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Note

Synthesis of methyl α-L-callipeltoside

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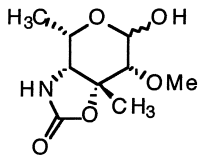
Abstract

The synthesis of callipeltose, a novel amino sugar with the proposed structure, 4-amino-4,6-dideoxy-2,*O*-3-*C*-dimethyl-L-talopyranosyl-3,4-urethane, from L-rhamnose is described. Oxime reduction, carbamate cyclization and selective methylation are key steps. The synthesis supports the assignment of the relative stereochemistry of callipeltose.

Keywords: Callipeltose; Methyl α-L-callipeltoside

Callipeltins are a new class of cyclodepsipeptides recently isolated by Minale and co-workers from the marine sponge *Callipelta* sp. Extracts of the sponge were found to inhibit in vitro proliferation of KB and P388 cells and to protect cells infected with HIV. Further studies of the same extract led to the isolation of three biologically active macrolides, callipeltosides A–C, which consist of a macrocyclic lactone linked to a dienyne cyclopropane side chain [1]. The novel macrocycle is also linked, in each case, to a different deoxy sugar. In callipeltoside A, the carbohydrate component is a new amino sugar whose structure has been proposed as 4-amino-4,6-dideoxy-2,*O*-3-*C*-dimethyl-L-talopyranosyl-3,4-urethane (**1**). Callipeltoside B contains an analogous *N*-formyl amino sugar **2**, while the authors have proposed that callipeltoside C contains 6-deoxy-2,*O*-3-*C*-dimethyl-β-mannopyranose (**3**) [2]. The 2-hydroxy, D-form of **3** is known as evalose and is found in the oligosaccharide antibiotic everninomicin [3] B; however, only the relative configurations of the carbohydrates found in callipeltosides A–C have been established.

The synthesis of callipeltose (**1**) has not been reported. As part of our ongoing efforts to synthesize carbohydrate components of antibiotics, we have synthesized methyl α-L-callipeltoside **11** from L-rhamnose. The ^{1}H NMR data obtained for **11** match that assigned for the carbohydrate component in the naturally occurring glycoside, providing confirmation of the structure proposed.



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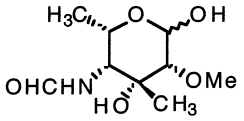

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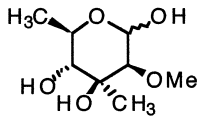

