Natural Products

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Total Synthesis of (−)-Isatisine A**

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Isatisine A (**1**; Figure 1) was isolated in 2007 by Chen et al. whilst searching for anti-HIV compounds from the leaves of *Isatis indigotica* Fort. (Cruciferae).[1] This biennial herbaceous

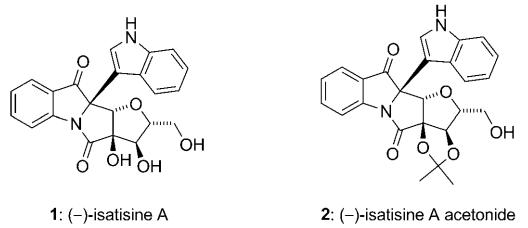
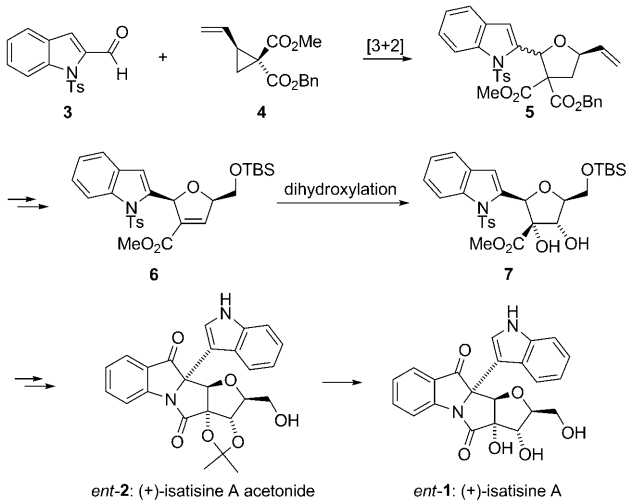


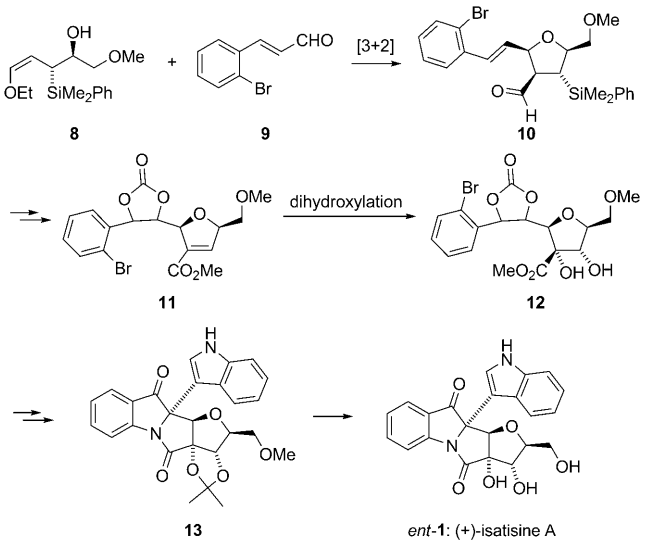
Figure 1. Structures of isatisine A (**1**) and its acetonide **2** showing the absolute configuration that was established by Kerr's group.

plant is widely used in traditional Chinese medicine for the prevention and treatment of viral diseases such as influenza, viral pneumonia, mumps, and hepatitis.[2] Interestingly, its derivative isatisine A acetonide (**2**) was identified first, and was later proved to be an artifact of the isolation process.[1] Extensive NMR spectroscopic analyses and X-ray crystallographic analysis of **2** revealed that isatisine A (**1**) features an unprecedented fused tetracyclic framework with five contiguous stereogenic centers, two of which are fully substituted, and a densely functionalized tetrahydrofuran core. The absolute configuration of these two bisindole alkaloids was established by the first total synthesis of (+)-isatisine A (*ent*-**1**), which was reported by Karadeolian and Kerr (Scheme 1),[3] and later was confirmed by the total synthesis of *ent*-**1** by Lee and Panek (Scheme 2).[4]

Apart from the challenging structural features of isatisine A (**1**), its uncharacterized bioactivity makes this compound an unusually appealing synthetic target. Isatisine A acetonide (**2**), the abundant artifact which arises from the isolation process of isatisine A, was shown to be cytotoxic against C8166 ($CC_{50} = 302\ \mu M$) and also displayed anti-HIV-1_{IIIB} activity ($EC_{50} = 37.8\ \mu M$).[1] Given these findings, the



Scheme 1. Total synthesis of (+)-isatisine A by Karadeolian and Kerr. Bn = benzyl, TBS = tert-butyldimethylsilyl, Ts = *p*-toluenesulfonyl.



