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Efficient synthesis of the 6,6-spiroacetal of spirofungin A

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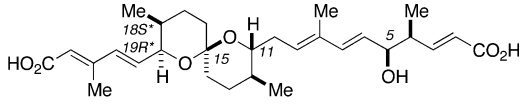
Abstract—The 6,6-spiroacetal segment of spirofungin A, an antifungal antibiotic isolated from *Streptomyces violaceusniger* Tü 4113, was efficiently prepared via the coupling reaction of the Weinreb amide and the alkyne which are readily available from the common intermediate. The synthesis includes the unsymmetrization through a stereoinversion at the C11 position and the transacetalization as the key steps. © 2003 Elsevier Science Ltd. All rights reserved.

Spirofungins A (**1**) and B (**2**) are novel polyketide-type antibiotics isolated from *Streptomyces violaceusniger* Tü 4113 as a 4:1 mixture of **1**:**2** and show various antifungal activities, particularly against yeasts.[1] The molecular structures of **1** and **2** are characterized by a 6,6-spiroacetal core bearing two unsaturated side chains ending in carboxylic acid units and two methyl groups. The relative configuration of the spiroacetal core in **1** is quite similar to reveromycin A (**3**), a potent inhibitor of mitogenic activity induced by the epidermal growth factor.[2] The absolute configuration depicted for **1** was proposed by analogy with **3** and remains unconfirmed (Fig. 1).[3,4] We have already reported the first asymmetric total synthesis of **3** (Fig. 2).[5] In connection of our studies concerning the chemical modifications and structure–activity relationships of **3**,[6] we planned to synthesize **1** and to confirm the relative and absolute configuration of **1**.



Spirofungin A (**1**)
B (**2**) (18*R**,19*S**)

Figure 1. Provisional structures of spirofungins A (**1**) and B (**2**).

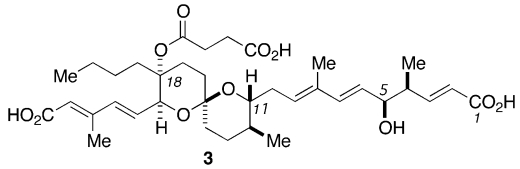
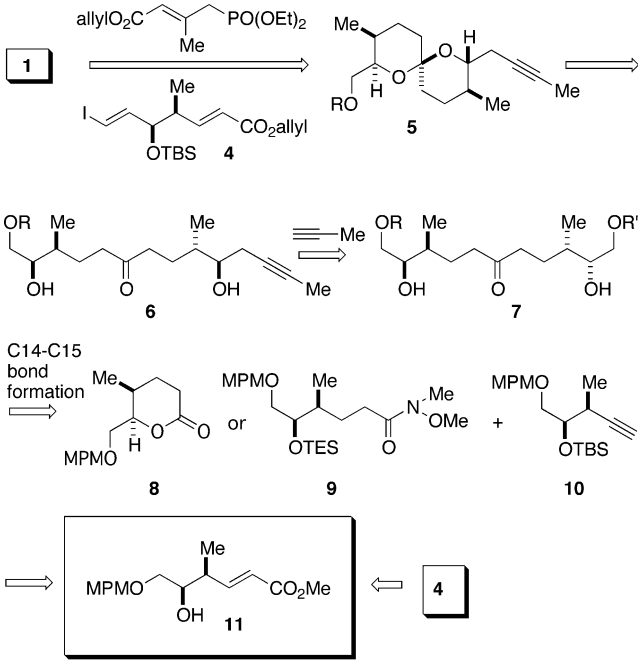


Figure 2. Structure of reveromycin A (**3**).

Our retrosynthetic analysis of spirofungin A (**1**) is shown in Scheme 1. The unsaturated left and right side chains should be produced by the Horner–Wadsworth–Emmons reaction and Negishi coupling reaction.[5,7] The



Scheme 1. Retrosynthetic analysis of spirofungin A (**1**).

Keywords: spirofungin A; antifungal; 6,6-spiroacetal; Weinreb amide.

