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► To cite this version:

Yangguang Gao, Zhou Cao, Chengzhong Chen, Zefeng Chen, Xianran He, et al.. Chiron Approaches to the Antitumor Natural Product Fuzanin D. *Synthesis: Journal of Synthetic Organic Chemistry*, 2016, 48 (24), pp.4471 - 4476. 10.1055/s-0036-1588343 . hal-01446170

HAL Id: hal-01446170

<https://hal.sorbonne-universite.fr/hal-01446170>

Submitted on 25 Jan 2017

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Chiron Approaches to Anti-tumor Natural Product Fuzanin D

Yangguang Gao^{a,b,*}

Zhou Cao^b

Chengzhong Su^b

Zefeng Chen^c

Xianran He^{a,b}

Fei Ding^{a,b}

Hang Li^{a,b}

Yongmin Zhang^{a,d,*}

^aInstitute for Interdisciplinary Research, Jiangnan University, Wuhan Economic and Technological Development Zone, Wuhan 430056, People's Republic of China

^bKey Laboratory of Optoelectronic Chemical Materials and Devices of Ministry of Education, Jiangnan University, Wuhan Economic and Technological Development Zone, Wuhan 430056, People's Republic of China

^cChimie, IUT d'Orsay, Université Paris sud, plateau de Moulon, 91400 Orsay, France

^dInstitut Parisien de Chimie Moléculaire, CNRS UMR 8232, Université Pierre et Marie Curie-Paris 6, 4 Place Jussieu, 75005 Paris, France

e-mail_gaoyangguang@126.com; yongmin.zhang@upmc.fr.

Abstract Fuzanin D, a pyridine-containing natural product, which exhibits cytotoxic activity against DLD-1 cells, has been synthesized in a concise manner using L-arabinose or ethyl L-lactate as chiral pool over 6–9 steps. Key steps involved olefin cross-metathesis and Wittig olefination.

Key words Synthesis; Chiral pool; Anti-tumor; Cytotoxicity; Olefination

Pyridine-containing natural products which mainly originate from animals, plants, eukaryotes and prokaryotes fascinate chemical community due to their various biological activities,¹ such as cytotoxic,² antimicrobial,³ antifungal,⁴ anti-HIV,⁵ neurotoxic,⁶ anti-inflammatory activities.⁷ Fuzanin D, a disubstituted pyridine-containing natural product, incorporated a long chain with a *E,E*-conjugated diene moiety, continuous hydroxyl groups, and one methyl group, was isolated from the culture supernatant of *Kitasatospora* sp. IFM10917 by Ishibashi and the coworkers in 2009.⁸ The biological activities determination of Fuzanin D in vitro displayed inhibitory activity against DLD-1 cells with IC₅₀ value of 41.2 μM. Besides, it also displayed moderate inhibition of Wnt signal transcription at 25 mM.

Recently, the Rao's group has achieved the syntheses of Fuzanins C, D and their derivatives as well as preformed biological evaluation on anticancer in vitro (Scheme 1).⁹ On the basis of synthesis, the original absolute configuration of Fuzanin D was suggested to be reassigned. In the synthesis of Fuzanin D, Sharpless epoxidation was utilized to set the chiral centers, and Julia olefination was utilized to construct carbon carbon double bond. Herein, we would like to describe an alternative synthesis of Fuzanin D using L-arabinose or ethyl L-lactate as chiral pool.

Scheme 1 Structures of Fuzanin C and Fuzanin D.

As shown in Scheme 2, synthesis of Fuzanin D (**1**) could be achieved by Wittig olefination between building block **2** and 3-methylpicolininaldehyde **3** followed by removal of cyclohexylidene group.

Compound **2** was prepared from commercially available L-arabinose through several conventional manipulations, while compound **3** could be easily obtained by selective oxidation of 2,3-dimethyl pyridine according to a literature procedure.¹⁰

