



The stereochemistry of baishouwubenzophenone, a unique atropisomer from *C. wilfordii*

Zhixu Zhou^{a,b}, Zhiqiang Wang^c, Linwei Li^a, Ke Zhang^a, Qing Peng^a, Shuyun Wang^a, Jinhui Wang^a, Jian Huang^{a,**}, Tiemin Sun^{a,*}

^a Key Laboratory of Structure-Based Drug Design and Discovery, Shenyang Pharmaceutical University, Ministry of Education, Shenyang 110016, PR China

^b School of Pharmaceutical Sciences, Guizhou University, Guiyang 550025, PR China

^c College of Chemistry & Chemical Engineering, Harbin Normal University, Harbin 150025, PR China

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ABSTRACT

Baishouwubenzophenone (**1**), possessing a unique atropisomeric feature, has been isolated from the roots of *Cynanchum wilfordii*. The congested structure makes it showing optical activity and consequently the absolute configuration was identified by experimental CD and computational approaches. Configurational assignment was further confirmed by exciton chirality method. The structural features in baishouwubenzophenone molecule allow it to be a potential atropisomeric ligand in asymmetric synthesis.

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1. Introduction

The genus *Cynanchum*, containing the largest number among the 180 species in *Asclepiadaceae*, is distributed around the world [1]. *Cynanchum wilfordii*, belonging to the family *Apocynaceae*, is a famous traditional medicine used as a blood tonic, enriching vitality and enhancing immunity [2]. According to the current knowledge, more than 300 compounds have been isolated from *Cynanchum* species, including steroids, alkaloids, terpenes, flavonoids, benzophenones, polysaccharides, and steroidal glycosides [1]. Among these, baishouwubenzophenone was often regarded as an important active component.

Baishouwubenzophenone (**1**, Fig. 1) was isolated from the roots of *C. wilfordii*. Although the compound has been reported previously [3], the stereochemistry has not been investigated in spite of the obvious existence of steric effects. Many compounds with similar planar structures or substructures to baishouwubenzophenone were reported, such as graphisin A (**2**) [4], sutural element

of Balanol (**3**) [5,6], *ortho*-benzoylbenzoic acid (**4**) [7], however not enough attention was paid to their stereochemistry. In our research, we have found that baishouwubenzophenone showed unique optical activity which aroused our interest of its stereochemistry. We assumed that the two phenyl rings in the molecular structure are flanked by two *ortho* substituents thus exhibiting hindered rotation about the Ar-CO-Ar group. Moreover, the most of atropisomeric compounds used in asymmetric synthesis are derived from biaryls, such as the BINOL [8–12], BINAP [8,13] and their derivatives, while the use of non-biaryl atropisomeric ligands in asymmetric catalysis is in its infancy [14–16]. Some benzophenone-derived diphosphine ligands, such as DPBP (2,2'-bis(diphenylphosphino)benzophenone) [17], which could be controlled into a single enantiomeric conformation, have been used in asymmetric synthesis. It is reported that the levels of enantioselectivity observed with the benzophenone-based catalyst are superior to those observed with BINAP-based catalytic systems in asymmetric ketone hydrogenation [18].

In the present paper, we tried to investigate the stereochemistry of baishouwubenzophenone systematically, considering that the atropisomeric feature and multiple hydroxyl groups would allow it to be potential as an atropisomeric ligand in asymmetric synthesis. The chemical structure of **1** as well as the absolute configuration (AC) was elucidated by spectroscopic methods, electronic circular

* Corresponding author.

** Corresponding author.

E-mail address: suntiemini@126.com (T. Sun).

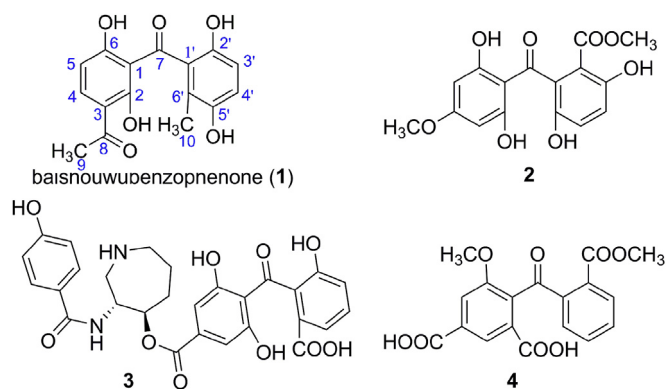


Fig. 1. Structures of baishouwubenzophenone and its analogs.

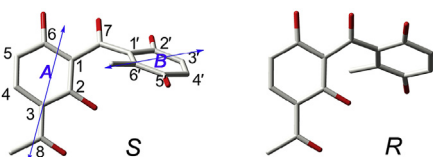


Fig. 2. Possible configurations of 1, hydrogen atoms are omitted.

dichroism (ECD), and theoretical calculations.

