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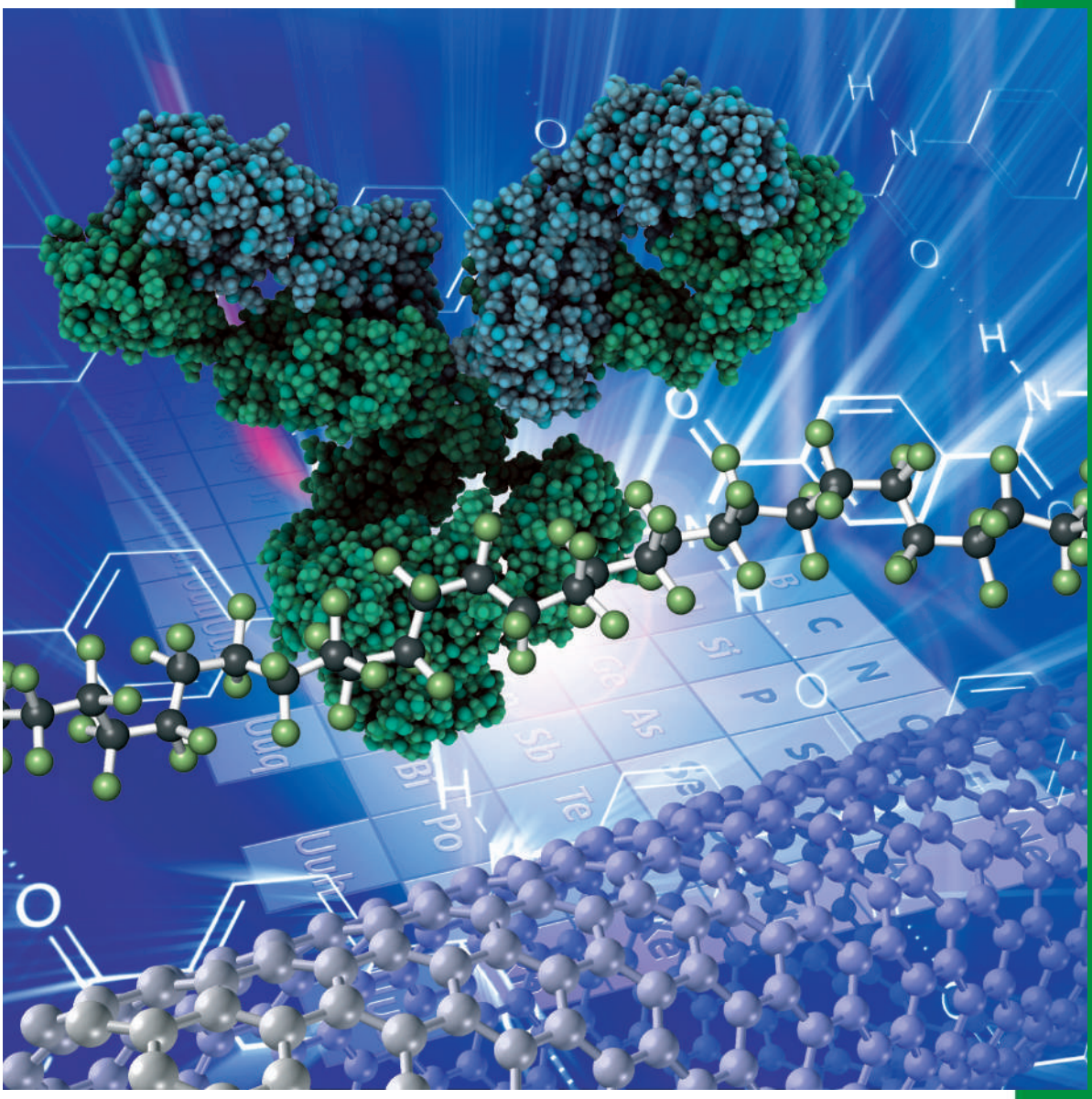

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Chemistry SELECT Reviews

Organic & Supramolecular Chemistry

Total Synthesis of Xyloketals and Related Natural Product Alboatrin: Strategies and Tactics

Biswajit Panda*[a]

Dedicated to my teacher Dr. Subhas Chandra Maity to celebrate his 48th birthday

Molecular Architectures: Xyloketals are an interesting class of natural products showing various potent and notable bioactivities like acetylcholine esterase inhibition, antioxidant activity, L-calcium channel inhibition, radical-scavenging activity, suppression of glioblastoma cell proliferation, reduction of neonatal hypoxic-ischemic brain injury, etc. A significant number of reports have appeared in the literature regarding the synthesis and biological activity of xyloketals and structurally related natural compound, alboatrin which insist to review thoroughly on this topic. Here the delights and difficulties of all synthetic strategies to concoct these molecules along with the comparative studies of various approaches and wherever necessary, the uniqueness of the synthetic protocols have been discussed thoroughly.

1. Introduction

Nature gifts us immeasurable numbers of natural products with complex and fascinating architectures having useful biological and medicinal properties. Total synthesis, the imitation of nature's molecules in the laboratory reveals and signifies the state of the art of synthesis in general.[1] Xyloketals are a family of natural products which were isolated from a mangrove fungus of the *Xylaria* species.[2] *Xylaria* is large and first described genus of the xylariaceae,[3] a large and relatively well known Ascomycetes family found in most countries contain 35 genera.[4] *Xylaria* is characterized by sac-like perithecium, ascocarp, and long asci with variable number of the ascospores. Majorities of the Xylaria species are host-specific but many questions about the *Xylaria* species remain unanswered, especially with regard to the colonization of hosts.[5]

Xyloketals belong to one comparatively small but exciting class of natural products displaying many different bioactivities. The chiral nonracemic and polycyclic molecular framework of these molecules, as well as the high symmetry of several members of the family, makes these natural products attractive targets for total synthesis. In addition, several of these compounds were shown to have potent and notable biological activity. Therefore, these compounds could serve as potential lead compounds for drug discovery.

The joy and challenges in total syntheses of xyloketals and structurally related natural product, alboatrin will be discussed here; only those stratagems that led to effective total syntheses will be emphasized. In discussing the total syntheses of these natural products, the methods used for ketal formation is naturally highlighted. The other significant facet will be the reactions engaged for xyloketal synthesis, particularly on regio- and, stereoselectivity of ketal formation.

Although several racemic and some chiral syntheses of these biologically active natural products have been reported, this is the first review article which is going to appear in the literature. Since Alboatrin is a single molecule, whereas xyloketals are a series of compounds, we will start our discussion about alboatrin first and then about xyloketals.

2. Alboatrin (2)

2.1. Isolation and Structural Characterization of Alboatrin (2)

In 1988, the phytotoxic metabolite alboatrin was first isolated from the culture filtrate of fungus *verticillium albo-atrum* (Figure 1) by Ichihara et al.[6] The structure of isolated alboatrin had been determined by spectroscopic and degradative methods. The stereochemistry at the three adjoining chiral centres is a crucial feature of the alboatrin molecule, and the relative configurations have been determined by nuclear over-

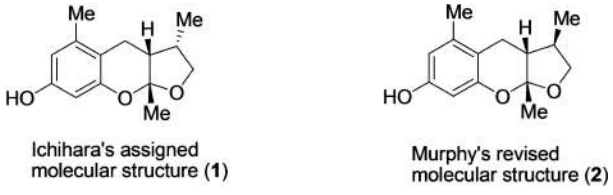

Figure 1. Ichihara's Assigned Molecular Structure (**1**) and Murphy's Revised Molecular Structure (**2**) of Alboatrin

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hauser experiments(NOE). The assigned structure (**1**) contained a 5,6-bicyclic acetal moiety that was fused to an aromatic core. This time, the stereochemistry of C-5 methyl substituent was assigned as being *anti* to the *cis*-ring junction of the bicyclic acetal. In this initial report, the authors made no comment regarding the absolute stereochemistry of the natural product.

In the year 1999, Murphy et al. finished a total synthesis of the assigned structure of alboatrin (**1**).[7] Surprisingly, they found that major product obtained in the reaction was the diastereomer of the natural product as reported by Ichihara et al. X-Ray crystal structure analysis of their synthetic material confirmed that the major reaction product tallied with the structure reported by Ichihara et al. The spectral data for their synthetic material did not tally with the data reported for the natural product. The NMR studies of the crude reaction mixture showed the presence of a mixture of two, different diastereomers (6.7: 1 ratio). And the data matching those of naturally obtained alboatrin were shown by the minor reaction product **2**, the C-5 epimer of the assigned structure for alboatrin. Therefore, the originally assigned molecular structure for alboatrin was revised. Note that the correct molecular structure of alboatrin (**2**) incorporates an identical 5,6-bicyclic acetal moiety as to that found in the xyloketal family of natural products.

2.2 Biological Properties of Alboatrin[8]

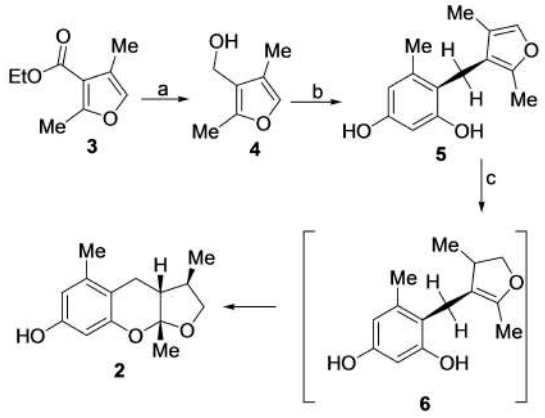
Alboatrin (**2**) is related to the vascular-wilt disease of alfalfa. It has been reported that alboatrin (**2**) at a concentration of 50 ppm, inhibits the root growth of the host plant, *Maris Kabul* by 49%. This disease causes stunted growth, reduced quality, wilted and dead foliage as well as a decrease in life span of the plant. This causes crop production to become profligate after two to three years in infected alfalfa fields. In addition, infected plants are more prone to death from environmental stresses such as the lack of precipitation and temperature.

2.3 Literature Syntheses of Alboatrin

2.3.1 Ichihara's Synthesis of Racemic Alboatrin (2)[6]

The earliest total synthesis of racemic alboatrin (**2**) was described by Ichihara et al. in conjunction with their report on the isolation of the natural product (Scheme 1).

An electrophilic aromatic substitution process and a subsequent hydrogenation step are the key steps in this



Scheme 1. Ichihara's Synthesis of Racemic Alboatrin (**2**)
Reagents and conditions: (a) LAH, Et_2O, 85%; (b) 1-methyl-3,5-dihydroxybenzene (**7**), $BF_3.Et_2O$, $CHCl_3$, 10%; (c) H_2, Pd/C, AcOH, 64%.

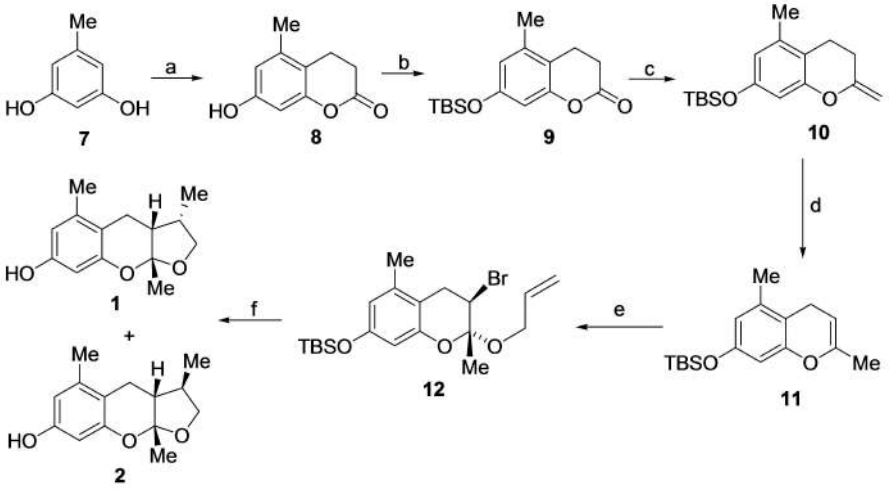
synthesis. Probably, the less substituted double bond of the furan **5** was reduced selectively, based on steric factors, which led to the spontaneous formation of the bicyclic acetal moiety. The relative stereochemistry of the C-5 methyl substituent was *syn* to the bridgehead hydrogen atom of the acetal moiety. Note that this racemic product was resolved by chiral HPLC to obtain both enantiomers of alboatrin (**2**). The similar biological activity was shown to exhibit by the enantiomers.

2.3.2 Murphy's Synthesis of Racemic Alboatrin (2)[7]

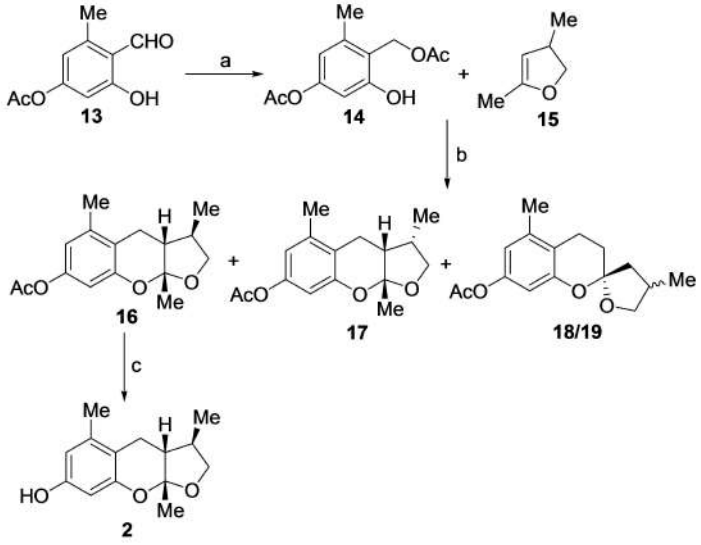
In 1999, Murphy and co-workers have also described a total synthesis of racemic alboatrin (**2**) (Scheme 2).