Synthesis of building block **2** was commenced with a known compound 3,4-*O*-isopropylidene-L-arabopyranose **4** (Scheme 3).¹¹ Oxidative cleavage of compound **4** with NaIO₄ followed by treatment of the crude product with Na₂CO₃ gave protected L-erythrose **5**.¹² Without further purification, compound **5** was subjected to Wittig olefination¹³ with *in-situ* generated methyl Wittig reagent in toluene at reflux to provide enol **6** in 52% yield for 2 steps. To note, ring-opening reaction by Wittig reagent gave a low yield of **6** when using THF as solvent at 0 °C to room temperature. Iodination of enol **6** using standard Appel reaction condition¹⁴ gave compound **7** in a high yield (90%). Reduction of iodide **7** was carried out smoothly with an excess amount of LiAlH₄ (10 eq) to give terminal methyl-containing compound **8** in 82% yield. In consideration of low boiling point of compound **8**, isopropylidene group was replaced by bulky cyclohexylidene group through a 2-step conversion in a yield of 88%. Olefin cross-metathesis (OCM) between compound **9** and allyl bromide under a catalytic amount of Grubbs II exclusively generated *trans* olefin **2** (*J* = 15.6 Hz) in 81% yield.

Scheme 2 Retrosynthetic analysis of Fuzanin D.

An alternative synthesis of building block **2** was summarized in Scheme 4. The required secondary allylic alcohol **10** as a 20:1

mixture of diastereoisomers was obtained from ethyl L-lactate over 3 steps superior to a literature procedure¹⁵ when using DCM as solvent instead of Et₂O. After that, compound **10** and allyl bromide was subjected to the similar OCM as described for **2** to give *trans* olefin **11** in 75% yield. Compound **11** was converted into compound **2** in a high yield (89%) through unblocking of silyl ether under acidic condition followed by protection with cyclohexylidene group.

Scheme 3 Synthesis of compound **2**. *Reagents and conditions:* (a) NaIO₄, MeOH-H₂O, then Na₂CO₃; (b) Ph₃P⁺-CH₃Br, *n*-BuLi, toluene, 0 °C to reflux, 52% yield for 2 steps; (c) I₂, PPh₃, imidazole, THF, reflux, 90% yield; (d) PTSA, MeOH, then CH₃CN, cyclohexanone, 88% yield; (e) LiAlH₄, THF, 82% yield; (f) Allyl bromide, Grubbs II, DCM, 81% yield.

Scheme 4 Alternative synthesis of compound **2**. *Reagents and conditions:* (a) (i) TBSCl, imidazole, DCM, 96% yield; (ii) DIBAL-H, DCM, -98 °C, then vinylmagnesium chloride (1.9M), -98 °C to rt, 83% yield; (b) Allyl bromide, Grubbs II, DCM, 75% yield; (c) PTSA, MeOH, then CH₃CN, cyclohexanone, 89% yield.

With building block **2** and 3-methylpicolinaldehyde **3** in hand, assembly of them became our next goal. As shown in Scheme 5, treatment of compound **2** with PPh₃ in CH₃CN at reflux gave the corresponding alkyltriphenylphosphonium salt **12**. Without purification, the alkyltriphenylphosphonium salt **12** was deprotonated by *n*-BuLi at -78 °C in THF to provide *in-situ* Wittig reagent, which reacted with 3-methylpicolinaldehyde **3** to give an inseparable *E,Z*-mixture in a ratio of 1.7:1 according to H-NMR analysis. Fortunately, the *E,Z*-mixture could be purified at the subsequent deprotection step. Thus, the natural product Fuzanin D (**1**) was obtained in 42% yield for 3 steps. The value of optical rotation and spectral data were in good accordance with the previously reported literature.⁹

Scheme 5 Synthesis of Fuzanin D (**1**). *Reagents and conditions:* (a) PPh₃, CH₃CN, 80 °C; (b) (i) *n*-BuLi (2.5M), THF, then 3-methylpicolinaldehyde **3**, -78 °C; (ii) PTSA, MeOH, 42% yield for 3 steps.

In conclusion, synthesis of Fuzanin D (**1**) has been achieved from L-arabinose, ethyl L-lactate in 9 steps, 6 steps, respectively. Highlight of the protocol was using natural chiral pool to set stereogenic centers, and adopting Wittig olefination and OCM as

crucial steps. Our scheme was flexible and facile, and could be applied to synthesize homologs or derivatives of Fuzanin D, which would be reported in due course.

The experimental section has no title; please leave this line here.

All reagents were commercially available and used directly without further purification unless otherwise stated. Column chromatography was carried out by using silica gel (100–200 mesh). Routine monitoring of reactions was used silica gel 60 F254 TLC plates. ¹H and ¹³C NMR spectra were recorded with Bruker Avance III spectrometer at 400 MHz, 100 MHz respectively, relative to Me₄Si (δ = 0 ppm) as internal standard. HRMS were measured with a Bruker micro-TOFQ II mass spectrometer. IR spectra were recorded on neat samples with a NICOLET iS 10 infrared spectrometer. Optical rotations were recorded with a AUTOPOL IV automatic polarimeter.

