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Total Synthesis of (+)-Isatisine A

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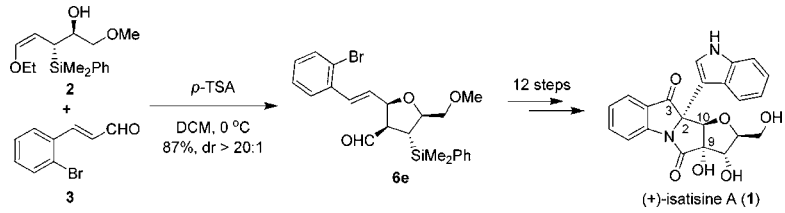
ABSTRACT



Total synthesis of (+)-isatisine A is described based on the application of a silyl-directed Mukaiyama-type [3 + 2]-annulation for the preparation of a fully substituted furan core. The indole branch forming the quaternary carbon center at C2 was constructed by addition to an intermediate N-acyliminium ion derived from aminal 4. In addition, the fused tetracyclic framework including furan core was built up using modified Buchwald amidation conditions.

The roots and leaves of *Isatis indigotica* Fort. (Cruciferae), a plant species widely cultivated in China and East Asia, have been traditionally used for treatment of viral diseases such as influenza, viral pneumonia, mumps, and hepatitis. In 2007, Chen and co-workers reported isolation of isatisine A (**1**), which was the only alkaloid among 12 compounds isolated from *I. Indigotica*.[1] Initially, it was isolated as its acetonide derivative **2**, and the structure elucidation was established by 1D and 2D NMR experiments, then subsequent X-ray crystallographic analysis secured the structure assignment, as well as the relative and absolute stereochemistries. Biological evaluation of the acetonide derivative **2** reveals that this material exhibits cytotoxicity against C8166 with CC_{50} = 302 μM and anti-HIV activity of EC_{50} = 37.8 μM. However, its unusual dioxolane group which is rarely found in natural products led to further investigations to determine whether the acetonide derivative **2** was an artifact formed during the isolation processes using acetone as an eluent, which lead to the natural product, isatisine A (**1**). Recently, the first total synthesis, achieved by Kerr revealed that the assignment of absolute configuration originally provided by Chen's group is antipodal to the natural product.[2]

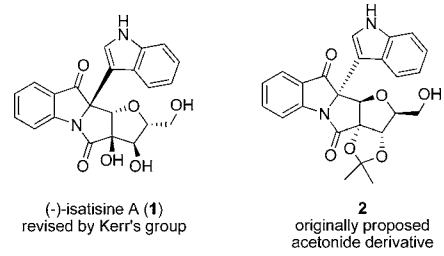


Figure 1. Revised structure of isatisine A (**1**) and original proposed structure of its acetionide **2**.

The challenging structural features of isatisine A (**1**) include a fused tetracyclic framework containing a densely substituted furan subunit and two fully substituted carbon centers (C2 and C9) embedded in the core. In addition, an indole branch forms the C-2 quarternary carbon center. Our interest in this alkaloid arose from its challenging tetracyclic skeleton, as well as its potent anti-HIV activity, and a successful approach to developing an efficient synthetic

(1) Liu, J.-F.; Jiang, Z.-Y.; Wang, R.-R.; Zheng, Y.-T.; Chen, J.-J.; Zhang, X.-M.; Ma, Y.-B. *Org. Lett.* **2007**, *9*, 4127–4129.

(2) (a) Karadeolian, A.; Kerr, M. A. *Angew. Chem., Int. Ed.* **2010**, *49*, 1133–1135. (b) Karadeolian, A.; Kerr, M. A. *J. Org. Chem.* **2010**, *75*, 6830–6841.

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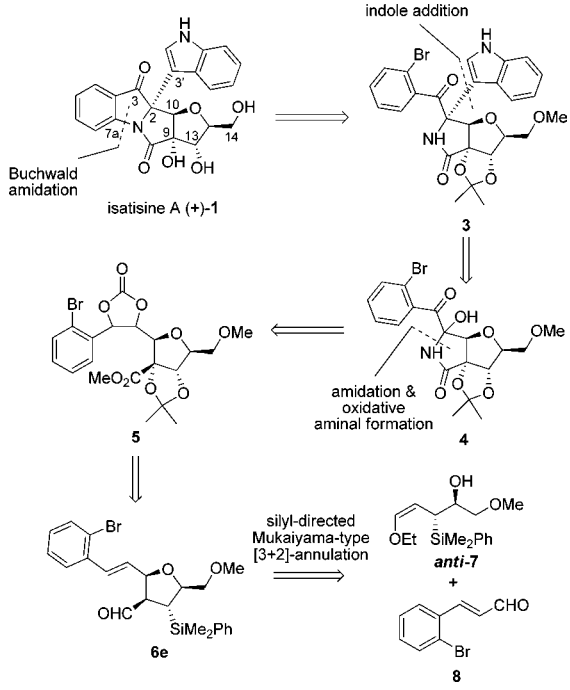
strategy would allow further SAR (structure−activity relationship) and SSAR (stereostructure activity relationship) studies.

