Synthesis of (3*R*,4*R*,5*R*)-1-(*tert*-Butoxycarbonyl)-3,4-isopropylidenedioxy-5-methoxymethyl-2-pyrrolidinone from (*S*)-Pyroglutaminol

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(3*R*,4*R*,5*R*)-1-(*tert*-Butoxycarbonyl)-3,4-isopropylidenedioxy-5-methoxymethyl-2-pyrrolidinone (6), a useful chiral intermediate for the preparation of calyculins, was synthesized starting from (*S*)-pyroglutaminol *via* the *O*-methylation of 1c with diazomethane in the presence of fluoboric acid and *cis*-dihydroxylation of the α,β-unsaturated lactam (4) as the key reactions.

Keywords (*S*)-pyroglutaminol; calyculin; chiral synthesis; fluoboric acid; *O*-methylation; *cis*-dihydroxylation

Earlier we have reported the synthesis of optically active polyhydroxylated amines by empolying *cis*-dihydroxylation of α,β-unsaturated lactams derived from chiral (*S*)- and (*R*)-pyroglutamic acid.[1] Recently, Smith, III *et al.*[2] and Shioiri *et al.*[3] have reported the synthesis of (3*R*,4*R*,5*R*)-1-(*tert*-butoxycarbonyl)-3,4-isopropylidenedioxy-5-methoxymethyl-2-pyrrolidinone (**6**), a useful intermediate for the preparation of calyculins,[4] from D-isoascorbic acid and from (*S*)-pyroglutaminol respectively. In these procedures the *p*-methoxybenzyl group was used as the lactam *N*-protecting group for the *O*-methylation of the alcohol, and then the *p*-methoxybenzyl group was replaced with a *tert*-butoxycarbonyl group. In a continuation of our studies on the utility of chiral pyroglutamic acid derivatives for natural product synthesis, we describe here a synthesis of **6** from (*S*)-1-(*tert*-butoxycarbonyl)-5-hydroxymethyl-2-pyrrolidinone (**1c**).

Compound **1c** (mp 91—92 °C; $[\alpha]_D^{20}$ −68° (*c*=1, $CHCl_2$), lit.[5] mp 98—99 °C, $[\alpha]_D^{25}$ −63° (*c*=0.61, $CHCl_3$)) was prepared from either (*S*)-pyroglutaminol (**1a**)[6] or (*S*)-1-(*tert*-butoxycarbonyl)-5-trityloxymethyl-2-pyrrolidinone (**1d**).[1d] Successive treatment of **1a** with *tert*-butyldimethylsilyl chloride, di-*tert*-butyl dicarbonate, and tetrabutylammonium fluoride gave **1c** in 76% overall yield. Acid hydrolysis of **1d** with concentrated HCl–methanol (1 : 50) at 30—35 °C gave **1c** in 48% yield. Treatment of **1c** with sodium hydride in tetrahydrofuran (THF)–*N*,*N*-dimethylformamide (DMF) (1 : 1) followed by addition of methyl iodide did not afford the *O*-methyl compound **2**, while the reaction with a large excess of methyl iodide and silver oxide gave a mixture of **2** (about 15%) and an inseparable by-product with 35% recovery of the starting alcohol **1c**. However, when treated with diazomethane in the presence of fluoboric acid[7] in methylene chloride at 0 °C, **1c** furnished the *O*-methyl compound **2** in 74% yield. Then, selenenylation of **2** using lithium diisopropylamide (LDA) and phenylselenenyl chloride afforded a diastereomeric mixture of the 3-phenylseleno-2-pyrrolidinone derivative **3** (2.5 : 1 by ^{1}H-NMR) in 63% yield. Treatment of **3** with 30% H_2O_2 in ethyl acetate gave the α,β-unsaturated lactam **4** in 73% yield. The lactam **4** was also obtained from **7a**,[1d,g] a major diastereomer synthesized from **1d** by selenenylation with LDA and phenylselenenyl bromide. Acid hydrolysis of **7a** with concentrated HCl–methanol (1 : 50) at 35 °C followed by *O*-methylation with diazomethane in the presence of fluoboric acid and subsequent deselenenylation provided **4** in 26% yield. *cis*-Dihydroxylation of **4** with a catalytic amount of OsO_4 in the presence of *N*-methylmorpholine *N*-oxide in aqueous acetone produced the diol **5** in 68% yield as a single diastereomer. Protection of the *cis*-diol in **5** with an isopropylidene group provided **6** ($[\alpha]_D^{20}$ −91.1° (*c*=1, $CHCl_3$), lit.[3] $[\alpha]_D^{24}$ −92.3° (*c*=1, $CHCl_3$)) in 80% yield. Its spectral data (^{1}H-NMR and IR) were identical with those reported.[3]

Thus, *O*-methylation of **1c** with diazomethane and fluoboric acid provided a facile route to **6**.

