α-Amino Polyhydroxy Tetronic and Pentonic Acids from Bromodeoxyaldonolactones*

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Treatment of either 2-bromo-2-deoxy-L-threo- (3) or L-erythro-1,4-lactone (6) with NaN₃ gave identical mixtures of 2-azido-2-deoxy-L-threo- (7) and L-erythro-1,4-lactone (8). Similar treatment of 2-bromo-2-deoxy-d-xylono-1,4-lactone (13) gave a 1:1 mixture of 2-azido-2-deoxy-d-xylono- (15) and d-lyxono-1,4-lactone (16), while the 2-bromo-2-deoxy-d-arabino-1,4-lactone (24) gave a 1:1 mixture of 2-azido-2-deoxy-d-arabino- (26) and d-ribono-1,4-lactone (27). All isomers could be separated by either flash chromatography or crystallization. Catalytic hydrogenation of the azido lactones gave the corresponding amino lactones, as hydrochlorides, or the α-amino acids. The azido lactone 15 was converted into 2-acetamido-2-deoxy-d-xylono (21), while 26 gave 2-amino-2-deoxy-d-arabinono · HCl (35). The epimeric mixtures of azido lactones (15, 16) or (26, 27) were converted in a one-pot synthesis into 2-acetamido-5-O-acetyl-2,3-dideoxy-d-threo-pentono-1,4-lactone (37). The intermediate was shown to be 2-acetamido-5-O-acetyl-2,3-dideoxy-D-glycero-pent-2-eno-1,4-lactone (36), which was prepared from the fully acetylated amino lactones (32, 33). The 2-bromo lactones, as well as the 2-azido lactones, were shown to equilibrate under basic conditions.

The α-amino-β-hydroxy acids are an important class of amino acids which are fundamental components in peptidases, but may act as enzyme inhibitors or can be used as pharmaceuticals. The necessity of having only one enantiomer has resulted in the appearance of several methods for the enantioselective synthesis of such compounds. Optically active α-amino polyhydroxy acids may also be obtained from aldonic acids having the appropriate stereochemistry. Thus, using bromodeoxyaldonolactones, readily available from aldonic acids, we have recently described the preparation of amino acids and amino sugars by nucleophilic substitution with the azide ion. Continuing this work, we now describe the reactions of 2-bromo-2-deoxy-tetronic- and -pentono-lactones with azide ion.

Results and discussion

2-Bromo-2-deoxy-d-xylono- (13) and d-arabino-1,4-lactone (24) were obtained by treatment of d-lyxono- and d-ribono-1,4-lactone, respectively, with hydrogen bromide in acetic acid (HBA). Treatment of either potassium L-erythronate (1) or calcium L-threonoate (4) with HBA yielded the 2,4-dibromo-2,4-dideoxy-L-threonic (2) and L-erythronic acid (5), respectively, previously isolated as their methyl esters. When the acids 2 and 5 were kept in aqueous solution at a pH of ca. 3, an intramolecular nucleophilic attack by the carboxylate on C-4 took place, leading to the 1,4-lactones 3 and 6, respectively.

When either of the 2-bromo-2-deoxylactones (3) or (6) was treated with sodium azide in acetonitrile, the same mixture of the 2-azido-2-deoxy-L-threono- (7) and L-erythro-1,4-lactone (8) in a 2:3 ratio was obtained. The azido lactones could be separated by chromatography. Treatment of

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either 2-bromo-2-deoxy-δ-xylono- (13) or δ-arabinino-1,4-lactone (24) under similar conditions gave 1:1 mixtures of 2-azido-2-deoxy lactones 15 and 16, and 26 and 27, respectively. Chromatographic separation yielded the pure isomers, the xylo (15) and arabino (26) isomers being crystalline. Direct crystallization from the crude mixture of 26 and 27 gave 26 in 30–35% yield. Catalytic hydrogenation of the azido lactones afforded the corresponding amino lactones in admixture with the α-amino acids. Thus, from the three azido lactone 7 the 2-amino lactone 9 as well as the amino acid 10 could be prepared and isolated in a crystalline state. Similarly, the erythro isomer 8 gave the crystalline 2-amino lactone 12 and the amino acid 11. These four isomers of α-amino-β-γ-dihydroxy butyric acid, as well as of their γ-lactone hydrochloride, have been described, thus proving the 1-threo configuration of 9 and 10 as well as the 1-erythro configuration of 11 and 12 (the data for the compounds with D- and L-threo- configurations have been interchanged in Ref. 10).

