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Studies directed towards synthesis of leprostatic agent desoxyfructoserotonin

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Leprosy is an infectious chronic disease and a neglected tropical disease induced by *Mycobacterium leprae*, and mainly affects the skin, peripheral nerves, upper respiratory mucosa and eyes. The prolonged physical deformities associated with leprosy get progressively worse with delayed diagnosis and increasing age. In this paper we report synthesis of Desoxyfructoserotonin which is a leprostatic agent, using 5-methoxy indole and the desired chiral centres have been incorporated using naturally obtained sugar moiety (D)-mannitol employing Vilsmeier-Haack reaction and Henry reactions.

Keywords: Hanson's disease, Desoxyfructoserotonin, Vilsmeier-Haack reaction, Henry reaction

Hansen's disease or leprosy is a chronic bacterial infection caused by the *M.leprae* or *M. lepromatosis* which was first identified by G. A. Hansen in 1873. Leprosy is a contagious disease in human mainly affects the skin, nerves and upper respiratory tract[1-6]. In 1940, Sodium glufosinate[7] is the first drug used to treat leprosy and was later replaced by diamino diphenyl sulphone (DDS) also called as Dapsone in 1950[7]. In order to eradicate the leprosy disease though it is seen in 5% of population due to low immunity, World Health Organization (WHO) put forth the multi-drug therapy (MDT) treatment soon after its early diagnosis and detection. Multi Drug Therapy (MDT)[8] of leprosy includes the dapsone (**2**),[9] clofazimine (**3**),[10] ehtionamide (**4**)[11], rifampicin (**5**),[12] and antibiotics like ofloxacin (**6**) (Fig. 1)[13].

Results and Discussion

Herein, we report the studies directed towards the synthesis of Desoxyfructoserotonin. The key steps in our convergent strategy involve Vilsmeier-Haack reaction and Henry reaction[14,15]. The key precursor (**5**) could be synthesized from commercially available 5-methoxy indole (Scheme 1a).

The synthesis of Desoxyfructoserotonin was begun with commercially available starting material 5-methoxyindole. The 5-methoxyindole was subjected to vilsmeier reaction with phosphorus oxychloride in DMF/CH_3CN which afforded the corresponding aldehyde, followed by the Henry reaction to afford the nitroalkene on dehydration. Thus obtained nitroalkene was reduced with LAH to afford the respective amine as shown in Scheme 1b.

The aliphatic chiral moiety was deduced from commercially available sugar moiety D-Mannitol. D-Mannitol was subjected to triketalization followed by the regioselective deprotection of one of the terminal isopropylidene group and selective tosylation of primary alcohol gave us the hydroxyl compound. The hydroxyl compound was subjected to oxidation with Dess-Martin- Periodinane in DCM which afforded the ketone **14** as shown in Scheme 2.

Further, the two fragments amine and aliphatic chiral ketone was coupled in the presence of K_2CO_3 using CH_3CN to furnish the compound **15** as shown in Scheme 3.

Finally the compound **15** was subjected to acetonide deprotection and simultaneous demethylation using BBr_3 in various possible conditions (Table 1) to afford the target molecule Desoxyfructoserotonin **7**.

Experimental Section

All the air and moisture sensitive reactions were carried out under inert atmosphere (nitrogen or argon). Oven-dried glass apparatus were used to perform all the reactions. Freshly distilled anhydrous solvents were used for air and moisture sensitive reactions. Commercially available reagents were used as such. Purification of compounds was carried out

