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Alternative Synthesis of Tadalafil: PDE5 Inhibitor

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Abstract: Two-step alternative synthesis of tadalafil (**1**) is described. The synthesis features Pictet–Spengeler type reaction and DCC (*N,N′*-dicyclohexylcarbodiimide)/HOBt (*N*-hydroxybenzotriazole)–mediated double amidation employing sarcosine ethyl ester hydrochloride.

Keywords: Double amidation, erection, phosphodiesterase, Pictet–Spengeler reaction

INTRODUCTION

Tadalafil **1** (Fig. 1) is a phosphodiesterase type 5 (PDE5) inhibitor used in the management of erectile dysfunction in men. Inhibition of PDE5 allows cyclic guanosine monophosphate (cGMP) to remain functional in penile tissue, thereby relaxing the smooth muscle in the corpus cavernosum, which leads to increase in blood flow, strengthening the erection.[1]

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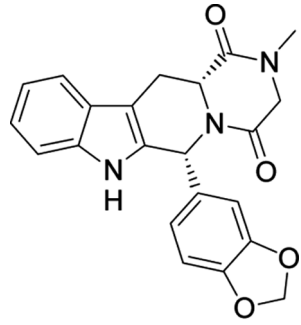

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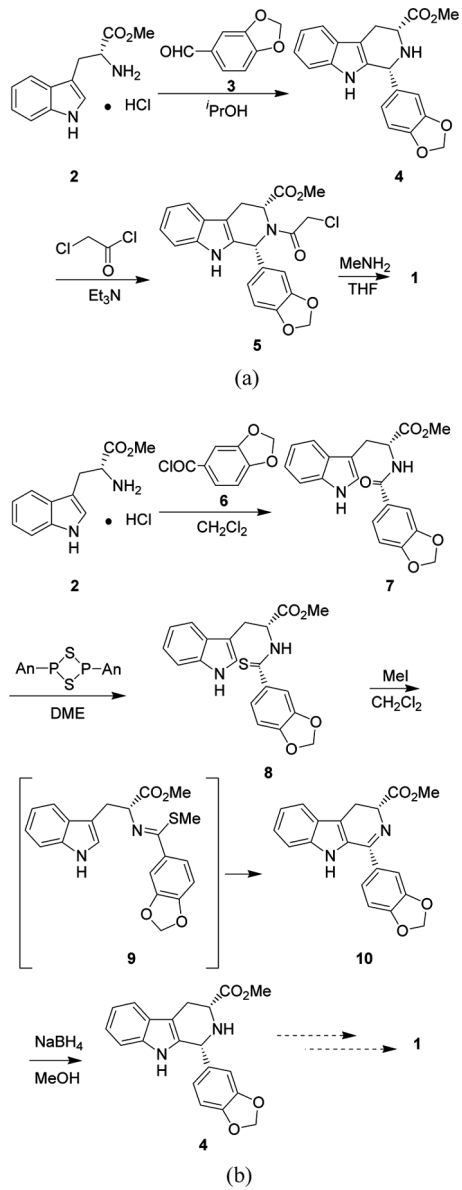
Figure 1. Structure of tadalafil.

Precedented medicinal chemistry and large-scale synthetic routes[2] for tadalafil **1** involve classical Pictet–Spengler-type reaction between methyl ester of D-tryptophan **2** (racemic starting material used in medicinal chemistry route) or its hydrochloride salt (to avoid the use of trifluoroacetic acid [TFA]) and piperonal **3** to obtain cyclic intermediate **4**, which was treated with chloroacetyl chloride to afford amide **5**. Intermediate **5** was further reacted with methyl amine as shown in Scheme 1a.

