RSC Advances



REVIEW

View Article Online
View Journal | View Issue



Cite this: RSC Adv., 2017, 7, 24470

Total synthesis of natural products containing benzofuran rings

Majid M. Heravi, **D* Vahideh Zadsirjan, **D* Hoda Hamidi and Parvin Hajiabbas Tabar Amiri

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.

Received 27th March 2017 Accepted 26th April 2017

DOI: 10.1039/c7ra03551a

rsc.li/rsc-advances

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

Department of Chemistry, School of Sciences, Alzahra University, Vanak, Tehran, Iran. E-mail: mmh1331@yahoo.com 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 antibacterial,⁷ antimicrobial,⁸ antitumor,⁹ anticonvulsant antiinflammatory,¹⁰ antidiabetic¹¹ and antineophobic agents.¹² Furthermore, certain derivatives of benzofuran present in natural products show high cytotoxicity.¹³ The exceptional structural features of benzofuran and its wide assortment of biological as well as pharmacological activities make it



Majid M Heravi was born in 1952 in Mashhad, Iran. He received his B. Sc. degree from the National University of Iran in 1975 and his M. Sc. and Ph. D. degrees from Salford University, England in 1977 and 1980, respectively. He completed his doctoral thesis under the supervision of the late Jim Clarck in Salford University, England. He started his career as a research fellow in Daroupakhsh (a phar-

maceutical company) in 1981 Tehran, Iran and joined as an assistant professor to Ferdowsi University of Mashhad, Iran in 1983, and was promoted to associate professor in 1993 and full professor in 1997 in the aforementioned university. In 1999 he moved to Alzahra University of Tehran, Iran as professor of chemistry where he still works. He has previously been a visiting professor at UC Riverside, California, USA and Hamburg University, Hamburg, Germany. His research interests focus on heterocyclic chemistry, catalysis, organic methodology and green synthetic organic chemistry.



Vahideh Zadsirjan was born in Shiraz, Iran in 1979. She received her B. Sc. in Pure Kharazmi Chemistry from University in 2002, and her M. Sc by course in 2007 and Ph. D degrees in organic chemistry in 2016 under the supervision of Professor Majid M. Heravi from Alzahra University Tehran, Iran. His research is focused on heterocyclic chemistry, catalysis, organic methodology and green synthetic organic chemistry.

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

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

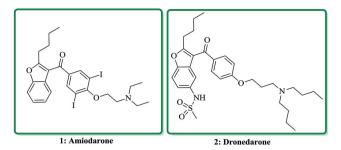


Fig. 1 The structure of amiodarone 1 and dronedarone 2.

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 ailanthoidos*. ³¹ Studies on the constituents of plants of *Zanthoxylum ailanthoidos*, they are used in Chinese traditional herbal medicine. These compounds exhibit different interesting pharmacological activities. ^{32,33} Ailanthoidol 5, a neolignan derivative, demonstrated antiviral, antioxidant and antifungal potencies (Fig. 4). ³⁴⁻³⁹

Significantly, the benzofuran derivatives containing the pyrazole nucleus were reported to be analgesic, antiinflammatory, 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) acidcatalyzed cyclization of compounds continuing carbonyl group by dehydration,54,55 (b) palladium56,57 or platinum58-



Hoda Hamidi was born in1984 in Ramsar, Mazandaran, Iran. She obtained her B.Sc. degree in applied chemistry from Mohaghdas Ardebili University, Ardebil, Iran, in 2006 and her M.Sc. degree in 2010 and Ph. D degree in 2015 in organic chemistry from Alzahra University, Tehran, Iran, in 2010 and 2015 under the supervision of Professor Hossein Abdi Oskooei and Professor Majid M. Heravi.

Her research interests are in the area of the synthesis of organic compounds particularly heterocycles and synthetic methodology.



Parvin Hajiabbasi was born in1984 in Babol, Mazandaran, Iran. She received her B.Sc. degree in chemistry from Tehran University, Tehran, Iran in 2006, her M.Sc. degree in organic chemistry from Tehran University, Tehran, Iran, in 2010 and her Ph.D degree in organic chemistry at Alzahra University, Tehran, Iran under supervision of Professor Ghodsi Mohammadi Ziarani in 2015.

She is presently enduring her researches in the synthesis of organic compounds, heterocycles, natural products and medicinal compounds.

3: Psoralen

Fig. 2 The structure of psoralen 3.

Fig. 3 The structure of machicendiol 4.

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

catalyzed⁵⁹ ring closure by an intramolecular Wittig reaction⁶⁰⁻⁶² or o-(acyloxy)benzyl anions,⁶³ (c) condensation of activated methylene following Dieckmann reaction condtiions^{64,65} or ketene intermediate involved cyclization,⁶⁶ (d) acid-catalyzed ring construction of α -aryloxycarbonyls⁶⁷ or (e) intramolecular Friedel–Crafts reaction,⁶⁸ (f) photolytic cyclization of α -phenyl-ketones,⁶⁹ and (g) gold(α)-catalyzed tandem reaction of α -arylhydroxylamines with 1,3-dicarbonyl substrates.⁷⁰ Moreover, a one-pot reaction for the transformation of allyl aryl ethers to 2-methylbenzofurans via sequential reaction involving Claisen rearrangement/oxidative cyclization has been reported.⁷¹ 3-Acyl-2-aminobenzofurans give 2-(cycanomethyl) phenyl esters using catalytic quantity of Pd(OAc)₂, PCy₃, and Zn.⁷²

Recently, the role of benzofuran and its derivatives present in natural products as emerging framework for antimicrobial agents, antibreast cancer agents and in other natural lead molecules with diverse pharmacological properties have been comprehensively, revealed. We are especially interested in heterocyclic chemistry and heterocyclic compounds showing high biological activity. 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.

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 neolignans98,99 have been considered following the biomimetic routes. In this approach, initially an appropriate 4-furyl-3alkoxy-3-butenoic acid 10 was synthesized. As illustrated in Scheme 1, the aldehyde 7 (ref. 7) was reacted with the lithium salt of protected propynol 8 to afford the corresponding carbinol, which was then transformed into the 3-bromofuran 9 involving sequential reactions including oxidation of propargylic carbinol/selective deprotection of tetrahydropyranyl ether/acid-catalyzed cyclization to afford 3-bromofuran 9 in moderate overall yield. 3-Bromofuran 9 was then converted into the benzofuran 11 via the formation of 4-furyl-3-alkoxy-3butenoic 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-4hydroxycinnamate) to form the benzofuran skeleton has also been reported. 103 This strategy gave only low overall yield (34%) and showed no flexibility for the synthesis of other analogs. An improved and efficient strategy for the total synthesis of ailanthoidol 5 has been reported by Lütjens and co-workers in 1998. This approach for the total synthesis found being attractive and practical. In this protocol, the total synthesis of ailanthoidol

Scheme 1 Total synthesis of ailanthoidol 5.

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

Notably, the synthesis of XH-14 **6** was accomplished using a similar protocol, employing the Sonogashira coupling reaction conditions. Nevertheless, in the case of the generation of the intermediate *ortho*-hydroxytolan, it was isolated preceding to cyclization and then subjected into Pd-catalyzed carbonylative cyclization reaction was to construct the benzofuran ring system with simultaneous acylation at the 3-position. Ethyl-3-methoxy-4-hydroxy-5-iodocinnamate **12b** was protected as MOM ether and then coupled with the various substituted alkyne to provide the corresponding MOM protected *ortho*-hydroxytolan in high yield (92%). For the removal of the MOM protecting group oxalic acid in aqueous methanol was used to afford virtually quantitative yield of the *ortho*-hydroxytolan **16**. Using a catalytic amount of PdCl₂ to solution of **16** and NaOAc/MeOH under atmosphere of CO imposed cyclization to a vinyl-

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 ₂ O, Py, reflux	62
3	12a	PdCl ₂ (PPh ₃) ₂ , CuI, NEt ₃ , MeCN	69
4	12a	Pd(PPh ₃) ₄ , CuI, NEt ₃ , MeCN	52
5	12b	Pd(PPh ₃) ₂ , CuI, NEt ₃ , MeCN	88

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 reoxidized 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 K2CO3 was employed instead of Na₂CO₃. 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 ailanthoidol was also accomplished in 12 steps manipulating different functional transformations in a 17% overall yield starting from vanillin 19. A convenient method for the synthesis of ailanthoidol from vanillin is established, using trimethylsilyl diazomethane lithium salt to generate diphenyl acetylene which followed by oxymercuration cyclization of the resulting alkyne using mercury acetate in acetic acid as key steps. The mercurial intermediate 21 is found to be a very useful intermediate for the syntheses of analogs by the direct replacement of the mercurial moiety with a variety of functional groups. The desired intermediate 20 upon treatment with mercury acetate in acetic acid and then quenching with saturated sodium chloride solution afforded 2-(p-benzyloxy-m-methoxyphenyl)-3-chloromercurio-5-(5',5'-dimethyl-1',3'-dioxan-2'-yl)-7-methoxybenzofuran 21. The chloromercurial intermediate 21 without further purification was isolated and reduced with NaBH4 in THF to afford benzofuran 22 in high yields. After several steps the latter was converted into the desired natural product ailanthoidol 5 (Scheme 4).106

RSC Advances Review

Scheme 2 Total synthesis of ailanthoidol 5.

Scheme 3 Total synthesis of XH-14 6.

Furthermore, ailanthoidol 5, was also synthesized via a route which is the longest linear sequence is only six steps in 48% overall yield. This pathway started from commercially available 5-bromo-2-hydroxy-3-methoxybenzaldehyde 23. The key transformation in the synthesis is the Stille coupling reaction of benzofuranyl bromide with stannanyl compounds. This synthetic strategy can be modified to give access to a variety of different ailanthoidol analogues. With the aim of developing a successful route to ailanthoidol 5, an alternative method of construction was examined. Accordingly, the removal of the benzyl protecting group with $TiCl_4$ followed by DIBAL or 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-arylbenzofurans moiety in their structures such as, egonol **31a**, homoegonol **31b**, and demethoxyegonol **31c** were also isolated from *Styrax japonicum*, *Styrax officinalis* L., and *Styrax obassia*. They were found exhibiting cytostatic activity towards human leukemic HL-60 cells. The brief total synthesis of all three naturally occurring **31a**, **31b**, and **31c** was achieved only in five steps in overall yields of 40, 40, and 34%, respectively. The bromobenzofuran **28** present in these natural products were all also provided in two steps *via* selective cross MacMurry coupling in good yields. The introduction of 3-hydroxypropy moiety on the benzofuran rings was accomplished *via* Sonogashira cross coupling reaction with subsequent hydrogenation

Scheme 4 Total synthesis of ailanthoidol 5.

Scheme 5 Total synthesis of ailanthoidol 5.

followed by hydrolysis. The total synthesis started from readily available 23 and 26 which are coupled by means of selective MacMurry cross coupling 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 ailanthoidol 5, XH-14 6 and the other three natural products 31a-c (Scheme 6).¹¹¹

Yang and co-workers have carried out the total synthesis, which could also substantiate unambiguously the structure of XH-14 **6**. A key feature of this synthetic program was the conventional coupling 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 debenzylation of **39** the desired natural product XH-14 **6** is obtained in very high yield (90%) (Scheme 8).¹¹⁶

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

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

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

The first total synthesis of a norneolignan isolated from Ratanhia, 5-(3-hydroxypropyl)-2-(2'-methoxy-4'-hydroxyphenyl) benzofuran **46**, is described in 2002. The key steps contain the one-pot reaction for a 2-arylbenzofuran from methyl 3-(4-hydroxyphenyl)propionate **43** with 2-chloro-2-methylthio-(2'-methoxy-4'-acetoxy)acetophenone **44** in the presence of ZnCI₂, 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.

RSC Advances Review

Scheme 10 Total synthesis of a norneolignan 46.

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

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

Scheme 11 Total synthesis of eupomatenoids 50.

Scheme 12 Total synthesis of eupomatenoids 50.

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

The suggested synthetic pathway has three main problems: (a) highly conjugated enol ether derivative 55 is not stable, (b) the Dötz reaction^{134,135} is competitive due to the formation of naphthol 58 (Scheme 13) with the desired benzofuran-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 dienyne **55** and an enediyne **56** can be used as starting materials. ^{137,138}

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

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

Scheme 13 Proposed pathway for the synthesis of compound 59

Scheme 14 Total synthesis of egonol 31a.