In order to prove the configurations of the 2-azido lactones 15 and 16, one of them (15) was treated with sodium borohydride to give a 2-azido-2-deoxy pentose (20). A 1H NMR spectrum showed the presence of two anomers having $J_{13}$ 4.0 and 8.0 Hz, respectively, confirming the xylo configuration. Furthermore, hydrogenation and acetylation gave the known 2-acetamido-2-deoxy-δ-xylene (21). The azido lactone 15 was hydrogenated in aqueous hydrochloric acid yielding the syrupy 2-amino-γ-lactone hydrochloride (17), together with a small amount of the δ-lactone, as seen from the $^{13}$C NMR spectrum. The 2-amino-2-deoxy-δ-xylono-γ- and δ-lactones, as a mixture, have been synthesised, together with the δ-arabinino isomer, from δ-glyceraldehyde. The free amino acid (23) was obtained as an amorphous substance by basifying the hydrochloride (17). Treatment of 23 in methanol with acetic anhydride gave the crystalline 2-acetamido-γ-lactone (18). The L-enantiomer of 18 has been described, together with other derivatives of the naturally occurring 2-amino-2-deoxy-δ-xylosic acid and of the corresponding D-isomer (23). The L-enantiomer of 23, the so-called polyoxamic acid, is a constituent of polyoxines, a family of antifungal antibiotics.

The 2-azido-2-deoxy-δ-lyxonolactone (16) was similarly converted into the amino lactone 19 and 2-amino-2-deoxy-δ-lyxonic acid (22). From the mixture of azido lactones, having arabino (26) and ribo (27) configuration, one isomer (26) could be crystallized directly. Conversion to the 2-azido sugar (34), and subsequent reduction to 2-amino-2-deoxy-δ-arabinose hydrochloride (35) proved the arabino configuration of 26. Hence, 27 was shown to be the ribo isomer. Cata-
lytic hydrogenation of 26 and 27 produced the crystalline hydrochlorides of the 2-amino lactones 28\(^{13}\) and 29, respectively.

The convenient synthesis of 3-deoxyaldonolactones from acetylated aldonolactones\(^{14}\) might be extended to the preparation of 2-amino-2,3-dideoxyaldonolactones from 2-azido lactones. All four isomers, 26 and 27, and 15 and 16, would be expected to give the same compound (37). Thus, the crude mixture of 26 and 27 was hydrogenated in the presence of acetic anhydride to give the acetamido compounds 30 and 31, which were subsequently O-acetylated to 32 and 33, respectively. Elimination of acetic acid by treatment with potassium fluoride in ethyl acetate gave the crystalline 2,3-unsaturated 2-acetamido lactone.

\[ R_1 \quad R_2 \quad R \]
- 14: Br \quad H \quad 20: N\(_3\)
- 15: H \quad N\(_3\) \quad 21: NHAc
- 16: N\(_3\) \quad H
- 17: H \quad NH\(_2\)-HCl
- 18: H \quad NHAc
- 19: NH\(_2\)-HCl \quad H

\[ R_1 \quad R_2 \quad R \]
- 25: H \quad Br \quad H
- 26: N\(_3\) \quad H \quad H
- 27: H \quad N\(_3\) \quad H
- 28: NH\(_2\)-HCl \quad H \quad H
- 29: H \quad NH\(_2\)-HCl \quad H
- 30: NHAc \quad H \quad H
- 31: H \quad NHAc \quad H
- 32: NHAc \quad H \quad Ac
- 33: H \quad NHAc \quad Ac

\[ R_1 \quad R_2 \quad R \]
- 34: R = N\(_3\)
- 35: R = NH\(_2\)-HCl
(36). Hydrogenation of the double bond yielded 2-acetamido-5-O-acetyl-2,3-dideoxy-α-threo-
pentono-1,4-lactone (37). More conveniently, the synthesis of 37 could be performed as a one-
pot procedure by catalytic hydrogenation of the crude mixture of azido lactones (26 and 27, or 15
and 16) in the presence of acetic anhydride and triethylamine. A derivative of 2-amino-2,3-dide-
oxoy-α-threo-pentono-1,4-lactone has previously been synthesised from α-xylene with the aim of
preparing clavalin, a β-lactam antibiotic.

