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Note

Synthesis of methyl α-L-vancosaminide

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Abstract

The synthesis of methyl α-L-vancosaminide from di-*O*-acetyl-L-rhamnal is described. The allylic alcohol methyl 2,3,6-trideoxy-3-*C*-methyl-α-L-*threo*-hex-2-enopyranoside was prepared from the glycal, 1,5-anhydro-1,2,6-trideoxy-3-*C*-methyl-L-*ribo*-hex-1-enitol, and converted to its *N*,*N*-dimethylisourea derivative. The *cis* amino alcohol functionality in vancosamine was introduced by the electrophilic cyclization of the isourea, followed by hydrolysis of the resulting oxazoline.

Keywords: Vancosamine; Methyl α-L-vancosaminide; Isourea cyclization

The amino sugar L-vancosamine [1], its C-3 epimer [2], and its 4-keto derivative [3] are found in the glycopeptide antibiotics vancomycin, A35512B, and balhimycin, respectively, while *N*,*N*-dimethylvancosamine [4] occurs in kidamycin and related *C*-glycoside antibiotics. Vancomycin is an important drug used to treat antibiotic-resistant infections caused by Gram-positive bacteria [5]. The emergence of vancomycin-resistant strains of *Staphylococcus aureus* and *Enterococcus faecalis* has resulted in renewed interest in the chemistry and biology of this valuable antibiotic [6]. Of particular interest to our laboratory was the recent discovery that carbohydrate-modified derivatives of vancomycin are active against these resistant strains [7], a finding that clearly demonstrates that the glucose–vancosamine disaccharide of vancomycin is involved in the mechanism of action, and that carbohydrate modification by synthesis can be pursued as a means of developing useful vancomycin analogs [8,9].

The key problem in the synthesis of vancosamine and related 3-methyl branched amino and nitro sugars is the introduction of the functionality at the 3-position with the correct stereochemistry [10]. Several syntheses of vancosamine have been described from carbohydrate and non-carbohydrate precursors [11], the first being that reported in 1979 by Thang, Lukacs, and co-workers, which was based on the addition of HCN to a 3-keto sugar [12] and subsequent transformation of the cyanomesylate derivative to a spiroaziridine. In vancosamine and in other amino and nitro sugars in which the nitro or amino group is *cis* to an adjacent hydroxyl group, the electrophilic cyclization of allylic imidates [13], carbamates [14], or isoureas [15] has been an effective method for controlling the stereochemistry at the critical C-3 position (Eq. (1)) [16]. Hydrolysis of the resulting oxazoline provides the *cis* amino alcohol functionality.

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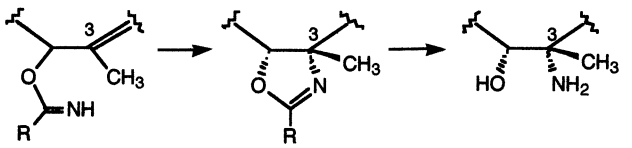
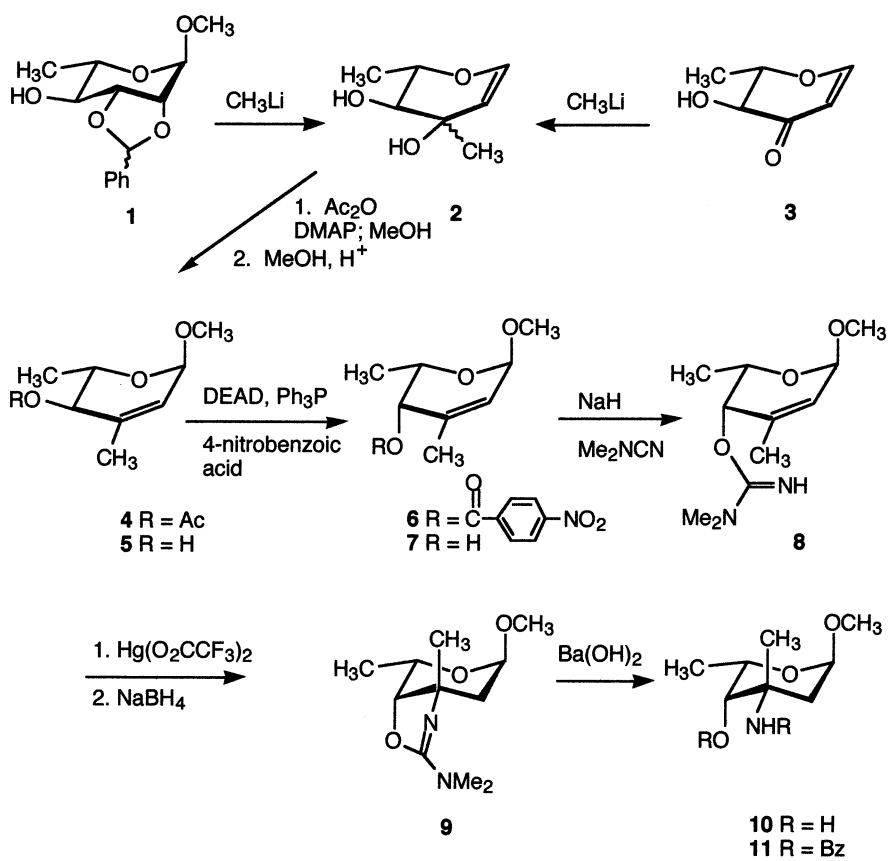


