

Total Synthesis

Total Synthesis of (+)-Isatisine A**

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In memory of Keith Fagnou

Traditional Chinese medicine has yielded a plethora of diverse naturally occurring bioactive compounds for many years.^[1] *Isatis indigotica* Fort. is a plant species cultivated in China for its antiviral properties which include activity against influenza, viral pneumonia, and hepatitis.^[2] Recently Chen and co-workers reinvestigated this organism in search of anti-HIV compounds and reported the isolation of 64 mg of the bis-indole **2** (Figure 1) from 50 kg of the dried leaves of *I.*

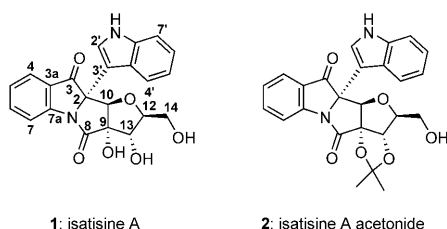


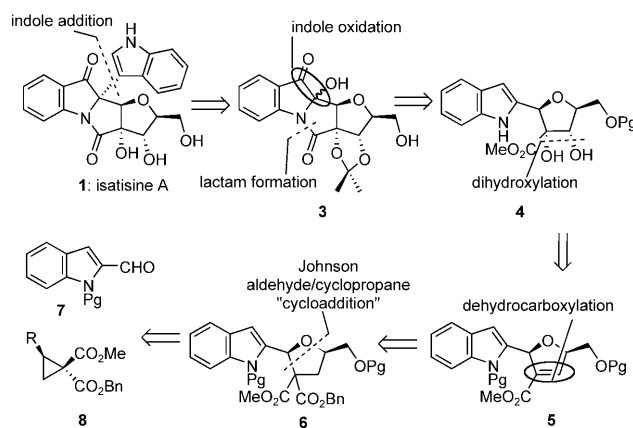
Figure 1. Isatisine A (**1**) and its acetonide derivative (**2**).

indigotica.^[3] Interestingly it became apparent that acetonide **2** was not in fact the native natural product but an artefact arising from purification with an acetone eluent on silica gel. Upon this realization and reinvestigation, compound **1**, named isatisine A was determined to be the native plant constituent.

Acetonide **2**, however, did provide a convenient compound for full characterization which included unambiguous structure determination by single crystal X-ray diffraction. Although an optical rotation was obtained for **2**, the absolute stereochemical configuration was not reported. The only reports of bioactivity in the isolation paper^[3] are for the acetonide **2**, which showed an EC₅₀ anti-HIV-1 activity of 37.8 μ M. Isatisine A itself was not screened for bioactivity, however, it is reasonable to assume that its activity may be promising. Herein we report a concise synthesis of isatisine A (**1**) (through its acetonide **2**) capable of providing significant

quantities of product for medicinal and biological investigation as well as clarifying the absolute configuration.

A retrosynthetic analysis for isatisine A is shown in Scheme 1. The final step is an acid-catalyzed indole addition to the hemiaminal **3** (which may have biomimetic implica-



Scheme 1. Retrosynthesis of isatisine A (**1**).

