A Concise Synthesis of *rac*-Staurosporine Glycon

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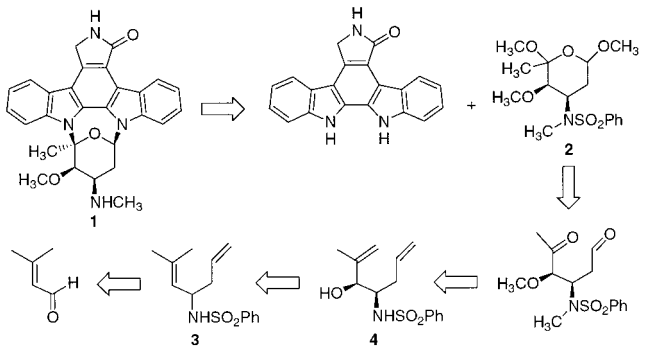
Staurosporine **1** is a bioactive alkaloid isolated[1] from *Streptomyces staurosporeus*. The unique combination of its wide range of promising pharmacological properties such as hypotensive,[1] antimicrobial,[1] cell cytotoxic,[2] nanomolar inhibition of protein kinase C(IC_{50} 2.7 nM),[2] and novel pyranosylated indolocarbazole structure inspired several synthetic chemists to take up its total synthesis.[3−10] The intriguing aspect of this total synthesis is the fashioning of its unusual bis-*N*-glycosidic linkage between aglycon and glycon units.

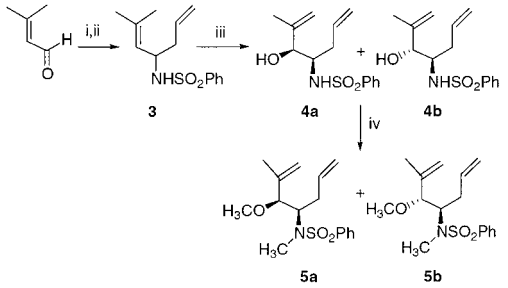
As part of our ongoing approach toward the total synthesis of **1**, we have chosen 3-benzenesulfonamido hexose **2** as an ideal pyranose derivative (Scheme 1). Apart from having the required structural and stereochemical features, its two labile methoxy groups at C_2 and C_6 would facilitate linkup with the weakly nucleophilic indole nitrogens of the aglycon unit in one step. The benzenesulfonyl group meant for the protection of the amino function can be subsequently removed after linkup.

We report herein an efficient synthesis of pyranose derivative **2**. Our retrosynthesis of **2** identified 3-methyl-2-butenal as an apt synthon that was submitted to a condensation step with benzenesulfonamide in the presence of a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS). Without isolating the corresponding benzenesulfonylimine intermediate, it was further reacted with allylmagnesium bromide at −78 °C in THF to provide *N*-(1-allyl-3-methyl-2-butenyl)benzenesulfonamide **3** in a single flask reaction in 79% overall yield. We have earlier reported a diastereoselective ene reaction[11] using singlet oxygen as a key step in the synthesis of a 2,6-dideoxyhexopyranose derivative. Now that methodology is utilized in the present synthesis. When a carbon tetrachloride solution of compound **3** was bubbled with oxygen and irradiated with 400 W sodium lamp in the presence of 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine at 0 °C, singlet oxygen reacted stereoselectively and yielded a mixture of erythro and threo isomers **4a** and **4b** in a 4:1 ratio, respectively,[12] after workup with dimethyl sulfide (Scheme 2). This mixture was methylated using methyl iodide in THF in the presence of sodium hydride at room temperature. After aqueous workup followed by flash chromatography, the corresponding dimethylated derivatives **5a** and **5b** were obtained in 75% and 18% yields, respectively.

Scheme 1



Scheme 2[a]



[a] Reagents and conditions: (i) NH_2SO_2Ph, PPTS, benzene, reflux, 1.5 h; (ii) 1 M allylmagnesium bromide, THF, −78 °C, 79% (for two steps); (iii) $^1O_2$, CCl_4, 0 °C; DMS, 71%; (iv) NaH, THF, CH_3I, rt, 14 h.

