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Sugar Lactams and Lactim Ethers, Useful Precursors of Cyclic Amidines, from Intramolecular Nucleophilic Displacements

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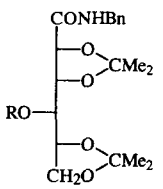
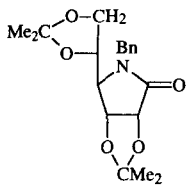
Abstract: The cyclisation of the conjugate base of N-aryl-2,3:5,6-di-O-isopropylidene-4-O-methanesulfonyl-D-gulonamides gave the D-allonolactam acetals. Sodium methoxide-promoted cyclisation of 2,3:5,6-di-O-isopropylidene-4-O-methanesulfonyl-D-mannononitrile gave the D-talonolactim ether. Tetrazole formation without isolation of the intermediate azide was illustrated by the conversion of the aforementioned nitrile sulfonate into the D-talonotetrazole. Cyclic amidines were prepared from the lactam and lactim ether derivatives. The D-allono derivatives were also converted into D-ribono-1,4 lactam and amidine derivatives.

The ability of sugar-related alkaloids and related compounds, such as lactams, cyclic amidines and tetrazoles, to inhibit glycosidases, and their potential use as antiviral and anticancer agents has stimulated attempts to find new synthetic routes to such compounds.[1] Earlier attempts in this laboratory to exploit the intramolecular nucleophilic displacement reactions of aldononitrile and aldonamide sulfonates with O-benzyl protecting groups to form respectively lactim ethers and lactams were unsuccessful due to several competing reactions.[2] It was reasoned that the formation of five-membered rings would be easier especially if a cyclic acetal protecting group were used to lock the carbon skeleton in a conformation favourable for cyclisation.

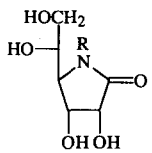
Thus N-benzyl-2,3:5,6-di-O-isopropylidene-D-gulonamide (**1**), prepared by reaction of the known 2,3:5,6-di-O-isopropylidene-D-gulono-1,4-lactone with benzylamine, was converted into the O-methanesulfonate (**2**), which, on treatment with sodium hydride in DMF, gave the crystalline D-allonolactam derivative (**3**) in good yield. The expected *allo* configuration of (**3**)[3] was confirmed by the small coupling ($J < 1$ Hz) between the trans related protons H3 and H4. Acid hydrolysis gave the tetrol (**4**, R=Bn) and partial hydrolysis led to the isolation of the diol (**5**) which was converted into the D-ribonolactam derivative (**6**) by periodate oxidation followed by reduction with sodium borohydride. Acid hydrolysis of (**6**) gave the free lactam (**7**). Formation of the unsubstituted lactam using 2,3:5,6-di-O-isopropylidene-D-gulonamide was not possible because reaction of the amide with methanesulfonyl chloride gave a mixture from which the 4-mesylate could not be isolated.



(**1**) R = H
(**2**) R = Ms

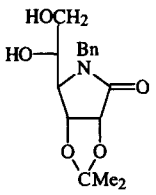


(**3**)
[Bn = CH_2Ph]

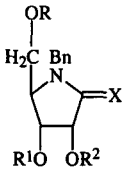


(**4**)

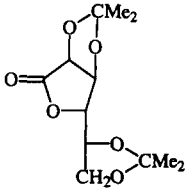
Debenzylation of the N-benzyl lactam (**3**) proved to be difficult; many methods were tried, and eventually an oxidative method was successful.[4] Oxidation of the tetraacetate of (**4**) with chromium trioxide in acetic acid gave the crystalline N-benzoyl lactam tetraacetate (55% yield after chromatography), and acid hydrolysis gave the deprotected 4-amino-4-deoxy-D-allonolactam (**4**, R=H) in 33% yield (not optimised). The p-methoxybenzyl analogue of (**3**) was prepared in the hope that removal of the p-methoxybenzyl group would be easier. However the deprotection, by means of potassium persulfate, was only accomplished in low yield (28%).



(**5**)



(**6**) R = H, X = O, R^1R^2 = CMe_2
(**7**) X = O, R = R^1 = R^2 = H
(**18**) R = H, X = NH, R^1R^2 = CMe_2
(**19**) R = Ac, X = O, R^1R^2 = CMe_2

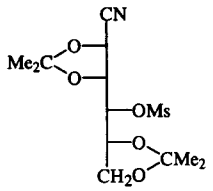


(**8**)