Scheme 1. Retrosynthetic Analysis of (+)-Isatisine A (**1**)



In our synthetic plan described in Scheme 1, we intended to apply a Mukaiyama-type [3 + 2]-annulation of silane ***anti*-7** with a suitably functionalized aldehyde to construct tetrahydrofuran core. Subsequent use of a CuI-mediated aryl amidation[3] would assemble the tetracyclic skeleton of isatisine A. Accordingly, our retrosynthetic plan began with disconnection of C7a-N to afford an advanced intermediate aryl bromide **3**. Further disconnection occurred at the indole side chain C2−C3′, which led to an indole and aminal **4**. This intermediate aminal would spontaneously form in the course of oxidation of the amido-diol. Disconnection between the amide nitrogen N1 and C2 led to protected furan **5**, which possesses the required oxidation state to access the aminal **4**. The tetrahydrofuran intermediate **6e** would be constructed from silyl-directed Mukaiyama-type [3 + 2]-annulation of silane ***anti*-7** with bromocinnamyl aldehyde **8**.

Mukaiyama [3 + 2]-annulation strategy to construct functionalized furans was initially developed by Hoppe.[4] In that context, we have learned that enantioenriched silane reagents bearing C-centered chirality can participate in stereoselective [3 + 2]-annulation sequence resulting in stereochemically well-defined and highly functionalized furans. In this regard, use of the allyl silanes **7**,[5] prepared from the known epoxy-silanes[6] in two steps, as a reaction partner afforded silyl-substituted furans with an aryl and aliphatic aldehyde (eqs 1 and 2 in Figure 2). The annulations

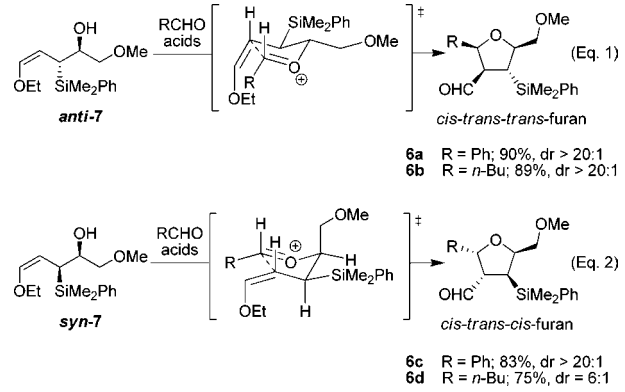


Figure 2. Asymmetric Mukaiyama-type [3 + 2]-annulation of *anti*- and *syn*-ethoxy allyl silane **7**.

took place with high levels of selectivity, which illustrates that the configuration of the C-SiR_3 bond functions as a reliable stereocontrol element during the reaction. In this synthesis, we describe examples of a silyl-directed [3 + 2]-annulation and how it's used in the synthesis of a complex natural product.

Our synthesis began with the preparation of *tetra*-substituted furan **6e** through [3 + 2]-annulation of silane ***anti*-7** with 2-bromocinnamyl aldehyde **8** (Scheme 2). Thus, using 2.0 equiv of aldehyde **8**[7] in the presence *p*-TSA (1.0 equiv) at 0 °C afforded desired furan **6e** in 87% yield with high dr (>20:1). Selective α-bromination in the presence of the conjugated olefin was achieved using PTAB (phenyltrimethylammonium tribromide),[8] that material was directly treated with TBAF at 0 °C to form an α,*β*-unsaturated aldehyde. This resulting unstable intermediate unsaturated aldehyde was immediately subjected to oxidation with MnO_2 in the presence of NaCN to afford the α,*β*-unsaturated methyl ester **9** in 57% yield from tetrahydrofuran **6e**.[9]

The styrene-like olefin of **9** was selectively oxygenated by a catalytic OsO_4 dihydroxylation using 1.0 equiv of NMO, which afforded diol **10** as a 1.5:1 mixture of diastereomers. Formation of the undesired diol was not detected by spectroscopic methods. Conversion of the mixture of diols to a cyclic carbonate and subsequent dihydroxylation of α,*β*-unsaturated ester **11** still gave 1.5:1 mixture of diasteromers,

(3) (a) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727–7729. (b) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421–7428.

