

Biomimetic Total Synthesis of (–)-Isatisine A

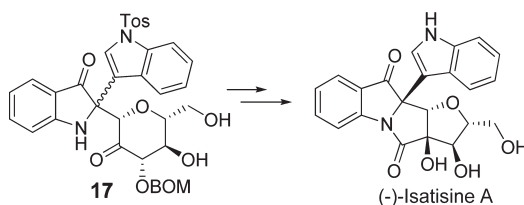
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ABSTRACT



The biomimetic total synthesis of (–)-isatisine A, a novel alkaloid with an unprecedented fused tetracyclic skeleton, was accomplished in 8 steps from indole and 4,6-*O*-isopropylidene-protected glucal. The synthesis features a convergent synthetic strategy which relies on nucleophilic addition and a biomimetic benzilic ester rearrangement as key reactions.

The leaves and root of *Isatis indigotica* Fort., named “Da-Qing-Ye” and “Ban-Lan-Gen” respectively in Chinese, have been used in traditional Chinese medicine for the treatment of viral diseases for hundreds of years in China.¹ Chemical investigations of its root and leaves have led to the isolation of compounds with diverse structures and significant biological activities.² In 2007, Chen and co-workers reported the isolation of isatisine A acetonide (**1**) from the leaves (Da-Qing-Ye) (Figure 1).³ This compound showed moderate anti-HIV-1 activity with EC_{50} = 37.8 μ M and selectivity index (SI) = 7.98. Isatisine A acetonide (**1**) also exhibited cytotoxicity against C8166 with CC_{50} = 302 μ M.

The structure and relative configuration of **1** was elucidated by NMR experiments and finally determined by single-crystal X-ray diffraction.³ The structural features of **1** possess a fused pentacyclic framework containing a densely substituted furan subunit, one aza-quaternary carbon center, and one oxo-quaternary carbon center. In

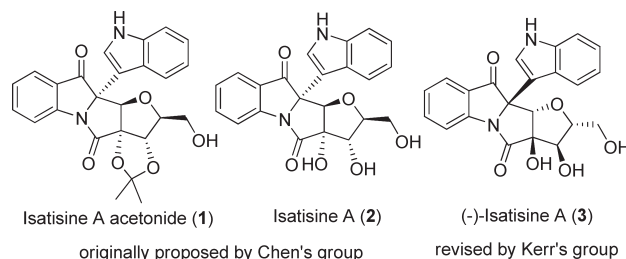


Figure 1. Original proposed structure of isatisine A (**2**) and its acetonide (**1**) and revised structure of isatisine A (**3**).

addition, an unusual isopropylidenyl group was embedded in the core. The isopropylidenyl group that has been relatively rare in natural products prompted further investigation by Chen and co-workers, which indicated acetonide derivative **1** was an isolation artifact, and isatisine A (**2**) was proposed as the genuine natural product.³ However, the bioactivity of **2** was not reported due to limited supply. Its uncharacterized bioactivity and intriguing molecular architecture have drawn a great amount of attention from the synthetic community. In 2010, Kerr et al. reported the first total synthesis and structural revision of (–)-isatisine A (**3**).⁴ The revised structure was further confirmed by the total syntheses of (+)-isatisine