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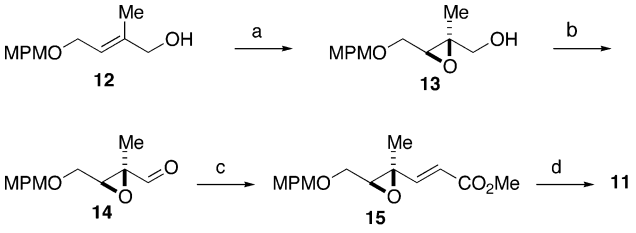


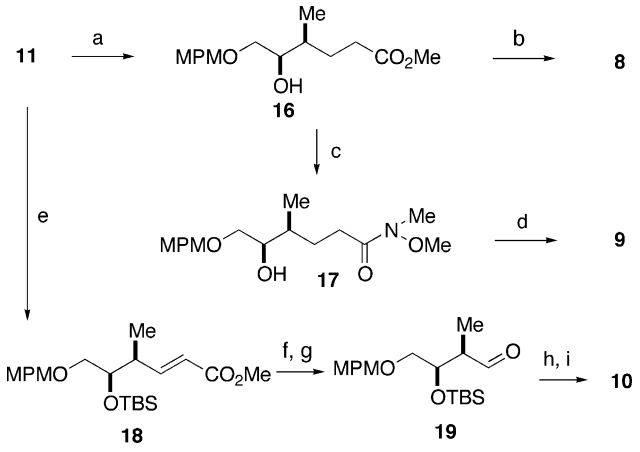
Scheme 2. *Reagents and conditions*: (a) (+)-DET, Ti(O*i*-Pr)$_4$, *t*-BuOOH, MS-4A, CH_2Cl_2, −25°C (88%); (b) $(COCl)_2$, DMSO, CH_2Cl_2, −78°C; Et_3N, −78°C to rt; (c) $Ph_3P{=}CHCO_2Me$, benzene, rt (82%, two steps); (d) $Pd_2(dba)_3{\cdot}CHCl_3$, *n*-Bu_3P, HCO_2H–Et_3N, dioxane, rt (96%).

construction of **5** could be achieved by the intramolecular acetalization of the ketone **6** derived from ketone **7** through a stereoinversion at the C11 position. The symmetrical ketone **7** would be synthesized via the coupling reaction of the lactone **8** or Weinreb amide **9** and alkyne **10**, which in turn might be prepared from a common precursor **11**. The vinyl iodide **4** for the Negishi coupling could also be prepared from **11**.

First, the common precursor **11** was prepared. The Sharpless epoxidation[8] of the allyl alcohol **12**[9], which was readily prepared from *cis*-2-buten-1,4-diol, with *t*-BuOOH in the presence of (+)-DET and Ti(O*i*-Pr)$_4$ gave the epoxide **13** in 88% yield (90% ee).[10] The Swern oxidation of **13** followed by the Wittig reaction with $Ph_3P{=}CHCO_2Me$ afforded the ester **15** in 82% yield in two steps. The palladium-catalyzed hydrogenolysis of **15** was performed with $Pd_2(dba)_3{\cdot}CHCl_3$ in the presence of *n*-Bu_3P–HCO_2H–Et_3N to stereoselectively afford the *syn*-alcohol **11** (96%) (Scheme 2).[11]

