Total Synthesis of (+)-Madindoline A and (−)-Madindoline B, Potent, Selective Inhibitors of Interleukin 6. Determination of the Relative and Absolute Configurations

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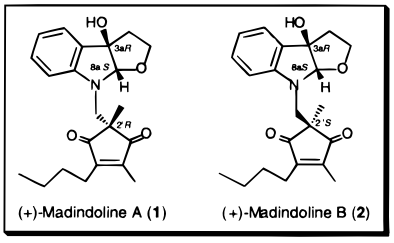
Interleukin 6 (IL-6), a multifunctional cytokine, plays a central regulatory role in host defense mechanisms.[1] However, in tumor cells IL-6 stimulates cell proliferation in an autocrine/paracrine manner and is responsible for much of the metabolic change known as cancer cachexia.[2] Control of IL-6 activity thus holds great promise both for the suppression of IL-6-dependent tumor cell growth and for the relief of cancer cachexia.[3]

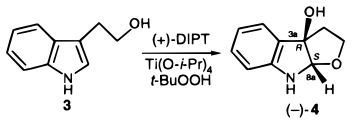
In our program to discover new IL-6 modulators, we recently reported the isolation and planar structures of (+)-madindolines A and B (**1** and **2**),[4] novel antibiotics comprised of a 3a-hydroxyfuroindoline ring connected at nitrogen via a methylene bridge to a cyclopentene-1,3-dione ring. Structural assignments were based on extensive 1- and 2-D NMR studies, in conjunction with IR, UV, and MS data; the relative and absolute configurations, however, remained undefined. Bioassays revealed potent, selective inhibition of IL-6 activity in the IL-6-dependent cell line MH60; importantly the response was dose-dependent.[4] In addition, (+)-madindoline A (**1**), the more potent congener, inhibited the differentiation of osteoblast cells.[4] Preliminary studies suggest that **1** interacts with the IL-6 receptor.[5] Unfortunately, the original source, *Streptomyces nitrosporeus* K93-0711, no longer produces these antibiotics.[5]



Intrigued by the novel architecture, the significant IL-6 inhibitory activity, and the scarcity of these natural products, we recently undertook their total synthesis. Herein we report the first total synthesis and assignment of the relative and absolute configurations of (+)-madindoline A (**1**) and (−)-madindoline B (**2**), the latter the enantiomer of natural madindoline B (vide infra).

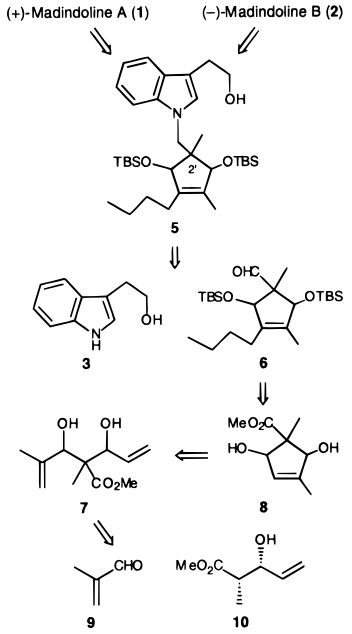
As prelude to total synthesis, we devised an efficient, asymmetric synthesis of the 3a-hydroxyfuroindoline ring system.[6] On the basis of our observation that *m*-CPBA oxidation of tryptophol (**3**) furnished 3a-hydroxyfuroindoline (**4**) in 75% yield, we explored the Sharpless asymmetric epoxidation protocol.[7] Stoichiometric oxidation [2.5 equiv *t*-BuOOH, 1.2 equiv (+)-DIPT, 1.0 equiv Ti(O*i*-Pr)$_4$, CH_2Cl_2 (0.01 M)] for 6 h at −20 °C led to (−)-**4**[8] in 72% yield and 99% ee (Scheme 1); catalytic protocols proved less effective (e.g., 37% yield; 28% ee). The absolute configuration of (−)-**4** (3a*R*,8a*S*), determined by single-crystal X-ray analysis of the *N*-methyl-*O*-MTPA ester, proved consistent with the Sharpless epoxidation mnemonic.[7]

Scheme 1



Having secured a viable asymmetric protocol to access the 3a-hydroxyfuroindoline ring, we envisioned the total synthesis of **1** and **2** to entail reductive coupling of aldehyde **6** (Scheme 2) with tryptophol (**3**), followed by the stereocontrolled introduction of the 3a-hydroxyfuroindoline ring, exploiting the Sharpless protocol. Aldehyde **6** in turn would derive from **8**, the product of a ring-closing metathesis reaction[9] on diene **7**, followed by conjugate introduction of an *n*-butyl group and oxidation state adjustments. Diene **7** required for ring metathesis would be constructed beginning with an initial Evans asymmetric aldol[10] on acrolein

Scheme 2



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(2) Strassmann, G.; Masui, Y.; Chizzoniti, R.; Fong, M. *J. Immunology* **1993**, *150*, 2341−2345 and references therein.

