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Tetrahedron Letters
Tetrahedron Letters 47 (2006) 6761–6764

# Synthetic applications of a three-component Mannich reaction. Total synthesis of IL-6 inhibitor (+)-madindoline A and B

Tomoyasu Hirose, Toshiaki Sunazuka, Daisuke Yamamoto, Eisuke Kaji and Satoshi Ōmura*

*The Kitasato Institute and Kitasato Institute for Life Sciences and Pharmaceutical Sciences, Kitasato University, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8642, Japan*

Received 27 June 2006; accepted 17 July 2006
Available online 8 August 2006

**Abstract**—A three-component Mannich reaction of 3a-hydroxyfuroindoline (**3**), β-ketoester and formaldehyde was employed as an efficient and concise method to synthesize naturally-occurring (+)-Madindolines A (**1**) and B (**2**). The scope and limitations of the Mannich reaction with **3** are described.


In 1996, we reported the isolation of two novel indole alkaloids from a culture broth of *Streptomyces nitrosporeus* K93-0711, (+)-madindolines A (**1**) and B (**2**) (Fig. 1), both proved selective inhibitors of interleukin-6 (IL-6).[1,2] Both (+)-**1** and **2** specifically inhibited the growth of the IL-6 dependent MH60 cell line; importantly the response was dose-dependent, without any cytotoxicity.[3] More detailed biological studies revealed oral administration of (+)-**1** to ovariectomized mice significantly suppressed the decrease in bone mass and increase in serum $Ca^{2+}$ level after ovariectomy.[3]

The design and development of practical and efficient strategies for (+)-madindolines (**1**) and (**2**) synthesis have been an important objective in our group[4–6] and other groups[7–10] since the original source, *Streptomyces nitrosporeus* K93-0711, no longer produces these antibiotics. We have been involved in the first[4,6] and second generation[5,6] of total synthesis and determination of the absolute configurations of (+)-**1** and **2**, as well as the SAR studies of madindolines.[11] In the course of the continuation of these studies, we were interested in the application of a three-component Mannich reaction[12] to build β-aminocarbonyl moieties of madindolines. Mannich's methodology for the construction of β-aminocarbonyls has been a very useful tool of the synthetic organic chemistry. Indeed, the Mannich reactions, including asymmetric versions, have been investigated and applied to natural products synthesis by several research groups.[13–17] We present here a very quick synthesis of the title compounds as well as the limitation and scope for the Mannich reaction of sensitive amines, such as 3a-hydroxyfuroindoline (−)-**3**.

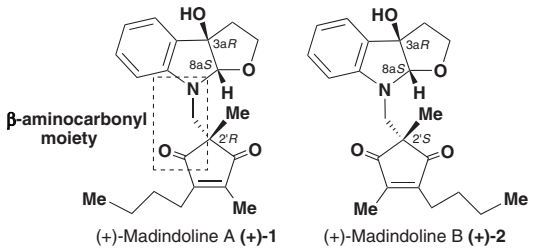


**Figure 1.** Structure of (+)-madindolines A (**1**) and B (**2**).

Our synthetic strategy for madindolines after second generation synthesis feature three-component coupling (−)-**3**, β-ketoester and formaldehyde (Scheme 1). Stereochemistry of the quaternary carbon of cyclopentenedione is not important to supply madindolines for bioassay, because both (+)-madindolines A and B show selective inhibitory activity of IL-6.

Before we embarked upon the synthesis of (+)-**1** and **2** via a third generation strategy, it was necessary to examine the general applicability of the Mannich reaction of acid-sensitive (−)-**3** with formaldehyde and ethyl

* Corresponding author. Tel.: +81 3 5791 6101; fax: +81 3 5791 6380; e-mail: omura-s@kitasato.or.jp