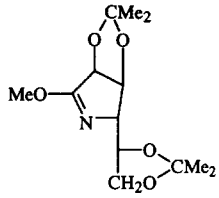
A similar sequence of reactions in the D-mannose series was unsuccessful because of the instability of sulfonate esters of 2,3:5,6-di-O-isopropylidene-D-mannonamide and its N-benzyl derivative. The rate of esterification of the 4-OH group was slow and the sulfonate ester, when formed, readily reacted to form the inverted lactone, 2,3:5,6-di-O-isopropylidene-D-talono-1,4-lactone (**8**), as a result of nucleophilic attack by the amide oxygen and hydrolysis of the resulting iminolactone. The ease with which this cyclisation took place implied that other cyclisations of acyclic 2,3:5,6-di-O-isopropylidene-4-O-methanesulfonyl-D-mannonic acid derivatives would be favourable. Sodium methoxide-promoted cyclisation of 2,3:5,6-di-O-isopropylidene-4-O-methanesulfonyl-D-mannononitrile (**9**)[5] was thus attempted, and the lactim ether (**10**) was isolated in good yield as a stable gum In contrast sugar-derived six- and seven-membered ring imidates were recently reported to be too unstable to be isolated.[6] It was not possible to deprotect (**10**) by partial acid hydrolysis without hydrolysing the lactim ether function. The resulting 4-amino-4-deoxy-D-talonolactam (**11**) was isolated crystalline in good yield and was also characterised as the crystalline 2,3:5,6-di-O-isopropylidene derivative (**12**). The lactim ether was also a convenient precursor of the corresponding amidine (**13**) which was isolated crystalline in 71% yield after reaction of (**10**) with ammonium chloride in methanol. Acid hydrolysis gave the deprotected amidine.

The relative ease with which 2,3:5,6-di-O-isopropylidene-D-talonic acid derivatives are formed in cyclisations was further illustrated by the conversion of the nitrile mesylate (**9**) into the tetrazole (**14**) in 89% yield by reaction with sodium azide. The tetrazole was presumably formed by cycloaddition of a 4-azido-4-deoxy-D-talononitrile intermediate.[7] Acid hydrolysis of (**14**) gave the deprotected tetrazole (**15**). The *talo*

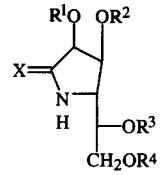
configuration was confirmed by the value of $J_{3,4}$ (< 1 Hz) for the lactim ether (**10**), lactam (**12**), amidine (**13**) and tetrazole (**14**).



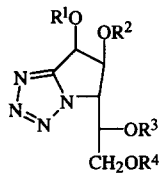
(**9**)



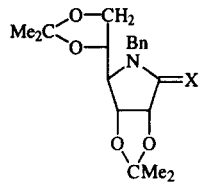
(**10**)



(**11**) X = O, $R^1 = R^2 = R^3 = R^4 = H$
(**12**) X = O, $R^1R^2 = R^3R^4 = CMe_2$
(**13**) X = NH, $R^1R^2 = R^3R^4 = CMe_2$



(**14**) $R^1R^2 = R^3R^4 = CMe_2$
(**15**) $R^1 = R^2 = R^3 = R^4 = H$



(**16**) X = S
(**17**) X = NH

In order to form cyclic amidine derivatives in the D-allono series the thionolactam route[8] was explored. Thus, the protected D-allonolactam (**3**) was reacted with Lawesson's reagent to form the thionolactam (**16**), isolated crystalline in 39% yield after chromatography. The action of ammonia in methanol in the presence of mercuric oxide converted the thionolactam into the amidine (**17**), which was isolated crystalline in high yield provided that triethylamine was present.[9] The D-ribono-amidine (**18**) was similarly prepared from the 5-O-acetyl-4-amino-4-deoxy-2,3-O-isopropylidene-D-allonolactam (**19**). The alternative route to amidines, involving reaction of lactam acetals with ammonia or amines,[10] failed in the case of 4-amino-4-deoxy-2,3:5,6-di-O-isopropylidene-N-(p-methoxybenzyl)-D-allonolactam (also the N-benzyl derivative) because the dimethyl acetal was too unstable to be isolated.

In conclusion these results suggest that cyclisation of the conjugate base of protected aldonamide sulfonates should be a general route to five-membered ring lactams when a cyclic acetal protecting group is present at positions 2,3 and provided that the aldonamide sulfonate can be isolated without decomposition to form the inverted lactone. In the latter case cyclisation of the corresponding aldononitrile sulfonate, readily prepared from the protected aldose oxime,[5] should succeed giving rise to the lactim ether which can be readily hydrolysed to the lactam. When lactim ether formation is possible this provides the most efficient route to the corresponding cyclic amidines.

