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Note

Synthesis of L-3-(3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranos-3-yl)alanine*

ALEX ROSENTHAL AND ABRAHAM J. BRINK†
Department of Chemistry, The University of British Columbia, Vancouver, B.C. V6T 1W5 (Canada)
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In continuation of studies[1,2] on the synthesis of branched-chain glycosyl α-amino acids that are structural analogues of the sugar moiety of the polyoxins[3], we now report the synthesis of L-3-(3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranos-3-yl)alanine, wherein the terminal carbon atom of the L-alanine moiety is attached to C-3 of the furanosyl ring. The present work stemmed from the recent publication of an elegant synthesis of α-amino acids from nitriles[4]. In this synthesis, the carbanion derived from methyl (methylthio)methyl sulfoxide was shown to add to nitriles to form an enamino sulfoxide. Sequential treatment of the latter with acetic anhydride, followed by reductive desulfurization with Raney nickel, afforded the protected α-amino acid. Because branched-chain glycos-3-yl nitriles are readily available via addition of acetonitrile to ketoses[5], and by application of the Wittig reaction to ketoses[6], it therefore appeared that application of the procedure[4] of Ogura and co-worker's to a glycosyl nitrile might provide a facile procedure for preparing a glycosylalanine derivative.

Treatment of 3-*C*-cyanomethyl-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose[6](**1**) with the carbanion derived from methyl (methylthio)methyl sulfoxide in tetrahydrofuran afforded a glycosyl enamino sulfoxide, which was immediately acetylated with acetic anhydride and pyridine to yield a diastereoisomeric mixture of the L and D methanethiol esters of *N*-acetyl-3-(glycos-3-yl)-2-(methylthio)alanines **2** and **3** in 66% yield (based on consumed **1**; the ratio of **2**:**3** was 5:1). Treatment of compound **2** with triethylamine in methanol led to a base-catalyzed ester exchange to afford the *N*-acetyl-2-(methylthio)alanate **4** in 87% yield. Reductive desulfurization of **4** with Raney nickel yielded the methyl *N*-acetyl-3-glycos-3-ylalanate **5** in 81% yield. Treatment of **5** with aqueous barium hydroxide afforded the glycosyl α-amino acid **6** in 77% yield. Because compound **6** exhibited a positive optical rotatory dispersion spectrum that was similar to that of L-alanine[7] and of L-2-(3-deoxy-1,2;5,6-

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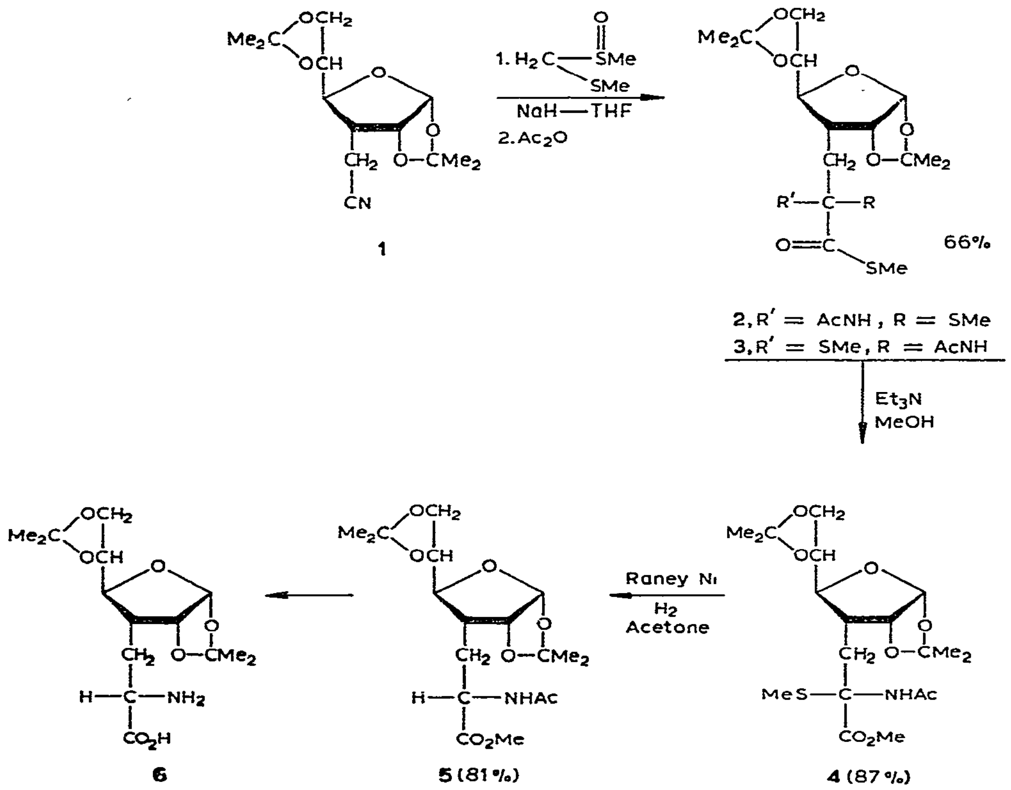
[*] Glycos-3-yl-α-amino acids. Part VII. The term glycosyl is used in an extended sense, through the indicated, non-anomeric carbon atom.

