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An expedient synthesis of honokiol and its analogues as potential neuropreventive agents

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ABSTRACT

An efficient synthesis of honokiol with Suzuki–Miyaura cross coupling obtained an overall yield of 45%. The proposed approach successfully synthesized several structurally similar alkyl, alkenyl and alkynyl analogues, seven of which showed potential neuropreventive activity against MPP^+-induced and CHP/TBHP oxidative stress induced neuroblastoma cell death.

The search for natural sources of chemical entities with therapeutic and chemo-preventive activities has been a major focus of scientific research in recent decades. Most of these natural products have complex structural features that inhibit rapid industrial synthesis. Therefore, reports of structurally simple small molecule natural products (SMNPs)[1] with wide-spectrum biological activities and low toxicity are exceptionally rare in the literature. Honokiol, a biphenolic neolignan that is isolated from the stem bark of *Magnolia* species precisely meets these criteria and is known to exhibit a wide range of biological activities, including anticancer,[2] anti-inflammatory,[3] anti-viral,[4] and anxiolytic properties.[5] One recently discovered biological activity of honokiol has motivated a recent surge of biological studies of the compound.

Symptoms of Parkinson's disease (PD), which is a motor control disorder, include akinesia, tremor, and rigidity, which are largely attributable to a dopamine (DA) deficit in the putamen and caudate nucleus, which is caused by dysfunction and neurodegeneration of the dopaminergic neurons in the substantia nigra.[6,7] This neurodegenerative disorder is characterized by several abnormalities, including inflammation,[8–11] mitochondrial dysfunction,[12,13] iron accumulation and oxidative stress.[14–16] Considerable evidence suggests that cellular oxidative damage in PD might also be caused by nitric oxide (NO).[17,18] Indeed, both human and animal studies of PD reveal high levels of neuronal and inducible NO synthase (NOS) in the substantia nigra.[19,20]

The compounds honokiol and magnolol significantly decrease Amyloid β peptide (Aβ)-induced cell death.[21] Their neuroprotective effects may involve reductions in reactive oxygen species (ROS) production, intracellular calcium and caspase-3 activity. The synthetic neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) causes a Parkinsonian syndrome in humans and animals. Formation of ROS (e.g., superoxide or hydroxyl radicals)[22] induced by its active metabolite, 1-methyl-4-phenyl pyridinium (MPP^+), suggests that oxidative stress underlies MPTP neurotoxicity. An MPTP-based animal model can therefore reveal compounds that mitigate ROS effects and have potential use as neuroprotective agents for treating PD.[23] This study explores the neuroprotective activity of honokiol and its analogues against oxidative stress forced by CHP/TBTH and MPP^+-induced neuroblastoma cell death.

Few approaches[5c,24] for synthesizing honokiol **1** have been documented, and a simple high-yield strategy is still needed. This study therefore developed a general method for synthesizing honokiol **1** and several of its analogues for use in biological screening.

Retrosynthesis of **1** and its analogues reveals that the biphenolic core is easily formed by Suzuki–Miyaura cross coupling between the respective bromo aromatic compounds and aryl boronates or boronic acids (Scheme 1). Hence, if the flexibility of the substituents of bromo aromatic compounds is maintained, coupling of the same boronate **4** would enable synthesis of numerous analogues that are structurally similar to honokiol **1** and would reveal whether interacting functional groups exhibit typical biological activities.

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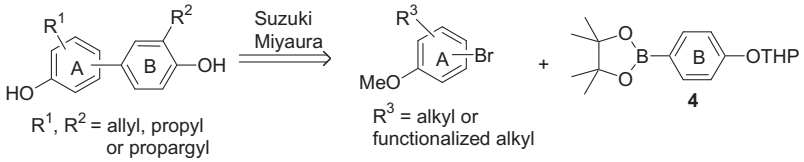


Scheme 1. Retrosynthesis of honokiol and its analogues.