The nucleophilic substitution of 2-bromo-2-deoxytetrono and -pentono lactones with azide ion
gave ca. 1:1 mixtures of 2-azido lactones; this contrasts with the corresponding reactions of bro-
modeoxyhexonolactones,7 for which the epimeric ratio was found to be ca. 95:5. We did observe7
that an epimerisation at C-2 of the 2-bromo-2-deoxyhexonolactones took place in DMF in the
presence of bromide ions. Similarly, a mixture of 3 and 6 was obtained when the 2-bromo-2-deoxy-
λ-threono lactone (3) was boiled in acetonitrile in the presence of 0.1 molar equiv. of sodium bro-
mide; the reaction is probably an S2 displacement. However, we have also observed that a base
may cause a similar isomerisation. Thus, the 2-bromoxylono lactone (13) in the presence of
sodium azide in water showed, after 1.5 h at room temperature, the presence of the lyxo
isomer (14) (13:14 ~ 3:2), while the arabino
isomer (24) in acetonitrile in the presence of
triethylamine instantaneously gave a 1:1 mixture of
24 and the ribo isomer (25). These reactions probably proceed via abstraction of the α-hydro-
gen atom to give the carbanion 38 (X = Br) as an intermediate. The same intermediate (38, X =
N₃) is probably responsible for the isomerisation of pure 2-azido lactones in the presence of azide
ions. Thus, 8 was stable in boiling acetonitrile,
but addition of sodium azide gave, after 3 h, 8
and 7 in the ratio 2:1.

Preparation of α-azido lactones by nucleophilic
displacement has been reported to be an S₂ process
with no isomerisation.16 The leaving group used
was the reactive triflate, allowing the reaction
to take place at −20°C. However, a similar substitution was reported17 to proceed
with retention. The use of lithium azide to sub-
stitute a (4-chlorophenyl)sulfonyl group was re-
ported to give pure inversion.15 When the 2-bro-
omaxyxono lactone (13) was treated in DMF with
lithium azide at −10°C → +25°C, the 2-azido
lactones with lyxo (16) and xylo (15) configura-
tion were formed in the ratio 4:1, while the ratio
was 1:1 when sodium azide was used. Other ex-
periments have indicated that lithium azide is
more reactive, allowing substitutions to proceed
at lower temperatures and thus with less isomer-
isation.

In conclusion, a nucleophilic substitution α to a
carboxyl function may, in principle, always give
two isomeric products, the ratio varying between
9:0.5 and 1:1. But, as described in this paper and
in the preceding paper in this series,7 optically
pure azido lactones, and hence α-amino hydroxy
acids and aminodeoxy sugars, can easily be ob-
tained from bromodeoxy lactones.

Experimental

Melting points are uncorrected. Optical rotations
were measured using a Perkin Elmer 241 polari-
meter. NMR Spectra were recorded on Bruker
WH-90 and AM-500 NMR instruments. Dioxane
(67.40 ppm) was used as internal reference for
13C NMR spectra, and acetone (δ 2.22) for 1H
NMR spectra in D₂O. TMS was used as the refe-
rence for spectra in CDCl₃. Column chromatog-
raphy was performed on silica gel 60 (40–63 μm,
Merck 9385) using the flash technique. Evapo-
rations were carried out in vacuum at 50°C, un-
less otherwise indicated. Microanalyses were per-
formed by NOVO Microanalytical Laboratory,
Bagsværd, Denmark.

