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Total synthesis of (−)-isatisine A via a biomimetic benzilic acid rearrangement

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ABSTRACT

The biomimetic total synthesis of potential anti-HIV (−)-isatisine A, a novel alkaloid with an unprecedented fused tetracyclic skeleton, was accomplished in eight steps from indole and known 4,6-*O*-isopropylidene-protected glucal. The synthetic strategy was inspired primarily by the proposed biogenetic hypothesis that indole *C*-furanoside would be derived from indole *C*-glucoside via a ring contractive benzilic acid rearrangement. The biogenetic hypothesis was enabled by model studies: the *O*-glucoside was converted to *O*-furanoside via a benzilic acid rearrangement.

1. Introduction

As a fundamental traditional Chinese medicine, *Isatis indigotica Fort.* (Cruciferae) has been used for the treatment of viral diseases for hundreds of years in China.[1] Chemical investigation of its root and leave, respectively named 'Ban-Lan-Gen' and 'Da-Qing-Ye' in Chinese, has led to the isolation of diverse structures and significant biological activities compounds.[2] In 2007 Chen and co-workers have reinvestigated and isolated isatisine A acetionide (**1**) from the leaves (Da-Qing-Ye) (Fig. 1).[3] This compound showed moderate anti-HIV-1 activity with EC_{50}=37.8 μM and selectivity index (SI)= 7.98. Furthermore, isatisine A acetionide (**1**) exerted cytotoxicity against C8166 with CC_{50}=302 μM.

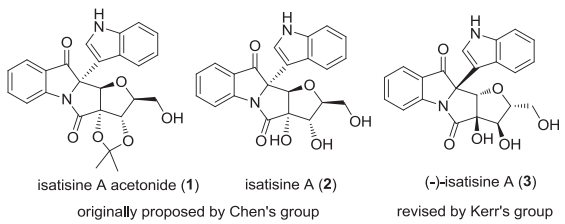

Fig. 1. Original proposed structure of isatisine A (**2**) and its acetionide (**1**) and revised structure of isatisine A (**3**).

The structure and relative configuration of **1**was elucidated by 1D and 2D NMR experiments and finally determined by single-crystal X-ray diffraction. The unique bisindole alkaloid possessed an unprecedented fused pentacyclic framework containing a densely substituted furan subunit and five contiguous stereocenters. Furthermore, an isopropylidenyl group was embedded in the core. Natural compounds containing the isopropylidenyl group have often been reported, however, the use of acetone as a solvent in their purification process made Chen and co-workers doubt whether the acetonide derivative **1** was an artifact. They did further investigations and confirmed that isatisine A (**2**) was a genuine natural product in the leaves of Isatis indigotica.[3] Unfortunately, the bioactivity of natural isatisine A (**2**) was not reported in the paper that described its isolation due to the scarcity of the isolated material.

Its uncharacterized bioactivity and intrigued molecular architecture has drawn the attention of organic chemists to make this compound as an unusually appealing synthetic target.[4] In 2010, Kerr reported the first total synthesis of (+)-isatisine A (**2**), and revised the absolute configuration of the natural alkaloids as (−)-isatisine A (**3**) (Scheme 2).[4a–b] Their strategy involved the use of a Lewis acid-catalyzed cyclization of homochiral (S)-vinylcycopropane diester (**4**) and N-tosylindole-2-carboxaldehyde (**5**) to construct the tetrahydrofuran ring and an indole oxidation, followed by an electrophilic aromatic substitution to install the second indole moiety. Following this, Panek[4c] and Liang[4d] reported the total synthesis of (+)-isatisine A (**2**) and (−)-isatisine A (**3**), respectively. A key feature of Panek's synthesis was the application of

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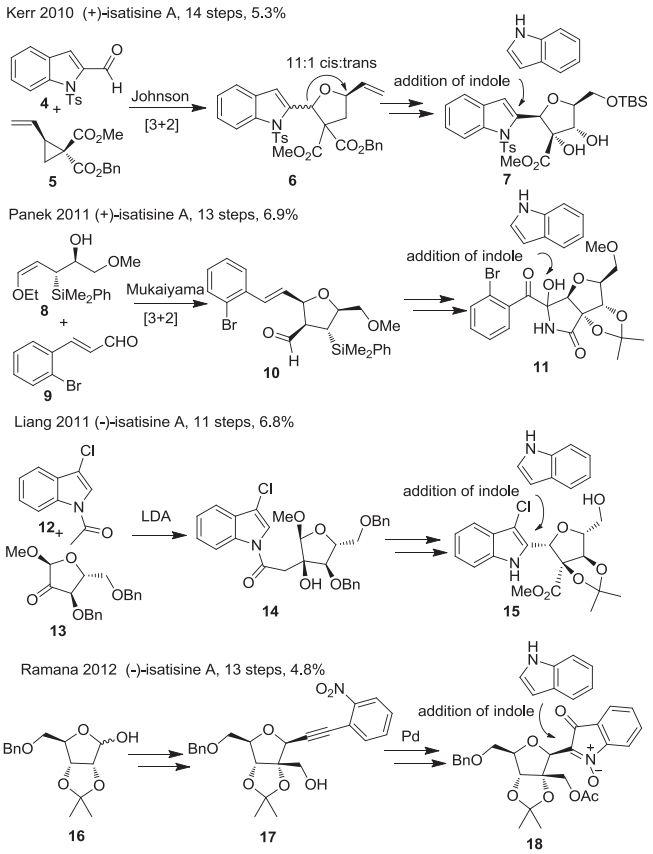
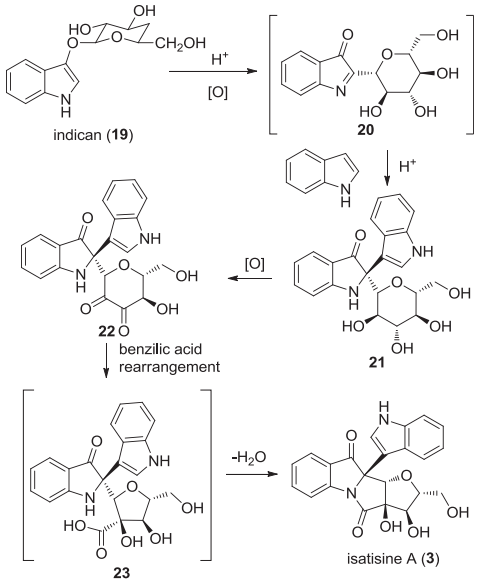
a silyl-directed Mukaiyama-type [3+2]-annulation for the preparation of a fully substituted furan core and a nucleophilic addition of indole to an intermediate N-acyliminium ion to form the quaternary center. Liang's synthesis featured an aldol reaction of acetylindole (**12**) and D-ribose derivative ketone (**13**), an unprecedented intramolecular *C* glycosylation of an indole, and a subsequent oxidative ring contraction. In 2012, Ramana[4f] reported their employment of late-stage four consecutive metal-mediated transformations to achieve (−)-isatisine A. All these elegant strategies had a common feature that a late-stage nucleophilic addition of indole was adopted to install the second indole moiety (Scheme 1).



Scheme 1. Total synthesis of (+)- and (−)-isatisine A.

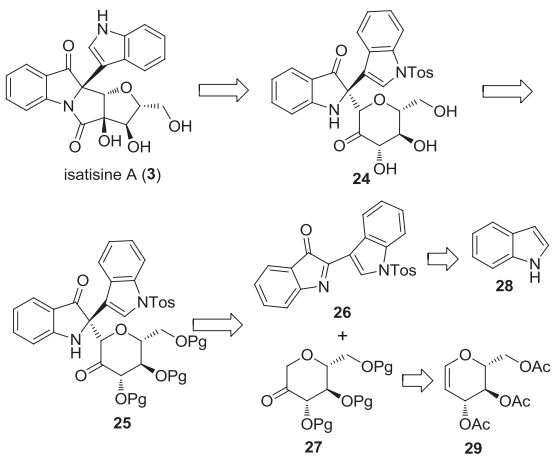
Fascinated by the unprecedented molecular structures of isatisine A, and the interesting hypothesis regarding their origins, we contemplated its biomimetic synthesis. We felt an endeavor that could lead to new synthetic strategies toward the indole *C*-glycoside species. For this novel alkaloid possessing an unprecedented fused tetracyclic skeleton, Chen did not give explanation of the source from the biogenetic view.[3] Studies suggest that the polyhydroxy core of some natural products is likely to arise in nature from glycosides.[5] We envisioned that indican (**19**), isolated from the same species, could be the precursor of isatisine A (**3**). After further survey, indican (**19**) was found in higher concentration in the young leaves than the old leaves of *I. indigotica* and as an important precursor for other compounds.[6] Thus, a plausible biogenetic pathway for (−)-isatisine A (**3**) was proposed by us, as shown in Scheme 2. Indican (**19**) may be first subjected to a rearrangement and subsequent oxidation to afford iminium **20**, which is immediately converted to bisindole *C*-glucoside **21** via a nucleophilic addition of indole.[7] Selective oxidation of **21** would provide 1, 2-diketone **22**,



Scheme 2. Proposed biogenetic pathway of isatisine A.

an intermediate that would undergo a benzilic acid rearrangement,[8] dehydration, to afford isatisine A.

Our retrosynthetic analysis of isatisine A is outlined in Scheme 3. To support this biogenetic pathway, the benzilic acid rearrangement was devised as a key biomimetic reaction for the synthesis of (−)-isatisine A. We envisioned that isatisine A would be afforded via selective oxidation of the α-hydroxy of **24** and the immediate benzilic acid rearrangement of the corresponding 1,2-diketone. Bisindole-glycoside **25** would be derived from the addition of D-glucal derivative **27** to 2-indolyl-3-one-3H-indole **26** and the stereochemistry of the newly formed aza-quaternary center would be induced by the stereostructure of **27**. Known 2-Indolyl-3-one-3*H*-indole **26** and D-glucal derivative **27** could be obtained from commercial available indole **28** and triacetyl-D-glucal **29**, respectively.



