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Improved Synthesis of (2*R*,3*S*,4*R*)-3,4-Dihydroxy-2-Hydroxymethylpyrrolidine Derivatives

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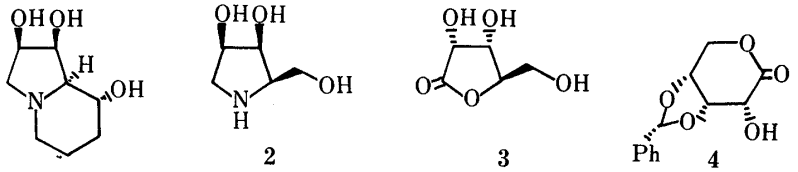
An improved and facile synthesis of (2*R*,3*S*,4*R*)-2-hydroxymethyl-3,4-dihydroxypyrrolidine derivatives (**11** and **15**), which are important intermediates for the synthesis of (−)-swainsonine, from D-ribonolactone was developed.

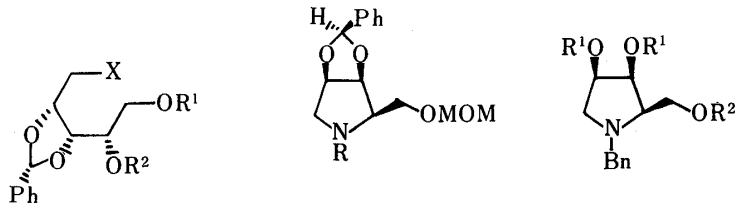
Keywords——(−)-swainsonine; chiral synthesis; (2*R*,3*S*,4*R*)-3,4-dihydroxy-2-hydroxymethylpyrrolidine; D-ribonolactone; Zinner's lactone; selective methoxymethylation

In the previous communications,[1,2] we reported the synthesis of (−)-swainsonine (**1**) and its stereoisomers, which possess α-mannosidase inhibitory activity. In our synthesis of **1**, (2*R*,3*S*,4*R*)-3,4-dihydroxy-2-hydroxymethylpyrrolidine derivatives were important intermediates, and in particular **15**, having a di-*O*-benzyl protecting group, was successfully used in a highly diastereoselective allylation for the preparation of **1**, and was synthesized from (*S*)- or (*R*)-glutamic acid. On the other hand, D-ribonolactone is also an inexpensive, readily available sugar. Although the synthesis of (2*R*,3*S*,4*R*)-4-benzyloxy-2-benzyloxymethyl-3-hydroxy-*N*-toluene-*p*-sulfonylpyrrolidine from D-ribonolactone in nine steps[3] has been reported, we describe here an imporved and facile synthesis of polyhydroxylated pyrrolidine derivatives (**2**, **11**, and **15**) from D-ribonolactone.

Reduction of Zinner's lactone (**4**),[4–6] prepared from D-ribonolactone (**3**), with lithium



1 **2** **3** **4**



5: R^1,R^2=H, X=OH
6: R^1=MOM, R^2=H, X=OH
7: R^1=MOM, R^2=H, X=OMOM
8: R^1,R^2=H, X=OMOM
9: R^1=MOM, R^2=Ms, X=OMs
10: R^1=MOM, R^2=Ms, $X=N_3$
MOM=$-CH_2OCH_3$ Ms=$-SO_2CH_3$

11: R=H
12: R=Bn
Bn=$-CH_2C_6H_5$

13: R^1=H, R^2=MOM
14: R^1=Bn, R^2=MOM
15: R^1=Bn, R^2=H

Chart 1

aluminum hydride in tetrahydrofuran (THF) afforded a triol **5** in 92% yield. The reaction of **5** with 1.3 eq of chloromethyl methyl ether in the presence of *N*,*N*-diethylaniline in methylene chloride at −10— −20 °C gave the mono-methoxymethyl ether (**6**) as a major product in 53% yield, and the di-methoxymethyl ether (**7**) and the mono-methoxymethyl ether (**8**) were also obtained as minor products in 10.5% and 5% yields, respectively. The desired mono-methoxymethyl ether (**6**) was easily isolated by column chromatography. Mesylation of **6** with methanesulfonyl chloride (2.6 eq) in pyridine afforded the dimesylate (**9**) in quantitative yield, followed by displacement of the primary mesylate in **9** by sodium azide in dimethylformamide (DMF) to afford the azidomesylate **10**. Hydrogenation of the azide group in **10** with palladium black in EtOH gave the pyrrolidine derivative **11** with intramolecular S_N2 displacement in 51% yield from **6** and in six steps from **3**. The structure and the optical purity of **11** was confirmed by the conversion of **11** into the hydrochloride of **2** (mp 154—155 °C, $[\alpha]_D^{20}$ +20.8° (c=0.4, H_2O) by acidic hydrolysis. It was identical with an authentic sample previously prepared.[1] Compound **11** was transformed into **15** by the following procedure. *N*-Benzylation of **11** with benzyl bromide in the presence of K_2CO_3, selective cleavage of the benzylidene group in **12** under acidic condition (MeOH : 10% aqueous HCl = 1 : 1, 40 °C), di-*O*-benzylation of **13** with benzyl bromide in the presence of sodium hydride in THF–DMF, and acidic hydrolysis of the methoxymethyl group in **14** afforded **15** in 54% overall yield from **11**. Thus, the selective methoxymethylation of **5** resulted in the facile preparation of (2*R*,3*S*,4*R*)-3,4-dihydroxy-2-hydroxymethylpyrrolidine derivatives.