1-Ethylpiperidine hypophosphite mediated radical cyclization process is the key step in this synthesis to install the 5,6-bicyclic acetal moiety. From the beginning of this synthesis, it was expected that this reaction would afford predominately compound **1**, which was the originally assigned structure of alboatrin (**2**), based on the steric arguments that are associated with 5-exo-trig radical cyclizations. As stated earlier, on the comparison of the spectral data of the major product of this reaction with that reported for alboatrin was it discovered that the minor reaction product corresponded to the correct molecular structure of naturally obtained alboatrin.

Dr. Biswajit Panda did his Ph.D in 2012 under the supervision of Prof. Tarun K. Sarkar at Indian Institute of Technology, Kharagpur (IIT KGP), India. His doctoral work was based on the synthesis of xyloketal natural products and Pd-Au dual catalytic synthetic methodology developments. After completion of doctoral work, he joined as a postdoctoral fellow in the laboratory of Prof. Tien Y. Luh at National Taiwan University, Taiwan. There he worked on the development of new cyclopropene based conducting polymers. In May 2015, he returned to India and joined as an Assistant Professor of Chemistry, City College, Kolkata-700009, under the University of Calcutta. His main research interests are stereoselective synthesis of bioactive natural products and development of new synthetic organic methodologies.



Scheme 2. Murphy's Synthesis of Racemic Alboatrin (**2**)
Reagents and conditions: (a) Acrylic acid, Arnberlyst 15® resin, PhMe, 4 h, 87%; (b) TBSCl, Et_3N, CH_2Cl_2, rt, 6 h, 97%; (c) Tebbe reagent, PhMe, −40 °C to rt, 4 h, 70%; (d) Amberlyst 15® resin, $CHCl_3$, 60 °C, 12 h, 100%; (e) ally1 alcohol, NBS, CH_2Cl_2, 0 °C to rt, 6 h, 72%; (f) 1-ethyl piperidine hypophosphite, AIBN, PhH, 4 h, 77%, dr = 7:l (**1**: **2**).



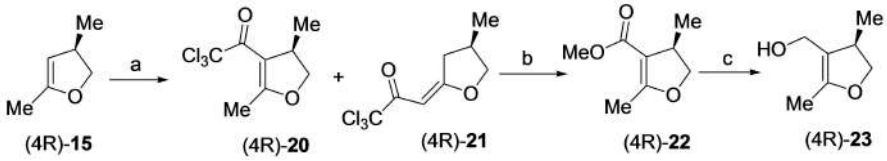
Scheme 3. Baldwin's Synthesis of Racemic Alboatrin (**2**)
Reagents and conditions: (a) BH_3-DMS, THF, 0 °C to rt, 1 h, 84 %; (b) PhH, reflux, 36 h, 68 %, dr = 13:l (**16**: **17**), 25 %, dr = 3:2 [**18**:**19**]; (c) K_2CO_3, CH_2C1_2: MeOH: H_2O (12:7:10), rt, 6 h, 90 %.

2.3.3 Baldwin's Synthesis of Racemic Alboatrin (2)[9,10]

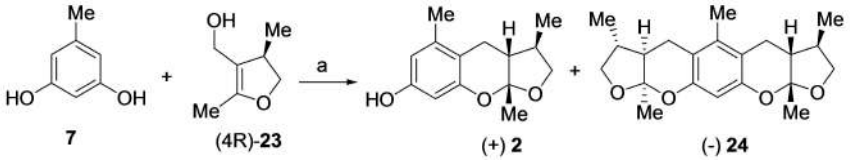
Baldwin and co-workers have reported a new and efficient strategy for the formation of o-quinone methide intermediate from o-methyleneacetoxy-phenols that have been used to the biomimetic synthesis of racemic alboatrin (**2**) as per Scheme 3. An inverse electron demand hetero Diels-Alder reaction between an ortho-quinone methide and a dihydrofuran was the significant step in this synthesis. Although, this reaction proceeded in high yield and in good diastereoselectivity (dr = 13: 1) for the desired reaction product alboatrin (**2**). However, during this key step, a considerable quantity (25%) of the undesired spiroacetals **18** and **19** were also formed (vide infra). It is worthy of mention that the known acetate **13** was synthesized in two steps from 5-methyl-1,3-dihydroxybenzene (**7**). This compound was then converted into the ortho-quinone methide precursor **14** in a one-pot reaction sequence that involved reduction of the formyl group and migration of the adjacent acetate.

2.3.4 Wilson's Asymmetric Synthesis of Alboatrin [(+)-2][11]

Wilson and Pettigrew reported the asymmetric synthesis of (+)-alboatrin from 5-methyl-1,3-dihydroxybenzene (**7**) and the



Scheme 4. Synthesis of (4*R*) (2,4-Dimethyl-4,5-dihydro-furan-3-yl)-methanol (**23**)
Reagents and conditions: (a) $C1_3CCOC1$, py, CH_2C1_2, rt, 30 min, 45 % [(4*R*)-**20**], 46 % [(4*R*)-**21**] *or* $C1_3CCOC1$, py, CH_2C1_2, -78 °C to rt, 21 h, 93 % [(4*R*)-**20**]; (b) trichloroketone (4*R*)-**20**, $NaHCO_3$, MeOH, reflux, 1 h, 98 %. (c) LAH, Et_2O, 0 °C to rt, 20 min, 34 %.



Scheme 5. Total Synthesis of (+)-Alboatrin (**2**)
Reagents and conditions: (a) (4*R*)-**23** (1.05 equiv.), $BF_3.Et_2O$ (0.3 equiv.), $MgSO_4$, Et_2O, 0 °C to rt, 48 h, 36 % [(+)-**2**], 14 % [(-)-**24**].

chiral alcohol (4*R*)-**23**. The alcohol (4*R*)-**23** was prepared from chiral dihydrofuran (4*R*)-**15**. The dihydrofuran (4*R*)-**15** was allowed to react with trichloroacetyl chloride and pyridine at room temperature thus affording a readily separable mixture of the desired trichloroketone (4*R*)-**20** (45%) and a considerable amount of the regioisomeric trichloroketone (4*R*)-**21** (46%). Subsequent methanolysis of the trichloroketone (4*R*)-**20** furnished the methyl ester (4*R*)-**22** in excellent yield. The ester (4*R*)-**22** was reduced to the alcohol (4*R*)-**23** with lithium aluminum hydride (Scheme 4).

2.3.5 Venkateswaran's Synthesis of Racemic Alboatrin (2)

First Generation Approach:[12]

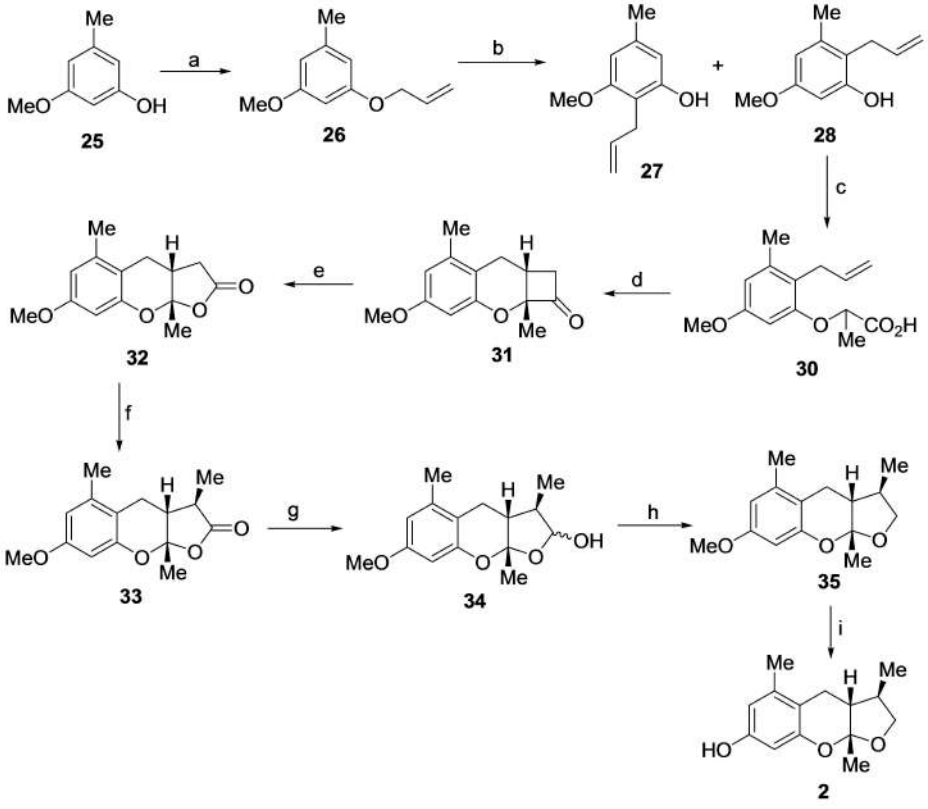
The synthesis commenced with orcinol monomethyl ether **25**, which was subjected to alkylation with allyl bromide followed by a thermal Claisen rearrangement of the allylphenyl ether **26** to give a mixture of rearranged phenols in 1:2 ratio (Scheme 6). The major product **28** was subjected to alkylation with α-bromo propionic acid (**29**) to furnish the carboxylic acid **30**, which on heating with *p*-toluenesulfonyl chloride and in presence of base triethylamine in benzene solvent subjected to an intramolecular ketene-alkene cycloaddition to deliver the tricyclic cyclobutanone **31** in moderate yields. The oxidative ring-enlargement with *m*-CPBA furnished the lactone **32**, which was then methylated with methyl iodide in presence of LDA. DIBAL–H mediated reduction of lactone **33** to lactol **34** followed by reductive removal of the hydroxyl group by triethylsilane in presence of trifluoroacetic acid furnished the *O*-methyl alboatrin **35**. Demethylation of *O*-methyl alboatrin **35** with boron tribromide afforded alboatrin (**2**) in good yield. Although it is a unique strategy but this approach suffers from several weaknesses. Primarily, the Claisen rearrangement of the allylphenyl ether was not regioselective which affected the yield of the desired compound. Secondly, the intramolecular ketene-alkene cycloaddition step was also a low-yielding step. Lastly, the reductive removal of the lactone carbonyl also proved to be a less productive exercise impacting the overall yield factor.

Second Generation Approach:[13]

To overcome all aforementioned weaknesses in first generation approach, Venkateswaran et al. reported an elegant route to obtain alboatrin in very good yield. The synthesis started with resacetophenone (**36**), which was monomethylated with methyl iodide followed by condensation with diethyl oxalate and dehydration to furnish chromone carboxylate **38** (Scheme 7). Sodium cyanoborohydride and $BF_3.OEt_2$ mediated removal of ketone afforded the desired product **40** in poor yield. A better yield, however, was obtained via a two-step procedure, first total hydrogenation to the chroman carboxylate **39**, then double bond reinstatement taking benefit of the ester functionality owing to phenyl selenylation accompanied by oxidative elimination. The reduction of **40** with LAH followed by Johnson orthoester Claisen rearrangement using triethyl orthopropionate furnished a mixture of γ, δ- unsaturated esters **42 a, 42 b** in 9:1 ratio. The major isomer after chromatographic separation was subjected to reduction with LAH giving the expected alcohol **43**, which was then undergoing to acid catalyzed cyclization to afford *O*-methyl alboatrin (**35**). Demethylation with boron tribromide finally gave the target molecule alboatrin (**2**) in good yield.

2.3.6 Sarkar-Panda Synthesis of Alboatrin (2)[14]

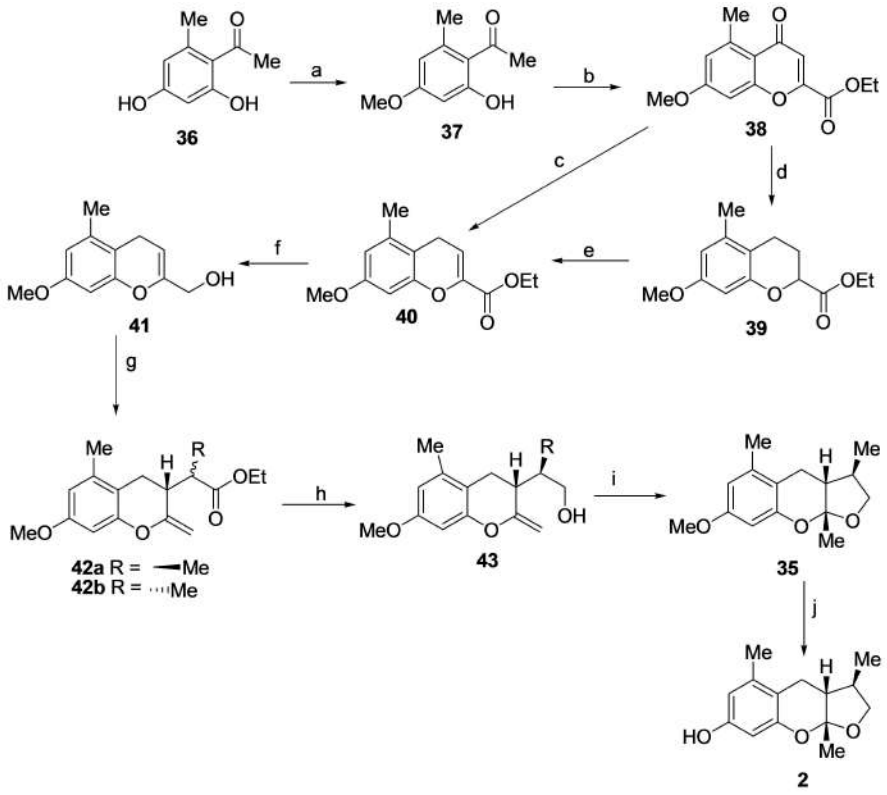
The synthesis of alboatrin was reported from our group via one-pot desilylation – gold catalyzed cycloisomerization of pendant alkynes having a silyl-protected phenolic –OH and a free alcoholic –OH component leading selectively to the construction of tetrahydrofuranobenzopyran ring system. Tradi-



