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Chiron Approaches to the Antitumor Natural Product Fuzanin D

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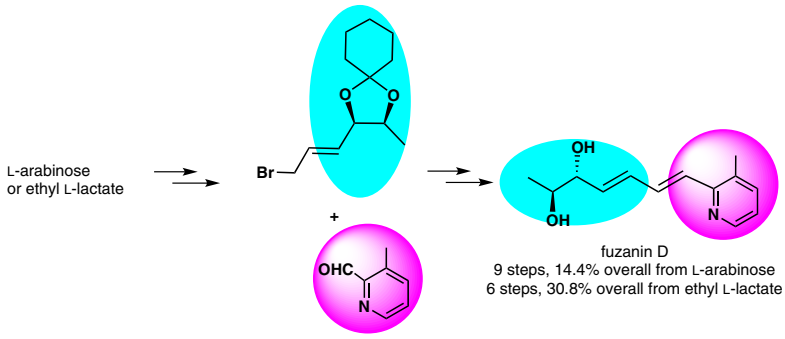

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Abstract Fuzanin D, a pyridine-containing natural product, which exhibits cytotoxic activity against DLD-1 cells, is synthesized in a concise manner using L-arabinose or ethyl L-lactate as chiral pool substrates in nine steps (14.4% overall yield) and six steps (30.8% overall yield), respectively. The key steps involve Wittig olefination and olefin cross-metathesis.

Key words synthesis, chiral pool, antitumor, cross-metathesis, olefination

Pyridine-containing natural products, which mainly originate from animals, plants, eukaryotes and prokaryotes, fascinate the chemical community due to their wide spectrum of biological activity,[1] such as cytotoxic,[2] antimicrobial,[3] antifungal,[4] anti-HIV,[5] neurotoxic,[6] and anti-inflammatory.[7] Fuzanin D, a disubstituted pyridine-containing natural product, incorporating a long chain with an *E*,*E*-conjugated diene moiety and adjacent hydroxy groups was isolated from the culture supernatant of *Kitasatospora* sp. IFM10917 by Ishibashi and co-workers in 2009.[8] The *in vitro* determination of the biological activity of fuzanin D revealed inhibitory activity against DLD-1 cells with an IC_{50} value of 41.2 μM. Besides, it also displayed moderate inhibition of Wnt signal transcription at 25 mM.

Recently, Rao's group achieved the syntheses of fuzanins C and D and their derivatives, and performed an *in vitro* biological evaluation of their anticancer activity (Figure 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 a Julia olefination was utilized to construct the carbon–carbon double bond. Herein, we describe an alternative syntheses of fuzanin D using L-arabinose or ethyl L-lactate as chiral pool substrates.

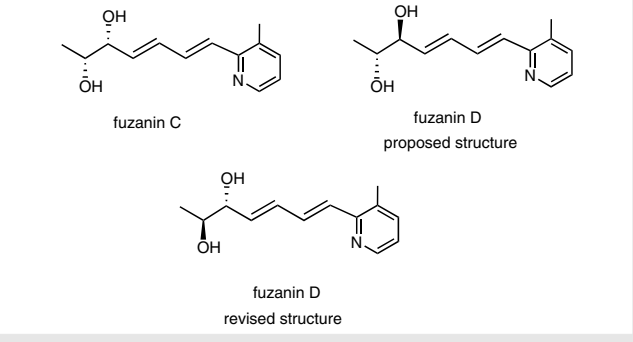
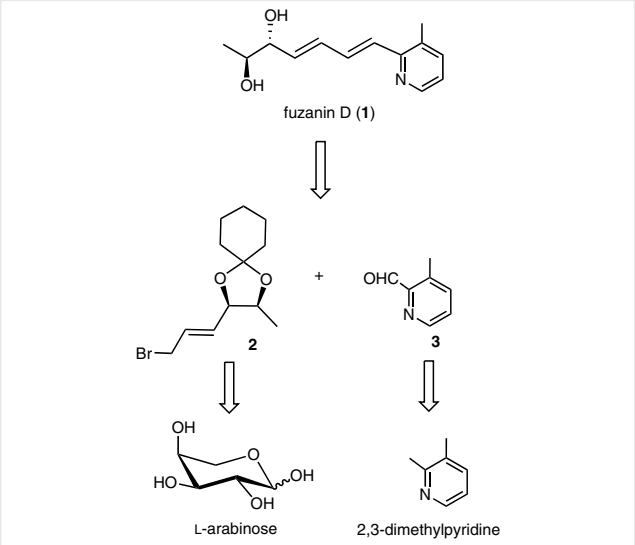


