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A Concise Stereoselective Route to the Indoline Spiroaminal Framework of Neoxaline and Oxaline

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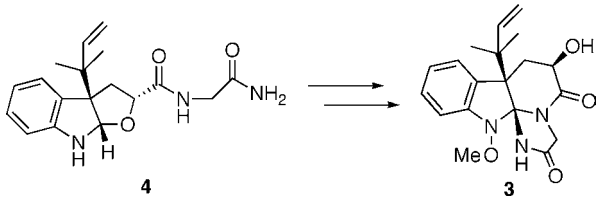
ABSTRACT



The stereoselective synthesis of tetracyclic intermediate, the indoline spiroaminal 3 for neoxaline (1) and oxaline (2), has been accomplished. The key step of the stereoselective synthesis of 3 was the Lewis acid mediated transcyclization of 4 to the diaminal 18, and the tungstate-catalyzed oxidation of 18 to obtain the nitrone 19, which easily cyclizes to the indoline spiroaminal framework 3.

During the course of our chemical screening of microbial metabolites, neoxaline (**1**)[1] was isolated from the culture broth of *Aspergillus japonicus* Fg-551, together with the structurally related known compound oxaline (**2**)[2]. Neoxaline (**1**) and oxaline (**2**) (Figure 1) are members of a novel class of biologically active indole alkaloids, (including meleagrin[3] and glandicolins[4]) characterized by a unique indoline spiroaminal framework and substitution of a 1,1-dimethylallyl ("reverse-prenyl") group at the benzylic ring junction. The relative stereochemistry of **2** has been previously established by X-ray analysis.[5] Hence, the structure of **1** was determined by comparison with **2**; however, the relative and absolute configurations of **1** remain undefined. Compound **1** did not present antibacterial or antifungal activity, although it did weakly stimulate the central nervous system (dose: 100 mg/kg, mice, p.o.). Recently, **1** and **2** were found to inhibit cell proliferation and arrest the cell cycle during M phase in Jarkat

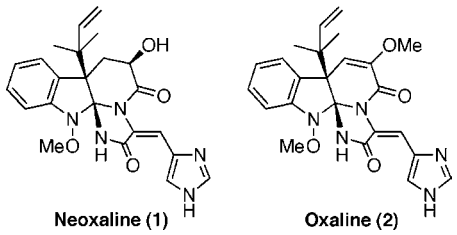


Figure 1. Structures of neoxaline (**1**) and oxaline (**2**).

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(1) (a) Hirano, A.; Iwai, Y.; Masuma, R.; Tei, K.; Ōmura, S. *J. Antibiot.* **1979**, *32*, 781−785. (b) Konda, Y.; Onda, M.; Hirano, A.; Ōmura, S. *Chem. Pharm. Bull.* **1980**, *28*, 2987−2993.
(2) Steyn, P. S. *Tetrahedron* **1970**, *26*, 51−57.
(3) Nozawa, K.; Nakajima, S. *J. Nat. Prod.* **1979**, *42*, 374−377.
(4) Kozlovsky, A. G.; Vinokurova, N. G.; Reshetilova, T. A.; Sakharovsky, V. G.; Baskunov, B. P. *Prikl. Biokhim. I Mikrobiol.* **1994**, *30*, 410−414.
(5) Nagel, D. W.; Pachler, K. G. R.; Steyn, P. S.; Wessels, P. L.; Gafner, G.; Kruger, G. J. *J. Chem. Soc., Chem. Commun.* **1974**, 1021−1022.

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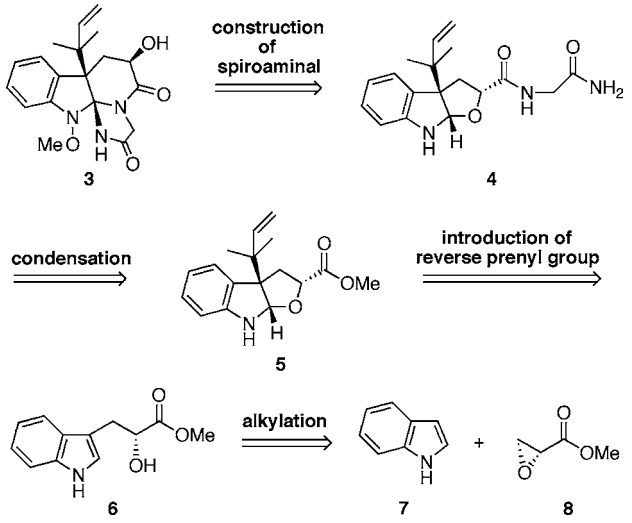
cells.[6] Compounds **1** and **2** bind to tublin at, or near, the colchicine binding site, which results in inhibition of tubulin polymerization.[6] The highly complex indoline spiroaminal framework of the neoxalines was recognized as an attractive target for total synthesis. In conjunction with our continuing structural and synthetic studies of important bioregulatory products,[7] we report herein the concise stereoselective synthesis of the indoline spiroaminal framework **3** of **1** and **2**.

