



Synthesis of Dibenzofuran Derivatives Possessing Anticancer Activities: A Review



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THIS review focuses on reports concerning the isolation and/or synthesis of dibenzofuran derivatives' isolation and synthesis (whether one of them or both occurs simultaneously) existing naturally while exhibiting evident biological anticancer activity. While not a comprehensive approach to all relevant compounds, the review intends to demonstrate anticancer activity's reach related to said compounds instead and the various natural origins and synthetic methods from which and by which the compounds are to be secluded and prepared. Compounds with reduced benzene rings, e.g., morphine as well as its derivatives, are omitted, same for compounds with aromaticity disrupted by alkylation, as with usnic acid.

Keywords: Dibenzofuran derivatives, Anticancer activities, Polychlorinated dibenzo-p-dioxins, Polychlorinated biphenyl.

Synthesis of Dibenzofuran Derivatives

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.

Two more soluble alternative electron donors have been f (refer to Modern Literature). The method in the current report improves output at a shorter reaction time (**scheme 1**).

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**) [1].

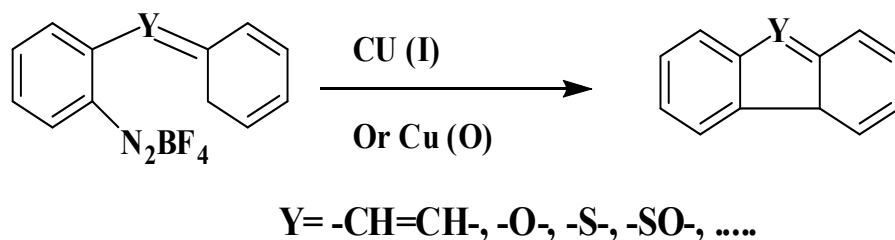
Intramolecular palladium (II) catalyzes the formation of carbon– and oxidized carbon bonds under air in the presence of pivalic acid where in the reaction's solvent, rather than the acetic acid, leads to more reproduction and productivity and wider substrate range. The reaction allows the conversion of both electron-rich electron amines and electron deficiency (**scheme 3**) [2].

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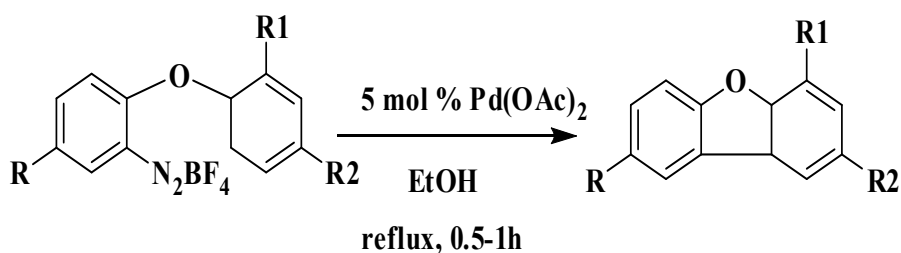
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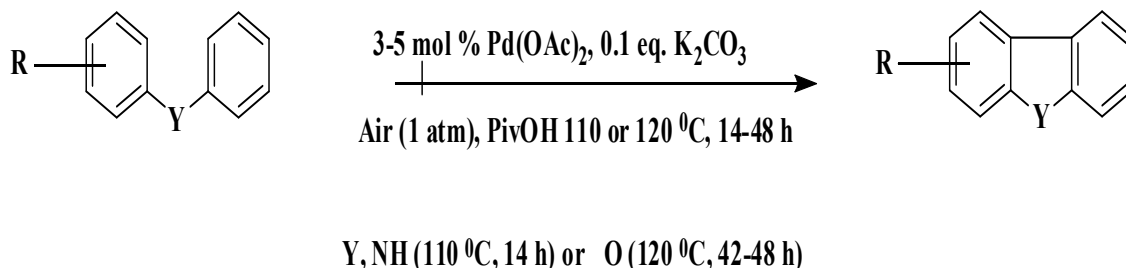
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Scheme 1. Synthesis of biaryl tricyclics



Scheme 2. Synthesis of dibenzofurans



Scheme 3. Synthesis of dibenzofurans and / or dibenzopyrrols

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*-Iododiaryl ether synthesis in one vessel was accomplished through serial iodine and *o*-Arylation of phenol under moderate reaction conditions (**scheme 4**) [3].