This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

Open Access Article. Published on 05 2017. Downloaded on 05/11/2025 11:32:56

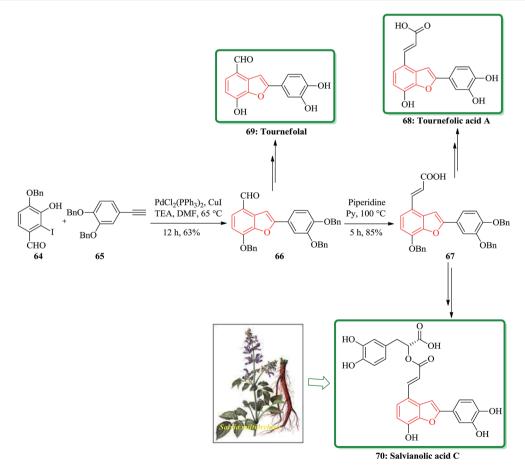
RSC Advances Review

HIV activities.140 Salvianolic acid C 70, is actually one of the salvianolic acids, which are present in the structure of 2-phenylbenzofuran neolignan tournefolic acid A 68.141 The total synthesis of the naturally occurring compounds salvianolic acid C 70, tournefolal 69 and tournefolic acid A 68 have been achieved and reported in 2012. Noticeably, the key benzofuran framework were synthesized via selective iodination to obtain 64 followed by Sonogashira coupling¹⁴² in which 3-hydroxy-2iodobenzaldehyde 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 debenzylation of 67 and 66, are converted into tournefolic acid A 68 and tournefolal 69 respectively (Scheme 15).143

A novel and efficient synthetic approach for the synthesis of biologically potent natural benzofurans is reported in 2007 by Naito and co-workers. 144 The important step of this protocol is the well-known [3,3]-sigmatropic rearrangement. TFAA has been established as the best reagent to promote [3,3]sigmatropic rearrangement for the preparation of cyclic or acyclic dihydrobenzofurans. Alternatively, the TFAT-DMAP

system was proved as the most efficient system for the synthesis of different benzofurans. This method is particularly practical since the protection of the phenolic hydroxy groups in the synthesis of hydroxylated 2-arylbenzofurans is non-

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 6 50g,146 and coumestan 83 were achieved.147 These compounds showed various biological activities. For the synthesis of compounds 75, 50g and 83 with no hydroxy group, this synthetic approach was especially remarkable since they can be accomplished without any protection of the phenolic hydroxy groups (Scheme 16). Initially, the synthesis of stemofuran A 75, which had been isolated from Stemona collinsae, 145 was attempted. The synthesis of stemofuran A was achieved through condensation of ketones with aryloxyamine followed by reaction with TFAT-DMAP in sequential reactions involving four steps giving the desired products in 72% yield. This reported synthesis of stemofuran A by Pasturel and co-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 tournefolic acid A 68, tournefolal 69 and salvianolic acid C 70.

Scheme 16 Total synthesis of stemofuran A 75.

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

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

The third desired target was coumestan 83.¹⁴⁷ That is a basic pharmacophore having coumestanes such as coumestrol, ¹⁴⁹ which exhibits estrogenic potency. Due to its unique and remarkable structure, coumestan 83 has attracted the attention of several organic chemists who were attempting independently different approaches. ^{150,151} One of successful reported synthetic

strategies involved the synthesis of the benzofuran moiety in the second step. Initial condensation of readily available *O*-phenylhydroxylamine 72 with 4-chromanone *via* sequential acylation/rearrangement of the resulting oxime ether **81** gave the desired tricyclic benzofuran **82** in 73% yield in only two steps. Finally, the carbonyl group was introduced upon the treatment of tricyclic benzofuran **82** with PCC to furnish coumestan **83** in good yield (Scheme 18).¹⁴³

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

RSC Advances

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 $\rm ZnCl_2$ 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 I₂/Ag₂SO₄ in EtOH at room temperature to give iodovanillin **100** in 80% yields. Sonogashira coupling of **100** with 3,4-methylenedioxyphenylacetylene **101** which was easily prepared from piperonal *via* Colvin rearrangement,¹⁶⁴ by using Pd(PPh₃)₄/CuI/Et₃N 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.

RSC Advances

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 crosscoupling 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 vield (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-p-glucopyranoside. Ribisin A has a highly oxygenated benzofuran scaffold, thus for its total synthesis, it was taken advantages of the intrinsic chirality of p-glucose. The important features of this total synthesis are applying some name reactions. It involved the Ferrier carbocyclization, Johnson iodination, Suzuki crosscoupling reaction, and Wacker oxidative cyclization. In this total synthesis, initially the commercially available methyl α -Dglucopyranoside 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 H₂O₂ 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 heterocyclic conversation and synthesis via antioxypalladation.172 It was successfully applied to oxidative cyclization of 120 by using PdCl₂/CuCl/O₂. 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, R₂ = OH). Palladium-catalyzed coupling of the more reactive aryl acetylenes175-177 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 2methoxy-4,5-methylenedioxybenzyltriphenylphosphonium bromide and 2,4-di-tert-butyldimethylsiloxy-benzaldehyde. An alternative pathway to cicerfuran 126a involves epoxidation and

110: Ribisin A

Scheme 27 Total synthesis of ribisin A 110

122 123 124

HO
$$R^2$$
 epoxidation

124 126a: $R^1 = OMe$, $R^2 = OH$

126b: $R^1 = H$, $R^2 = H$

126c: $R^1 = OMe$, $R^2 = H$

126c: $R^1 = OMe$, $R^2 = H$

126c: $R^1 = OMe$, $R^2 = H$

126c: $R^1 = Me$, $R^2 = H$

126e: $R^1 = H$, $R^2 = H$

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 ${\bf 131a-c}$ (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 ${\bf 132a-c}$. These epoxides can be easily converted to the desired compound by using a few crystals of p-toluenesulphonic acid in chloroform (Scheme 32). 178

Sonogashira coupling/cyclization reaction of aryl iodide **134** with 2-methyl-3-butyn-2-ol **135** was achieved in the presence of Pd(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

HO
$$\frac{124i: R = OMe}{R}$$
 $\frac{3-CPBA, CH_2Cl_2}{R}$ $\frac{125a: R = OMe, 67\%}{125b: R = Me}$ $\frac{126c: R = OMe, 76\%}{126d: R = Me, 50\%}$

Scheme 29 Total synthesis of cicerfuran 126c, d.

$$\begin{array}{c} R^{3} \\ R^{2} \\ \end{array} + \begin{array}{c} HO \\ \\ \end{array} \\ \begin{array}{c} Pd(Ph_{3}P)_{2}Cl_{2} \\ \hline \\ CuI, Et_{3}N, DMF \end{array} \\ \begin{array}{c} R^{3} \\ \end{array} \\ \begin{array}{c} R^{2} \\ \end{array} \\ \begin{array}{c} R^{3} \\ \end{array} \\ \begin{array}{c} R^{3}$$

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 coworkers (25% overall yield).¹⁸² Eidamshaus and Burch in 2008 accomplished a four-step total synthesis of **50g**, in a three-pot approach. Initially, 2-bromo-4-chlorophenol **138** was coupled with 4'-methoxypropiophenone **139**, which was followed by concurrent cyclization under optimized reaction conditions to afford compound **140** containing a benzofuran moiety in 45% yield. The latter was then transformed to the desired natural product **50g** *via* a cascade reaction involving Stille reaction and demethylation with ethanethiolate in one-pot fashion (Scheme **34**).¹⁸³

The aglyconic part, which is also called eupomatenoid-6 **50g**, is a naturally occurring compound. It was initially isolated from

extract of the leaves of Piper fulvescens. Compound 146 can be subjected into glycodiversification, 184-186 thus can create a set of diverse modulators of Hsp90 activity. 187-189 For glycol diversification, eupomatenoid-2 of the 2-(4'-hydroxyphenyl)benzofuran aglycon (a.k.a. eupomatenoid-6) was subjected into glycosylation. Glycosylation of the phenol by glycosylbromides under basic conditions afforded the desired products in the gluco-, galactoand 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 5chlorobenzofuran 145. Finally, the latter was transformed to the desired natural product 146 in several steps. 190

Review

Scheme 32 Synthesis of the natural products 126

Scheme 33 Total synthesis of cicerfuran 126.

Scheme 34 Total synthesis of eupomatenoid 6 50g.

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

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

147,¹⁹² which is easily available from citronellene. Compound 147 is transformed into ketone 148 in several steps including palladium(0)-mediated rearrangement. The latter was then subjected to acid-catalyzed formation of the furan ring which concomitantly removes the 3-OMOM group to give 149 which was oxidized to carboxylic acid 150 (Scheme 36). After several steps, involving functional groups transformations compound 50g was converted into the desired natural product 151.¹⁹³

A pathway for the total synthesis of the bacterial metabolite kendomycin **151** was reported in 2014. Furthermore, an efficient strategy for the total synthesis of **151** was achieved starting from readily available 2-methoxy-3-methylbenzene-1,4-diol **152**, which was initially transformed into cycloalkyne **153**. The latter was then underwent to a gold-catalyzed hydroalkoxylation resulting in benzofuran **155**, which contains benzofuran moiety in its structure. Worthy to mention that benzofuran **155** had been utilized as an intermediate en route to **151**. In this strategy, cycloalkyne **153** was submitted to saponification of the

remaining acetate. Noticeably, upon treatment of cycloalkyne 153 with 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.

RSC Advances Review

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 (+)-liphagal 200 has also been accomplished in 13 steps with 9% overall yield and reported.

The total synthesis was started from a natural product (+)-sclareolide **161**. In this approach, the key step is a ring expansion involving the generation of a highly stabilized benzylic carbocation, which is converted into the sevenmembered 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 rearmament in 74% overall yield. Then, the synthesis of (+)-liphagal, the desired natural product **160** was accomplished after two steps (Scheme 39).²⁰¹

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

Scheme 38 Total synthesis of liphagal 160.

OMe

MeO

OTHP

MeO

OH

1. H, -H₂O

2. pinacol
rearrangement
3. -H₂O

161

162

163

160: Liphagal

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*-butyldimethylsilanyloxy)-5-ethynylbenzene 171 employing Sonogashira cross coupling under basic conditions and *in situ* cyclization afforded 172 which upon final deprotection with HF-pyridine provided (–)-moracin O 173 in a 75% yield. The

NMR spectra of synthetic (-)-173 were identical to the spectra of the corresponding natural products (Scheme 41).²⁰⁴

Then, the synthesis of (–)-176 was started from 2,4-dihydroxybenzaldehyde 169 is converted into dihydrochomarine. 174 The latter was reacted with alkyne 171 under Sonogashira cross coupling conditions followed by *in situ* cyclization in dioxane to afford benzo[*b*]furan intermediate 175 in a 36% yield. Early attempts to remove the TBDMS groups from benzofuran derivative 175 using TBAF yielded a mixture of products, possibly due to the strong basic conditions and/or the long reaction time which either permitted group 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 hypoxiainducible factor (HIF-1), a mediator, which is a key important during adaptation of cancer cells to tumor hypoxia. Systematic studies revealed the significance of presence of the 2-arylbenzofuran ring and particularly the core framework should have (*R*)-configuration. The 2-arylbenzofuran is a common unit, consisting of B, C, and D rings. All the benzofuran derivatives **179–191** were

Scheme 40 Total synthesis of liphagal 160.

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

173: (±)-Moracin O

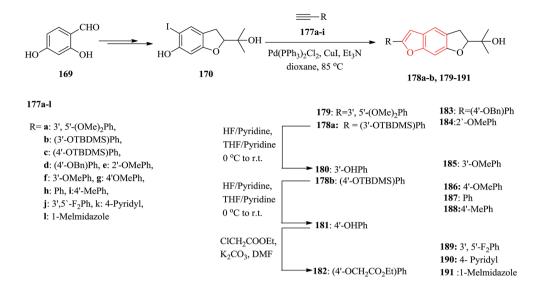
Scheme 42 Total synthesis of (-)-moracin P 176.

synthesized as outlined in Scheme 43. The key and important intermediates for the synthesis of moracin O or P derivatives as shown in Scheme 43 is dihydrobenzofuran 170 which can be synthesized from 2,4-dihydroxybenzaldehyde in several steps. The terminal acetynyl derivatives either were purchased from commercial sources 177e-l or synthesized 177a-d. The acetynyl compounds can be provided *via* a procedure developed by Ramirez-Corey-Fuchs, in which compounds 177a-d were synthesize in three steps.²⁰⁷ The Sonogashira catalyzed coupling of terminal acetylenes 177a-l with substituted *o*-iodophenol 170 afforded the moracin O analogues 178a, b and 179–191. Compounds 178a, b were deprotected using HF/pyridine to yield the corresponding phenol analogues 180 and 181 in satisfactory yields. Treatment of compound 181 with ethyl chloroacetate gave the alkylated product 182.²⁰⁸

It has been reported that the (R)-isomer of moracin O was more active than its (S)-isomer. Unpleasantly, the stereogenic center of the synthesized analogues was generated in a non-stereospecific fashion. Thus, it was desirable to synthesize the corresponding (R)-stereoisomer of the analogues 181 asymmetrically in optically pure form for further biological screening. The asymmetric synthetic approach was outlined in

Scheme 44. In this pathway, the key intermediate is an optically pure iodobenzofuran derivative (R)-(-)-**170** which can be obtained from the prenylated derivative **192** in five steps including a stereoselective synthesis. (R)-(-)-**170** reacted with the protected ethynyl benzene compound **177c** *via* Sonogashira reaction to provide (R)-(-)-**178** with subsequent deprotection with HF/pyridine, which gave the desired target (R)-(-)-**181**.²⁰⁸

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



Scheme 43 Total synthesis of compounds 179–191.