Another very close to formal synthesis[3] of **1** is also reported describing the acylation of hydrochloride salt of **2** with piperonyloyl chloride **6** to afford amide **7**, which was treated with Lawesson's reagent to obtain thioamide **8**. Intermediate **8** was subjected to alkylation with methyl iodide to give thioimidate **9**, which undergoes cyclization affording pentacyclic structure **10**. Intermediate **9** was reduced by employing sodium borohydride to afford advanced intermediate **4** as shown in Scheme 1b. There are a few more syntheses reported along the lines of concept depicted in Scheme 1.[4]

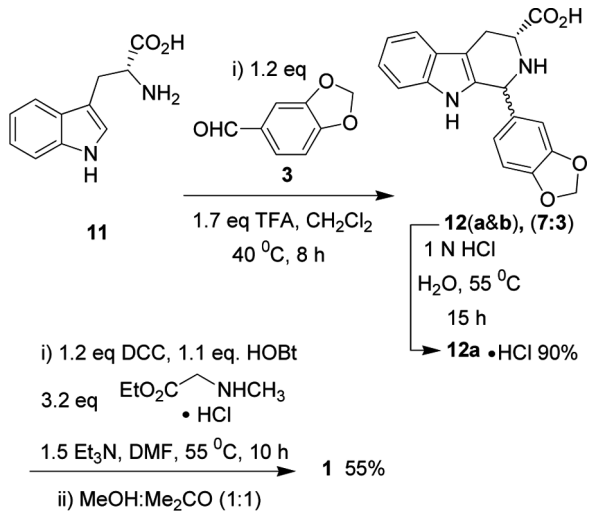
RESULTS AND DISCUSSION

In our endeavor, as shown in Scheme 2, we started the synthesis with commercially available D-tryptophan **11** analogous to the reported synthesis, Pictet–Spengeler-type reaction between **11** and **3**, in the presence of triflouroacetic acid, which allowed us to access a mixture of diastereomers **12a** and **b** [$dr = 7(cis):3(trans)$] in 90% yield. These two diastereomers are found to be in dynamic equilibrium; hydrochloric acid salt of *cis*-isomer is less soluble in aqueous media that shifts the equilibrium toward the conversion of *trans*- to *cis*-isomer. We were able to



Scheme 1. Precedented synthetic approach.

obtain **12a**, *cis*-isomer, predominantaly (90% yield; >98% chiral HPLC purity) in the salt-formation event. Intermediate **12a** was subjected to amidation conditions (N,N′-dicyclohexylcarbodiimide/N-hydrobenzotriazole



Scheme 2. Novel Synthesis of **1**.

[DCC/HOBt]) in the presence of commercially available sarcosine ethyl ester hydrochloride, which afforded crude tadalafil with good yield and purity. Crystallization of crude tadalafil with a methanol and acetone mixture afforded the optically pure API **1** in 85% yields. We have successfully implemented this synthesis in plants on a kilogram scale.

The Aforementioned synthesis has certain advantages over the reported one: i) it avoids the use of toxic chloroacetyl chloride, ii) it avoids column chromatography, which is required for separation of isomers to meet the International Conference on Hormonization (ICH) standards, and iii) this synthesis does not require relatively expensive solvents.

CONCLUSIONS

We have developed an alternative synthesis for tadalafil **1** that appears to be more compatible with industrial scale and has some advantages over the existing synthesis.

EXPERIMENTAL

Solvents and reagents were obtained from commercial sources and used without further purification. The ^{1}H and ^{13}C spectra were measured

in DMSO-d_6 using 200 or 400 MHz on a Varian Gemini and Varian Mercury Plus 2000 FT NMR spectrometer; the chemical shifts were reported in δ ppm. IR spectrum was recorded in the solid state as KBr dispersion using a Perkin-Elmer 1650 FT IR spectrometer. The mass spectrum (70 eV) was recorded on a HP 5989 A LC MS spectrometer. The melting points were determined using the capillary method on a Polmon (model MP-96) melting-point apparatus. The solvents and reagents were used without further purification.

Preparation of (1*R*,3*R*)-1,2,3,4-Tetrahydro-1-(3,4-methylene dioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylic Acid Hydro Chloride (12a)

Trifluoroacetic acid (808 mol; 6 L) was added to a solution of D-tryptophan **11** (10.0 kg, 490 mol) and piperonal **3** (8.8 kg, 586 mol) in dichloromethane (100 L), and the reaction mass was heated to 40 °C. After stirring for 10 h at 40 °C, the mixture was allowed to cool down to 35 °C, and a mixture of dichloromethane/methanol (50 L each) was added. The reaction mass was then quenched with 8% sodium bicarbonate solution (50 L). The organic layer was separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were concentrated on a rotary evaporator to afford **12a** and **b**. To a suspension of **12a** and **b** in water, 1 N hydrochloric acid (150 L) was added slowly. After stirring for 15 h at 55 °C, toluene (30 L) was added, and the reaction mass was cooled to 15–20 °C. After 30 min, the precipitated solid was filtered, washed with toluene (10 L), and dried at 75 °C for 6 h to afford **12a** (16.6 kg) in 90% yield and >98% HPLC purity.