Scheme 3. Retrosynthetic analysis of isatisine A.

In previous communication,[4e] our group disclosed the biomimetic total synthesis of (−)-isatisine A (**3**), in which a convergent nucleophilic addition for installation of the indole moiety and an unprecedented benzilic acid rearrangement for construction of the densely substituted furan subunit were applied. In this article, we provided a full account of our investigation that led to the biomimetic total synthesis of (−)-isatisine A.

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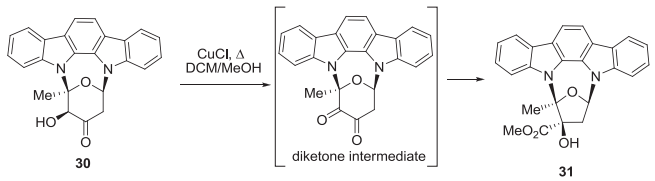
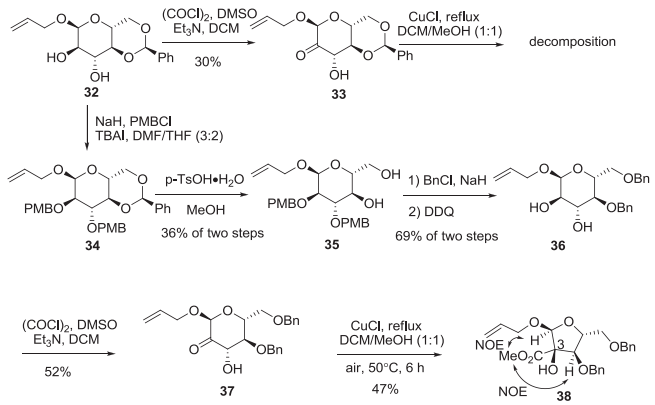
2. Results and discussion

Benzilic acid rearrangement[8] (BAR) was discovered by Liebig in 1883 and since then a number of theoretical studies were proceeded, however, few applications was found in synthesis of natural product. In 1996, Stoltz and Wood[8e] reported the unexpected employment of an efficient, highly stereoselective benzilic acid rearrangement on the pyranosylated indolocarbazole **30** to give the K252a tetrahydrofuran moiety **31** via a putative α-diketone intermediate using methanolic CuCl (Scheme 4). More early, one example of tetrahydropyran ring contracting to tetrahydrofuran ring was reported by Hanessian via an α-ketol rearrangement in the total synthesis of spectinoic acid.[9]



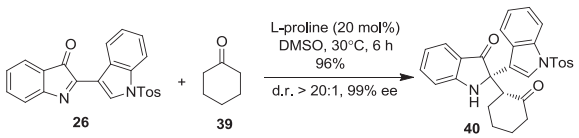
Scheme 4. Application of BER by Stoltz and Wood.



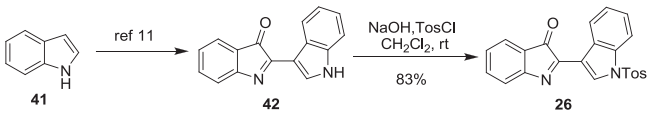
Scheme 5. Model studies of benzilic acid rearrangement.

Thus, we initially conducted the model studies. The known benzylidene-protected glucose derivative **32**[10] underwent Swern oxidation to afford α-hydroxy ketone **33**. Under Stoltz and Wood's conditions,[8e] α-Hydroxy ketone **33** was refluxed in DCM/MeOH (1:1) in the presence of excess CuCl to obtain the deprotection product, and further heating led to the decomposition. The additional six-membered ring in **33** would presumably prevent the rearrangement due to restrict in the respect of stereo-chemical configuration. Therefore, the benzyl group was chose to selectively protect the dihydroxy. Benzyl-protection of **34**, followed cleavage of the isopropylidene group, gave diol **36** in 69% yield. Swern oxidation of **36** afforded α-hydroxy ketone **37** in 52% yield. The benzilic acid rearrangement of **37** in DCM/MeOH (1:1) in the presence of CuCl successfully gave the desired product **38** as a single isomer. The configuration of **38** was determined by ^{1}H NOE spectroscopy. The successful ring contractive rearrangement of *O*-glucoside to *O*-furanoside increased our confidence in the biomimetic synthesis of isatisine A.

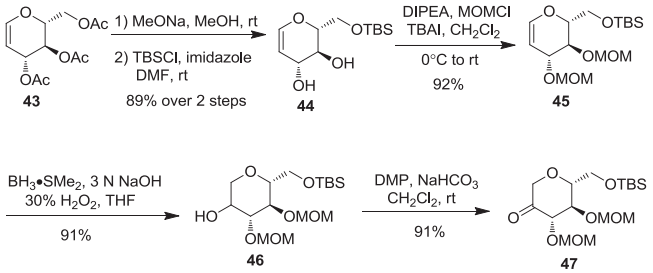
In our previous studies,[11] we reported a Mannich reaction of 2-aryl-3*H*-indol-3-ones with aldehydes or ketones in the presence of L-proline as a catalyst, giving the corresponding aza-quaternary carbon addition product in good yield with excellent regio- and enantioselectivity. Although the Mannich reaction proceeded well between iminium **26** and aldehyde or ketone (Scheme 6), we doubted that whether D-glucal derivative **47** was suitable for it. According to reported methods,[11,12] 2-indolyl-3-one-3*H*-indole **26** could be obtained from indole in three steps. Meanwhile, the cleavage of the acetyl group of commercial triacetyl-D-glucal **43**, followed by selective TBS-protection of the primary hydroxyl, gave **44** in 89% overall yield. The ketone **47** was obtained via MOM group protection of the remaining dihydroxy, regioselective hydroboration-oxidation, and Dess–Martin oxidation (Schemes 7 and 8).



Scheme 6. Asymmetric Mannich reaction between 2-Indolyl-3-one-3*H*-indole **26** and cyclohexanone **39.**

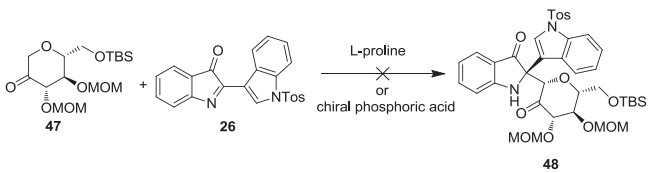


Scheme 7. Synthesis of compound **26**.



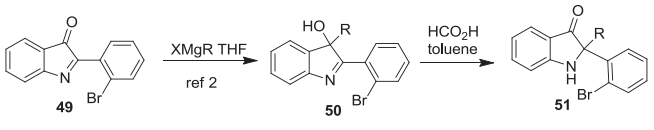
Scheme 8. Synthesis of compound **47**.

After a number of surveys, the addition of **47** to the 2-indolyl-3-one-3*H*-indole **26** in the presence of L-proline[11] or chiral phosphoric acid failed (Scheme 9). The different electron and steric effects might account for this. At this point, another addition method should be adopted. We envisioned that the enolate of ketone **47** would be an active intermediate that could be added to the carbonyl or the iminium carbon of **26**. According to McWhorter's report,[13] the product from addition to the carbonyl carbon could be in turn rearranged to yield the product from addition to the iminium carbon under acid conditions (Scheme 10 and 11).

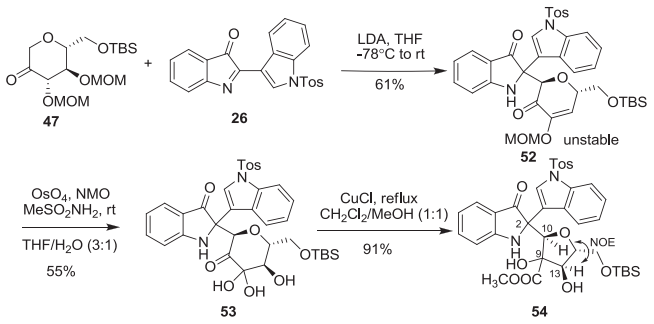


Scheme 9. Mannich reaction of **47** and **26**.

To our delight, the enolate of **47**, in situ formed by LDA, was added to the iminium carbon rather than the carbonyl carbon to afford **52** in 61% yield as a sole diastereoisomer. Although the β-hydroxy was eliminated, the hydroxyl could be reintroduced via



Scheme 10. The rearrangement of **50** to **51**.



Scheme 11. Synthesis of compound **55**.

dihydroxylation to furnish **53**. Treatment of **53** with CuCl in CH_2Cl_2/MeOH (1:1)[8e] uneventfully gave ring contraction product, α, β-dihydroxy ester **54**, in 91% yield. The stereochemistry of C10 and C13 were established by NOE experiment. Obviously, the stereostructure of C10 was inconsistent with that of isatisine A. We surmised that the negative result could be attributed to the E1cb elimination of OMOM group before addition. The elimination would result in the configuration change of lithium enolate to favor attack to iminium carbon of **26** from more sterically accessible enolate α-face. Unfortunately, endeavors toward the epimerization of **52** were unfruitful, due to the unstable nature of **52**.

