ORGANIC LETTERS

2002
Vol. 4, No. 14
2337−2340

Synthesis of (±)-Madindolines and Chemical Models. Studies of Chemical Reactivity

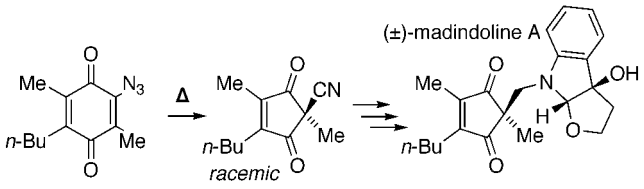
Casey C. McComas,[†] Joe B. Perales, and David L. Van Vranken*

Department of Chemistry, University of California, Irvine, California 92697-2025

dlvanvra@uci.edu

Received April 15, 2002

ABSTRACT



The madindolines are believed to inhibit cytokine signaling through the gp130 receptor. Model compounds of madindolines were synthesized and tested for thiol reactivity. The heterocyclic moiety of madindoline was shown to form thiol adducts via the Savige–Fontana reaction. The enedione moiety was found to be unreactive toward simple thiols unless the quaternary center was removed. Using the powerful Moore reaction, we have synthesized (±)-madindoline A and B in 11 steps.

In 1996, two metabolites of *Streptomyces nitrosporeus* K93-0711 were shown to selectively inhibit the growth of IL-6-dependent cell lines.[1] Madindoline A and B possess the same tricyclic indoline moiety but differ in the position of the butyl and methyl groups on the cyclopentene ring. The importance of the madindolines is their selectivity; they inhibit signaling through IL-6 and IL-11 but not IL-2, IL-4, IL-8, or LIF. An elegant series of inhibition experiments points to the extracellular domain of gp130 as the target of madindoline.[2]

The extracellular domain of gp130 has two free cysteines (Cys279 and Cys469) that are hypothesized to form a disulfide during cytokine activation.[3] The structure of madindoline is reminiscent of two key functional groups that are known to react with cysteine thiols: maleimides and 3a-hydroxypyrrolidino-indolines. In light of these circumstantial facts, it is conceivable that madindoline could act covalently on its target. We set out to create models of madindoline, study their thiol reactivity, and use the chemistry to synthesize madindolines A and B.

Streptomyces nitrosporeus K93-0711 has stopped producing madindolines, so new material must be obtained by total synthesis.[4] Quaternary centers represent a continuing challenge for synthetic organic chemistry, and the quaternary center of madindoline proves to be a major obstacle. There are three elegant enantioselective syntheses of madindoline A.[4,5] We hoped to exploit the powerful Moore ring contraction of azidoquinones to construct models of the madindolines and ultimately the natural products.

Under acidic conditions, cysteine thiols in peptides and proteins react with 3a-hydroxypyrrolidino[2,3-*b*]indolines derived from tryptophan, leading to irreversible formation of tryptathionine cross-links (the Savige−Fontana reaction, Scheme 1).[6] Saito has shown that tetrahydrofuro[2,3-*b*]indol-

[†] Scripps Research Institute.

(1) (a) Hayashi, M.; Kim, Y. P.; Takamatsu, S.; Enomoto, A.; Shinose, M.; Takahashi, Y.; Tanaka, H.; Komiyama, K.; Omura, S. *J. Antibiot.* **1996**, *49*, 1091−5. (b) Takamatsu, S.; Kim, Y. P.; Enomoto, A.; Hayashi, M.; Tanaka, H.; Komiyama, K.; Omura, S. *J. Antibiot.* **1997**, *50*, 1069−72.

(2) Omura, S.; Hayashi, M.; Tomoda, H. *Pure Appl. Chem.* **1999**, *71*, 1673−81.

(3) Moritz, R. L.; Hall, N. E.; Connolly, L. M.; Simpson, R. J. *J. Biol. Chem.* **2001**, *276*, 8244−53.

