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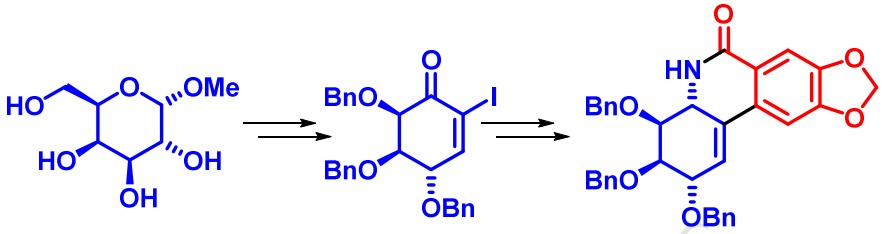

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ABSTRACT

A highly stereoselective total synthesis of Amaryllidaceae alkaloid starting from α-D-galactopyranoside has been described. The salient features of this total synthesis are Ferrier carbocyclization reaction for the synthesis of ring A and Suzuki Miyaura coupling of chiral α-iodo enone fragment with aromatic boronic acid followed by modified Bischler-Napieralski cyclization reaction to form the lactam ring.

1. Introduction

The *Amaryllidaceae* alkaloids, which contains lycorine type of structures such as (+)-lycoricidine **1**, (+)-narciclasine **2**, and (+)-pancratistatin **3** have been isolated from the plants of the genus *Amaryllidaceae* including the bulbs of narcissi and daffodils.[1] The structural elucidation of these molecules was done in 1970[2] showing highly oxygenated benzophenanthridone-type of skeletons with four or six contiguous stereogenic centers in the C-ring. The extensive biological properties of these compounds, particularly their anticancer and antiviral activities, have led them to being considered as therapeutic agents.[3] For instance, (+)-pancratistatin and some of its analogues (fig. 1) have been the subject of preclinical development studies as agents for the treatment of certain cancers.[2] Owing to their biological importance and limited availability through the natural resources, a significant body of work toward development of synthetic routes to these class of molecules and various analogues has been a challenging task to synthetic chemists.[4] However, among the various synthetic routes reported so far many of them have drawbacks such as harsh conditions, poor stereoselectivity, long reaction series and incompetent protecting group chemistry in the late stages resulting overall low yield. In continuation of our passion in total synthesis of natural products or biologically important molecules by utilizing monosaccharide derived chiral building blocks[5,6] polyhydroxylated alkaloids, and iminosugars,[7] motivated us to take an attempt toward a chiron approach to total synthesis of (+)-lycoricidine (**1**).

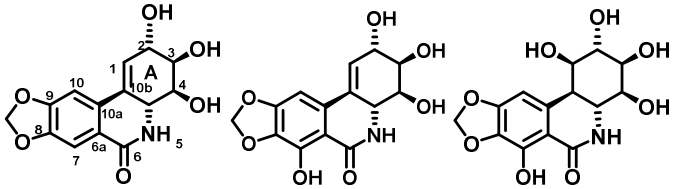

Figure 1: Structures of important *Amaryllidaceae* alkaloids.

The retrosynthetic strategy for the target molecule (+)-lycoricidine **1** is depicted in Scheme 1. We envisaged that **1** could be elaborated from **4** by electrophilic ring cyclization under modified conditions of Bischler–Napieralski reaction[8] followed by debenzylation. The precursor **4** could be synthesized either by Overmann rearrangement of **5** or inversion of sterocenter C4 of the alcohol **6**. The respective precursors of **5** and **6** (**7** and **8**) could be anticipated by Suzuki-Miyaura coupling of the substituted commercially available phenyl boronic acid **9** and carbohydrate derived iodine partners **10** and **11** which could be derived from methyl-α-D-mannopyranoside **14** and methyl-α-D-galactopyranoside **15** respectively.

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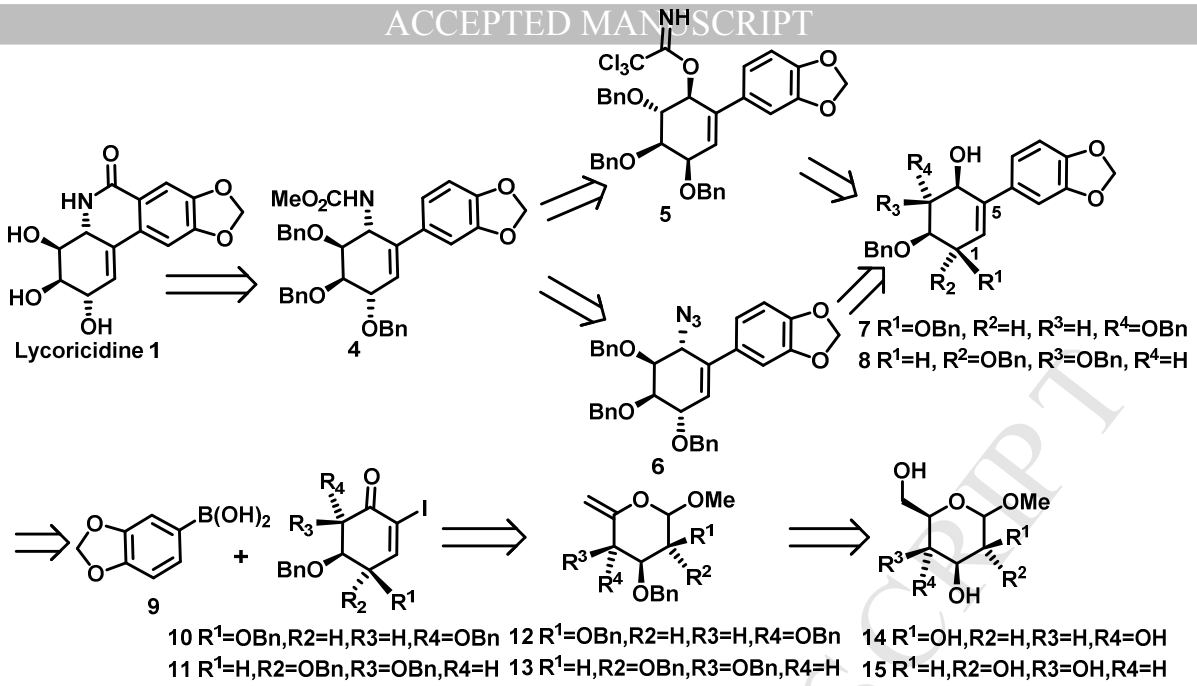
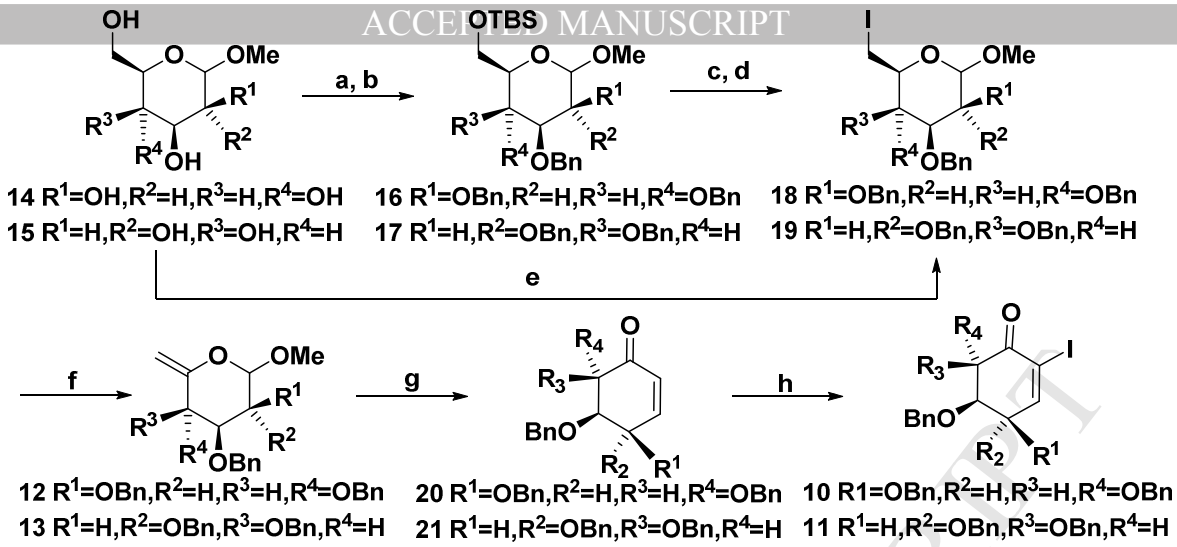


