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First Total Synthesis of (±)-Latifolin and Its Antioxidant Mechanism

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The first total synthesis of (±)-latifolin has been accomplished in six steps and 47.8% overall yield. To understand the relative importance of phenolic O—H and benzhydryl C—H hydrogen on the antioxidant activity of latifolin, 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assay and density functional theory (DFT) studies were carried out. On scavenging DPPH radical in ethanol, the activity of latifolin (**1**) bearing phenolic hydrogen is remarkably higher than analogue **10** bearing no phenolic hydrogen. Therefore, Phenolic hydrogen is responsible for latifolin's antioxidant activity rather than benzhydryl C—H hydrogen. Furthermore, the 5-OH BDE is lower than 2'-OH and 7-CH BDEs by a DFT calculation, respectively. Based on theoretical results it is definitely concluded that the phenolic 5-OH plays a major role in the antioxidant activity of latifolin.

Keywords total synthesis, latifolin, antioxidant, DPPH-scavenging, density functional theory

Introduction

Latifolin (**1**), a naturally occurring phenolic compound, was first isolated from the heartwood of *Dalbergia latifolia* in 1962.[1] It has been reported to deliver a variety of biological and pharmacological activities, including inhibition of *β*-amyloid production,[2] antifungal,[3,4] anticarcinogenic[5] and antioxidant activity.[6] It is obvious that benzhydryl C—H bond (Figure 1, highlighted in **1**) on latifolin is very weak due to delocalization of the π electrons on the adjacent phenyl or alkenyl group. Thus, the free radical scavenging activity of latifolin can arise from the highly activated benzhydryl C—H hydrogen. On the other hand, latifolin also contains two phenolic hydrogens, which are usually responsible for antioxidant properties of plant phenolic compound.[7-9] Having a very similar antioxidant structure as curcumin, latifolin contains acidic protons in the benzhydryl carbon and phenolic group. Contradictory opinions have been proposed to explain the radical-attacking sites in curcumin. The main argument was whether the phenolic hydrogen or the central methylenic hydrogen in the heptadienone moiety is responsible for its antioxidant activity.[10-14] Focusing on kinetics and mechanisms of curcumin and its synthetic analogues, our previous work has showed that the phenolic group is responsible for its antioxidant activity.[15-18] In addition, although the synthesis of (±)-latifolin dimethyl ether has been reported by Kumari *et al.* from 1,2,4-trimethoxybenzene and *o*-methoxycinnamyl cation,[19] no total synthesis of latifolin has been reported. We have been interested in the synthesis of benzhydryl natural products, such as cassumunin C.[20] In order to study the relative importance of the phenolic O—H and the benzhydryl C—H hydrogen on the antioxidant activity of latifolin, we describe here the first total synthesis of (±)-latifolin.

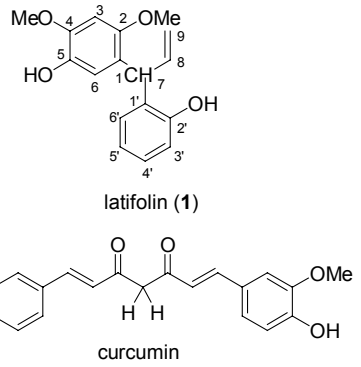

Figure 1 Structures of latifolin and curcumin.

Experimental

Oxygen- and moisture-sensitive reactions were carried out under an argon atmosphere. Solvents were purified and dried by standard methods prior to use. All commercially available reagents were used without fur-

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ther purification, unless otherwise noted. Column chromatography was carried out on silica gel (200－300 mesh). ^{1}H (400 MHz) and ^{13}C (100 MHz) spectra were recorded with TMS as an internal standard on a Bruker AV-400 MHZ instrument. The EIMS were recorded on a Trance 2000 DSQ mass spectrometer. The ESI-MS were recorded with an LCQ advantage mass spectrometer. High-resolution MS were recorded on a Thermo Scientific LTQ Orbitrap XL spectrometer. IR spectra were recorded on a Nicolet 5700 spectrometer. Melting points are uncorrected. 2,4-Dimethoxyphenol was prepared according to a literature procedure.[21] All calculations were performed with the Gaussian09 suites of programs.[22] The DFT calculations employed the B3LYP functional using the standard 6-31G(d,p) basis set.

