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Total Synthesis of (−)-Isatisine A

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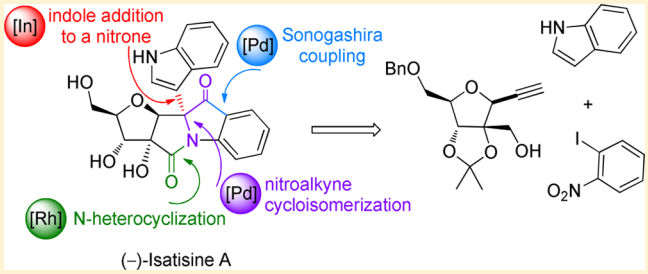
Supporting Information

ABSTRACT: A modular total synthesis of (−)-isatisine A is described in which four consecutive metal-mediated transformations have been employed at the final stage. These include [Pd]-catalyzed Sonogashira coupling, [Pd]-catalyzed nitroalkyne cycloisomerization leading to isatogens, and addition of indoles to isatogens using $InCl_3$- and [Rh]-catalyzed oxidative N-heterocyclization of amino alcohol to form the key amide bond. In addition to these, the removal of the protecting groups has also been carried out in a selective fashion employing either catalytic or stoichiometric metal/metal-based reagents.



INTRODUCTION

The structural complexity and skeletal diversity of natural products have served as inspirations to organic chemists for the discovery and design of new synthetic methods en route to their chemical synthesis.[1] In recent years, methods for new carbon−carbon and carbon−heteroatom bond formation mediated by transition metal complexes have found enormous applications in natural product synthesis.[2] The development of modular strategies involving metal-mediated reactions that enable the synthesis of structural variants of the targeted natural product is an active ongoing program in our group.[3] In this context, herein we document a highly modular total synthesis of (−)-isatisine A,[4−9] featuring four consecutive metal-mediated transformations at the final stage—a couple of reactions having been developed indigenously.

In 2007, Chen and co-workers reported the isolation of (−)-isatisine A (**1**), a complex alkaloid having a bisindole skeleton, from the leaves of *Isatis indigotica* Fort, an herbaceous plant species used in Chinese folk medicine.[4] The acetonide derivative **2**, which is an artifact during the isolation, was found to exhibit cytotoxicity against C8166 with CC_{50} = 302 μM and anti-HIV activity of EC_{50} = 37.8 μM. The challenging structural features of isatisine A (**1**) is characterized by the presence of a fused tetracyclic system comprising mainly furanose and indolin-3-one units. These two units are connected through a C-anomeric linkage at the C(2) position of the indolin-3-one and an amide bridge between the C(2) of furanose and nitrogen of the indolinone. There is an indole unit as a substituent at the C(2) position of indolinone connected with its C(3). Keeping the promising biological activity in mind, taken together with its unique structure, several programs aimed at its total synthesis were initiated immediately after its isolation. In 2010, Kerr's group reported the first total synthesis of isatisine A and revised its absolute configuration, as shown in Figure 1.[5] Following this, Panek[6] and Liang[7] reported the total synthesis of isatisine A. Very recently, Xie et al. have reported its biomimetic synthesis, which is characterized by its short sequence.[8]

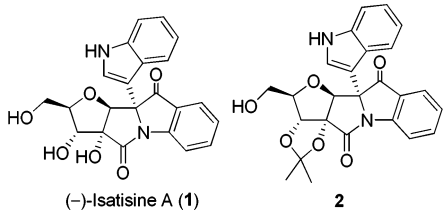


Figure 1. Revised structure of (−)-isatisine A (**1**) and its acetonide (**2**).

Scheme 1 outlines the salient features of our retrosynthetic disconnections. The construction of the central lactam ring has been planned as the final key event in our total synthesis featuring a metal-mediated oxidative N-heterocyclization of the amino alcohol **3**.[10,11] The synthesis of amino alcohol **3** features the addition of indole to the isatogen **4**. The nitroalkyne **5** has been identified as an advanced intermediate for the synthesis of **4** which, in turn, has been planned from the alkyne **6**. Alkyne **6** can be prepared from the known ribose derivative **7** by simple functional group manipulation. In the context of this total synthesis, we have developed methods for the synthesis of isatogens[9a] and spiroindolin-3-one derivatives[9b] based upon the [Pd]-mediated nitroalkyne cycloisomerization. We have also developed methods for the addition of indole to isatogens. A model study exploiting the indole addition to isatogens has resulted in the synthesis of 10-deoxyisatisine A.[9c]

RESULTS AND DISCUSSION

The synthesis commenced with the preparation of key alkyne **6** from the known compound **7** (Scheme 2). Compound **7** was prepared from D-ribose following the established procedures.[12] The C(2) hydroxymethylation of **7** was carried out with an excess of 40% formaldehyde solution and potassium carbonate

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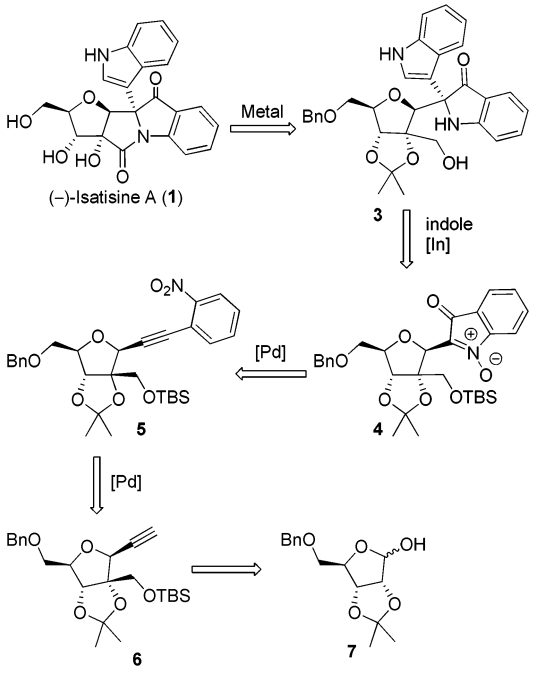
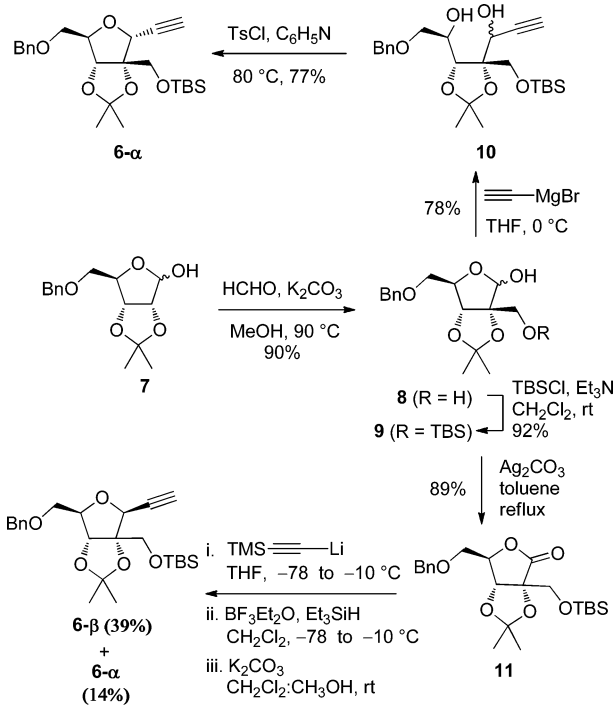
Scheme 1. Key Retrosynthetic Disconnections for (−)-Isatisine A