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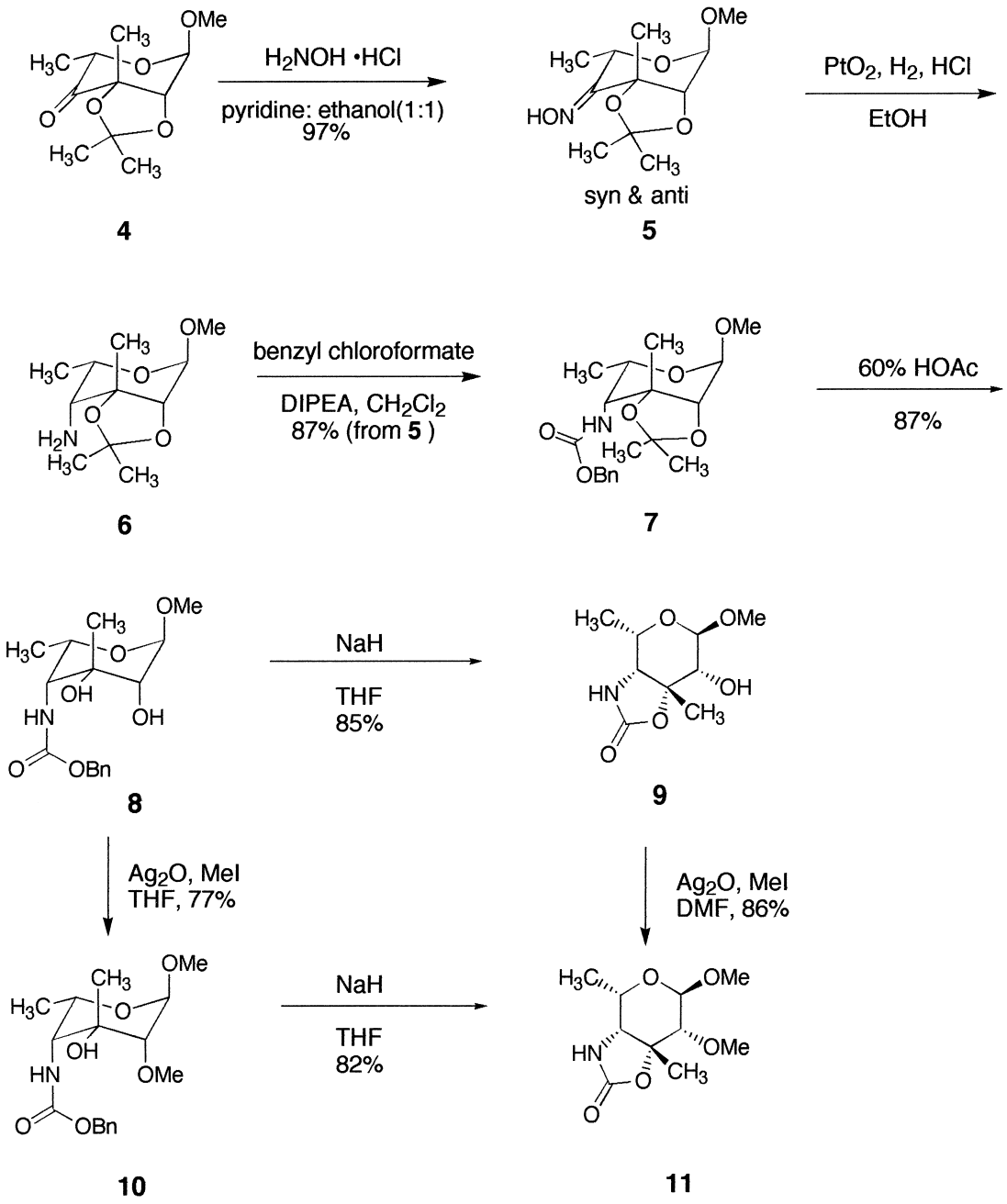
The 3-*C*-methyl branched sugar **4** was prepared from methyl α-L-rhamnopyranoside [4] as described by Klemer [5], by alkylation of the lithium enolate of methyl 6-deoxy-2,3-*O*-isopropylidene-α-L-*lyxo*-hexopyranoside-4-ulose. The resulting 3-*C*-methyl-branched derivative was converted to the oxime **5** (Scheme 1), which was previously synthesized [6] by Yoshimura and co-workers as a precursor to the amino sugar sibirosamine. Reduction of the oxime was attempted using the method described by the authors, with hydrogen in the presence of 10% palladium-on-charcoal, to give the product with the L-*talo* configuration. We observed that reduction of **5** under these conditions proved to be extremely slow. The use of reduced platinum oxide as the catalyst resulted in facile reduction to give amino sugar **6**, which was isolated as its benzyl carbamate derivative **7** in 87% yield. Consistent with the previously reported results, the reduction of the oxime occurred with complete stereoselectivity to give **8** as the only isomer. Partial cleavage of the isopropylidene group



4 **5** **6** **7** **8** **9** **10** **11**

Scheme 1. Synthesis of methyl α-L-callipeltoside.

occurred during reduction to give diol **8**, which could be separated for purposes of characterization of both **7** and **8**. Products resulting from transglycosylation with solvent (ethanol) were not observed. Treatment of the crude reduction product with 60% acetic acid resulted in complete removal of the isopropylidene group. Completion of the synthesis of callipeltose required selective methylation of the C-2 hydroxyl group in the presence of the carbamate nitrogen and cyclization. The conditions used for these transformations proved to be problematic, owing to the propensity of the nitrogen to undergo alkylation. The cyclization of **8** to **9** occurred efficiently in the presence of sodium hydride, using conditions described by Sugawara and Narisada [7] for a different system. However, **9** underwent conversion to its *N*-methyl derivative when treated with sodium hydride and one equivalent of iodomethane. It was found that methylation of either **8** or **9** occurred selectively using silver oxide and iodomethane in DMF [6,8] to give the corresponding 2-*O*-methyl derivatives **10** and **11**. Methylation of **8** stopped short of completion, and the formation of side products was observed. The yield of 77% for this step is based on recovered starting material. Methylation of **9** occurred more cleanly to give methyl α-L-callipeltoside **11**. The ^{1}H NMR spectrum of **11** was remarkably similar to that reported for the carbohydrate in the natural glycoside. A comparison is given in Table 1. These data support the original assignment of relative stereochemistry for callipeltose.

