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# Total synthesis of madindoline A

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**Abstract**

The total synthesis of madindoline A was achieved. The key step of the synthesis is a reductive coupling of an acid-sensitive hydroxyfuroindoline derivative and a sterically hindered aldehyde using $Sn(OTf)_2$–$NaBH(OAc)_3$. After the reductive coupling, the derived trione was subjected to intramolecular condensation to construct a madindoline skeleton. 

*Keywords:* madindoline A; total synthesis; reductive coupling; tin(II) triflate; intramolecular condensation.

Interleukin 6 (IL-6) is a multifunctional cytokine which acts on immune response and also participates in inflammation, cancer cachexia, and stimulation of the proliferation of tumor cells in an autocrine/paracrine manner.[1] Thus, an inhibitor of IL-6 activity is considered to be a promising candidate for treatment of these diseases. We have been interested in a search for an inhibitor of IL-6 activity and investigated the synthesis of several natural products such as norzoanthamine.[2] Madindoline A (**1**) and B (**2**) were isolated from the culture of *Streptomyces nitrosporeus* K93-0711 by Ōmura in 1996 as a selective inhibitor of IL-6 activity.[3] Further, Ōmura's group recently achieved the first total synthesis of madindolines and determined the absolute stereochemistry as shown in Fig. 1.[4] During their synthetic investigations they developed

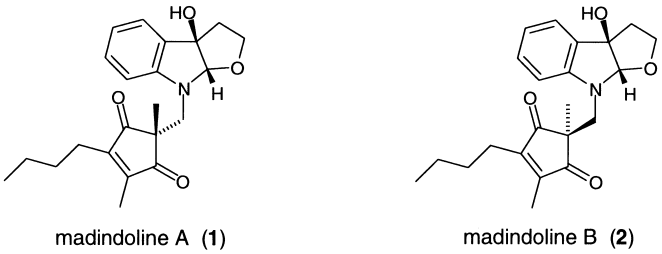


Figure 1.

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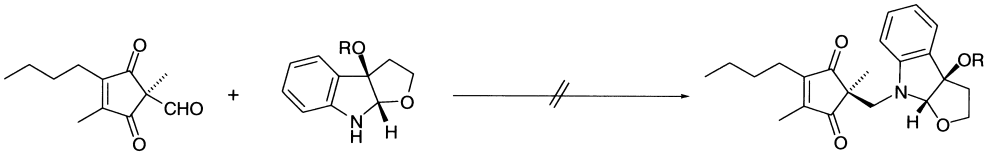
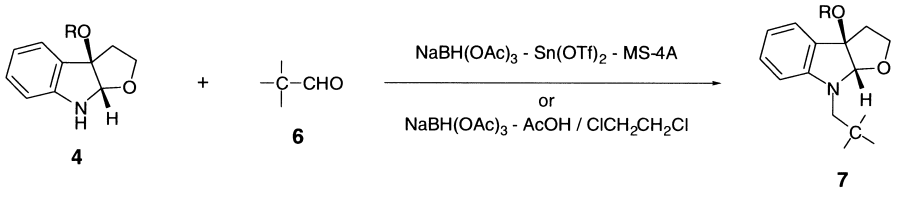
an excellent methodology for enantioselective preparation of the hydroxyfuroindoline moiety.[4] This method, however, was less stereoselective in application to the total synthesis. Thus, we became interested in an alternative approach utilizing the chiral hydroxyfuroindoline as a starting material. In the preceding paper,[5] we described an enantioselective synthesis of cyclopentenedione by developing a new method for the construction of a quaternary chiral carbon and regioselective intramolecular condensation of triketone leading to a cyclopentenedione skeleton. Here, we report the total synthesis of madindoline A.

Our initial attempts towards the total synthesis of madindolines were focused on a reductive coupling of the cyclopentenedione aldehyde **3**[5] and hydroxyfuroindoline **4**,[6] which would directly afford the madindoline skeleton (Eq. (1)).[7,8] Although cyclopentenedione aldehyde **3** could be isolated by the oxidation of the corresponding alcohol, we were not able to achieve the reductive coupling of **4** and **3** under various conditions mainly due to the ready deformylation of **3**. Therefore, we were forced to change to an alternative approach which involved the cyclopentenedione formation being carried out after coupling with furoindolidine **4**. Another difficulty we observed during the above attempts was the instability of the furoindolidine **4** under acidic conditions. Therefore, it became necessary to develop a new methodology for the reductive coupling of acid-sensitive **4** and a sterically hindered aldehyde.