(4) (a) Hoppe, D.; Kramer, T.; Erdbriigger, C. F.; Egert, E. *Tetrahedron Lett.* **1989**, *30*, 1233–1236. (b) Brüns, A.; Wibbeling, B.; Fröhlich, R.; Hoppe, D. *Synthesis* **2006**, 3111–3121. (c) Kollmann, S.; Fröhlich, R.; Hoppe, D. *Synthesis* **2007**, 883–892. (d) Becker, J.; Fröhlich, R.; Salorinne, K.; Hoppe, D. *Eur. J. Org. Chem.* **2007**, 3337–3348.

(5) For the preparation of *syn* and *anti*-ethoxy allyl silane **7**, see the Supporting Information.

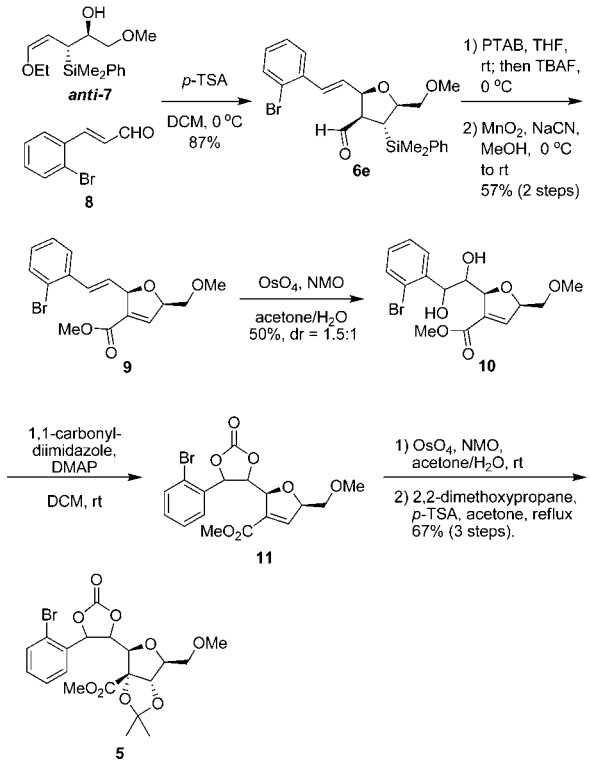
(6) Lowe, J. T.; Youngsaye, W.; Panek, J. S. *J. Org. Chem.* **2006**, *71*, 3639–3642.

(7) Kim, J. H.; Lee, S.; Kwon, M.-G.; Park, Y. S.; Choi, S.-K.; Kwon, B.-M. *Synth. Commun.* **2004**, *34*, 1223–1228.

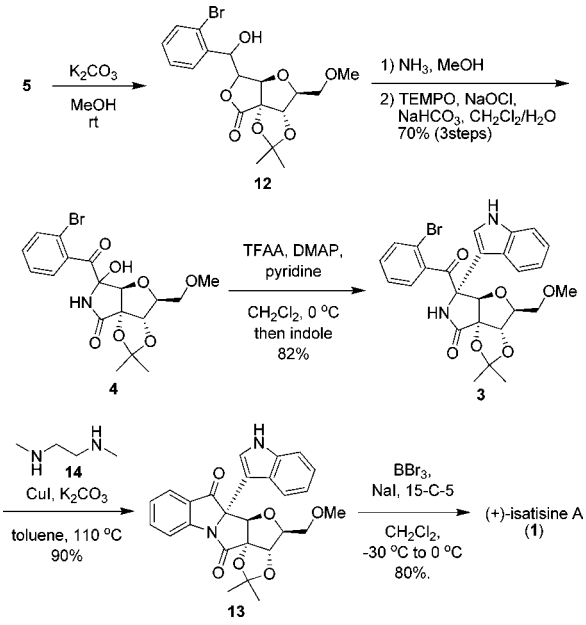
(8) Ager, D. J.; Fleming, I.; Patel, S. K. *J. Chem. Soc., Perkin Trans 1* **1981**, 2520–2526.

(9) Corey, E. J.; Posner, G. H. *J. Am. Chem. Soc.* **1968**, *90*, 5616–5617.

Scheme 2. Preparation of Intermediate **5**



Scheme 3. Completion of Synthesis of (+)-Isatisine A (**1**)



which means this second dihydroxylation proceeded in a fully stereoselective manner. Subsequent acetonide protection of the resulting diol afforded an intermediate **5** in 67% yield (3 steps) from diol **10**. The relative configuration of bicyclic dioxolane **5** was confirmed by NOE measurement after separation of the two diastereomers.[10]

Removal of carbonate of **5** under basic conditions also resulted in the cleavage of the methyl ester to form an intermediate dihydroxy acid which is spontaneously latonized in $CHCl_3$ to give bicyclic lactone **12** (Scheme 3). Treatment of this material with anhydrous NH_3 solution in MeOH provided an intermediate amide, which was subjected to oxidation with TEMPO and NaOCl at room temperature.[11] As we anticipated, the oxidation of the dihydroxy amide spontaneously cyclized to afford a key intermediate aminal **4** as a single diastereomer.