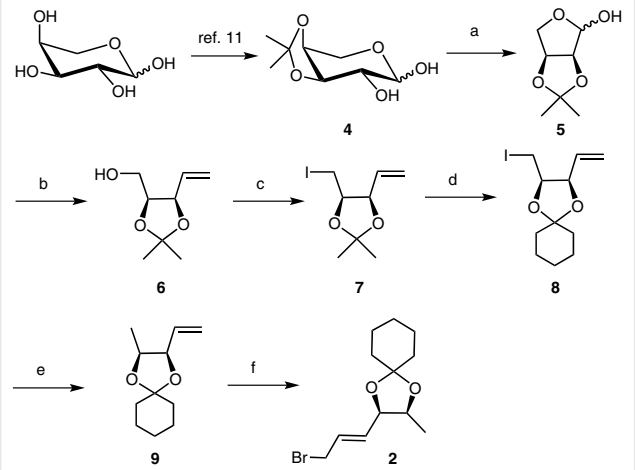
Figure 1 Structures of fuzanin C and fuzanin D

As shown in Scheme 1, the synthesis of fuzanin D (**1**) could be achieved by Wittig olefination between building block **2** and 3-methylpicolinaldehyde (**3**), followed by removal of the cyclohexylidene group. Compound **2** can be prepared from commercially available L-arabinose through several conventional manipulations, while aldehyde **3** can be easily obtained by selective oxidation of 2,3-dimethylpyridine according to a literature procedure.[10]



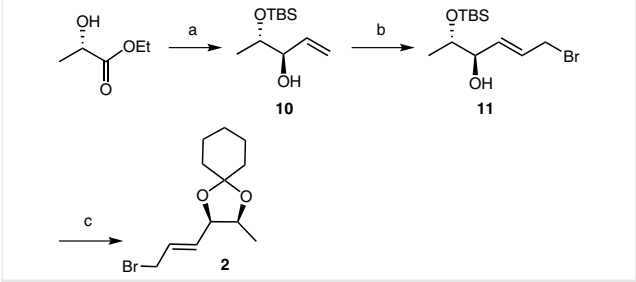
Scheme 1 Retrosynthetic analysis of fuzanin D

The synthesis of building block **2** was commenced from the known compound 3,4-*O*-isopropylidene-L-arabinopyranose (**4**) (Scheme 2).[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 an in situ generated methyl Wittig reagent in toluene at reflux to provide enol **6** in 52% yield over two steps. It should be noted that the ring-opening reaction with the Wittig reagent gave a low yield of **6** when using THF as the solvent at 0 °C to room temperature. Iodination of enol **6** using standard Appel reaction conditions[14] gave compound **7** in a high yield (90%). Reduction of iodide **8** was carried out smoothly with an excess amount of $LiAlH_4$ (10 equiv) to give terminal-methyl-containing compound **9** in 82% yield. In consideration of the low boiling point of the direct reduction product of iodide **7** by $LiAlH_4$, the isopropylidene group was replaced by a bulky cyclohexylidene group via a two-step conversion in a yield of 88%. Olefin cross-metathesis (OCM) between compound **9** and allyl bromide using a catalytic amount of Grubbs' second-generation catalyst (Grubbs II) exclusively generated *trans*-olefin **2** (J = 15.2 Hz) in 81% yield.



