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Total Synthesis of the Proposed Structure of Mycosporulone: Structural Revision and an Unexpected Retro-Aldol/Aldol Reaction

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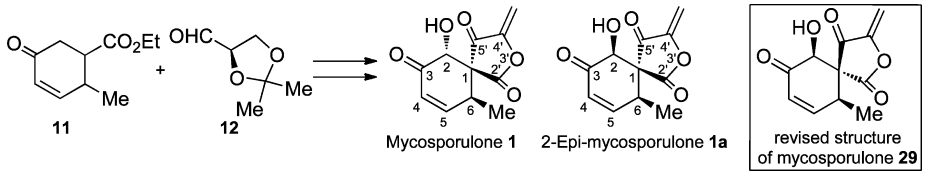
ABSTRACT



The proposed structure of the fungal metabolite, mycosporulone 1, was prepared starting from the cyclohexenone ester 11 and the D-(*R*)-glyceraldehyde acetonide 12. The spectroscopic data for both 1 and its C2 epimer 1a did not match those reported for the natural product. A revised structure 29 for mycosporulone is proposed.

Mycosporulone **1** (Figure 1), a polyketide-derived fungal metabolite first reported in 1993,[1a] has shown activity against several bacterial, fungal, and cancer strains while exhibiting no toxicity toward human lung fibroblasts (MRC5).[1b] It belongs to the 3-methylidene-2-oxaspiro-[4.5]decan-1-one class of compounds which all possess similar carbon connectivity and varying degrees of oxidation (Figure 2).[2] With the exception of an analogue synthesis by Kraus and co-workers,[3] no member of this class has been synthesized; moreover, very little is known about their biological activity. The structure of mycosporulone **1** was determined by ^{1}H and ^{13}C NMR and mass spectrometric fragmentation patterns, with the relative stereochemistry being assigned by NOE and Dreiding model analysis. Investigation of the reported data revealed an NOE between the protons on C2 and C6, suggesting a *cis* and not a *trans* relationship as depicted. According to calculations, the *cis* diastereomer **1a** would be the lowest energy conformation by approximately 2.5 kcal/mol.[4] Due to its varied biological activity and questionable structural assignment, we therefore sought to develop a synthesis of mycosporulone **1** that would prove its structure and that also could be applied to its structural congeners.

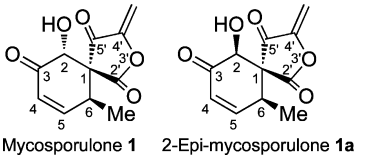


Figure 1. Structures of mycosporulone and its 2-epimer.

The retrosynthetic analysis (Scheme 1) suggested that the methylene tetrahydrofurandione moiety of **1** could be prepared by dehydration of the lactone **8**, which would

(1) (a) Kaouadji, M.; de Gusmao, N. B.; Steiman, R.; Seigle-Murandi, F. *J. Nat. Prod.* **1993**, *56*, 2189–2192. (b) Guiraud, P.; Steiman, R.; Seigle-Murandi, F.; Buarque de Gusmao, N. *J. Nat. Prod.* **1999**, *62*, 1222–1224.

(2) (a) Ayer, W. A.; Craw, P. A.; Neary, J. *Can. J. Chem.* **1992**, *70*, 1338–1347. (b) Hirota, A.; Nakagawa, M.; Hirota, H. *Agric. Biol. Chem.* **1991**, *55*, 1187–1188. (c) Abdel-Wahab, M. A.; Asolkar, R. N.; Inderbitzin, P.; Fenical, W. *Phytochemistry* **2007**, *68*, 1212–1218. (d) Sun, Z.-L.; Zhang, M.; Zhang, J.-F.; Feng, J. *Phytomedicine* **2011**, *18*, 859–862. (e) Albinati, A.; Bruckner, S.; Camarda, L.; Nasini, G. *Tetrahedron* **1980**, *36*, 117–21.

(3) For a synthesis of desmethyl mycosporulone, see: Kraus, A. G.; Cui, W. *Synlett* **2003**, *1*, 95–96.

(4) Liu, P.; Houk, K. H. UCLA, private communication.

