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Studies on the total synthesis of sanglifehrin A: stereoselective synthesis of the C(29)–C(39) fragment

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Abstract—A highly stereoselective synthesis of the C(29)–C(39) fragment of the potent immunosuppressant sanglifehrin A has been accomplished by a sequence involving 16 steps (18% overall yield) from *N*-propionyloxazolidinone **9**. Key steps are a diastereoselective hydroboration, and a diastereoselective epoxidation of an allylic alcohol followed by a 1,5-anti boron-mediated aldol reaction of methyl ketone **4** with chiral aldehyde **5**.

1. Introduction

The potent immunosuppressant sanglifehrin A (SAF) was isolated from the culture broths of *Streptomyces flaveolus* in 1997 by scientists at Novartis (Fig. 1).[1] Sanglifehrin A (**1**) shows a remarkably high affinity for cyclophilin A with an $IC_{50} = 2$–4 nM.[2,3] SAF has a complex molecular structure, consisting of a 22-membered macrocyclic lactone, which incorporates piperazic, aliphatic, and aromatic amino acid fragments. One of the remarkable features of this molecule is the presence of a highly substituted spirobicyclic oxaazaspiro[5,5]-undecanone system (C(33)–N(42)). This spirobicycle contains seven stereogenic centers, six of which are contiguous (C(33)–C(38)). The significant biological properties of sanglifehrin A have prompted numerous studies directed toward its synthesis.[4] Nicolaou and co-workers described the first total synthesis of sanglifehrin A, which was followed by the synthesis of Paquette and co-workers.[4] In addition, many research groups have reported studies directed toward the synthesis of fragments of sanglifehrin A.[5]

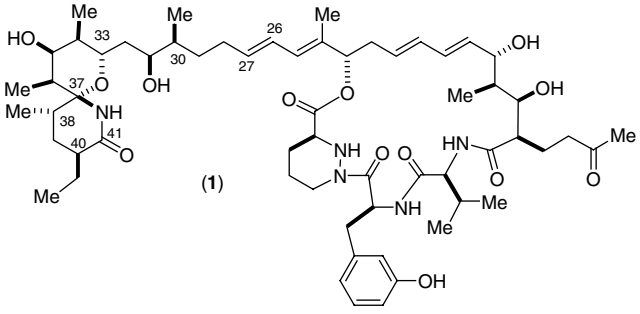

Figure 1. Sanglifehrin A (**1**).

To provide material for further biological studies as well as access to novel analogues, we initiated a study toward the synthesis of the spirobicyclic oxaazaspiro[5,5]-undecanone system of sanglifehrin A. We wish to describe here our successful efforts toward the preparation of the C(29)–C(39) fragment, via a diastereoselective boron-mediated 1,5-anti aldol reaction of methyl ketone **4** with chiral aldehyde **5** as the key step.

2. Results and discussion

Our disconnection strategy summarized in Scheme 1, involved cleavage of the C(39)–C(40), O–C(37), and N–C(37) bonds in **2** to give the β-hydroxy ketone **3**. Further synthetic analysis involved the cleavage of the C(31)–C(32) bond in **3** to give methyl ketone **4** (C(32)–C(39) fragment) and aldehyde **5** (C(29)–C(31) fragment). Methyl ketone **4** is viewed as arising from allylic alcohol **6**, available from lactone **7**. Key steps in this approach are a diastereoselective hydroboration of aldol adduct **8** to give lactone **7**, selective epoxidation of allylic

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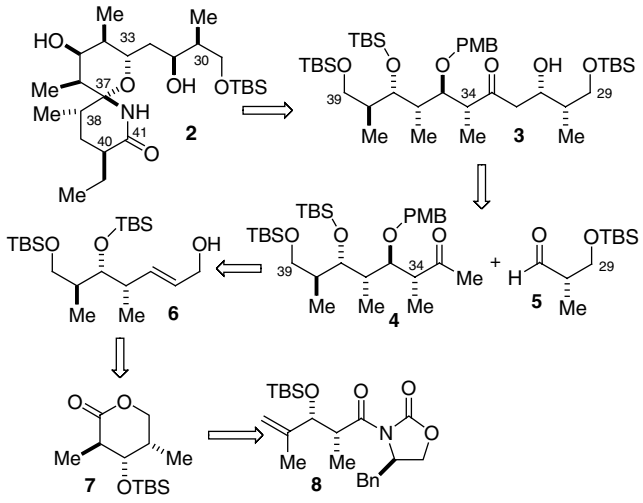
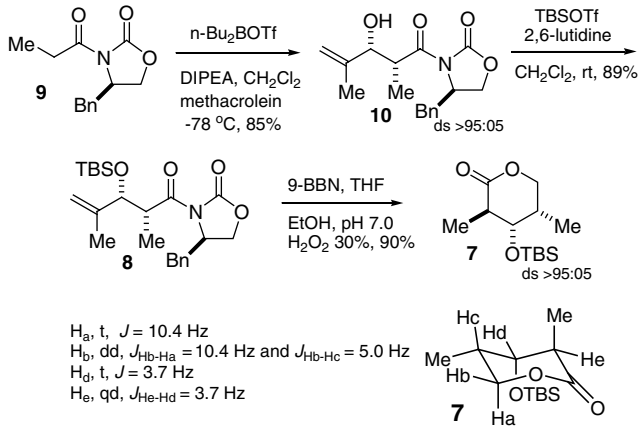


Scheme 1. Retrosynthetic analysis.