(3) Stein, B.; Kung Sutherland, M. S. *Drug Discovery Today* **1998**, *3*, 202.

(4) (a) Hayashi, M.; Kim, Y.-P.; Takamatsu, S.; Enomoto, A.; Shinose, M.; Takahashi, Y.; Tanaka, H.; Komiyama, K.; Ōmura, S. *J. Antibiot.* **1996**, *49*, 1091. (b) Takamatsu, S.; Kim, Y.-P.; Enomoto, A.; Hayashi, M.; Tanaka, H.; Komiyama, K.; Ōmura, S. *J. Antibiot.* **1997**, *50*, 1069.

(5) Hayashi, M., unpublished results.

(6) Racemic 3a-hydroxyfuroindoline (±)-**4** had been prepared previously by photosensitized oxygenation of tryptophol (**3**), see: Saito, I.; Imuta, M.; Nakada, A.; Matsugo, S.; Matsuura, T. *Photochem. Photobiol.* **1978**, *28*, 531 and references therein.

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(8) The structural assignment to each new compound is in accord with its IR, ^{1}H, and ^{13}C, and high-resolution mass spectra.

(9) For recent reviews, see: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (b) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371.

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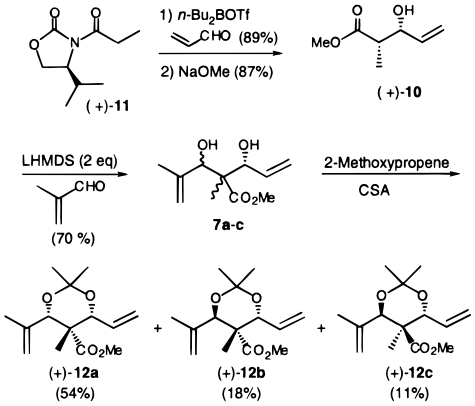
to furnish **10**; a second diastereoselective aldol[11] with methacrolein would complete the diene synthesis, establishing the key stereogenicity at C(2′). Importantly, this strategy held the promise of controlled access to each of the possible stereoisomers of the madindoline skeleton, thereby permitting establishment of the relative and absolute configurations of **1** and **2**.

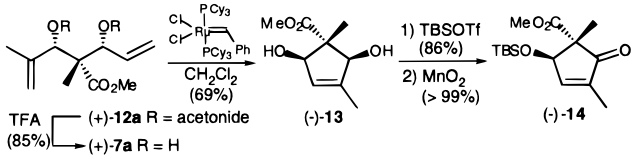
With this scenario in mind, aldol reaction of oxazolidinone (+)-**11**[10,12] with acrolein proceeded in 89% yield with >99% de (Scheme 3); methanolysis afforded *β*-hydroxyester (+)-**10**.[8] A second aldol with methacrolein,[11] furnished a difficultly separable mixture of diols (**7a**−**c**) in 70% yield. To establish the relative stereochemistry of **7a**−**c**, the corresponding 1,3-acetonides **12a**−**c**[8] were prepared and separated by flash chromatography; NOE analysis permitted stereochemical assignment.

Scheme 3



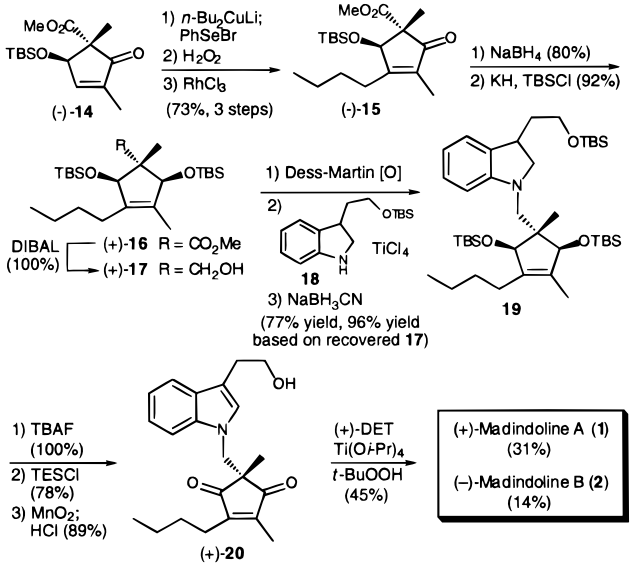
Hydrolysis of the major acetonide (+)-**12a** (Scheme 4), followed by ring-closing metathesis[9] of (+)-**7a**[8] (0.2 equiv Grubbs catalyst, CH_2Cl_2) furnished cyclopentene (−)-**13**[8] in 69% yield. Selective silylation (TBSOTf) of the less hindered allylic hydroxyl and oxidation (MnO_2) then provided (−)-**14**[8] in 86% yield (2 steps). For material advancement, the mixture of diols (**7a**−**c**) was subjected directly to metathesis, protection, and oxidation; flash chromatography afforded (−)-**14** in 53% overall yield.