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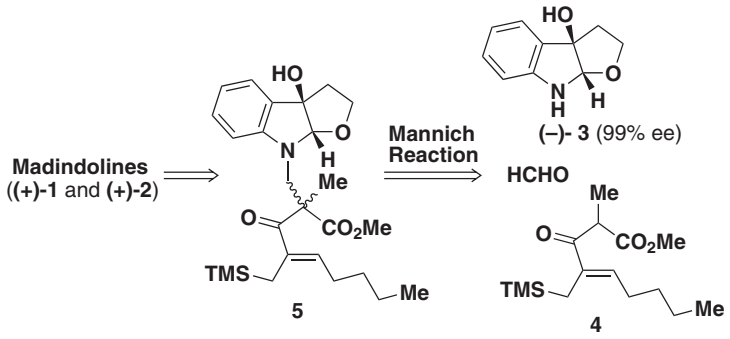
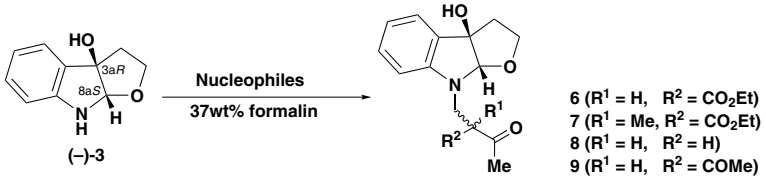
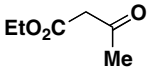
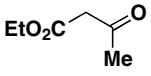
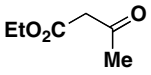
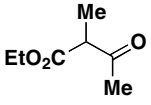
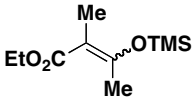
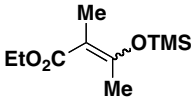
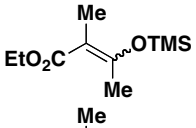
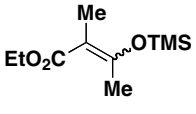
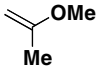
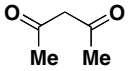
doi:10.1016/j.tetlet.2006.07.083




**Scheme 1.** Synthetic strategy of madindolines.

**Table 1.** Results and scope of Mannich reaction of 3a-hydroxyfuroindoline, nucleophiles and formaldehyde

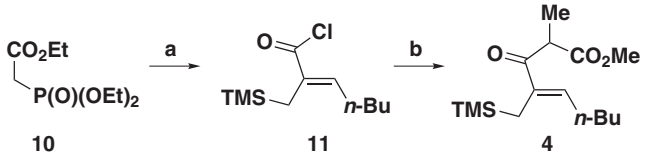



| Entry[a] | Nucleophiles | Conditions (acids, solvents) | Temperature; time | Results (yield%) |
|---|---|---|---|---|
| 1 |  | AcOH (1.0 equiv), EtOH | 0 °C; 1 h | Decomposed |
| 2 |  | Without acid, EtOH | 0 °C; 1 h | Decomposed |
| 3 |  | $Yb(DS)_3$ (0.1 equiv), $H_2O$ | 0 °C; 3 h | **6** (78%)[b,c] |
| 4 |  | $Yb(DS)_3$ (0.1 equiv), $H_2O$ | 0 °C; 3 h | **7** (Trace) |
| 5 |  | $Yb(DS)_3$ (0.1 equiv), $H_2O$ | rt; 1 day | No reaction[d] |
| 6 |  | $Sc(DS)_3$ (0.1 equiv), $H_2O$ | rt; 1 day | No reaction[d] |
| 7 |  | $Sc(OTf)_3$ (0.1 equiv) + $Yb(DS)_3$ (0.2 equiv), $H_2O$ | rt; 1 day | **7** (52%)[b,c] |
| 8 |  | $Sc(OTf)_3$ (0.1 equiv) + $Sc(DS)_3$ (0.2 equiv), $H_2O$ | rt; 1 day | **7** (97%)[b,c] |
| 9 |  | $Yb(DS)_3$ (0.1 equiv), $H_2O$ | 0 °C; 3 h | **8** (98%)[b] |
| 10 |  | $Yb(DS)_3$ (0.1 equiv), $H_2O$ | 0 °C; 3 h | **9** (Trace) |

[a] All the runs were carried out by using 3.0 equiv of nucleophiles and 1.0 equiv of 37 wt % formalin.
[b] Isolated yields.
[c] As a diastereomixture of the quaternary carbon center.
[d] Starting material was recovered.

