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Synthetic Studies on Aculeximycin: Synthesis of C24−C40 Segment by Kobayashi Aldolization and Epoxide Rearrangements

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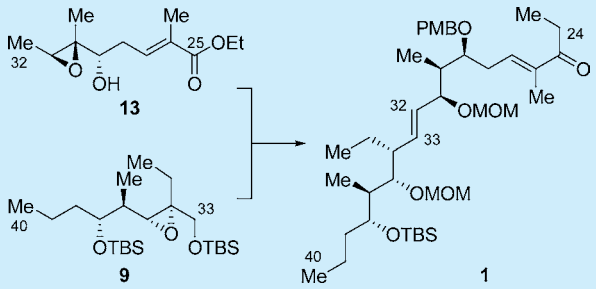
Supporting Information

ABSTRACT: Stereoselective synthesis of the C24−C40 segment of aculeximycin has been achieved by using the Kobayashi aldol reactions and epoxy-opening rearrangement reactions. The C33−C40 segment was synthesized by the Kobayashi aldol reaction followed by epoxidation and Jung rearrangement of epoxide **9**, while the C25−C32 segment was constructed by the Kobayashi aldol reaction followed by epoxidation and the epoxy-opening rearrangement reaction of epoxide **13**. These segments were connected by the aldol reaction and the sequential dehydration, reduction, and conversion of ethyl ester to ethyl ketone to give the C24−C40 segment **1**. All stereogenic centers were constructed by substrate-controlled stereoselective reactions.



Aculeximycin was isolated as an antibiotic from the culture broth of *Streptosporangium albidum*, by the Haneishi group in 1983 (Figure 1).[1] In 1995, the Harada group disclosed the impressive structure of this compound by degradation and derivatization studies as well as spectroscopic methods.[2] Aculeximycin possesses a 30-membered ring attaching triose, *β*-mannose, and vancosamine. This compound was found to be a potent uncoupler of the oxidative phosphorylation of rat-liver mitochondria.[3] The structure of aculeximycin has attracted and inspired us to synthesize this compound. Herein, we present a concise synthesis of the C24−C40 segment of aculeximycin by combination of the remote asymmetric induction reaction and an epoxide-opening strategy.

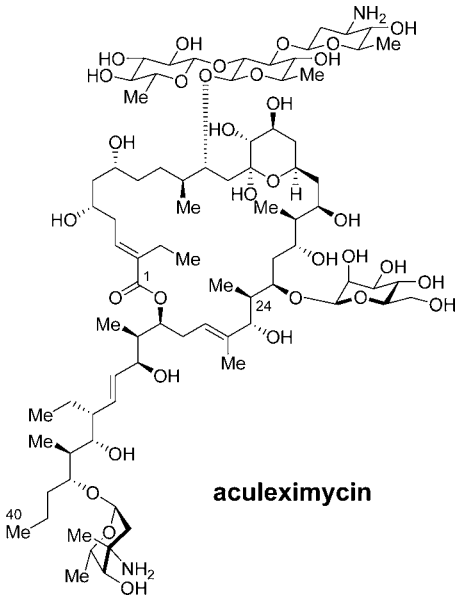
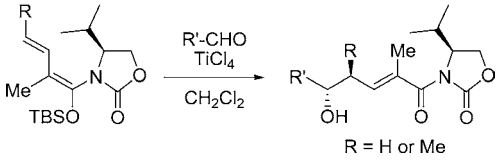


Figure 1. Structure of aculeximycin.

In the course of our studies on polyketides, we have developed the remote asymmetric induction reaction using the vinylketene silyl *N,O*-acetal having a chiral auxiliary (Kobayashi aldol reaction, Scheme 1).[4] Since the reaction performs the construction of stereogenic centers and introduction of a carbon chain simultaneously, it has been applied to natural product synthesis to accomplish syntheses in a few steps.[5,6] We decided to apply this reaction to the synthetic studies on aculeximycin to establish an efficient route.

Scheme 1. Remote Asymmetric Induction Reactions Using the Chiral Vinylketene Silyl *N,O*-Acetals



Our strategy to synthesize the C24−C40 segment **1** is disclosed in Scheme 2. The C24−C40 segment would be synthesized by an aldol condensation between C33−C40 segment **2** and C25−C32 segment **3** (Scheme 2). These oligoketides might be constructed in a few steps by combining the Kobayashi aldol reaction (Scheme 1) and two kinds of

