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Synthesis of the spiroacetal fragments of spirofungins A and B, antibiotics isolated from *Streptomyces violaceusniger* Tü 4113

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Abstract: The spiroacetal [C(9)–C(20)] fragments of spirofungins A and B, antibiotics isolated from *Streptomyces violaceusniger* Tü 4113, were prepared from a known bromo alcohol derived from (*S*)-citronellal, using thermodynamically controlled iodolactonization and spiroacetalization as the key steps.

Keywords: acetylide; antibiotics; iodolactonization; selenolactonization; spiroacetalization; spirofungins A and B; *Streptomyces violaceusniger* Tü 4113; synthesis.

Introduction

Spirofungins A and B are antifungal polyketides bearing a spiroacetal ring, isolated from culture extracts of *Streptomyces violaceusniger* Tü 4113 (Figure 1) [1]. Total synthesis has been achieved by several groups [2–7], and other synthetic studies have been reported to date [8–13]. In a preliminary communication, we have reported the synthesis of a spirofungins A C(9)–C(20) fragment (A core, **1**) and incorrectly proposed B [(15*S*,18*R*,19*S*)-isomer of A] by addition reaction of a racemic alkyne **Y** to an optically active lactone **X** [8]. Later, an optically active alkyne **Y** has been used instead for the preparation of **1** [11]. Here we describe the synthetic details of **1** and **2** as a continuation of the previous reports [8, 11].

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Results and discussion

(*S*)-Citronellal was converted to the known epoxy bromide **3** [14] (Scheme 1). Oxidative cleavage of the epoxy ring with $NaIO_4$ followed by reduction with $NaBH_4$ afforded alcohol **4** in 86% yield [15]. The resulting hydroxy group was protected with a triphenylmethyl (Tr) group to give **5**, which was subjected to dehydrobromination using KO*t*-Bu in DMSO, leading to the olefinic compound **6**. Oxidation of the double bond was performed by Lemieux-Johnson oxidation or ozonolysis to afford the aldehyde, which was treated with $Ph_3P{=}CHCO_2Me$ to give ester **7**. The ester carbonyl group was reduced using DIBAL to furnish **8**, and the newly formed hydroxy group was protected as a benzyl ether to produce **9**. After removal of the trityl group, the resulting alcohol **10** was oxidized to carboxylic acid **11a**, the precursor for the key halolactonization. The corresponding *p*-methoxybenzyl and *p*-bromobenzyl derivatives, **11b** and **11c**, were also prepared.

The trials of halolactonization are listed in Table 1. Several reagents releasing iodonium or bromonium ions were examined for **11a** (entries 1–6). The desired *trans*-isomer was preferentially obtained using I_2 under thermodynamic

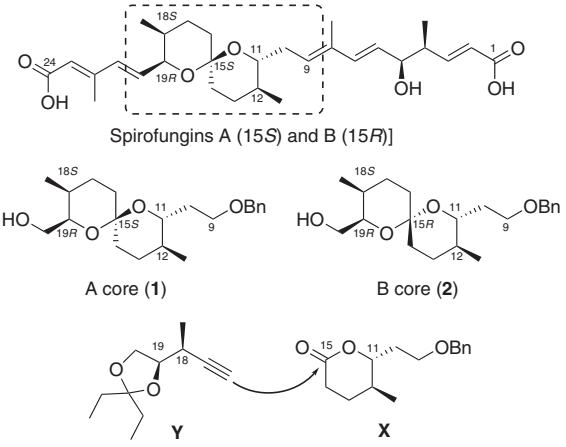
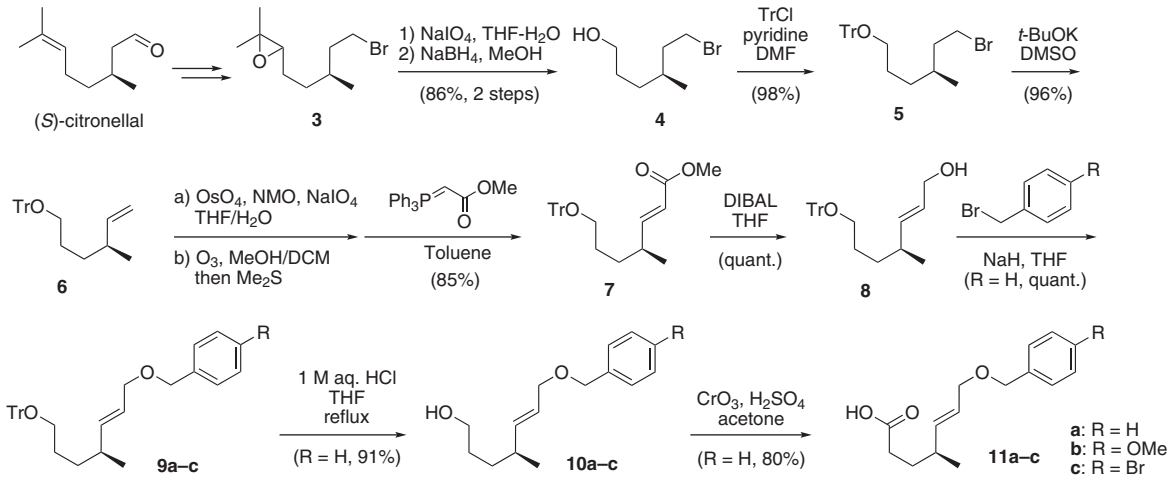
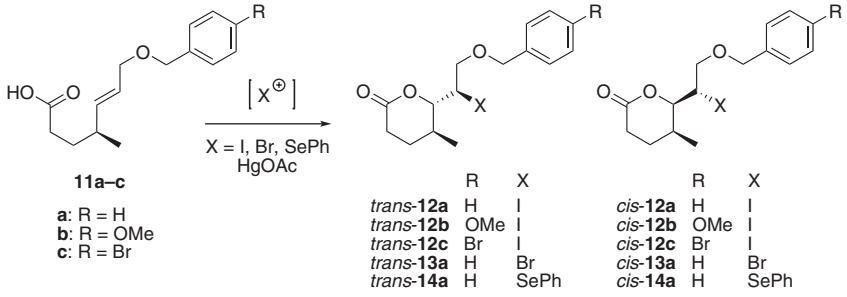


Figure 1 Spirofungins A and B, and the spiroacetal fragments prepared in this study.