Scheme 1: Retrosynthetic analysis of (+)-lycoricidine**1.**

2. Results and Discussion

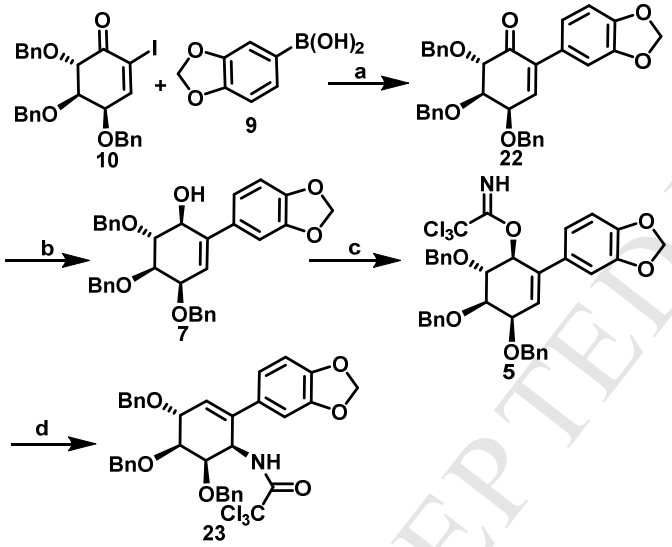
As per the above retrosynthetic analysis (Scheme 1), the stereoselective total synthesis of the title molecule **1** was commenced with methyl-α-D-mannopyranoside **14**. Initially, the pyranoside **14** was converted into the 6-deoxy-6-iodo-2,3-di-O-benzyl-α,D-mannopyranoside **18** through sequential four step reactions[9] involving silyl protection of primary alcohol followed by benzyl protection of remaining hydroxyl groups to obtain a globally protected sugar **16**. Its silyl removal with TBAF at 0 °C and subsequent iodination following regular protocol produced the iodide **18** with overall 66% yield starting from **14**. The compound **18** was also prepared in 90% yield by following the modified Pongdee et al protocol[10] from mannopyranoside **14**. According to which, **14** was subjected to regioselective iodination of C(6)-OH by using triphenylphosphine, imidazole and I_2 at 70 °C. The resulting iodide was purified by filter column which on benzylation produced 6-iodo derivative **18** (Scheme 2). It was subjected to dehydrohalogenation with potassium tertiarybutoxide (^{t}BuOK) in THF to furnish exocyclic tetrahydro-2*H*-pyran **12** in 82% yield.[11,12] The olefin **12** was subjected to the Ferrier's carbocyclization reaction[12] in the presence of mercuric (II) trifluoroacetate ($Hg(OCOCF_3)_2$) in acetone/water (1/1 V/V) and subsequent dehydration of the resultant with mesyl chloride and Et_3N produced enone **20** in 76% yield over two steps. Finally, α-iodo enone **10**, a chiral fragment for the synthesis of (+)-lycoricidine **1** was prepared by α-iodination of **20** with iodine in the presence of K_2CO_3 and DMAP in THF/H_2O (1/1) in 89% yield.[13] The formation of **10** from **20** was also possible by its treatment with iodine in pyridine/CCl_4 in the presence of catalytic amount of DMAP, but the yield was comparatively low (75%).[12]

Now, we switch on to palladium catalyzed Suzuki Miyaura coupling between **9** and **10**.[14] First, we screened various palladium catalysts under different conditions for the coupling reaction. We realized that performing the reaction in presence of palladium on carbon with sodium carbonate as a base and DME and water as a solvent in 1:1 ratio at 50 °C was found to be the most favorable condition for the coupling of **9** with **10** to obtain the coupled product **22** in 83% yield. The Luche's reduction of its α,β-unsaturated carbonyl group at 0 °C produced the corresponding alcohol **7** with the required stereochemical orientation of the OH functionality along with its diastereomer in the ratio of 2.5:1 in 81% yield (HPLC). However, the highly stereoselective reduction of **22** was performed successfully with DIBAL-H at -78 °C to produce the desired alcohol **7** almost exclusively in 79% yield (10:1, HPLC).[15] The allylic alcohol **7** was treated with trichloroacetonitrile (CCl_3CN) in the presence of base DBU at 0 °C to give the corresponding imidate **5** in 90% yield. Overmann rearrangement[16] of compound **5** with K_2CO_3 at 90 °C for 30 min in microwave conditions gave **23** in trace amounts and the most of the starting material was found untreated.[16d] Further changing the conditions like increasing the temperature or reaction time was futile and the starting material was decomposed. Therefore, we redesigned our synthetic strategy based on retrosynthetic scheme 1. According to it, we planned to carry out Mitsunobu reaction of the alcohol **7** to introduce nitrogen functionality at C4. However, before arrive to this stage, we need to move on to galactose derived **15** in order to set the remaining sterocenters of natural product **1** (scheme 3)**.**



Scheme 2: Synthesis of chiral fragment **10** and **11** from manno and galactopyranoside **14** and **15**.