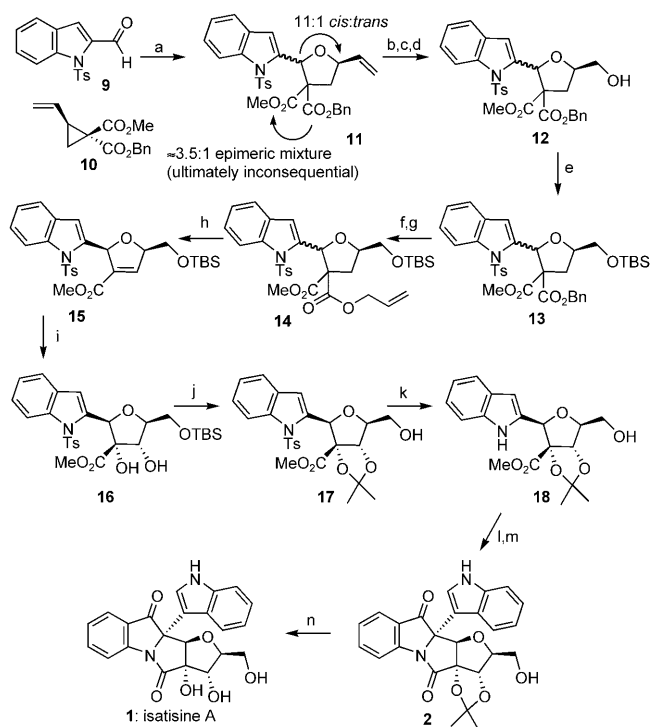
tions).^[4] The masked 1,2-dicarbonyl in **3** would be installed through oxidation of the 2,3-indole double bond in a substrate such as **4**.^[5] The requisite dihydroxy moiety would arise from a diastereoselective dihydroxylation of enoate **5**, the olefin of which coming from dehydrocarboxylation of one of the geminal diesters in **6**. The tetrahydrofuran ring in **6**, which represents a central structural feature of the natural product, would be prepared through the elegant cyclopropane–aldehyde cycloaddition developed by Johnson and co-workers,^[6] between an indole-2-carboxaldehyde **7** and a suitable cyclopropane-1,1-diester **8**. The *S* configuration of the cyclopropane as shown would set the C10 and C12 stereocenters as *R* and *S*, respectively, by virtue of stereospecific inversion upon ring-opening in the cycloaddition process and a *cis* diastereoselectivity in the tetrahydrofuran synthesis. This enantiomeric choice of starting material would prepare the enantiomer of isatisine A depicted herein (and in the isolation paper^[3]).

Our synthesis commenced with the key Johnson tetrahydrofuran synthesis^[6b] using the indole-2-carboxaldehyde **9** and the homo-chiral (*S*)-vinylcyclopropane diester **10**^[7] under catalytic influence of Sn(OTf)₂ (Scheme 2). The tetrahydrofuran **11** was isolated in 89% yield as an 11:1 mixture of the 2,5-*cis*:2,5-*trans* (furan numbering) isomers. There was moderate selectivity at the geminal diester center, however this

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Scheme 2. Synthesis of (+)-isatisine A (**1**). a) $\text{Sn}(\text{OTf})_2$, CH_2Cl_2 (89%); b) methanesulfonamide, NMO, OsO_4 , THF/ H_2O /acetone; c) NaIO_4 , THF/ H_2O , 0°C ; d) NaBH_4 , THF/ H_2O /EtOH (87%, 3 steps); e) TBSCl, imidazole, CH_2Cl_2 (94%); f) Pd/C , H_2 (1 atm), THF; g) PPh_3 , allyl alcohol, DIAD, THF (99%, 2 steps); h) $[\text{Pd}_2(\text{dba})_3]$, CH_3CN , 80°C (45–55%); i) methanesulfonamide, NMO, OsO_4 , acetone/ H_2O (62%); j) 2,2-dimethoxypropane, *p*-toluenesulfonic acid, acetone (83%, >98% ee); k) Mg^0 , NH_4Cl , MeOH (77%); l) *m*CPBA, CH_2Cl_2 ; m) indole, CSA, CH_2Cl_2 , 42 h (50%, >98% ee); n) 1 N HCl, MeOH (82%). NMO = *N*-methylmorpholine-*N*-oxide, TBS = *tert*-butyldimethylsilyl, DIAD = diisopropyl azodicarboxylate, dba = dibenzylideneacetone, *m*CPBA = *m*-chloroperbenzoic acid, CSA = 10-camphorsulfonic acid, Ts = toluene-4-sulfonyl, Bn = benzyl.

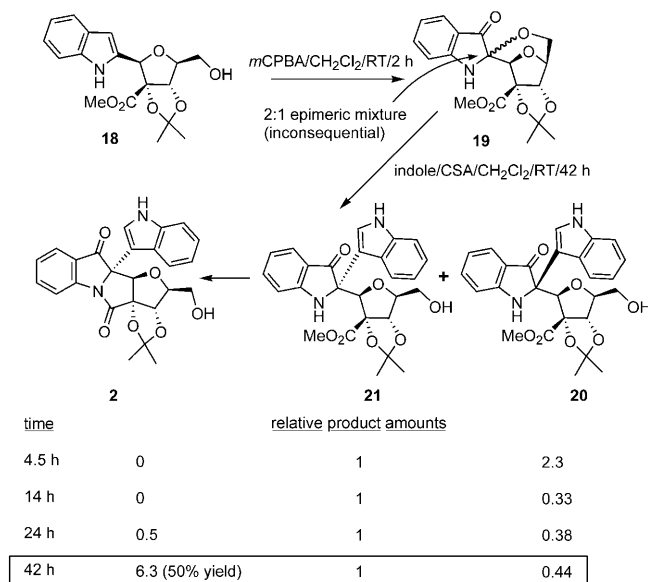
would prove to be inconsequential since this carbon would become sp_2 hybridized in subsequent steps.

