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Synthesis of Dibenzofurans Possessing Anti-Allergy, Antioxidant, Anti-Inflammatory, Antimalarial and Treatment of Skin Conditions

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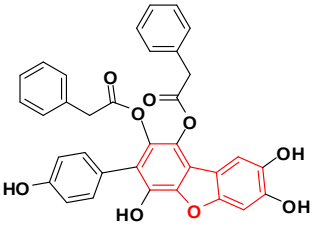
Abstract

This review focuses on reports regarding the isolation and/or synthesis of naturally occurring dibenzofurans with demonstrated anti-allergy, antioxidant, anti-inflammatory, antimalarial and treatment of skin conditions. It is not a comprehensive discussion of all such compounds, but is instead intended to illustrate the range of biological activity possessed by such compounds, the variety of sources from which they can be isolated, and the various synthetic methods by which they can be prepared.

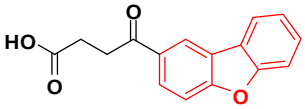
Keywords: dibenzofuran derivatives; anti-allergy; antioxidant, anti-inflammatory; antimalarial**.**

1. Introduction

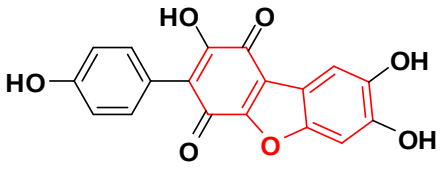
Dibenzofurans can be found in a wide range of natural products; they are used as pharmaceutical candidates [1, 2] because of their unique properties, such as anticancer, antibacterial, antiallergy, antimalarial, and anti-inflammatory activities (fig 1) [3-9]. In addition, fused dibenzofuran skeletons are considered to be potential photoelectronic materials in blue phosphorescent organic light-emitting diodes [10, 11]. As a result, many research groups devoted themselves to developing new approaches to construct dibenzofuran motifs [12-25].



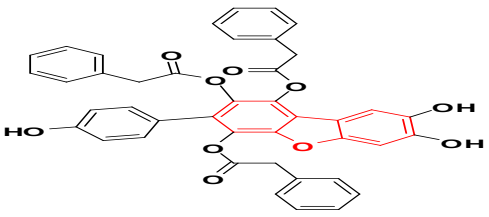
Vialinin B, [4, 7, 8-trihydroxy-3-(4-hydroxyphenyl)-1-(2-phenylacetyl) oxydibenzofuran-2-yl] 2-phenylacetate, potent inhibitor of TNF-alpha production, Anti-allergic agent [26, 27].



Furobufen, 4-(Dibenzo[b,d]furan-2-yl)-4-oxobutanoic acid, anti-inflammatory agent [28].



Cycloleucomelone, 2, 7, 8-Trihydroxy-3-(4-hydroxyphenyl) dibenzofuran-1, 4-dione, potent inhibitor



ganbajunin B, [7,8-dihydroxy-3-(4-hydroxyphenyl)-1,2-bis[(2-phenylacetyl)oxy] dibenzofuran-4-yl] 2-

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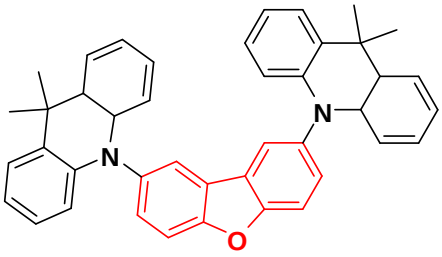
of TNF-alpha production. Anti-inflammatory and Antimicrobial agents [29-31].

phenylacetate, potent inhibitor of TNF-alpha production, anti-allergic agent [32].



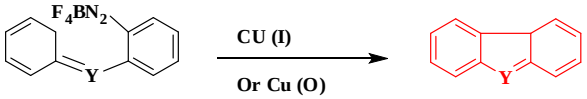
Phosphine oxide, 2,8-bis(9,9-dimethyl-9,9a-dihydroacridin-10(4aH)-yl) dibenzo[b,d]furan, host material in blue pholeds dibenzofurans [33]

Fig. 1. Selected active dibenzofurans

2. Synthesis of Dibenzofuran Derivatives

2.1. Pschorr Reaction

The preparation of biaryltricyclics rings is facilitated by the Pschorr Reaction via intramolecular means by substituting one arene by the aryl radical. The said radical is created in situ from the aryl diazonium salt by a copper catalysis. Despite the use of excess copper salts, the yield is optimally moderate. Alternative one-electron donors that are more soluble have recently been discovered [34]. The method in the current report improves output at a shorter reaction time (scheme 1).

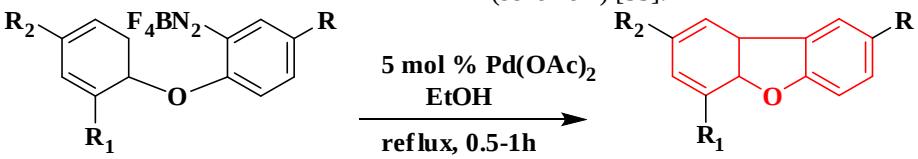


Y= -CH=CH-, -O-, -S-, -SO-, ...