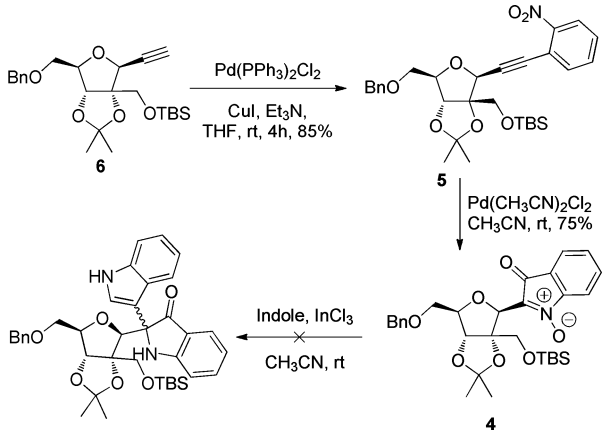
Scheme 2. Synthesis of Key Alkyne Intermediate 6



in methanol at 90 °C for 30 h to procure the diol **8** in 90% yield.[13] The primary hydroxyl group was selectively protected as its TBS ether **9**. Our initial attempts to synthesize the β-alkyne **6** following a two-step sequence involving the addition of acetylene Grignard to the lactol **9** and subsequent treatment of the intermediate alkynol with *p*-TsCl and pyridine at 80 °C gave the cyclic alkyne **6** in 77% yield as a single diastereomer.[14] The 2D NMR spectral analysis revealed that compound **6** was the undesired α-anomer. Nevertheless, Kishi's[15] strategy involving addition of trimethylsilylethynyllithium to the lactone **11** followed by reduction of the crude hemiketal using Et_3SiH in the presence of $BF_3{\cdot}Et_2O$ in dichloromethane at −78 °C and subsequent C-TMS deprotection using K_2CO_3 in a 1:1 mixture of methanol and dichloromethane furnished the β-alkyne **6** (39%) along with the α-anomer (14%) in a ∼3:1 ratio (overall yields for three steps).

Next, the Sonogashira coupling of **6** with 2-iodonitrobenzene under standard conditions furnished the nitroalkyne **5** in 85% yield. The key nitroalkyne cycloisomerization of **5** proceeded smoothly with 5 mol % of $Pd(CH_3CN)_2Cl_2$, and the isatogen **4** was obtained in 75% yield (Scheme 3).[9a] The next concern was

Scheme 3. Attempted Synthesis of (−)-Isatisine A



executing the alkylation of isatogen with indole and the subsequent N−O reduction by employing $InCl_3$ as a reagent.[9c] Accordingly, compound **5** was treated with indole in the presence of 20 mol % of $InCl_3$ in acetonitrile solvent, which led to an intractable complex reaction mixture. Varying the temperature, solvent, and the amounts of $InCl_3$ had no effect on the reaction outcome, and also, the use of other Lewis acids did not lead to the desired product. In the majority of the cases, the reaction ended with either deprotection of the TBS group or formation of a complex reaction mixture. We reasoned that the presence of a bulky and acid-labile TBS group might be the possible reason for this.[16]

We resorted next to switching the protecting group from TBS to acetate. For this, the alkynol **12** was prepared from lactone **11** following a three-step procedure (Scheme 4), which involves addition of trimethylsilylethynyllithium to the lactone **11** followed by reduction of the crude hemiketal using Et_3SiH in the presence of $BF_3{\cdot}Et_2O$ in dichloromethane at −78 °C, and subsequent deprotection of both silyl groups using TBAF in THF furnished the β-alkynol **12** (37%) along with the α-anomer (13%) in a ∼3:1 ratio (overall yields for three steps). Sonogashira coupling of **12** with 2-iodonitrobenzene under standard conditions furnished the nitroalkyne **13** in 90% yield. Protection of the free −OH group of **13** as its acetate **14** followed by the [Pd]-mediated nitroalkyne cycloisomerization gave the corresponding isatogen **15** in 72% yield. The key indole addition reaction with the isatogen **15** needed a substantial optimization. It was realized that the reaction in acetonitrile at room temperature in the presence of catalytic amounts of $InCl_3$ was sluggish. The optimized conditions involve the treatment of **15** with 2 equiv of indole in the presence of 1 equiv of $InCl_3$ in acetonitrile at 70 °C for 12 h.[17] As the deacetylation was a side reaction under

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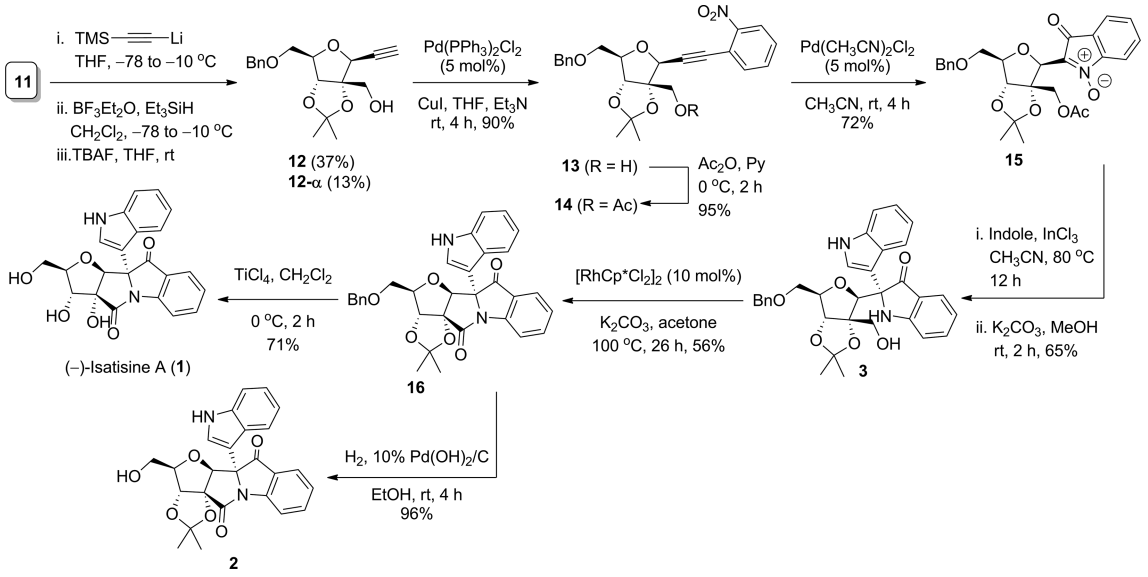
Scheme 4. Total Synthesis of (−)-Isatisine A (1) and Its Acetonide 2



these conditions, the intermediate addition product was treated immediately with K_2CO_3 in methanol to obtain the key amino alcohol intermediate **3** in 65% yield over two steps as a single diastereomer.

