

MINI-REVIEW ARTICLE

Synthetic Evolution Toward the Total Synthesis of the Bioactive Natural Polyphenol Cynandione A

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Abstract: Cynandione A (CA) is a natural bioactive polyphenol isolated from *Cynanchum wilfordii*, which has attracted considerable attention owing to its notable anti-inflammatory activity and multi-functional pharmacological potential. CA has been reported to exhibit immunomodulatory, neuroprotective, and hepatoprotective activities in various models. However, its limited natural abundance and structural complexity hinder extensive biological exploration. Consequently, the total synthesis of CA has been studied extensively. The first total synthesis of CA was reported in 2005, and the original six-step synthesis has evolved into more efficient approaches, including a scalable two-step synthesis and a recently developed one-pot method, which enable gram-scale production with high yield and operational simplicity. A key feature of these strategies is the regioselective conjugate addition of acetylphenol derivatives to an *in situ*-generated benzoquinone intermediate, governed by electronic and steric factors. This review outlines the synthetic evolution of CA and summarizes its pharmacological activities. The integration of advanced synthetic design with mechanistic pharmacology underscores the value of CA as a promising lead compound for further drug development. Continued optimization of its synthesis and biological validation will facilitate its translation into therapeutic applications.

Keywords: Cynandione A, total synthesis, natural polyphenol, anti-inflammatory activity, regioselectivity, conjugate addition.

1. INTRODUCTION

Cynandione A (CA, **1**) is a principal bioactive constituent of the dried roots (Radix) of *Cynanchum wilfordii* and *Cynanchum taiwanianum*, among other species of the genus *Cynanchum* [1,2]. Structurally, **1** is a biaryl compound characterized by two differently substituted aromatic rings linked via a carbon-carbon bond between the C1 and C1' positions (Fig. 1A). Initially upon isolation, the structure of **1** was misassigned, having been originally proposed as a biphenyl where in the phenolic hydroxyl groups were placed at the C2, C3, C2', and C6' positions (Fig. 1B) [3]. However, subsequent nuclear magnetic resonance (NMR) spectroscopic analysis revealed that the correct structure features hydroxyl groups at the C3, C6, C2', and C6' positions, thereby establishing its true unsymmetrical substitution pattern [4,5]. Along with phenolic hydroxyl groups, each acetophenone ring contains an aryl ketone moiety, forming a non-symmetrical diaryl diketone framework. Although the aromatic rings are planar, the molecule as a whole exhibits partial conjugation owing to the rather flexible interconnecting

bond. The presence of phenolic and carbonyl functionalities provides potential sites for hydrogen bonding, which could affect its physicochemical properties and intra- and intermolecular interactions. Density functional theory (DFT)-optimized structures revealed three intramolecular hydrogen bonds—3-OH...7-CO, 2'-OH...7'-CO, and 6-OH...2'-OH—with bond lengths ranging from 1.608 to 1.914 Å, which contribute to the conformational rigidity and overall structural stability of the molecule (Fig. 1A) [6].

Plants of the genus *Cynanchum*, including *C. wilfordii* (Fig. 2) and *C. bungei*, are perennial climbing vines widely distributed in East Asia [7-10]. Among them, the dried root of *C. wilfordii* (*Cynanchi wilfordii* Radix), long used in traditional medicine, is typically dried and decocted to treat a broad range of ailments, including menopausal disorders, cardiovascular dysfunction, and age-related degenerative conditions, and has also been applied for the management of fatigue, osteoporosis, and constipation [11-18]. Recent pharmacological studies have supported these traditional claims by demonstrating that *Cynanchum wilfordii* root extracts exert notable anti-inflammatory, antioxidant, hepatoprotective, and immunomodulatory effects in diverse models, including RAW264.7 macrophages, dextran sulfate sodium (DSS)-induced colitis, and high-fat diet-induced hepatic

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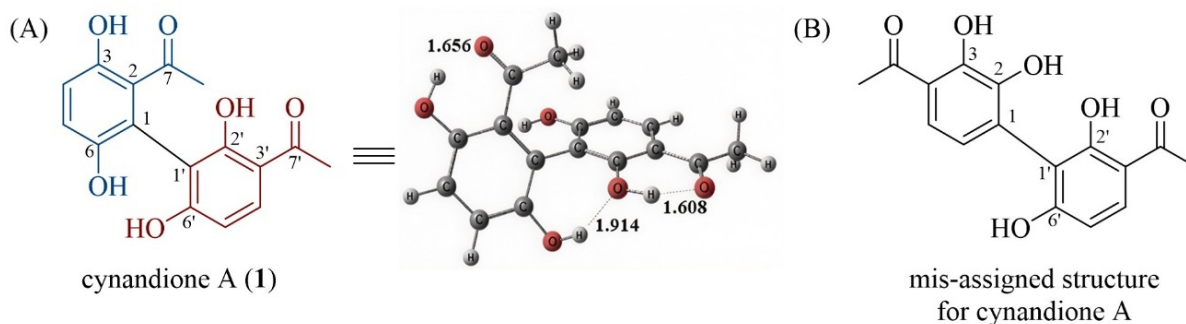


Fig. (1). Structural representation of **1**. (A) Structure of **1** and its optimized 3D structure [5]. (B) Originally mis-assigned structure of **1**.