Scheme 1. Synthesis of biaryl tricyclics

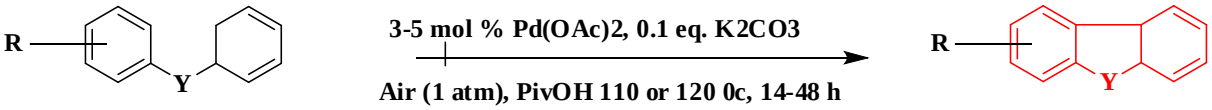
2.2. Recent Methods

Catalysis of palladium provides an intracellular cycle for ethyl diazonium salts of diaryl ether to produce dibenzofurans. This process uses 3% molpalladium acetate as an aid in refluxing ethanol without a base (scheme 2) [35].



Scheme 2. Synthesis of dibenzofurans

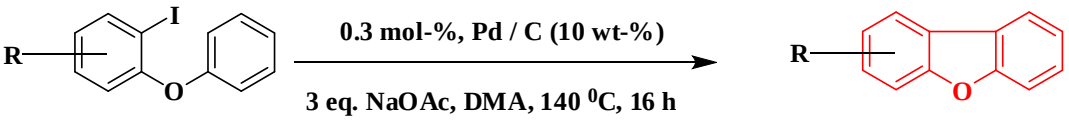
Intramolecular palladium (II) catalyzes the formation of carbon– and oxidized carbon bonds under air in the presence of pivalic acid where in the reaction‘s solvent, rather than the acetic acid, leads to more reproduction and productivity and wider substrate range. The reaction allows the conversion of both electron-rich electron amines and electron deficiency (scheme 3) [36].



Y, NH (110 0C, 14 h) or O (120 0C, 42-48 h)

Scheme 3. Synthesis of dibenzofurans and / or dibenzopyrols

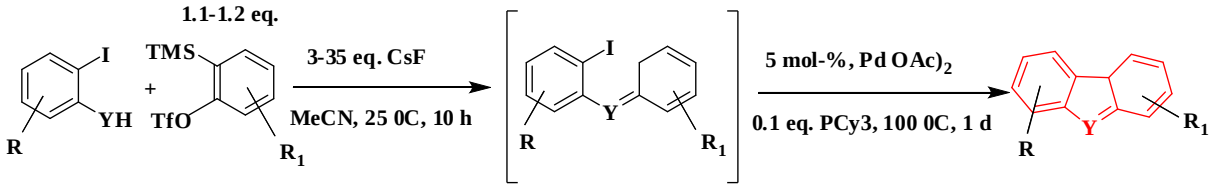
An effective method to synthesize dibenzofurans from O-iododiaryl ethers is to let it be stimulated by reusable Pd/C considering bonding- and ligand-free circumstances. O-ododiaryl ether synthesis in one vessel was accomplished through serial iodine and O-arylation of phenol under moderate reaction conditions (scheme 4) [37].



R, EWG, H

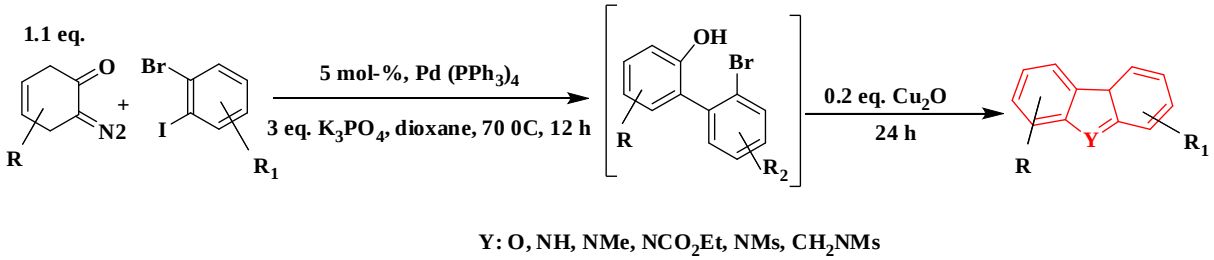
Scheme 4. Synthesis of dibenzofurans from o-iododiaryl ethers

An effective route has been developed to formulating carbazoles and dibenzofurans. O-iodoanilines or o-iodophenols' reaction with silylaryltriflates followed by exposure to CsF to provide N- or O-arylated products by cyclization using the Pd catalyst to carbazoles and dibenzofurans in acceptable to flawless yields; different functional groups were tolerated (scheme 5) [38].



Scheme 5. Synthesis of dibenzofurans and carbazoles

A novel and efficient protocol for the rapid construction of dibenzofuran motifs from 6-diazo-2-cyclohexenones and ortho-haloiodobenzenes involves one-pot Pd-catalyzed cross-coupling/aromatization and Cu-catalyzed Ullmann coupling (scheme 6) [39].



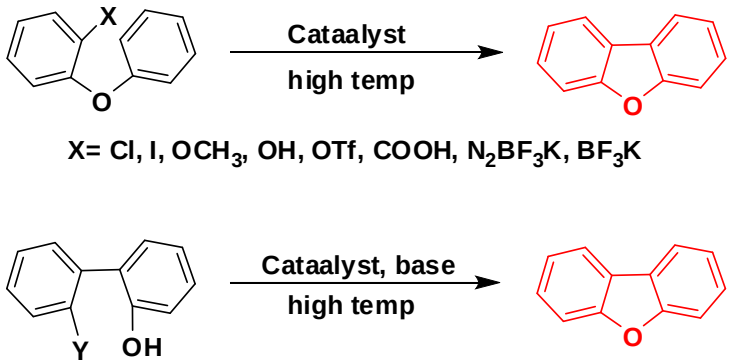
Scheme 6. Synthesis from dibenzofurans 6-diazo-2-cyclohexenones and ortho-haloiodobenzenes