2-Bromo-2-deoxy-λ-threono-1,4-lactone (3). Potas-
sium λ-erythronate (1)8,18 (16.6 g) was stirred with
170 ml of a 32% solution of hydrogen bro-
mide in acetic acid (HBA) for 1.5 h at room

temperature. Water (400 ml) was then added and
the mixture was allowed to stand for 2 h. Con-
centration left a residue containing the dibromo
acid (2). 13C NMR (D₂O): 171.5 ppm (C-1), 71.4
(C-3), 52.6 (C-2), 35.3 (C-4). An aqueous
solution of Na₂CO₃ was added until pH = 3. Con-
centration left a residue which was dissolved in
water (60 ml); the aqueous solution was extracted
with EtOAc (6×50 ml). The combined extracts
were dried (Na₂SO₄), treated with activated car-
bon, and concentrated to give the syrup
2-bromo lactone (3) (13.7 g, 79%), which was
pure as judged from 13C NMR spectra (D₂O):
174.9 ppm (C-1), 75.0 (t, J 155 Hz, C-4), 74.5 (d,
J 158 Hz, C-3), 42.6 (d, J 163 Hz, C-2). A sample
was purified further by distillation, b.p. 150–160°C/2 mm Hg; [α]D^20 +14° (c 5.0, CHCl₃). Anal. C₃H₈BrO₢; C, H, Br.

2-Bromo-2-deoxy-L-erythroono-1,4-lactone (6). Calcium L-threonate₃⁶ (4) (10.0 g) was treated with HBA (100 ml) for 1.5 h at room temperature as described above. The residue containing the dibromide acid (5) [¹³C NMR (D₂O): 171.7 ppm (C-1), 71.2 (C-3), 46.7 (C-2), 36.8 (C-4)] was adjusted to pH 3 and worked up as described above to give the 2-bromo lactone (6) (8.5 g, 73%) as a syrup, which was pure as judged from ¹³C NMR spectra (D₂O): 170.7 ppm (s, C-1); 71.1 (t, J 155 Hz, C-4); 66.1 (d, J 159 Hz, C-3), 44.5 (d, J 154 Hz, C-2). A sample was distilled, b.p. 135–145°C/1–2 mm Hg; [α]D^20 +5.0° (c 4, CHCl₃). Anal. C₃H₈BrO₢; C, H, Br.

2-Azido-2-deoxy-L-threono- (7) and L-erythrono-1,4-lactone (8). a: From 3. The 2-bromo lactone 3 (8.6 g) was boiled under reflux in acetonitrile (125 ml) together with Na₂S₂O₈ (15 g) for 2.5 h with protection from light. After filtration and concentration, the residue was dissolved in EtOAc (50 ml) and the solution was washed twice with water (10 ml). The organic layer was dried (Na₂SO₄) treated with activated carbon and concentrated to give a product (5.9 g, 87%) containing the two azido lactones 7 and 8 in the ratio 2:3, as seen from a ¹³C NMR spectrum. The compounds were separated by flash chromatography (EtOAc/Hexane, 1:1) to give 2-azido-2-deoxy-L-threono-1,4-lactone (7) (1.3 g, 19%) as a syrup. ¹³C NMR (D₂O): 174.3 ppm (C-1), 71.1 (d and t, C-3 and C-4), 63.8 (d, C-2). A mixed fraction (1.0 g, 14%) was then isolated, followed by syrupy 2-azido-2-deoxy-L-erythroono-1,4-lactone (8) (2.0 g, 30%). ¹³C NMR (D₂O): 174.5 ppm (C-1), 74.2 (t, C-4), 69.6 (d, C-3), 61.3 (d, C-2).

b: From 6. The bromo lactone 6 (14.3 g) was boiled under reflux in acetonitrile (150 ml) together with sodium azide (28 g) for 5 h with protection from light. Filtration and concentration gave a residue which was worked up as described above to give 7.5 g (66%) of a mixture of the 2-azido lactones 7 and 8 in the ratio 2:3, as seen from the ¹³C NMR spectrum.