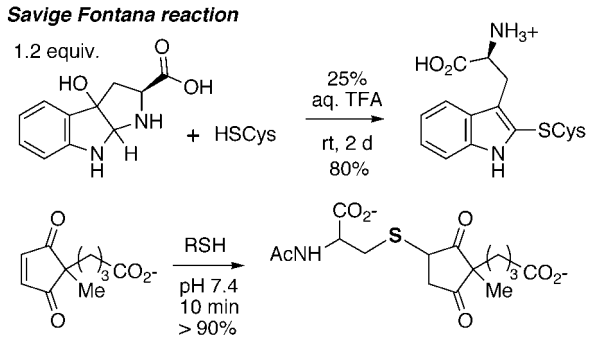
(4) Sunazuka, T.; Hirose, T.; Shirahata, T.; Harigaya, Y.; Hayashi, M.; Komiyama, K.; Omura, S.; Smith, A. B., III. *J. Am. Chem. Soc.* **2000**, *122*, 2122−3.

(5) (a) Hosokawa, S.; Sekiguchi, K.; Hayase, K.; Hirukawa, Y.; Kobayashi, S. *Tetrahedron Lett.* **2000**, *41*, 6435−9. (c) Hosokawa, S.; Sekiguchi, K.; Enemoto, M.; Kobayashi, S. *Tetrahedron Lett* **2000**, *41*, 6429−33. (c) Hirose, T.; Sunuzaka, T.; Shirata, T.; Yamamoto, D.; Harigaya, Y.; Kuwajima, I.; Omura, S. *Org. Lett.*, **2002**, *4*, 501−3.

10.1021/ol026015e CCC: $22.00
Published on Web 06/13/2002

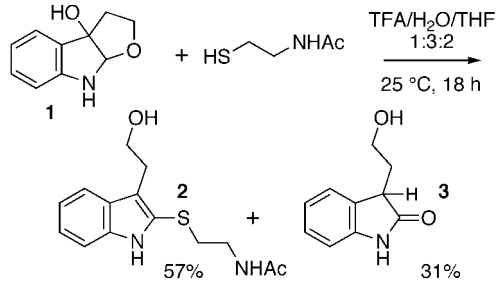
3a-ol **1** reacts with tryptophan in the presence of Lewis acids to form 2,2′-biindole cross-links.[7] In theory, the heterocyclic moiety of madindoline could react with either tryptophan or cysteine side chains.

Scheme 1. Precedent for the Thiophilicity of Madindoline Subunits



Under acidic conditions indoline **1** condenses with *N*-acetylcysteamine to produce the adduct **2** in 57% yield (Scheme 2). Water competes with the thiol so the corresponding oxindole was also isolated in 31% yield. The Savige−Fontana reaction of indoline **1** does not proceed at an appreciable rate at pH 7.4, consistent with the highly specific biological profile of madindoline.

Scheme 2. Savige−Fontana Reaction of Indoline **1**

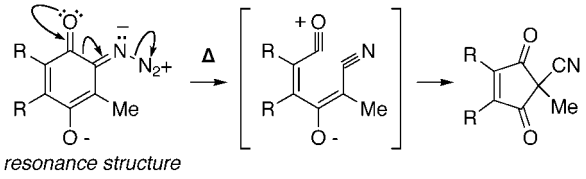


N-Alkylmaleimides exhibit exceptional reactivity and selectivity toward protein thiols. Miyadera has compared the reactivity of *N*-ethylmaleimide with its 3,4-dimethyl analogue and shown that the extra methyl groups slow the brisk reaction rate by over 5 orders of magnitude.[8] While the rates are undoubtedly slowed, 3,4-dialkylmaleimides still form cysteine[9] and glutathione[10] adducts under physiological conditions. Substituents on the 3 and 4 positions of the maleimide tetramethrin destabilize 1,4-thiol adducts, yet covalent bond formation has been proposed to account for the high potency of tetramethrin toward insect ion channels.[10] The alkyl substituents on the cyclopent-4-ene-1,3-dione moiety of madindoline should slow the rate of Michael addition, conferring the selectivity observed in the biological studies.

Billington and co-workers have shown that cyclopent-4-ene-1,3-diones, close analogues of maleimides, also react rapidly in high yield with *N*-acetylcysteine at pH 7.4 (Scheme 1).[11] However, based on analogy to studies of maleimides, it is expected that the methyl and butyl substituents of madindoline should slow thiol addition.

To test the potential thiophilicity of the madindoline cyclopentene unit, a symmeterical analogue was needed that would simplify the studies with thiols. The Moore azidoquinone ring contraction offers an ideal approach to these analogues.[12] The mechanism of the Moore rearrangement (Scheme 3) is believed to involve formation of a zwitterionic acylium-enolate that rapidly cyclizes.