2.3. Synthetic Strategies of dibenzofurans

As a result, many research groups devoted themselves to developing new approaches to construct dibenzofuran motifs [12-25], which can be divided into intermolecular and intramolecular categories:

2.3.1. Intramolecular Synthetic Strategies

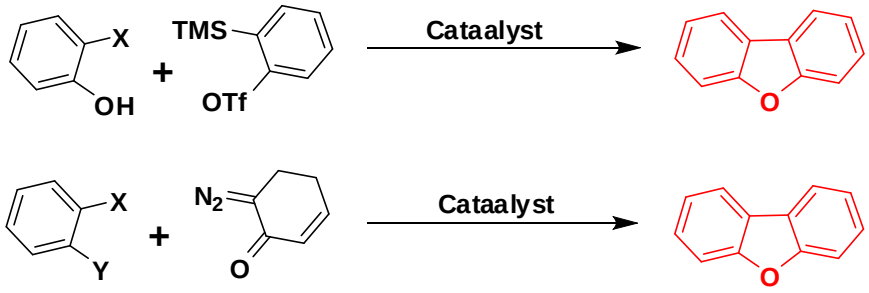
intramolecular synthesis strategy: cyclization of diaryl ether derivatives [40-48], formation of C−O bonds using biaryls (scheme 7) [49].



Scheme 7. Synthesis of dibenzofuran via intramolecular synthetic strategies

2.3.2. Intermolecular Synthetic Strategies

reaction of ortho-iodophenols with silylaryl triflates in the presence of CsF to afford the O-arylated products, which are subsequently cyclized using a Pd catalyst to dibenzofurans [50]; reaction between 6-diazo-2-cyclohexenone and an ortho-haloiodobenzene through tandem Pd-catalyzed cross-cou- pling/aromatization followed by a Cu-catalyzed Ullmann coupling reaction (scheme 8) [51]. However, these strategies suffer from hash reaction conditions, tedious steps, limited substrate scope, and use of molar excess of catalyst.



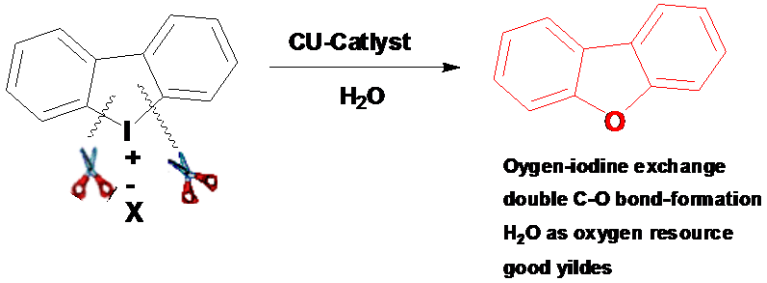
X= Cl, I, OCH_3, OH, OTf, COOH, N_2BF_3K, BF_3K

Y = NO_2, OH, Cl, H, NH_2

Scheme 8. Synthesis of dibenzofuran via intermolecular synthetic strategies

2.3.3. Recent Synthetic Strategies

Cyclic diaryliodoniums have emerged as a new paradigm to synthesis of dibenzothiophenes [52-56], dibenzopyrroles [57-59], and dibenzoselenophens [60-62], which avoids poor atom economy by generating 1 equiv of an iodoarene as waste. Considering our continuous interest in developing application of hypervalent iodine reagent in organic synthesis, we were focused mainly on construction of heterocyclic to exploit diverse diaryliodonium salt transformations [63]. Accordingly, intramolecular cyclizations of dibenziodolium triflates were established by our group for the synthesis of dibenzothiophenes [64] and fluorenones [65]. An efficient synthesis of a variety of dibenzofuran derivatives via Cu-catalyzed cyclization diaryliodonium salts in water is achieved (scheme 9). Various dibenzofuran derivatives could be obtained in good to excellent yields via this oxygen-iodine exchange approach. A concise synthesis of organic semiconducting material molecule has been achieved using this method [66].



Scheme 9. Synthesis of dibenzofuran via recent synthetic strategies

3. Anti-allergy dibenzofurans

Also, in general, it has been observed during recent references that synthetic organic chemistry has a distinct biological activity in all different applied directions [67-101]. Therefore, in this review, the focus will be on reports relating to the isolation and/or naturally occurring synthesis of dibenzofuran derivatives with possessing anti-allergy, antioxidant, anti-inflammatory, antimalarial and the treatment of skin conditions.

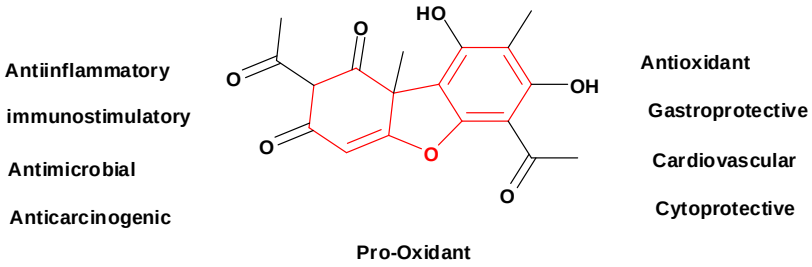
Structurally very similar to the boletopsins are vialinins B and C (Fig. 9), which are essentially the same molecular framework as boletopsin 7 **57**, in which the acetate esters have been replaced by esters of phenylacetic acid and p-hydroxybenzoic acid, respectively. Vialinin B was isolated from the edible mushroom, Thelephora vialis, and was found to inhibit release of TNF-a (tumor necrosis factor) from RBL-2H3 cells [102]. Since TNF-α is involved in inflammation (among other things), inhibition of its release is viewed as a potential route to the suppression of allergic responses. In the assay utilized, vialinin B had an IC_{50} value of 0.02 nM, as compared to a value of 0.25 nM in the same assay for the known immunosuppressant agent FK-506 [102]. Vialinin C was isolated from the same mushroom, and had an IC_{50} value of 0.89 mMin the same assay [103].

