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An expedient synthesis of D-callipeltose

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Abstract—Methyl D-callipeltose 12 and D-callipeltose 4 were synthesized from D-glucal 5 in 10 and 11 steps, respectively. The synthesis features an azide displacement reaction of an α-nosyloxy ketone 7 and a highly diastereoselective C-methylation of α-azido ketone 8. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Callipeltoside A 1 belongs to a new class of cyclodepsipeptides called callipeltins. The molecules were isolated in 1996 from the shallow water lithistid sponge Callipelta sp., a native of New Caledonia.1,2 They were found to inhibit in vitro proliferation of KB and P338 cells and to protect cells infected with HIV. Structurally, 1 consists of a macrocyclic lactone linked to a unique dienyne cyclopropane side chain and the deoxy amino sugar, callipeltose, 4 (Fig. 1). The absolute stereochemistry of the molecule has not been established.

There has been considerable synthetic interest in 1 although no total synthesis has been reported to date.3–7 The deoxy amino sugar 4 contains an unusual five-membered oxazolidinone ring fused to the sugar backbone at positions 3 and 4. Both enantiomers of 4 have been synthesized—methyl L-callipeltose in 10 steps from L-rhamnose8 and methyl D-callipeltose in 14 steps from methyl D-mannose.9 Herein we report an expedient synthesis of α-D-callipeltose 4 from D-glucal 5.

2. Results and discussion

The α,β-unsaturated ketone 6 was synthesized from D-glucal in three steps (Scheme 1).10 A sequence of tosylation (TsCl, pyr.)11 and reduction with LiAlH412,13 effected deoxygenation of the 6-position of D-glucal 5.
Scheme 1. Synthesis of α-callipeltose. Reagents and conditions: (a) TsCl, py, CH₂Cl₂, 0°C→rt, 78%; (b) LiAlH₄, THF, Δ, 59%; (c) MnO₂, CH₂Cl₂, rt, 66%; (d) NsCl, py, CH₂Cl₂, 0°C→rt, 80%; (e) n-Bu₃N⁺, CH₂Cl₂, 0°C→rt, 95%; (f) MeLi, THF, −100°C, 77%; (g) m-CPBA, NaHCO₃, MeOH, 0°C→rt, 60%; (h) MeI, Ag₂O, EtOAc, rt, 62%; (j) t-BuOK, THF, 0°C→rt, 69%; (k) 2 M H₂SO₄ in 1:1 H₂O/dioxane, 60–70°C, 48%. Rt = room temperature, NsCl = nosyl chloride, py = pyridine, m-CPBA = m-chloroperbenzoic acid, Boc = t-butoxycarbonyl.

The resulting D-rhamnal was oxidized with MnO₂ to give α,β-unsaturated ketone 6. The next task was to introduce a nitrogen atom at the 4-position of the sugar by azide displacement of a suitable leaving group.

For this purpose, several leaving groups, including mesylate, triflate, imidazolyl sulfonate, were examined, but only the nosylate group could be displaced at an acceptable rate without decomposition. The nosylate 7 was obtained by the action of nosyl chloride and pyridine on the carbonyl, and the electronegativity of the nitrogen posed azide group prevents attack from the opposite face of the ketone. Reaction of the newly created alcohol with MeI and Ag₂O furnished the desired azide 8 in 90% yield along with 5% of its C-(4) epimer. Sodium azide was found to be too basic for the displacement reaction; stirring overnight in DMSO with NaN₃ at room temperature gave, in addition to recovered starting material, ca. 1:1 mixture of both epimers of 8, presumably due to product enolization. However, tetra-n-butylammonium azide furnished the desired azide 8 in 90% yield along with 5–10% of its C-(4) epimer. The C-methylation with methyllithium in THF at −100°C gave the tertiary alcohol 9 in 77% yield as a single diastereomer. The observed selectivity is rationalized through a synergy of steric and stereoelectronic considerations, as described in Fig. 2: the axially disposed azide group prevents attack from the Re face of the carbonyl, and the electronegativity of the nitrogen favors attack from the opposite (Si) face.