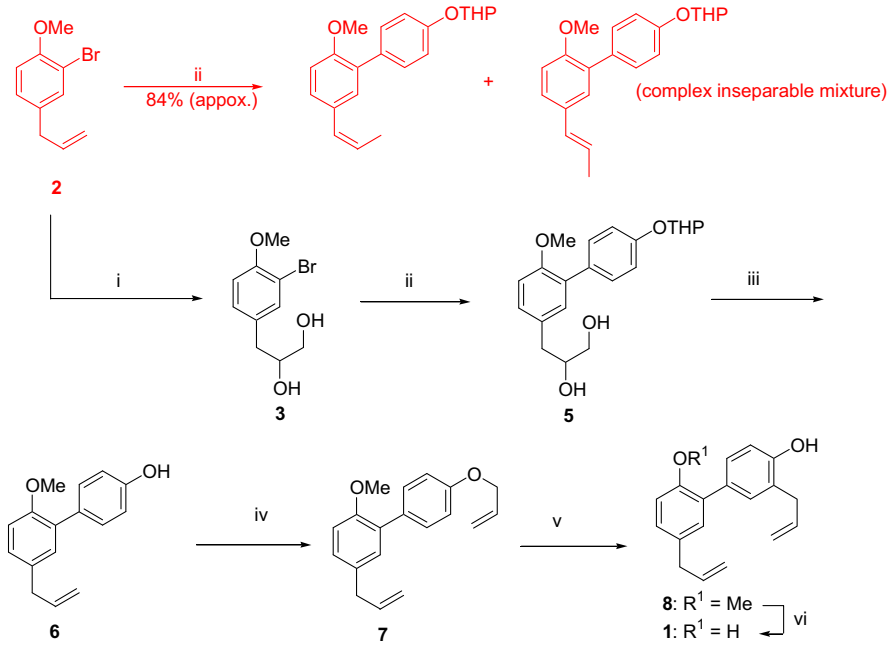
Commercially available 4-allylanisole **9** was used to synthesize the known 2-bromo-4-allyl anisole **2**[25] in a two-step process with 70% isolated yield. In accordance with procedures reported in the literature,[26b] the other coupling component, pinacol boronate **4**, was easily obtained with an excellent yield from the corresponding known boronic acid.[26a] In this study, the first attempt at cross coupling of **2** with **4** in the presence of the Pd(II) catalyst under Suzuki–Miyaura conditions failed to yield the desired product. Instead, a mixture of *cis* and *trans* isomers was obtained, presumably via isomerization of the double bond of the allyl substituent of the coupled product (Scheme 2). This process required the temporary functionalization of the terminal double bond before the coupling reaction to prevent isomeratization resulting from its interaction with the Pd(II) catalyst. Fortunately, the Suzuki–Miyaura cross coupling of dihydroxylated bromo compound **3** with **4** under the same reaction conditions efficiently produced **5** in a nearly quantitative yield. The terminal double bond was smoothly regenerated by an iodide-induced demesylation–iodination–deiodination sequence in the presence of Zn in DMF at an elevated temperature on the crude dimesylated derivative of **5**, which eventually produced the phenol **6** with associated THP deprotection in situ.

The *ortho* allylic substituent was successfully incorporated by the quantitative Et_2AlCl-catalyzed Claisen rearrangement[27] of the allylic ether **7** in hexanes at room temperature. The final demethylation step by BBr_3 was optimized by performing the reaction at various temperatures with various equivalents of BBr_3 because prolonged exposure of the BBr_3 to substrate produced inseparable impurities that adversely affected the final yield. The reaction finished within 25 min with 90% yield at room temperature and with 2.5 equiv of BBr_3. Therefore, honokiol **1** was synthesized (Scheme 2) at a sufficiently high overall yield (45%) for industrial synthesis. Although Lewis and co-workers[24c] reported a similar approach for synthesizing **1**, the method described here is superior in terms of the simplicity and efficiency of the intermediate synthetic steps, which are essential for large-scale production of this synthetic product.