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

heptenoic acid 193 with ethyl formate in the presence of LDA in THF. The formyl ester 194 upon treatment with the butenolide 195 in 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 furoventalene 200 by comparison of its spectroscopic data with those obtained from the original natural product (Scheme 45). 210

Khellin **207** is one of several furochromones that was isolated from *Ammi visnaga* L., a perennial herbaceous plant that cultivates desolate in several Eastern Mediterranean countries. 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*-dimethyformamide 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 *Tephrosiapurpurea*.²¹⁵ *T. IanceolotaPongamia glabra*²¹⁶ and *T. hamiltonii*.²¹⁷ The structure of pongamol was established as the enol by X-ray crystallography.²¹⁸ Lanceolatin B was isolated from *P. pinnata*²¹⁹ and *T. purpurea*.²²⁰ A new method for dipolar cycloaddition of diazocyclohexane-1,3-diones, leading to benzofuran derivatives has been applied to the tota1 synthesis of natural products from *Tephrosia* and *Pongamia*. Total synthesis of pongamol 211 and lanceolatin B 212 started from 6,7-dihydrobenzofuran-4(5*H*)-one 208, which initially reacted with acetone, DME in the presence of NaH or KH to give compound 209 upon carboxylation and then subjected to dehydrogenation to be converted into methoxy derivative 210. The latter was

Scheme 45 Total synthesis of furoventalene 200.

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

Total synthesis of garcifuran B 217, which is the constituents of plants of the *Garcinia* genus (Guttiferae) was achieved and reported. This plant has been used in traditional herbalmedicines in areas of southeastern Asia, shown later to contain a number of toxic components. 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. The total synthesis of garcifuran B 217 started with 5-bromo-2-hydroxybenzaldehyde 213 which was reacted with

BrCH(CO₂Et)₂ in the presence of K_2CO_3 to provide benzofuran 214 and after 2 steps is converted into 5-bromobenzofuran 216. The reactive trimethylstannyl 215 reacted smoothly with 5-bromobenzofuran 216 to give the desired benzofuran in 44% yield, which was then deprotected by heating under reflux in AcOH/ H_2O to afford the natural product, garcifuran B 217 (Scheme 48).²²⁴

Benzofuran derivative **220** was isolated from various yeasts as an 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

Br CHO BrCH(CO₂Et)₂, Br CO₂Et
$$\frac{1. \text{ KOH, H}_2\text{SO}_4}{2. \text{ Cu, quinoline,}}$$
 $\frac{1. \text{ Pd}(\text{PPh}_3)_4}{2. \text{ H}_3^{\circ} \text{ , } \Delta}$ $\frac{1. \text{ Pd}(\text{PPh}_3)_4}{2. \text{ H}_3^{\circ} \text{ , } \Delta}$ $\frac{1. \text{ Pd}(\text{PPh}_3)_4}{2. \text{ H}_3^{\circ} \text{ , } \Delta}$ $\frac{217: \text{ Garcifuran B}}{217: \text{ Garcifuran B}}$

Scheme 48 Total synthesis of garcifuran B 217.

This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

Open Access Article. Published on 05 2017. Downloaded on 05/11/2025 11:32:56

Review

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 gave 5-hydroxy-2-(4-methoxyphenyl)-2,3dihydrobenzofuran 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 1aryloxypropan-2-ones 233a-c with DMFDMA, with subsequent addition of the catalyst, providing a route that was literally onestep 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 1aryloxypropan-2-ones 233a-f with DMFDMA. The intramolecular cyclization of 3-aryloxy-4-dimethylamino-3-buten-2ones 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 potential utility in the treatment of human

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

RSC Advances

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 2,4dihydroxybenzaldehyde and nitromethane was stirred in AcOH in the presence of NH₄OAc to give 5-hydroxy-2-(2-nitroethenyl) phenol 236 (ref. 248) in 84% yield. The unsaturated compound 236 was then converted into the desired product 237 (ref. 248) in 87% yields by treatment with NaBH₄ in i-PrOH-THF (1:4) at room temperature. It is well known that a nitro group can be easily converted to a carbonyl by the Nef reaction. 4-(2-Nitroethyl)benzene-1,3-diol 237 was thus subjected to the Nef reaction. Interestingly, the predicted aldehyde 238 was not obtained, while the required benzofuran-6-ol 239,249 was produced directly in a one-pot reaction under the reaction conditions. It is visualized that benzofuran-6-ol 239 could produce the intermediate 238 via an intramolecular cyclocondensation under Nef conditions. Based on this finding, a major attempt was there after made to modify the Nef reaction conditions aiming to improve the yield of benzofuran-6-ol 239, which is the key intermediate for the synthesis of diversified furocoumarins 240a (Scheme 54).250

The dibenzofuran-1,4-dione core is found being present in many naturally occurring compounds, some showing interesting biological activities. Some of them are cytotoxic popolohuanone E,251 antipruritic balsaminone A252 and violetquinone.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 4,5dimethoxy-7-methylnaphthalen-1-ol 241 via a two-step sequential reaction. Relied on, these back grounds, the oxidative cyclization of quinone-arenols 242 was conducted by using benzoquinone 228 as an efficient oxidant in the presence of molecular oxygen, giving raise in 243 in satisfactory yield. Ultimately, MgBr2-iodide-catalyzed selective demethylation of the C4- and C11-OMe motives of 243 gave the desired target violet-quinone 244 in high vield (Scheme 55).254

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

No₂ NaBH₄,
$$i$$
-PrOH/THF NO₂ NaBH₄, i -PrOH/THF NO₂ NaBH₄, i -ProH/THF NO₂ No₂ NaBH₄, i -ProH/THF NO₂ NaBH₄, i -ProH/THF NO₂ No₂ NaBH₄, i -ProH/THF NO₂ No₂ NaBH₄, i -ProH/THF No₂ No₃ NaBH₄, i -ProH/THF No₂ No₃ NaBH₄, i -ProH/THF No₂ No₃ NaBH₄, i -ProH/THF No₂ NaBH₄, i -ProH/THF No₂ No₃ NaBH₄, i -ProH/THF No₂ NaBH₄, i -ProH/THF No₃ No₄ NaBH₄, i -ProH/THF No₄ No₅ No₅ No₅ No₅ No₅ No₅ NaBH₄, i -ProH/THF No₅ No₅

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 pivalovl and a trimethylsilylethoxymethyl group. The resulting crude product from 250 was subjected to an intramolecular etherification under standard conditions to complete the construction of tetracyclic framework of erypoegin H 251, which was obtained in a respectable 28% yield over the nine steps of the longest linear sequence. The resulting compound 249, upon exposure to catalytic amounts of PtCl₂ in toluene under a CO atmosphere, 257,258 underwent a clean cycloisomerization with the formation of the desired benzofuran derivative 250. This reaction was best performed in the presence of powdered molecular sieves to sequester traces of water that might protonate the putative organo platinum intermediate of type C and/or D and hence reduce the efficiency of the $O \rightarrow C$ 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 alterpalladium-catalyzed Sonogashira deprotection and ring closing step. Initially, a suitable Omethyl-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-Sonogashira cascade coupling based strategy (Scheme 57).262

Scheme 56 Total synthesis of erypoegin H 251

Scheme 57 Total synthesis of vignafuran 255

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

The first total synthesis of glycyrol, isolated from glycyrrhizae radix, with a unique skeleton of a benzofuran coumarin was reported in 2008. Glycyrrhizae radix is a traditional medicine in the East Asia, and contains biologically active natural products such as glycyrrhizin, glycyrol, glycycoumarin, and liquoric acid.263 Glycyrol has antibacterial activity against upper airway respiratory tract pathogens.264 The key steps are Smiles rearrangement and selective introduction of prenyl and O-methyl groups. Preparation of O-benzyl-(diacetoxyiodo)arene 257 as a Smiles rearrangement precursor for the construction of benzofuran coumarin had unexpected difficulties. Benzylation of commercially available 2-iodophenol was achieved and after several steps, a crude 1-benzyloxy-3-(diacetoxyiodo)benzene 257 was provided. However, 1-benzyloxy-3-(diacetoxyiodo)benzene 257 was more unstable than commercially available 3methoxy-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 2iodo-4-phenoxycoumarin 261 in 87% yield by refluxing in DMF via Smiles rearrangement. The palladium-mediated intramolecular coupling reaction of vinyl iodide with the phenyl group in 261 was readily achieved by using palladium(II) acetate

Gnetuhainin B 272 was initially isolated from the lianas of Gnetum hainanense by Lin and co-workers.266 The structure of viniferifuran as the congerer of gnetuhainin, extracted from Vitis vinifera 'Kyohou' was fully characterized based on the widespread 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 cyclodehydration was performed for the facile access to 3-arylbenzofuran moiety. Consequently, for the introduction of aryl group at the C-2 position of benzofuran a Pd-catalyzed direct C-H activation of benzofuran followed by cross-coupling with

Scheme 58 Total synthesis of glycyrol 263

aryl halide is a key reaction. In an approach towards the total synthesis of these analogues, Chakraborty and co-workers synthesized aryloxyketone **266**, which was in turn can be readily synthesized from the treatment of phenol **264** (ref. 271) with α -bromoketone **265** (ref. 272) mediated by K_2CO_3 . Upon the treatment of ketone **266** with BCl₃ 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 coppermediated 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 ptoluene-sulfonate, 2-iodoxybenzoic acid, and silver(1)oxidethionyl chloride, providing the desired target 279 in 98% yield (Scheme 60).277

(\pm)-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(\mathfrak{l})-catalyzed construction of a bis(benzo[\mathfrak{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(\mathfrak{l}) iodide under the conditions of a modified Stephens–Castro reaction. After several steps, phenol **284**, was transformed into the desired natural product (\pm)-**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, sevenmembered 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 (\pm) -laetirobin 285.

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

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

Syah and co-workers reported the isolation and characterization of a novel oligostilbenoid from the tree bark of *Hopea mengarawan*. This natural product exhibited potent

immunosuppressive activity.²⁸³ As a matter of fact, several of oligomeric stilbenes have been isolated and recognized having divergent means of connectivity of their basic 1,2-diphenylethylene scaffold. Several remarkable biological functions of this family have been acknowledged comprising antibacterial

RSC Advances Review

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 BCl₃ in CH₂Cl₂ undergoes regioselective demethylation to give the tetracyclic 6*H*-anthra[1,9-*bc*]furan-6-one G. In fact, treatment of **289** with BCl₃, 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-butyn-1-ol at ambient

Scheme 63 Total synthesis of diptoindonesin G 293

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

Scheme 65 Synthesis of 301a, b.

temperature. After two steps, 302 afforded 303a and 303b in high yields. Compound 303a underwent the mixed-metalmediated 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-Benzovlbenzo[b]furans and aurones (2-benzylidene-3-(2H)benzofuran-3-ones) are occurring in nature and bearing the same carbon unit scaffold (C6-C3-C6). 2-Benzovlbenzo[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(2H)-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 Zisomers, in respective to the configuration of naturally

occurring aurones. The reduction of aurones was conducted with sodium borohydride in methanol at ambient temperature corresponding allylic the alcohols 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.

RSC Advances Review

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 (+)-fulicineroside **315** as the desired target *via* multi-steps reaction through different functional group transformations (Scheme 68).³⁰¹

Coumestrol **319** is an essential dietary ingredient found in forage plants, cabbages and soybeans.³⁰² Due to its importance in human nutrition, it has been extensively studied.^{303,304} The total synthesis of **319** based on the iron-catalyzed cross-dehydrogenative coupling (CDC) was achieved and revealed in 2013. In this approach, a modified aerobic oxidative cross-coupling applied for the construction of benzofuran, a moiety present in coumestrol **319**. Ethyl 2-(2,4-dimethoxybenzoyl)

acetate **317** and 3-methoxy phenol **316**, were reacted in DCE as solvent at 70 °C in the presence of $FeCl_3$ as the catalyst and 2,2′-bipyridine as additives to give compound **318**. The latter was then submitted to sequential deprotection/lactonization giving the desired natural product in good (59%) overall yield (Scheme 69).³⁰⁵

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

Scheme 68 Total synthesis of fulicineroside 315.

Review RSC Advances

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 coworkers¹⁰² 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)propiolic acid or propiolic acid and *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride or dicyclohexylcarbodiimide. The total synthesis of pimpinellin **328** started from vanillin **19**, which was transformed to substituted arene **325** in 84% yield. The latter was then submitted to a Sonogashira cross-coupling ³¹³ reaction with triisopropylsilylacetylene to afford a 1:8 mixture of acetylene **326** (5%) and the isomeric benzofuran **327** (39%). Delightfully,

they could be separated by column chromatographically. The rather moderate yields linked with the transformed $325 \rightarrow 326 + 327$ 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).