2,3-*O*-isopropylidene-L-erythrose (**5**)

To a solution of 3,4-*O*-isopropylidene-L-arabopyranose **4** (10.4 g, 54.71 mmol) in MeOH (100 mL) was added NaIO₄ solution (16 g dissolved in 90 mL water) by dropping funnel, and the mixture was allowed to stir at room temperature. After the reaction completed (monitoring by TLC), the solution was basified (pH 9) by the addition of Na₂CO₃ powder, and stirred for another 1 h. The undissolved white solid was filtered and the filtrate was extracted with DCM (3 × 150 mL). The combined organic layer was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether–EtOAc, 3 : 1) to give compound **5** as a syrup. The spectral data agreed with the reported literature.¹²

((4*S*,5*R*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)methanol (**6**)

To a suspension of methyl triphenyl phosphoniumbromide (15 g, 42.13 mmol) in dried toluene (100 mL) was added dropwise *n*-BuLi solution (2.5 M in hexane, 19.3 mL, 48.25 mmol) at 0 °C under a nitrogen atmosphere. The formed yellow suspension was stirred for 45 min at the same temperature, then compound **5** (3 g, 18.74 mmol) in 10 mL of toluene solution was added dropwise. After the addition completed, the ice bath was replaced by an oil bath. The mixture was heated at reflux, and quenched with saturated aqueous NH₄Cl (100 mL) until TLC indicated a complete consumption of the starting material. The organic layer was removed and the water phase was extracted with EtOAc (3 × 100 mL), and the combined organic layer was concentrated in vacuo. Column chromatography of the residue on silica gel (petroleum ether–EtOAc, 3 : 1) generated compound **6** as a yellow oil (1.54 g, 52% yield for 2 steps).

[α]_D²⁵ = -39.2 (c 0.35, CHCl₃).

IR (neat): 1637, 1376, 1215, 1164, 1039 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 5.91–5.83 (m, 2H), 5.39 (d, 1H, *J* = 17.2 Hz), 5.28 (d, 1H, *J* = 14.0 Hz), 4.65 (t, 1H, *J* = 6.8 Hz), 4.26 (q, 1H, *J* = 6.0 Hz), 3.58 (d, 1H, *J* = 5.6 Hz), 1.51 (s, 3H), 1.39 (s, 3H) ppm.

¹³C NMR (100 MHz, CDCl₃): δ = 133.11, 119.15, 109.02, 78.43, 78.39, 62.21, 27.93, 25.37 ppm.

HRMS (ESI): *m/z* [M - H]⁻ calcd for C₈H₁₃O₃: 157.0865; found: 157.0842.

(4*R*,5*R*)-4-(iodomethyl)-2,2-dimethyl-5-vinyl-1,3-dioxolane (**7**)

To a solution of compound **6** (410 mg, 2.59 mmol) in THF (10 mL) was added I₂ (1.18 g, 4.65 mmol), PPh₃ (1.22 g, 4.65 mmol), imidazole (530 mg, 8.54 mmol) in sequence. The mixture was heated at reflux till the completion of the reaction monitoring by TLC. Saturated Na₂S₂O₃ solution (10 mL) was added to quench the reaction, the organic layer was separated, extracted with EtOAc (3 × 10 mL), and the combined organic layer was concentrated. The residue was purified by silica gel column chromatography (petroleum ether–EtOAc, 50 : 1) to furnish compound **7** (625 mg, 90% yield) as a yellow oil.

[α]_D²⁵ = -1.45 (c 0.76, CHCl₃).

IR (neat): 2986, 2931, 1428, 1380, 1215, 1042, 870 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 5.87–5.80 (m, 1H), 5.43 (d, 1H, *J* = 17.2 Hz), 5.33 (d, 1H, *J* = 10.4 Hz), 4.63 (t, 1H, *J* = 6.0 Hz), 4.46–4.41 (m, 1H), 3.14 (dd, 1H, *J* = 10.4, 7.6 Hz), 3.06 (dd, 1H, *J* = 10.0, 6.4 Hz), 1.51 (s, 3H), 1.38 (s, 3H) ppm.