(1)

We have utilized this method with allylic *N*,*N*-dimethylisoureas (R = NMe_2) in the synthesis of the nitro sugars rubranitrose [15], decilonitrose [17], and kijanose [18]. For the synthesis of vancosamine, cyclization of allylic isourea **8** would be expected to produce the desired *lyxo* stereochemistry. In this paper, we report the stereoselective synthesis of methyl α-L-vancosaminide by the electrophilic cyclization of **8**, which was prepared from the 3-*C*-methyl glycal 1,5-anhydro-1,2,6-trideoxy-3-*C*-methyl-L-*ribo*-hex-1-enitol **2**.

Glycal **2** was synthesized by two different routes in this study. In one sequence, benzylidene acetal **1** [19] was prepared from methyl α-L-rhamnopyranoside and converted to **2** by the addition of excess methyllithium, as described by Jung and Klemer [20]. Alternatively, **2** was prepared by the addition of methyllithium to enone **3**, as reported by Thiem and Elvers [21]. Enone **3** was prepared from di-*O*-acetyl-L-rhamnal by deacetylation and oxidation with silver carbonate-on-Celite [22]. These two routes afforded **2** in overall yields of 44 and 34%, respectively. While the route from **1** is more efficient in terms of overall yield, we prefer the alternative synthesis of **2** from the enone, as it is more convenient to carry out.

Both routes provide glycal **2** as a mixture of epimers, with the *arabino* isomer being the major product in each case. This is of no consequence as both alcohols smoothly undergo acylation and Ferrier rearrangement in the presence of methanol to give allylic ester **4**, as described by Parker and Meschwitz [23] (Scheme 1). The β anomer of **4** is also obtained (α:β = 1:1); however, equilibration of the mixture in the presence of acid, as reported, provides α anomer **5** as the major product in 49% overall yield from glycal **2**.



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

Deacylation of **4** with ion-exchange resin gave the key allylic alcohol **5**, which is epimeric at C-4 with vancosamine. Inversion of configuration at C-4 in **5** was previously carried out by the Mitsunobu reaction by Dyong et al. [24]. Use of the Martin-modified Mitsunobu reaction [25], in which 4-nitrobenzoic acid in tetrahydrofuran was substituted for benzoic acid in benzene, gave **6** in similar yield, and enabled the labile nitrobenzoyl group to be cleaved by treatment with basic ion-exchange resin.