1. Experimental

General methods.—^{1}H NMR spectra were recorded on a Varian XL 300 spectrometer at 300 MHz with Me_4Si as an internal reference in $CDCl_3$, unless otherwise noted. ^{13}C NMR spectra were recorded on a Varian XL 300 spectrometer at 75 MHz and referenced with $CDCl_3$. Melting points were determined in an open capillary tube with a Thomas–Hoover apparatus and are uncorrected. TLC analyses were conducted on silica gel (Kieselgel 60 F_{254}, E. Merck) glass plates and visualized by $UV_{254\,nm}$ or with ammonium molybdate–ceric sulfate reagent. Column chromatography was carried out with J. T. Baker's silica gel. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter as $[\alpha]_D$ values at 23 °C. Elemental analysis were carried out at Merck Research Laboratories. High-resolution mass spectra were measured at Merck Research Laboratories using ES-FT/ICR/MS with propylene glycol as internal standard on a Bruker ES-FT mass spectrometer.

*Methyl 4-(benzyloxycarbonylamino)-4,6-dideoxy-2,3-*O*-isopropylidene-3-*C*-methyl-*α*-*L*-talopyranoside* (**7**). A solution of methyl 6-deoxy-2,3-*O*-isopropylidene-3-*C*-methyl-α-L-*lyxo*-hexopyranosid-4-ulose oxime[5] (**5**, 3.1 g) in 95% ethanol (120 mL) containing HCl (1 M, 25 mL) and platinum(IV) oxide (1.4 g) was shaken on a Parr apparatus for 48 h. The reaction was filtered over Celite and was made neutral with basic ion-exchange resin (hydroxide, 6 g) and was again filtered through Celite. The reaction mixture was concentrated

Table 1
Comparison of NMR data for methyl α-L-callipeltoside and the carbohydrate portion of callipeltoside A

	Methyl α-L-callipeltoside	Callipeltoside A
H-1	4.74 (d, *J* 6.1 Hz)	4.48 (d, *J* 6.2 Hz)
H-2	3.42 (d, *J* 6.1 Hz)	3.39 (d, *J* 6.2 Hz)
H-4	3.48 (d, *J* 1.7 Hz)	3.46 (d, *J* 1.7 Hz)
H-5	3.99 (dq, *J* 6.5, 1.7 Hz)	3.94 (dq, *J* 6.4, 1.7 Hz)
H-6	1.12 (d, *J* 6.5 Hz)	1.12 (d, *J* 6.4 Hz)
3-CH_3	1.54 (s)	1.50 (s)
2-OCH_3	3.63 (s)	3.53 (s)
C-1	103.6	103.5
C-2	83.2	82.3
C-3	83.8	83.7
C-4	62.7	62.6
C-5	65.3	65.5
C-6	15.9	15.9
3-CH_3	23.0	23.1
2-OCH_3	62.0	61.0
C=O	161.2	161.1

