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Synthesis of the spiroacetal parts of spirofungin A and B

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Abstract

The C9–C20 spiroacetal parts of spirofungin A and B, antifungal antibiotics from *Streptomyces violaceusniger* Tü 4113, were synthesized simultaneously from (*S*)-citronellyl bromide and (±)-epoxy alcohol via alkyne–lactone coupling reaction and diastereomeric separation.

Keywords: spiro compounds; antibiotics; lactonization; polyketides.

Spirofungin A and B were isolated from the culture extracts of *Streptomyces violaceusniger* Tü 4113 as new polyketide-type antibiotics (Fig. 1).[1] These compounds showed various antifungal activities especially against yeasts.[1] The relative configuration of them quite resembles reveromycin A,[2] an inhibitor of the mitogenic activity of epidermal growth factor (EGF), except C18 position: spirofungins lack succinate residue and have methyl group instead of *n*-butyl group. As homologues of promising anticancer agents reveromycins, total synthesis and structure confirmation of spirofungins are to be expected. For the total synthesis of spirofungins, we planned that the whole structures were disconnected to a core spiroacetal part and two side chains. Here we describe the synthesis of the spiroacetal cores of spirofungin A and B.

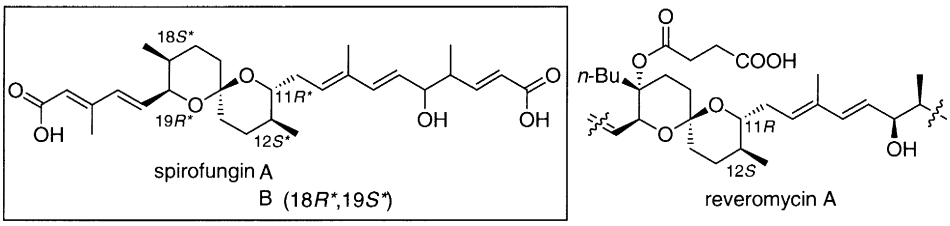

Fig. 1.

Our synthetic plan is shown in Scheme 1. We assumed the absolute configurations of the spiroacetal cores of spirofungin A (**1**) and B (**2**) to be (11*R*,12*S*,15*S*,18*S*,19*R*) and (11*R*,12*S*,15*S*,18*R*,19*S*), respec-

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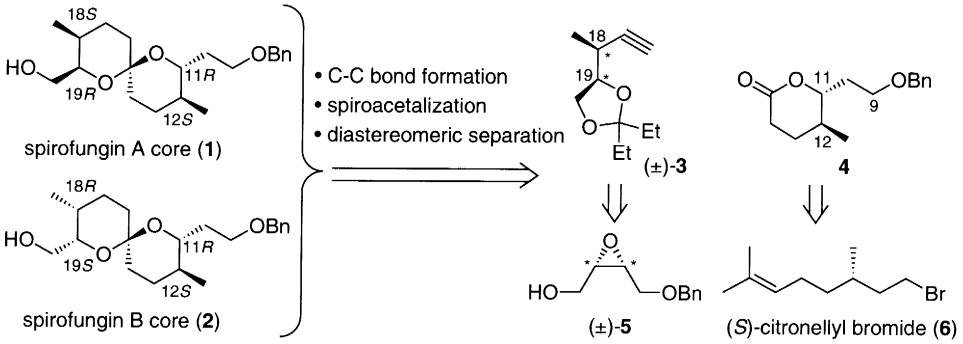
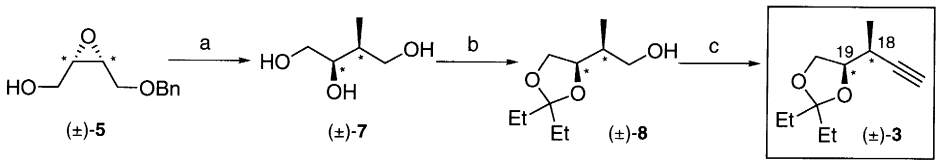
tively, by analogy to reveromycin A.[3] As our targets **1** and **2** were expected to be normally separable due to the diastereomeric nature, we planned to synthesize these cores as a diastereomeric mixture from a coupling reaction of a racemic part [(±)-**3**] and an optically active counterpart (**4**).[4] The racemic alkyne (±)-**3** was to be prepared from the known epoxy alcohol (±)-**5** according to the literature,[5,6] and the lactone **4** could be converted from (*S*)-citronellyl bromide (**6**).



