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Stereoselective Synthesis of the C27–C48 Moiety of Aflastatin A by a Carbohydrate Strategy Using a Tin(II)-Mediated Aldol Reaction

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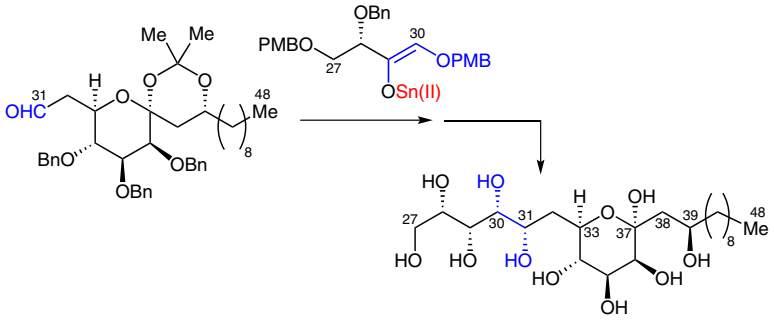

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Abstract The C27–C48 segment of aflastatin A was synthesized by using D-mannoside and L-erythrulose derivatives as chiral building blocks. The aldol reaction of undecan-2-one with mannolactone and a subsequent reduction gave the C37 and C39 stereogenic centers with high selectivity. Another aldol reaction of a tin(II) enolate of a protected erythrulose (C27–C30 segment) with a C31–C48 aldehyde segment gave the C30,C31-*syn* adduct with the desired stereochemistry. Deprotection of the assembled product proceeded smoothly to give the C27–C48 segment of aflastatin A containing a contiguous polyol moiety.

Key words stereoselectivity, aflastatin A, aldol reactions, polyols, carbohydrates

Aflastatin A (**1**; Figure 1), first isolated from *Streptomyces* sp. MRI142 by Sakuda and co-workers,[1] is an inhibitor of aflatoxin produced by *Aspergillus parasiticus*. The structure of aflastatin A features a variety of polyketide motifs including polypropionate, polyacetate, and contiguous polyol structures; consequently, it has become an attractive target molecule for organic synthesis.[2] In the course of our studies on polyketide synthesis,[3] aflastatin A became one of our target molecules, as its preparation might lead to a general and efficient strategy for the synthesis of complex polyketides. Contiguous polyol moieties of various polyketides, including aflastatin A, have been synthesized by several groups. Evans and co-workers employed aldol reactions to construct the C9–C27 and C33–C36 moieties of aflastatin A.[2a,b] McDonald and co-workers also reported a synthesis of the C9–C27 segment by using alkyne–epoxide cross coupling followed by intramolecular hydrosilation.[2c] Ramana and co-workers synthesized the C31–C48 segment[2d] and the C27–C38 segment[2e] by palladium-catalyzed dihydropyran formation. These studies indicate that the preparation of contiguous polyol structures, such as the C27–C39 moiety of aflastatin A, is a problem in organic synthesis.

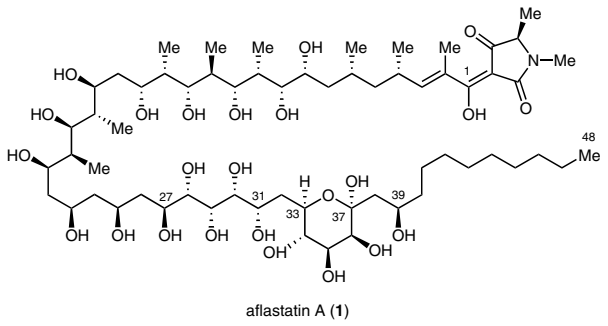
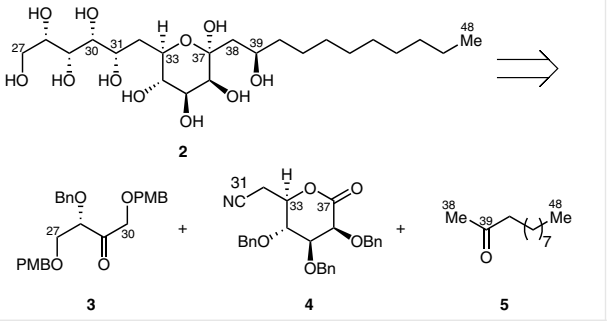