Reagents and conditions: (a) TBSCl, imidazole, DMF, RT, 6 h (b) NaH, BnBr, DMF, 0 °C -RT, 24 h (86% for **16** and 85% for **17** over 2 steps) (c) TBAF, THF, 0 °C-RT, 3 h (d) PPh_3, imidazole, I_2, toluene, 45 °C, 2 h (77% for **18** and 80% for **19** over 2 steps). (e) PPh_3, imidazole, I_2, toluene, 70 °C, 2 h then NaH, BnBr, DMF, 0 °C -RT, 24 h (90% over 2 steps for both **18** and **19**) (f) ^{t}BuOK, dry THF, 0 °C –RT (82% for **12** and 85% for **13**) (g) $Hg(OCOCF_3)_2$, acetone:water (2:1), RT, overnight then MsCl, Et_3N, dry DCM, 0 °C -RT, 3 h (76% for **20** and 72% for **21** over two steps). (h) K_2CO_3, DMAP, I_2, THF:H_2O (1:1), 0 °C -RT, 12 h (89% for **10** and 91% for **11**).



Scheme 3: Attempt to synthesis of *ent*-lycoricidine through Overmann rearrangement.

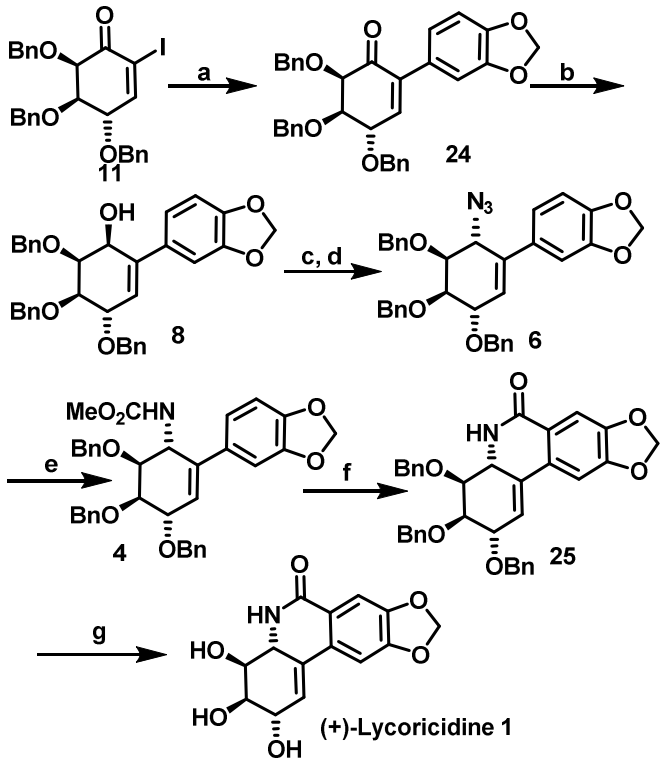
Reagents and conditions: (a) Pd/C (10%), Na_2CO_3, DME:H_2O (1:1), RT, 50 °C, overnight, 83% (b) DIBAL-H, THF, -78 °C, 3 h, 79% (c) CCl_3CN, DBU, DCM, 0 °C, 90% (d) K_2CO_3, 1,2-dichlorobenzene, microwave, 90 °C, 30 min (in trace amount).

The α-iodo enone **11** (50% yield) was synthesized starting from methyl α-D-galactopyranoside **15** by using similar reaction sequences which were used in the case of mannose derived chiral intermediate **10** (scheme 2). Its Suzuki-Miyaura coupling reaction with boronic acid **9** in the presence of palladium charcoal and Na_2CO_3 furnished enone **24** in 88% yield (Scheme 4). Its ketone functionality was subjected to DIBAL-H reduction at -78 °C to obtain the alcohol **8** with required stereochemistry in 85% yield along with a trace amount of its diastereomer (10:1 ratio). Its Mitsunobu reaction to introduce nitrogen functionality at C4-position was realized by treating it with diphenylphosphoryl azide (DPPA) and diisopropyl azodicarboxyelate (DIAD) at -20 °C.[6a] Unfortunately the reaction led to give the desired product **6** in poor yield (30-40%). Therefore, we switched over to a conventional method, in which the alcoholic group in **8** was converted into its corresponding mesylate which on azidation with sodium azide in DMF at room temperature produced the desired azide **6** comparatively in very good yields (83%).[4m] The stereochemistry of the newly created stereocenter was established by its 2D-NMR spectroscopy (COSY and NOESY). The azide **6** was reduced with PPh_3 to an amine whose subsequent protection with methyl chloroformate and DMAP afforded the protected amine **4** in 78% yield over two steps. It was then subjected to modified Bischler-Napieralski cylization reaction (Tf_2O, DMAP at 0 °C) to furnish the cyclized lactam **25** in 62% yield (scheme 4). Finally, its debenzylation with BCl_3 at 0 °C, led to produce the final title natural product **1** in 55% yield (Scheme 4). The spectral data of **1** was exactly matched with the reported[4c,f,n]

3. Conclusion

In summary, we have developed a new route for the total synthesis of *Amaryllidaceae* alkaloid (+)-lycoricidine **1** in 12 steps and with 7.8% overall yield and it is better approach compared to the some previous reports in terms of yields and number of steps.[4] The synthesis involved Ferrier carbocyclization reaction of the tetrahydro-2*H*-pyran **13** to form chiral carbocyclic fragment **21**, followed by Suzuki Miyaura coupling of α-iodo enone **11** with aromatic boronic acid **9** to form **24** and its Mitsunobu reaction to establish the

desired stereochemistry of title natural product. The carbamate (**4**) cyclization followed by global deprotection of cyclic lactam **25** led to give the target alkaloid **1**.



Scheme 4: Attempts to the preparation of (+)-lycoricidine **1.** **Reagents and conditions:** (a) Pd/C (10%), Na_2CO_3, DME:H_2O (1:1), 50 °C6 h, 88%. (b) DIBAL-H, THF, -78 °C, 3 h, 85% (c) MsCl, Et_3N, dry DCM, 0 °C-RT (d) NaN_3, DMF, RT, 24 h, 83% (over two steps). (e) (i) PPh_3, THF-H_2O, RT. (ii) $ClCO_2Me$, DMAP, DCM, RT, 78%. (f) Tf_2O, DMAP, dry DCM, 0 °C to RT, 12 h, 62%. (g) BCl_3, DCM, 0 °C, 6 h, 55%.

