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Synthesis of the Spirofungin B Core by a Reductive Cyclization Strategy

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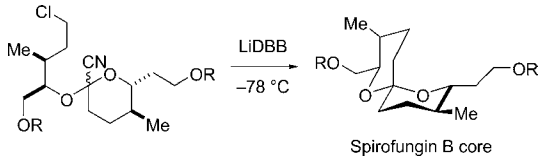
ABSTRACT



Spirofungin B core

A reductive decyanation approach to the synthesis of the core of spirofungin B has been developed. Spirofungin B has only one anomeric stabilization in the spiroacetal and was isolated along with its spiroacetal epimer, spirofungin A. The cyclization precursor was constructed from readily available starting materials. The reductive cyclization reaction was both efficient and stereoselective. The reductive cyclization strategy to spiroacetals is convergent and effective.

The spirofungin family of natural products was isolated from a *Streptomyces* strain Tü 4113 collected in the Australian Otway National Park as a 4:1 mixture of spirofungin A (**1**) and spirofungin B (**2**).[1] Rizzacasa and co-workers recently reported the total synthesis of spirofungin B (**2**) and found that NMR data for the natural product did not match that for their synthetic material (Figure 1).[2] Rizzacasa proposed a revised structure for spirofungin B (**3**) that is epimeric with spirofungin A (**1**) at the C15 spiroacetal center. Thus spirofungin B (**3**) would be a spiroacetal with a single anomeric stabilization. Rizzacasa's reassignment of spirofungin B was further supported by the report of Dias, who synthesized a spirofungin A and B spiroacetal.[3] Dias' spirofungin model was isolated as a 30:70 equilibrium mixture of spiroacetals **5** and **4**, corresponding to the spirofungin A and spirofungin B spiroacetals, respectively.[3] The revised structure of spirofungin B (**3**) as a spiroacetal with only one anomeric stabilization appears to be secure.

We recently reported a new reductive cyclization strategy to access spiroketals with a single anomeric stabilization.[4] The reductive cyclization method appears well suited to the synthesis of the revised spirofungin B structure. Described herein is a synthesis of the spirofungin B spiroacetal core using a stereoselective reductive cyclization strategy.

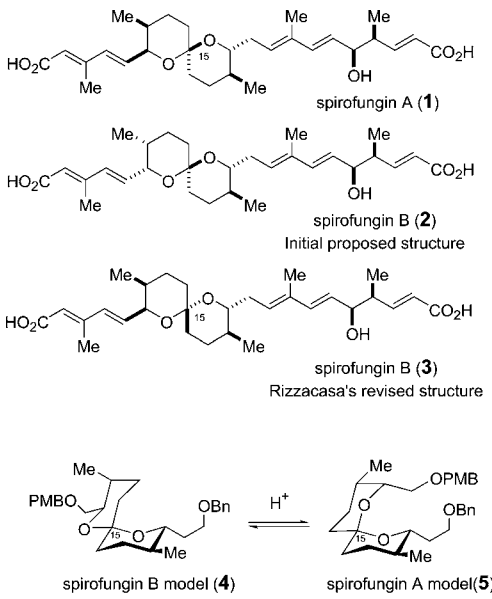


Figure 1. The originally proposed structure of spirofungin B (**2**) and Rizzacasa's revised structure (**3**), as well as Dias' synthetic spirofungin A/B model (**5**/**4**).

(1) Holtzel, A.; Kempter, C.; Metzger, J. W.; Jung, G.; Groth, I.; Fritz, T.; Fiedler, H.-P. *J. Antibiot.* **1998**, *51*, 699−707.

(2) Rizzacasa, M. A.; White, J. M.; Zanatta S. D. *Org. Lett.* **2004**, *6*, 1041−1044.

(3) Dias, L. C.; de Oliveira, L. G. *Org. Lett.* **2004**, *6*, 2587−2590.

(4) Buckmelter, A. J.; La Cruz, T. E.; Rychnovsky, S. D.; Takaoka, L. R. *J. Am. Chem. Soc.* **2005**, *127*, 528−529.

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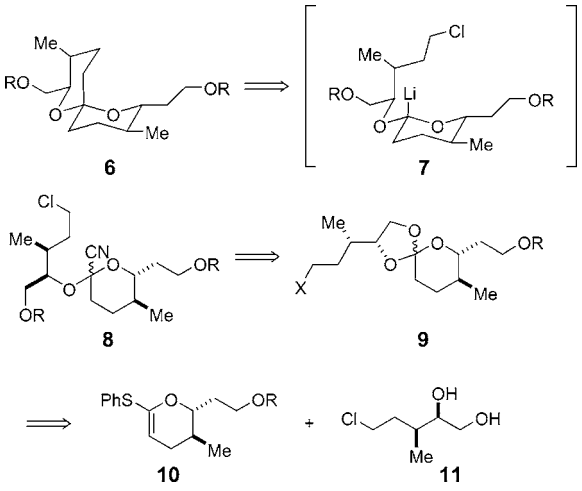
The disconnection strategy employed for the synthesis of the spirofungin B spiroacetal **6** is illustrated in Scheme 1.