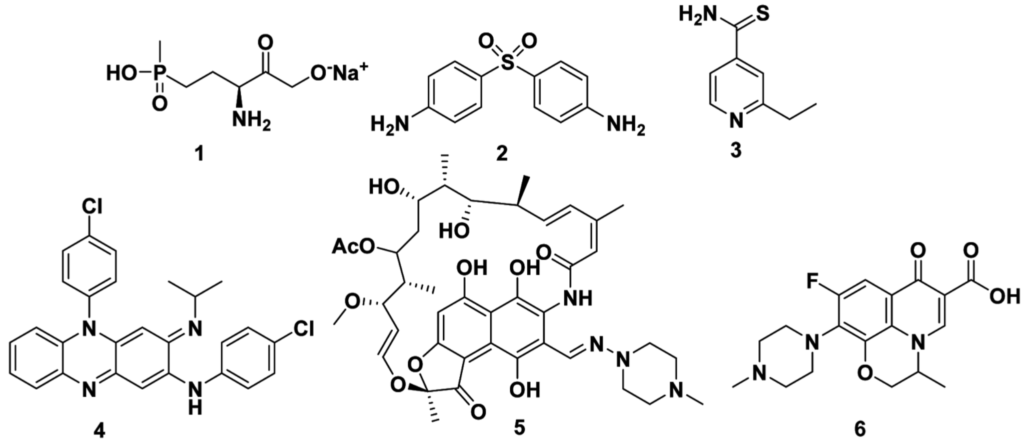
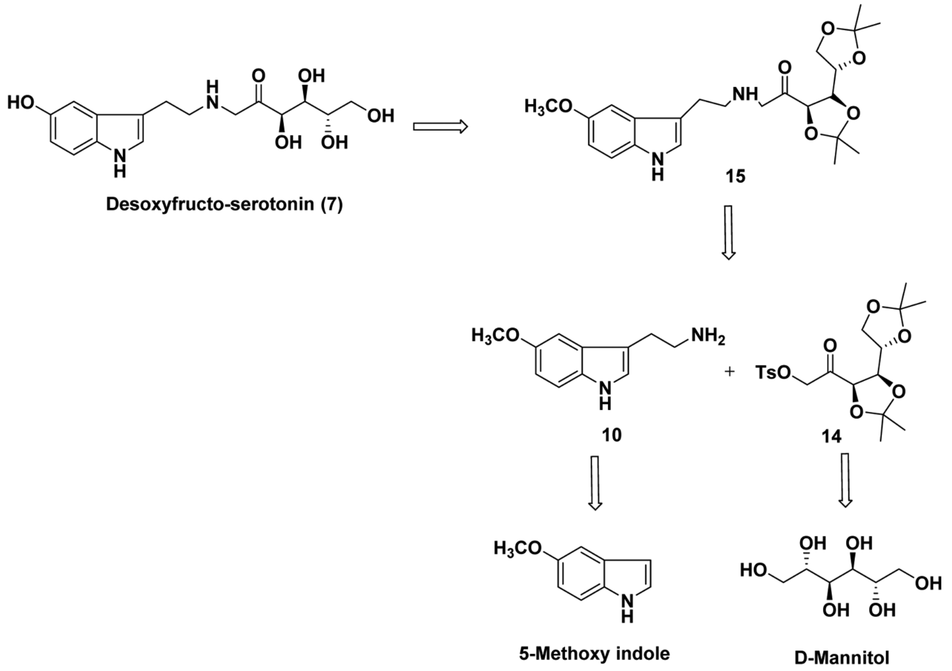
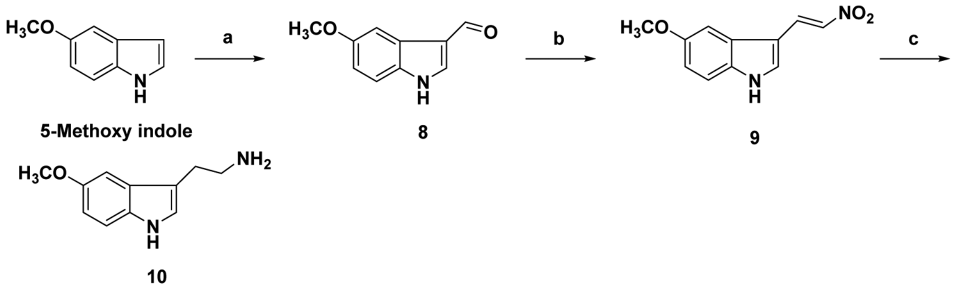


