Adv. Heterocycl. Chem.*, 2015, **114**, 77–145; (*d*) M. M. Heravi and B. Talaei, *Adv. Heterocycl. Chem.*, 2014, **113**, 143–244.
78 M. M. Heravi and V. Zadsirjan, *Adv. Heterocycl. Chem.*, 2015, **117**, 261–376.
79 M. M. Heravi, S. Khaghaninejad and N. Nazari, *Adv. Heterocycl. Chem.*, 2014, **112**, 183–234.
80 M. M. Heravi, S. Khaghaninejad and M. Mostofi, *Adv. Heterocycl. Chem.*, 2014, **112**, 1–50.
81 S. Khaghaninejad and M. M. Heravi, *Adv. Heterocycl. Chem.*, 2014, **111**, 95–146.
82 M. M. Heravi and T. Alishiri, *Adv. Heterocycl. Chem.*, 2014, **113**, 1–66.
83 M. M. Heravi and B. Talaei, *Adv. Heterocycl. Chem.*, 2017, **122**, 43–114.
84 V. Zadsirjan, M. Shiri, M. M. Heravi, T. Hosseinnejad, S. A. Shintre and N. A. Koorbanally, *Res. Chem. Intermed.*, 2017, **43**, 2119–2142.
85 (*a*) R. Mirsafaei, M. M. Heravi and S. Ahmadi, *J. Mol. Catal. A: Chem.*, 2015, **402**, 100–108; (*b*) M. M. Heravi, E. Hashemi, Y. S. Beheshtiha, S. Ahmadi and T. Hosseinnejad, *J. Mol. Catal. A: Chem.*, 2014, **394**, 74–82.
86 M. M. Heravi, E. Hashemi, Y. S. Beheshtiha, K. Kamjou, M. Toolabi and N. Hosseintash, *J. Mol. Catal. A: Chem.*, 2014, **392**, 173–180.
87 M. M. Heravi, F. Mousavizadeh, N. Ghobadi and M. Tajbakhs, *Tetrahedron Lett.*, 2104, **55**, 1226–1228.
88 M. M. Heravi, M. Khorasani and F. Derikvand, *Catal. Commun.*, 2007, **8**, 1886–1890.
89 M. M. Heravi, M. Daraie and V. Zadsirjan, *Mol. Diversity*, 2015, **15**, 577–623.
90 M. M. Heravi and V. F. Vavsari, *RSC Adv.*, 2015, **5**, 50890–50912.
91 M. M. Heravi, T. B. Lashaki and N. Poorahmad, *Tetrahedron: Asymmetry*, 2015, **26**, 405–495.
92 M. M. Heravi, E. Hashemi and N. Nazari, *Mol. Diversity*, 2014, **18**, 441–472.
93 M. M. Heravi, E. Hashemi and F. Azimian, *Tetrahedron*, 2014, **70**, 7–21.
94 M. M. Heravi, E. Hashemi and N. Ghobadi, *Curr. Org. Chem.*, 2013, **17**, 2192–2224.
95 M. M. Heravi and E. Hashemi, *Tetrahedron*, 2012, **68**, 9145–9178.
96 M. M. Heravi, V. Zadsirjan and M. Dehghani, *Curr. Org. Chem.*, 2016, **20**, 1069–1134.
97 M. M. Heravi and V. Zadsirjan, *Curr. Org. Synth.*, 2016, **13**, 780–833.
98 R. S. Ward, *Chem. Soc. Rev.*, 1982, **11**, 75–125.
99 R. S. Ward, *Tetrahedron*, 1990, **46**, 5029–5041.
100 Z. Yang, H. B. Liu, C. M. Lee, H. M. Chang and H. N. C. Wong, *J. Org. Chem.*, 1992, **57**, 7248–7257.
101 S. A. Hutchinson, H. Liitjens and P. J. Scammells, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 3081–3084.
102 P. J. Scammells, S. P. Baker and A. R. Beauglehole, *Bioorg. Med. Chem.*, 1998, **6**, 1517–1524.
103 Y. H. Kuo and C. H. Wu, *J. Nat. Prod.*, 1996, **59**, 625–628.
104 M. M. Heravi and S. Sadjadi, *Tetrahedron*, 2009, **65**, 7761–7775.
105 H. Lütjens and P. J. Scammells, *Tetrahedron Lett.*, 1998, **39**, 6581–6584.
106 M. Inoue, M. W. Carson, A. J. Frontier and S. J. Danishefsky, *J. Am. Chem. Soc.*, 2001, **123**, 1878–1889.
107 R. Segal, I. M. Goldzweig, S. Sokolo and D. V. Zaitschek, *J. Chem. Soc. C*, 1967, 2402–2404.
108 (*a*) Q. L. Li, B. G. Li, H. Y. Qi, X. P. Gao and G. L. Zhang, *Planta Med.*, 2005, **71**, 847–851; (*b*) M. Takanashi, Y. Takizawa and T. Mitsuhashi, *Chem. Lett.*, 1974, 869.
109 T. Hirano, M. Goto and K. Oka, *Life Sci.*, 1994, **55**, 1061–1069.
110 M. M. Heravi and Z. Faghihi, *Curr. Org. Chem.*, 2012, **16**, 2097–2123.
111 X. F. Duan, G. Shen and Z. B. Zhang, *Synthesis*, 2010, **7**, 1181–1187.
112 C. E. Castro, E. J. Gaughan and D. C. Owsley, *J. Org. Chem.*, 1966, **31**, 4071.
113 R. D. Stephens and C. E. Castro, *J. Org. Chem.*, 1963, **28**, 3313–3315.
114 (*a*) A. Galet, *J. Am. Chem. Soc.*, 1946, **68**, 376–377; (*b*) H. Hellmann and W. Elser, *Justus Liebigs Annalen der Chemie*, 1961, **639**, 77.

