

## Novel Applications of Vinylogous Mannich Reactions. Total Synthesis of Rugulovasines A and B

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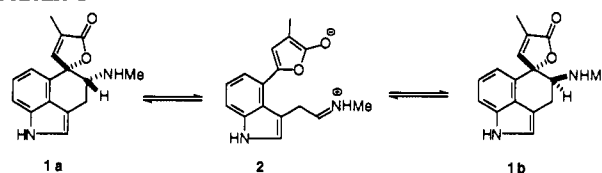
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The rugulovasines A and B (**1a,b**), which were first isolated from *Penicillium concavorugulosium*<sup>1</sup> and then from *Penicillium islandicum*,<sup>2</sup> represent novel structural types within the family of the *Ergot* alkaloids.<sup>3</sup> Interestingly, the rugulovasines A and B were isolated in racemic form, and they were also observed to interconvert upon warming. To account for these facts, the mechanism depicted in Scheme I was proposed, in which **1a** and **1b** undergo interconversion *via* the achiral intermediate **2**.<sup>2</sup> That this hypothesis was indeed feasible was convincingly demonstrated by Rebek, who completed the first and only total synthesis of rugulovasine A and then studied its equilibration to form a mixture of **1a** and **1b**.<sup>4</sup>

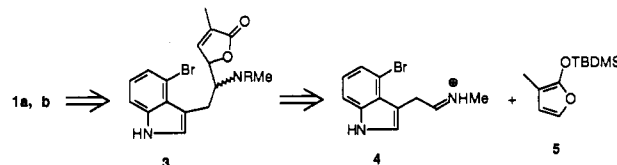
The conversion of **2** into **1a** and **1b** is an example of a vinylogous Mannich reaction, a transformation that we have recently begun to evaluate as a general tactic for the construction of structural subunits common to different alkaloid natural products.<sup>5,6</sup> For example, we have formulated a novel entry to alkaloids that contain 5-aminomethylbutenolide and -butyrolactone rings by a strategy that features inter- and intramolecular vinylogous Mannich reactions of 2-((trialkylsilyloxy)furan with iminium and *N*-acyliminium ions.<sup>6,7</sup> A biomimetic approach to the rugulovasines A and B might then be envisioned as proceeding *via* the intermediacy of **2**, and we are currently exploring this possibility. We have also devised an alternate approach to these and related *Ergot* alkaloids that features an intermolecular addition of the 2-((trialkylsilyloxy)furan **5**<sup>8,9</sup> to the iminium ion **4** to give the 5-aminoalkylbutenolide **3**, cyclization of which *via* a photostimulated S<sub>RN1</sub> reaction<sup>10</sup> would then deliver the natural products **1a,b** (Scheme II). The reduction of this strategy to practice constitutes the subject of this report.

The first step of the synthesis involved the introduction of a functionalized side chain onto the 3-position of commercially available 4-bromoindole (**6**)<sup>11</sup> by classical methods to give the