The oxidative lactamization of **3** has been examined by screening various transition metal catalysts that have been prescribed for this purpose.[10] The $[Cp^*RhCl_2]_2$ complex was the most fruitful catalyst in this regard.[18] The optimized conditions involve the use of $[RhCp^*Cl_2]_2$ (10 mol %) and catalytic potassium carbonate in acetone at 100 °C for 26 h to furnish the lactam compound **16** in moderate yields. Having the complete skeleton in hand, the stage was now set for the completion of the total synthesis of (−)-isatisine A by deprotection of the benzyl and acetonide groups. To this end, the global deprotection of **16** using $TiCl_4$ resulted in the isolation of (−)-isatisine A (**1**) in 71% yield.[19] The spectral and analytical data for (−)-isatisine A were in accordance with the data reported by the other groups. The specific rotation of the synthetic (−)-isatisine A (**1**) was $[\alpha]_D^{25} = -276$ (c = 0.21, MeOH), which is essentially equal and opposite in sign to that reported by Kerr ($[\alpha]_D^{14} = +274$) for its enantiomer.[5] Alternatively, to have the access for the acetonide **2**, which showed promising anti-HIV activity, we explored the possibility of selective debenzylation. This can be smoothly effected by hydrogenolysis of **16** with $Pd(OH)_2$ in ethanol at balloon pressure to furnish acetonide **2** in 96% yield. The spectral and analytical data of acetonide **2** are in accordance with the data reported in the isolation paper.[4]

CONCLUSION

To conclude, a modular total synthesis of (−)-isatisine A starting from D-ribose has been completed featuring four consecutive metal-catalyzed/mediated transformations at the final stage. The reactions address two of each of the C−C and C−heteroatom bond formations. Also, the present synthesis documents the first application of a [Rh]-catalyzed oxidative N-heterocyclization of amino alcohol leading to the γ-lactam in the synthesis of a complex natural product. Efforts to optimize the final synthetic events in a continuous flow manner[20] and the synthesis of (−)-isatisine A related small molecules are currently underway.

EXPERIMENTAL SECTION

5-*O*-Benzyl-2-*C*-(hydroxymethyl)-2,3-*O*-isopropylidene-D-ribofuranose (8). A suspension of lactal **7** (20 g, 71.4 mmol) and K_2CO_3 (14.8 g, 107 mmol) in MeOH (150 mL) was treated with 37% aqueous formaldehyde (150 mL) and stirred for 30 h at 90 °C. After completion of the reaction as indicated by TLC, the reaction mixture was cooled in an ice bath and neutralized with 10% aqueous HCl. The reaction mixture was concentrated and extracted with ethyl acetate. The combined organic layer was dried (Na_2SO_4), concentrated, and purified by column chromatography (35% EtOAc/petroleum ether) to afford the diol **8** (19.9 g, 90%) as a colorless liquid: R_f (50% ethyl acetate/petroleum ether) 0.3; $[\alpha]_D^{25}$ = 10.6 (c 2.77, $CHCl_3$); IR ($CHCl_3$) ν 3428, 2989, 2936, 2870, 1715, 1496, 1455, 1372, 1216, 1075, 860, 755 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.43 (s, 3H, major), 1.47 (s, 2.3H, minor), 1.5 (s, 3H, major), 1.58 (s, 2.3H, minor), 2.18−2.24 (m, 0.7H, minor), 2.33−2.39 (m, 1H, major), 3.58−3.68 (m, 3.3H), 3.7−3.83 (m, 4H), 4.23−4.27 (m, 0.8H, minor), 4.34−4.37 (m, 1H, major), 4.51−4.61 (m, 4.7H), 4.64−4.68 (m, 1.4H), 4.73 (s, 0.7H), 5.24 (d, J = 10.3 Hz, 1H, minor), 5.31 (d, J = 10.9 Hz, 1H, major), 7.28−7.4 (m, 8.8H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.1 (q, minor), 27.3 (q, minor), 27.5 (q, major), 28.1 (q, major), 62.6 (t, major), 62.9 (t, minor), 70.9 (t, major), 71.5 (t, minor), 73.7 (t, minor), 74.1 (t, major), 80.9 (d, minor), 83.9 (d, minor), 84.6 (d, major), 85.8 (d, major), 91.4 (s, minor), 94.8 (s, major), 98.8 (d, minor), 104.6 (d, major), 113.3 (s, major), 114.1 (s, minor), 127.8 (d, minor), 127.9 (d, minor), 128.2 (d, major), 128.5 (d, minor), 128.6 (d, major), 128.8 (d, major), 135.9 (s, major), 137.2 (s, minor) ppm; MS (ESI) m/z 333.2 ($[M + Na]^+$); HRMS (ESI) calcd for $C_{16}H_{22}O_6$ $[M + Na]^+$ 333.1313, found 333.1308.

5-*O*-Benzyl-2-*C*-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,3-*O*-isopropylidene-D-ribofuranose (9). At 0 °C, a solution of alcohol **8** (15 g, 48.3 mmol) in CH_2Cl_2 (30 mL) was treated with triethylamine (13.5 mL, 96.7 mmol) followed by TBDMSCl (7.28 g, 48.3 mmol). The reaction mixture was slowly allowed to reach room temperature and was stirred for 8 h. After the completion of the reaction, ice was added to the reaction mixture and stirred for 5 min. The contents were diluted with CH_2Cl_2 (60 mL), and the resulting layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The crude product was purified by flash column chromatography (9% EtOAc/petroleum ether) to afford lactols **9** (18.88 g, 92%) as colorless oil: R_f (15% ethyl acetate/petroleum ether) 0.3; $[\alpha]_D^{25}$ = 14.1 (c 3.24, $CHCl_3$); IR ($CHCl_3$) ν 3432, 2931, 2858, 1725, 1496, 1457, 1381, 1251, 1212, 1090, 838, 777 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.0 (s, 6H, major), 0.03 (s, 3H, minor), 0.86

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(s, 9H, major), 0.89 (s, 4.5H, minor), 1.42 (s, 1.5H, minor), 1.45 (s, 3H, major), 1.47 (s, 1.5H, minor), 1.55 (s, 3H, major), 3.55 (d, J = 4.3 Hz, 2H, major), 3.62 (d, J = 3.0 Hz, 1H, minor), 3.5 (dd, J = 5.4, 10.2 Hz, 1H), 3.55 (dd, J = 5.4, 10.2 Hz, 1H), 3.7 (br s, 2H), 4.2−4.25 (m, 1H), 4.23 (dt, J = 1.3, 4.3 Hz, 1H, major), 4.32 (dt, J = 1.1, 4.3 Hz, 0.5H, minor), 4.55 (d, J = 12.0 Hz, 1H), 4.62 (d, J = 1.4 Hz, 1H), 5.14 (d, J = 10.7 Hz, 1H, major), 5.22 (d, J = 11.4 Hz, 0.5H, minor), 7.27−2.37 (m, 7.5H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ −5.7 (q), −5.5 (q), 18.3 (s, major), 18.4 (s, minor), 25.8 (q, major), 25.9 (q, minor), 27.3 (q, major), 27.6 (q, major), 27.9 (q, minor), 27.9 (q, minor), 62.3 (t, minor), 62.8 (t, major), 70.8 (t, major), 71.2 (t, minor), 73.6 (t, major), 74.1 (t, minor), 81.0 (d, major), 83.7 (d, major), 84.4 (d, minor), 85.8 (d, minor), 91.4 (s, major), 95.0 (s, minor), 98.4 (d, major), 105.1 (d, minor), 113.4 (s, minor), 114.1 (s, major), 127.7 (d, major), 127.8 (d, minor), 128.2 (d, minor), 128.4 (d, major), 128.7 (d, minor), 136.2 (s, minor), 137.6 (s, major) ppm; MS (ESI) m/z 447.2 ([M + Na]$^+$); HRMS (ESI) calcd for $C_{22}H_{36}O_6Si$ ([M + Na]$^+$) 447.2179, found 447.2163.