[†] Visiting Scientist, National Chemical Research Laboratory, Council for Scientific and Industrial Research, Pretoria, South Africa.



di-*O*-isopropylidene-α-D-allofuranos-3-yl)glycine[8], compound **6** is therefore considered to be L-3-(3-deoxy-1,2;5,6-di-*O*-isopropylidene-α-D-allofuranos-3-yl)alanine.

EXPERIMENTAL

General methods. — As previously described[1].

Methyl L(*and* D)-N-*acetyl-3-(3-deoxy-1,2;5,6-di-*O*-isopropylidene-α-*D*-allofuranos-3-yl)-2-(methylthio)thioalanate* (**2**) *and* (**3**). — To a suspension of sodium hydride (37 mg, 1.5 mmol) in tetrahydrofuran (30 ml) was added a solution of anhydrous methyl (methylthio)methyl sulfoxide (188 mg, 1.5 mmol) in the same solvent (10 ml), and the mixture was stirred under anhydrous conditions for 20 h at room temperature. To this mixture was then added a solution of 3-*C*-cyanomethyl-3-deoxy-1,2;5,6-di-*O*-isopropylidene-α-D-allofuranose[6] (**1**) (428 mg, 1.5 mmol) in anhydrous tetrahydrofuran (10 ml), and the mixture was stirred for 24 h at room temperature. The solution was evaporated to dryness under vacuum and the residue extracted with 50 ml of chloroform. The chloroform extract was washed with water (2 × 25 ml), dried (calcium sulfate), and evaporated under vacuum to yield an oil (580 mg). The (glycosyl)enamino sulfoxide was immediately acetylated with acetic anhydride (3 ml) and pyridine (5 ml) for 20 h at room temperature. After removal of the volatile components under vacuum, the product (610 mg) was twice chromatographed on silica gel, with 40:1 chloroform–methanol as developer to yield the diastereoisomeric protected glycos-3-yl-α-amino acids **2** and **3**, together with unchanged glycosyl nitrile **1** (325 mg).

Compound **2** (55 mg) was a syrup, $[\alpha]_{\mathrm{D}}^{25}$ +48° (*c* 0.9, chloroform); $\nu_{\max}^{\mathrm{CHCl_3}}$ 3390 (NH), 1695 (COSMe), and 1675 cm^{-1} (amide); $\tau^{\mathrm{CDCl_3}}$ 2.99 (s, 1, exchanges with D_2O, NH), 4.29 (d, 1, $J_{1,2}$ 3.8 Hz, H-1), 5.31 (t, 1, $J_{2,3}$ 4.0 Hz, H-2), 5.86–6.45 (m, 4, H-4,5,6,6′), 7.18–7.60 (m, 3, H-5, CH_2), 7.71 (s, 3, SMe), 7.82 (s, 3, COSMe), 8.04 (s, 3, N-Ac), 8.51, 8.59, 8.69 (s, 12, CH_3).

Compound **3** (11 mg) was a syrup, $[\alpha]_{\mathrm{D}}^{25}$ +38° (*c* 0.4, chloroform); $\nu_{\max}^{\mathrm{CHCl_3}}$ 3420 (NH), 1700 (COSMe), and 1680 cm^{-1} (amide); $\tau^{\mathrm{CDCl_3}}$ 3.02 (s, 1, exchanges with D_2O, NH), 4.30 (d, 1, $J_{1,2}$ 3.8 Hz, H-1), 5.59 (t, 1, $J_{2,3}$ 4.0 Hz, H-2), 5.90–6.43 (m, 4, H-4,5,6,6′), 7.38–7.54 (m, 3, H-3, CH_2), 7.73 (s, 3, SMe), 7.90 (s, 3, COSMe), 8.03 (s, 3, NAc), 8.54, 8.58, 8.66, 8.74 (s, 12, CH_3).