Scheme 3. Mechanism of the Moore Reaction



The symmetrical dione **6**[13] was constructed using the Moore azidoquinone ring contraction (Scheme 4). In theory the Moore rearrangement could proceed in situ during the azide substitution reaction. However, the addition−elimination with sodium azide was most effective in alcoholic solvents, whereas the Moore rearrangement was most effective in nonpolar, nonnucleophilic solvents. Since the azidoquinone deflagrates on heating it was carried directly to the rearrangement without separation from unreacted starting material.

When madindoline model **6** was treated with 1 equiv of *N*-acetylcysteamine, the thiol adduct **8** was formed in 15% yield (as an inseparable mixture of diastereomers) along with starting material and other products (Scheme 5). However, the more complete model **7** failed to form thiol adducts, even when heated. Thus, all three alkyl substituents on madindoline conspire to inhibit nonspecific Michael addition by thiols.

(6) (a) Savige, W. E.; Fontana, A. *J. Chem. Soc., Chem. Commun.* **1976**, 600−1. (b) Savige, W. E.; Fontana, A. *Int. J. Pept. Protein Res.* **1980**, *15*, 102−12. (c) Wieland, T. B., B.; Zanotti, G. *Chem. Pept. Proteins* **1989**, *4*, 95−100.

(7) Saito, I.; Morii, T.; Matsugo, S.; Matsuura, T. *J. Chem. Soc., Chem. Commun.* **1982**, 977−9.

(8) Miyadera, T.; Kosower, E. M.; Kosower, N. S. *J. Med. Chem.* **1971**, *14*.

(9) Tressl, R.; Wondrak, G.; Kersten, E.; Rewicki, D. *J. Agric. Food Chem.* **1994**, *42*, 2692−7.

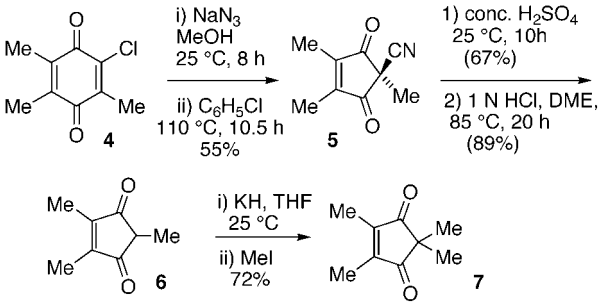
(10) Smith, I. H.; Wood, E. J.; Casida, J. E. *J. Agric. Food Chem.* **1982**, *30*, 598−600.

(11) Billington, S.; Mann, J.; Quazi, P.; Alexander, R.; Eaton, M. A. W.; Millar, K.; Millican, A. *Tetrahedron* **1991**, *47*, 5231−6.

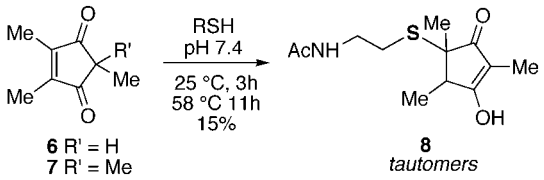
(12) (a) Moore, H. W.; Shelden, H. R. *J. Org. Chem.* **1968**, *33*, 4019−24. (b) Moore, H. W.; Weyler, W., Jr.; Shelden, H. R. *Tetrahedron Lett.* **1969**, 3947−50. (c) Weyler, W., Jr.; Pearce, D. S.; Moore, H. W. *J. Am. Chem. Soc.* **1973**, *95*, 2603−10. (d) Hamdan, A. J.; Moore, H. W. *Heterocycles* **1989**, *29*, 51−6.

(13) Cyclopent-4-ene-1,3-diones have been broadly patented for fragrance applications; dione **7** lacks fragrant properties. Isaac, B. O.; Chan, C. O.; Marr, I. M. U.S. Patent 5,407,910, 1995.