Synthesis of 2-(methoxymethoxy)benzaldehyde (3)[23]

To a suspension of NaH (60% in oil, 1.58 g, 39.50 mmol) in dry THF (5.0 mL) was added dropwise a solution of 2-hydroxybenzaldehyde (4.00 g, 32.75 mmol) in DMF (4.5 mL) at 0 ℃. After stirring for 30 min, a solution of methoxymethyl chloride (3.00 mL, 39.50 mmol) in THF (10.0 mL) was added dropwise to the reaction mixture at 0 ℃. After stirring for 2 h, the reaction mixture was diluted with hexane. The organic phase was washed with NaOH (aq., 20%) and H_2O, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The crude material was purified by column chromatography on silica gel column [*V*(hexane)∶*V*(EtOAc)＝30∶1] to give **3** (5.03 g, 30.27 mmol) as a light yellow liquid, yield 92%. ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 10.49 (s, 1H) 7.83 (d, *J*= 7.7 Hz, 1H), 7.52 (t, *J*＝7.5 Hz, 1H), 7.19 (d, *J*＝8.4 Hz, 1H), 7.06 (t, *J*＝7.5 Hz, 1H), 5.29 (s, 2H), 3.51 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 189.8, 159.7, 135.9, 128.3, 125.4, 121.8, 115.0, 94.6, 56.5; MS (70 eV, EI) *m*/*z*: 166 (M^+, 79), 135 (54), 121(100).

Synthesis of 1-(2-(methoxymethoxy)phenyl)-3-(trimethylsilyl)prop-2-yn-1-ol (4)

To a solution of trimethylsilylacetylene (0.60 mL, 4.25 mmol) in dry THF (20.0 mL) was added dropwise *n*-BuLi (1.40 mL, 2.5 mol/L in hexane, 3.50 mmol) at −78 ℃. The reaction was stirred at this temperature for 20 min then r.t. for 1 h. After cooling to −78 ℃, aldehyde **3** (0.54 g, 3.25 mmol) was added dropwise to the mixture. The solution was allowed to warm to r.t. gradually and stirred for an additional hour before quenched with aqueous NH_4Cl. The mixture was extracted with EtOAc, and the organic phases were washed with water and brine, dried over anhydrous Na_2SO_4. The crude material was purified by column chromatography on silica gel column [*V*(hexane)∶*V*(EtOAc)＝15∶1] to give **4** (794 mg, 3.00 mmol) as a colorless liquid, yield 92%. ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.60 (dd, *J*＝7.6, 1.3 Hz, 1H), 7.33－7.25 (m, 1H), 7.12 (d, *J*＝8.2 Hz, 1H), 7.05 (t, *J*＝7.5 Hz, 1H), 5.73 (s, 1H), 5.24 (ABq, *J*＝6.7 Hz, 2H), 3.50 (s, 3H), 3.29 (br s, 1H), 0.21 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 154.4, 129.6, 129.5, 128.0, 122.1, 114.5, 105.1, 94.5, 90.3, 61.1, 56.2, −0.1. ESI-HRMS $[M+Na]^+$ calcd for $C_{14}H_{20}NaO_3Si$: 287.1079, found 287.1106.

Synthesis of 2,4-dimethoxy-5-(1-(2-(methoxymethoxy)phenyl)-3-(trimethylsilyl)prop-2-ynyl)phenol (6) and 5-(1-(2-hydroxyphenyl)-3-(trimethylsilyl)prop-2-ynyl)-2,4-dimethoxyphenol (7)

To a solution of compound **4** (187 mg, 0.71 mmol) and **5** (111 mg, 0.72 mmol) in dry acetonitrile (4.0 mL) was added iodine (11 mg, 0.04 mmol) at −10 ℃. The reaction was allowed to warm to r.t. and stirred for 0.5 h. The mixture was diluted with EtOAc. The organic phase was washed with saturated $Na_2S_2O_3$, water and brine, dried over anhydrous Na_2SO_4. The crude material was purified by column chromatography on silica gel column [*V*(hexane)∶*V*(EtOAc)＝4∶1] to give **6** (199 mg, 0.50 mmol, yield 70%) as a white solid and **7** (24 mg, 0.07 mmol, yield 10%) as a yellow oil.

