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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 antidiabetic¹¹ and antineoplastic 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.*

Naaltrindole (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

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

been found to inhibit the growth of malignant cells and they also showed antibiotic properties (Fig. 3).^{28,29}

Ailanthoidol **5** (ref. 30) and XH-14 **6** were isolated from the chloroform-soluble fraction of stem woods of *Zanthoxylum ailanthoides*.³¹ Studies on the constituents of plants of *Zanthoxylum ailanthoides*, 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 containing carbonyl group by dehydration,^{54,55} (b) palladium^{56,57} or platinum⁵⁸.

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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.

catalyzed⁵⁹ ring closure by an intramolecular Wittig reaction^{60–62} or *o*-(acyloxy)benzyl anions,⁶³ (c) condensation of activated methylene following Dieckmann reaction conditions^{64,65} or ketene intermediate involved cyclization,⁶⁶ (d) acid-catalyzed ring construction of α -aryloxy-carbonyls⁶⁷ 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-(cyanomethyl) phenyl esters using catalytic quantity of Pd(OAc)₂, PCy₃, and Zn.⁷²

Recently, the role of benzofuran and its derivatives present in natural products as emerging framework for antimicrobial agents,⁷³ antibreast cancer agents⁷⁴ 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 benzofurans⁹⁶ 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-butenic 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-butenic 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 aianthoidol 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 $\text{PdCl}_2(\text{PPh}_3)_2$ is more efficient catalyst than $\text{Pd}(\text{PPh}_3)_4$ and also iodophenol **12b** was proved to react better than bromophenol **12a**. The resultant benzofuran **14** was then converted into aianthoidol 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 vinyl-

palladium(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

In another attempt, the total synthesis of aianthoidol 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 aianthoidol 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 aianthoidol **5** (Scheme 4).¹⁰⁶

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	$\text{PdCl}_2(\text{PPh}_3)_2$, CuI, NEt_3 , MeCN	69
4	12a	$\text{Pd}(\text{PPh}_3)_4$, CuI, NEt_3 , MeCN	52
5	12b	$\text{Pd}(\text{PPh}_3)_2$, CuI, NEt_3 , MeCN	88

Scheme 2 Total synthesis of ailantheidol 5.

Scheme 3 Total synthesis of XH-14 6.

Furthermore, ailantheidol 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 ailantheidol analogues. With the aim of developing a successful route to ailantheidol 5, an alternative method of construction was examined. Accordingly, the removal of the benzyl protecting group with TiCl₄ followed by DIBAL or LiAlH₄ 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-aryl-benzofurans moiety in their structures such as, egonol 31a, homoegonol 31b, and demethoxyegonol 31c were also isolated from *Styrax japonicum*, *Styrax officinalis* L., and *Styrax obasica*.^{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 ailantheidol 5.

Scheme 5 Total synthesis of ailantheidol 5.

followed by hydrolysis. The total synthesis started from readily available **23** and **26** which are coupled by means of selective MacMurry cross coupling reaction¹¹⁰ 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 ailantheidol **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 reaction¹¹² 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 BCl₃ is used for debenzoylation 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*-hydroxyaryalkynes 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 ailantheidol 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-tri-bromobenzofuran **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 allyl 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 starting 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-formation¹³⁵ 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 diyne **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 anti-tumor, 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 tournefollic acid A **68**.¹⁴¹ The total synthesis of the naturally occurring compounds salvianolic acid C **70**, tournefollic acid A **68** and tournefollic 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 coupling¹⁴² in which 3-hydroxy-2-iodobenzaldehyde **64** was coupled to the ethynylbenzene analogues **65** in a catalyzed-Pd(Ph₃P)₂Cl₂ 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 debenzoylation of **67** and **66**, are converted into tournefollic acid A **68** and tournefollic acid A **68** 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 protocol¹⁴⁴ the synthesis of naturally occurring compounds containing benzofuran moiety such as stemofuran A **75** (ref. 145) eupomatenoid **650g**,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-workers¹⁴⁸ 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 tournefollic acid A **68**, tournefollic acid **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*-hydroxypropiofenone afforded the oxime ether **79**, which upon reaction with TFAT-DMAP in dichloromethane 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 CH₂Cl₂ 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 LiAlH₄ 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/Et₃N 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 BF₃·Et₂O (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 Kawai¹⁶² 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 $\text{I}_2/\text{Ag}_2\text{SO}_4$ 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 $\text{Pd}(\text{PPh}_3)_4/\text{CuI}/\text{Et}_3\text{N}$ 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 disclosed¹⁶⁷ 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 coupling¹⁷⁹ 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-buten-2-ol **135** was achieved in the presence of Pd(PPh₃)₂Cl₂ 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'-methoxypropiphenone **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 endothelial