In 2009, Takahashi and coworkers reported their synthesis of vialinin B [104]. It will not be discussed in detail here, as it is virtually identical to the synthetic approach utilized by Beekman and Barrow five years later for the synthesis of boletopsin **7** 57 (Schemes 10 and 11), with the exception that Takahashi used benzyloxy groups where Barrow used methoxy groups, and of course, Takahashi used

phenylacetyl chloride where Barrow used acetyl chloride. Since benzyl ethers were utilized in Takahashi's synthesis of vialinin B, the catalytic hydrogenation step that removed the benzyloxycarbonyl protecting group also deprotected the other phenols in the same step. Yields were comparable to those reported by Barrow.

4. Antioxidant dibenzofurans

Usnic acid (UA) is one of the most common and abundant lichen metabolites. It belongs to the dibenzofuran family and can be isolated from Usnea longissima, U. articulate, U. complanata, U. meridionalis, U. barbata and Cladonia arbuscula, among other species [105-110]. Several biological properties have been observed from this compound, such as gastroprotective [105], cardiovascular [107] and cytoprotective [105, 111], immunostimulatory [108], antimicrobial [109], anti-inflammatory [112] and anticarcinogenic activities [109, 113-115], mostly through its antioxidant action in reducing oxidative damage [107, 115-117] (Figure 2).



Usnic acid, 2, 6-Diacetyl-7, 9-dihydroxy-8, 9b-dimethyldibenzo[b, d] furan-1, 3 (2H, 9bH)-dione

Figure 2. Usnic acid structure and biological activities.

Structurally related to vialinin B is ganbajunin B, which differs only in that an additional phenol group has been acylated with a phenylacetyl group (Fig. 10). Like vialinin B, it has been isolated from Thelephora vialis [103], as well as two other species of the Thelephora genus [118-120].

The ability of ganbajunin B to scavenge radicals has led to interest in it as an antioxidant [9]. Liu and coworkers found that ganbajunin B inhibited lipid peroxidation in rat liver homogenate with an IC_{50} value of 54 mM, as compared to values of 295 mM and 222 mM for vitamin E (a-tocopoherol) and BHA (butylated hydroxyanisole), respectively [118]. Likewise it was found to scavenge both superoxide radicals and DPPH (2, 2-diphenyl-1-(2, 4, 6-trinitrophenyl)hydrazyl) radicals with EC_{50} values of 204 mM and 55 mM, respectively. Under the same conditions, the EC_{50} values for BHA were 424 mM and 110 mM [118].

That same year Liu and coworkers also measured DPPH radical scavenging ability by a slightly different assay [121]. In this assay the EC_{50} values were expressed in terms of the mole ratio (antioxidant to DPPH radical) required to reduce the DPPH radical concentration 50% in 30 min. Once again vitamin E and BHA were used as positive controls, with EC_{50} values of 0.25 and 0.09, respectively, being reported for these compounds. Ganbajunin B was found to be superior to vitamin E but inferior to BHA in this assay, with an EC_{50} value of 0.13.

Other dibenzofurans were found to be effective antioxidants in that same study [121]. For example, an EC_{50} value of 0.12 was reported for boletopsin **6** (Fig. 11) with the most active compound tested being boletopsin **7** (Scheme 11), which had an EC_{50} value of 0.07 [122].

A synthesis of ganbajunin B was recently reported by Takahashi and coworkers (Scheme 12) [118]. Starting from intermediate **59** used in their synthesis of vialinin B, acylation of the corresponding lithium phenolate was accomplished in 88% yield (use of bases such as triethylamine or pyridine gave poor results). Removal of the methylenedioxy group was initiated by oxidation of **60** with lead tetraacetate, which produced acetate **61** in 73% yields. This intermediate was then hydrolyzed with aqueous acetic acid, and without further purification, the liberated the 1, 2-diol was acylated once again via the corresponding lithium phenolate. Removal of the benzyl protecting groups was accomplished by catalytic hydrogenation, giving ganbajunin B in 30% yield from **61**.

5. Anti-inflammatory dibenzofurans

Lichens are interesting plant-like, composite, symbiotic organisms that arise from cohabitations between green algae or cyanobacteria in filamentous fungi, and ubiquitously reside on rock surfaces, tundra, and

even deserts. To date, more than 20,000 species have been identified. Lichens produce several secondary metabolites, such as depside, depsidone, xanthone, and dibenzofuran, which have been used in foods, perfumes, and medicines, and as dyes [123–125]. Furthermore, the metabolites produced by lichens exhibit antioxidant, antimicrobial, anticancer, antiviral, and anti-inflammatory effects [126–130].