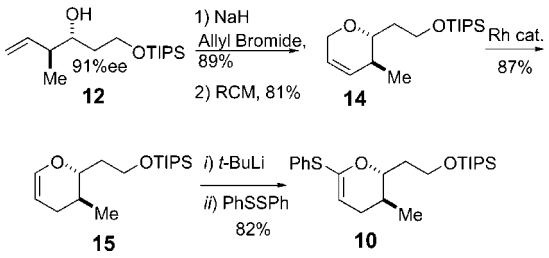
Scheme 1. Retrosynthetic Analysis



The intermediate synthetic goal is the preparation of ortho ester **9**. Opening the ortho ester **9** to a cyano acetal **8**, followed by reductive lithiation using lithium di-*tert*-butylbiphenylide (LiDBB) would produce the axial organolithium species **7**. Intramolecular alkylation of organolithium **7** should deliver spiroacetal **6** stereoselectively, with a single anomeric stabilization. The synthesis of ortho ester **9** derives from the combination of hemithio ketene acetal **10** and diol **11**, both of which should be readily available using standard synthetic transformations.

Synthesis of hemithio ketene acetal **10** began with known alcohol **12**, available in 91% ee using Brown's enantioselective crotylation reaction.[5,8a] Alcohol **12** was esterified with allyl bromide in 89% yield (Scheme 2). Ring closing

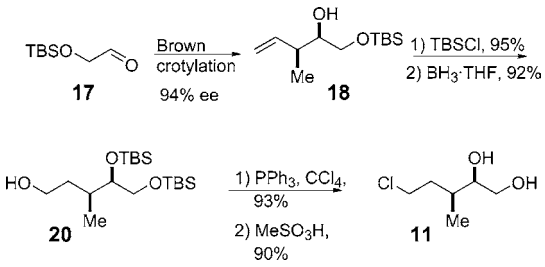
Scheme 2. Synthesis of Hemithio Ketene Acetal **10**



metathesis of allyl ether **13** with Grubb's first generation catalyst generated dihydropyran **14** in 81% yield. Alkene isomerization with Wilkinson's catalyst to enol ether **15**, followed by lithiation of dihydropyran **15** with *t*-BuLi and quenching of the organolithium species with diphenyl disulfide, gave hemithio ketene acetal **10**.[6,7] Compound **10** was prepared with a TIPS protecting group because previous experience had shown that it was suitable for both the metalation reaction and the reductive cyclization.[4]

Scheme 3 summarizes the synthesis of diol **11**. Homo-

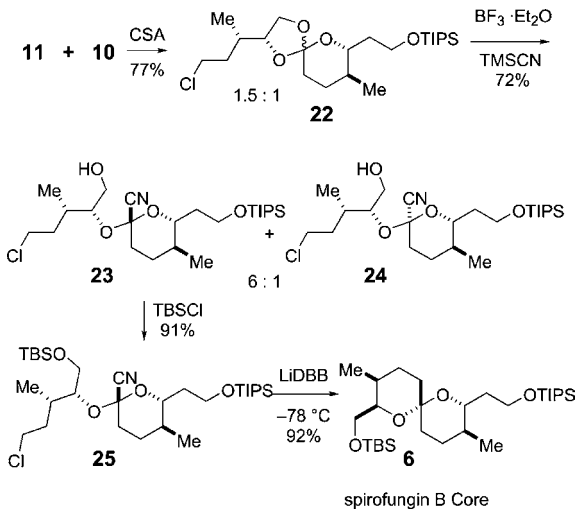
Scheme 3. Synthesis of Chloro Diol **11**



allylic alcohol **18** was synthesized by Brown crotylation of aldehyde **17** in 86% yield and 94% ee.[8] Alcohol **18** was protected as the bis-TBS ether **19**, which upon hydroboration gave the primary alcohol **20**. Treatment of this primary alcohol with triphenylphosphine and carbon tetrachloride, followed by removal of the TBS ethers under acidic conditions, gave chloro diol **11**.[9]

With the hemithio ketene acetal **10** and the diol **11** in hand, synthesis of the spiroacetal could commence. The cyclization precursor was assembled as outlined in Scheme 4. Acid-

Scheme 4. Combining the Fragments and Reductive Cyclization



catalyzed addition of chloro diol **11** to hemithio ketene acetal **10** gave an inseparable mixture of ortho esters **22** consisting

(5) Dreher, S. D.; Leighton, J. L. *J. Am. Chem Soc.* **2001**, *123*, 341−342.

(6) Leeuwenburgh, M. A.; Overkleeft, H. S.; van der Marel, G. A.; van Boom, J. H. *Synlett* **1997**, 1263−1264.