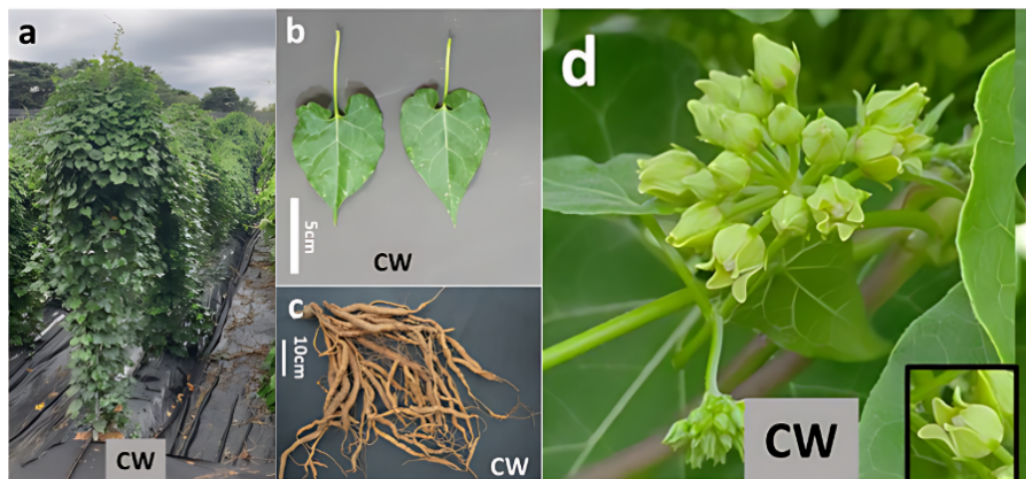


Fig. (2). Morphological features of *Cynanchum wilfordii* (CW): (a) whole plant, (b) leaves, (c) roots, and (d) flowers [20]. Reprinted from Lee et al., BMC Plant Biology, 22, 4 (2022), licensed under CC BY 4.0. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

injury [19-23]. In addition, phytochemical investigations have confirmed the presence of bioactive phenolics such as **1** [24, 25].

Along with **1**, several structurally related congeners, cynanchone A (**2**) and cynandiones B through E (**3-6**), have been isolated from species of the genus *Cynanchum* [1-3, 26-31] (Fig. 3). These compounds share a biaryl origin with **1** and are believed to be dimeric derivatives formed through oxidative coupling of acetophenone-type precursors. Notably, studies have demonstrated that cynandiones B (**3**) and C (**4**) can be formed by stirring **1** in methanol in the presence of silica, suggesting that both **3** and **4** may be artifacts generated during the isolation process rather than genuine natural products [3,32]. Compound **3**, nonetheless, exhibits notable biological activity, including dose-dependent inhibition of β -glucuronidase and lysozyme release in fMLP-stimulated rat neutrophils ($IC_{50} = 1.5 \pm 0.2$ and 1.6 ± 0.2 μ M, respectively), as well as suppression of superoxide anion generation in PMA-stimulated neutrophils ($IC_{50} = 78.0 \pm 8.1$ μ M) [2]. It has also shown *in vitro* cytotoxicity against the human T-24 bladder carcinoma and PLC/PRF/5 hepatoma cell lines [30], highlighting its potential anti-inflammatory and anticancer properties. These findings point to further opportunities for expanding both synthetic approaches and biological evaluation within this class of polyphenolic compounds.

Compound **1** remains the most abundant and well-characterized natural component in *Cynanchi wilfordii* Ra-

dix. It exhibits a broad range of pharmacological activities, including antioxidant, anti-inflammatory, neuroprotective, and anti-lipogenic effects [33-50]. However, the amount of **1** obtainable from natural sources is insufficient for sustained research and development, as extraction from plant materials remains limited in terms of efficiency and scalability. Along with its intriguing structural characteristics, this limitation highlights the importance of synthetic approaches to compensate for the low natural availability.