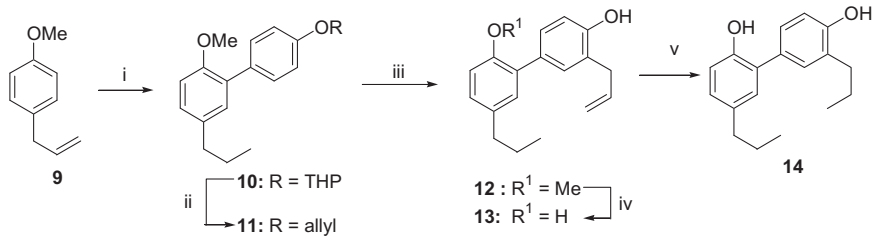
Honokiol analogues were synthesized using the same method. However, the position and functionality of the substituents of the two aromatic rings were varied in order to determine an appropriate screening for biological activity. The two strategies were (i) using the same biphenolic framework reported in **1** but synthetically modifying the allyllic substituents and (ii) varying the position of the aromatic coupling with flexibile positioning and judicious synthetic modification of the substituents. Although the hydrogenated derivatives **13**, **14** and **19**[5c,24b] were also obtainable by hydrogenation of **1**, their exclusive synthetic has not been reported in the literature.

Hydrogenation of **9** followed by bromination yielded the desired chromatographically unstable bromo compound, which was subjected to Suzuki–Miyaura cross coupling with **4** to furnish **10**. Then the compound **10** was ultimately converted to the partially- and fully-hydrogenated analogues **13** and **14** in high yield following the simple reaction sequence of THP deprotection, allylation, rearrangement and demethylation by BBr_3 (Scheme 3).

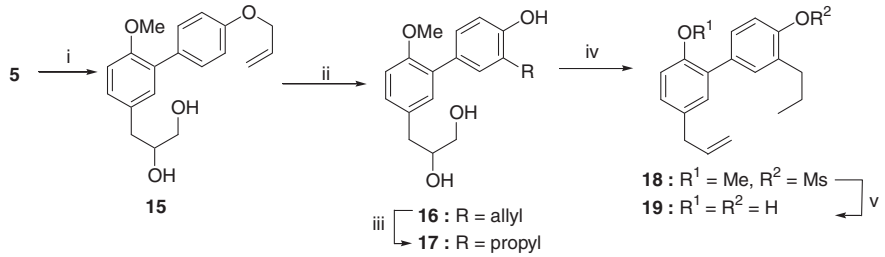
The other partially-hydrogenated analogue **19**, an allyl group, was generated at a later stage from its diol precursor **17**, by the same method used to generate the parent compound (Scheme 4). The greater acidity of phenol compared to alcohol was exploited



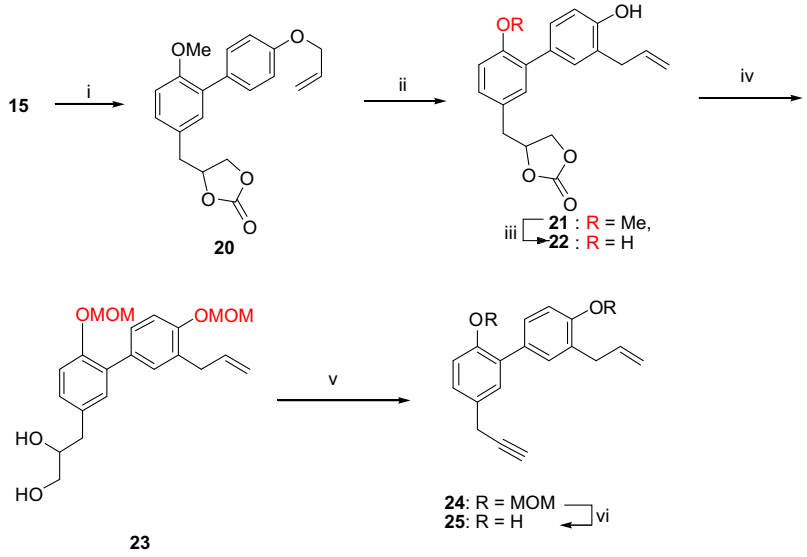
Scheme 2. Synthesis of compound **1**. Reagents and conditions: (i) OsO_4, 91%; (ii) Compound **4**, $PdCl_2$(dppf), DME, Na_2CO_3, 99%; (iii) (a) MsCl, TEA; (b) Zn, NaI, 85%; (iv) allyl bromide, K_2CO_3, acetone; (v) Et_2AlCl, 100%; (vi) BBr_3, 90%.



