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Chiral discrimination of natural isoflavanones using (*R*)- and (*S*)-BINOL as the NMR chiral solvating agents

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ABSTRACT

Commercially available chiral solvating agents (*R*)- and (*S*)-BINOL were applied to the enantiodifferentiation of natural isoflavanones via ^{1}H NMR spectroscopy. The absolute configurations of the enantiomers of isoflavanones including sativanone **1**, 3′-*O*-methylviolanone **2**, and homoferreirin **3** were assigned by comparing the corresponding δ^R and δ^S values. This approach provided a simple and general means to tentatively assign the enantiomeric purity and absolute configuration of isoflavanones.

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1. Introduction

Isoflavonoids, which are based on a 3-phenylchromene skeleton, form a distinctive subclass of flavonoids.[1] Isoflavonoids mainly occur in the subfamily Papilionoideae of the Leguminosae.[2] Isoflavonoids and their derivatives play a role as phytoalexins in plants, helping the plant fight microbial disease.[3] There are several beneficial properties to human health associated with the isoflavonoids, including a reduction in osteoporosis and cardiovascular disease. Moreover, dietary isoflavonoids can act as phytoestrogens in animals to exert estrogenic effects because of the similarity in structure[3] and reduce the incidence of some distinct cancer forms that are hormone-dependent, such as breast, prostate, and lung cancer.[4]

There have been more than 1600 naturally occurring isoflavonoids reported, which can be divided into 11 major subclasses including isoflavones, pterocarpanoids, rotenoids, isoflavanones, isoflavans, as well as less common ones such as coumestans, 3-arylcoumarins, isoflavonoid oligomers, coumaronochromones, isoflav-3-enes, etc.[4,5] Among them, isoflavanones are considerably rare, with a rather limited taxonomic distribution. The chemical characteristic of isoflavanones, which is based on the 2,3-dihydro-2-phenyl-benzopyran-4-one moiety, is the presence of a single C-3 stereogenic center (Fig. 1). Therefore, finding a convenient means to define the absolute configuration of isoflavanones is crucial for further studies of isoflavanones.

Some analytic techniques have been reported for the chiral discrimination of isoflavanones. For example, optical rotatory dispersion (ORD) and circular dichroism (CD) are widely used to define the stereochemistry of chiral isoflavanones.[6] However, CD signals are not observed if a molecule is present in its racemic form. For X-ray diffraction analysis, obtaining a high-quality crystal is always the prerequisite, and is thus a limitation.[7] Nuclear magnetic resonance (NMR) spectroscopy is one of the indirect or relative methods to achieve a quick determination of the enantiomeric excess of chiral compound when the amount of the compounds is only a few milligrams; it also possesses other advantages such as easy performance, small sample size, and low cost.[8] Three NMR technologies have been used in the determination of the enantiomeric purity including chiral derivatizing agents method, chiral lanthanide shift reagents method and chiral solvating agents method.[9] Among them, the chiral solvating agents method is generally more attractive because of the advantages that it is quick and simple to perform, with no problems in terms of kinetic resolution or sample racemization, provided that the complexes remain in solution. The chiral solvating agent can bind with test compounds through noncovalent, intermolecular forces, allowing for the separation of the signals of the enantiomers in the ^{1}H NMR spectrum. A wide number of chiral solvating agents such as alkaloids,[10] porphyrins,[11] cyclodextrins,[12] binols,[13] trianglamines[14] and diamines[15] have been studied for various applications.[16] It has

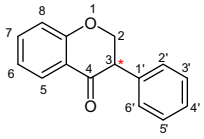

Figure 1. Chemical backbone of isoflavanones.

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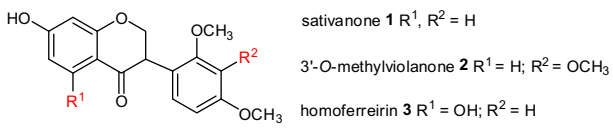


Figure 2. Structures of three isoflavanones isolated from *Dalbergia odorifera*.

been reported that enantiopure BINOL was a good NMR chiral solvating agent for the determination of the enantiomeric purity of different chiral compounds, including antitumor alkaloid crispine A,[17] promethazine,[18] *O*-heterocycles,[19] and antiasthmatic drug montelukast.[20]

In our previous study, we reported that the enantiomeric purity and absolute configuration of flavanones could be determined by using (*S*)-3,3-dibromo-1,1-bi-2-naphthol as a chiral solvating agent by means of ^{1}H NMR spectroscopy.[21] Herein, three isoflavanones sativanone **1**, 3′-*O*-methylviolanone **2**, homoferreirin **3** (Fig. 2) isolated from *Dalbergia odorifera*, were chosen as representatives. Their enantiomeric purity and absolute configuration were determined using commercially available binaphthyl-type