115 Z. Yang, P. M. Hon, K. Y. Chui, Z. L. Xu, H. M. Chang, C. M. Lee, Y. X. Cui, H. N. C. Wong, C. D. Poon and B. M. Fung, *Tetrahedron Lett.*, 1991, **32**, 2061–2064.
116 H. B. Bang, S. Y. Han, D. H. Choi, D. M. Yang, J. W. Hwang, H. S. Lee and J.-G. Jun, *Synth. Commun.*, 2009, **39**, 506–515.
117 K. Kawazu, *Agric. Biol. Chem.*, 1980, **44**, 1367–1372.
118 Y. Fukuyama, M. Nakahara, H. Minami and M. Kodama, *Chem. Pharm. Bull.*, 1996, **44**, 1418–1420.
119 (*a*) F. Toda and M. Nakagawa, *Bull. Chem. Soc. Jpn.*, 1959, **32**, 514–516; (*b*) I. Candiani, S. DeBemardinis, W. Cabri, M. Marchi, A. Bedeschi and S. Penco, *Synlett*, 1993, 9–69; (*c*) K. Hiroya, K. Hashimura and K. Ogasawara, *Heterocycles*, 1994, **38**, 2463–2472.
120 A. Sakai, T. Aoyama and T. Shioiri, *Tetrahedron Lett.*, 1999, **40**, 4211–4214.
121 H.-D. Choi, P. J. Seo and B.-W. Son, *Arch. Pharmacal Res.*, 2002, **25**, 786–789.
122 (*a*) B. F. Bowden, E. Ritchie and W. C. Taylor, *Aust. J. Chem.*, 1972, **25**, 2659–2669; (*b*) K. Picker, E. Ritchie and W. C. Taylor, *Aust. J. Chem.*, 1973, **26**, 1111–1119; (*c*) R. W. Read and W. C. Taylor, *Aust. J. Chem.*, 1979, **32**, 2317–2321; (*d*) A. R. Carroll and W. C. Taylor, *Aust. J. Chem.*, 1991, **44**, 1615–1626; (*e*) A. R. Carroll and W. C. Taylor, *Aust. J. Chem.*, 1991, **44**, 1627–1633.
123 T. A. Engler and W. Chai, *Tetrahedron Lett.*, 1996, **37**, 6969–6970.
124 W. J. Gensler and J. E. Stouffer, *J. Org. Chem.*, 1958, **23**, 908–910.
125 T. Bach and M. Bartels, *Tetrahedron Lett.*, 2002, **43**, 9125–9127.
126 (*a*) R. Ahmed and R. Stevenson, *Phytochemistry*, 1975, **14**, 2710–2712; (*b*) B. A. McKittrick and R. Stevenson, *J. Chem. Soc., Perkin Trans. 1*, 1983, 475–482; (*c*) T. A. Engler, W. Chai and K. O. LaTessa, *J. Org. Chem.*, 1996, **61**, 9297–9308; (*d*) T. A. Engler and W. Chai, *Tetrahedron Lett.*, 1996, **37**, 6969–6970.
127 T. Benincori, E. Brenna, F. Sannicolo, L. Trimarco, P. Antognazza, E. Cesarotti, F. Demartin and T. Pilati, *J. Org. Chem.*, 1996, **61**, 6244–6251.
128 T. Bach and M. Bartels, *Synthesis*, 2003, **6**, 925–939.
129 (*a*) T. J. Jackson and J. W. Herndon, *Tetrahedron*, 2001, **57**, 3859–3868; (*b*) J. W. Herndon, Y. Zhang, H. Wang and K. Wang, *Tetrahedron Lett.*, 2000, **41**, 8687–8690; (*c*) J. W. Herndon and A. Hayford, *Organometallics*, 1995, **14**, 1556–1558; (*d*) J. W. Herndon and H. Wang, *J. Org. Chem.*, 1998, **63**, 4562–4563; (*e*) Y. Zhang and J. W. Herndon, *Tetrahedron*, 2000, **56**, 2175–2184; (*f*) M. L. Waters, M. E. Bos and W. D. Wulff, *J. Am. Chem. Soc.*, 1999, **121**, 6403–6413.
130 A. Rahm and W. D. Wulff, *J. Am. Chem. Soc.*, 1996, **118**, 1807–1808.
131 R. S. Ward, *Nat. Prod. Rep.*, 1999, **16**, 75–96.
132 (*a*) R. S. Mali and A. P. Massey, *J. Chem. Res., Synop.*, 1998, 230–231; (*b*) Y. Aoyagi, T. Mizusaki, A. Hatori, T. Asakura, T. Aihara, S. Inaba, K. Hayatsu and A. Ohta, *Heterocycles*, 1995, **41**, 1077–1084; (*c*) F. G. Schreiber and R. Stevenson, *Chem. Lett.*, 1975, 1257–1258; (*d*) E. Ritchie and R. Taylor, *Aust. J. Chem.*, 1969, 1329–1330.
133 A. M. Puentes de Diaz, *Phytochemistry*, 1997, **44**, 345–346.
134 A. De Meijere, H. Schirmer and M. Duetsch, *Angew. Chem., Int. Ed.*, 2000, **39**, 3964–4002.
135 K. H. Dotz and P. Tomuschat, *Chem. Soc. Rev.*, 1999, **28**, 187–198.
136 A. De Meijere, *Pure Appl. Chem.*, 1996, **68**, 61–72.
137 G. B. Stone and L. S. Liebeskind, *J. Org. Chem.*, 1990, **55**, 4614–4622.
138 J. Zhang, Y. Zhang, Y. Zhang and J. W. Herndon, *Tetrahedron*, 2003, **59**, 5609–5616.
139 (*a*) T. O. Cheng, *Int. J. Cardol.*, 2007, **121**, 9–22; (*b*) X. B. Wang, S. L. Morris-Natschke and K. H. Lee, *Med. Res. Rev.*, 2007, **27**, 133–148; (*c*) L. Zhou, Z. Zuo and M. S. Chow, *J. Clin. Pharmacol.*, 2005, **45**, 1345–1359.
140 (*a*) Y. R. Lu and L. Y. Foo, *Tetrahedron Lett.*, 2001, **42**, 8223–8225; (*b*) X. N. Yang, Y. J. Wang, Y. S. Liu and X. Tang, *J. Ethnopharmacol.*, 2008, **117**, 408–414; (*c*) X. S. Ouyang, K. Takahashi, K. Komatsu, N. Nakamura, A. H. Baba and J. Azuma, *Jpn. J. Pharmacol.*, 2001, **87**, 289–296; (*d*) Y. T. Wu, Y. F. Chen, Y. J. Hsieh, I. Jaw, M. S. Shiao and T. H. Tsai, *Int. J. Pharm.*, 2006, **326**, 25–31; (*e*) J. F. Zhao, C. H. Liu, Y. Y. Hu, L. M. Xu, P. Liu and C. Liu, *Hepatobiliary Pancreatic Dis. Int.*, 2004, **3**, 102–105.
141 Y. L. Lin, Y. Y. Chang, Y. H. Kuo and M. S. Shiao, *J. Nat. Prod.*, 2002, **65**, 745–747.
142 (*a*) C. H. Cho, B. Neuenswander, G. H. Lushington and R. C. Larock, *J. Comb. Chem.*, 2008, **10**, 941–947; (*b*) H. B. Bang, S. Y. Han, D. H. Choi, J. W. Hwang and J. G. Jun, *ARKIVOC*, 2009, **2**, 112–125; (*c*) J. R. Hwu, K. S. Chuang, S. H. Chuang and S. C. Tsay, *Org. Lett.*, 2005, **7**, 1545–1548.
143 S. D. Shen, G. P. Zhang, M. Leib and L. H. Hu, *ARKIVOC*, 2012, **4**, 204–213.
144 N. Takeda, O. Miyata and T. Naito, *Eur. J. Org. Chem.*, 2007, 1491–1509.
145 T. Pacher, C. Seger, D. Engelmeier, S. Vajrodaya, O. Hofer and H. Greger, *J. Nat. Prod.*, 2002, **65**, 820–827.
146 D. C. Chauret, C. B. Berrnard, J. T. Arnason and T. J. Durst, *J. Nat. Prod.*, 1996, **59**, 152–155.
147 S. B. Pandit and S. Y. Gadre, *Synth. Commun.*, 1988, **18**, 157–166.
148 J. Y. Pasturel, G. Solladie and J. Maignan, *Chem. Abstr.*, 2003, **139**, 36375–36377.
149 E. M. Bickoff, R. L. Lyman, A. L. Livingston and A. N. Booth, *J. Am. Chem. Soc.*, 1958, **80**, 3969–3971.
150 G. A. Kraus and N. Zhang, *J. Org. Chem.*, 2000, **65**, 5644–5646.
151 Y. R. Lee, J. Y. Suk and B. S. Kim, *Org. Lett.*, 2000, **2**, 1387–1389.
152 (*a*) I. Muhammad, X.-C. Li, M. R. Jacob, B. L. Tekwani, D. C. Dunbar and D. Ferreira, *J. Nat. Prod.*, 2003, **66**, 804–809; (*b*) I. Muhammad, X.-C. Li, D. C. Dunbar, M. A. ElSohly and I. A. Khan, *J. Nat. Prod.*, 2001, **64**, 1322–1325.