Scheme 3. Synthesis of compounds **13** and **14**. Reagents and conditions: (i) (a) H_2, Pd/C, MeOH; (b) Br_2, AcOH; (c) **4**, $PdCl_2$(dppf), 65%; (ii) (a) PTSA, MeOH; (b) allyl bromide, K_2CO_3, acetone; (iii) Et_2AlCl, 99%; (iv) BBr_3, 88%; (v) H_2, Pd/C, MeOH, 99%.



Scheme 4. Synthesis of compound **19**. Reagents and conditions: (i) (a) PTSA; (b) allyl bromide, 89%; (ii) Et_2AlCl, 98%; (iii) H_2, Pd/C, MeOH, 100%; (iv) (a) MsCl, TEA; (b) NaI, DMF, Zn, 85%; (v) (a) BBr_3; (b) NaOH, 87%.

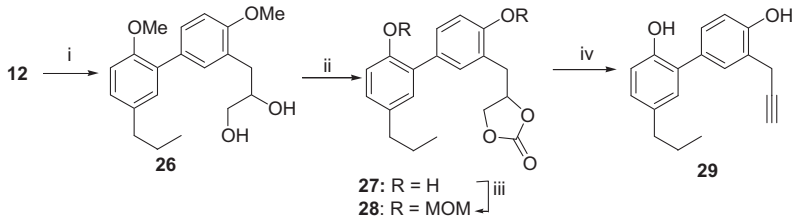


Scheme 5. Synthesis of compound **25**. Reagents and conditions: (i) $COCl_2$, 99%; (ii) Et_2AlCl, 98%; (iii) BBr_3, 96%; (iv) (a) MOMBr; (b) NaOH, 83%; (v) (a) $NaIO_4$; (b) CBr_4, PPh_3; (c) *t*-BuLi, 67%; (vi) HCl, 92%.

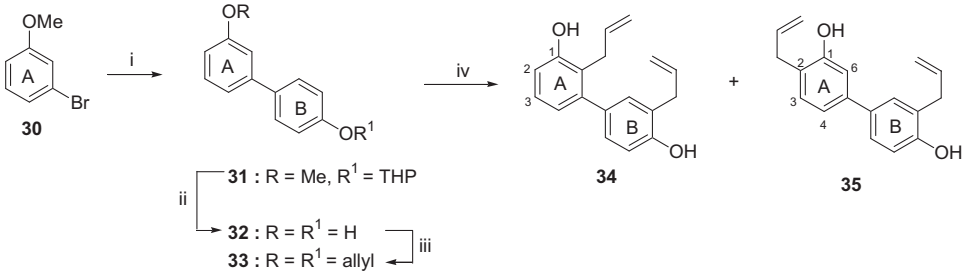
to obtain the allyl ether **15** with excellent yield and chemoselectivity; after rearrangement and hydrogenation, the desired propyl group was installed at the *ortho* position of **15**. The allyl group was then regenerated as before, and the subsequent removal of phenolic protections gave **19** in a satisfactory overall yield.

The versatility of intermediate **15** was confirmed by the finding that its vicinal diol moiety could be transformed into a terminal alkyne through oxidative cleavage with periodate and application of Corey–Fuchs protocol[28] to the resultant aldehyde. This strategy again failed at the BBr_3 demethylation stage, which obtained a mixture of unidentifiable products, possibly because of the bromination[29] of the terminal alkyne by BBr_3. Other demethylation methods such as those using TMSI,[30] $AlBr_3$-EtSH[31] and LiI[32] in collidine and others were also attempted but resulted in either a mixture of products or the complete recovery of starting material. Finally, **15** was protected as a cyclic carbonate **20**, which was converted to two phenolic hydroxyl groups by Claisen rearrangement and demethylation by BBr_3. The phenolic hydroxyl groups of **22** were further protected as their MOM ethers (**23**), which were implemented by Corey–Fuchs protocol to produce a terminal alkyne **24** in excellent yield. Final acid treatment to remove MOM protection successfully produced the desired analogue **25** (Scheme 5).