Scheme 1 Preparation of lactonization precursors **11a–c**.

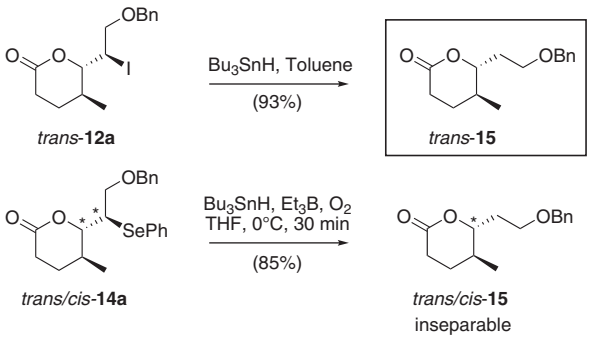
Table 1 Lactonization of carboxylic acid precursors **11a–c.**



Entry	R	Conditions	Yield (%)	*trans*/*cis*
1	H	I_2 (3 eq), MeCN, 0°C, 6 h	44	3/1
2	H	I_2 (3 eq), $NaHCO_3$, MeCN, 0°C, 3 h	23	1/2.5
3	H	NIS (2.3 eq), 2,6-lutidine, DCM, 0 to 20°C, 24 h	35	1.2/1
4	H	IBr (3 eq), MeCN, 0°C, 6 h	53	3/1
5	H	NBS (2 eq), MeCN, 0°C, 12 h	41	1.3/1
6	H	NBS (2 eq), *t*-BuOK (1 eq), DMF, -20 to 20°C	13	2.4/1
7	H	$Hg(OAc)_2$ (1.1 eq), MeOH, 0°C, 12 h	0	–
8	H	PhSeCl, Et_3N, DCM	80	5/1[a]
9	OMe	I_2 (1.5 eq), MeCN, 0°C, 12 h	10	–
10	OMe	I_2 (3 eq), $NaHCO_3$, MeCN, 0°C, 24 h	70	1.2/1
11	Br	I_2 (1.2 eq), MeCN, 0°C, 6 h	22	7/1
12	Br	IBr (1.2 eq), MeCN, 0°C, 6 h	74	6/1

[a]Inseparable mixture: determined by ^1H NMR.

conditions (entry 1), but the yield was 44%. The products *trans/cis*-**12a** were easily separated using silica gel column chromatography. Attempted mercuriolactonization produced no lactonic product (entry 7). Selenolactonization [16] using PhSeCl afforded the desired lactones, *trans*-**14a** and *cis*-**14a**, in 80% yield (entry 8); however, these isomers were inseparable even after deselenenylation (Bu_3SnH, Et_3B, O_2, THF, 85%; Scheme 2). We also tried halolactonization using the substrates with *p*-methoxy (**11b**) or *p*-bromo (**11c**) substituent on the benzene ring (entries 9–12), to change the electrostatic nature of the double bond. The yield was improved with the *p*-methoxy derivative **11b**, but the stereoselectivity was lower (entry 10). The best result was obtained with the *p*-bromo derivative **11c** using IBr under thermodynamic conditions (entry 12). However, the parent Bn compound *trans*-**12a** was used in the following steps due to the expected difficulty in deprotection of the *p*-bromobenzyl group.

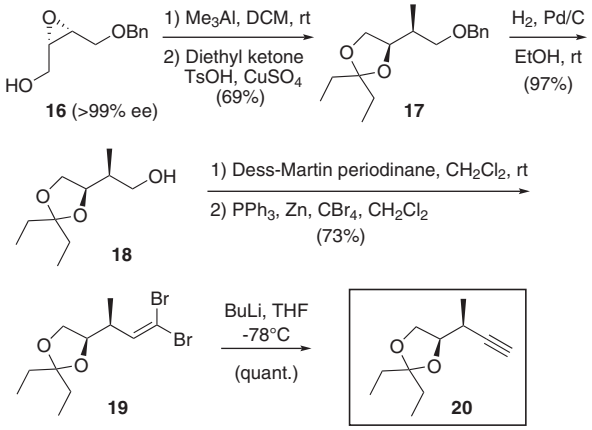


Scheme 2 Synthesis of *trans*-**15** (= **X**).

Deiodination of *trans*-**12a** was performed using Bu_3SnH in 93% yield to give the desired lactone *trans*-**15** (Scheme 2). The overall yield was 18% over 10 steps from **4**.

The optically active alkyne **20** was prepared in a similar manner as described in the previous report (Scheme 3) [8], starting from the epoxide **16** [17]. The enantiomeric purity of **16** was increased to >99% ee after crystallization of the corresponding *p*-nitrobenzoyl ester. The epoxy ring of **16** was cleaved by methylation with Me_3Al and the resulting diol [18] was isolated as an acetal **17** [8]. The benzyl group was removed by hydrogenolysis and the deprotected alcohol **18** was converted to the dibromo olefin **19** under Corey-Fuchs reaction conditions. Treatment of **19** with BuLi afforded the alkyne **20**.

