

Synthesis of C3–C21 Segment of Aflastatin A Using Remote Asymmetric Induction Reactions

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S Supporting Information



ABSTRACT: The C3–C21 segment of aflastatin A has been synthesized by converging three segments including the C3–C8 segment, the C9–C15 segment, and the C16–C21 segment. Each segment has been synthesized from a vinylketene silyl *N*,*O*-acetal possessing a chiral auxiliary by a wide-range stereocontrol strategy. The C3–C8 segment was constructed in seven steps including the stereoselective vinylogous Mukaiyama alkylation, while the C9–C15 segment and the C16–C21 segment were synthesized using the vinylogous Mukaiyama aldol reaction in seven and eight steps, respectively.

flastatin A (1, Figure 1) is a giant acyclic polyketide isolated as an inhibitor of aflatoxin production by Sakuda



Figure 1. Structure of aflastatin A (1).

and co-workers.¹ The structure of aflastatin A (1) involves many types of polyketide motifs including polypropionate, deoxypropionate, polyacetate, and contiguous polyol structures. Therefore, the structure attracts chemists, and several groups have been challenged to achieve its synthesis.² However, only one total synthesis has been reported as a doctoral thesis.³ Aflastatin A is still an attractive and challenging target molecule because the complexity and large size of this compound require efficient methodologies and adequate strategies to achieve total synthesis.

During the course of our synthetic studies on polyketides, we have developed the remote asymmetric induction reactions with vinylketene silyl *N*,*O*-acetals⁴ and the wide range

stereocontrol strategy which is based on the initial construction of the central part of the molecule and a subsequent functionalization of the surroundings (Scheme 1).⁵ We have already achieved short-step syntheses of several polyketides by





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Scheme 2. Synthetic Plan of Aflastatin A (1)



combining the remote asymmetric induction reactions and wide-range stereocontrol strategy.⁵ With these backgrounds, we have been interested in the structure of aflastatin A possessing a variety of polyketide motives. We have already synthesized the C27–C48 moiety **5**, the contiguous polyol segment, by developing the Sn(II)-mediated aldol reaction.⁶ Herein, we present a synthesis of C3–C21 segment, the polypropionate moiety, of aflastatin A.

Our synthetic plan for aflastatin A is disclosed in Scheme 2. The tetramic acid moiety (C5'-C2 part) would be installed in the final stage due to its lability. The remaining structure was divided into two parts including C3–C21 segment 3 and C22–C48 segment 4. The C3–C21 segment would be synthesized by connection of three segments including C3–C8 segment 6, C9–C15 segment 7, and C16–C21 segment 8. These segments might be synthesized by employing the remote asymmetric induction reactions with vinylketene silyl N,O-acetals (9 and *ent-*9) and the wide range stereocontrol strategy.

Synthesis of C3–C8 segment started from vinylketene silyl N,O-acetal 9 (Scheme 3). Allylation of 9 proceeded at the γ position in a stereoselective manner to afford adduct 10.^{4f} α,β -Unsaturated imide 10 was subjected to the Birch reduction, which was quenched by 2-methylbenzimidazole,^{4f} a bulky proton source, to give the 4,6-syn (aflastatin A numbering) product 11 with excellent stereoselectivity. When ammonium chloride was employed as the protonation reagent in the Birch reduction, moderate stereoselectivity (dr = 5:1) was observed. Reduction of imide 11 with LiBH₄ and benzylation of the resulting hydroxy group afforded benzyl ether 12, which underwent ozonolysis followed by reduction to yield primary alcohol 13. Subsequent Mitsunobu reaction with 1-phenyl-1*H*-tetrazole-5-thiol and oxidation in the presence of ammonium

Scheme 3. Synthesis of C3-C8 Segment (6)



heptamolybdate⁷ gave 1-phenyl-1H-tetrazole-5-yl sulfone 6, the C3–C8 segment.

