Bioorganic Chemistry of Alternaric Acid: Stereochemistry, Total Synthesis and Bioactivity

Akitami Ichihara

Department of Bioscience and Chemistry, Faculty of Agriculture, Hokkaido University

Abstract: Absolute stereostructure of alternaric acid (I) has been determined by the synthesis of four diastereomers of the degradation product, which had been obtained in the course of structural studies. The key synthetic steps incorporated into the total synthesis of I were the Julia olefination of tertiary aldehyde 6 and phenylsulfone 7 and novel one-pot construction of 3-acyl-4-hydroxy-5,6-dehydro-2-pyrone 1b via Fries-type rearrangement of the O-enol acyl group of β-keto-δ-valerolactone toward the α-position of the δ-lactone. The structure-activity relationship of analogues of I and synthetic intermediates has been investigated.

1. Introduction

In 1960, the planar structure of alternaric acid (1), a phytotoxin isolated from Alternaria solani, causal fungus in the early bright disease of potato and tomato, was determined by using classical chemical methods (ref. 1). However, the total stereostructure of I remained to be elucidated. A. solani also produces several secondary metabolites, and some of them were isolated in our laboratory (ref. 2). After that, alternaric acid (1) was shown to contribute to disease development of the host by A. solani in a manner similar to the mode of action of the group of compounds classified as host-specific toxins, although all of the requirements as a primary disease determinant were not fulfilled (ref. 3). This phytotoxin I was also shown to delay the occurrence of hypersensitive death of potato cells infected by an incompatible race of Phytophthora infestans (ref. 4). Recently we have disclosed details concerning the isolation, structural elucidation, and determination of the stereochemistries of three new metabolites 2, 3, and 4 as a strategy for structurally identifying alternaric acid (1) (ref. 5) and understanding its biosynthetic route (ref. 6).

In this paper, we shall discuss the determination of the complete stereochemistry, total synthesis and structure-activity relationship, of alternaric acid (1) (ref. 7).

2. Synthetic Plan

Retrosynthetic analysis of I generated three building blocks: aldehyde 6 (segment A), phenylsulfone 7 (segment B) and β-keto-δ-valerolactone 8 (segment C) (Scheme 1), in which aldehyde 6 is considered to be combined with phenylsulfone 7 by Julia olefination (Ref. 8). However, this condensation proved to be a far more challenging than originally anticipated because aldehyde 6
contains a chiral centre at the α-position, and has a methoxycarbonyl group, which could be easily attacked by a nucleophilic reagent. There may be no precedents for such a case in Julia olefination. Construction of 3-acyl-4-hydroxy-5, 6-dehydro-2-pyrone from carboxylic acid 5 and β-keto-δ-valerolacton 8 via a newly developed Fries type rearrangement was achieved by O-enol acyl group formation of the β-keto-δ-valerolactone at the α-position of the δ-lactone when medicated in the presence of DCC and DMAP (ref. 9).

Scheme 1

From the values of the optical rotations of the degradation products 9 and 11 of 1, the stereochemistry at C(12) and C(17) positions was presumed to be 12-S and 17-R. Since the stereochemistry at the C(10) and C(11) positions were undetermined at this stage, we elucidated the stereochemistry of 1 through the syntheses of four possible diastereoisomers of the degradation product 10, C(9)-C(14) fragment, of 1.

3. Synthesis of Segment A and Stereochemistry of Alternaric Acid

The synthesis of the four possible diastereoisomers of degradation product 10 was achieved as follows: The starting material, (S)-(+) -2-methylbutanal (9), was prepared by Swern oxidation or

Scheme 1

\[ \begin{align*}
1 & \xrightarrow{\text{DCC and DMAP}} \text{segment A (6)} \\
& \quad \downarrow \\
& \text{segment AB (5)} \\
& \quad \downarrow \\
& \text{segment C (8)} \\
& \quad \downarrow \\
& \text{segment B (7)}
\end{align*} \]

From the values of the optical rotations of the degradation products 9 and 11 of 1, the stereochemistry at C(12) and C(17) positions was presumed to be 12-S and 17-R. Since the stereochemistry at the C(10) and C(11) positions were undetermined at this stage, we elucidated the stereochemistry of 1 through the syntheses of four possible diastereoisomers of the degradation product 10, C(9)-C(14) fragment, of 1.