153 (*a*) O. Miyata, N. Takeda and T. Naito, *Org. Lett.*, 2004, **6**, 1761–1763; (*b*) N. Takeda, O. Miyata and T. Naito, *Eur. J. Org. Chem.*, 2007, 1491–9150.
154 H. J. Lee, Y. R. Lee and S. H. Kim, *Helv. Chim. Acta*, 2009, **92**, 1404–1412.
155 J. D. Lambert, R. O. Meyers, B. N. Timmermann and R. T. Dorr, *Cancer Lett.*, 2001, **171**, 47–56.
156 (*a*) O. Dann, J. Lang and H. Vohl, *Justus Liebigs Ann. Chem.*, 1960, **631**, 116–128; (*b*) S. Johann, B. B. Cota, E. M. Souza-Fagundes, M. G. Pizzolatti, M. A. Resende and C. L. Zani, *Mycoses*, 2009, **52**, 499–506.
157 L. Ruan, M. Shi, S. Mao, L. Yu, F. Yang and J. Tang, *Tetrahedron*, 2014, **70**, 1065–1070.
158 H. D. Choi, M. C. Ha, P. J. Seo, B. W. Son and J. C. Song, *Arch. Pharmacal Res.*, 2000, **23**, 438–440.
159 H. Okada, *J. Pharm. Soc. Jpn.*, 1915, 657–666.
160 C. Y. Hopkins, D. F. Ewing and M. J. Chisholm, *Can. J. Chem.*, 1967, **45**, 1425–1429.
161 Y. Luo, Z. He and H. Li, *Fitoterapia*, 2007, **78**, 211–214.
162 S. Kawai, T. Nakamura and N. Sugiyama, *Ber. Dtsch. Chem. Ges. A*, 1939, **72**, 1146–1149.
163 M. Takanashi and Y. Takizawa, *Phytochemistry*, 1988, **27**, 1224–1226.
164 E. W. Colvin and B. J. Hamill, *J. Chem. Soc., Perkin Trans. 1*, 1977, 869–874.
165 H. L. Teles, J. P. Hemerly, P. M. Pauletti, J. R. C. Pandolfi, A. R. Araujo, S. R. Valentini, M. C. M. Young, V. S. Bolzani and D. H. S. Silva, *Nat. Prod. Res.*, 2005, **19**, 319–323.
166 X. F. Duan, J. X. Feng and Z. B. Zhang, *Synthesis*, 2010, **3**, 0515–0519.
167 Y. Liu, M. Kubo and Y. Fukuyama, *J. Nat. Prod.*, 2012, **75**, 2152–2157.
168 (*a*) I.-K. Lee, J.-H. Lee and B.-S. Yun, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 4566–4568; (*b*) Y. Liu and F. Wang, *Carbohydr. Polym.*, 2007, **70**, 386–392.
169 P. Lan, M. G. Banwell and A. C. Willis, *J. Org. Chem.*, 2014, **79**, 2829–2842.
170 (*a*) M. G. Banwell, B. L. Flynn and S. G. Stewart, *J. Org. Chem.*, 1998, **63**, 9139–9144; (*b*) B. L. Flynn and M. G. Banwell, *Heterocycles*, 2012, **84**, 1141–1170.
171 C. Zhang, J. Liu and Y. Du, *Tetrahedron Lett.*, 2014, **55**, 959–961.
172 (*a*) M. Reiter, S. Ropp and V. Gouverneur, *Org. Lett.*, 2004, **6**, 91–94; (*b*) M. Reiter, H. Turner, R. Mills-Webb and V. Gouverneur, *J. Org. Chem.*, 2005, **70**, 8478–8485; (*c*) X. Liao, H. Zhou, X. Z. Wearing, J. Ma and J. M. Cook, *Org. Lett.*, 2005, **7**, 3501–3504; (*d*) T. Hayashi, K. Yamasaki, M. Mimura and Y. Uozumi, *J. Am. Chem. Soc.*, 2004, **126**, 3036–3037.
173 P. C. Stevenson and N. C. Veitch, *Phytochemistry*, 1998, **48**, 947–951.
174 Z. Novak, G. Timari and A. Kotschy, *Tetrahedron*, 2003, **59**, 7509–7513.
175 N. G. Kundu, M. Pal, J. S. Mahanty and M. De, *J. Chem. Soc., Perkin Trans. 1*, 1997, 2815–2820.
176 A. Arcadi and E. Marinelli, *Synthesis*, 1986, 749–751.
177 S. Torii, L. H. Xu and H. Okumoto, *Synlett*, 1992, 515–516.
178 S. N. Aslam, P. C. Stevenson, S. J. Phythian, N. C. Veitch and D. R. Hall, *Tetrahedron*, 2006, **62**, 4214–4226.
179 R. T. Scannell and R. Stevenson, *J. Heterocycl. Chem.*, 1980, **17**, 1727–1728.
180 Y. Jiang, B. Gao, W. Huang, Y. Liang, G. Huang and Y. Ma, *Synth. Commun.*, 2009, **39**, 197–204.
181 R. Stevenson and B. A. McKittrick, *J. Chem. Soc., Perkin Trans. 1*, 1983, 475–482.
182 T. Bach and M. Bartels, *Synthesis*, 2003, 925–939.
183 C. Eidamshaus and J. D. Burch, *Org. Lett.*, 2008, **10**, 4211–4214.
184 J. Jiang, J. B. Biggins and J. S. Thorson, *J. Am. Chem. Soc.*, 2000, **122**, 6803–6804.
185 J. M. Langenhan, B. R. Griffith and J. S. Thorson, *J. Nat. Prod.*, 2005, **68**, 1696–1711.
186 C. J. Thibodeaux, C. E. Melancon and H. W. Liu, *Angew. Chem., Int. Ed.*, 2008, **47**, 9814–9859.
187 S. M. Patel, M. d. l. Fuente, S. Ke and A. M. R. Guimaraes, *Chem. Commun.*, 2011, **47**, 10569–10571.
188 C. Albermann, A. Soriano, J. Jiang and H. Vollmer, *Org. Lett.*, 2003, **5**, 933–936.
189 H. Cheng, X. Cao, M. Xian and L. Fang, *J. Med. Chem.*, 2004, **48**, 645–652.
190 L. Morelli, A. Bernardi and S. Sattin, *Carbohydr. Res.*, 2014, **390**, 33–41.
191 (*a*) H. B. Bode and A. Zeeck, *J. Chem. Soc., Perkin Trans. 1*, 2000, 323–328; (*b*) H. B. Bode and A. Zeeck, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2665–2670.
192 Y. Yu, H. Men and C. Lee, *J. Am. Chem. Soc.*, 2004, **126**, 14720–14721.
193 T. Magauer, H. J. Martin and J. Mulzer, *Angew. Chem., Int. Ed.*, 2009, **48**, 6032–6036.
194 T. Magauer, H. J. Martin and J. Mulzer, *Chem.–Eur. J.*, 2010, **16**, 507–519.
195 P. Magnus and C. Lescop, *Tetrahedron Lett.*, 2001, **42**, 7193–7196.
196 L. Hoffmeister, P. Persich and A. Fürstner, *Chem.–Eur. J.*, 2014, **20**, 4396–4402.
197 F. Marion, D. E. Williams, D. O. Patrick, I. Hollander, R. Mallon, S. C. Kim, D. M. Roll, L. Feldberg, R. V. Soest and R. J. Andersen, *Org. Lett.*, 2006, **8**, 321–324.
198 H. Landelle, A. M. Godard, D. Laduree, E. Chenu and M. Robba, *Chem. Pharm. Bull.*, 1991, **39**, 3057–3060.
199 G. Mehta, N. S. Likhite and C. S. A. Kumar, *Tetrahedron Lett.*, 2009, **50**, 5260–5262.
200 A. C. Anderson and D. L. Wright, *Org. Biomol. Chem.*, 2009, **7**, 840–850.
201 J. H. George, J. E. Baldwin and R. M. Adington, *Org. Lett.*, 2010, **12**, 2394–2397.
202 (*a*) B. Vanhaesebroeck, L. Stephens and P. Hawkins, *Nat. Rev. Mol. Cell Biol.*, 2012, **13**, 195–203; (*b*) M. P. Wymann and C. Schultz, *ChemBioChem*, 2012, **13**, 2022–2035.
203 (*a*) V. Deore, M. Kumar Lohar, R. Mundada, A. Roychowdhury, R. Vishwakarma and S. Kumar, *Synth. Commun.*, 2011, **41**, 177–183; (*b*) T. Kamishima, T. Kikuchi, K. Narita and T. Katoh, *Eur. J. Org. Chem.*, 2014, 3443–3450.