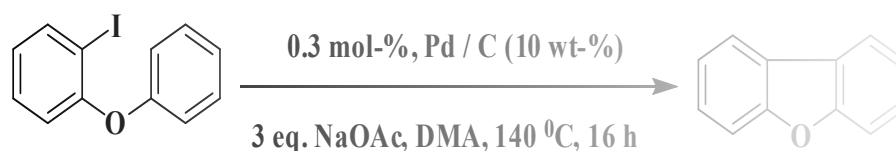
An effective route has been developed to formulating carbazoles and dibenzofurans. *o*-Iodoanilines or *o*-Iodophenols' reaction with silylaryltriflates followed by exposure to Caesium Fluoride (CsF) to provide *N*- or *o*-Arylated products by cyclization using the Pd catalyst to carbazoles and dibenzofurans in acceptable to

flawless yields; different functional groups were tolerated (**scheme 5**) [4].

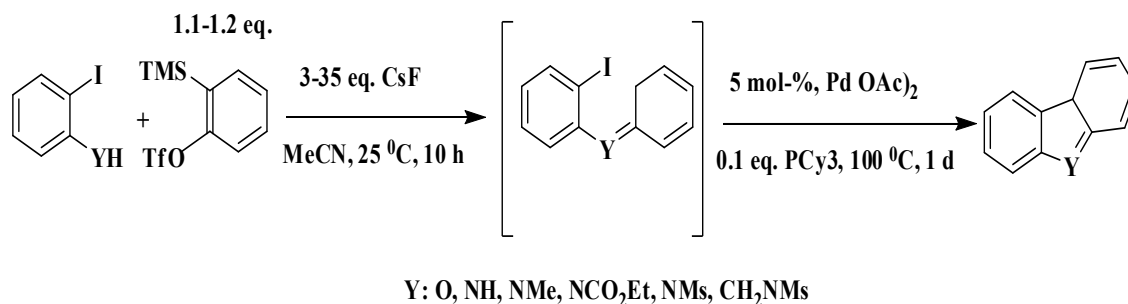
Includes a new effective protocol for the rapid construction of 6-diazo-2-cyclohexanone and *o*-halo bi-benzenes formations, including coupling/stirring, one Pd catalyst, Pd catalyst, and copper catalyst, Ullmann coupling (**scheme 6**) [5].

Anticancer Dibenzofurans

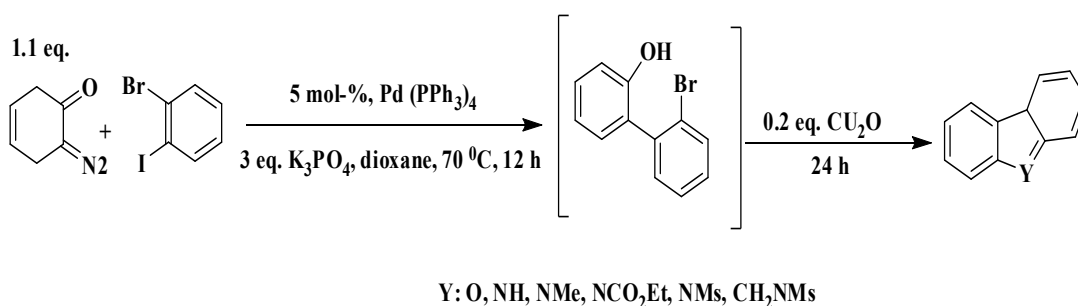
Amongst diseases, cancer stands as one of the most terrible diseases, these increases with lifestyle, global warming, and nutrition. Treatments for cancer do not contain an effective drug because the medications currently available cause side effects in some cases.



Scheme 4. Synthesis of dibenzofurans from o-iododiaryl ethers



Scheme 5. Synthesis of dibenzofurans and carbazoles



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

In this context, the synthetic compounds that depend on the dibenzofuran moiety and natural products extracted from medicinal plants are of rising prominence in treating cancer. The World Health Organization found out that 80% of the world's population relies mainly on plant-derived medicines from developing countries for health care [6]. Potential antioxidant and anticancer properties of plant extracts or products isolated from plants' sources can be experimented to develop anticancer drugs [7].