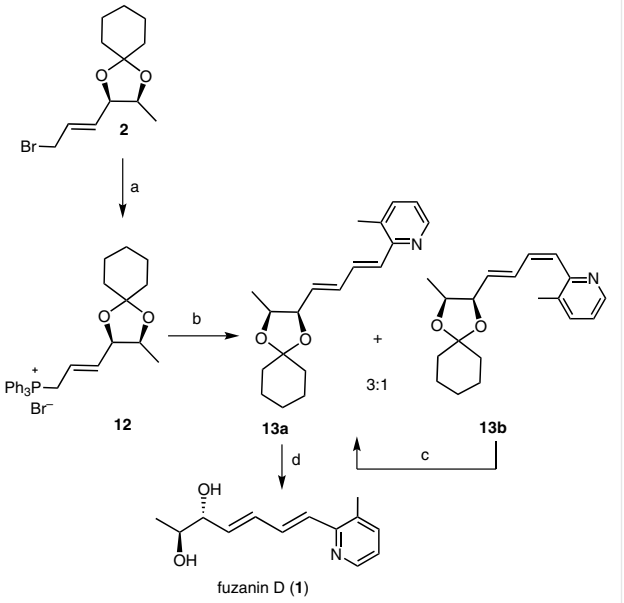
Scheme 2 Synthesis of compound **2**. *Reagents and conditions*: (a) $NaIO_4$, MeOH–H_2O, then Na_2CO_3; (b) $Ph_3P^+CH_3Br^-$, *n*-BuLi, toluene, 0 °C to reflux, 52% over 2 steps; (c) I_2, PPh_3, imidazole, THF, reflux, 90%; (d) PTSA, MeOH, then MeCN, cyclohexanone, 88%; (e) $LiAlH_4$, THF, 82%; (f) allyl bromide, Grubbs II, CH_2Cl_2, 81%.

An alternative synthesis of building block **2** is summarized in Scheme 3. The required secondary allylic alcohol **10** was obtained as a 20:1 mixture of diastereoisomers from ethyl L-lactate over three steps, being superior to the literature procedure[15] when using CH_2Cl_2 as the solvent instead of Et_2O. Next, compound **10** and allyl bromide were subjected to a similar OCM as described for **2** (see Scheme 2) to give *trans*-olefin **11** in 75% yield. Compound **11** was converted into compound **2** in a high yield (89%) through unblocking of the silyl ether under acidic conditions followed by protection with a cyclohexylidene group.



Scheme 3 An alternative synthesis of compound **2**. *Reagents and conditions*: (a) (i) TBSCl, imidazole, CH_2Cl_2, 96%; (ii) DIBAL-H, CH_2Cl_2, –98 °C, then vinylmagnesium chloride (1.9 M), –98 °C to r.t., 83%; (b) allyl bromide, Grubbs II, CH_2Cl_2, 75%; (c) PTSA, MeOH, then MeCN, cyclohexanone, 89%.

With building block **2** and 3-methylpicolinaldehyde (**3**) in hand, their assembly into fuzanin D became our next goal. As shown in Scheme 4, treatment of compound **2** with PPh_3 in MeCN at reflux temperature gave the corresponding alkyltriphenylphosphonium salt **12**. Without purification, the alkyltriphenylphosphonium salt **12** was deprotonated by *n*-BuLi at –78 °C in THF to provide the *in situ* Wittig reagent, which reacted with 3-methylpicolinaldehyde (**3**) in the presence of LiBr[16] to give a separable *E*/*Z*-mixture in a ratio of 3:1. Fortunately, the *Z*-isomer (J = 11.2 Hz) could be converted into the desired compound **13a** in 67% yield via a radical-induced isomerization using a slightly modified literature procedure.[17] Finally, deprotection of compound **13a** gave the natural product fuzanin D (**1**) in 92% yield. The value of the optical rotation and the spectral data were in good accordance with those previously reported in the literature.[9]



Scheme 4 Synthesis of fuzanin D (**1**). *Reagents and conditions*: (a) PPh_3, MeCN, 80 °C; (b) *n*-BuLi (2.5 M), LiBr, THF, then 3-methylpicolinaldehyde (**3**), –78 °C, 63% over 2 steps; (c) see ref. 17, 67%; (d) PTSA, MeOH, 92%.

In conclusion, the synthesis of fuzanin D (**1**) has been achieved starting from either L-arabinose or ethyl L-lactate in nine steps (14.4 overall yield) and six steps (30.8 overall yield), respectively. The highlight of the protocol was the use of the natural chiral pool to set the stereogenic centers, and adopting Wittig olefination and olefin cross-metathesis reactions as crucial steps. Our method is flexible and facile, and can be applied to synthesize homologues or derivatives of fuzanin D, the results of which will be reported in due course.