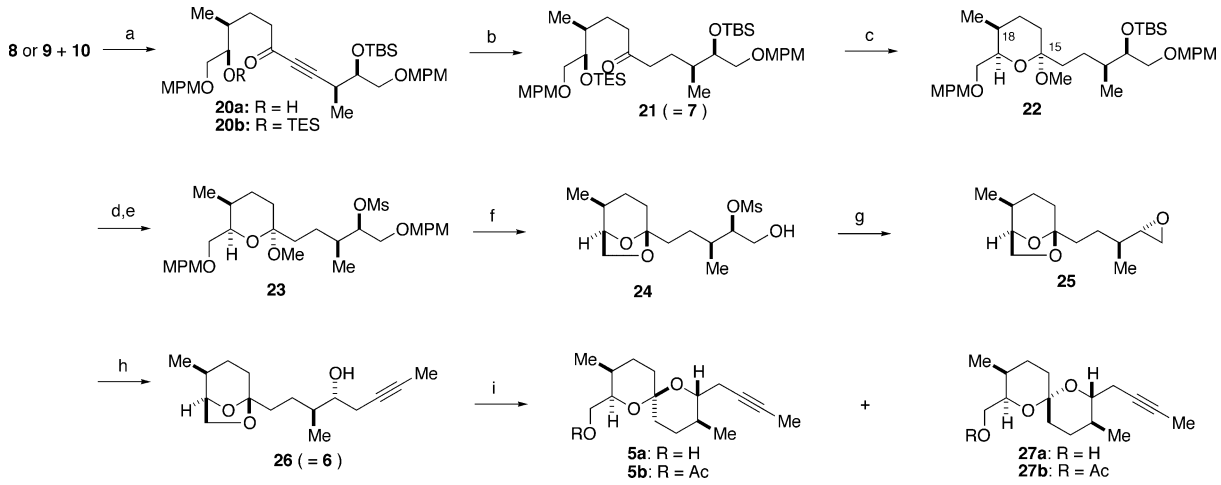
Next, all of the segments **8**, **9** and **10** were prepared from **11**. The hydrogenation of **11** on Pd/C gave the saturated alcohol **16** (99%), which was then treated with CSA to afford the lactone **8** (72%). The methyl ester **16** was converted into the Weinreb amide **9** by treatment with Me_2AlCl–(MeO)MeNH·HCl[12] followed by silylation with TESCl. The alkyne **10** was synthesized from **11**. After protection of the hydroxyl group in **11** as the TBS ether (99%), the olefin **18** was oxidatively cleaved by successive treatment with OsO_4-NMO and $Pb(OAc)_4$ to afford the aldehyde **19**. The aldehyde **19** was then treated with CBr_4–Ph_3P in the presence of Et_3N to produce the dibromoolefin (93%, three steps), which was converted into the alkyne **10** by treatment with 2 equiv. of *n*-BuLi (Scheme 3).[13]

The stage was then set for the construction of the 6,6-spiroacetal. The treatment of **10** with *n*-BuLi followed by the addition of **8** afforded the coupling product **20a** in 23% yield together with the recovered **10** (65%). On the other hand, **9** produced **20** in 81% yield by a similar treatment with **10**. Then, **20b** was hydrogenated on Pd/C to give the saturated ketone **21** (99%), which is a latent C_2 symmetric compound. Selective cleavage of the TES group in **21** followed by simultaneous acetalization was performed with PPTS in MeOH at room temperature to give the acetal **22** in



Scheme 3. *Reagents and conditions*: (a) H_2, Pd/C, AcOEt, rt (99%); (b) CSA, benzene, 70°C (72%); (c) Me_2AlCl, (MeO)MeNH·HCl, CH_2Cl_2, 0°C to rt; (d) TESCl, imidazole, DMAP, DMF, rt (92%, two steps); (e) TBSCl, imidazole, DMF, 0°C to rt (99%); (f) OsO_4, NMO, acetone-H_2O-*t*-BuOH, rt; (g) $Pb(OAc)_4$, toluene, rt; (h) CBr_4, Ph_3P, Et_3N, CH_2Cl_2, 0°C to rt (93%, three steps); (i) *n*-BuLi, THF, −78°C to rt (91%).

95% yield. It is important to note that the C19-hydroxyl group forms the acetal with the C15-carbonyl group distinguished from the C11-hydroxyl group. The next task is the introduction of propyne through a stereoinversion at the C11 position. The TBS group in **22** was deprotected with *n*-Bu_4NF to give the alcohol, which was immediately treated with MsCl in pyridine to afford the mesylate **23**. The treatment of **23** with DDQ effected deprotection of both MPM groups and simultaneous transacetalization to give the stable hydroxyl bicyclic acetal **24** (80%, three steps). The mesylate was treated with K_2CO_3 in MeOH to provide the epoxide **25** in 93% yield. The epoxide **25** was reacted with propyne and *n*-BuLi in the presence of $BF_3{\cdot}OEt_2$ to afford the alcohol **26** with the desired configuration at the C11 position.[14] The remaining task is formation of the 6,6-spiroacetal core by the transacetalization of **26**. The treatment of **26** with CSA in CH_2Cl_2 at room temperature gave an equilibrium mixture of **26** and the 6,6-spiroacetal alcohols **5a** and **27a** (3:3:2) which was selectively acetylated by an addition of collidine and AcCl at −78°C to provide a mixture of the secondary alcohol **26** and the 6,6-spiroacetal acetates **5b** and **27b**.[15] These successive treatments were repeated four times in one pot and the desired 6,6-spiroacetal **5b**[16] and the isomer **27b** were obtained in 46 and 30% yields, respectively (Scheme 4). The stereostructures of **5b** and **27b** were confirmed by the extensive NMR analyses (^1H, ^{13}C NMR, NOE and HMBC). The vicinal coupling constant between H11 and H12 ($J=10.8$ Hz) in **5b** reflects the diaxial position of the two protons. The vicinal coupling constant between H18 and H19 ($J=4.4$ Hz) as well as the chemical shift of the C18-Me (15.0 ppm) indicate that H18 is axial and H19 is equatorial. The NOEs between H20 and H11, H17 axial also proved that **5b** has the same conformation as that of spirofungin A (**1**) as shown in Figure 3.