3. Synthesis of Segment A and Stereochemistry of Alternaric Acid

The synthesis of the four possible diastereoisomers of degradation product 10 was achieved as follows: The starting material, (S)-(+) -2-methylbutanal (9), was prepared by Swern oxidation or
nitroxyl radical oxidation (2, 2, 6, 6-tetramethylpiperidin-1-oxyl, NaOCl, pH 9.5, KBr, 0–15°C) of (S)-(−)-2-methylbutanol (ref. 10). Condensation of the aldehyde 9 with vinyl lithium reagent 12 which was prepared from 1.7 equiv. of 2-bromo-3,3-diethoxy-1-propene (ref. 11) and 1.7 equiv. of n-butyllithium, yielded a diastereomeric mixture of 13a and 13b in a ratio of 64:36 (59% yield) (Scheme 2) (ref. 13). The stereochemistry of the newly formed stereocenters at C(11) in 13a and 13b was confirmed by chemical correlation of 13b with L-isoleucine.

Scheme 2

\[

gennin oxyl radical oxidation (2, 2, 6, 6-tetramethylpiperidin-1-oxyl, NaOCl, pH 9.5, KBr, 0–15°C) of (S)-(−)-2-methylbutanol (ref. 10). Condensation of the aldehyde 9 with vinyl lithium reagent 12 which was prepared from 1.7 equiv. of 2-bromo-3,3-diethoxy-1-propene (ref. 11) and 1.7 equiv. of n-butyllithium, yielded a diastereomeric mixture of 13a and 13b in a ratio of 64:36 (59% yield) (Scheme 2) (ref. 13). The stereochemistry of the newly formed stereocenters at C(11) in 13a and 13b was confirmed by chemical correlation of 13b with L-isoleucine.

Scheme 2

\[
\begin{align*}
&\text{(++)9} \\
&\text{THF, } -78°C \text{, 59%} \\
&\text{LiCH(OEt)₂} \quad 12 \\
&\text{13a} \\
&\text{OH} \\
&\text{CH(OEt)₂} \\
&\text{13b} \\
&\text{13a : 13b = 64 : 36}
\end{align*}
\]

\[
\begin{align*}
&\text{OH} \\
&\text{CH(OEt)₂} \\
&\text{Me₂C(OMe)₂} \quad \text{CSA,} \quad 72%, \text{ from 9} \\
&\text{16a} \\
&\text{16b} \\
&\text{16a : 16b : other isomers} \\
&\text{= 60 : 34 : 6}
\end{align*}
\]

Figure 1

\[
\begin{align*}
&\text{NOE} \\
&\text{16a} \\
&\text{16b}
\end{align*}
\]
Dihydroxylation of the mixture of 13a and 13b with catalytic amount of osmium tetroxide, followed by selective protection of the primary hydroxyl group as silyl ether, and subsequent acetonide formation, furnished a mixture of four diastereoisomers in 72% overall yield (16a : 16b : other diastereoisomers = 60 : 34 : 6). The mixture was separated by flash silica gel column chromatography to give pure 16a and 16b. The relative configuration of the stereocenters at C(10) and C(11) in 16a and 16b was elucidated by difference NOE experiments in the 1H-NMR spectrum (Fig. 1). Thus, the NOE was observed between 9-H and 12-H, and between 11-H and 20-H on 16a and 16b. These stereochromatic assignments are consistent with the predicted values based on Kishi's empirical formulation (ref. 14) that dihydroxylation of 13a and 13b with osmium tetroxide would occur from opposite side of allylic hydroxyl group to give 14a and 14b, respectively. In addition, the coupling constants due to 11-H, J = 6.7 Hz in 16a and 9.4 Hz in 16b, are in accordance with stable conformers arising from previously assigned configurations of 13a and 13b.

