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Short Total Synthesis of (+)-Madindolines A and B

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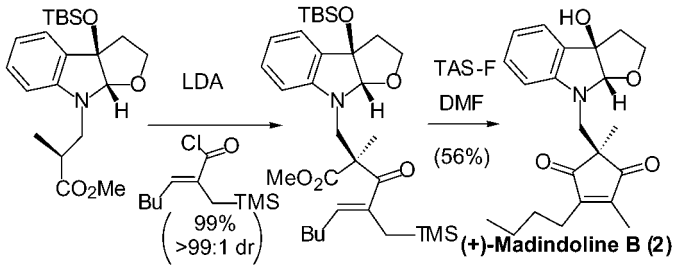
ABSTRACT



A short and efficient total synthesis of (+)-madindolines A (1) and B (2), potent and selective inhibitors of interleukin 6, has been achieved. The synthesis features a key chelation-controlled 1,4-diastereoselective acylation to generate the quaternary carbon and an intramolecular acylation of allylsilane to build up the cyclopentene unit.

(+)-Madindolines A and B (**1** and **2**) are metabolites isolated by our group[1] from *Streptomyces nitrosporeus* K93-0711 that strongly and selectively inhibit IL-6 activity. From NMR analyses, the madindolines are shown to be a 3a-hydroxyfuroindoline ring connected at the nitrogen via a methylene bridge to the cyclopentene-1,3-dione ring, and madindoline A (**1**) is a stereoisomer of B (**2**) at the C-2′ position.[2] Furthermore, we reported the first total synthesis of (+)-madindoline A (**1**) and (−)-madindoline B (**2**), the latter being the enantiomer of natural madindoline B, to define for the first time their relative and absolute configuration.[3] Unfortunately, the original culture of the streptomyces no longer produces these compounds. Herein, we report a more efficient and shorter synthesis of these compounds.[4]

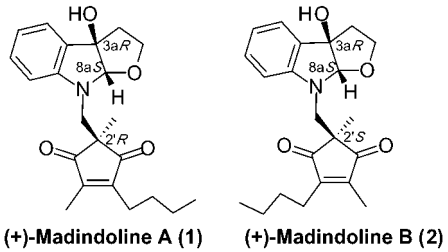


Figure 1. Structure of madindolines.

The retrosynthesis analysis of the second generation is shown in Scheme 1. The key reaction is the stereoselective acylation of ester **III** with α,β-unsaturated acid chloride **II**. We assume the lithium enolate of compound **III** would

(1) Hayashi, M.; Kim, Y.-P.; Takamatsu, S.; Enomoto, A.: Shinose, M.; Takahashi, Y.; Tanaka, H.; Komiyama, K.; Ōmura, S. *J. Antibiot.* **1996**, *49*, 1091−1095.
(2) Takamatsu, S.; Kim, Y.-P.; Enomoto, A.; Hayashi, M.; Tanaka, H.; Komiyama, K.; Ōmura, S. *J. Antibiot.* **1997**, *50*, 1069−1072.
(3) Sunazuka, T.; Hirose, T.; Shirahata, T.; Harigaya, Y.; Hayashi, M.; Komiyama, K.; Ōmura, S.; Smith, A. B., III. *J. Am. Chem. Soc.* **2000**, *122*, 2122−2123.
(4) For another total synthesis of madindoline A, see: Hosokawa, S.; Sekiguchi, K.; Hayase, K.; Hirukawa, Y.; Kobayashi, S. *Tetrahedron Lett.* **2000**, *41*, 6435−6439.