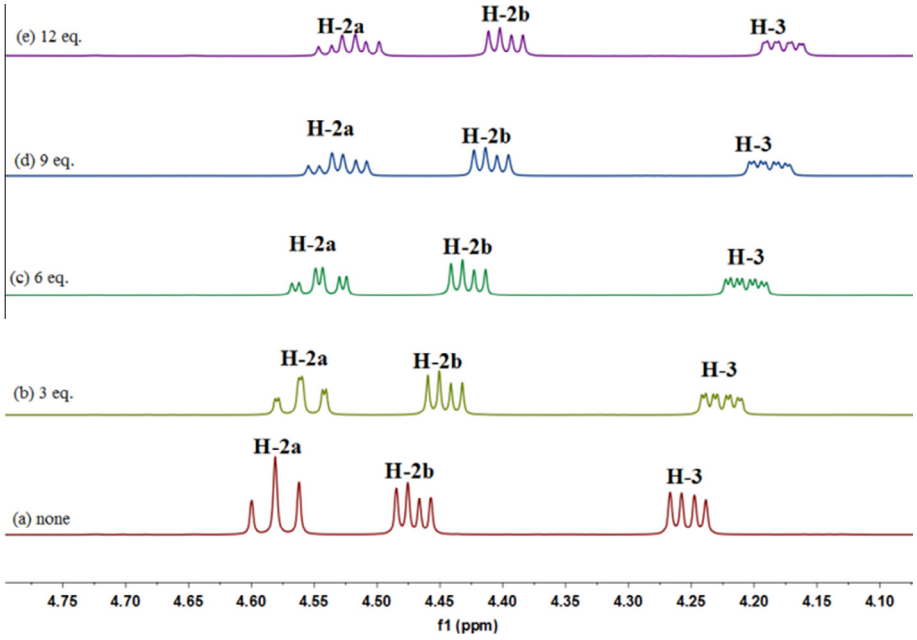


Figure 3. Overlaid ^{1}H NMR spectra (600 MHz in $CDCl_3$) of natural sativanone **1** (3.5 mg) in the presence of (*S*)-BINOL (0–12 equiv).

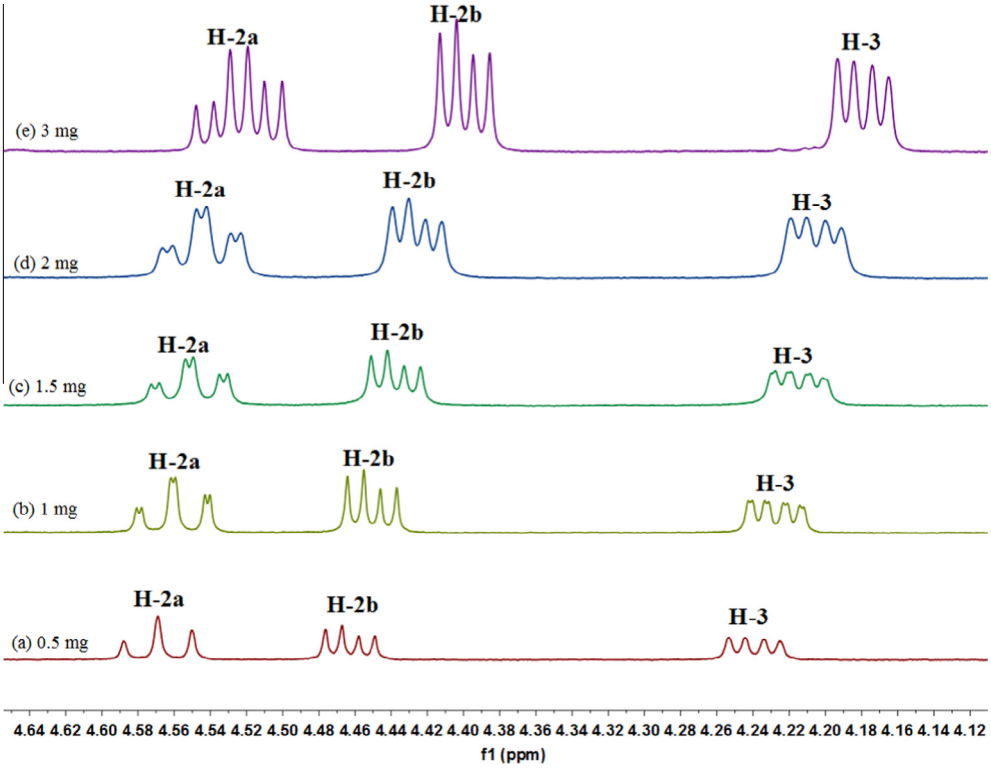


Figure 4. Overlaid ^{1}H NMR spectra (600 MHz in $CDCl_3$) of natural sativanone **1** (0.5–3.0 mg) in the presence of 9 equiv of (*S*)-BINOL.

binaphthol (BINOL) as a chiral solvating agent. To the best of our knowledge, this is the first successful attempt to develop an approach for the enantiomeric purity determination of isoflavanones using an NMR method.