Experimental[7]

3,4-*O*-Benzylidene-D-ribitol (5)——$LiAlH_4$ (216 mg, 5.7 mmol) was added to a solution of Zinner's lactone (**4**) (1.23 g, 5.21 mmol) in THF (120 ml) and the whole was stirred at ambient temperature for 2 h. Then, $LiAlH_4$ (120 mg, 3.2 mmol) was added, and the mixture was stirred for a further 3 h, then neutralized with 10% aqueous HCl. The insoluble materials were filtered off and washed with THF. The combined filtrates were dried over $MgSO_4$ followed by evaporation and column chromatography (silica gel, AcOEt : MeOH = 10 : 1) to afford **5** (1.55 g, yield 92%) as a colorless oil. $[\alpha]_D^{20}$ −13.0° (c=0.4, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1050, 3400. ^{1}H-NMR ($CDCl_3$): 3.45—4.5 (9H, m), 4.7 (1H, br s, 1H), 5.65 (1H, br s). ^{13}C-NMR ($CDCl_3$): 60.52 (t), 64.08 (t), 69.54 (d), 77.53 (d), 77.68 (d), 103.16 (d), 126.41 (d), 128.26 (d), 129.48 (d), 136.34 (s). MS m/z: 240 (M^+).

3,4-*O*-Benzylidene-1-*O*-methoxymethyl-D-ribitol (6)——A solution of **5** (940 mg, 3.92 mmol), *N*,*N*-diethylaniline (820 mg, 5.49 mmol), and chloromethyl methyl ether (410 mg, 5.1 mmol) in CH_2Cl_2 (15 ml) was kept at −10— −20 °C for 32 h. After dilution with AcOEt, the mixture was washed with 10% aqueous HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl. Drying followed by evaporation and column chromatography (silica gel, AcOEt : $CHCl_3$ = 1 : 2) afforded **6** (620 mg, yield 53%), **7** (142 mg, yield 10.5%) and **8** (56 mg, yield 5%). **6**: mp 37 °C. $[\alpha]_D^{20}$ −33.6° (c=1, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1030, 3450. ^{1}H-NMR ($CDCl_3$): 3.38 (3H, s, OCH_3), 3.4—4.6 (9H, m), 4.66 (2H, s, OCH_2O), 5.77 (1H, s, C<u>H</u>Ph), 7.38 (5H, s, aromatic protons). ^{13}C-NMR ($CDCl_3$): 55.26 (q), 60.43 (t), 68.61 (d), 70.61 (t), 77.14 (d), 78.26 (d), 97.02 (t), 103.11 (d), 126.31 (d), 128.16 (d), 129.33 (d), 136.49 (s). MS m/z: 284 (M^+). **7**: Oil. $[\alpha]_D^{20}$ −11.9° (c=0.8, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1030, 3500. ^{1}H-NMR ($CDCl_3$): 3.38 (6H, s, 2 × OCH_3), 3.38 (1H, OH), 3.58—4.63 (7H, m), 4.68 (2H, s, OCH_2O), 4.69 (2H, s, OCH_2O), 5.81 (1H, s, C<u>H</u>Ph), 7.38 (5H, m, aromatic protons). ^{13}C-NMR ($CDCl_3$): 55.11 (q), 55.41 (q), 65.93 (t), 68.32 (d), 69.83 (t), 76.55 (d), 77.58 (d), 96.58 (t), 96.83 (t), 103.41 (d), 126.36 (d), 128.06 (d), 129.18 (d), 136.69 (s). MS m/z: 327 (M^+ − 1), 310 (M^+ − 18). **8**: Oil. $[\alpha]_D^{20}$ −4.2° (c=0.7, $CHCl_3$). IR ν_{max}^{film} cm^{-1} :1050, 3450. ^{1}H-NMR ($CDCl_3$): 1.96 (2H, br s, 2 × OH), 3.41 (3H, s, OCH_3), 3.66—4.86 (7H, m), 4.71 (2H, s, OCH_2O), 5.80 (1H, s, C<u>H</u>Ph), 7.39 (5H, s, aromatic protons). ^{13}C-NMR ($CDCl_3$): 55.75 (q), 64.27 (t), 65.93 (t), 69.0 (d), 75.68 (d), 78.50 (d), 96.78 (t), 103.45 (d), 126.36 (d), 128.20 (d), 129.37 (d), 136.49 (s). MS m/z: 284 (M^+).