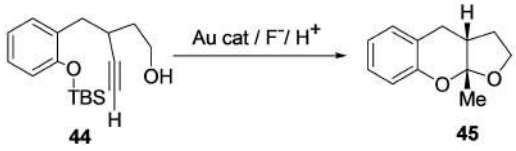
Scheme 6. Synthesis of Alboatrin (**2**) through Ketene-Olefin Cycloaddition
Reagents and conditions: (a) K_2CO_3, allyl bromide, acetone, reflux, 5 h, 96 %; (b) 200 °C, 1 h, 86 %; (c) NaH, $CH_3CH(Br)CO_2H$ (**29**), THF, reflux, 10 h, 83 %; (d) *p*-TsCl, Et_3N, benzene, reflux, 12 h, 50 %; (e) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, rt, 6 h, 80 %; (f) LDA, HMPA, MeI, THF, -78 °C to rt, 10 h, 94 %; (g) DIBAL-H, Et_2O, -78 °C, 2 h, 95 %; (h) CF_3CO_2H, Et_3SiH, CH_2Cl_2, -40 °C to rt, 15 min, 38 %; (i) BBr_3, CH_2Cl_2, -78 °C, 5 h, 80 %.

tionally, to construct a ketal, a ketone is made to react with two hydroxyl groups. Yet in our approach, we felt that a triple bond could be employed as the oxidation state equivalent to a ketone as has been recorded in several contemporary publications.[15] Thus, the linear tricyclic tetrahydrofuranobenzopyran ring system **45** as treasured in xyloketals and related natural product, alboatrin was formed through activation of alkyne **44** by a gold catalyst and followed by addition of two hydroxyl groups, one alcoholic-OH and another phenolic-OH (Scheme 8). The catalyst screening revealed that AuCl and $AuCl_3$ are the catalysts of choice with fluoride ion for this transformation. Thus, when $HgCl_2$, $FeCl_3$, and $CuCl_2$ were employed no traces of the anticipated product could be detected from the crude reaction mixture by TLC; the only decomposition of starting material was found in these cases. On the other hand, the softer catalysts $AuCl(PPh_3)$ and $PdCl_2(PPh_3)_2$ were proven to be completely inactive these reactions having yielded the desilylated product almost completely. The desired product was formed using other carbophilic Lewis acids such as AgOTf and $PtCl_2$ in low yields (11% and 44% respectively). Also, it was found that PPTS in absence of metal salts was totally inactive for this cycloisomerisation reaction and the desilylated starting material was isolated as the sole product. Albeit spiroketalization of alkynes with alcohols using metal-catalysts are documented in the literature,[16] *this type of construction of linear cyclic ketal namely, xyloketalization was reported from our group for the first time.*

For the synthesis of alboatrin, γ-butyrolactone **48**, prepared from citraconic anhydride(**46**) following literature procedure,[17] underwent aldol condensation with aldehyde **49** to provide the β-hydroxy lactone **50** in 89% isolated yield (Scheme 9). Excitingly, the aldol condensation reaction is extremely stereoselective and we got only one diastereomer. The stereochemistry of the product was established by a single crystal x-ray analysis. Reduction of **50** with triethylsilane in presence of Lewis acid $BF_3.OEt_2$ gave **51** in excellent yield. Demethylation of **51** using BBr_3 at room temperature provide a dihydroxy compound which was protected with TBSCl without purification in the usual manner to obtain **52** in 78% overall yield. It has been observed that in absence of a beta-methyl group in lactone **52**, the conversion into corresponding acetylene compound via selective DIBAL–H reduction from lactone to lactol and followed by Colvin rearrangement using TMS-diazomethane in presence of strong base LDA was obtainable in good yield at low temperature (-78 °C). Whereas conversion of **52** to corresponding alkyne **53** was found to be unsuccessful under the previously mentioned conditions (Scheme 9). Reactions under low temperature (-78 °C), prolonged time (12-18 h) and gradually warming to room temperature or reactions at even room temperature and overnight stirring returned the



Scheme 7. Venkateswaran's Synthesis of Racemic Alboatrin (**2**)
Reagents and conditions: (a) K_2CO_3, MeI, acetone, reflux, 3 h, 92%; (b) (i) NaH, $(CO_2C_2H_5)_2$, THF, 0 °C to rt, 8 h; (ii) PTSA, C_6H_6, reflux, 90% (over all yield); (c) $BF_3.Et_2O$, $Na(CN)BH_3$, THF, reflux, 4 h, 25%; (d) Pd/C, H_2, C_2H_5OH, 3 h, 95%; (e) (i) LDA, PhSeBr, THF, −78 °C, 92%; (ii) H_2O_2, CH_2Cl_2 : THF (2:1), 0 °C to rt, 90%; (f) LAH, THF, −40 °C to 0 °C, 1 h, 93%; (g) $C_2H_5C(OEt)_3$, C_2H_5COOH(cat.), xylene, 140 °C, 6 h, 97%; (h) LAH, THF, 0 °C, 1 h, 90%; (i) H_2SO_4(cat.), THF, 0 °C to rt, 2 h, 96%; (j) BBr_3, CH_2Cl_2, −78 °C, 1 h, 80%.



Scheme 8. Formation of the Tetrahydrofuranobenzopyran Ring System

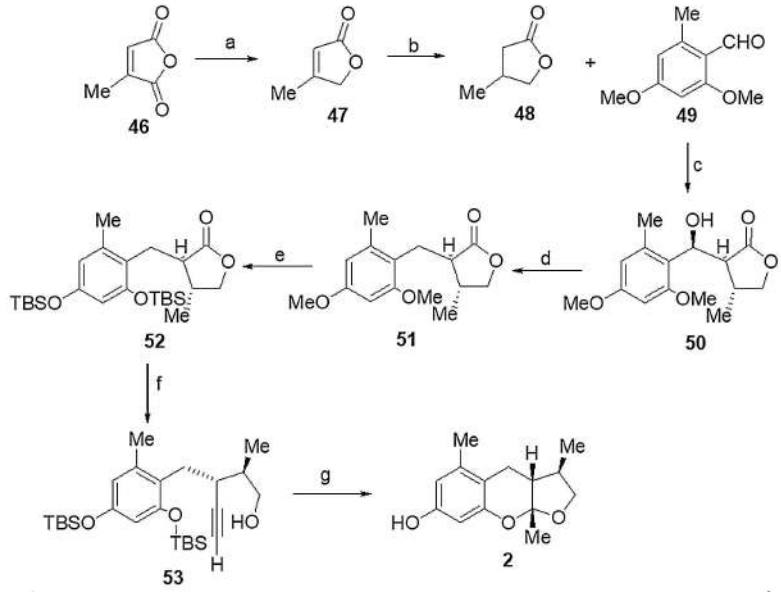
lactol derivative in adequate yield. We chalk up this failure to likely Thorpe-Ingold type effect of the methyl substituent in the lactol thus avoiding its ring opening and producing sufficient of the free aldehyde in solution. However, the alkyne derivative **53** was obtained in 72% isolated yield upon refluxing the reaction mixture for 3 h and using excess reagents. Obviously, higher temperature is essential here to cross the higher activation energy barrier needed for ring opening (shifting the equilibrium) of the lactol ring. Now the stage was ready to apply our gold/fluoride mediated ketalization process to achieve our target molecule alboatrin (**2**). Using our ketalization process, a methanol solution of alkyne **53** was added to a mixture of $AuCl_3$ (3 mol%), TBAF (2.1 equiv.) and PPTS (2.2 equiv.) in methanol followed by stirring for 1 h at room temperature furnished the desired target molecule alboatrin **2** in 92% isolated yield. This is a 7- step facile synthesis of alboatrin having 40% overall yield.

3. Xyloketals

3.1 Isolation and Structural Elucidation of the Xyloketal Natural Products

In the year of 2001, Lin and co-workers reported the isolation and characterization of structurally similar five natural products, namely xyloketal A (**54**), B (**55**), C (**56**), D (**57**), and E (**58**). These natural products were isolated from mangrove fungus *Xylaria* species from South China Sea coast (Figure 2).[18] Later, an improved isolation procedure has been documented by Xiaobo et al.[19] Furthermore, the isolation and structural elucidation of xyloketal F(**59**) and G (**60**), two other members of these ancestors of natural products have lately reported by Lin et al.[20,21] They also depict the isolation of another metabolite later named as xyloketal H[22] from the fungus *Xylaria* sp. 2508. The structure of xyloketal H(**61**) was resolved by NMR spectroscopy and mass spectrometry.

The molecular structures and relative stereochemistries of these naturally occurring molecules were elucidated through the extensive spectroscopic examinations as well as by X-ray



Scheme 9. Synthesis of Alboatrin (**2**)
Reagents and conditions: (a) $NaBH_4$ (2.5 equiv.),THF, 0 °C, 2 h, 92% (b)H_2 (1 atm), 10% Pd/C (10% wt/wt), EtOAc, 12 h, 97% (c) LDA (1.5 equiv.), −78 °C to 0 °C, 7 h, 89%. (d) Et_3SiH (1.5 equiv.), $BF_3.OEt_2$ (1.2 equiv.), 0 °C, 1.5 h, 96% (e) (i) BBr_3 (1 M in CH_2Cl_2) (4 equiv.), CH_2Cl_2, 0 °C, 1 h, rt, 12 h; (ii) TBSCl (2.4 equiv.), Imidazole (3 equiv.), DMF, rt, 24 h, 80% (f) (i) DIBAL–H (1.2 equiv.), PhMe, −78 °C, 2 h. (ii) LDA (10 equiv.), −78 °C, TMS-diazomethane (10 equiv.), −78 °C to rt, 1 h, reflux 3 h, 72%. (g) $AuCl_3$ (3 mol%), TBAF (2.1 equiv.), PPTS (2.2 equiv.), rt, 1 h, 92%.

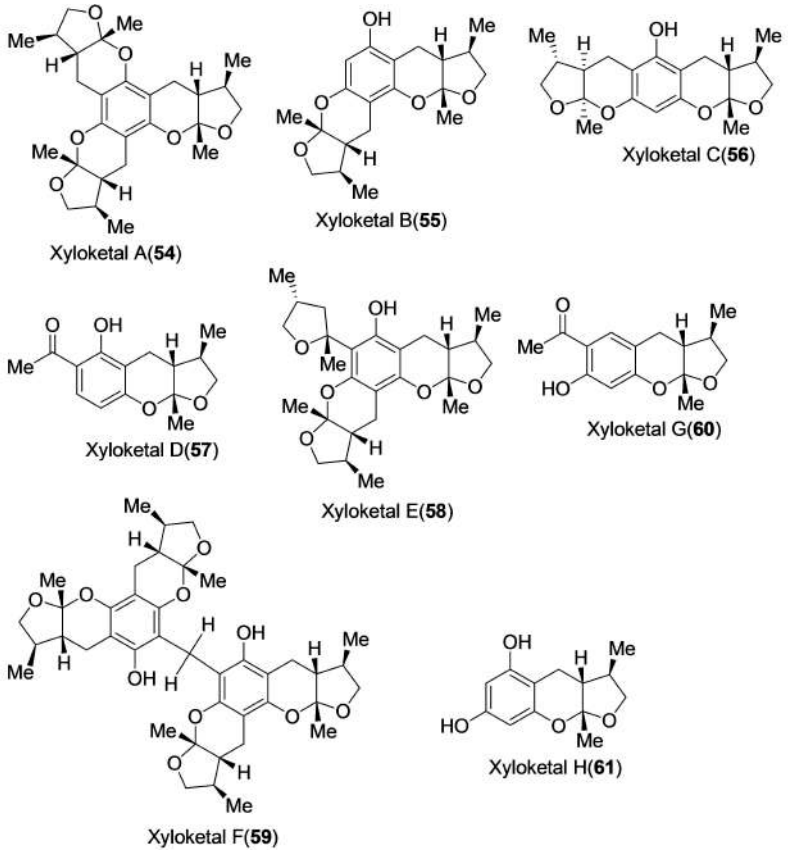


Figure 2. Structures of Xyloketal A (**54**), B (**55**), C (**56**), D (**57**), E (**58**), F (**59**), G (**60**) and H (**61**)

crystallography. Through the analysis of their Circular Dichroism(CD) spectra, the absolute stereochemistries of xyloketal A (**54**), D (**57**), F (**59**) and G (**60**) were established. The absolute stereochemistries of the residual members of this class of natural molecules were consigned by analogy. All the xyloketal molecules incorporate identical 5,6-bicyclic acetal moieties that are bonded to an aromatic core. It was found that in all cases, the stereochemistries of ring junctions are *cis*-fused and the bicyclic acetals are in a syn configuration with the methyl groups at the C-5 position of the five-membered rings. Xyloketal A (**54**) has a unique C_3-symmetric molecular architecture that fuses three bicyclic acetal moieties. It was noted that Xyloketal B (**55**) and the minor C_2-symmetric component, xyloketal C (**56**), consolidate two bicyclic acetal moieties. Xyloketal D (**57**) and the analogous regioisomer, xyloketal G (**60**) contain one bicyclic acetal moiety. Xyloketal C (**56**) is relatively unstable as compared to the regioisomeric natural product, xyloketal B (**55**), and it undergoes isomerization to give the latter substance in solution. It is reasonable to assume that this is a result of unfavorable dipole interactions which are limited on account of xyloketal B (**55**).

The isolation and elucidation of the structure of xyloketal E (**58**), a sibling of xyloketal B (**55**), suggests that (4*R*)-2, 4-dimethyl-4, 5-dihydrofuran is a typical biogenic antecedent to all of these naturally occurring molecules. Presumably, this natural product is formed through a direct substitution reaction of the electron-rich aromatic ring of xyloketal B (**55**) on protonation of the previously mentioned dihydrofuran antecedent. Additionally, acid catalyzed condensation of xyloketal B (**55**) with formaldehyde afforded xyloketal F (**59**), further supports a common biogenic source of all of this unique secondary metabolites.[20]

3.2 Biological Properties of the Xyloketal Natural Products

3.2.1 Acetylcholine Esterase Inhibition[23]

The preliminary biological evaluation of the xyloketals showed that xyloketal A, B, C and D were shown to inhibit acetylcholine esterase with IC_{50} values of 29.9, 137.4, 109.3 and 425.6 μmol/L, respectively.[24] Acetylcholine(ACh) is the most plenteous neurotransmitter in the body and the essential in the cerebrum which is in charge of cholinergic transmission. The enzyme acetylcholinesterase (AChE) plays a vital character in the metabolic saponification of the active neurotransmitter acetylcholine to inactive choline within the human nervous system. It was found that the patients suffering from neurological disorders like Alzheimer's disease show a lower level of acetylcholine in their brain tissue. The most used therapeutic strategy[25] for the treatment of this disorder is to inhibit acetylcholinesterase. The acetylcholinesterase inhibitor (AChEI) is a chemical or a drug molecule which inhibit the activity of acetylcholinesterase enzyme-catalyzed hydrolysis of acetylcholine, thereby cumulating both the level and period of action of acetylcholine. AChEI were used for the treatment of Alzheimer's, the Lewy body dementia and Parkinson's disease. In these neurodegenerative situations, AChEIs are mainly used for the treatment of cognitive (mainly memory and learning deficits) symptoms of dementia. The cognition in the central nervous system reduces these symptoms because of the action of acetylcholine. There is some proof to suggest that AChEIs may weaken psychotic symptoms, particularly visual hallucinations in Parkinson's disease.