2. Result and discussion

Natural sativanone **1** was chosen as the model substrate during the chiral discrimination experiments of isoflavanones using (*S*)-BINOL as the chiral solvating agent. Firstly, the effect of the amount of (*S*)-BINOL on the signal separation was investigated. Natural sativanone **1** with (*S*)-BINOL displayed dramatic changes in the chemical shift values of the ^{1}H NMR signals for H-2a (*trans* to H-3). A gradual increase in the amount of (*S*)-BINOL resulted in a gradual increase in the chemical shift difference between the two enantiomers. The results obtained using 9 equiv and 12 equiv of (*S*)-BINOL were more satisfactory than those obtained using less (*S*)-BINOL (Fig. 3). Since the addition of 9 equiv and 12 equiv of

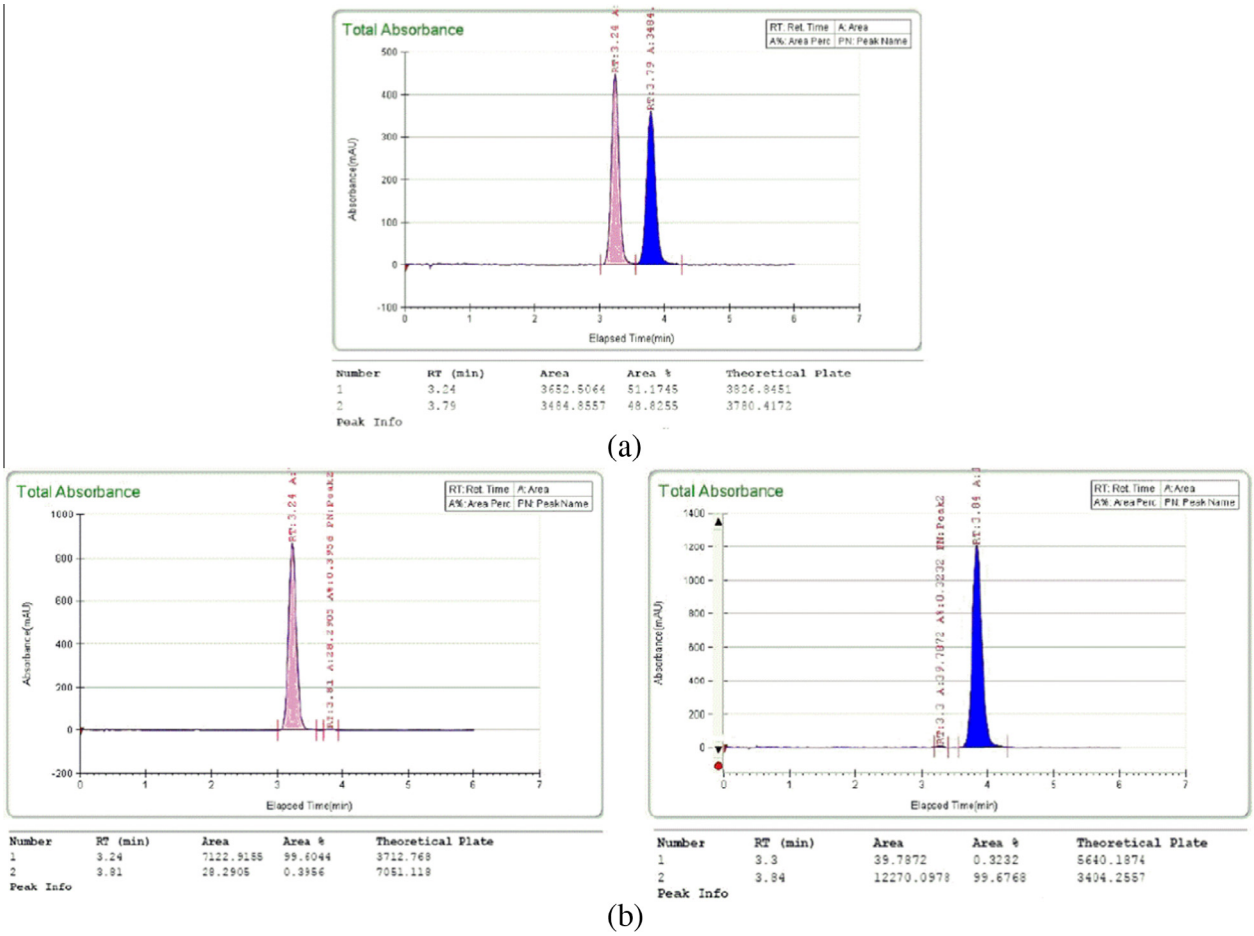


Figure 5. Chiral-SFC analysis of sativanone enantiomers: (a) chiral-SFC analysis of sample sativanone **1**; (b) purity check of (*S*)-sativanone and (*R*)-sativanone.

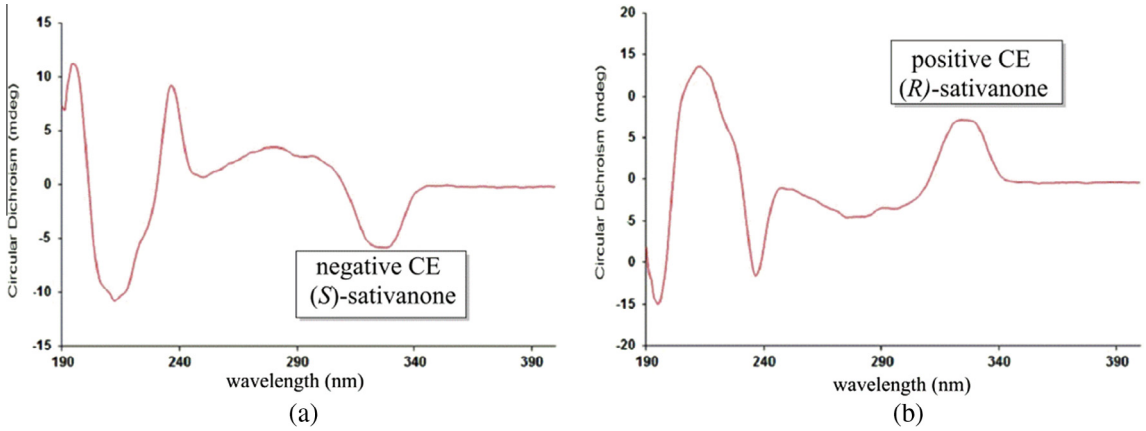


Figure 6. CD spectra analysis of sativanone enantiomers: (a) (*S*)-sativanone; (b) (*R*)-sativanone. The samples were dissolved in methanol and the concentration was 0.167 mg/mL; the measurement temperature was 25 °C.