Fig. 1 — Synthetic anti-leprotic agents

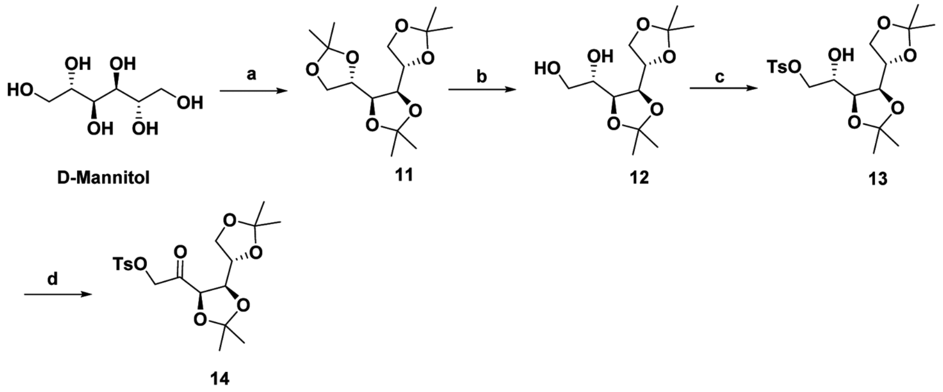


Scheme 1a — Retrosynthetic analysis of Desoxyfructoserotonin



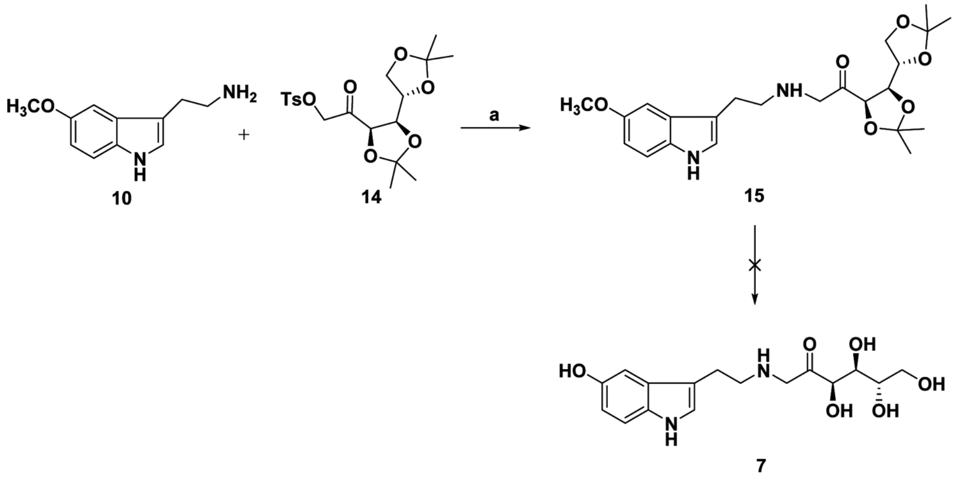
Reagents and Conditions: (a) (i)$POCl_3$, DMF, CH_3CN, 0°C-5°C, 2 h. (ii) H_2O, 50°C, 1 h, 77% (b) NO_2CH_3, $AcONH_4$, reflux, 90 min, 88% (c) LAH, THF, 0°C- RT, 1h, 77%.