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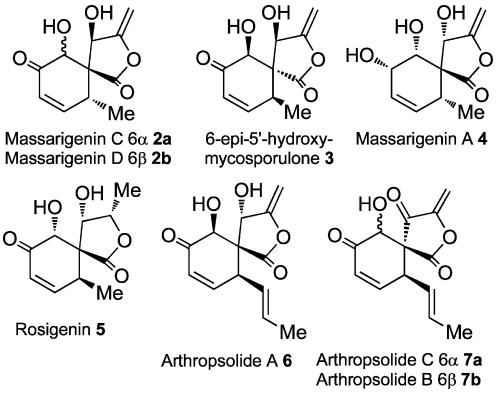
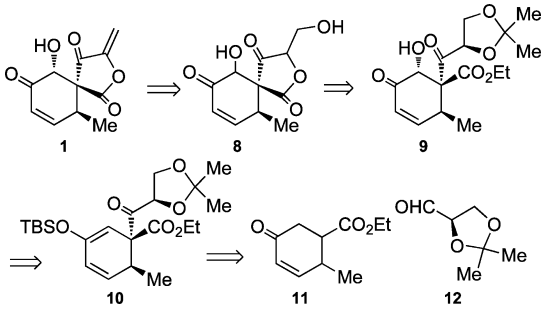


Figure 2. 3-Methylidene-2-oxaspiro[4.5]decan-1-one class.

arise from an acid-mediated acetonide hydrolysis/lactonization of the acyloin **9**. We noted that these acidic conditions might epimerize the acyloin functionality by the Lobry de Bruyn–Alberda van Ekenstein reaction to give two diastereomers.[5] The acyloin group would be introduced by a Rubottom oxidation of the silyl enol ether **10**,[6] which would result from an aldol reaction of the kinetic silyl enol ether of the cyclohexadienone **11** and the enantiopure D-(*R*)-glyceraldehyde acetonide **12**.

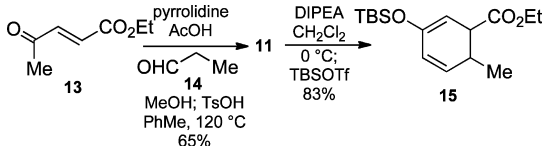
Scheme 1. Mycosporulone Retrosynthetic Analysis



Condensation of ethyl 4-oxo-2-pentenoate **13**[7] and propionaldehyde **14** employing pyrrolidine as an organocatalyst followed by standard Dean–Stark dehydration conditions[8] afforded the enone **11** in 65% yield as a mixture of diastereomers (Scheme 2). Soft enolization[9] of the enone **11** in the presence of TBSOTf gave the silyloxy cyclohexadiene **15** in 83% yield as a mixture of diastereomers.

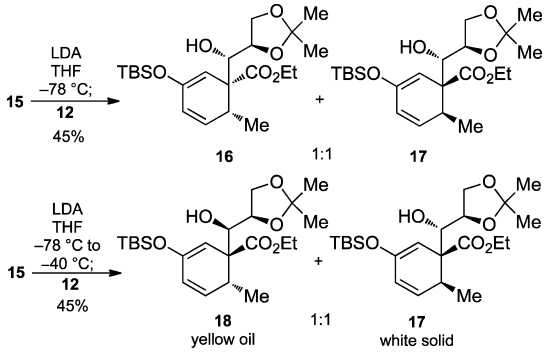
This observed regioselectivity is predicated on the increased basicity of the enone over the ester carbonyl.

Scheme 2. Preparation of Silyl Enol Ether **15**



The silyloxy cyclohexadiene **15** was deprotonated with LDA at −78 °C, trapped with D-(*R*)-glyceraldehyde acetonide **12**, and quenched at the same temperature to produce a 1:1 mixture of the aldol diastereomers **16** and **17** (Scheme 3). These diastereomers differ in the absolute stereochemistry about the methyl and ethyl ester groups but have the same alcohol configuration consistent with a Felkin–Ahn approach of the aldehyde *trans* to the methyl group.[10] When the same mixture was allowed to warm to −40 °C and then quenched, a different 1:1 mixture of products was obtained, namely a yellow oil, **18**, along with **17**. An X-ray crystal structure of **17** shows the stereochemistry[11] (Figure 3). The aldol product **17** possesses the requisite stereodiad for the synthesis of mycosporulone.