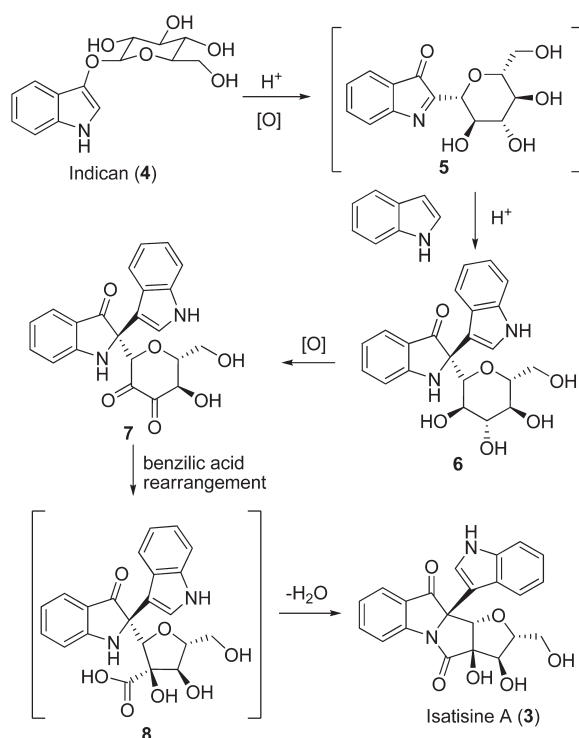
(1) Zheng, H. Z.; Dong, Z. H.; Yu, Q. *Modern Study of Traditional Chinese Medicine*; Xueyuan Press: Beijing, 1997; Vol. 1, p 328.

(2) (a) Huang, Q. S.; Yoshihira, K.; Natori, S. *Planta Med.* **1981**, *42*, 308. (b) Wu, X. Y.; Liu, Y. H.; Sheng, W. Y.; Sun, J.; Qin, G. W. *Planta Med.* **1997**, *63*, 55. (c) Wu, X. Y.; Qin, G. W. *Tetrahedron* **1997**, *53*, 13323. (d) Mak, N. K.; Leung, C. Y.; Wei, X. Y.; Shen, X. L.; Wong, R. N.; Leung, K. N.; Fung, M. C. *Biochem. Pharmacol.* **2004**, *67*, 167. (e) Peng, S. P.; Gu, Z. L. *Chin. Wild Plant Resources* **2005**, *24*, 4. (f) Shi, X.; Ni, Y.; Liu, Y. H. *Chin. Hosp. Pharm. J.* **2006**, *26*, 1397.

(3) 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.

A (**2**) and (–)-isatisine A (**3**) by Panek⁵ and Liang,⁶ respectively. Interesting, Kerr, Panek, and Liang demonstrated elegant synthetic strategies that first constructed the densely substituted furan subunit and, subsequently, installed the second indole moiety by a nucleophilic addition.^{4–6} Herein, we report our biomimetic total synthesis of (–)-isatisine A (**3**). Our biomimetic synthetic strategy features a convergent nucleophilic addition for installation of the indole moiety and, subsequently, an unprecedented benzilic ester rearrangement for construction of the densely substituted furan subunit.

Scheme 1. Biogenetic Pathway Proposed for (–)-Isatisine A



We became interested in (–)-isatisine A (**3**) as a novel alkaloid possessing an unprecedented fused-tetracyclic skeleton which cannot be well explained from a biogenetic point of view.³ Studies suggest that the polyhydroxy core of some natural products is likely to arise in nature from glycosides.⁷ Inspired by the multiple hydroxy groups and indole moiety of (–)-isatisine A (**3**), indican (**4**), isolated from the same species, seems to be the precursor of **3**. After further survey, indican (**4**) was found in higher concentration in the young leaves than the old leaves of *I. indigotica* and as an important precursor for other compounds.⁸

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

(5) Lee, J.; Panek, J. S. *Org. Lett.* **2011**, *13*, 502.