4. Experimental Section

4.1. General

The organic solvents were made anhydrous by standard methods before their use. TLC plates coated with silica gel (60F-254) 2.5 × 5 cm and 0.25 mm thickness were used to monitor the progress of the reaction. Visualization of the spots was done by spraying the plate with $Ce(SO_4)_2$ (1% in 2N H_2SO_4) and subsequent charring over hot plate. Silica gel (60–120 mesh) and silica gel (230-400 mesh) were used for column chromatography. All the intermediates were characterized by NMR, IR, ESI-HRMS and the identifications of known compounds were done by comparing their optical rotation with those reported in the literature. NMR experiments were recorded in $CDCl_3$ and CD_3OD at 25 ºC. Chemical shift values are given on δ scale with reference to TMS at 0.00 ppm for proton and carbon. The reference $CDCl_3$ appeared at 77.26 ppm for ^{13}C NMR. NMR spectra were recorded on Bruker Avance 400 MHz spectrometer at 400 MHz (^1H) and 100 MHz (^{13}C). Optical rotations were determined on HORIBA, high sensitive polarimeter, SEPA-300 using a 1 dm cell at 17 ºC-32 ºC in chloroform; concentrations mentioned are in g/100 mL. For IR spectra were recorded on Perkin–Elmer 881 and FTIR-8210 PC Shimadzu Spectrophotometers. Mass spectra were recorded on a JEOL JMS-600H high resolution spectrometer using EI mode at 70 eV. ESI-HRMS were recorded on a JEOL-AccuTOF, JMS-T100LC spectrometer.

tert-butyldimethyl(((2R,3S,4S,5R)-3,4,5-tris(benzyloxy)-6-methoxytetrahydro-2H-pyran-2-yl)methoxy)silane (Compound 17): To a solution of methyl α-D-galactopyranoside **15** (5.00 g, 0.026 mmol) and imidazole (3.5 g, 0.052 mmol) in DMF (50 mL) at room temperature was added TBSCl (5.75 g, 0.038 mmol) and the reaction was stirred at the same temperature for 4 h. The reaction was diluted with EtOAc (50 mL) and quenched with cold water (50 mL). The organic layer was extracted with EtOAc (3 x 50 mL) and the combined organic layers were concentrated in vacuo. The residue was placed on a high vacuum manifold to afford methyl α-D-6-O-silylgalactopyranoside as colorless compound. It was subjected to filter column to remove unreacted silyl reagent.

To the stirred solution of above crude compound (9.74 g, 0.032 mmol) in THF at 0 °C, was added sodium hydride (3.8 g, 0.158 mmol) in portion wise followed by dropwise addition of benzyl bromide by using dropping funnel. The reaction was shifted to room temperature and allowed to stir for overnight. After completion of the reaction, the reaction mixture was quenched with methanol and then it was evaporated in rotavapour to a solid mass. After that it was diluted with EtOAc, and washed with water and brine solution. The combined organic layers were dried on Na_2SO_4 and concentrated in vacuum. The crude material was subjected to silica gel column chromatography by using EtOAc/Hexane (1:9) as a solvent to obtain a pure compound **17** in 85% yield (16 g, 0.028 mmol). R_f 0.4 (1/4, EtOAc/ Hexane). $[\alpha]_D^{22}$ +31.5 (c 0.1, $CHCl_3$). IR (Neat): ν_{max}= 3117, 2986, 1721, 1630, 1415, 1205, 1120 cm^{-1}. ^1H (400 MHz, $CDCl_3$): δ 7.24-7.40 (m, 15H), 4.96 (d, *J*=15.2 Hz, 1H), 4.81-4.88 (m, 2H), 4.67-4.75 (m, 3H), 4.55-4.60 (m, 1H), 4.03 (dd, J_1=3.56, J_2=9.42 Hz 1H), 3.91-3.94 (m, 2H), 3.68-3.72 (m, 1H), 3.57-3.64 (m, 2H), 3.36 (s, 3H), 0.87 (s, 9H), 0.02 (s, 6H). ^{13}C (100 MHz, $CDCl_3$): δ 139.14, 139.05, 138.81, 128.59, 128.55, 128.42, 128.37, 128.33, 127.89, 127.74, 98.97, 79.42, 76.76, 75.39, 74.99, 73.77, 73.51, 71.27, 62.21, 55.41, 26.11, 18.42, -5.16, -5.24. ESI-HRMS: m/z $[M+Na]^+$ calcd for $C_{34}H_{46}NaO_6Si^+$ 601.2961, measured 601.2950.

(2S,3R,4S,5R)-3,4,5-tris(benzyloxy)-2-(iodomethyl)-6-methoxytetrahydro-2H-pyran (Compound 19): TBAF (28.5 mL,1.0 M solution in THF, 0.028 mmol) was added drop wise to a stirred solution of compound **17** (11 g, 0.019 mmol) in THF (10 mL) at 0 °C and the stirring was continued for 3 h. After completion of the reaction, the mixture was quenched with water and the organic layer was separated. The aqueous layer was extracted with EtOAc (3 x 30 mL) and the

combined organic layers were dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude reaction mixture was used for iodination without its column purification.

To the above stirred solution of crude compound (5.5 g, 0.012 mmol) in toluene were added PPh_3 (4.6 g, 0.02 mmol), imidazole (1.6 g, 0.02 mmol) and molecular iodine (4.5 g, 0.02 mmol) at room temperature. The temperature of the reaction was raised to 70 °C and stirring was continued for 2 h. After completion of the reaction, the mixture was quenched with $Na_2S_2O_3.5H_2O$. The aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated in vacuum. The crude compound was subjected to column chromatography (EtOAc/Hexane, 8:92) to obtain a pure compound **19** in 80% yield (9.4 g, 0.02 mmol) over two steps. R_f 0.4 (1/5, EtOAc/ Hexane). $[\alpha]_D^{22}$ +25.5 (c 0.3, $CHCl_3$). IR (Neat): ν_{max}=3015, 2930, 2855, 1645, 1472, 1216, 1014 cm^{-1}. ^1H (400 MHz, $CDCl_3$): δ 7.24-7.41 (m, 15 H), 5.03 (d, J=11.08, 1H), 4.62-4.91 (m, 6H),4.0-4.03 (m, 2H), 3.91-3.94 (m, 1H), 3.82-3.86 (m, 1H), 3.41 (s, 3H), 3.22 (dd, J_1=7.53, J_2=9.98 Hz, 1H), 3.07 (dd, J_1=6.21, J_2=9.98 Hz, 1H). ^{13}C (100 MHz, $CDCl_3$): δ 138.89, 138.61, 138.50, 128.67, 128.35, 128.05, 128.01, 127.85, 127.76, 99.09, 79.31, 76.24, 76.05, 75.26, 73.85, 71.54, 55.98, 3.8. ESI-HRMS: m/z $[M+Na]^+$ calcd for $C_{28}H_{31}INaO_5^+$ 597.1114, measured 597.1105.