¹³C NMR (100 MHz, CDCl₃): δ = 132.43, 119.49, 109.12, 79.20, 78.56, 28.21, 25.62, 3.91 ppm.

HRMS (ESI): *m/z*[M + Na]⁺ calcd for C₈H₁₃INaO₂: 290.9858; found: 290.9862.

(2*R*,3*R*)-2-(iodomethyl)-3-vinyl-1,4-dioxaspiro[4.5]decane (8)

Treatment of compound **7** (600 mg, 2.24 mmol) in MeOH (10 mL) with *p*-toluenesulfonic acid (PTSA) (20 mg, 0.105 mmol), the mixture was allowed to stir at room temperature until the complete consumption of the starting material monitoring with TLC. The solution was concentrated in vacuo, and the residue was dissolved in CH₃CN (20 mL). Cyclohexanone (550 mg, 5.6 mmol) was added subsequently. The resulting solution was stirred for additional 2 h at room temperature, neutralized with Et₃N and concentrated. Column chromatography of the residue on silica gel (petroleum ether–EtOAc, 50 : 1) provided compound **8** (607 mg, 88% yield) as a colorless oil.

[α]_D²⁵ –1.0 (c 1.08, CHCl₃).

IR (neat): 2932, 2854, 1448, 1280, 1108, 928 cm^{–1}.

¹H NMR (400 MHz, CDCl₃): δ = 5.87–5.79 (m, 1H), 5.41 (d, 1H, *J* = 16.8 Hz), 5.31 (d, 1H, *J* = 10.4 Hz), 4.61 (t, 1H, *J* = 6.0 Hz), 4.41 (q, 1H, *J* = 6.4 Hz), 3.14 (dd, 1H, *J* = 10.0, 7.6 Hz), 3.03 (dd, 1H, *J* = 10.0, 6.4 Hz), 1.69–1.64 (m, 4H), 1.62–1.56 (m, 4H), 1.39–1.38 (m, 2H) ppm.

¹³C NMR (100 MHz, CDCl₃): δ = 132.69, 119.33, 109.76, 78.78, 78.03, 38.09, 35.05, 25.09, 24.08, 23.75, 4.13 ppm.

HRMS (ESI): *m/z*[M + Na]⁺ calcd for C₁₁H₁₇INaO₂: 331.0171; found: 331.0167.

(2*S*,3*R*)-2-methyl-3-vinyl-1,4-dioxaspiro[4.5]decane (9)

To a solution of compound **8** (200 mg, 0.649 mmol) in dry THF (8 mL) was added LiAlH₄ (246 mg, 6.49 mmol) powder under a nitrogen atmosphere. The suspension was stirred at room temperature for 2 h, then quenched by the addition of saturated solution of K/Na tartrate (10 mL) cautiously, extracted with EtOAc (3 × 10 mL), and the combined organic layer was concentrated. The residue was purified by silica gel column chromatography (petroleum ether–EtOAc, 50 : 1) to furnish compound **9** (96.9 mg, 82% yield) as a colorless oil.

[α]_D²⁵ +12.3 (c 0.3, CHCl₃).

IR (neat): 2927, 2854, 1448, 1366, 1112, 926 cm^{–1}.

¹H NMR (400 MHz, CDCl₃): δ = 5.84–5.75 (m, 1H), 5.30 (d, 1H, *J* = 17.2 Hz), 5.22 (d, 1H, *J* = 10.0 Hz), 4.47 (t, 1H, *J* = 6.8 Hz), 4.35–4.29 (m, 1H), 1.68–1.64 (m, 4H), 1.62–1.58 (m, 4H), 1.40–1.39 (m, 2H), 1.14 (d, 3H, *J* = 6.4 Hz) ppm.

¹³C NMR (100 MHz, CDCl₃): δ = 134.91, 118.10, 108.78, 79.74, 73.66, 38.18, 35.13, 25.27, 24.19, 23.88, 16.31 ppm.

HRMS (ESI): *m/z*[M + Na]⁺ calcd for C₁₁H₁₈NaO₂: 205.1204; found: 205.1212.

(2*R*,3*S*)-2-((*E*)-3-bromoprop-1-en-1-yl)-3-methyl-1,4-dioxaspiro[4.5]decane (2)

Method A: To a solution of compound **9** (615 mg, 3.376 mmol) and allyl bromide (840 mg, 6.94 mmol) in DCM (10 mL) was added Grubbs II catalyst (85.9 mg, 0.101 mmol). The mixture was allowed to stir at reflux until the completion of the reaction, and concentrated in vacuo. Column chromatography of the residue on silica gel (petroleum ether–EtOAc, 50 : 1) provided compound **2** (749 mg, 81% yield) as a colorless oil.