The desired pyranose derivative **2** was smoothly obtained by the ozonolysis of **5a** in dichloromethane−methanol mixture at −78 °C and subsequent treatment with dimethyl sulfide followed by trifluoromethanesulfonic acid at room temperature. In this reaction, methyl ketone **6**, an open-chain isomer of **2**, was formed as a byproduct. Obviously, the dione resulting from the ozonolysis of **5a** was transformed into **6** on reacting with methanol, which cyclized to pyranose **2** under acidic conditions. Conversion of **6** into **2** was demonstrated by placing **6** in acidified methanol and isolating **2** and **6** in 2:1 ratio. The stereochemical structure of **2** was confirmed by XRD studies. It evidenced the cis orientation of C_3 and C_4 protons, which supports the erythro configuration of major isomer **4a**.

In conclusion, we have designed a novel protocol for pyranose derivative **2**, in which the oxygenation pattern

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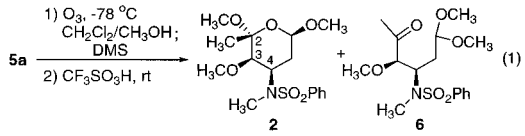

(1)

and stereochemistry at C_3 and C_4 are already placed correctly, proceeding further toward the total synthesis of staurosporine. Efforts to synthesize indolocarbazole unit and its subsequent linkup with **2** are in progress.

Experiment Section

The NMR spectra were run at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR and are referenced to internal standard TMS (tetramethylsilane) in ppm units. Unless otherwise mentioned, $CDCl_3$ is used as solvent for recording the NMR spectra. In the column chromatography, silica gel (Merck Art. No.9385) was used.

***N*-[1-(2-Propenyl)-3-methyl-2-butenyl]benzenesulfonamide 3.** A solution of benzenesulfonamide (2.84 g, 18.1 mmol) and PPTS (0.46 mg, 1.81 mmol) in benzene (30 mL) was refluxed for 30 min. 3-Methyl-2-butenal (2.3 mL, 24.2 mmol) was added to this solution, and refluxing continued for 1 h. The mixture was cooled to room temperature, and PPTS was destroyed with potassium carbonate. The solution was concentrated in vacuo, and to the residue was added THF (30 mL). Allylmagnesium bromide (40 mL, 1.0 M in THF, 40 mmol) was slowly added to this solution at −78 °C, and after the addition the reaction was allowed to continue for 5 h. The reaction mixture was cooled to 0 °C, saturated ammonium chloride solution (20 mL) was added to it, and the reaction mixture was extracted with ethyl acetate (3 × 20 mL). The organic phase was washed with brine (30 mL), dried using anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by flash chromatography eluting with ethyl acetate/hexane (1:4) to furnish compound **3** (3.77 g, 79%): IR (neat) 3274, 1642 cm^{-1}; ^{1}H NMR δ 1.42 (s, 3H), 1.45 (s, 3H), 2.11−2.27 (m, 2H), 3.98−4.09 (m, 1H), 4.50 (d, J = 6.8 Hz, 1H), 4.68−4.73 (m, 1H), 5.03 (d, J = 16.8 Hz, 1H), 5.04 (d, J = 10.4 Hz, 1H), 5.55−5.67 (m, 1H), 7.41−7.55 (m, 3H), 7.78−7.83 (m, 2H); ^{13}C NMR δ 17.9, 25.3, 40.4, 51.6, 118.4, 124.0, 127.1, 128.6, 132.2, 133.3, 134.9, 141.1; HRMS calcd for $C_{14}H_{19}NO_2S$, 265.1136, found 265.1141. Anal. Calcd for $C_{14}H_{19}NO_2S$: C, 63.36; H, 7.22; N, 5.28; S, 12.08. Found: C, 63.38; H, 7.24; N, 5.32; S, 12.11.

***N*-[1-(2-Propenyl)-2-hydroxy-3-methyl-3-butenyl]benzenesulfonamide 4.** Compound **3** (8.07 g, 30.4 mmol) was dissolved in carbon tetrachloride (100 mL), 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine (0.11 g, 0.18 mmol) was added, and the reaction mixture was irradiated at 0 °C with 400 W sodium lamp in an oxygen atmosphere for 6 days. After the reaction was quenched with DMS, the reaction mixture was brought to room temperature and concentrated in vacuo. The residue was subjected to flash chromatography eluting with ethyl acetate/hexane (1:3) to provide compounds **4a** and **4b** (6.02 g, 71%; **4a**/**4b** = 4:1).