In order to explore the last reaction conditions and synthesize the isomer of isatisine A, we conducted the subsequent experiment. Attempts (Mg/MeOH, Na/aphthalene, SmI_2, and TBAF)[14] to cleave the Tos group of **54** were unfruitful. The acid **55** was obtained in 82% yield via deprotected the Tos group and hydrolysis of the methyl ester in the presence of K_2CO_3/MeOH.[14h] We tried a number of condensation conditions (DIC/NHS, BOP/Et_3N, EDC, EDCI, DEPBT, and Mukaiyama reagent), but did not obtain the desired lactam **56**. We wondered whether the lactamization could realize before the deprotection of the Tos group. Gratifyingly, treatment of **54** with PTSA in refluxing toluene gave compound **57** in 64% yield, accompanying the cleavage of TBS group. On the base of previous surveys, photo-assisted cleavage of Tos group[15] afforded lactam **56** in 27% yield. We have synthesized the *p*-bromobenzoyl derivative of **56**, but the single crystal of which could not be obtained after many trials.

In order to elucidate the stereochemistry of C2 and C9 in **56**, the electronic circular dichroisms (ECD) of four possible candidate stereoisomers of **56** were performed (Fig. 2) (See Supplementary data). The experimental spectra match those calculated for structure **56a** and **56b** as can be seen from the comparison of positive CEs at 230. Therefore, compound **56** is more likely to be the structure of **56a** or **56b**. Given the model study of benzilic acid rearrangement shown in Scheme 5, the hydroxyl group at C3 in compound **38** is *R* configuration, conforming to that of the hydroxyl group at C9 in compound **56a**. Thus, the structure of **56** was proposed to be **56a**. The configuration of C9 in **56a** was also in consistency with the experimental result that the lactamization of **55** to form the *trans*-fused five member ring was difficult (Scheme 12) because such a process in the present case would experience high strain.

Although the correct stereostructure of isatisine A was not achieved, the enolate addition to the iminium carbon was

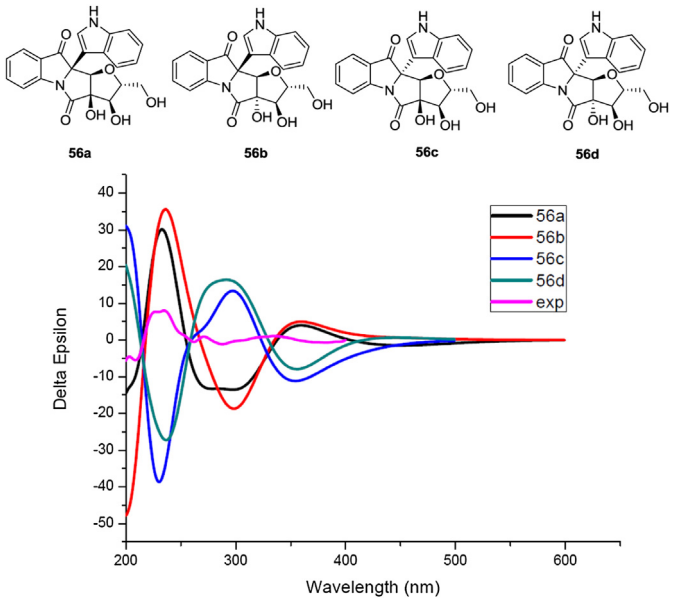
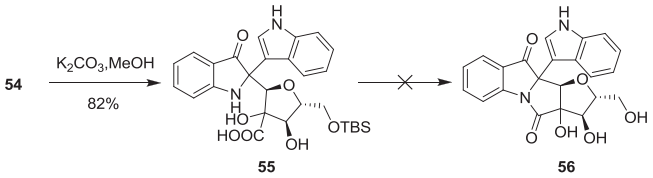


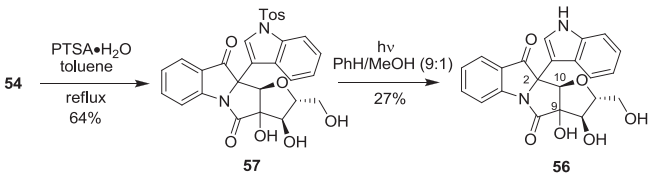
Fig. 2. The CD and ECD spectra of **56**.

successfully tested and biomimetic benzilic acid rearrangement was realized in the synthesis. Those studies lay a solid foundation to achieve the biomimetic synthesis of isatisine A.

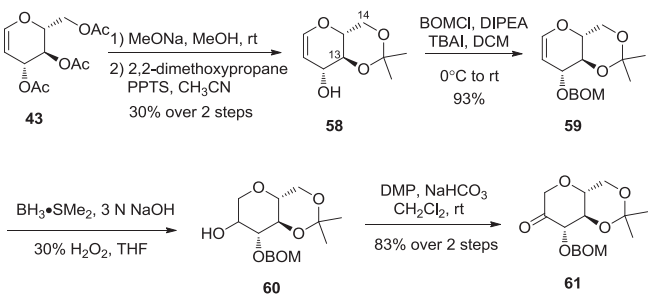
According to Kerr's report,[4a–b] the C2-epimer could be isomerized to the desired stereochemistry under acid conditions. Thus, controlling the stereochemistry of C10 was the key step to synthesize isatisine A and the stereochemistry of C9 was expected to be induced by the correct 2*H*-pyran-3-one configuration. We



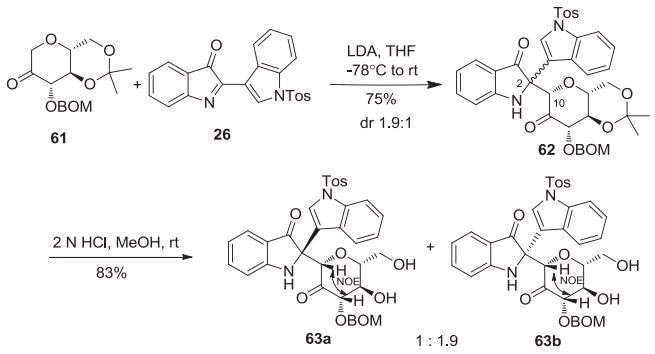
Scheme 12. Attempts to the synthesis of lactam **56**.



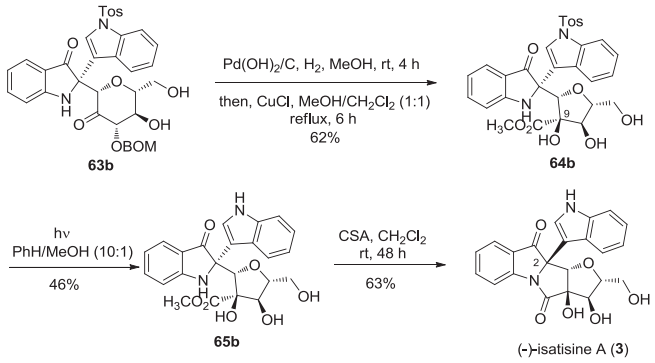
Scheme 13. Synthesis of lactam **56**.



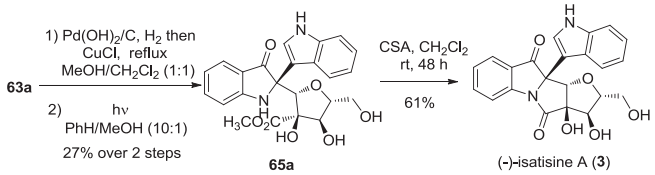
Scheme 14. Synthesis of 2*H*-pyran-3-one **61**.



Scheme 15. Synthesis of **63a** and **63b**.



Scheme 16. Total synthesis of (−)-isatisine A from **63b**.



Scheme 17. Total synthesis of (−)-isatisine A from **63a**.

envisioned that the configuration of C10 would be desired, if the E1cb elimination was avoided. Therefore, the isopropylidene group was chose to protect the diol at C13 and C14. It is believed that the newly installed six-membered ring would make the group at C13 hard to leave.

The known isopropylidene protected D-glucal **58** was obtained from triacetyl-D-glucal **43** according to the literature.[16] The screen of protecting group of the remaining hydroxyl expended a lot of time. BOM was found to be the best protecting group. For others, such as SEM, MOM and TBS, confronted the failure of addition to the iminium or the decomposition of the starting material in the deprotection procedure. Regioselective hydroboration-oxidation of **60**, followed by Dess–Martin oxidation, afforded the 2*H*-pyran-3-one **61** in 83% yield of two steps.

The lithium enolate of **61** was added to iminium carbon of **26** to give a 1.9:1 mixture of **62** in 75% yield. To the best of our knowledge, this reaction represents the first addition of a glucoside derivative to the iminium carbon of indolone. After cleavage of the isopropylidene group, **63a** and **63b** were isolated, and the stereochemistry of the newly formed C10 stereocenter was identified by NOE experiment and the configuration at C2 was distributed by experimental and computational optical rotation data.[17] As we expected, the configuration of C10 was consistent with that of isatisine A.

63b was chose to explore the subsequent route. The BOM group of **63b** was removed under hydrogenation in the presence of $Pd(OH)_2/C$ to give the corresponding triol, which was treated with CuCl in refluxing $MeOH/CH_2Cl_2$ (1:1)[8e] to furnish the desired β-hydroxy ester **64b** in overall 62% yield. It is worth to note that the precursor, which was only removed the BOM group with isopropylidene group retained could not be rearranged under the same condition. We envisioned that the stereochemistry of newly formed C9 stereocenter via benzilic acid rearrangement would be closely related to the stereostructure of 2*H*-pyran-3-one ring. According to the previous study, deprotection of the Tos group prior to lactamization was better. Finally, cleavage of the Tos group, subsequent lactamization by treatment with CSA for 48 h, gave (−)-isatisine A in 29% yield from **64b**. As Kerr's report,[4a–b] the inappropriate configuration of C2 was epimerized under acid conditions. The spectral data of the synthetic **3** were in accord with those reported for the natural (−)-isatisine A.[3]

In addition, **63a** was converted to (−)-isatisine A in overall 16% yield from **63a** under a same protocol (Schemes 13–17).