1-((4*S*,5*R*)-5-((*R*)-2-(Benzyloxy)-1-hydroxyethyl)-4-(((*tert*-butyldimethylsilyl)oxy)meth-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)prop-2-yn-1-ol (10). Flame-dried Mg (86 mg, 3.53 mmol) was treated with dry THF (4 mL) and a few crystals of iodine. To it was added *n*-BuCl (327 mg, 3.53 mmol), and the contents were refluxed until the generation of Grignard reagent. Heating was removed, and stirring was continued at room temperature until all of the magnesium was consumed. Then the reaction mixture was cooled to 0 °C, and acetylene gas was bubbled into it for 15 min. At the same temperature, a solution of lactals **9** (300 mg, 0.706 mmol) in THF (3 mL) was added and stirred for 30 min at 0 °C. The reaction was quenched with saturated NH_4Cl solution, diluted with water, and extracted with ethyl acetate. The combined organic layer was dried over Na_2SO_4, concentrated, and purified on silica gel chromatography (8% EtOAc/petroleum ether) to give the diol **10** (340 mg, 78%) as colorless oil: R_f (15% ethyl acetate/petroleum ether) 0.4; $[\alpha]_D^{25}$ = −2.3 (c 1.2, $CHCl_3$); IR ($CHCl_3$) ν 3447, 2988, 2931, 2861, 1725, 1603, 1496, 1454, 1381, 1217, 1071, 757 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.09 (s, 3H), 0.09 (s, 3H), 0.90 (s, 9H), 1.37 (s, 3H), 1.46 (s, 3H), 2.46 (d, J = 2.3 Hz, 1H), 3.54−3.68 (m, 3H), 3.77 (dd, J = 2.4, 10.1 Hz, 1H), 3.87 (d, J = 10.6 Hz, 1H), 4.07 (d, J = 10.6 Hz, 1H), 4.58−4.65 (m, 3H), 7.29−7.36 (m, 5H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ −5.7 (q), −5.5 (q), 18.3 (s), 25.9 (q, 3C), 26.1 (q), 27.7 (q), 63.8 (d), 64.0 (t), 68.5 (d), 71.9 (t), 73.4 (t), 74.3 (s), 77.8 (d), 82.5 (s), 84.6 (d), 108.8 (s), 127.6 (d), 127.7 (d, 2C), 128.3 (d, 2C), 138.1 (s) ppm; MS (ESI) m/z 473.1 ([M + Na]$^+$); HRMS (ESI) calcd for $C_{24}H_{38}O_6Si$ ([M + Na]$^+$) 473.2335, found 473.2334.

(((3a*S*,4*R*,6*R*,6a*R*)-6-((Benzyloxy)methyl)-4-ethynyl-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-3a-yl)methoxy)(*tert*-butyl)dimethylsilane (6-*α*). To a solution of diol **10** (200 mg, 0.44 mmol) in dry pyridine (2 mL) was added tosyl chloride (169 mg, 0.88 mmol), and the resulting solution was heated at 50−60 °C for 3 h. To this was added water, and the contents were extracted with CH_2Cl_2. The combined organic phase was dried with $MgSO_4$ and concentrated to dryness under reduced pressure. The crude was purified by silica gel column chromatography (4% EtOAc/petroleum ether) to procure alkyne **6-*α*** (148 mg, 77% yield) as colorless oil: R_f (10% ethyl acetate/petroleum ether) 0.5; $[\alpha]_D^{25}$ = −12.1 (c 4.03, $CHCl_3$); IR ($CHCl_3$) ν 3306, 2931, 2858, 2118, 1727, 1496, 1455, 1381, 1253, 1218, 1060, 839, 756 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.87 (s, 9H), 1.43 (s, 3H), 1.58 (s, 3H), 2.58 (d, J = 2.3 Hz, 1H), 3.5 (dd, J = 5.4, 10.2 Hz, 1H), 3.55 (dd, J = 5.4, 10.2 Hz, 1H), 3.7 (br s, 2H), 4.26−4.31 (m, 1H), 4.58 (d, J = 12.0 Hz, 1H), 4.55 (d, J = 12.0 Hz, 1H), 4.62 (d, J = 1.4 Hz, 1H), 4.69 (br d, J = 2.3 Hz, 1H), 7.26−2.34 (m, 5H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ −5.7 (q), −5.5 (q), 18.3 (s), 25.8 (q, 3C), 27.3 (q), 27.9 (q), 63.2 (t), 69.4 (t), 72.9 (d), 73.4 (t), 76.2 (d), 78.5 (s), 83.6 (d), 85.2 (d), 93.5 (s), 114.2 (s), 127.7 (d, 2C), 127.8 (d), 128.4 (d, 2C), 137.7 (s) ppm; MS (ESI) m/z 455.2 ([M + Na]$^+$); HRMS (ESI) calcd for $C_{24}H_{36}O_5Si$ ([M + Na]$^+$) 455.2229, found 455.2225.

(3a*R*,6*R*,6a*R*)-6-((Benzyloxy)methyl)-3a-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,2-dimethyldihydrofuro[3,4-*d*][1,3]dioxol-4(3a*H*)-one (11). A suspension of TBS lactals **9** (5 g, 16.1 mmol) and Ag_2CO_3 impregnated on Celite (36.7 g, 64.4 mmol, contains 1 mmol of Ag_2CO_3 per 0.57 g of prepared reagent) in dry toluene (50 mL) was refluxed for 6 h. After completion of reaction as indicated by TLC, the contents were cooled to room temperature and filtered through a pad of Celite. The Celite pad was washed with toluene, and the combined filtrate was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (3% EtOAc/petroleum ether) to procure lactone **11** (4.43 g, 89% yield) as crystalline solid: R_f (5% ethyl acetate/petroleum ether) 0.2; mp 83 °C; $[\alpha]_D^{25}$ = −12 (c 1.27, $CHCl_3$); IR ($CHCl_3$) ν 2931, 2858, 1789, 1727, 1496, 1463, 1383, 1253, 1214, 1108, 1080, 838, 780 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.0 (s, 3H), 0.02 (s, 3H), 0.86 (s, 9H), 1.40 (s, 3H), 1.44 (s, 3H), 3.67 (d, J = 4.5 Hz, 2H), 3.80 (d, J = 10.6 Hz, 1H), 3.97 (d, J = 10.6 Hz, 1H), 4.50 (d, J = 12.2 Hz, 1H), 4.56 (d, J = 12.2 Hz, 1H), 4.60 (t, J = 4.5 Hz, 1H), 4.72 (s, 1H), 7.26−7.38 (m, 5H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ −5.7 (q), −5.5 (q), 18.3 (s), 25.8 (q, 3C), 26.7 (q), 27.1 (q), 61.8 (t), 69.0 (t), 73.7 (t), 79.7 (d), 82.5 (d), 86.0 (s), 113.4 (s), 127.8 (d, 2C), 128.0 (d), 128.5 (d, 2C), 137.1 (s), 174.7 (s) ppm; MS (ESI) m/z 445.1 ([M + Na]$^+$); HRMS (ESI) calcd for $C_{22}H_{34}O_6Si$ ([M + Na]$^+$) 445.2022, found 445.2027.