Also, in general, it has been observed during recent references that synthetic organic chemistry has a distinct biological activity in all different applied directions [8-28]. Therefore, in this review, the focus will be on reports relating to the isolation and/or naturally occurring synthesis

of dibenzofuran derivatives with demonstrated anticancer activity.

The Polychlorinated Dibenzo-p-Dioxins (PCDD/Fs) and Polychlorinated Biphenyl (PCBs) create similar types of toxic results and seem to work by employing a common mechanism of action, although they vary widely in efficacy [29,30]. Toxicity responses include skin toxicity, teratogenicity, bodyweight loss, immune- and neurotoxicity, and carcinogenicity [31]. Biochemical and genetic studies both imply that Aryl Hydrocarbon Receptor (AhR) halts most anticancer responses by TCDD (2, 3, 7, 8-Tetrachlorodibenzo-p-dioxin) and affiliated compounds [32,33].

The common PCDD/Fs mechanism and the common-level PCBs have been used in the

development of AhR to develop the concept of Toxic Equivalence Factor (TEF) wherein the effectiveness of a given constructor is present within the most effective congeners: 2, 3, 7, 8-TCDD [34]. TEF values at present are mainly extracted from *in vitro* as well as short-term *in vivo* experimentation [35] and are currently utilized in risk assessment of complex compounds combination. Structural Activity Relationships (SAR) for the various chemical responses and toxicity mediated by AbR indicated that the TEF approach applies to all alternative PCDD/Fs 2, 3, 7 and 8 PCBDFs, planar PCBs, and some relatively planar PCBs homogeneous.

However, it is unclear whether all toxic responses to organic halogen elements mediate the AhR pathway. For example, SARs for anticancer responses related to carcinogenicity [36] and neurotoxicity [37] appear to swerve from the AbR pathway. The promotion of liver tumors was increased *in vivo* after exposure to Polyhalogenated Aromatic Hydrocarbons (PAHs) in experimental animal studies [38,39].

All the Polychlorinated Biphenyl (PCB) and Polychlorinated Dibenzo-p-Dioxins (PCDD/F) congeners tested in this study showed the inhibition capabilities of Intercellular Communication (IC), except for 2,2', 4,4' and 5,5'-HxCB, at least two different mechanisms, for example, independent paths based on AhR may contribute to IC inhibition. The PCDD/Fs and coplanar PCBs are likely to raise their impact through a pathway based on the AhR receptor, a bidirectional PCB, however, applying an autonomous mechanism (AhR) and monochrome PCBs most likely by a mixture of both tracks.

The provided information suggests that current values of TEF based on intermediate effects of the used AhR to assess the risks of carcinogenic implications may instigate serious risks for individuals prone to complicated combinations of PCBs and PCDD/Fs. Moreover, *in vitro* inhibition seems to be a beneficial model for anticipating the potential for tumor acceleration potential, for example, organic halogens and machine studies in the cause of IC inhibition by these compounds [40].

Multiple naturally occurring dibenzofurans exhibited activity against different cancer types. For example, a dibenzofurans series known as kekokorins A-E was secluded from two differing types of *Trichiafavoginea*, a slime mold [41,42].

Three kekokorins, A, D, and E, showed counter-HeLa cells activity and maintained IC₅₀ values of a range of 1.5 mg/mL for kekokorin A to 6.1 mg/mL for kekokorin D. No other studies reported on the given compounds (**Fig. 1**). Two dibenzofurans dubbed Pf-1 and Pf-2 were recently secluded from *dictyostelium discoideum*, another slime mold [43,44].

The given compounds structurally resembled AB0022A, a compound isolated from other types of slime mold, *Dictyostelium purpureum* K1001 and was confirmed to possess antibacterial properties [45].

On the other hand, Pf-2 was found to lack any substantial cytotoxicity. Pf-1 and AB0022A exhibited the constraint of the tested cell lines (K562, HeLa and 3T3-L1), which indicates that a free phenolic group connected to carbonyl is necessary for activity. Despite the lack of IC₅₀ values reports, AB0022A proved effectual against the three cell lines compared to Pf-1 [44] (**Fig. 2**).

