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Total Synthesis of the Oxopolyene Macrolide (−)-Marinisporolide C

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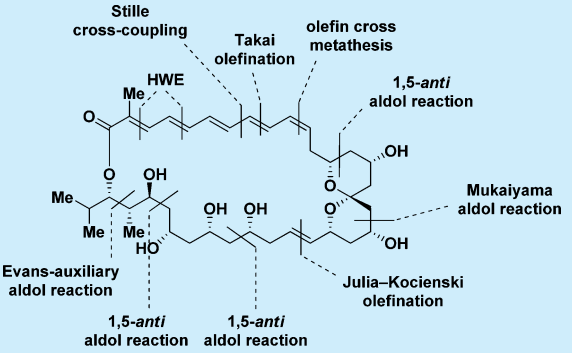
Supporting Information

ABSTRACT: The first total synthesis of (−)-marinisporolide C was performed in 25 steps (longest linear sequence) and an overall yield of 1%. Due to the high degree of convergence and robustness, the C9−C35 fragment that corresponds to the polyol portion was obtained in gram quantity. Highlights of this synthesis include five highly stereoselective aldol reactions responsible for the construction of five C−C bonds and six stereogenic centers. Additionally, a very efficient Julia−Kocieński reaction was used to install a C22−C23 double bond, and the macrocyclic ring was closed using an intramolecular Horner−Wadsworth−Emmons olefination.



Marinisporolides A and B (**1** and **2**) were isolated in 2009 from a saline culture of the marine actinomycete Marinispora, strain CNQ-140 (Figure 1). The structure of

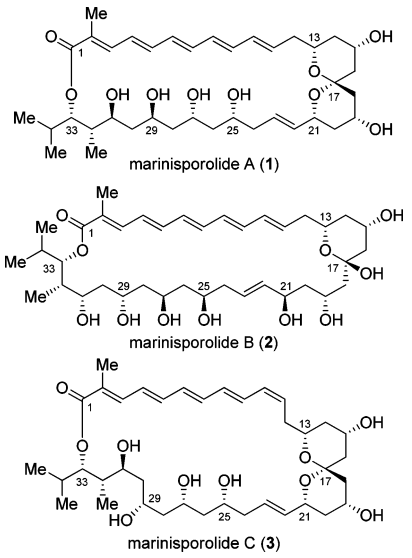


Figure 1. Marinisporolides A−C.

marinisporolide A consists of 11 stereogenic centers within a 34-membered macrolide, containing an internal spiroketal with one anomeric effect, and a conjugated pentaene system. The marinisporolide B is the corresponding hemiketal of the marinisporolide A. Due to readily photoisomerization, marinisporolide C (**3**), which is an olefin geometric isomer of marinisporolide A, was also isolated.[1]

Herein, we describe our synthetic efforts which culminated in the total synthesis of marinisporolide C (**3**) and the confirmation of the stereochemical assignment by Fenical and co-workers.[2,3]

Our retrosynthetic analysis[4] began with an intramolecular Horner−Wadsworth−Emmons olefination involving phosphonate-aldehyde **6** (Scheme 1). Compound **6** could be disconnected into stannane **7** (C3−C7 fragment), aldehyde **8** (C10−C22 fragment), and sulfone **9** (C23−C35 fragment). We envisioned that compounds **8** and **9** could be prepared using several aldol reactions as key steps.[5]

Synthesis of sulfone **9** commenced with the protection of commercially available (*R*)-4-penten-2-ol (**10**) with *para*-methoxybenzyl 2,2,2-trichloroacetimidate (PMBTCA), followed by a Wacker oxidation that delivered methylketone **11** in 59% yield over two steps (Scheme 2).[6] An aldol reaction between methylketone **11** and aldehyde **12** afforded the desired 1,5-*anti* aldol adduct **13** as a 95:05 mixture of diastereoisomers.[7] This mixture was reduced with Et_2BOMe and $LiBH_4$ (70% over two steps, *dr* > 95:05),[8] followed by protection with 2,2-DMP to furnish the acetonide **14** in 81% yield. Removal of PMB ether of the compound **14** with DDQ (91%) and a Swern oxidation provided methylketone **15** in 97% yield.[9]