Synthesis of Compounds 6 and 12 from Lactone 11. A solution of trimethylsilyl acetylene (3.23 mL, 22.7 mmol) in THF (15 mL) was cooled to −78 °C under argon and treated with *n*-BuLi (13.6 mL, 1.6 M in hexane) and stirred at −78 °C for 45 min. To this was introduced a solution of lactone **11** (4.0 g, 9.47 mmol) in THF (15 mol) added dropwise, and stirring was continued for another 5 min at −78 °C and then at −10 °C for 30 min. The reaction mixture was quenched with saturated aqueous NH_4Cl solution and partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The resulting crude product was used for the next step without any further purification.

To a cooled (−78 °C) solution of the 500 mg of crude hemiacetal and triethylsilane (1.6 mL, 9.6 mmol) in anhydrous CH_2Cl_2 (20 mL) was added dropwise $BF_3{\cdot}OEt_2$ (0.57 mL, 4.8 mmol), and stirring was continued at the same temperature for 30 min. When all of the starting material was completely consumed as indicated by TLC, the reaction mixture was neutralized with triethylamine and extracted with dichloromethane. The combined organic layer was dried (Na_2SO_4), filtered, and concentrated to obtain 600 mg of crude product. The crude was subjected for next step without further purification.

(((3a*S*,4*S*,6*R*,6a*R*)-6-((Benzyloxy)methyl)-4-ethynyl-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-3a-yl)methoxy)(*tert*-butyl)dimethylsilane (6-*β*). Potassium carbonate (0.6 g, 3.44 mmol) was added to a stirred solution of crude compound (0.5 g) in a 1:1 mixture of methanol−CH_2Cl_2 (30 mL) at room temperature, and the reaction mixture was stirred for 4 h. The reaction mixture was concentrated and then extracted with dichloromethane. The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was subjected to column chromatography purification (3% EtOAc/petroleum ether) to afford **6-*β*** (190 mg, 39%) and **6-*α*** (72 mg, 14%); **6-*β*** as colorless liquid; R_f (10% ethyl acetate/petroleum ether) 0.6; $[\alpha]_D^{25}$ = −34.5 (c 1.55, $CHCl_3$); IR ($CHCl_3$) ν 3932, 2858, 2139, 1722, 1612, 1586, 1513, 1463, 1370, 1250, 1104, 1006, 838, 758 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.06 (s, 3H), 0.90 (s, 9H), 1.41 (s, 3H), 1.52 (s, 3H), 2.53 (d, J = 2.1 Hz, 1H), 3.55 (dd, J = 5.2, 10.1 Hz, 1H), 3.60 (dd, J = 5.2, 10.1 Hz, 1H), 3.76 (d, J = 11.3 Hz, 1H), 4.02 (d, J = 11.3 Hz, 1H), 4.21 (dt, J = 2.6, 5.2 Hz, 1H), 4.53 (d, J = 2.1 Hz, 1H), 4.55 (d, J = 12.2 Hz, 1H), 4.59 (d, J = 12.2 Hz, 1H), 4.64 (d, J = 2.6 Hz, 1H), 7.26−2.33 (m, 5H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ −5.6 (q), −5.4 (q), 18.4 (s), 25.9 (q, 3C), 26.8 (q), 28.3 (q), 61.7 (t), 69.7 (t), 73.5 (t), 75.5 (d), 76.6 (d), 77.6 (s), 82.0 (d), 83.3 (d), 92.0 (s), 114.8 (s), 127.7 (d), 127.8 (d, 2C), 128.4 (d, 2C), 137.9 (s) ppm; MS (ESI) m/z 433.1 ([M + H]$^+$); HRMS (ESI) calcd for $C_{24}H_{36}O_5Si$ [M + K]$^+$ 471.1969, found 471.1965.

((3a*S*,4*S*,6*R*,6a*R*)-6-((Benzyloxy)methyl)-4-ethynyl-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-3a-yl)methanol (12-*β*). At 0 °C, the reduced crude product (0.6 g) in THF (10 mL) 1 M TBAF solution in THF (2.54 mL, 2.54 mmol) was added and stirred for 4 h at the same temperature. After completion, the reaction mixture was

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quenched with saturated NH_4Cl (20 mL) and the contents were partitioned between ethyl acetate and water. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (20 mL × 3). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue obtained was purified by column chromatography (18% EtOAc/petroleum ether) to afford alkynol **12-*β*** (133 mg, 37% yield) and **12-*α*** (44 mg, 13%) as colorless oil: R_f (40% ethyl acetate/petroleum ether) 0.5; $[\alpha]_D^{25} = -26$ (*c* 1.37, $CHCl_3$); IR ($CHCl_3$) ν 3479, 3291, 2990, 2936, 2862, 2121, 1723, 1496, 1455, 1382, 1217, 1152, 1072, 755 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.42 (s, 3H), 1.55 (s, 3H), 2.12 (br s, 1H), 2.61 (d, *J* = 2.2 Hz, 1H), 3.65 (br d, *J* = 4.5 Hz, 2H), 3.86 (d, *J* = 12.3 Hz, 1H), 4.01 (d, *J* = 12.3 Hz, 1H), 4.26 (dt, *J* = 2.0, 4.5 Hz, 1H), 4.55 (d, *J* = 12.1 Hz, 1H), 4.6 (d, *J* = 12.1 Hz, 1H), 4.62 (d, *J* = 2.2 Hz, 1H), 4.64 (d, *J* = 2.0 Hz, 1H), 7.28–2.35 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.9 (q), 28.1 (q), 61.9 (t), 69.7 (t), 73.6 (t), 75.3 (d), 77.1 (d), 78.0 (s), 83.1 (d), 83.2 (d), 91.9 (s), 114.5 (s), 127.8 (d, 3C), 128.4 (d, 2C), 137.6 (s) ppm; MS (ESI) *m*/*z* 341.3 ([M + Na]$^+$); HRMS (ESI) calcd for $C_{18}H_{22}O_5$ [M + Na]$^+$ 341.1365, found 341.1368.

(((3a*S*,4*S*,6*R*,6a*R*)-6-((Benzyloxy)methyl)-2,2-dimethyl-4-((2-nitrophenyl)ethynyl)-tetrahydrofuro[3,4-*d*][1,3]dioxol-3a-yl)-methoxy)(*tert*-butyl)dimethylsilane (5). To a solution of alkyne **6-*β*** (500 mg, 1.16 mmol) and aryl iodide (345 mg, 1.39 mmol) in Et_3N/THF (2:1, 9 mL) were added TPP (30 mg, 0.115 mmol) and $Pd(PPh_3)_2Cl_2$ (80 mg, 0.115 mmol), and the suspension was degassed with argon for 10 min. To this CuI (22 mg, 0.115 mmol) was introduced and degassed with argon for 10 min and stirred at rt for 4 h. The reaction mixture was filtered through a Celite pad, and the filtrate was concentrated under reduced pressure. The residue obtained was purified by column chromatography (7% EtOAc/petroleum ether) to afford the nitroalkyne **5** (547 mg, 85% yield) as yellow oil: R_f (15% ethyl acetate/petroleum ether) 0.4; $[\alpha]_D^{25} = -90.5$ (*c* 0.34, $CHCl_3$); IR ($CHCl_3$) ν 2996, 2912, 2857, 1645, 1496, 1412, 1380, 1256, 1120, 1070, 838, 757 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.09 (s, 6H), 0.90 (s, 9H), 1.44 (s, 3H), 1.56 (s, 3H), 3.59 (dd, *J* = 5.2, 10.4 Hz, 1H), 3.64 (dd, *J* = 5.2, 10.4 Hz, 1H), 3.88 (d, *J* = 11.6 Hz, 1H), 4.18 (d, *J* = 11.6 Hz, 1H), 4.28 (dt, *J* = 2.4, 5.2 Hz, 1H), 4.57 (d, *J* = 12.2 Hz, 1H), 4.60 (d, *J* = 12.2 Hz, 1H), 4.7 (d, *J* = 2.4 Hz, 1H), 4.82 (s, 1H), 7.24–7.34 (m, 5H), 7.47 (ddd, *J* = 1.5, 7.4, 7.5 Hz, 1H), 7.56 (dt, *J* = 1.5, 7.5 Hz, 1H), 7.61 (dd, *J* = 1.5, 7.6 Hz, 1H), 8.03 (dd, *J* = 1.3, 7.6 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.7 (q), −5.4 (q), 18.4 (s), 25.9 (q, 3C), 26.9 (q), 28.4 (q), 61.9 (t), 69.7 (t), 73.5 (t), 76.4 (d), 82.2 (d), 83.0 (s), 83.6 (d), 91.0 (s), 93.1 (s), 114.8 (s), 117.6 (s), 124.6 (d), 127.7 (d), 127.8 (d, 2C), 128.4 (d, 2C), 129.2 (d), 132.7 (d), 135.2 (d), 137.9 (s), 149.7 (s) ppm; MS (ESI) *m*/*z* 576.2 ([M + Na]$^+$); HRMS (ESI) calcd for $C_{30}H_{39}NO_7Si$ [M + Na]$^+$ 576.2394, found 576.2389.