3. Summary

In conclusion, the biomimetic total synthesis of (−)-isatisine A has been achieved in eight steps from known **58**. A convergent nucleophilic addition of 2-indolyl-3-one-3*H*-indole **26** with lithium enolate of D-glucal derivative was developed and applied to assemble the biindole-glucal structure, and a biomimetic benzilic acid rearrangement was used to construct the densely substituted 4H-furan subunit. The stereochemistry of all newly formed stereocenters in the two reactions was found to be controlled by the stereostructure of pyranone ring. Our synthetic efforts have established an efficient route towards indole *C*-glycoside and conspicuously demonstrated the utility of benzilic acid rearrangement for diastereoselective preparation of densely substituted furan subunit from glucal derivative.

4. Experimental section

4.1. General

All moisture-sensitive reactions were performed under an atmosphere of Ar. Glassware was flame dried prior to use. THF was dried by distillation over Na/K. CH_2Cl_2 was dried by distillation over CaH_2. Unless otherwise stated, solvents and reagents were used as received. Column chromatography was generally performed on silica gel (200–300 mesh) and TLC inspections were on silica gel GF254 plates. ^1H NMR spectra were recorded at 400 MHz spectrometers. Chemical shifts (δ) are reported in parts per million downfield from $Si(CH_3)_4$ with the partially deuterated solvent as the internal standard ($CDCl_3$ δ 7.26). Data are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, dd=doublet of doublet, b=broad, q=quartet, m=multiplet). ^{13}C NMR spectra were recorded at 100 MHz spectrometers. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard ($CDCl_3$ δ 77.0, CD_3OD δ 49). IR spectra were recorded on a Nicolet 670 FTIR spectrophotometer and reported in wave numbers (cm^{-1}). HRMS data were determined on a Bruker Daltonics APEXII 47e FT-ICR spectrometer. Optical rotation calculations were performed using Gaussian 09 package.

4.2. Experimental procedures and data of synthetic intermediates

*4.2.1. (2R,4aR,6S,8S,8aS)-6-(Allyloxy)-8-hydroxy-2-phenyltetrahydropyrano[3,2-d][1,3]dioxin-7(6H)-one (**33**).* To a solution of DMSO (97 μL, 1.4 mmol) in DCM (5 mL), was slowly added

$(COCl)_2$ (55 μL, 0.65 mmol) at −78 °C, and the mixture was stirred at this temperature for 15 min, then a solution of **32**(168 mg, 0.54 mmol) in DCM (3 mL) was added dropwise. After 1 h at −78 °C, Et_3N (0.38 mL, 2.7 mmol) was added and the reaction was warmed to rt over 30 min, then saturated aq NH_4Cl was added. The mixture was extracted by EtOAc. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, filtered, concentrated in vacuo. Purification by flash column chromatography (petroleum ether/ethyl acetate 3:1 to 2:1) yielded alcohol **33** (50 mg, 30%) as a white flocculent solid. mp 180–182 °C. $[\alpha]_D^{26.3}$ +159.0 (*c* 1.00, $CHCl_3$). ^1H NMR (400 MHz, DMSO-d_6): δ 7.43–7.45 (m, 2H), 7.39–7.40 (m, 3H), 5.86–5.94 (m, 1H), 5.67 (s, 1H), 5.50 (d, *J*=8.0 Hz, 1H), 5.34 (dq, *J*=1.6, 17.2 Hz 1H), 5.23 (d, *J*=4.4 Hz, 1H), 5.18 (dd, *J*=2.0, 10.4 Hz, 1H), 4.60 (dd, *J*=1.6, 9.6 Hz, 1H), 4.44–4.48 (m, 1H), 4.32 (dd, *J*=4.4, 9.6 Hz, 1H), 4.16–4.21 (m, 1H), 4.00–4.06 (m, 1H), 3.92 (*t*, *J*=10.0 Hz, 1H), 3.81–3.87 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.0, 137.6, 134.5, 129.5, 128.6, 126.8, 117.8, 102.4, 101.0, 81.4, 75.1, 68.9, 68.6, 66.0. IR (thin film, cm^{-1}) ν_{max}: 3407.9, 3076.1, 2958.0, 2921.6, 2866.2, 1744.7, 1643.3, 1549.0, 1498.3, 1452.3, 1213.2, 1077.1, 1041.7, 996.7, 755.1, 697.4. HRMS (ESI): calcd for $C_{16}H_{22}NO_6$ $[M+NH_4]^+$: 324.1442; found 324.1439.

*4.2.2. (2R,4aR,6S,7R,8S,8aR)-6-(Allyloxy)-7,8-bis((4-methoxy benzyl) oxy)-2-phenylhexahydropyrano[3,2-d][1,3]dioxine (**34**).* The diol **33** (1.4 g, 4.6 mmol) dissolved in DMF (6 mL) and THF (4 mL) was added dropwise at 0 °C (ice bath) to a suspension of NaH (392 mg, 70%, 11.4 mmol) in DMF (6 mL) and THF (4 mL), followed by addition of PMBCl (1.4 mL, 10.1 mmol) and TBAI (338 mg, 0.92 mmol). The mixture was stirred at 0 °C for 10 min, and then at rt overnight (12 h). The reaction was quenched by water, then extracted by EtOAc. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, filtered, concentrated in vacuo. Purification by flash column chromatography (petroleum ether/ethyl acetate 4:1) yielded alcohol **34** (1.1 g, 45%) as a colorless oil. $[\alpha]_D^{26.5}$ −10.0 (*c* 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, *J*=6.4 Hz, 2H), 7.26–7.37 (m, 7H), 6.84 (*t*, *J*=8.4 Hz, 4H), 5.88–5.98 (m, 1H), 5.53 (s, 1H), 5.32 (d, *J*=17.2 Hz, 1H), 5.22 (d, *J*=10.0 Hz, 1H), 4.74–4.85 (m, 4H), 4.60 (d, *J*=11.6 Hz, 1H), 4.14–4.26 (m, 2H), 4.00–4.06 (m, 2H), 3.84–3.90 (m, 1H), 3.76 (d, *J*=4.4 Hz, 6H), 3.67 (*t*, *J*=10.4 Hz, 1H), 3.51–3.59 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.23, 159.03, 137.35, 133.56, 130.88, 130.18, 129.49, 129.47, 128.72, 128.04, 125.89, 118.09, 113.65, 113.55, 101.05, 96.70, 82.03, 78.73, 78.17, 74.86, 73.04, 68.86, 68.30, 62.41, 55.07. IR (thin film, cm^{-1}) ν_{max}: 3053.5, 2926.3, 2866.4, 1686.7, 1612.4, 1586.1, 1513.4, 1461.9, 1265.0, 1248.6, 1087.0, 1035.0, 1001.5, 738.3, 701.1. HRMS (ESI): calcd for $C_{32}H_{36}O_8Na$ $[M+Na]^+$: 571.2302; found 571.2296.

*4.2.3. (2R,3R,4S,5R,6S)-6-(Allyloxy)-2-(hydroxymethyl)-4,5-bis((4-methoxybenzyl)oxy)tetrahydro-2H-pyran-3-ol (**35**).* To a solution of **34**(1.1 g, 2.0 mmol) in MeOH (10 mL) was added *p*-TsOH·H_2O (190 mg, 1.0 mmol), and the mixture was stirred at rt for 4 h. The reaction was quenched by Et_3N, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate 1:1 to 1:2) to afford alcohol **35** (762 mg, 80%) as a colorless oil. $[\alpha]_D^{26.8}$ +24.0 (*c* 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.26 (d, *J*=8.4 Hz, 4H), 6.85 (d, *J*=8.0 Hz, 4H), 5.87–5.96 (m, 1H), 5.31 (dd, *J*=1.6, 17.2 Hz, 1H), 5.19–5.22 (m, 1H), 4.90 (d, *J*=10.8 Hz, 1H), 4.75 (d, *J*=3.6 Hz, 1H), 4.65 (dd, *J*=1.6, 11.2 Hz, 2H), 4.55 (d, *J*=11.6 Hz, 1H), 4.14 (dd, *J*=5.2, 13.2 Hz, 1H), 3.98 (dd, *J*=6.4, 12.8 Hz, 1H), 3.72–3.80 (m, 7H), 3.60–3.64 (m, 2H), 3.50 (*t*, *J*=9.2 Hz, 1H), 3.45 (dd, *J*=3.6, 9.6 Hz, 2H), 2.93 (s, 1H), 2.49 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.23, 159.13, 133.65, 130.84, 130.10, 129.46, 129.41, 117.95, 113.78, 113.70, 95.62, 80.89, 79.33, 74.82, 72.42, 70.93, 70.13, 68.09, 61.97, 55.09, 55.08. IR (thin film, cm^{-1}) ν_{max}: 3431.9, 3054.5, 2924.3, 2838.5, 1612.5, 1586.0, 1513.6, 1463.1, 1265.3, 1249.0, 1094.9, 1057.6, 1035.2, 823.7, 738.6, 703.7. HRMS (ESI): calcd for $C_{25}H_{32}O_8Na$ $[M+Na]^+$: 483.1989; found 483.1982.