Compound 6 m.p. 136－138 ℃ after crystallization from hexane and EtOAc; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.41 (d, *J*＝7.6 Hz, 1H), 7.18 (t, *J*＝8.4 Hz, 1H), 7.03 (d, *J*＝8.2 Hz, 1H), 7.01 (s, 1H), 6.97 (t, *J*＝7.5 Hz, 1H), 6.47 (s, 1H), 5.70 (s, 1H), 5.34 (br s, 1H), 5.15 (ABq, *J*＝6.7 Hz, 2H), 3.84 (s, 3H), 3.73 (s, 3H), 3.39 (s, 3H), 0.17 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 154.1, 150.2, 145.7, 139.4, 130.5, 129.1, 127.8, 122.5, 121.7, 115.4, 114.2, 107.5, 97.5, 94.2, 86.4, 57.1, 56.1, 55.8, 31.3, 0.2; IR (neat film) *v*: 3574, 2956, 2172, 1515, 1207, 1152, 1099, 1035, 995, 843, 748 cm^{-1}. ESI-HRMS $[M+Na]^+$ calcd for $C_{22}H_{28}NaO_5Si$: 423.1604, found 423.1617.

Compound 7 ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.55 (dd, *J*＝7.7, 1.5 Hz, 1H), 7.15 (s, 1H), 7.11 (td, *J*＝7.9, 1.6 Hz, 1H), 6.99 (br s, 1H), 6.90 (td, *J*＝7.6, 1.1 Hz, 1H), 6.83 (dd, *J*＝8.0, 1.1 Hz, 1H), 6.46 (s, 1H), 5.46 (s, 1H), 5.31 (br s, 1H), 3.90 (s, 3H), 3.84 (s, 3H), 0.21 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 153.4, 148.0, 146.1, 140.6, 128.5, 128.3, 127.2, 121.5, 120.8, 116.9, 114.9, 106.3, 96.7, 88.4, 57.1, 56.2, 31.2, 0; IR (neat film) *v*: 3578, 3490, 2958, 2167, 1514, 1455, 1200, 1030, 846, 750 cm^{-1}; ESI-HRMS $[M+Na]^+$ calcd for $C_{20}H_{24}NaO_4Si$: 379.1342, found 379.1342.

Synthesis of compound 7 from 6

To a solution of compound **6** (92 mg, 0.23 mmol) in MeOH (25.0 mL) was added 4 mol/L HCl (5.0 mL) at r.t. The mixture was stirred at 50 ℃ for 12 h. After removal of most of the solvent, the crude product was extracted with EtOAc. The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4. The crude material was purified by column chromatography over a silica gel column [*V*(hexane)∶*V*(EtOAc)＝4∶1] to give **7** (77 mg, 0.21 mmol) as a yellow oil, yield 91%.

Synthesis of 5-(1-(2-hydroxyphenyl)prop-2-ynyl)-2,4-dimethoxyphenol (8)

To a solution of compound **7** (66 mg, 0.19 mmol) in THF (2.0 mL) was added TBAF in THF (0.24 mL, 1 mol/L, 0.20 mmol) at 0 ℃. After stirring for 30 min, the reaction mixture was quenched with 10% HCl (0.54 mL), extracted with EtOAc, washed with water and brine, dried over anhydrous Na_2SO_4. The crude material was purified by column chromatography over a silica gel column [*V*(hexane)∶*V*(EtOAc)=2∶1] to give **8** (50 mg, 0.18 mmol) as a yellow oil, yield 94%. ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.62 (dd, *J*=7.7, 1.6 Hz, 1H), 7.16 (s, 1H), 7.12 (td, *J*=7.8, 1.7 Hz, 1H), 6.92 (td, *J*=7.6, 1.1 Hz, 1H), 6.83 (dd, *J*=8.0, 1.1 Hz, 1H), 6.46 (s, 1H), 5.48 (d, *J*=2.6 Hz, 1H), 3.90 (s, 3H), 3.83 (s, 3H), 2.43 (d, *J*=2.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 153.1, 147.9, 146.2, 140.6, 128.5, 128.4, 127.0, 121.1, 120.9, 116.9, 114.8, 96.6, 84.3, 71.9, 57.2, 56.2, 29.9; IR (neat film) *v*: 3396, 3287, 2937, 2482, 1600, 1505, 1456, 1200, 1030, 878, 756 cm^{-1}. ESI-HRMS $[M+Na]^+$ calcd for $C_{17}H_{16}NaO_4$: 307.0946, found 307.0947.