Procedure for the preparation of 19 directly from 15: To a solution of methyl α- D-glucopyranoside **15** (5.00 g, 25.8 mmol) in toluene (500 mL) at room temperature was added triphenylphosphine (10.1 g, 38.6 mmol) followed by imidazole (5.30 g, 3.00 mmol) and iodine (9.15 g, 1.40 mmol) and the reaction was heated to 70 ºC for 2 h. It was cooled to room temperature and water (50 mL) was added to it. The resulting mixture was stirred vigorously for 10 min. The organic layer was extracted with water (1 X 50 mL) and the combined aqueous layers were concentrated in vacuo. The residue was placed on a high vacuum manifold to afford 11.0 g of methyl α-D-6-deoxy-6-iodoglucopyranoside as an off-white solid.

To the above crude compound (11 g, 0.035 mmol) in THF at 0 °C, was added sodium hydride (4.2 g, 0.175 mmol) in portion wise for 30 min followed by dropwise addition of benzyl bromide by using dropping funnel at the same temperature. The reaction was warmed to room temperature and allowed to stir for overnight. The reaction mixture was diluted with methanol followed by evaporation of the solvent in rotavapour to a solid mass. It was dissolved in EtOAc, and washed with water and brine solution. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuum. The crude material was subjected to silica gel column chromatography by using EtOAc/Hexane (1:9) as a solvent to obtain a pure compound **19** in 90% yield over two steps (17 g, 0.03 mmol).

(3R,4S,5R)-3,4,5-tris(benzyloxy)-2-methoxy-6-methylenetetrahydro-2H-pyran (Compound 13): ^{t}BuOK (1.04 g, 9.3 mmol) was added to a stirred solution of iodide **19** (3 g, 0.01 mmol) in THF (40 mL) in portion wise at 0 °C over 2 h and the reaction was allowed to stir at room temperature for 24 h. The reaction mixture was diluted with ethyl acetate (50 mL) and the organic layer was washed with H_2O (2 x 25 mL) followed by brine solution (2 x 25 mL). The organic layer was separated, dried (Na_2SO_4), and concentrated under reduced pressure to give a residue. Its silica gel column chromatography furnished pure olefin **13** in 85% yield (2 g, 0.005 mmol). R_f 0.4 (1/5, EtOAc/ Hexane). $[\alpha]_D^{22}$ +7.6 (c 0.2, $CHCl_3$). IR (Neat): ν_{max} =3020, 2361, 1663, 1216, 1051 cm^{-1}. ^1H (400 MHz, $CDCl_3$): δ 7.17-7.29 (m, 15H), 4.53-4.93 (m, 9H), 3.82-3.96 (m, 1H), 3.45-3.54 (m, 1H), 3.34-3.41 (m, 4H), 3.21-3.28 (m, 1H). ^{13}C (100 MHz, $CDCl_3$): δ 153.89, 138.79, 138.27, 138.25, 128.74, 128.70, 128.64, 128.60, 128.24, 127.98, 127.94, 127.85, 99.30, 97.07, 79.76, 76.02, 75.99, 75.59, 74.72, 73.84, 73.68, 55.75. ESI-HRMS: m/z $[M+H]^+$ calcd for $C_{28}H_{31}O_5^+$ 447.2171, measured 447.2160.

(4S,5R,6R)-4,5,6-tris(benzyloxy)cyclohex-2-en-1-one (Compound 21): To a stirred suspension of the exocyclic olefin **13** (900 mg, 2.02 mmol) in acetone/water (30 mL, 2:1, v/v) at room temperature was added Mercury (II) trifluoroacetate (90 mg, 0.220 mmol). The reaction mixture was allowed to stir for overnight, after completion the reaction, the solvent was concentrated at reduced pressure to a residue. Then it was dissolved in ethyl acetate (30 mL) and washed with water (3 x 15 mL) and brine (3 x 15 mL) solutions. The combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure to obtain clear oil (890 mg), which was used without further purification.

Triethyl amine (2.5 mL) and methanesulfonyl chloride (0.64 mL, 4.6 mmol) were added to the above crude residue (890 mg) dissolved in DCM (15 mL) at 0 °C. The reaction mixture was shifted to room temperature and continued the stirring for 2 h. The reaction was quenched with saturated aqueous solution of NH_4Cl (15 mL) and the resulting solution was extracted with DCM (4 x 15 mL). The organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure to a residue, which on silica gel column chromatography furnished the enone **21** in 72% yield (585 mg, 1.41 mmol) over two steps. R_f 0.4 (1/4, EtOAc/ Hexane). $[\alpha]_D^{22}$ +137.6 (c 0.2, $CHCl_3$). IR (neat): ν_{max} =3020, 2361, 1693, 1648, 1216, 1024 cm^{-1}. ^1H (400 MHz, $CDCl_3$): δ 7.27-7.34 (m, 15H), 6.77 (dd, J_1=3.18, J_2=10.20 Hz, 1H), 5.99 (d, J=10.31 Hz, 1H), 4.80-4.83 (m, 1H), 4.52-4.72 (m, 5H), 4.42 (bs, 1H), 4.23-4.24 (m, 1H), 3.95-3.97 (m, 1H). ^{13}C (100 MHz, $CDCl_3$): δ 196.34, 138.13, 138.00, 137.80, 128.76, 128.62, 128.61, 128.29, 128.23, 128.09, 128.05, 80.23, 79.16,

75.35, 73.47, 72.94, 72.63. ESI-HRMS: m/z $[M+Na]^+$ calcd for $C_{27}H_{26}NaO_4^+$ 437.1729, measured 437.1722.

General procedure for the α-iodination of compounds 10 and 11: K_2CO_3 (664 mg, 4.8 mol) and DMAP (10 mg, 0.08 mmol) were added to the stirred solution of 2-cyclohexenone derivative **20** or **21** (1.6 g, 0.004 mmol) in a 1:1 mixture of THF/H_2O at 0 °C then continue the stirring at the same temperature for 10 min. A series of colours were observed before finally turning to brown. After that, I_2 (1.22 g, 0.005 mol) was added slowly to avoid forming a solid mass at the bottom of the flask. The reaction turned black and was stirred for 12 h open to the atmosphere at room temperature. Then the mixture was partitioned between EtOAc and washed sequentially with 0.1 M aqueous HCl, saturated aqueous $Na_2S_2O_3.5H_2O$, and brine solutions. The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was subjected to silica gel column chromatography to afford a pure 2-iodoenone.

(4R,5R,6S)-4,5,6-tris(benzyloxy)-2-iodocyclohex-2-en-1-one (Compound 10): 89% yield (1.7 g, 0.0035 mmol) as a yellow oil. R_f 0.5 (1/4, EtOAc/ Hexane). $[\alpha]_D^{22}$ +286.1 (c 0.77, $CHCl_3$); IR (neat): ν_{max} =3427, 3022, 2927, 2363, 1698, 1218 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, J=3.5 Hz, 1H), 7.39-7.26 (m, 15H), 4.82-4.56 (m, 6H), 4.40-4.34 (m, 2H), 4.01 (dd, 1H, J_1=3.0, J_2=6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.6, 154.9, 138.1, 137.8, 137.6, 128.9, 128.8, 128.5, 128.4, 128.3, 103.9, 78.7, 78.4, 75.4 , 73.9, 73.7, 73.0; ESI-HRMS: m/z $[M]^+$ calcd for $C_{27}H_{25}IO_4^+$ 540.0798, found 540.0798.

