Carbohydrate Research, 232 (1992) 341–348
Elsevier Science Publishers B.V., Amsterdam

Note

Synthesis of methyl 3-amino-deoxy-D-alluronate *

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(Received October 22nd, 1991; accepted January 11th, 1992)

Aminodeoxyuronic acids have been identified as constituents of bacterial polysaccharides [1] and antibiotics [2]. In addition, the C-3/6 segment of 3-amino-3-deoxy-D-glycopyranuronic acids is closely similar to the structure of the antiepileptic and hypotensive drug 4-amino-3-hydroxybutyric acid and carnitine (vitamin B_T, β-hydroxy-γ-butyrotrimethylbetaine).

3-Amino-3-deoxy-D-glucuronic acid has been synthesised [3] and, because of their potential biological importance, syntheses of other stereoisomers are desirable. Moreover, such compounds of their derivatives could serve as chiral building blocks [4]. We now report a synthesis or methyl 3-amino-3-deoxy-D-alluronate.

Treatment of 3-azido-3-deoxy-1,2 : 5,6-di-*O*-isopropylidene-α-D-allofuranose [5] (**1**) with aqueous 77% acetic acid (3 h, 60°) removed the 5,6-*O*-isopropylidene group to give the diol **2** (80%). Tritylation of **2** followed by acetylation gave an almost quantitative yield of the 6-*O*-trityl derivative **3**. Oxidation of **3** with the Jones reagent [6,7] followed by methylation of the resulting uronic acid under phase-transfer conditions [8] gave the methyl uronate **4** (52% from **3**). This route to **4** was more reproducible than the well-known method of regioselective Pt-catalysed oxidation of the primary hydroxyl group [3]. Zemplén *O*-deacetylation of **4** gave **5**, from which the target methyl 3-amino-3-deoxy-D-alluronate (**8**) was obtained by two routes.

Hydrogenation (Pd black) of **5** gave the amine **6** (96%), which was deisopropylidenated by Dowex 50 (H^+) resin in methanol (3 h, 60°) to give the mixture **8a–8d** contaminated by the corresponding methyl glycosides (total yield, 30%). However, the reverse sequence of reactions was more convenient. Thus, treatment of **5** with aqueous 90% trifluoroacetic acid quantitatively afforded a mixture (**7a–7d**) of α,β-pyranose and α,β-furanose forms of methyl 3-azido-3-deoxy-D-alluronate,

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* Presented at the 6th European Symposium on Carbohydrate Chemistry, Edinburgh, September 8–13th, 1991.

1
2 R¹ = R² = H
3 R¹ = Ac, R² = Tr
4 R = Ac
5 R = H
6
7a R = N₃
8a R = NH₂
7b R = N₃
8b R = NH₂
7c R = N₃
8c R = NH₂
7d R = N₃
8d R = NH₂

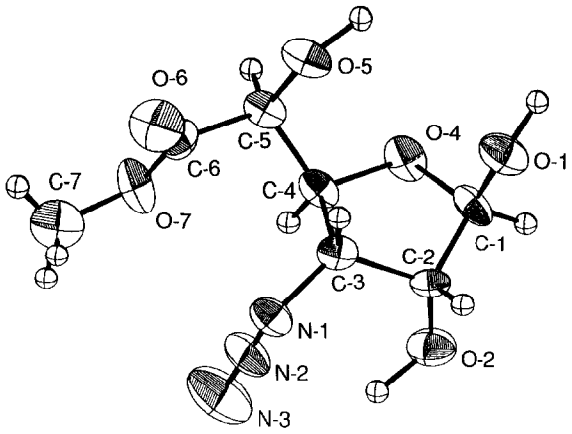

Fig. 1. A view of the molecule of methyl 3-azido-3-deoxy-β-D-allofuranuronate (**7a**).

from which the β-furanose form **7a** crystallised. In the FAB mass spectra of **2–5** and **7**, the fragments $(M + H - 28)^+$ and/or $(M + H - 26)^+$, which are characteristic for azido compounds [9], were observed.

Compound **7a** mutarotates on dissolution in water. The ^{1}H- and ^{13}C-NMR spectra of an equilibrium mixture revealed **7a–7d** in the ratios ~30:15:50:5. Thus, **7a** (β-furanose form) has characteristic, downfield signals for C-1 and C-4 at 102.9 and 82.5 ppm, respectively, and **7b** (α-furanose) was identified on the basis of the signals for C-1 and C-4 98.1 and 83.1 ppm, respectively. The relatively upfield signals for C-1 (95.4 and 93.2 ppm) were assigned to **7c** (β-pyranose) and **7d** (α-pyranose), respectively. The spectra of **2–7** were assigned on the basis of data for 3-azido-3-deoxy- and 3-amino-3-deoxy-allose derivatives [10].