Method B: To a solution of compound **11** (900 mg, 2.92 mmol) in MeOH (10 mL) was added *p*-toluenesulfonic acid (PTSA) (25 mg, 0.131 mmol), the mixture was allowed to stir at room temperature until the

completion of the reaction monitoring with TLC. The solution was concentrated under reduced pressure, and the residue was dissolved in CH₃CN (20 mL). After that, cyclohexanone (0.76 g, 7.74 mmol) was added. The resulting solution was stirred for another 2 h at room temperature, neutralized by the addition of Et₃N and concentrated. Column chromatography of the residue on silica gel (petroleum ether–EtOAc, 50 : 1) gave compound **2** (0.71 g, 89% yield) as a colorless oil.

[α]_D²⁵ +6.1 (c 0.41, CHCl₃).

IR (neat): 2929, 1608, 1416, 1243, 1025 cm^{–1}.

¹H NMR (400 MHz, CDCl₃): δ = 5.94 (dt, 1H, *J* = 15.2, 7.2 Hz), 5.71 (dd, 1H, *J* = 15.2, 7.2 Hz), 4.49 (t, 1H, *J* = 6.4 Hz), 4.32 (dt, 1H, *J* = 12.8, 6.4 Hz), 3.94 (d, 2H, *J* = 7.6 Hz), 1.68–1.61 (m, 4H), 1.60–1.52 (m, 4H), 1.39–1.38 (m, 2H), 1.12 (d, 3H, *J* = 6.4 Hz) ppm.

¹³C NMR (100 MHz, CDCl₃): δ = 131.93, 129.61, 109.05, 78.02, 73.82, 38.12, 35.03, 31.68, 25.22, 24.17, 23.85, 16.24 ppm.

HRMS (ESI): *m/z*[M + H]⁺ calcd for C₁₂H₂₀BrO₂: 275.0647; found: 275.0640.

(3*R*,4*S*)-4-((*tert*-butyldimethylsilyl)oxy)pent-1-en-3-ol (10)

To a solution of ethyl L-lactate (2.36 g, 20 mmol) in DCM (20 mL) was added TBSCl (4.50 g, 30 mmol), imidazole (3.60 g, 60 mmol) in sequence. The solution was allowed to stir for 2 h at room temperature, then poured into water (10 mL) and extracted with DCM (2 × 15 mL), the combined organic layer was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether–EtOAc, 50 : 1) to afford TBS-protected ethyl L-lactate (4.46 g, 96% yield) as a colorless oil. To a solution of TBS-protected lactate (7 g, 30.15 mmol) in dry DCM (100 mL) was added DIBAL-H (1.1 M in hexane, 33 mL, 36.3 mmol) *via* dropping funnel at –98 °C under a nitrogen atmosphere. After 15 min, vinylmagnesium chloride (1.9 M in toluene, 30 mL, 57 mmol) was added dropwise to the above solution. The solution was allowed to warm to room temperature and stirred overnight. The saturated solution of K/Na tartrate (40 mL) was added slowly to quench the reaction. The aqueous layer was extracted with DCM (3 × 100 mL). The combined organic layer was concentrated in vacuo. The residue was purified by silica gel column chromatography (petroleum ether–EtOAc, 50 : 1) to provide compound **10** (5.4 g, 83% yield) as a yellow oil.

¹H NMR (400 MHz, CDCl₃): δ = 5.83–5.76 (m, 1H), 5.27 (d, 1H, *J* = 17.6 Hz), 5.17 (m, 1H, *J* = 9.2 Hz), 4.03–3.86 (m, 1H), 3.85–3.81 (m, 1H), 2.32 (d, 1H, *J* = 4.4 Hz), 1.14 (d, 3H, *J* = 6.0 Hz), 0.88 (s, 9H), 0.07 (s, 6H) ppm.

¹³C NMR (100 MHz, CDCl₃): δ = 136.66, 116.51, 76.73, 71.37, 25.85, 18.11, 17.69, –4.39, –4.80 ppm.