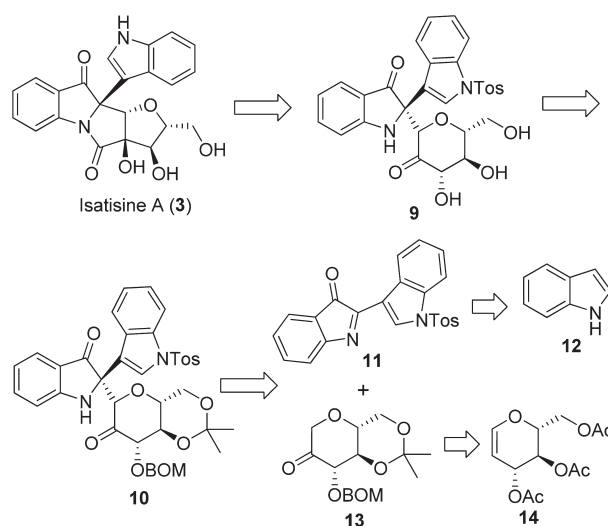
(6) Zhang, X.; Mu, T.; Zhan, F. X.; Ma, L. J.; Liang, G. X. *Angew. Chem., Int. Ed.* **2011**, *50*, 6164.

(7) Watanabe, H.; Nakada, M. *J. Am. Chem. Soc.* **2008**, *130*, 1150.

(8) (a) Kokubun, T.; Edmonds, J.; John, P. *Phytochemistry* **1998**, *49*, 79. (b) Maugarda, T.; Enauda, E.; Choisyb, P.; Legoya, M. D. *Phytochemistry* **2001**, *58*, 897.

Thus, a plausible biogenetic pathway for (–)-isatisine A (**3**) was proposed by us as shown in Scheme 1. In the proposed biogenetic route, indican (**4**) is first converted to compound **5** via rearrangement and subsequent oxidation. **5** then undergoes a rapid nucleophilic addition by an indole molecule to afford compound **6**.^{4b,9} The key intermediate, 1,2-diketone **7**, is expected to be obtained by selective oxidation of compound **6**. Finally, biogenetic benzilic acid rearrangement¹⁰ of compound **7** could give rise to the compound **8**, which is converted to (–)-isatisine A (**3**) through dehydration.

Scheme 2. Retrosynthesis Analysis of (–)-Isatisine A



In order to support this biogenetic pathway, benzilic ester rearrangement was devised as a key biomimetic reaction for the synthesis of (–)-isatisine A. As shown in retrosynthesis analysis (Scheme 2), we reasoned that the synthesis of (–)-isatisine A (**3**) could be achieved from compound **9** by a biomimetic oxidation, benzilic ester rearrangement, and cyclization. The α -hydroxy ketone **9** would be prepared easily by deprotection from diketone **10**. We envisioned that if electrophilic **11** and nucleophilic **13** could be merged together by base, a short, convergent,

(9) (a) Young, T. E.; Auld, D. S. *J. Org. Chem.* **1963**, *28*, 418. (b) Chien, C. S.; Takanami, T.; Kawasaki, T.; Sakamoto, M. *Chem. Pharm. Bull.* **1985**, *33*, 1843. (c) Ling, K. Q. *Synth. Commun.* **1996**, *26*, 149. (d) Clawson, R. W., Jr.; Dacko, C. A.; Deavers, R. E., III; Akhmedov, N. G.; Söderberg, B. C. G. *Tetrahedron* **2009**, *65*, 8786. (e) Higuchi, K.; Sato, Y.; Kojima, S.; Tsuchimochi, M.; Sugiura, K.; Hatori, M.; Kawasaki, T. *Tetrahedron* **2010**, *66*, 1236. (f) Rueping, M.; Raja, S.; Núñez, A. *Adv. Synth. Catal.* **2011**, *353*, 563.