Since the ^{1}H- and ^{13}C-NMR data did not definitely identify the structure of crystalline **7a** due to mutarotation, we used X-ray crystallographic analysis for this purpose (see Fig. 1, Tables I and II, and Experimental).

Hydrogenation (Pd black) of the azide **7a** gave an almost quantitative yield of methyl 3-amino-3-deoxy-D-alluronate as a mixture of β-furanose (**8a**), α-furanose (**8b**), β-pyranose (**8c**), and α-pyranose (**8d**) in the ratios ~20:10:50:20. These proportions were determined on the basis of intensities of the H-1 and C-1 signals.

EXPERIMENTAL

General methods.—Melting points were determined with a Boetius apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 141 polarimeter on solutions in $CHCl_3$ at 20 ± 2°. NMR spectra were recorded with Bruker WH-90/DS and WM-360 instruments on solutions in $CDCl_3$ (internal Me_4Si). IR spectra were recorded for Nujol mulls with a Perkin–Elmer spectrometer (580 V). Mass spectra were recorded with a Kratos MS-50 instrument equipped with an FAB-11 NF (Ion Tech. Ltd.) FAB source (the ionisation gas was Ar, and

TABLE I

Fractional co-ordinates ($\times 10^4$) of non-hydrogen atoms of **7a** with estimated standard deviations in parentheses

Atom	*x*	*y*	*z*
O-1	−1895 (11)	553 (7)	5293 (3)
O-2	532 (14)	2647 (6)	5950 (3)
O-3	3544 (17)	2060 (8)	7009 (4)
O-4	944 (15)	410 (7)	7317 (3)
O-5	848 (14)	−1893 (6)	4956 (4)
O-6	530 (15)	1360 (6)	4371 (3)
N-1	3884 (17)	−894 (8)	6084 (4)
N-2	2753 (18)	−1822 (9)	6337 (4)
N-3	1964 (24)	−2711 (11)	6607 (6)
C-2	−297 (18)	334 (9)	5910 (5)
C-3	2401 (19)	−49 (9)	5623 (5)
C-4	1756 (18)	−605 (8)	4913 (5)
C-5	−455 (19)	250 (9)	4675 (5)
C-6	−236 (19)	1560 (9)	6337 (5)
C-7	1638 (23)	1399 (11)	6928 (5)
C-8	2624 (33)	75 (13)	7878 (7)

TABLE II

Interatomic distances (Å) and angles (°) of **7a** (standard deviations in parentheses)

Bond distances		Bond angles	
C-2–O-1	1.465 (0.011)	O-1–C-2–C-3	104.3 (0.7)
C-5–O-1	1.439 (0.011)	O-1–C-2–C-6	109.0 (0.7)
C-6–C-2	1.408 (0.011)	C-2–O-1–C-5	110.9 (0.7)
C-7–O-3	1.202 (0.014)	O-1–C-5–O-6	111.0 (0.7)
C-7–O-4	1.320 (0.013)	O-1–C-5–C-4	105.0 (0.7)
C-8–O-4	1.428 (0.016)	O-2–C-6–C-2	112.7 (0.8)
C-4–O-5	1.415 (0.011)	O-2–C-6–C-7	108.4 (0.8)
C-5–O-6	1.386 (0.011)	O-3–C-7–O-4	125.9 (1.0)
N-2–N-1	1.224 (0.012)	O-3–C-7–C-6	123.7 (1.0)
C-3–N-1	1.462 (0.013)	O-4–C-7–C-6	110.4 (0.9)
N-3–N-2	1.133 (0.015)	C-7–O-4–C-8	117.4 (0.9)
C-3–C-2	1.541 (0.013)	O-5–C-4–C-3	112.0 (0.8)
C-6–C-2	1.515 (0.013)	O-5–C-4–C-5	109.0 (0.7)
C-4–C-3	1.526 (0.014)	O-6–C-5–C-4	110.1 (0.8)
C-5–C-4	1.509 (0.013)	N-1–N-2–N-3	172.3 (1.1)
C-7–C-6	1.502 (0.014)	N-2–N-1–C-3	117.9 (0.8)
		N-1–C-3–C-2	113.6 (0.8)
		N-1–C-3–C-4	115.8 (0.8)
		C-2–C-3–C-4	103.1 (0.8)
		C-3–C-2–C-6	113.2 (0.8)
		C-2–C-6–C-7	109.6 (0.8)
		C-3–C-4–C-5	102.5 (0.7)
		N-1–C-3–C-4	115.8 (0.8)
		C-2–C-3–C-4	103.1 (0.8)
		C-3–C-2–C-6	113.2 (0.8)
		C-2–C-6–C-7	109.6 (0.8)
		C-3–C-4–C-5	102.6 (0.7)

the matrix was thioglycerol). TLC was carried out on Silufol and column chromatography on Silasorb 600 (LC 30 μm).