The next objective was to install the final two stereocenters of the sugar. Epoxidation accompanied by concomitant stereo- and regioselective opening of the epoxide is a useful method to functionalize the double bond in glucals. Thus, reaction of 9 with m-CPBA in methanol in the presence of NaHCO₃ led to the stereoselective formation of 10 in 60% yield. Methylation of the newly created alcohol with MeI and Ag₂O cleanly alkylated the secondary hydroxyl group. Subsequent palladium-catalyzed hydrogenation reduced the azide to the corresponding amine, which, in the presence of Boc-anhydride, furnished amide 11, setting the stage for the oxazolidinone ring closure. Thus, exposure of the tertiary alcohol 11 to potassium t-butoxide in THF, following the procedure of Davies et al., furnished the methyl glycoside 12. Finally, the glycoside was hydrolyzed with 2 M sulfuric acid in water/dioxane (1:1) at 60°C, concluding the synthesis of D-callipeltose 4 in 11 steps from commercially available D-glucal 5.

3. Conclusion

In conclusion, methyl D-callipeltose 12 and D-callipeltose 4 were synthesized in a highly selective manner starting from D-glucal 5 in 10 and 11 steps, respectively. Key features of this synthesis, the shortest reported to date for 4, include: (i) readily available starting materials; (ii) use of an α-nosyloxy ketone 7 en route to azide 8; and (iii) a highly diastereoselective C-methylation rationalized in Fig. 2.

4. Experimental

All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, if
necessary. Anhydrous solvents were obtained by passing them through commercially available activated alumina columns. Yields refer to chromatographically and spectroscopically (1H NMR) homogeneous materials, unless otherwise stated. All reagents were purchased at highest commercial quality and used without further purification, unless otherwise stated. All reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and acidic PMA (2.5% phosphomolybdic acid, 1.5% phosphoric acid and 5% sulfuric acid in water) or 1% aqueous potassium permanganate solution and heat as developing agents. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. NMR spectra were recorded on Bruker DRX-600, DRX-500 or AMX-400 instruments and calibrated using residual undeuterated solvents as an internal reference (CDCl3, 7.26 ppm, MeOH 3.34 ppm). The following abbreviations are used to explain the multiplicities: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; b = broad. IR spectra were recorded on a Perkin–Elmer 1600 series FT-IR spectrometer. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter. High resolution mass spectra (HRMS) were recorded on an IonSpec mass spectrometer under MALDI-FTMS conditions with NBA or DHB as the matrix. Low resolution mass spectra were recorded on a Hewlett Packard 5971A benchtop GC/MS. Melting points (mp) are uncorrected and were recorded on a Thomas–Hoover Unimelt capillary melting point apparatus.

### 4.1. d-Rhamnal

To a stirred solution of D-glucal 5 (2.50 g, 17.1 mmol) in pyridine (42 mL) and CH2Cl2 (42 mL), cooled at 0°C, was added tosyl chloride (4.89 g, 25.7 mmol) and the cooling bath was removed. After stirring for 2.5 h at ambient temperature, the reaction mixture was cooled again to 0°C, quenched with water (5 mL) and stirred for 30 min. More water (20 mL) was added, the organic layer was separated and washed with sat. aq. CuSO4 (3×20 mL) and water (3×20 mL). The combined aqueous phases (excluding the first water layer) were extracted with CH2Cl2 (2×20 mL) and those organic extracts were washed with water (2×10 mL). The combined organic extracts were washed with brine (20 mL), dried (Na2SO4), filtered and concentrated to provide crude 6-O-tosyl-d-glucal as a yellow oil (3.99 g, 78% yield). Rf 0.55 (EtOAc); 1H NMR (400 MHz, CDCl3) δ 7.81 (d, J = 8.2 Hz, 2H), 7.36 (d, J = 8.2 Hz, 2H), 6.24 (dd, J = 6.1, 1.6 Hz, 1H), 4.74 (dd, J = 6.1, 2.1 Hz, 1H), 4.48 (dd, J = 11.4, 3.8 Hz, 1H), 4.27 (app. d, J = 11.4 Hz, 2H), 3.91 (ddd, J = 10.0, 3.8, 2.1 Hz, 1H), 3.77 (dd, J = 10.0, 7.3 Hz, 1H), 2.45 (s, 3H).