2-Amino-2-deoxy-L-threono-1,4-lactonehydro-

chloride (9). The azido lactone 7 (900 mg) in water (25 ml) and 12 M HCl (1 ml) was hydrogenated (70 atm. H₂) in the presence of 5% palladium-on-carbon (100 mg) over night. Filtration and concentration gave a residue which contained the lactone 9 together with the acid hydrochloride. Crystallization from EtOH gave 9 (300 mg, 31%); m.p. 173–175°C. Recrystallization from EtOH/EtOAc/CHCl₃ gave a product with m.p. 174–176°C; [α]D^20 +27.3° (c 0.6, H₂O); [lit.⁶] m.p. 175–175.5°C; [α]D^20 +26° (α and 1 are interconverted); cf.¹⁰ m.p. 165°C; [α]D^20 −29.5° for the d enantiomer. ¹³C NMR (D₂O): 172.4 ppm (C-1), 71.8 (C-4), 69.9 (C-3), 56.1 (C-2). The mother-liquid from crystallization of 9 was boiled in water (20 ml) for 1.5 h and the solution was poured on a column of ion-exchange resin (Amberlite IR-120, H⁺, 20 ml). Elution with water until neutral, followed by elution with aqueous ammonia (12.5%, 250 ml) gave, after concentration of the ammoniacal eluate, 2-amino-2-deoxy-L-threonic acid (10) (0.26 g, 31%); m.p. 208–212°C. Recrystallization from H₂O/MeOH gave 10 with m.p. 210–212°C; [α]D^20 +12.8° (c 0.6, H₂O); [lit.¹¹] m.p. 214–215°C, [α]D^20 +13.1° (c 4.8, H₂O).

2-Amino-2-deoxy-L-erythroono-1,4-lactone hydro-

chloride (12). The 2-azido lactone 8 (1.0 g) in water (25 ml) and 12 M HCl (1 ml) was hydrogenated, and the reaction mixture worked up as described above to give a crystalline residue (~1 g). Crystallization from EtOH gave 12 (750 mg, 70%); m.p. 170–174°C. Recrystallization from EtOH/EtOAc gave a product with m.p. 175–177°C; [α]D^20 +54.3° (c 0.5, H₂O); [lit.¹⁰] m.p. 176°; [α]D^20 +55.6° (c 1.5, H₂O). ¹³C NMR (D₂O): 173.6 ppm (C-1), 75.9 (C-4), 67.1 (C-3), 52.9 (C-2). The mother-liquor was treated as described above to give 2-amino-2-deoxy-L-erythrionic acid (11), which was crystallized from H₂O/MeOH (70 mg, 7%); m.p. 190–193°C. Recrystallization from the same solvent gave 11 with m.p. 192–194°C; [α]D^20 −7.8° (c 0.7, H₂O); [lit.¹⁰] m.p. 194–195°C; [α]D^20 −11.3° (c 7.2, H₂O).

2-Azido-2-deoxy-D-xylono- (15) and D-lyx-

ono-1,4-lactone (16). The 2-Bromo-2-deoxy-D-xylono-1,4-lactone (13) (5.0 g) and NaN₃ (5 g) in CH₃CN (50 ml) were boiled for 6 h with protection from light. Filtration and concentration gave a residue to which EtOAc (50 ml) was added,
followed by filtration and concentration. The resulting syrup was dissolved in water (10 ml) and the solution was extracted with EtOAc (10×20 ml). The combined extracts were dried (Na₂SO₄) and concentrated to give 3.9 g (95%) of a mixture of the azido lactones 15 and 16 in ca. 1:1 ratio. Flash chromatography (EtOAc/hexane, 3:1) gave 1.2 g (29%) of the xylol isomer 14. ¹³C NMR (D₂O): 174.9 ppm (C-1), 82.1 (C-4), 72.5 (C-3), 64.0 (C-5), 59.8 (C-2). Crystallization from ether gave 0.57 g (14%); m.p. 80-82°C; [α]D +222° (c 1.5, EtOAc). Anal. C₅H₇N₂O₂; C, H, N. A mixture (0.74 g, 18%) of 15 and 16 was then isolated, followed by the byxol isomer (16) (1.27 g, 31%) which was pure as judged from a ¹³C NMR spectrum (D₂O): 175.5 ppm (C-1), 83.9 (C-4), 71.0 (C-3), 63.2 (C-5), 60.6 (C-2).