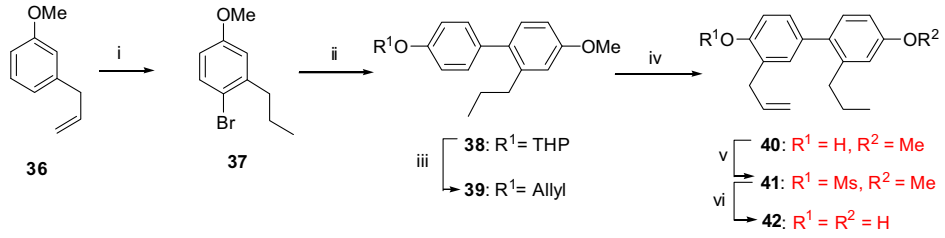
The intermediate **12** was used as the starting material for the synthesis of the other alkyne analogue, **29**. The **12** was converted to diol **26** in excellent yield by successive methylation and dihydroxylation with OsO_4. To avoid further complications in the final demethylation stage, the methyl ethers were cleaved after the diol



Scheme 6. Synthesis of compound **29**. Reagents and conditions: (i) (a) MeI; (b) OsO_4, 89%; (ii) (a) $COCl_2$; (b) BBr_3, 86%; (iii) MOMBr, 90%; (iv) (a) NaOH, (b) $NaIO_4$, (c) CBr_4, PPh_3; (d) *t*-BuLi, (e) HCl, 56%.



Scheme 7. Synthesis of compounds **34** and **35**. Reagents and conditions: (i) **4**, $PdCl_2$(dppf), DME, Na_2CO_3, 80%; (ii) (a) PTSA; (b) BBr_3, 90%; (iii) allyl bromide, 87%; (iv) Et_2AlCl.



Scheme 8. Synthesis of compound **42**. Reagents and conditions: (i) (a) H_2, Pd/C, MeOH; (b) NBS; (ii) **4**, $PdCl_2$(dppf), DME, 89%; (iii) (a) PTSA; (b) allyl bromide, 94%; (iv) Et_2AlCl, 96%; (v) MsCl, TEA, 95%; (vi) (a) BBr_3; (b) NaOH, 80%.

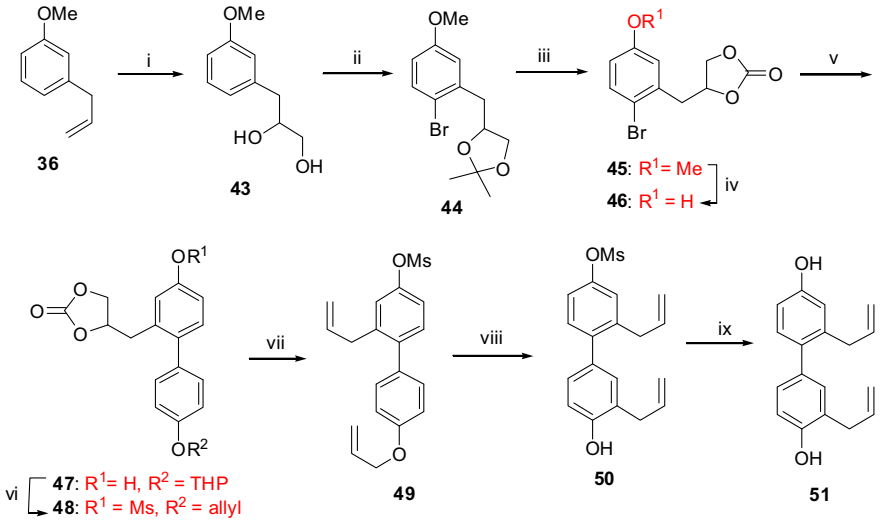
26 had been protected by formation of its carbonate derivative, and the target alkyne analogue **29** was produced following the same reactions used to generate **25** (Scheme 6).