All reagents were commercially available and were used directly without further purification unless otherwise stated. Column chromatography was carried out using Haiyang brand silica gel (100–200 mesh). Routine monitoring of reactions was carried out using Huanghai brand silica gel 60 F254 TLC plates. Optical rotations were recorded with an AUTOPOL IV automatic polarimeter. IR spectra were recorded as neat samples with a NICOLET iS 10 infrared spectrometer. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker Avance III spectrometer at 400 MHz and 100 MHz, respectively, relative to Me_4Si (δ = 0) as an internal standard. HRMS were measured with a Bruker micro-TOFQ II mass spectrometer.

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

To a solution of 3,4-*O*-isopropylidene-L-arabinopyranose (**4**) (10.4 g, 54.71 mmol) in MeOH (100 mL) was added a solution of $NaIO_4$ [16 g dissolved in H_2O (90 mL)] via a dropping funnel, and the mixture was allowed to stir at r.t. After the reaction was complete (monitoring by TLC), the solution was basified (pH 9) by the addition of Na_2CO_3 powder, and stirred for another 1 h. The undissolved white solid was filtered and the filtrate was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layer was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (PE–EtOAc, 3:1) to give compound **5** (6.30 g, 72%) as a syrup. The spectral data agreed with those reported in the literature.[12]

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

To a suspension of methyltriphenylphosphonium bromide (15 g, 42.13 mmol) in anhydrous toluene (100 mL) was added dropwise *n*-BuLi solution (19.3 mL, 2.5 M in hexane, 48.25 mmol) at 0 °C under a nitrogen atmosphere. The resulting yellow suspension was stirred for 45 min at the same temperature, then a solution of compound **5** (3 g, 18.74 mmol) in toluene (10 mL) was added dropwise. After the addition was complete, the ice bath was replaced by an oil bath. The mixture was heated at reflux until TLC indicated complete consumption of the starting material, and was then quenched with sat. aq NH_4Cl (100 mL). The organic layer was separated and the aq phase was extracted with EtOAc (3 × 100 mL). The combined organic layer was concentrated in vacuo and column chromatography of the residue on silica gel (PE–EtOAc, 3:1) afforded compound **6** (1.54 g, 52% over 2 steps) as a yellow oil.

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

IR (neat): 3420, 1637, 1376, 1215, 1164, 1039 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.87–5.78 (m, 1 H), 5.35 (dt, *J* = 17.2, 1.2 Hz, 1 H), 5.29 (dt, *J* = 10.4, 1.6 Hz, 1 H), 4.61 (t, *J* = 7.6 Hz, 1 H), 4.23 (q, *J* = 5.6 Hz, 1 H), 3.54 (t, *J* = 4.4 Hz, 2 H), 2.23 (br s, 1 H), 1.48 (s, 3 H), 1.36 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 133.11, 119.15, 109.02, 78.43, 78.39, 62.21, 27.93, 25.37.

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) were added sequentially I_2 (1.18 g, 4.65 mmol), PPh_3 (1.22 g, 4.65 mmol) and imidazole (530 mg, 8.54 mmol). The mixture was heated at reflux until the completion of the reaction (monitoring by TLC). Sat. $Na_2S_2O_3$ solution (10 mL) was added to quench the reaction, the organic layer was separated and extracted with EtOAc (3 × 10 mL), and the combined organic layer was concentrated. The residue was purified by silica gel column chromatography (PE–EtOAc, 50:1) to furnish compound **7** (625 mg, 90%) as a yellow oil.

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

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

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.87–5.80 (m, 1 H), 5.43 (dt, *J* = 17.2, 1.2 Hz, 1 H), 5.33 (dt, *J* = 10.4, 1.6 Hz, 1 H), 4.63 (t, *J* = 6.0 Hz, 1 H), 4.46–4.41 (m, 1 H), 3.14 (dd, *J* = 10.4, 7.6 Hz, 1 H), 3.06 (dd, *J* = 10.0, 6.4 Hz, 1 H), 1.51 (s, 3 H), 1.38 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 132.43, 119.49, 109.12, 79.20, 78.56, 28.21, 25.62, 3.91.