204 (*a*) A. Shirata, K. Takahashi, M. Taksugi, S. Nago, S. Ishikawa, S. Ueno, L. Munoz and T. Masamune, *Bull. Seric. Exp. Stn.*, 1983, **28**, 793; (*b*) F. Ferrari, F. D. Monache, R. S. Compagnone, A. I. Suarez and S. Tillett, *Fitoterapia*, 1998, **69**, 554–555; (*c*) L. Cui, M. Na, H. Oh, E. Y. Bae, D. G. Jeong, S. E. Ryu, S. Kim, B. Y. Kim, W. K. Oh and J. S. Ahn, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 1426–1429.
205 R. Kakarla, M. Ghosh, J. A. Anderson, R. G. Dulina and M. J. Sofia, *Tetrahedron Lett.*, 1999, **40**, 5–8.
206 N. Kaur, Y. Xia, Y. Jin, N. T. Dat, K. Gajulapati, Y. Choi, Y. S. Hong, J. J. Lee and K. Lee, *Chem. Commun.*, 2009, 1879–1881.
207 T. Gibtner, F. Hampel, J. P. Gisselbrecht and A. Hirsch, *Chem.–Eur. J.*, 2002, **8**, 408–432.
208 Y. Xia, Y. Jin, N. Kaur, Y. Choi and K. Lee, *Eur. J. Med. Chem.*, 2011, **46**, 2386–2396.
209 A. J. Weinheimer and P. H. Washecheck, *Tetrahedron Lett.*, 1969, 3315–3318.
210 F. Kido, Y. Noda, T. Maruyama, C. Kabuto and A. Yoshikoshi, *J. Org. Chem.*, 1981, **46**, 4264–4266.
211 S. Danishefsky, J. F. Kerwin and S. Kobayashi, *J. Am. Chem. Soc.*, 1982, **104**, 358–360.
212 S. Danishefsky, E. R. Larson and D. Askin, *J. Am. Chem. Soc.*, 1982, **104**, 6457–6458.
213 R. B. Gammill and B. R. Hyde, *J. Org. Chem.*, 1983, **48**, 3863–3865.
214 S. Narayanaswamy, S. Rangaswami and T. R. Scshadri, *J. Chem. Soc. C*, 1954, 187l–l873.
215 A. Pelter, R. S. Ward, E. V. Rao and N. R. Raju, *J. Chem. Soc., Perkin Trans. 1*, 1981, 2491–2498.
216 S. Rangaswami and V. Sasuy, *Curr. Sci.*, 1955, **24**, 13–14.
217 P. Rajani and P. N. Sarma, *Phytochemistry*, 1988, **27**, 648–649.
218 V. S. Parmar, J. S. Ratho, R. Jain, D. A. Henderson and J. F. Malone, *Phytochemistry*, 1989, **28**, 59l–593.
219 T. Tanaka, M. Iinuma, K. Yuki, Y. Fujii and M. Mizuno, *Phytochemistry*, 1992, **31**, 993–998.
220 S. Rangaswti and B. V. Ramasastry, *Bull Inst. Nat. Sci.*, 1955, **4**, 149.
221 M. C. Pirrung and Y. R. Lee, *Tetrahedron Lett.*, 1994, **35**, 6231–6234.
222 M. Niwa, K. Terashima and M. Aqil, *Heterocycles*, 1993, **36**, 671–673.
223 M. Niwa, K. Terashima, J. Ito and M. Aqil, *Heterocycles*, 1994, **38**, 1071–1076.
224 T. R. Kelly, A. Szabados and Y.-J. Lee, *J. Org. Chem.*, 1997, **62**, 428–429.
225 M. Forbes, F. Zilliken, G. Roberts and P. Gyrgy, *J. Am. Chem Soc.*, 1958, **80**, 385–389.
226 M. A. P. Meisinger, F. A. Kuehl, E. L. Rickes, N. G. Brink, K. Folkers, M. Forbes, F. Zilliken, G. Roberts and P. Gyorgy, *J. Am. Chem. Soc.*, 1959, **81**, 4979–4982.
227 A. F. Wagner, E. Walton, A. N. Wilson, J. O. Rodin, F. W. Holly, N. G. Brink and K. Folkers, *J. Am. Chem. Soc.*, 1959, **81**, 4983–4989.
228 B. A. McKittrick and R. Stevenson, *J. Chem. Soc., Perkin Trans. 1*, 1984, 709–712.
229 S. Jinno, T. Okita and K. Inouye, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 1029–1032.
230 M. V. Sargent, P. O. Stransky, V. A. Patrick and A. H. White, *J. Chem. Soc., Perkin Trans. 1*, 1983, 231–239.
231 T. Sawada, M. Aono, S. Asakawa, A. Ito and K. Awano, *J. Antibiot.*, 2000, **53**, 959–966.
232 A. D. Patil, A. J. Freyer, L. Killmer, P. Offen, B. Carte, A. J. Jurewicz and R. K. Johnson, *Tetrahedron*, 1997, **53**, 5047–5060.
233 R. C. Hock, I. U. Schraustätter and C. G. Cochrane, *J. Lab. Clin. Med.*, 1996, **128**, 134–145.
234 M. Inoue, A. J. Frontier and S. J. Danishefsky, *Angew. Chem.*, 2000, **112**, 777–780.
235 S. H. von Reuß and W. A. König, *Phytochemistry*, 2004, **65**, 3113–3118.
236 A. G. Ober, F. R. Fronczek and N. H. Fischer, *J. Nat. Prod.*, 1985, **48**, 242–248.
237 A. G. González, B. M. Fraga, M. G. Hernández and V. P. García, *Phytochemistry*, 1982, **21**, 1826–1827.
238 M. d. Carmen Cruz and J. Tamariz, *Tetrahedron*, 2005, **61**, 10061–10072.
239 D. Bethea, B. Fullmer, S. Syed, G. Seltzer, J. Tiano, C. Rischko, L. Gillespie, D. Brown and F. P. Gasparro, *J. Dermatol. Sci.*, 1999, **19**, 78–88.
240 K. M. Grundmann, R. Ludwig, T. M. Zollner, F. Ochsendorf, D. Thaci, W. H. Boehncke, J. Krutmann, R. Kaufmann and M. Podda, *J. Am. Acad. Dermatol.*, 2004, **50**, 734–739.
241 (*a*) P. E. Grimes, *Clin. Dermatol.*, 1997, **15**, 921–926; (*b*) H. Petering, C. Breuer, R. Herbst, A. Kapp and T. Werfel, *J. Am. Acad. Dermatol.*, 2004, **50**, 68–72.
242 (*a*) P. V. M. M. Diederen, H. Weelden, C. J. G. Sanders, J. Toonstra and W. A. Vloten, *J. Am. Acad. Dermatol.*, 2003, **48**, 215–219; (*b*) G. Miolo, R. Tomanin, A. D. Rossi, A. F. Dall, F. Zacchello and M. Scarpa, *J. Photochem. Photobiol., B*, 1994, **26**, 241–247; (*c*) C. Lage, M. Pádula, T. A. M. Alencar, S. R. F. Gonçalves, L. S. Vidal, J. Cabral-Neto and A. C. Leitão, *Mutat. Res., Rev. Mutat. Res.*, 2003, **544**, 143–157.
243 G. D. Cimino, H. B. Gamper, S. T. Isaacs and J. E. Hearst, *Annu. Rev. Biochem.*, 1985, **54**, 1151–1193.
244 R. L. Edelson, *Arch. Dermatol.*, 1999, **135**, 600–601.
245 (*a*) J. J. Goupil, French Patent, 2, 698, 270–319, 1994; (*b*) J. L. Goaster, French Patent, 691, 629–691, 1993.
246 A. Wiesmann, A. Weller, G. Lischka, T. Klingebiel, L. Kanz and H. Einsele, *Bone Marrow Transplant.*, 1999, **23**, 151–155.
247 P. Ceccherelli, M. Curini, M. C. Marcotullio, F. Epifano and O. Rosati, *Synth. Commun.*, 1998, **28**, 3057–3064.
248 D. Dauzonne and R. Royer, *Synthesis*, 1984, 1054–1057.
249 P. J. Coleman, K. M. Brashear, B. C. Askew, J. H. Hutchinson, C. A. McVean, L. T. Duong, B. P. Feuston, C. Fernandez-Metzler, M. A. Gentile, G. D. Hartman, D. B. Kimmel, C. T. Leu, L. Lipfert, K. Merkle, B. Pennypacker, T. Prueksaritanont, G. A. Rodan, G. A. Wesolowski, S. B. Rodan and M. E. Duggan, *J. Med. Chem.*, 2004, **47**, 4829–4837.