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2. Williams, J. M., Pickles, D., Gravestock, M. B., A search for new routes to sugar lactams and lactim ethers, Abstract B.15, 6th European Symposium on Carbohydrate Chemistry, Heriot-Watt University, Edinburgh, 1991.
3. All new compounds gave spectra and elemental compositions consistent with their structure; see note 11.
4. We are indebted to Mr G. Llewellyn for the exploratory experiments.
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11. Representative data for some new compounds: **3**, m.p. 119-121°C, ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 7.25 (m, 5H), 5.07 (d, 1H, *J* 15.3 Hz, PhC$\underline{H}_2$), 4.74 (d, 1H, *J* 5.7 Hz, H-2), 4.53 (d, 1H, *J* 5.7 Hz, H-3), 4.32 (dt, 1H, H-5), 4.08 (d, 1H, *J* 15.3 Hz, PhC$\underline{H}_2$), 4.07 (dd, 1H, *J* 8.7, 7.9 Hz, H-6), 3.75 (dd, 1H, *J* 5.8, 8.7 Hz, H-6'), 3.48 (d, 1H, *J* 2.0 Hz, H-4), 1.4, 1.4, 1.3, 1.2 (4s, 12H, 4Me); MS (EI) 347 M^+.
10, oil, ^{1}H-NMR (400 MHz $CDCl_3$) δ 5.11 (d, 1H, *J* 5.5 Hz, H-2), 4.82 (d, 1H, H-3), 4.43 (dt, 1H, H-5), 4.19 (d, 1H, *J* 2.7 Hz, H-4), 4.17 (dd, 1H, *J* 6.9, 7.9 Hz, H-6), 4.08 (dd, 1H, *J* 6.9, 7.9 Hz, H-6'), 3.89 (s, 3H, OMe), 1.47, 1.38, 1.37, 1.33 (4s, 12H, 4Me); MS (CI) 272 $(M+H)^+$.
11, m.p. 68-69°C, ^{1}H-NMR (400 MHz, d_5-pyridine) δ 9.2-5.3 (5 s, 5H, NH + OH) 5.15 (d, 1H, *J* 5.5Hz, H-2), 4.93 (bd, 1H, *J* 5.5 Hz, H-3), 4.41 (m, 1H, H-4), 4.36 (m, 1H, H-5), 4.19 (m, 2H, H-6); ^{13}C-NMR 178.2 (CO), 73.69, 73.04, 71.90 (3 CH), 64.90 (CH_2), 63.38 (CH); MS (CI) 178 $(M+H)^+$.
13, m.p. 208-209°C, ^{1}H-NMR (400 MHz, d_5-pyridine) δ 5.54 (d, 1H, *J* 5.2 Hz,H-2), 4.94 (d, 1H, *J* 5.2 Hz, H-3), 4.58 (dd, 1H, *J* 7.5, 8.8 Hz, H-6), 4.46 (d, 1H, *J* 2.0 Hz, H-4), 4.40 (dt, 1H, H-5), 4.20 (dd, 1H, *J* 6.6, 8.8 Hz), 1.52, 1.42, 1.36(x2) (3s, 12H, 4 Me) (NH not detected, broad weak signals were detected in $CDCl_3$ solution, ν_{KBr} 3400-3100 cm^{-1} (broad) NH; MS (CI) 257 $(M+H)^+$.
14, m.p. 126.5-127.5°C, ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.63 (d, 1H, *J* 5.3 Hz, H-2), 5.41 (d, 1H, *J* 5.3 Hz, H-3), 4.86 (d, 1H, *J* 1.6 Hz, H-4), 4.61 (dt, 1H, H-5), 4.33 (dd, 1H, *J* 6.0, 9.1 Hz, H-6), 4.26 (dd, 1H, *J* 7.0, 9.1 Hz, H-6'), 1.45, 1.28, 1.25, 0.78 (4s, 12H, 4 Me); MS (CI) 283 $(M+H)^+$.
17, m.p. 83.5-85°C, ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.3-7.2 (m, 6H, ArH+NH), 5.01 (d, 1H, *J* 15.8 Hz, PhC$\underline{H}_2$), 4.83 (d, 1H, *J* 5.3 Hz, H-2),4.49 (d, 1H, *J* 5.3 Hz, H-3), 4.28 (m, 1H, H-5), 4.23 (d, 1H, *J* 15.8 Hz, PhC$\underline{H}_2$),4.03 (dd, 1H, *J* 7.5, 8.6 Hz, H-6), 3.71 (dd, 1H, *J* 6.1, 8.6 Hz, H-6'), 3.53 (d, 1H, *J* 2.2 Hz, H-4), 1.45, 1.42, 1.38, 1.27 (4s, 12H, 4 Me); MS (EI) 346 M^+.
18, m.p. 151.5-153 C, ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.26-7.14 (m, 5H, ArH), 4.99 (d, 1H, *J* 15.3 Hz, PhC$\underline{H}_2$), 4.68 (d, 1H, *J* 5.6 Hz, H-2), 4.56 (d, 1H, *J* 5.6 Hz, H-3), 4.25 (bs, 1H, OH), 3.94 (d, 1H, *J* 15.3 Hz, PhC$\underline{H}_2$), 3.80 (dd, 1H, *J* 1.9, 12.4 Hz, H-5), 3.55 (bd, 1H, *J* 12.4 Hz, H-5'), 3.44 (bs, 1H, H-4), 1.36, 1.27 (2s, 6H, 2 Me) (NH not detected); ν_{KBr} 3430 cm^{-1} (broad) OH, NH; MS (CI) 277 $(M+H)^+$.

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