This review summarizes the recent advances in the pharmacological investigation and chemical synthesis of **1**, with an emphasis on its strategic evolutions in efficiency and scalability (Fig. 4). The first total synthesis, reported by Kraus and co-workers, established a concise six-step route. Subsequently, significant advancements have been achieved through a streamlined two-step synthesis featuring a one-pot tandem oxidation/regioselective arylation approach. More recently, a highly efficient one-pot synthetic methodology has further improved scalability, sustainability, and overall yield, complemented by computational insights from DFT calculations elucidating the regioselectivity in the key step. Together, these synthetic advancements have improved access to **1** and facilitated more extensive biological studies.

2. BIOLOGICAL ACTIVITIES OF **1**

More recent studies have extended traditional use and earlier pharmacological observations by investigating the

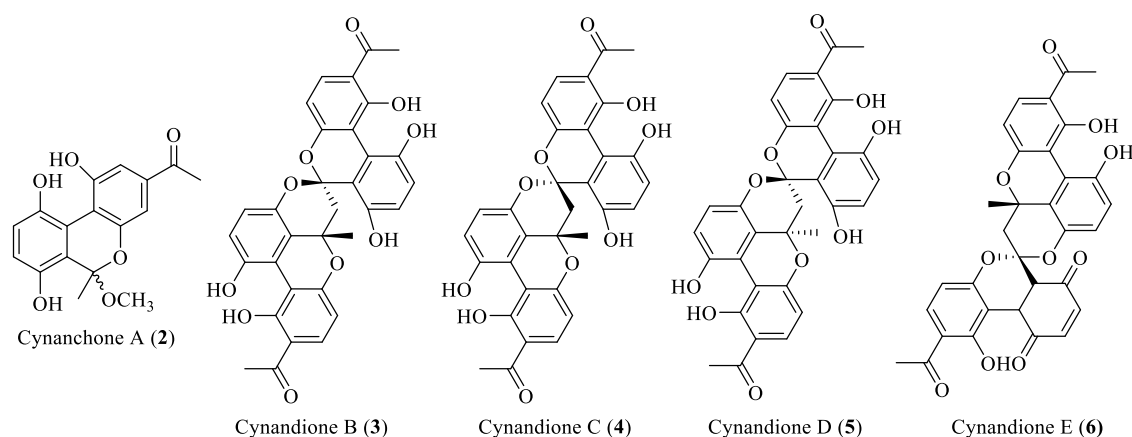


Fig. (3). Chemical structures of related congeners of **1**.

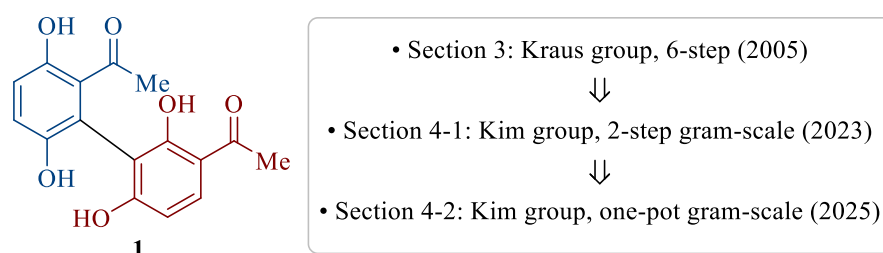


Fig. (4). Schematic summary of the evolution of synthetic strategies toward **1** discussed in this review.

biological activities of **1** in greater depth. These studies have demonstrated a broad spectrum of bioactivities, particularly in the areas of inflammation, metabolism, and neuroprotection, which are summarized in Table 1.

The Kim group demonstrated the potent anti-inflammatory properties of **1** in both *in vitro* and *in vivo* models. In lipopolysaccharide (LPS)-stimulated BV-2 microglial cells, **1** significantly inhibited the production of nitric oxide (NO) and pro-inflammatory cytokines, including TNF- α , IL-6, and IL-1 β . In LPS-induced septic mouse models, **1** reduced plasma cytokine levels and inhibited activation of ERK1/2 and p38 MAPKs. These findings suggest that **1** modulates systemic inflammatory responses through the downregulation of iNOS and the suppression of the NF- κ B signaling pathway [33,34].

The Wang group investigated the neuroprotective, antinociceptive, and anti-inflammatory activities of **1**. In a rat model of neuropathic pain, administration of **1** significantly alleviated both mechanical allodynia and thermal hyperalgesia. Mechanistically, **1** increased the expression of β -endorphin in spinal microglia and activated postsynaptic μ -opioid receptors, thus contributing to pain relief. These effects were dependent on the activation of $\alpha 7$ nicotinic acetylcholine receptors ($\alpha 7$ -nAChRs), which also played a key role in modulating neuroinflammatory responses. In LPS-stimulated microglial cells and hippocampal tissue slices, **1** suppressed microglial activation and pro-inflammatory cytokine release through $\alpha 7$ -nAChR-dependent pathways. Furthermore, in systemic inflammation models using LPS-challenged mice, **1** reduced the circulating levels of TNF- α , IL-6, and IL-1 β by activating the cholinergic anti-

inflammatory pathway. This was accompanied by phosphorylation of STAT3 and increased expression of IL-10, indicating a dual mechanism that involved both central and peripheral regulation of inflammation [31, 35-38].