Scheme 2. Total synthesis of (+)-isatisine A by Lee and Panek.

plant constituent **1**, was speculated to possess comparable or even stronger antiviral activity than its derivative **2**.

Unfortunately, the bioactivity of isatisine A was not reported in the paper that described its isolation because of the scarcity of the isolated material.[5] An efficient total synthesis of this natural product is expected to facilitate the charactization of its bioactivity and future medicinal chemistry studies.

Karadeolian and Kerr (Scheme 1), and Lee and Panek (Scheme 2) demonstrated elegant synthetic strategies that applied two different [3+2] annulations for the construction

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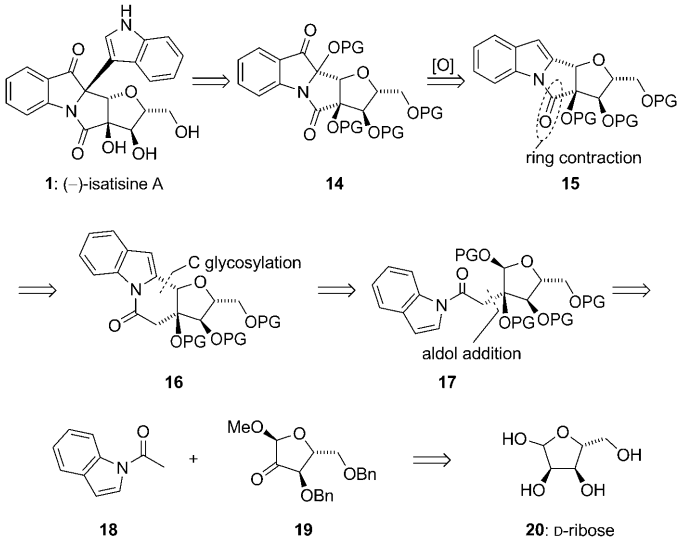
of the tetrahydrofuran core and used a dihydroxylation to install the *cis*-diol moiety found in the natural product. Subsequently, the second indole moiety was installed by a nucleophilic addition to a rather reactive acyl iminium ion to prepare *ent*-**1**.[3,4,6]

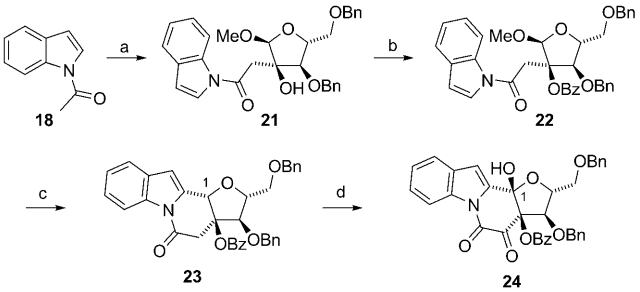
Herein, we report our total synthesis of (−)-isatisine A (**1**), the natural enantiomer of the alkaloid. Our synthetic strategy was inspired by the multiple hydroxy groups and their relative stereochemistry on the tetrahydrofuran core of **1**, which reminded us of D-ribose. We decided to take advantage of this feature by synthesizing **1** from this furanose. A retrosynthetic analysis for **1** from D-ribose (**20**) is shown in Scheme 3. The final installation of the indole onto the indoxyl



Scheme 3. Retrosynthetic analysis of (−)-isatisine A (**1**). Bn = benzyl, PG = protecting group.