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

328: Pimpinellin

Scheme 72 Total synthesis of xylarianaphthol-1 336

resulting in the formation of compound 332. The latter was further treated with sodium acetate to produce acetate 333, which can be used as the precursor of the key intramolecular arylation. Among several efforts to find optimal conditions the combination of Pd(PPh₃)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 silvlether 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 AlCl₂. 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 2substituted-3-functionalized benzofuran through molecular 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. 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.

tative yield (Scheme 75).326

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

Moreover, the synthesis of (\pm) -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.

genation step provided the natural product virtually in quanti-

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 (\pm) -anastatins B 347.

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

Review RSC Advances

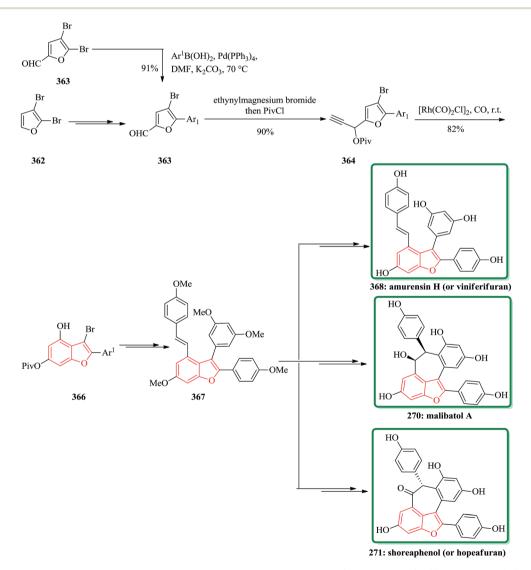
Scheme 77 Total synthesis of vialinin C 355 and ganbajunin B 356.

a ketone and three phenolic OH groups and also involves an additional E-ring bearing one more phenolic OH group. Dip G 293 exhibited anti-proliferation effect in murine leukemia P-388 cells.282 A convergent synthetic approach for the total synthesis of diptoindonesin G 293 has been achieved and reported by Tang and co-workers in 2009.330 The protocol comprises a regioselective dehydrative cyclization of arylacetals, a regioselective bromination of benzofurans, a sequential cross-coupling of bromo-benzofurans with aryl boronicacids and a BBr₃mediated 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 crosscoupling with 3,5-dimethoxyphenyl boronic acid, which occurred at high temperature. The desired target Dip G 293 was synthesized from 361 via BBr3 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 routs333,334 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 Ar₂B(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.

Review

OMe 1. Tf₂O 2. Ar₁CH=CHB(OH)₂

Scheme 80 Synthesis of PPA 370 and fuliginosin A 371

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

Conclusion

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

Abbreviations

(PTP-1B) Protein tyrosine phosphatase inhibitors (NTI) Naltrindole

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

Acknowledgements

The authors are grateful to Department of Chemistry of Alzahra University for the encouragements and Alzahra University Research Council, for partial financial support. MMH is thankful to Iran National Research Foundation (INSF) for the partial financial supports.

References

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

8 M. Koca, S. Servi, C. Kirilmis, M. Ahmedzade, C. Kazaz,

RSC Advances

B. Özbek and G. Ötük, Eur. J. Med. Chem., 2005, 40, 1351-1358.

- 9 L. Pieters, S. V. Dyck, M. Gao, R. Bai, E. Hamel, A. Vlietinck and G. Lemiére, J. Med. Chem., 1999, 42, 5475-5481.
- 10 K. M. Dawood, H. Abdel-Gawad, E. A. Rageb, M. Ellithey and H. A. Mohamed, Bioorg. Med. Chem., 2006, 14, 3672-3680.
- 11 K. Tsujihara, M. Hongu, K. Saito, H. Kawanishi, K. Kuriyama, M. Matsumoto, A. Oku, K. Ueta, M. Tsuda and A. Saito, J. Med. Chem., 1999, 42, 5311-5324.
- 12 Y. Liao, A. P. Kozikowski, A. Guidotti and E. Costa, Bioorg. Med. Chem. Lett., 1998, 8, 2099-2102.
- 13 A. H. Banskota, Y. Tezuka, K. Midorikawa, K. Matsushige and S. Kadota, J. Nat. Prod., 2000, 63, 1277-1279.
- 14 M. Ono, H. Kawashima, A. Nonaka, T. Kawai, M. Haratake, H. Mori, M. Kung, H. F. Kung, H. Saji and M. Nakayama, I. Med. Chem., 2006, 49, 2725-2730.
- 15 D. Manish, B. K. Tripathi, A. K. Tamrakar, A. K. Srivastava, B. Kumar and A. Goel, Bioorg. Med. Chem., 2007, 15, 727-
- 16 D. H. Choi, J. W. Hwang, H. S. Lee, D. M. Yang and J. G. Jun, Bull. Korean Chem. Soc., 2008, 29, 1594-1596.
- 17 Z. Liu, G. Xia, S. Chen, Y. Liu, H. Li and Z. She, Mar. Drugs, 2014, 12, 3669-3680.
- 18 F. Xu, Y. Zhang, J. Wang, J. Pang, C. Huang, X. Wu, Z. She, L. L. P. Vrijmoed, E. B. Gareth Jones and Y. Lin, J. Nat. Prod., 2008, 71, 1251-1253.
- 19 P. Dawson, J. Opacka-Juffry, J. D. Moffatt, Y. Daniju, N. Dutta, J. Ramsey and C. Davidson, Biol. Psychiatry, 2014, 48, 57-63.
- 20 N. Maggi, C. R. Pasqualucci, R. Ballotta and P. Sensi, Chemotherapy, 1966, 11, 285-292.
- 21 M. Sofuoglu, P. S. Portoghese and A. E. Takemori, J. Pharmacol. Exp. Ther., 1991, 257, 676-680.
- 22 G. V. Naccarelli, D. L. Wolbrette, H. M. Patel and J. C. Luck, Current Opinion in Cardiology, 2000, 15, 64-72.
- 23 S. Kathofer, D. Thomas and C. A. Karle, Cardiovasc. Drug Rev., 2005, 23, 217-230.
- 24 Q. Wu, L. A. Christensen, R. J. Legerski and K. M. Vasquez, EMBO Rep., 2005, 6, 551-557.
- 25 E. G. Schneiders and R. Stevensonm, J. Org. Chem., 1979, 44, 4710-4711.
- 26 F. G. Schreiber and R. Stevenson, J. Chem. Soc., Perkin Trans. 1, 1976, 1, 1514-1518.
- 27 R. L. Shriner and P. McCutchan, J. Am. Chem. Soc., 1929, 81, 2193-2195.
- 28 M. W. Rathke, J. Am. Chem. Soc., 1970, 92, 3222-3223.
- 29 M. W. Rathke and D. F. Sullivan, J. Am. Chem. Soc., 1973, 95, 3050-3051.
- 30 S. Y. Lin, C.-L. Chen and Y.-J. Lee, J. Org. Chem., 2003, 68, 2968-2971.
- 31 W. S. Sheen, I. L. Tsai, C. M. Teng and I. S. Chen, Phytochemistry, 1994, 36, 213-215.
- 32 C. L. Kao and J. W. Chern, Tetrahedron Lett., 2001, 42, 1111-1113.
- 33 C. L. Kao and J. W. Chern, J. Org. Chem., 2002, 67, 6772-6787.
- 34 C. Fuganti and S. A. Serra, *Tetrahedron Lett.*, 1998, **39**, 5609–5610.

- 35 R. Basawaraj, B. Yadav and S. S. Sangapure, Indian J. Heterocycl. Chem., 2001, 11, 31-34.
- 36 S. M. Rida, S. A. M. El-Hawash, H. T. Y. Fahmy, A. A. Hazzaa and M. M. M. El-Meligy, Arch. Pharmacal Res., 2006, 29, 826-
- 37 R. K. Ujjinamatada, R. S. Appala and Y. S. Agasimundin, J. Heterocycl. Chem., 2006, 43, 437-441.
- 38 S. Wachi, K. Takagi, G. Menichi and M. Hubert-Habart, Bull. Soc. Chem., 1978, 56, 230-233.
- 39 D. V. Singh, A. R. Mishra, R. M. Mishra, A. K. Pandey, C. R. Singh and A. K. Dwivedi, Indian J. Heterocycl. Chem., 2005, 14, 319-322.
- 40 A. M. Farag, A. S. Mayhoub, S. E. Barakat and A. H. Bayomi, Bioorg. Med. Chem., 2008, 16, 4569-4578.
- 41 B. Insuasty, A. Tigreros, F. Orozco, J. Quiroga, R. Abonia, M. Nogueras, A. Sanchez and J. Cobo, Bioorg. Med. Chem., 2010, 18, 4965-4974.
- 42 A. M. Farag, A. S. Mayhoub, S. E. Barakat and A. H. Bayomi, Bioorg. Med. Chem., 2008, 16, 881-889.
- 43 I. M. El-Deeb and S. H. Lee, Bioorg. Med. Chem., 2010, 18, 3961-3973.
- 44 B. S. Holla, P. M. Akberali and M. K. Shivananda, *Il Farmaco*, 2000, 55, 256-263.
- 45 A. Mustafa, C. A. Hismat and M. M. J. Yannis, J. Prakt. Chem., 1970, 312, 1011-1019.
- 46 M. H. Elnagdi, M. R. H. Elmoghayor, E. A. A. Hafez and H. H. Alnima, J. Org. Chem., 1975, 40, 2604-2607.
- 47 H. G. Garg, J. Med. Chem., 1972, 15, 446-447.
- 48 F. Manna, F. Chementi, R. Fioravanti and A. Bolasco, Bioorg. Med. Chem. Lett., 2005, 15, 4632-4635.
- 49 J. H. Ahn, H. M. Kim, S. H. Jung, S. K. Kang, K. R. Kim, S. D. Rhea, S. D. Yong, H. G. Cheon and S. S. Kim, Bioorg. Med. Chem. Lett., 2004, 14, 4461-4465.
- 50 R. V. Ragavan, V. Vijayakumar and N. S. Kumari, Eur. J. Med. Chem., 2010, 45, 1173-1180.
- 51 Y. R. Prasad, A. L. Rao, L. Prasoona, K. Murali and K. P. Ravi, Bioorg. Med. Chem. Lett., 2005, 15, 5030-5034.
- 52 J. C. Jung, E. B. Watkins and M. A. Avery, Heterocycles, 2005, 65, 77-94.
- 53 A. E. Rashad, M. I. Hegab, R. E. Abdel-Megeid, J. A. Micky and F. M. E. Abdel-Megeid, Bioorg. Med. Chem., 2008, 16, 7102-7106.
- 54 P. D. Seemuth and H. Zimmer, J. Org. Chem., 1978, 43, 3063-3065.
- 55 B. Ledoussal, A. Gorgues and A. Le Coq, J. Chem. Soc., Chem. Commun., 1986, 171-172.
- 56 L. Abmann and W. Friedrichsen, Heterocycles, 1989, 29, 1003-1004.
- 57 A. Arcadi, S. Cacchi, M. Del Rosario, G. Fabrizi and F. Marinelli, J. Org. Chem., 1996, 61, 9280-9288.
- 58 I. Nakamura, Y. Mizushima and Y. Yamamoto, J. Am. Chem. Soc., 2005, 127, 15022-15023.
- 59 X. Z. Jiang, W. L. Liu, W. Zhang, F. Q. Jiang, Z. Gao, H. Zhuang and L. Fu, Eur. J. Med. Chem., 2011, 46, 3526-
- 60 A. Hercouet and M. Le Corre, Tetrahedron, 1981, 37, 2867-2873.