*4.2.4. (2S,3R,4R,5S,6R)-2-(Allyloxy)-5-(benzyloxy)-6-((benzyloxy) methyl)tetrahydro-2H-pyran-3,4-diol (**36**).* To a solution of **35** (677 mg, 1.5 mmol) in DMF (10 mL) was added NaH (110 mg, 80%, 3.7 mmol), and after 10 min, BnBr (0.42 mL, 3.5 mmol) was added. The reaction was stirred for 4 h at rt, then it was quenched by water, followed by extraction with EtOAc. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, filtered, concentrated in vacuo. Purification by flash column chromatography (petroleum ether/ethyl acetate 6:1) yielded Bn-protected product **35′** (840 mg, 89%) as a colorless oil. $[\alpha]_D^{26.2}$ +21.0 (*c* 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.31–7.40 (m, 12H), 7.22–7.30 (m, 2H), 6.92 (d, *J*=8.4 Hz, 4H), 5.96–6.06 (m, 1H), 5.38 (d, *J*=17.2 Hz, 1H), 5.27 (d, *J*=10.4 Hz, 1H), 4.99 (d, *J*=10.4 Hz, 1H), 4.92 (d, *J*=10.8 Hz, 1H), 4.77–4.87 (m, 3H), 4.67 (d, *J*=11.6 Hz, 2H), 4.51–4.56 (m, 2H), 4.23 (dd, *J*=5.2, 12.8 Hz, 1H), 4.05–4.11 (m, 2H), 3.83–3.89 (m, 1H), 3.81 (d, *J*=3.6 Hz, 6H), 3.78 (d, *J*=3.6 Hz, 1H), 3.68–3.72 (m, 2H), 3.62 (dd, *J*=3.6, 9.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.19, 158.99, 138.20, 137.81, 133.68, 130.94, 130.19, 129.47, 129.40, 128.14, 127.65, 127.61, 127.44, 127.43, 117.87, 113.64, 113.60, 95.62, 81.66, 79.44, 77.55, 75.18, 74.79, 73.22, 72.62, 70.08, 68.37, 67.99, 55.01. IR (thin film, cm^{-1}) ν_{max}: 3054.9, 2924.2, 2858.7, 1655.1, 1611.5, 1545.8, 1513.3, 1458.8, 1264.8, 1094.7, 1067.7, 1034.9, 739.3, 703.6. HRMS (ESI): calcd for $C_{39}H_{44}O_8Na$ $[M+Na]^+$: 663.2928; found 663.2913.

To a solution of Bn-protected product **35′** (651 mg, 1.0 mmol) in DCM (8 mL) and buffer solution (3 mL, 0.4 M Na_2HPO_4/0.4M NaH_2PO_4, 2:1), was added DDQ (578 mg, 2.5 mmol). The reaction was stirred at rt for 18 h, and then quenched by saturated aq NH_4Cl, followed by extraction by EtOAc. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, filtered, concentrated in vacuo. Purification by flash column chromatography (petroleum ether/ethyl acetate 6:1) yielded **36** (313 mg, 77%) as a colorless oil. $[\alpha]_D^{26.7}$ +117.0 (*c* 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.21–7.30 (m, 10H), 5.83–5.93 (m, 1H), 5.27 (dd, *J*=1.6, 17.2 Hz, 1H), 5.16 (dd, *J*=1.2, 10.4 Hz, 1H), 4.92 (d, *J*=3.6 Hz, 1H), 4.82 (d, *J*=11.2 Hz, 1H), 4.62 (d, *J*=12 Hz, 1H), 4.48–4.55 (m, 2H), 4.18 (dd, *J*=5.2, 12.8 Hz, 1H), 4.00 (dd, *J*=6.4, 12.8 Hz, 1H), 3.87 (*t*, *J*=9.2 Hz, 1H), 3.71–3.79 (m, 2H), 3.64–3.68 (m, 1H), 3.50–3.57 (m, 2H), 3.19 (s, 1H), 2.65 (d, *J*=9.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.24, 137.85, 133.51, 128.30, 128.27, 127.83, 127.79, 127.64, 127.60, 117.72, 97.25, 77.36, 75.05, 74.56, 73.39, 72.45, 70.30, 68.48, 68.37. IR (thin film, cm^{-1}) ν_{max}: 3413.1, 3056.2, 2923.0, 2865.4, 1637.7, 1597.8, 1545.5, 1496.2, 1454.1, 1265.5, 1149.1, 1118.4, 1048.2, 738.7, 702.4. HRMS (ESI): calcd for $C_{23}H_{28}O_6Na$ $[M+Na]^+$: 423.1778; found 423.1772.

*4.2.5. (2S,4S,5S,6R)-2-(Allyloxy)-5-(benzyloxy)-6-((benzyloxy) methyl)-4-hydroxydihydro-2H-pyran-3(4H)-one (**37**).* To a solution of DMSO (73 μL, 1.0 mmol) in DCM (5 mL), was slowly added $(COCl)_2$ (43 μL, 0.51 mmol) at −78 °C, and the mixture was stirred at this temperature for 15 min, then a solution of **36** (136 mg, 0.34 mmol) in DCM (2 mL) was added dropwise. After 1 h at −78 °C, Et_3N () was added and the reaction was warmed to rt over 30 min, then saturated aq NH_4Cl was added. The mixture was extracted by EtOAc. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, filtered, concentrated in vacuo. Purification by flash column chromatography (petroleum ether/ethyl acetate) yielded alcohol **37** (70 mg, 52%) as colorless oil. $[\alpha]_D^{27.0}$ +132.7 (*c* 0.52, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.33–7.37 (m, 5H), 7.28–7.32 (m, 5H), 5.79–5.89 (m, 1H), 5.25–5.30 (m, 2H), 5.19 (dd, *J*=1.2, 10.4 Hz, 1H), 4.88 (d, *J*=11.2 Hz, 1H), 4.63 (d, *J*=12.4 Hz, 1H), 4.52 (d, *J*=12.0 Hz, 1H), 4.44 (d, *J*=11.2 Hz, 1H), 4.37 (dq, *J*=1.2, 4.4 Hz, 1H), 4.32 (dd, *J*=1.2, 9.6 Hz, 1H), 4.14–4.19 (m, 1H), 3.98–4.06 (m, 2H), 3.72–3.81 (m, 2H), 3.31 (d, *J*=8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.6, 137.8, 137.1, 132.9, 128.4, 128.3, 128.1, 127.9, 127.8, 118.1, 100.2, 78.1,

77.2, 75.0, 73.6, 73.3, 68.8, 68.1 IR (thin film, cm^{-1}) ν_{max}: 3447.7, 3061.1, 3032.0, 2924.7, 2854.6, 1739.1, 1612.9, 1546.2, 1496.4, 1454.8, 1264.8, 1074.7, 1049.2, 1027.8, 739.1, 700.4. HRMS (ESI): calcd for $C_{23}H_{26}O_6Na$ $[M+Na]^+$: 421.1622; found 421.1617.

*4.2.6. (2S,4R,5R)-Methyl 2-(allyloxy)-4-(benzyloxy)-5-((benzyl oxy) methyl)-3-hydroxytetrahydrofuran-3-carboxylate (**38**).* To a solution of **37** (22 mg, 0.055 mmol) in MeOH (2 mL) and DCM (2 mL), was added CuCl (109 mg, 1.11 mmol). The reaction was refluxed at 50 °C for 6 h under air. The solid was filtered over a short silica column chromatography with DCM. The organic solvent was concentrated in vacuo, and the residue was purified by flash column chromatography (petroleum ether/ethyl acetate) to afford alcohol **38** (11 mg, 47%) as a colorless oil. $[\alpha]_D^{27.2}$ +120.0 (*c* 0.10, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.26–7.30 (m, 10H), 5.84–5.94 (m, 1H), 5.29 (dd, *J*=1.2, 17.2 Hz, 1H), 5.18–5.21 (m, 2H), 4.70 (d, *J*=12.0 Hz, 1H), 4.46–4.57 (m, 3H), 4.29–4.34 (m, 1H), 4.20–4.24 (m, 1H), 4.09–4.14 (m, 2H), 3.74 (s, 3H), 3.63–3.66 (m, 2H), 3.55 (dd, *J*=5.2, 10.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2, 138.0, 137.3, 133.5, 128.4, 128.3, 128.1, 128.0, 127.7, 127.6, 117.9, 102.4, 80.8, 80.0, 79.7, 73.4, 73.0, 69.1, 69.0, 52.8. IR (thin film, cm^{-1}) ν_{max}: 3297.2, 3059.2, 3032.0, 2918.4, 2850.3, 1741.2, 1658.6, 1597.0, 1544.2, 1511.7, 1454.4, 1265.6, 1106.7, 1072.5, 1043.3, 738.6, 701.0. HRMS (ESI): calcd for $C_{24}H_{28}O_7Na$ $[M+Na]^+$: 451.1727; found 451.1719.

*4.2.7. (4R,5R,6R)-6-(((tert-Butyldimethylsilyl)oxy)methyl)-4,5-bis(methoxymethoxy)tetrahydro-2H-pyran-3-ol (**46**).* To a stirred solution of compound **45**(800 mg, 2.3 mmol) in THF (20 mL) cooled in an ice bath, was added an excess of $BH_3 \cdot SMe_2$ complex (0.81 mL, 2 M in THF, 1.6 mmol). After stirring for 12 h at rt, excess borane was destroyed by careful addition of water (1.1 mL). Sodium hydroxide solution (3 M, 4.6 mL) was then added all at once, followed by dropwise addition of aq hydrogen peroxide (30%, 11.5 mL). After 1 h, the solution was diluted with ethyl acetate. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, filtered, concentrated in vacuo. Purification by flash column chromatography (petroleum ether/ethyl acetate 4:1) yielded alcohol **46** (766 mg, 91%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 4.77–4.80 (m, 1H), 4.73 (d, *J*=2.8 Hz, 3H), 4.34 (s, 1H), 4.00–4.04 (m, 1H), 3.86 (d, *J*=11.6 Hz, 1H), 3.73–3.77 (m, 1H), 3.50–3.55 (m, 2H), 3.45 (s, 3H), 3.37 (d, *J*=2.8 Hz, 3H), 3.25–3.29 (m, 1H), 3.10–3.16 (m, 2H), 0.87 (s, 9H), 0.06 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 98.4, 97.9, 90.4, 80.3, 74.3, 69.1, 62.5, 56.0, 55.8, 25.8, 18.3, −5.2, −5.5. IR (thin film, cm^{-1}) ν_{max}: 3439.1, 2930.8, 2855.9, 1467.5, 1385.9, 1253.1, 1150.4, 1102.0, 1027.9, 835.9, 778.7. HRMS (ESI): calcd for $C_{16}H_{34}O_7NaSi$ $[M+Na]^+$: 389.1966; found 389.1962.