14 could be achieved through an acid-catalyzed nucleophilic addition, which was used in the synthesis of *ent*-**1** reported by Karadeolian and Kerr.[3,6] It also has been previously demonstrated that the indole precursor **15** can be oxidized to give indoxyl **14**.[3,6,7] The tetracyclic indole precursor **15** could arise from a ring contraction of compound **16**, which should be readily prepared by an intramolecular C-glycosylation reaction. The substrate **17** for this key C–C bond formation could be formed by an aldol addition of the enolate of **18** to the D-ribose-derived ketone **19**.

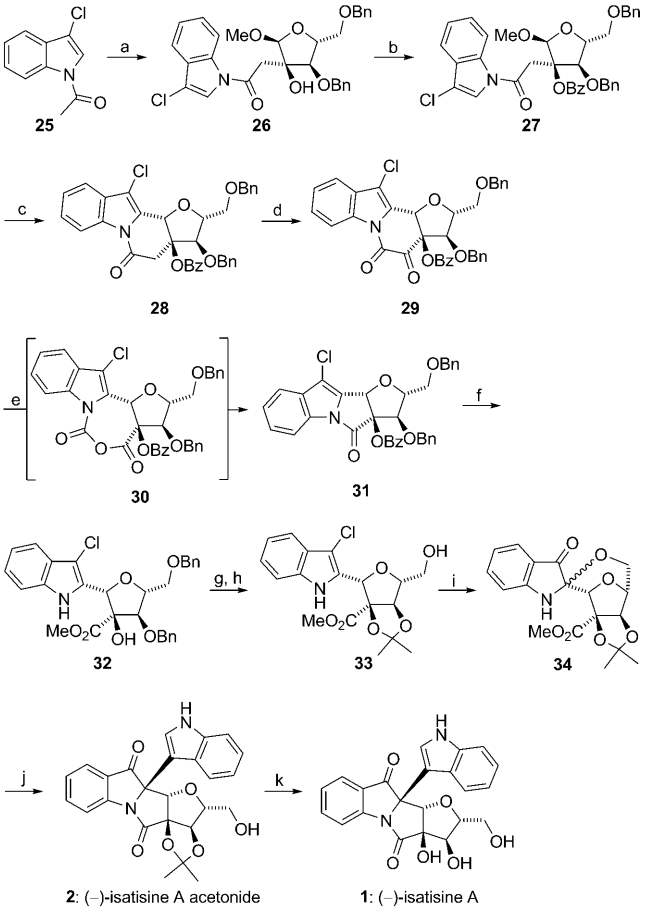
Our synthesis commenced with the D-ribose derivative ketone **19**, which was readily prepared from D-ribose (**20**) in four steps by using published procedures.[8] Initially, we used acetylindole **18**[9] as the substrate for the aldol reaction (Scheme 4). The reaction between the enolate of **18** and ketone **19** successfully afforded the adduct **21** in 76% yield as a single diastereomer. Protection of the tertiary alcohol **21** with a benzoyl group smoothly produced the C-glycosylation precursor **22**. Investigation of several Lewis acidic conditions for this reaction revealed that $BF_3{\cdot}OEt_2$ in nitromethane produced **23** in a useful yield. When **22** was subjected to these reaction conditions, the intramolecular C glycosylation



Scheme 4. Initial synthetic efforts starting with **18**. a) LDA, −78 °C, THF; then **19** (76%); b) BzCl, Et_3N, DMAP, CH_2Cl_2 (87%); c) $BF_3{\cdot}OEt_2$, $MeNO_2$, 0 °C to RT (61%); d) SeO_2, 1,4-dioxane, 135 °C (48%). Bz = benzoyl, DMAP = 4-dimethylaminopyridine, LDA = lithium diisopropylamide, THF = tetrahydrofuran.

smoothly afforded the cyclized product **23** in 61% yield. To the best of our knowledge, this reaction represents the first C glycosylation at the 2-position of an indole with an unactivated anomeric center of a furanose.[10] With the key intermediate **23** in hand, we chose to use the well-established SeO_2 oxidation to oxidize the position α to the carbonyl group in **23**.[11] However, when **23** was treated with SeO_2 in 1,4-dioxane in a sealed tube at 135 °C, not only did oxidation occur at the α position to give the desired carbonyl group, but it also occurred at the anomeric center (C1) to give **24**. Variation of the reaction conditions did not improve the result. To solve the problem, we decided to try a different substrate, which contained a chlorine atom at the 3-position of the indole moiety, in the hope that the adjustment of the electronic properties of the indole would change the reactivity at the anomeric center.