The Nakajima group reported that **1** promotes adipogenesis and induces a beige adipocyte-related phenotype in 3T3-L1 preadipocytes. This process is accompanied by increased expression of key thermogenic genes, including Ucp1, Pgc-1 α , and Prdm16, as well as enhanced mitochondrial biogenesis. Recently, the same group found that **1** induces beige adipocyte differentiation and mitochondrial biogenesis in mice fed with a high-fat diet (personal communication). These observations suggest the potential of **1** as a metabolic regulator and aid in the treatment of obesity-related disorders. [39-41].

Compound **1** also exhibited significant hepatoprotective activity against carbon tetrachloride (CCl₄)-induced oxidative injury in primary rat hepatocytes [42]. This highlights the antioxidant and membrane-protective properties of **1**. Pharmacokinetic studies indicated that **1** is rapidly absorbed and widely distributed across tissues, with particularly high concentrations in the liver, and that it is eliminated quickly, supporting its potential for hepatoprotective applications [43,44]. In neuronal models, **1** exhibited neuroprotection against H₂O₂-induced oxidative damage in rat cortical neurons by directly scavenging reactive oxygen species (ROS) and preserving antioxidant enzyme activities, while also protecting from excitotoxicity mediated by AMPA/kainate receptors [45]. In ischemic stroke models involving middle cerebral artery occlusion, **1** significantly reduced the infarct volume and improved neurological outcomes by reducing

Table 1. Summary of the reported biological activities of **1**.

Study Group	Biological Activity	Model	Mechanism of Action
Kim group [33,34]	Anti-inflammatory	BV-2 microglial cells, septic mice	• ↓ NO, TNF-α, IL-6, IL-1β • iNOS downregulation • NF-κB, ERK1/2, p38 MAPK inhibition
Wang group [31,35-38]	Neuroprotective, antinociceptive, anti-inflammatory	Neuropathic pain rat model; LPS-stimulated microglia; hippocampal slices; LPS-induced systemic inflammation	• ↑ β-Endorphin • μ-Opioid receptor activation • α7-nAChR activation • ↑ IL-10, p-STAT3 • ↓ TNF-α, IL-6, IL-1β
Nakajima group [39-41]	Metabolic modulatory	3T3-L1 preadipocytes	• Beige adipocyte differentiation • ↑ Beige adipocyte-related genes (e.g., <i>Ucp1</i>, <i>Pgc-1α</i>, <i>Prdm16</i>) • ↑ Mitochondrial biogenesis-related genes (e.g., <i>Tfam</i>, <i>Sirt3</i>)
Other studies [42-50]	Hepatoprotective	HepG2 cells; CCl ₄ -induced hepatic injury (mice)	• ↑ GSH • ↓ MDA • ↑ SOD, catalase, GPx • ↓ Lipid peroxidation
	Neuroprotective (antioxidant-based)	Primary cortical neurons; SH-SY5Y cells	• ↓ ROS • Mitochondrial protection • ↓ Caspase-3, PARP cleavage • H₂O₂ decomposition

oxidative stress, mitigating mitochondrial dysfunction, and restoring antioxidant enzymes [46]. Furthermore, network-based analyses confirmed the protective effect of **1** against ischemic injury in neuronal cells by modulating key molecular pathways involved in stroke pathology, notably suppressing KHSRP and HMGB1 expression in glutamate-induced neurotoxicity models [47]. Collectively, these findings indicate that **1** suppresses vascular inflammation by inhibiting VCAM-1 expression and NF- κ B/MAPK signaling, thereby reducing monocyte adhesion to endothelial cells [48].

3. FIRST TOTAL SYNTHESIS BY THE KRAUS GROUP

The first total synthesis of **1** was accomplished by Kraus and co-workers and reported in 2005 (Scheme 1) [51]. Their strategy employed a regioselective and modular approach that exploited the reactivity of quinone to construct the biphenyl core structure.

The synthesis began with a two-step sequence in which the enol silyl ether of cyclohexane-1,3-dione underwent a regioselective conjugate addition to acetylbenzoquinone **7**, followed by *O*-methylation of the resulting conjugate addition product to yield β -methoxy enone **8**. This regioselective and modular strategy exploited the inherent reactivity of quinones to construct the skeletal core of **1** via a key carbon-carbon bond formation achieved during the conjugate addition step [52].