Scheme 3. Aldol Reaction of **15** and **12**



The configuration of the aldol product **18** was assigned as follows. First, the lowest energy conformations of the four possible lithium alkoxides were calculated (Scheme 4).[12] The alkoxide **19** arises from Felkin–Ahn addition of the aldehyde *trans* to the methyl group of the (*S*)-enolate eventually leading to the aldol product **17**. The alkoxide **20** corresponds to the same aldehyde addition on the opposite (*R*)-enolate leading to **16**. The alkoxides **21** and **22** would be generated from either Felkin–Ahn or Cram-chelation addition of the aldehyde *cis* to the methyl group on the (*R*)-enolate, respectively. Second, the observed proton–proton

(5) For examples of the Lobry de Bruyn–Alberda van Ekenstein reaction in synthesis, see: (a) Grieco, P. A.; Nargund, R. P.; Parker, D. T. *J. Am. Chem. Soc.* **1989**, *111*, 6287–6294. (b) White, J. D.; Cutshall, N. S.; Kim, T.-S.; Shin, H. *J. Am. Chem. Soc.* **1995**, *117*, 9780–9781.

(6) Rubottom, G. M.; Vazquez, M. A.; Pelegrina, D. R. *Tetrahedron Lett.* **1975**, *15*, 4319–4322.

(7) McMurry, J. E.; Blaszczak, L. C. *J. Org. Chem.* **1974**, *39*, 2217–2222.

(8) Wang, J.; Ma, A.; Ma, D. *Org. Lett.* **2008**, *10*, 5425–5428.

(9) Jung, M. E.; Ho, D. *Org. Lett.* **2007**, *9*, 375–378.

(10) For selectivity in enolate additions to D-(*R*)-glyceraldehyde acetonide, see: Heathcock, C. H.; Young, S. D.; Hagan, J. P.; Pirrung, M. C.; White, C. T.; VanDerveer, D. *J. Org. Chem.* **1980**, *45*, 3846–3856.

(11) Since the absolute stereochemistry of the acetonide carbon was established from **12**, one can assign the absolute stereochemistry of **17**.

(12) Pham, H. V.; Houk, K. H. UCLA, private communication.

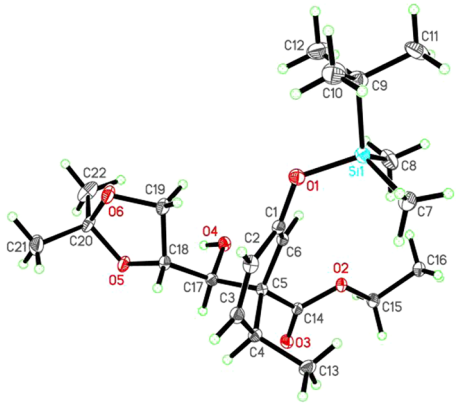
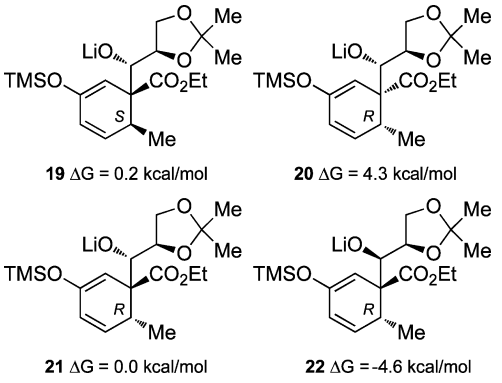


Figure 3. X-ray crystallographic structure of **17**.

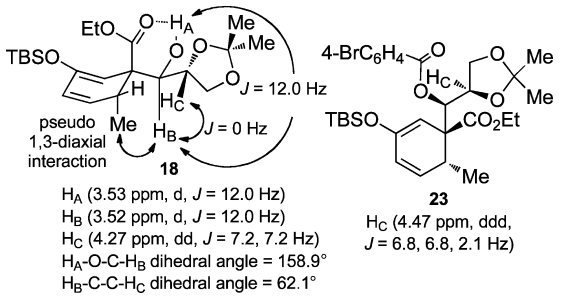
Scheme 4. Calculated Lowest Energy Conformations



coupling constants of the aldol product **18** (Scheme 5) also are consistent with the assigned structure, i.e., a large coupling (J = 12.0 Hz) for both H_A and H_B, implying an anticoplanar orientation of the two protons. This is supported by the structure minimization, which indicates a H_A–O–C–H_B dihedral angle of 159°. Furthermore, H_C exists as a doublet of doublets (dd) due to the coupling between it and the protons on the adjacent methylene group with no coupling observed with H_B, implying that H_C and H_B are nearly orthogonal. This is again borne out by the structure minimization which shows that the H_B–C–C–H_C dihedral is 62°.[13] In contrast, proton H_C of the ester **23** now exists as a ddd, J = 6.8, 6.8, 2.1 Hz. Several conditions were screened for the oxidation of the aldol **18**, but all resulted in unreacted starting material. After the initial alcohol activation, the inability to remove the proton H_B, which is sterically hindered due to a pseudo 1,3-diaxial interaction with the methyl group, presumably prevents the second E_2 elimination step. Accordingly, the