Figure 1 Structure of aflastatin A (**1**)

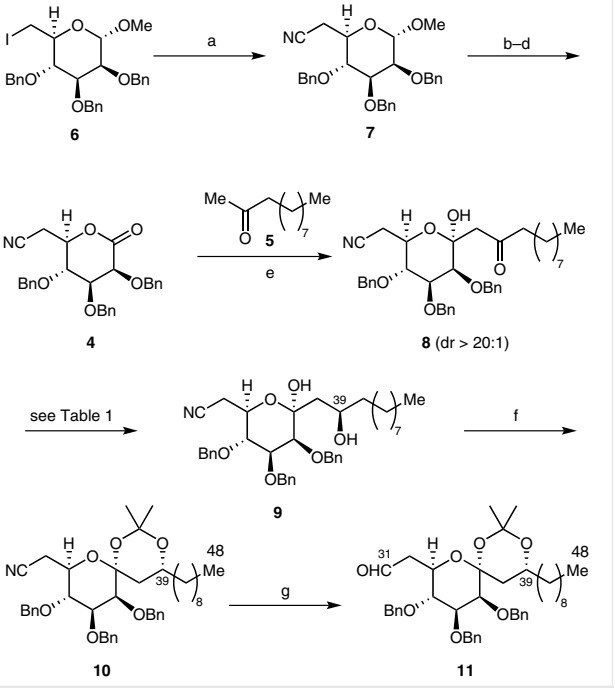
Here, we present an alternative synthesis of the C27–C48 segment of aflastatin A. To establish a straightforward route, the starting materials should reflect the polyol alignment of the target compound. We therefore decided to synthesize the polyol segment from carbohydrates. Our synthetic plan is shown in Scheme 1. On the basis of the strategy of using easily available polyols as starting materials, we divided the C27–C48 moiety **2** into three segments: the protected L-erythrulose **3** (C27–C30), the mannose derivative **4** (C31–C37), and undecan-2-one (**5**; C38–C48). We intended to connect these segments by aldol reactions, which needed to be stereoselective to establish an efficient route. This strategy should form a straightforward method for synthesizing contiguous polyol compounds.

The synthesis of the C31–C48 segment **11** is shown in Scheme 2. The mannose derivative **6**[4] was converted into the cyanide **7**,[5] which was transformed into the lactone **4** by sequential acetolysis, methanolysis, and oxidation reac-



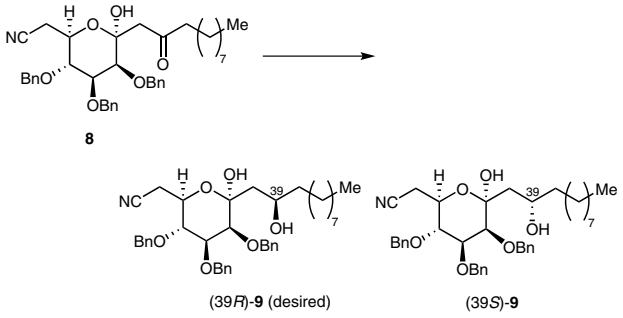
Scheme 1 Synthetic plan toward the C27–C48 segment **2**

tions. The nucleophilic addition of the lithium enolate of undecan-2-one (**5**) to lactone **4** proceeded stereoselectively to give adduct **8** as a single isomer. The ketone group in **8** was then reduced stereoselectively. Treatment of adduct **8** with sodium borohydride in ethanol gave (39*S*)-**9** with high stereoselectivity, whereas reduction of adduct **8** by using tetramethylammonium triacetoxyborohydride[6] in the presence of acetic acid gave (39*R*)-**9** in excellent yield and high stereoselectivity (Table 1).