Considerable interest in dibenzofuran quinone popolohuanone E was raised following its 1993 isolation report [46] due to its anticancer potency. Secluded from the *Dysidea* sponge, it exhibited suppressive behavior toward topoisomerase II (IC₅₀ ¼ 400 nM) same for human lung cancer cells A549 (IC₅₀ ¼ 2.5 mg/mL) [46].

Tremendous work has been dedicated towards its synthesis; however—and up to this report, whole compound synthesis has not been reported yet (**Fig. 3**).

Early efforts towards the complete synthesis of popolohuanone E were conducted by Terashima, Katoh, and co-workers where a series of typical compounds of the five assorted isotopes were readied: the most common in popolohuanone E structure was compound (11) as shown. [47]. (**scheme 7**).

The synthesis method of Terashima began with 3, 4-dimethoxyphenol, converted to methoxymethyl ether 1, *tert*-butyllithium was used to lithiate 1 which was then followed by reaction with (4aR, 8aR)-1-formyl-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydro-8a-methyl-naphthalene 2 that yielded alcohol 3, yielded only at a 24% yield. Catalytic hydrogenation diminished the benzylic alcohol, and the MOM group, undergoing acidic removal, led to the production of alternative phenol, compound (4), at a yield of 78%.

MOM-protected 3-methoxyphenyl 5 was used to prepare phenol, compound (7), by a similar sequence of transformations; the resulting yields were more in comparison. Phenol 7 was converted to quinone, compound (8), through molecular oxygen oxidation. Salcomine was used to catalyze the oxidation, and then thionylchloride was used

to chlorinate quinone 8 to yield intermediate, compound (9). Sodium salt from 4 C-alkylated product, compound (10) was used to condense this medium. Previous model studies on much plainer compounds concluded that a phenolic methoxy group was necessary for this reaction in C-6 of 4 rather than phenolic oxygen.