(10) For reviews, see: (a) Selman, S.; Easthan, J. F. *Quart. Rev. Chem. Soc.* **1960**, *14*, 221. (b) Rubin, M. B. *Chem. Rev.* **1975**, *75*, 177. (c) Burke, A. J.; Marques, C. S. *Mini-Rev. Org. Chem.* **2007**, *4*, 310. For recent examples: (d) Rajyaguru, I.; Rzepa, H. S. *J. Chem. Soc., Perkin Trans. 2* **1987**, 1819. (e) Stoltz, B. M.; Wood, J. L. *Tetrahedron Lett.* **1996**, *37*, 3929. (f) Hotchkiss, D. J.; Jenkinson, S. F.; Storer, R.; Heinz, T.; Fleet, G. W. J. *Tetrahedron Lett.* **2006**, *47*, 315. (g) Marques, C. S.; Moura, N.; Burke, A. J. *Tetrahedron Lett.* **2006**, *47*, 6049. (h) Yamabe, S.; Tsuchida, N.; Yamazaki, S. *J. Org. Chem.* **2006**, *71*, 1777. (i) Umland, K. D.; Palisse, A.; Haug, T. T.; Kirsch, S. F. *Angew. Chem., Int. Ed.* **2011**, *50*, 9965.

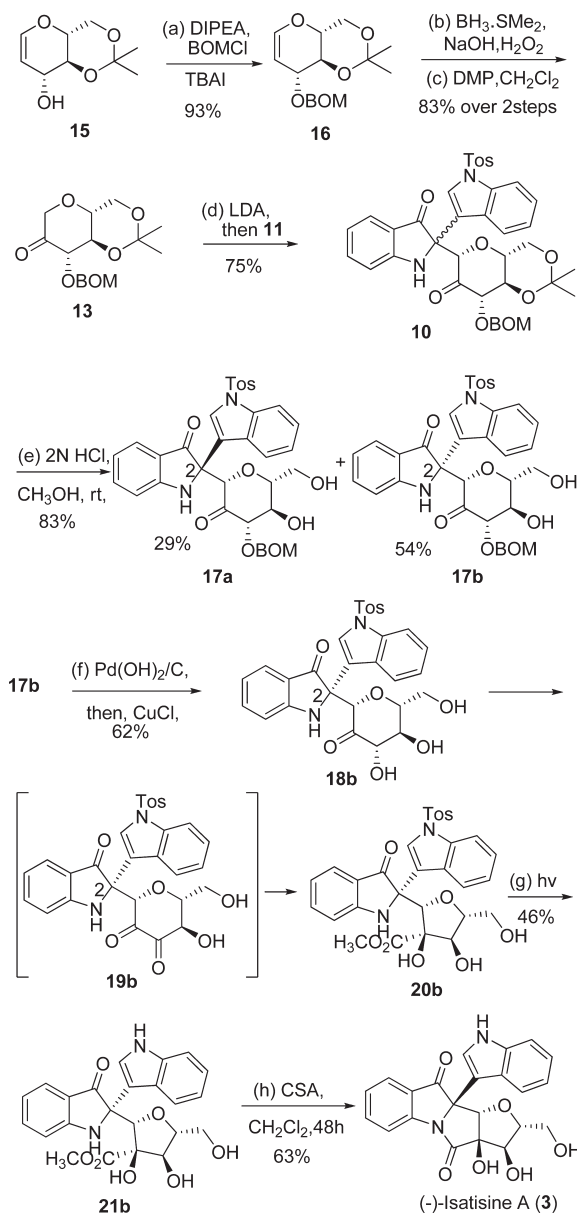
and efficient synthesis of key intermediate **10** would be developed. Compounds **11** and **13** could be synthesized from commercially available indole (**12**) and triacetyl-D-glucal (**14**), respectively.

As shown in Scheme 3, nucleophilic partner **13** was efficiently synthesized from the known compound **15**,¹¹ which was prepared from triacetyl-D-glucal in two steps. Compound **15** was first protected with BOM to afford **16** in 93% yield. The subsequent hydroboration of enol ether **16** with BH_3 and oxidative workup (H_2O_2 , NaOH , 50°C), followed by DMP oxidation, afforded compound **13**. Another electrophilic precursor **11** was synthesized from indole according to the literature reported method.¹²