Scheme 1. Retrosynthetic plan for spirofungin A and B

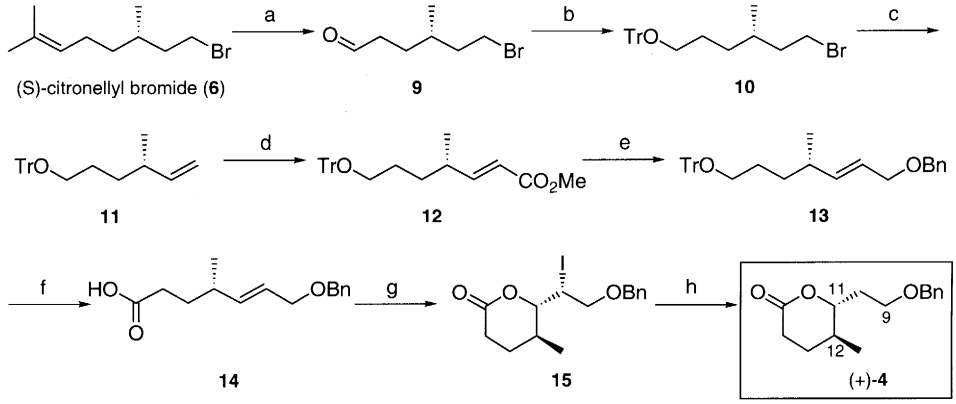
Synthesis of the alkyne part [(±)-**3**] started from (±)-**5** (Scheme 2). The epoxy ring was substituted with methyl group[5] and the resulting 1,2- and 1,3-diols were converged to a single triol (±)-**7**[6] after the removal of benzyl group. The vicinal diol part was selectively protected as dioxolane acetal[7] to give (±)-**8**. The remaining hydroxy group was converted to the desired alkyne [(±)-**3**] via Corey–Fuchs method.[8] The yield from (±)-**5** was 40% in six steps.



Scheme 2. Synthesis of racemic alkyne part. (a) (i) MeMgI, CuI, THF, −78~20°C (86%, 1,3-/1,2-diol=3.5/1); (ii) H_2, Pd–C, EtOH. (b) 3-Pentanone, TsOH, rt (83%, two steps). (c) (i) Dess–Martin oxidation, 0°C; (ii) Ph_3P, CBr_4, Zn, CH_2Cl_2 (70%, two steps); (iii) *n*-BuLi, THF, −78°C (81%)