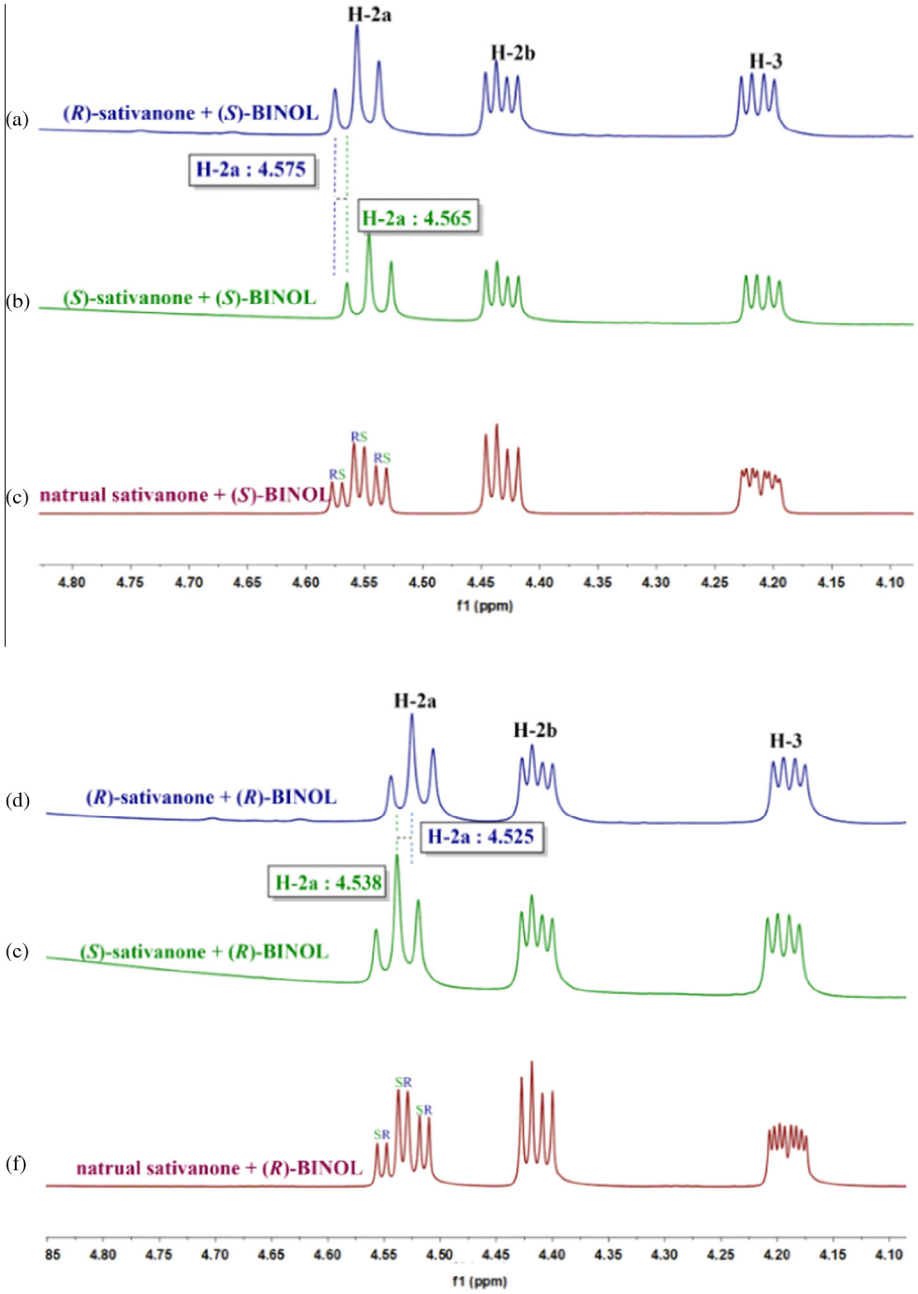


Figure 7. The δ^R and δ^S signs of H-3a: sativanone **1** (3.5 mg) with 9 equiv of BINOL in $CDCl_3$ (600 MHz). (a) (*R*)-sativanone and (*S*)-BINOL; (b) (*S*)-sativanone and (*S*)-BINOL; (c) natural sativanone and (*S*)-BINOL; (d) (*R*)-sativanone and (*R*)-BINOL; (e) (*S*)-sativanone and (*R*)-BINOL; (f) natural sativanone and (*R*)-BINOL.

(*S*)-BINOL resulted in a similarly distinct signal separation, the optimum amount of (*S*)-BINOL to be used for the chiral discrimination of natural sativanone was 9 equiv.