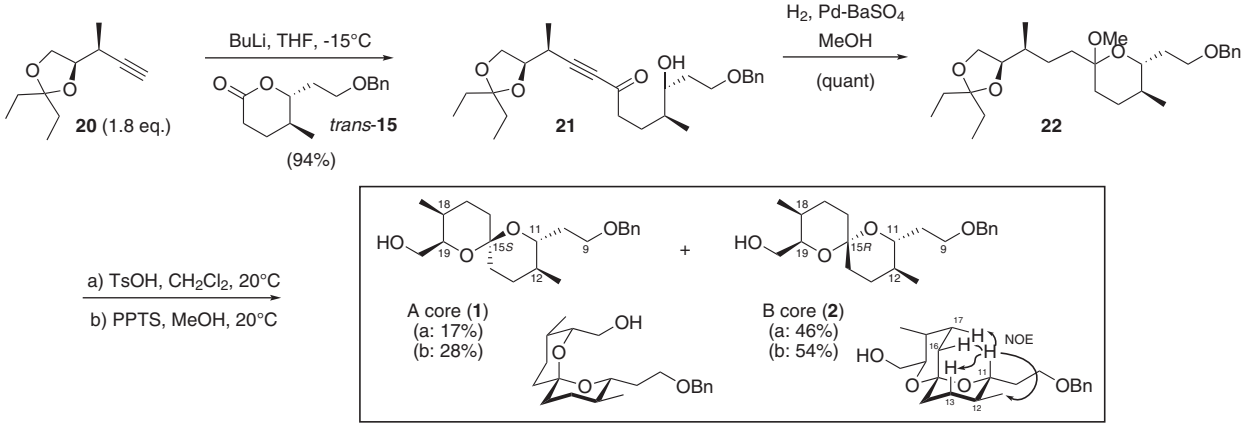
With both fragments, *trans*-**15** (= **X**) and **20** (= **Y**), in our hands, lithium acetylide derived from **20** (1.8 eq.) was treated with *trans*-**15** lactone to furnish hydroxy ketone **21** in 94% yield (Scheme 4). The tautomeric hemiacetal was not observed. Selective reduction of the compound **21** triple bond using $Pd/BaSO_4$ as a catalyst in MeOH gave the methyl acetal **22** as a single diastereomer in quantitative yield. The stereochemistry of the acetal carbon could not be determined. Finally, deprotection of the terminal acetal group under acidic conditions accompanied by spiroacetal formation produced the desired A core (**1**) and B core (**2**). The ratio of two spiroacetals (A core/B core = 1.0:2.7 or 1.0:1.9) is similar to Diaz's results on the corresponding PMB ethers (1.0:2.3) [11]. The spectroscopic data for **2** coincides with those reported [8, 11]. Studies towards total synthesis are underway.



Scheme 3 Synthesis of **20** (= **Y**).

Experimental

IR spectra were recorded using neat compounds on a Jasco IR Report-100 spectrometer. ^1H NMR spectra were recorded with a Varian GEMINI-300 spectrometer (300 MHz) using $CDCl_3$ as solvent and internal standard (δ_H 7.26 ppm). ^{13}C NMR spectrum was recorded with a Varian Inova-600 spectrometer (150 MHz) using $CDCl_3$ as solvent and internal standard (δ_C 77.00 ppm). Mass spectra in a positive ion mode (EI^+) were recorded with a Jeol JMS-700 spectrometer. Merck silica gel 60 (70–230 mesh) was used for column chromatography. Merck silica gel 60 F_{254} (0.25 mm thickness) was used for TLC analysis.



Scheme 4 Synthesis of spirofungins A core (**1**) and B core (**2**).

The enantiomeric purity of compound **16** (>99% ee) was determined by HPLC analysis [column Daicel Chiralcel OD (4.6×250 mm)] eluting with hexane/*i*-PrOH, 4:1, flow rate 1.0 mL/min at 20°C, t_R = 7.60 min (*ent*-**16**) and 9.20 min (**16**)].

(*S*)-6-Bromo-4-methylhexan-1-ol (4) [15]

To a solution of epoxide **3** [14] (11 g, 47 mmol) in THF/H_2O (2:1, 120 mL) was added $NaIO_4$ (20 g, 95 mmol), and the mixture was stirred at 50°C for 4 h. After removing the precipitate by filtration, the mixture was concentrated *in vacuo*. The residue was diluted with ether, washed with saturated aqueous $NaHCO_3$ solution followed by saturated aqueous $Na_2S_2O_3$ solution, dried with $MgSO_4$, and concentrated *in vacuo*. To a solution of the resulting crude oil in MeOH (80 mL), $NaBH_4$ (0.62 g, 16 mmol) was gradually added at 0°C, and the mixture was stirred at 20°C for 1 h. After the pH value of the solution was adjusted to 6 with 2 M aqueous HCl, the solvent was removed *in vacuo*. The residue was diluted with ether, washed with water and brine, dried with $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane/EtOAc, 3:1) to give **4** (7.9 g, 40 mmol, 86%) as a colorless oil, $[\alpha]_D^{23}$ = +5.0° (*c* = 1.2, *i*-Pr_2O) {$[\alpha]_D^{32}$ = +7.40 (*c* = 1.16 g/mL) [15]}; IR (film): ν_{max} 3350, 2950, 2920, 2850, 1740, 1720, 1650, 1450, 1440, 1380, 1260, 1240, 1220, 1060 cm^{-1}; ^1H NMR: δ 0.92 (d, 3H, *J* = 6.6 Hz, CH_3), 1.19–1.75 (m, 6H), 1.89 (m, 1H, H-4), 3.37–3.52 (m, 2H, H-6), 3.65 (t, 2H, *J* = 6.6 Hz, H-1). EI-HR-MS. Calcd for $C_7H_{16}{}^{79}BrO$ $(M+H)^{+\cdot}$: *m/z* 195.0385. Found: *m/z* 195.0389.