Selective removal of the diethyl acetal and silyl ether groups, and traversing the compound through several subsequent oxidative reactions in both acetonides 16a and 16b afforded four possible diastereoisomers of the degradation product of 1. Thus, hydrolysis of 16a (TMSCI, SiO2, acetone, rt, 8 h) gave aldehyde 17 (Scheme 3). In this step, treatment of 16a with protonic acid failed to give 17 because of hydrolysis of the acetonide moiety. Sodium chlorite oxidation (ref. 15) of the resultant aldehyde 17 followed by methylation with diazomethane afforded methyl ester 18. Removal of the silyl protecting group (n-Bu4NF, AcOH, THF, rt, 44 h) of methyl ester 18 and subsequent Swern oxidation of the alcohol 19 provided aldehyde 6. In the removal of the silyl protecting group, acetic acid is necessary to prevent the hydrolysis of methyl ester group because of the basicity due to tetrabutylammonium fluoride. Sodium chlorite oxidation of the resultant aldehyde 6 yielded carboxylic acid 10a, which was treated with an aqueous solution of 2-benzyl-2-thiopseudourea hydrochloride to form 20a; R = H, 20b; R = H-2N=S=NH=Sb.
give the corresponding salt 10b. Similarly, using the reactions from 16a to 10b, acetonide isomer 16b was converted to 20b.

On the other hand, removal of the silyl protecting group of 16a gave alcohol 21 which was converted to 25, the C-10 epimer of 10, as follows (Scheme 4): Thus, Swern oxidation of the aldehyde 22 followed by methylation with diazomethane afforded methyl ester 23. In the hydrolysis of 23, it was essential to use a stronger Lewis acid, such as trimethylsilyltriflate, instead of the usual protic acid.

Scheme 4

Oxidation of the resultant aldehyde 24 provided carboxylic acid 25a, which was treated with an aqueous solution of 2-benzyl-2-thiopseudourea hydrochloride, affording the corresponding salt 25b. According to the procedure from 16a to 25b, the acetonide isomer 16b was converted to 26b. The optical rotations and melting points of 10b and all other diastereomers thus obtained, are summarized in Table 1, in which the physical data of 10b are in fair agreement with those of the degradation product 10b (natural) of alternaric acid (1). From the above results, we concluded that the absolute configuration of alternaric acid must be that as depicted in 1.
4. Synthesis of Segments B and C

As shown in Scheme 5, segment B (7) was synthesized from dimethyl itaconate (27). Direct reduction of 27 failed to give the corresponding diol 32 due to the predominance of a 1,4-reduction side reaction. This problem could be overcome by protection of the olefin moiety according to a retro-Diels-Alder procedure (ref. 16). Diels-Alder reaction of 27 with cyclopentadiene gave a diastereomeric mixture of adduct 28. Without recourse to isolation, reduction of 28 with lithium aluminum hydride to diol 29 and subsequent acetylation yielded diacetate 30. Deprotection of 30 by heating (270 ~ 280 °C) furnished olefin 31 (54% yield, 4 steps). A ratio of 2.3 : 1 in adduct 28endo and 28exo was revealed by difference NOE experiments in the 1H-NMR spectrum of the mixture of diacetate 30endo and 30exo.

\[
\begin{align*}
\text{MeO}_2\text{C} & \quad \text{CO}_2\text{Me} \\
\text{O} & \quad \text{AlCl}_3 \\
\arrow & \quad \text{CO}_2\text{Me} \\
\text{LiAlH}_4 & \Rightarrow \\
\end{align*}
\]

Palladium catalyzed allylic alkylation (ref. 17) of 31 with sodium dimethyl malonate gave dimethyl ester 33, and decarboxylation of 33 by heating with sodium chloride in wet DMSO at 150 °C afforded the corresponding ester 34 without hydrolysis of methyl ester. The acetoxyl group of 34 was converted into the phenylsulfonyl group via three conventional reactions. Thus, treatment of 34 with p-toluenesulfonic acid in methanol yielded alcohol 35, and treatment of 35 with diphenyl disulfide and tri-n-butylphosphine in pyridine (ref. 19), followed by selective oxidation of sulfide group of 36 with

Table 1  Optical rotations and melting points of salts 10b, 20b, 25b and 26b

<table>
<thead>
<tr>
<th>salts</th>
<th>optical rotation* [α]d (EtOH)</th>
<th>mp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10b (natural)</td>
<td>+ 64*</td>
<td>141~141.5</td>
</tr>
<tr>
<td>10b</td>
<td>+ 59.2*</td>
<td>139~141</td>
</tr>
<tr>
<td>20b</td>
<td>- 40.4*</td>
<td>136~138</td>
</tr>
<tr>
<td>25b</td>
<td>+ 24.7*</td>
<td>127~129</td>
</tr>
<tr>
<td>26b</td>
<td>- 15.3*</td>
<td>143~145</td>
</tr>
</tbody>
</table>

* Optical rotations were measured at 22 °C for salts 10b, 20b, 26b and at 23 °C for salts 10b (natural) and 25b.