Subsequent oxidation of **8** using DDQ in refluxing dioxane generated biphenyl intermediate **9** in 48% yield [53]. Initial efforts to directly install the second acetyl group onto

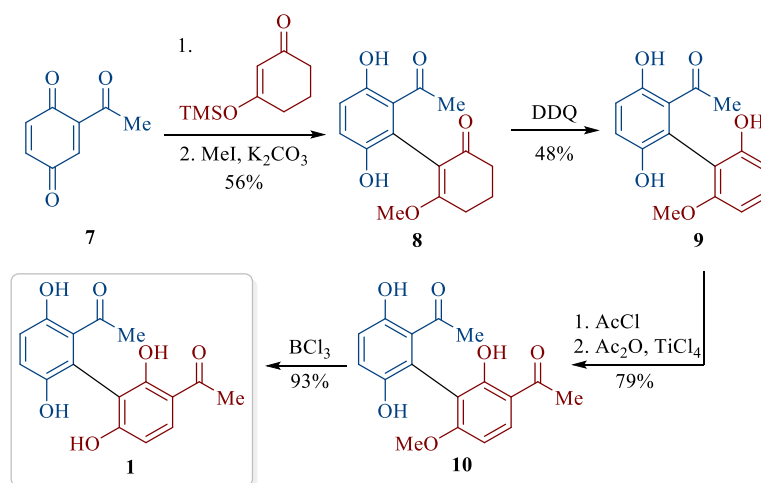
9 via Friedel-Crafts acylation were unsuccessful, likely owing to steric hindrance and electronic deactivation of the aromatic system. Consequently, a stepwise *O*-acylation and Friedel-Crafts acylation strategy was adopted to achieve regioselective functionalization of the phenolic hydroxyl groups. Mono-*O*-acetylation of **9** was achieved by treating it with acetyl chloride and pyridine. Subsequently, the intermediate was acylated under Friedel-Crafts reaction conditions using titanium tetrachloride and acetic anhydride, affording compound **10** in an overall yield of 79% from compound **9** [54]. Finally, the methoxy substituent was demethylated using boron trichloride in dichloromethane at 0 °C to obtain the fully deprotected **1** in 93% yield.

The overall synthesis was achieved in six linear steps starting from commercially available cyclohexane-1,3-dione, with a total isolated yield of 13%. Kraus' synthesis provides a strong foundation for future **1** research and remains a significant achievement.

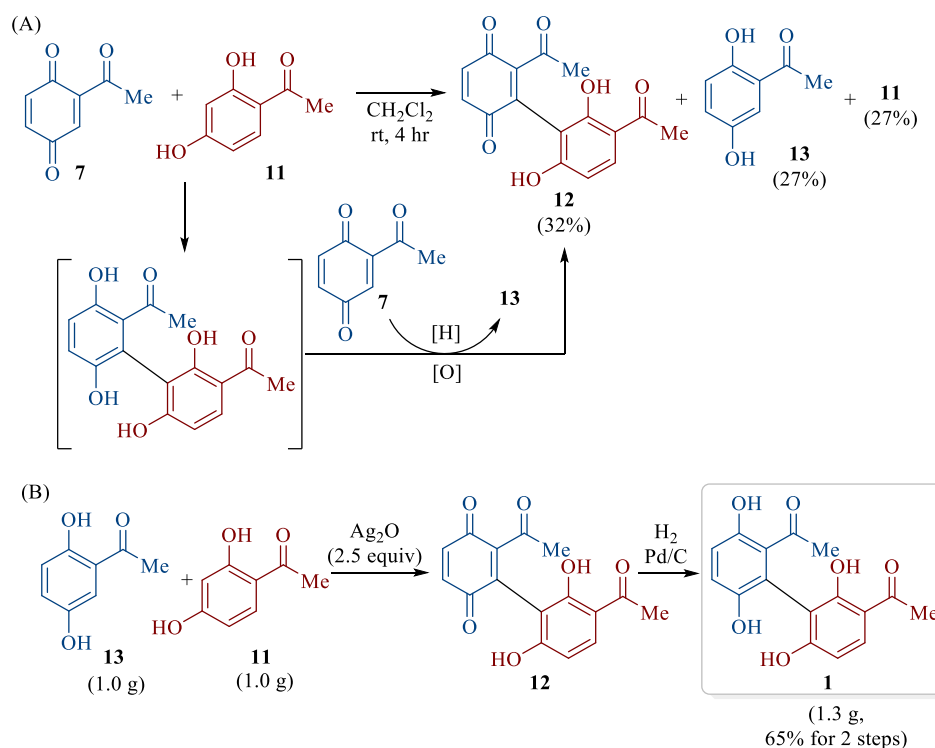
4. SCALABLE SYNTHESIS OF **1**

4.1. Two-step Synthesis of **1**

The first total synthesis of **1**, developed by the Kraus group [51], was significant because it provided excellent regiochemical control and validated the structural assignment. However, its modest overall yield and milligram-scale output (44 mg) limited its applicability in broader biological studies and preclinical investigations. Approximately two decades later, the Kim group developed a concise and scalable two-step synthesis (Scheme 2), which substantially increased the efficiency and production capacity [55].



