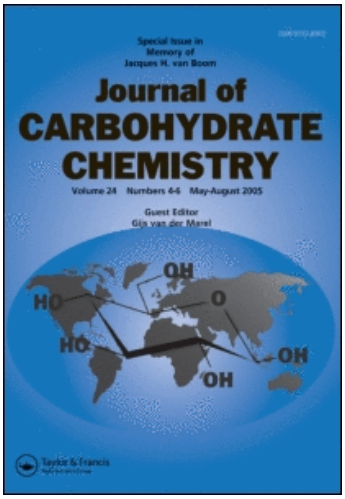

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An Allylic Rearrangement Arising from Reaction of Fluoride Ion and A 3-Chloro, 4,5-Unsaturated Uronate Derivative

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AN ALLYLIC REARRANGEMENT ARISING FROM REACTION OF FLUORIDE ION AND A 3-CHLORO, 4,5-UNSATURATED URONATE DERIVATIVE

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ABSTRACT

Reaction of methyl [benzyl 2-[(benzyloxycarbonyl)-amino]-3-chloro-2,3,4-trideoxy-ß-L-threo-hex-4-enopyranosid]uronate (7) with silver fluoride gave the 5-fluoro, 3,4-unsaturated uronate derivative 8, which, on treatment with methanolic ammonia, afforded the corresponding 5-methoxy, uronamide 9. The structures of 8 and 9 were confirmed by spectral data and by x-ray crystallographic analysis of 8. ^{1}H NMR spectroscopy parameters for 9 and its diastereomer 11 have been used to probe the conformational preferences in solution.

INTRODUCTION

In a previous communication[1] we reported the base-induced, allylic rearrangement of the 3,4-di-O-methylsulfonyl hexopyranosiduronate derivative 1. This reaction

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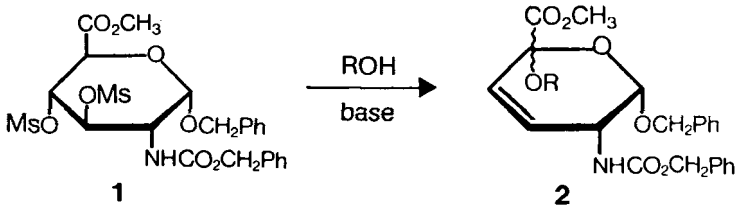


1 2

Scheme 1

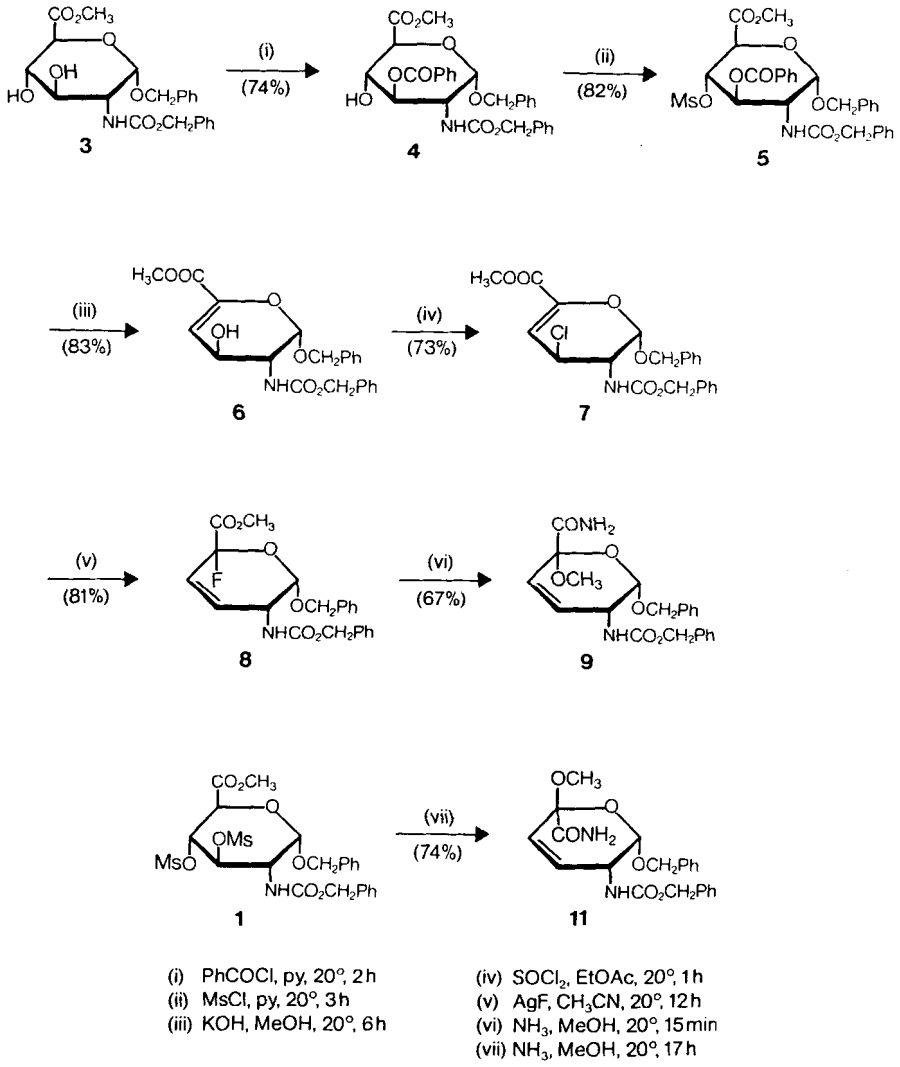
was conducted in alcoholic solution and yielded the 5-alkoxy, 3,4-unsaturated hexopyranosiduronate derivative 2 (Scheme 1).