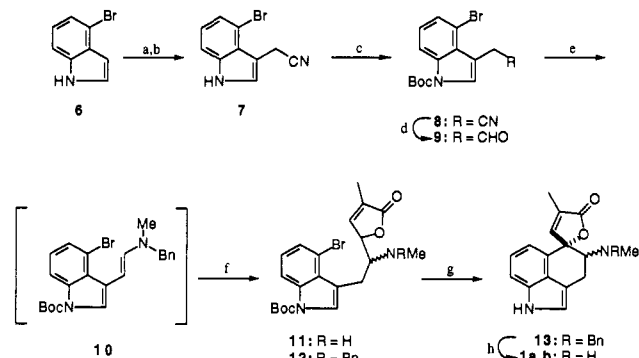
### Scheme I



### Scheme II



### Scheme III<sup>a</sup>



<sup>a</sup> (a) Aqueous Me<sub>2</sub>NH, aqueous HCHO, AcOH, 0 °C → 25 °C. (b) KCN, DMF-H<sub>2</sub>O, 140 °C, 2 h; 71% overall. (c) (Boc)<sub>2</sub>O, DMAP, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 25 °C, 2 h; 91%. (d) DIBAL, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C → 25 °C. (e) Benzylmethylamine, CH<sub>2</sub>Cl<sub>2</sub>, 25 °C, 7 h. (f) CSA, then **5**, benzene 80 °C, 1 h; 45% overall from **8**. (g) *tert*-BuOK, NH<sub>3</sub>, reflux, hv, 1 h; 51%. (h) HCl, EtOH, H<sub>2</sub> (1 atm), 20% Pd(OH)<sub>2</sub>/C, 25 °C, 9 h; 74%.

3-indolylacetonitrile derivative **7** in 71% overall yield (Scheme III).<sup>12</sup> After **7** was converted into the derived *tert*-butyl carbamate **8**, the nitrile function was reduced with diisobutylaluminum hydride to give the aldehyde **9**, which was used in subsequent steps without purification; if the indole N-H was not protected prior to reduction, the resultant aldehyde was too unstable<sup>13</sup> and could not be efficiently elaborated further. Condensation of **9** with methylamine followed by exposure of the intermediate imine to (silyloxy)furan **5** in the presence of acids under a variety of conditions afforded no detectable quantities of the desired adduct **11**. However, the reaction of crude **9** with benzylmethylamine cleanly furnished the enamine **10**, which was treated *in situ* with the (silyloxy)furan **5** and camphorsulphonic acid in refluxing benzene to provide a mixture (1:2) of diastereomeric adducts in 45% overall yield from the nitrile **8**.

The stage was now set to explore cyclization of **12** by an intramolecular S<sub>RN1</sub> reaction to create the spirocyclic lactone moiety and complete the skeletal construction of the rugulovasines. Although such processes have found only limited application in the syntheses of natural products,<sup>14</sup> irradiation of **12** in refluxing ammonia in the presence of sublimed potassium *tert*-butoxide proceeded smoothly to deliver an inseparable mixture (1:2) of the protected rugulovasines **13** in 51% yield; the desired cyclization had proceeded with concomitant removal of the *tert*-butyl

(12) Somei, M.; Kizu, K.; Kunimoto, M.; Yamada, F. *Chem. Pharm. Bull.* 1985, 33, 3996.

(13) For example, see: Burkard, S.; Borschberg, H.-J. *Helv. Chim. Acta* 1989, 72, 254.

(14) (a) Semmelhack, M. F.; Chong, B. P.; Stauffer, R. D.; Rogerson, T. D.; Chong, A.; Jones, L. D. *J. Am. Chem. Soc.* 1975, 97, 2507. (b) Goehring, R. R. *Tetrahedron Lett.* 1992, 33, 6045.

(1) Abe, M.; Ohmono, S.; Ohashi, T.; Tabuchi, T. *Agric. Biol. Chem.* 1969, 33, 469.

(2) Cole, R. J.; Kirksey, J. W.; Clardy, J.; Eickman, N.; Weinreb, S. M.; Singh, P.; Kim, D. *Tetrahedron Lett.* 1976, 3849.

(3) For an excellent review of the *Ergot* alkaloids, see: Ninomiya, I.; Kiguchi, T. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: San Diego, CA, 1990; Vol. 38, p 1.

(4) (a) Rebek, J.; Shue, Y.-K. *J. Am. Chem. Soc.* 1980, 102, 5426. (b) Rebek, J.; Shue, Y.-K.; Tai, D. F. *J. Org. Chem.* 1984, 49, 3540.

(5) Martin, S. F.; Hunter, J. E.; Benage, B.; Geraci, L. S.; Mortimore, M. *J. Am. Chem. Soc.* 1991, 113, 6161.

(6) Martin, S. F.; Corbett, J. W. *Synthesis* 1992, 55.

