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SYNTHESIS OF TWO STEREOISOMERS OF SWAINSONINE

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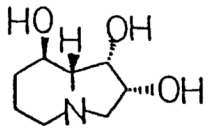
Two stereoisomers of swainsonine, (1S,2S,8S,8aR)-1,2,8-trihydroxyoctahydroindolizine and the corresponding (1S,2R,8S,8aR) derivative, were synthesized from D-glucose via one step cyclization to the 5-oxo-1,2,8-trihydroxyoctahydroindolizine derivative.

In the previous paper,[1] we reported total synthesis of swainsonine(1), (1S,2R,8R,8aR)-1,2,8-trihydroxyoctahydroindolizine, which possesses immunoregulative activity.[2] We became much interested in biological activity of stereoisomers of 1 and their syntheses. In this paper, we wish to report synthesis of two stereoisomers of 1, the corresponding (1S,2S,8S,8aR) isomer(2) and (1S,2R,8S,8aR) isomer(3).

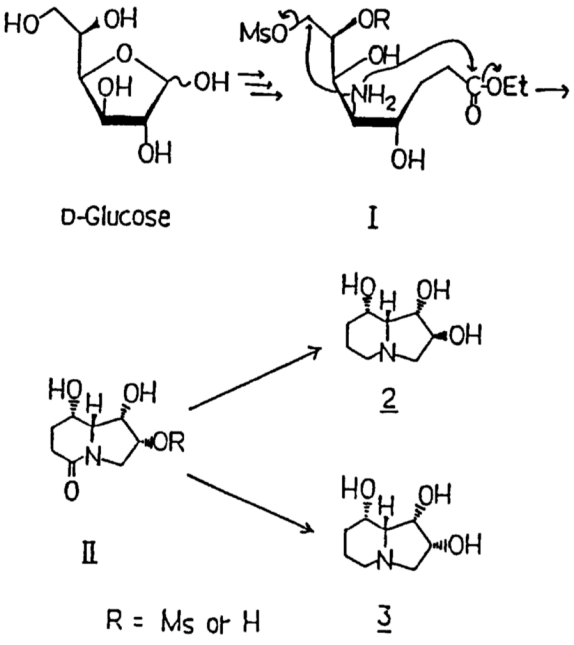


Swainsonine(1)

Our synthetic strategy is to build up a key intermediate, 5-oxo-1,2,8-trihydroxyoctahydroindolizine derivative(II), by one-step cyclization from an acyclic compound, 5-amino-7-O-mesyloctanate derivative(I), which could be obtained from D-glucose. Our target compounds, 2 and 3, could be afforded from II (Scheme 1).

Treatment of 3-azido-3-deoxy-1,2-O-isopropylidene-α-D-glucofuranose(4)[3] with excess mesyl chloride in pyridine gave the corresponding 5,6-di-O-mesyl derivative(5) (mp 104-108 °C; IR (nujol) 2130 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.33 (s, Me), 1.50 (s, Me), 3.07 (s, Ms), 3.17 (s, Ms), and 5.87 (d, $J_{1,2}$=4 Hz, H-1)) in 78% yield. Deprotection of the isopropylidene group in 5 with trifluoroacetic acid and water (9:1) at room temperature for 5.5 h, followed by treatment of (carboethoxymethylene)triphenylphosphorane in THF under reflux for 2 h, gave ethyl (2E)-5-azido-7,8-di-O-mesyl-2,3,5-trideoxy-D-gluco-2-octenate(6) as syrup (IR (neat) 2250, 1700, and 1660 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 1.33 (t, J=8 Hz, Et), 3.03 (s, Ms), 3.10 (s, Ms), 4.20 (q, J=8 Hz, Et), 6.27 (d, $J_{2,3}$=16 Hz, H-2), 6.93 (dd, $J_{2,3}$=16 Hz, $J_{3,4}$=5 Hz, H-3)) in 71% yield. Hydrogenation of 6 in methanol in the

