Total Synthesis of Madindoline A

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Abstract: The total synthesis of madindoline A was achieved. Stereoselective construction of the quaternary carbon in the cyclopentenedione moiety was accomplished by alkylation of dienolate bearing a chiral auxiliary. The coupling of sterically hindered aldehyde 17 and acid-sensitive amine 30 was achieved by developing a new reductive amination method using Sn(OTf)2 and NaBH(OAc)3. After the reductive coupling, the cyclopentenedione skeleton of madindoline was constructed by intramolecular condensation of triketone 5.

1. Introduction

Interleukin 6 (IL-6) is a multifunctional cytokine which participates in immune response and also participates in inflammation, cancer cachexia, and stimulation of tumor cells proliferation in autocrine/paracrine manner. Thus, an inhibitor of IL-6 activity would be promising candidates for treatment of these diseases. We have been interested in the synthesis of natural products that exhibit selective inhibition of IL-6 activity. Madindoline A (1) and B (2) were isolated from the culture of Streptomyces nitrosporeus K93-0711 by Omura in 1996 and were determined to be inhibitors of IL-6 activity. They possess furoindoline and cyclopentenedione skeleton including a chiral quaternary carbon. The first total syntheses of madindolines were recently achieved by Omura’s group, who determined the absolute configurations as shown in Figure 1. Intrigued by their structures and bioactivities, we embarked on a synthetic study of 1. We herein report the total synthesis of madindoline A via the synthetic strategy shown in Figure 1.

2. Synthesis of the Cyclopentenedione Moieties of Madindolines

Our synthetic strategy for madindolines feature coupling furoindoline 4 and cyclopentenedione 3 or its precursor (Scheme 1). The quaternary carbon of cyclopentenedione 3 is chiral because the side chains differ in length. Even though there are some methods for construction of a chiral quaternary carbon, this remains to be a challenge in synthetic organic chemistry. Our synthetic strategy for cyclopentenedione 3 is shown in Scheme 2. We envisioned that the cyclopentenedione skeleton might be constructed by a regioselective intramolecular condensation of triketone 5. The requisite triketone 5, in turn, could be derived from olefin 6.
the synthesis of 6, we expected that the key quaternary carbon formation can be achieved by regio- and stereoselective alkylation of α, β-unsaturated carbonyl derivative 8 bearing a chiral auxiliary.

2.1 Construction of the Chiral Quaternary Carbon

Prior to the synthesis of 3, we examined a stereoselective construction of a quaternary carbon using a tiglic acid derivative as a model substrate (Scheme 3). Among the several chiral substrates examined, Evans' oxazolidone derivative 9 showed high stereoselectivity when alkylated with benzyloxymethyl chloride or methoxymethyl chloride (Table 1). In these reactions, the regioselectivity of the alkylation was excellent, affording an α-alkylation product exclusively. In a separate experiment, the intermediate dienolate anion was trapped as TBDMS ether 11 which was isolated as a single isomer in 90% yield (Scheme 4). The E stereochemistry was unambiguously determined by an NOE experiment in which NOE's were observed between the vinyl and isopropyl methyl protons as well as between the methyl and TBDMS protons. From these results, we speculate that the electrophile approach from the side opposite to the i-Pr group of dienolate 12, and we tentatively assigned the absolute configuration of 10 as shown below.

![Scheme 3](image)

**Scheme 3**

![Scheme 4](image)

**Table 1.** α-Alkylation of α,β-unsaturated imide 9

<table>
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<th>entry</th>
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<th>selectivity</th>
</tr>
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<td>toluene</td>
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2.2 Synthesis of the Cyclopentenedione Derivative Possessing a Chiral Quaternary Carbon

With the promising results of the model studies in hand, we began the synthesis of cyclopentendione moiety 3 (Scheme 5). Hexanal 13 was converted to acid chloride 14 which was reacted with lithio-oxazolidone to give α, β-unsaturated oxazolidone 15 (Scheme 6). Alkylation of 15 proceeded with 11:1 diastereoselectivity to afford 16 in 65% yield, whose olefin was exclusively the E isomer (J1,2 = 16.1Hz). The stereochemistry of the quaternary carbon was tentatively assigned to be S with the same rationale as in the model study and was confirmed when the total synthesis of madindolone A was achieved. The chiral auxiliary of 16 was reductively removed and the resulting primary alcohol was oxidized to aldehyde 17 (Scheme 6). Aldehyde 17 was transformed to ethyl ketone 18 in a two-step sequence consisting of ethylation and PCC oxidation. Following the protection of ketone 18 as ethylene acetal, 19 the olefin was oxidized in to steps to α,β-diketone, namely, dihydroxylated with osmium tetroxide and the subsequent Swern oxidation. Deprotection of ethylene acetal of 19 gave triketone 20 (13C-NMR: δ 208.1, 199.9, 197.5) in 85% yield. When the triketone 20 was treated with DBU in benzene at room temperature, cyclopentendione 21 (13C-NMR: δ 205.9, 205.6; 1H-NMR: δ 2.04 (3H, s, vinyl-CH3)) was isolated in 91% yield as a single product. Next, the removal of the benzyl group with BCl3 followed by oxidation gave unstable cyclopentenedione aldehyde 22 (1H-NMR: δ 9.36 (H, s, CHO)) which rapidly decomposed at room temperature.