2-((3a*S*,4*S*,6*R*,6a*R*)-6-((Benzyloxy)methyl)-3a-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,2-dimethyltetrahydrofuro-[3,4-*d*][1,3]dioxol-4-yl)-3-oxo-3*H*-indole 1-oxide (4). The compound **5** (500 mg, 0.9 mmol) was dissolved in acetonitrile (50 mL) and degassed under argon atmosphere for 10 min, and Pd-$(CH_3CN)_2Cl_2$ (12 mg, 5 mol %) was introduced and stirred for 8 h at room temperature. The reaction mixture was concentrated under reduced pressure. The crude was subjected to column chromatography purification (9% EtOAc/petroleum ether) to procure isatogen **4** (375 mg, 75%) as yellow oil: R_f (20% ethyl acetate/petroleum ether) 0.5; $[\alpha]_D^{25} = -120$ (*c* 0.42, $CHCl_3$); IR ($CHCl_3$) ν 3283, 3104, 2929, 2857, 1689, 1600, 1451, 1307, 1264, 1235, 917, 757 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ −0.20 (s, 3H), −0.15 (s, 3H), 0.65 (s, 9H), 1.40 (s, 3H), 1.67 (s, 3H), 3.70 (dd, *J* = 5.2, 10.4 Hz, 1H), 3.76 (dd, *J* = 5.2, 10.4 Hz, 1H), 3.78 (d, *J* = 11.3 Hz, 1H), 3.92 (d, *J* = 11.3 Hz, 1H), 4.31–4.33 (m, 1H), 4.45 (d, *J* = 3.4 Hz, 1H), 4.64 (d, *J* = 12.2 Hz, 1H), 4.70 (d, *J* = 12.2 Hz, 1H), 5.41 (s, 1H), 7.27 (br d, *J* = 7.1 Hz, 1H), 7.34 (t, *J* = 7.3 Hz, 2H), 7.40 (br d, *J* = 7.6 Hz, 2H), 7.51–7.64 (m, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.9 (q), −5.6 (q), 18.2 (s), 25.6 (q, 3H), 27.5 (q), 28.5 (q), 64.2 (t), 69.9 (t), 73.6 (t), 78.0 (d), 83.7 (d), 83.9 (d), 94.9 (s), 114.1 (d), 115.2 (s), 121.5 (d), 123.4 (s), 127.6 (d), 127.8 (d, 2C), 128.3 (d, 2C), 131.4 (d), 134.2 (d), 134.6 (s), 138.0 (s), 146.9 (s), 184.5 (s) ppm; MS (ESI) *m*/*z* 576.2 ([M + Na]$^+$); HRMS (ESI) calcd for $C_{30}H_{39}NO_7Si$ [M + Na]$^+$ 576.2393, found 576.2388.

((3a*S*,4*S*,6*R*,6a*R*)-6-((Benzyloxy)methyl)-2,2-dimethyl-4-((2-nitrophenyl)ethynyl)tetrahydrofuro[3,4-*d*][1,3]dioxol-3a-yl)-methanol (13). The Sonogashira coupling of alkynol **12-*α*** (200 mg, 0.32 mmol) and 2-nitroiodobenzene (187 mg, 0.753 mmol) was carried out according to the procedure used for the preparation of **5**. Purification of the crude by column chromatography (20% EtOAc/petroleum ether) gave the nitroalkynol **13** (249 mg, 90%) as yellow syrup: R_f 0.6 (petroleum ether/EtOAc 7:3); $[\alpha]_D^{25} = -154$ (*c* = 0.5, $CHCl_3$); IR ($CHCl_3$) ν 3453, 2990, 2935, 2862, 2839, 1667, 1611, 1516, 1463, 1345, 1248, 1162, 1075, 853, 754 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.45 (s, 3H), 1.58 (s, 3H), 2.26 (br s, 1H), 3.69 (d, *J* = 5.2 Hz, 2H), 3.98 (br d, *J* = 12.2 Hz, 1H), 4.12 (br d, *J* = 12.2 Hz, 1H), 4.34 (dt, *J* = 2.2, 5.1 Hz, 1H), 4.56 (d, *J* = 12.2 Hz, 1H), 4.62 (d, *J* = 12.2 Hz, 1H), 4.7 (d, *J* = 2.0 Hz, 1H), 4.94 (s, 1H), 7.25–7.35 (m, 5H), 7.44–7.66 (m, 3H), 8.06 (dd, *J* = 1.3, 7.7 Hz, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.0 (q), 28.0 (q), 62.3 (t), 69.6 (t), 73.5 (t), 76.4 (d), 83.5 (s), 83.7 (d, 2C), 91.5 (s), 92.9 (s), 114.5 (s), 117.5 (s), 124.7 (d), 127.7 (d), 127.7 (d, 2C), 128.3 (d, 2C), 129.3 (d), 132.9 (d), 135.2 (d), 137.6 (s), 149.4 (s) ppm; MS (ESI) *m*/*z* 462.1 ([M + Na]$^+$); HRMS (ESI) calcd for $C_{24}H_{25}NO_7$ [M + Na]$^+$ 462.1529, found 462.1514.