(2*S*,3*R*,*E*)-6-bromo-2-((*tert*-butyldimethylsilyl)oxy)hex-4-en-3-ol (11)

To a solution of compound **10** (2.5 g, 11.56 mmol) and allyl bromide (3.5 g, 28.93 mmol) in DCM (10 mL) was added Grubbs II catalyst (310 mg, 0.365 mmol). The mixture was stirred for 5 h at reflux, and concentrated in vacuo. Column chromatography of the residue on silica gel (petroleum ether–EtOAc, 50 : 1) provided compound **11** (2.67 g, 75% yield) as a yellow oil.

[α]_D²⁵ +10.3 (c 0.92, CHCl₃).

IR (neat): 1634, 1378, 1253, 970 cm^{–1}.

¹H NMR (400 MHz, CDCl₃): δ = 5.99–5.91 (m, 1H), 5.74 (dd, 1H, *J* = 15.2, 6.0 Hz), 4.05–4.03 (m, 1H), 3.95 (d, 2H, *J* = 7.6 Hz), 3.87–3.81 (m, 1H), 2.33 (d, 1H, 4.0 Hz), 0.89 (s, 9H), 0.07 (s, 6H) ppm.

¹³C NMR (100 MHz, CDCl₃): δ = 133.59, 128.30, 75.26, 71.25, 32.15, 25.84, 18.09, 17.88, –4.37, –4.81 ppm.

HRMS (ESI): m/z [M + Na]⁺ calcd for C₁₂H₂₅BrNaO₂Si: 331.0705; found: 331.0718.

Fuzanin D (1)

PPh₃ (630 mg, 2.40 mmol) was added to a solution of compound **2** (600 mg, 2.19 mmol) in CH₃CN (20 mL), the mixture was heated at reflux under a nitrogen atmosphere till a complete consumption of the starting material. The solution was concentrated in vacuo to furnish compound **12** as a white powder, which was directly subjected to the coming Wittig olefination without further purification. To a suspension of compound **12** (587 mg, 1.09 mmol) in dried THF (10 mL) was added *n*-BuLi (2.5 M in THF, 0.5 mL, 1.25 mmol) via a syringe at -78 °C under a nitrogen atmosphere. After stirring for 45 min at the same temperature, 3-methylpicolinaldehyde **3** (110 mg, 0.91 mmol) dissolved in 5 mL of dried THF was added. The mixture was allowed to warm to room temperature gradually, and quenched with saturated aqueous NH₄Cl (8 mL) till the completion of the reaction. The organic layer was separated, and the water phase was extracted with EtOAc (3 × 10 mL), the combined organic layer was dried over anhydrous Na₂SO₄, concentrated in vacuo. The residue was dissolved in MeOH (10 mL), then PTSA (10 mg, 0.05 mmol) was added to the above solution. The reaction was quenched by the addition of Et₃N till the reaction finished, concentrated. Column chromatography of the residue on silica gel (petroleum ether–EtOAc, 2 : 1) furnished Fuzanin D (100 mg, 42% yield for 3 steps) as an amorphous solid.

$[\alpha]_D^{25}$ –23.7 (c 0.18, CHCl₃).

IR (neat): 3227, 2921, 1614, 1583, 1449, 1417, 1372, 1297, 1072, 989 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 8.40 (d, 1H, *J* = 3.6 Hz), 7.44–7.37 (m, 2H), 7.04 (dd, 1H, *J* = 7.6, 4.4 Hz), 6.80 (d, 1H, *J* = 14.8 Hz), 6.55 (dd, 1H, *J* = 15.2, 10.8 Hz), 6.00 (dd, 1H, *J* = 15.6, 6.8 Hz), 4.24–4.21 (m, 1H), 3.93–3.91 (m, 1H), 2.36 (s, 3H), 1.16 (d, 3H, *J* = 6.4 Hz) ppm.

¹³C NMR (100 MHz, CDCl₃): δ = 153.15, 146.72, 138.71, 134.82, 133.73, 132.49, 131.10, 127.90, 122.22, 76.03, 70.40, 18.85, 17.72 ppm.

HRMS (ESI): m/z [M + H]⁺ calcd for C₁₃H₁₈NO₂: 220.1338; found: 220.1324.

Acknowledgment

We are grateful to the financial support from Natural Science Foundation of Hubei Province of China (No. 2015CFB333) for Youth Fund and Hubei Chengguang Talented Youth Development Foundation, China.

Supporting Information

NO (this text will be deleted prior to publication)

Primary Data

NO (this text will be deleted prior to publication)

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