250 B. L. Zhang, F. D. Wang and J. M. Yue, *Synlett*, 2006, **4**, 567–570.

251 J. R. Carney and P. J. Scheuer, *Tetrahedron Lett.*, 1993, **34**, 3727–3730.

252 K. Ishiguro, Y. Ohira and H. Oku, *J. Nat. Prod.*, 1998, **61**, 1126–1129.

253 A. V. B. Sankaram, V. V. N. Reddy and G. S. Sidhu, *Phytochemistry*, 1981, **20**, 1093–1096.

254 T. Takeya, H. Kondo, T. Otsuka, K. Tomita, I. Okamoto and O. Tamura, *Org. Lett.*, 2007, **9**, 2807–2810.

255 (*a*) H. Tanaka, M. Sato, T. Oh-Uchi, R. Yamaguchi, H. Etoh, H. Shimizu, M. Sako and H. Takeuchi, *Phytomedicine*, 2004, **11**, 331–337; (*b*) H. Tanaka, M. Sato, S. Fujiwara, M. Hirata, H. Etoh and H. Takeuchi, *Lett. Appl. Microbiol.*, 2002, **35**, 494–498.

256 F. L. Weitl, *J. Org. Chem.*, 1976, **41**, 2044–2045.

257 A. Fürstner and P. W. Davies, *J. Am. Chem. Soc.*, 2005, **127**, 15024–15025.

258 (*a*) A. Fürstner, P. W. Davies and T. Gress, *J. Am. Chem. Soc.*, 2005, **127**, 8244–8245; (*b*) A. FPrstner and C. A. Wssa, *J. Am. Chem. Soc.*, 2006, **128**, 6306–6307.

259 A. Furstner, E. K. Heilmann and P. W. Davies, *Angew. Chem., Int. Ed*, 2007, **46**, 4760–4763.

260 (*a*) N. W. Preston, K. Chamberlain and R. A. Skipp, *Phytochemistry*, 1975, **14**, 1875–1876; (*b*) R. P. Duffley and R. Stevenson, *J. Chem. Soc., Perkin Trans. 1*, 1977, 802–804; (*c*) M. Meyer, C. Deschamps and D. Molho, *Bull. Soc. Chim. Fr.*, 1991, 91–99; (*d*) M. Na, D. M. Hoang, D. Njamen, J. T. Mbafor, Z. T. Fomun, P. T. Thuong, J. S. Ahn and W. K. Oh, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 3868–3871; (*e*) T. Kinoshita and K. Ichinose, *Heterocycles*, 2005, **65**, 1641–1654.

261 M. A. Khalizadeh, A. Hosseini, M. Shokrollahzadeh, M. R. Halvagar, D. Ahmadi, F. Mohannazadeh and M. Tajbakhsh, *Tetrahedron Lett.*, 2006, **47**, 3525–3528.

262 M. Csekei, Z. Novak and A. Kotschy, *Tetrahedron*, 2008, **64**, 8992–8996.

263 (*a*) E. E. Shul'ts, T. N. Petrova, M. M. Shakirov, E. I. Chernyak and G. A. Tolstikov, *Chem. Nat. Compd.*, 2000, **36**, 362–368; (*b*) T. Shiozawa, S. Urata, T. Kinoshita and T. Saitoh, *Chem. Pharm. Bull.*, 1989, **37**, 2239–2240.

264 Y. Tanaka, H. Kikuzaki, S. Fukuda and N. Nakatani, *J. Nutr. Sci. Vitaminol.*, 2001, **47**, 270–273.

265 Y. L. Jin, S. Kim, Y. S. Kim, S. A. Kim and H. S. Kim, *Tetrahedron Lett.*, 2008, **49**, 6835–6837.

266 K.-S. Huang, Y.-H. Wang, R.-L. Li and M. Lin, *J. Nat. Prod.*, 2000, **63**, 86–89.

267 (*a*) J. Ito, Y. Takaya, Y. Oshima and M. Niwa, *Tetrahedron*, 1999, **55**, 2529–2544; (*b*) I. Kim and J. Choi, *Org. Biomol. Chem.*, 2009, **7**, 2788–2795.

268 J.-R. Dai, Y. F. Hallock, J. H. Cardellina and M. R. Boyd, *J. Nat. Prod.*, 1998, **61**, 351–353.

269 (*a*) A. Saraswathy, K. K. Purushothaman, A. Patra, A. K. Dey and A. B. Kundu, *Phytochemistry*, 1992, **31**, 2561–2562; (*b*) T. Tanaka, T. Ito, Y. Ido, K. Nakaya, M. Iinuma and V. Chelladurai, *Chem. Pharm. Bull.*, 2001, **49**, 785–787.

270 (*a*) Y. Takaya and M. Niwa, *Trends Heterocycl. Chem.*, 2001, **7**, 41–54; (*b*) E.-K. Seo and A. D. Kinghorn, *Stud. Nat. Prod. Chem.*, 2000, **23**, 531.

271 (*a*) T. K. Chakraborty and G. V. Reddy, *J. Org. Chem.*, 1992, **57**, 5462–5469; (*b*) N. Hoffmann and J.-P. Pete, *Synthesis*, 2001, 1236–1242; (*c*) S. Inoue, C. Nakagawa, H. Hayakawa, F. Iwasaki, Y. Hoshino and K. Honda, *Synlett*, 2006, 1363–1366.

272 L. Chen, Q. Ding, P. Gillespie, K. Kim, A. J. Lovey, W. W. McComas, J. G. Mullin and A. Perrota, World Pat.WO 02057261 A2, 2005.

273 M. M. Heravi, F. Dirkwand, H. A. Oskooie and M. Ghassemzadeh, *Heterocycl. Commun.*, 2005, **11**, 75–78.

274 I. Kim and J. Choi, *Org. Biomol. Chem.*, 2009, **7**, 2788–2795.

275 A. Yaron and F. Naider, *Crit. Rev. Biochem. Mol. Biol.*, 1993, **28**, 31–81.

276 T. Aoyagi, T. Wada, M. Nagai, F. Kojima, S. Harada, T. Takeuchi, H. Takahashi, K. Hirokawa and T. Tsumita, *Experientia*, 1990, **46**, 94–97.

277 L. Y. Yang, C. F. Chang, Y. C. Huang, Y. J. Lee, C. C. Hu and T. H. Tseng, *Synthesis*, 2009, **7**, 1175–1179.

278 M. J. Lear, O. Simon, T. L. Foley, M. D. Burkart, T. J. Baiga, J. P. Noel, A. G. DiPasquale, A. L. Rheingold and J. J. La Clair, *J. Nat. Prod.*, 2009, **72**, 1980–1987.