In addition to its antioxidant properties, boletopsin 6 has also been found to possess anti-inflammatory activity, as evidenced by its ability to inhibit 5-lipoxygenase with an IC_{50} value of 0.35 mM [131]. Boletopsins 1, 4, and 5 (Fig.12) also inhibited this enzyme with IC_{50} values ranging from 1.04 to 1.29 mM, while boletopsin **7** was somewhat less effective, its IC_{50} value being 4.95 mM [131]. No synthesis of these boletopsins has been reported.

The anti-inflammatory activity of other dibenzofurans was assessed by determining their inhibition of superoxide anion generation by human neutrophils [131]. Lucidafuran and eriobofuran (Fig. 13), both isolated from the deciduous tree Pourthiaea lucida, were found to inhibit superoxide generation with IC_{50} values of 18.7 mMand 32.7 mM, respectively. The IC_{50} value of ibuprofen using the same assay was 27.5 mM [132].

These same two dibenzofurans have been identified as phytoalexins generated by apples that have been infected with Erwinia amylovora, the bacteria responsible for "fire blight" [133]. No synthesis of eriobofuran or lucidafuran (also known as noreriobofuran) has yet been reported, though biosynthetic pathways for both have been proposed [134].

6. Antimalarial dibenzofurans

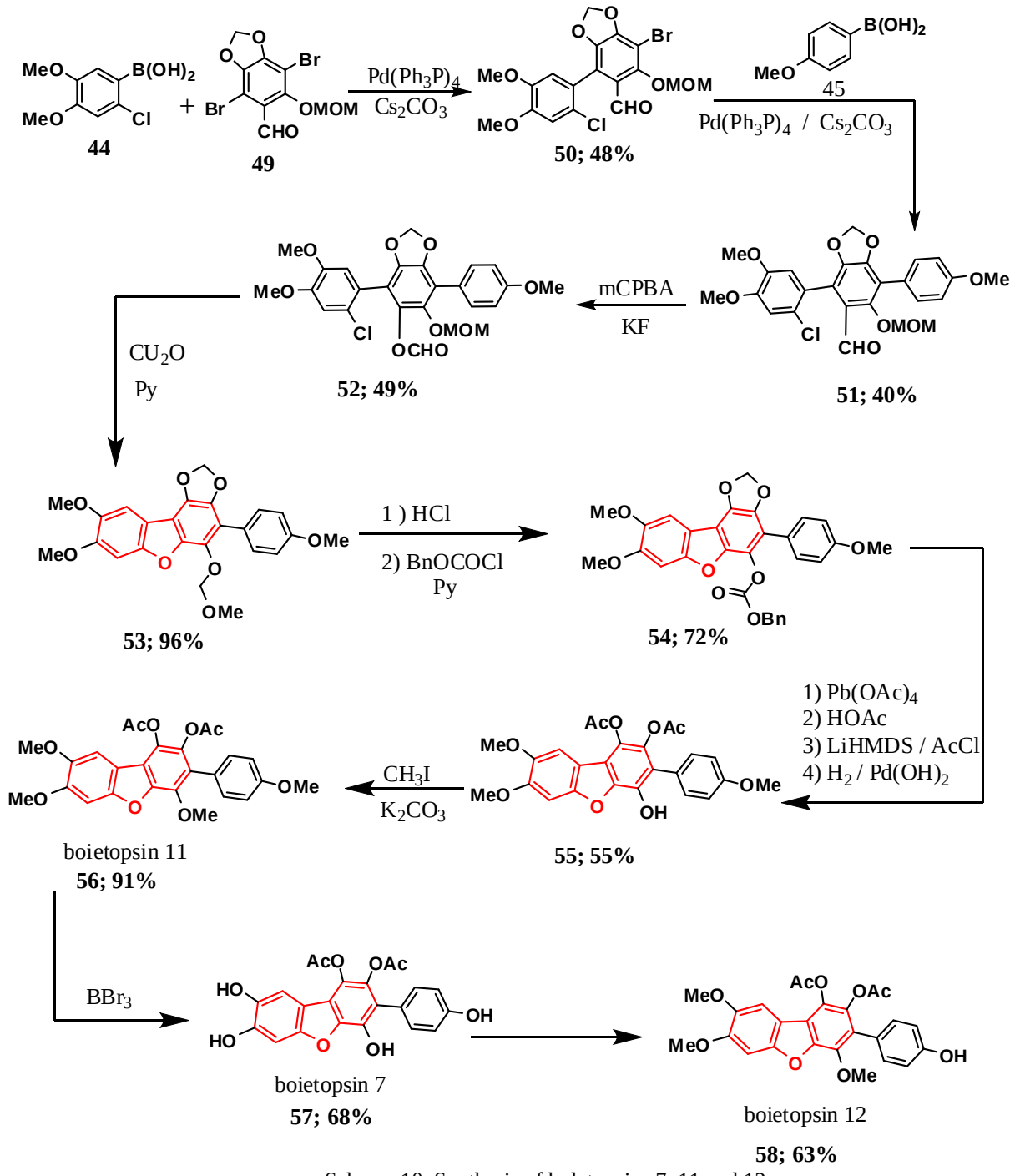
In Nigeria, several studies reported the antioxidant activities and furthermore, anti-diabetic activities of the acetone fraction of stem bark and these activities were attributed to the presence of resorcinol and dibenzofuran [135-137]. Also, the root bark showed promising antimalarial activity against Plasmodium berghei as well as antipyretic and antinociceptive activities, and the authors related these activities to the presence of tannins, saponins and some traces of anthraquinones [138]. Furthermore, the leaves from Northern Ethiopia showed promising antimalarial activities alone or in a combination with chloroquine [139].