2-Amino-2-deoxy-d-xylonic acid (23). A mixture of the azido lactone 15 (500 mg), water (10 ml) and 4 M HCl (1.1 ml) was stirred in an H₂ atmosphere in the presence of 5% palladium-on-carbon (100 mg) overnight. Filtration and concentration gave a syrupy residue (~700 mg) containing 2-amino-2-deoxy-d-xylono-1,4-lactone hydrochloride (17), as seen from a ¹³C NMR spectrum (D₂O): 171.8 ppm (C-1), 81.9 (C-4), 70.2 (C-3), 59.3 (C-5), 55.2 (C-2). A minor component was present, probably the corresponding 1,5-lactone: 170.8 ppm (C-1), 73.3 (C-4), 68.0 (C-3), 63.0 (C-5), 57.2 (C-2). The product was basified on a column of ion-exchange resin (Amberlite IR 120 H⁺, 15 ml) by elution with aqueous ammonia as described above to give 23 (200 mg, 42%) as a syrup. ¹³C NMR (D₂O): 173.5 ppm (C-1), 73.9 (C-4), 69.0 (C-3), 63.3 (C-5), 58.8 (C-2). The amino acid could not be induced to crystallize.

2-Azetido-2-deoxy-d-xylonic acid (21). A mixture of the azido sugar 20 (470 g), CH₃OH (20 ml) and Ac₂O (1.0 ml) was stirred in an H₂ atmosphere overnight in the presence of 5% palladium-on-carbon (100 mg). Filtration and concentration gave a residue (530 mg, ~100%) which crystallized on addition of EtOH to give α-21; m.p. 176-184°C. Recrystallization from ethanol/hexane gave a product with m.p. 182-184°C; [α]D +26.8° → +6.0° (c 1.2, H₂O); [lit.¹² m.p. 186-190°C; [α]D +55° → 7.8° (c 0.64, H₂O)]. ¹³C NMR (D₂O): α-anomer: 92.0 ppm (C-1), 71.8, 70.8 (C-3, C-4), 62.0 (C-5), 54.9 (C-2), 173.5 and 22.9 (NAc); β-anomer: 96.6 (C-1), 70.4, 66.1 (C-3, C-4, C-5), 57.5 (C-2), 177.8 and 23.1 (NAc).

2-Azetido-2-deoxy-d-lyxonic acid (22). A mixture of 2-azido lactone 16 (2.58 g), water (40 ml) and 4M HCl (5.6 ml) was stirred in an H₂ atmosphere for 8 h in the presence of 5% palladium-on-carbon (200 mg). Filtration and concentration gave the syrupy 2-amino lactone hydrochloride (19) (2.12 g, 77%), as seen from the ¹³C NMR spectrum (D₂O): 173.1 ppm (s, C-1), 84.4 (d, C-4), 67.9 (d, C-3), 60.2 (t, C-5), 53.7 (d, C-2). The product could not be crystallized. The product (650 mg) was basified on a column of Amberlite IR 120 (H⁺, 20 ml) as described above. This gave 2-amino-2-deoxy-d-lyxonic acid (22) as a syrup (500 mg, 65%). ¹³C NMR (D₂O): 172.6 ppm (C-1), 72.8 (C-4), 68.5 (C-3), 63.5 (C-5), 59.7 (C-2).
2-Azido-2-deoxy-d-arabinono- (26) and -d-ribo-n-1,4-lactone (28). The 2-bromo-2-deoxy-d-arabinono lactone (24) (5.0 g) was treated with NaN₃ (5.0 g) in boiling CH₂CN (7 h) as described above to give a syrup (3.5 g, 85%) consisting of the 2-azido lactones 26 and 27 in a ratio of ca. 1:1. Addition of ether gave 1.3 g (32%) of the arabinono isomer (26); m.p. 105–111°C. Recrystallization from ethyl acetate/hexane gave 26 with m.p. 118–120°C; [α]D²⁰ −76° (c 1.6, EtOAc). Anal. C₇H₇N₂O₄; C, H, N. ¹³C NMR (D₂O): 173.8 ppm (C-1), 83.5 (C-4), 72.0 (C-3), 65.3 (C-2), 60.0 (C-5). The mother-liquor from crystallization of 26 contained 26 and the ribo isomer (27) in a ca. 1:4 ratio. ¹³C NMR (D₂O) of 27: 175.7 ppm (C-1), 88.5 (C-4), 71.7 (C-3), 61.9, 61.5 (C-2, C-5). Pure 27 is reported to be crystalline.¹³

2-Amino-2-deoxy-d-arabinono-1,4-lactone hydrochloride (28). The 2-azido lactone 26 (1.0 g) was hydrogenated for 2 h as described above. The residue, which crystallized on addition of EtOH, gave the amino lactone hydrochloride 28 (800 mg, 75%); m.p. 166–170°C. Recrystallization from water/acetonitrile gave a product with m.p. 172–173°C; [α]D²⁰ +45.0° (c 1.8, H₂O); (lit.¹² for the amino lactone: m.p. 175°C; [α]D +44°). Anal. C₅H₁₀ClNO₄; C, H, Cl, N. ¹³C NMR (D₂O): 171.0 ppm (C-1), 84.1 (C-4), 70.0 (C-3), 59.7 (C-5), 56.7 (C-2).