((3a*S*,4*S*,6*R*,6a*R*)-6-((Benzyloxy)methyl)-2,2-dimethyl-4-((2-nitrophenyl)ethynyl)tetrahydrofuro[3,4-*d*][1,3]dioxol-3a-yl)-methyl acetate (14). To a stirred solution of nitroalkynol **13** (300 mg, 0.68 mmol) in pyridine (1 mL) and Ac_2O (1.5 mL) was added cat. DMAP at room temperature and stirred for 2 h at rt. The reaction was diluted with ethyl acetate (30 mL). The organic layer was separated, washed with saturated $CuSO_4$ solution and brine, dried (Na_2SO_4), and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (15% EtOAc/petroleum ether) to afford the compound **14** (313 mg, 95%) as a yellow liquid: R_f 0.5 (petroleum ether/EtOAc 7:3); $[\alpha]_D^{25} = -144$ (*c* = 0.35, $CHCl_3$); IR ($CHCl_3$) ν 3358. 2925, 2854, 1916, 1720, 1622, 1458, 1282, 1089, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 3H), 1.58 (s, 3H), 2.07 (s, 3H), 3.68 (dd, *J* = 5.2, 10.5 Hz, 1H), 3.71 (dd, *J* = 5.2, 10.5 Hz, 1H), 4.33 (dt, *J* = 2.0, 5.2 Hz, 1H), 3.41 (d, *J* = 12.3 Hz, 1H), 4.55 (d, *J* = 12.1 Hz, 1H), 4.60 (d, *J* = 12.1 Hz, 1H), 4.67 (d, *J* = 2.0 Hz, 1H), 4.75 (d, *J* = 12.3 Hz, 1H), 4.93 (s, 1H), 7.25–7.32 (m, 5H), 7.47–7.51 (m, 1H), 7.58 (dt, *J* = 1.3, 7.8 Hz, 1H), 7.61 (dd, *J* = 1.7, 7.8 Hz, 1H), 8.06 (dd, *J* = 1.2, 8.2 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8 (q), 26.7 (q), 28.1 (q), 62.9 (t), 69.5 (t), 73.5 (d), 76.5 (t), 83.4 (d), 83.7 (d), 90.7 (s), 91.4 (s), 114.9 (s), 117.3 (s), 124.7 (d), 127.7 (d, 3C), 128.3 (d, 2C), 128.5 (s), 129.3 (d), 132.9 (d), 135.1 (d), 137.7 (s), 149.5 (s), 170.4 (s) ppm; MS (ESI) *m*/*z* 482.1 ([M + H]$^+$); HRMS (ESI) calcd for $C_{26}H_{27}NO_8$ [M + Na]$^+$ 504.1635, found 504.1637.

2-((3a*S*,4*S*,6*R*,6a*R*)-3a-(Acetoxymethyl)-6-((benzyloxy)-methyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-3-oxo-3*H*-indole 1-oxide (15). The cycloisomerization of nitroalkyne **14** (300 mg, 0.42 mmol) using $Pd(CH_3CN)_2Cl_2$ (5 mol %) was carried out according to the procedure used for the preparation of **4**. Purification of the crude by column chromatography (35% EtOAc/petroleum ether) **17** gave **15** (216 mg, 72%) as yellow syrup: R_f 0.5 (petroleum ether/EtOAc 7:3); $[\alpha]_D^{25} = -162$ (*c* = 0.87, $CHCl_3$); IR ($CHCl_3$) ν 3394, 2927, 2850, 1746, 1690, 1606, 1527, 1457, 1382, 1233, 1086, 755 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.40 (s, 3H), 1.68 (s, 3H), 1.79 (s, 3H), 3.68 (dd, *J* = 4.6, 10.7 Hz, 1H), 3.71 (dd, *J* = 4.9, 10.7 Hz, 1H), 4.32–4.38 (m, 3H), 4.62 (d, *J* = 12.2 Hz, 1H), 4.67 (d, *J* = 3.0 Hz, 1H), 4.71 (d, *J* = 12.2 Hz, 1H), 5.41 (s, 1H), 7.30–7.38 (m, 5H), 7.57–7.68 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2 (q), 27.0 (q), 28.4 (q), 63.6 (t), 69.7 (t), 73.7 (t), 77.7 (d), 83.5 (d), 84.0 (d), 92.3 (s), 114.3 (d), 115.6 (s), 121.7 (d), 123.1 (s), 127.7 (d), 127.8 (d, 2C), 128.4 (d, 2C), 131.9 (d), 133.3 (s), 134.5 (d), 137.9 (s), 146.8 (s), 170.1 (s), 184.6 (s) ppm; MS (ESI) *m*/*z* 482.1 ([M + H]$^+$); HRMS (ESI) calcd for $C_{26}H_{27}NO_8$ [M + Na]$^+$ 504.1635, found 504.1641.

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(*S*)-2-((3a*S*,4*S*,6*R*,6a*R*)-6-((Benzyloxy)methyl)-3a-(hydroxymethyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-2-(1*H*-indol-3-yl)indolin-3-one (3). To a solution of compound **15** (100 mg, 0.122 mmol) and indole (22 mg, 0.182 mmol) in acetonitrile (2 mL) was added anhydrous $InCl_3$ (27 mg, 0.122 mmol) degassed under argon atmosphere for 5 min. Reaction mixture was allowed to stir at 60 °C for 12 h. After completion of the reaction, acetonitrile was evaporated under reduced pressure and the crude was used for the next step without any further purification.

To a solution of the above crude product (130 mg) in methanol (3 mL) was added K_2CO_3 (0.5 equiv of the crude mass), and the mixture was stirred for 30 min at room temperature. After completion of reaction, methanol was removed and the residue was purified by column chromatography (33% EtOAc/petroleum ether) to afford alcohol **3** (73 mg, 65% over two steps) as yellow oil: R_f 0.2 (40% ethyl acetate/petroleum ether); $[\alpha]_D^{25}$ = −132 (*c* 0.16, $CHCl_3$); IR ($CHCl_3$) ν 3363, 3215, 2932, 2852, 1627, 1487, 1461, 1382, 1321, 1216, 1095, 750 cm^{-1}; ^1H NMR (500 MHz, MeOD) δ 1.36 (s, 3H), 1.64 (s, 3H), 3.44 (d, *J* = 12.5 Hz, 1H), 3.63 (dd, *J* = 4.9, 10.4 Hz, 1H), 3.65 (dd, *J* = 4.9, 10.4 Hz, 1H), 3.87 (d, *J* = 12.5 Hz, 1H), 4.14 (dt, *J* = 2.2, 4.9 Hz, 1H), 4.55 (d, *J* = 11.9 Hz, 1H), 4.59 (d, *J* = 11.9 Hz, 1H), 4.65 (d, *J* = 2.2 Hz, 1H), 4.96 (s, 1H), 6.77 (d, *J* = 7.4 Hz, 1H), 6.90−6.93 (m, 2H), 7.05 (br t, *J* = 8.1 Hz, 1H), 7.31−7.37 (m, 7H), 7.49−7.52 (m, 2H), 7.75 (d, *J* = 8.2 Hz, 1H), ppm; ^{13}C NMR (100 MHz, CD_3OD) δ 27.0 (q), 29.2 (q), 59.3 (t), 71.0 (s), 71.4 (t), 74.6 (t), 82.5 (d), 84.3 (d), 88.5 (d), 93.8 (s), 112.6 (d), 113.3 (d), 114.2 (s), 115.6 (s), 119.2 (d), 119.9 (d), 120.6 (s), 121.9 (d), 122.5 (d), 124.6 (d), 125.8 (d), 126.2 (s), 128.8 (d), 128.9 (s), 129.0 (d, 2C), 129.3 (s), 129.4 (d, 2C), 139.1 (d), 162.5 (s), 201.1 (s) ppm; MS (ESI) *m*/*z* 563.2 ($[M + Na]^+$); HRMS (ESI) calcd for $C_{32}H_{32}N_2O_6$ $[M + H]^+$ 541.2339, found 541.2341.