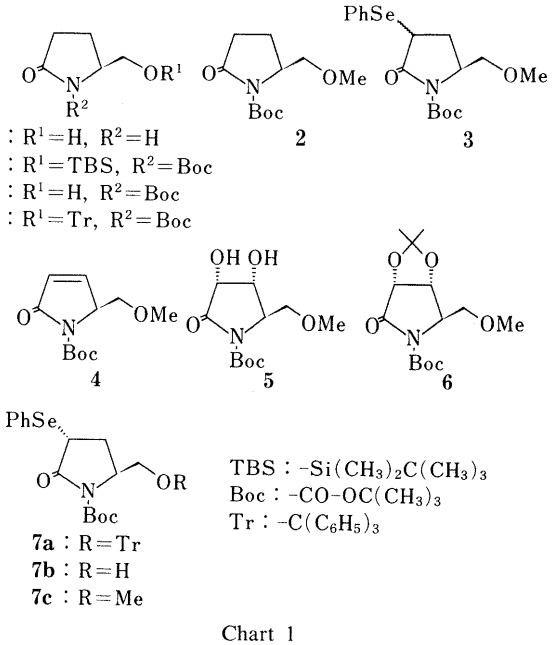

Chart 1

Experimental

Melting points were measured on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectral measurements were performed on a JEOL JIR-110 FT-IR spectrophotometer. Proton and carbon-13 nuclear magnetic resonance (^{1}H- and ^{13}C-NMR) spectra were measured with a JEOL JNM FX-100 (100 MHz) spectrometer. Data were recorded in parts per million (ppm) downfield from internal tetramethylsilane (TMS). The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). Optical rotations were determined with a JASCO DIP-360 digital polarimeter. Mass spectra (MS) were recorded with JEOL JMS-D302 and JEOL JMS-HX110 mass spectrometers. Organic extracts were dried over $MgSO_4$ before vacuum evaporation.

(*S*)-1-(*tert*-Butoxycarbonyl)-5-[(*tert*-butyldimethylsilyloxy)methyl]-2-pyrrolidinone (1b) A mixture of (*S*)-5-hydroxymethyl-2-pyrrolidinone (**1a**) (760 mg, 6.6 mmol), *tert*-butyldimethylsilyl chloride (1.09 g, 7.23 mmol), and imidazole (1.12 g, 16.5 mmol) in DMF (9 ml) was stirred at

0 °C for 12 h. After dilution with AcOEt–benzene (3 : 1, 300 ml), the mixture was washed with half-saturated aqueous NaCl. Drying followed by evaporation gave a crude silyl ether (1.5 g, yield quant.), which was treated with di-*tert*-butyl dicarbonate (2.88 g, 13.2 mmol), triethylamine (0.92 ml, 6.6 mmol), and 4-dimethylaminopyridine (810 mg, 6.6 mmol) in CH_2Cl_2 (16 ml) at room temperature for 5 h. After removal of the volatiles *in vacuo*, the residue was purified by column chromatography (silica gel, AcOEt : hexane = 1 : 1) to afford **1b** (1.75 g, yield 81%) as an oil. $[\alpha]_D^{20}$ −68.5° (c = 0.7, $CHCl_3$) (lit.[5] $[\alpha]_D^{20}$ −61° (c = 1.1, $CHCl_3$)). IR ν_{max}^{film} cm^{-1}: 1787, 1753, 1712. ^{1}H-NMR ($CDCl_3$): 0.015 (6H, br s, 2 × CH_3), 0.85 (9H, s, *tert*-Bu), 1.50 (9H, s, *tert*-Bu), 1.81—2.91 (4H, m, 2 × CH_2), 3.65 (1H, dd, J = 2.3, 10.3 Hz, CH), 3.91 (1H, dd, J = 3.8, 10.3 Hz, CH), 4.16 (m, 1H, CH). MS m/z: 329 (M^+).