The next set of analogues was prepared by changing the Suzuki coupling, and the precursor bromo compounds were selected accordingly. Therefore, the synthesis of analogues **34** and **35** began with commercially available 3-bromo anisole **30** as the Suzuki coupling precursor (Scheme 7). The Suzuki coupling product **31** was fully deprotected to bisphenol **32**, which, on allylation and Claisen rearrangement, produced two chromatographically-separable isomers in a 3:2 ratio and with allylic moieties in different positions in the aromatic ring A. The structure of the two regioisomers was fully elucidated by their respective ^{1}H NMR spectra. The appearance of a clear singlet peak at 7.01 ppm was attributed to the aromatic proton H-6 located between the phenolic hydroxyl group and the aryl substituent. Although the structure was identical to that of **35**, the signal from the H-3 proton of compound **34** in ring A appeared as a triplet owing to coupling with the two adjacent *ortho* protons, which was indeed observed from its ^{1}H NMR.

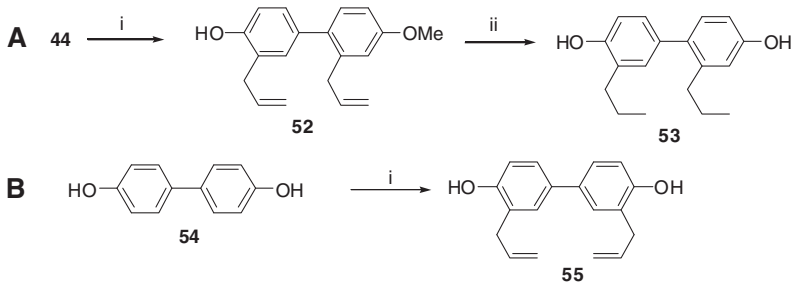
The Suzuki coupling precursors for the remaining analogues with 4,4′-biphenolic cores (**42**, **51**, and **53**), were synthesized as described in the literature. Thus, bromo compound **37**,[33] obtained in two steps from known 3-allyl anisole **36**[34] by sequential hydrogenation and bromination was subjected to Suzuki–Miyaura cross coupling with **4** to furnish **38**, which was ultimately converted to the partially-hydrogenated analogue **42** in good yield following the simple reaction sequence, THP deprotection, allylation, rearrangement and demethylation by BBr_3 (Scheme 8).

The bromo compound **44** was prepared in three steps from **36**[34] in excellent overall yield. The steps were sequential dihydroxylation, acetonide protection and regioselective bromination by NBS. Removal of acetonide followed by Suzuki coupling gave the desired biphenolic core in the analogue **51**. Similar synthetic processes smoothly produced the diallyl compound **52**. We attempted to cleave the methyl ether of **52** by BBr_3 or by other established methods to obtain **51**, but we did not succeed. Involvement of allyl groups in the BBr_3 reaction by initiating side reactions was suspected. After its diol functionality was protected by forming its cyclic carbonate derivative **45** as described above, Suzuki coupling performed at a reduced temperature with a shortened reaction time produced the coupled product **47** in 70% yield. Thereafter, the precursor bromo compound was demethylated. Under prolonged exposure to the basic Suzuki conditions at high temperatures, concomitant deprotection of cyclic carbonate reduced overall yield. The remaining steps in synthesizing **51** resulted in high yield and are elucidated in Scheme 9. The study hypothesis was further supported by evidence that totally hydrogenated derivative of **52** underwent smooth demethylation by BBr_3, which produced analogue **53** in excellent yield (Scheme 10, A). Analogue **55** was synthesized from commercially available bisphenol **54** using established procedures[4] (Scheme 10, B).

Since phenolic compounds are known to exert cytoprotective effects, the aim of this study was to investigate whether the new synthetic biphenolic neolignans are neuroprotective. For this purpose, two in vitro models of neuronal death were performed: (1) the SH-SY5Y human neuroblastoma cells exposed to cumene



Scheme 9. Synthesis of compounds **51**. Reagents and conditions: (i) OsO_4, 91%; (ii) (a) acetone, PTSA; (b) NBS, 86%; (iii) (a) PTSA; (b) $COCl_2$, 88%; (iv) BBr_3, 94%; (v) **4**, $PdCl_2$(dppf), DME, 70%; (vi) (a) MsCl, TEA; (b) PTSA, (c) allyl bromide, 79%; (vii) (a) NaOH, (b) MsCl, TEA; (c) Zn, NaI, 76%; (viii) Et_2AlCl, 97%; (ix) NaOH, 90%.