Retrosynthetic analysis of the indoline spiroaminal framework **3** is shown in Scheme 1.

Scheme 1



We anticipated that the spiroaminal framework **3** could be prepared from furoindoline **4** via oxidative transcyclization. Compound **4** would be obtained via condensation of glycine amide with **5**, generated from the chiral indole lactic acid derivative **6**, according to the procedure of Marsden et al.[8] Compound **6** would be prepared via alkylation of commercially available indole **7** with chiral epoxide **8**. The first step of the synthesis, regioselective alkylation[9] of indole **7** with chiral epoxide **8**[10] was examined. Initially $SnCl_4$ was used, however in low yield(52%). Using a $Sc(OTf)_3$ gave complex mixture, $Cu(OTf)_3$ in 21% yield. $Yb(OTf)_3$ proved the most efficient and afforded indole lactic acid ester **6** in 77% yield (Scheme 2). Silylation of the secondary hydroxy group, followed by Boc protection of the α-amino group and desilylation, afforded the alcohol **9**.

Next, selenylation-induced ring closure with *N*-phenylselenophthalimide (*N*-PSP)[11] provided the separable diastereo

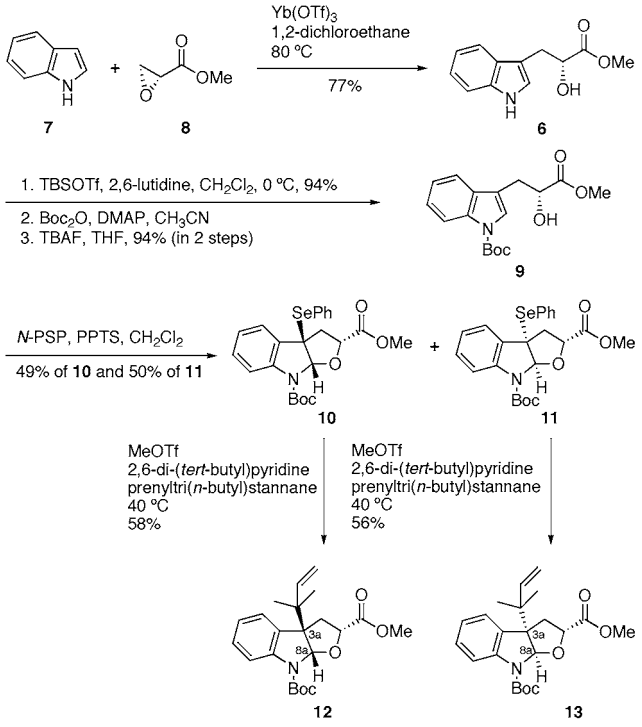
(6) Koizumi, Y.; Arai, M.; Tomoda, H.; Ōmura, S. *Biochim. Biophys. Acta*−*Mol. Cell Res.* **2004**, in press.

(7) 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.

(8) (a) Depew, K. M.; Marsden, S. P.; Zatorska, D.; Zatorski, A.; Bornmann, W. G.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11953−11963. (b) Marsden, S. P.; Depew, K. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1994**, *116*, 11143−11144.

(9) Akita, H.; Kawaguchi, T.; Enoki, Y.; Oishi, T. *Chem. Pharm. Bull.* **1990**, *38*, 323−328.

Scheme 2 [a]

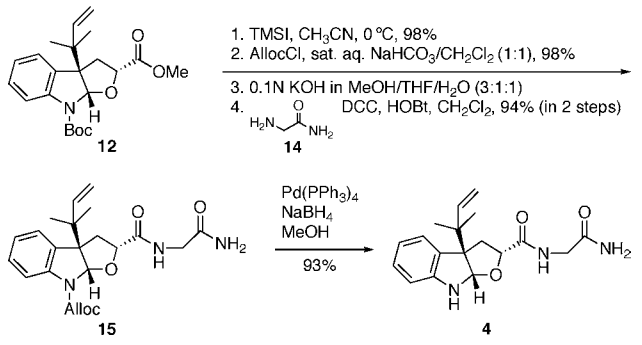


[a] Boc = *tert*-butoxycarbonyl, DMAP = 4-dimethylaminopyridine, TBAF = tetrabutylammonium fluoride, *N*-PSP = *N*-phenylselenophthalimide, PPTS = pyridinium *p*-toluenesulfonate.

mixture (1:1) of 3-selenylated furoindolines **10** and **11**.[12] Treatment of each compound with methyl triflate and prenyltri(*n*-butyl)stannane[13] introduced the reverse prenyl group to the desired position to give compounds **12** and **13**, respectively, with either stereochemistry[14] (Scheme 2).