(*S*)-1-(*tert*-Butoxycarbonyl)-5-hydroxymethyl-2-pyrrolidinone (1c) A) From **1b**: A 1 M solution of tetrabutylammonium fluoride in THF (4.5 ml) was added to a solution of **1b** (900 mg, 2.73 mmol), and the mixture was stirred at room temperature for 30 min. After dilution with AcOEt, the mixture was washed with H_2O. Drying, followed by evaporation and purification of the residue by column chromatography (silica gel, AcOEt : hexane = 2 : 3), gave **1c** (554 mg, 94% yield) as crystals, mp 91—92 °C (ether–hexane), $[\alpha]_D^{20}$ −68° (c = 1, $CHCl_3$). IR ν_{max}^{Nujol} cm^{-1}: 3440, 1781, 1697. ^{1}H-NMR ($CDCl_3$): 1.46 (9H, s, *tert*-Bu), 1.77—2.86 (4H, m, 2 × CH_2), 3.14—4.00 (3H, m, CH_2, OH), 4.15 (m, 1H, CH). ^{13}C-NMR ($CDCl_3$): 20.56 (t), 27.78 (q), 31.87 (t), 59.16 (d), 63.64 (t), 82.84 (s), 150.09 (s), 175.18 (s). *Anal.* Calcd for $C_{10}H_{17}NO_4$. C, 55.80; H, 7.96; N, 6.51. Found: C, 55.56; H, 8.09; N, 6.38. B) From **1d**: A mixture of (*S*)-1-(*tert*-butoxycarbonyl)-5-trityloxymethyl-2-pyrrolidinone (**1d**) (1.65 g, 3.61 mmol) and 20 ml of concentrated HCl–MeOH (1 : 50) was stirred at 30—35 °C for 1 h. After neutralization with $NaHCO_3$, the methanol was removed *in vacuo* to give a residue, which was dissolved in AcOEt (200 ml), and the solution was washed with half-saturated aqueous NaCl. Drying, followed by evaporation and purification of the residue by column chromatography (silica gel, AcOEt : hexane = 3 : 1), gave **1c** (372 mg, 48% yield) as crystals. Physical and spectral data were identical with those obtained from **1b**.

(*S*)-1-(*tert*-Butoxycarbonyl)-5-methoxymethyl-2-pyrrolidinone (2) Ethereal diazomethane was added to a mixture of concentrated fluoboric acid[7a] (100 mg) and **1c** (550 mg, 2.56 mmol) in CH_2Cl_2 (6 ml) at 0 °C, and the whole was stirred at 0 °C for 3 min. After further addition of concentrated fluoboric acid (100 mg), ethereal diazomethane was added until the starting material had almost disappeared. After neutralization with saturated aqueous $NaHCO_3$, the mixture was diluted with AcOEt and washed with half-saturated aqueous NaCl. Drying, followed by evaporation and purification of the residue by column chromatography (silica gel, AcOEt : hexane = 2 : 3), gave **2** (433 mg, 74% yield) as an oil, $[\alpha]_D^{20}$ −58.8° (c = 1, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1786, 1751, 1713. ^{1}H-NMR ($CDCl_3$): 1.45 (9H, s, *tert*-Bu), 1.84—2.76 (4H, m, 2 × CH_2), 3.26 (3H, s, OCH_3), 3.45 (2H, m, CH_2), 4.17 (1H, m, CH). ^{13}C-NMR ($CDCl_3$): 20.86 (t), 27.58 (q), 31.53 (t), 56.87 (d), 58.82 (q), 73.00 (t), 82.26 (s), 149.40 (s), 174.40 (s). HR-MS m/z: Calcd for $C_{11}H_{20}NO_4$ (M^+ + 1): 230.1392. Found: 230.1430.

