Chiron Approaches to the Antitumor Natural Product Fuzanin D

Yangguang Gao, Zhou Cao, Chengzhong Chen, Zefeng Chen, Xianran He, Fei Ding, Hang Li, Yongmin Zhang

▶ **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

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

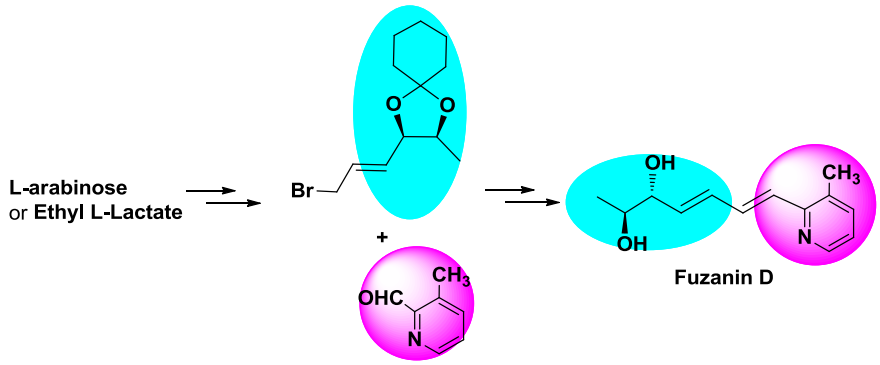
L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Chiron Approaches to Anti-tumor Natural Product Fuzanin D

YangguangGao[a,b,*]
Zhou Cao[b]
Chengzhong Su[b]
Zefeng Chen[c]
Xianran He[a,b]
Fei Ding[a,b]
Hang Li[a,b]
YongminZhang[a,d,*]

[a]Institute for Interdisciplinary Research, Jianghan University, Wuhan Economic and Technological Development Zone, Wuhan 430056, People's Republic of China
[b] Key Laboratory of Optoelectronic Chemical Materials and Devices of Ministry of Education, Jianghan University,Wuhan Economic and Technological Development Zone,Wuhan 430056, People's Republic of China
[c]Chimie, IUT d'Orsay, Université Paris sud, plateau deMoulon, 91400 Orsay, France
[d]InstitutParisien de ChimieMoléculaire, CNRS UMR 8232, Université Pierre et Marie Curie-Paris 6, 4 Place Jussieu, 75005Paris, France

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

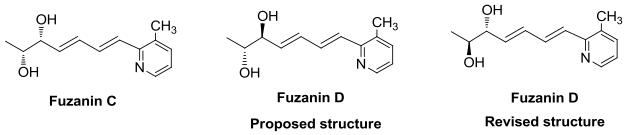


AbstractFuzanin D, a pyridine-containing natural product, which exhibitscytotoxic activity against DLD-1 cells, has been synthesized in a concise manner usingL-arabinose or ethyl L-lactate as chiral pool over 6-9 steps. Key steps involved olefin cross-metathesis and Wittig olefination.

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-inflammatoryactivities.[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 IC_{50} value of 41.2 μM. Besides, it also displayed moderate inhibition of Wntsignal transcription at 25 mM.

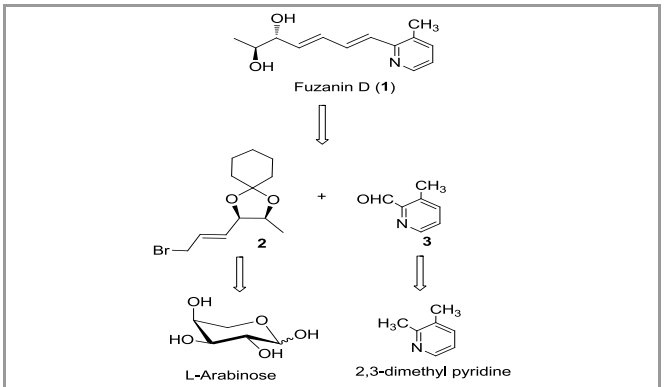
Recently, the Rao's group has achieved the syntheses of Fuzanins C, D and their derivatives as well as preformed biological evaluation on anticancer in vitro (Scheme 1).[9] On the basis of synthesis, the original absolute configuration of Fuzanin D was suggested to be reassigned. In the synthesis of 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-methylpicolinaldehyde**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]