Scheme 2 Synthesis of the C31–C48 segment **11**. *Reagents and conditions*: (a) NaCN, DMSO, 60 °C, 17 h, 98%; (b) Ac_2O, TFA, r.t., 2 d; (c) K_2CO_3, MeOH, r.t., 30 min, 78% (2 steps); (d) IBX, DMSO, toluene, 70 °C, 1 h, 82%; (e) LiHMDS, THF, –70 °C, 1.5 h, 72%; (f) $Me_2C(OMe)_2$, $TsOH·H_2O$, 0 °C to r.t., 15 min, 97%; (g) DIBAL-H, CH_2Cl_2, –70 °C, 15 min, 97%.

Table 1 Reduction of the C-39 Keto Group of **8**



Entry	Reductant	Solvent	Temp	Time (h)	Yield (%)	dr[a] (*R*/*S*)
1	$NaBH_4$	EtOH	r.t.	1	95	1:18
2	$Me_4NBH(OAc)_3$–AcOH	MeCN	0 °C to r.t.	2	97	13:1

[a] Determined by ^1H NMR.

The stereochemistry of diol **9** was determined through conversion into the acetonide **10** (Figure 2). With (39*R*)-**10**, an NOE was observed between H-39 and one of methyl groups of the acetonide, which also showed an NOE with H-33. On the other hand, with (39*S*)-**10**, an NOE was observed between H-39 and H-36, as well as between H39 and the methyl group of the acetonide opposite to the one correlating with H33. Because β-hydroxy lactol groups occur widely in natural products,[7] the procedure involving an aldol reaction between a lactone and a ketone followed by stereoselective reduction should be a powerful tool for the synthesis of such natural products. Reduction of the cyanide group of **10** with diisobutylaluminum hydride gave aldehyde **11**, the required C31–C48 segment.

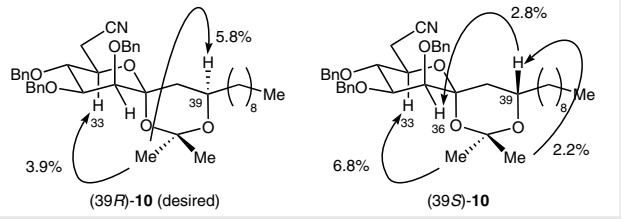
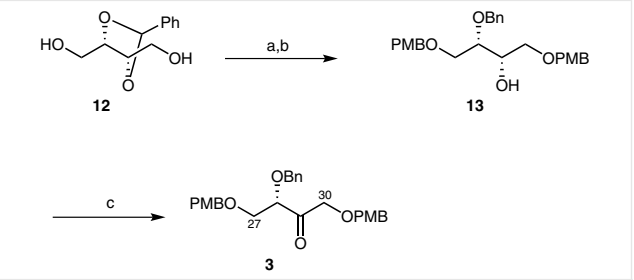


Figure 2 Structural determination of (39*R*)-**10** and (39*S*)-**10**

Next, we prepared the C27–C30 segment **3** from the known tartrate derivative **12** (Scheme 3).[8] Protection of the primary alcohol groups of **12** as *p*-methoxybenzyl ethers and subsequent reduction with diisobutylaluminum hydride gave the secondary alcohol **13**. Oxidation of alcohol **13** with 1-hydroxy-1λ⁵,2-benziodoxol-1,3-dione (IBX) gave the ketone **3**. The three-step sequence gave the C27–C30 segment **3** in high yield.