Synthesis of latifolin

To a solution of alkyne **8** (50 mg, 0.18 mmol) in EtOAc (2.0 mL) was added quinoline (6 mg, 46.45 μmol) and 5% palladium on barium sulfate (6 mg, 2.82 μmol). The mixture was hydrogenated at r.t. and atmospheric pressure for 12 h. The mixture was filtered through celite, concentrated, and purified by column chromatography over a silica gel column [*V*(hexane)∶*V*(EtOAc)=2∶1] to give latifolin (47 mg, 0.17 mmol) as a light brown oil, yield 94%. ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.18 (d, *J*=7.6 Hz, 1H), 7.11 (t, *J*=7.6 Hz, 1H), 6.92−6.80 (m, 2H), 6.76 (s, 1H), 6.52 (s, 1H), 6.33 (ddd, *J*=16.9, 10.2, 5.8 Hz, 1H), 6.02 (br s, 1H), 5.27 (d, *J*=10.2 Hz, 1H), 5.23 (br s, 1H), 5.19 (d, *J*=5.8 Hz, 1H), 5.05 (dd, *J*=17.1, 1.1 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 153.7, 149.5, 145.5, 140.1, 139.0, 129.4, 128.5, 127.7, 122.6, 120.6, 116.7, 116.3, 115.2, 97.1, 57.2, 56.2, 40.1; IR (neat film) *v*: 3432, 2859, 2172, 1602, 1489, 1457, 1251, 1154, 1040, 843, 758 cm^{-1}. ESI-HRMS $[M+Na]^+$ calcd for $C_{17}H_{18}NaO_4$: 309.1103, found 309.1112.

Synthesis of dihydrolatifolin (9)

To a mixture of compound **8** (30 mg, 0.11 mmol) in EtOAc (1.0 mL) was added Pd/C (20% *w*/*w*, 30 mg, 0.06 mmol). The mixture was hydrogenated at r.t. and atmospheric pressure for 12 h. The mixture was filtered through celite, concentrated, and purified by column chromatography over a silica gel column [*V*(hexane)∶*V*(EtOAc)=2∶1] to give **9** (29 mg, 0.10 mmol) as a light brown oil, yield 91%. ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.28 (dd, *J*=7.7, 1.3 Hz, 1H), 7.06 (td, *J*=7.6, 1.5 Hz, 1H), 6.88 (dd, *J*=7.6, 0.8 Hz, 1H), 6.87 (s, 1H), 6.83 (dd, *J*=7.9, 0.8 Hz, 1H), 6.82 (s, 1H), 6.48 (s, 1H), 5.26 (s, 1H), 4.26 (t, *J*=7.7 Hz, 1H), 3.91 (s, 3H), 3.84 (s, 3H), 2.05−2.12 (m, 2H), 0.88 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 154.1, 148.9, 145.0, 140.6, 130.6, 127.2, 126.2, 124.8, 120.6, 116.3, 113.2, 96.7, 57.2, 56.1, 36.2, 26.8, 12.6. ESI-HRMS $[M+Na]^+$ calcd for $C_{17}H_{20}NaO_4$: 311.1259, found 311.1263.