2. Experimental details

2.1. General remarks

Column chromatography: Silica gel (200–300 mesh; Qingdao Marine Chemical Group, Co.); ODS (30–50 μm ; YMC CO. Ltd. Japan). Mass spectra were recorded on Varian QFT-ESI and Bruker micro-TOF-Q mass spectrometer (for HR-ESI/MS). NMR spectra were recorded on Bruker AV-300 and Bruker AV-600 spectrometers (Bruker, Germany), TMS as internal standard, δ in ppm, J in Hz; CD spectrum were gotten on Biologic MOS-450 CD spectrometer.

2.2. Plant material

The roots of *C. wilfordii* were purchased from Changfu medicines Ltd (Anhui), China, in July 2007 and identified by Prof. Qishi Sun of Shenyang Pharmaceutical University. The voucher sample (WF-20070713) was deposited in the Department of Natural Products

Chemistry, Shenyang Pharmaceutical University, Shenyang, China.

2.3. Extraction and isolation

Air-dried roots of *C. wilfordii* (20 kg) were extracted three times by 95% ethanol (3×100 L) after refluxing for 3 h. The combined EtOH extracts were concentrated in vacuo to yield a residue (920 g), which was suspended in water and extracted successively with light-petroleum, chloroform, ethyl acetate and *n*-butyl alcohol. Part of the ethyl acetate extract was subjected to column chromatography over silica gel and using a $\text{CHCl}_3 - \text{MeOH}$ gradient (from 100:0 \rightarrow 94:6 v/v) to afford 76 mg of baishouwubenzophenone.

2.4. Computational details

The conformational searching was performed using the Spartan 08 program with the MMFF94. Then all of the possible conformers were optimized at B3LYP level of theory using 6-311 + G(d, p) basis sets. Relative population of each conformer was valued on the basis of Boltzmann weighting factor at 298 K.

The geometries used for the ECD calculation are optimized by DFT calculations at the B3LYP/6-311 + G(d, p) levels. The ECD were then simulated by the TDDFT method at the level of CAM-B3LYP/TZVP. ECD curves were generated by Specdis using half bandwidth of 0.25 eV. To generate the final spectrum of ECD, all the simulated spectra of the lowest energy conformations were averaged according to the Boltzmann distribution theory in which their Gibbs free energy (G) was adopted.

3. Results and discussion

3.1. Structure confirmation

Baishouwubenzophenone (1) was obtained as colorless needles, $[\alpha]_D^{25} = 30$ ($c = 0.1$ M, MeOH). The molecular formula of 1 was determined as $\text{C}_{16}\text{H}_{14}\text{O}_6$ by its HR-ESI-MS (m/z 301.0710 $[\text{M} - \text{H}]^-$, calcd for $\text{C}_{16}\text{H}_{13}\text{O}_6$ 301.0712). The UV absorption at 285 nm suggesting the existence of phenolic hydroxyl chromophore, The IR bands at 3442, 3419, 2926, 2856, 1629 and 1620 cm^{-1} suggested the presence of OH, CH_3 and carbonyl chromophore. The ^1H NMR spectrum (300 MHz, $\text{DMSO}-d_6$) showed the presence of two methyls at δ_{H} 2.21 (3H, s, phenyl- CH_3) and 2.52 (3H, s, COCH_3), four protons of aromatic ring at δ_{H} 6.44 (1H, d, $J = 9$ Hz, H-5), 6.75 (1H, d, $J = 8.7$ Hz, H-3'), 6.69 (1H, $J = 8.7$ Hz, H-4'), 7.71 (1H, d, $J = 8.9$ Hz, H-4), four hydroxyl group at δ_{H} 8.50 (1H, s, $\text{C}_5'-\text{OH}$), 9.31 (1H, s, $\text{C}_6'-\text{OH}$), 10.30 (1H, s, C_2-OH), 12.88 (1H, s, C_2-OH). The ^{13}C NMR

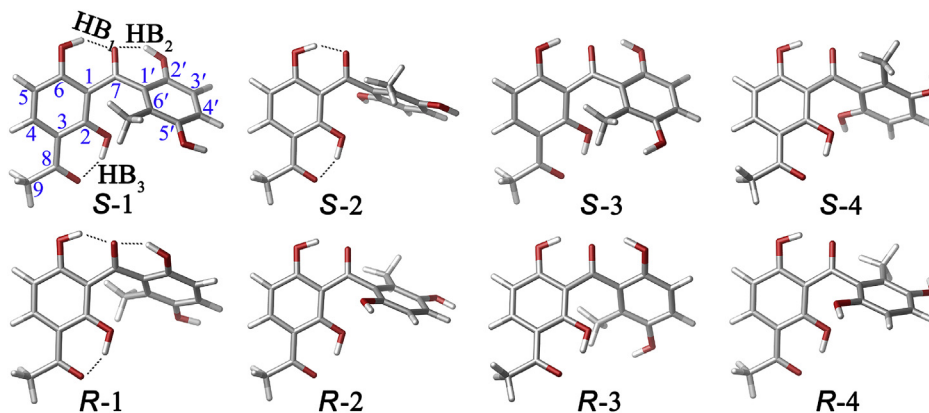


Fig. 3. Relatively stable conformers of R and S configurations.

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