Palladium catalyzed allylic alkylation (ref. 17) of 31 with sodium dimethyl malonate gave dimethyl ester 33, and decarboxylation of 33 by heating with sodium chloride in wet DMSO at 150 °C afforded the corresponding ester 34 without hydrolysis of methyl ester. The acetoxyl group of 34 was converted into the phenylsulfonyl group via three conventional reactions. Thus, treatment of 34 with p-toluenesulfonic acid in methanol yielded alcohol 35, and treatment of 35 with diphenyl disulfide and tri-n-butylphosphine in pyridine (ref. 19), followed by selective oxidation of sulfide group of 36 with
diphenyl diselenide and hydrogen peroxide provided phenylsulfone 37 (ref. 20). Reduction of methyl ester group of 37 with lithium aluminum hydride and following primary alcohol protection using t-butyldimethylsilyl chloride provided the C(3)-C(8) phenylsulfone 7 (segment B) (Scheme 5).

Scheme 5

\[
\begin{array}{c}
\text{Pd(dba)\textsubscript{2}}, \text{dpe} \\
\text{dimethyl malonate, NaH} \\
\text{77%}
\end{array} \quad \begin{array}{c}
\text{AcO} \\
\text{CO\textsubscript{2}Me} \\
\text{79%}
\end{array} \quad \begin{array}{c}
\text{NaCl, DMSO, H\textsubscript{2}O, 150 °C} \\
\end{array}
\]

\[
\begin{array}{c}
\text{RO} \\
\text{CO\textsubscript{2}Me} \\
\text{83%}
\end{array} \quad \begin{array}{c}
\text{(PhS)}_{3}, \text{pyridine} \\
\text{Bu$_3$P} \\
\end{array} \quad \begin{array}{c}
\text{X} \\
\text{CO\textsubscript{2}Me} \\
\text{79%}
\end{array} \quad \begin{array}{c}
\text{RO} \\
\text{PhSO\textsubscript{2}O} \\
\text{7; R = TBS, (segment B)}
\end{array}
\]

\[
\begin{array}{c}
\text{p-TsOH, MeOH} \\
\text{90%}
\end{array} \quad \begin{array}{c}
\text{X} \\
\text{36; X = SP} \quad \text{37; X = SO\textsubscript{2}Ph}
\end{array}
\]

β-Keto-δ-valerolactone 8, segment C, could be prepared by two different routes. One of these started from D-glucose, but this route proved to be circuitous. Alternatively, therefore, the carbon skeleton of segment C was constructed according to literature (ref. 21) as follows: Claisen condensation of (R)-(−)-methyl 3-hydroxybutanoate and lithium t-butyl acetate gave δ-hydroxy-β-keto ester (79% yield), and hydrolysis of the keto ester with trifluoroacetic acid afforded β-keto-δ-valerolactone 8, segment C, in 89% yield. Evidently, the latter route was more effective because of a reduction in the number of steps taken and an enhancement in the overall yield.