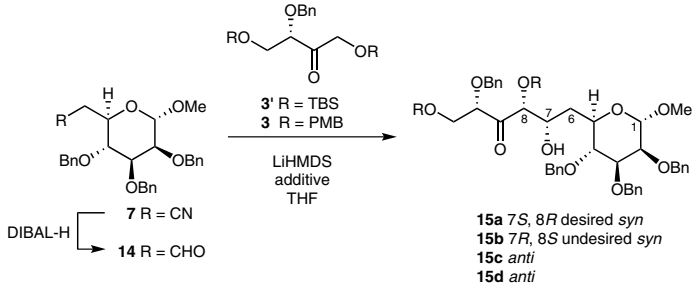


Scheme 3 Synthesis of the C27–C30 segment **3**. *Reagents and conditions:* (a) NaH, PMBCl, DMF, 0 °C, 1 h, 91%; (b) DIBAL-H, toluene, 0 °C to r.t., 30 min, 97%; (c) IBX, DMSO, toluene, 40 °C, 1 h, 97%.

Attachment of the polyol aldehyde to the polyol ketone by an aldol reaction was examined by using the aldehyde **14**, derived from cyanide **7**, and the protected ketones **3** (Table 2). We also prepared the *tert*-butyl(dimethyl)silyl ether **3′**[9] for comparison with the *p*-methoxybenzyl ether **3**. Because the aldol reaction of the dicyclohexylborane enolate of **3′** with the polyol aldehyde **14**[10] under Marco's conditions[11] did not work well, we examined aldol reactions of other enolates (Table 2). The aldol reaction between these polyoxygenated compounds was markedly influenced by the nature of the countercation, whereas the protecting group of the primary alcohols had only a slight effect. In the lithium-mediated aldol reaction (entries 1 and 5), the undesired *syn*-adduct was obtained as the major product.[12] Addition of zinc chloride gave the adducts in high yields, but the selectivity was not good (entries 2 and 6). In the case of triisopropoxytitanium chloride,[13] an *anti*-adduct (stereochemistry not determined)[14] was obtained with good selectivity (entries 3 and 7). The desired stereoisomer was, however, obtained by addition of tin(II) chloride (entries 4 and 8).[15] In the tin(II)-mediated aldol reaction (entries 4 and 8), the *p*-methoxybenzyl-protected ketone **3** gave better results than did the *tert*-butyl(dimethyl)silyl-protected **3′**. To avoid the equilibrium between the lithium enolate and the tin(II) enolate, we added 12-crown-4 to trap the lithium ion (entry 9). The transformation gave the adducts in excellent yield, which included the desired isomers in high selectivity. These results indicate that the aldol reaction with a tin(II) enolate is useful for the synthesis of the contiguous polyoxygenated compounds. We therefore used ketone **3** and the conditions shown in entry 9 of Table 2 to synthesize the C27–C48 moiety of aflastatin A.

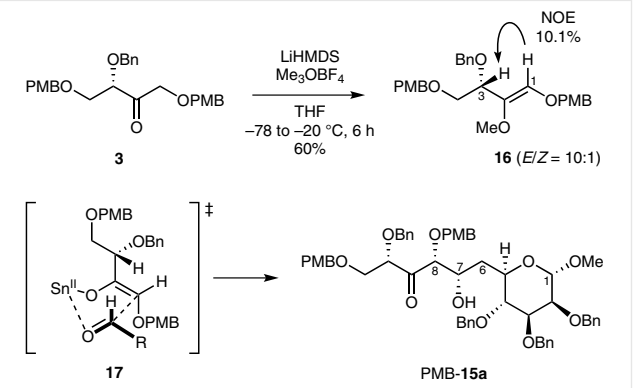
To investigate the origin of the stereoselectivity, we trapped the enolate derived from **3** (Scheme 4). Treatment of the lithium enolate with Meerwein reagent gave methyl ether **16**, which showed an NOE between the vinylic proton at the C1 position and C3 proton, indicating it to be the (*Z*)-vinyl ether. These results suggest that the reaction under the conditions of Table 2, entry 9 proceeds via the transition state **17**, in which tin(II) is not chelated with the nearby ether oxygen atoms.