To a stirred solution of 6-O-tosyl-d-glucal (3.99 g, 13.3 mmol) in THF (30 mL) at 0°C was added LiAlH4 (0.9 M solution in THF, 44.2 mL, 39.9 mmol) dropwise and the reaction mixture was heated to reflux. After stirring the reaction for 1 h, the mixture was cooled to 0°C and quenched slowly with H2O (1.5 mL), 15% NaOH (1.5 mL) and H2O (4.5 mL). The resulting slurry was diluted with EtO, filtered through a pad of Celite (EtO rinse) and concentrated. Purification by dry-column flash chromatography (silica, 20–100% EtOAc/hexanes) provided d-rhamnal as a white solid (1.02 g, 59% yield). Rf 0.37 (EtOAc); mp 72–73°C (EtOAc/hexanes) (lit.35 71–73°C (EtOAc/hexanes)); 1H NMR (500 MHz, CDCl3) δ 6.32 (dd, J = 6.0, 1.6 Hz, 1H), 4.72 (dd, J = 6.0, 2.2 Hz, 1H), 4.21 (app. d, J = 6.3 Hz, 1H), 3.87 (dq, J = 9.8, 6.3 Hz, 1H), 3.43 (app. t, J = 8.6 Hz, 1H), 1.39 (d, J = 6.3 Hz, 3H).

### 4.2. 1,5-Anhydro-2,6-dideoxy-ð-erythro-hex-1-enitol-uloside 6

To a stirred solution of d-rhamnal (100 mg, 0.768 mmol) in CH2Cl2 (7.5 mL) at room temperature was added MnO2 (200 mg, 2.30 mmol). After 3 h, more MnO2 (200 mg, 2.30 mmol) was added and the stirring was continued. After 15 h, the reaction mixture was diluted with CH2Cl2 (10 mL), filtered through a pad of Celite (EtOAc rinse) and concentrated. Purification by flash chromatography (silica, 40–50% EtOAc/hexanes) provided 65 mg of 6 as a white volatile solid (66% yield). Rf 0.66 (EtOAc); mp 91–92°C (EtOAc/hexanes) (lit.36 92–93°C); 1H NMR (500 MHz, CDCl3) δ 7.39 (app. d, J = 5.7 Hz, 1H), 5.46 (d, J = 5.7 Hz, 1H), 4.20 (dq, J = 12.9, 6.4, 0.7 Hz, 1H), 3.54 (s, 1H), 1.57 (d, J = 6.4 Hz, 3H).

### 4.3. 1,5-Anhydro-2,6-dideoxy-4-ð-nosyl-ð-erythro-hex-1-enitol-3-uloside 7

To a stirred solution of 6 (0.212 g, 1.65 mmol) in CH2Cl2 (8.0 mL) at 0°C were added pyridine (0.667 mL, 8.25 mmol) and nosyl chloride (0.733 g, 3.31 mmol). The reaction mixture was allowed to warm to room temperature over 2 h, and after stirring the mixture for a further 3 h more nosyl chloride (0.367 g, 1.66 mmol) and pyridine (0.667 mL, 8.25 mmol) were added. After 12 h the reaction mixture was cooled to 0°C and water (2 mL) was added. After stirring for 30 min more water (10 mL) was added, the aqueous layer was separated and extracted with CH2Cl2 (2×10 mL), the combined organic layers were washed with brine (5 mL), dried (Na2SO4), filtered and concentrated. Purification by dry-column flash chromatography (silica, 15–30% EtOAc/hexanes) provided 7 as a yellow crystalline solid (0.411 g, 80% yield). Rf 0.60 (50% EtOAc/hexanes); mp 93°C; [x]D +138.8 (c 1.07, CHCl3); IR (film) 3108, 1695, 1598, 1533, 1353, 1256, 1188, 1026, 854, 780 cm−1; 1H NMR (500 MHz, CDCl3) δ 8.39 (app. d, J = 9.2 Hz, 2H), 8.19 (app. d, J = 9.2 Hz, 2H), 7.35 (d, J = 5.9 Hz, 1H), 5.37 (d, J = 5.9 Hz, 1H), 5.02 (d, J = 12.1 Hz, 1H), 4.54 (dq, J = 12.1, 6.2 Hz, 1H), 1.63 (d, J = 6.2 Hz, 3H); 13C NMR (125 MHz, CDCl3) δ 180.0, 163.5, 150.8, 142.1, 129.7, 124.1, 105.0, 79.6, 77.4, 17.4; HRMS (MALDI) calcd for C12H11NO7S (M+) m/z: 313.0256, found 313.0286.
4.4. 1,5-Anhydro-4-azido-2,6-dideoxy-\(\alpha\)-threo-hex-1-enitol-3-ulose \(8\)