Scheme 4. Synthesis of Models of Madindoline Cyclopent-4-ene-1,3-dione

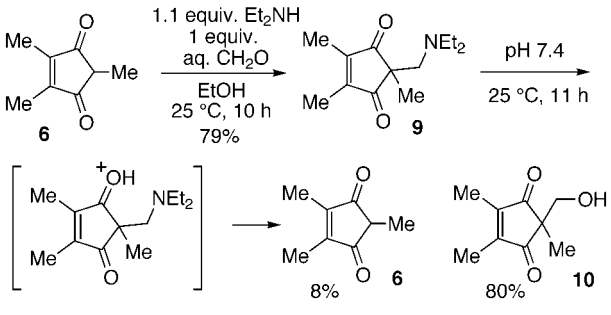


Scheme 5. Thiol Addition to Cyclopent-4-ene-1,3-diones



1,3-Diketones that form stable enols are poor substrates for Mannich reactions because of a sparing equilibrium and the extreme facility of retro-Mannich fragmentation.[14] Cyclopentane-1,3-dione, which exists as the enol tautomer, does not form stable Mannich products under acidic or basic conditions. In contrast, cyclopentene-1,3-diones such as **6** exist in the keto form. Gas-phase DFT calculations (SVWN/DN*) predict that the 4,5-double bond of 1,3-dione **6** destabilizes the enol tautomer by over 17 kcal/mol,[15] and not surprisingly, diketone **6** readily forms a Mannich adduct with diethylamine under basic conditions (Scheme 6). However, the Mannich product **9** is unstable under aqueous conditions. Presumably, retro-Mannich cleavage of madindoline is inhibited by the presence of the double bond in the cyclopentenedione moiety and the attenuated reactivity of the indoline nitrogen.

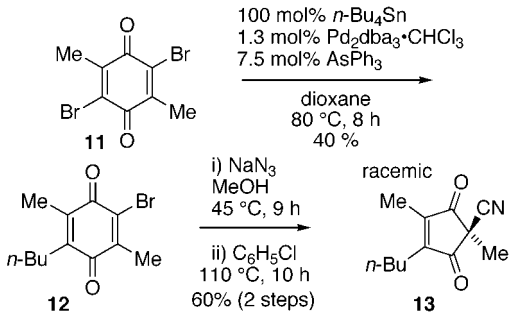
Scheme 6. Mannich and Retro-Mannich Reactions of Cyclopent-4-ene-1,3-diones



A Mannich reaction between an indoline and a cyclopent-4-ene-1,3-dione could offer a simple approach to synthesize racemic madindolines. Unfortunately, an attempted Mannich reaction of enedione **6** with indoline and formalin led to rapid generation of the *N*,*N*-aminal and decomposition of the enedione. Even though the Mannich approach appeared untenable we hoped to exploit the Moore rearrangement by retaining the nitrile carbon and using it to form the key neopentyl linkage of madindoline.

For the synthesis of the madindolines, the required *n*-butyl substituent was introduced through a statistical Stille reaction of 2,5-dibromo-3,6-dimethylbenzoquinone (Scheme 7). What this approach lacked in efficiency it made up for in directness. The bromoquinone **12** was substituted with azide and heated to induce rearrangement. Thus, a fully functionalized cyclopentene core was available in three steps from the readily available dibromoquinone **11**.

Scheme 7. Application of the Moore Azidoquinone Ring Contraction to Construction of the Madindoline Core



The cyclization step sets the stereochemistry of the cyclopentene moiety. In theory a metal coordinated to the nitrile could exert enantiocontrol in the cyclization step; the gold-catalyzed aldol reaction of isonitrile enolates generates high levels of enantioselection through this kind of coordination.[16] Unfortunately, attempts to induce the Moore rearrangement using transition metals such as $Rh_2(OAc)_4$ and $Cu(OTf)_2$ were ineffective at accelerating the Moore reaction.[17] Thus, the Moore reaction is promising for the construction of symmetric cyclopentenediones rather than asymmetric cyclopentenediones.

One price to be paid for such a direct route comes in the attachment to the indoline ring system. Sadly, the nitrogen present in the cyano group could not be incorporated into the indoline ring system. Thus, the carbonyl groups were protected by stereoselective Luche reduction and TBS ether formation. Nitrile **14** was reduced to aldehyde **15** and coupled to the indoline moiety using the reductive amination approach developed by Smith and Omura in the first synthesis.[4]

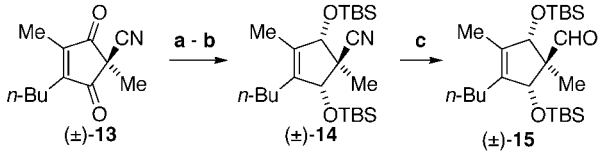
(14) (a) Hellmann, H.; Opitz, G. α-*Aminoalkylierung*. Verlag: Weinheim, 1960; p 214. (b) Levchenko, N. K.; Sviridova, A. P.; Segal, G. M.; Torgov, I. V. *J. Chem. Res. Miniprint* **1978**, 5001−27.