acetoacetate or ethyl 2-methylacetoacetate. A series of experiments were carried out to identify appropriate reaction conditions and the results are listed in Table 1. When the reaction was carried out with or without AcOH in EtOH, (−)-**3** was quickly decomposed, and no desired product was observed (entries 1 and 2). Next, we tried to use a lanthanide-catalyzed Mannich reaction in aqueous media, which was developed by Kobayashi's group.[18,19] The reaction of (−)-**3** and acetoacetyl ester in the presence of 10 mol % of ytterbium tridodecylsulfate ($Yb(DS)_3$) proceeded smoothly at 0 °C to afford the desired **6** in satisfactory yield (entry 3). Though good yield was obtained in the case of acetoacetyl ester, the use of 2-methylacetoacetyl ester led to very low yield (entry 4). Thus, TMS enol ether of 2-methylacetoacetyl ester[20] was employed instead of 2-methylacetoacetyl ester in the presence of $Yb(DS)_3$ or scandium tridodecylsulfate ($Sc(DS)_3$). However, the reaction did not proceed completely (entries 5 and 6). The reaction was further carried out in the presence of 20 mol % of $Yb(DS)_3$ with another 10 mol % of $Sc(OTf)_3$, and comparable yield was obtained (entry 7). Moreover, the combination of 10 mol % of $Sc(OTf)_3$ and 20 mol % of $Sc(DS)_3$ led to desired **7** in almost quantitative yield (entry 8).[21] The other simple nucleophiles were also examined under the condition of 10% $Yb(OTf)_3$ in $H_2O$, and though excellent yield was obtained in the case of 2-methoxypropene as a nucleophile (entry 9), 2,4-pentadione was not produced under this condition (entry 10).

After achieving satisfactory yields for the Mannich reaction of (−)-**3** and 2-methylacetoacetate, we turned our attention to the applicability of the construction of β-amino carbonyl moiety of madindolines. We have already reported a practical method to prepare acid chloride (**11**) from commercially available **10** in four steps.[5,6] Therefore, allylsilane β-ketoester (**4**) was prepared from **11** by *C*-acylation with lithium enolate of methyl propionate in 67% yield (Scheme 2).




10 11 4

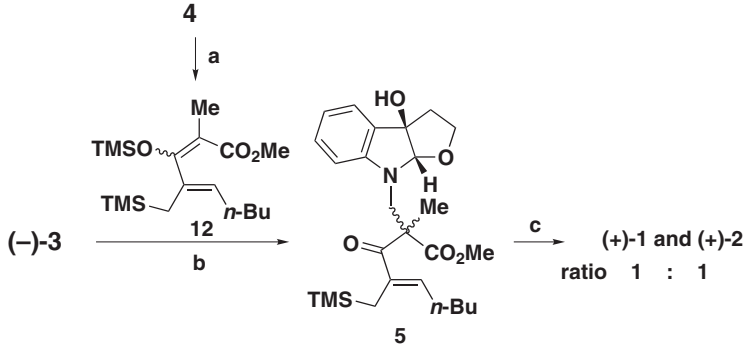
**Scheme 2.** Preparation of β-ketoester ether **4**: (a) Refs. 5,6; (b) methyl propionate, LDA, THF, −78 °C, 10 min, 67%.

We next tried a three-component Mannich reaction of (−)-**3** and TMS enolate of **4** under suitable conditions, as shown in Table 1, entry 8. At first, TMS enolate (**12**) was prepared by using LDA and TMSCl, then subjected to the next reaction without purification. Mannich reaction of (−)-**3**, formaldehyde and **12** in the presence of 10 mol % of $Sc(OTf)_3$ and 20 mol % of $Sc(DS)_3$ led to Mannich adduct (**5**) in 11% yield.[22] Though many examinations of this reaction condition were carried out, we could not improve this yield. We suspect that this is caused by instability of **12** against Lewis acids, and high hydrophobicity of **12** may be difficult to approach scandium atom as the active center of the micelle complex of $Sc(DS)_3$ and $Sc(OTf)_3$. Finally, an intramolecular *endo* cyclization of allylsilane (**5**) using tris(dimethylamino)sulfur(trimethylsilyl)difluoride (TAS-F), directly led to (+)-madindolines A (**1**) and B (**2**) in 39% and 38% yields, respectively (Scheme 3).[23] Synthetic (+)-**1** and (+)-**2** were very easy to separate and purify by standard separation conditions (Preparative TLC; hexane–ethyl acetate = 1:1) from the crude reaction mixture and identical in all respects with authentic (+)-**1** and (+)-**2**.