4a: IR (neat) 3510, 3285, 1642 cm^{-1}; ^{1}H NMR δ 1.62 (s, 3H), 1.89 (s, 1H), 2.10 (dd, J = 6.6,6.6 Hz, 2H), 3.32−3.41 (m, 1H), 4.06 (d, J = 3.2 Hz, 1H), 4.85 (d, J = 7.6 Hz, 1H), 4.88−4.96 (m, 3H), 5.01 (s, 1H), 5.36−5.50 (m, 1H), 7.46−7.60 (m, 3H), 7.83−7.89 (m, 2H); ^{13}C NMR δ 19.2, 32.5, 55.4, 76.3, 112.1, 118.2 127.2, 129.0, 132.7, 134.1, 140.5, 143.6; HRMS calcd for $C_{14}H_{19}NO_3S$ 281.1086, found 281.1095.

4b: IR (neat) 3491, 3274, 1645 cm^{-1}; ^{1}H NMR δ 1.49 (s, 3H), 1.89 (s, 1H), 2.15−2.33 (m, 2H), 3.28−3.37 (m, 1H), 3.98 (d, J = 4.4 Hz, 1H), 4.78−4.87 (m, 2H), 4.93−5.04 (m, 2H), 5.50−5.64 (m, 1H), 7.44−7.51 (m, 2H), 7.52−7.59 (m, 1H), 7.80−7.86 (m, 2H); ^{13}C NMR δ 18.1, 37.1, 55.2, 75.0, 113.2, 118.8, 127.2, 129.5, 133.4, 140.7, 143.8; HRMS calcd for $C_{14}H_{19}NO_3S$ ($M + 1^+$), 282.1164, found 282.1169. Anal. Calcd for $C_{14}H_{19}NO_3S$: C, 59.76; H, 6.81; N, 4.98; S, 11.40. Found: C, 59.65; H, 6.74; N, 4.93; S, 11.57.

***N*-[(1*S**,2*R**)-1-(2-Propenyl)-2-methoxy-3-methyl-3-butenyl]-*N*-methylbenzenesulfonamide 5a and *N*-[(1*S**,2*S**)-1-(2-Propenyl)-2-methoxy-3-methyl-3-butenyl]-*N*-methylbenzenesulfonamide 5b.** A stirred suspension of sodium hydride (60%, 4.42 g, 110 mmol) in THF (80 mL) was cooled to 0 °C, and to this was added slowly the mixture of **4a** and **4b** (5.90 g, 21 mmol) dissolved in THF (40 mL). After completion of the addition, the reaction mixture was brought to room temperature and stirred for 20 min. Methyl iodide (5.5 mL) was added to this, and the reaction mixture was stirred at room temperature for 14 h. After being cooled to 0 °C, the reaction mixture was quenched by addition of water (100 mL) and extracted with ethyl acetate (3 × 200 mL). The combined organic extracts were washed with brine (30 mL), dried (anhydrous Na_2SO_4), and concentrated in vacuo. The residue was subjected to flash chromatography, eluting with ethyl acetate/hexane (1:1), to furnish **5a** (4.99 g, 77%) and **5b** (1.14 g, 18%).

5a: IR(neat) 3072, 2979, 1642, 1447 cm^{-1}; ^{1}H NMR δ 1.71 (s, 3H), 2.14−2.35 (m, 2H), 2.82 (s, 3H), 3.15 (s, 3H), 3.51 (d, J = 4.6 Hz, 1H), 4.00 (ddd, J = 9.6, 4.6, 4.6 Hz, 1H) 4.73 (d, J = 9.6 Hz, 1H), 4.88 (d, J = 16.8 Hz, 1H), 4.89 (s, 1H), 4.94 (s, 1H), 5.30−5.43 (m, 1H), 7.42−7.56 (m, 3H), 7.75−7.81 (m, 2H); ^{13}C NMR δ 18.2, 29.5, 30.7, 56.6, 58.1, 87.6, 113.8, 116.7, 127.1, 128.6, 132.1, 135.1, 140.2, 141.5; HRMS calcd for $C_{16}H_{23}NO_3S$ 309.1399, found 309.1399. Anal. Calcd for $C_{16}H_{23}NO_3S$: C, 62.11; H, 7.49; N, 4.53; S, 10.36; Found: C, 62.18; H, 7.42; N, 4.64; S, 10.42.