Secondly, the effect of the concentration of sativanone **1** with 9 equiv of (*S*)-BINOL on signal separation was addressed (Fig. 4). When the addition of sativanone **1** was less than 3 mg/0.5 mL (0.02 mmol/mL), it showed no obvious signal separation for H-2a. This result possibly contributed to the weak ability of the hydroxy group in (*S*)-BINOL group to form a hydrogen bond at low concentrations. Moreover, increasing the amount of BINOL when sativanone **1** was present in lower concentrations also resulted in incomplete signal separation. Therefore, the appropriate concentration of sativanone **1** to be used for chiral discrimination was established as no less than 0.02 mmol/mL.

Next, in order to obtain (*S*)- and (*R*)-sativanone, the chiral separation of natural sativanone on a preparative scale was achieved by using supercritical fluid chromatography (Fig. 5). The determination of their configurations was based on the detection of CD spectra (Fig. 6), in which an obvious Cotton effect (CE) was observed. (*S*)-Sativanone showed negative CE at 320–340 nm, while (*R*)-sativanone showed a positive CE at same absorption.[6]

The experimental results of (*S*)- or (*R*)-sativanone associated respectively with one enantiomer of BINOL and are shown in Figure 7. According to the results, when (*S*)- and (*R*)-sativanone were associated with (*S*)-BINOL as the chiral solvating agent, the chemical shift value of H-2a of (*R*)-sativanone was greater than that of H-2a of (*S*)-sativanone (H-2a: $\delta^R > \delta^S$). Conversely, when associated with (*R*)-BINOL, the chemical shift value of H-2a of (*S*)-sativanone

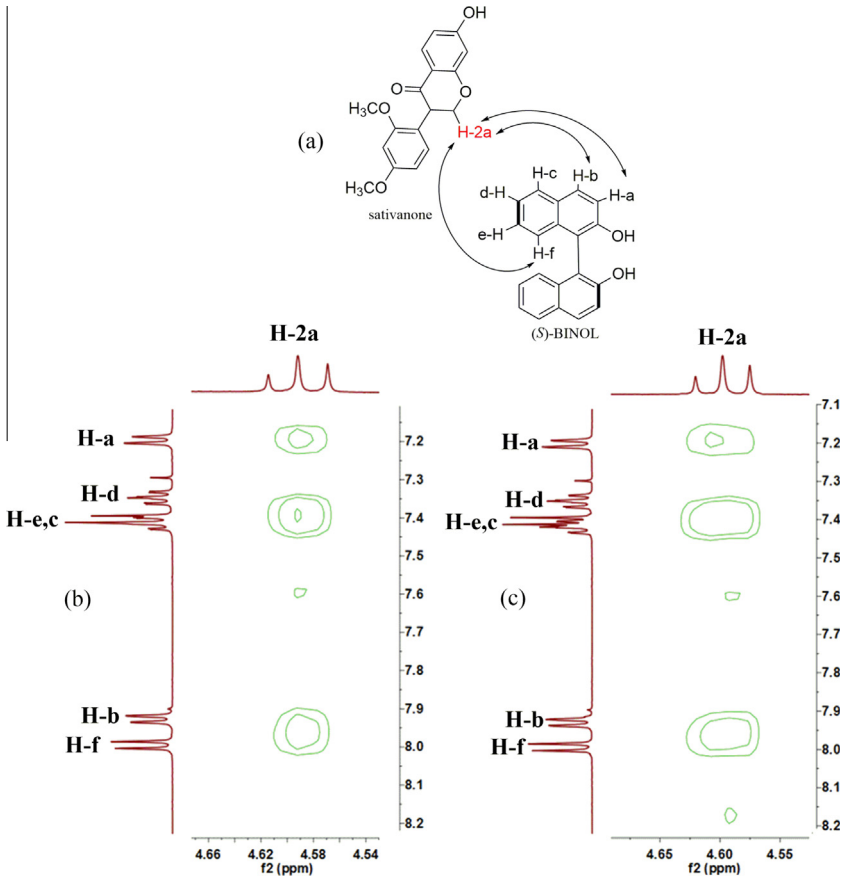


Figure 8. (a) Structures of sativanone **1** and (*S*)-BINOL. The arrows represent the observed intermolecular NOEs; (b) 2D NOESY spectrum of (*S*)-sativanone (3.5 mg) and 9 equiv of (*S*)-BINOL; (c) (*R*)-sativanone (3.5 mg) and 9 equiv of (*S*)-BINOL (500 MHz in $CDCl_3$).

was greater than that of H-2a of (*R*)-sativanone (H-2a: $\delta^S > \delta^R$). These results indicated that the chemical shifts were affected by strong aromatic shielding effects or weak shielding effects produced by the BINOL, which depended on the spatial location of that hydrogen atom with regards to the naphthyl rings. Therefore, when two enantiomers of an isoflavanone is associated with one enantiomer of chiral solvating agent through noncovalent bonds, a comparison of the chemical shift values of H-2a for two diastereomeric complexes can determine their absolute configuration ($\delta^R > \delta^S$ or $\delta^S > \delta^R$), i.e., the absolute configuration of isoflavanone can be constructed by comparing the chemical shifts of H-2a in the presence of enantiopure BINOL.