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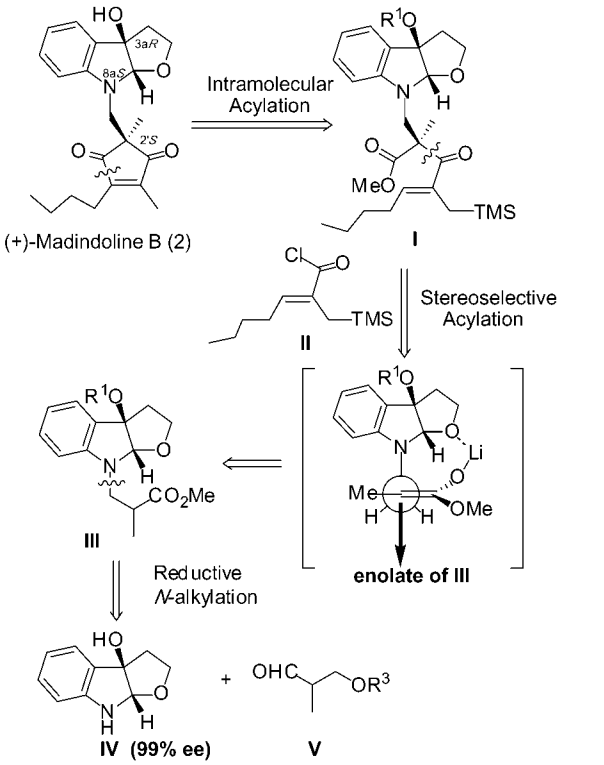
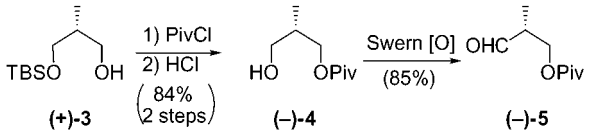
Scheme 1



coordinate with the oxygen on the chiral 3a-hydroxyfuroindoline to make a rigid conformation, and stereoselective acylation would occur to afford **I**, stereoselectively. Then, at the final stage, intramolecular acylation would occur with allylsilane compound **I** to give (+)-madindoline B (**2**), directly. Compound **III** would be obtained via the reductive amination of **IV** with **V**. The chiral 3a-hydroxyfuroindoline **IV** is available by our asymmetric oxidative ring closure.[3]

First, the synthesis of aldehyde (−)-**5** started with the known compound (+)-**3**[5] (Scheme 2). Acylation of (+)-**3**,

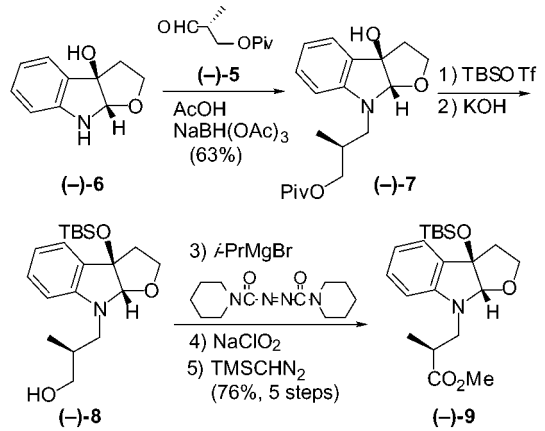
Scheme 2



followed by acid hydrolysis gave (−)-**4**, which was oxidized to aldehyde (−)-**5**.

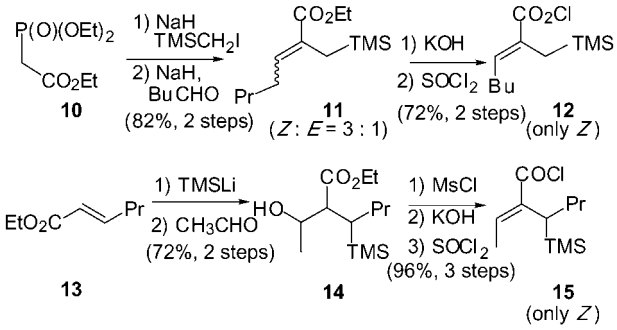
Next, reductive amination[6] of 3a-hydroxyfuroindoline (−)-**6** with aldehyde (−)-**5** using acetic acid in dichloroethane, followed by iminium reduction with sodium triacetoxyborohydride,[7] gave the desired compound (−)-**7** in 63% yield. Silylation of the tertiary hydroxy group and hydrolysis of the pivaloyl ester afforded the alcohol (−)-**8**. In the basic oxidation, (*i*-propylmagnesium bromide and 1,1′-(azodicarbonyl)dipiperidine[8]), aldehyde was obtained. Then sodium chlorite oxidation followed by esterification afforded methyl ester (−)-**9**[3](Scheme 3).