3-Azido-3-deoxy-1,2-O-isopropylidene-α-D-allofuranose (**2**).—A solution of 3-azido-3-deoxy-1,2:5,6-*O*-isopropylidene-α-D-allofuranose [5] (**1**; 8.50 g, 30.0 mmol) in aq 77% acetic acid (20 mL) was heated for 3 h at 60–65°C, then concentrated. Column chromatography (2:1 EtOAc–hexane) of the residue gave **2** (5.90 g, 80%). After crystallisation from EtOAc–hexane, **2** had mp 75–76°, $[\alpha]_D$ +106° (*c* 1.17); ν_{max} 2110 cm^{-1} (N_3). ^{1}H-NMR data: δ 5.78 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 4.76 (dd, 1 H, $J_{2,3}$ 4.5 Hz, H-2), 4.11–3.82 and 3.84–3.44 (2 m, 5 H, H-3,4,5,6a,6b), 2.73 and 2.33 (2 bs, 2 H, HO-5,6), 1.56 and 1.36 (2 s, 6 H, CMe_2). FAB-mass spectrum: *m/z* 246 $(M + H)^+$, 230 $(M - 15)^+$, 220 $(M + H - 26)^+$.

Anal. Calcd for $C_9H_{15}N_3O_5$ (245.2): C, 44.08; H, 6.12; N, 17.13. Found: C, 44.08; H, 6.18; N, 16.33.

5-O-Acetyl-3-azido-3-deoxy-1,2-O-isopropylidene-6-O-trityl-α-D-allofuranose (**3**).—A mixture of **2** (5.00 g, 20.41 mmol), dry pyridine (45 mL), and chlorotriphenylmethane (9.28 g, 33.26 mmol) was stirred at 60° for 3 h. Acetic anhydride (20 mL) was added, and the mixture was kept overnight at room temperature, then concentrated with the addition of portions of water and MeOH. Column chromatography (1:6 EtOAc–hexane) of the residue gave amorphous **3** (10.47 g, 97%), $[\alpha]_D$ +29° (*c* 1.37); ν_{max} 2110 cm^{-1} (N_3). ^{1}H-NMR data: δ 7.27 (m, 15 H, 3 Ph), 5.67 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 5.27 (m, 1 H, H-5), 4.64 (pseudo t, 1 H, *J* 4 Hz, H-2), 4.31 (dd, 1 H, $J_{3,4}$ 10, $J_{4,5}$ 6 Hz, H-4), 3.33 (m, 3 H, H-3,6a,6b), 2.09 (s, 3 H, Ac), 1.56, 1.33 (2 s, 6 H, CMe_2). FAB-mass spectrum: *m/z* 502 $(M + H - 28)^+$.

Anal. Calcd for $C_{30}H_{31}N_3O_6$ (529.6): C, 68.03; H, 5.90; N, 7.93. Found: C, 67.84; H, 5.93; N, 7.22.

Methyl 5-O-acetyl-3-azido-3-deoxy-1,2-O-isopropylidene-α-D-allofuranuronate (**4**).—To a solution of **3** (2.00 g, 3.78 mmol) in acetone (9 mL) and CH_2Cl_2 (6 mL) at 0° was added a solution of chromium trioxide (1.6 g, 16 mmol) in 3.2 M H_2SO_4 (7 ml) dropwise with stirring, and the mixture was allowed to attain room temperature. After 4–4.5 h, the mixture was poured into ice–water and extracted thrice with $CHCl_3$. The combined extracts were washed twice with water and concentrated. Saturated $NaHCO_3$ (5 mL), tetrabutylammonium iodide (1.0 g, 2.71 mmol), and a solution of MeI (1 mL, 16 mmol) in CH_2Cl_2 (20 mL) were added to the residue. The mixture was stirred overnight at room temperature, then diluted with CH_2Cl_2, and the organic layer was washed three times with water, dried, and concentrated. Column chromatography (1:4 EtOAc–hexane) of the residue gave **4** (0.62 g, 52%), mp 64–66° (from $CHCl_3$–hexane), $[\alpha]_D$ +117.5° (*c* 1.12); ν_{max} 2110 cm^{-1} (N_3). ^{1}H-NMR data: δ 5.78 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 5.40 (d, 1 H, $J_{4,5}$ 2.7 Hz, H-5), 4.73 (dd, 1 H, $J_{2,3}$ 4.5 Hz, H-2), 4.45 (dd, 1 H, $J_{3,4}$ 10 Hz, H-4), 3.78 (s, 3 H, COOMe), 3.72 (m, 1 H, H-3), 2.16 (s, 3 H, Ac), 1.58, 1.33 (2 s, 6 H, CMe_2). FAB-mass spectrum: *m/z* 300 $(M - 15)^+$, 290 $(M + H - 26)^+$, 288 $(M + H - 28)^+$.