Therefore, xyloketal A, B, C, and D are potential lead molecules for drug discovery for the treatment of these neurological diseases.

3.2.2 Antioxidant Activity[26]

Xyloketal B effectively enters cell membranes because of its low molecular weight and high liposolubility. As confirmed by the weakening of Ang II-induced toxicity in HUVECs and concealment of NADPH oxidase action in zebrafish embryos, xyloketal B is a strong natural HO-1 inducer, and xyloketal B-instigated HO-1 articulation plays an essential role in the antioxidative activities of that natural product. Activation of Nrf-2 and PI3 K/Akt and Erk pathways are mostly in charge of xyloketal B-prompted HO-1 articulation. Hence, xyloketal B has a strong potential as a medication possibility to treat oxidative stress-related diseases.

3.2.3 L–Calcium Channel Inhibition[20,27]

Abundant studies reported in recent years have revealed that the vascular function is compromised in several of pathological conditions such as hypertension and atherosclerosis. Hypertension is a chronic heart disease related to a changed balance in the proportion of biological endeavor of vasodilator and vasoconstrictor molecules and modifications in vascular tissue. Calcium channel blockers are several drug molecules that interrupt the motion of calcium ion (Ca^{2+}) over calcium channels. In subsequent biological evaluations, it was shown that at the concentration of 0.03 μmol/ L, xyloketal A, B and F block L-calcium channels by 21, 12 and 50%, respectively. L-type calcium channels are accountable for regulating the movement of calcium ions in and out of skeletal, smooth, cardiac muscle and for aldosterone discharge in endocrine cells of the adrenal cortex. Since the high concentration of these channels is present in heart muscle and the movement of calcium ions is directly associated with heart muscle contraction. As a result, calcium channel blockers are employed to decrease blood pressure in patients with hypertension. Therefore, it was found that xyloketal A, B, and F are potential lead drug molecules for the treatment of numerous cardiovascular diseases.

3.2.4 Radical-Scavenging Activity[28]

In the biological redox reactions, free radicals and other reactive oxygen species (ROS) have unavoidable side products and they show significant roles in health disorder and cellular damage. Accordingly, the selection of effective antioxidants to scavenge free radicals has stimulated great interest. The antioxidant property and the protective action on the mito-

chondria can explain its neuroprotective nature. With the help of absorption spectrometry, Peng et al. reported that a number of synthetic xyloketals and related chromanes shows radical-scavenging activities of toward 2,2-diphenyl-1-picrylhydrazyl (DPPH) and 2,2′-azino-bis(3- ethylbenzothiazoline-6-sulfonic acid) (ABTS). In their research, the results displayed that most of the xyloketals had high radical scavenging properties, and among them, xyloketal B showed substantial antioxidative activity toward DPPH and ABTS.

3.2.5. Protective Effects Against MPP+- Induced Neurotoxicity

The neuroprotective nature of xyloketal B counter to MPP^+-induced neurotoxicity was investigated by Chen et al. in Caenorhabditis elegans and PC12 cells.[29] The viability and DA neuro-deterioration were evaluated in C. elegans by discriminate expression of the green fluorescent protein (GFP) in DA neurons. Employing MTT and nuclear morphology, PC12 cell injury was assessed. They have evaluated the reactive oxygen species (ROS) within the cell and mitochondrial membrane potential as well as total GSH. The studies revealed that in the case of C. elegans, xyloketal B protected against MPP+-induced reduction of viability and DA neurodegeneration dose-dependently.

On the other hand, Peng et al. prepared 39 different xyloketal derivatives in addition with xyloketal B.[30] All 40 synthetic compounds were examined for neuroprotective action *in vivo* through respiratory burst assays and longevity-extending assays. Some of the compounds show strong neuroprotective activity and some of the compounds with benzopyrano pyran skeleton show antioxidant activity.

3.2.6 Reduction of Oxygen-Glucose Deprivation (OGD)-Induced Cell Injury [31]

Oxygen-Glucose Deprivation (OGD) in PC12 cell line has been employed as a fast and responsive in vitro model of ischemic stroke in the advancement of probable neuroprotective agents. Initially, PC12 cells are exposed to a small duration of OGD (ischemia) after that a long time of re-oxygenation and reappearance of normal culture medium (reperfusion) to mimic cerebral ischemia-reperfusion injury. Hence this model is supposed to superior mimic the pathological situations of stroke. Xyloketal B can protect PC12 cells towards OGD-induced cell injury in a concentration-dependent manner and therefore it may be a good medicinal compound for stroke treatment.

3.2.7. Reduction of Neonatal Hypoxic-Ischemic Brain Injury

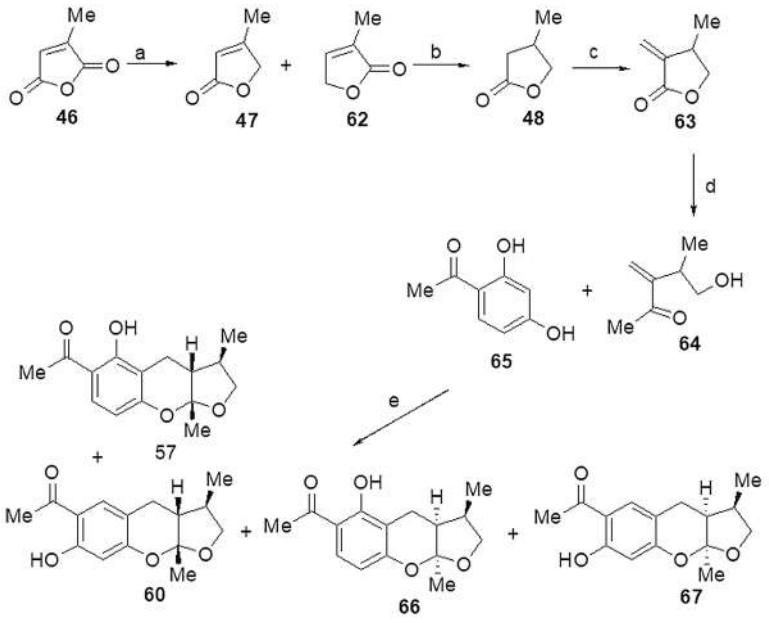
It is generally found that the neonatal hypoxic-ischemic encephalopathy[32–34] due to neurodegeneration and brain injury produces sensorimotor dysfunction. In their study, Sun et al. investigated[35] the responses and mechanistic pathway of xyloketal B against oxygen-glucose deprivation-induced neuronal cell death in mouse essential cortical culture and on hypoxic-ischemic cerebrum damage in neonatal mice in vivo. They observed that *in vitro,* anoxia-induced neuronal cell death was decreased in presence of xyloketal B. Moreover, xyloketal B enhanced functional behavioral recuperation of the animals following hypoxic-ischemic affront. Additionally, xyloketal B considerably reduced calcium entrance, decreased the amount of TUNEL-positive cells, decreased the levels of cleaved caspase-3 and Bax proteins, and extended the component of Bcl-2 protein after the hypoxic-ischemic damage. Their discoveries show that xyloketal B is viable in models of hypoxia-ischemia and thus has a potential lead compound for the treatment of hypoxic-ischemic brain injury.

3.2.8. Reduction of Atherosclerotic Plaque Formation and Endothelial Dysfunction[36]

Atherosclerosis is as of now the main reason behind mortality among the cardiovascular diseases around the world. Endothelial dysfunction is an initial key incident around the atherogenesis and has been perceived as a typical connection of all cardiovascular threat factors in the vascular framework comprising dyslipidemia, hyperhomocysteinemia, hypertension, diabetes, and smoking. Two essential functions of the endothelium associated with injury improvement in athero-susceptible areas consist of preservation of the vascular penetrability barrier and assurance of nitric oxide (NO) bioavailability. The purpose behind the loss of NO bioavailability is primarily because of reduced synthesis of NO and further accumulation of responsive oxygen species (ROS) and is a cardinal element of endothelial dysfunction all along the growth of atherosclerosis. The searching of compounds that increase NO bioavailability and eNOS activity is the area of interest for therapeutic use. Wang et al. found in their investigation that the addition of xyloketal B dose-dependently reduced the atherosclerotic plaque region both in the aortic sinus and all through the aorta in apoE−/− mice fed a high-fat diet. Additionally, xyloketal B markedly decreased the intensities of vascular oxidative stress, along with repairing the damaged epithelium integrity and NO-dependent arterial blood vessel vasorelaxation in hardening of the arteries of mice. Also, in cultured human umbilical vein endothelial cells (HUVECs), xyloketal B considerably changed the phosphorylation intensities of endothelial nitric oxide synthase (eNOS) and Akt without changing the expression of total eNOS and Akt. Therefore their examination shows that xyloketal B has a powerful anti-atherosclerotic effect in vivo, which is to some extent because of its antioxidant nature and as well as potential improvement of endothelial function.

3.2.9. Suppression of Glioblastoma Cell Proliferation[37]

Glioblastoma is the most well-known and hostile type of brain tumors and has terribly propagative and intrusive characteristics. The necessity for finding a unique and explicit drug target is earnest as the present methodologies have restricted therapeutic impacts for the treatment of glioblastoma. In their examination, Sun et al. utilized a glioblastoma U251 cell line firstly to investigate the impacts of xyloketal B on cell viability, propagation, and migration; and furthermore, examine the



Scheme 10. Krohn's Synthesis of Racemic Xyloketal D (**57**) and G (**60**)
Reagents and conditions: (a) LAH, Et_2O, 73% (**47**:**62**), 3:17; (b) H_2, 10% Pd/C, 72%; (c) NaH, HCO_2Et, EtOH, Et_2O, rt, 30 min, $(HCHO)_n$, Et_2O, reflux, 1 h, 63%; (d) MeLi, Et_2O, −50 °C to 0 °C, 1.5 h, 75%; (e) **64**, PhMe, reflux, 4 h, 80%, dr = 17:3 [**57**:**66**], 9% [**60** + **67**].

essential molecular mechanisms as well as signaling pathways. In those studies, several techniques were used like MTT assay, colony formation, wound healing, western blot, and patch clamp etc. They discover that xyloketal B diminished cell viability, proliferation, and relocation of U251 cells. Additionally, they have also uncovered that; xyloketal B diminished the p-Akt and p-ERK1/2 protein expressions. Thus, the marine natural product xyloketal B found to be a potential drug molecule for the treatment of glioblastoma, although further research, particularly in vivo studies, are crucial before its use.

3.3 Literature Syntheses of Xyloketal Natural Products

There have been several reports regarding the synthesis of members of the xyloketal family of natural products. A brief summary of these investigations is presented below.

3.3.1 Literature Syntheses of Xyloketal D(57) and Xyloketal G (60) Natural Products

Xyloketal D (**57**) and G (**60**) are regioisomers. A number of groups reported the total synthesis of xyloketal D(**57**) and G (**60**) were described below.

3.3.1.1. Krohn's Synthesis of Racemic Xyloketal D (57) and G (60)[38]

Krohn and co-workers synthesized the racemic enone **64** and used this material to prepare racemic xyloketal D (**57**) and G (**60**) (Scheme 10).

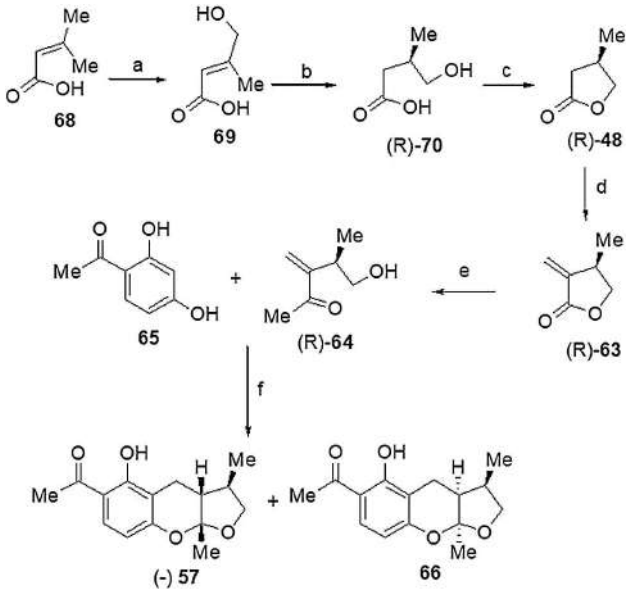
Although the enone **64** was prepared concisely, the initial LAH reduction of citraconic anhydride led to the formation of undesired the regioisomer **62** as the main product. The final step of the reaction sequence gave xyloketal D (**57**) along with undesired three side products. Moreover, the bicyclic acetal moiety was *cis*-fused and relative to the stereogenic centre at *C*-5, good diastereoselectivity was observed (dr = 17:3). The authors made no comment on the selectivity between the formation of xyloketal G (**60**) and its epimer **67**.

3.3.1.2 Krohn's Asymmetric Synthesis of (-)-Xyloketal D (57)[39]

After completion of total synthesis of racemic xyloketal D (**57**), Krohn et al. subsequently completed the asymmetric synthesis of that natural product (Scheme 11). The absolute stereo-chemistry in this synthesis was introduced by ruthenium/BINAP catalytic asymmetric hydrogenation reaction of the carboxylic acid **69**. The obtained alcohol (*R*)-**70** was converted to the chiral lactone (*R*)-**48** which corresponded to an intermediate in the achiral synthesis as discussed above. This compound was then used to afford α,β-unsaturated lactone **63**. The methyl lithium mediated ring opening of lactone **63** provides chiral unsaturated enone **64** in moderate yield. The reaction of resorcinol derivative **65** with enone **64** under toluene refluxing condition afford (-)-xyloketal D (**57**) and the 2, 6-epimer **66** in a 17:3 ratio.