An aldol reaction between **15** and the known aldehyde **16** (90%, *dr* > 95:05),[7] followed by a reduction with Et_2BOMe and $LiBH_4$ (99%, *dr* > 95:05),[8] and a protection with 2,2-DMP gave compound **17** in 87% yield (Scheme 3). Compound **17** was next transformed into sulfone **9** by removal of the C23 TBS group with TBAF (99%),[10] Mitsunobu reaction of the resulting primary alcohol with 1-phenyl-1*H*-tetrazole-5-thiol (PTSH), and oxidation with $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ and H_2O_2 of the resulting sulfide.[11] Overall, the C23−C35 sulfone **9** (more than

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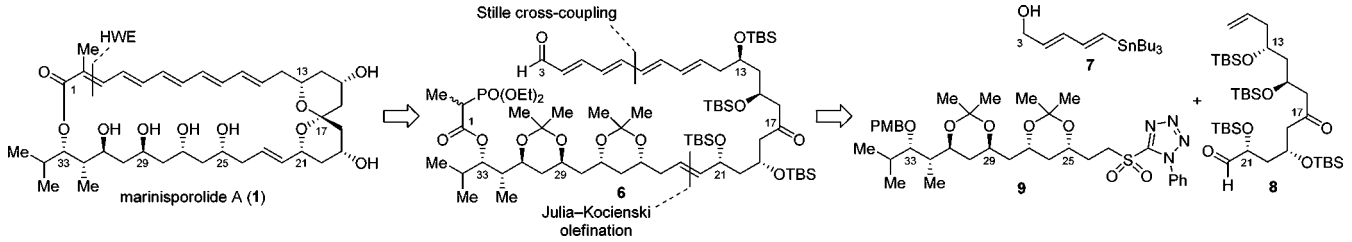
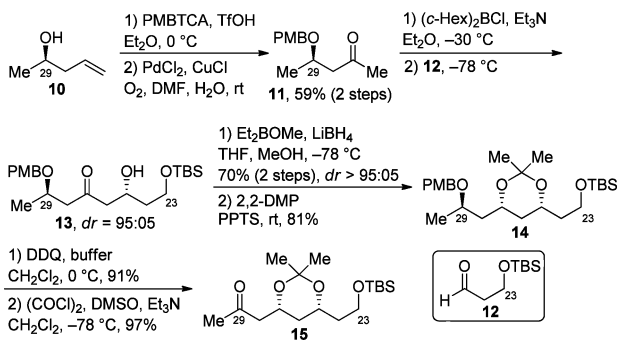
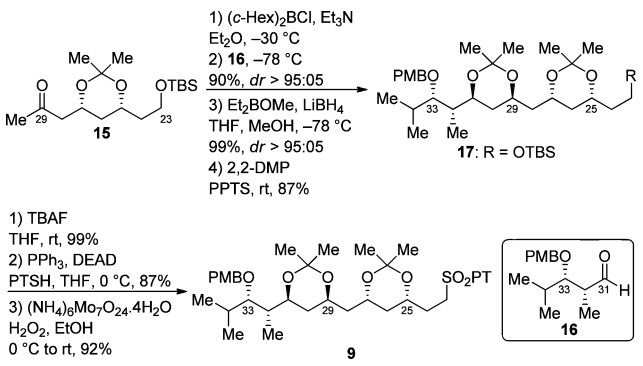
Scheme 1. Retrosynthetic Analysis



Scheme 2. Synthesis of C23–C30 Fragment 15



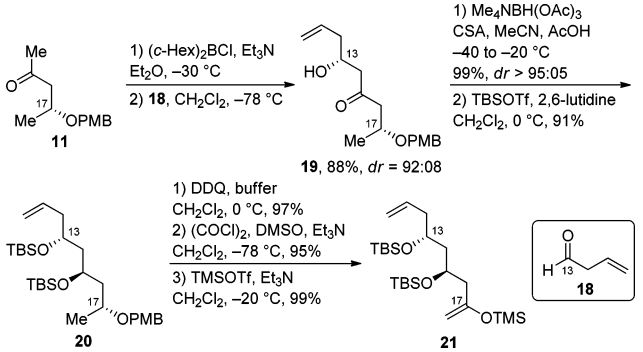
Scheme 3. Synthesis of C23–C35 Fragment 9



1.5 g prepared) was obtained in 13 steps and 18% yield from alcohol **10**.[12]