at reduced pressure, and the resulting methyl 4-amino-4,6-dideoxy-2,3-*O*-isopropylidene-3-*C*-methyl-α-L-talopyranoside (**6**) (2.9 g, 12.5 mmol) was dissolved in dichloromethane (60 mL) at 0 °C and treated with benzyl chloroformate (2.15 mL, 15.0 mmol) and diisopropylethylamine (3.1 mL, 17.6 mmol). The resulting solution was allowed to warm to ambient temperature for 1.5 h, after which time it was diluted with dichloromethane (50 mL) and poured into satd aq $NaHCO_3$ (50 mL). The layers were separated, and the aqueous layer was extracted again with dichloromethane (30 mL). The organic layers were combined, dried (Na_2SO_4), filtered and concentrated at reduced pressure. The resulting oil was purified by flash chromatography on silica gel with 1:4 ethyl acetate–hexane to give 3.3 g of a colorless oil as well as 0.60 g of the 2,3-deprotected product (87%): $[\alpha]_D$ −37.4° (*c* 1.00; chloroform); R_f 0.82 in 1:1 hexanes–ethyl acetate; ^{1}H NMR (300 MHz) δ 7.40–7.25 (m, 5 H, Ar), 5.18 (br. d, $J_{NH,4}$ 10.3 Hz, 1 H, NH), 5.12 (d, *J* 2.5 Hz, 2 H, $PhCH_2$), 4.85 (s, 1 H, H-1), 3.97 (br q, $J_{5,6}$ 6.6 Hz, 1 H, H-5), 3.71 (s, 1 H, H-2), 3.52 (br d, $J_{NH,4}$ 10.4 Hz, 1 H, H-4), 3.37 (s, 3 H, OCH_3), 1.47 (s, 3 H, 3-CH_3), 1.34, 1.39 (each s, 3 H, CH_3), 1.21 (d, $J_{5,6}$ 6.5 Hz, 3 H, H-6); ^{13}C NMR (75 MHz) δ 155.64 (C=O), 127.86, 128.02, 128.09 (Ar), 135.52 (Ar ipso), 108.46 (Cq, acetal), 98.37 (C-1), 77.77 (C-2), 66.62 ($PhCH_2$), 63.27 (C-5), 57.55 (C-3), 56.22 (C-4), 54.84 (OCH_3), 25.38, 25.87 (2xCH_3), 24.62 (3-CH_3), 17.28 (C-6). HRMS: Calcd for $C_{19}H_{28}NO_6$ (M+1), 366.1911. Found, 366.1917.

*Methyl 4-(benzyloxycarbonylamino)-4,6-dideoxy-3-*C*-methyl-α-*L*-talopyranoside* (**8**). A stirred solution of methyl 4-(benzyloxycarbonylamino)-4,6-dideoxy-2,3-*O*-isopropylidene-3-*C*-methyl-α-L-talopyranoside (700 mg) in 60% acetic acid (15 mL) was heated at 70–75 °C for 13 h. The reaction mixture was then concentrated at reduced pressure to yield an amber oil that was concentrated from toluene (3 mL) twice. The resulting oil was purified by flash chromatography on silica gel (200 g) with 2:3 ethyl acetate–hexane to give 540 mg of a colorless oil which crystallized on standing (87%): mp 111–113 °C; $[\alpha]_D$ −72.5° (*c* 1.13, chloroform); R_f 0.31 in 1:1 hexanes–ethyl acetate; ^{1}H NMR (300 MHz) δ 7.38–7.25 (m, 5 H, Ar), 5.85 (br d, $J_{NH,4}$ 10.3 Hz, 1 H, NH), 5.10 (AB_q, *J* 21.3 Hz, 12.2 Hz, 2 H, $PhCH_2$), 4.71 (s, 1 H, H-1), 4.03 (br q, $J_{5,6}$ 6.6 Hz, 1 H, H-5), 3.55 (br d, $J_{NH,4}$ 10.3 Hz, 1 H, H-4), 3.39 (br s, 1 H, H-2), 3.34 (s, 3 H, OCH_3), 1.40 (s, 3 H, 3-CH_3), 1.17 (d, $J_{5,6}$ 6.5 Hz, 3 H, H-6); ^{13}C NMR (75 MHz) δ 157.65 (C=O), 136.33 (Ar ipso), 127.83, 127.91, 128.28, 128.33 (Ar), 101.39 (C-1), 72.75 (C-2), 69.28 (C-3), 66.80 ($PhCH_2$), 64.26 (C-5), 58.59 (C-4), 55.11 (OCH_3), 24.39 (3-CH_3), 17.05 (C-6). Anal. Calcd for $C_{16}H_{23}NO_6$: C, 59.07; H, 7.13, N, 4.30. Found: C, 58.87; H, 7.16; N, 4.20.