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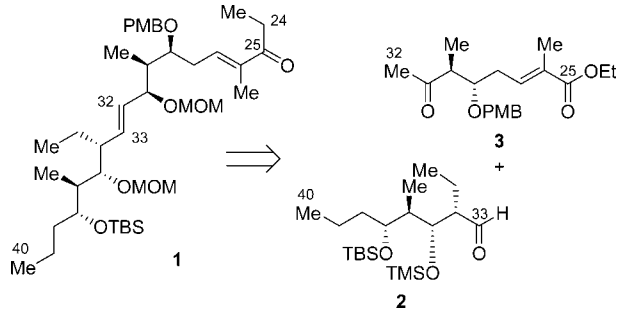
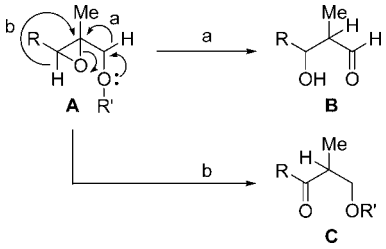
Scheme 2. Synthetic Plan of Aculeximycin C24−C40 Segment 1



epoxide-rearrangement reactions (Scheme 3). One of the rearrangement reactions is the semipinacol rearrangement

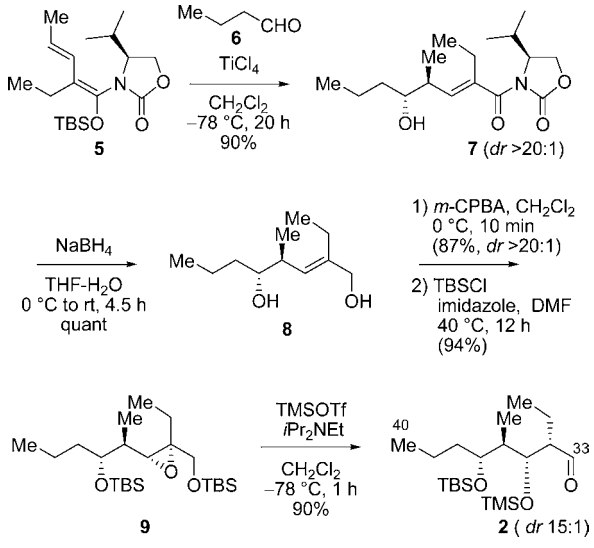
Scheme 3. Epoxide-Opening Hydride Shift Reactions To Give Aldols



(path a), and another is the epoxide-carbonyl isomerization (path b). While path a known as Jung's method[7] has been employed in natural product synthesis,[8] the rearrangement of path b has rarely been applied. Proper use of these reactions would realize construction of a variety type of polyketides.

Synthesis of the C33−C40 segment **2** started from silyl dienol ether **5** (Scheme 4). The remote asymmetric induction reaction (Kobayashi aldol reaction) of dienol ether **5** with butanal **6** proceeded efficiently to afford **7** in high yield and excellent selectivity. The chiral auxiliary was removed by hydride reduction to give allylic alcohol **8**. Epoxidation[9] of the diol **8** made smooth progress in high selectivity, and the

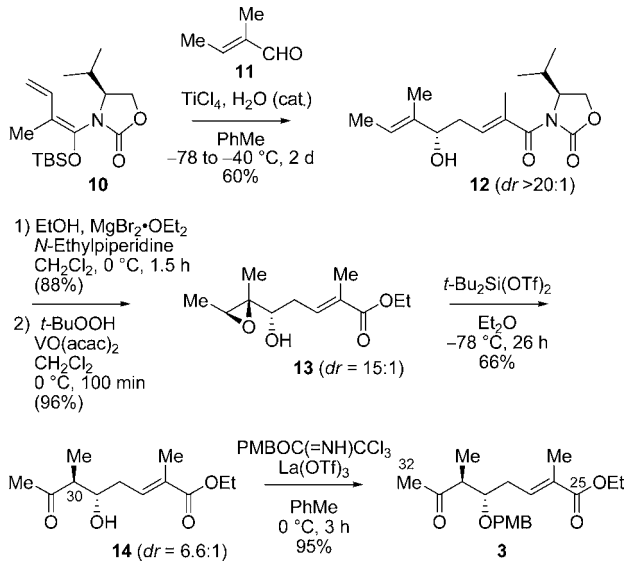
Scheme 4. Synthesis of C33−C40 Segment 2



resulting diol was protected as TBS ether **9**. Treatment of TBS-protected epoxy alcohol **9** with TMSOTf in the presence of a Hünig base promoted semipinacol rearrangement to give aldehyde **2**, the C33−C40 segment.[10]

Yet, the synthesis of C25−C32 segment **3** was performed as shown in Scheme 5. The synthesis began with a Kobayashi

Scheme 5. Synthesis of C25−C32 Segment 3



aldol reaction using *exo*-olefin **10** and tiglic aldehyde **11** in the presence of H_2O[11] to obtain allylic alcohol **12** with excellent selectivity.[12] After conversion of the imide moiety to an ester function,[13] vanadium-mediated epoxidation[14] proceeded with high selectivity. Epoxy alcohol **13** was treated with *t*-$Bu_2Si(OTf)_2$ as a Lewis acid to promote the epoxide-carbonyl rearrangement.[15] The resulting *anti* β-hydroxy-α-methyl ketone **14** was protected as PMB ether **3**.[16] Although a stereoisomer resulted from the epoxide-carbonyl rearrangement reaction could not be separated from our desired compound, ketone **3** including a minor stereoisomer was submitted to the coupling reaction between the C33−C40 and C25−C32 segments.