presence of 10% palladium on carbon under 3.5 atmospheric pressure of hydrogen at room temperature gave the expected compound, (1S,2R,8S,8aR)-2-O-mesyl-5-oxo-1,2,8-trihydroxyoctahydroindolizine(7) (mp 169-171 °C; IR (nujol) 1610 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 1.60-2.02 (m, H-7) and 3.27 (s, Ms)) in 19% yield, together with 5,8-imino-7-O-mesyl-2,3,5,8-tetradeoxy-D-gluco-octano-1,4-lactone(8) (mp 153 °C (decomp); IR (nujol) 1770, 1210, and 1180 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 3.20 (s, Ms); FD-MS 266 (M^++1)) in 30% yield. The lactone 8 gave 7 in 89% yield on heating it in a mixture of DMF and EtOH (1:4). Trimethylsilylation of 7 with a mixture of hexamethyldisilazane and trimethylchlorosilane, followed by reduction with boran dimethylsulfide complex in THF under reflux, gave (1S,2R,8S,8aR)-2-O-mesyl-1,2,8-trihydroxyoctahydroindolizine(9) (mp 117-118 °C; $[\alpha]_D^{23}$-7.95° (c 4.0, MeOH); ^{1}H-NMR (DMSO-d_6) δ 3.13 (s, Ms); FD-MS 251 (M^+)) in 28% yield. Treatment of 9 with sodium benzoate in DMF at 120 °C for 2 h afforded (1S,2S,8S,8aR)-2-O-benzoyl-1,2,8-trihydroxyoctahydroindolizine(10) as syrup ($[\alpha]_D^{28}$+16.4° (c 2.65, MeOH); IR (neat) 1710, 1600, and 1550 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 7.33-7.77 and 7.87-8.17 (each m, 1 X Bz); FD-MS 277 (M^+)) in 54% yield. Removal of the benzoyl group in 10 with sodium methoxide in methanol at room temperature gave (1S,2S,8S,8aR)-1,2,8-trihydroxyoctahydroindilizine(2), a stereoisomer of swainsonine, (mp 122 °C(decomp); $[\alpha]_D^{24}$+5.03° (c 0.71, MeOH); ^{13}C-NMR (CD_3OD) δ 20.5, 32.0, 54.4, 62.3, 67.5, 68.1, 78.3, and 82.2; FD-MS 173 (M^+)) in 38% yield.

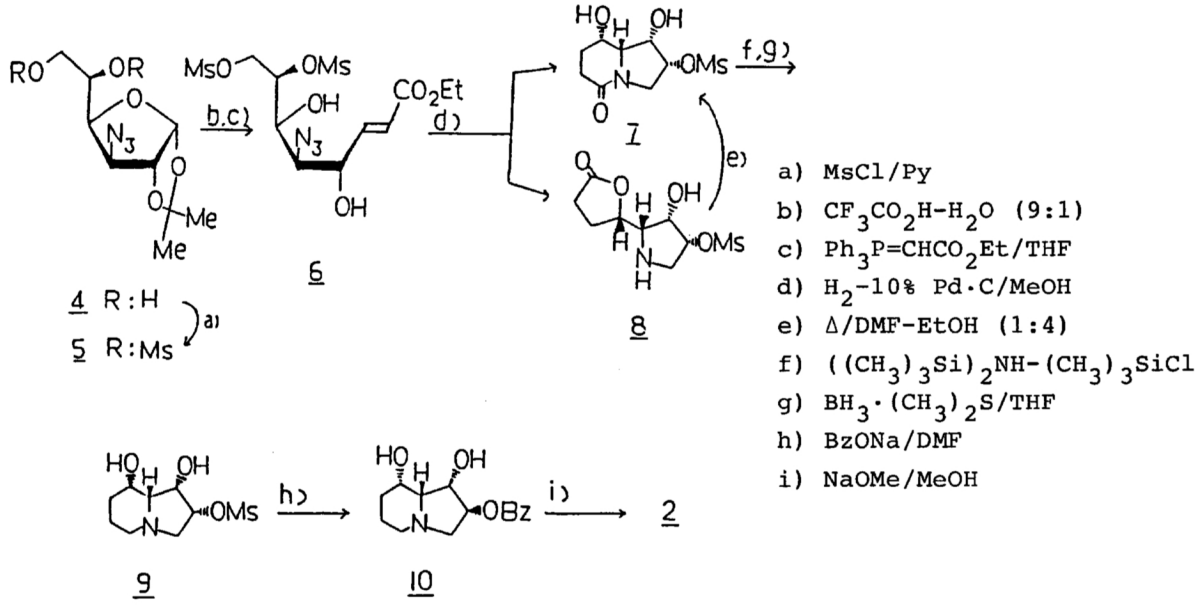


Scheme 1. Our strategy for synthesis of two stereoisomers of swainsonine.