5b: IR (neat) 3073, 2979, 1644, 1446 cm^{-1}; ^{1}H NMR δ 1.65 (s, 3H), 1.93−2.03 (m, 1H), 2.14−2.24 (m, 1H), 2.69 (s, 3H), 2.81 (s, 3H), 3.32 (d, J = 8.0 Hz, 1H), 4.10 (ddd, J = 9.4, 9.0, 5.0 Hz, 1H), 4.91 (s, 1H), 5.00 (s, 1H), 5.02 (d, J = 10.0 Hz, 1H), 5.12(d, J = 16.0 Hz, 1H), 5.69−5.81 (m, 1H), 7.40−7.53 (m, 3H), 7.78−7.83 (m, 2H); ^{13}C NMR δ 16.7, 28.6, 30.1, 55.6, 58.5, 85.0, 116.1, 117.2, 127.6, 1281, 131.7, 134.5, 140.1, 141.5; HRMS calcd for $C_{16}H_{23}NO_3S$ 309.1399, found 309.1400.

***N*-Methyl-*N*-[(2*S**,3*S**,4*S**,6*S**)-2,3,6-trimethoxy-2-methyltetrahydro-2*H*-4-pyranyl]benzenesulfonamide 2 and *N*-[(1*S**,2*S**)-1-(2,2-Dimethyloxyethyl)-2-methoxy-3-oxobutyl]-*N*-methylbenzenesulfonamide 6.** Compound **5a** (1.01 g, 3.27 mmol) was dissolved in a mixture of dichloromethane (15 mL) and methanol (1.5 mL), and ozone gas was passed in to this solution at −78 °C for 10 min until the solution turned blue. After being stirred at −78 °C for an additional 5 min, the mixture was treated with DMS (3 mL) and then warmed to 25 °C and concentrated in vacuo. The resultant residue was dissolved in methanol (30 mL), trifluoromethanesulfonic acid (0.25 mL) was added, and the solution was stirred at room temperature for 4 days. Potassium carbonate (160 mg) was added to neutralize trifluoromethanesulfonic acid. The solvent was removed in vacuo, and the residue was purified by flash chromatography, eluting with ethyl acetate/hexane (1:2) to furnish compounds **2** (606.4 mg, 52%) and **6** (326.7 mg, 28%).

2: IR (neat) 3065, 2990, 2940, 1447, 1343 cm^{-1}; ^{1}H NMR (benzene-d_6) δ 1.16−1.23 (m, 1H), 1.20 (s, 3H), 2.01 (ddd, J = 14, 11.6, 10.0 Hz, 1H), 2.73 (s, 3H), 3.00 (s, 3H), 3.06 (s, 3H), 3.21 (s, 3H), 3.28 (d, J = 3.0 Hz, 1H), 4.40 (dd, J = 10.0, 2.4 Hz, 1H), 4.66 (ddd, J = 14.0, 4.4, 3.0 Hz, 1H), 6.86−6.95 (m, 3H), 7.73−7.78 (m, 2H); ^{13}C NMR (benzene-d_6) δ 19.3, 30.1, 31.4, 48.1, 52.5, 56.1, 61.1, 84.1, 98.2, 102.4, 127.6, 129.5, 132.5, 141.0. Anal. Calcd for $C_{16}H_{25}NO_6S$: C, 53.46; H, 7.01; N, 3.90; S, 8.92. Found: C, 53.40; H, 7.06; N, 3.94; S, 8.89.

6: IR (neat) 3065, 2987, 1724, 1447 cm^{-1}; ^{1}H NMR (benzene-d_6) δ 1.73 (ddd, J = 14.4, 8.8, 4.4 Hz, 1H), 1.88 (ddd, J = 14.4, 7.2, 5.2 Hz, 1H), 1.98 (s, 3H), 2.65 (s, 3H), 2.83 (s, 3H), 2.99 (s, 3H), 3.04 (s, 3H), 3.52 (d, J = 3.6 Hz, 1H), 4.28 (dd, J = 7.2, 4.4 Hz, 1H), 4.71 (ddd, J = 8.8, 5.2, 3.6 Hz, 1H), 6.88−6.95 (m, 3H), 7.81−7.87 (m, 2H); ^{13}C NMR (benzene-d_6) δ 26.4, 30.5, 31.7, 53.0, 53.2, 55.1, 58.4, 91.1, 102.2, 128.1, 129.5, 141.1, 207.0; CIMS m/z (rel intensity) 359 (M^+, 49), 141 (100).

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Supporting Information Available: Tables of X-ray structural data for compound **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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