receptor antagonist and antiosteoporotic 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 PtCl₂ 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 rearrangement¹⁹⁵ 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 suggested¹⁹⁷ 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 annulation¹⁹⁸ 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 (+)-liphagal²⁰⁰ 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/CH₂Cl₂ at -78 °C and then gradual warming to ambient temperature the ring-expanded product **163** was obtained in two steps *via* pinacol rearrangement 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 liphagal²⁰² 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, ¹H-NMR and ¹³C-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*-butyldimethylsilyloxy)-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 migration²⁰⁵ 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 hypoxia-inducible 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–I** or synthesized **177a–d**. The acetynyl compounds can be provided *via* a procedure developed by Ramirez–Corey–Fuchs, in which compounds **177a–d** were synthesized in three steps.²⁰⁷ The Sonogashira catalyzed coupling of terminal acetylenes **177a–I** 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 built up from methyl 2-fomyl-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 Me₂SO 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 furoentalene **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 (CH₃I/K₂CO₃/18-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 *Tephrosia purpurea*,²¹⁵ *T. lanceolata*,²¹⁶ *Pongamia 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 total 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

$\text{BrCH}(\text{CO}_2\text{Et})_2$ 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 $\text{AcOH}/\text{H}_2\text{O}$ to afford the natural product, garcifuran B **217** (Scheme 48).²²⁴

Benzofuran derivative **220** was isolated from various yeasts as an antioxidant²²⁵ 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. Regio-selective 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 1,9-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(m)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 ¹H-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 disease²⁴⁵ 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-nitroethyl) 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 popo-luanone **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 rise 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

Erypoeigin **H** **251** is the most active of flavonoid 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 erypogin 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 $\text{O} \rightarrow \text{C}$ 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 erypogin 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, glycoumarin, 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-phenoxy coumarin **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 congener of gnetuhainin, extracted from *Vitis vinifera* 'Kyohou' was fully characterized based on the widespread ¹H-NMR and ¹³C-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 Oligostilbenes²⁷⁰ 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 cyclo-dehydration 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 oxidation²⁷³ 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 BBr₃ 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 (±)-laetiobin 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-diphenyl-ethylene 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 arylation²⁸⁵ to assemble an aryl group at the C2 position of the benzofuran²⁸⁶ 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 reaction²⁸⁹ 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-butyne-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 method²⁹⁵ 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 MnO₂ 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 coupling²⁹⁸ 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 conditions²⁹⁹ 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 (+)-fulcineroside **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 FeCl₃ 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 fulcineroside **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-workers¹⁰² to give the 2-arylbenzo[*b*]furan core 322 (51% yield). Finally, reaction of 323 and 324, in the presence of Et₃N 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)propionic acid or propionic 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-coupling³¹³ 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 K₂CO₃ in DMSO³¹⁷ to afford a C–O coupling product. Upon reduction of the quinone moiety, present in acetonitrile using aqueous Na₂S₂O₄, 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 $\text{Pd}(\text{PPh}_3)_4$ 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 silyl ether 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 reaction³²¹ 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 ($\pm$)-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 ($\pm$)-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 Ag₂O 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 Ag₂O, 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 Indonesia²⁸² 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 diptioindonesin 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 boronic acids 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 routes^{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 $\text{Ar}_2\text{B}(\text{OH})_2$ 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 from 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)	Naaltrindole

(DMAP)	<i>N,N</i> -dimethylpyridin-4-amine
(DEAD)	Diethyl azodicarboxylate
(DMF-DMA)	<i>N,N</i> -Dimethylformamide dimethyl acetal
(DDQ)	2,3-Dichloro-5,6-dicyano- <i>p</i> -benzoquinone
(PEP)	Prolyl endopeptidase
(CDC)	Cross-dehydrogenative coupling
(MW)	Microwave irradiation
(IMHA)	Intramolecular hydroarylation
(Dip)	Diptoindonesin

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