To elucidate the association of the complexes of BINOL and (*S*)- and (*R*)-sativanone, some attempts were made to achieve additional structural information via 2D NOESY experiments on the BINOL/sativanone complex. In Figure 8, correlation peaks between several BINOL aryl signals and the H-2a signals of (*S*)- and (*R*)-sativanone were clearly detected, thus indicating the close intermolecular association of BINOL and the sativanone enantiomers.

The separating results inspired us to apply this NMR method to other natural isoflavanones from *Dalbergia odorifera*. We chose 3′-*O*-methylviolanone to screen (*S*)-BINOL as a chiral solvating agent by using ^{1}H NMR spectrum, recorded in $CDCl_3$. To make this method suitable for more polar compounds which are difficult to dissolve in a nonpolar solvent, we recorded the ^{1}H NMR spectrum of the mixture of homoferreirin and (*S*)-BINOL in a $CDCl_3$/acetonitrile-d_3 mixture (*v*/*v*, 9:1). In addition, ^{1}H NMR analysis and chiral HPLC were compared for the determination of the enantiomeric purity (Table 1). The enantiomeric purity was determined by integrating the corresponding H-2a signals in the ^{1}H NMR spectra and HPLC-UV absorption peaks for the (*S*)- and (*R*)-configuration. The results suggested that the data obtained using NMR methods closely matched those obtained using chiral HPLC analysis.

3. Conclusion

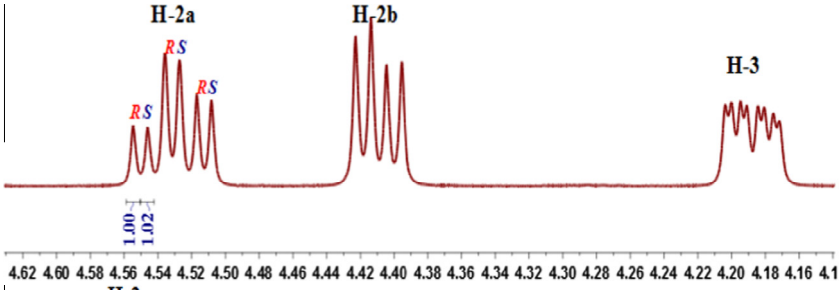
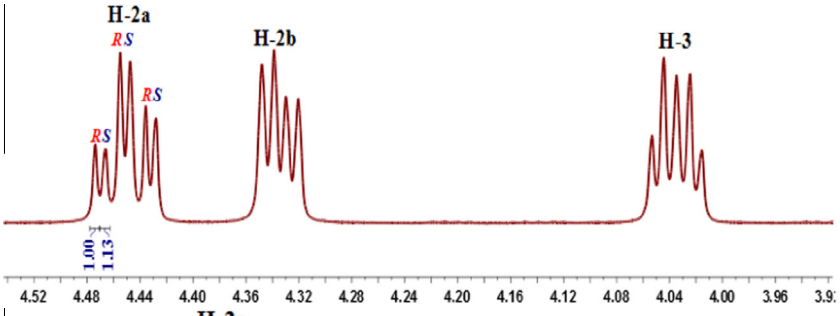
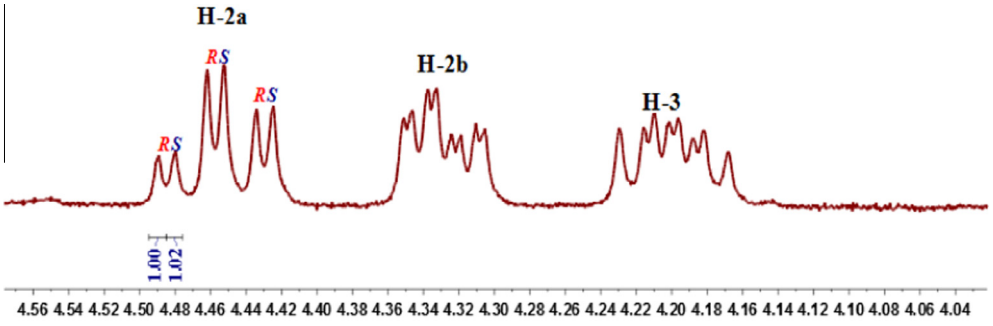
The absolute configuration of most natural isoflavanones was often established as (*R*)- or (*S*)- by the CD method. However, an incorrect result could be obtained when an enantiomeric molecule is present. In our study, isoflavanones when associated with commercially available chiral solvating agents (*R*)- or (*S*)-BINOL permitted their enantiodifferentiation via ^{1}H NMR spectroscopy. The absolute configuration of enantiomers isoflavanones was assigned by comparing the corresponding δ^R and δ^S with the models. The formation of H-bond complexes of (*S*)- and (*R*)-isoflavanones with BINOL was supported by the NOE results. In conclusion, the NMR approach provides a simple and general means to tentatively assign the enantiomeric purity and absolute configuration of isoflavanones.

4. Experimental

4.1. General

^{1}H, ^{13}C and 2D NMR spectra were obtained using a Bruker AV-400, 500 or a 600 instrument. Circular dichroism (CD) spectra were recorded on Chirascan CS30049 instrument. Optical rotatory dispersion (ORD) values were measured on an Autopol VI instrument, manufactured by Rudolph Research Analytical, Hackettstown, NJ.