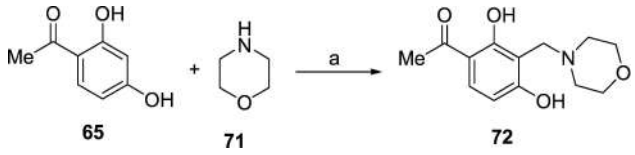
3.3.1.3. Wilson's Synthesis of Racemic Xyloketal D (57)[11]

Wilson and Pettigrew used a cycloaddition reaction of an appropriately functionalized ortho-quinone methide generated



Scheme 11. Krohn's Asymmetric Synthesis of (-)-Xyloketal D (**57**)
Reagents and conditions: (a) SeO_2, AcOH, reflux, 4 h, 37%; (b) H_2, (*R*)-BINAP–$Ru(OAc)_2$, MeOH, rt, 12 h, l00%, 93% ee; (c) HCl (aq), $CHCl_3$, reflux, 75%; (d) NaH, HCO_2Et, EtOH, Et_2O, rt, 30 min, $(HCHO)_n$, Et_2O, reflux, 1 h; (e) MeLi, Et_2O, −50 °C to 0 °C, 1.5 h, 54% (over two steps); (f) PhMe, reflux, 4 h, 81%, dr = 17:3 [(-)- **57**:**66**].

from a Mannich base and a dihydrofuran to furnish xyloketal D (**57**). The Mannich base **72** was prepared by heating a solution of 2,4-dihydroxyacetophenone (**65**) and formaldehyde with morpholine (**71**) in aqueous methanol (Scheme 12).



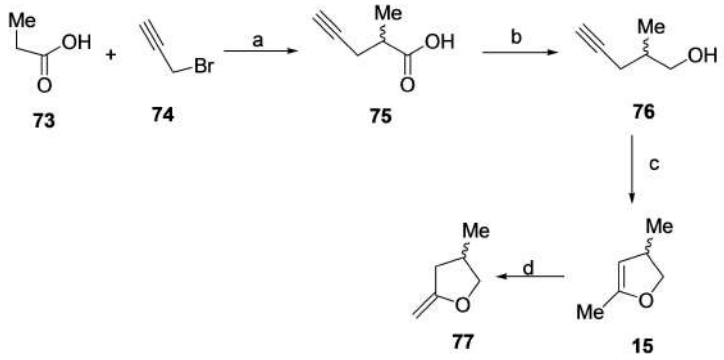
Scheme 12. Synthesis of Mannich Base **72** from 2,4-Dihydroxyacetophenone **65**
Reagents and conditions: (a) $(CH_2O)_n$, H_2O, MeOH, reflux, 3 h, 82%.

On the other hand, the synthesis of the racemic dihydrofuran **79** began from propionic acid (**73**) and propargyl bromide (**74**). This involved generation of the corresponding dianion of propionic acid (**73**) with excess LDA (2.3 equiv.) in a mixture of HMPA and THF. This dianion was then treated with propargyl bromide (**74**) (1.2 equiv.) to access the desired product **75** in good yield (68%). Compound **75** was subsequently reduced to the corresponding acetylenic alcohol **76** with LAH. The neat alcohol **76** was then heated at reflux with a substoichiometric amount of sodium amide. This induced a 5-exo-dig cyclization to afford dihydrofuran **77** containing an exocyclic double bond, which was isomerized to the desired 2,4-dimethyl-4,5- dihydrofuran **15** upon heating at reflux in the absence of solvent (Scheme 13). Cycloaddition of ortho-quinone methide generated from **72** and **15** gave xyloketal D (**57**) as shown in Scheme 14.

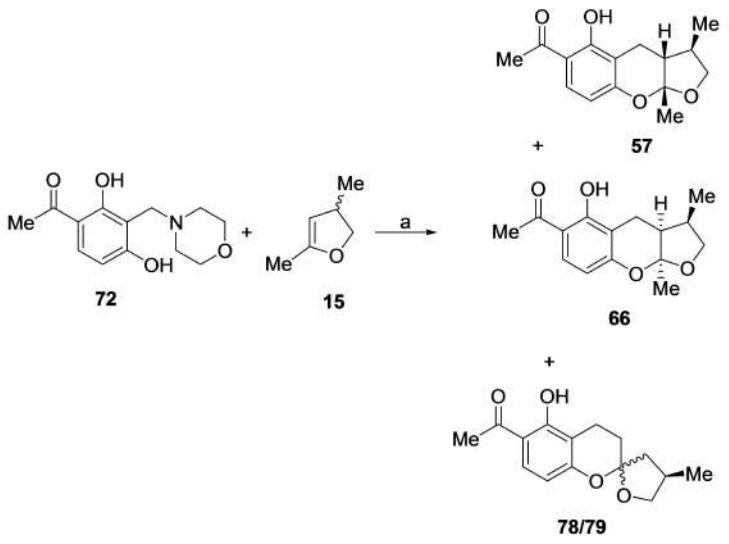
3.3.1.4 Wilson's Synthesis of (-)-Xyloketal D (57)[40]

The synthesis of (-)-xyloketal D (**57**) commenced from racemic carboxylic acids **75** via chiral resolution procedure (Scheme 15). It was observed that the amides (-)-**81** and (-)-**82** made from (*R*)-phenylglycinol (**80**) and these diastereoisomeric amides could be readily separated by flash chromatography on a multigram scale. Acid-mediated hydrolysis of amides (-)-**81** and (-)-**82**, provided the chiral nonracemic carboxylic acids (2*R*)-**75** and (2 *S*)-**75** respectively. Thus, the amide (-)-**82** had an appropriate absolute stereochemistry to prepare the enantiomer of the natural product, (+)-xyloketal D(**57**), and the amide (-)-**81** had the appropriate absolute stereochemistry to prepare the natural product(-)-xyloketal D(**57**). Lithium aluminum hydride reduction of chiral nonracemic carboxylic acid (2*R*)-**75** afforded the corresponding alcohol (2*R*)-**76** in good yield. As depicted previously in the case of the racemic compound, alcohol **76** was used in the synthesis of dihydrofuran (4*R*)-**15** (Scheme 15). This compound (4*R*)-**15** has served as the precursor molecule of (-)-xyloketal D (**57**).

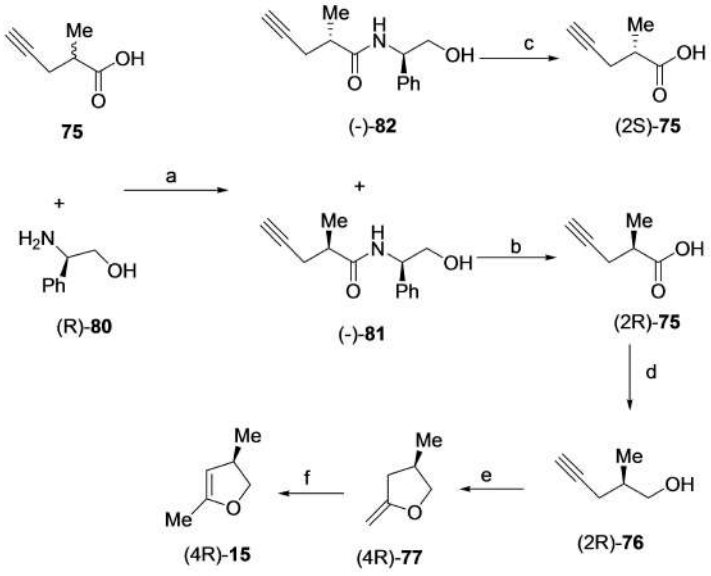
Heating the reaction mixture containing chiral nonracemic dihydrofuran (4*R*)-**15** (3 equiv.) and the Mannich base **72** (1 equiv.) in benzene at reflux in presence of methyl iodide



Scheme 13. Synthesis of 2, 4-Dimethy1-4, 5-dihydrofuran (**15**)
Reagents and conditions: (a) LDA, HMPA, THF, 0 °C to rt, 1 h, propargyl bromide (**74**), 0 °C to rt, 3 h, 68%; (b) LAH, THF, 0 °C to rt, 16 h, 82%; (c) $NaNH_2$ (cat.), reflux, 2 h, 66%; (d) reflux, 16 h, 87%.



Scheme 14. Synthesis of Racemic Xyloketal D (**57**)
Reagents and conditions: a) MeI, PhMe, reflux, 5 days, 54%, [**57**: **66**: **78**: **79** = 11: 1: 3: 3].

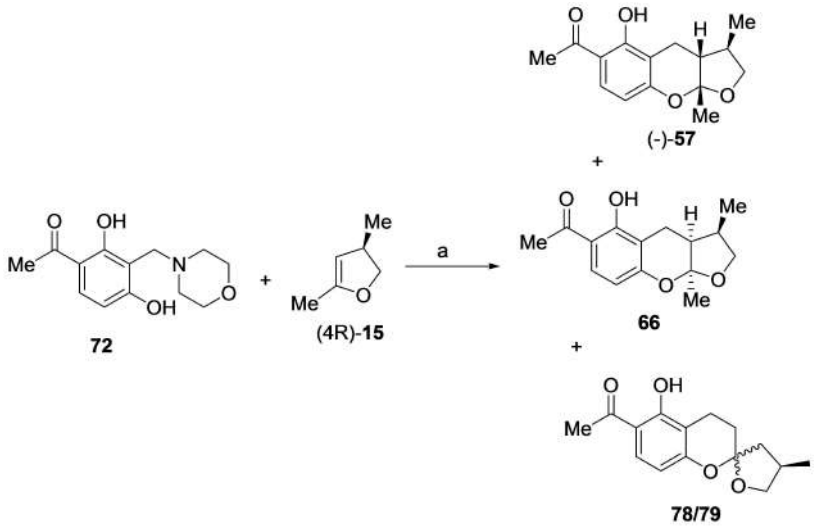


Scheme 15. Synthesis of (4*R*)-2,4-Dimethyl-4,5-dihydrofuran (**15**)
Reagents and conditions: (a) $(COCl)_2$, CH_2Cl_2, DMF (cat.), 0 °C to rt, 2 h, (*R*)-**80**, Et_3N, CH_2Cl_2, 0 °C to rt, 16 h, 36% [(-)-**81**], 34% [(-)-**82**]; (b) 3 M H_2SO_4, *p*-dioxane, reflux, 7 h, 76%; (c) 3 M H_2SO_4, *p*-dioxane, reflux, 7 h, 86% ; (d) LAH, THF, 0 °C to rt, 16 h, 89%; (e) $NaNH_2$ (cat.), reflux, 2 h; (f) reflux, 2 h, 44% (over two steps).

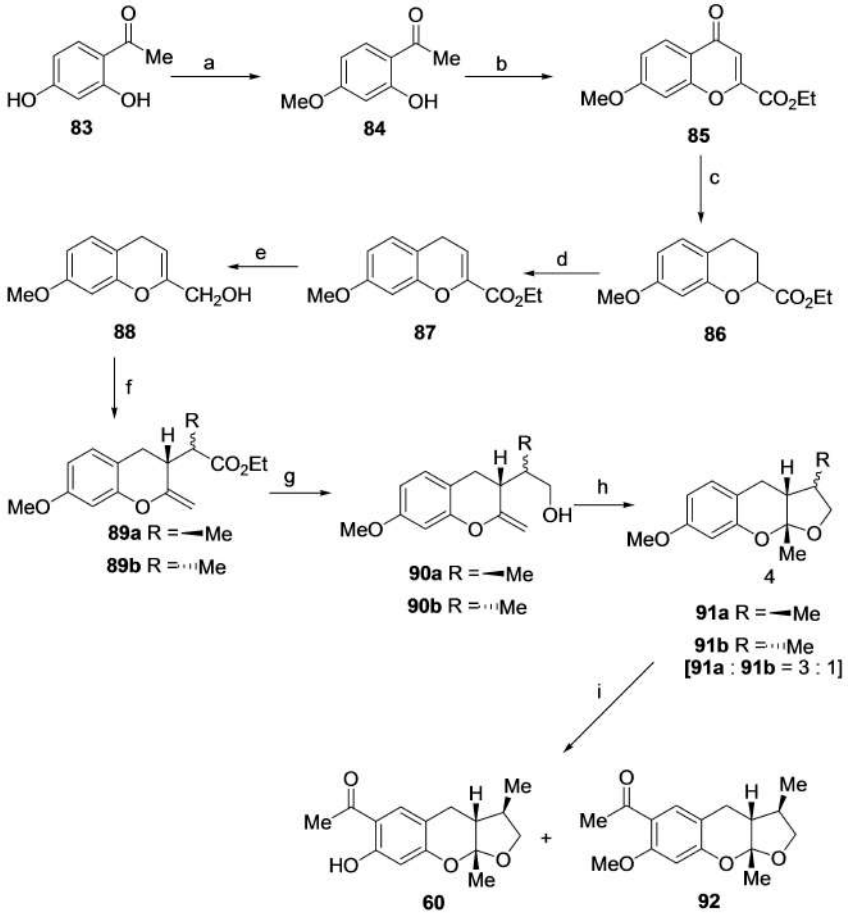
(1 equiv.) for eight days gave a mixture of compounds having (-)-xyloketal D (**57**), 2, 6-epi-xyloketal D (**66**) and the diastereoisomeric spiroacetals **78** and **79** in a collective yield of 40% (Scheme 16). Although this strategy is certainly a good and effective one, however the formation of undesired isomers in a considerable amount was the demerits of this synthetic protocol.