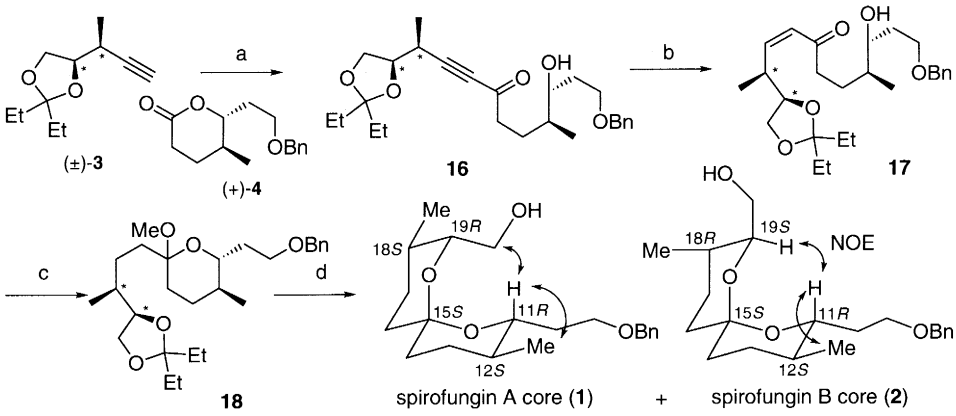
The asymmetric center of the lactone part (**4**) was derived from (*S*)-citronellyl bromide (**6**) (Scheme 3).[9] The double bond of **6** was cleaved to give bromoaldehyde **9**.[10] Dehydrobromination of **9** to form the olefin with *t*-BuOK was successful only after conversion to the corresponding trityl ether (**10**). In the cases of ethylene acetal and *O*,*O*′-xylenedioxy acetal of **9**, undesired *t*-butoxy ether formation competed. After the double bond was oxidized with OsO_4 and cleaved with $NaIO_4$, the resulting aldehyde was coupled with Wittig reagent ($Ph_3P{=}CHCO_2Me$) to afford unsaturated ester **12**. The ester group was reduced and the formed hydroxy group was protected as benzyl ether. Then, removal of trityl group and Jones oxidation gave carboxylic acid **14**. This was subjected to thermodynamically controlled iodolactonization to give **15**. Undesired *cis*-isomer was easily separated by silica gel chromatography. Finally, the iodo group was removed to give the lactone **4** {$[\alpha]_D$ +84° (*c* 1.0, *i*-Pr_2O)}. The yield from **6** was 19% in 14 steps.

As the required segments were prepared, coupling reaction was examined. Alkynyl anion derived from (±)-**3** was treated with the lactone (+)-**4** to afford the desired alkynyl ketone **16** in 78% yield (Scheme 4). Since direct reduction of the triple bond to single bond was unsuccessful (giving a complex mixture), we did this reduction step by step. Treatment of **16** with hydrogen in the presence of Lindlar catalyst



Scheme 3. Synthesis of lactone part [(+)-**4**]. (a) (i) MCPBA, $CHCl_3$; (ii) $NaIO_4$, THF/H_2O. (b) (i) $NaBH_4$, MeOH; (ii) TrCl, pyridine, DMAP, DMF (74% from **6**). (c) *t*-BuOK, DMSO, pentane (95%). (d) (i) OsO_4, NMO, $THF–H_2O$; (ii) $NaIO_4$ (pH 6); (iii) methyl (triphenylphosphoranylidene)acetate, toluene (79%, *E*/*Z*=95/5; and 20% of **11**); (iv) separation (SiO_2 column). (e) (i) DIBAL, THF; (ii) BnBr, NaH, THF (93%). (f) (i) 1 M HCl aq.–THF; (ii) Jones oxidation (70%). (g) (i) I_2, CH_3CN, 0°C; (ii) separation (SiO_2) (42%). (h) $(n\text{-Bu})_3SnH$, toluene (quant.)

gave enone **17**. Spiroacetalization from this enone also failed in the formation of a tricyclic compound by the initial 1,4-addition of the primary hydroxy group to the enone moiety followed by spiroacetalization with the remaining secondary hydroxy group. Thus, the double bond was further hydrogenated over Pd–$BaSO_4$ catalyst. In this reaction, acetal exchange with MeOH occurred to form monocyclic acetal **18**. Finally, treatment with TsOH afforded the desired spiroacetals **1**[11] and **2**,[12] which were easily separated by silica gel column chromatography: the R_f of **1** was 0.71 while that of **2** was 0.43 (SiO_2 coated TLC, hexane:EtOAc=1:1). The stereochemistry of **1** and **2** was confirmed by $^1H–^1H$ COSY, HMQC and NOE experiments. The total yields were 6.7% for **1** and 3.4% for **2** from (*S*)-citronellyl bromide. Preparation of other side chain parts and total synthesis of spirofungin A and B are in progress.