15-*O*-Benzyl Isatisine A Acetonide (16). Under an atmosphere of argon in a Teflon-sealed tube, compound **3** (40 mg, 0.074 mmol), $[Cp^*RhCl_2]_2$ (4.5 mg, 10 mol %), K_2CO_3 (~2 mg, 5 mol %), and acetone (3 mL) were placed. The tube was sealed and was heated at 110 °C (oil bath temp) for 26 h. The reaction mixture was concentrated, and the resulting crude was purified by column chromatography (9% EtOAc/petroleum ether) to obtain the lactam **16** (22 mg, 56% yield) as yellow foam: R_f (20% ethyl acetate/petroleum ether) 0.5; $[\alpha]_D^{25}$ = −232.0 (*c* 0.16, $CHCl_3$); IR ($CHCl_3$) ν 3363, 2929, 2868, 1794, 1620, 1487, 1456, 1372, 1321, 12156, 1080, 750 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.39 (s, 3H), 1.52 (s, 3H), 3.33 (dd, *J* = 2.7, 10.7 Hz, 1H), 3.36 (dd, *J* = 3.3, 10.7 Hz, 1H), 3.81 (d, *J* = 12.8 Hz, 1H), 3.92 (d, *J* = 12.8 Hz, 1H), 4.32−4.33 (m, 1H), 4.86 (d, *J* = 2.4 Hz, 1 H), 4.91 (s, 1H), 6.96 (br dd, *J* = 1.8, 7.9 Hz, 2H), 7.17−7.26 (m, 7H), 7.33−7.35 (m, 1H), 7.58 (br t, *J* = 7.4 Hz, 1H), 7.65 (d, *J* = 7.4, 1H), 7.99 (d, *J* = 8.2 Hz, 1H), 8.16−8.17 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.6 (q), 27.0 (q), 68.9 (t), 73.0 (t), 75.0 (s), 84.6 (d), 85.6 (d), 87.2 (d), 98.2 (s), 111.5 (d), 111.8 (s), 116.4 (d), 117.7 (s), 120.6 (d), 121.0 (d), 122.5 (d), 122.9 (d), 124.5 (s), 125.4 (d), 125.5 (d), 126.1 (s), 127.5 (d), 127.6 (d, 2C), 128.2 (d, 2C), 136.2 (d), 137.2 (s), 137.5 (s), 149.9 (s), 169.9 (s), 194.0 (s) ppm; MS (ESI) *m*/*z* 559.2 ($[M + H]^+$); HRMS (ESI) calcd for $C_{32}H_{28}N_2O_6$ $[M + Na]^+$ 559.1845, found 559.1849.

(−)-Isatisine A (1). To an ice-cooled solution of **16** (10 mg, 0.019 mmol) in CH_2Cl_2 (1 mL) was added a solution of $TiCl_4$ (8 μL) in CH_2Cl_2 (1 mL) and stirred for 2 h at the same temperature. The reaction was quenched with ice and extracted with CH_2Cl_2 (20 mL × 3); the combined organic layer was dried (Na_2SO_4), concentrated, and the crude was subjected for column chromatography (5% MeOH/dichloromethane) to procure isatisine A (4.6 mg, 71%) as yellow solid: R_f (methanol/dichloromethane 1:9) 0.5; $[\alpha]_D^{25}$ = −275 (*c* 0.21, CH_3OH); IR ($CHCl_3$) ν 3432, 2913, 2879, 1712, 1635, 1466, 1458, 1386, 1315,, 1282, 1089, 750 cm^{-1}; ^1H NMR (500 MHz, MeOD) δ 3.33 (dd, *J* = 4.9, 11.8 Hz, 1H), 3.4 (dd, *J* = 4.9, 11.8 Hz, 1H), 3.83−3.86 (m, 1H), 4.07 (d, *J* = 4.3 Hz, 1H), 4.89 (s, 1H), 7.05 (t, *J* = 7.5 Hz, 1H), 7.12 (t, *J* = 7.3 Hz, 1H), 7.29 (s, 1H), 7.3−7.35 (m, 2H), 7.64 (d, *J* = 7.3 Hz, 1H), 7.77 (br t, *J* = 8.0 Hz, 1H), 7.93 (d, *J* = 7.9 Hz, 1H), 7.99 (d, *J* = 8.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, MeOD) δ 63.2 (t), 74.4 (d), 76.8 (s), 84.7 (d), 89.0 (d), 99.0 (s), 110.7 (s), 112.9 (d), 117.8 (d), 120.7 (d), 121.6 (d), 123.2 (d), 124.6 (d), 126.1 (s), 126.3 (d), 127.0 (d), 127.4 (s), 138.0 (d), 139.1 (s), 151.9 (s), 174.7 (s), 196.8 (s) ppm; MS (ESI) *m*/*z* 429.01 ($[M + Na]^+$); HRMS (ESI) calcd for $C_{22}H_{18}N_2O_6$ $[M + Na]^+$ 429.1063, found 429.1020.

(−)-Isatisine A Acetonide (2). A suspension of compound **16** (10 mg, 0.019 mmol) and 10% $Pd(OH)_2/C$ in ethanol (1.5 mL) was flushed with hydrogen gas and stirred under hydrogen (20 psi) atmosphere at rt for 4 h. The reaction mixture was filtered through a plug of filter aid, washed with ethyl acetate thoroughly (3 × 10 mL), and concentrated. Purification of crude product by column chromatography (30% ethyl acetate in petroleum ether) yielded product **2** (8 mg, 96%) as yellow solid: R_f 0.2 (petroleum ether/EtOAc 5:2); $[\alpha]_D^{25}$ = −278 (*c* 0.21, CH_3OH); IR ($CHCl_3$) ν 3425, 2989, 2915, 2859, 2830, 1720, 1615, 1470, 1376, 1265, 1246, 1215, 1148, 1087, 1055, 875 cm^{-1}; ^1H NMR (500 MHz, MeOD) δ 1.36 (s, 3H), 1.49 (s, 3H), 3.43 (dd, *J* = 11.9, 4.4 Hz, 1H), 3.49 (dd, *J* = 11.9, 4.2 Hz, 1H), 4.16 (dd, *J* = 7.7, 4.2 Hz, 1H), 4.79 (d, *J* = 3.4 Hz, 1H), 4.90 (s, 1H), 7.08 (t, *J* = 7.2 Hz, 1H), 7.14 (t, *J* = 7.2 Hz, 1H), 7.24 (s, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.80−7.74 (m, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 8.01 (d, *J* = 8.1 HZ, 1H) ppm; ^{13}C NMR (125 MHz, MeOD) δ = 26.4 (q), 27.4 (q), 62.6 (t), 76.4 (s), 86.1 (d), 87.2 (d), 87.9 (d), 99.6 (s), 111.1 (s), 113.1 (d), 117.6 (d), 119.6 (s), 120.9 (d), 121.4 (d), 123.4 (d), 124.4 (d), 125.8 (s), 126.3 (d), 127.1 (d), 127.4 (s), 138.0 (d), 139.2 (s), 151.3 (s), 171.6 (s), 195.8 (s) ppm; MS (ESI) *m*/*z* 469.1 ($[M + H]^+$); HRMS (ESI) calcd for $C_{25}H_{22}N_2O_6$ $[M + H]^+$ 447.1557, found 447.1553.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H, ^{13}C NMR, and HRMS spectra of all the new compounds; COSY and NOESY spectra of compounds ***6α*** and ***6β***. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This paper is dedicated to Professor Goverdhan Mehta on the occasion of his 70th birthday.

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