In conclusion, the third generation synthesis of (+)-madindolines A and B, has been achieved via a convergent strategy involving a three-component Mannich reaction (two linear steps from optically active (−)-3a-hydroxyfuroindoline (99% ee) (**3**) or eight linear steps from commercially available **10**). This synthetic route not only provides quick access to madindolines, but also broadens the chemical diversity of madindoline libraries. We believe that chemical diversity of madindolines will accelerate biological evaluation and lead to the discovery of a more potent IL-6 inhibitor.

## Acknowledgements

This work was supported by a Grant from the 21st Century COE Program, Ministry of Education, Culture, Sports, Science and Technology. We also thank Ms.




**Scheme 3.** Mannich reaction of (−)-**3** and **12**, and final cyclization. Reagents and conditions: (a) TMSCl, LDA, $Et_3N$, THF, −78 °C, 30 min; (b) **12**, 37 wt % formalin, $Sc(OTf)_3$, $Sc(DS)_3$, $H_2O$, rt, 24 h, 11%; (c) TAS-F, DMF, rt, 20 min, 39% for (+)-**1**, 38% for (+)-**2**.

A. Nakagawa, Ms. C. Sakabe and Ms. N. Sato for various instrumental analyses.

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21. Experimental procedure of preparation of (3a*R*,8a*S*)-3a-hydroxy-8-(2-methoxycarbonyl-2-methyl-3-oxobutyl)-3,3a,8,8a-tetrahydro-2*H*-furo[2,3-*b*]indole (**7**): (−)-**3** (51.6 mg, 0.291 mmol) was dissolved in a solution of $Sc(DS)_3$ (49.0 mg, 0.0582 mmol), $Sc(OTf)_3$ (14.3 mg, 0.0291 mmol), 37 wt % formalin (24 μL, 0.291 mmol) and 2-methyl-3-trimethylsilyloxy)-2-butenoic acid ethyl ester (188.9 mg, 0.873 mmol) in $H_2O$ (1.8 mL) at room temperature. The resulting reaction mixture was stirred for 24 h. The reaction mixture was quenched with satd aq $NaHCO_3$ solution (2.0 mL) and extracted with EtOAc (×3). The combined organic layers were washed with brine (×1), dried over $Na_2SO_4$, filtered and concentrated. The crude product was purified by preparative TLC ($CHCl_3$–acetone 2:1) to afford Mannich adduct **7** (94.1 mg, 97%) as a light brown oil; $R_f$ 0.57 ($CHCl_3$–acetone 2:1); IR (KBr) 3436 (OH), 1737 (–OC=O), 1710 (C=O), 1612, 1487, 1462 (arom.) $cm^{-1}$; NMR data for one of the diastereomer of **7**, $^1H$ NMR (270 MHz, $CDCl_3$) $\delta$ 7.22 (1H, d, $J = 7.3$ Hz, 4-H), 7.12 (1H, dd, $J = 7.9$, 7.6 Hz, 6-H), 6.70 (1H, dd, $J = 7.6$, 7.3 Hz, 5-H), 6.40 (1H, d, $J = 7.9$ Hz, 7-H), 5.03 (1H, s, 8a-H), 4.17 (2H, q, $J = 7.3$ Hz, $OCH_2CH_3$), 4.11 (1H, d, $J = 14.8$ Hz, 1′-H), 3.85 (1H, m, 2-H), 3.68 (1H, d, $J = 14.8$ Hz, 1′-H), 2.84 (1H, m, 2-H), 2.84 (1H, br s, OH), 2.34, 2.24 (each 1H, m, 3-$H_2$), 2.17 (3H, s, 4′-$H_3$), 1.39 (3H, s, 2′-$CH_3$), 1.25 (3H, t, $J = 7.3$ Hz, $OCH_2CH_3$); $^{13}C$ NMR (6.75 MHz, $CDCl_3$) $\delta$ 205.2 (C-3′), 172.1 (2′-$COOCH_2CH_3$) 151.1 (C-7a), 130.0 (C-3b), 130.0 (C-6), 123.8 (C-4), 118.4 (C-5), 106.5 (C-7), 104.5 (C-8a), 87.6 (C-3a), 66.9 (C-2), 61.6 ($OCH_2CH_3$), 60.4 (C-2′), 47.9 (C-1′), 41.2 (C-3), 26.5 (C-4′), 18.6 (2′-$CH_3$) 13.9 ($OCH_2CH_3$); HR-MS (FAB, NBA matrix) *m*/*z*: 333.1600 $[M]^+$, calcd for $C_{18}H_{23}O_5N$: 333.1576 [M].