(4S,5R,6R)-4,5,6-tris(benzyloxy)-2-iodocyclohex-2-en-1-one (Compound 11): 91% yield (1.89 g, 0.004 mmol) as a yellow oil. R_f 0.5 (1/4, EtOAc/ Hexane). $[\alpha]_D^{22}$ +155.3 (c 0.15, $CHCl_3$). IR (neat): ν_{max} =3028, 2924, 2865, 1698, 1593, 1083, 1015 cm^{-1}. ^1H (400 MHz, $CDCl_3$): δ 7.49 (d, J=3.79 Hz, 1H), 7.25-7.38 (m, 15H), 4.81-4.84 (m, 1H), 4.49-4.64 (m, 5H), 4.39 (d, J=2.40 Hz, 1H), 4.33 (bs, 1H), 3.96 (dd, J_1=2.32, J_2=5.36 Hz, 1H). ^{13}C (100 MHz, $CDCl_3$): δ 190.43, 154.25, 137.84, 137.52, 137.45, 128.84, 128.67, 128.41, 128.36, 128.19, 128.15, 128.09, 103.38, 79.88, 78.00, 73.46, 73.15, 72.97. ESI-HRMS: m/z $[M+Na]^+$ calcd for $C_{27}H_{25}INaO_4^+$ 563.0695, found 563.0670.

General procedure for the synthesis of 22 and 24: To a stirred solution of 2-iodoenone **10** or **11** (1.1 g, 0.002 mmol) in DME and H_2O (1:1, 10 mL) were added Na_2CO_3 (431 mg, 4.07 mol), boronate **9** (675 mg, 4.07 mmol), and 10% Pd/C (100 mg, 5 mol %). The mixture was stirred for the 4 h at room temperature. After completion of the reaction, Pd/C was filtered, and the filtrate was diluted with H_2O (10 mL) and extracted with Et_2O (3 x 15 mL). The collected organic extracts were dried over Na_2SO_4 and concentrated under vacuum. The crude was subjected to column chromatography (EtOAc/Hexane 12:88) to obtain a pure compound.

(4R,5R,6S)-2-(benzo[d][1,3]dioxol-5-yl)-4,5,6-tris(benzyloxy)cyclohex-2-en-1-one (Compound 22): The compound **22** was obtained in 83% yield (171 mg, 0.30 mmol) after column purification. Column eluent: EtOAc/hexane (18:72, v/v). R_f 0.3 (1/3, EtOAc/ Hexane); $[\alpha]_D^{22}$ +32.4 (c 0.3, $CHCl_3$). IR (KBr): ν_{max}=3021, 1746, 1644, 1217, 1072 cm^{-1}. ^1H (400 MHz, $CDCl_3$): δ 7.17-7.28 (m, 15H), 6.59-6.71 (m, 2H), 6.46 (d, J=7.55 Hz, 2H), 5.88 (s, 2H), 5.01-5.04 (m, 1H), 4.91-4.94 (m, 1H), 4.66-4.80 (m, 4H), 4.38 (dd, J_1=2.12, J_2=8.08 Hz, 1H), 3.94-4.09 (m, 2H); ^{13}C (100 MHz, $CDCl_3$): δ 196.16, 148.88, 144.37, 143.52, 138.39, 138.33, 137.97, 137.87, 135.85, 128.78, 128.62, 128.49, 128.37, 128.26, 128.17, 128.07, 128.01, 108.86, 103.17, 101.81, 84.72, 84.42, 78.80, 75.81, 74.74, 73.90. ESI-HRMS: m/z $[M+H]^+$ calcd for $C_{34}H_{31}O_6^+$ 535.2121, found 535.2135.

(4S,5R,6R)-2-(benzo[d][1,3]dioxol-5-yl)-4,5,6-tris(benzyloxy)cyclohex-2-en-1-one (Compound 24): The compound **24** was obtained in 88% yield (880 mg, 1.64 mmol). R_f 0.5 (1/4, EtOAc/ Hexane) $[\alpha]_D^{22}$ +50.6 (c 0.1, $CHCl_3$). IR (KBr): ν_{max} =3018, 2954, 2855, 1702, 1542, 1183, 1025 cm^{-1}. ^1H (400 MHz, $CDCl_3$): δ 7.24-7.39 (m, 15H), 6.71-6.79 (m, 4H), 5.89 (s, 2H), 5.02-504 (m, 1H), 4.92-4.95 (m, 1H), 4.63-4.80 (m, 4H), 4.37-4.39 (m, 1H), 3.95-4.10 (m, 2H). ^{13}C (100 MHz, $CDCl_3$): δ 196.30, 148.10, 147.73, 144.04, 138.47, 138.32, 138.04, 137.94, 128.81, 128.65, 128.54, 128.47, 128.40, 128.27, 128.18, 128.10, 128.03, 122.59, 109.40, 108.40, 101.43, 84.77, 84.50, 78.83, 75.85, 74.74, 73.87. ESI-HRMS: m/z $[M+H]^+$ calcd for $C_{34}H_{31}O_6^+$ 535.2121, found 535.2115.

General procedure for 7 or 8: Enone **22** or **24** (350 mg, 0.655 mmol) was dissolved in dry THF (4.0 mL), cooled to –78 °C under argon and 0.5 mL of DIBAL-H (1M solution in dichloromethane or hexanes) was added. The mixture was allowed to stir for two hours, warmed to room-temperature and EtOAc (1.0 mL) was added, followed by 3N HCl (0.3 mL) and water (5.0 mL). The mixture was extracted with EtOAc (3 x 20 mL). Organic phase was separated, washed with brine (3 x 20 mL), dried (Na_2SO_4), and solvent removed under vacuum.