(*S*)-1-Bromo-3-methyl-6-(triphenylmethyl)oxyhexane (5)

A solution of **4** (12.0 g, 61.5 mmol), pyridine (7.75 g, 8.00 mL, 98.0 mmol), triphenylmethyl chloride (18.1 g, 65.0 mmol) and DMAP (1.51 g, 12.0 mmol) in dry DMF (100 mL), was stirred at 70°C for 2 h. After cooling to room temperature the mixture was diluted with water and extracted with hexane. The organic layer was washed with 1 M aqueous HCl followed by water, dried with $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane/EtOAc, 19:1) to give **5** (26.2 g, 60.0 mmol, 98%) as a colorless oil; $[\alpha]_D^{24}$ = -3.2° (*c* = 1.1, *i*-Pr_2O); IR (film): ν_{max} 3070, 3050, 3010, 2950, 2920, 2850, 1950, 1480, 1440, 1380, 1320, 1280, 1220, 1180, 1150, 1080, 1030, 1000, 900 cm^{-1}; ^1H NMR: δ 0.88 (d, 3H, *J* = 6.3 Hz, CH_3), 1.15–1.69 (m, 6H), 1.73–1.82 (m, 1H, H-3), 3.05 (t, 2H, *J* = 6.6 Hz, H-6), 3.46–3.60 (m, 2H, H-1), 7.19–7.46 (m, 15H, Ph). EI-HR-MS. Calcd for $C_{26}H_{29}{}^{79}BrO$ $(M^{+\cdot})$: *m/z* 436.1402. Found: *m/z* 436.1402.

(*S*)-3-Methyl-6-(triphenylmethyl)oxyhex-1-ene (6)

To a solution of **5** (3.00 g, 6.86 mmol) in pentane (15 mL) was added a solution of KO*t*-Bu (1.54 g, 13.7 mmol) in DMSO (14 mL) at 0°C, and the mixture was stirred at room temperature for 1 h. Then the mixture was cooled to 0°C, and water (10 mL) was added. After stirring at room temperature for 30 min., the mixture was extracted with pentane. The organic layer was washed with 1 M aqueous HCl, a saturated aqueous $NaHCO_3$ solution and then water, dried with $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane/EtOAc, 100:1) to give **6** (2.30 g, 6.55 mmol, 96%) as a colorless oil; $[\alpha]_D^{24}$ = +6.8° (*c* = 1.0, *i*-Pr_2O); IR (film): ν_{max} 3050, 3000, 2950, 2910, 2850, 1630, 1590, 1480, 1440, 1410, 1380, 1360, 1310, 1220, 1180, 1150, 1070, 1030, 990, 900 cm^{-1}; ^1H NMR: δ 0.97 (d, 3H, *J* = 6.6 Hz, CH_3), 1.33–1.38 (m, 2H), 1.57–1.65 (m, 2H), 2.02–2.11 (m, 1H, 3-H), 3.03 (t, 2H, *J* = 6.7 Hz, 6-H), 4.88–4.95 (m, 2H, 1-H), 5.67 (ddd, 1H, *J* = 7.7, 10.4, 17.3 Hz, 2-H), 7.20–7.46 (m, 15H, Ph). EI-HR-MS. Calcd for $C_{26}H_{28}O$ $(M^{+\cdot})$: *m/z* 356.2140. Found: *m/z* 356.2141.

Methyl (2*E*,4*S*)-4-methyl-7-(triphenylmethyl)oxyhept-2-enoate (7)

Method A A solution of **6** (5.3 g, 15 mmol), OsO_4 (catalyst) and *N*-methylmorpholine *N*-oxide (3.0 g, 26 mmol) in THF/water (6:1, 30 mL) was stirred at room temperature for 3 h and then treated with a solution of $NaIO_4$ (8.1 g, 38 mmol) in THF/water (1:1, 20 mL). After adjusting the pH of the solution to 7, it was stirred at room temperature for 18 h. After removal of precipitates by filtration, the mixture was diluted with ether, washed twice with a saturated aqueous $Na_2S_2O_3$ solution, dried with Na_2SO_4 and concentrated *in vacuo* to obtain crude aldehyde.

Method B Ozone in oxygen gas was passed through a solution of **6** (3.4 g, 9.7 mmol) in dry MeOH/dry CH_2Cl_2 (5:3, 80 mL) at -78°C for 30 min. Then this solution was treated with Me_2S (1.5 mL) and the mixture was stirred until the temperature of the reaction reached room temperature. The mixture was concentrated *in vacuo* and the residue was diluted with ether, washed with water, dried with $MgSO_4$, and concentrated *in vacuo* to obtain crude aldehyde.

A mixture of crude aldehyde and methyl triphenylphosphoranylideneacetate [**A**, 9.6 g, 30 mmol; **B**, 6.1 g, 19 mmol] in dry toluene [**A**, 80 mL; **B**, 40 mL] was stirred at 50°C for 20 h. The mixture was concentrated *in vacuo* and the residue was chromatographed on silica gel (hexane/EtOAc, 9:1) to give **7** [**A**, 5.1 g, 12 mmol, 83%; **B**, 3.4 g, 8.2 mmol, 85%, *E*/*Z* = 95:5] as a colorless oil; $[\alpha]_D^{20}$ = +33° (*c* = 1.0, *i*-Pr_2O); IR (film): ν_{max} 3050, 3010, 2950, 2920, 2860, 1650, 1600, 1490, 1450, 1430, 1380, 1350, 1310, 1270, 1210, 1180, 1150, 1070, 1040, 980, 900 cm^{-1}; ^1H NMR: δ 1.03 (d, 3H, *J* = 6.6 Hz, CH_3), 1.39–1.48 (m, 2H), 1.57–1.64 (m, 2H), 2.25 (m, 1H, 4-H), 3.04 (dt, 2H, *J* = 1.5, 6.5 Hz, 7-H), 3.73 (s, 3H, OCH_3), 5.75 (dd, 1H, *J* = 1.0, 16 Hz, 2-H), 6.84 (dd, 1H, J = 8.0, 16 Hz, 3-H), 7.18–7.45 (m, 15H). EI-HR-MS. Calcd for $C_{28}H_{30}O_3$ $(M^{+\cdot})$: *m/z* 414.2195. Found: *m/z* 414.2197.