The dibenzofuranquinone designated xylariaquinone (Fig. 14) has been isolated from an endophytic fungus in the Xylaria genus [140]. Though it showed only weak activity against Plasmodium falciparum (an IC_{50} value of 6.68 mMas compared to an IC_{50} value of 3.3 nM for the positive control, dihydroartemisinine), its low cytotoxicity toward Vero cells (IC_{50} value > 184 mM) led the authors to conclude that further study might be warranted [140]. No synthesis of this compound has been reported.

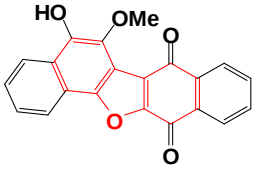
7. Dibenzofurans for the treatment of skin conditions

More recently, trace contaminants formed during the manufacture of PCBs and other polychlorinated compounds, especially herbicides, have been causally linked to chloracne development [141]. These include polyhalogenated dibenzofurans in association with PCBs, polychlorinated dibenzo-*p*-dioxins, and chlorinated azo- and azoxybenzenes which are contaminants of 3, 4-dichloraniline and related herbicides.

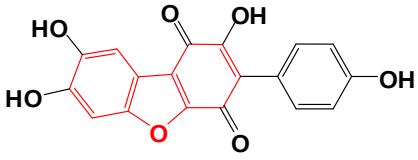
Another dibenzofuranquinone with demonstrated biological activity is balsaminone A (Fig. 15), which has been isolated from Impatiens balsamina, a plant that has been used in Chinese herbal medicine [142]. Both balsaminone A (fig. 3), and its b-D-glucoside, known as balsaminone B, have exhibited antipruritic activity in mice [142]. Moderate anti-tumor activity has also been reported for balsaminone A against four different cells lines (scheme 10) [143]. In tests on MCF-7, HeLa, HCT-116 and HT-29 cell lines, balsaminone A had IC_{50} values of 36.96, 7.63, 20.71, and 21.23 mM, respectively. In contrast, the positive control, 5-FU (5-fluorouracil), had values of 16.28, 7.34, 36.17, and 18.83 mM against the same cell lines.



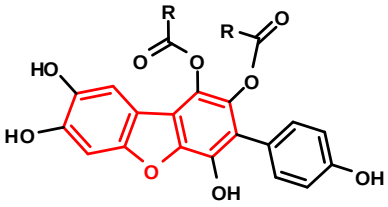
Scheme 10. Synthesis of boletopsins 7, 11 and 12.