Scheme 1b — Synthesis of key pharmacophore amino fragment **5**



Reagents and Conditions: (a) 2,2-DMP, acetone, RT, 2 h, 88%; (b) Conc. H_2SO_4, CH_3OH, RT, 30 min, 87%; (c) TsCl, , Bu_2SnO, TEA, CH_2Cl_2, 0°C-RT, 1 h, 82%; (d) DMP, $CH_2Cl_{2,}$ 0°C-RT, 1 h, 78%

Scheme 2 — Synthesis of aliphatic fragment



Reagents and Conditions: (a) K_2CO_3, CH_3CN, reflux, 14 h, 82%

Scheme 3 — Synthesis of Desoxyfructoserotonin

Table 1 — Various conditions attempted for acetonide deprotection and demethylation

S. No.	Various reagents	Condition	Solvents	Results
1	BBr_3 (1eq)	0°C – 20°C, 2 h	CH_2Cl_2	Decomposition
2	BBr_3 (1eq)	0°C, 2 h	CH_2Cl_2	Decomposition
3	BBr_3 (1eq)	–10°C, 2 h	CH_2Cl_2	Decomposition

via column chromatography by using silica gel (60-120meah) packed in glass columns. ^1H NMR and ^{13}C NMR were recorded in $CDCl_3$ on 400 MHz and 500MHz spectrometer, using TMS as an internal standard. IR spectra were recorded on a Perkin-Elmer FT-RT 240-c Spectro photometer using KBr / Thin Film optics. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70eV. Optical rotation values were recorded on Horiba sepa300 polarimeter. High resolution mass spectra (HRMS) [ESI+] were obtained using either a TOF or a double focusing spectrometer.

5-Methoxy-1*H*-indole-3-carbaldehyde, 8 [14]

To a stirred solution of N, N-dimethylformamide (3.5 g, 48.64 mmol) and acetonitrile (25 mL) was added phosphorus oxychloride (5.73 g, 37.41 mmol) dropwise at room temperature and stirred for 2 h. After the complete conversion of reaction mixture to vilsmeier reagent, indicated by clear and yellow colored solution, reaction mixture was added with 5-methoxy indole (5 g, 34.0 mmol) in 25 mL of acetonitrile at –15°C and allowed to stir at same temperature for about 30 mins. After the formation of precipitate (vilsmeier formamidinium phosphorochloridate), the solid was filtered and washed with ice cooled acetonitrile and dried.

To a stirred solution of above solid in water (50 mL) was heated to 50°C for 40 mins till the clear solution is formed. Then the reaction mixture was cooled to room temperature and quenched with 0.1 M hypo. The reaction mixture was stirred about 10 mins and filtered to obtain the solid which was then washed with cold water and air dried to afford compound **8** (4.58 g, 77%) as brown solid Mp: 178 -180°C. IR (neat): υ 3043, 2735 1624, 1578, 1446, 1262, 1135, 1069 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.02 (s, 1H), 8.85 (br s, 1H), 7.80 (d, 2H, *J* = 2.20 Hz), 7.32 (d, 1H, *J* = 8.91 Hz), 6.97 (dd, 1H, *J* = 8.92, 2.54 Hz), 3.89 (s, 3H),; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.1, 156.6, 135.5, 129.7, 125.1, 119.6, 115.0, 112.3, 103.1, 55.7. HRMS: m/z $[M + H]^+$ cald for $C_{10}H_{10}O_2N$: 176.07053; found: 176.07061.

(E)-5-Methoxy-3-(2-nitrovinyl)-1*H*-indole, 9 [15]

To stirred solution of **8** (3 g, 17.14 mmol) and ammonium acetate (0.66 g, 8.57 mmol) in nitromethane (30 mL) under inert atmosphere was refluxed for 90 mins. After the completion of the reaction (was monitored by TLC), reaction mixture was diluted with ethylacetate and washed with water (50 mL), then dried over Na_2SO_4. The solvent evaporated under reduced pressure to give crude compound which was then purified by column chromatography using silica gel (60-120 mesh) by eluting with EtOAc-Hexane (3: 7) mixture to afford compound **9** (3.28 g, 88%) as brown solid, Mp: 162-164°C. IR (neat): υ 3205, 1610, 1295, 1246, 1210, 1120 cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.74 (s, 1H), 8.29 (d, 1H, *J* = 13.54 Hz), 7.73 (d, 1H, *J* = 13.54 Hz), 7.64 (d, 1H, *J* = 3.00 Hz), 7.37 (d, 1H, *J* = 8.92 Hz), 7.18 (d, 1H, *J* = 2.35 Hz), 6.98 (dd, 1H, *J* = 8.92, 2.44 Hz), 3.92 (s, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.2, 133.7, 132.5, 132.4, 132.0, 125.5, 114.1, 113.0, 109.5, 102.7, 56.0.. HRMS: m/z $[M + H]^+$ cald for $C_{11}H_{11}O_3N_2$: 219.21119; found: 219.21125.