Indeed, this adjustment fulfilled our expectation and allowed us to finish the total synthesis of (−)-isatisine A (**1**; Scheme 5). The aldol reaction between the enolate of **25**[12] and **19**, and subsequent benzoylation, produced the C-glycosylation substrate **27** in good yield. Gratifyingly, compared with **22**, the chloroindole **27** showed a 23% improvement on the yield of the C-glycosylation product. Treatment of **28** with SeO_2 in 1,4-dioxane in a sealed tube at 135 °C afforded the desired dicarbonyl product **29** without any oxidation at the anomeric center. Interestingly, when **29** was treated with hydrogen peroxide and potassium carbonate in THF, a ring contraction was observed to afford the tetracyclic intermediate **31** directly, in good yield. Presumably, this transformation produced intermediate **30**, which is the usual product for an oxidative dicarbonyl cleavage reaction.[13] Debenzoylation and ring opening occurred simultaneously when **31** was subjected to NaOMe in methanol/THF (4:1). Hydrogenolysis of **32** removed the two benzyl protecting groups to produce a triol, which was then selectively protected as a ketal to give **33** in excellent yield. Oxidation of the chloroindole moiety in **33** with *m*CPBA[14] afforded **34** as a pair of diastereomers, the enantiomeric counterparts of which were used in the total synthesis of *ent*-**1** by Karadeolian and Kerr. By using their procedure,[3,6] we were able to obtain **2**. A mild hydrolysis of **2** with 1N HCl in MeOH readily afforded **1** in 88% yield.



Scheme 5. Total synthesis of (−)-isatisine A. a) LDA, −78 °C, THF; then **19** (80%); b) BzCl, Et_3N, DMAP, CH_2Cl_2 (93%); c) $BF_3{\cdot}OEt_2$, $MeNO_2$, 0 °C to RT (84%); d) SeO_2, 1,4-dioxane, 135 °C (67%); e) H_2O_2, K_2CO_3, THF (62%); f) NaOMe, MeOH/THF (4:1), 0 °C to RT (84%); g) 20% $Pd(OH)_2/C$, H_2 (1 atm), THF; h) 2,2-dimethoxypropane, *p*-toluenesulfonic acid, acetone (98%, 2 steps); i) *m*CPBA, CH_2Cl_2; j) indole, CSA, CH_2Cl_2 (36%, 2 steps); k) 1 N HCl, MeOH (88%). CSA = 10-camphorsulfonic acid, *m*CPBA = *m*-chloroperbenzoic aci.

The specific rotations of the synthetic acetonide **2** and **1** we obtained were $[\alpha]_D^{19} = -242\ deg\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 0.7\ g\,cm^{-3}$, MeOH) and $[\alpha]_D^{19} = -240\ deg\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 0.43\ g\,cm^{-3}$, MeOH) respectively. These specific rotations are close to the value but opposite to those reported by Karadeolian and Kerr ($[\alpha]_D^{25} = +271\ deg\,cm^3\,g^{-1}\,dm^{-1}$ and $[\alpha]_D^{25} = +274\ deg\,cm^3\,g^{-1}\,dm^{-1}$, respectively).[3] In addition, the specific rotation of our synthetic **2** compares well to that reported in the report describing the isolation of **2** ($[\alpha]_D^{14} = -283\ deg\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 0.46\ g\,cm^{-3}$, MeOH)).[1] Therefore, the isatisine A (**1**) we prepared is the natural enantiomer.

In conclusion, we have achieved a total synthesis of the natural enantiomer of isatisine A (**1**) in 11 steps with a 6.8% overall yield from the readily available D-ribose derivative **19**. The synthesis features an unprecedented intramolecular C glycosylation of an indole and an oxidative ring contraction. The success of the synthetic strategy allowed us to construct the rather complex alkaloid from common and inexpensive building blocks such as indole and D-ribose. Biological assessment of (−)-isatisine A and its analogues is underway in our laboratory.

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