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Preliminary communication

Synthesis of L-acosamine and 1-thio-L-acosamine derivatives by the stereoselective reduction of *O*-acetyloximes with borane*

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Derivatives of 3-amino-2,3,6-trideoxy-L-*arabino*-hexose (L-acosamine), one of the amino sugar components[1] of the vancomycin-type antibiotic actinoidin[2], have been synthesized by various groups[3—10] and have been used for the preparation of 4′-epidaunomycin and 4′-epiadriamycin. These two semisynthetic antibiotics are of interest because their anticancer activity is comparable to that of daunomycin and adriamycin. The two semisynthetic antibiotics also have comparatively low cardiotoxicity[11].

Herein, we describe a convenient synthesis of L-acosamine and 1-thio-L-acosamine derivatives suitable as starting materials for the preparation of the above mentioned antibiotics. Both were synthesized by stereoselective reduction of the corresponding *O*-acetyloximes (**2** and **9**) with the borane–tetrahydrofurane adduct[12].

In a recent report[9], it was shown that the catalytic hydrogenation of oxime **1**, prepared from methyl 2,6-dideoxy-α-L-*erythro*-hexopyranoside-3-ulose (**3**), gave, after acetylation, a 39:7 mixture of methyl 3-acetamido-4-*O*-acetyl-α-L-*ribo*-hexopyranoside (methyl *N*-acetyl-*O*-acetyl-α-L-ristosaminide[13]) and the C-3-epimeric L-*arabino*-analog (**4**, methyl *N*-acetyl-*O*-acetyl-α-L-acosaminide). Interestingly, when the *O*-diacetyl derivative **2** of the oxime **1** was reduced with borane, followed by acetylation, methyl 3-acetamido-4-*O*-acetyl-2,3,6-trideoxy-α-L-*arabino*-hexopyranoside {**4**, m.p. 161–162°, $[\alpha]_D^{21}$ – 188° (*c* 1.05, methanol); lit.[5] m.p. 163–164° $[\alpha]_D^{22}$ –191° (*c* 0.52, methanol)} was obtained as the major product, and only traces of the L-*ribo* epimer could be detected. Compound **4** was isolated in 57% yield (based on **3**). Reduction of **2** in the same way, followed by trifluoroacetylation and *O*-deacylation, gave methyl 2,3,6-trideoxy-3-trifluoroacetamido-α-L-*arabino*-hexopyranoside {**5**, m.p. 195–196° (subl.), $[\alpha]_D^{21}$ –110.8° (*c* 0.6, methanol); lit.[6] m.p. 195–197°, $[\alpha]_D$ –110° (*c* 0.2, methanol) in 67% yield (based on **3**)}.

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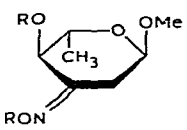
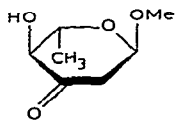


1 R = H
2 R = Ac



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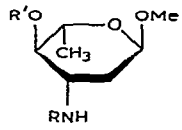
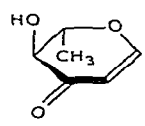


4 R = R' = Ac
5 R = $COCF_3$; R' = H



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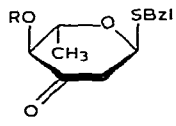
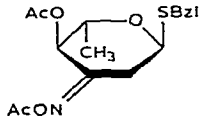


7 R = H
8 R = Ac



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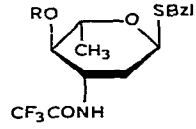

10 R = H
11 R = Ac

Thus, in agreement with previous results[9] and those described herein, both L-ristosamine and L-acosamine derivatives can be conveniently prepared from the oxime derivatives of the same starting material **3** by catalytic hydrogenation or reduction with borane, respectively.