2-(5-Methoxy-1*H*-indol-3-yl)ethan-1-amine, 10

To a stirred solution of LAH (3.48 g, 91.74 mmol) in dry THF (40 mL) was added a solution of nitro compound **10** (2 g, 9.17 mmol) in dry THF at 0°C and the resulting mixture was stirred for 2h. After completion of the reaction (was confirmed by TLC), the reaction mixture was quenched with Rochelle's salt and stirred until the formation of clear solution. The aqueous layer extract with Et_2O (2 × 30 mL) and the combined organic layer was washed with brine, dried over Na_2SO_4. The solvent evaporated under reduced pressure to give crude compound which was then purified by column chromatography by using silica gel (60-120 mesh) by eluting with MeOH-EtOAc (1: 9) mixture to afford compound **5** (1.3 g, 77%) as white solid, Mp: 118-120°C. IR (neat): υ 3335, 3294, 3050, 2885, 1629, 1589, 1495, 1245, 1220, 1015, 798, 645 cm.$^{-1}$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.72 (s, 1H), 7.22 (d, 1H, *J* = 8.76 Hz), 7.11 (d, 1H, *J* = 1.94 Hz), 7.02 (d, 1H, *J* = 2.41 Hz), 6.72 (dd, 1H, *J* = 8.72, 2.46 Hz), 3.76 (s, 3H), 2.91 – 2.87 (m, 2H), 2.83 – 2.79 (m, 2H), 1.77 (s, 2H).; ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.1, 153.5, 131.9, 127.9, 124.0, 112.5, 111.5, 100.6, 55.8, 41.5, 27.3.; HRMS: m/z $[M + NH_4]^+$ cald for $C_{11}H_{15}ON_2$: 191.11789; found : 191.11798.

(4*S*, 4'*S*,4''*S*,5'*R*)-2,2,2',2',2'',2''-Hexamethyl-4,4':5',4''-ter(1,3-dioxolane), 11

To a mixture of acetone (75 mL) and sulfuric acid (0.5 mL) was added D-mannitol (5.052 g, 27.77 mmol) in portions and stirred for 18 h at room temperature. The mixture was neutralized by addition of aqueous NH_4OH (1.75 mL) and then Na2CO3 (3.125 g, 29.48 mmol). The residue was filtered, and the filtrate was concentrated to a volume of 20 mL under vacuum. Then, the solution was immersed in an ice bath to precipitate the product as a white solid. The solid product was collected and recrystallized from acetone to give **11** (7.30 g, 88% yield, as white solid Mp; 65 -67°C. Optical rotation- $[\alpha]_D^{25}$ +15.69 (*c* 1.0, $CHCl_3$). IR (neat)- υ 2932, 2880, 1450, 1325, 1225, 1069, 905 cm.$^{-1}$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.19 (dd, 2H, *J* = 11.52, 5.55 Hz), 4.08 (dd, 2H, *J* = 8.32, 6.42 Hz), 4.00 – 3.94 (m, 4H), 1.43 (s, 6H), 1.39 (s, 6H), 1.35 (s, 6H).; ^{13}C NMR (100 MHz, $CDCl_3$): δ 110.2, 109.6, 79.4, 76.4, 66.3, 27.5, 26.5, 25.3. HRMS: m/z $[M + H]^+$ cald for $C_{15}H_{27}O_6$: 303.18022; found: 303.18002.