Scheme 4



Continuing with the synthesis, conjugate addition (*n*-Bu_2CuLi) (Scheme 5), followed by phenylselenylation (PhSeBr) of the derived enolate, and oxidative elimination (H_2O_2) furnished a mixture comprised of (−)-**15** and the exomethylene isomer (1:1). Treatment of the mixture with $RhCl_3$ converted the exo congener to (−)-**15**;[8] the overall yield for the three steps was 73%. Stereoselective reduction of (−)-**15** ($NaBH_4$),[8,13] silylation (TBSCl, KH), and reduction (DIBAL) to furnish (+)-**17**[8] (74%, 3 steps), set the stage for elaboration of the aldehyde and reductive coupling to tryptophol. Toward this end, the oxidation (Dess−Martin)[14] of (+)-**17** proceeded smoothly; however, all attempts to achieve reductive coupling of the derived aldehyde with tryptophol proved unsuccessful. Formation of the intermediate imine appeared to be the problem, presumably due to the poor nucleophilicity of the indole nitrogen. With the more nucleophilic indoline (**18**),

Scheme 5



reductive alkylation ($TiCl_4$, benzene; $NaBH_3CN$, MeOH)[15] furnished **19**[8] in 77% yield as a diastereomeric mixture.

Having achieved the union of (+)-**17** with indoline, all that remained to arrive at the madindolines was generation of the enedione and indole moieties and elaboration of the 3a-hydroxyfuroindoline ring. To this end, removal of the silyl groups in **19** (TBAF; 100% yield), followed in turn by selective silylation of the primary hydroxyl (TESCl; 78% yield), oxidation (MnO_2) and acid hydrolysis (89% yield, 2 steps) afforded indole (+)-**20**.[8] Oxidative ring-closure of (+)-**20** [(+)-DET, Ti(O*i*-Pr)$_4$, *t*-BuOOH] then yielded (+)-madindoline A (**1**) and (−)-madindoline B (**2**)[8] (2.2:1, 45% yield).[16] Synthetic crystalline (+)-madindoline A (**1**) was identical in all respects with natural (+)-**1** [400 MHz ^{1}H and 100 MHz ^{13}C NMR, IR, HRMS, optical rotation, mp, mmp].

Synthetic (−)-madindoline B (**2**) was also identical with natural madindoline B in all respects, except for the chiroptical properties {$[\alpha]^{29}_D$ −30.0° (*c* 0.03 MeOH); natural, $[\alpha]^{24}_D$ +25.6° (*c* 0.3 MeOH)}. Thus, (−)-madindoline B (**2**) is the enantiomer of natural (+)-**2**.[17] Confirmation of the relative configurations in **1** and **2** was achieved by X-ray analysis of synthetic (+)-**1**.

In summary, the first total synthesis of (+)-madindoline A (**1**) and (−)-madindoline B (**2**), has been achieved via an efficient and convergent strategy (19 linear steps, 7.8% overall yield). The synthetic route not only provides ready access to these rare natural products, but also defines for the first time their relative and absolute configurations. Further refinements of the synthetic scheme and preparation of analogues for biological evaluation will be reported in due course.

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Supporting Information Available: Experimental procedures and spectroscopic and analytical data for relevant compounds (PDF). This material is avilable free of charge via the Internet at http://pubs.acs.org.

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(12) The absolute stereochemistry of **11** was randomly selected.
(13) Stereoselectivity presumably derives from the OTBS moiety.
(14) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
(15) White, W. A.; Weingarten, H. *J. Org. Chem.* **1967**, *32*, 213.
(16) Use of (−)-DET furnished (+)-**1** and (−)-**2** in 15 and 34% yield, respectively. The lower selectivity vis-á-vis the model oxidation is presumably due to increased steric hindrance and/or the presence of the additional stereogenic centers in (+)-**20**. Oxidation with *m*-CPBA furnished a 1:1 mixture of (+)-**1** and (−)-**2**.
(17) The absolute configuration therefore of natural (+)-madindoline A is 3a*R*,8a*S*,2′*R* and (+)-madindoline B is 3a*R*,8a*S*,2′*S*.