5. Coupling of Segments A, B and C, and Total Synthesis of Alternarioc Acid (1)

The subsequent steps in the total synthesis involved a Julia olefination of aldehyde 6 (segment A) to phenylsulfone 7 (segment B). In general, the addition of sulfone anions to aldehydes can be capricious process, and depends on base, solvent and auxiliary reagents (ref. 22). In our case, segment A (6) is a tertiary aldehyde, and has a methoxycarbonyl group at the vicinal carbon, C(10), of the formyl group. A survey of the literature reveals that there may be no precedents for such a case in Julia olefination. In model experiments using pivalaldehyde, the reaction proceeds in good yield (96%) when using lithium dialkylamide rather than alkyl lithium as base. However, in the coupling of segments A(6) and B(7), the reaction yields are not only dependent on base but also on solvents. Thus, the reaction proceeds more smoothly in the existence of n-hexane as cosolvent. The results of some examinations of reaction conditions reveals that the following conditions gave optimal results; treatment of phenylsulfone 7 with 1.5 equivalent lithium disopropylamide at -78 °C in ether-n-hexane (1:1) afforded the corresponding sulfone anion, which reacted with aldehyde 6 to give the corresponding β-hydroxy sulfones 39 as a mixture of diastereomers. The mixture was acetylated to afford β-acetoxy sulfones 40, and 40 was subjected to an elimination reaction using sodium amalgam. The product 41 was obtained in 41% overall yield, and it consisted of a 14:1 mixture of E and Z isomers. These were separated by MPLC to give the desired major isomer 41.
Several methods for construction of 3-acyl-4-hydroxy-5, 6-dihydro-2-pyrone structure have been reported (ref. 23). However, most of them are not so convenient, since they require some steps, and the starting materials are not readily available. As part of our model studies, we discovered that the 3-acyl-4-hydroxy-5, 6-dihydro-2 pyrone structure was directly prepared from carboxylic acids and β-keto-δ-valerolactones under mild conditions. This reaction involves Fries type rearrangement of the O-enol

**Table 2** Synthesis of 3-Acy1-5,6-dihydro-4-hydroxy-2-pyrones from Carboxylic Acids and β-Keto-δ-valerolactone 8.

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>solvent</th>
<th>time</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>MEMO(CH₂)₂C(=CH₂)(CH₂)₂</td>
<td>CH₂Cl₂</td>
<td>24 h</td>
<td>65a</td>
</tr>
<tr>
<td>2.</td>
<td></td>
<td>acetone</td>
<td>24 h</td>
<td>50a</td>
</tr>
<tr>
<td>3.</td>
<td></td>
<td>THF</td>
<td>24 h</td>
<td>29a</td>
</tr>
<tr>
<td>4.</td>
<td>CH₃</td>
<td>CH₂Cl₂</td>
<td>53 h</td>
<td>77b</td>
</tr>
<tr>
<td>5.</td>
<td>CH₂CH₂</td>
<td>CH₂Cl₂</td>
<td>48 h</td>
<td>85b</td>
</tr>
<tr>
<td>6.</td>
<td>CH₃(CH₂)₆</td>
<td>CH₂Cl₂</td>
<td>10 h</td>
<td>78a</td>
</tr>
<tr>
<td>7.</td>
<td>(CH₃)₂CH</td>
<td>CH₂Cl₂</td>
<td>72 h</td>
<td>25a</td>
</tr>
<tr>
<td>8.</td>
<td>(CH₅)₃C</td>
<td>CH₂Cl₂</td>
<td>7 days</td>
<td>N.R. c</td>
</tr>
<tr>
<td>9.</td>
<td>CH₃(CH₂)₇CH=CH(CH₂)₇</td>
<td>CH₂Cl₂</td>
<td>24 h</td>
<td>86a</td>
</tr>
<tr>
<td>10.</td>
<td>CH₃(CH₂)₄CH=CHCH₂CH=CH(CH₂)₇</td>
<td>CH₂Cl₂</td>
<td>24 h</td>
<td>89a</td>
</tr>
</tbody>
</table>

a Yield after purification of product by flash chromatography; b Yield after recrystallization of product; c O-Acylation proceeds in quantitative yield.
acyl group of β-keto-δ-valerolactone toward the α-position of the lactone. Thus, a solution of carboxylic acid, β-keto-δ-valerolactone (1 equiv), DCC (1.1 equiv) and DMAP (0.1 equiv) in CH₂Cl₂ was stirred at room temperature to give the product in good yield. Several examples are summarized in Table 2.

At first, the solvent effects of the reaction were tested (entry 1, 2 and 3). The nonpolar solvent such as CH₂Cl₂ was shown to be effective, while polar solvent such as THF was not effective. The rearrangement of a low molecular weight acyl group gives the good yield, and in the case of a secondary or tertiary acyl group gives poor yield or no product, although the O-acyl products are given in quantitative yield (entry 7, 8). The rearrangement of acyl group depends on the chain length of carboxylic acid (entry 4, 5 and 6). Thus, the octanoyl group completely undergoes rearrangement in ten hours. However, acetyl group rearrangement requires a longer reaction time. It is interesting to note that this reaction proceeds in good yield in the case of an unsaturated carboxylic acid (entry 1, 9 and 10).