- 61 L. Capuano, S. Drescher, V. Hammerer and M. Hanisch, Chem. Ber., 1988, 121, 2259–2261.
- 62 (*a*) S. Ghosh and J. Das, *Tetrahedron Lett.*, 2011, **52**, 1112–1116; (*b*) S.-E. Syu, Y.-T. Lee, Y.-J. Jang and W. Lin, *Org. Lett.*, 2011, **13**, 2970–2973.
- 63 Y. Liu, H. K. Jacobs and A. S. Gopalan, *Tetrahedron Lett.*, 2011, 52, 2935–2939.
- 64 D. C. Schroeder, P. O. Corcoran, C. A. Holden and M. C. Mulligan, J. Org. Chem., 1962, 27, 586–591.
- 65 G. Lamotte, P. Demerseman and R. Royer, *Synthesis*, 1984, 1068–1070.
- 66 W. T. Brady and Y. F. Giang, *J. Org. Chem.*, 1986, **51**, 2145–2147.
- 67 J. K. MacLeod and B. R. Worth, *Tetrahedron Lett.*, 1972, **13**, 237–240.
- 68 J. Einhorn, P. Demerseman and R. Royer, *J. Heterocycl. Chem.*, 1985, 22, 1243–1247.
- 69 G. Pandey, A. Krishna and U. T. Bhalerao, *Tetrahedron Lett.*, 1989, 30, 1867–1870.
- 70 Y. Liu, J. Qian, S. Lou and Z. Xu, J. Org. Chem., 2010, 75, 6300–6303.
- 71 S. W. Youn and J. I. Eom, Org. Lett., 2005, 7, 3355-3358.
- 72 M. Murai, K. Miki and K. Ohe, *Chem. Commun.*, 2009, 3466–3468.
- 73 A. Hiremathad, M. R. Patil, K. R. Chethana, K. Chand, M. A. Santos and R. S. Keri, RSC Adv., 2015, 5, 96809–96828.
- 74 G. Khodarahmi, P. Asadi, F. Hassanzadeh and E. Khodarahmi, *J. Res. Med. Sci.*, 2015, **20**, 1094–1104.
- 75 C. Selvam, B. C. Jordan, S. Prakash, D. Mutisya and R. Thilagavathi, Eur. J. Med. Chem., 2017, 128, 219–236.
- 76 K. C. Rajeshwari, A. Hiremathad, M. Singh, M. A. Santos and R. S. Keri, *Pharmacol. Rep.*, 2017, **69**, 281–295.
- 77 (a) M. M. Heravi and B. Talaei, Adv. Heterocycl. Chem., 2016,
 118, 195-291; (b) M. M. Heravi and B. Talaei, Adv. Heterocycl. Chem., 2015, 114, 147-225; (c) M. M. Heravi and V. Fathi Vavsari, Adv. Heterocycl. Chem., 2015, 114, 77-145; (d) M. M. Heravi and B. Talaei, Adv. Heterocycl. Chem., 2014, 113, 143-244.
- 78 M. M. Heravi and V. Zadsirjan, *Adv. Heterocycl. Chem.*, 2015, 117, 261–376.
- 79 M. M. Heravi, S. Khaghaninejad and N. Nazari, *Adv. Heterocycl. Chem.*, 2014, 112, 183–234.
- 80 M. M. Heravi, S. Khaghaninejad and M. Mostofi, *Adv. Heterocycl. Chem.*, 2014, **112**, 1–50.
- 81 S. Khaghaninejad and M. M. Heravi, *Adv. Heterocycl. Chem.*, 2014, 111, 95–146.
- 82 M. M. Heravi and T. Alishiri, Adv. Heterocycl. Chem., 2014, 113, 1-66.
- 83 M. M. Heravi and B. Talaei, *Adv. Heterocycl. Chem.*, 2017, **122**, 43–114.
- 84 V. Zadsirjan, M. Shiri, M. M. Heravi, T. Hosseinnejad, S. A. Shintre and N. A. Koorbanally, *Res. Chem. Intermed.*, 2017, 43, 2119–2142.
- 85 (a) R. Mirsafaei, M. M. Heravi and S. Ahmadi, J. Mol. Catal. A: Chem., 2015, 402, 100–108; (b) M. M. Heravi, E. Hashemi,
 Y. S. Beheshtiha, S. Ahmadi and T. Hosseinnejad, J. Mol. Catal. A: Chem., 2014, 394, 74–82.

- 86 M. M. Heravi, E. Hashemi, Y. S. Beheshtiha, K. Kamjou, M. Toolabi and N. Hosseintash, *J. Mol. Catal. A: Chem.*, 2014, 392, 173–180.
- 87 M. M. Heravi, F. Mousavizadeh, N. Ghobadi and M. Tajbakhs, *Tetrahedron Lett.*, 2104, 55, 1226–1228.
- 88 M. M. Heravi, M. Khorasani and F. Derikvand, *Catal. Commun.*, 2007, **8**, 1886–1890.
- 89 M. M. Heravi, M. Daraie and V. Zadsirjan, *Mol. Diversity*, 2015, **15**, 577–623.
- 90 M. M. Heravi and V. F. Vavsari, RSC Adv., 2015, 5, 50890– 50912.
- 91 M. M. Heravi, T. B. Lashaki and N. Poorahmad, *Tetrahedron: Asymmetry*, 2015, **26**, 405–495.
- 92 M. M. Heravi, E. Hashemi and N. Nazari, *Mol. Diversity*, 2014, **18**, 441-472.
- 93 M. M. Heravi, E. Hashemi and F. Azimian, *Tetrahedron*, 2014, 70, 7–21.
- 94 M. M. Heravi, E. Hashemi and N. Ghobadi, *Curr. Org. Chem.*, 2013, 17, 2192–2224.
- 95 M. M. Heravi and E. Hashemi, *Tetrahedron*, 2012, **68**, 9145–9178.
- 96 M. M. Heravi, V. Zadsirjan and M. Dehghani, *Curr. Org. Chem.*, 2016, 20, 1069–1134.
- 97 M. M. Heravi and V. Zadsirjan, *Curr. Org. Synth.*, 2016, **13**, 780–833.
- 98 R. S. Ward, Chem. Soc. Rev., 1982, 11, 75-125.
- 99 R. S. Ward, Tetrahedron, 1990, 46, 5029-5041.
- 100 Z. Yang, H. B. Liu, C. M. Lee, H. M. Chang and H. N. C. Wong, *J. Org. Chem.*, 1992, 57, 7248–7257.
- 101 S. A. Hutchinson, H. Liitjens and P. J. Scammells, *Bioorg. Med. Chem. Lett.*, 1997, 7, 3081–3084.
- 102 P. J. Scammells, S. P. Baker and A. R. Beauglehole, *Bioorg. Med. Chem.*, 1998, 6, 1517–1524.
- 103 Y. H. Kuo and C. H. Wu, J. Nat. Prod., 1996, 59, 625-628.
- 104 M. M. Heravi and S. Sadjadi, *Tetrahedron*, 2009, **65**, 7761–7775.
- 105 H. Lütjens and P. J. Scammells, *Tetrahedron Lett.*, 1998, **39**, 6581–6584.
- 106 M. Inoue, M. W. Carson, A. J. Frontier and S. J. Danishefsky, *J. Am. Chem. Soc.*, 2001, **123**, 1878–1889.
- 107 R. Segal, I. M. Goldzweig, S. Sokolo and D. V. Zaitschek, *J. Chem. Soc. C*, 1967, 2402–2404.
- 108 (a) Q. L. Li, B. G. Li, H. Y. Qi, X. P. Gao and G. L. Zhang,
 Planta Med., 2005, 71, 847–851; (b) M. Takanashi,
 Y. Takizawa and T. Mitsuhashi, Chem. Lett., 1974, 869.
- 109 T. Hirano, M. Goto and K. Oka, Life Sci., 1994, 55, 1061–1069.
- 110 M. M. Heravi and Z. Faghihi, *Curr. Org. Chem.*, 2012, **16**, 2097–2123.
- 111 X. F. Duan, G. Shen and Z. B. Zhang, *Synthesis*, 2010, 7, 1181–1187.
- 112 C. E. Castro, E. J. Gaughan and D. C. Owsley, *J. Org. Chem.*, 1966, **31**, 4071.
- 113 R. D. Stephens and C. E. Castro, *J. Org. Chem.*, 1963, **28**, 3313–3315.
- 114 (a) A. Galet, J. Am. Chem. Soc., 1946, 68, 376-377; (b)
 H. Hellmann and W. Elser, Justus Liebigs Annalen der Chemie, 1961, 639, 77.

RSC Advances

- 115 Z. Yang, P. M. Hon, K. Y. Chui, Z. L. Xu, H. M. Chang, C. M. Lee, Y. X. Cui, H. N. C. Wong, C. D. Poon and B. M. Fung, *Tetrahedron Lett.*, 1991, 32, 2061–2064.
- 116 H. B. Bang, S. Y. Han, D. H. Choi, D. M. Yang, J. W. Hwang, H. S. Lee and J.-G. Jun, *Synth. Commun.*, 2009, **39**, 506–515.
- 117 K. Kawazu, Agric. Biol. Chem., 1980, 44, 1367-1372.
- 118 Y. Fukuyama, M. Nakahara, H. Minami and M. Kodama, *Chem. Pharm. Bull.*, 1996, 44, 1418–1420.
- 119 (a) F. Toda and M. Nakagawa, Bull. Chem. Soc. Jpn., 1959,
 32, 514–516; (b) I. Candiani, S. DeBemardinis, W. Cabri,
 M. Marchi, A. Bedeschi and S. Penco, Synlett, 1993, 9–69;
 (c) K. Hiroya, K. Hashimura and K. Ogasawara,
 Heterocycles, 1994, 38, 2463–2472.
- 120 A. Sakai, T. Aoyama and T. Shioiri, *Tetrahedron Lett.*, 1999, **40**, 4211–4214.
- 121 H.-D. Choi, P. J. Seo and B.-W. Son, *Arch. Pharmacal Res.*, 2002, **25**, 786–789.
- 122 (a) B. F. Bowden, E. Ritchie and W. C. Taylor, Aust. J. Chem.,
 1972, 25, 2659–2669; (b) K. Picker, E. Ritchie and W. C. Taylor, Aust. J. Chem., 1973, 26, 1111–1119; (c) R. W. Read and W. C. Taylor, Aust. J. Chem., 1979, 32, 2317–2321; (d) A. R. Carroll and W. C. Taylor, Aust. J. Chem., 1991, 44, 1615–1626; (e) A. R. Carroll and W. C. Taylor, Aust. J. Chem., 1991, 44, 1627–1633.
- 123 T. A. Engler and W. Chai, *Tetrahedron Lett.*, 1996, 37, 6969–6970.
- 124 W. J. Gensler and J. E. Stouffer, *J. Org. Chem.*, 1958, 23, 908–910.
- 125 T. Bach and M. Bartels, *Tetrahedron Lett.*, 2002, **43**, 9125–9127.
- 126 (a) R. Ahmed and R. Stevenson, Phytochemistry, 1975, 14, 2710–2712; (b) B. A. McKittrick and R. Stevenson, J. Chem. Soc., Perkin Trans. 1, 1983, 475–482; (c) T. A. Engler, W. Chai and K. O. LaTessa, J. Org. Chem., 1996, 61, 9297–9308; (d) T. A. Engler and W. Chai, Tetrahedron Lett., 1996, 37, 6969–6970.
- 127 T. Benincori, E. Brenna, F. Sannicolo, L. Trimarco, P. Antognazza, E. Cesarotti, F. Demartin and T. Pilati, J. Org. Chem., 1996, 61, 6244–6251.
- 128 T. Bach and M. Bartels, Synthesis, 2003, 6, 925-939.
- 129 (a) T. J. Jackson and J. W. Herndon, Tetrahedron, 2001, 57, 3859–3868; (b) J. W. Herndon, Y. Zhang, H. Wang and K. Wang, Tetrahedron Lett., 2000, 41, 8687–8690; (c) J. W. Herndon and A. Hayford, Organometallics, 1995, 14, 1556–1558; (d) J. W. Herndon and H. Wang, J. Org. Chem., 1998, 63, 4562–4563; (e) Y. Zhang and J. W. Herndon, Tetrahedron, 2000, 56, 2175–2184; (f) M. L. Waters, M. E. Bos and W. D. Wulff, J. Am. Chem. Soc., 1999, 121, 6403–6413.
- 130 A. Rahm and W. D. Wulff, *J. Am. Chem. Soc.*, 1996, **118**, 1807–1808.
- 131 R. S. Ward, Nat. Prod. Rep., 1999, 16, 75-96.
- 132 (a) R. S. Mali and A. P. Massey, *J. Chem. Res.*, *Synop.*, 1998, 230–231; (b) Y. Aoyagi, T. Mizusaki, A. Hatori, T. Asakura, T. Aihara, S. Inaba, K. Hayatsu and A. Ohta, *Heterocycles*, 1995, 41, 1077–1084; (c) F. G. Schreiber and R. Stevenson,