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)

A mixture of compound **7** (600 mg, 2.24 mmol) in MeOH (10 mL) and *p*-toluenesulfonic acid (PTSA) (20 mg, 0.105 mmol) was allowed to stir at r.t. until the starting material had been completely consumed (monitoring by TLC). The solution was concentrated in vacuo and the residue was dissolved in MeCN (20 mL). Cyclohexanone (550 mg, 5.6

mmol) was added subsequently and the resulting solution was stirred for an additional 2 h at r.t., neutralized with Et_3N and concentrated. Column chromatography of the residue on silica gel (PE–EtOAc, 50:1) provided compound **8** (607 mg, 88%) as a colorless oil.

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

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

^1H NMR (400 MHz, $CDCl_3$): δ = 5.87–5.79 (m, 1 H), 5.41 (d, *J* = 16.8 Hz, 1 H), 5.31 (d, *J* = 10.4 Hz, 1 H), 4.61 (t, *J* = 6.0 Hz, 1 H), 4.41 (q, *J* = 6.4 Hz, 1 H), 3.14 (dd, *J* = 10.0, 7.6 Hz, 1 H), 3.03 (dd, *J* = 10.0, 6.4 Hz, 1 H), 1.69–1.64 (m, 4 H), 1.62–1.56 (m, 4 H), 1.39–1.38 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 132.69, 119.33, 109.76, 78.78, 78.03, 38.09, 35.05, 25.09, 24.08, 23.75, 4.13.

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 anhyd THF (8 mL) was added $LiAlH_4$ powder (246 mg, 6.49 mmol) under a nitrogen atmosphere. The suspension was stirred at r.t. for 2 h, then quenched by the addition of a sat. 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 (PE–EtOAc, 50:1) to furnish compound **9** (96.9 mg, 82%) as a colorless oil.

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

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

^1H NMR (400 MHz, $CDCl_3$): δ = 5.82–5.75 (m, 1 H), 5.30 (dt, *J* = 17.2, 1.2 Hz, 1 H), 5.22 (ddd, *J* = 10.4, 1.6, 0.8 Hz, 1 H), 4.48 (t, *J* = 7.2 Hz, 1 H), 4.36–4.29 (m, 1 H), 1.69–1.64 (m, 4 H), 1.62–1.58 (m, 4 H), 1.41–1.39 (m, 2 H), 1.14 (d, *J* = 6.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.91, 118.10, 108.78, 79.74, 73.66, 38.18, 35.13, 25.27, 24.19, 23.88, 16.31.

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 (Step f, Scheme 2)

To a solution of compound **9** (615 mg, 3.376 mmol) and allyl bromide (840 mg, 6.94 mmol) in CH_2Cl_2 (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 then concentrated in vacuo. Column chromatography of the residue on silica gel (PE–EtOAc, 50:1) provided compound **2** (749 mg, 81% yield) as a colorless oil.

Method B (Step c, Scheme 3)

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), and the mixture was allowed to stir at r.t. until the completion of the reaction (monitoring with TLC). The solution was concentrated under reduced pressure and the residue was dissolved in MeCN (20 mL). Next, cyclohexanone (0.76 g, 7.74 mmol) was added. The resulting solution was stirred for another 2 h at r.t., then neutralized by the addition of Et_3N and concentrated. Column chromatography of the residue on silica gel (PE–EtOAc, 50:1) gave compound **2** (0.71 g, 89%) as a colorless oil.

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

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

^1H NMR (400 MHz, $CDCl_3$): δ = 5.94 (dt, *J* = 15.2, 7.2 Hz, 1 H), 5.71 (dd, *J* = 15.2, 7.2 Hz, 1 H), 4.49 (t, *J* = 6.4 Hz, 1 H), 4.32 (dt, *J* = 12.8, 6.4 Hz, 1 H), 3.94 (d, *J* = 7.6 Hz, 2 H), 1.68–1.61 (m, 4 H), 1.60–1.52 (m, 4 H), 1.39–1.38 (m, 2 H), 1.12 (d, *J* = 6.4 Hz, 3 H).