The pendant vinyl substituent in **11** was converted to a primary alcohol through dihydroxylation, oxidative cleavage, and reduction of the resulting aldehyde, producing **12** in 87% overall yield. Protection of the primary alcohol as a silyl ether was uneventful, providing **13** in 94% yield. It is worthy of note at this juncture that the obvious use of a cyclopropane bearing the required hydroxy substituent was not successful under a variety of conditions. The cycloaddition apparently requires the π -donor activity provided by the vinyl substituent.

In order to install the double bond necessary for formation of the 9,13-dihydroxyl moiety (isatisine A numbering; Figure 1), we initially considered the pedestrian strategy of decarboxylation, installation of a leaving group, and elimination. After some unsuccessful attempts along this line, we settled on a much more productive strategy—namely to eliminate one of the esters directly. To this end, hydrolysis of the benzyl ester and subsequent Mitsunobu allylation,^[8] gave a 99% yield of the allyl ester **14**. Treatment of **14** with $[\text{Pd}_2(\text{dba})_3]$ gave a 45–55% yield of enoate **15**.^[9,10]

This yield is more impressive than at first glance in that it represents the removal of the *trans*-furan diastereomer as well as some product resulting from the undesired regioisomeric elimination to the 2,3-unsaturated furan. Dihydroxylation of **15** under standard conditions gave diol **16** as a single diastereomer in 62% yield. Acetonide formation was concomitant with silyl ether removal giving **17** in 83% overall yield. In order to set up indole oxidation, the *N*-tosyl group was removed under the influence of magnesium metal in methanol,^[11] giving **18** in 77% yield. In what proved to be a wonderfully efficient strategy, isatisine A acetonide (**2**) was produced from **18** in a simple two-step procedure with no intermediate purification. Treatment of **18** with *m*CPBA in CH_2Cl_2 for 2 h at room temperature,^[5a] gave a crude oxidation product which, upon isolation was treated with indole and camphorsulfonic acid in CH_2Cl_2 for 42 h. Standard workup gave isatisine A acetonide (**2**) in 50% overall yield. Simple hydrolysis of the acetonide in acidic methanol produced the natural product **1** in 82% yield.

The key transformation of **18** to **2** deserves comment and is outlined in Scheme 3. Although, in practice it was used crude, the oxidation product of **18** with *m*CPBA was in fact



Scheme 3. Oxidation of **18** with indole addition.

characterized and found to be a 2:1 epimeric mixture of amins **19**. The diastereomers were separable and stable, however, the stereochemical configuration at the aminal carbon could not be unambiguously determined. This of course would prove to be inconsequential since treatment of **19** with indole and camphorsulfonic acid resulted in C3 indole alkylation through an *N*-acyliminium ion devoid of asymmetry at this carbon. After 4.5 h, a 2.3:1 mixture of indole addition products was formed in favor of the undesired diastereomer **20**. This indole addition is apparently reversible, since after 14 h, the ratio had readjusted to a 3:1 ratio in favor of the desired isomer **21**. After 24 h that ratio was constant and a small amount of the isatisine A acetonide (**2**) was

observed. A 42 h reaction time resulted in a 6.3:1:0.44 ratio of **2**, **21**, and **20**. While **20** and **21** could, in principle form more of the desired product, the yield of **2** diminished due to various acid mediated decomposition pathways involving the indole moiety. Thus the overall yield of **2** from **18** was 50 % without purification of intermediate **19**.