*4.2.8. (4S,5R,6R)-6-(((tert-Butyldimethylsilyl)oxy)methyl)-4,5-bis(methoxymethoxy)dihydro-2H-pyran-3(4H)-one (**47**).* To a solution of Dess-Martin periodinane (1.36 g, 3.2 mmol) in CH_2Cl_2 (20 mL) at rt was added $NaHCO_3$ (897 mg, 10.7 mmol) and alcohol **46** (782 mg, 2.1 mmol). The reaction was stirred for 2 h at rt, at, which point it was quenched with water. The mixture was extracted with CH_2Cl_2 for three times and the combined organic fractions were dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (petroleum ether/ethyl acetate, 4:1) to provide **47** (707 mg, 91%) as a colorless oil. R_f=0.20 (silica gel, petroleum ether/ethyl acetate 4:1) $[\alpha]_D^{17.9}$ +0.3 (*c* 0.94, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 4.80–4.85 (m, 2H), 4.72–4.77 (m, 2H), 4.36 (d, *J*=9.2 Hz, 1H), 4.15 (d, *J*=15.2 Hz, 1H), 3.95–3.99 (m, 2H), 3.88–3.93 (m, 2H), 3.82–3.86 (m, 1H), 3.43 (s, 3H), 3.39 (s, 3H), 0.68 (s, 9H), 0.04 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.3, 97.8, 96.8, 81.8, 80.4, 76.6, 72.6, 62.8, 56.3, 56.1, 25.8, 18.2, −5.4, −5.5. IR (thin film, cm^{-1}) ν_{max}: 2954.3, 2931.3, 2895.0, 2857.0, 1743.8, 1468.5, 1361.8, 1254.1, 1151.2, 1106.5, 1025.6, 837.2, 779.3. HRMS (ESI): calcd for $C_{16}H_{32}O_7NaSi$ $[M+Na]^+$: 387.1810; found 387.1811.

*4.2.9. 2-((2R,6S)-6-(((tert-Butyldimethylsilyl)oxy)methyl)-4-(methoxymethoxy)-3-oxo-3,6-dihydro-2H-pyran-2-yl)-2-(1-tosyl-1H-indol-3-yl)indolin-3-one (**52**).* To a solution of compound **47** (137 mg, 0.38 mmol) in anhydrous THF (3 mL) at −78 °C was added a THF solution of LDA (0.5 M, 1.1 mL). The mixture was stirred for 30 min at −78 °C. A solution of compound **26** (94 mg, 0.24 mmol) in THF (1 mL) was added dropwise. The resulting solution was warmed to −30 °C over 30 min, and then stirred for 4.5 h at rt, and then quenched with water. The resulting mixture was transferred to a separatory funnel and the phases were allowed to separate. The aqueous layer was extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel flash column chromatography (ethyl acetate/petroleum ether=1:2) to afford 101 mg (61%) of **52**. $[\alpha]_D^{17.8}$ −24.9 (*c* 0.82, CH_3OH). ^1H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, *J*=8.4 Hz, 1H),7.61–7.74 (m, 5H), 7.41 (*t*, *J*=0.8 Hz, 1H),7.43 (s, 2H), 7.39–7.43 (m, 4H), 6.83 (*t*, *J*=8.0 Hz, 2H), 6.25 (d, *J*=4.4 Hz, 1H), 5.70 (s, 1H), 5.50 (s, 1H), 4.99 (d, *J*=6.8 Hz, 1H), 4.94 (d, *J*=6.8 Hz, 1H),4.54–4.56 (m, 1H), 3.87–3.91 (m, 1H), 3.67–3.71 (m, 1H), 3.37 (s, 3H), 2.29 (s, 3H), 0.83 (s, 9H), 0.01 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.8, 187.6, 159.5, 147.3, 144.9, 136.7, 135.5, 134.9, 129.8, 128.3, 126.8, 125.2, 125.0, 124.6, 123.3, 121.7, 121.0, 120.1, 119.5, 118.7, 113.5, 111.8, 94.3, 82.4, 73.5, 70.3, 65.1, 56.2, 25.6, 21.5, 18.0, −5.75, −5.80. IR (thin film, cm^{-1}) ν_{max}: 3399.8, 2954.1, 2929.1, 2856.7, 1700.6, 1618.9, 1486.5, 1469.2, 1371.2, 1320.7, 1173.4, 1147.7, 967.6, 838.2, 750.5, 537.2. HRMS (ESI): calcd for $C_{37}H_{42}N_2NaO_8SSi$ $[M+Na]^+$: 725.2323; found 725.2314.

*4.2.10. 2-((2R,5R,6R)-6-(((tert-Butyldimethylsilyl)oxy)methyl)-4,4,5-trihydroxy-3-oxotetrahydro-2H-pyran-2-yl)-2-(1-tosyl-1H-indol-3-yl)indolin-3-one (**53**).* To a solution of **52** (225 mg, 0.32 mmol) in THF/H_2O (3:1, 8 mL) was added NMO (150 mg, 50%), $MeSO_2NH_2$ (36 mg, 0.38 mmol), catalytic amount of OsO_4 successively, and the mixture was stirred at room temperature for 2 h. Then aq $NaHSO_3$ was added, and the resulting mixture was extracted with EtOAc. The combined organic fractions were dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (petroleum ether/ethyl acetate, 4:1) to provide **53** (122 mg) in 55% yield. The product was unstable and the next step was undergone immediately.

*4.2.11. (2R,4R,5R)-Methyl 5-(((tert-butyldimethylsilyl)oxy) methyl)-3,4-dihydroxy-2-(3-oxo-2-(1-tosyl-1H-indol-3-yl)indolin-2-yl)tetrahydrofuran-3-carboxylate (**54**).* To a solution of **53** (122 mg, 0.18 mmol) in MeOH/CH_2Cl_2 (1:1, 6 mL) was added CuCl (454 mg, 4.6 mmol), and the mixture was refluxed for 2 h. Then, the reaction mixture was filtered over a short silica gel column using CH_2Cl_2. The filtrate was concentrated in vacuo and the residue was purified by column chromatography (petroleum ether/ethyl acetate, 2:1) to provide **54** (113 mg, 91%). $[\alpha]_D^{17.8}$ −1.5 (*c* 1.07, CH_3OH). ^1H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, *J*=8.4 Hz, 1H), 7.78 (s, 1H), 7.73–7.75 (m, 3H), 7.56 (d, *J*=7.6 Hz, 1H), 7.47–7.51 (m, 5H), 6.94 (d, *J*=8.0 Hz, 1H), 6.86 (*t*, *J*=7.2 Hz, 1H), 5.56 (s, 1H), 5.27 (s, 1H), 4.60–4.65 (m, 1H), 4.27 (s, 1H), 3.69–3.84 (m, 3H), 3.66 (s, 3H), 2.55 (d, *J*=11.2, 1H), 2.31 (s, 3H), 0.77 (s, 9H), −0.12 (s, 3H), −0.23 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.6, 172.1, 161.5, 144.9, 137.8, 135.6, 135.1, 129.8, 128.0, 1227.0, 125.1, 124.9, 124.6, 123.2, 121.7, 121.0, 119.9, 119.7, 113.5, 113.4, 83.7, 83.6, 81.2, 69.9, 62.4, 53.4, 25.6, 21.5, 18.1, −5.8, −5.8. HRMS (ESI): calcd for $C_{36}H_{43}N_2O_9SSi$ $[M+H]^+$: 707.2453; found 707.2443.

4.2.12. (2R,3R,10bR)-3,3a-Dihydroxy-2-(hydroxymethyl)-10a-(1-tosyl-1H-indol-3-yl)-3,3a-dihydro-2H-furo[2′,3′:3,4]pyrrolo [1,2-a]

*indole-4,10(10aH,10bH)-dione (**57**).* To a solution of **54** (125 mg, 0.18 mmol) in toluene (6 mL) was added *p*-TsOH·H_2O (84 mg, 0.44 mmol) and the solution was refluxed for 2.5 h aq $NaHCO_3$ was poured into the flask and the mixture was extracted by EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate, 1:2) to provide **57** (63 mg) in 64% yield. $[\alpha]_D^{17.8}$ −5.8 (*c* 1.06, CH_3OH). ^1H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, *J*=8.4 Hz, 1H), 7.76 (s, 1H), 7.72 (d, *J*=8.4 Hz, 2H), 7.66 (*t*, *J*=8.8 Hz, 2H), 7.52−7.56 (m, 1H), 7.29 (*t*, *J*=8.0 Hz, 1H) 7.17−7.20 (m, 3H), 7.12 (d, *J*=8.4 Hz, 1H), 7.06 (*t*, *J*=7.6 Hz, 1H), 6.17 (brs, 1H), 5.14 (s, 1H), 4.47 (s, 1H), 4.36 (d, *J*=12.4 Hz, 1H), 4.25−4.28 (m, 1H), 2.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.8, 173.0, 158.4, 145.4, 136.9, 135.5, 134.7, 130.0, 127.8, 127.0, 125.2, 125.1, 124.8, 123.9, 123.6, 122.6, 121.6, 117.9, 115.0, 113.8, 86.5, 80.3, 79.6, 74.0, 71.3, 70.6, 21.5. IR (thin film, cm^{-1}) ν_{max}: 3644.7, 3297.7, 3150.6, 2920.7, 1752.4, 1703.4, 1614.6, 1470.5, 1370.2, 1172.1, 1090.4, 930.9, 754.5, 575.3. HRMS (ESI): calcd for $C_{29}H_{25}N_2O_6S$ $[M+H]^+$: 561.1326; found 561.1319.