To a stirred solution of \(7\) (190 mg, 0.606 mmol) in CH\(_2\)Cl\(_2\) (3.3 mL) at 0°C was added \(n\)-Bu\(_4\)N\(_2\)O (0.651 g, 2.29 mmol) \[CAUTION\] in CH\(_2\)Cl\(_2\) (0.5 mL) via cannula. The reaction mixture was allowed to warm to room temperature for 1 h. Water (5 mL) was added, the aqueous layer was extracted with CH\(_2\)Cl\(_2\) (2×10 mL), the combined organic extracts were washed with brine (5 mL) and dried (Na\(_2\)SO\(_4\)), filtered and concentrated. Purification by dry-column flash chromatography (silica, 10–20\% EtOAc/hexanes) provided \(8\) as a yellow oil (88 mg, 95\% yield). \(R\_f\) 0.43 (33\% EtOAc/hexanes); \([\alpha]_D^\text{20°}\) = –78.0 (c 0.383, CHCl\(_3\)); IR (film) 3378, 2919, 2106, 1675, 1593, 1414, 1274, 1050 cm\(^{-1}\); \(1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.37 (d, \(J = 6.0\) Hz, 1H), 4.53 (qd, \(J = 6.6, 3.1\) Hz, 1H), 3.81 (d, \(J = 3.1\) Hz, 1H), 1.48 (d, \(J = 6.6\) Hz, 3H); \(13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 187.1, 163.6, 104.9, 76.9, 63.8, 15.3; HRMS (MALDI) calcd for \(C_7H_8NO_2\) (MH\(^+\)) \(m/z\): 126.0550, found 126.0549.

4.5. 1,5-Anhydro-4-azido-2,6-dideoxy-3-C-methyl-\(\alpha\)-lyxo-hex-1-enitol \(9\)

To a stirred solution of \(8\) (95 mg, 0.620 mmol) in THF (3.1 mL) at \(–100^\circ\)C was added MeLi (1.5 M solution in THF) (0.417 mL) \(0.967\) mmol). The reaction mixture was protected from light and heated to reflux. After stirring under reflux for 5 h, the reaction was diluted with EtOAc (10 mL), filtered through a pad of Celite (EtOAc rinse) and concentrated. Purification by flash chromatography (silica, 5–15\% EtOAc/hexanes) provided the azidomethyl glycoside as an oil (53 mg, 72\% yield). \(R\_f\) 0.33 (33\% EtOAc/hexanes); \([\alpha]_D^\text{20°}\) +164.8 (c 0.708, CHCl\(_3\)); IR (film) 3483, 2931, 1455, 1349, 1102, 1055, 597 cm\(^{-1}\); \(1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 6.0 Hz, 1H), 4.00 (qd, \(J = 6.5, 1.6\) Hz, 1H), 3.72 (d, \(J = 1.0\) Hz, 1H), 3.49 (s, 3H), 3.36 (s, 3H), 3.11 (br s, 1H) 2.90 (s, 1H), 1.40 (d, \(J = 1.0\) Hz, 3H), 1.35 (d, \(J = 6.5\) Hz, 3H); \(13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 98.4, 82.0, 70.1, 69.6, 64.3, 59.8, 55.2, 24.5, 17.9; HRMS (MALDI) calcd for \(C_6H_11NO_2\) (M+Na\(^+\)) \(m/z\): 254.1111, found 254.1112.