Table 1
Comparison of NMR spectra and chiral HPLC analysis of isoflavanones **1**–**3**

Isoflavanones	Spectra[a]	(*S*):(*R*) (%) (NMR)	(*S*):(*R*) (%) (HPLC)
1		50.5:49.5	50.1:49.9
2		53.1:46.9	54.8: 45.2
3		50.5:49.5	50.1:49.9

[a] Sativanone **1** and 3′-*O*-methylviolanone **2** in the presence of 9 equiv of (*S*)-BINOL in $CDCl_3$ 600 MHz; homoferreirin **3** in the presence of 9 equiv of (*S*)-BINOL in $CDCl_3$/acetonitrile-d_3 (9:1) 500 MHz.

The ESI-MS and HR-ESI-MS analysis were performed on a Finnigan LCQ Deca XP equipped with an electrospray ionization source mass ion-trap spectrometer. HPLC analysis was performed on an Agilent 1200 instrument equipped with a quaternary pump and multiple wavelength detectors (MWD). Supercritical fluid chromatography (SFC) analysis was performed on a SFC instrument (Thar, Waters).

(*S*)- and (*R*)-BINOL were obtained from Daicel Corporation (Shanghai, People's Republic of China) and used without further purification. The deuterated solvents were $CDCl_3$ (99.80%) from Cambridge Isotope Laboratories (USA) and acetonitrile-d_3 (99.80%) from Sigma–Aldrich (Germany). Ethanol, methanol, ammonia, (CINC, Shanghai, China) were of HPLC grade. High-purity carbon dioxide (CO_2, 99.999%) was from AP BAIF Gases (Beijing, China).

Three substrate compounds for NMR analysis were all naturally occurring isoflavanones, which were isolated from the plant *Dalbergia odorifera* using a procedure described previously.[22] Their structures were identified by comparing ^{1}H NMR and ^{13}C NMR data with those of literatures reported, as sativanone,[23] 3′-*O*-methylviolanone,[22] homoferreirin.[22]

4.1.1. Sativanone 1

^{1}H NMR (400 MHz, DMSO-d_6, δ): 10.59 (s, 1H, 7-OH), 7.68 (d, J = 8.7 Hz, 1H; H-5), 6.99 (d, J = 8.4 Hz, 1H; H-6′), 6.58 (d, J = 2.4 Hz, 1H; H-8), 6.52 (dd, J = 8.7, 2.2 Hz, 1H; H-6), 6.48 (dd, J = 8.4, 2.4 Hz, 1H; H-5′), 6.34 (d, J = 2. 2 Hz, 1H; H-3′), 4.52 (dd, J = 11.0, 11.3 Hz, 1H; H-2a), 4.41 (dd, J = 11.0, 5.3 Hz, 1H; H-2b), 4.15 (dd, J = 11.3, 5.3 Hz, 1H; H-3), 3.75 (s, 3H, 2′-OCH_3), 3.72 (s, 3H, 4′-OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6, δ): 190.3 (C=O), 164.2 (C-7), 163.2 (C-9), 159.9 (C-4′), 158.1 (C-2′), 130.6 (C-5), 128.9 (C-6′), 116.1 (C-1′), 113.9 (C-10), 110.5 (C-3′), 104.9 (C-5′), 102.3 (C-6), 98.8 (C-8), 70.3 (C-2), 55.6, 55.2 (2 × OCH_3), 46.6 (C-3); ESI-MS (m/z): 301 $[M+H]^+$; $[\alpha]_D^{20}$ = 0 (c 1.0, MeOH); (*S*)-sativanone: $[\alpha]_D^{20}$ = 26 (c 0.5, MeOH); (*R*)-sativanone: $[\alpha]_D^{20}$ = −28 (c 0.5, MeOH).[24]

4.1.2. 3′-*O*-Methylviolanone 2

^{1}H-NMR (400 MHz, DMSO-d_6, δ): 10.60 (s, 1H, 7-OH), 7.69 (d, J = 8.6 Hz, 1H; H-5), 6.85 (d, J = 8.6 Hz, 1H; H-6′), 6.74 (d, J = 8.5 Hz, 1H; H-5′), 6.53 (dd, J = 8.6, 2.2 Hz, 1H; H-6), 6.35 (d, J = 2.2 Hz, 1H; H-8), 4.51 (dd, J = 11.5, 11.2 Hz, 1H; H-2a), 4.44 (dd, J = 11. 2, 5.6 Hz, 1H; H-2b), 4.14 (dd, J = 11.5, 5.6 Hz, 1H; H-3), 3.78 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3). ^{13}C-NMR (100 MHz, DMSO-d_6, δ): 191.0 (C-4), 164.9 (C-7), 163.8 (C-9), 153.5 (C-4′), 151.9 (C-2′), 142.2 (C-3′), 129.5 (C-5), 125.0 (C-1′), 122.2 (C-6′), 114.4 (C-10), 111.1 (C-6), 108.2 (C-5′), 102.9 (C-8), 71.1 (C-2), 61.6 (OCH_3), 60.7 (OCH_3), 56.3 (OCH_3), 47.8 (C-3). ESI-MS (m/z): 331 $[M+H]^+$; $[\alpha]_D^{20}$ = +1 (c 1.0, MeOH).

