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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. 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.

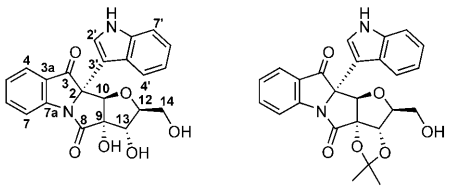
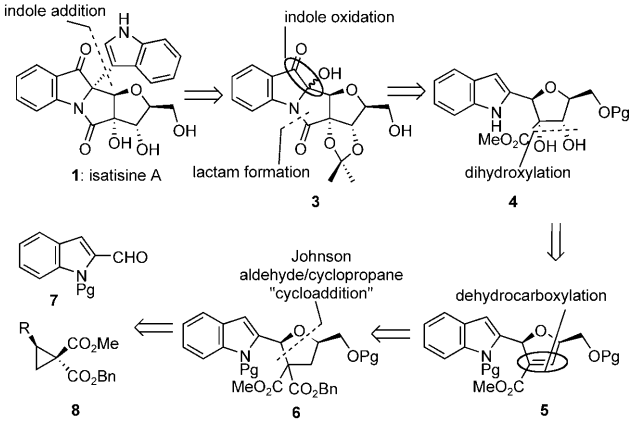


Figure 1. Isatisine A (**1**) and its acetonide derivative (**2**).

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 EC_{50} anti-HIV-1 activity of 37.8 μM. 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 implications).[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 dehydrocarbonylation 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]).



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

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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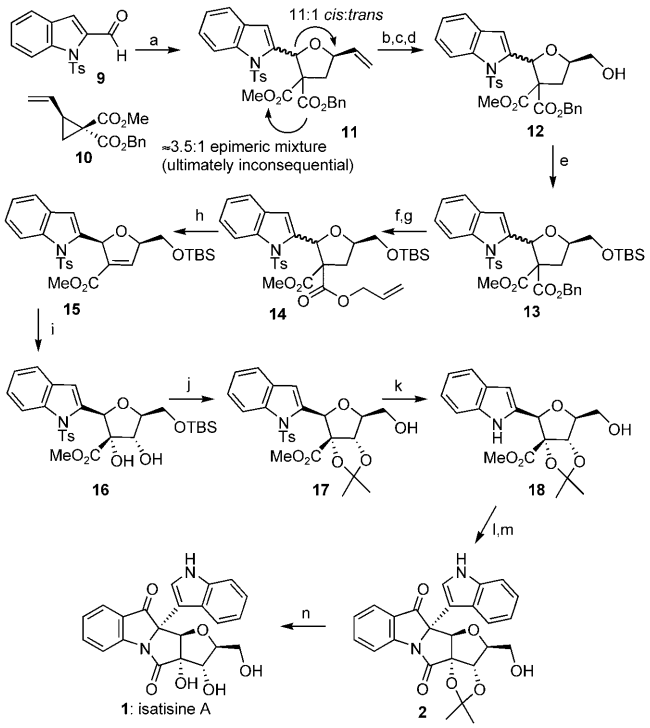


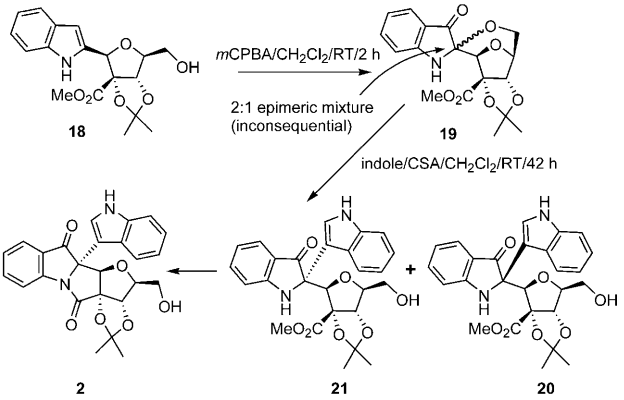
Scheme 2. Synthesis of (+)-isatisine A (**1**). a) $Sn(OTf)_2$, CH_2Cl_2 (89%); b) methanesulfonamide, NMO, OsO_4, THF/H_2O/acetone; c) $NaIO_4$, THF/H_2O, 0°C; d) $NaBH_4$, THF/H_2O/EtOH (87%, 3 steps); e) TBSCl, imidazole, CH_2Cl_2 (94%); f) Pd/C, H_2 (1 atm), THF; g) PPh_3, allyl alcohol, DIAD, THF (99%, 2 steps); h) $[Pd_2(dba)_3]$, 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, hydrogenolysis of the benzyl ester and subsequent Mitsunobu allylation,[8] gave a 99% yield of the allyl ester **14**. Treatment of **14** with $[Pd_2(dba)_3]$ 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



time	relative product amounts		
4.5 h	0	1	2.3
14 h	0	1	0.33
24 h	0.5	1	0.38
42 h	6.3 (50% yield)	1	0.44

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

characterized and found to be a 2:1 epimeric mixture of aminals **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 acetonide **2** and the synthetic isatisine A (**1**) were $[\alpha]_D^{25} = +271$ and $[\alpha]_D^{25} = +274$, respectively. Our value for acetonide **2** is essentially equal and opposite to that reported in the isolation paper ($[\alpha]_D^{14} = -283$ ($c = 0.46$, 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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