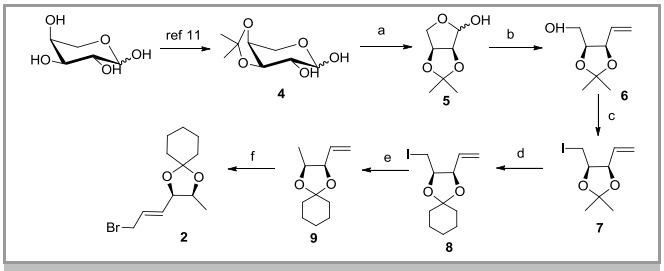
Synthesis of building block **2** was commenced with a known compound 3,4-*O*-isopropylidene-L-arabopyranose**4** (Scheme 3).[11] Oxidative cleavage of compound **4** with $NaIO_4$ followed by treatment of the crude product with Na_2CO_3 gave protected L-erythrose**5**.[12] Without further purification, compound **5** was subjected to Wittig olefination[13] 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 condition[14] gave compound **7** in a high yield (90%). Reduction of iodide **7** was carried out smoothly with an excess amount of $LiAlH_4$ (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.



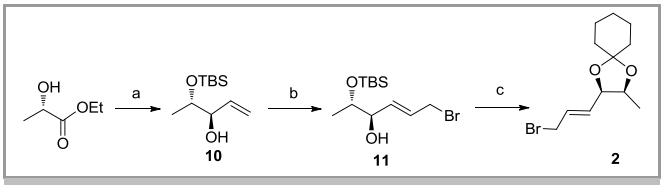
Scheme 2 Retrosynthetic analysis of Fuzanin D.

An alternative synthesis of building block **2** was summarized inScheme 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 procedure[15] when using DCM as solvent instead of Et_2O. 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.

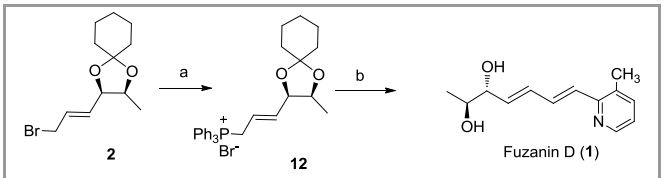


Scheme 3 Synthesis of compound **2**.*Reagents and conditions*: (a) $NaIO_4$, MeOH-H_2O, then Na_2CO_3; (b) Ph_3P^+·CH_3Br^-, *n*-BuLi, toluene, 0°C to reflux, 52% yield for 2 steps; (c) I_2, PPh_3, imidazole, THF, reflux, 90% yield; (d) PTSA, MeOH, then CH_3CN, cyclohexanone, 88% yield; (e) $LiAlH_4$, 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 CH_3CN, 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 PPh_3 in CH_3CN 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) PPh_3, CH_3CN, 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 ^{13}CNMR spectra were recorded with Bruker Avance III spectrometer at 400 MHz, 100 MHz respectively, relative to Me_4Si (δ = 0 ppm) as internal standard. HRMS were measured with a Bruker micro-TOFQ II mass spectrometer. IR spectra were recorded on neat sampleswith 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-*arabo*pyranose**4** (10.4 g, 54.71mmol) in MeOH (100mL) was added $NaIO_4$ 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 Na_2CO_3 powder, and stirred for another 1h. 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 °Cunder 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, andquenched with saturated aqueous NH_4Cl (100 mL) until TLCindicated a complete consumption of the starting material.The organic layer was removed and the water phase wasextracted with EtOAc (3 × 100 mL), and the combined organiclayer 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).