4.1.3. Homoferreirin 3

^{1}H NMR (400 MHz, DMSO-d_6, δ): 12.25 (s, 1H, OH), 10.80 (s, 1H, OH), 7.05 (d, J = 8.4 Hz, 1H; H-6′), 6.60 (d, J = 2.4 Hz, 1H; H-3′), 6.51

(dd, J = 8.4, 2.4 Hz, 1H; H-5′), 5.91 (d, J = 2.2 Hz, 1H; H-8), 5.90 (d, J = 2.2 Hz, 1H; H-6), 4.49 (dd, J = 11.1, 10.9 Hz, 1H; H-2a), 4.40 (dd, J = 10.9, 5.5 Hz, 1H; H-2b), 4.31 (dd, J = 11.1, 5.5 Hz, 1H; H-3), 3.76 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6, δ): 197.4 (C-4), 166.9 (C-7), 164.3 (C-9), 163.5 (C-5), 160.7 (C-4), 158.6 (C-2′), 131.4 (C-6′), 115.7 (C-1′), 105.5 (C-5′), 102.5 (C-10), 99.4 (C-3′), 96.4 (C-6), 95.3 (C-8), 70.2 (C-2), 56.2 (2′-OMe), 55.7 (4′-OMe), 46.4 (C-3). ESI-MS (m/z): 317 $[M+H]^+$; $[\alpha]_D^{20}$ = 0 (c 1.0, MeOH).

4.2. Preparation of (*S*)- and (*R*)-sativanone

(*S*)- and (*R*)-sativanone were obtained by separating natural sativanone via preparative supercritical fluid chromatography (SFC). Before the enantiomeric separation, an analytical SFC method was established. An aliquot of a 3 μL sample was injected for analysis. The sativanone **1** solution was separated on a Chiralpak IC column 4.6 × 100 mm, 5 μm (Daicel Industries) ((0–6 min, CO_2/C_2H_5OH = 85/15, v/v; 0.2% Methanol Ammonia). The flow rate was 4.0 mL/min, the back pressure regulation (BPR) pressure was 120 Bar, and the column temperature was 40 °C. The UV detection wavelength was set at 214–359 nm.

Similar to that used in the analytical method, the sativanone (50 mg) was dissolved in 12 mL MeOH and then separated on a preparative Chiralpak IC column (20 × 250 mm, 5 μm, Daicel Industries), and was detected at 214 nm. The flow rate was 80 g/min and the injection volume was 1.0 mL/4.17 mg. The BPR pressure was 100 bar, and the column temperature was 35 °C. An isocratic elution (CO_2/C_2H_5OH = 75/25, v/v; 0.2% methanol ammonia) was used to obtain (*S*)-sativanone (tR = 3.24 min, 24 mg) and (*R*)-sativanone (tR = 3.84 min, 15 mg). To determine the absolute configurations of sativanone enantiomers, their CD spectra and specific rotation values were recorded.

4.3. Procedures for chiral differentiation studies

All solutions were prepared by weighing the corresponding quantities of the substrates and the chiral solvating agents, dissolving the mixtures in the 0.5 mL deuterated solvent and then transferred to 5 mm NMR tubes at room temperature.

In the experiments of chiral solvating agent equivalent numbers effect, the samples were prepared by dissolving sativanone **1** (3.5 mg) with 3–12 equiv of (*S*)-BINOL in $CDCl_3$; in the experiments of substrate concentration effect, the samples were prepared by dissolving sativanone **1** from 0.5 mg to 3 mg with 9 equiv of (*S*)-BINOL in $CDCl_3$; in the experiments of NOE studies, the samples were prepared by dissolving (*S*)-sativanone (3.5 mg) and (*R*)-sativanone (3.5 mg) with 9 equiv of (*S*)-BINOL and (*R*)-BINOL in $CDCl_3$; in the experiments of the absolute configuration and enantiomeric purity analysis of two other natural isoflavanones, 3′-*O*-methylviolanone (3.5 mg) was dissolved with 9 equiv of (*S*)-BINOL in $CDCl_3$; homoferreirin (3.5 mg) was dissolved with 9 equiv of (*S*)-BINOL in $CDCl_3$ and acetonitrile-d_3 (v/v, 9:1).

4.4. Determination of the enantiomeric purity by traditional chiral HPLC

The proportions of the enantiomers of all natural isoflavanones were also determined using an Agilent 1200 HPLC instrument. Separations of compounds **1** and **3** were performed on a Chiral CD-Ph (5 μm, 4.6 mm i.d. × 250 mm; Shiseido, Japan) using mobile phase of methanol and H_2O (80:20, v/v) at a flow rate of 0.5 mL/min. The retention time of the (*S*)-enantiomer of **1** was 12.06 min while that of the (*R*)-enantiomer was 13.02 min. The retention time of the (*S*)-enantiomer of **3** was 9.66 min and that of the (*R*)-enantiomer was 10.72 min. Separation of compound **2** was performed on a Chiral OD-RH (5 μm, 4.6 mm i.d. × 150 mm; Daicel Corporation, China), using mobile phase of methanol and H_2O (80:20, v/v) at a flow rate of 0.5 mL/min. The retention time of *S* enantiomer of **2** was 17.35 min and that of *R* enantiomer was 18.07 min. The enantiomeric purity of isoflavanones **1**–**3** was determined by integrating HPLC-UV absorption peaks (280 nm) for the *S* and *R* configuration, respectively.

Acknowledgement

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