Methyl N-*acetyl*-L-*3-(3-deoxy-1,2;5,6-di*-O-*isopropylidene-α*-D-*allofuranos-3-yl)-2-(methylthio)alanate* (**4**). — To a solution of **2** (105 mg) in anhydrous methanol (10 ml) was added triethylamine (0.1 ml) and the mixture was heated for 20 h under reflux. The mixture was then evaporated under vacuum. The residue was crystallized from hexane–acetone to afford **4** (88 mg, 87%); m.p. 129–130°, $[\alpha]_{\mathrm{D}}^{28}$ +21.5° (*c* 0.2, chloroform); $\nu_{\max}^{\mathrm{CHCl_3}}$ 1750 (CO_2) and 1695 cm^{-1} (amide); $\tau^{\mathrm{CDCl_3}}$ 3.07 (s, 1, exchanges with D_2O, NH), 4.26 (d, 1, $J_{1,2}$ 3.7 Hz, H-1), 5.51 (t, 1, $J_{2,3}$ 4.0 Hz, H-2), 5.85–6.35 (m, 4, H-4,5,6,6′), 6.19 (s, 3, OMe), 7.30–7.43 (m, 2, CH_2), 7.91 (s, 3, SMe), 7.97 (s, 3, NAc), 8.51, 8.57, 8.63, 8.70 (s, 12, CH_3).

Anal. Calc. for $C_{19}H_{31}NO_8S$: C, 52.65; H, 7.21; N, 3.23. Found: C, 52.33; H, 7.45; N, 3.27.

Methyl N-*acetyl*-L-*3-(3-deoxy-1,2;5,6-di*-O-*isopropylidene-α*-D-*allofuranos-3-yl) alanate* (**5**). — Compound **4** (55 mg) in acetone (10 ml) was reductively desulfurized with deactivated Raney nickel (1 g) as catalyst for 24 h. The catalyst was filtered off and the filtrate evaporated to afford chromatographically pure **5** (40 mg, 81%) as a syrup, $[\alpha]_{\mathrm{D}}^{27}$ +36.7° (*c* 0.95, chloroform); $\nu_{\max}^{\mathrm{CHCl_3}}$ 1745 (CO_2) and 1680 cm^{-1} (amide); $\tau^{\mathrm{CDCl_3}}$ 3.59 (broad s, NH), 4.27 (d, 1, $J_{1,2}$ 3.8 Hz, H-1), 5.17–5.49 (m, 2, H-2, CH_2), 5.89–6.49 (m, 4, H-4,5,6,6′), 6.23 (s, 3, OMe), 7.73–8.17 (m, 3, CH_2, H-3), 7.99 (s, 3, NAc), 8.50, 8.60, 8.65, and 8.75 (s, 12, CH_3).

Anal. Calc. for $C_{18}H_{29}NO_8$: C, 55.80; H, 7.54; N, 3.62. Found: C, 55.50; H, 7.39; N, 3.66.

L-*3-(3-Deoxy-1,2:5,6-di*-O-*isopropylidene-α*-D-*allofuranos-3-yl)alanine* (**6**). — A solution of **5** (80 mg) in concentrated aqueous barium hydroxide solution (12 ml) was kept for 48 h at room temperature. The mixture was neutralized with dilute sulfuric acid and the barium sulfate removed by filtration. The filtrate was then passed through a column of Rexyn RG-51 (H^+) (polystyrenecarboxylic acid-type resin) that had been prewashed with 1% acetic acid and then water until the effluent was neutral. Elution of the column with water, and combination and evaporation of the ninhydrin-positive fractions, afforded the α-amino acid **6** (52 mg, 77%). An analytical sample was crystallized from ethanol–water, m.p. 226° (dec.), $[\alpha]_D^{25}$ +41.7° (*c* 1.0, methanol); o.r.d. (*c* 0.19, methanol): $[\Phi]_{220}$ +1680°, $[\Phi]_{216}$ +3180° (peak), and $[\Phi]_{213}$ +1680°.

Anal. Calc. for $C_{15}H_{25}NO_7$: C, 54.37; H, 7.60; N, 4.23. Found: C, 53.85; H, 7.50; N, 3.98.

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