(*S*)-1-((4*R*,4'*S*,5*S*)-2,2,2',2'-Tetramethyl-[4,4'-bi(1,3-dioxolan)]-5-yl)ethane-1,2-diol, 12

To a stirred solution of compound **11** (5 g, 16.55 mmol) in methanol (100 ml) was added H_2SO_4 adsorbed over silica (cat.) stirred for 30 min at room temperature. After the completion of reaction (was confirmed by TLC), quenching with solid sodium bicarbonate and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography using silica gel (60-120 mesh) by eluting with EtOAc-hexane (3:7) mixture to give **12** (3.77 g, 87%) as yellow oil. Optical rotation- $[\alpha]_D^{25}$ +14.37 (*c* 1.0, $CHCl_3$).: υ υ 3459, 1685, 1462, 1284, 1050 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 4.05 – 4.01 (m, 2H), 3.94 (dd, 1H, *J* = 8.42, 5.12 Hz), 3.84 – 3.81 (m, 2H), 3.78 – 3.73 (m, 2H), 3.67 – 3.61 (m, 3H), 1.38 (s, 3H), 1.30 (d, 9H, *J* = 3.82 Hz).; ^{13}C NMR (100 MHz, $CDCl_3$): δ 110.3, 109.6, 80.8, 72.2, 68.1, 63.9, 26.6, 26.3, 25.1. HRMS: m/z $[M + NH_4]^+$ cald for $C_{12}H_{23}O_6$: 263.14891; found: 263.14877.

(S)-2-Hydroxy-2-((4R,4'S,5S)-2,2,2',2'-tetramethyl-[4,4'-bi(1,3-dioxolan)]-5-yl)ethyl 4-methylbenzenesulfonate, 13

To a stirred mixture of **12** (3 g, 11.45 mmol) in dry DCM (10 mL) at 0°C was added Bu_2SnO (0.57 g, 2.29 mmol), TsCl (2.18 g, 11.45 mmol) and Et_3N (1.74 g, 17.17 mmol) and stirring continued for 1h. After completion of the reaction (monitored by TLC), quenched with cold water and extracted with DCM (3×30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure, the obtained crude product was purified by column chromatography using silica gel (60-120 mesh) by eluting with EtOAc-hexane (1:4) mixture to give **13** (4.5 g, 82%) as yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, 2H, *J* = 8.30 Hz), 7.33 (d, 2H, *J* = 8.02 Hz), 4.30 (d, 1H, *J* = 10.32 Hz), 4.12 – 4.08 (m, 2H), 4.06 – 3.98 (m, 1H), 3.97 (dd, 1H, *J* = 8.71, 5.16 Hz), 3.82 – 3.78 (m, 2H), 3.73 (dd, 2H, *J* = 8.41, 6.96 Hz), 2.44 (s,3H), 1.41 (s,3H), 1.34 (s, 9H), 1.31 (s, 6H).;^{13}C NMR (100 MHz,CDCl3): δ 144.7, 132.9, 129.8, 128.0, 110.3, 109.9, 80.8, 79.3, 76.2, 71.4, 70.7, 67.7, 26.8, 26.3, 25.0, 21.6.

2-oxo-2-((4R,4'S,5R)-2,2,2',2'-Tetramethyl-[4,4'-bi(1,3-dioxolan)]-5-yl)ethyl4-methylbenzenesulf onate, 14