3,4-*O*-Benzylidene-2,5-di-*O*-methanesulfonyl-1-*O*-methoxymethyl-D-ribitol (9)——A mixture of **6** (930 mg, 3.28 mmol) and methanesulfonyl chloride (976 mg, 8.53 mmol) in pyridine (15 ml) was stirred at 0 °C for 15 h. After dilution with ethyl acetate, the mixture was washed with 10% aqueous HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl. Drying followed by evaporation and column chromatography (silica gel, AcOEt : $CHCl_3$ = 1 : 4) gave **9** (1.44 g, yield quant.) as crystals. Recrystallization from AcOEt–hexane gave an analytically pure sample, mp 65 °C, $[\alpha]_D^{20}$ +35.6° (c=0.5, $CHCl_3$). IR ν_{max}^{nujol} cm^{-1}: 1170, 1360, 1380. ^{1}H-NMR ($CDCl_3$): 2.97 (3H, s, SO_2CH_3), 3.09 (3H, s, SO_2CH_3), 3.34 (3H, s, OCH_3), 3.66—4.23 (2H, m, C<u>H</u>$_2$$OCH_2O$), 4.3—4.85 (4H, m, 2 × C<u>H</u>, C<u>H</u>$_2$$OSO_2CH_3$), 4.63 (2H, s, OCH_2O), 3.98 (1H, s, C<u>H</u>Ph), 7.43 (5H, m, aromatic protons). ^{13}C-

NMR ($CDCl_3$): 37.28 (q), 38.94 (q), 55.41 (q), 66.32 (t), 67.32 (t), 67.98 (t), 75.48 (d), 77.53 (d), 96.34 (t), 103.50 (d), 126.31 (d), 128.26 (d), 129.62 (d), 135.52 (s). *Anal.* Calcd for $C_{16}H_{24}O_{10}S_2$: C, 43.64; H, 5.49. Found: C, 43.39; H, 5.45.

5-Azido-3,4-*O*-benzylidene-5-deoxy-2-*O*-methanesulfonyl-1-*O*-methoxymethyl-D-ribitol (10)——A mixture of **9** (1.3 g, 2.95 mmol) and sodium azide (384 mg, 5.9 mmol) in DMF (15 ml) was stirred at 110-120 °C for 2.5 h. After dilution with AcOEt–benzene (4 : 1), the mixture was washed with H_2O and saturated aqueous NaCl (×5). Drying followed by evaporation and column chromatography (silica gel, AcOEt : $CHCl_3$ = 1 : 10) gave **10** (788 mg, yield 69%) as a slightly yellow oil. $[\alpha]_D^{20}$ +52.2° (c = 1.2, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1180, 1350, 2055. ^{1}H-NMR ($CDCl_3$): 3.09 (3H, s, OSO_2CH_3), 3.34 (3H, s, OCH_3), 3.54—3.71 (2H, m, N_3CH_2), 3.71—4.09 (2H, m, CH_2OCH_2O), 4.26—4.51 (2H, m, 2xCH), 4.63 (2H, s, OCH_2O), 4.98 (1H, m, $CHOSO_2$), 5.83 (1H, s, CHPh), 7.40 (5H, m, aromatic protons). ^{13}C-NMR ($CDCl_3$): 39.18 (q), 50.48 (t), 55.50 (q), 66.52 (t), 75.68 (d), 78.26 (d), 96.49 (t), 103.41 (d), 126.36, 128.35, 129.57, 135.81 (s). MS m/z: 387 (M^+).