With compounds **11** and **13** in hand, we started to investigate the key coupling reaction. Although compound **11** was highly reactive toward a variety of nucleophiles,^{12c} the coupling reaction proved to be challenging due to the steric hindrance. Through extensive reaction screening, we identified a suitable condition, in which ketone **13** was treated with LDA for 0.5 h at -78°C and then coupled with electrophilic **11**, to provide diketone **10** as a diastereomeric mixture in 75% yield. The two diastereomers of **10** were unstable and could not be separated and purified. Further treatment of compound **10** with 2 N HCl in methanol at room temperature smoothly removed the acetonide protective group and generated **17a** and **17b**. By spectroscopic analysis of the two isolated compounds, we found that the major product isolated was compound **17b** in 54% yield along with a 29% yield of compound **17a**. The new formed stereocenters of **17a** and **17b** were established using its NOE experiment and the experimental and computational optical rotation data.¹³

Based on Kerr's report,^{4b} the configuration of C2 in compound **17b** tends to isomerize to give the configuration of C2 in **17a** when the Tos was removed. In order to support this assumption, we first use compound **17b** as a substrate for the next steps. Hydrogenation of **17b** in the presence of $\text{Pd}(\text{OH})_2$ provided the corresponding triol **18b**.¹⁴ **18b** was unstable, which was used without further purification and converted to **20b** in moderate yield with excellent chemo- and diastereoselectivity through CuCl -mediated tandem biomimetic oxidation and benzilic ester rearrangement.¹⁰ Due to the lability of compound **20b**, neutral conditions for deprotection were required. After screening several reaction conditions, we found that photoinduced deprotection of the Tos group afforded the desired compound **21b** in 46% yield.¹⁵ Ultimately, treating compound **21b** with CSA in CH_2Cl_2 at room temperature furnished **3**. The spectral data of synthetic

Scheme 3. Biomimetic Total Synthesis of (–)-Isatisine A



(–)-isatisine A (**3**) (^1H , ^{13}C NMR, IR, and HRMS) are consistent with those of the natural product.³ (–)-Isatisine A (**3**) was also synthesized from compound **17a** following the same procedure in 16% yield.¹⁶ Thus the separation of compound **17a** and **17b** was unnecessary. Compound **3** was obtained from the mixture of **17a** and **17b** in 18% yield by using the same procedure.

In summary, the biogenetic synthetic pathway toward (–)-isatisine A has been proposed. Based on the biogenetic pathway, the biomimetic total synthesis of (–)-isatisine A has been accomplished in 8 steps from 4,6-*O*-isopropylidene-protected glucal **15** in an overall yield of 8.6%. Our synthetic strategy relies on a nucleophilic addition and an unprecedented biomimetic benzilic ester rearrangement as

(11) Dötz, K. H.; Otto, F.; Nieger, M. *J. Organomet. Chem.* **2001**, *621*, 77.

(12) (a) Astolfi, P.; Panagiotaki, M.; Rizzoli, C.; Greci, L. *Org. Biomol. Chem.* **2006**, *4*, 3283. (b) Ottoni, O.; Cruz, R.; Alves, R. *Tetrahedron* **1998**, *54*, 13915. (c) Li, L. Q.; Han, M. Y.; Xiao, M. X.; Xie, Z. X. *Synlett.* **2011**, *12*, 1727.

(13) See the Supporting Information.

(14) Hirai, G.; Watanabe, M.; Yamaguchi, K.; Miyagi, T.; Sodeoka, M. *J. Am. Chem. Soc.* **2007**, *129*, 15420.

(15) (a) Li, Y. Z.; Zou, H. X.; Gong, J. X.; Xiang, J.; Luo, T. P.; Quan, J. M.; Wang, G. X.; Yang, Z. *Org. Lett.* **2007**, *9*, 4057. (b) Reed, D. D.; Bergmeier, S. C. *J. Org. Chem.* **2007**, *72*, 1024.

(16) See the Supporting Information.

key steps. The synthesis and biological investigation of isatisine A analogues are currently underway and will be reported in due course.

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

The authors declare no competing financial interest.