Synthesis of 3,3-diphenylpropene (10)

To a mixture of *t*-BuOK (0.62 g, 5.50 mmol) and methyltriphenyl phosphonium bromide (1.79 g, 5.00 mmol) was added dry THF (20.0 mL) at 0 ℃. The reaction mixture was stirred for 2 h at r.t. After cooling to 0 ℃, a solution of 2,2-diphenylacetaldehyde (0.98 mL, 5.00 mmol) was added to the reaction mixture slowly and the mixture was stirred for 24 h at r.t. The mixture was diluted with EtOAc and filtered. The filtrate was washed with water and brine, dried over anhydrous Na_2SO_4. The crude material was purified by column chromatography over a silica gel column [*V*(hexane)∶*V*(EtOAc)=50∶1] to give **10** (738 mg, 3.80 mmol) as a colorless liquid, yield 76%. ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.42−7.38 (m, 4H), 7.33−7.30 (m, 6H), 6.42 (ddd, *J*=17.1, 10.0, 7.2 Hz, 1H), 5.32 (d, *J*=9.3, 1H), 5.11 (dd, *J*=17.1, 1.2 Hz, 1H), 4.85 (d, *J*=6.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 143.4, 140.7, 128.7, 128.5, 126.5, 116.5, 55.1; MS (70 eV, EI) *m*/*z* (%): 194 (M^+, 100), 179 (44), 165 (40), 115 (71).

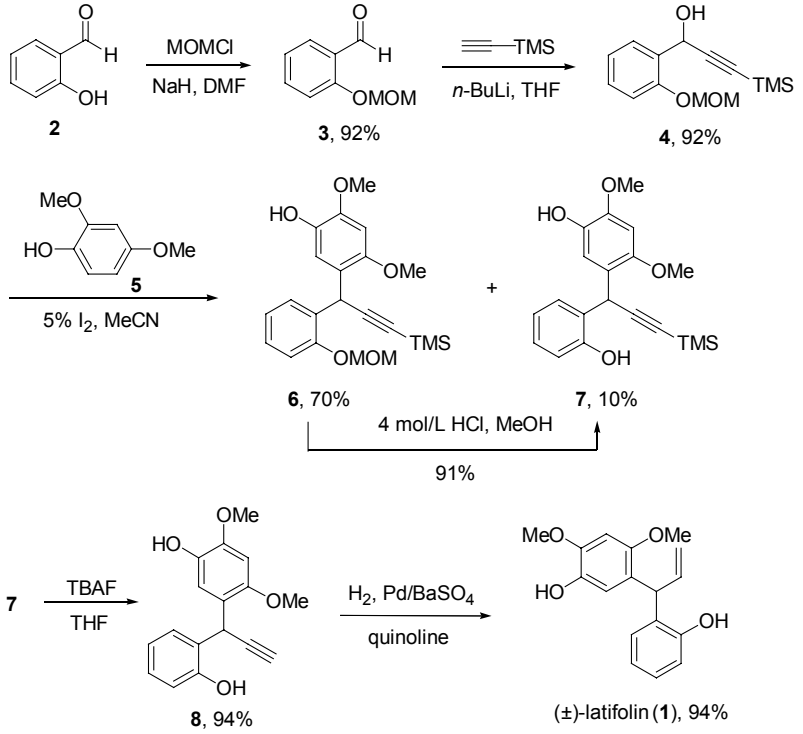
DPPH assay

The DPPH-scavenging assay[16] was carried out by monitoring the absorbance of an ethanolic solution of DPPH (100 μmol/L) at 517 nm at r.t. in the presence and absence of latifolin and its analogues. $IC_{0.20}$ represents the concentration of the test compound at which absorbance decreased by 0.20 of a unit during a 30-min observation and was taken as the free radical scavenging potency.

Results and Discussion

Our synthesis of latifolin is outlined in Scheme 1. 2-Hydroxybenzaldehyde (**2**) was protected with a methoxymethyl group under basic condition to give **3** (92%). Treatment of trimethylsilylacetylene with *n*-butyllithium followed by addition of **3** afforded the expected propargyl alcohol **4** (92%). Aromatic propargylation[20,24] of **4** with 2,4-dimethoxyphenol **5** using iodine as the catalyst in acetonitrile for 30 min gave alkyne **6** (70%) and deprotecting compound **7** (10%). Compounds **6** and **7** were easily separated using silica gel column chromatography, and **6** can be further converted into **7** (91%) in the presence of a concentrated HCl solution in methanol. The structure of **6** was unambiguously confirmed by X-ray crystallographic analysis (Figure 2). With key intermediate **7** in hand, removal of the TMS group with tetrabutylammonium fluoride (TBAF) gave **8** (94%). Catalytic hydrogenation in the presence of $Pd/BaSO_4$ and quinoline afforded (±)-latifolin (**1**) (94%). The ^{1}H and ^{13}C NMR spectra were in good agreement with the reported data of