(*S*)-1-(*tert*-Butoxycarbonyl)-5-methoxymethyl-2-oxo-3-pyrroline (4) A solution of LDA (2.18 mmol) was prepared in THF (4 ml) from diisopropylamine (0.31 ml, 2.18 mmol) and butyl lithium (1.85 ml of a 1.18 M solution in hexane), then cooled to −78 °C. A solution of **2** (400 mg, 1.75 mmol) in THF (4 ml) was added to the LDA solution and the mixture was stirred at −78 °C for 40 min. Then a solution of phenylselenenyl chloride (435 mg, 2.27 mmol) in THF (3.5 ml) was added and the mixture was stirred at −78 °C for 15 min. After addition of 10% aqueous NH_4Cl (3 ml), the mixture was diluted with ether and washed with 5% aqueous citric acid, H_2O, saturated aqueous $NaHCO_3$, and H_2O. Drying, followed by evaporation and purification of the residue by column chromatography (silica gel, AcOEt : hexane = 1 : 2), gave **3** (420 mg, 63% yield) as a mixture of diastereomers, $[\alpha]_D^{20}$ −75.7° (c = 0.6, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1780, 1716. ^{1}H-NMR ($CDCl_3$): 1.49 and 1.51 (9H, 2 × s, *tert*-Bu), 1.88—2.74 (2H, m, CH_2), 3.26 and 3.34 (3H, 2 × s, OCH_3), 3.38—3.68 (2H, m, CH_2), 3.80—4.30 (2H, m, 2 × CH). ^{13}C-NMR ($CDCl_3$): 27.73 (q), 28.75 and 29.82 (t), 40.79 and 41.37 (d), 55.60 and 55.75 (t), 58.77 and 59.01 (q), 72.56 and 72.90 (t), 82.79 and 82.94 (s), 126.99, 127.67, 128.06, 128.79 (aromatic carbons), 134.01 and 135.08 (d), 149.36 (s), 172.65 (s). HR-MS (FAB) m/z: Calcd for $C_{17}H_{24}NO_4{}^{80}Se$ (M^+ + 1): 386.0871. Found: 386.0840. A solution of **3** (390 mg, 1.02 mmol) in AcOEt (4.5 ml) was treated with 30% H_2O_2 (1 ml) at 0 °C, and the mixture was stirred at 15—20 °C for 15 min, then diluted with ether and washed with H_2O, saturated $NaHCO_3$, and H_2O. Drying, followed by evaporation and purification of the residue by column chromatography (silica gel, AcOEt : hexane = 1 : 1), gave **4** (167 mg, 73% yield) as an oil, $[\alpha]_D^{20}$ −208° (c = 0.8, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1778, 1740, 1714. ^{1}H-NMR ($CDCl_3$): 1.53 (9H, s, *tert*-Bu), 3.32 (3H, s, OCH_3), 3.47 (1H, dd, J = 7.2, 9.2 Hz, CH), 3.90 (H, dd, J = 3.7, 9.2 Hz, CH), 4.68 (1H, m, CH), 6.09 (1H, dd, J = 1.7, 6.1 Hz, vinyl proton), 7.27 (1H, dd, J = 2.0, 6.1 Hz, vinyl proton). ^{13}C-NMR ($CDCl_3$): 27.78 (q), 59.16 (q), 61.55 (d), 67.19 (t), 82.84 (s), 126.60 (d), 149.21 (d and s), 169.04 (s). HR-MS m/z: Calcd for $C_{11}H_{17}NO_4$ (M^+): 227.1157. Found: 227.1109.

Preparation of 4 from (3*R*,5*S*)-1-(*tert*-Butoxycarbonyl)-3-phenylseleno-5-trityloxymethyl-2-pyrrolidinone (7a) (3*R*,5*S*)-1-(*tert*-Butoxycarbonyl)-5-hydroxymethyl-3-phenylseleno-2-pyrrolidinone (**7b**) was obtained from **7a** in 71% yield as an oil after column chromatography (silica gel, AcOEt : hexane = 3 : 2) in the same manner as described above for the preparation of **1c** from **1d**, $[\alpha]_D^{20}$ −112° (c = 0.9, $CHCl_3$). ^{13}C-NMR ($CDCl_3$): 27.44 (q), 28.90 (t), 41.03 (d), 57.60 (d), 62.72 (t), 82.74 (s), 126.55, 127.87, 128.55 (aromatic carbons), 134.89 (d), 149.36 (s), 173.33 (s). MS m/z: 370 and 372 (M^+ + 1). (3*R*,5*S*)-1-(*tert*-Butoxycarbonyl)-5-methoxymethyl-3-phenylseleno-2-pyrrolidinone (**7c**) was obtained from **7b** in 45% yield as an oil after column chromatography (silica gel, AcOEt : hexane = 2 : 3) in the same manner as described above for the preparation of **2**, $[\alpha]_D^{20}$ −102° (c = 0.6, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 1.52 (9H, s, *tert*-Bu), 1.90—2.60 (2H, m, CH_2), 3.26 (3H, s, OCH_3), 3.49 (2H, m, CH_2), 3.93—4.30 (2H, m, 2 × CH), 7.09—7.75 (5H, m, aromatic protons). ^{13}C-NMR ($CDCl_3$): 27.73 (q), 29.83 (t), 41.37 (d), 55.80 (t), 59.02 (q), 72.90 (t), 82.79 (s), 127.04, 128.06, 128.80 (aromatic carbons), 135.08 (d), 149.36 (s), 172.65 (s). (*S*)-1-(*tert*-Butoxycarbonyl)-5-methoxymethyl-2-oxo-3-pyrroline (**4**) was obtained from **7c** in 80% yield as an oil after column chromatography (silica gel, AcOEt : hexane = 1 : 1) in the same manner as described above for the preparation of **4** from **3**.