Scheme 4. *Reagents and conditions*: (a) LHMDS, THF, −78°C to rt (**20a** from **8**, 23%; **20b** from **9**, 91%); (b) H_2, Pd/C, AcOEt, rt (99%); (c) PPTS, MeOH, rt (95%); (d) TBAF, DMF, rt; (e) MsCl, pyridine, 0°C to rt; (f) DDQ, CH_2Cl_2–H_2O, rt (80%, three steps); (g) K_2CO_3, MeOH, rt (93%); (h) propyne, *n*-BuLi, $BF_3{\cdot}OEt_2$, THF, −78°C to rt (99%); (i) CSA, CH_2Cl_2, rt then AcCl, collidine, −78°C (four times repeated) (**5b**, 46%; **27b**, 30%).

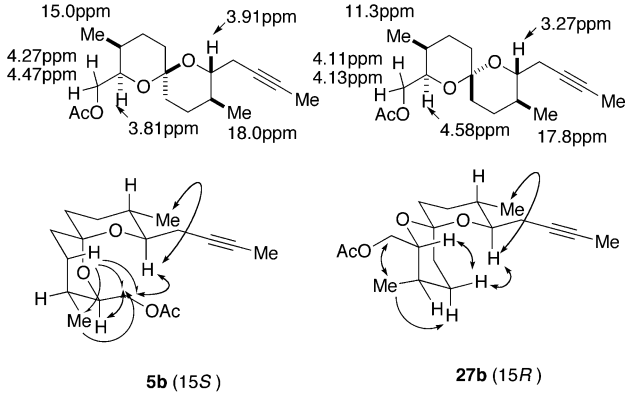


Figure 3. ^1H, ^{13}C NMR and NOE data of spiroacetals **5b** and **27b**.

In summary, the segments, Weinreb amide **9** and alkyne **10**, were readily prepared from the common intermediate **11**. In turn, the 6,6-spiroacetal core **5b** was efficiently synthesized via the coupling reaction of **9** and **10**, the unsymmetrization by the reaction of the epoxide with propyne through a stereoinversion at the C11 position and the transacetalization to form the 6,6-spiroacetal.

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16. Data for **5b**: $[\alpha]_D^{24}$: −69.1 (*c* 1.17, C_6D_6); IR (neat): ν_{max} = 2930, 1743, 1458, 1370, 1239 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 0.72 (d, J = 7.3 Hz, C18-Me), 0.81 (d, J = 6.9 Hz, C12-Me), 1.58 (t, J = 2.4 Hz, C8-Me), 1.75 (s, Ac), 2.40 (ddq, J = 17.1, 5.4, 2.4 Hz, H10), 2.55 (ddd, J = 17.1, 2.4, 2.4 Hz, H10), 3.81 (ddd, J = 8.3, 4.4, 4.4 Hz, H19), 3.91 (ddd, J = 10.8, 5.4, 2.4 Hz, H11), 4.27 (dd, J = 11.2, 4.4 Hz, H20), 4.47 (dd, J = 11.2, 8.3 Hz, H_20); ^{13}C NMR (150 MHz, C_6D_6) δ 3.6, 15.0, 18.0, 24.1, 25.4, 27.8, 31.2, 33.7, 34.2, 34.7, 64.8, 74.2, 74.5, 76.3, 76.9, 96.8, 170.0; HRMS (FAB) calcd for $C_{18}H_{29}O_4$ (M^++H^+) 309.2066, found 309.2084.