(1S,4R,5R,6R)-2-(benzo[d][1,3]dioxol-5-yl)-4,5,6-tris(benzyloxy)cyclohex-2-en-1-ol (Compound 7): The compound **22** was obtained in 79% yield (171 mg, 0.30 mmol) after column purification. Column eluent: EtOAc/hexane (18:72, v/v). R_f 0.3 (1/3, EtOAc/ Hexane). $[\alpha]_D^{22}$ +73.7 (c 0.2, $CHCl_3$). IR (Neat): ν_{max} =3432, 3020, 2959, 2363, 1637, 1216, 1044 cm^{-1}. ^1H (400 MHz, $CDCl_3$): δ 7.22-7.30 (m, 15H), 6.65 (s, 1H,), 6.46-6.48 (m, 2H), 5.85-5.94 (m, 3H), 4.77-4.93 (m, 3H), 4.59-4.70 (m, 4H), 4.16-4.25

(m, 1H), 3.80-3.83 (m, 1H), 3.52-3.68 (m, 1H). ^{13}C (100 MHz, $CDCl_3$): δ 149.23, 143.68, 139.67, 138.27, 135.40, 135.36, 133.94, 128.83, 128.78, 128.62, 128.59, 128.24, 128.13, 127.98, 127.84, 127.82, 126.71, 106.62, 101.51, 100.90, 80.04, 79.78, 79.35, 75.37, 75.21, 73.42, 72.61, 71.99, 68.33. ESI-HRMS: m/z $[M+H]^+$ calcd for $C_{34}H_{33}O_6^+$ 537.2277, found 537.2262;

(1S,4S,5R,6S)-2-(benzo[d][1,3]dioxol-5-yl)-4,5,6-tris(benzyloxy)cyclohex-2-en-1-ol (Compound 8): Pure compound was obtained in 85% yield (298 mg, 0.26 mmol) by using silica gel column chromatography. R_f0.5 (1/3, EtOAc/ Hexane). $[\alpha]_D^{22}$ +45.0 (c 0.1, $CHCl_3$). IR (Neat): ν_{max} =3427, 3022, 2927, 2363, 1698, 1218 cm^{-1}; ^{1}H (400 MHz, $CDCl_3$): δ 7.25-7.40 (m, 15H), 7.02-7.04 (m, 2H), 6.76-6.78 (m, 1H), 5.39-5.95 (m, 3H), 4.69-4.82 (m, 4H), 4.57-4.66 (m, 2H), 427-4.29 (m, 1H), 4.03-4.04 (m, 1H), 3.96-3.97 (m, 1H), 3.30 (d, *J*= 10.61 Hz, 1H); ^{13}C (100 MHz, $CDCl_3$): δ 147.94, 147.54, 141.33, 138.55, 138.14, 133.64, 128.72, 128.16, 127.98, 122.27, 120.65, 108.34, 107.46, 101.28, 79.00, 75.86, 73.57, 72.15, 67.60. ESI-HRMS: m/z $[M+H]^+$ calcd for $C_{34}H_{33}O_6^+$ 537.2277, found 537.2259.

(1S,4R,5R,6R)-2-(benzo[d][1,3]dioxol-5-yl)-4,5,6-tris(benzyloxy)cyclohex-2-en-1-yl 2,2,2-trichloroacetimidate (Compound 5): To the stirred solution of compound **7** (130 mg, 0.243 mmol) in dry DCM was added the trichloroacetonitrile (0.045 mL, 0.036 mmol) and DBU (0.054 mL, 0.036 mmol) at ice cold conditions. Then the reaction mixture was stirred for 3 h at room temperature. After completion of the reaction, solvent was evaporated in rota vapour. The crude mixture was subjected to silica gel column chromatography to obtain pure compound **5** in 90% yield. R_f 0.5 (1/5, EtOAc/ Hexane). $[\alpha]_D^{22}$ +72 (c 0.2, $CHCl_3$). IR (Neat): ν_{max} =3100, 3055, 2899, 2100, 1655, 1190 cm^{-1}; ^{1}H (400 MHz, $CDCl_3$): $_\delta$ 7.20-7.31 (m, 15 H), 6.81-6.88 (m, 3H), 6.69 (d, *J*=8.67 Hz, 1H), 6.08 (d, *J*= 3.83 Hz, 1H), 5.87 (s, 2H), 5.34 (dd, J_1=2.25, J_2=9.85 Hz, 1H), 4.78 (t, *J*=11.52 Hz, 2H), 4.59-4.67 (m, 3H), 4.52-4.55 (m, 1H), 4.10-4.11 (m, 1H), 3.74-3.76 (m, 2H); ^{13}C (100 MHz, $CDCl_3$): δ 162.29, 147.68, 147.56, 138.72, 138.40, 138.36, 137.79, 131.99, 128.70, 128.60, 128.53, 128.23, 128.02, 127.90, 127.86, 127.61, 120.59, 108.23, 107.50, 101.24, 91.65, 83.40, 82.67, 79.88, 78.40, 75.65, 72.87; ESI-HRMS: m/z $[M+H]^+$ calcd for $C_{36}H_{33}C_{l3}NO_6^+$ 680.1373, found 680.1390.

5-((3S,4R,5S,6R)-6-azido-3,4,5-tris(benzyloxy)cyclohex-1-en-1-yl)benzo[d][1,3]dioxole (Compound 6): Triethyl amine (0.13 mL, 1.5 mmol) and methanesulfonyl chloride (0.12 mL, 1.42 mmol) were added to the alcohol **8** (400 mg, 0.71 mmol) dissolved in DCM (15 mL) at 0 °C. The reaction mixture was shifted to room temperature and continued the stirring for 2 h. The reaction was quenched with saturated aqueous solution of $NaHCO_3$ (15 mL) and the resulting solution was extracted with DCM (4 x 15 mL). The organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure to a residue, which was used directly for the azidation without purification.

NaN_3 (109 mg, 0.17 mmol) was added to the above crude solution of mesylate compound in anhydrous DMF (5 mL) and the resulting mixture was stirred under nitrogen atmosphere at 18 °C for 10 h then diluted with diethyl ether (30 mL). The separated organic layer was washed with water (5 X 10 mL) then dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a yellow oil. Subjection of this material to flash column chromatography (20% v/v ethyl acetate/hexanes) and concentration of the relevant fractions gave the title compound **6** in 83% yield (362 mg, 0.6 mmol) as a clear, colorless oil. R_f 0.3 (1/4, EtOAc/ Hexane). $[\alpha]_D^{22}$ -66.4 (c 0.1, $CHCl_3$). IR (Neat): ν_{max} =3128, 2824, 2160, 1710, 1593, 1283, 1115 cm^{-1}. ^{1}H (400 MHz, $CDCl_3$): δ 7.29-7.37 (m, 15H), 6.76-6.85 (m, 3H), 5.99 (d, *J*=3.54 Hz, 1H), 5.96 (s, 2H), 4.64-4.81 (m, 6H), 4.45 (d, *J*=5.12 Hz, 1H), 4.29-4.31 (m, 1H), 3.98 (dd, J_1=2.16, J_2=5.48 Hz, 1H), 3.87 (dd, J_1=2.16, J_2=5.79 Hz, 1H). ^{13}C (100 MHz, $CDCl_3$): δ 148.08, 147.80, 138.75, 138.53, 138.40, 138.25, 132.85, 128.72, 128.70, 128.68, 128.21, 128.11, 128.08, 127.99, 120.45, 108.47, 107.29, 101.45, 78.52,75.24, 73.13, 72.89, 72.45, 61.29. ESI-HRMS: m/z $[M+Na]^+$ calcd for $C_{34}H_{31}N_3NaO_5^+$ 584.2161, found 584.2155.

methyl ((1R,4S,5R,6S)-2-(benzo[d][1,3]dioxol-5-yl)-4,5,6-tris(benzyloxy)cyclohex-2-en-1-yl)carbamate (4): To the stirred solution of azide **6** (20 mg, 0.0356 mmol) in THF (3 mL) was added the PPh_3 (19 mg, 0.07 mmol) and 2 drops of water. The resulting mixture was continued for stirring for 3 h. After completion of the reaction, it was concentrated under reduced pressure and the residue was dissolved in DCM (5 mL). The resulting solution was dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain a crude amine which was used directly without purification for the next step.