- *Chem. Lett.*, 1975, 1257–1258; (*d*) E. Ritchie and R. Taylor, *Aust. J. Chem.*, 1969, 1329–1330.
- 133 A. M. Puentes de Diaz, Phytochemistry, 1997, 44, 345-346.
- 134 A. De Meijere, H. Schirmer and M. Duetsch, *Angew. Chem.*, *Int. Ed.*, 2000, **39**, 3964–4002.
- 135 K. H. Dotz and P. Tomuschat, *Chem. Soc. Rev.*, 1999, **28**, 187–198.
- 136 A. De Meijere, Pure Appl. Chem., 1996, 68, 61-72.
- 137 G. B. Stone and L. S. Liebeskind, *J. Org. Chem.*, 1990, 55, 4614–4622.
- 138 J. Zhang, Y. Zhang, Y. Zhang and J. W. Herndon, *Tetrahedron*, 2003, **59**, 5609–5616.
- (a) T. O. Cheng, *Int. J. Cardol.*, 2007, 121, 9–22; (b)
 X. B. Wang, S. L. Morris-Natschke and K. H. Lee, *Med. Res. Rev.*, 2007, 27, 133–148; (c) L. Zhou, Z. Zuo and M. S. Chow, *J. Clin. Pharmacol.*, 2005, 45, 1345–1359.
- 140 (a) Y. R. Lu and L. Y. Foo, Tetrahedron Lett., 2001, 42, 8223–8225; (b) X. N. Yang, Y. J. Wang, Y. S. Liu and X. Tang, J. Ethnopharmacol., 2008, 117, 408–414; (c) X. S. Ouyang, K. Takahashi, K. Komatsu, N. Nakamura, A. H. Baba and J. Azuma, Jpn. J. Pharmacol., 2001, 87, 289–296; (d) Y. T. Wu, Y. F. Chen, Y. J. Hsieh, I. Jaw, M. S. Shiao and T. H. Tsai, Int. J. Pharm., 2006, 326, 25–31; (e) J. F. Zhao, C. H. Liu, Y. Y. Hu, L. M. Xu, P. Liu and C. Liu, Hepatobiliary Pancreatic Dis. Int., 2004, 3, 102–105.
- 141 Y. L. Lin, Y. Y. Chang, Y. H. Kuo and M. S. Shiao, *J. Nat. Prod.*, 2002, **65**, 745–747.
- 142 (a) C. H. Cho, B. Neuenswander, G. H. Lushington and R. C. Larock, *J. Comb. Chem.*, 2008, 10, 941–947; (b) H. B. Bang, S. Y. Han, D. H. Choi, J. W. Hwang and J. G. Jun, *ARKIVOC*, 2009, 2, 112–125; (c) J. R. Hwu, K. S. Chuang, S. H. Chuang and S. C. Tsay, *Org. Lett.*, 2005, 7, 1545–1548.
- 143 S. D. Shen, G. P. Zhang, M. Leib and L. H. Hu, *ARKIVOC*, 2012, 4, 204–213.
- 144 N. Takeda, O. Miyata and T. Naito, *Eur. J. Org. Chem.*, 2007, 1491–1509.
- 145 T. Pacher, C. Seger, D. Engelmeier, S. Vajrodaya, O. Hofer and H. Greger, *J. Nat. Prod.*, 2002, **65**, 820–827.
- 146 D. C. Chauret, C. B. Berrnard, J. T. Arnason and T. J. Durst, *J. Nat. Prod.*, 1996, **59**, 152–155.
- 147 S. B. Pandit and S. Y. Gadre, *Synth. Commun.*, 1988, **18**, 157–166.
- 148 J. Y. Pasturel, G. Solladie and J. Maignan, *Chem. Abstr.*, 2003, **139**, 36375–36377.
- 149 E. M. Bickoff, R. L. Lyman, A. L. Livingston and A. N. Booth, J. Am. Chem. Soc., 1958, 80, 3969–3971.
- 150 G. A. Kraus and N. Zhang, *J. Org. Chem.*, 2000, **65**, 5644–5646.
- 151 Y. R. Lee, J. Y. Suk and B. S. Kim, *Org. Lett.*, 2000, **2**, 1387–1389.
- 152 (a) I. Muhammad, X.-C. Li, M. R. Jacob, B. L. Tekwani,
 D. C. Dunbar and D. Ferreira, J. Nat. Prod., 2003, 66, 804–809; (b) I. Muhammad, X.-C. Li, D. C. Dunbar,
 M. A. ElSohly and I. A. Khan, J. Nat. Prod., 2001, 64, 1322–1325.

- 153 (a) O. Miyata, N. Takeda and T. Naito, *Org. Lett.*, 2004, 6, 1761–1763; (b) N. Takeda, O. Miyata and T. Naito, *Eur. J. Org. Chem.*, 2007, 1491–9150.
- 154 H. J. Lee, Y. R. Lee and S. H. Kim, *Helv. Chim. Acta*, 2009, **92**, 1404–1412.
- 155 J. D. Lambert, R. O. Meyers, B. N. Timmermann and R. T. Dorr, *Cancer Lett.*, 2001, **171**, 47–56.
- 156 (a) O. Dann, J. Lang and H. Vohl, Justus Liebigs Ann. Chem., 1960, 631, 116–128; (b) S. Johann, B. B. Cota, E. M. Souza-Fagundes, M. G. Pizzolatti, M. A. Resende and C. L. Zani, Mycoses, 2009, 52, 499–506.
- 157 L. Ruan, M. Shi, S. Mao, L. Yu, F. Yang and J. Tang, *Tetrahedron*, 2014, **70**, 1065–1070.
- 158 H. D. Choi, M. C. Ha, P. J. Seo, B. W. Son and J. C. Song, *Arch. Pharmacal Res.*, 2000, 23, 438–440.
- 159 H. Okada, J. Pharm. Soc. Jpn., 1915, 657-666.
- 160 C. Y. Hopkins, D. F. Ewing and M. J. Chisholm, *Can. J. Chem.*, 1967, 45, 1425–1429.
- 161 Y. Luo, Z. He and H. Li, Fitoterapia, 2007, 78, 211-214.
- 162 S. Kawai, T. Nakamura and N. Sugiyama, *Ber. Dtsch. Chem. Ges. A*, 1939, **72**, 1146–1149.
- 163 M. Takanashi and Y. Takizawa, *Phytochemistry*, 1988, 27, 1224–1226.
- 164 E. W. Colvin and B. J. Hamill, *J. Chem. Soc., Perkin Trans.* 1, 1977, 869–874.
- 165 H. L. Teles, J. P. Hemerly, P. M. Pauletti, J. R. C. Pandolfi, A. R. Araujo, S. R. Valentini, M. C. M. Young, V. S. Bolzani and D. H. S. Silva, *Nat. Prod. Res.*, 2005, **19**, 319–323.
- 166 X. F. Duan, J. X. Feng and Z. B. Zhang, *Synthesis*, 2010, 3, 0515–0519.
- 167 Y. Liu, M. Kubo and Y. Fukuyama, *J. Nat. Prod.*, 2012, 75, 2152–2157.
- 168 (a) I.-K. Lee, J.-H. Lee and B.-S. Yun, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 4566–4568; (b) Y. Liu and F. Wang, *Carbohydr. Polym.*, 2007, **70**, 386–392.
- 169 P. Lan, M. G. Banwell and A. C. Willis, J. Org. Chem., 2014, 79, 2829–2842.
- 170 (a) M. G. Banwell, B. L. Flynn and S. G. Stewart, J. Org. Chem., 1998, 63, 9139–9144; (b) B. L. Flynn and M. G. Banwell, Heterocycles, 2012, 84, 1141–1170.
- 171 C. Zhang, J. Liu and Y. Du, *Tetrahedron Lett.*, 2014, 55, 959-961.
- 172 (a) M. Reiter, S. Ropp and V. Gouverneur, Org. Lett., 2004, 6, 91–94; (b) M. Reiter, H. Turner, R. Mills-Webb and V. Gouverneur, J. Org. Chem., 2005, 70, 8478–8485; (c) X. Liao, H. Zhou, X. Z. Wearing, J. Ma and J. M. Cook, Org. Lett., 2005, 7, 3501–3504; (d) T. Hayashi, K. Yamasaki, M. Mimura and Y. Uozumi, J. Am. Chem. Soc., 2004, 126, 3036–3037.
- 173 P. C. Stevenson and N. C. Veitch, *Phytochemistry*, 1998, **48**, 947–951.
- 174 Z. Novak, G. Timari and A. Kotschy, *Tetrahedron*, 2003, **59**, 7509–7513.
- 175 N. G. Kundu, M. Pal, J. S. Mahanty and M. De, *J. Chem. Soc., Perkin Trans.* 1, 1997, 2815–2820.
- 176 A. Arcadi and E. Marinelli, Synthesis, 1986, 749-751.
- 177 S. Torii, L. H. Xu and H. Okumoto, Synlett, 1992, 515-516.

- 178 S. N. Aslam, P. C. Stevenson, S. J. Phythian, N. C. Veitch and D. R. Hall, *Tetrahedron*, 2006, **62**, 4214–4226.
- 179 R. T. Scannell and R. Stevenson, J. Heterocycl. Chem., 1980, 17, 1727–1728.
- 180 Y. Jiang, B. Gao, W. Huang, Y. Liang, G. Huang and Y. Ma, *Synth. Commun.*, 2009, **39**, 197–204.
- 181 R. Stevenson and B. A. McKittrick, J. Chem. Soc., Perkin Trans. 1, 1983, 475-482.
- 182 T. Bach and M. Bartels, Synthesis, 2003, 925-939.
- 183 C. Eidamshaus and J. D. Burch, *Org. Lett.*, 2008, **10**, 4211–4214.
- 184 J. Jiang, J. B. Biggins and J. S. Thorson, *J. Am. Chem. Soc.*, 2000, **122**, 6803–6804.
- 185 J. M. Langenhan, B. R. Griffith and J. S. Thorson, *J. Nat. Prod.*, 2005, **68**, 1696–1711.
- 186 C. J. Thibodeaux, C. E. Melancon and H. W. Liu, Angew. Chem., Int. Ed., 2008, 47, 9814–9859.
- 187 S. M. Patel, M. d. l. Fuente, S. Ke and A. M. R. Guimaraes, *Chem. Commun.*, 2011, 47, 10569–10571.
- 188 C. Albermann, A. Soriano, J. Jiang and H. Vollmer, *Org. Lett.*, 2003, 5, 933–936.
- 189 H. Cheng, X. Cao, M. Xian and L. Fang, *J. Med. Chem.*, 2004, 48, 645–652.
- 190 L. Morelli, A. Bernardi and S. Sattin, *Carbohydr. Res.*, 2014, **390**, 33–41.
- 191 (a) H. B. Bode and A. Zeeck, *J. Chem. Soc., Perkin Trans.* 1, 2000, 323–328; (b) H. B. Bode and A. Zeeck, *J. Chem. Soc., Perkin Trans.* 1, 2000, 2665–2670.
- 192 Y. Yu, H. Men and C. Lee, J. Am. Chem. Soc., 2004, 126, 14720-14721.
- 193 T. Magauer, H. J. Martin and J. Mulzer, *Angew. Chem., Int. Ed.*, 2009, **48**, 6032–6036.
- 194 T. Magauer, H. J. Martin and J. Mulzer, *Chem.-Eur. J.*, 2010, 16, 507–519.
- 195 P. Magnus and C. Lescop, *Tetrahedron Lett.*, 2001, **42**, 7193–7196.
- 196 L. Hoffmeister, P. Persich and A. Fürstner, *Chem.-Eur. J.*, 2014, **20**, 4396–4402.
- 197 F. Marion, D. E. Williams, D. O. Patrick, I. Hollander, R. Mallon, S. C. Kim, D. M. Roll, L. Feldberg, R. V. Soest and R. J. Andersen, *Org. Lett.*, 2006, **8**, 321–324.
- 198 H. Landelle, A. M. Godard, D. Laduree, E. Chenu and M. Robba, *Chem. Pharm. Bull.*, 1991, 39, 3057–3060.
- 199 G. Mehta, N. S. Likhite and C. S. A. Kumar, *Tetrahedron Lett.*, 2009, **50**, 5260–5262.
- 200 A. C. Anderson and D. L. Wright, *Org. Biomol. Chem.*, 2009, 7, 840–850.
- 201 J. H. George, J. E. Baldwin and R. M. Adington, *Org. Lett.*, 2010, 12, 2394–2397.
- 202 (a) B. Vanhaesebroeck, L. Stephens and P. Hawkins, *Nat. Rev. Mol. Cell Biol.*, 2012, **13**, 195–203; (b) M. P. Wymann and C. Schultz, *ChemBioChem*, 2012, **13**, 2022–2035.
- 203 (a) V. Deore, M. Kumar Lohar, R. Mundada, A. Roychowdhury, R. Vishwakarma and S. Kumar, *Synth. Commun.*, 2011, 41, 177–183; (b) T. Kamishima, T. Kikuchi, K. Narita and T. Katoh, *Eur. J. Org. Chem.*, 2014, 3443–3450.