Synthesis of C10–C22 aldehyde **8** began with the aldol reaction between methylketone **11** (a common intermediate in the synthesis of C23–C35 fragment **9**) and known aldehyde **18** to deliver the 1,5-*anti* aldol adduct **19** in 88% yield with high diastereoselectivity (*dr* = 92:08) (Scheme 4).[7] This mixture was reduced with $Me_4NBH(OAc)_3$ to afford the desired 1,3-*anti*

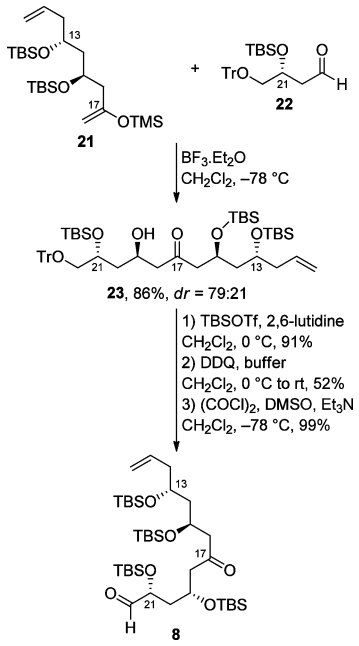
Scheme 4. Synthesis of C10–C18 Fragment 21



diol (99%, *dr* > 95:05),[13] which was protected with TBSOTf to furnish compound **20** in 91% yield.[14] Removal of PMB ether with DDQ (97%), followed by a Swern oxidation (95%), and the treatment of corresponding methylketone with TMSOTf and Et_3N gave enolsilane **21** in 99% yield.[15]

The $BF_3{\cdot}Et_2O$-catalyzed Mukaiyama aldol reaction between enolsilane **21** and known aldehyde **22** (see Supporting Information) yielded the desired 1,3-*anti* aldol adduct **23** in 86% yield with a good level of diastereoselectivity (*dr* = 79:21) (Scheme 5).[16] Protection of compound **23** with TBSOTf

Scheme 5. Synthesis of C10–C22 Fragment 8



(91%),[14] followed by the removal of a trityl group with DDQ, gave the corresponding primary alcohol as only one diastereoisomer in 52% yield after silica flash column chromatography.[17] Finally, a Swern oxidation provided aldehyde **8** in 99% yield.[9] Additionally, the C10–C22 aldehyde **8** (more than 1.5 g prepared) was obtained in 10 steps and 29% yield from methylketone **11**.[12]

Having assembled sulfone **9** and aldehyde **8**, these fragments were coupled by using the Julia–Kocieński olefination to provide compound **24** in 74% yield with high diastereoselectivity (*dr* > 95:05) (Scheme 6).[18] Removal of C33 PMB ether with DDQ (91%), followed by an olefin cross-metathesis using the second-generation Hoveyda–Grubbs catalyst, furnished aldehyde **25** in excellent yield and diastereoselectivity (89%, *dr* > 95:05).[19] Compound **25** that corresponds to the C9–C35 fragment of marinisporolides was prepared in more than 1.5 g. Finally, Takai–Utimoto olefination of aldehyde **25**