The rationale for the regioselectivity of intramolecular condensation is shown in Scheme 7. We propose that the relative stabilities of the intermediates 23 and 24 ultimately determine the course of the reaction. Thus, intermediate 23 suffers from a sterical repulsion between the substituents on the quaternary carbon and its adjacent carbon, besides assuming an electronically unstable α,β-diketone form. Intermediate 24, on the other hand, has neither of such problems. Thus, the equilibrium favored the formation of 24 which leads to the exclusive formation of the desired cyclopentenedione 21.

3. Reductive Amination of a Sterically Hindered Aldehyde with an Acid-sensitive Amine

Our initial strategy for the total synthesis of madindolines involved a reductive coupling of cyclopentenedione aldehyde 22 and furoindoline 4, 5 which would directly afford the madinedolone skeleton. 13, 14 Thus, we next examined the reductive coupling of aldehydes with unprotected furoindoline 4 (Scheme 8). Although the use of NaBH4CN as the hydride source for the coupling of 4 and isobutyraldehyde gave undesired indole 25, presumably produced via alkylated indoline 26, the use of NaBH(OAc)3 as the hydride source provided alkylated furoindoline 27 in high yield. However, when pivaloylaldehyde was used under the same condition, only indole 28 was obtained in low yield. Thus, we used protected furoindoline 31 for the coupling with aldehyde 22 (Scheme 9). Unfortunately, we were not able to achieve the reductive coupling of 30 or 31 and 22 to afford madindolone skeleton 32 under various conditions mainly due to the facile dehydronylation of 22 to produce 33. Therefore, we sought an alternative approach in which the cyclopentenedione formation would be carried out after the coupling with furoindoline 30 or 31. Another difficulty we encountered during the attempts above was the instability of the protected furoindoline 30 or 31. Under acidic conditions, therefore, it became necessary to develop a new methodology for the reductive coupling of acid-sensitive furoindoline and sterically hindered aldehyde.
The coupling of sterically hindered aldehydes and furoindolines were very difficult. The lability of furoindoline was such that when AcOH was used as acid, for example, we obtained only alcohol 35 (Scheme 10). After carrying out a number of experiments with varying aldehydes, acids and reaction conditions, we found that a combination of Sn(OTf)2 - NaBH(OAc)3 gives the desired furoindoline 36 in 66% yield. Thus, aldehyde 17 was treated with furoindoline 30 (1.35 eq for 17) in the presence of Sn(OTf)2 - NaBH(OAc)3 with MS-4A in dichloroethane at 0 °C. In this manner, we succeeded in the construction of the madindoline skeleton by carrying out the coupling reaction prior to cyclopentendion formation as shown in Scheme 11.

4. Total Synthesis of Madindoline A

The final route to madindoline A is shown in Scheme 12.14 The benzyl group in 36 was removed by treatment with BCl3 at -78 °C. Dess–Martin oxidation of 39 gave aldehyde 40 which was converted to 41 by alkylation with ethyllithium and the subsequent acetylation of the resulting alcohol. The C–C double bond of 41 was oxidized with a catalytic amount of OsO4 in the presence of N-methylmorpholine N-oxide, and subsequent hydrolysis gave a diastereomeric mixture of triol 42 in 75% yield (2 steps). The key intermediate triketone 38 was obtained in 70% yield by Swern oxidation,10 which underwent regioselective cyclization upon treatment with DBU in benzene at room temperature to produce cyclopentenedione derivative 43 in high yield. The presence of a singlet corresponding to vinyl-Me protons in NMR spectrum at δ 2.01 strongly supported its structure. Finally, a treatment of 43 with TBAF removed the TBS group and afforded madindoline A. The structure of synthetic madindoline A was confirmed by comparing the 1H- and 13C-NMR spectra with those of natural madindoline A, which was kindly provided by Professor S. Omura.

<table>
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<tr>
<td>THF</td>
<td>65</td>
<td>11 : 1</td>
</tr>
<tr>
<td>toluene</td>
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Table 2. α-Alkylation of imide 15
5. Conclusion

We have achieved the total synthesis of madindoline A with the development of novel methodology. The characteristic features of the present study are (1) a novel method for the stereoselective construction of a quaternary carbon, (2) a novel effective $\text{Sn(OTf)}_2$–$\text{NaBH(OAc)}_3$ method for reductive coupling of sterically hindered aldehyde and acid-sensitive amine, and (3) regio-selective intramolecular cyclization of triketone to construct the cyclopentenedione. Further correlation of 16 to madindoline A, but not madindoline B, unambiguously established the absolute stereochemistry of 16 which
was tentatively assigned based on mechanistic considerations.

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References


6) For excellent reviews which present most the methods for asymmetric construction of quaternary carbon centers; (a) Fuji, K. Chem. Rev. 1993, 93, 2037. (b) Corey, E.J.; Guzman-Perez, A. Angew. Chem. Int. Ed. 1998, 37, 388.


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