3.3.1.5 Venkateswaran's Synthesis of Racemic Xyloketal G (60)[41]

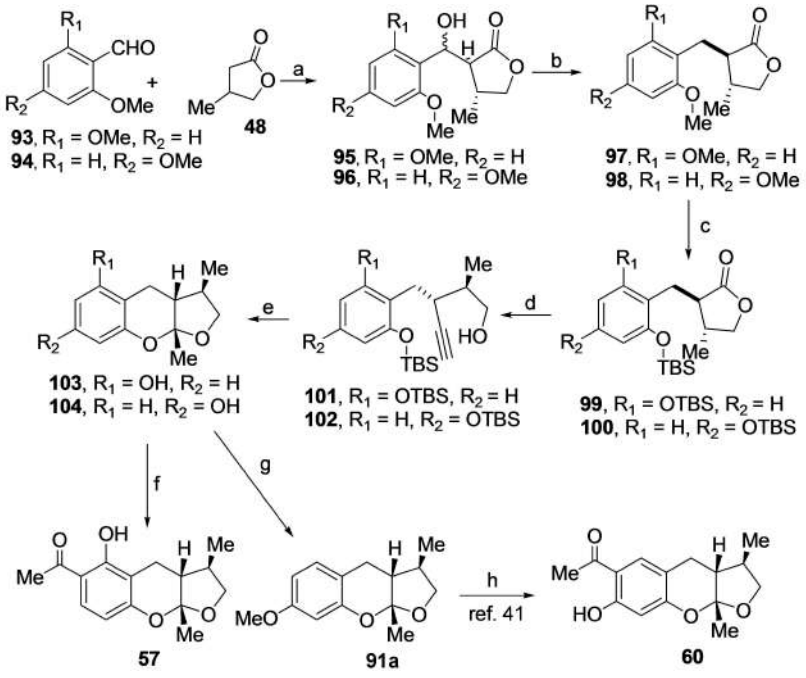
Venkateswaran and Sarkar reported the synthesis of xyloketal G in the year 2011(Scheme 17). The synthesis started with selective methylation of resacetophenone **83** in the less hindered phenolic group. Condensation of methyl ether **83** with diethyl oxalate and subsequent *in situ* dehydration provided the chromone carboxylate **85**. Hydrogenolysis/hydrogenation followed by re-installation of the endocyclic double bond provided the chromene carboxylate **87**.



Scheme 16. Wilson's Synthesis of (-)-Xyloketal D (**57**)
Reagents and conditions: (a) Dihydrofuran (4*R*)-**15** (3 equiv.), Me1 (1 equiv.), PhH, reflux, 8 days, 40%, 8:1:2:2 [(-)-**57**:**66**:**78**:**79**].



Scheme 17. Venkateswaran's Synthesis of Racemic Xyloketal G (**60**)
Reagents and conditions: (a) K_2CO_3, acetone, MeI, reflux, 1.5 h, 90%; (b) (i) NaH, $(CO_2Et)_2$, THF, 0 °C to rt, 18 h; (ii) PTSA, C_6H_6, reflux, 70% (overall yield); (c) Pd/C, H_2, EtOH, 9 h, 90%; (d) (i) LDA, PhSeBr, THF, −78 °C to 0 °C; (ii) H_2O_2, CH_2Cl_2:THF (2:1), 0 °C to rt, 3 h, 90% (overall yield); (e) LAH, THF, −40 °C to 0 °C, 1 h, 93%; (f) $C_2H_5C(OEt)_3$, C_2H_5COOH (cat), xylene, 140 °C, 8 h, 97%; (g) LAH, THF, 0 °C, 1 h, 85%; (h) H_2SO_4 (cat), THF, 0 °C to rt, 2 h, 96%; (i) CH_3COCl, $AlCl_3$, DCM, −78 °C to rt, 2 h, 70%.



Scheme 18. Synthesis of Xyloketal D (**57**) and Xyloketal G (**60**)
Reagents and conditions: (a) LDA, −78 °C, 5 h, 90% [**95**], 93% [**96**]; (b) Et_3SiH, $BF_3.OEt_2$, 0 °C,1.5 h, 98% [**97**], 96% [**98**]; (c) (i) BBr_3, CH_2Cl_2, rt, 12 h (ii) TBSCl, imidazole, DMF, rt, 24 h, 76% [**99**], 79% [**100**]; (d) (i) DIBAL–H, tol., −78 °C, 2 h; (ii) LDA, −78 °C, TMS-diazomethane, reflux, 3 h, 70% [**101**], 73% [**102**]; (e) $AuCl_3$ (3 mol %), PPTS, TBAF, rt, 1 h, 94% [**103**], 93% [**104**]; (f) $TiCl_4$, AcCl, 1,2-DCE, rt, 24 h, 82%; (g) Me_2SO_4, K_2CO_3, acetone, rt, 12 h, 86%; (h) $AlCl_3$, AcCl, DCM, rt, 2 h, 70%.

The allylic alcohol **88** obtained through LAH reduction of the ester **87** was used to an orthoester Claisen rearrangement with triethyl orthopropionate to furnish the ester(s) **89** in 97% yield as a diastereomeric mixture (3:1). LAH reduction of the ester(s) provides the olefinic alcohol(s) **90**, which was converted to a mixture of **91 a** and **91 b** on acid treatment. $AlCl_3$ mediated Friedel-Crafts acylation with acetyl chloride afforded xyloketal G (**60**) along with traces amount of *O*-methyl xyloketal G (**92**). Interestingly, in this protocol three reactions, such as acetylation, isomerization and demethylation occurred in one pot which certainly claims the merits of this approach, although it is a strategy for the synthesis of racemic xyloketal G(**60**).

3.3.1.6. Sarkar-Panda Synthesis of Xyloketal D (57) and G (60)[14]

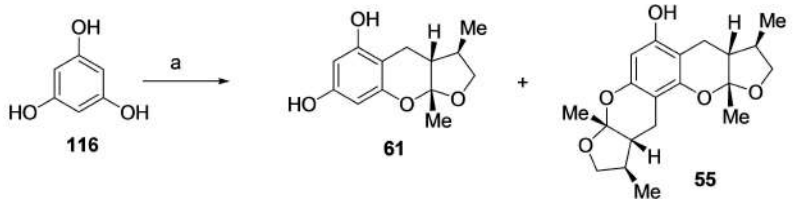
The effective synthesis of alboatrin (**2**) propelled us to use identical strategy to the synthesis of xyloketal D (**57**) and G (**60**). Structurally Xyloketal D (**57**) and G (**60**) are positional or regioisomers, since the hydroxyl group occupy two different positions in this molecule. We commenced their synthesis using known aromatic aldehydes **93** and **94**. In contrast within the case alboatrin (**2**), aldol reaction of **93** and **94** was not fully stereoselective. Although, both the carbinols **95** and **96** was obtained in high yield where two side chains of the lactone ring are *trans* stereochemistry there was no stereocontrol in the generation of the residual stereocentre. This was, in fact, no concern as the reduction of **95** and **96** afforded compounds **97** and **98** as single diastereomers. Demethylation after that silyl protection provided **99** and **100** which were then converted into **101** and **102**, the final precursors for cycloisomerization. Cycloisomerization (xyloketalization) of **101** and **102** then passed off smoothly under the hitherto stated conditions depicted for alboatrin (**2**) to **103** and **104** in proximate quantitative yields. Lastly, $TiCl_4$ Lewis acid mediated selective acylation of **103** furnished our targeted compound xyloketal D (**57**) in good yield. Consequently, methylation of phenolic compound **104** with dimethyl sulfate leads to methyl ether **105** (86%). This compound is the precursor in the Venkateswaran synthesis of xyloketal G (**60**)[41] described in Scheme 17. Thus, we have completed a formal total synthesis of xyloketal G (**60**) as well. Our synthetic strategy is applicable to the chiral synthesis of the xyloketal natural products which is the beauty of our approach.

3.3.2. Literature Synthesis of Racemic Xyloketal H (61)

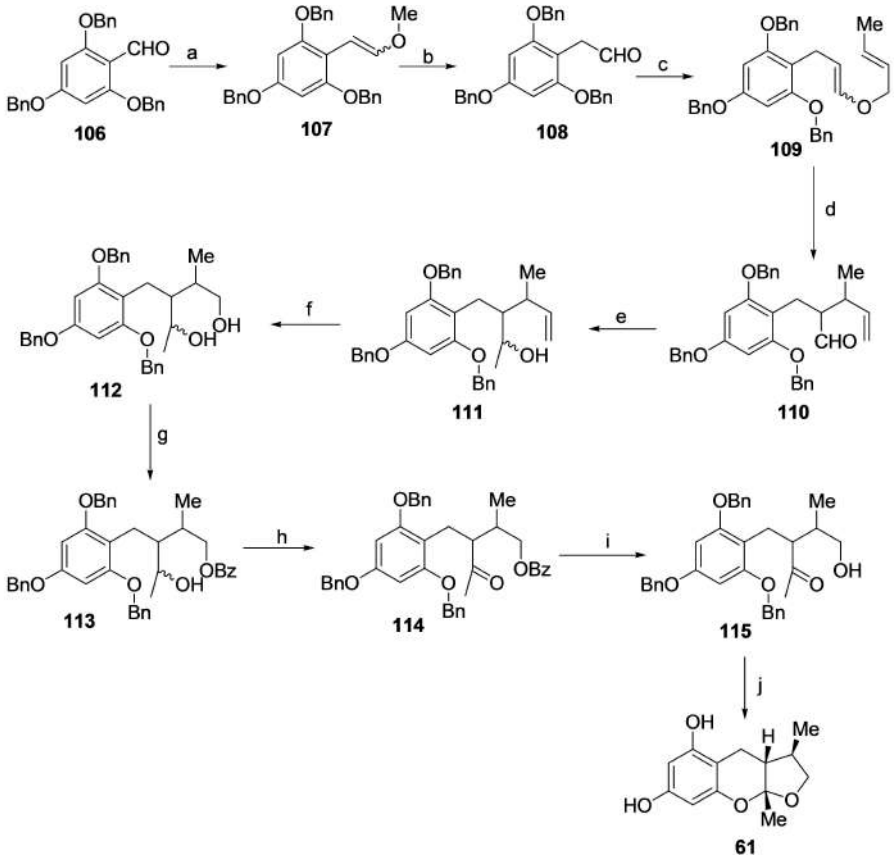
Three reports are available for the synthesis of xyloketal H. Both Krohn et al. method and Pang-Lin et al. method provide xyloketal H(**61**) mixed with other products. Only Kulkarni's procedure gave a clean synthesis of xyloketal H(**61**).

3.3.2.1. Krohn's Synthesis of Racemic Xyloketal H (61)[38]

Krohn et al. obtained xyloketal H (**61**), before its isolation, as a component of an epimeric mixture intermediate in the course



Scheme 19. Pang and Lin's Synthesis of (-)- Xyloketal H(**61**)
Reagents and conditions: (a) Alcohol (4R)-**23** (2 equiv), $BF_3.Et_2O$ (0.7 equiv), $MgSO_4$, Et_2O, 0 °C to rt, 24 h, 43.7% [(-)-**61**], 51.2% [(-)-**55**]



Scheme 20. Kulkarni's Synthesis of Racemic Xyloketal H (**61**)
Reagents and conditions: (a) Ph3P + CH_2OCH_3Cl (**105**), t BuOK, dry THF, 0°C, 82%; (b) 2 M HCl, acetone, reflux, 30 min, 88%; (c) $Ph_3P^+CH_2OCH_2CH_2CHCH_3Cl^-$, tBuOK, dry THF, 0 °C, 77%; (d) xylene, reflux, 12 h, 94%; (e) CH_3MgBr, dry THF, 0 °C, 83%; (f) O_3, MeOH, −78 °C, $NaBH_4$ (3.0 equiv) 75%; (g) PhCOCl, pyridine, DCM, 0 °C, 3 h, 91%; (h) IBX, EtOAc : DMSO (1:1), rt, 73%; (i) K_2CO_3, MeOH, rt, 2 h, 94%; (j) (i) 20 mol% Pd/C, H_2, MeOH, rt, 12 h; (ii) p-TSA, MeOH, $MgSO_4$, rt, 14 h, 61% (over two steps).

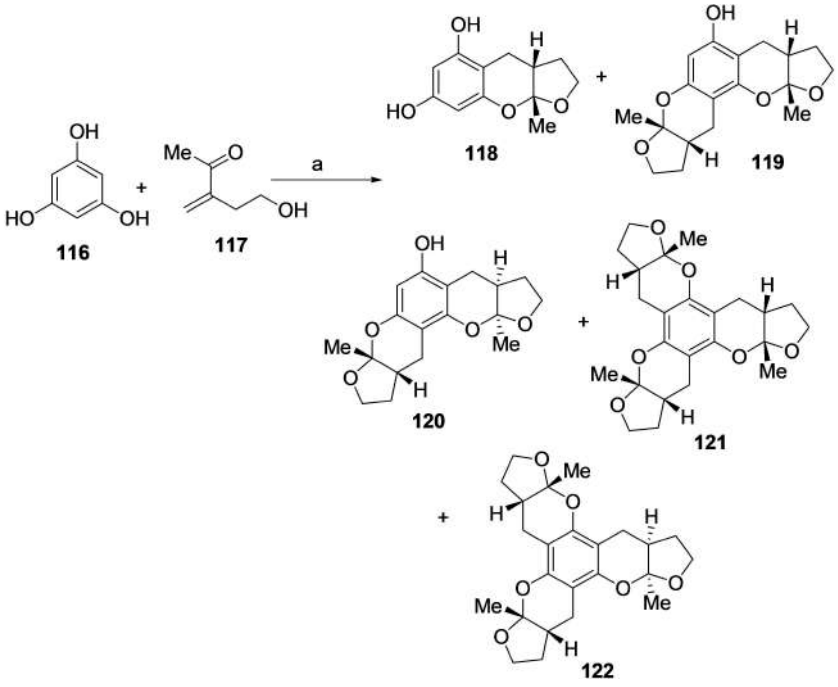
of non-enantioselective synthesis of xyloketals A(**54**) and B(**55**) (see, Scheme 22).

3.3.2.2. Pang and Lin's Synthesis of (-)- Xyloketal H (61)[42]

The reaction of phloroglucinol with two equivalent of 2,4-dimethyl-3-hydroxymethyl-4,5-dihydrofuran (**23**) and boron trifluoride diethyl etherate in presence of anhydrous magnesium sulfate in ether afforded a mixture of xyloketal H(**61**) (43.7%) as a yellow solid with xyloketal B(**55**) (51.2%) as a white solid (Scheme 19).