Table 2 The Aldol Reaction of Aldehyde **14** with the Enolates of Ketone **3**



Entry	R	Additive (1.6 equiv)	Temp (°C)	Time (h)	Yield (%)	dr[a] **15a**/**15b**/**15c**/**15d**
1	TBS	–	–30	3	62	11:73:16:0
2	TBS	$ZnCl_2$	–30 to –10	5	85	38:49:14:0
3	TBS	$(i\text{-PrO})_3TiCl$	–30	5	70	13:26:61:0
4	TBS	$SnCl_2$	–30 to –10	12	59	61:27:13:0
5	PMB	–	–30	2	70	21:43:28:7
6	PMB	$ZnCl_2$	–30	2	95	33:42:23:2
7	PMB	$(i\text{-PrO})_3TiCl$	–30	1	90	4:8:72:16
8	PMB	$SnCl_2$	–30 to –10	24	78[b]	75:17:6:2
9	PMB	$SnCl_2$, 12-crown-4	–30 to –10	20	96	82:14:4:0

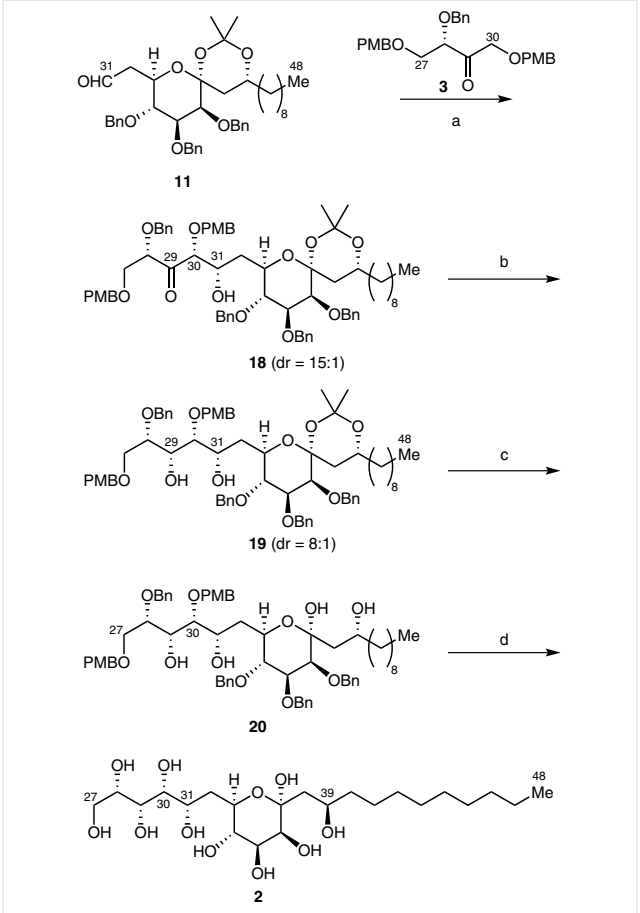
[a] Ratios of diastereomers were determined by 400 MHz ^1H NMR.
[b] 12% of the starting material **14** was recovered.



Scheme 4 Trapping of the lithium enolate and the proposed transition state

The C31–C48 segment **11** was coupled with the C27–C30 segment **3** to construct the C27–C48 segment (Scheme 5). Aldehyde **11** was treated with the tin(II)-enolate of ketone **3** in the presence of 12-crown-4 to give the desired adduct **18** in high yield and with high selectivity. Reduction of the keto group of adduct **18** with sodium triacetoxyborohydride[16] gave the desired 29*R*-isomer **19**, in which all stereogenic centers were identical with those of the natural product.[1e,17] This two-step sequence accomplished the connection of the segments and alignment of stereogenic centers to construct the C27–C48 moiety of aflastatin A. With the partially protected C27–C48 moiety **19** in hand, we completed the synthesis of the C27–C48 moiety **2** by two-step deprotection. The acetonide group bridging the C37 and C39 oxygen atoms was removed by hydrolysis with 1 M aqueous hydrochloric acid at 50 °C to give tetraol **20** in good yield. Hydrogenolysis of the six benzyl ethers then afforded the C27–C48 moiety **2** in high yield.[18]