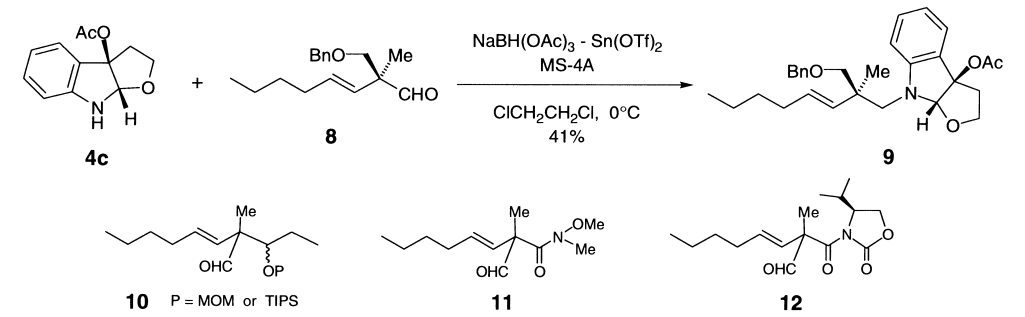

(1)



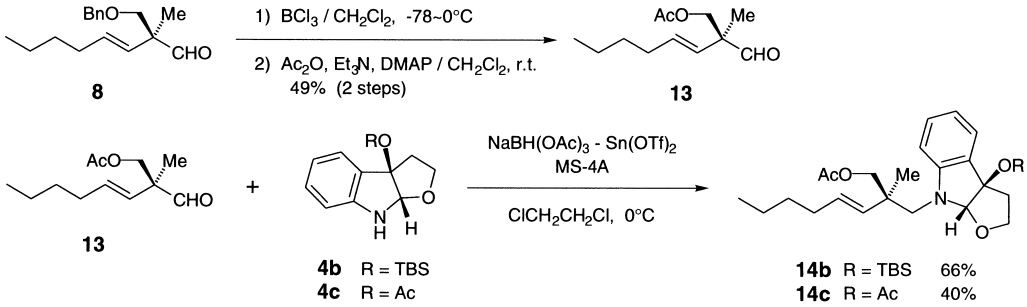

(2)

After a number of experiments by varying aldehydes, acids, additives, and reaction conditions, we were able to develop $NaBH(OAc)_3$–$Sn(OTf)_2$ and $NaBH(OAc)_3$–AcOH methods (Eq. (2)).[9] Particularly, the $NaBH(OAc)_3$–$Sn(OTf)_2$ method was found to be effective for the reductive coupling of furoindoline derivative **4**. For example, coupling of acetoxyfuroindoline **4c** and tertiary aldehyde **8**[5] gave the corresponding alkylated furoindoline **9** in 41% yield (Scheme 1). Unfortunately the present methods were not successful for the coupling with aldehydes such as **3**, **10**–**12** which are more straightforward for the synthesis of madindolines.

Since deprotection of the benzyl group in **9** was difficult, acetyl derivative **13** was prepared from **8**, and subjected to the reductive coupling with **4**. Scheme 2 shows the preparation and reaction of **13**.




Scheme 1.

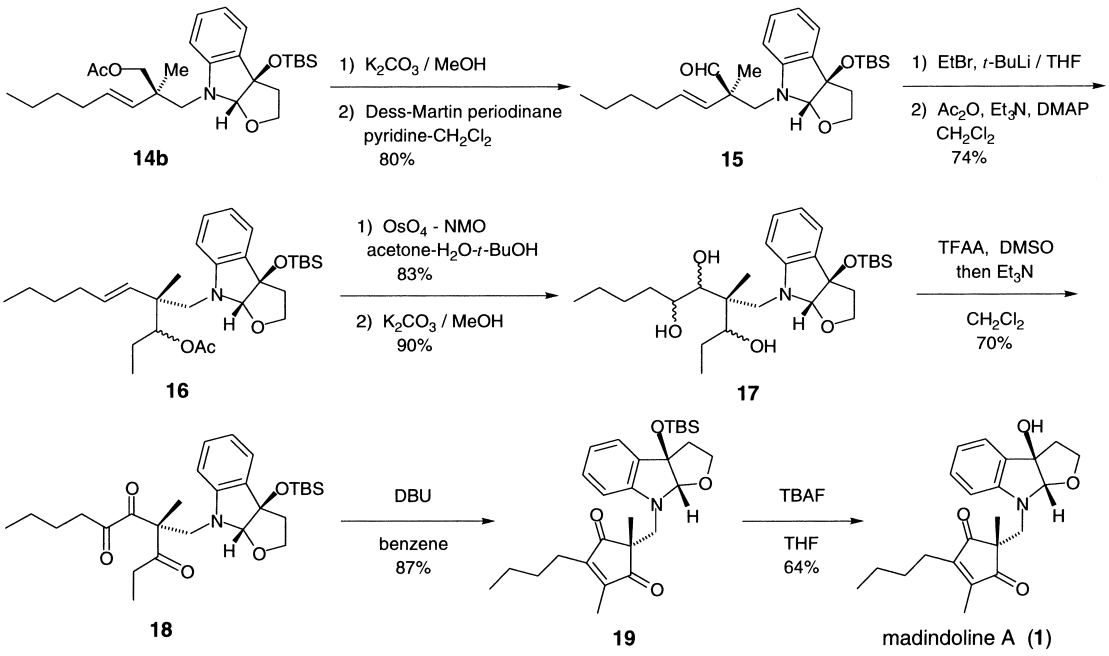



Scheme 2.

As shown in Scheme 2, reductive coupling of **13** with furoindoline **4b** and **4c** gave **14b**[10] and **14c** in 66 and 40% yields, respectively. TBS derivative **14b** eventually served as the key intermediate for madindoline A.