To stirred mixture of **13** (3 g, 7.21 mmol) in dry CH_2Cl_2 (10 mL) at 0°C under an inert atmosphere was added Dess-Martin-Periodinane (6.10 g, 14.42 mmol). The reaction mixture was stirred at 0°C for 12 h. After completion of the reaction (monitored by TLC), quenched with sodium bicarbonate and hypo solution, allowed to stir for 30 mins. The reaction mixture was extracted with DCM (3×30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure, the obtained crude was purified by column chromatography using silica gel (60-120 mesh) by eluting with EtOAc-hexane (1:4) mixture to give **14** (2.3 g, 78%) as yellow oil. Optical rotation- $[\alpha]_D^{25}$ +14.65 (*c* 1.0, $CHCl_3$).: υ υ 3459, 1685, 1462, 1284, 1050 cm^{-1}; ^1H NMR (400 MHz, CDCl3): δ 7.84 (s, 2H), 7.37 (s, 2H), 4.98 (dd, 2H , *J* = 8.80, 2.41 Hz), 4.41 (d, 1H , *J* = 8.31 Hz), 4.15 (d, 2H, *J* = 12.80 Hz), 4.11- 4.08 (m, 1H), 3.93 (dd, 1H, *J* = 12.16, 7.35 Hz), 2.45 (s, 1H), , 1.43 (s, 3H), 1.39 (s, 3H), 1.33 (s, 6H). ^{13}C NMR (100 MHz, CDCl3): δ 199.7, 145.3, 136.1, 133.2, 132.6, 131.3, 129.8, 129.3, 129.0, 128.1, 111.9, 110.0, 80.6, 78.3, 76.1, 70.1, 66.5, 29.6, 26.7, 26.4, 25.9, 25.0, 21.6.; HRMS: m/z $[M + H]^+$ cald for $C_{19}H_{27}O_8S$: 415.18431; found: 415.18308.

2-((2-(5-Methoxy-1*H*-indol-3-yl)ethyl)amino)-1-((4R,4'S,5R)-2,2,2',2'-tetramethyl-[4,4'-bi(1,3-dioxolan)]-5-yl)ethan-1-one, 15

To the stirred solution of compound **10** (0.9 g, 2.05 mmol) in CH_3CN (5 mL) was added amine compound **14** (0.3 g, 1.58 mmol) and potassium carbonate (0.43 g, 3.15 mmol). The reaction mixture was allowed to stir for 12 h at 80°C. After completion of the reaction (monitored by TLC), the reaction mixture was filtered and washed with acetonitrile. The combined organic layer was washed with brine, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography using silica gel (60-120 mesh) by eluting with EtOAc-hexane (4:1) mixture to give **15** (0.56 g, 82%) as yellow oil. Optical rotation- $[\alpha]_D^{25}$ –13.9 (*c* 1.0, $CHCl_3$).: υ υ 3459, 1685, 1462, 1284, 1050 cm^{-1}; 1H NMR (400 MHz, CDCl3): δ 7.88 (s, 1H), 7.24 (s, 1H), 7.04 (dd, 2H *J* = 11.92, 2.30 Hz), 6.86 (dd, 1H , *J* = 8.80, 2.41 Hz), 4.16 (dd, 1H , *J* = 8.24, 6.15 Hz), 4.08 (dd, 1H, *J* = 12.86, 6.27 Hz), 3.99 (dd, 1H, *J* = 8.49, 5.46 Hz), 3.86 (s, 3H), 3.81- 3.75 (m, 4H), 3.02- 2.92 (m, 4H), 1.43 (s, 3H), 1.33 (s, 9H).; ^{13}C NMR (100 MHz, CDCl3): δ 203.5, 154.0, 131.6, 127.6, 123.2. 112.3, 112.0, 110.0, 109.8, 100.6, 81.6, 80.4, 76.4, 69.8, 67.4, 56.0, 51.5, 49.3, 29.7, 27.0, 26.4, 25.1, 24.7.; HRMS: m/z $[M + H]^+$ cald for: $C_{23}H_{33}N_2O_6$: 433.24896; found: 433.24841.

Conclusion

In summary, we have developed a route to synthesize Desoxyfructoserotonin in 9 steps using Vilsmeier-Haack reaction and Henry reaction and unfortunately we could not able to achieve the final compound. All the reactions are easy to handle and all the synthesized compounds were confirmed by their spectral data.

Supplementary Information

Supplementary information is available in the website http://nopr.niscpr.res.in/handle/123456789/58776.

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