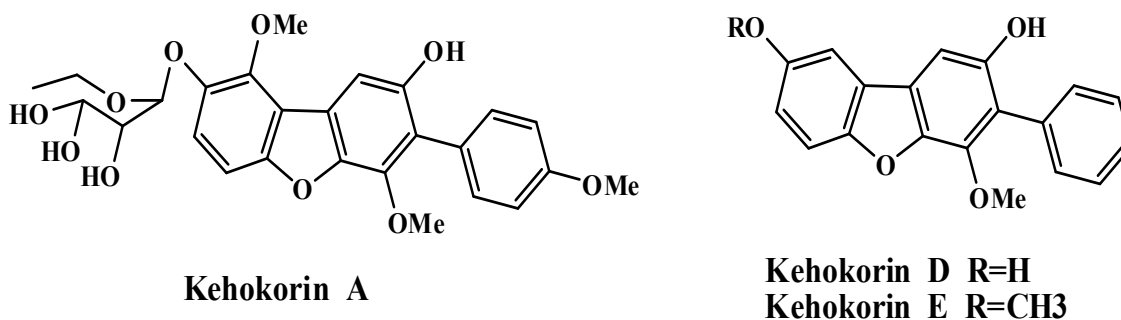


Fig. 1. Structures of kehokorins

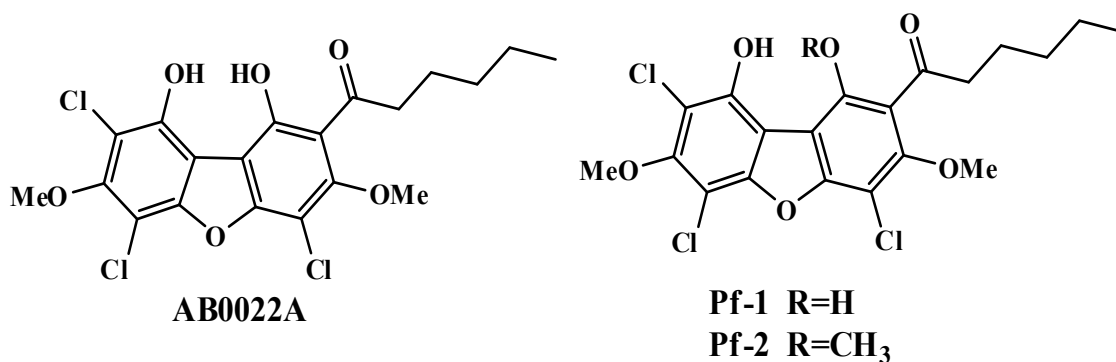


Fig. 2. Cytotoxically active chlorinated dibenzofurans

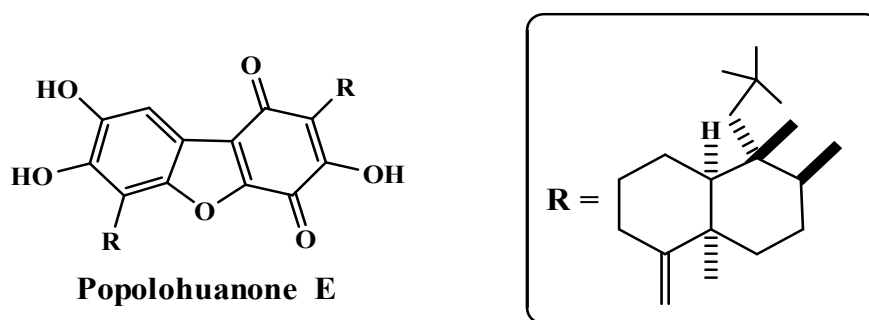
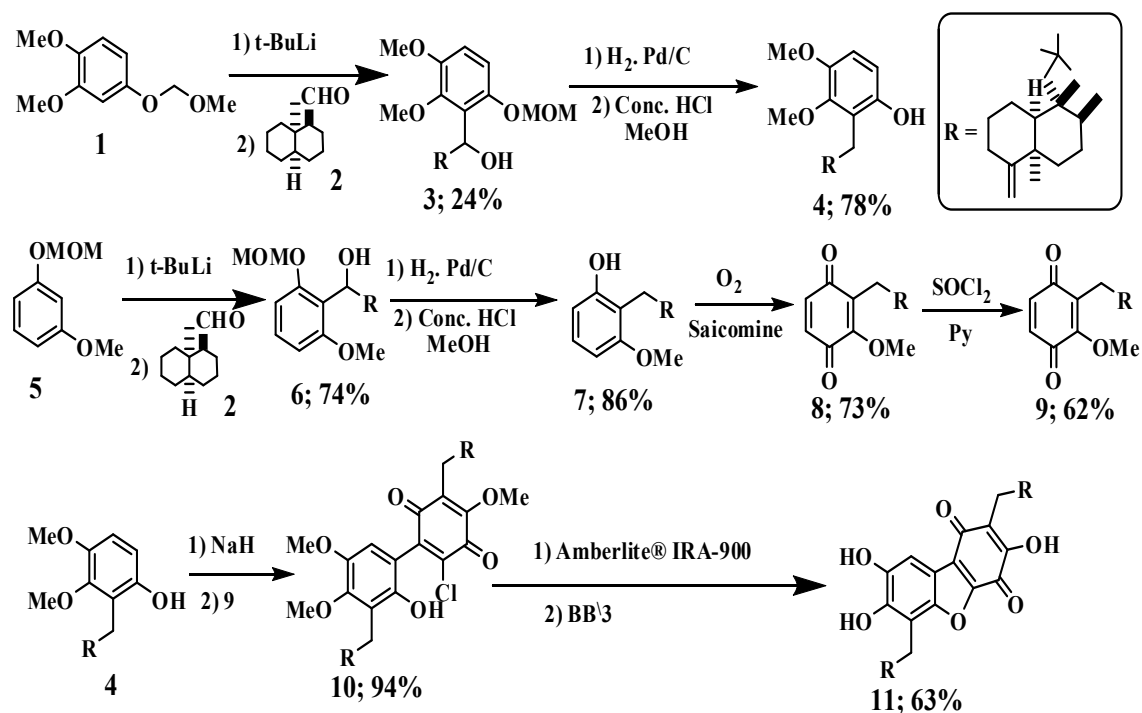


Fig. 3. Structure of popolohuanone E.



Scheme 7. Synthesis of popolohuanone E analog.

Cyclization of compound (**10**) took place via basic ion exchange resins, and demethylation was derived from methoxy three groups via boron propoxide, resulting in representative E-popolohuanon, compound (**11**). Ion exchange resins have been suggested to be used for the cyclization of compound (**10**) through yields in previous model studies wherein “traditional” rules did not result in the desired cyclized outcome by more than 20%.