Scheme 1 Synthesis of (±)-latifolin



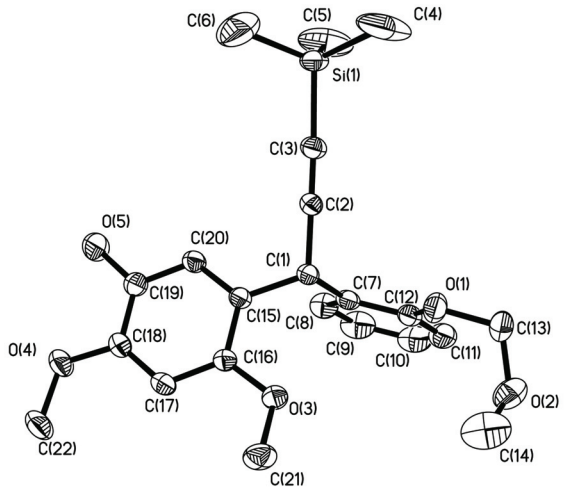
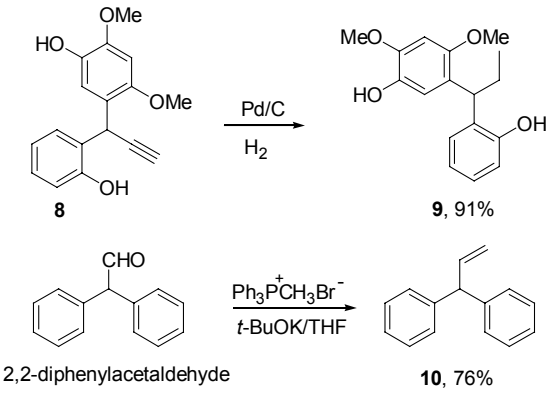


Figure 2 ORTEP view of the crystal structure of **6**.

Scheme 2 Synthesis of analogues **9** and **10**



natural latifolin.[4]

Analogues **9** and **10** were also synthesized to study the antioxidant mechanism of latifolin. As shown in Scheme 2, Pd/C-catalyzed hydrogenation of **8** gave the dihydrolatifolin (**9**) (91%). The synthesis of 3,3-diphenylpropene **10** from 2,2-diphenylacetaldehyde was reported in low yield (33%—46%) using *n*-butyllithium as a base.[25,26] We modified the Wittig reaction using potassium *tert*-butoxide as a base to afford **10** in a satisfied yield (76%).

Antioxidant mechanism

Herein, we investigated the antioxidant effect of latifolin (**1**) and analogues **9**, **10** on the DPPH-scavenging assay. The capacity of antioxidant to scavenge the DPPH radical, can be expressed as its magnitude of antioxidation ability.[27,28] Table 1 showed the scavenging activities of the tested compounds expressed as $IC_{0.2}$ value. Compared with vitamin C that has an $IC_{0.2}$ value of 9.53 μmol/L, latifolin and analogue **9** were considered as strong DPPH-scavengers with $IC_{0.2}$ value of 8.19 μmol/L and 8.63 μmol/L, respectively. While the activity of **10** which bears no phenolic hydrogen was negligible (~6200 times less than latifolin). In our previous work, the antioxidant effects of curcumin and synthetic analogues were studied in micelles, human low density lipoprotein (LDL), human red blood cell (RBC) and rat liver mitochondria.[15-18] We found that the antioxidative activities of analogues which bear no phenolic group are also inactive. Therefore, phenolic hydrogen is responsible for latifolin's antioxidant activity, which agrees well

CHINESE JOURNAL OF CHEMISTRY

with the conclusion from our previous work on the radical-scavenging mechanism of curcumin.[15-18] In addition, there was no significant difference between latifolin and analogue **9** in the DPPH-scavenging activities, suggesting that the teminal double bond has limited influence on antioxidant activity of latifolin.