On the other hand, C9–C15 segment was synthesized from vinylketene silyl *N*,*O*-acetal *ent-*9 (Scheme 4). The vinylogous Mukaiyama aldol reaction with methacrylaldehyde proceeded-stereoselectively to give *anti* adduct **15** in good yield.⁸ Reduction of imide **15** afforded diol **16**, which underwent the stereoselective epoxidation with *m*-CPBA⁹ followed by the

Scheme 4. Synthesis of C9-C15 Segment (7)



selective protection of the primary alcohol to furnish mono-TBS ether **18**. Hydroboration of the *exo* olefin of **18** proceeded in good stereoselectivity to give diol **19**.^{10,11} The hydroxy groups of **19** were converted into silyl ethers, and the resulting epoxide **20** underwent the semipinacol rearrangement¹² to give C9–C15 segment (7), which was subjected immediately to the next reaction due to its lability.

With both the C3–C8 segment (6) and C9–C15 segment (7) in hand, connection of these segments and sequential oxidation of the resulting adduct were deduced to synthesize the C3–C15 segment (Scheme 5). The Kocienski reaction¹³ between sulfone 6 and aldehyde 7 and exposure of the adduct under the acidic conditions promoted the selective O-desilylation to furnish the diol 21.¹⁴ Sharpless asymmetric dihydroxylation afforded tetraol 22, which was treated with an excess amount of TESOTf and 2,6-lutidine to give silyl ether 23. The selective de-O-silylation of the primary triethylsilyl ether afforded the primary alcohol 24, which underwent Dess–Martin oxidation to yield C3–C15 segment (25). The resulting aldehyde 25 was immediately subjected to the next reaction to avoid undesired cyclization to afford δ -lactol.

The third segment, C16–C21 segment (8), was synthesized from 9 (Scheme 6). The vinylogous Mukaiyama aldol reaction with paraldehyde (26) proceeded to give *anti* adduct 27 predominantly.¹⁵ Reduction of the imide followed by epoxidation, the same procedure as Scheme 4, gave epoxy alcohol 29 in excellent stereoselectivity. The diol 29 was converted into bisTBS ether 30 which was submitted to the one-pot sequence including the semipinacol rearrangement, reduction, and methanolysis to afford diol 32. Acetalization of diol 32 with *p*-methoxybenzaldehyde dimethylacetal gave 1,3-dioxane 33. De-O-silylation of 33 gave the secondary alcohol 34, which was oxidized to furnish the methyl ketone, C16–C21 segment (8).

The sequence from connection between C3-C15 (25) segment and C16-C21 (8) segment to the synthesis of C3-C21 segment is disclosed in Scheme 7. Treatment of methyl





Scheme 6. Synthesis of C16-C21 Segment



ketone 8 with LiHMDS to prepare the corresponding terminal enolate and addition of a solution of aldehyde 25 promoted the aldol reaction in a stereoselective manner. The resulting adduct 35 was subjected to the Narasaka reduction¹⁶ to give *syn* diol 36. Acetalization followed by the site-selective

Scheme 7. Synthesis of C3-C21 Segment



reduction of the *p*-methoxybenzylidene acetal¹⁷ afforded the primary alcohol **37** in good yield. The resulting alcohol **37** was subjected to Dess-Martin oxidation to give C3-C21 segment (**3**).

In conclusion, a stereoselective and convergent synthesis of the C3–C21 segment of aflastatin A has been achieved. All segments were prepared in six to eight steps using the remote asymmetric reactions including the allylation reaction (C3–C8 segment) and the vinylogous Mukaiyama aldol reactions (C9– C15 and C16–C21 segments). Therefore, the C3–C21 segment of aflastatin A was synthesized in 17 steps of longest linear sequence from vinylketene silyl *N*,*O*-acetal **9**.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.8b04008.

Experimental procedures, spectral data of compounds, ¹H and ¹³C NMR spectra, and structural determination (PDF)

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