Scheme 10. Synthesis of compounds **53** and **55**. Reagents and conditions: (A) (i) (a) HCl; (b) **4**, $PdCl_2$(dppf), DME, Na_2CO_3; (c) MsCl, TEA; (d) Zn, NaI; (e) allyl bromide, acetone; (f) Et_2AlCl, 62%; (ii) (a) H_2, MeOH; (b) BBr_3, 92%. (B) (i) (a) allyl bromide, K_2CO_3; (b) BCl_3, CH_2Cl_2.

hydroperoxide (CHP) and *tert*-butyl hydroperoxide (TBHP), for oxidative stress; and (2) the SH-SY5Y human neuroblastoma cells treated with 1-methyl-4-phenylpyridium (MPP^+), for neurotoxicity. Cell death was evaluated by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. CHP and TBHP are the lipophilic form of hydrogen peroxide that approaches to the plasma membrane causing oxidative stress and lipid peroxidation, participating in cellular damage or death.[35–37] Three hours neuroblastoma cell exposure to CHP and TBHP at 300 μM, cell viability was reduced to 64% and 72%, respectively, compared with control (Fig. 1). Administration of seven synthesized neolignans, including honokiol (**1**), **13**, **14**, **19**, **25**, **34** and **55** at 10 μM to SH-SY5Y cells 30 min prior to the commencement of CHP and TBHP exposure for 3 h significantly prevented cell death (Fig. 1). Our results showed that these honokiol derivatives have different potencies and efficacies to prevent neuronal cell death provoked by oxidative stress.

Parkinsonian toxins are known to be particularly toxic to dopaminergic neuronal cells. The exposure of SH-SY5Y neuroblastoma cells to MPP^+ (1 mM) for 24 h reduced cell viability and resulted in cytotoxicity.[38] The following experimental model of neuroprotection was challenged by seven synthesized neolignans, including honokiol (**1**), **13**, **14**, **19**, **25**, **34** and **55** at concentrations of 10 and 30 μM. The cells were treated by MPP^+ at the same time as neolignans (10–30 μM) for 24 h. As Figure 2 shows, the neolignans moderated the cytotoxicity of MPP^+ in the culture cells in a concentration-dependent manner.[39] The rates of cell survival in medium that containing 30 μM neolignan **14**, **19**, **13**, **34** or **25** and 1 mM MPP^+ were 91%, 87%, 83%, 79% and 80%, respectively. These

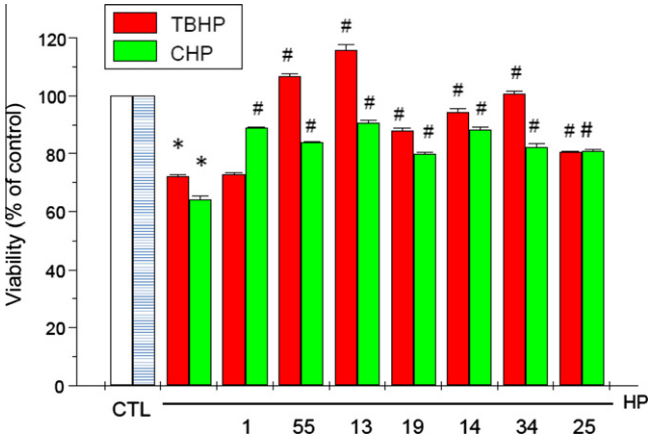


Figure 1. Effects of neolignans on cell viability exposed to oxidative stress in vitro. SH-SY5Y cells were treated with honokiol analogues at 10 μM, including honokiol (**1**), **13**, **14**, **19**, **25**, **34**, and **55**, 30 min before exposure to CHP and TBHP (300 μM) for 3 h. Cell viability was assessed by MTT assay. Results are expressed as mean ± SEM ($n = 3$). Cell viability in control cultures was treated as 100%. *P* values were calculated using ANOVA. *Indicates a significant difference from the control group, $^*p < 0.05$. $^\#p < 0.05$ versus CHP or TBHP alone treated cell groups.