Benzyl 1-thio-α-L-acosaminide derivatives, new representatives of the daunosamine-type sugars, were synthesized as follows: The addition of phenylmethanethiol to 1,5-anhydro-2,6-dideoxy-L-*erythro*-hex-1-en-3-ulose[9] **6** resulted in benzyl 2,6-dideoxy-1-thio-α-L-*erythro*-hexopyranosid-3-ulose (7) which was characterized in form of the crystalline 4-acetate {8, m.p. 98–99°, $[\alpha]_D^{21}$ –436.8° (*c* 0.77, methanol); ^{1}H-n.m.r.: δ 7.34–7.25 (m, 5H, aromatic), 5.40 (d, 1H, $J_{1,2''}$ 7.7 Hz, H-1), 4.88 (d, 1 H, $J_{4,5}$ 10.6 Hz, H-4), 4.56–4.42 (m, 1 H, H-5), 3.78–3.62 (2 d, $J_{H,H}$ 7.7 Hz, PhCH_2S), 3.1 (dd, 1 H, $J_{1,2''}$ 7.7, $J_{2',2''}$ 14.8 Hz, H-2''), 2.55 (d, 1 H, H-2'), 2.20 (s, 3 H, OAc), and 1.32 (d, 3 H, $J_{5,6}$ 7.7 Hz, CH_3-5)}. This is the first example of a 2-deoxy-1-thioglycoside prepared by a Michael addition.

Reaction of **7** with hydroxylamine and subsequent acetylation gave the *O*-acetyloxime **9**, the reduction of which with borane, followed by trifluoroacetylation and *O*-deacylation, resulted in 60.2% (based on **6**) of benzyl 2,3,6-trideoxy-3-trifluoroacetamido-1-thio-α-L-*arabino*-hexopyranoside {**10**, m.p. 154–155°, $[\alpha]_D^{21}$ –272° (*c* 0.85, methanol)}. The ^{1}H-n.m.r. spectrum of the corresponding 4-acetate, obtained by acetylation {**11**, m.p. 165–166°, $[\alpha]_D^{21}$ –290° (*c* 0.8 methanol), ^{1}H-n.m.r. data (200 MHz): δ 7.34–7.27 (m, 5 H, aromatic), 6.63 (d, 1 H, $J_{3,NH}$ 8 Hz, N*H*), 5.16 (d, 1 H, $J_{1,2a}$ 5.6 Hz, H-1), 4.53 (t, 1 H, $J_{3,4} = J_{4,5}$ = 10.0 Hz, H-4), 4.45–4.22 [($\delta_{H\text{-}5}$ 4.29) m, 2 H, H-3 and -5], 3.77–3.68 (2 d, 2 H, $J_{H,H}$ 7.6 Hz, PhCH_2S), 2.70 (m, 1 H, $J_{1,2e}$ 1.6, $J_{2e,3a}$ = 4, $J_{2a,3a}$ 9.6, $J_{2e,2a}$ 14 Hz, H-2e), 2.08 (s, 1 H, OAc), 2.02–1.92 (m, 1 H, H-2a), and 1.16 (d, 3 H, $J_{5,6}$ 6.4 Hz, CH_3-5)} unequivocally supported the L-*arabino* configuration of both **10** and **11**. The C-3 epimeric L-*ribo* compound, formed in traces, could not be isolated in pure form.

As the only example hitherto reported for the reduction of a C-3 oxime derivative of a 2,3-dideoxy sugar with borane, Rosenthal and Catsoulacos[14] obtained a 3 : 1 mixture of methyl 3-acetamido-4,6-*O*-benzylidene-2,3-dideoxy-α-D-*arabino*- and -D-*ribo*-hexopyranoside from the corresponding *O*-acetyloxime-3. In the 2-amino-2-deoxy sugar series, the reaction has been examined by Lemieux *et al.*[15]. They found the reduction of isopropyl 2-acetoximino-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranoside with borane highly stereoselective, providing the corresponding 2-amino-2-deoxy-glucopyranoside and -mannopyranoside derivatives in a 19 : 1 ratio.

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