This improved method was applied to the synthesis of alternaric acid (1). Thus, removal of the silyl protecting group in E-olefin 41 yielded alcohol 42 (Scheme 6). Swern oxidation of the alcohol 42, was followed by sodium chlorite oxidation of resultant aldehyde 43 to furnish carboxylic acid 5 (segment AB). Rather fortuitously it was observed that O-enolacylation of β-keto-δ-valerolactone 8 (segment C) with carboxylic acid 5 in the presence of DDC and DMAP afforded 3-acyl-4-hydroxy-5,6-dehydropyrone 45, [α]₂⁰D-3.8° (c 3.70, EtOH), [natural, [α]₂⁰D-5.2° (c 3.68, EtOH) (ref. 1f), in good yield (75%).

The hydrolysis of 1b was not easy because of its instability to acid. The hydrolysis of acetonide moiety of 1b with 1N hydrochloric acid in methanol-THF gave the corresponding diol in only 21% yield, but we were unable to obtain the target compound by further hydrolysis of the methyl ester.
Eventually, however, the problem was overcome by changing the order of hydrolysis reactions (Scheme 6). Thus, hydrolysis of methyl ester of 1b with 2N lithium hydroxide in methanol-THF (1:2) smoothly yielded the corresponding carboxylic acid 45 and following hydrolysis of acetonide by heating at 120°C in autoclave provided alternaric acid (1), [α]_D^24 0° (c 1.00, acetone), [natural, optically inactive] (ref. 1d), in 45% yield (2 steps). To effect cleanly the hydrolysis of the acetonide moiety of 45, an increased pressure and the presence of the carboxyl group were essential. Such a hydrolysis condition involved using an intramolecular carboxyl group without adding acid or base is very mild and neutral reaction condition. The spectroscopic data of synthetic 1 thus obtained was identical in all respects with those of natural 1.

6. Structure-Activity Relationship

Alternaric acid (1) shows phytotoxic activity on tomato seedlings inducing necrosis and curling. It was also found that the phytotoxicity depends on the oxidation levels of the molecules, in which the exomethylene group at C-6 and the hydroxy group at C-10 in 1 play an important role (Table 3). Very recently, from the results of the bioassay with the synthetic samples (Fig. 2), it has been clarified that the side chain moiety consisting of segments A and B induces necrosis and the pyrone moiety causes curling of hypocotyl (Fig. 3). Details of the bioactivity results will be reported elsewhere.

Table 3 Effect of alternaric acids on punctured potato leaves

(125 ppm, 5 days, 25 °C)

<table>
<thead>
<tr>
<th></th>
<th>control</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 days</td>
<td>-</td>
<td>++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>5 days</td>
<td>-</td>
<td>+++</td>
<td>++</td>
<td>-</td>
</tr>
</tbody>
</table>

phytotoxic activity; +++: very strong, ++: strong, +: weak, -: no activity

Figure 2 Test samples for tomato seedlings assay

<table>
<thead>
<tr>
<th>segment AB'</th>
<th>segment BC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>segment A'</th>
<th>segment B'</th>
<th>segment C'</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
7. Conclusion

The determination of the stereochemistry and the first total synthesis of altemaric acid 1 have been accomplished. In addition, an advanced method for the construction of tricarbonylmethane structures was developed. These studies made possible the synthesis of analogs of altemaric acid for the study of their structure-activity relationship.

Acknowledgement

The author is greatly indebted to Dr. Hiroyasu Tabuchi who has contributed much throughout the research work. We are also grateful to our coworkers, Mr. Taisuke Hamamoto, Dr. Shokyo Miki, Mr. Takeshi Tejima whose accomplishments in the above experiments were crucial to the success of this project. The research was supported by a Grant-in-Aid for Scientific Research from Ministry of Education, Science and Culture of Japan.

References and Notes


(12) The ratio was determined by 1H NMR (500 MHz) spectrum.

(13) It is known that the condensation of the vinyllithium reagent 12 and chiral α-methylaldehyde gives Cram (syn) adduct as major product (61:39→63:37). Kinoshita, M.; Nakata, M. *Yuki Gosei Kagaku Kyokai-shi*, 1986, 44, 206.


(Received June 29, 1995)