neolignans had two hydroxyl groups in the 2- and 4′-positions, and the allyl or propyl groups were in the 5- and 3′-positions (Fig. 3). Allyl groups were at the 5- and the 3′-positions of honokiol (**1**) whereas propyl groups were at these positions in neolignans **14**. In neolignan **19**, the allyl group was at the 5-position, and

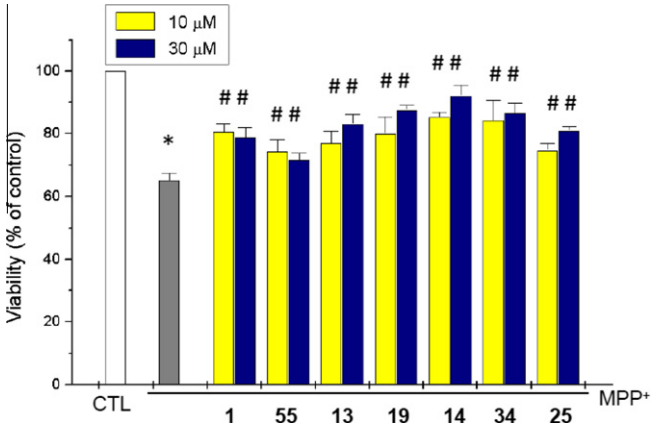


Figure 2. Effects of neolignans on MPP^+-induced SH-SY-5Y cell death. Cell viability was assessed by MTT assay in SH-SY-5Y neuroblastoma cells exposed to neurotoxin MPP^+ (1 mM) for 24 h. Cultured cells were also exposed to MPP^+ (1 mM) with or without neolignans (10–30 μM) for 24 h to test the neuroprotective efficiency of neolignans including honokiol (**1**), **13**, **14**, **19**, **25**, **34**, and **55**. The data represent the percent of cell viability compared to control (CTL, no MPP^+ exposure). Results are expressed as mean ± SEM ($n = 4$). *P* values were calculated using ANOVA. *Indicates a significant difference from the control group, $^*p < 0.05$. $^\#p < 0.05$ versus MPP^+ alone treated cell groups.

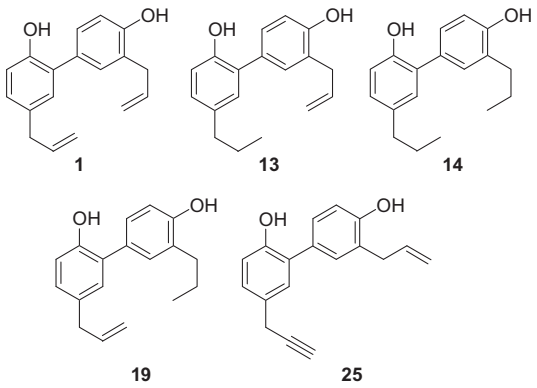


Figure 3. The structures of compounds **1**, **13**, **14**, **19** and **25**.

the propyl group was at the 3′-position whereas, in neolignan **13**, the propyl group was in the 5-position and the allyl group was in the 3′-position. In neolignan **25**, the propagyl group was at the 5-position, and the allyl group was at the 3′-position. The similar cell survival in neolignans **1** and **25** implied that the double bonds did not have a π–π-interaction with the biomolecular target. Thus, the data is indicative of the fact that honokiol and its analogues may confer a neuroprotective effect against MPP^+-induced neuroblastoma cell death even though a more rigorous study in this direction is needed.

In conclusion, this study developed a simple, practical and inexpensive gram-scale synthesis of honokiol. Judicious application of the general approach successfully synthesized analogues structurally similar to honokiol, several of which are showed a hint of neuropreventive activity against Perkinsonian toxins. A more detailed study of this effect is currently underway.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2011.11.030.

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