3.3.2.3. Kulkarni's Synthesis of Racemic Xyloketal H (61)[43]

Kulkarni et al. described a pleasant total synthesis of (±) Xyloketal H.The initial Wittig olefination followed by Claisen rearrangement protocol were used as the strategic approaches for the synthesis of this natural product. Wittig olefination of aldehyde **106** with methoxy -methylenetriphenylphosphonium chloride affords the required enol ether **107** (Scheme 20). Then compound **107** upon acid-mediated hydrolysis lead to the phenylacetaldehyde derivative **108** in good yield. Now the Wittig olefination of aldehyde **108** with crotyloxymethylene triphenylphosphonium chloride provides crotyl vinyl ether **109**



Scheme 21. Synthesis of the Xyloketal A and B Analogues
Reagents and conditions: (a) Enone **117** (0.5 equiv), PhMe, reflux, 4 h, 50% **118**, 27%(**119** and **120**), 6% (**121** and **122**) *or* enone **117** (3.0 equiv), PhMe, reflux, 4 h, 19% **118**, 63% (**119** and **120**), 7% (**121** and **122**) ***or*** enone **117** (6.0 equiv), PhMe, reflux, 20 h, 7% **118**, 22% (**119** and **120**), 58% (**121** and **122**).

as an inseparable diastereomeric mixture (E: Z = 2.55:1). The Claisen rearrangement of ether **109** gave the corresponding 4-pentenals **110** in 94% yield as an inseparable mixture of diastereomers in 1:1.01 ratio. The reaction of methyl magnesium bromide with aldehyde **110** in THF at low temperature afforded alcohol **111** in good yield. Ozonolysis of alkene **111** and subsequent reduction of the ozonide with $NaBH_4$ in situ gave 1,4 diol **112**. Primary alcohol of 1,4 diol **112** was protected selectively with benzoyl chloride to obtain **113**. The IBX oxidation of secondary alcohol **113** at ambient temperature gave ketone **114** in good yield. Further, debenzoylation of **114** provided alcohol **115** in excellent yield. Finally, palladium/charcoal catalyzed hydrogenolysis of **115** followed by acid-mediated ketalization produced the anticipated (±) Xyloketal H (**61**) in 61% yield.

3.3.3 Literature Syntheses of Xyloketal A, B, and its analogs

Xyloketal A (**54**) has a distinct and amazing C_3-symmetric molecular structure that fuses three bicyclic acetal moieties. An anomeric effect enforces this molecule to adopt a bowl-shaped conformation in the solid state.

3.3.3.1 Krohn's Synthesis of the Xyloketal A and B Analogues[38]

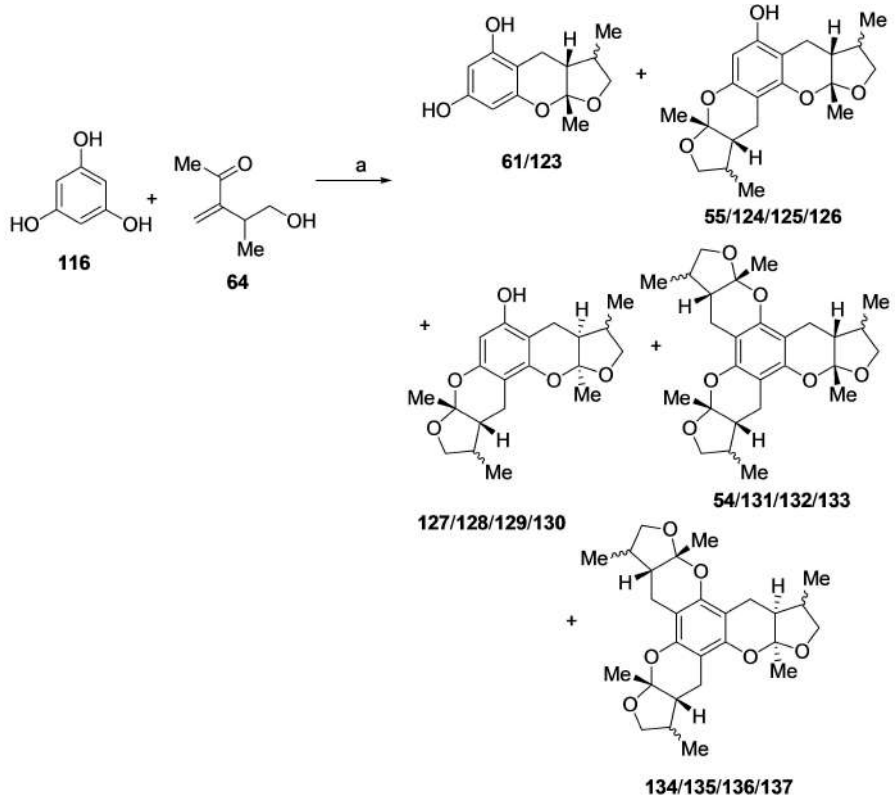
After successful synthesis of xyloketal D(**57**) and G(**60**), Krohn and co-workers have extended the same synthetic strategy to prepare the xyloketal A analogs **121** and **122** as well as xyloketal B analogs **119** and **120**, from enone **118** and phloroglucinol **116** (Scheme 21).

Varying the number of equivalents of the enone **117** used relative to phloroglucinol **116**, it was observed that the ratio of the resultant mono-, bis- and tris-adducts could be controlled. The xyloketal B analogs **119** and **120** were isolated as an inseparable mixture (dr = 2:3) with the syn, anti-isomer **120** being the major product. Interestingly, none of the regioisomeric bis-adducts related to xyloketal C **(56)**, were obtained in this reaction. Again, in the case of the xyloketal A analogs **121** and **122**, were formed as an inseparable mixture (dr = 1:4). Unfortunately, the unsymmetric syn, syn, anti-isomer **122** was the major product.

3.3.3.2 Krohn's Attempted Synthesis of Racemic Xyloketal A, B and H[38]

Krohn and co-workers, after getting the success on the synthesis of xyloketal A and xyloketal B analogs, applied the same synthetic protocol towards the preparation of racemic xyloketal A (**54**) and B (**55**) from phloroglucinol (**116**) (Scheme 22).

The reaction of phloroglucinol(**116**) with enone **64** provided the mono-adducts, later isolated an as xyloketal H(**61**) and **123** along with the bis-adducts **55** and **124–130** as well as deemed the tris-adducts **54** and isomers **131–137**. It was found that the xyloketal H(**61**) and **123** were obtained as an inseparable mixture of epimers (dr = 17:3). Similarly, the bis-adducts **55** and **124–130** were also obtained as an inseparable



Scheme 22. Krohn's Attempted Synthesis of Racemic Xyloketal A, B and H
Reagents and conditions: (a) Enone **64** (1 equiv), PhMe, reflux, 4 h, 50% (**61** and **123**), 3 1% (**55** and **124–130**), 6% (**54** and **131–137**)

mixture of eight compounds. Additionally, the desired tris-adducts were isolated in low yield (6%) as an inseparable mixture of eight compounds.

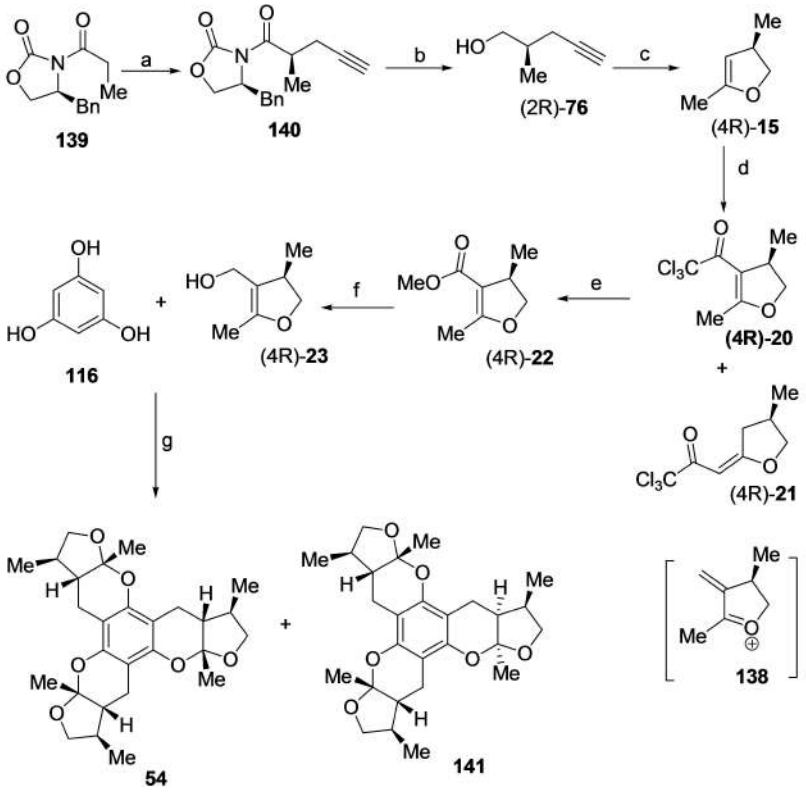
3.3.3.3 Wilson Synthesis of (-)-Xyloketal A(54)[44]

Wilson and co-worker reported the earliest total synthesis of the C_3-symmetric and powerful bioactive natural product, (-)-xyloketal A(**54**) by a threefold electrophilic aromatic substitution reaction of phenolic compound phloroglucinol **116** and the reactive intermediate **138**. The cis-fused bicyclic acetal moieties are thermodynamically stable and generated through the initial electrophilic substitution followed by appropriate acid promoted cyclization. Interestingly, the steric influence of the stereogenic C4-methyl substituent of the reactive intermediate **138** generated on ionization of the corresponding chiral nonracemic alcohol (4R)-**23** plays a vital role on the stereochemistry of the acetal formation reactions. The compound (4R)-**23 was** prepared from the known oxazolidinone **139** (Scheme 23). Base mediated propargylation followed by reduction provides chiral alcohol (2R)-**76** in good yield. Heating of acetylenic alcohol **76** with sodium amide followed by thermal isomerization of the corresponding *exo*-cyclic dihydrofuran afforded the known *endo*-cyclic dihydrofuran (4R)-**15**.

For the synthesis of necessary methyl ester (4R)-**22**, the dihydrofuran (4R)-**15** was reacted with trichloroacetyl chloride and pyridine at −78 °C to afford the trichloroketone (4R)-**20** in very good yield (93%) along with trace amount of regioisomeric trichloroketone **21**. The methanolysis of (4R)-**20** gave the methyl ester (4R)-**22** in excellent yield. They found that the lithium aluminum hydride mediated reduction of methyl ester (4R)-**22** cleanly provide required alcohol (4R)-**23**, although the compound (4R)-**23** was found to be quite unstable to isolation and purification and was used for next step directly. Finally, the boron trifluoride diethyl etherate mediated reaction of phloroglucinol **116** and alcohol (4R)-**23** in the presence of anhydrous magnesium sulfate in ether at 0 °C gave desired xyloketal A(**54**) along with 2,6-*epi*xyloketal A (**141**) in 85% yield (dr) 5:2) within 20 min of the reaction time. Interestingly, there is no evidence was found for the formation of mono- or bis-addition products in this reaction. This may be due to the relative instability of the alcohol (4R)-**23** and the high reactivity of the more electron-rich mono- and bis-addition products towards electrophilic aromatic substitution reaction. In this strategy, the borontrifluoride diethyletherate-promoted triple electrophilic aromatic substitution reaction is the key step for the facile and diastereoselective formation of this intricate architecture.

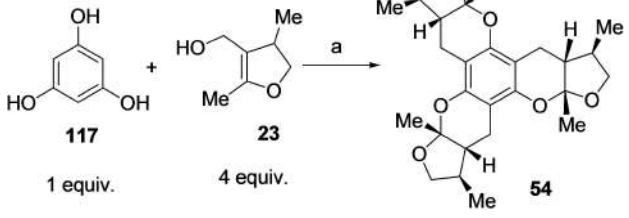
3.3.3.4 Pang and Lin's Synthesis of Racemic Xyloketal A (54)[42]

The reaction of phloroglucinol (**116**) with four equivalent of 2,4-dimethyl-3-hydroxymethyl-4,5-dihydrofuran (**23**) and boron trifluoride diethyl etherate in presence of anhydrous magne-



Scheme 23. Synthesis of (-)-Xyloketal A(**54**)
Reagents and conditions: (a) LDA, HMPA, THF, -78 °C, 30 min, proargyl bromide(**74**), -78 °C, 20 h, 77% (b) $LiAlH_4$, THF, 0 °C, 45 min, 73% (c) $NaNH_2$, reflux,4 h, distill; reflux, 18 h, 74% (d) Pyridine, CH_2Cl_2, rt, 30 min, 45%(**20**), 46%(**21**) or pyridine,CH_2Cl_2, -78 °C to rt, 21 h, 93%(**20**) (e) $NaHCO_3$, MeOH, reflux, 1 h, 98% (f) $LiAlH_4$, Et_2O, 0 °C to rt, 20 min (g) $BF_3.Et_2O$, $MgSO_4$, Et_2O, 0 °C 20 min, 85% (over two steps), dr = 5:2 (**54**:**141**) or $BF_3.Et_2O$, $MgSO_4$, Et_2O, -78 °C, 20 min, 79% (over two steps), dr = 4:1 (**54**:**141**)

sium sulfate in ether afforded a mixture of xyloketal A(**54**) as a white solid (Scheme 24).