Anal. Calcd for $C_{12}H_{17}N_3O_7$ (315.3): C, 45.71; H, 5.44; N, 13.33. Found: C, 45.98; H, 5.40; N, 13.16.

Methyl 3-azido-3-deoxy-1,2-O-isopropylidene-α-D-allofuranuronate (**5**).—A solution of **4** (0.38 g, 1.21 mmol) in MeOH (4 mL) was treated with methanolic M NaOMe (0.1 mL), then kept for 15 min at room temperature. A few drops of glacial acetic acid were added and the solution was concentrated. Column chromatography (1:3 EtOAc–hexane) of the residue gave **5** (0.29 g, 88.5%), mp 82–84° (from $CHCl_3$–hexane), $[\alpha]_D$ +159° (*c* 1.30); ν_{max} 2110 cm^{-1} (N_3). ^{1}H-NMR data: δ 5.80 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 4.73 (pseudo t, 1 H, *J* 4 Hz, H-2), 4.47 (m, 2 H, H-4,5), 3.87 (s, 3 H, COOMe), 3.58 (m, 1 H, H-3), 3.04 (d, 1 H, *J* 5 Hz, HO-5), 1.56, 1.33 (2 s, 6 H, CMe_2). FAB-mass spectrum: *m/z* 274 $(M + H)^+$, 258 $(M - 15)^+$, 248 $(M + H - 26)^+$, 246 $(M + H - 28)^+$.

Anal. Calcd for $C_{10}H_{15}N_3O_6$ (273.3): C, 43.96; H, 5.53; N, 15.38. Found: C, 44.22; H, 5.58; N, 15.14.

Methyl 3-azido-3-deoxy-β-D-allofuranuronate (**7a**).—A solution of **5** (0.25 g, 0.91 mmol) in aq 90% trifluoroacetic acid (3 mL) was kept at room temperature for 20 min, then concentrated, and water was evaporated twice from the residue (0.21 g, 99%). Crystallisation from EtOAc–hexane gave **7a**. The mother liquors were concentrated, the residue was crystallised, and this procedure was repeated twice to give more **7a** (total yield, 0.13 g, 60%), mp 98–100°, $[\alpha]_D$ +44° (after 10 min), +29.5° (after 60 min) (*c* 1.05, H_2O); ν_{max} 2120 cm^{-1} (N_3). FAB-mass spectrum: *m/z* 234 $(M + H)^+$, 206 $(M + H - 28)^+$.

Anal. Calcd for $C_7H_{11}N_3O_6$ (233.1): C, 36.07; H, 4.72; N, 18.02. Found: C, 36.46; H, 4.66; N, 17.70.

(a) Crystal data. $C_7H_{11}N_3O_6$: $M = 233.1$, orthorombic, space group $P2_12_12_1$, $a = 5.121$ (2), $b = 10.355$ (3), $c = 19.346$ (6) Å, $V = 1025.9$ (6) Å^3, $D_c = 1.51$ g cm^{-3}, $Z = 4$, $F(000) = 488$, $\mu = 0.9$ cm^{-1}.

(b) Data collection. Intensities of 825 independent reflections were measured on four circles with a Syntex-$P2_1$ difractometer (MoK_α radiation, graphite monochromator, $\theta/2\theta$-scan, $2\theta_{max} = 45°$). Lattice parameters were refined from 17 reflections; one standard reflection showed no significant decay.

(c) Structure analysis. The structure was solved by the direct method. For refinement, 695 reflections with $I > 2\sigma(I)$ were employed. The structure was refined by a full-matrix least-squares method with anisotropic thermal parameters for carbon, nitrogen, and oxygen atoms. The hydrogen atoms of methyl and hydroxyl groups were located by a difference Fourier map. The co-ordinates of other hydrogen atoms were calculated geometrically. The H atoms were not refined. The final *R* factor was 0.0717. All calculations were carried out with the help of programme complex AREN [11].