$[\alpha]_D^{25}$–39.2 (c 0.35, $CHCl_3$).

IR (neat):1637, 1376, 1215, 1164, 1039 cm^{-1}.

^1HNMR (400MHz, $CDCl_3$): 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.

^{13}C NMR (100MHz, $CDCl_3$): 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 $C_8H_{13}O_3$: 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 I_2 (1.18 g, 4.65 mmol), PPh_3 (1.22g, 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 $Na_2S_2O_3$ solution (10 mL) was added to quench the reaction, the organic layer was seperated, extracted with EtOAc (3 × 10 mL), and the combined organiclayer 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.

$[\alpha]_D^{25}$–1.45 (c 0.76, $CHCl_3$).

IR (neat): 2986, 2931, 1428, 1380, 1215, 1042, 870cm^{-1}.

^{1}HNMR (400MHz, $CDCl_3$): 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.

^{13}C NMR (100MHz, $CDCl_3$): 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 $C_8H_{13}INaO_2$: 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 CH_3CN (20 mL). Cyclohexanone (550 mg, 5.6 mmol) was added subsequently. The resulting solution was stirred for additional 2h at room temperature,neutralized with Et_3N 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.

$[\alpha]_D^{25}$ –1.0 (c 1.08, $CHCl_3$).

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

^{1}HNMR (400MHz, $CDCl_3$): 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.

^{13}C NMR (100MHz, $CDCl_3$): 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 $C_{11}H_{17}INaO_2$: 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 $LiAlH_4$ (246 mg, 6.49 mmol) powder under a nitrogen atmosphere. The suspension was stirred at room temperature for 2h, then quenched by the addition of saturated solution of K/Na tartrate (10 mL) cautiously, extracted with EtOAc (3 × 10 mL), and the combined organiclayer 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.

$[\alpha]_D^{25}$ +12.3 (c 0.3, $CHCl_3$).

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

^{1}HNMR (400MHz, $CDCl_3$): 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.

^{13}C NMR (100MHz, $CDCl_3$): 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 $C_{11}H_{18}NaO_2$: 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 CH_3CN (20 mL). After that, cyclohexanone (0.76 g, 7.74 mmol) was added. The resulting solution was stirred for another 2h at room temperature, neutralized by the addition of Et_3N 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.

$[\alpha]_D^{25}$ +6.1 (c 0.41, $CHCl_3$).

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

^{1}HNMR (400MHz, $CDCl_3$): 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.

^{13}C NMR (100MHz, $CDCl_3$): 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 $C_{12}H_{20}BrO_2$: 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 2h 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) wasadded dropwise to the above solution. The solution was allowed to warmtoroom 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.

^{1}HNMR (400MHz, $CDCl_3$): 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.

^{13}C NMR (100MHz, $CDCl_3$):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.

$[\alpha]_D^{25}$ +10.3 (c 0.92, $CHCl_3$).

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

^{1}HNMR (400MHz, $CDCl_3$): 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.

^{13}C NMR (100MHz, $CDCl_3$): 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 $C_{12}H_{25}BrNaO_2Si$: 331.0705; found: 331.0718.

Fuzanin D (1)

PPh_3 (630 mg, 2.40 mmol) was added to a solution of compound **2** (600 mg, 2.19 mmol) in CH_3CN (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 NH_4Cl (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 Na_2SO_4, 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 Et_3N 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, $CHCl_3$).

IR (neat): 3227, 2921, 1614, 1583, 1449, 1417, 1372, 1297, 1072, 989 cm^{-1}.

^{1}HNMR (400MHz, $CDCl_3$): 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.

^{13}C NMR (100MHz, $CDCl_3$): 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 $C_{13}H_{18}NO_2$: 220.1338; found: 220.1324.