(13) Although this dihedral angle is not 85°, the J for the two protons is close to zero which may be due to the fact that the two heteroatoms on the adjacent carbons change the Karplus equation values.

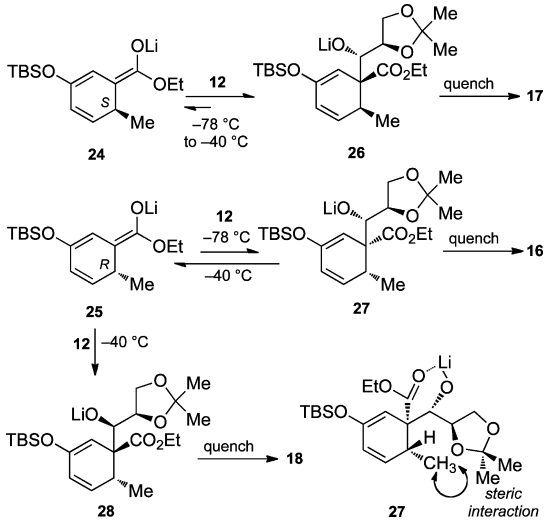
Scheme 5. NMR Coupling Constant Analysis of **18**



stereochemical configuration of the aldol product **18** was assigned based on this analysis.

When the racemic silyloxycyclohexadiene **15** was deprotonated, the two enantiomeric enolates **24** and **25** were formed in solution (Scheme 6). Each one added to the glyceraldehyde acetonide **12** at −78 °C to give the lithium alkoxides **26** and **27**, leading to the aldol products **17** and **16** upon quenching. The alkoxide **27** is 4.1 kcal/mol higher in energy than the alkoxide **26** which can be attributed to a *syn*-pentane-like interaction between the methyl and acetonide substituent in **27**. Upon warming to −40 °C, this interaction in the lithium alkoxide **27** is alleviated by undergoing a retro-aldol/aldol sequence to give the alkoxide **28**, which when quenched forms the aldol **18**.[14]

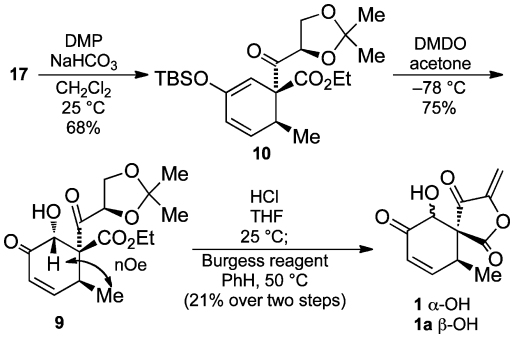
Scheme 6. Retro-Aldol/Aldol Sequence



(14) For examples of retro-aldol/aldol sequences, see: (a) Silverman, R. B. *J. Org. Chem.* **1981**, *46*, 4789–4791. (b) Brocksom, T. J.; Coelho, F.; Deprés, J.-P.; Greene, A. E.; Freire de Lima, M. E.; Hamelin, O.; Hartmann, B.; Kanazawa, A. M.; Wang, Y. *J. Am. Chem. Soc.* **2002**, *124*, 15313–15325. (c) Wang, J.; Cole, K. P.; Wei, L.-L.; Zehnder, L. R.; Hsung, R. P. *Tetrahedron Lett.* **2002**, *43*, 3337–3340. (d) Xu, K.; Lalic, G.; Sheehan, S. M.; Shair, M. D. *Angew. Chem., Int. Ed.* **2005**, *44*, 2259–2261. (e) Akai, S.; Tsujino, T.; Fukuda, N.; Iio, K.; Takeda, Y.; Kawaguchi, K.-I.; Naka, T.; Higuchi, K.; Akiyama, E.; Fujioka, H.; Kita, Y. *Chem.—Eur. J.* **2005**, *11*, 6286–6297. (f) Flock, A. M.; Reucher, C. M. M.; Bolm, C. *Chem.—Eur. J.* **2010**, *16*, 3918–3921.