22. Mannich adduct **5** as a light brown oil; $R_f$ 0.53 ($CHCl_3$–acetone 5:1); IR (KBr) 3438 (OH), 1740 (OC=O), 1728 (C=C–*C*=O), 1661 (C=C), 1616, 1487, 1464 (arom.) $cm^{-1}$; NMR data for one of the diastereomer of **5**, $^1H$ NMR (270 MHz, $CDCl_3$) $\delta$ 7.16 (1H, d, $J = 7.3$ Hz, 4-H), 7.13 (1H, dd, $J = 7.9$, 7.3 Hz, 6-H), 6.69 (1H, dd, $J = 7.3$, 7.3 Hz, 5-H), 6.44 (1H, d, $J = 7.9$ Hz, 7-H), 6.28 (1H, t, $J = 7.3$ Hz, 5′-H), 5.08 (1H, s, 8a-H), 4.13 (1H, d, $J = 15.2$ Hz, 1′-H), 3.97 (1H, m, 2-H), 3.63 (3H, s, $OCH_3$), 3.61 (1H, d, $J = 15.2$ Hz, 1′-H), 3.38 (1H, m, 2-H), 2.44, 2.25 (each 1H, m, 3-$H_2$), 2.14 (2H, m, 6′-$H_2$), 1.84, 1.73 (each 1H, d, $J = 13.5$ Hz, $CH_2Si(CH_3)_3$), 1.61 (3H, s, 2′-$CH_3$), 1.36 (4H, m, 7′-, 8′-$H_2$), 0.93 (3H, t, $J = 6.9$ Hz, 9′-$H_3$), 0.86 (9H, s, $Si[(CH_3)_2]C(CH_3)_3$), 0.00 (9H, s, $Si(CH_3)_3$), −0.12, −0.16 (each 3H, s, $Si[(CH_3)_2]C(CH_3)_3$); $^{13}C$ NMR (67.5 MHz, $CDCl_3$) $\delta$: 199.3 (C-3′), 175.2 (2′-$COOCH_3$), 153.0 (C-7a), 140.5 (C-5′), 138.8 (C-4′), 131.6 (C-3b), 130.7 (C-6), 125.4 (C-4), 119.0 (C-5), 107.5 (C-7), 103.6 (C-8a), 90.6 (C-3a), 67.6 (C-2), 58.5 (C-2′), 54.1 (C-1′), 53.2 (2′-$COOCH_3$), 44.9 (C-3), 31.8 (C-7′), 30.5 (C-6′), 26.6 ($Si[(CH_3)_2]C(CH_3)_3$), 23.4 (C-8′), 22.6 (2′-$CH_3$), 18.9 ($Si[(CH_3)_2]C(CH_3)_3$), 17.6 ($CH_2Si(CH_3)_3$), 14.8 (C-9′), 0.0 ($Si(CH_3)_3$), −2.3, −2.9 ($Si[(CH_3)_2]C(CH_3)_3$); HR-MS (FAB, NBA matrix) *m*/*z*: 496.25 $[M+Na]^+$, calcd for $C_{26}H_{39}O_5NSiNa$: 496.2495 [M+Na].
23. Experimental procedure of preparation of (+)-madindolines A (**1**) and B (**2**): At room temperature, a solution of **5** (4.3 mg, 9.08 μmol) in DMF (0.91 ml) was treated with tris(dimethylamino)sulfur(trimethylsilyl)difluoride (12.5 mg, 0.0455 mmol). The reaction mixture was stirred for 20 min, and then quenched with $H_2O$ (2 ml), extracted with hexane–EtOAc (1:1) solution (×3), and the combined extracts were washed with brine (×1), dried over $Na_2SO_4$, filtered and concentrated. Preparative TLC (hexane–EtOAc 1:1) furnished (+)-madindoline A (+)-**1** (1.3 mg, 39%) as a light yellow crystal and (+)-madindoline B (+)-**2** (1.1 mg, 38%) also as a light yellow crystal: All physical data for (+)-**1** and (+)-**2** were matched with the data of synthetic (+)-madindolines in our previous papers (Refs. 4–6).