The required Aldehyde, compound (**2**), which was vital for these studies, was prepared across the Wieland-Meiser, compound (**12**), optically pure ketone seven steps (**scheme 8**). Although **2** is illustrated in scheme 7 as a single isomer; it has actually been used as a mélange of epimers; segregation of the stereoisomers taking place after interaction with the aryllithium reagent.

Years later, Katoh, Terashima, and his research group stated their work to apply a correspondent combination of conversions to consolidate popolohuanone E itself [48]. Ketone, compound (**13**), was used to prepare Aldehyde, compound (**14**), across fifteen steps [49,50]. Aldehyde, compound (**14**), was converted to the derivative of methoxyphenol **15a** before albeit some changes were applied to the experiment’s conditions.

The most important change was benzylic alcohol reduction which was accomplished by using the Barton reaction (converting alcohol into a matching xanthate, succeeded by a radical depreciation with tributyltin hydride) rather than catalysis by hydrogenation. Also, within these sequences of experiments, aryllithium reagents were created by exchanging halogen lithium with the matching bromoarene instead of immediate lithiation as shown in scheme 7. In the end, **15** in the 65% yields of **14** were obtained across five steps.

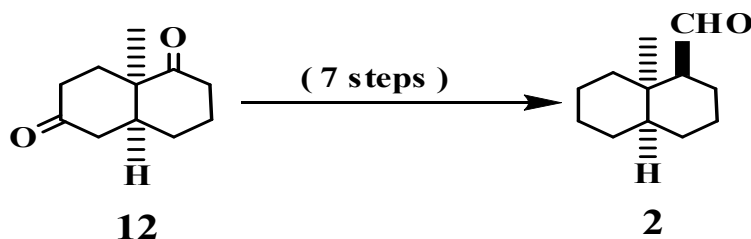
Coupling partner, compound (**16**), was created in a similar way immediately to **15** and then transformed to quinone, compound (**17**), as previously stated for the preparation of compound (**9**). Coupling and then cyclization were performed similarly to typical compounds, yielding dibenzofuran quinone, compound (**18**), at 75% yield (**scheme 9**).

Hydrolysis of acetal protecting groups on **18** took place in a quantitative yield, but transfiguration of the ketones produced to the corresponding methylene groups was shown to be a problem. The use of Wittig and Tebbe reagents causes the starting material to be consumed with no desired product formed as planned; while

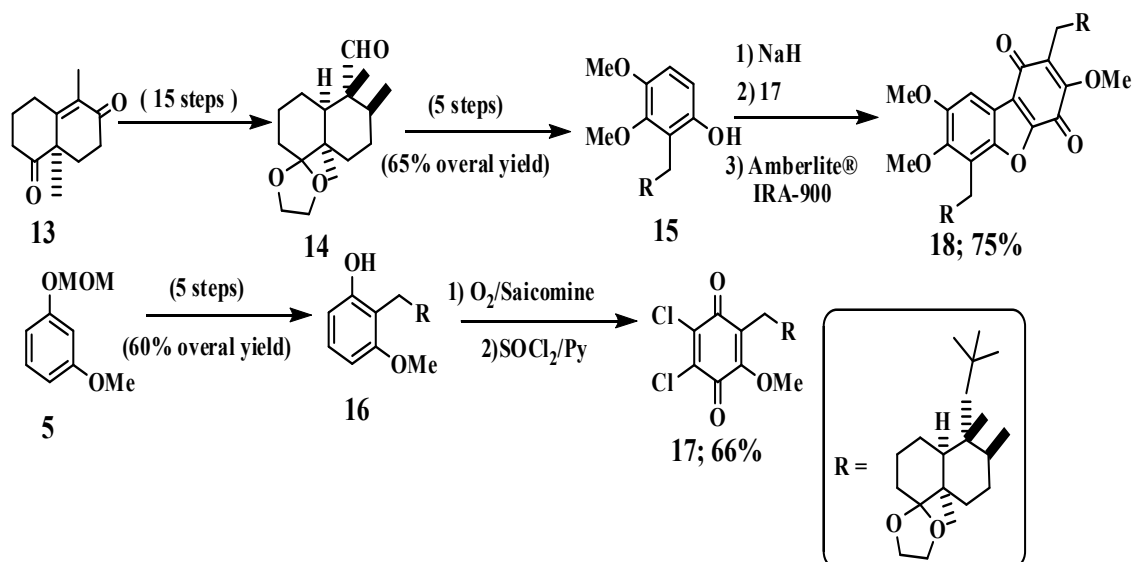
the Peterson olefination attempt only returns the initial material. Eventually, applying Oshima and his research group's reported protocol [51] produced (**19**) in a 26% yield (**scheme 10**).