- 204 (a) A. Shirata, K. Takahashi, M. Taksugi, S. Nago, S. Ishikawa, S. Ueno, L. Munoz and T. Masamune, Bull. Seric. Exp. Stn., 1983, 28, 793; (b) F. Ferrari, F. D. Monache, R. S. Compagnone, A. I. Suarez and S. Tillett, Fitoterapia, 1998, 69, 554–555; (c) L. Cui, M. Na, H. Oh, E. Y. Bae, D. G. Jeong, S. E. Ryu, S. Kim, B. Y. Kim, W. K. Oh and J. S. Ahn, Bioorg. Med. Chem. Lett., 2006, 16, 1426–1429.
- 205 R. Kakarla, M. Ghosh, J. A. Anderson, R. G. Dulina and M. J. Sofia, *Tetrahedron Lett.*, 1999, **40**, 5–8.
- 206 N. Kaur, Y. Xia, Y. Jin, N. T. Dat, K. Gajulapati, Y. Choi, Y. S. Hong, J. J. Lee and K. Lee, *Chem. Commun.*, 2009, 1879–1881.
- 207 T. Gibtner, F. Hampel, J. P. Gisselbrecht and A. Hirsch, *Chem.-Eur. J.*, 2002, **8**, 408-432.
- 208 Y. Xia, Y. Jin, N. Kaur, Y. Choi and K. Lee, Eur. J. Med. Chem., 2011, 46, 2386–2396.
- 209 A. J. Weinheimer and P. H. Washecheck, *Tetrahedron Lett.*, 1969, 3315–3318.
- 210 F. Kido, Y. Noda, T. Maruyama, C. Kabuto and A. Yoshikoshi, *J. Org. Chem.*, 1981, **46**, 4264–4266.
- 211 S. Danishefsky, J. F. Kerwin and S. Kobayashi, *J. Am. Chem. Soc.*, 1982, **104**, 358–360.
- 212 S. Danishefsky, E. R. Larson and D. Askin, *J. Am. Chem. Soc.*, 1982, **104**, 6457–6458.
- 213 R. B. Gammill and B. R. Hyde, *J. Org. Chem.*, 1983, **48**, 3863–3865.
- 214 S. Narayanaswamy, S. Rangaswami and T. R. Scshadri, J. Chem. Soc. C, 1954, 187l–1873.
- 215 A. Pelter, R. S. Ward, E. V. Rao and N. R. Raju, *J. Chem. Soc., Perkin Trans.* 1, 1981, 2491–2498.
- 216 S. Rangaswami and V. Sasuy, Curr. Sci., 1955, 24, 13-14.
- 217 P. Rajani and P. N. Sarma, *Phytochemistry*, 1988, **27**, 648-649.
- 218 V. S. Parmar, J. S. Ratho, R. Jain, D. A. Henderson and J. F. Malone, *Phytochemistry*, 1989, **28**, 59l–593.
- 219 T. Tanaka, M. Iinuma, K. Yuki, Y. Fujii and M. Mizuno, *Phytochemistry*, 1992, 31, 993–998.
- 220 S. Rangaswti and B. V. Ramasastry, *Bull Inst. Nat. Sci.*, 1955, 4, 149.
- 221 M. C. Pirrung and Y. R. Lee, *Tetrahedron Lett.*, 1994, 35, 6231–6234.
- 222 M. Niwa, K. Terashima and M. Aqil, *Heterocycles*, 1993, **36**, 671–673.
- 223 M. Niwa, K. Terashima, J. Ito and M. Aqil, *Heterocycles*, 1994, **38**, 1071–1076.
- 224 T. R. Kelly, A. Szabados and Y.-J. Lee, *J. Org. Chem.*, 1997, **62**, 428–429.
- 225 M. Forbes, F. Zilliken, G. Roberts and P. Gyrgy, *J. Am. Chem. Soc.*, 1958, **80**, 385–389.
- 226 M. A. P. Meisinger, F. A. Kuehl, E. L. Rickes, N. G. Brink, K. Folkers, M. Forbes, F. Zilliken, G. Roberts and P. Gyorgy, J. Am. Chem. Soc., 1959, 81, 4979–4982.
- 227 A. F. Wagner, E. Walton, A. N. Wilson, J. O. Rodin, F. W. Holly, N. G. Brink and K. Folkers, *J. Am. Chem. Soc.*, 1959, **81**, 4983–4989.

- 228 B. A. McKittrick and R. Stevenson, J. Chem. Soc., Perkin Trans. 1, 1984, 709–712.
- 229 S. Jinno, T. Okita and K. Inouye, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 1029–1032.
- 230 M. V. Sargent, P. O. Stransky, V. A. Patrick and A. H. White, *J. Chem. Soc.*, *Perkin Trans.* 1, 1983, 231–239.
- 231 T. Sawada, M. Aono, S. Asakawa, A. Ito and K. Awano, I. Antibiot., 2000, 53, 959–966.
- 232 A. D. Patil, A. J. Freyer, L. Killmer, P. Offen, B. Carte, A. J. Jurewicz and R. K. Johnson, *Tetrahedron*, 1997, 53, 5047–5060.
- 233 R. C. Hock, I. U. Schraustätter and C. G. Cochrane, *J. Lab. Clin. Med.*, 1996, **128**, 134–145.
- 234 M. Inoue, A. J. Frontier and S. J. Danishefsky, *Angew. Chem.*, 2000, **112**, 777–780.
- 235 S. H. von Reuß and W. A. König, *Phytochemistry*, 2004, **65**, 3113–3118.
- 236 A. G. Ober, F. R. Fronczek and N. H. Fischer, *J. Nat. Prod.*, 1985, **48**, 242–248.
- 237 A. G. González, B. M. Fraga, M. G. Hernández and V. P. García, *Phytochemistry*, 1982, **21**, 1826–1827.
- 238 M. d. Carmen Cruz and J. Tamariz, *Tetrahedron*, 2005, **61**, 10061–10072.
- 239 D. Bethea, B. Fullmer, S. Syed, G. Seltzer, J. Tiano, C. Rischko, L. Gillespie, D. Brown and F. P. Gasparro, J. Dermatol. Sci., 1999, 19, 78–88.
- 240 K. M. Grundmann, R. Ludwig, T. M. Zollner, F. Ochsendorf, D. Thaci, W. H. Boehncke, J. Krutmann, R. Kaufmann and M. Podda, J. Am. Acad. Dermatol., 2004, 50, 734–739.
- 241 (a) P. E. Grimes, Clin. Dermatol., 1997, 15, 921–926; (b)
 H. Petering, C. Breuer, R. Herbst, A. Kapp and T. Werfel,
 J. Am. Acad. Dermatol., 2004, 50, 68–72.
- 242 (a) P. V. M. M. Diederen, H. Weelden, C. J. G. Sanders, J. Toonstra and W. A. Vloten, J. Am. Acad. Dermatol., 2003, 48, 215–219; (b) G. Miolo, R. Tomanin, A. D. Rossi, A. F. Dall, F. Zacchello and M. Scarpa, J. Photochem. Photobiol., B, 1994, 26, 241–247; (c) C. Lage, M. Pádula, T. A. M. Alencar, S. R. F. Gonçalves, L. S. Vidal, J. Cabral-Neto and A. C. Leitão, Mutat. Res., Rev. Mutat. Res., 2003, 544, 143–157.
- 243 G. D. Cimino, H. B. Gamper, S. T. Isaacs and J. E. Hearst, *Annu. Rev. Biochem.*, 1985, **54**, 1151–1193.
- 244 R. L. Edelson, Arch. Dermatol., 1999, 135, 600-601.
- 245 (a) J. J. Goupil, French Patent, 2, 698, 270–319, 1994; (b) J. L. Goaster, French Patent, 691, 629–691, 1993.
- 246 A. Wiesmann, A. Weller, G. Lischka, T. Klingebiel, L. Kanz and H. Einsele, *Bone Marrow Transplant.*, 1999, 23, 151–155.
- 247 P. Ceccherelli, M. Curini, M. C. Marcotullio, F. Epifano and O. Rosati, Synth. Commun., 1998, 28, 3057–3064.
- 248 D. Dauzonne and R. Royer, Synthesis, 1984, 1054-1057.
- 249 P. J. Coleman, K. M. Brashear, B. C. Askew,
 J. H. Hutchinson, C. A. McVean, L. T. Duong,
 B. P. Feuston, C. Fernandez-Metzler, M. A. Gentile,
 - G. D. Hartman, D. B. Kimmel, C. T. Leu, L. Lipfert, K. Merkle, B. Pennypacker, T. Prueksaritanont,
 - G. A. Rodan, G. A. Wesolowski, S. B. Rodan and M. E. Duggan, *J. Med. Chem.*, 2004, 47, 4829–4837.

Review

250 P. I. Thong F. D. Wang and I. M. Vuo. Sunlett. 2006, 4, 567. 270 (c

- 250 B. L. Zhang, F. D. Wang and J. M. Yue, *Synlett*, 2006, **4**, 567–570.
- 251 J. R. Carney and P. J. Scheuer, *Tetrahedron Lett.*, 1993, 34, 3727–3730.
- 252 K. Ishiguro, Y. Ohira and H. Oku, *J. Nat. Prod.*, 1998, **61**, 1126–1129.
- 253 A. V. B. Sankaram, V. V. N. Reddy and G. S. Sidhu, *Phytochemistry*, 1981, **20**, 1093–1096.
- 254 T. Takeya, H. Kondo, T. Otsuka, K. Tomita, I. Okamoto and O. Tamura, *Org. Lett.*, 2007, **9**, 2807–2810.
- 255 (a) H. Tanaka, M. Sato, T. Oh-Uchi, R. Yamaguchi, H. Etoh, H. Shimizu, M. Sako and H. Takeuchi, *Phytomedicine*, 2004,
 11, 331–337; (b) H. Tanaka, M. Sato, S. Fujiwara, M. Hirata, H. Etoh and H. Takeuchi, *Lett. Appl. Microbiol.*, 2002, 35, 494–498.
- 256 F. L. Weitl, J. Org. Chem., 1976, 41, 2044-2045.
- 257 A. Fürstner and P. W. Davies, J. Am. Chem. Soc., 2005, 127, 15024–15025.
- 258 (a) A. Fürstner, P. W. Davies and T. Gress, *J. Am. Chem. Soc.*, 2005, **127**, 8244–8245; (b) A. FPrstner and C. A. Wssa, *J. Am. Chem. Soc.*, 2006, **128**, 6306–6307.
- 259 A. Furstner, E. K. Heilmann and P. W. Davies, *Angew. Chem., Int. Ed*, 2007, **46**, 4760–4763.
- 260 (a) N. W. Preston, K. Chamberlain and R. A. Skipp, *Phytochemistry*, 1975, 14, 1875–1876; (b) R. P. Duffley and R. Stevenson, *J. Chem. Soc., Perkin Trans.* 1, 1977, 802–804; (c) M. Meyer, C. Deschamps and D. Molho, *Bull. Soc. Chim. Fr.*, 1991, 91–99; (d) M. Na, D. M. Hoang, D. Njamen, J. T. Mbafor, Z. T. Fomun, P. T. Thuong, J. S. Ahn and W. K. Oh, *Bioorg. Med. Chem. Lett.*, 2007, 17, 3868–3871; (e) T. Kinoshita and K. Ichinose, *Heterocycles*, 2005, 65, 1641–1654.
- 261 M. A. Khalizadeh, A. Hosseini, M. Shokrollahzadeh, M. R. Halvagar, D. Ahmadi, F. Mohannazadeh and M. Tajbakhsh, *Tetrahedron Lett.*, 2006, 47, 3525–3528.
- 262 M. Csekei, Z. Novak and A. Kotschy, *Tetrahedron*, 2008, 64, 8992–8996.
- 263 (a) E. E. Shul'ts, T. N. Petrova, M. M. Shakirov, E. I. Chernyak and G. A. Tolstikov, *Chem. Nat. Compd.*, 2000, 36, 362–368; (b) T. Shiozawa, S. Urata, T. Kinoshita and T. Saitoh, *Chem. Pharm. Bull.*, 1989, 37, 2239–2240.
- 264 Y. Tanaka, H. Kikuzaki, S. Fukuda and N. Nakatani, *J. Nutr. Sci. Vitaminol.*, 2001, 47, 270–273.
- 265 Y. L. Jin, S. Kim, Y. S. Kim, S. A. Kim and H. S. Kim, *Tetrahedron Lett.*, 2008, **49**, 6835–6837.
- 266 K.-S. Huang, Y.-H. Wang, R.-L. Li and M. Lin, *J. Nat. Prod.*, 2000, **63**, 86–89.
- 267 (a) J. Ito, Y. Takaya, Y. Oshima and M. Niwa, *Tetrahedron*, 1999, 55, 2529–2544; (b) I. Kim and J. Choi, *Org. Biomol. Chem.*, 2009, 7, 2788–2795.
- 268 J.-R. Dai, Y. F. Hallock, J. H. Cardellina and M. R. Boyd, *J. Nat. Prod.*, 1998, **61**, 351–353.
- 269 (a) A. Saraswathy, K. K. Purushothaman, A. Patra, A. K. Dey and A. B. Kundu, *Phytochemistry*, 1992, 31, 2561–2562; (b)
 T. Tanaka, T. Ito, Y. Ido, K. Nakaya, M. Iinuma and V. Chelladurai, *Chem. Pharm. Bull.*, 2001, 49, 785–787.