(7) For other recent examples of the reactions of furans with iminium electrophiles, see: (a) Harding, K. E.; Coleman, M. T.; Liu, L. T. *Tetrahedron Lett.* 1991, 32, 3795. (b) Casiraghi, G.; Rasso, G.; Spanu, P.; Pinna, L.; Ulgheri, F. *J. Org. Chem.* 1993, 58, 3397.

(8) Jefford, C. W.; Sledeski, A. W.; Rossier, J.-C.; Boukouvalas, J. *Tetrahedron Lett.* 1990, 31, 5741.

(9) For leading references to accounts of the related additions of 2-(trialkylsilyloxy)furan to aldehydes, see: (a) Jefford, C. W.; Jaggi, D.; Boukouvalas, J. In *Studies of Natural Products Chemistry, Stereoselective Synthesis (Part B)*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1989; Vol. 3, p 163. (b) Casiraghi, G.; Rasso, G. In *Studies of Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1992; Vol. 11, p 429.

(10) For reviews on the S<sub>RN1</sub>, see: (a) Bunnett, J. F. *Acc. Chem. Res.* 1978, 11, 413. (b) Wolfe, J. F.; Carver, D. R. *Org. Prep. Proc. Int.* 1978, 10, 225. (c) Rossi, R. A.; de Rossi, R. H. In *Aromatic Substitution by the S<sub>RN1</sub> Mechanism*; ACS Monograph Series 178; American Chemical Society: Washington, DC, 1983.

(11) 4-Bromoindole may also be prepared from 2-bromo-6-nitrotoluene. See: Moyer, M. P.; Shiurba, J. F.; Rapoport, H. *J. Org. Chem.* 1986, 51, 5106.

carbamate Boc group, thereby obviating the need for a separate deprotection step. The transformation **12** → **13** appears to occur by an  $S_{RN}1$  mechanism, since several attempts to effect the cyclization in the absence of light under the typical reaction conditions required for aryne-type reactions (LDA, THF,  $-23\text{ }^{\circ}\text{C} \rightarrow 25\text{ }^{\circ}\text{C}$ ) failed.<sup>15</sup>

The final removal of the *N*-benzyl protecting group from **13** proved to be a more challenging task than originally anticipated. Attempted debenylation of **13** under oxidative conditions<sup>16</sup> or with use of various chloroformates<sup>17</sup> either returned starting material or gave unacceptable mixtures of products. However, the debenylation proceeded smoothly by hydrogenolysis of the hydrochloride salt of **13** over Pearlman's catalyst to give a mixture (1:2) of the rugulovasines A and B (**1a,b**) in 74% yield. The spectral characteristics of **1a** and **1b** were identical with those of an authentic sample.<sup>18</sup>

The sequence of reactions described above concludes a concise total synthesis of the rugulovasines A and B by a general strategy

(15) Cf.: Flann, C. J.; Overman, L. E.; Sarkar, A. K. *Tetrahedron Lett.* **1991**, 32, 6993.

(16) (a) Monkovic, T.; Wong, H.; Bachand, C. *Synthesis* **1985**, 770. (b) Gao, X.; Jones, R. A. *J. Am. Chem. Soc.* **1987**, 109, 1275.

(17) For example, see: Olofson, R. A.; Martz, J. T.; Senet, J.-P.; Piteau, M.; Malfroot, T. J. *J. Org. Chem.* **1984**, 49, 2081 and references therein.

featuring an intermolecular vinylogous Mannich reaction of a 2-((trialkylsilyl)oxy)furan with an iminium ion followed by a  $S_{RN}1$  cyclization. Extensions of this general approach to other *Ergot* alkaloids as well as the applications of vinylogous Mannich reactions to the syntheses of other alkaloids constitute the basis of several current investigations, the results of which will be disclosed in due course.

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**Supplementary Material Available:** Complete experimental procedures for the preparation of compounds **7-9**, **12**, **13**, and **1a,b** and copies of their  $^1\text{H}$  NMR spectra (12 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the Journal, and can be ordered from the ACS. Ordering information is given on any current masthead page.

(18) We thank Professor Julius Rebek (Massachusetts Institute of Technology) for spectra of rugulovasines A and B.