(2*R*,3*S*,4*R*)-3,4-Benzylidenedioxy-2-(methoxymethoxy)methylpyrrolidine (11)——A solution of **10** (600 mg, 1.55 mmol) in EtOH (10 ml) in the presence of palladium black (150 mg) was stirred under hydrogen at atmospheric pressure for 15 h and then filtered. The filtrate was concentrated *in vacuo* to give an oily residue, which was dissolved in AcOEt, and washed with 10% aqueous NaOH and saturated aqueous NaCl. Drying followed by evaporation and column chromatography of the residue (silica gel, AcOEt) gave **11** (301 mg, yield 73%) as a colorless oil. $[\alpha]_D^{20}$ −76.1° (c = 0.5, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 2.14 (1H, s, NH), 2.72 (1H, dd, J = 3.4, 13 Hz, H-5), 3.01 (1H, m, $CHCH_2OCH_2$), 3.30 (1H, d, J = 13 Hz, H-5), 3.36 (3H, s, OCH_3), 3.45—4.07 (2H, m, CH_2OCH_2O), 4.66 (2H, s, OCH_2O), 4.50—4.85 (2H, m, 2 × CH), 5.68 (1H, s, CHPh), 7.40 (5H, m, aromatic protons). ^{13}C-NMR ($CDCl_3$): 52.73 (t), 55.02 (q), 63.15 (d), 65.54 (t), 81.77 (d), 82.55 (d), 96.39 (t), 104.23 (d), 126.36, 128.11, 129.33, 135.73 (s). MS m/z: 264 (M^+).

(2*R*, 3*S*, 4*R*)-3,4-Dihydroxymethyl-2-hydroxymethylpyrrolidine Hydrochloride (Hydrochloride of 2)——A mixture of **11** (30 mg, 0.11 mmol), 10% aqueous HCl (2 ml), and MeOH (2 ml) was stirred at 70 °C for 2 h. After removal of the methanol *in vacuo*, the aqueous layer was washed with ether (×2), then evaporated *in vacuo* to dryness. The residue was crystallized from methanol–ether to give hydrochloride of **2** (16 mg, yield 83%) as needles, mp 154—155 °C. Spectroscopic data and the $[\alpha]_D$ value were identical with those of an authentic sample.