Scheme 3



On the other hand, the synthesis of allylsilane **12** started with ethyl diethylphosphonoacetate **10** (Scheme 4). Alkyla-

Scheme 4



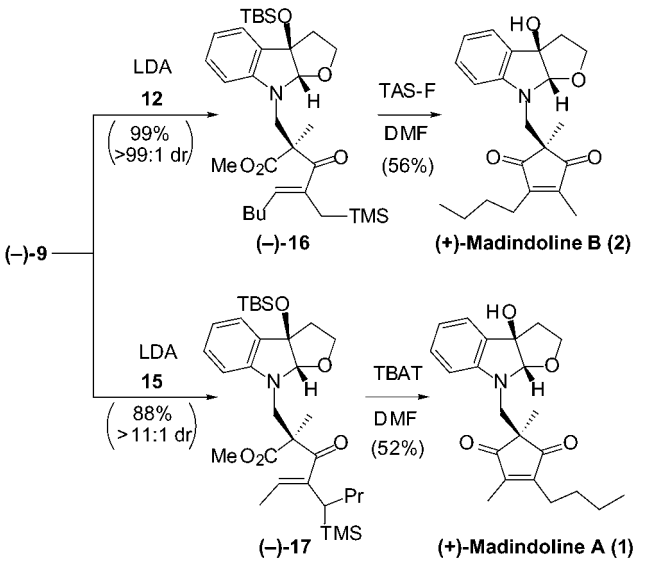
tion of **10** with iodomethyltrimethylsilane,[9] followed by the Wittig−Horner reaction[10] with valeraldehyde, led to the corresponding unsaturated ester **11** (*Z*:*E* = 3:1). Ethyl ester **11** was hydrolyzed, followed by chlorination with thionyl chloride, to afford (*Z*)-α,*β*-unsaturated acid chloride **12** as the only geometrical isomer.[11,12] For the synthesis of another allylsilane **15**, Michael addition of ethyl 1-hexenoate **13** with

(5) Mori, K.; Koseki, K. *Tetrahedron* **1988**, *44*, 6013−6020.
(6) Michael addition of (−)-**6** to methyl methacrylate or acrylate to afford **9** was unsuccessful under several conditions.
(7) (a) Ramanjulu, J. M.; Joullié, M. M. *Synth. Commun.* **1996**, *26*, 1379−1384. (b) Abdel-Magid, A. F.; Maryanoff, C. A.; Carson, K. G. *Tetrahedron Lett.* **1990**, *31*, 5595−5598.
(8) Narasaka, K.; Morikawa, A.; Saigo, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2773−2776.
(9) Hosomi, A.; Hashimoto, H.; Sakurai, H. *Tetrahedron Lett.* **1980**, *21*, 951−954.
(10) Martin, H.; Hoffmann, R.; Rabe, J. *J. Org. Chem.* **1985**, *50*, 3849−3859.
(11) (*E*)-Isomers changed to more thermodynamically stable (*Z*)-isomers during the reaction.

trimethylsilyllithium[13] followed by aldol reaction with acetaldehyde afforded β-hydroxyester **14**. Mesylation of **14** followed by alkali hydrolysis gave the corresponding unsaturated acid, which was treated with thionyl chloride to afford (*Z*)-α,β-unsaturated acid chloride **15** as the only geometrical isomer.[11,12]

The key reaction is the stereoselective acylation of ester **(−)-9**[14] with allylsilane **12** (Scheme 5). The ester (−)-**9** was

Scheme 5



treated with LDA followed by treatment with α,β−unsaturated acid chloride **12** to afford the desired compound (−)-**16** as a single isomer, in 99% yield (>99% dr).[15]

The final reaction, an intramolecular endo cyclization of allylsilane (−)-**16** using tris(dimethylamino)sulfur(trimethylsilyl)difluoride (TASF),[16] led to (+)-madindoline B (**2**) in 56% yield, directly. The synthetic (+)-madindoline B (**2**) was identical in all respects with a sample of the natural product (^{1}H and ^{13}C NMR, IR, HRMS, optical rotation, mp, and mobility on TLC). Furthermore, confirmation of the relative and absolute stereochemistry in **2** was achieved by X-ray analysis of synthetic (+)-**2** (Figure 2).