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

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 CH_2Cl_2 (20 mL) were sequentially added TBSCl (4.50 g, 30 mmol) and imidazole (3.60 g, 60 mmol). The solution was allowed to stir for 2 h at r.t., then poured into H_2O (10 mL) and extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layer was concentrated under reduced pressure and the residue purified by column chromatography on silica gel (PE–EtOAc, 50:1) to afford TBS-protected ethyl L-lactate (4.46 g, 96%) as a colorless oil.

To a solution of the TBS-protected lactate (7 g, 30.15 mmol) in anhyd CH_2Cl_2 (100 mL) was added DIBAL-H (33 mL, 1.1 M in hexane, 36.3 mmol) via a dropping funnel at –98 °C under a nitrogen atmosphere. After 15 min, vinylmagnesium chloride (30 mL, 1.9 M in toluene, 57 mmol) was added dropwise to the above solution. The solution was allowed to warm to r.t. and stirred overnight. A sat. solution of K/Na tartrate (40 mL) was added slowly to quench the reaction and the aq layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layer was concentrated in vacuo. The residue was purified by silica gel column chromatography (PE–EtOAc, 50:1) to provide compound **10** (5.4 g, 83%) as a yellow oil.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.83–5.76 (m, 1 H), 5.27 (dt, *J* = 17.6, 1.6 Hz, 1 H), 5.17 (dt, *J* = 10.8, 1.6 Hz, 1 H), 4.03–3.86 (m, 1 H), 3.85–3.81 (m, 1 H), 2.32 (d, *J* = 4.4 Hz, 1 H), 1.14 (d, *J* = 6.0 Hz, 3 H), 0.88 (s, 9 H), 0.07 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.66, 116.51, 76.73, 71.37, 25.85, 18.11, 17.69, –4.39, –4.80.

(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 CH_2Cl_2 (10 mL) was added Grubbs II catalyst (310 mg, 0.365 mmol). The mixture was stirred for 5 h at reflux, and then concentrated in vacuo. Column chromatography of the residue on silica gel (PE–EtOAc, 50:1) provided compound **11** (2.67 g, 75%) as a yellow oil.

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

IR (neat): 3306, 1634, 1378, 1253, 970 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.99–5.91 (m, 1 H), 5.74 (dd, *J* = 15.2, 6.0 Hz, 1 H), 4.05–4.03 (m, 1 H), 3.95 (d, *J* = 7.6 Hz, 2 H), 3.87–3.81 (m, 1 H), 2.33 (d, *J* = 4.0 Hz, 1 H), 1.07 (d, *J* = 6.4 Hz, 3 H), 0.89 (s, 9 H), 0.07 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 133.59, 128.30, 75.26, 71.25, 32.15, 25.84, 18.09, 17.88, –4.37, –4.81.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{25}BrNaO_2Si$: 331.0705; found: 331.0718.

3-Methyl-2-{(1*E*,3*E*)-4-[(2*R*,3*S*)-3-methyl-1,4-dioxaspiro[4.5]decan-2-yl]buta-1,3-dien-1-yl}pyridine (13a) and 3-Methyl-2-{(1*Z*,3*E*)-4-[(2*R*,3*S*)-3-methyl-1,4-dioxaspiro[4.5]decan-2-yl]buta-1,3-dien-1-yl}pyridine (13b)

PPh_3 (630 mg, 2.40 mmol) was added to a solution of compound **2** (600 mg, 2.19 mmol) in MeCN (20 mL), and the mixture was heated at reflux under a nitrogen atmosphere until 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 Wittig olefination without further purification.

To a suspension of compound **12** (587 mg, 1.09 mmol) and LiBr (473 mg, 5.45 mmol) in anhyd THF (10 mL) was added *n*-BuLi (0.5 mL, 2.5 M in THF, 1.25 mmol) via a syringe at –78 °C under a nitrogen atmosphere. After stirring for 45 min at the same temperature, a solution of 3-methylpicolinaldehyde (**3**) (110 mg, 0.91 mmol) in anhyd THF (5 mL) was added. The mixture was allowed to warm to r.t. gradually and quenched with MeOH (8 mL) after completion of the reaction. The mixture was further stirred overnight and the solvent was removed under reduced pressure. Column chromatography of the residue on silica gel (PE–EtOAc, 25:1) furnished **13a** (171.5 mg, 63% over 2 steps) as an amorphous solid, and **13b** (57.2 mg, 21% over 2 steps) as a colorless oil.