(3*R*,4*R*,5*R*)-1-(*tert*-Butoxycarbonyl)-3,4-dihydroxy-5-methoxymethyl-2-pyrrolidinone (5) A mixture of **4** (200 mg, 0.88 mmol), OsO_4 (21 mg, 0.08 mmol) and *N*-methylmorpholine *N*-oxide monohydrate (150 mg, 1.11 mmol) in acetone (4.5 ml) and H_2O (2 ml) was stirred at room temperature for 14 h. After addition of sodium hydrosulfite (400 mg), the mixture was diluted with AcOEt (250 ml) and washed with half-saturated NaCl. Drying, followed by evaporation and purification of the residue by column chromatography (silica, gel, AcOEt : hexane = 6 : 1), gave **5** (155 mg, 68% yield) as an oil, $[\alpha]_D^{20}$ −16.7° (c = 1.5, MeOH). IR ν_{max}^{film} cm^{-1}: 3424, 1785, 1716. ^{1}H-NMR ($CDCl_3$): 1.54 (9H, s, *tert*-Bu), 3.32 (3H, s, OCH_3), 3.63 (2H, m, CH_2), 4.10 (1H, m, CH), 4.18—4.65 (2H, br, 2 × OH), 4.33 (1H, d, J = 5 Hz, CH), 4.62 (1H, d, J = 5 Hz, CH). ^{13}C-NMR ($CDCl_3$): 27.87 (q), 59.26 (q), 63.01 (d), 69.05 (d), 70.76 (t), 71.44 (d), 83.52 (s), 149.51 (d and s), 174.40 (s). HR-MS (FAB) m/z: Calcd for $C_{11}H_{20}NO_6$ (M^+ + 1): 262.1281. Found: 262.1291.

(3*R*,4*R*,5*R*)-1-(*tert*-Butoxycarbonyl)-3,4-isopropylidenedioxy-5-methoxymethyl-2-pyrrolidinone (6) A mixture of **5** (120 mg, 0.46 mmol) and 2,2-dimethoxypropane (1 ml) in acetone (1 ml) was stirred in the presence of a catalytic amount of *p*-TsOH at room temperature for 1.5 h. After dilution with AcOEt, the mixture was washed with saturated aqueous $NaHCO_3$ and half-saturated NaCl. Drying, followed by evaporation and purification of the residue by column chromatography (silica gel, AcOEt : hexane = 1 : 3), gave **6** (110 mg, 80% yield) as an oil, $[\alpha]_D^{20}$ −91.1° (c = 1, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1791, 1792, 1716. ^{1}H-NMR ($CDCl_3$): 1.38 (3H, s, CH_3), 1.46 (3H, s, CH_3), 1.56 (9H, s, *tert*-Bu), 3.32 (3H, s, OCH_3), 3.63 (2H, m, CH_2), 4.28 (1H, m, CH), 4.52 (1H, d, J = 5.4 Hz, CH), 4.68 (1H, d, J = 5.4 Hz, CH). ^{13}C-NMR ($CDCl_3$): 25.53 (q), 27.00 (q), 27.87 (q), 59.35 (q), 60.18 (d), 70.76 (t), 75.38 (d), 77.92 (d), 83.47 (s), 111.79 (s), 150.68 (s), 171.14 (s). HR-MS m/z: Calcd for $C_{14}H_{23}NO_6$ (M^+): 301.1526. Found: 301.1552.

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