(15) There is no evidence of the enol in the IR spectrum of diketone **6**.

(16) Hayashi, T.; Sawamura, M.; Ito, Y. *Tetrahedron* **1999**, *48*, 1999−2012.

(17) Azidoquinones have been shown to participate in metal-catalyzed intramolecular nitrene-like cycloadditions with tethered dienes. However, Moore rearrangement products were not reported in these studies. Naruta, Yoshinori; Nagai, Naoshi; Arita, Yoshihiro; Maruyama, Kazuhiro *J. Org. Chem.* **1987**, *52*, 3956−3967.

Scheme 8. Synthesis of Key Aldehyde (±)-**15**[a]



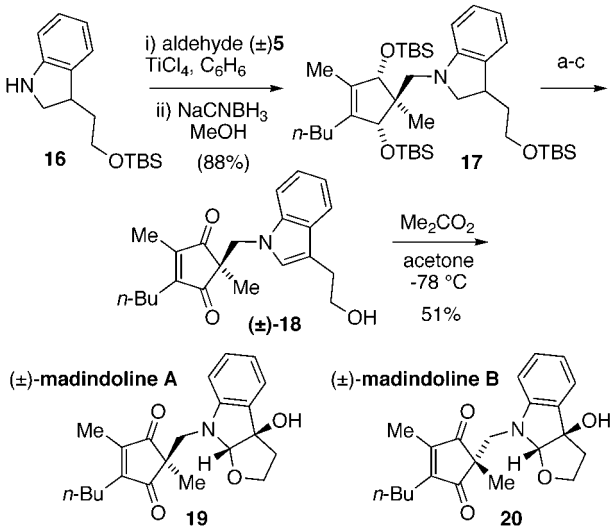
[a] Conditions: (a) $NaBH_4$, $CeCl_3 \cdot 7H_2O$ (89%), (b) TBSOTf, 2,6,-lutidine, DMF (91%), (c) DIBAL-H (84%).

Aldehyde (+)-**15** was used by Smith and co-workers in the synthesis of (+)-madindoline A. We followed the Smith route to complete the synthesis of madindolines A and B. The final oxidative cyclization under Sharpless conditions proceeds in modest yield with only 38% stereoselection. Thus, even under ideal conditons, we would not be able to obtain optically pure material using the Sharpless reaction. Instead, the more reliable DMDO oxidation was employed in the final oxidative cyclization. Madindoline A **19**, the more active isomer, was formed in preference to madindoline B **20** in a 80:20 ratio.

The level of stereoselection is somewhat surprising when one considers that the asymmetry in the starting material is solely due to the methyl and butyl substituents, far removed from the indole ring.

Cysteines have been implicated in the mechanism of gp130 signaling, so two substructural models of madindoline were prepared and their reactivity toward thiols was studied. The furanoindoline core of the madindolines was shown to cross-link with thiols via a Savige−Fontana reaction. We have used the Moore azidoquinone ring contraction to synthesize (±)-madindoline A, (±)-madindoline B, and model compounds. The Moore reaction allowed rapid construction of the cyclopent-3-ene-1,4-dione core of madindoline but did not allow control of absolute stereochemistry. The alkyl substituents of madindoline were found to inhibit Michael addition by thiols. Madindoline has the potential to form covalent bonds with its target and such reactions would be facilitated by preorganization, but confirmation of this hypothesis awaits further studies.

Scheme 9. Synthesis of (±)-Madindoline A and (±)-Madinoline B Using the Smith and Omura Route[a]



[a] Conditions: (a) TBAF, THF, 3 h, 60 °C (75%), (b) TESCl, Et_3N, CH_2Cl_2, rt (66%), (c) MnO_2, CH_2Cl_2, 1 N HCl (75%).

Acknowledgment. We gratefully acknowledge the support of the UC Cancer Research Coordinating Committee, the NIH (GM54523), and GlaxoSmithKine for a graduate fellowship (J.B.P.).

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

OL026015E