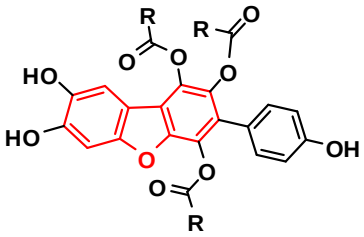
balsaminone A



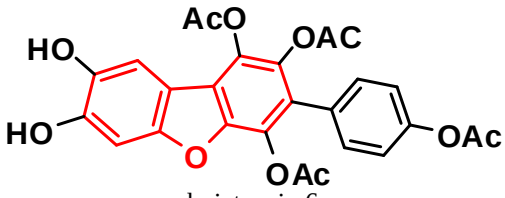
cycloleucomelone



vialinin B R= CH2Ph; Vialinin C R= P(OH)Ph



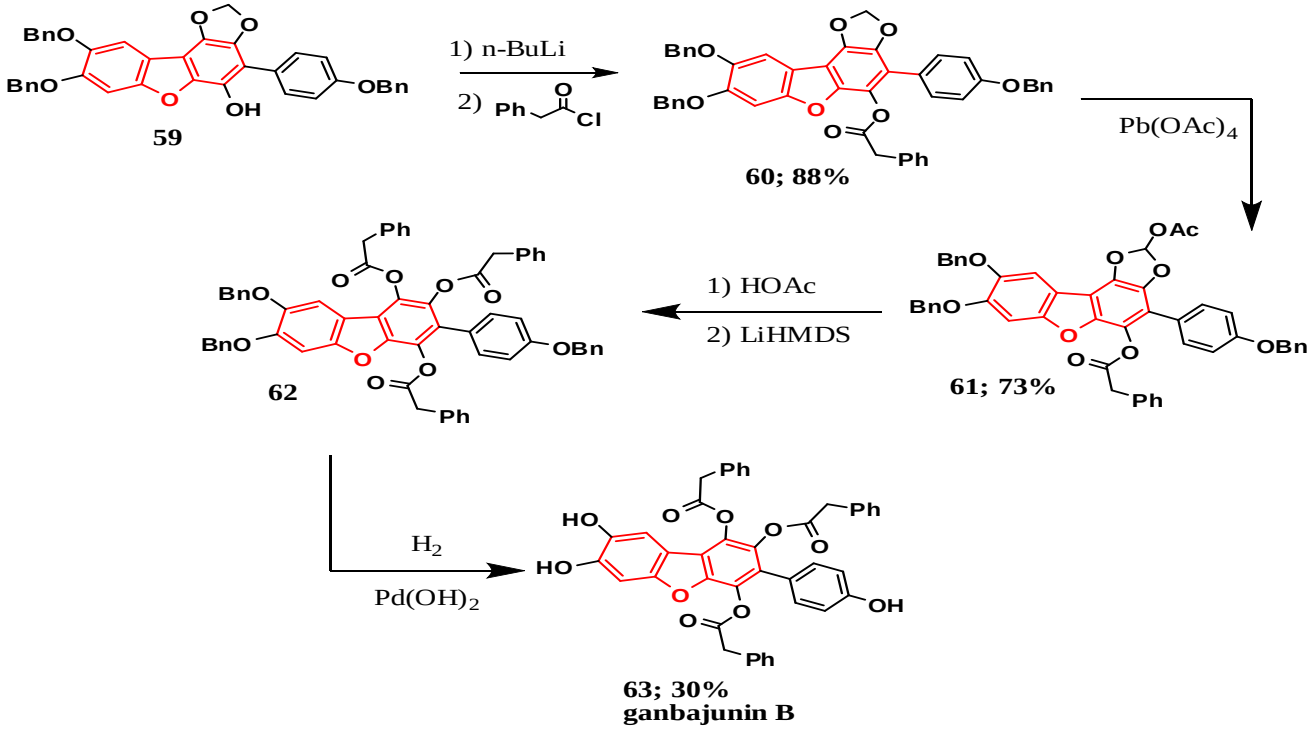
ganbajunin B R= CH2Ph



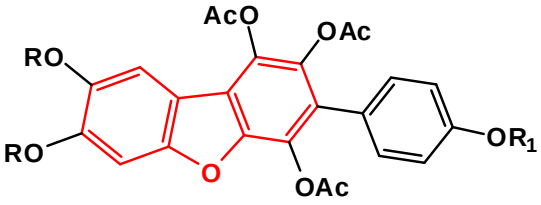
boietopsin 6

Fig. 4. Structure of selected active dibenzofuran derivatives.

Moody and coworkers have reported a synthesis of balsaminone A starting from 2-bromo-1, 4-naphthoquinone **64** and 2, 3-dichloro-1, 4-naphthoquinone **68** (Scheme 12) [144]. Reduction of **64** with sodium dithionite followed by methylation with dimethyl sulfate produced **65** in 80% yields. Lithiumehalogen exchange followed by formylation with DMF then produced aldehyde 66, which was demethylated with boron tribromide to give **67**. Base-promoted cyclization with 2, 3-dichloro-1, 4-naphthoquinone **68** produced pentacyclic quinone **69**, which provided the complete ring system of balsaminone A, essentially only requiring conversion of the aldehyde into a methoxy group to complete the synthesis. This was accomplished by first protecting the phenol as a benzyl ether and then conducting a Baeyer-Villiger oxidation, followed by basic hydrolysis to give **71** in 60% yield from **69**. Straightforward methylation of the phenol and removal of the benzyl ether via catalytic hydrogenation then completed the synthesis of balsaminone A. This synthesis is notable in that yields in every step except one.

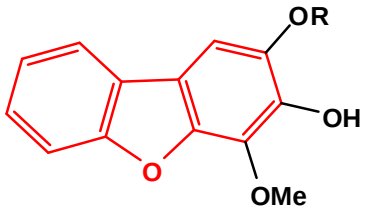


Scheme 11. Synthesis of ganbajunin B.



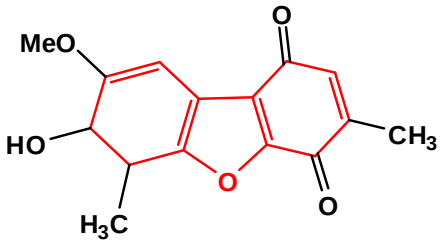
boietopsin 1; R, R_1 = Ac
boietopsin 4; R, R_1 = H
boietopsin 5; R = AC, R_1 = H

Fig. 5. Structures of boletopsins 1, 4, and 5.



Lucidafuran; R = H
Eriobofuran; R = CH_3

Fig. 6. Structures of lucidafuran and eriobofuran.