The required aldol product **17** was next oxidized with Dess–Martin periodinane to give the ketone **10** in 68% yield (Scheme 7). The ketone **10** was then oxidized with DMDO[15] to give the acyloin **9** as a single diastereomer, the structure of which was assigned by NMR, especially the NOE between the methyl and the acyloin proton. The acyloin **9** was treated with concentrated HCl in THF at 25 °C followed by dehydration with the Burgess reagent[3] to give the proposed structure of mycosporulone as a mixture of the alcohol epimers **1** and **1a** in 21% yield. The spectral data of the mixture of **1** and **1a** were not consistent with the data reported for mycosporulone, strongly suggesting a structural misassignment. We were able to access both epimers **1** (OH *trans* to Me) and **1a** (OH *cis* to Me) and can conclude that neither has the required spectral data of mycosporulone. It should be pointed out that the steps in the synthesis from the aldol product **17** to the epimers **1** and **1a** cannot epimerize the quaternary center; had that occurred by some unknown route, one would have expected to see four final products instead of two. Based on these observations, we postulate that the quaternary center (C1) is of the wrong configuration.

Scheme 7. Completion of Synthesis of **1** and **1a**

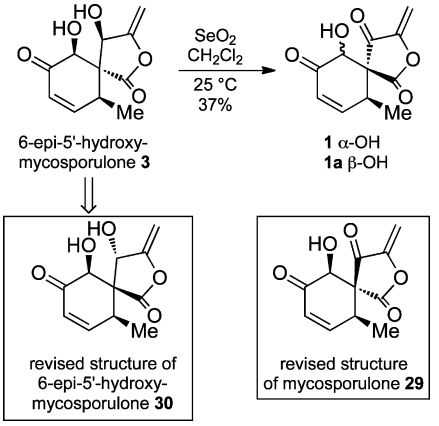


In an attempt to prove that the revised structure of mycosporulone was indeed **29**, we requested and received a gift of the known natural product, 6-epi-5′-hydroxymycosporulone **3**. After screening several conditions (Scheme 8), we found that oxidation with SeO_2 gave a mixture of epimers in 37% yield (59% brsm) that was spectroscopically consistent with the previously synthesized proposed structure for mycosporulone **1**. Consequently, we concluded that 6-epi-5′-hydroxymycosporulone **3** also has the configuration in which the methyl group and the ester of the lactone are *cis* to one another, leading us to believe that it has likewise been misassigned. The revised structure **30** as drawn is consistent with the NOE data reported for 6-epi-5′-hydroxymycosporulone **3**.[2c,16]

(15) Murray, R. W.; Singh, M. *Org. Synth.* **1997**, *74*, 91.

(16) (a) Fukami, A.; Taniguchi, Y.; Nakamura, T.; Rho, M.-C.; Kawaguchi, K.; Hayashi, M.; Komiyama, K.; Omura, S. *J. Antibiot.* **1999**, *52*, 501–504. (b) Roll, D. M.; Tischler, M.; Williamson, R. T.; Carter, G. T. *J. Antibiot.* **2002**, *55*, 520–523.

Scheme 8. Synthesis of **1** from **3** and Structural Reassignment



In summary, a total synthesis of the proposed structure of mycosporulone **1** and its C2-epimer **1a** has been completed. The synthetic material **1** does not correspond to the reported data for mycosporulone, strongly suggesting that there has been a structural misassignment. Based on the current synthesis and the previously reported spectroscopic data, we propose the structural revision of mycosporulone to compound **29**. While attempting to access **29** via oxidation of the known 6-epi-5′-hydroxymycosporulone **3**, the previously synthesized mixture of **1** and **1a** was produced instead. Thus we have reason to believe that 6-epi-5′-hydroxymycosporulone **3** has also been misassigned and now propose its structure to be that of compound **30**. Lastly, a retro-aldol/aldol reaction sequence was observed, generating the aldol products **17** and **18**. The retro-aldol reaction takes place to alleviate the *syn*-pentane-like interactions found in the lithium alkoxide **27**. Future efforts will be focused on elaborating the aldol product **18** by an analogous synthesis to the revised structure of mycosporulone **29**.

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Supporting Information Available. Experimental procedures and proton and carbon NMR for all new compounds. This material is free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.