Scheme 1. First total synthesis of **1** by the Kraus group (2005).

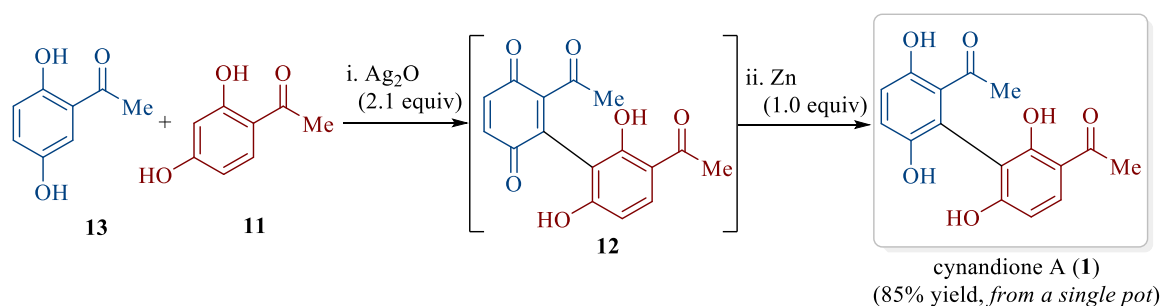


Scheme 2. Two-step synthesis of **1** by the Kim group (2023). (A) Initial synthetic route for **1**. (B) One-pot tandem oxidation/arylation strategy for the two-step synthesis of **1**.

Initially, analogous to the strategy reported by the Kraus group, acetylbenzoquinone (**7**) was used as the key electrophilic partner in the conjugate addition step. However, the Kim group directly used 2,4-dihydroxyacetophenone (**11**) as the nucleophilic coupling partner, thereby avoiding additional manipulations such as protection/deprotection, acetyl group installation, and redox adjustments. Owing to the presence of ortho- and para-hydroxyl groups in 2,4-dihydroxyacetophenone, the concurrent formation of undesired regioisomers *via* nucleophilic attack at both the C3 and C5 positions was anticipated, which were expected to be readily separable.

In initial attempts (Scheme 2A), the direct conjugate addition of compound **11** to benzoquinone **13** resulted in only a trace amount of **1**. Instead, compound **12** was obtained as a major product along with **13** and unreacted **11**. This was later confirmed to originate from an unexpected competing redox reaction between **1** and the starting material **7**, leading to the loss of the former [56,57].

To address this issue and improve the overall efficiency, hydroquinone **13** was instead used as the starting material, enabling a one-pot oxidation/conjugate addition/oxidation sequence in the presence of excess oxidant [58-61]. In the first step, Ag₂O-mediated oxidation of **13** generated benzo-



Scheme 3. One-pot gram-scale synthesis of **1** by the Kim group (2025).

quinone **7** *in situ*, which subsequently underwent a conjugate addition of **11** at the C3 position, furnishing the key intermediate **12** in high yield. This conjugate addition was exceptionally regioselective and prevented the formation of isomers. This regiochemical preference of C3 over C5 was governed by the electronic effects, as supported by the natural bond orbital (NBO) charge analysis and DFT calculations (*vide infra*).

The synthesis was further validated by demonstrating its reproducibility on a gram scale (Scheme **2B**). First, 1.0 g of each starting material (**11** and **13**) was treated with 2.5 equivalents of Ag_2O , and the unstable intermediate compound **12** was directly subjected to catalytic hydrogenation after filtration, without chromatographic purification. This streamlined procedure produced **1** with an overall yield of 65% over two steps, demonstrating its practicality and robustness. Notably, only one chromatographic step was required throughout the process.

4.2. One-pot Synthesis of **1**

As previously outlined, the two-step process significantly enhanced the synthetic accessibility of **1**. However, further optimization was required to improve the pot economy and adhere to the principles of green chemistry [62,63]. Accordingly, a one-pot gram-scale synthesis (Scheme **3**) was developed [64].