- 270 (a) Y. Takaya and M. Niwa, *Trends Heterocycl. Chem.*, 2001,
 7, 41–54; (b) E.-K. Seo and A. D. Kinghorn, *Stud. Nat. Prod. Chem.*, 2000, 23, 531.
- 271 (a) T. K. Chakraborty and G. V. Reddy, J. Org. Chem., 1992,
 57, 5462–5469; (b) N. Hoffmann and J.-P. Pete, Synthesis,
 2001, 1236–1242; (c) S. Inoue, C. Nakagawa, H. Hayakawa,
 F. Iwasaki, Y. Hoshino and K. Honda, Synlett, 2006, 1363–1366.
- 272 L. Chen, Q. Ding, P. Gillespie, K. Kim, A. J. Lovey, W. W. McComas, J. G. Mullin and A. Perrota, World Pat.WO 02057261 A2, 2005.
- 273 M. M. Heravi, F. Dirkwand, H. A. Oskooie and M. Ghassemzadeh, *Heterocycl. Commun.*, 2005, **11**, 75–78.
- 274 I. Kim and J. Choi, Org. Biomol. Chem., 2009, 7, 2788-2795.
- 275 A. Yaron and F. Naider, *Crit. Rev. Biochem. Mol. Biol.*, 1993,28, 31–81.
- 276 T. Aoyagi, T. Wada, M. Nagai, F. Kojima, S. Harada, T. Takeuchi, H. Takahashi, K. Hirokawa and T. Tsumita, *Experientia*, 1990, **46**, 94–97.
- 277 L. Y. Yang, C. F. Chang, Y. C. Huang, Y. J. Lee, C. C. Hu and T. H. Tseng, *Synthesis*, 2009, 7, 1175–1179.
- 278 M. J. Lear, O. Simon, T. L. Foley, M. D. Burkart, T. J. Baiga, J. P. Noel, A. G. DiPasquale, A. L. Rheingold and J. J. La Clair, *J. Nat. Prod.*, 2009, 72, 1980–1987.
- 279 M. Sridhar, B. A. Kumar and R. Narender, *Tetrahedron Lett.*, 1998, 39, 2847–2850.
- 280 O. Simon, B. Reux, J. J. La Clair and M. J. Lear, *Chem.-Asian J.*, 2010, 5, 342–351.
- 281 D. Y. K. Chen, Q. Kang and T. R. Wu, *Molecules*, 2010, 15, 5909–5927.
- 282 L. D. Juliawaty, E. H. Hakim, S. A. Achmad, Y. M. Syah, J. Latip and I. M. Said, *Nat. Prod. Commun.*, 2009, 4, 947– 950.
- 283 H. M. Ge, W. H. Yang, Y. Shen, N. Jiang, Z. K. Guo, Q. Luo, Q. Xu, J. Ma and R. X. Tan, *Chem.-Eur. J.*, 2010, **16**, 6338–6345.
- 284 (a) K.-S. Huang, M. Lin and G.-F. Cheng, *Phytochemistry*, 2001, 58, 357–362; (b) Y. Meng, P. C. Bourne, P. Whiting, V. Sik and L. Dinan, *Phytochemistry*, 2001, 57, 393–400; (c) H.-F. Luo, L.-P. Zhang and C.-Q. Hu, *Tetrahedron*, 2001, 57, 4849–4854; (d) C. Privat, J. P. Telo, V. Bernades-Genisson, A. Vieira, J. P. Souchard and F. Nepveu, *J. Agric. Food Chem.*, 2002, 50, 1213–1217; (e) S. Wang, D. Ma and C. Hu, *Helv. Chim. Acta*, 2005, 88, 2315–2321.
- 285 (a) I. V. Seregin and V. Gevorgyan, Chem. Soc. Rev., 2007, 36, 1173–1193; (b) B.-J. Li, S.-D. Yang and Z.-J. Shi, Synlett, 2008, 949–957; (c) X. Chen, K. M. Engle, D.-H. Wang and J.-Q. Yu, Angew. Chem., Int. Ed., 2009, 48, 5094–5115; (d) L. Ackermann, R. Vicente and A. R. Kapdi, Angew. Chem., Int. Ed., 2009, 48, 9792–9826; (e) C.-L. Sun, B.-J. Li and Z.-J. Shi, Chem. Commun., 2010, 46, 677–685.
- 286 (a) N. S. Nandurkar, M. J. Bhanushali, M. D. Bhor and B. M. Bhanage, *Tetrahedron Lett.*, 2008, 49, 1045–1048; (b) S.-D. Yang, C.-L. Sun, Z. Fang, B.-J. Li, Y.-Z. Li and Z.-J. Shi, *Angew. Chem., Int. Ed.*, 2008, 47, 1473–1476; (c) H.-Q. Do, R. M. K. Khan and O. Daugulis, *J. Am. Chem. Soc.*, 2008, 130, 15185–15192; (d) S. Matsuda,

RSC Advances

- M. Takahashi, D. Monguchi and A. Mori, Synlett, 2009, 1941-1944; (e) M. Ionita, J. Roger and H. Doucet, ChemSusChem, 2010, 3, 367-376.
- 287 K. Kim and I. Kim, Org. Lett., 2010, 12, 5314-5317.
- 288 C. W. Chang and R. J. Chein, J. Org. Chem., 2011, 76, 4154-4157.
- 289 (a) R. C. Larock, E. K. Yum, M. J. Doty and K. K. C. Sham, J. Org. Chem., 1995, 60, 3270-3271; (b) B. C. Bishop, I. F. Cottrell and D. Hands, Synthesis, 1997, 1315-1320.
- 290 B. M. Trost, S. A. Godleski and J. P. Genet, J. Am. Chem. Soc., 1978, 100, 3930-3931.
- 291 S. Paul, S. Pattanayak and S. Sinha, Tetrahedron Lett., 2011, 52, 6166-6169.
- 292 (a) R. Hänsel, H. Rimpler and R. Schwar, Tetrahedron Lett., 1965, **6**, 1545–1548; (b) Z.-F. Hu, L.-L. Chen, J. Oi, Y.-H. Wang, H. Zhang and B.-Y. Yu, Fitoterapia, 2011, 82, 190-192.
- 293 (a) M. W. Khan, M. J. Alam, M. A. Rashid and R. Chowdhury, Bioorg. Med. Chem., 2005, 13, 4796-4805; (b) I. Hayakawa, R. Shioya, T. Agatsuma, H. Furukawa, S. Naruto and Y. Sugano, Bioorg. Med. Chem. Lett., 2004, 14, 455-458.
- 294 M. R. Saberi, T. K. Vinh, S. W. Yee, B. J. Griffiths, P. J. Evans and C. Simons, J. Med. Chem., 2006, 49, 1016-1022.
- 295 (a) C. Beney, A.-M. Mariotte and A. Boumendjel, Heterocycles, 2001, 55, 967-972; (b) V. Wallez, S. Durieux-Poissonnier, P. Chavatte, J. A. Boutin, V. Audinot, J.-P. Nicolas, C. Bennejean, P. Delagrange, P. Renard and D. Lesieur, J. Med. Chem., 2002, 45, 2788-2800.
- 296 S. Yahiaoui, M. Peuchmaur and A. Boumendjel, Tetrahedron, 2011, 67, 7703-7707.
- 297 T. Rezanka, L. O. Hanus, P. Kujan and V. M. Dembitsky, Eur. J. Org. Chem., 2005, 2708-2714.
- 298 D. Ma and Q. Cai, Org. Lett., 2003, 5, 3799-3802.
- 299 B. Liégault, D. Lee, M. P. Huestis, D. R. Stuart and K. Fagnou, J. Org. Chem., 2008, 73, 5022-5028.
- 300 (a) A. Shiotani and H. Itatani, J. Chem. Soc., Perkin Trans. 1, 1976, 1236-1241; (b) H. Hagelin, J. D. Oslob and B. kermark, Chem.-Eur. J., 1999, 5, 2413-2416; (c) T. Gensch, M. Rennefahrt, R. Czerwonka, A. Jäger, O. Kataeva, I. Bauer and H.-J. Knçlker, Chem.-Eur. J., 2012, 18, 770-776.
- 301 R. Bartholomaus, F. Dommershausen, M. Thiele, N. S. Karanjule, K. Harms and U. Koert, Chem.-Eur. J., 2013, 19, 7423-7436.
- 302 E. M. Bickoff, A. N. Booth, R. L. Lyman, A. L. Livingston, C. R. Thompson and F. Deeds, Science, 1957, 126, 969-970.
- 303 M. S. Kurzer and X. Xu, Annu. Rev. Nutr., 1997, 17, 353-381.
- 304 M. S. Kurzer, J. Nutr., 2003, 133, 1983S-1986S.
- 305 U. A. Kshirsagar, R. Parnes, H. Goldshtein, R. Ofir, R. Zarivach and D. Pappo, Chem.-Eur. J., 2013, 19, 13575-13583.
- 306 R. J. Y. Chen, T. Jinn, Y. Chen, T. Chung, W. Yang and J. T. C. Tzen, Acta Pharmacol. Sin., 2011, 32, 141-151.
- 307 Y. Lu and L. Foo, Phytochemistry, 2002, 59, 117-140.
- 308 R. Jiang, K. Lau, P. Hon, T. C. W. Mak, K. Woo and K. Fung, Curr. Med. Chem., 2005, 12, 237-246.

- 309 T. o. Cheng, Int. J. Cardiol., 2007, 121, 9-22.
- 310 B. L. Alford and H. M. Hügel, Org. Biomol. Chem., 2013, 11, 2724-2727.
- 311 (a) W. Steck, Phytochemistry, 1970, 9, 1145-1146; (b) M. Vanhaelen and R. Vanhaelen-Fastré, *Phytochemistry*, 1974, 13, 306-307; (c) J. Reisch, A. Wickramasinghe and V. Kumar, J. Nat. Prod., 1989, 52, 1379-1382; (d) A. H. Muller, L. R. O. Degáspari, P. C. Vieira, M. F. da Silva, J. B. Fernandes and J. R. Pirani, Phytochemistry, 1993, 34, 585-586; (e) F. M. Oliveira, A. E. G. Sant'ana, L. M. Conserva, J. G. S. Maia and G. M. P. Guilhon, Phytochemistry, 1996, 41, 647-649.
- 312 (a) A. E. Desjardins, G. F. Spencer and R. D. Plattner, Phytochemistry, 1989, 28, 2963-2969; (b) C. C. Wang, J. E. Lai, L. G. Chen, K. Y. Yen and L. L. Yang, Bioorg. Med. Chem., 2000, 8, 2701-2707; (c) J. Singhuber, I. Baburin, G. F. Ecker, B. Kopp and S. Hering, Eur. J. Pharmacol., 2011, 668, 57-64.
- 313 K. Sonogashira, J. Organomet. Chem., 2002, 653, 46-49.
- 314 A. Cervi, P. Aillard, N. Hazeri, L. Petit, C. L. L. Chai, A. C. Willis and M. G. Banwell, J. Org. Chem., 2013, 78, 9876-9882.
- 315 E. Gellert, R. Hamet and E. Schlittler, Helv. Chim. Acta, 1951, 34, 642-651.
- 316 T. Matsui, Y. Sowa, H. Murata, K. Takagi, R. Nakanishi, S. Aoki, M. Yoshikawa, M. Kobayashi, T. Sakabe, T. Kubo and T. Sakai, Int. J. Oncol., 2007, 31, 915-922.
- 317 M. L. Bolognesi, F. Lizzi, R. Perozzo, R. Brun and A. Cavalli, Bioorg. Med. Chem. Lett., 2008, 18, 2272-2276.
- 318 N. Kotoku, K. Higashimoto, M. Kuriok, M. Arai, A. Fukud, Y. Sumii, Y. Sowa, T. Sakai and M. Kobayashi, Bioorg. Med. Chem. Lett., 2014, 24, 3389-3391.
- 319 (a) M. D. Clift, C. N. Taylor and R. J. Thomson, Org. Lett., 2007, 9, 4667-4669; (b) C. T. Avetta, L. C. Konkol, C. N. Taylor, K. C. Dugan, C. L. Stern and R. J. Thomson, Org. Lett., 2008, 10, 5621-5624; (c) M. D. Clift and R. J. Thomson, J. Am. Chem. Soc., 2009, 131, 14579-14593.
- 320 B. T. Jones, C. T. Avetta and R. J. Thomson, Chem. Sci., 2014, 5, 1794-1798.
- 321 M. M. Heravi and A. Fazeli, Heterocycles, 2010, 81, 1979-2026.
- 322 H. Yuan, K. Bi, W. Chang, R. Yue, B. Li, J. Yea, Q. Sun, H. Jin, L. Shan and W. Zhang, Tetrahedron, 2014, 70, 9084-9092.
- 323 M. M. Heravi and E. Hashemi, Monatsh. Chem., 2012, 143, 861-880.
- 324 M. M. Heravi and P. Hajiabbasi, Mol. Diversity, 2014, 18,
- 325 X. Zheng, W. D. Meng and F. L. Qing, Tetrahedron Lett., 2004, 45, 8083-8085.
- 326 G. Pan, Y. Ma, K. Yang, X. Zhao, H. Yang, Q. Yao, K. Lu, T. Zhu and P. Yu, Tetrahedron Lett., 2015, 56, 4472-4475.
- 327 Y. Q. Ye, C. Negishi, Y. Hongo, H. Koshino, J.-i. Onose, N. Abe and S. Takahashi, Bioorg. Med. Chem., 2014, 22,
- 328 Y.-Q. Ye, H. Koshino, J. Onose, K. Yoshikawa, N. Abe and S. Takahashi, Org. Lett., 2009, 11, 5074-5077.

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