279 M. Sridhar, B. A. Kumar and R. Narender, *Tetrahedron Lett.*, 1998, **39**, 2847–2850.

280 O. Simon, B. Reux, J. J. La Clair and M. J. Lear, *Chem.–Asian J.*, 2010, **5**, 342–351.

281 D. Y. K. Chen, Q. Kang and T. R. Wu, *Molecules*, 2010, **15**, 5909–5927.

282 L. D. Juliawaty, E. H. Hakim, S. A. Achmad, Y. M. Syah, J. Latip and I. M. Said, *Nat. Prod. Commun.*, 2009, **4**, 947–950.

283 H. M. Ge, W. H. Yang, Y. Shen, N. Jiang, Z. K. Guo, Q. Luo, Q. Xu, J. Ma and R. X. Tan, *Chem.–Eur. J.*, 2010, **16**, 6338–6345.

284 (*a*) K.-S. Huang, M. Lin and G.-F. Cheng, *Phytochemistry*, 2001, **58**, 357–362; (*b*) Y. Meng, P. C. Bourne, P. Whiting, V. Sik and L. Dinan, *Phytochemistry*, 2001, **57**, 393–400; (*c*) H.-F. Luo, L.-P. Zhang and C.-Q. Hu, *Tetrahedron*, 2001, **57**, 4849–4854; (*d*) C. Privat, J. P. Telo, V. Bernades-Genisson, A. Vieira, J. P. Souchard and F. Nepveu, *J. Agric. Food Chem.*, 2002, **50**, 1213–1217; (*e*) S. Wang, D. Ma and C. Hu, *Helv. Chim. Acta*, 2005, **88**, 2315–2321.

285 (*a*) I. V. Seregin and V. Gevorgyan, *Chem. Soc. Rev.*, 2007, **36**, 1173–1193; (*b*) B.-J. Li, S.-D. Yang and Z.-J. Shi, *Synlett*, 2008, 949–957; (*c*) X. Chen, K. M. Engle, D.-H. Wang and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2009, **48**, 5094–5115; (*d*) L. Ackermann, R. Vicente and A. R. Kapdi, *Angew. Chem., Int. Ed.*, 2009, **48**, 9792–9826; (*e*) C.-L. Sun, B.-J. Li and Z.-J. Shi, *Chem. Commun.*, 2010, **46**, 677–685.

286 (*a*) N. S. Nandurkar, M. J. Bhanushali, M. D. Bhor and B. M. Bhanage, *Tetrahedron Lett.*, 2008, **49**, 1045–1048; (*b*) S.-D. Yang, C.-L. Sun, Z. Fang, B.-J. Li, Y.-Z. Li and Z.-J. Shi, *Angew. Chem., Int. Ed.*, 2008, **47**, 1473–1476; (*c*) H.-Q. Do, R. M. K. Khan and O. Daugulis, *J. Am. Chem. Soc.*, 2008, **130**, 15185–15192; (*d*) S. Matsuda,