(2*E*,4*S*)-4-Methyl-7-(triphenylmethyl)oxyhept-2-en-1-ol (8)

To a solution of **7** (12.1 g, 29.1 mmol) in dry THF (100 mL) was added DIBAL (1.0 M in toluene, 64 mL, 64 mmol) at -78°C, and the mixture was stirred at this temperature for 20 min. Then MeOH (3 mL) was added, followed by a saturated aqueous Rochelle salt solution (10 mL), and the mixture was stirred for 2 h at room temperature. Next, the mixture was diluted with ether, washed with a saturated aqueous NH_4Cl solution, water and then brine, dried with $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane/EtOAc, 10:1) to give **8** (11.2 g, 29.0 mmol, quantitative yield) as a colorless oil; $[\alpha]_D^{24}$ = +11°(*c* = 1.1, *i*-Pr_2O); IR (film): ν_{max} 3350, 3080, 3050, 3020, 2950, 2920, 2860, 1740, 1600, 1490, 1450, 1370,

1240, 1220, 1180, 1150, 1070, 1040, 1000, 900 cm^{-1}; ^1H NMR: δ 0.98 (d, 3H, *J* = 6.9 Hz, CH_3), 1.31–1.39 (m, 2H), 1.58–1.66 (m, 2H), 2.10 (m, 1H, 4-H), 3.04 (dt, 2H, *J* = 6.7 Hz, 7-H), 4.08–4.14 (m, 3H), 5.54 (m, 2H, 2-H, 3-H), 7.23–7.46 (m, 15H, Ph). EI-HR-MS. Calcd for $C_{27}H_{30}O_2$ ($M^{+\cdot}$): *m/z* 386.2246. Found: *m/z* 386.2248.

(2*E*,4*S*)-1-Benzyloxy-4-methyl-7-(triphenylmethyl) oxyhept-2-ene (9a)

To a suspension of NaH (60% oil dispersion, washed with hexane before use, 0.9 g, 22 mmol) in dry THF (70 mL), a solution of **8** (2.6 g, 6.7 mmol) in dry THF (15 mL) and benzyl chloride (2.9 g, 2.6 mL, 23 mmol) were added dropwise at 20°C, and the mixture was stirred at 50°C for 12 h. After cooling to 0°C, water (10 mL) was added and THF was removed *in vacuo*. The residue was diluted with ether, washed with a saturated aqueous NH_4Cl solution, water and then brine, dried with $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane/EtOAc, 10:1) to give **9a** (3.2 g, 6.7 mmol, quantitative yield) as a colorless oil; $[\alpha]_D^{23}$ = +12° (*c* = 1.0, *i*-Pr_2O); IR (film): ν_{max} 3075, 3050, 3020, 2925, 2860, 1590, 1485, 1445, 1355, 1215, 1150, 1070, 1025, 970 cm^{-1}; ^1H NMR: δ 0.98 (d, 3H, *J* = 6.9 Hz, CH_3), 1.31–1.42 (m, 2H), 1.57–1.66 (m, 2H), 2.11 (sep., 1H, *J* = 6.9 Hz, H-3), 3.03 (t, 2H, *J* = 6.6 Hz, H-7), 3.96 (d, 2H, *J* = 5.0 Hz, H-1), 4.50 (s, 2H, PhCH_2), 5.43–5.61 (m, 2H, H-2, 3), 7.19–7.45 (m, 15H, Tr).

(4*E*,5*S*)-7-Benzyloxy-4-methylhept-5-en-1-ol (10a)

A solution of **9a** (1.00 g, 2.10 mmol) in THF/1 M aqueous HCl (14:1, 30 mL) was stirred under reflux for 6 h. After removal of the solvent, the residue was diluted with ether, washed with a saturated aqueous $NaHCO_3$ solution followed by brine, dried with $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane/EtOAc, 10:1) to give **10a** (470 mg, 1.92 mmol, 91%) as a colorless oil; $[\alpha]_D^{24}$ = +19° (*c* = 1.1, *i*-Pr_2O); IR (film): ν_{max} 3400, 3010, 2920, 2850, 1490, 1450, 1370, 1250, 1210, 1100, 1070, 1030, 980, 910 cm^{-1}; ^1H NMR: δ 1.02 (d, 3H, *J* = 6.9 Hz, CH_3), 1.32–1.40 (m, 2H), 1.51–1.61 (m, 2H), 2.18 (m, 1H, 4- H), 3.63 (t, 2H, *J* = 1.5, 6.5 Hz, 1-H), 3.98 (d, 2H, *J* = 4.7 Hz, 7-H), 4.51 (s, 2H, PhCH_2), 5.77–5.59 (m, 2H, 5, 6-H), 7.26–7.35 (m, 5H, Ph). EI-HR-MS. Calcd for $C_{15}H_{22}O_2$ ($M^{+\cdot}$): *m/z* 234.1620. Found: *m/z* 234.1621.

(4*E*,5*S*)-7-Benzyloxy-4-methylhept-5-enoic acid (11a)

To a solution of **10a** (5.39 g, 23.0 mmol) in acetone (30 mL) was titrated with Jones reagent (2.67 M) at 0°C until the color of the solution became pale orange, and then the mixture was stirred at room temperature for an additional 3 h. The mixture was treated with *i*-PrOH until the color of the solution changed to green. Then, solids were removed by filtration through a Celite pad, and the filtrate was concentrated *in vacuo*. The residue was diluted with ether and extracted twice with a saturated aqueous $NaHCO_3$ solution. After acidification with 2 M aqueous HCl, the aqueous layer was extracted four times with EtOAc. The combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated *in vacuo* to give **11a** (4.60 g, 18.5 mmol, 80%) as a pale green oil. This carboxylic acid was used in the next step without further purification. IR (film): ν_{max} 3675–3050 (br.), 3025, 2950, 2925, 2860, 1705, 1450, 1410, 1355, 1280, 1175, 1115, 1090, 1075, 1025, 975 cm^{-1}; ^1H NMR: δ 1.03 (d, 3H, *J* = 6.6 Hz, CH_3), 1.55–1.75 (m, 2H), 2.16–2.25 (m, 1H, 4-H), 2.31–2.37 (m, 2H, H-2), 3.98 (d, 2H, *J* = 4.8 Hz, H-7), 4.51 (s, 2H, PhCH_2), 5.57–5.60 (m, 2H, H-5, 6), 7.35–7.40 (m, 5H, Ph).