2-Amino-2-deoxy-d-ribo-n-1,4-lactone hydrochloride (29). Crude 2-azido-2-deoxy- d-ribo-n lactone (27) (2.4 g) (obtained as described above from crystallization of 26, and containing ~20% of the latter) was hydrogenated for 5 h as usual. Work-up gave a crystalline residue (1.7 g, 67%); m.p. 183–185°C. Recrystallization from H₂O (a few drops)/acetone gave 29 with m.p. 190–191°C; [α]D²⁰ +6.0° (c 1.9, H₂O). Anal. C₃H₇NO₃Cl; C, H, N, Cl. ¹³C NMR (D₂O): 173.1 ppm (C-1), 88.9 (C-4), 67.9 (C-3), 60.4 (C-5), 51.9 (C-2).

2-Azido-2-deoxy-d-arabino (34). To a solution of borane dimethylsulfide adduct (3.5 ml, 10 M) in THF (10 ml) was slowly added 2-methyl-2-buten-1-ol (7.5 ml) under N₂, and the mixture was then kept at room temperature for 5 h. The azido lactone 26 (1.0 g) in THF (10 ml) was added slowly at 0°C, and the mixture was allowed to reach room temperature overnight. Water (10 ml) was then added and the mixture was boiled for 1 h. Concentration gave a residue which was dissolved in water and extracted three times with dichloromethane. The aqueous phase was concentrated to give syrupy 2-azido-2-deoxy-d-arabino (34) (800 mg, 79%). ¹³C NMR (D₂O): α-anomer: 96.7 ppm (C-1), 72.1 (C-3), 68.6, 67.4, 65.6 (C-2, C-4, C-5); β-anomer: 92.5 (C-1), 69.2, 68.1 (C-3, C-4), 63.4, 61.4 (C-2, C-5). ¹H NMR (500 MHz, D₂O): α-anomer: δ 4.61 (d, H-1, J₁₂ 8.0 Hz), 3.54 (dd, H-2, J₂₃ 10.5 Hz), 3.6–4.2 (m, H-3, H-4, H-5); β-anomer: δ 5.42 (d, H-1, J₁₂ 3.5 Hz), 3.6–4.2 (m, H-2, H-3, H-4, H-5).

2-Amino-2-deoxy-d-arabino hydrochloride (35). A solution of the azido sugar 34 (800 mg) in water (20 ml) containing 1.2 ml 4 M HCl was stirred in a hydrogen atmosphere overnight in the presence of palladium-on-carbon (5%, 200 mg). Filtration and concentration gave a product which crystallized on addition of EtOH. This gave 35 (500 mg, 59%); m.p. 151–153°C; [α]D⁰ −153° (3 min) → −120° (20 h) (c 1.4, H₂O); (lit.¹² m.p. 154–157°C; [α]D −158° → −120°). ¹³C NMR (D₂O): 94.1 ppm (C-1, β), 90.2 (C-1, α), 69.7, 68.7, 68.2, 67.5, 66.3, 63.2 (C-3, C-4, C-5), 55.4, 52.1 (C-2).