*4.2.13. (2R,3R,10bR)-3,3a-Dihydroxy-2-(hydroxymethyl)-10a-(1H-indol-3-yl)-3,3a-dihydro-2H-furo[2′,3′:3,4]pyrrolo[1,2-a]indole-4,10(10aH,10bH)-dione (**56**).* The compound **57** (20 mg, 0.036 mmol) in CH_3OH/PhH (1:9, 10 mL) was carefully sealed and irradiated using a UV lamp for 2.5 h. The resulting mixture was concentrated in vacuo and then purified by flash column chromatography (silica gel, CH_2Cl_2/MeOH 50:1) to give compound **56** (4 mg) in 27% yield. $[\alpha]_D^{17.8}$ −12.4 (*c* 0.42, CH_3OH). ^1H NMR (400 MHz, CD_3OD): δ 7.51−7.57 (m, 3H), 7.45 (s, 1H), 7.31 (d, *J*=8.0 Hz, 1H), 7.15 (d, *J*=8.4 Hz, 1H), 7.04 (*t*, *J*=7.6 Hz, 1H), 6.97 (*t*, *J*=7.6 Hz, 1H), 6.89 (*t*, *J*=8.0 Hz, 1H), 5.30 (s, 1H), 4.44 (s, 1H), 4.33 (s, 2H), 4.08 (s, 1H). ^{13}C NMR (100 MHz, CD_3OD): δ 202.6, 175.3, 162.0, 139.0, 137.6, 126.4, 125.6, 125.4, 125.3, 122.7, 122.1, 121.9, 120.3, 115.9, 112.9, 112.7, 88.0, 82.4, 81.4, 75.2, 72.9, 72.8. IR (thin film, cm^{-1}) ν_{max}: 3429.6, 2924.0, 2855.0, 1744.4, 1705.7, 1617.1, 1466.9, 1321.7, 1289.5, 1171.5, 1094.7, 749.8. HRMS (ESI): calcd for $C_{22}H_{19}N_2NaO_6$ $[M+H]^+$: 407.1238; found 407.1240.

*4.2.14. (4aR,8R,8aS)-8-((Benzyloxy)methoxy)-2,2-dimethyl-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3]dioxine (**59**).* To a solution of compound **58** (1.55 g, 8.33 mmol) in CH_2Cl_2 (15 mL) was added DIPEA (3.59 mL, 20.82 mmol), BOMCl (2.31 mL, 16.66 mmol) and TBAI (306.27 mg, 0.83 mmol) at 0 °C. The resulting mixture was stirred under rt for 10 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution, and extracted with ethyl acetate. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, filtered, concentrated in vacuo. Purification by flash column chromatography (petroleum ether/ethyl acetate 25:1) yielded compound **59** (2.37 g, 93%) as a colorless oil. $[\alpha]_D^{27.9}$ +19.6 (*c* 0.51, $CHCl_3$) ^1H NMR (400 MHz, $CDCl_3$): δ 7.25−7.38 (m, 5H), 6.31 (dd, *J*=1.6, 6.4 Hz, 1H), 4.93 (d, *J*=6.8 Hz, 1H), 4.84 (d, *J*=7.2 Hz, 1H), 4.76 (dd, *J*=2.0, 6.0 Hz, 1H), 4.61−4.68 (m, 2H), 4.39−4.42 (m, 1H), 3.86−4.00 (m, 2H), 3.72−3.83 (m, 2H), 1.51 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.4, 137.8, 128.3, 127.9, 127.6, 102.4, 99.6, 93.6, 71.9, 71.7, 69.7, 69.3, 61.6, 29.0, 19.0; IR (thin film, cm^{-1}) ν_{max}: 2887.8, 1639.5, 1382.9, 1268.1, 1091.0, 1043.5; HRMS (ESI): calcd for $C_{17}H_{26}NO_5$ $[M+NH_4]^+$: 324.1805; found 324.1813.

*4.2.15. (4aR,8R,8aR)-8-((Benzyloxy)methoxy)-2,2-dimethylhexahydropyrano[3,2-d][1,3]dioxin-7-ol (**60**).* According to the similar procedure for **46**, **60** (2.27 g) was afforded as a colorless oil by flash column chromatography (petroleum ether/ethyl acetate 4:1) in 87% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 7.26−7.36 (m, 5H), 4.99 (d, *J*=6.8 Hz, 1H), 4.87 (d, *J*=7.2 Hz, 1H), 4.78 (d, *J*=11.6 Hz, 1H), 4.62 (d, *J*=11.6 Hz, 1H), 4.01−4.06 (m, 1H), 3.88−3.93 (m, 2H), 3.64−3.70 (m, 2H), 3.57 (*t*, *J*=9.2 Hz, 1H), 3.44 (*t*, *J*=8.8 Hz, 1H), 3.16−3.29 (m, 2H), 1.49 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.9, 128.5, 128.0, 127.9, 99.4, 95.9, 84.6, 72.5, 72.4, 70.2, 70.1, 69.8, 62.2, 29.0, 19.0; IR (thin film, cm^{-1}) ν_{max}: 3435.3, 2881.8, 1376.9, 1103.4, 1032.4; HRMS (ESI): calcd for $C_{17}H_{24}NO_6$ $[M+NH_4]^+$: 342.1911; found 342.1903.

*4.2.16. (4aR,8S,8aR)-8-((Benzyloxy)methoxy)-2,2-dimethyltetrahydropyrano[3,2-d][1,3]dioxin-7(6H)-one (**61**).* According to the similar procedure for **47**, **61** (2.14 g) was afforded as a colorless oil by flash column chromatography (petroleum ether/ethyl acetate 10:1 to 4:1) in 95% yield. $[\alpha]_D^{27.9}$ −31.5 (*c* 0.54, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.26−7.39 (m, 5H), 4.96 (dd, *J*=6.8, 10.8 Hz, 2H), 4.80 (d, *J*=11.2 Hz, 1H), 4.63 (d, *J*=11.2 Hz, 1H), 4.41 (d, *J*=10.4 Hz, 1H), 4.19 (d, *J*=15.2 Hz, 1H), 4.00−4.04 (m, 2H), 3.95 (*t*, *J*=9.6 Hz, 1H), 3.80 (*t*, *J*=10.0 Hz, 1H), 3.58−3.64 (m, 1H), 3.16−3.29 (m, 2H), 1.53 (s, 3H), 1.43 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.3, 137.5, 128.4, 128.3, 127.8, 99.5, 94.4, 74.7, 74.2, 71.9, 69.5, 62.1, 29.0, 19.0; IR (thin film, cm^{-1}) ν_{max}: 2922.7, 1737.0, 1380.4, 1113.4, 1040.3, 699.5; HRMS (ESI): calcd for $C_{17}H_{26}NO_6$ $[M+NH_4]^+$: 340.1755; found 340.1762.

*4.2.17. 2-((4aR,6S,8S,8aR)-8-((Benzyloxy)methoxy)-2,2-dimethyl-7-oxohexahydropyrano[3,2-d][1,3]dioxin-6-yl)-2-(1-tosyl-1H-indol-3-yl)indolin-3-one (**62**).* According to the similar procedure for **52**, **62** (117 mg) was afforded as a colorless oil by flash column chromatography (petroleum ether/ethyl acetate 9:2) in 75% yield. The product is unstable, so ^1H NMR and ^{13}C NMR of pure **62** could not be obtained, R_f=0.38 (silica gel, petroleum ether: ethyl acetate 2:1).

*4.2.18. (S)-2-((2S,4S,5R,6R)-4-((Benzyloxy)methoxy)-5-hydroxy-6-(hydroxymethyl)-3-oxotetrahydro-2H-pyran-2-yl)-2-(1-tosyl-1H-indol-3-yl)indolin-3-one (**63a**) and (R)-2-((2S,4S,5R,6R)-4-((benzyloxy)methoxy)-5-hydroxy-6-(hydroxymethyl)-3-oxotetrahydro-2H-pyran-2-yl)-2-(1-tosyl-1H-indol-3-yl)indolin-3-one (**63b**).* To a solution of compound **62** (147 mg, 0.204 mmol) in MeOH (5 mL) at rt was added HCl (2 N, 0.5 mL). The mixture was stirred for 2 h at, which point the solvent was removed. The remaining yellow-orange residue was preadsorbed onto silica and purified by flash column chromatography (ethyl acetate/petroleum=1.5:1) to yield compound **63a** (39.7 mg) and **63b** (75.3 mg) as a light yellow solid, R_f=0.20 (silica gel, petroleum ether: ethyl acetate 1; 2).