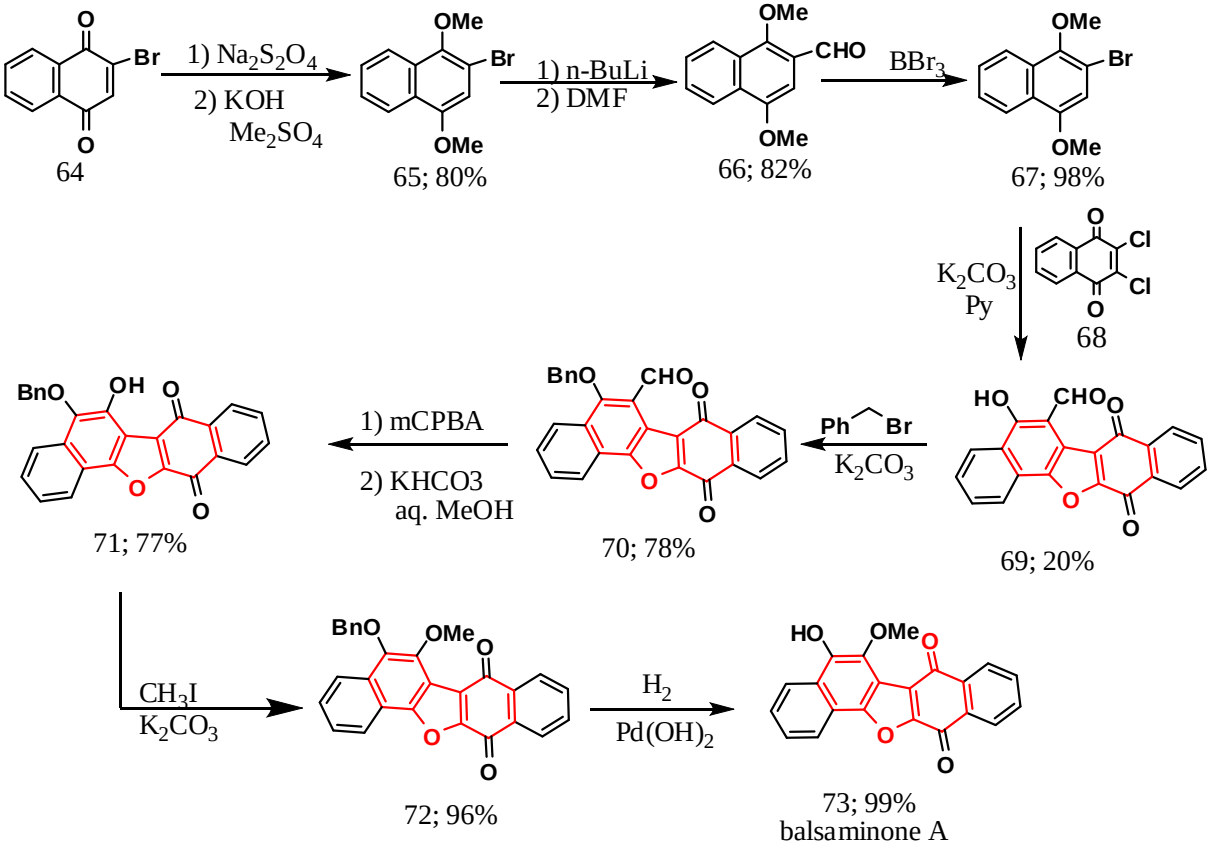
Xylariaquinone

Fig. 7. Structure of xylariaquinone.

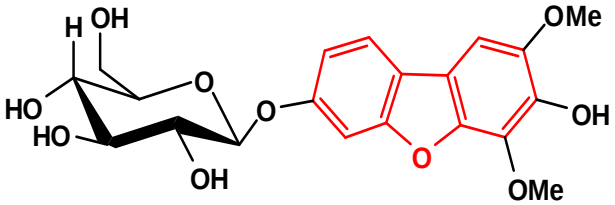
(The cyclization) were close to 80% or higher. Indeed, an earlier reaction in which an acetyl group was used in place of the formyl group had undergone the analogous cyclization in 73% yield, but the benzyl ether of the resulting product could not be induced to undergo the Baeyer-Villiger oxidation. Likewise, condensation of **68** with naphthohydroquinones with oxygen-based substituents at C-2 (which would remove the need for the Baeyer-Villiger oxidation) all failed to undergo the cyclization. Nevertheless, following the sequence outlined above, Moody and coworkers were able to obtain balsaminone A in greater than 7% overall yield starting from 2-bromo-1, 4-naphthoquinone 64. Aqueous ethanol extraction of the dried fruit of Pyracantha fortuneana produced six structurally similar dibenzofurans (mostly as their b-D-glucosides) designated as fortuneanosides G through L [145]. Four of these compounds were found to be potent inhibitors of tyrosinase. Since tyrosinase is significant in the production of melanin, inhibitors of this enzyme are of interest in the treatment of certain skin disorders, and also cosmetically as skin lighteners. The most active of the fortuneanosides was found to be fortuneanoside G (Fig. 16), which had an IC_{50} value of 0.08 mM. This compares favorably with arbutin, another tyrosinase inhibitor found in many current skin lightening agents, which had an IC_{50} value of 0.23mMunder the same conditions. No synthesis of any of the fortuneanosides has been reported.

Tyrosinase inhibition has also been exhibited by oxygenated dibenzofurans isolated from the evergreen tree Distylium racemosum [146, 147]. The most active was 4-methoxy-1, 8-dimethyl-3, 7-dibenzofurandiol **74** (Fig. 17), which had an IC_{50} value of 76.4 mg/mL, although this did not compare favorably to that measured for arbutin, whichwas 48.8 mg/mL using the same assay [147]. (Since the molecular mass of arbutin is slightly larger than that of **74**, this difference would only be greater if expressed in terms of molarity).

Dibenzofuran **74** did show significant inhibition of porcine pancreatic elastase, however, with an IC_{50} value of 7.7 mg/mL, as compared to 9.7 mg/mL, the value reported for the positive control, oleanolic acid [147]. Since elastase is involved in the degradation of elastin in the dermis, compounds such as **74** may find use in the maintenance of skin elasticity.

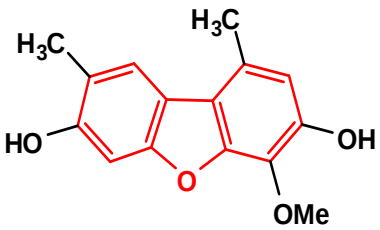


Scheme 12. Synthesis of balsaminone A.



fortuneanoside G.

Fig. 16. Structure of fortuneanoside G.



74

Fig. 8. Structure of 4-methoxy-1, 8-dimethyl-3, 7-dibenzofurandiol

8. Conclusions

The previous literature reports conclude that dibenzofurans may be extracted from many natural sources; many members of this group of compounds have exhibited significant anti-allergy, antioxidant, aanti-inflammatory, antimalarial and treatment of skin conditions, which has led to various efforts focusing on their wholesome synthesis.

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