Treatment of allylic alcohol **7** with sodium hydride in neat dimethylcyanamide gave isourea **8** in 90% yield after purification by column chromatography on Florisil. The isourea was not stable, so the purified product was immediately subjected to the conditions for electrophilic cyclization. Treatment of **8** with mercuric trifluoroacetate followed by sodium borohydride gave oxazoline **9**. The complete regio- and stereoselectivity of this cyclization was consistent with that observed in previous studies with structurally related carbohydrate isoureas, and **9** was obtained as the single product in high yield. Hydrolysis of the oxazoline in refluxing saturated barium hydroxide solution provided methyl α-L-vancosaminide **10** in 93% yield. Conversion of **10** to the known dibenzoyl derivative **11** was carried out with benzoyl chloride in pyridine, and gave a product for which the ^{1}H NMR spectrum matched that reported [1a]. The synthesis of **10** from di-*O*-acetyl-L-rhamnal required a total of nine steps, with an overall yield of 6.5%. Synthetic transformations of **10** at the anomeric position and the amino group will be investigated in due course.

1. Experimental

General methods.—^{1}H NMR spectra were recorded on a Varian XL-300 MHz spectrometer with Me_4Si as an internal reference in $CDCl_3$ unless otherwise noted. ^{13}C NMR spectra were recorded on a Varian XL-300 MHz 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 F254, E. Merck) glass plates and visualized by W 254 nm or with ammonium molybdate–ceric sulfate reagent. Flash chromatography [26] was carried out with J.T. Baker silica gel. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter as $[\alpha]_D$ values at 23 °C. Elemental analyses 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 2,3,6-trideoxy-3-C-methyl-4-O-(4-nitrobenzoyl)-α-L-threo-hex-2-enopyranoside (**6**).—To a stirring soln of methyl 2,3,6-trideoxy-3-*C*-methyl-α-L-*erythro*-hex-2-enopyranoside **5** (1.3 g, 8.16 mmol) in anhyd THF (40 mL) under nitrogen was added PPh_3 (4.3 g, 16.3 mmol) and 4-nitrobenzoic acid (2.73 g, 16.3 mmol). To the resulting soln was added diethyl azodicarboxylate (2.6 mL, 16.3 mmol) over 15 min, and the reaction mixture was stirred for 18 h at room temperature (rt). The solvent was removed by concn at reduced pressure, and the resulting oil was diluted with diethyl ether (150 mL) and washed with satd aq $NaHCO_3$ (70 mL), then with satd aq NaCl (50 mL). The organic layer was dried ($MgSO_4$), filtered, and concd at reduced pressure. The resulting oil was purified by flash column chromatography over silica gel with 3:1 hexanes–EtOAc to yield 1.54 g of a white solid (61%): mp 122–124 °C; $[\alpha]_D$ +173° (*c* 1.02, $CHCl_3$); R_f 0.49 (1:3 EtOAc–hexanes); ^{1}H NMR (300 MHz): δ 8.28 (bd, 4 H, Ar), 5.80 (m, 1 H, H-2), 5.27 (d, $J_{4,5}$ 2.5 Hz, 1 H, H-4), 4.96 (bs, 1 H, H-1), 4.31 (dq, $J_{5,6}$ 6.6 Hz, 1 H, H-5), 3.45 (s, 3 H, OCH_3), 1.78 (bs, 3 H, 3-CH_3), 1.22 (d, 3 H, H-6); ^{13}C NMR (75 MHz): δ 164.6 (C=O), 134.9 (ipso), 133.8 (C-3), 130.9, 123.5 (Ar), 125.5 (C-2), 95.5 (C-1), 69.8 (C-4), 64.8 (C-5), 55.5 (OCH_3), 20.1 (3-CH_3), 15.9 (C-6). Anal. Calcd for $C_{15}H_{17}NO_6$: C, 58.63; H, 5.58; N, 4.56. Found: C, 58.80; H, 5.69; N, 4.40.