At this point, what remained was the removal of methyl from the three methoxy groups to produce the E-polyphuanone. Unfortunately, this

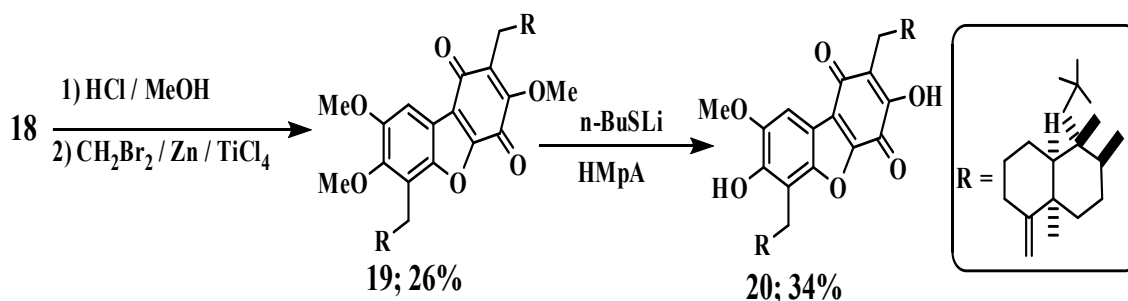
shift was not achieved, and the closest result was 8-O methyl popolohuanone E, compound (**20**), production at 34% of the yield when heating compound (**19**), at 110 °C with Lithium n butyl thiolate. Till now, no conditions have been reported to remove the conclusive methyl group from 20 to obtain popolohuanone E or to use other protection groups.



Scheme 8. Preparation of aldehyde 2.



Scheme 9. Synthesis of popolohuanone E precursor.



Scheme 10. Synthesis of 8-O-methylpopolohuanone E.

During Terashima and Katoh's investigation to create populothanone E, Anderson and coworkers were trying to totally synthesize it. Yet again, they were preceded by a model study. 1, 2, 4-trimethoxybenzene lithiation was followed by addition to pivaldehyde created the anticipated benzylic alcohol (**scheme 11**), which was then diminished to compound (**22**), via triethylsilane and trifluoroacetic acid [52]. Demethylation via trimethylsilyl iodide then furnished triol, compound (**23a**); an excellent yield was formed as a result.

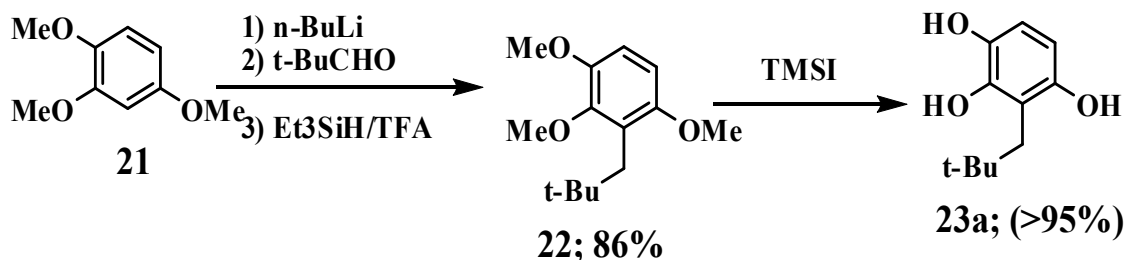
This triol could be oxidatively dimerized using Silica-supported iron trichloride can be used to oxidatively dimerize this triol, enabling the result of diquinone, compound (**24a**), in an 81% yield. Then diquinone, compound (**24a**), is treated with potassium carbonate and then the production of analog E-25P in a single step within a 79% yield (**scheme 12**).