Compound 13a

$[\alpha]_D^{25}$ –12.7 (*c* 0.525, $CHCl_3$).

IR (neat): 2932, 2859, 1735, 1581, 1448, 1367, 1231, 1100, 997 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.41 (d, *J* = 4.4 Hz, 1 H), 7.44–7.42 (m, 2 H), 7.06–7.03 (m, 1 H), 6.78 (d, *J* = 15.2 Hz, 1 H), 6.53–6.47 (m, 1 H), 5.92 (dd, *J* = 14.8, 7.6 Hz, 1 H), 4.61 (t, *J* = 7.2 Hz, 1 H), 4.38–4.31 (m, 1 H), 2.35 (s, 3 H), 1.71–1.57 (m, 8 H), 1.41–1.38 (m, 2 H), 1.13 (d, *J* = 6.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.28, 146.90, 138.47, 133.45, 133.18, 132.71, 130.92, 128.03, 122.13, 108.91, 78.91, 74.05, 38.21, 35.15, 25.27, 24.20, 23.89, 18.85, 16.48.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{25}NNaO_2$: 322.1783; found: 322.1780.

Compound 13b

$[\alpha]_D^{25}$ +9.28 (*c* 0.28, $CHCl_3$).

IR (neat): 2931, 2859, 1580, 1447, 1365, 1280, 1100, 992 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.45 (d, *J* = 4.4 Hz, 1 H), 7.44 (d, *J* = 8.0 Hz, 1 H), 7.39 (dd, *J* = 15.6, 10.8 Hz, 1 H), 7.05 (dd, *J* = 7.6, 4.8 Hz, 1 H), 6.49 (t, *J* = 11.2 Hz, 1 H), 6.43 (t, *J* = 11.2 Hz, 1 H), 5.84 (dd, *J* = 15.2, 8.4 Hz, 1 H), 4.60 (t, *J* = 8.0 Hz, 1 H), 4.36–4.30 (m, 1 H), 2.30 (s, 3 H), 1.70–1.56 (m, 8 H), 1.40–1.36 (m, 2 H), 1.16 (d, *J* = 6.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.87, 146.49, 137.73, 133.88, 132.88, 131.83, 130.84, 126.25, 121.76, 108.74, 79.08, 74.03, 38.15, 35.11, 25.21, 24.14, 23.81, 19.13, 16.41.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{25}NNaO_2$: 322.1783; found: 322.1795.

Isomerization of 13b into 13a

To a solution of compound **13b** (30 mg, 0.10 mmol) in anhyd toluene (4 mL) was added *p*-toluenethiol (62 mg, 0.50 mmol) and AIBN (82 mg, 0.50 mmol). The mixture was heated at reflux for 3 h, then concentrated in vacuo. The residue was purified by silica gel column chromatography (PE–EtOAc, 10:1) to give compound **13a** (20 mg, 67%).

Fuzanin D (1)

Compound **13a** (100 mg, 0.334 mmol) was dissolved in MeOH (10 mL), then PTSA (19 mg, 0.10 mmol) was added and the mixture stirred for 3 h. After completion, the reaction was quenched by the addition of Et_3N and then concentrated. Column chromatography of the residue on silica gel (PE–EtOAc, 1:2) furnished fuzanin D (67.4 mg, 92%) 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}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.40 (d, *J* = 3.6 Hz, 1 H), 7.44–7.37 (m, 2 H), 7.04 (dd, *J* = 7.6, 4.4 Hz, 1 H), 6.80 (d, *J* = 14.8 Hz, 1 H), 6.55 (dd, *J* = 15.2, 10.8 Hz, 1 H), 6.00 (dd, *J* = 15.6, 6.8 Hz, 1 H), 4.24–4.21 (m, 1 H), 3.93–3.91 (m, 1 H), 2.36 (s, 3 H), 1.16 (d, *J* = 6.4 Hz, 3 H).

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

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{18}NO_2$: 220.1338; found: 220.1324.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588343.

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