Methyl 2,3,6-trideoxy-3-C-methyl-α-L-threo-hex-2-enopyranoside (**7**).—A soln of nitrobenzoate **6** (2.0 g, 6.5 mmol) in MeOH (60 mL) was stirred with Amberlite IRA 400 (OH)

resin (1.4 g) for 30 h at rt. The resulting slurry was then filtered through Celite, and the resulting clear soln was concd at reduced pressure to yield 0.87 g of a white solid (85%): mp 84–86 °C; $[\alpha]_D$ +110° (*c* 1.03, MeOH); R_f 0.45 in 1:1 EtOAc–hexanes; ^{1}H NMR (300 MHz): δ 5.52 (m, 1 H, H-2), 4.82 (bs, 1 H, H-1), 4.06 (dq, $J_{4,5}$, $J_{5,6}$ 2.0, 6.6 Hz, 1 H, H-5), 3.36 (s, 3 H, OCH_3), 3.34 (dd, $J_{4,OH}$ 10.8 Hz, 1 H, H-4), 1.93 (d, 1 H, OH), 1.88 (bs, 3 H, 3-CH_3), 1.32 (d, 3 H, H-6); ^{13}C NMR (75 MHz): δ 139.2 (C-3), 121.7 (C-2), 95.7 (C-1), 68.2 (C-4), 66.3 (C-5), 55.3 (OCH_3), 20.3 (3-CH_3), 15.8 (C-6). HRMS Calcd for $C_8H_{14}O_3$ $[M+Na]^+$: 181.0835. Found: 181.0842.

*Methyl 4-*O*-(*N,N*-dimethyl-1-oxa-3-azo-prop-2-eno)-2,3,6-trideoxy-3-*C*-methyl-α-*L*-threo-hexopyranoside* (**9**).—To a stirring soln of allylic alcohol **7** (230 mg, 1.46 mmol) in *N*,*N*-dimethylcyanamide (1.8 mL, 22 mmol) under nitrogen was added NaH (60% dispersion in mineral oil, 70 mg, 1.76 mmol) at rt. After 0.5 h, MeOH (0.5 mL) in hexanes (10 mL) was added, followed by water (3 mL). The aq phase was extracted with $CHCl_3$ (5 × 15 mL), and the combined organic extracts were dried (Na_2SO_4), filtered and concd at reduced pressure. The resulting oil was then purified by flash column chromatography over Florisil (35 g) with EtOAc to yield unstable isourea **8** as a colorless oil (300 mg, 90%), which was used without further purification. To a soln of **8** (300 mg, 1.31 mmol) in anhyd THF (5 mL) under nitrogen was added mercury(II) trifluoroacetate (673 mg, 1.58 mmol), and the reaction mixture was stirred for 20 h at ambient temperature. The reaction mixture was cooled to 0 °C, and aq NaOH (2 N) was added until a pH of 12 was reached. A soln of $NaBH_4$ in 2 N aq NaOH (4 N, 2 mL) was added slowly, resulting in the precipitation of mercury. After stirring for 2 h, the slurry was washed with diethyl ether (4 × 25 mL), and the combined extracts were dried ($MgSO_4$), filtered and concd at reduced pressure. The residual mercury was removed by dissolving the oil in diethyl ether and filtering by gravity through a short column of Celite. Concentration of the clear, colorless filtrate gave 290 mg of oil (96%): $[\alpha]_D$ −0.8° (*c* 1.2, $CHCl_3$); R_f 0.57 (MeOH); ^{1}H NMR (300 MHz): δ 4.72 (d, 1 H, H-1), 3.98 (d, 1 H, H-4), 3.91 (dq, $J_{5,4}$ 1.5 Hz, 1 H, H-5), 3.37 (s, 3 H, OCH_3), 2.91 (s, 6 H, $N(CH_3)_2$), 2.22 (dd, $J_{2a,1}$ 5.7 Hz, 1 H, H-2a), 1.58 (dd, $J_{2e,1}$ 7.9 Hz, $J_{2e,2a}$ 14.7 Hz, 1 H, H-2e), 1.29 (s, 3 H, 3-CH_3), 1.25 (d, $J_{6,5}$ 6.6 Hz, 3 H, H-6); ^{13}C NMR (75 MHz): δ 160.6 (C=N), 98.5 (C-1), 85.8 (C-4), 64.6 (C-3), 64.3 (C-5), 54.6 (OCH_3), 37.4 (C-2), 36.9 ($N(CH_3)_2$), 29.7 (3-CH_3), 16.0 (C-6). HRMS Calcd for $C_{11}H_{20}N_2O_3$ $[M+1]^+$: 229.1547. Found: 229.1554.