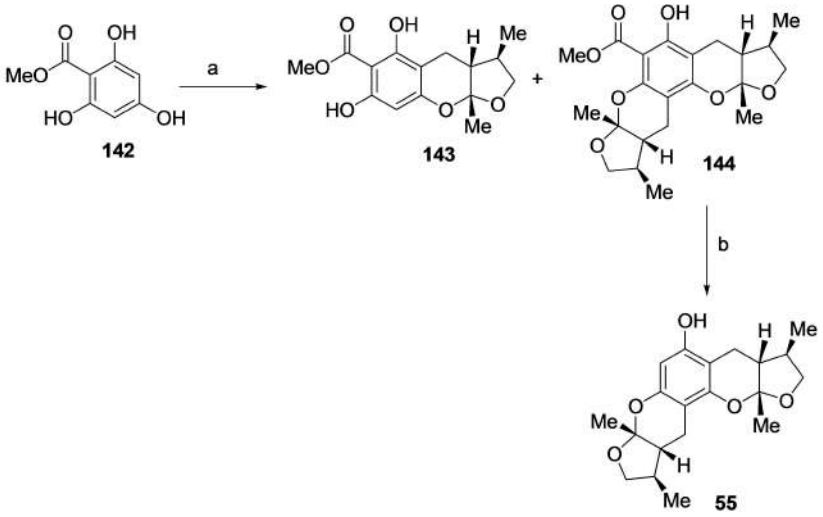
Scheme 24. Pang and Lin's Synthesis of Racemic Xyloketal A (**54**)
Reagents and conditions: (a) $BF_3.Et_2O$ (1 equiv), $MgSO_4$, Et_2O, 0 °C to rt, 24 h, 84.2%

3.3.3.5. Wilson Synthesis of (-)-Xyloketal B [(-)-55][11]

Wilson et al. reported the synthesis of the natural products xyloketal B from phloroglucinol ester **142** as per scheme 25. Reaction of ester **142** (1 equiv.) with the alcohol (4R)-**23** (4 equiv.) and boron trifluoride diethyl etherate (0.7 equiv.) in the presence of anhydrous magnesium sulfate for 38 h afforded chromatographically separable mixture of the bis-adduct (-)-**144** (73%) along with mono-adduct (-)-**143** (17%). They found that extending the duration of reaction from 38 h to 46 h afforded the bis-adduct (-)-**144** in excellent yield (91%). Significantly, a single diastereoisomer was obtained in the above reaction. Additionally, none of the regioisomer, e.g. linear isomer, corresponding to the thermodynamically unstable natural product xyloketal C (**56**) was isolated in these reactions. The subsequent hydrolysis and decarboxylation of bis-adduct (-)-**144** with sodium hydroxide in aqueous methanol at refluxing condition afforded (-)-xyloketal B (**55**) in excellent yield (95%). Wilson et al. have found that the sign of the optical rotation of the man-made (-)-xyloketal B [(-)-**55**] was opposite to that reported. They have thoroughly investigated and revealed that the optical rotation reported for the natural product was incorrect.

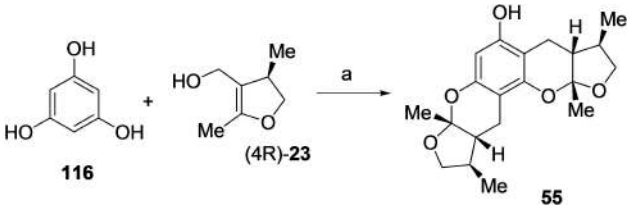
3.3.3.6. Pang and Lin Synthesis of Racemic Xyloketal B [(-)-55][42]

An electrophilic aromatic substitution reaction between the compound (4R)-**23** and phloroglucinol (**116**) promoted by



Scheme 25. Wilson Synthesis of (-)-Xyloketal B
Reagents and conditions: (a) Alcohol (4R)-**23** (4 equiv), $BF_3.Et_2O$ (0.7 equiv), $MgSO_4$, Et_2O, 0 °C to rt, 38 h, 17% [(-)-**143**], 73% [(-)-**144**] *or* alcohol (4R)-**23** (4 equiv), $BF_3.Et_2O$ (0.7 equiv), $MgSO_4$, Et_2O, 0 °C to rt, 46 h, 91% [(-)-**144**]. (b) NaOH, H_2O, MeOH, reflux, 3.5 h, 95%.

$BF_3.Et_2O$ provides racemic xyloketal B(**55**) in excellent yield(93%) was reported by Lin et al (Scheme 26).



Scheme 26. Pang and Lin Synthesis of (-)-Xyloketal B
Reagents and conditions: (a) $BF_3.Et_2O$ (0.7 equiv), $MgSO_4$, Et_2O, 0°C to rt, 24 h, 93%

3.3.4 Literature Synthesis of Xyloketal E(58)

Xyloketal E(**58**) is a tetrahydrofuran-linked angular structure related to xyloketal B(**55**). To the best of our knowledge, only one synthesis of xyloketal E is reported till date by Wilson group.

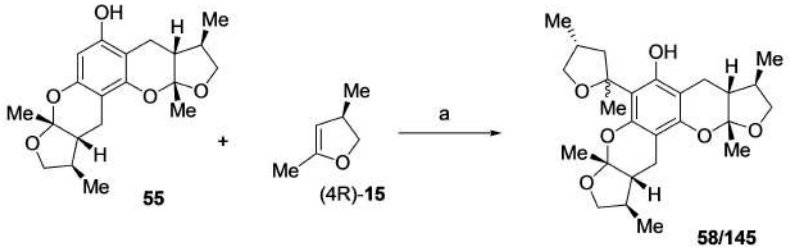
3.3.4.1 Wilson's Synthesis of Xyloketal E (58) from (-)-Xyloketal B [(-)-55][11]

Wilson et al. reported the total synthesis of xyloketal E(**58**) from xyloketal B(**55**) as per Scheme 27. The reaction of xyloketal B (**55**) with chiral nonracemic (4R)- **15** and pyridinium p-toluenesulfonate afforded an inseparable mixture (dr = 2:9) of xyloketal E (**58**) and 14-epi-xyloketal E (**145**).

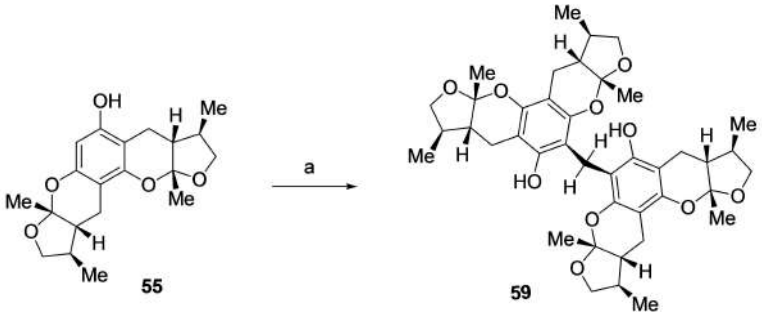
The diastereoselectivity of this process (dr = 2:9) was readily established by inspection of the ^{1}H NMR spectra as the signals corresponding to the two hydrogen-bonded phenol moieties of the reaction products **58** and **145** were well resolved at δ 10.81 and 10.86 ppm, respectively.

3.3.5 Literature Syntheses of Xyloketal F[(-)-59]

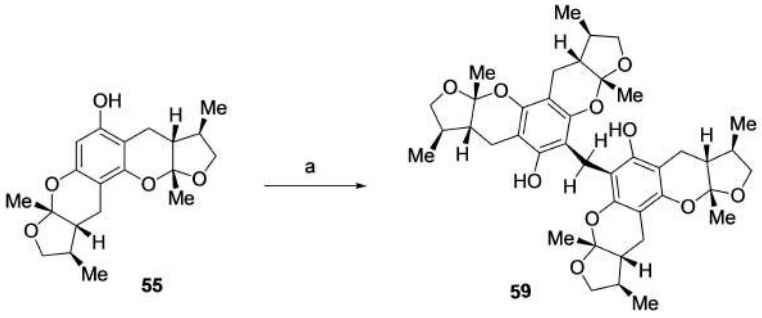
The complete planar structure of xyloketal F(**59**), is a dimeric type of xyloketal B connected by a methylene group. The four furan rings are in *cis* configurations. The phenolic hydroxyl



Scheme 27. Total Synthesis of the Xyloketal E (**58**) from (-)-Xyloketal B [(-)-**55**]
Reagents and conditions: (a) PPTS, CH_2Cl_2, room temperature, 21 h, 82%, dr = 2:9 (**58:145**).



Scheme 28. Krohn's Synthesis of (-)-Xyloketal F [(-)-**59**] from (-)-Xyloketal B [(-)-**55**]
Reagents and conditions: (a) Parafomaldehyde, 2(N) HCl, THF, 20 °C, 24 h, 80%.



Scheme 29. Synthesis of (-)-Xyloketal F [(-)-**59**] from (-)-Xyloketal B [(-)-**55**]
Reagents and conditions: (a) Parafomaldehyde, PPTS, CH_2Cl_2, rt, 23 h, 84%.

groups and oxygen atoms of the pyran rings formed the two hydrogen bonds in this molecule. These hydrogen bonds appear to enhance the stability of this conformation. The isolation of xyloketal F unequivocally recommends that its biosynthesis in the fungus occurs by means of the reaction of two molecules of xyloketal B(**55**) and one molecule of formaldehyde (or a biological congener). There are many pieces of evidences which support the existance of formaldehyde in biosynthetic system in nature.

3.3.5.1 Krohn's Syntheses of (-)-Xyloketal F [(-)-59][20]

The earliest total synthesis of non-racemic xyloketal F (**59**) was described by Krohn et al. in conjunction with their report on the isolation of the natural product (Scheme 28). In their synthesis, xyloketal B (**55**) subjected to react with paraformaldehyde in presence of 2 (N) HCl in THF solvent for 24 h at 20 °C to afford xyloketal F (**59**) (80%). They found that the optical rotation and NMR spectra of their prepared product matched with the isolated xyloketal F (**59**).

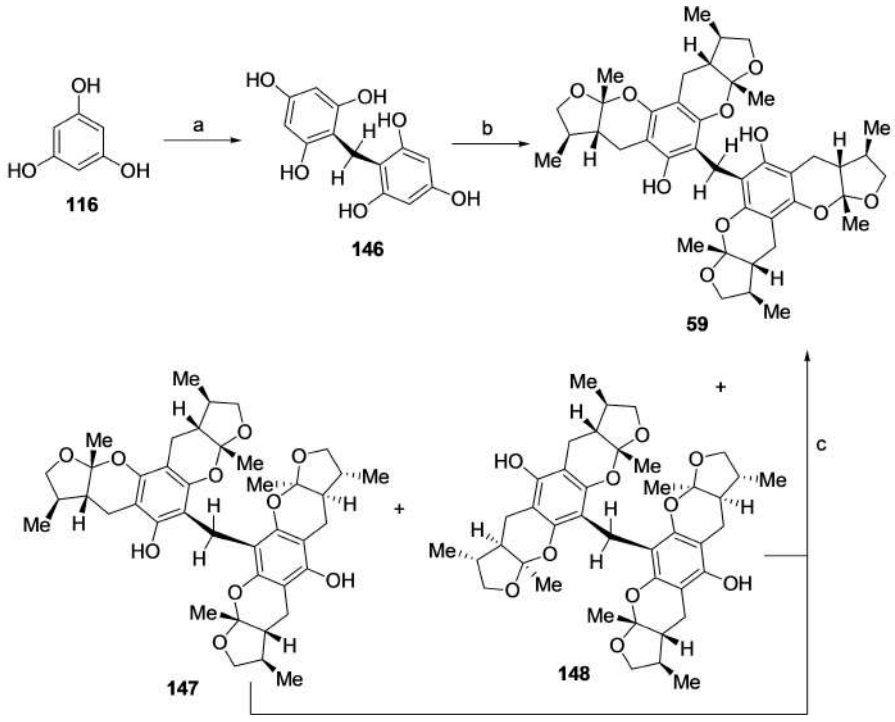
3.3.5.2 Wilson Syntheses of (-)-Xyloketal F [(-)-59][11]

First Generation Approach: Wilson et al. initially furnished the synthesis of xyloketal F **(-)-59** through the coupling of two equivalents of xyloketal B (**55**). The reaction of two equivalent of (-)-Xyloketal B [(-)-**55**] with paraformaldehyde under mildly acidic conditions at room temperature afforded (-)-xyloketal F [(-)-**59**] in good yield (84%) (Scheme 29).

Second Generation Approach: They have explored an alternative and more direct synthesis of xyloketal F [(-)-**59**]. The synthesis started with phloroglucinol (**116**), which was subjected to react with paraformaldehyde to afforded known biaryl compound **146** in one step according to literature procedures.[45,46] Although the overall yield of this method was low (34%), the ready availability, inexpensive starting materials and straightforward isolation of product were the benefits to follow that procedure. The electrophilic aromatic substitution reaction compound **146** with chiral alcohol (4R)-**23** (8 equiv.) in presence of $BF_3.Et_2O$ (1.3 equiv.) afforded an inseparable mixture (10:7:3) of xyloketal F [(-)-**59** and the regioisomers **147** and **148** in well-combined yield (7 1%) (Scheme 30).

4. Conclusion and Perspectives

Clearly, the biological evaluation, and application of various tactics and strategies for the synthesis of xyloketals and structurally related natural products, alboatrin is found to be a highly active area of interest among organic chemist community. Although the earliest synthetic efforts toward these nature's molecules were reported in 1988 for alboatrin and in 2004 for xyloketals, their highly functionalized architecture still leaves large space for further improvement. The construction of the aromatic core containing *cis*-fused 5,6-bicyclic acetal moieties



Scheme 30. Total Synthesis of (-)-Xyloketal F [(-)-**59**] from Phloroglucinol (**116**)
Reagents and conditions: (a) Paraformaldehyde (0.5 equiv.), HCl, H_2O, 4 °C, 16 h, 34%; (b) alcohol (4R)-**23** (8 equiv.), $BF_3.Et_2O$ (1.3 equiv.), $MgSO_4$, Et_2O, 0 °C to rt, 75 min, 71% [(-)-**59:147:148**], 10:7:3; (c) p-TsOH.H_2O, $CDCl_3$, 23 °C, 18 h, > 99%.

syn to the methyl substituents at C-5 of the five-membered ring in enantio- and diastereoselective manner for each target molecules is certainly the key synthetic challenge. Xyloketals shows various biological activities like acetylcholine esterase inhibition, L-calcium channel inhibition, these molecules can relax blood vessels, increase angiogenesis, stimulate endothelial cell NO production, and weaken the oxLDL-induced oxidative stress, etc. Thus the advances in the synthesis of xyloketals and evolution of additional biological activities and their action pathways are the active research area for organic chemists. Additionally, the developments in the synthesis of xyloketals will contribute to expediting access to other more intricate molecules.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Alboatrin · Bioactive Molecules · Natural Products · Total Synthesis · Xyloketals

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