Total synthesis of madindoline A is summarized in Scheme 3. Deprotection of the acetyl group of **14b** followed by Dess–Martin oxidation gave aldehyde **15**, which was converted into **16** by alkylation with EtLi following protection of the resulting alcohol. The carbon–carbon double bond of **16** was oxidized with a catalytic amount of $OsO_4$ in the presence of *N*-methylmorpholine *N*-oxide, and the resulting diol was further hydrolyzed to give a diastereomeric mixture of triol **17** in 75% yield (2 steps). The key intermediate triketone **18** was obtained in 70% yield by Swern oxidation.[11] On treatment with DBU in benzene, triketone **18** underwent regioselective cyclization to produce cyclopentenedione derivative **19**[12] in 87% yield. The presence of vinyl-*Me* protons, which appeared at $\delta$ 2.01 as a singlet, strongly supported its structure. Finally, deprotection of **19** with TBAF completed the total synthesis of madindoline A. The structure of synthetic madindoline A (m.p. 123–124°C; $[\alpha]_D^{23} = +144°$ ($c = 0.273$, MeOH), $[\alpha]_D^{24} = +125°$ ($c = 0.353$, $CHCl_3$)) was confirmed by comparing $^1$H- and $^{13}$C-NMR spectra with those of natural madindoline A, kindly provided by Professor S. Ōmura.

We have thus succeeded in the total synthesis of madindoline A. The key features of the present synthesis are: (1) development of a novel $Sn(OTf)_2$–$NaBH(OAc)_3$ method for reductive coupling of a sterically hindered aldehyde and acid-sensitive furoindoline; and (2) regioselective cyclization of the triketone affording the requisite cyclopentenedione. Further correlation of **8** to madindoline A unambiguously established the absolute stereochemistry of **8** which was tentatively assigned based on mechanistic consideration.[5]




Scheme 3.

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9. Details of this method will be published elsewhere in due course.
10. $[\alpha]_D^{25} = -74.9^\circ$ ($c = 0.57$, $CHCl_3$); $^1$H-NMR (400 MHz, $CDCl_3$): $\delta$ –0.21 (3H, s), –0.14 (3H, s), 0.86 (9H, s), 0.88 (3H, d, $J = 7.1$ Hz), 1.11 (3H, s), 1.23–1.35 (4H, m), 2.00 (2H, q, $J = 7.1$ Hz), 2.10 (3H, s), 2.28 (1H, td, $J = 7.6$, 11.7 Hz), 2.44 (1H, ddd, $J = 1.5$, 5.1, 11.7 Hz), 3.15 (1H, d, $J = 14.9$ Hz), 3.37 (1H, d, $J = 14.9$ Hz), 3.45 (1H, ddd, $J = 5.1$, 9.3, 11.7 Hz), 3.97 (1H, ddd, $J = 1.5$, 7.6, 9.3 Hz), 4.04 (2H, s), 5.11 (1H, s), 5.45–5.51 (2H, m), 6.49 (1H, d, $J = 7.6$ Hz), 6.71 (1H, t, $J = 7.6$ Hz), 7.13 (1H, td, $J = 1.0$ Hz), 7.18 (1H, dd, $J = 1.0$, 7.6 Hz). $^{13}$C-NMR (100 MHz, $CDCl_3$): $\delta$ –3.6, –3.1, 14.0, 18.0, 20.8, 21.0, 22.2, 25.7, 31.5, 32.7, 41.4, 43.5, 54.4, 66.8, 69.1, 89.4, 104.6, 107.1, 117.8, 124.5, 129.7, 130.0, 130.2, 133.6, 152.4, 171.0.
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12. $[\alpha]_D^{25} = +73.3^\circ$ ($c = 0.40$, $CHCl_3$); $^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ –0.31 (3H, s), –0.24 (3H, s), 0.76 (9H, s), 0.81 (9H, s), 1.13 (3H, s), 1.16–1.36 (4H, m), 2.01 (3H, s), 2.15 (1H, dd, $J = 3.7$, 12.8 Hz), 2.32 (1H, td, $J = 7.4$, 11.6 Hz), 2.36 (2H, t, $J = 7.4$ Hz), 3.04 (1H, ddd, $J = 4.6$, 8.8, 11.6 Hz), 3.45 (1H, d, $J = 14.3$ Hz), 3.73 (1H, d, $J = 14.3$ Hz), 4.84 (1H, s), 6.64 (1H, d, $J = 7.9$ Hz), 6.71 (1H, t, $J = 7.4$ Hz), 7.10 (1H, d, $J = 7.4$ Hz), 7.17 (1H, t, $J = 7.9$ Hz).; $^{13}$C-NMR (75 MHz, $CDCl_3$): $\delta$ –3.8, –3.2, 9.4, 13.6, 17.3, 17.9, 22.7, 23.5, 25.6, 29.9, 43.1, 50.6, 54.0, 66.2, 89.4, 105.7, 107.8, 118.6, 124.4, 129.5, 130.1, 150.8, 156.7, 157.6, 180.4, 206.4, 206.5.