Both of the absolute configurations of C11 in six-member ring of **63a** and **63b** were determined by its NOE experiments. Meanwhile, the absolute configuration of C2 in **63a** and **63b** were determined by the experimental and computational optical rotation data (the B3LYP/6-31G method). Giving **63a** as our desired configuration and **63b** as its diastereomer, the sum of optical rotation data for candidate **63a** is −274.44 and **63b** is 233.78. The optical rotation of minor and major product was measured to be −92.0 and 90.0, respectively. The desired **63a** was matched with the experimental minor product, which suggested the configuration of minor product. Thus, the minor S7 and major product was elucidated as **63a** and **63b**, respectively. (Optical rotation calculations were performed using PCM method of salvation and the methanol was specified as the solvent, which was in agreement with the experiment condition). Compound **63a** $[\alpha]_D^{19.3}$ −92.0 (*c* 0.10, CH_3OH); ^1H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, *J*=8.4 Hz, 1H), 7.84 (d, *J*=8 Hz, 1H), 7.28 (s, 1H), 7.68 (d, *J*=8.4 Hz, 2H), 7.48 (d, *J*=7.6 Hz, 1H), 7.39−7.43 (m, 3H), 7.15−7.28 (m, 4H), 7.10 (d, *J*=8.4 Hz, 2H), 6.82 (d, *J*=8.4 Hz, 1H), 6.76 (*t*, *J*=7.2 Hz, 1H), 5.78 (s, 1H), 5.02 (s, 1H), 4.92 (d, *J*=7.2 Hz, 1H), 4.69−4.72 (m, 2H), 4.55 (d, *J*=11.6 Hz, 1H), 4.33 (d, *J*=8.8 Hz, 1H), 3.97 (b, 1H), 3.75−3.91 (m, 3H), 3.62−3.66 (m, 1H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.1, 198.4, 161.0, 145.0, 137.9, 136.6, 135.5, 134.7, 129.9, 128.6, 128.2, 127.7, 126.8, 125.0, 124.8, 124.6, 123.5, 121.8, 119.2, 119.1, 117.9, 113.8, 111.8, 95.0, 85.7, 82.0, 80.1, 74.1, 70.6, 69.1, 61.9, 21.5; IR (thin film, cm^{-1}) ν_{max}: 3516.2, 3411.9, 1712.7,

1621.9, 1423.5, 1362.7,1223.3, 1092.5756.4; HRMS (ESI): calcd for $C_{37}H_{34}N_2NaO_9S$ $[M+Na]^+$: 705.1877; found 705.1872. Compound **63b** $[\alpha]_D^{19.3}$ +90.0 (*c* 0.10, CH_3OH); ^1H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, *J*=8.4 Hz, 1H), 7.75 (s, 1H), 7.67–7.72 (m, 3H), 7.60 (d, *J*=7.6 Hz, 1H), 7.35–7.39 (m, 1H), 7.22–7.31 (m, 5H), 7.11–7.16 (m, 3H), 6.81 (*t*, *J*=7.6 Hz, 1H), 6.75 (d, *J*=8.4 Hz, 1H), 5.90 (s, 1H), 4.86 (s, 1H), 4.86 (d, *J*=6.8 Hz, 1H), 4.73 (d, *J*=7.2 Hz, 1H), 4.67 (d, *J*=11.6 Hz, 1H), 4.54 (d, *J*=11.6 Hz, 1H), 4.22 (d, *J*=9.6 Hz, 1H), 3.93 (*t*, *J*=9.2 Hz, 2H), 3.72 (s, 2H), 3.63–3.66 (b, 1H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.4, 160.1, 145.2, 137.2, 136.8, 135.5, 134.5, 129.9, 128.44, 128.10, 128.07, 127.93, 126.7, 125.3, 124.8, 123.4, 121.6, 120.6, 119.1, 118.7, 113.7, 112.0, 95.3, 84.6, 79.7, 71.5, 70.3, 68.7, 61.4, 21.4; IR (thin film, cm^{-1}) ν_{max}: 3392.6, 1698.6, 1619.6, 1447.5, 1370.0, 1174.1, 1094.2, 749.0, 575.9; HRMS (ESI): calcd for $C_{37}H_{34}N_2NaO_9S$ $[M+Na]^+$: 705.1877; found 705.1869.

*4.2.19. (2S,3R,4R,5R)-Methyl 3,4-dihydroxy-5-(hydroxymethyl) -2-((R)-3-oxo-2-(1-tosyl-1H-indol-3-yl)indolin-2-yl)tetrahydro-furan-3-carboxylate (**64b**).* To a solution of **63b** (64 mg, 0.094 mmol) in methanol (5 mL) was added 20w% $Pd(OH)_2/C$ (13 mg). After stirring for 4 h under hydrogen atmosphere at room temperature, the reaction mixture was filtrated. The filtrate was concentrated under reduced pressure, then copper(I) chloride (279.2 mg, 2.82 mmol) was added to a solution of the residue in 1:1 $MeOH/CH_2Cl_2$ (6 mL), and the mixture was warmed to reflux for 6 h. The resulting mixture was then directly subjected to flash column chromatography (silica gel, CH_2Cl_2/MeOH 30:1) to give the desired **64b** (34 mg) in 62% yield, R_f=0.59 (silica gel, CH_2Cl_2/MeOH 10:1) $[\alpha]_D^{19.2}$ +60.0 (*c* 0.10, CH_3OH). ^1H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, *J*=8.0 Hz, 1H), 7.87 (d, *J*=8.4 Hz, 1H), 7.72 (s, 1H), 7.65 (d, *J*=8.0 Hz, 2H), 7.53 (d, *J*=7.6 Hz, 1H), 7.44 (*t*, *J*=7.2 Hz, 1H), 7.24 (*t*, *J*=8.0 Hz, 1H), 7.17 (*t*, *J*=7.6 Hz, 1H), 7.11 (d, *J*=8.0 Hz, 2H), 6.93 (d, *J*=8.4 Hz, 1H), 6.81 (*t*, *J*=7.6 Hz, 1H), 6.26 (s, 1H), 4.88 (s, 1H), 4.53 (b, 1H), 4.15 (b, 1H), 3.81–3.87 (b, 3H), 3.11 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.3, 172.0, 160.0, 145.1, 137.7, 135.7, 134.7, 129.9, 128.1, 126.8, 125.4, 124.8, 124.7, 123.5, 122.1, 119.7, 119.6, 119.64, 113.7, 112.2, 87.9, 83.8, 79.9, 73.6, 69.9, 61.4, 52.6, 21.5; IR (thin film, cm^{-1}) ν_{max}: 3394.1, 2922.8, 1726.3, 1619.0, 1446.5, 1370.1, 1174.4, 748.7; HRMS (ESI): calcd for $C_{30}H28N_2NaO_9S$ $[M+Na]^+$: 615.1408; found 615.1398.

*4.2.20. (2S,3R,4R,5R)-Methyl 2-((R)-2-(1H-indol-3-yl)-3-oxoindolin-2-yl)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-furan-3-carboxylate (**65b**).* The compound **64b** (62 mg, 0.105 mmol) in CH_3OH/PhH (44 mL, 1:10) was carefully sealed and irradiated using a UV lamp for 2.5 h. The resulting mixture was then directly subjected to flash column chromatography (silica gel, CH_2Cl_2/MeOH 18:1) to give compound **65b** (32.5 mg) in 46% yield, R_f=0.29 (silica gel, CH_2Cl_2/MeOH 10:1). $[\alpha]_D^{20.9}$ 350.5 (*c* 0.39, CH_3OH); ^1H NMR (400 MHz, CD_3OD): δ 7.89 (d, *J*=7.6 Hz, 1H), 7.43–7.48 (m, 2H), 7.29 (d, *J*=8.8 Hz, 1H), 7.25 (s, 1H), 7.05 (*t*, *J*=7.6 Hz, 1H), 6.86 (d, *J*=8.0 Hz, 2H), 6.74 (*t*, *J*=7.2 Hz, 1H), 5.04 (s, 1H), 4.44 (d, *J*=7.2 Hz, 1H), 3.73–3.84 (m, 3H), 3.14 (s, 3H), 2.37 (s, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ 200.7, 173.2, 162.5, 138.9, 138.3, 130.9, 128.3, 125.9, 124.5, 122.5, 122.1, 121.0, 120.0, 119.1, 113.0, 112.6, 90.4, 84.2, 81.7, 75.3, 72.2, 62.6, 52.4; IR (thin film, cm^{-1}) ν_{max}: 3356.2, 2922.8, 1695.7, 1616.6, 1326.0, 1248.1,1084.6; HRMS (ESI): calcd for $C_{23}H_{23}N_3O_7$ $[M+H]^+$: 439.1500; found 439.1497.

*4.2.21. (−)-Isatisine A (**3**).* To a solution of compound **65b** (11 mg, 0.025 mmol) in CH_2Cl_2 (8 mL) CSA (17.5 mg, 0.075 mmol) was added. The solution was stirred at room temperature for 48 h. The resulting mixture was then directly subjected to flash column chromatography (silica gel, CH_2Cl_2/MeOH 20:1) to give the desired isatisine A (6.4 mg) in 63% yield. R_f=0.48 (silica gel, CH_2Cl_2/MeOH 10:1) $[\alpha]_D^{19.2}$ −235.0 (*c* 0.50, CH_3OH). ^1H NMR (400 MHz, CD_3OD): δ 7.92 (d, *J*=8.0 Hz, 1H), 7.86 (d, *J*=8.0 Hz, 1H), 7.68–7.73 (m, 1H), 7.57 (d, *J*=7.6 Hz, 1H), 7.23–7.28 (m, 2H), 7.22 (s, 1H), 7.05 (td, *J*=0.8, 7.2 Hz, 1H), 6.98 (td, *J*=0.8, 7.2 Hz, 1H), 4.82 (s, 1H), 3.98 (d, *J*=4.0 Hz, 1H), 3.78 (dd, *J*=4.8, 6.0 Hz, 1H), 3.27–3.33 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ 196.7, 174.6, 151.8, 139.0, 137.8, 127.3, 126.8, 126.1, 126.0, 124.5, 123.0, 121.4, 120.5, 117.7, 112.8, 110.5, 89.8, 88.9, 84.6, 76.7, 74.2, 63.1; IR (thin film, cm^{-1}) ν_{max}: 3392.4, 2923.4, 1716.3, 1602.3, 1468.6, 1374.4, 1073.7, 747.5; HRMS (ESI): calcd for $C_{22}H_{22}N_3O_6$ $[M+NH_4]^+$: 424.1503; found 425.1568.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.09.028.

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17. See Experimental section.

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