According to the optimistic results attained with the typical compound (**23a**), hydroxyarenarol, compound (**23b**), was derived and exposed to the same oxidation circumstances. However, the required diquinone, compound

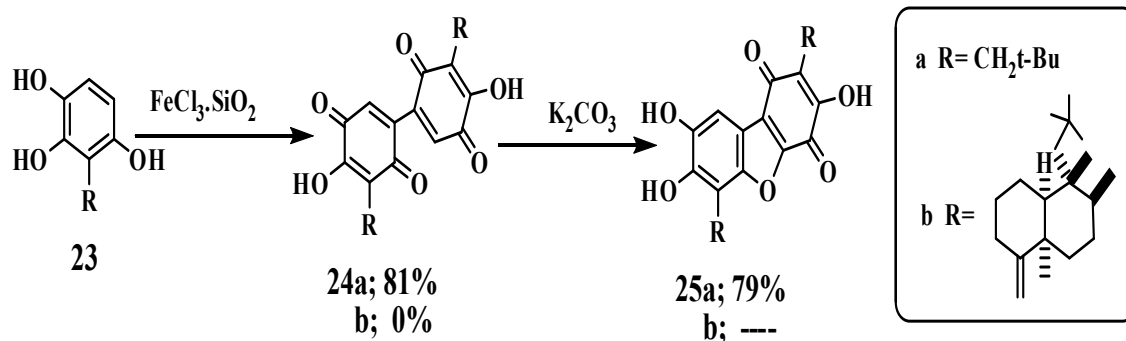
(**24b**), has not been created, and the affiliated hydroxyl benzonine was created instead [53]. Likewise, the testing of other oxidants failed to produce diquinone, compound (**24b**). Therefore, it was not possible to attempt the cyclization to populothanone E.

The last dipenzofuran to exhibit anticancer properties is rhodomartoxin B, extracted from *pylidostigmatropicum's* bark extract [54] and also from Australian cherry, *rhodomartus macrocarpa* [55]. The said compound demonstrated behavior against Hep-G2 and MDA-MB-231 cell lines with a value of LC50 of 19.0 (\pm 9.0) μ m previous and 2.50 (\pm 0.27) μ m last arrow [31,56].

Setzer and coworkers suggest that anticancer activity is caused by the intersection of rhodomeroxin B in cytosine base pairs. Djaballah and collaborators also found that rhodomeretoxin B stints the outgrowth of NCEB1 cells with an IC₅₀ value of ca. 9 μ m [57,58]. Despite the lack of appearance of combinations of rhodomeretoxin B in modern literature, rhodomeretoxin C has been reported and exhibited a similar structure (**Fig. 4**).



Scheme 11. Synthesis of triol 23a.



Scheme 12. Oxidative dimerizations of triols

Conclusions

The previous literature reports conclude that highly oxygenated dibenzofurans may be extracted from many natural sources, whether marine or terrestrial and could be done from slime molds to humongous evergreen trees. Many members of this group of compounds have exhibited significant anticancer activity, which has led to various efforts focusing on their wholesome synthesis. Plenty of these natural products were made exclusively by organisms that were isolated from them, and thus they continued to present artificial challenges for the future.

Acknowledgements

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تشبيد مشتقات الداينزوفوران التي لها نشاطا كمضادات للسرطان: استعراض مرجعي

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يهتم هذا البحث المرجعي بعرض الأبحاث المتعلقة بتشبيد مشتقات الداينزوفوران (سواء حدث أحدهما أو كلاهما في وقت واحد) الموجودة بشكل طبيعي مع عرض نشاطها البيولوجي كمضادات للسرطانات البشرية المختلفة.

يركز البحث المرجعي على إظهار مدى النشاط البيولوجي (مضاد للسرطان) لهذه المركبات سألقة الذكر فيما يتعلق بالمركبات المذكورة، وكذلك يتعرض البحث المرجعي للأصول الطبيعية المختلفة والأساليب التركيبية التي يتم من خلالها فصل المركبات وتجهيزها. وفي هذا البحث المرجعي لم تتم دراسة المركبات ذات حلقات البنزين المنخفضة، مثل المورفين ومشتقاته، كما هو الحال بالنسبة للمركبات الأروماتية التي حجب تكوينها نتيجة لعملية الألكلة، كما هو الحال مع حمض الأوثنك.