A solution of methyl chloroformate (0.2 mL, 0.12 mmol) and DMAP (20 mg, 0.16 mmol) were added slowly to a vigorously stirred mixture of the above crude amine (20 mg, 0.03 mmol) in CH_2C1_2 (3 ml). The reaction mixture was then allowed to stir at 18 °C for a further 3 h and afterward water (4 mL) and CH_2Cl_2 (4 ml) were added to it. The separated organic phase was washed with water (1 x20 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to obtain a pure compound **4** in 78% (16 mg, 0.027 mmol) over two steps. R_f 0.3 (1/4, EtOAc/ Hexane). $[\alpha]_D^{22}$ +61.8 (c 0.2, $CHCl_3$). IR (Neat): ν_{max} =3018, 2931, 2231, 1742, 1584, 1216, 1152 cm^{-1}. ^{1}H (400 MHz, $CDCl_3$): δ 7.18-7.28 (m, 15H), 6.82 (d, *J*=9.6 Hz, 1H), 6.47-6.48 (m, 2H), 6.04 (d, *J*=2.37 Hz, 1H), 5.86-5.88 (m, 2H), 5.09 (dd, J_1=5.31, J_2=9.39 Hz, 1H), 4.72-4.75 (m, 1H), 4.61-4.65 (m,

5H), 4.16-4.17 (m, 1H), 3.86-3.89 (m, 1H), 3.77-3.79 (m, 4H). ^{13}C (100 MHz, $CDCl_3$): δ 149.09, 143.65, 138.32, 137.99, 137.78, 136.57, 135.50, 132.55, 128.73, 128.68, 128.39, 128.29, 128.19, 128.15, 128.09, 128.03, 125.64, 106.07, 101.80, 100.86, 79.15, 78.59, 76.45, 74.25, 74.14, 72.23, 56.71. ESI-HRMS: m/z $[M+H]^+$ calcd for $C_{36}H_{35}NNaO_7^+$ 616.2311, found 616.2355.

(2S,3R,4S,4aR)-2,3,4-tris(benzyloxy)-3,4,4a,5-tetrahydro-[1,3]dioxolo[4,5-j]phenanthridin-6(2H)-one (Compound 25): To a solution of methyl carbamate **4** (55 mg 0.09 mmol) and DMAP (35 mg, 0.3 mmol) in CH_2Cl_2 (4 mL) cooled to -10 °C was added trifluoromethanesulfonic anhydride (0.7 mL, 0.4 mmol). The reaction mixture was stirred for 5 h at -10 °C to -5 °C and further continued for 12 h at 0 °C. After total consumption of starting material (TLC analysis), the solvents were removed under reduced pressure, and THF (2 mL) was added. The reaction mixture was cooled to 0 °C and two drops of 2 M aq HCl was added. The mixture was stirred for 2 h, and solid sodium bicarbonate was added. The solvent was removed under reduced pressure and the residue purified by flash column chromatography affording lactam **25** as a yellow oil (13.8 mg, 62%); R_f 0.1 (ethyl acetate/hexanes, 2:1); IR (Neat): ν_{max} =3490, 2940, 2858, 1660, 1613 cm^{-1}; $[\alpha]_D^{22}$ +22.4 (c 0.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (s, 1H), 7.18-7.27 (m, 15H), 7.04 (s, 1H), 6.01-6.02 (m, 1H), 5.85 (dd, J_1=1.26, J_2=4.78 Hz, 2H), 5.06 (dd, J_1=5.10, J_2=9.44 Hz, 1H), 4.71-4.74 (m, 1H), 4.57-4.66 (m, 5H), 4.15-4.17 (m, 1H), 3.87 (dd, J_1=4.53, J_2=6.58 Hz, 1H), 3.79-3.81 (m, 1H); ^{13}C (100 MHz, $CDCl_3$): δ 161.37, 148.02, 147.87, 138.40, 138.08, 137.82, 136.73, 132.21, 128.73, 128.69, 128.37, 128.28, 128.23, 128.14, 128.06, 128.02, 125.42, 120.47, 108.42, 107.19, 101.38, 78.98, 78.27, 76.32, 74.14, 74.05, 72.16, 52.07; ESI-HRMS: m/z $(M+Na)^+$ calcd. for $C_{35}H_{31}NNaO_6^+$ 584.2049, found: 584.2055.

(+)-Lycoricidine (1): To the stirred solution of above lactam **25** (32 mg) dissolved in dry DCM (2 mL) at 0 °C was added BCl_3 (0.4 mL, 1 M solution in DCM) under argon atmosphere and stirring of the reaction mixture was continued at same temperature for 4 h. After completion of reaction, methanol (2 mL) was added to the reaction mixture. Solvent evaporation of reaction mixture at reduced pressure furnished a residue, which was purified using silica gel column chromatography to afford a pure compound (+)-lycoricidine **1** as a white solid in 55% yield (8 mg); R_f0.5 (1/4, MeOH/ DCM). m.p 220-223 °C; (lit^{4n}. m.p 217-221 °C); $[\alpha]_D^{22}$ +187 (c 0.50, pyridine); [lit^{4n} $[\alpha]_D^{22}$ +180 (c 0.45, pyridine)]; IR (KBr): ν_{max} =3380, 2923, 1712, 1643, 1470, 1396, 1129, 1032 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD): δ 7.39 (s, 1H), 7.15 (s, 1H), 6.15-6.17 (m, 1H), 6.05 (d, J = 1.0 Hz, 1H), 6.02(d, J = 1.0 Hz, 1H),, 4.34 (dd, J_1=2.6, J_2=8.5 Hz, 1H), 4.22 (dd, J_1 =2.6, J_2=4.8 Hz, 1H), 3.88-3.95 (m, 2H); ^{13}C (100 MHz, CD_3OD): δ 166.23, 153.24, 149.90, 133.88, 133.10, 124.08, 123.20, 108.62, 105.04, 103.90, 74.25, 70.68, 70.63, 53.26; ESI-HRMS: m/z $(M+H)^+$ calcd. for $C_{14}H_{14}NO_6^+$ 292.0816, found: 292.0829.

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