(7) Boeckman, R. K.; Bruza, K. J. *Tetrahedron* **1981**, *37*, 3997−4006.

(8) (a) Bhat, K. S.; Brown, H. C. *J. Am. Chem. Soc.* **1986**, *108*, 5919−5923. (b) Gravel, M.; Hall, D. G.; Lachance, H.; Lu, X. *J. Am. Chem. Soc.* **2003**, *125*, 10160−10161. (c) Ardisson, J.; Berque, I.; Brion, J.-D.; Férézou, J.-P.; Le Ménéz, P.; Mahuteau, J.; Pancrazi, A.; Razon, P. *J. Org. Chem.* **1999**, *64*, 373−381.

of two predominant isomers (1.5:1 ratio) that were epimeric at the spiro center. We found this mixture to be contaminated with at least one other diastereomeric ortho ester (~5%) that would arise from the coupling of the minor enantiomer of hemithio ketene acetal **10** or chloro diol **11**. Treatment of the ortho ester mixture **22** with TMSCN and BF_3 etherate afforded cyano acetals **23** and **24** in 77% yield as a 6:1 mixture of epimers. However, once again a third minor isomer was present in this mixture. The major cyano acetal **23** could be readily separated from the other cyano acetals by flash chromatography and was carried forward as a single diastereomer.[10] The primary hydroxyl group was protected as the TBS ether to give the cyclization precursor **25**.

Cyano acetal **25** was treated with LiDBB in THF at −78 °C to generate an axial organolithium reagent corresponding to compound **7** in Scheme 1. The organolithium reagent cyclized to give the spiroacetal core of spirofungin B, compound **6**. Spiroacetal **6** was produced as a single diastereomer. The relative configuration of spiroacetal **6** was determined by 1D and 2D NMR analysis[11,12] and by comparing the spectroscopic data of **6** with Dias' spirofungin B segment (Figure 2).[3] The chemical shift of the spiro carbon of **6** was found to be 97.4 ppm ($CDCl_3$), which is in good agreement with both the structure of spirofungin B (97.1 ppm), and of Dias' spiroacetal (97.5 ppm).[13] The methyl groups of **6** also shared similar chemical shifts as those reported for Dias' spiroacetal. When spiroacetal **6** was dissolved in $CDCl_3$, equilibration ensued to produce a 70:30 mixture of **6** and its C15 epimer. This outcome is in accord with the behavior Dias observed with his spirofungin B spiroacetal and lends further support to the structural assignment of spiroacetal **6**.[11,13]

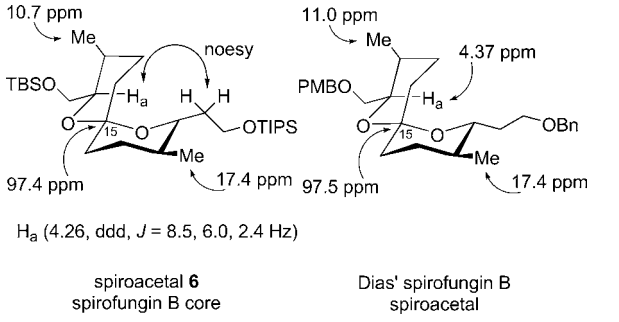


Figure 2. Spectroscopic data for spiroacetal **6** and Dias' analogue.

A reductive cyclization approach to the synthesis of the spirofungin B spiroacetal was developed. The spiroacetal has only a single anomeric stabilization, and it has not been prepared as a single diastereomer previous to this work. The reductive cyclization strategy is inherently convergent, and in this example the cyclization precursor was constructed efficiently from readily available starting materials. The cyclization reaction was highly stereoselective and produced the spirofungin B core as a single diastereomer. We will continue to investigate the potential of reductive cyclization strategies in natural product syntheses.

Acknowledgment. This work was supported by the National Institute of General Medical Sciences (GM-65338). Brian Patterson initially developed the route to enol ether **15** in this laboratory.

Supporting Information Available: Preparation and characterization of the described compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL050589C

(9) Garegg, P. J.; Johansson, R.; Samuelsson, B. *Synthesis* **1984**, 168−170.

(10) The configuration of the nitrile motif is inconsequential to the outcome of the cyclization reaction (ref 4).

(11) 1D and 2D proton NMR data of spiroacetal **6** were collected in C_6D_6. However, the spectroscopic data shown in Figure 2 was collected in $CDCl_3$, the same solvent used by Dias. In $CDCl_3$ spiroacetal **6** equilibrated with its C15 epimer rapidly, and equilibrium was achieved in approximately 10 min.

(12) Equilibration of spiroacetal **6** with its C15 epimer was prevented if ^1H NMR and ^{13}C NMR data were obtained using C_6D_6.

(13) The chemical shift of the C15 epimer of **6** was observed to be 96.6 ppm ($CDCl_3$). Dias' spirofungin A model showed an identical ^{13}C NMR shift at the corresponding carbon atom (ref 3).