(4*S*,5*S*,6*R*)-7-Benzyloxy-6-iodo-4-methylheptan-5-olide (*trans*-12a)

To a solution of **11a** (560 mg, 2.26 mmol) in dry CH_3CN (5 mL) was added I_2 (1.72 g, 6.78 mmol) at 0°C, and the mixture was stirred at 0°C for 12 h. The mixture was poured into a saturated aqueous $Na_2S_2O_3$ solution (1:1, 20 mL), and stirred until the color of I_2 diminished. The aqueous layer was separated and extracted three times with EtOAc. The combined organic layers were washed with water and then brine, dried with $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed twice on silica gel (hexane/EtOAc, 4:1) to give *trans*-**12a** (281 mg, 0.750 mmol, 33%) as a colorless oil; $[\alpha]_D^{24}$ = +22° (*c* = 0.98, *i*-Pr_2O); IR (film): ν_{max} 3400, 3010, 2950, 2920, 2850, 1730, 1490, 1450, 1360, 1340, 1240, 1200, 1180, 1100, 1040 cm^{-1}; ^1H NMR: δ 1.09 (d, 3H, *J* = 6.6 Hz, CH_3), 1.49–1.62 (m, 1H, 3-H), 1.81–1.90 (m, 1H, 3-H), 2.18–2.29 (m, 1H, 4-H), 2.38–2.65 (m, 2H, 2-H), 3.79–3.92 (m, 2H, 7-H), 4.25 (dd, 1H, *J* = 3.0, 8.5 Hz, 5-H), 4.50–4.59 (m, 3H, H-6, PhCH_2), 7.27–7.36 (m, 5H, Ph). EI-HR-MS. Calcd for $C_{15}H_{19}IO_3$ ($M^{+\cdot}$): *m/z* 374.0379. Found: *m/z* 374.0457.

(4*S*,5*R*)-7-Benzyloxy-4-methylheptan-5-olide [(4*S*,5*R*)-1 or *trans*-15] [8]

To a solution of *trans*-**12a** (160 mg, 0.43 mmol) in dry toluene (1 mL) was added tributyltin hydride (0.64 mL, 400 mg, 1.37 mmol) at 0°C, and the mixture was stirred at room temperature for 2 h. After the mixture was diluted with ether, KF (100 mg, 1.7 mmol) was added, and the mixture was stirred at room temperature for 24 h. After removal of precipitates with a Celite pad, the filtrate was washed with brine, dried with $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed twice on silica gel (hexane/EtOAc, 10:1, then 4:1) to give (4*S*,5*R*)-**1** (100 mg, 0.40 mmol, 93%) as a pale yellow oil; $[\alpha]_D^{24}$ = +84° (*c* = 1.0, *i*-Pr_2O); IR (film): ν_{max} 3450, 3010, 2950, 2910, 2850, 1730, 1490, 1450, 1380, 1360, 1240, 1200, 1090, 1030 cm^{-1}; ^1H NMR: δ 1.02 (d, 3H, *J* = 6.6 Hz, CH_3), 1.49–1.62 (m, 1H, H-3), 1.68–1.96 (m, 3H, H-3, 6), 2.04–2.17 (m, 1H, H-4), 2.41–2.67 (m, 2H, H-2), 3.63–3.75 (m, 2H, H-7), 4.13 (dt, 1H, *J* = 2.5, 9.6 Hz, H-5), 4.51, 4.52 (s, s, 2H, PhCH_2), 7.27–7.38 (m, 5H, Ph). EI-HR-MS. Calcd for $C_{15}H_{20}O_3$ ($M^{+\cdot}$): *m/z* 248.1412. Found: *m/z* 248.1415.

(2*S*,3*R*)-1-Benzyloxy-3,4-(pentane-3,3-diyl)dioxy-2-methylbutane (17)

To a solution of **16** (800 mg, 4.12 mmol) in dry CH_2Cl_2 (25 mL) was added Me_3Al (1.0 M in CH_2Cl_2, 15 mL, 15 mmol) at 20°C, and the mixture was stirred at 20°C for 14 h. After addition of 2 M aqueous HCl the mixture was stirred for 30 min. Product was extracted with EtOAc and the extract was washed with water, a saturated aqueous $NaHCO_3$

solution followed by brine. Final concentration *in vacuo* gave a pale yellow oil (0.98 g) that was used in the next step without further purification. A solution of this oil (0.93 g), $CuSO_4$ (1.5 g) and TsOH (40 mg) in diethyl ketone (8 mL) was stirred at 20°C for 18 h. The mixture was filtered through a Celite pad and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane/EtOAc, 10:1) to give **17** (750 mg, 2.69 mmol, 69%) as a colorless oil; ^{1}H NMR: δ 0.89 (t, 3H, *J* = 7.4 Hz, C*H*$_3$CH$_2$), 0.90 (q, 3H, *J* = 7.4 Hz, C*H*$_3$CH$_2$), 1.04 (d, 3H, *J* = 6.9 Hz, 3-CH$_3$), 1.55–1.70 (m, 4H, CH$_3$C*H*$_2$ × 2), 1.95 (m, 1H, H-2), 3.37 (d, 2H, *J* = 5.9 Hz, H-4), 3.64 (t, 1H, *J* = 7.9 Hz, H-3), 4.00 (m, 1H, H-3), 4.48 (m, 2H, C*H*$_2$Ph).