M. Takahashi, D. Monguchi and A. Mori, *Synlett*, 2009, 1941–1944; (*e*) M. Ionita, J. Roger and H. Doucet, *ChemSusChem*, 2010, **3**, 367–376.
287 K. Kim and I. Kim, *Org. Lett.*, 2010, **12**, 5314–5317.
288 C. W. Chang and R. J. Chein, *J. Org. Chem.*, 2011, **76**, 4154–4157.
289 (*a*) R. C. Larock, E. K. Yum, M. J. Doty and K. K. C. Sham, *J. Org. Chem.*, 1995, **60**, 3270–3271; (*b*) B. C. Bishop, I. F. Cottrell and D. Hands, *Synthesis*, 1997, 1315–1320.
290 B. M. Trost, S. A. Godleski and J. P. Genet, *J. Am. Chem. Soc.*, 1978, **100**, 3930–3931.
291 S. Paul, S. Pattanayak and S. Sinha, *Tetrahedron Lett.*, 2011, **52**, 6166–6169.
292 (*a*) R. Hänsel, H. Rimpler and R. Schwar, *Tetrahedron Lett.*, 1965, **6**, 1545–1548; (*b*) Z.-F. Hu, L.-L. Chen, J. Qi, Y.-H. Wang, H. Zhang and B.-Y. Yu, *Fitoterapia*, 2011, **82**, 190–192.
293 (*a*) M. W. Khan, M. J. Alam, M. A. Rashid and R. Chowdhury, *Bioorg. Med. Chem.*, 2005, **13**, 4796–4805; (*b*) I. Hayakawa, R. Shioya, T. Agatsuma, H. Furukawa, S. Naruto and Y. Sugano, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 455–458.
294 M. R. Saberi, T. K. Vinh, S. W. Yee, B. J. Griffiths, P. J. Evans and C. Simons, *J. Med. Chem.*, 2006, **49**, 1016–1022.
295 (*a*) C. Beney, A.-M. Mariotte and A. Boumendjel, *Heterocycles*, 2001, **55**, 967–972; (*b*) V. Wallez, S. Durieux-Poissonnier, P. Chavatte, J. A. Boutin, V. Audinot, J.-P. Nicolas, C. Bennejean, P. Delagrange, P. Renard and D. Lesieur, *J. Med. Chem.*, 2002, **45**, 2788–2800.
296 S. Yahiaoui, M. Peuchmaur and A. Boumendjel, *Tetrahedron*, 2011, **67**, 7703–7707.
297 T. Rezanka, L. O. Hanus, P. Kujan and V. M. Dembitsky, *Eur. J. Org. Chem.*, 2005, 2708–2714.
298 D. Ma and Q. Cai, *Org. Lett.*, 2003, **5**, 3799–3802.
299 B. Liégault, D. Lee, M. P. Huestis, D. R. Stuart and K. Fagnou, *J. Org. Chem.*, 2008, **73**, 5022–5028.
300 (*a*) A. Shiotani and H. Itatani, *J. Chem. Soc., Perkin Trans. 1*, 1976, 1236–1241; (*b*) H. Hagelin, J. D. Oslob and B. kermark, *Chem.–Eur. J.*, 1999, **5**, 2413–2416; (*c*) T. Gensch, M. Rçnnefahrt, R. Czerwonka, A. Jäger, O. Kataeva, I. Bauer and H.-J. Knçlker, *Chem.–Eur. J.*, 2012, **18**, 770–776.
301 R. Bartholomaus, F. Dommershausen, M. Thiele, N. S. Karanjule, K. Harms and U. Koert, *Chem.–Eur. J.*, 2013, **19**, 7423–7436.
302 E. M. Bickoff, A. N. Booth, R. L. Lyman, A. L. Livingston, C. R. Thompson and F. Deeds, *Science*, 1957, **126**, 969–970.
303 M. S. Kurzer and X. Xu, *Annu. Rev. Nutr.*, 1997, **17**, 353–381.
304 M. S. Kurzer, *J. Nutr.*, 2003, **133**, 1983S–1986S.
305 U. A. Kshirsagar, R. Parnes, H. Goldshtein, R. Ofir, R. Zarivach and D. Pappo, *Chem.–Eur. J.*, 2013, **19**, 13575–13583.
306 R. J. Y. Chen, T. Jinn, Y. Chen, T. Chung, W. Yang and J. T. C. Tzen, *Acta Pharmacol. Sin.*, 2011, **32**, 141–151.
307 Y. Lu and L. Foo, *Phytochemistry*, 2002, **59**, 117–140.
308 R. Jiang, K. Lau, P. Hon, T. C. W. Mak, K. Woo and K. Fung, *Curr. Med. Chem.*, 2005, **12**, 237–246.
309 T. o. Cheng, *Int. J. Cardiol.*, 2007, **121**, 9–22.
310 B. L. Alford and H. M. Hügel, *Org. Biomol. Chem.*, 2013, **11**, 2724–2727.