Mp: 215–220 °C; ^{1}H NMR (200 MHz, DMSO-d_6) 10.8 (s, 1H), 7.55 (d, 1H, $J = 7.0$ Hz), 7.28 (d, 1H, $J = 7.2$ Hz), 6.9–7.2 (m, 5H), 6.19 (s, 2H), 5.8 (s, 1H), 2.4–3.6 (m, 3H); ^{13}C NMR (50 MHz (DMSO-d_6) 206.6, 168.7, 148.5, 147.2, 136.8, 128.9, 127.1, 125.5, 124.9, 122.1, 119.2, 118.3, 111.7, 110.2, 108.3, 106.7, 101.6, 57.6, 55.4, 22.2; IR (KBr) 2927, 1757, 1626, 1205, 1040 cm^{-1}. MS (CI) calcd. for $C_{19}H_{16}N_2O_4$ (M^+) 336.3; found (MH^+) 337.1.

Preparation of (6R, 12aR)-2,3,6,7,12,12A-Hexahydro-2-methyl-6-(3,4-methylene Dioxyphenyl)-pyrazino[2′,1′:6,1]pyrido[3,4-b]indole-1,4-dione (1)

Triethyl amine (10 kg, 1020 mol) was added to a solution of dimethyl formamide (65 L) and methylamino-acetic acid ethyl ester hydrochloride

(13.2 kg, 860 mol), and then the mixture was stirred at 25–30 °C for 20 min. The separated solid (triethyl amine hydrochloride) was filtered out and washed with 15 L of dimethyl formamide. To a solution of filtrate **12a** (10 kg, 270 mol), dicyclohexylcarbodiimide (6.6 kg, 320 mol), 1-hydroxybenzotriazole (5.4 kg, 400 mol), and triethyl amine (4.1 kg, 400 mol) were added at 25–35 °C, and then reaction mass was heated to 50–55 °C. After stirring for 10 h at 50–55 °C, the mixture was allowed to cool down to 10 °C and unwanted dicyclohexylurea (DCU) was filtered out. A mixture of dichloromethane/water (100 L each) was added to the filtrate. The reaction mass was then quenched with 8% sodium bicarbonate solution (80 L). The organic layer was separated, and aqueous layer was extracted with dichloromethane. The combined organic layers were concentrated on rotary evaporator, cooled to 0–5 °C, and recrystallized in mixture of methanol and acetone (1:1) to afford **1** (5.5 kg, 52.6%) with 99.9% purity.

^{1}H NMR (400 MHz, DMSO-d_6) 11.0 (s, 1H), 7.54 (d, 1H, J = 7.4 Hz), 7.29 (d, 1H, J = 8.0 Hz), 7.07 (t, 1H, J = 7.8 Hz), 7.03 (t, 1H, J = 7.8 Hz), 6.86 (s, 1H), 6.79 (s, 2H), 6.13 (s, 1H), 5.92 (s, 2H), 4.40 (dd, 1H, J = 4.6 Hz, J = 11.6 Hz), 4.17 (d, 1H, J = 16.8 Hz), 3.94 (d, 1H, J = 16.8 Hz), 3.50 (dd, 1H, J = 4.6 Hz, J = 16.0 Hz), 2.97 (m, 1H), 2.93 (s, 3H); ^{13}C NMR (400 MHz, DMSO-d_6) 166.8, 165.5, 147.0, 146.0, 136.9, 136.2, 133.9, 125.7, 121.2, 119.3, 118.8, 118, 111.3, 107.9, 107, 104.7, 100.8, 55.5, 55.3, 51.4, 32.8, 23.1; IR (KBr) 3325, 2904, 1678, 1650, 1439, 1322, 1242, 1040 cm^{-1}. HRMS (CI) calcd. for $C_{22}H_{19}N_3O_4$ (M^+) 389.4; found (MH^+) 390.5.

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