Coupling of the two segments and construction of the C24−C40 segment **1** are shown in Scheme 6. The lithium enolate of **3** was reacted with aldehyde **2** to give an aldol adduct, which was further converted to α,β-unsaturated ketone **15** *in one pot* by sequential mesylation and elimination. The aldol reaction proceeded stereoselectively (the resulting configuration of the C33 position was not determined), and sequential dehydration gave *E* isomers stereoselectively. Luche reduction of the resulting ketone **15** proceeded stereoselectively to yield the desired isomer **16**.[17] Removal of TMS under acidic conditions gave diol **17**, which was separated from other stereoisomers including derivatives of the stereoisomer of **3** by column chromatography. After protection of the diol as methoxymethyl ethers, the ester group at the C25 position was converted to ethyl ketone by the sequence of preparation of a Weinreb amide[18] and introduction of ethyl group with ethylmagnesium bromide. The six-step sequence gave a very straightforward route to C24−C40 segment **1**.

In conclusion, we achieved the synthesis of the C24−C40 segment of aculeximycin in a few steps. Both C25−C32 and C33−C40 segments were synthesized by the Kobayashi aldol reaction and epoxide-opening rearrangement reactions. In

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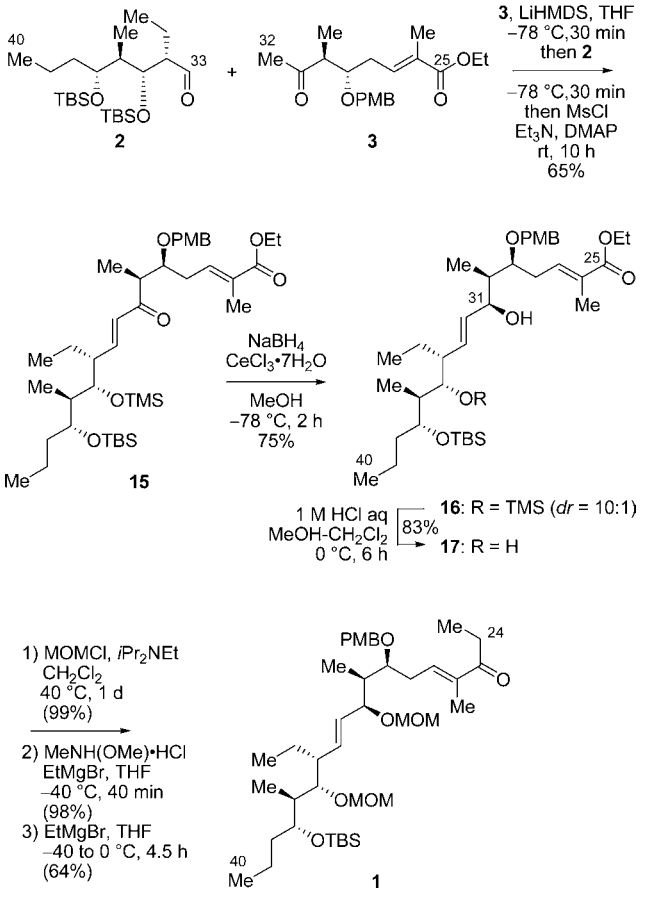
Scheme 6. Coupling of Segments and Synthesis of C24−C40 Segment 1



preparation of the C25−C32 segment the internal epoxyalcohol received an epoxide-ketone rearrangement, while semipinacol rearrangement of TBS-protected external epoxyalcohol was employed to the synthesis of C33−C40 segment. Coupling of these segments by an aldol reaction and subsequent dehydration to construct the double bond was accomplished in one pot. After separation of the stereoisomers, the desired major compound was converted to C24−C40 segment **1** by protection of the hydroxy groups and conversion of the ethyl ester into the ethyl ketone. This route shows the efficient and straightforward synthesis of medium-size polypropionates including multiple stereogenic centers and hydroxy groups. Further studies toward the total synthesis of aculeximycin are in progress.

■ ASSOCIATED CONTENT

Supporting Information

The experimental procedure and physical property of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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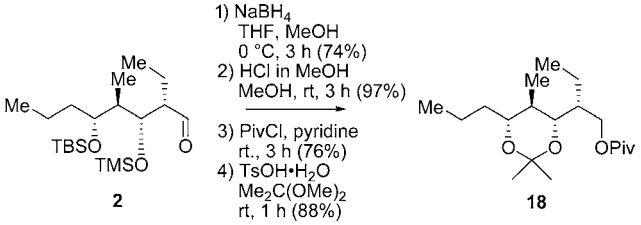

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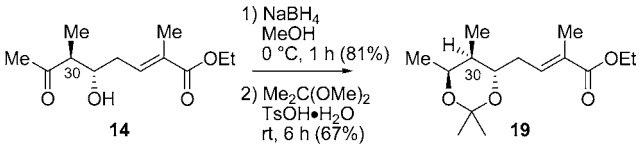

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