(2*S*,3*R*)-3,4-(Pentane-3,3-diyl)dioxy-2-methylbutan-1-ol (18)

A suspension of **17** (3.12 g, 11.2 mmol) and Pd/C (10%, 300 mg) in EtOH (100 mL) was stirred under a hydrogen atmosphere for 2 days. The solution was filtered through a Celite pad and the filtrate was concentrated *in vacuo*. The residue was chromatographed on silica gel to separate **18** (950 mg, 5.05 mmol) and **17** as colorless oils. A suspension of the recovered **17** and Pd/C (10%, *ca*. 150 mg) in EtOH (50 mL) was stirred under a hydrogen atmosphere for 3 days. The solution was filtered through a Celite pad and the filtrate was concentrated *in vacuo*. The residue was chromatographed on silica gel to give **18** (1.09 g, 5.79 mmol). The combined yield was 97%; IR (film): ν_{max} 3400, 2950, 2920, 2850, 1740, 1720, 1450, 1370, 1350, 1260, 1200, 1160, 1130, 1070, 1040, 960, 920 cm^{-1}; ^{1}H NMR: δ 0.88 (t, 3H, *J* = 7.4 Hz, C*H*$_3$CH$_2$), 0.92 (q, 3H, *J* = 7.4 Hz, C*H*$_3$CH$_2$), 0.99 (d, 3H, *J* = 6.9 Hz, 3-CH$_3$), 1.59–1.70 (m, 4H, CH$_3$C*H*$_2$ × 2), 1.97 (m, 1H, H-2), 3.52–3.65 (m, 2H, H-1), 4.02 (dd, 1H, *J* = 6.3, 8.0 Hz, H-3), 4.10–4.17 (m, 2H, H-4).

(3*S*,4*R*)-1,1-Dibromo-4,5-(pentane-3,3-diyl)dioxy-3-methylpent-1-ene (19)

A suspension of **18** (152 mg, 0.807 mmol), $NaHCO_3$ (140 mg, 1.75 mmol) and Dess-Martin periodinane (515 mg, 1.21 mmol) in dry CH_2Cl_2 (7 mL) was stirred at 20°C for 10 min. The mixture was diluted with Et_2O and washed with a saturated aqueous $Na_2S_2O_3$ solution and then a saturated aqueous $NaHCO_3$ solution, dried with $MgSO_4$ and concentrated *in vacuo* to give crude aldehyde; ^{1}H NMR: δ 0.90 (t, 6H, *J* = 7.5 Hz, C*H*$_3$CH$_2$), 1.23 (m, 3H, 2-CH$_3$), 1.59–1.65 (m, 4H, CH$_3$C*H*$_2$ × 2), 2.63 (quint, 1H, *J* = 6.6 Hz, H-2), 3.64 (t, 1H, *J*-7.5 Hz, H-4), 4.16 (m, 1H), 4.29 (q, 1H, *J* = 6.3 Hz), 9.74 (s, 1H, H-1).

A suspension of Zn powder (105 mg, 1.60 mmol) and PPh_3 (420 mg, 1.60 mmol) in dry CH_2Cl_2 (2 mL) was stirred for 5 min at 20°C. After the mixture had been cooled to 0°C, a solution of CBr_4 (540 mg, 1.60 mmol) in dry CH_2Cl_2 (2 mL) was added, and the mixture was stirred for 30 h, during which time the temperature was gradually increased to 20°C. This mixture was treated with the aldehyde described above in dry CH_2Cl_2 (2 mL), and the mixture was stirred for an additional 12 h. Pentane was then added and the resulting crystals were removed by filtration. The filtrate was concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane/EtOAc, 10:1) to give **19** (201 mg, 0.586 mmol, 73%) as a colorless oil; IR (film): ν_{max} 2960, 2930, 2860, 1610, 1450, 1380, 1360, 1350, 1330, 1270, 1230, 1200, 1170, 1130, 1080, 1060, 1020, 1000, 970, 940, 920 cm^{-1}; ^{1}H NMR: δ 0.86–0.95 (m, 6H, C*H*$_3$CH$_2$ × 2), 1.10 (d, 3H, *J* = 8.2 Hz, 3-CH$_3$), 1.56–1.70 (m, 4H, CH$_3$C*H*$_2$ × 2), 2.66 (m, 1H, H-3), 3.68 (m, 1H, H-4), 3.92–4.02 (m, 2H, H-5), 6.25 (dd, 1H, *J* = 1.8, 9.6 Hz, H-2). EI-HR-MS. Calcd for $C_{11}H_{19}{}^{79}Br{}^{81}BrO_2$ (M+H$^+$): *m/z* 342.9731. Found: *m/z* 342.9736.

(3*S*,4*R*)-4,5-(Pentane-3,3-diyl)dioxy-3-methylpent-1-yne (20)

To a solution of **19** (590 mg, 1.72 mmol) in dry THF (7 mL) was added BuLi (1.6 M in hexane, 3.5 mL, 5.5 mmol) at -78°C and the mixture was stirred for 30 min at -78°C. The mixture was diluted with a saturated aqueous NH_4Cl solution and extracted twice with ether. The combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane/EtOAc, 10:1) to give **20** (314 mg, 1.72 mmol, quantitative yield) as a colorless oil; IR (film): ν_{max} 3300, 2950, 2920, 2860, 2100, 1640, 1460, 1370, 1350, 1330, 1290, 1280, 1260, 1200, 1170, 1120, 1080, 960, 920 cm^{-1}; ^{1}H NMR: δ 0.87–0.94 (m, 6H, C*H*$_3$CH$_2$ × 2), 1.27 (d, 3H, *J* = 6.9 Hz, 3-CH$_3$), 1.57–1.70 (m, 4H, CH$_3$C*H*$_2$ × 2), 2.06 (d, 1H, H-1), 2.55–2.65 (m, 1H, H-3), 3.84 (dd, 1H, *J* = 6.6, 8.0 Hz, H-5), 3.96 (dd, 1H, *J* = 6.5, 8.0 Hz, H-4), 4.13 (dd, 1H, *J* = 6.0, 8.0 Hz, H-5). EI-HR-MS. Calcd. for $C_{11}H_{17}O_2$ (M−H$^+$): *m/z* 181.1229. Found: *m/z* 181.1292.