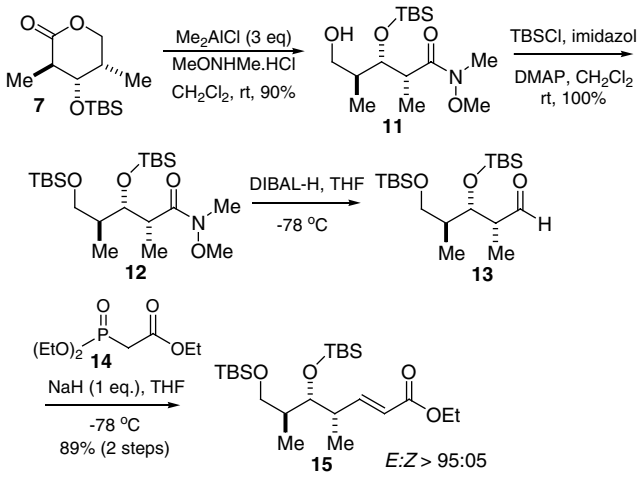
alcohol **6**, and a 1,5-anti boron-mediated aldol reaction between **4** and **5**.

Our approach to the C(29)–C(39) fragment of sanglifehrin A began with the asymmetric aldol addition of the boron enolate derived from *N*-propionyloxazolidinone **9** with methacrolein to give the corresponding aldol adduct **10** in 85% yield (ds >95:5) (Scheme 2).[6] Silylation of aldol **10** with TBSOTf and 2,6-lutidine gave **8** in 89% yield. We were very pleased to find that hydroboration of aldol **8** with 9-BBN in THF led directly to lactone **7** in 90% isolated yield and >95:05 diastereoselectivity for the two-step sequence (hydroboration and lactonization).[7] The corresponding chiral auxiliary was easily recovered. The relative stereochemistry for lactone **7** was determined by coupling constant analysis in its ^{1}H NMR spectra.[7] The coupling constants for H_a/H_c (10.4 Hz), H_c/H_d (3.7 Hz), and H_d/H_e (3.7 Hz) confirmed the stereochemistry of lactone **7**. In these stereochemical assignments, both the C(2)-methyl and the C(3)-OTBS stereocenter configurations served as important reference points.

The next step involved opening of lactone **7** with *N*,*O*-dimethylhydroxylamine in the presence of Me_2AlCl



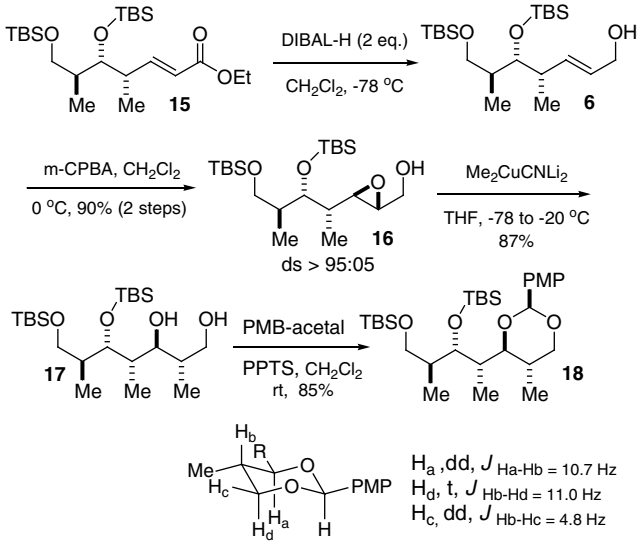
Scheme 2. Synthesis of lactone **7**.



Scheme 3. Lactone opening and HWE reaction.

leading to Weinreb amide **11** in 90% yield (Scheme 3).[8] Protection of the primary OH-function in **11** as its TBS ether gave Weinreb amide **12**, which, after reduction with DIBAL-H in THF at low temperature provided aldehyde **13**. The unpurified aldehyde was directly subjected to a Horner–Waddsworth–Emmons homologation with ketophosphonate **14** to give the (*E*)-α,β-unsaturated ester **15** in 89% yield over two steps (*E*:*Z* >95:5 diastereoselectivity).[9]

Ester **15** was smoothly converted to allylic alcohol **6** on treatment with excess DIBAL-H (Scheme 4). It is noteworthy that epoxidation of allylic alcohol **6** with *m*-CPBA gave the *anti*-epoxy alcohol **16** in 90% overall yield and >95:05 diastereoselectivity.[10,11] Treatment of epoxy alcohol **16** with $Me_2CuCNLi_2$ gave diol **17** in 87% yield.[12] At this point, the relative stereochemistry for 1,3-diol **17** was determined after conversion to the PMP-acetal **18**.[13] Formation of *p*-methoxybenzylidene acetal **18** was accomplished by treatment of the diol **17** with *p*-methoxybenzaldehyde dimethyl acetal and a cat-



Scheme 4. Diastereoselective epoxidation.