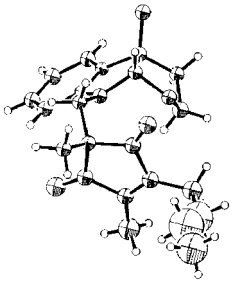


Figure 2. ORTEP plot for (+)-madindoline B (**2**).

On the other hand, for the total synthesis of (+)-madindoline A (**1**), the stereoselective acylation of (−)-**9** with α,β-unsaturated acid chloride **15** afforded the desired compound (−)-**17**, in 88% yield, predominantly (>11:1). The intramolecular endo cyclization of allylsilane (−)-**17** with tetrabutylammonium triphenyldifluorosilicate (TBAT)[17] led to (+)-madindoline A (**1**) in 52% yield. The synthetic (+)-madindoline A (**1**) was also identical in all respects with a sample of the natural product (^{1}H and ^{13}C NMR, IR, HRMS, optical rotation, mp, and mobility on TLC).

Synthetic madindoline A markedly inhibited osteoclastogenesis in vitro and inhibited bone resorption in ovariectomized mice in vivo.[18]

In summary, the second generation of the total synthesis of madindolines is stereoselective and very efficient via highly 1,4-diastereoselective acylation and intramolecular acylation, and proceeds in a practical route. A total of 11 steps is involved, and the overall yields are 16% (for **1**) and 19% (for **2**).

Further refinement of the synthetic scheme and the preparation and biological evaluation of madindoline analogues will be reported in due course.

Acknowledgment. We are grateful to Professor Amos B. Smith, III for his helpful suggestions. This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture, Japan and the Japan Keirin Association, and a Kitasato University Research Grant for Young Researchers (T.S.). We also thank the JSPS for a predoctoral fellowship to T.H.

Supporting Information Available: Spectroscopic and analytical data for compounds and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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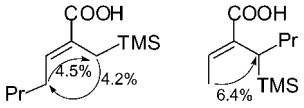
(12) The *Z*-stereochemistry for **12** and **15** was determined by NOE as show here.



(13) Still, W. C. *J. Org. Chem.* **1985**, *41*, 3063−3064.

(14) During the formation of the enolate of **9**, the chiral center of **5** is destroyed. So, it is not necessary to employ the optical active **5**. We used the chiral form of **5** in order to get the data of compounds **7**, **8**, and **9** easily.

(15) When we used KDA for the formation of its enolate, the selectivity was 2:1. Also, when we used LDA in the presence of HMPA, the selectivity was 2.3:1. On the basis of these results, there should be chelation during enolate formation of ester **9**.

(16) (a) Fujita, M.; Obayashi, M.; Hiyama, T. *Tetrahedron* **1988**, *44*, 4135−4145. (b) Scheidt, K. A.; Chen, H.; Follows, B. C.; Chemler, S. R.; Coffey, D. S.; Roush, W. R. *J. Org. Chem.* **1998**, *63*, 6436−6437.

(17) (a) Pilcher, A. S.; DeShong, P. *J. Org. Chem.* **1996**, *61*, 6901−6905. (b) Pilcher, A. S.; Ammon, H. L.; DeShong, P. *J. Am. Chem. Soc.* **1995**, *117*, 5166−5167.

(18) Hayashi, M.; Fukami, A.; Rho, M.-C.; Sekiguchi, Y.; Sunazuka, T.; Hirose, T.; Komiyama, K.; Ōmura, S. *Proc. Natl. Acad. Sci. U.S.A.* In preparation.