Scheme 4. Synthesis of spiroacetal parts of spirofungin A and B. (a) *n*-BuLi, Et_2O, −20°C, 30 min, then (+)-**4** (78%). (b) H_2, Lindlar cat., MeOH (quant.). (c) H_2, Pd–$BaSO_4$, MeOH (quant.). (d) TsOH, $CHCl_3$, rt 24 h (45% for **1** and 23% for **2**)

Acknowledgements

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9. (*S*)-Citronellyl bromide was prepared from (*S*)-citronellal in three steps [(i) $NaBH_4$, MeOH; (ii) TsCl, Et_3N; (iii) NaBr, DMF (total 80%)].
10. Preparation of racemic **9** was reported: Molander, G. A.; Harris, C. R. *J. Org. Chem.* **1997**, *62*, 7418–7429.
11. Compound **1**: $[\alpha]_D^{19}$ +68° (*c* 0.14, *i*-Pr_2O). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (d, 3H, *J*=6.5 Hz, 12-Me), 0.89 (d, 3H, *J*=7.0 Hz, 18-Me), 1.33 (m, 1H, H-12), 1.35 (m, 1H, H-13), 1.41 (m, 1H, H-14), 1.48 (m, 1H, H-16), 1.52 (m, 1H, H-17), 1.55 (m, 1H, H-17), 1.57 (m, 1H, H-10), 1.63 (m, 1H, H-14), 1.65 (m, 1H, H-18), 1.66 (m, 1H, H-16), 2.03 (m, 1H, H-13), 2.06 (m, 1H, H-10), 3.39 (m, 1H, H-20), 3.43 (m, 1H, H-11), 3.56 (m, 1H, H-20), 3.65 (m, 1H, H-9), 3.74 (m, 1H, H-9), 3.77 (m, 1H, H-19), 4.50 (s, 2H, CH_2OPh), 7.26–7.38 (m, 5H, Ph). ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.57 (18-Me), 17.76 (12-Me), 26.59 (C-13), 28.09 (C-17), 28.15 (C-18), 30.25 (C-14), 33.17 (C-10), 35.15 (C-12), 35.64 (C-16), 64.57 (C-20), 67.11 (C-9), 71.26 (C-12), 71.69 (C-19), 73.05 (CH_2OPh), 95.51 (C-15), 127.57, 127.71, 128.36, 138.45 (Ph). FABMS (NOBA) *m/z*: 349 $(M+H)^+$; HR-EIMS calcd for $C_{21}H_{32}O_4$: 348.2301, found: 348.2303.
12. Compound **2**: $[\alpha]_D^{19}$ +35° (*c* 0.10, *i*-Pr_2O). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 (d, 3H, *J*=6.5 Hz, 12-Me), 0.92 (d, 3H, *J*=7.0 Hz, 18-Me), 1.31 (m, 1H, H-13), 1.33 (m, 1H, H-17), 1.37 (m, 1H, H-12), 1.37 (m, 1H, H-16), 1.56 (m, 1H, H-14), 1.64 (m, 1H, H-14), 1.65 (m, 1H, H-10), 1.65 (m, 1H, H-13), 1.73 (m, 1H, H-18), 1.82 (m, 1H, H-17), 2.03 (m, 1H, H-10), 2.07 (m, 1H, H-16), 3.25 (dd, 1H, *J*=9.5, 10.5 Hz, H-11), 3.48 (m, 1H, H-20), 3.63 (m, 1H, H-20), 3.65 (m, 1H, H-9), 3.72 (m, 1H, H-9), 4.24 (m, 1H, H-19), 4.51 (s, 2H, CH_2OPh), 7.28–7.40 (m, 5H, Ph). ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.38 (18-Me), 18.15 (12-Me), 23.36 (C-16), 26.48 (C-17), 28.97 (C-18), 30.21 (C-13), 34.54 (C-10), 36.07 (C-12), 37.19 (C-14), 65.17 (C-20), 67.82 (C-9), 73.52 (C-19), 75.55 (C-11), 73.84 (*C*H_2OPh), 98.11 (C-15), 128.25, 128.51, 129.07, 139.35 (Ph). FABMS (NOBA) *m/z*: 349 $(M+H)^+$; HR-EIMS calcd for $C_{21}H_{32}O_4$: 348.2301, found: 348.2298.