4.6. Methyl 4-azido-4,6-dideoxy-3-C-methyl-\(\alpha\)-d-talo-pyranoside \(10\)

To a stirred solution of \(9\) (76 mg, 0.601 mmol) in THF (0.50 mL) at 0°C was added \(t\)-BuOK (0.9 M solution in THF, 0.204 mL, 0.183 mmol) dropwise and
the cooling bath was removed. After 4 h at room temperature more t-BuOK (0.051 mL, 0.46 mmol) was added. After 1 h sat. aq. NH₄Cl (1 mL) was added, the aqueous layer was extracted with EtOAc (2×5 mL), the combined organic extracts were washed with brine (5 mL) and dried (Na₂SO₄), filtered and concentrated. Purification by flash chromatography (silica, 1–3% MeOH/CH₂Cl₂) provided 15 mg of 12 as a white solid (69% yield). Rᵣ 0.28 (5% MeOH/CH₂Cl₂); mp 145–146°C (hexanes) (lit. 8 147–148°C); [ξ]D +91.6 (c 1.06, CHCl₃) (lit. 9 [ξ]D +76 (c = 1.0, CHCl₃); IR (film) 3295, 2931, 1747, 1376, 1267, 1104, 1060, 670 cm⁻¹; ¹H NMR (500 MHz, MeOH-d₄) δ 4.48 (d, J = 6.1 Hz, 1H), 3.94 (qd, J = 6.5, 2.0 Hz, 1H), 3.52 (s, 3H), 3.45 (d, J = 2.0 Hz, 1H), 3.41 (s, 3H), 3.38 (d, J = 6.1 Hz, 1H), 1.50 (s, 3H), 1.12 (d, J = 6.5 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 159.1, 101.6, 81.9, 81.1, 63.7, 61.4, 60.6, 55.0, 23.3, 15.6; HRMS (MALDI) calcd for C₁₀H₁₆NO₂Na (M+Na⁺) m/z: 254.0999, found 254.1001.

4.10. α-d-Callipeltose 4

A solution of 12 (4.3 mg, 0.186 mmol) in H₂SO₄ (2 M in H₂O/1,4-dioxane (1:1), 0.20 mL) was heated to 60°C for 30 h. Saturated aq. NaHCO₃ (1 mL) was added, the solution was saturated with NaCl and extracted with 25% EtOH/CHCl₃ (20×1 mL). The combined organic extracts were washed with brine and dried (Na₂SO₄), filtered and concentrated. Purification by flash chromatography (silica, 5% MeOH/CH₂Cl₂) afforded d-callipeltose 4 as a film (1.9 mg, 48% yield). Rᵣ 0.13 (5% MeOH/CH₂Cl₂); [ξ]D +25.3 (c 0.150, CHCl₃); IR (film) 3313, 2924, 1737, 1449, 1273, 1261, 1061, 667 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.56 (s, 1H), 5.13 (d, J = 5.9 Hz, 1H), 4.06 (qd, J = 6.5, 1.9 Hz, 1H), 3.60 (s, 3H), 3.38 (d, J = 1.9 Hz, 1H), 3.24 (d, J = 5.9 Hz, 1H), 2.99 (br s, 1H), 1.56 (s, 3H), 1.17 (d, J = 6.5 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 158.3, 95.0, 81.9, 81.8, 63.6, 61.3, 60.8, 23.3, 15.8; HRMS (MALDI) calcd for C₁₀H₁₆NO₂Na (M+Na⁺) m/z: 240.0842, found 240.0843.

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References

10. On a larger scale, d-glucal can be prepared from tri-O-acetyl-d-glucal by saponification of the three acetyl groups with K₂CO₃ in MeOH.