With availibity of intermediate hydroxyl-lactam **4**, we turned our attention to the stereoselective indole incorporation. This type of addition is typically carried out under acidic conditions and presumably proceeds through the formation and trapping of an acyl iminium ion.[12] In this case, it was expected that the indole would approach the iminium ion from the less hindered convex face of the bicycle. In our evaluation of this reaction, indole addition was initially conducted under Lewis and Brönsted acidic conditions ($In(OTf)_3$, $BF_3{\cdot}OEt_2$, CSA, and *p*-TSA). However, addition to hydroxyl-lactam **4** failed to afford the desired adduct. In order to convert the aminal into a better leaving group, a mesylate was generated *in situ* by treatment of **4** with MsCl (1.2 equiv) at 0 °C, and subsequent addition of a solution of indole (5.0 equiv) in CH_2Cl_2 gave the desired indole adduct **3** in 54% yield as a single diastereomer. Optimal conversion was acquired upon using TFAA instead of MsCl, which afforded **3** in 82% yield as a single stereoisomer. The stereochemistry and absolute configuration of the indole branched quarternary carbon center of **3** was confirmed by single crystal X-ray crystallographic analysis (Figure 3).

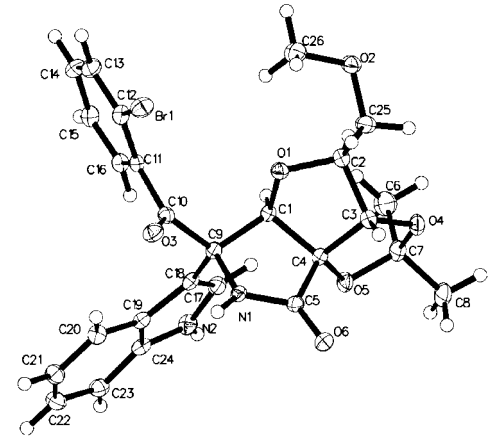


Figure 3. X-ray structure of the indole adduct **3**.

A modified Buchwald intramolecular amidation in the presence of CuI was used to assemble the fused tetracylclic

(10) For the spectroscopic anlysis, see the Supporting Information.

(11) (a) Slee, D. H.; Romano, S. J.; Yu, J.; Nguyen, T. N.; John, J. K.; Raheja, N. K.; Axe, F. U.; Jones, T. K.; Ripka, W. C. *J. Med. Chem.* **2001**, *44*, 2094–2107. (b) Tron, G. C.; Pagliai, F.; Grosso, E. D.; Genazzani, A. A.; Sorba, G. *J. Med. Chem.* **2005**, *48*, 3260–3268.

framework. This type of amidation has been studied and used previously by us as a strategy for macrocyclization.[13] In the present case, the advanced tetracyclic intermediate **13** was successfully generated through CuI-mediated coupling in 90% yield. Subsequent cleavage of the primary methyl ether[14] and acetonide with excess BBr_3 (9.0 equiv, added in three portions) in the presence of 15-crown-5 and NaI (3.0 equiv) provided (+)-isatisine A (**1**) in 80% yield.

In conclusion, a total synthesis of (+)-isatisine A has been achieved in 13 steps with a 6.9% overall yield starting from allyl silane ***anti*-7**. A key element of our synthesis includes the formation of highly substituted tetrahydrofuran using a silyl-directed Mukaiyama-type [3 + 2]-annulation strategy. In addition, construction of nitrogen-containing tetracyclic skeleton through CuI-mediated amidation demonstrated that this method can be useful for fused polycyclic systems in complex molecule synthesis. Further studies and applications of stereoselective [3 + 2]-annuation are currently underway.

Acknowledgment. Financial support was obtained from NIH CA 53604. We are grateful to Dr. Paul Ralifo, Dr. Norman Lee, and Dr. Jeffrey Bacon (Chemical Instrumentation Center at Boston University) for helpful discussions and assistance with NMR, HRMS, and X-ray crystallographic analysis experiments.

Note Added after ASAP Publication. Figure 2 contained errors in the version published ASAP December 28, 2010; the correct version reposted December 31, 2010.

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

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(13) (a) Wrona, I. E.; Gabarda, A. E.; Evano, G.; Panek, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 15026–1502. (b) Qin, H.-L.; Panek, J. S. *Org. Lett.* **2008**, *10*, 2477–2479.

(14) (a) Niwa, H.; Hida, T.; Yamada, K. *Tetrahedron Lett.* **1981**, *22*, 4239–4240. (b) Su, Q.; Panek, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 2425–2430.