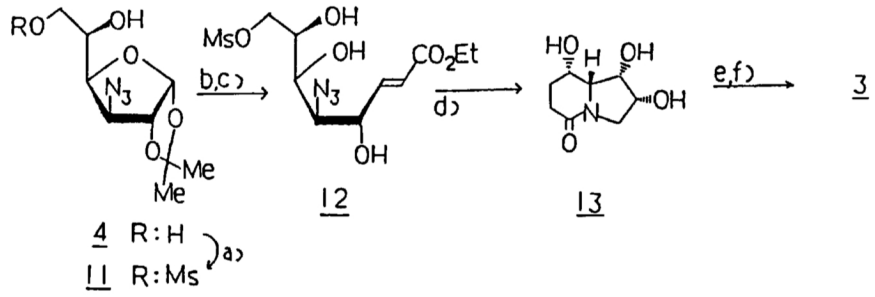
Next, we considered that the other stereoisomer 3 could be synthesized from 3-azido-3-deoxy-1,2-O-isopropylidene-6-O-mesyl-α-D-glucofuranose(11) according to a similar manner described above.

Regioselective mesylation of 4 gave the our starting material(11) as syrup

(IR (neat) 2160 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.33 (s, Me), 1.50 (s, Me), 3.07 (s, Ms), 4.63 (d, J=3 Hz, OH), and 5.87 (d, $J_{1,2}$=3 Hz, H-1)) in 93% yield. Deprotection of the isopropylidene group in 11, followed by Wittig reaction, gave ethyl (2E)-5-azido-8-O-mesyl-2,3,5-trideoxy-D-gluco-2-octenate(12) as syrup (IR (neat) 2120, 1700, and 1655 cm^{-1}; ^{1}H-NMR (CD_3OD) δ 1.23 (t, J=7 Hz, Et), 4.23 (q, J=7 Hz, Et), 6.20 (dd, $J_{2,3}$=15 Hz, $J_{2,4}$=2 Hz, H-2), and 7.07 (dd, $J_{2,3}$=15 Hz, $J_{3,4}$=6 Hz, H-3)) in 8% yield.[4] Hydrogenation of 12 gave (1S,2R,8S,8aR)-5-oxo-1,2,8-trihydroxyoctahydroindolizine(13) as syrup ($[\alpha]_D^{25}$+44.0° (c 1.95, MeOH); IR (neat) 1640-1590 cm^{-1}; ^{1}H-NMR (CD_3OD) δ 1.70-2.20 (m, H-7) and 2.20-3.36 (m, H-3)) in 36% yield.



Scheme 2. Synthetic scheme of (1S,2S,8S,8aR)-1,2,8-trihydroxyoctahydroindolizine(2).



Scheme 3. Synthetic scheme of (1S,2R,8S,8aR)-1,2,8-trihydroxyoctahydroindolizine(3).

Trimethylsilylation of 13, followed by reduction and repeated column chromatography (i, silica gel (Wakogel C-200, 1-butanol-ethanol-chloroform-25% aqueous ammonia 4:4:4:1 (v/v)); ii, CM-Sephadex G-25; iii, silica gel (Wakogel C-200, the same eluant system as i)), gave (1S,2R,8S,8aR)-1,2,8-trihydroxyoctahydroindolizine(3) as syrup ($[\alpha]_D^{21}$-3.43° (c 0.9, MeOH); ^{13}C-NMR (CD_3OD) δ 17.9, 24.5, 44.4, 61.5, 64.3, 72.2, 75.2, and 82.1; FD-MS 174 (M^++1)) in 8% yield.

Biological activity of both stereoisomers(2 and 3) is now under investigation.

References

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2) M.Hino, Y.Tsurumi, T.Shibata, H.Terano, M.Kohsaka, H.Aoki, and H.Imanaka, Annual Meeting of the Agricultural Chemical Society of Japan, Abstract, No.3V-3, Tokyo, Apr.1-4 (1984); O.Nakayama, T.Kino, T.Goto, K.Nakahara, H.Terano, M.Kohsaka, H.Aoki, and H.Imanaka, ibid., No.3V-4, Tokyo, Apr.1-4 (1984).

3) W.M.zu Reckendorf, Chem. Ber., 101, 3802 (1968).

4) This reaction condition was not optimized. Many by-products were observed on TLC.

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