In conclusion, we have synthesized the C27–C48 moiety of aflastatin A by a highly convergent route using aldol reactions to connect the L-erythrulose derivative **3**, the D-mannose derivative **4**, and undecan-2-one (**5**). The aldol reaction between mannolactone **4** and undecan-2-one (**5**) proceeded smoothly to give adduct **8** in a stereoselective manner. Subsequent reduction gave the β-hydroxy lactols (39*R*)-**9** and (39*S*)-**9** stereoselectively. In the next aldol reaction between the contiguous polyol ketone **3** and the contiguous polyol aldehyde **11**, the tin(II) enolate method was found to be useful in obtaining the desired stereoisomer **18**. Deprotection proceeded smoothly to afford the C27–C48 moiety of aflastatin A (**2**). This synthesis suggests an efficient and straightforward methodology for the preparation of compounds with contiguous polyoxygenated segments. Studies toward a synthesis of aflastatin A are in progress in our laboratory.



Scheme 5 Synthesis of the C27–C48 moiety of aflastatin A **2**. *Reagents and conditions*: (a) LiHMDS, THF, –30 °C, 1 h, then $SnCl_2$, 12-crown-4, –78 to –5 °C, 23 h, 84%; (b) $NaBH(OAc)_3$, $CHCl_3$, 0 °C to r.t., 1.5 h, 84%; (c) 1 M HCl, THF, 50 °C, 1 h, 83%, then H_2, $Pd(OH)_2$/C, THF, r.t., 13 h, 90%.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560572.

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(12) For the determination of the absolute stereochemistry of **15a** and **15b**, see the Supporting Information.

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(17) For the determination of the absolute configuration of **19**, see the Supporting Information.

(18) **C27–C48 Fragment 2**

20% Pd(OH)$_2$/C (1.0 mg) was added to a solution of compound **20** (4.2 mg, 3.9 μmol) in THF (1.0 mL), and the mixture was stirred for 13 h under H_2. The mixture was filtered through a pad of Celite and the filtrate was concentrated in vacuo. The residue was purified by column chromatography [silica gel, $CHCl_3$–MeOH (1:1)] to give a white solid; yield: 1.7 mg (3.5 μmol, 90%); mp 126–127 °C; R_f = 0.30 ($CHCl_3$–MeOH, 1:1); $[\alpha]_D^{25}$ +13.8 (*c* 1.34, MeOH). IR (thin film, KBr): 3535, 3073, 2959, 2924, 1260, 1124, 796, 668 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.16–6.12 (br s, 1 H), 5.26 (d, *J* = 3.9 Hz, 1 H), 4.59 (d, *J* = 5.2 Hz, 1 H), 4.54 (d, *J* = 5.2 Hz, 1 H), 4.49 (dd, *J* = 5.6, 5.6 Hz, 1 H), 4.48 (d, *J* = 4.1 Hz, 1 H), 4.37 (d, *J* = 5.2 Hz, 1 H), 4.17 (d, *J* = 5.0 Hz, 1 H), 4.16 (d, *J* = 5.0 Hz, 1 H), 4.11 (d, *J* = 6.1 Hz, 1 H), 3.94–3.81 (m, 2 H), 3.63 (ddd, *J* = 9.8, 9.8, 3.8 Hz, 1 H), 3.61–3.53 (m, 3 H), 3.48–3.34 (m, 4 H), 3.19 (ddd, *J* = 9.2, 9.2, 5.6 Hz, 1 H), 2.09–2.01 (m, 1 H), 1.86–1.79 (m, 1 H), 1.53–1.38 (m, 2 H), 1.37–1.15 (m, 16 H), 0.85 (t, *J* = 6.9 Hz, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 98.4, 73.1, 71.9, 71.7, 71.3, 70.7, 70.2, 69.3, 67.4, 62.8, 41.6, 38.2, 35.8, 31.3, 29.2, 29.1, 29.0, 28.7, 24.8, 22.1, 14.0. HRMS (ESI): *m/z* [M + Na]$^+$calcd for $C_{22}H_{44}NaO_{11}$: 507.2776; found: 507.2778.