In the two-pot process, the first step involved three sequential transformations—oxidation, regioselective arylation, and *in situ* oxidation—and the second step involved the reduction of the resulting compound **12** to **1**. Reduction conditions that could tolerate residual oxidants or byproducts had to be established to develop a successful one-pot reaction. Common reducing agents such as Pd/C-H_2 and NaBH_4 were found to be insufficiently reactive or poorly chemoselective for the reduction of intermediate **12** in the one-pot process [65–68]. Zinc in a $\text{CH}_2\text{Cl}_2/\text{AcOH}/\text{H}_2\text{O}$ co-solvent system was found to be the most effective option with excellent functional group tolerance. The use of 2.1 equivalents of Ag_2O for the first step and a stoichiometric amount (1.0 equiv) of zinc for the reduction of intermediate **12** was also found to be beneficial. The optimized one-pot synthesis of **1**, which involves four sequential steps—oxidation, regioselective arylation, *in situ* oxidation, and reduction—within a single vessel, enables gram-scale preparation with an overall yield of 82% (Scheme **3**). By avoiding intermediate isolations and reducing solvent consumption, this protocol offers a more efficient and scalable route suitable for medicinal

chemistry and biological studies [69–72]. Notably, the conjugate addition consistently occurs at the C3 position of the nucleophile, a preference that reflects electronic bias and is further supported by theoretical studies (Section 4.3).

4.3. Mechanistic Insights into the Regioselectivity

Regioselectivity is a key factor in directing the formation of the desired product among the other possible regioisomers. In the two-step or one-pot synthesis of **1** described in Sections 4.1 and 4.2, the conjugate addition step exhibited exceptional regioselectivity, exclusively yielding the C3 adduct. Kim's group investigated this selectivity using two computational techniques: NBO charge analysis [73, 74] and DFT calculations [75, 76].

To examine the electronic origin of the observed regioselectivity, NBO charge analysis was initially conducted by investigating the electronic factors of acetyl bisphenol **11** [52] (Fig. **5a**). The electron density varied across the three potential nucleophilic sites. Among them, the C3 position exhibited the highest negative charge (−0.370), followed by C5 (−0.336), whereas C6 displayed a significantly less negative value (−0.121). These values indicate that the C3 carbon has the greatest electron density and is thus the most nucleophilic among the three carbons. Although the difference between C3 and C5 was moderate ($\Delta = 0.034$), it correlated with the experimentally observed regioselectivity.

DFT calculations were performed on the reaction pathways leading to the addition at the C3, C5, and C6 positions to gain a deeper understanding of the regioselectivity [6,61] (Fig. **5b**). The energy profiles of the transition states (TS) reveal that the C3 position has the lowest activation energy, with a transition state energy of 15.7 kcal/mol, compared to 19.5 and 37.3 kcal/mol for the C5 and C6 pathways, respectively. Accordingly, addition at the C3 position is associated with the lowest energetic barrier among the three pathways, consistent with experimental observations. The Boltzmann-weighted analysis of transition state (TS) energies predicted that at room temperature, 99.8% of the reactants proceed *via* the C3 addition pathway (TS-3), with only 0.2% and 0.0% following the C5 (TS-5) and C6 (TS-6) pathways, respectively. These results further support the experimentally observed regioselectivity.

Together, the NBO charge analysis and DFT calculations provided a comprehensive mechanistic explanation for the regioselectivity observed in the conjugate addition of acetyl bisphenol to benzoquinone.

(a)

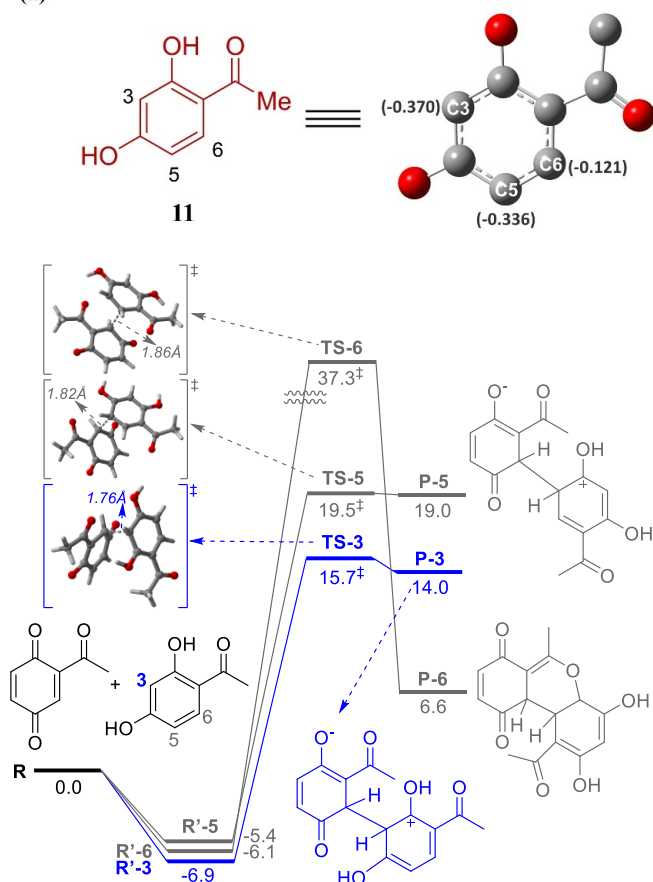


Fig. (5). Computational techniques for explaining regioselectivity in the conjugate addition step. (a) NBO charge analysis of **11**. (b) DFT calculations on the reaction pathways leading to the addition at the C3, C5, and C6 positions of **11**.