5-O-Acetyl-2-acetamido-2,3-dideoxy-d-gluco-pent-2-en-1,4-lacton (36). The 2-bromo lactone 24 (or the isomeric bromo lactone 13) (5.0 g) was treated with sodium azide as described above to give a mixture of the 2-azido lactones 26 and 27 (3.85 g, 94%). The mixture was dissolved in CH₃OH (50 ml) together with acetic anhydride (8 ml) and stirred in a hydrogen atmosphere for 3 h in the presence of palladium-on-carbon (5%, 500 mg). Filtration and concentration gave a ca. 1:1 mixture of the acetamido compounds 30 and 31 (~5 g). ¹⁳C NMR (D₂O): 177.5, 174.1, 175.2, 175.0 ppm (C-1 and carboxyl), 88.6, 83.8 (C-4), 71.4, 69.7 (C-3), 61.6, 60.7 (C-5), 58.2, 53.6 (C-2), 22.6 (NaOAc), 21.4 (OAc). Acetic anhydride (15 ml) and 60% aqueous HClO₄ (a few drops) were added, and after 1 h water was added; after a further 15 min NaOAc was added until neutral. The residue obtained on concentration was dissolved in EtOAc and the solution was filtered through silica gel. The filtrate was concentrated to give the acetates 32 and 33 (~6.4 g) (ca. 1:1). ¹³C NMR (CDCl₃): 172.6, 170.8, 170.1, 169.8, 169.4 ppm (C-1 and carbonyl), 80.3, 77.8 (C-4), 73.1, 70.1 (C-3), 62.7, 62.4 (C-5), 54.8, 49.4

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(C-2), 21.7 (NAc), 20.0 (OAc). The product was stirred in dry EtOAc (100 ml) with KF (10 g) for 5 h, after which the solution was filtered and concentrated to give a crystalline residue (3.6 g) of 36; addition of ether gave 3.0 g (59 %) of 36, m.p. 150–154°C. Recrystallization from ethyl acetate/hexane gave 36 with m.p. 153–154.5°C; \([\alpha]_D^{20} +35.8^\circ \, (c \, 0.7, \, \text{EtOAc})\) (Reported\(^2\) for the L-isomer: m.p. 160–161°C; \([\alpha]_D\) was not reported). Anal. C\(_9\)H\(_9\)N\(_2\)O\(_2\)· C, H, N. \(^{13}\)C NMR (CDCl\(_3\)): 170.0, 169.2, 168.8 ppm (C-1 and carbonyl), 126.7 (C-2), 124.7 (C-3), 78.8 (C-4), 63.2 (C-5), 23.0 (NAc) and 20.1 (OAc).

5-O-Acetyl-2-acetamido-2,3-dideoxy-\(D\)-threopentono-1,4-lactone (37). \(a\): From azido lactones. A crude mixture of the azido lactones 26 and 27 (4.2 g) was hydrogenated in EtOAc (100 ml) containing Et,N (16.8 ml), acetic anhydride (8.0 ml) and palladium-on-carbon (5 %, 600 mg) at ca. 50 atm. overnight. Filtration and concentration gave a residue which was dissolved in water (200 ml). The solution was extracted with CH\(_2\)Cl\(_2\) (10 ml) which was discarded. The CH\(_2\)Cl\(_2\) probably contained a small portion of 2,3-oxazolidines. The aqueous phase was then subjected to continuous extraction with EtOAc for 3 h. The organic phase was dried (Na\(_2\)SO\(_4\)), filtered and concentrated to give syrupy 37 (3.0 g, 58 %), which was pure as seen from a \(^{13}\)C NMR spectrum (CDCl\(_3\)): 174.1, 170.6, 170.2 ppm (C-1 and carbonyl), 74.5 (C-4), 64.2 (C-5), 49.1 (C-2), 30.1 (C-3), 22.0 (NAc), 20.1 (OAc). A sample was purified by kugelrohr distillation: bp ~240–250°C/0.5 mmHg; \([\alpha]_D^{20} +46.9^\circ \, (c \, 0.7, \, \text{EtOAc})\). Anal. C\(_9\)H\(_9\)N\(_2\)O\(_2\), C, H, N. Starting from the xylo,lxyo azide lactones (15 and 16) (4.0 g) and using the same procedure, 2.4 g (48 %) of 37 was obtained. A \(^{13}\)C NMR spectrum was identical with that of the product described above.

\(b\): From 36. The unsaturated lactone 36 (1.0 g) was hydrogenated in EtOH (50 ml) in the presence of palladium-on-carbon (5 %, 100 mg) at 100 atm. Filtration and concentration gave 37 (1.0 g, 99 %), which was pure as seen from a \(^{13}\)C NMR spectrum, identical with that described above. \([\alpha]_D^{20} +46.3^\circ \, (c \, 0.24, \, \text{EtOAc})\).

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References


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