BOC deprotection (TMSI, CH_3CN) of **12**, reprotection with Alloc group, methyl ester hydrolysis, and condensation with glycine amide **14**, afforded **15**. Subsequent deprotection of the Alloc group gave **4** in high yield (Scheme 3).

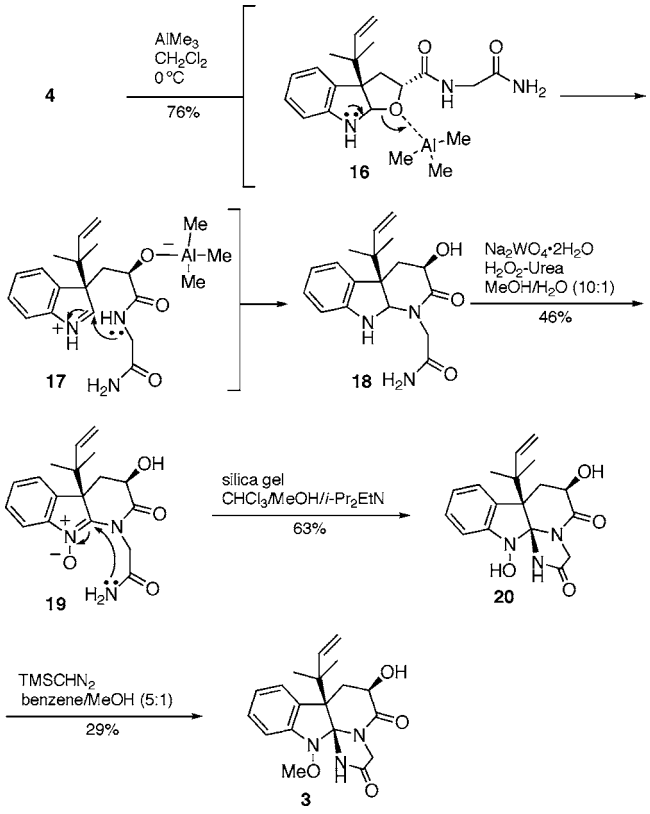
Scheme 3 [a]



[a] TMSI = trimethylsilyl iodide, Alloc = allyloxycarbonyl, DCC = dicyclohexylcarbodiimide, HOBt = 1-hydroxybenzotriazole.

Treatment of aminal **4** with $AlMe_3$ in CH_2Cl_2 at 0 °C facilitated transcyclization to afford diaminal **18**, through the

Scheme 4



iminium intermediate **17**, in 76% yield. Subsequent tungstate-catalyzed oxidation[15] of **18** gave nitrone **19**, which was then treated with silica gel ($CHCl_3$−MeOH−*i*-Pr_2NEt) to afford spiroaminal **20**. Methylation of **20** ($TMSCHN_2$, benzene/MeOH (5:1)) afforded the desired indoline spiroaminal framework **3** (Scheme 4). Compound **3** is a versatile intermediate for the synthesis of the neoxaline family of compounds.

In summary, we describe a concise route to the indoline spiroaminal framework of neoxaline and oxaline via nitrone intermediate. Efforts to complete the total syntheses of neoxaline and oxaline using this synthetic approach are currently underway.

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

OL050077Y

(10) Schaus, S. E.; Brandes, D. B.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307−1315.

(11) (a) Nicolaou, K. C.; Magolda, R. L.; Sipio, W. J.; Barnette, W. E.; Lysenko, Z.; Joullie, M. M. *J. Am. Chem. Soc.* **1977**, *99*, 3185−3187. (b) Clive, D. L. J. *Tetrahedron* **1978**, *34*, 1049−1132.

(12) In Marsden's case[8] Bis(BOC)tryptophan methyl ester reacted with *N*-phenylselenophthalimide and *p*-TsOH to give a 78% yield of 3-selenylated pyrroindole as a 9:1 mixture of diastereomers. On the other hand, *N*-BOC indolelactic acid **9** gave a 1:1 mixtire of 3-selenylated furoindoline. The difference of these selectivity is due to the nucleophilicity between *N*-BOC of bis(BOC)tryptophan and the hydroxyl group of **9**.

(13) Naruta, Y.; Nishigaichi, Y.; Maruyama, K. *Org. Synth.* **1993**, *71*, 118−124.

(14) The 3a−8a *cis*-configuration in compound **13** was determined by NOE proton correlations using a *de*-Boc compound of **13**. The NOE experimental details for the stereochemistry are given in the Supporting Information.

(15) (a) Murahashi, S.; Mitsui, H.; Shiota, T.; Tsuda, T.; Watanabe, S. *J. Org. Chem.* **1990**, *55*, 1736−1744. (b) Murahashi, S.; Oda, T.; Sugahara, T.; Masui, Y. *J. Org. Chem.* **1990**, *55*, 1744−1749.