(2*R*, 3*S*, 4*R*)-3,4-Dibenzyloxy-2-hydroxymethyl-*N*-benzylpyrrolidine (15)——A mixture of **11** (640 mg, 2.42 mmol) and benzyl bromide (0.57 ml, 4.84 mmol) in acetone (15 ml) was stirred in the presence of anhydrous K_2CO_3 (2 g) at room temperature for 2 h and filtered. The filtrate was concentrated *in vacuo* and the residue was chromatographed (silica gel, AcOEt : hexane = 1 : 4) to afford (2*R*,3*S*,4*R*)-3,4-benzylidenedioxy-2-(methoxymethoxy)methyl-*N*-benzylpyrrolidine (**12**, 816 mg, yield 95%) as a colorless oil. $[\alpha]_D^{20}$ −30.0° (c = 0.5, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 2.10 (1H, dd, J = 11.1, 4 Hz, H-5), 2.4—2.7 (1H, m, $CHCH_2OCH_2O$), 3.22 (1H, d, J = 11 Hz, H-5), 3.25, 4.20 (2H, AB, J = 13.4 Hz, CH_2Ph), 3.32 (3H, s, OCH_3), 3.71—4.1 (2H, m, $CHCH_2O$), 4.5—4.85 (2H, m, 2 × CH), 4.63 (2H, s, OCH_2O), 5.73 (1H, s, CHPh), 7.1—7.7 (5H, m, aromatic protons). ^{13}C-NMR ($CDCl_3$): 54.87 (q), 57.36 (t), 58.87 (t), 66.18 (t), 66.76 (d), 78.39 (d), 81.04 (d), 96.39 (t), 104.87 (d), 126.50, 126.94, 127.81, 129.13, 136.93 (s), 138.29 (s). A mixture of **12** (800 mg, 2.25 mmol) in MeOH (6 ml) and 10% aqueous HCl (6 ml) was stirred at 40 °C for 2 h. After removal of the methanol *in vacuo*, the aqueous layer was basified with 10% aqueous NaOH, and extracted with AcOEt (×3). The organic layer was washed with saturated aqueous NaCl. Drying followed by evaporation and column chromatography (silica gel, AcOEt) gave (2*R*,3*S*,4*R*)-3,4-dihydroxy-2-(methoxymethoxy)methyl-*N*-benzylpyrrolidine (**13**, 384 mg, yield 64%) as a colorless oil. $[\alpha]_D^{20}$ −18.2° (c = 0.4, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1035, 1100, 3450. ^{1}H-NMR ($CDCl_3$): 2.44 (1H, dd, J = 4, 11.4 Hz, H-5), 2.7—3.0 (4H, m, H-2, 2 × OH, H-5), 3.39 (3H, s, OCH_3), 3.50, 3.88 (2H, AB, J = 13.7 Hz, CH_2Ph), 3.5—3.62 (2H, m, CH_2OCH_2O), 3.85—4.02 (1H, m, CH), 4.12—4.32 (1H, m, CH), 4.61, 4.69 (2H, AB, J = 6.5 Hz, CH_2OCH_2O), 7.29 (5H, s, aromatic protons). ^{13}C-NMR ($CDCl_3$): 55.54, 57.34, 58.36, 63.42, 65.31, 70.57, 73.09, 96.63, 126.88, 128.40, 128.00, 138.01. MS m/z: 267 (M^+). A solution of **13** (370 mg, 1.39 mmol) in THF (10 ml) was added to a suspension of sodium hydride (166 mg, 60% oil suspension, washed with hexane, 4.16 mmol) in DMF (10 ml) at 0 °C. The mixture was stirred at room temperature for 40 min, then benzyl bromide (0.5 ml, 4.16 mmol) was added, and the mixture was stirred at room temperature for 4 h. After dilution with AcOEt–benzene, the mixture was washed with H_2O (×3) and saturated aqueous NaCl (×3). Drying followed by evaporation and column chromatography of the residue (silica gel, AcOEt : hexane = 1 : 4) afforded (2*R*,3*S*,4*R*)-3,4-dibenzyloxy-2-(methoxymethoxy)methyl-*N*-benzylpyrrolidine (**14**, 570 mg, yield 92%) as a colorless oil. $[\alpha]_D^{20}$ −35.2° (c = 1.6, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 2.61 (2H, dd, J = 5.7, 11.4 Hz, H-5), 2.98—3.38 (2H, m, H-5, H-2), 3.38 (3H, s, OCH_3), 3.66, 4.10 (2H, AB, J = 13.7 Hz, CH_2Ph), 3.75—4.14 (4H, m, 2 × CH, $CHCH_2O$), 4.55—4.92 (6H, m, 2 × CH_2Ph, OCH_2O), 7.35 (15H, s, aromatic protons). ^{13}C-NMR ($CDCl_3$): 54.53 (t), 54.92 (q), 59.50 (t), 63.88 (d), 67.88 (t), 71.29 (t), 72.51 (t), 77.04 (d), 78.50 (d), 96.58 (t), 126.5, 127.14, 127.38, 127.92, 128.40, 138.19 (s), 138.25 (s), 138.65 (s). A mixture of **14** (550 mg, 1.23 mmol) in MeOH (6 ml) and 10% aqueous HCl (3 ml) was stirred at 70 °C for 2 h. After removal of the methanol *in vacuo*, the aqueous layer was basified with 10% aqueous NaOH followed by extraction with AcOEt. Drying followed by evaporation and column chromatography of the residue (silica gel, AcOEt : hexane = 1 : 1) afforded **15** (477 mg, yield 96%) as a colorless oil. $[\alpha]_D^{20}$ −56.0° (c = 1.5, $CHCl_3$), (lit.[1]) $[\alpha]_D^{20}$ −58.3° (c = 1.6 $CHCl_3$)). IR ν_{max}^{film} cm^{-1}: 690, 730, 1020, 1130, 1340, 3450. ^{1}H-NMR ($CDCl_3$): 2.44 (1H, dd, J = 4, 11 Hz, H-5), 2.9—3.3 (3H, m, OH, H-5, H-2), 3.59, 3.91 (2H, AB, J = 13.7 Hz, CH_2Ph), 3.6—3.8 (2H, m, CH_2OH),

3.95—4.12 (2H, m, 2 × CH), 4.32—4.7 (4H, m, 2 × $C\underline{H}_2$Ph), 7.29 (5H, s, aromatic protons). ^{13}C-NMR ($CDCl_3$): 53.94 (t), 58.18 (t), 60.04 (t), 63.45 (d), 71.0 (t), 71.58 (d), 75.38 (d), 78.94 (d), 126.6, 127.0, 127.2, 127.8, 128.0, 128.31, 137.5 (s), 138.1 (s). MS *m/z*: 401 (M^+).

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7) Melting points were measured on a hot stage apparatus and are uncorrected. Infrared (IR) spectra measurements were performed with a JASCO IRA-1 grating infrared spectrometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra and carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectra were measured with a JNM-FX-100 (100 MHz) spectrometer. Data are recorded in parts per million (ppm) downfield from internal tetramethylsilane. The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). Optical rotations were determined with a JASCO DIP-SL. Mass spectra (MS) were recorded with a JEOL JMS-01 5G-Z mass spectrometer. The organic solvents were dried over $MgSO_4$ before vacuum evaporation.