311 (*a*) W. Steck, *Phytochemistry*, 1970, **9**, 1145–1146; (*b*) M. Vanhaelen and R. Vanhaelen-Fastré, *Phytochemistry*, 1974, **13**, 306–307; (*c*) J. Reisch, A. Wickramasinghe and V. Kumar, *J. Nat. Prod.*, 1989, **52**, 1379–1382; (*d*) A. H. Muller, L. R. O. Degáspari, P. C. Vieira, M. F. da Silva, J. B. Fernandes and J. R. Pirani, *Phytochemistry*, 1993, **34**, 585–586; (*e*) F. M. Oliveira, A. E. G. Sant'ana, L. M. Conserva, J. G. S. Maia and G. M. P. Guilhon, *Phytochemistry*, 1996, **41**, 647–649.
312 (*a*) A. E. Desjardins, G. F. Spencer and R. D. Plattner, *Phytochemistry*, 1989, **28**, 2963–2969; (*b*) C. C. Wang, J. E. Lai, L. G. Chen, K. Y. Yen and L. L. Yang, *Bioorg. Med. Chem.*, 2000, **8**, 2701–2707; (*c*) J. Singhuber, I. Baburin, G. F. Ecker, B. Kopp and S. Hering, *Eur. J. Pharmacol.*, 2011, **668**, 57–64.
313 K. Sonogashira, *J. Organomet. Chem.*, 2002, **653**, 46–49.
314 A. Cervi, P. Aillard, N. Hazeri, L. Petit, C. L. L. Chai, A. C. Willis and M. G. Banwell, *J. Org. Chem.*, 2013, **78**, 9876–9882.
315 E. Gellert, R. Hamet and E. Schlittler, *Helv. Chim. Acta*, 1951, **34**, 642–651.
316 T. Matsui, Y. Sowa, H. Murata, K. Takagi, R. Nakanishi, S. Aoki, M. Yoshikawa, M. Kobayashi, T. Sakabe, T. Kubo and T. Sakai, *Int. J. Oncol.*, 2007, **31**, 915–922.
317 M. L. Bolognesi, F. Lizzi, R. Perozzo, R. Brun and A. Cavalli, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 2272–2276.
318 N. Kotoku, K. Higashimoto, M. Kuriok, M. Arai, A. Fukud, Y. Sumii, Y. Sowa, T. Sakai and M. Kobayashi, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 3389–3391.
319 (*a*) M. D. Clift, C. N. Taylor and R. J. Thomson, *Org. Lett.*, 2007, **9**, 4667–4669; (*b*) C. T. Avetta, L. C. Konkol, C. N. Taylor, K. C. Dugan, C. L. Stern and R. J. Thomson, *Org. Lett.*, 2008, **10**, 5621–5624; (*c*) M. D. Clift and R. J. Thomson, *J. Am. Chem. Soc.*, 2009, **131**, 14579–14593.
320 B. T. Jones, C. T. Avetta and R. J. Thomson, *Chem. Sci.*, 2014, **5**, 1794–1798.
321 M. M. Heravi and A. Fazeli, *Heterocycles*, 2010, **81**, 1979–2026.
322 H. Yuan, K. Bi, W. Chang, R. Yue, B. Li, J. Yea, Q. Sun, H. Jin, L. Shan and W. Zhang, *Tetrahedron*, 2014, **70**, 9084–9092.
323 M. M. Heravi and E. Hashemi, *Monatsh. Chem.*, 2012, **143**, 861–880.
324 M. M. Heravi and P. Hajiabbasi, *Mol. Diversity*, 2014, **18**, 411–439.
325 X. Zheng, W. D. Meng and F. L. Qing, *Tetrahedron Lett.*, 2004, **45**, 8083–8085.
326 G. Pan, Y. Ma, K. Yang, X. Zhao, H. Yang, Q. Yao, K. Lu, T. Zhu and P. Yu, *Tetrahedron Lett.*, 2015, **56**, 4472–4475.
327 Y. Q. Ye, C. Negishi, Y. Hongo, H. Koshino, J.-i. Onose, N. Abe and S. Takahashi, *Bioorg. Med. Chem.*, 2014, **22**, 2442–2446.
328 Y.-Q. Ye, H. Koshino, J. Onose, K. Yoshikawa, N. Abe and S. Takahashi, *Org. Lett.*, 2009, **11**, 5074–5077.

329 N. Radulovic, D. N. Quang, T. Hashimoto, M. Nukada and Y. Asakawa, *Phytochemistry*, 2005, **66**, 1052–1059.
330 J.-T. Liu, T. J. Do, C. J. Simmons, J. C. Lynch, W. Gu, Z.-X. Ma, W. Xu and W. Tang, *Org. Biomol. Chem.*, 2016, **14**, 8927–8930.
331 I. Kim, S.-H. Lee and S. Lee, *Tetrahedron Lett.*, 2008, **49**, 6579–6584; J. H. Lee, M. Kim and I. Kim, *J. Org. Chem.*, 2014, **79**, 6153–6163.
332 J.-t. Liu, C. J. Simmons, H. Xie, F. Yang, X. Zhao, Y. Tang and W. Tang, *Adv. Synth. Catal.*, 2016, **358**, 1–6.
333 G. A. Kraus and V. Gupta, *Tetrahedron Lett.*, 2009, **50**, 7180–7182.
334 D. Y. K. Chen, Q. Kang and T. R. Wu, *Molecules*, 2010, **15**, 5909–5927.