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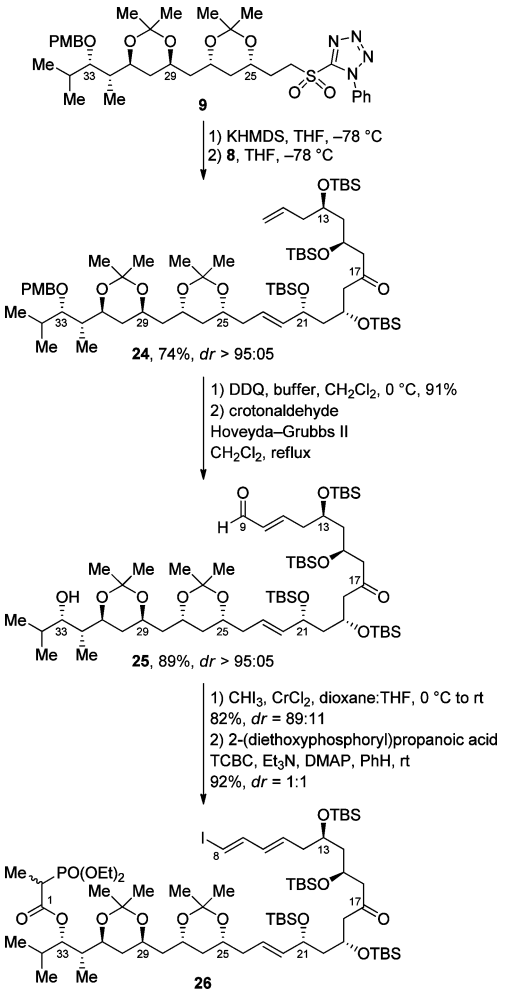
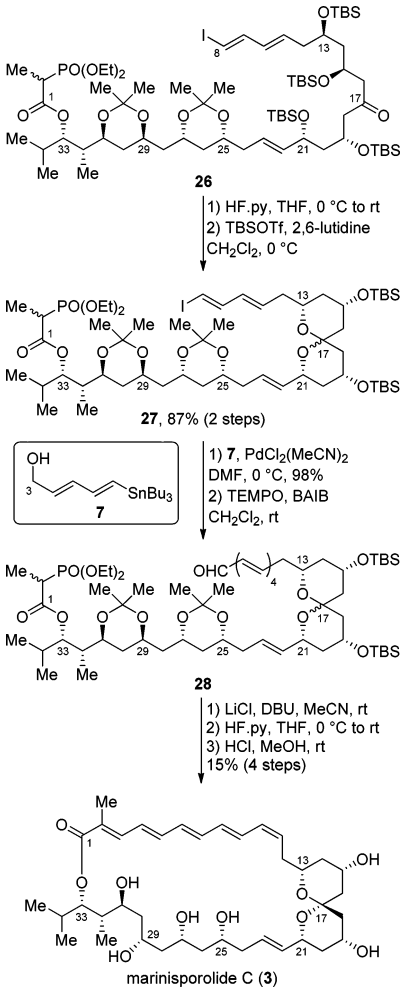
Scheme 6. Synthesis of C8−C35 Fragment 26



Scheme 7. Completion of the Total Synthesis of Marinisporolide C (3)



(82%, *dr* = 89:11),[20] followed by a Yamaguchi esterification, gave compound **26** in 92% yield and a 1:1 mixture of stereoisomers.[21]

Our initial strategy involved performing macrocyclization prior to spiroketalization. However, the compounds with the C17 free ketone were quite unstable and did not provide consistent data for the completion of the total synthesis. Thus, we decided to carry out the spiroketalization prior to the macrocyclization step. At this point, a series of C17 epimers were obtained; however, as the last step of synthesis would involve the removal of acetonides groups in an acidic medium, the initial mixture of spiroketals could be reisomerized or equilibrated in favor of the desired compound.

Therefore, the removal of the TBS ethers of compound **26** with HF·py formed a mixture of spiroketals,[22] which was protected with TBSOTf to provide compound **27** in 87% yield over two steps (Scheme 7).[14] The Stille cross-coupling between vinyl iodide **27** and known stannane **7** (98%),[23] followed by an oxidation with TEMPO and BAIB, provided aldehyde **28**.[24] Compound **28** was submitted to a Horner−Wadsworth−Emmons macrocyclization under Masamune−Roush conditions to furnish the desired macrolactone.[25] To our complete surprise, after full deprotection, first with HF·py and then with HCl, (−)-marinisporolide C (**3**) was obtained in 15% yield (over four steps).

Synthetic and natural marinisporolide C were found to be identical by a variety of analytical methods (^{1}H and ^{13}C NMR, HRMS, UV/vis, and circular dichroism), and this total synthesis confirms the relative and absolute stereochemical assignment by Fenical and co-workers.[1]

In conclusion, the first total synthesis of oxopolyene macrolide (−)-marinisporolide C (**3**) was accomplished in 25 steps (longest linear sequence) and 1% overall yield, which corresponds to an average yield of 83% per step. The pivotal five aldol reactions, responsible for the construction of five C−C bonds and six stereogenic centers, provide a straightforward approach to the convergent synthesis of the marinisporolide C skeleton. Furthermore, a very efficient Julia−Kocieński reaction was used to install the C22−C23 double bond and an intramolecular Horner−Wadsworth−Emmons reaction was used to build the very hindered macrolactone.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03352.

Experimental details and spectra data for all new compounds (^{1}H and ^{13}C NMR, IR, and HRMS) (PDF)

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Notes

The authors declare no competing financial interest.

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DEDICATION

We dedicate this paper to Professor Mauricio Gomes Constantino (FFCLRP/USP) for his contributions to the field of organic synthesis in Brazil.

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