*Methyl 3-amino-2,3,6-trideoxy-3-*C*-methyl-α-*L*-lyxo-hexopyranoside (methyl α-*L*-vancosaminide)* (**10**).—A soln of oxazoline **9** (280 mg, 1.23 mmol) in aq BaOH (2 N, 1.5 mL) was stirred for 22 h under reflux. The reaction mixture was then cooled to rt, diluted with water, and extracted with $CHCl_3$ until no more product was removed (8 × 5 mL). The combined extracts were dried (Na_2SO_4), decanted, and concd at reduced pressure to yield 200 mg of a waxy solid (93%): $[\alpha]_D$ −132° (*c* 1.4, MeOH); lit. $[\alpha]_D$ −118° (*c* 0.09, MeOH) [1a]; ^{1}H NMR (300 MHz): δ 4.74 (d, $J_{1,2a}$ 4.4 Hz, 1 H, H-1), 4.01 (q, $J_{6,5}$ 6.6 Hz, 1 H, H-5), 3.32 (s, 3 H, OCH_3), 3.02 (bs, 1 H, H-4), 1.78 (dd, $J_{2e,2a}$ 13.6 Hz, 1 H, H-2a), 1.54 (d, 1 H, H-2e), 1.32 (s, 3 H, 3-CH_3), 1.29 (d, 3 H, H-6); ^{13}C NMR (75 MHz): δ 98.3 (C-1), 74.9 (C-4), 63.5 (C-5), 54.7 (OCH_3), 49.8 (C-3), 37.5 (C-2), 27.5 (3-CH_3), 17.3 (C-6).

*Methyl 3-benzamido-*O*-benzoyl-2,3,6-trideoxy-3-*C*-methyl-α-*L*-lyxo-hexopyranoside* (**11**).—To a soln of methyl α-*L*-vancosaminide **10** (28 mg, 0.16 mmol) in pyridine (0.5 mL) under nitrogen was added BzCl (70 mL), and the reaction mixture was stirred for 20 h at ambient temperature. Ethyl acetate was added, and the soln was washed with 1 M HCl, then satd aq $NaHCO_3$. The organic layer was dried ($MgSO_4$), filtered, and concd at reduced pressure to an oil that was purified by flash column chromatography over silica gel with 3:1 hexanes–EtOAc to yield 38 mg of a white solid (62%), which was not crystallized: $[\alpha]_D$ −179° (*c* 0.16, MeOH); lit. $[\alpha]_D$ −191° (*c* 0.1, MeOH) [1a]; R_f 0.24 in 3:1 hexanes–EtOAc; ^{1}H NMR (300 MHz): δ 6.70 (s, 1 H, NH), 5.15 (bs, 1 H, H-4), 4.92 (d, $J_{1,2a}$ 4.4 Hz, 1 H, H-1), 4.29 (dq, $J_{4,5}$ 0.9 Hz, $J_{5,6}$ 6.5 Hz, 1 H, H-5), 3.40 (s, 3 H, OCH_3), 2.83 (d, $J_{2e,2a}$

14.0 Hz, 1 H, H-2e), 2.21 (dd, 1 H, H-2a), 1.90 (s, 3 H, 3-CH_3), 1.26 (d, 3 H, H-6); ^{13}C NMR (75 MHz): δ 167.9, 166.6 (OC=O, NC=O), 133.2, 135.0 (Ar ipso), 133.6, 131.0, 129.9, 128.5, 128.3, 128.3, 126.6 (Ar), 98.5 (C-1), 75.8 (C-4), 62.6 (C-5), 55.1 (C-3), 55.0 (OCH_3), 35.1 (C-2), 23.6 (3-CH_3), 17.4 (C-6).

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