Spectroscopic identification of **7a–7d**.—The ^{1}H-NMR spectrum of a solution of **7a** in D_2O contained H-1 signals with ratios of intensities of 15:30:5:50 at δ 5.27 (d, *J* 3.9 Hz), 5.12 (s), 5.05 (d, *J* 3.5 Hz), and 4.76 (d, *J* 7.9 Hz) for α-furanose **7b**, β-furanose **7a**, α-pyranose **7d**, and β-pyranose **7c**, respectively. Two singlets in the ratio 9:5 for COOMe were attributed tentatively to **7c** + **7b** (δ 3.77) and **7d** + **7a** (δ 3.75), respectively. All the other signals in the range δ 4.35–3.90 were poorly resolved.

Signals in the ^{13}C-NMR spectrum of a solution of **7a–7d** in D_2O were assigned as follows: **7a** δ 102.9 (C-1), 82.5 (C-4), 77.3 (C-2), 72.2 (C-5), 62.3 (C-3); **7b** δ 98.1 (C-1), 83.1 (C-4), 72.2, 71.9 (C-2,5), 61.6 (C-3); **7c** δ 95.4 (C-1), 74.8, 71.7, 70.0, 67.6 (C-2,3,4,5); **7d** δ 93.2 (C-1), 69.5, 69.4, 68.4, 65.7 (C-2,3,4,5). The spectrum also contained two weak signals at 174.6 and 173.0 ($COCH_3$), and three signals at 54.5 (2 C), 54.4, and 54.3 ($COCH_3$).

Methyl 3-amino-3-deoxy-1,2-O-isopropylidene-α-D-allofuranuronate (**6**).—A solution of **5** (0.15 g, 0.55 mmol) in MeOH (7 mL) was hydrogenated in the presence of Pd black (20 mg) for 1.5 h, then filtered, and concentrated. Column chromatography (95 : 5 chloroform–2-propanol) of the residue gave amorphous **6** (0.13 g, 96%), $[\alpha]_D$ +66.5° (*c* 0.63, MeOH). ^{1}H-NMR data: δ 5.76 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 4.42 (m, 2 H, H-2,5), 3.89 (dd, 1 H, $J_{3,4}$ 10, $J_{4,5}$ 4 Hz, H-4), 3.76 (s, 3 H, COOMe), 3.36 (m. 1 H, H-3), 2.36 (bs, 3 H, NH_2, OH), 1.51, 1.31 (2 s, 6 H, CMe_2). FAB-mass spectrum: *m/z* 248 $(M + H)^+$.

Anal. Calcd for $C_{10}H_{17}NO_6$ (247.3); C, 48.58; H, 6.93; N, 5.66. Found: C, 48.63; H, 6.64; N, 5.28.

Hydrogenolysis of **7a**.—A solution of **7a** (0.15 g, 0.64 mmol) in MeOH (7 mL) was hydrogenated in the presence of Pd black (20 mg) for 3 h, then filtered, and concentrated to give a solid mixture of **8a–8d** (0.13 g, 98%), mp 138–153°, $[\alpha]_D$ +35° (after 10 min), +27° (after 60 min) (*c* 0.75, H_2O). FAB-mass spectrum: *m/z* 208 $(M + H)^+$.

Anal. Calc. for $C_7H_{13}NO_6$ (207.2): C, 40.58; H, 6.32; N, 6.76. Found: C, 40.55; H, 6.44; N, 6.68.

Spectroscopic identification of **8a–8d**.—The ^{1}H-NMR spectrum of a solution of **8a–8d** in D_2O contained H-1 signals with ratios of intensities of 10 : 20 : 20 : 50 at δ 5.25 (d, *J* 4 Hz), 5.06 (s), 5.00 (d, *J* 3.5 Hz), and 4.80 (d, *J* 8.1 Hz) for α-furanose **8b**, β-furanose **8a**, α-pyranose **8d**, and β-pyranose **8c**, respectively, as well as signals at δ 3.72, 3.75, 3.76, and 3.78 ppm (4 s, 4 COOMe). The ^{13}C-NMR (D_2O) spectrum contained peaks, *inter alia*, at δ 103.4 (C-1), 85.1 (C-4), and 77.8 (C-2) for **8a**, δ 98.7 (C-1) and 85.5 (C-4) for **8b**, δ 95.3 (C-1) for **8c**, and δ 93.9 (C-1) for **8d**. The spectrum also contained eight peaks at 56.7, 56.0, 55.3, 54.9, 54.8, 54.6, 54.5, and 54.4 ppm, representing $COOCH_3$ and C-3 resonances of four isomers, as well as two weak peaks at 172.3 and 171.3 ppm ($COOCH_3$).

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