The specific rotation of the synthetic acetone **2** and the synthetic isatisine A (**1**) were $[\alpha]_{\text{D}}^{25} = +271$ and $[\alpha]_{\text{D}}^{25} = +274$, respectively. Our value for acetone **2** is essentially equal and opposite to that reported in the isolation paper ($[\alpha]_{\text{D}}^{14} = -283$ ($c=0.46$, MeOH)).^[3] Since our product is C2(*R*), C9(*S*), C10(*R*), C12(*S*), C13(*S*), the natural material must be C2(*S*), C9(*R*), C10(*S*), C12(*R*), C13(*R*) which is antipodal to the structural depictions in the isolation paper. Clearly, the route described herein starting with the *R*-cyclopropane **10** would yield the natural enantiomer.

In summary, we have successfully completed the total synthesis of (+)-isatisine A in 14 steps from homochiral cyclopropane **10** in an overall yield of 5.8%. The synthesis and biological investigation of isatisine A analogues is underway and will be reported in due course.

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[1] J. Zhou, G. Xie, X. Yan in *Traditional Chinese Medicines*, 2nd ed., Ashgate, England, **2003**.

[2] H. Z. Zheng, Z. H. Dong, Q. Yu in *Modern Study of Traditional Chinese Medicine, Vol. 1*, Xueyuan, Beijing, **1997**, p. 328–334.

- [3] J.-F. Liu, Z.-Y. Jiang, R.-R. Wang, Y.-T. Zeng, J.-J. Chen, X.-M. Zhang, Y.-B. Ma, *Org. Lett.* **2007**, 9, 4127–4129.
- [4] a) P. Astolfi, L. Creci, C. Rizzoli, P. Sgarabotto, G. Marrosu, *J. Chem. Soc. Perkin Trans. 2* **2001**, 1634–1640; b) C. I. Altinis Kiraz, T. J. Emge, L. S. Jimenez, *J. Org. Chem.* **2004**, 69, 2200–2202.
- [5] a) M. J. Buller, T. G. Cook, Y. Kobayashi, *Heterocycles* **2007**, 72, 163–166; b) Z. Wang, L. S. Jimenez, *Tetrahedron Lett.* **1996**, 37, 6049–6052; c) V. J. Colandrea, S. Rajaraman, L. S. Jimenez, *Org. Lett.* **1996**, 37, 6049–6052; d) C.-S. Chien, T. Suzuki, T. Kawasaki, M. Sakamoto, *Chem. Pharm. Bull.* **1984**, 32, 3945.
- [6] a) P. D. Pohlhaus, J. S. Johnson, *J. Am. Chem. Soc.* **2005**, 127, 16014–16015; b) P. D. Pohlhaus, S. D. Sanders, A. T. Parsons, W. Li, J. S. Johnson, *J. Am. Chem. Soc.* **2008**, 130, 8642–8650; c) A. T. Parsons, M. J. Campbell, J. S. Johnson, *Org. Lett.* **2008**, 10, 2541–2544; d) A. T. Parsons, J. S. Johnson, *J. Am. Chem. Soc.* **2009**, 131, 3122–3123; e) S. D. Sanders, A. Ruiz-Olalla, J. S. Johnson, *Chem. Commun.* **2009**, 5135–5137; f) M. J. Campbell, J. S. Johnson, *J. Am. Chem. Soc.* **2009**, 131, 10370–10371.
- [7] Prepared from the dimethyl ester (see Supporting Information). For the synthesis of the (*S*)-vinylcyclopropane-1,1-dimethyl ester see C. A. Carson, M. A. Kerr, *Angew. Chem.* **2006**, 118, 6710–6713; *Angew. Chem. Int. Ed.* **2006**, 45, 6560–6563.
- [8] O. Mitsunobu, M. Yamada, *Bull. Chem. Soc. Jpn.* **1967**, 40, 2380–2382.
- [9] I. Shimizu, T. Tsuji, *J. Am. Chem. Soc.* **1982**, 104, 5844–5846.
- [10] We thank Professor Jeffrey Manthorpe for this helpful suggestion.
- [11] a) Y. Yokoyama, T. Matsumoto, Y. Murakami, *J. Org. Chem.* **1995**, 60, 1486–1487; b) A. M. Elder, D. H. Rich, *Org. Lett.* **1999**, 1, 1443–1446.

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