Synthesis of the C10–C22 Fragment of Marinisporolide A

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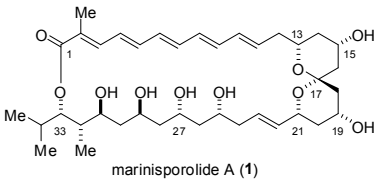
INTRODUCTION

Marinisporolide A (**1**) is an oxopolyene macrolide isolated in 2009 from the saline culture of the marine actinomycete *Marinispora*, strain CNQ-140 (Figure 1). The structure of marinisporolide A (**1**) consists of a total of 11 stereogenic centers within a 34-membered macrolide, containing a bicyclic spiro-*bis*-tetrahydropyran ketal and a conjugated pentaene.[1]



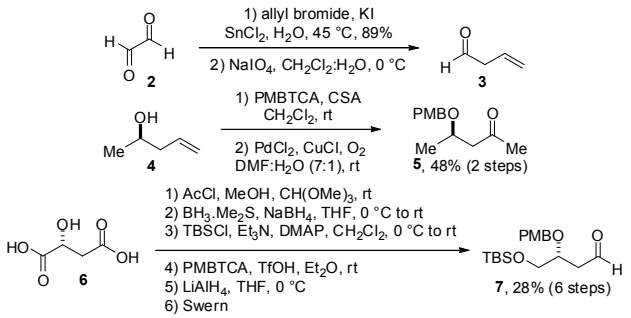
marinisporolide A (**1**)

Figure 1: Marinisporolide A.

This work aimed to the synthesis of C10–C22 fragment of marinisporolide A.

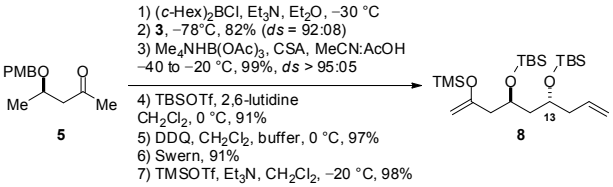
RESULTS AND DISCUSSION

Treatment of glyoxal (**2**) with allyl bromide and $SnCl_2$ (89%) followed by oxidative cleavage gave aldehyde **3** (Scheme 1). The reaction between alcohol **4** and PMB 2,2,2-trichloroacetimidate (PMBTCA) followed by Wacker oxidation provided the formation of methylketone **5** in 48% yield (2 steps). The esterification of (*R*)-malic acid (**6**) with MeOH, AcCl, and $CH(OMe)_3$ followed by regioselective reduction with $BH_3.Me_2S$ and $NaBH_4$, selective monoprotection of the diol with TBSCl, Et_3N, and DMAP, protection of the secondary alcohol with PMBTCA and TfOH, reduction of the ester with $LiAlH_4$, and Swern oxidation provided the formation of aldehyde **7**.



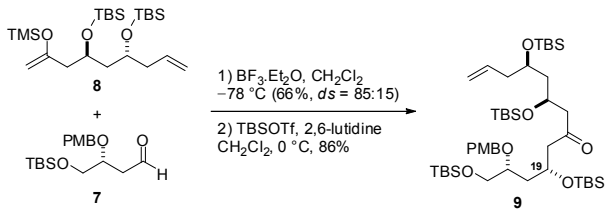
Scheme 1: Preparation of aldehyde **3**, methylketone **5**, and aldehyde **7**.

The aldol reaction[2] between the boron enolate of methylketone **5** with aldehyde **3** (82%, *dr* = 92:08), followed by 1,3-*anti* reduction (99%, *dr* > 95:05), treatment with TBSOTf and 2,6-lutidine (91%), DDQ (97%), Swern oxidation (91%), and treatment with TMSOTf and Et_3N provided enolsilane **8** in 98% yield (Scheme 2).



Scheme 2: Preparation of enolsilane **8**.

The Mukaiyama aldol reaction[2] between enolsilane **8** and aldehyde **7** mediated by $BF_3.Et_2O$ provided the corresponding 1,3-*anti* aldol adduct (66%, *ds* = 85:15). Finally, treatment of the aldol adduct with TBSOTf and 2,6-lutidine provided compound **9**, that corresponds to the C10–C22 fragment of marinisporolide A, in 86% yield (Scheme 3).



Scheme 3: Preparation of the C10–C22 fragment.

CONCLUSION

In summary, we have achieved a stereoselective synthesis of the C10–C22 fragment of marinisporolide A in 10 steps with an overall yield of 17%. Notable features of the present route are a 1,5-*anti* aldol reaction to install the stereogenic center at C13 and a Mukaiyama aldol reaction to install the stereocenter at C19.

ACKNOWLEDGEMENTS

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REFERENCES

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