*Methyl 4-amino-3-*O*,4-*N*-carbonyl-4,6-dideoxy-3-*C*-methyl-α-*L*-talopyranoside* (**9**). A stirred solution of methyl 4-(benzyloxycarbonylamino)-4,6-dideoxy-3-*C*-methyl-α-L-talopyranoside (500 mg, 1.54 mmol) in tetrahydrofuran (14 mL) under nitrogen was cooled to 0 °C. To this solution was added sodium hydride (44 mg, 1.84 mmol) in one portion, and the resulting suspension was allowed to warm to ambient temperature for 1.5 h. The reaction was quenched with satd aq $NaHCO_3$ (5 mL), and the resulting mixture was extracted with ethyl acetate (6×30 mL). The organic layers were combined, dried (Na_2SO_4), decanted, and concentrated at reduced pressure to yield a solid. This solid was triturated with ethyl ether (5 mL) and filtered to yield 297 mg of a white powder (89%): mp 234–236 °C; $[\alpha]_D$ −87.5° (*c* 0.92; methanol); R_f 0.38 in 95:5 ethyl acetate–methanol; ^{1}H NMR (300 MHz, CD_3OD) δ 4.41 (d, 1 H, H-1), 3.93 (dq, 1 H, H-5), 3.65 (d, $J_{1,2}$ 6.3 Hz, 1 H, H-2), 3.45 (d, $J_{4,5}$ 1.7 Hz, 1 H, H-4), 3.40 (s, 3 H, OCH_3), 1.49 (s, 3 H, 3-CH_3), 1.11 (d, $J_{5,6}$ 6.4 Hz, 3 H, H-6); ^{13}C NMR (75 MHz, CD_3OD) δ 161.1 (CO), 103.8 (C-1), 83.9 (C-3), 73.0 (C-2), 65.5 (C-5), 62.7 (C-4), 55.7 (OCH_3), 23.2 (3-CH_3), 16.0 (C-6). Anal. Calcd for $C_9H_{15}NO_5$: C, 49.76; H, 6.96; N, 6.45. Found: C, 49.36; H, 6.76; N, 6.26.

*Methyl 4-amino-3-*O*,4-*N*-carbonyl-4,6-dideoxy-3-*C*,2-*O*-dimethyl-α-*L*-talopyranoside* (**11**). To a stirring solution of methyl 4-amino-3-*O*,4-*N*-carbonyl-4,6-dideoxy-3-*C*-methyl-α-L-talopyranoside (50 mg, 0.23 mmol) in *N*,*N*-dimethylformamide (0.5 mL) was added silver oxide (213 mg, 0.92 mmol) and iodomethane (143 μL, 2.3 mmol), and the resulting mixture was warmed at 40–45 °C for 20 h. The reaction mixture was allowed to cool to room temperature and was then diluted with ethyl acetate and filtered through Celite. The resulting clear solution was washed with deionized water (2 mL) and extracted with ethyl acetate (5×5 mL). The organics were combined, dried (Na_2SO_4), decanted, and concentrated at reduced pressure to yield 46 mg of a white solid (86%): mp 147–148 °C; $[\alpha]_D$ = −88.5° (*c* 0.76; methanol); R_f

0.49 in 95:5 ethyl acetate–methanol; ^{1}H NMR (300 MHz, CD_3OD) δ 4.48 (d, $J_{1,2}$ 6.2 Hz, 1 H, H-1), 3.94 (dq, $J_{4,5}$ 1.7 Hz, $J_{5,6}$ 6.4 Hz, 1 H, H-5), 3.53 (s, 3 H, 2-OCH_3), 3.46 (d, $J_{4,5}$ 1.7 Hz, 1 H, H-4), 3.40 (s, 3 H, 1-OCH_3), 3.39 (d, $J_{1,2}$ 6.2 Hz, 1 H, H-2), 1.50 (s, 3 H, 3-CH_3), 1.12 (d, $J_{5,6}$ 6.4 Hz, 3 H, H-6); ^{13}C NMR (75 MHz, CD_3OD) δ 161.1 (CO), 103.5 (C-1), 83.7 (C-3), 82.3 (C-2), 65.5 (C-5), 62.6 (C-4), 61.0 (2-OCH_3), 55.2 (1-OCH_3), 23.1 (3-CH_3), 15.9 (C-6). Anal. Calcd for $C_{10}H_{17}NO_5$: C, 51.94; H, 7.41; N, 6.06. Found: C, 52.13; H, 7.06; N, 5.93. HRMS: Calcd for $C_{10}H_{18}NO_5$ (M + 1): 232.1182. Found: 232.1179.

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