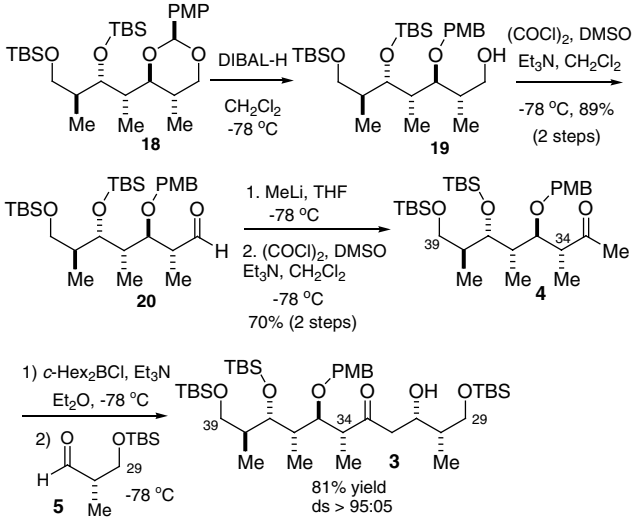
alytic amount of PPTS (85% yield).[13] Coupling constants between H_a–H_b (10.7 Hz), H_b–H_d (11.0 Hz), and H_b–H_c (4.8 Hz) confirmed the relative stereochemistry for **18**.

Treatment of PMP-acetal **18** with DIBAL-H in CH_2Cl_2 at −78 °C followed by oxidation of the resulting primary alcohol **19** under standard Swern conditions gave aldehyde **20** (89%, two steps) (Scheme 5).[14] Addition of MeLi in THF followed by Swern oxidation led to methyl ketone **4** in 70% for the two-step sequence.[14,15]

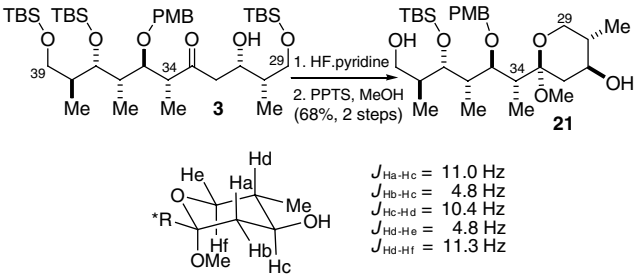
At this point, aldehyde **5**, corresponding to the C(29)–C(31) fragment was prepared in three steps and 77% overall yield from (*R*)-methyl-3-hydroxy-propanoate following protection with TBSCl and imidazole, reduction of the ester to the primary alcohol with excess DIBAL-H followed by Swern oxidation.[16]

With the requisite C(32)–C(39) and C(29)–C(31) fragments in hand, their coupling was undertaken (Scheme 5).[17] This was done by using a 1,5-anti selective boron-mediated aldol reaction providing β-hydroxyketone **3**, corresponding to the C(29)–C(39) fragment of sanglifehrin A in 81% yield and >95:05 diastereoselectivity.[17–20]

This aldol adduct appeared ideally suited for stereochemical analysis by using the very simple method for assigning the relative stereochemistry of β-hydroxy ketones reported in 2002 by Roush and co-workers.[20] However, we have reported a refinement of the Roush's model, in which we show that ^{1}H HMR ABX pattern analysis is not applicable to β-hydroxy ketones (e.g., aldols) deriving from aldehydes lacking β-branches.[21] The relative stereochemistry for aldol adduct **3** was then determined after conversion to the corresponding acetal **21** (68%, two steps) by treatment of **3** with HF·pyr followed by PPTS in MeOH (Scheme 6).[20] Analysis of the ^{1}H NMR coupling constants, specifically $J_{H_a–H_c} = 11.0$ Hz, $J_{H_c–H_d} = 10.4$ Hz, and $J_{H_d–H_f} = 11.3$ Hz,



Scheme 5. Boron-mediated aldol reaction of methyl ketone **4** with chiral aldehyde **5**.



Scheme 6. Determination of the relative stereochemistry for aldol adduct **3**.

proved that H_a, H_c, H_d, and H_f are all axial in **21**. This indicates that acetal **21** derives from a 1,5-anti (Felkin) aldol product.

3. Conclusions

This approach to the C(29)–C(39) fragment of sanglifehrin A requires 16 steps and produced the desired β-hydroxy ketone 3 in 18% overall yield. The key step in this approach involved a 1,5-anti boron-mediated aldol reaction of methyl ketone **4** with chiral aldehyde **5**. As a result, the route to the C(29)–C(39) fragment of sanglifehrin A presented here is, in principle, readily applicable for the preparation of the spirolactam fragment of sanglifehrin A as well as to additional analogues.[22] Extension of this work to the synthesis of the spirolactam fragment of sanglifehrin A and analogues is underway.

Acknowledgments

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