(2*R*,3*S*,9*S*,10*R*)-12-Benzyloxy-10-hydroxy-3,9-dimethyl-1,2-(pentane-3,3-diyl)dioxydodec-4-yn-6-one (21)

To a solution of **20** (91.0 mg, 0.50 mmol, 1.8 equiv.) in ether (0.9 mL) was added BuLi (1.6 M in hexane, 0.32 mL, 0.50 mmol) at -15°C and the mixture was stirred for 15 min at this temperature. This mixture was added dropwise to a solution of *trans*-**15** (63.8 mg, 0.275 mmol) in ether (1 mL) at -15°C and the resulting mixture was stirred for 20 min at this temperature. Then the mixture was poured into a saturated aqueous NH_4Cl solution and extracted with EtOAc. The organic layer was dried with $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane/EtOAc,4:1) to give **21** (111 mg, 0.258 mmol, 94%) as a colorless oil; ^{1}H NMR: δ 0.84–0.96 (m, 12H, C*H*$_3$CH$_2$ × 2, 3,9-CH$_3$), 1.40–1.80 (m, 9H, H-8,9,11, CH$_3$C*H*$_2$ × 2), 2.46–1.70 (m, 2H), 2.80 (quint, 1H, *J* = 7.3 Hz), 3.07 (br. s, 1H, OH), 3.62 (m, 2H), 3.74 (m, 1H), 3.81 (m, 1H), 4.00 (m, 1H), 4.13 (dd, 1H, *J* = 8.0, 6.0 Hz), 4.53 (s, 2H, C*H*$_2$Ph), 7.28–7.38 (m, 5H, Ph).

(2*R*,3*S*,9*S*,10*R*)-12-Benzyloxy-6,10-epoxy-6-methoxy-3,9-dimethyl-1,2-(pentane-3,3-diyl)dioxydodecane (22)

A suspension of **21** (18.0 mg, 0.042 mmol) and Pd-$BaSO_4$ (catalyst) in MeOH (0.5 mL) was stirred under a hydrogen atmosphere for 15 h. The mixture was filtered through a Celite pad and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane/EtOAc, 4:1) to give **22** (15.6 mg, 0.035 mmol, 83.1%) as a colorless oil; ^{1}H NMR: δ 0.83–0.92 (m, 9H, C*H*$_3$CH$_2$ × 2, 3-CH$_3$), 1.00 (d, 3H, *J* = 6.5 Hz, 9-Me), 1.40–1.80 (m, 11H), 2.02 (m, 1H), 3.09 (s, 3H, OCH$_3$), 3.36 (tt, 1H, *J* = 10.2, 2.1 Hz), 3.56 (dt, 1H, *J* = 3.0, 8.0 Hz), 3.60–3.70 (m, 2H), 3.85 (m, 1H), 4.00 (ddd, 1H, *J* = 8.0, 6.1, 4.2 Hz), 4.50 (s, 2H, C*H*$_2$Ph), 7.28–7.38 (m, 5H, Ph). HR-MS (FAB$^+$). Calcd for $C_{27}H_{44}O_5Na$ (M+Na$^+$): *m/z* 471.3086. Found: *m/z* 471.3093.

(2*R*,3*S*,6*S*,8*R*,9*S*)-8-(2-Benzyloxyethyl)-3,9-dimethyl-1.7-dioxaspiro[5.5]undecane-2-methanol [spirofungin numbering: (11*R*,12*S*,15*S*,19*R*,18*S*)-9-Benzyloxy-11,15: 15,19-diepoxy-12,18-dimethyldodecan-20-ol] (spirofungin A core, 1) and its 6*R*-epimer (spirofungin B core, 2)]

A solution of **22** (31.0 mg, 0.069 mmol) and TsOH (catalyst) in CH_2Cl_2 (1 mL) was stirred at 20°C for 5 min. A saturated aqueous $NaHCO_3$ solution was then added, and the separated organic layer was dried with $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane/EtOAc, 4:1) to give **1** (4.0 mg, 0.011 mmol, 17%) and **2** (11 mg, 0.032 mmol, 46%) as colorless oils. Data for **1**: ^{1}H NMR: δ 0.85 (d, 3H, *J* = 6.6 Hz), 0.90 (d, 3H, *J* = 6.9 Hz), 1.2–1.35 (m, 2H), 1.4–1.7 (m, 8H), 1.9–2.1 (m, 2H), 2.13 (dd, 1H, *J* = 14.3, 3.8 Hz), 3.56–3.66 (m, 2H), 3.66–3.76 (m, 2H), 4.10 (m, 2H), 4.25 (d, 1H, *J* = 9.6 Hz), 4.50 (d, 1H, *J* = 11.8 Hz, C*H*$_2$Ph), 4.56 (d, 1H, *J* = 11.8 Hz, C*H*$_2$Ph), 7.4–7.2 (m, 5H, Ph); ^{13}C NMR: δ 14.6 (Me), 17.8 (Me), 27.9, 29.6, 33.6, 34.8, 38.6, 42.1, 44.7, 66.9, 69.4, 72.3, 72.8, 77.2, 96.4 (C-15), 127.5 (*p*-Ph), 127.7 (*o*-Ph), 128.7 (*m*-Ph), 138.8 (*ipso*-Ph). HRMS (FAB$^+$). Calcd for $C_{21}H_{33}O_4$ (M+H$^+$): *m/z* 359.2379. Found: *m/z* 349.2382. Data for **2**: see refs. [8, 11].

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