Table 1 DPPH-scavenging activities of latifolin and its analogues[a]

Compound	$IC_{0.20}$/(μmol•L^{-1})
Latifolin (**1**)	8.19±0.16
9	8.63±0.25
10	(5.14±0.11)×10^4
Vc	9.53±0.19

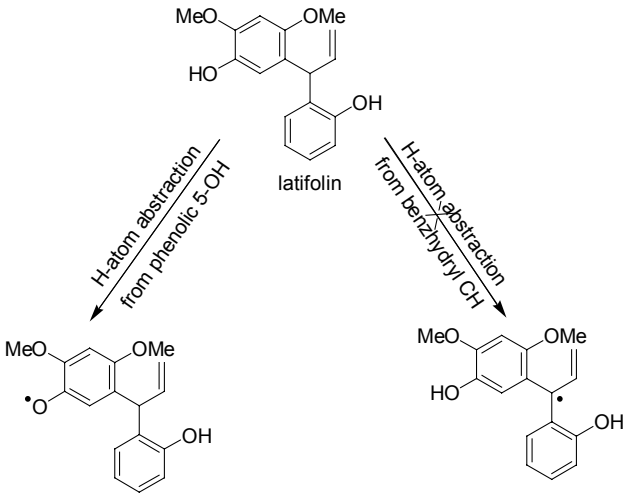
[a] The DPPH-scavenging assay was carried out by monitoring the absorbance of an ethanolic solution of DPPH (100 μmol/L) at 517 nm in the presence and absence of the test compounds at r.t. The concentration ($IC_{0.20}$) of the test compounds at which absorbance decreased by 0.20 of a unit during a 30-min observation was taken as the free radical scavenging potency.

In antioxidant mechanism, the evaluation of the antioxidant activity is also usually done by determining the bond dissociation enthalpy (BDE). In fact, low values of BDE suggest an easier dissociation or proton abstraction, a better interaction with the free radicals and consequently a higher antioxidant activity of the compound. To elucidate the antioxidant activity-structure relationship of latifolin, the BDE of the phenolic O—H bonds and benzhydryl C — H bond was calculated at B3LYP/6-31G* level of theory (Table 2). The results show that not only 5-OH BDE (*ca.* 271 kJ•mol^{-1}) but also 2'-OH BDE (*ca.* 279 kJ•mol^{-1}) is lower than benzhydryl 7-CH BDE (*ca.* 280 kJ•mol^{-1}), indicating that the phenolic OH plays a major role in the activity of latifolin. On the other hand, the 5-OH BDE is lower by 7.37 and 9.27 kJ•mol^{-1} than 2'-OH and 7-CH BDEs, respectively. This is due to the electron-rich phenol ring containing both *ortho*- and *para*-MeO groups. It has been proved that the *ortho*-methoxyl group can form intramolecular hydrogen bond with the phenolic hydrogen, making the H-atom abstraction from the *ortho*-methoxyphenols surprisingly easy.[29] Thus, the first H-atom abstraction of latifolin should take place in the phenolic 5-OH rather than benzhydryl 7-CH (Scheme 3).

Table 2 BDEs for latifolin calculated at B3LYP/6-31G* level of theory in kJ•mol^{-1}

Substitution	BDE
5-OH	271.16
2'-OH	278.53
7-CH	280.43

Scheme 3 Antioxidant mechanism of latifolin



Conclusions

The first concise and efficient total synthesis of latifolin has been accomplished in six steps and 47.8% overall yield. This synthetic process should be able to pave the way for further biological and pharmacological studies of latifolin and analogues. Latifolin (**1**) and dihydrolatifolin (**9**) that bear phenolic hydrogen were considered as strong DPPH-scavengers, and they are better antioxidants than **10** possessing no phenolic hydrogen. Therefore, Phenolic hydrogen is responsible for latifolin's antioxidant activity rather than benzhydryl C-H hydrogen. Furthermore, the 5-OH BDE is lower than 2'-OH and 7-CH BDEs by a DFT calculation, respectively. Based on theoretical results it is definitely concluded that the phenolic 5-OH plays a major role in the antioxidant activity of latifolin.

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