Acknowledgment

We are grateful tothe financial support from Natural Science Foundation of Hubei Province of China (No. 2015CFB333) for Youth Fund and Hubei Chenguang 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)

References

(1) Majumdar, K. C.; Chattopadhyay, S. K. *Heterocycles in Natural Product Synthesis*; Wiley-VCH: Weinheim, **2011**, 267.

(2) (a) Takekawa, Y.; Matsunaga, S. ; van Soest,R.W.M. ; Fusetani, N.*J. Nat. Prod.*, **2006**, *69*, 1503. (b) Tsukamoto, S.; Takahashi, M.; Matsunaga, S.; Fusetani, N.; vanSoest, R.W.M.*J. Nat. Prod.*, **2000**, *63*, 682. (c) Schmidt, G.; Timm, C.; Köck, M.*Org.Biomol. Chem.*,**2009**, *7*, 3061.

(3) Arai, M.; Ishida, S.; Setiawan, A.; Kobayashi, M.*Chem.Pharm. Bull.*, **2009**, *57*, 1136.

(4) (a) Musiol,R.; Serda,M.; Hensel-Bielowka, S.; Polanski, J.; *Curr. Med. Chem.*, **2010**, *17*, 1960. (b) Nicholas, G.M.; Molinski, T.F.*Tetrhedron*, **2000**, *56*, 2921.

(5) (a) Cheng, X.-F. ; Meng, Z.-M.; Chen,Z.-L.; *Phytochemistry*,**1998**, *49*, 2193. (b) Eun, J. S.; Seo, S.-Y. *Arch. Pharm. Res.*, **2009**, *32*, 1673.

(6) Kem , W.R.; Scott , K.N.; Duncan,J.H.*Experientia*, **1976**, *32*, 684.

(7) (a)Mukherjee,S.; Pal, M.;*Drug Discovery Today*, **2013**, *18*, 389.(b) De Marino, S.; Iorizzi, M.; Zollo, F.; Debitus, C.; Menou, J. L.; Ospina, L.F.; Alcaraz , M.J.; Payá , M.*J. Nat. Prod.*, **2000**, *63*, 322.

(8) Aida,W.; Ohtsuki, T.; Li, X.; Ishibashi, M. *Tetrahedron*,**2009**, *65*, 369.

(9) Kumar,S. N.; Sai Pavan Kumar, C. H. N. S.; Srihari, E.;Kancharl, S.; Srinivas,K.;Shrivastav, S.; Naidu, V. G. M.; Rao, V. J.*RSC Adv.*, **2014**, *4*, 8365.

(10) Dunn, A. D. *Organic Preparations and Procedures International : The New Journal for OrganicSynthesis*, **1999**, *31*, 120.

(11) (a)Hollingsworth, R. I. *J. Org. Chem.*,**1999**, *64*, 7633.(b) Gao, Y.-G.; Liu, J.; Wang, L.-L; Xiao, M.; Du, Y.-G. *Eur. J. Org. Chem.*,**2014**, 2092.

(12) Thompson,D. K.; Hubert, C. N.; Wightman, R. H. *Tetrahedron*, **1993**, *49*, 3827.

(13) (a) Rao, B. V.; LahiriIrgolic, S. *J. Carbohyd. Chem.*, **1996**, *15*, 975. (b) Joshi,B. V.; Moon, H. R.; Fettinger, J. C.; Marquez, V. E.; Jacobson, K. A.*J. Org. Chem.*, **2005**, *70*, 439.

(14) Chavan,S. P.; Praveen, C.; Ramakrishna, G.; Kalkote, U. R. *Tetrahedron Lett.*, **2004**, *45*, 6027.

(15) (a) Schmidt, B.; Biernat, A. *Chem. Eur. J.*, **2008**, *14*, 6135; (b) Liu,J.; Liu,Y.; Zhang, X.; Zhang, C.-L.; Gao,Y.-G.; Wang, L.-L.; Du, Y.-G. *J. Org. Chem.*, **2012**, *77*, 9718.