CONCLUSION

This review highlights the synthetic evolution toward the total synthesis of **1**, focusing on conciseness, scalability, and environmental sustainability. Following the initial six-step synthesis developed by the Kraus group, recent efforts have led to the development of a highly optimized protocol that enables gram-scale production with high yield and minimal purification. Both synthetic approaches share a common modular framework based on two acetophenone-derived fragments of compound **1**; however, the building blocks differ in two key aspects. First, Kraus used benzoquinone **7** as a Michael acceptor, whereas the Kim group used its precursor, hydroquinone **13**, as the starting material, which was oxidized *in situ* to produce compound **7**. Second, Kraus used a cyclohexadione derivative, and the Kim group used pre-acetyl equipped dihydroxyacetophenone as a nucleophilic Michael donor. These improvements reduce unnecessary waste and improve overall process efficiency.

Gram-scale synthesis of **1** proceeded with high regioselectivity in the conjugate addition step. By integrating experimental and computational approaches, including NBO charge analysis and DFT calculations, the regioselectivity was rationalized. The exclusive reactivity at the C3 position of acetyl bisphenol was attributed to both electronic and en-

ergetic factors, providing mechanistic insights that informed the design of a regioselective and efficient synthetic route.

Given the documented anti-inflammatory, neuroprotective, antioxidant, hepatoprotective, and metabolic regulatory properties of **1**, reliable access to **1** at the gram scale supports more extensive *in vivo* evaluation and further assessment of its therapeutic potential. The synthetic logic described here may also be applicable to related biaryl natural products.

AUTHOR'S CONTRIBUTIONS

The authors confirm their contribution to the paper as follows: study conception and design: JK. and HJP.; data collection: EZ.; data analysis and interpretation: AS.; draft manuscript: MN. and JHK. All authors reviewed the results and approved the final version of the manuscript.

LIST OF ABBREVIATIONS

AcOH	=	Acetic Acid
Ag ₂ O	=	Silver(I) Oxide
BV-2	=	Murine Microglial Cell Line
CA	=	Cynandione A
CCl ₄	=	Carbon Tetrachloride
CH ₂ Cl ₂	=	Dichloromethane
DFT	=	Density Functional Theory
ERK1/2	=	Extracellular Signal-Regulated Kinases 1 and 2
fMLP	=	N-Formylmethionine-leucyl-phenylalanine
GPx	=	Glutathione Peroxidase
GSH	=	Glutathione
H ₂ O ₂	=	Hydrogen Peroxide
HepG2	=	Human Hepatocellular Carcinoma Cell Line
HMGB1	=	High Mobility Group Box 1
IC ₅₀	=	Half Maximal Inhibitory Concentration
IL-10	=	Interleukin-10
IL-1β	=	Interleukin-1 Beta
IL-6	=	Interleukin-6
iNOS	=	Inducible Nitric Oxide Synthase
KHSRP	=	KH-Type Splicing Regulatory Protein
LPS	=	Lipopolysaccharide
MAPKs	=	Mitogen-Activated Protein Kinases
MCAO	=	Middle Cerebral Artery Occlusion
MDA	=	Malondialdehyde
NaBH ₄	=	Sodium Borohydride
NBO	=	Natural Bond Orbital

NF-κB	=	Nuclear Factor-kappa B
NMR	=	Nuclear Magnetic Resonance
NO	=	Nitric Oxide
PARP	=	Poly (ADP-ribose) Polymerase
Pd/C	=	Palladium on Carbon
Pgc-1α	=	Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-α
PLC/PRF/5	=	Human Liver Cancer Cell Line
PMA	=	Phorbol 12-myristate 13-acetate
Prdm16	=	PR Domain Containing 16
RAW264.7	=	Murine Macrophage Cell Line
ROS	=	Reactive Oxygen Species
SOD	=	Superoxide Dismutase
STAT3	=	Signal Transducer and Activator of Transcription 3
T-24	=	Human Bladder Carcinoma Cell Line
TNF-α	=	Tumor Necrosis Factor-α
TS	=	Transition State
Ucp1	=	Uncoupling Protein 1
α7-nAChR	=	Alpha-7 Nicotinic Acetylcholine Receptor
β-Endorphin	=	Beta-Endorphin
μ-Opioid receptor	=	Mu-Opioid Receptor

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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