We would like to report here a similar reaction involving fluoride ion and methyl [benzyl 2-[(benzyloxycarbonyl)amino]-3-chloro-2,3,4-trideoxy-ß-L-threo-hex-4-enopyranosid]uronate (7) to give a new fluorine-containing sugar (8) (Scheme 2).

RESULTS AND DISCUSSION

Methyl [benzyl 2-[(benzyloxycarbonyl)amino]-3-chloro-2,3,4-trideoxy-ß-L-threo-hex-4-enopyranosid]uronate (7) was prepared in three steps[2] from methyl [benzyl 2-[(benzyloxycarbonyl)amino]-2-deoxy-α-D-glucopyranosid]-uronate (3). Treatment of 3 with 1 equivalent of benzoyl chloride in pyridine gave the monobenzoylated derivative 4 as an oil which, on mesylation, afforded crystalline 5[3]. In the next step the alkene 6 was obtained by treatment of 5 with methanolic potassium hydroxide. Finally, reaction of 6 with thionyl chloride in ethyl acetate gave the desired chloro compound 7.

In the ^{1}H NMR spectrum of 7 H-3 was observed at δ 4.57 as a doublet of doublets ($J_{2,3}$ ~8 Hz and $J_{3,4}$ ~2.5 Hz), reflecting trans-diaxial coupling to H-2 and three-bond allylic coupling with a quasi-axial allylic proton[4]. The observed values are very similar to or identical with



Scheme 2

those reported for the 2-hydroxy compound 6 ($J_{2,3}$ ~9 Hz and $J_{3,4}$ = 2.5 Hz)[3] and for methyl 1,2,3-tri-O-acetyl-4-deoxy-ß-L-threo-hex-4-enopyranuronate ($J_{2,3}$ = 7 Hz and $J_{3,4}$ = 3 Hz)[5], and may be interpreted in terms of a $^2H_1$ half-chair conformation[6] (10, Figure 1).

Reaction of 7 with silver fluoride in acetonitrile then afforded the crystalline fluoro derivative 8 in 81%

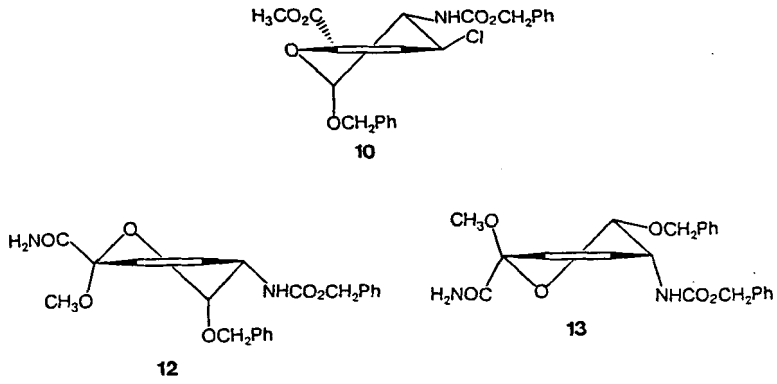


Figure 1

yield. The fluoro substituent in the new uronate 8 is linked to C-5; thus its reactivity should be similar to a glycosyl fluoride. The fluorine in 8 is additionally activated because it is allylic. Due to this "double" activation, the sugar was expected to be very reactive. Accordingly, it was converted within minutes into the corresponding 5-C-methoxyuronamide 9 when treated with methanolic ammonia at room temperature. The structures of 8 and 9 were proved by elemental analysis and spectral data (UV, CD and NMR), and by X-ray crystallographic analysis of 8. A projection of the structure indicating atom numbering, and a stereographic view are given in Figures 2 and 3, respectively. The absorption at ~240 nm in the UV spectra of 6 and 7 was not observed in that of 8, indicating that the double bond is isolated in this latter compound. The NMR-signal of H-3 (δ6.0) of 8 appeared at a 1.4-ppm lower field than that (δ 4.57) of the chloro compound 7, which is consistent with a vinylic proton. The circular dichroism spectra of 8 and 9 showed negative bands at 217 nm (8), and 236 and 206 nm (9), suggesting that both compounds have the same ring-conformation. In contrast, a positive band was observed at 233 nm for the diastereomer of 9 (11), obtained as the major product of the reaction of the 3,4-di-O-methylsulfonyl derivative 1

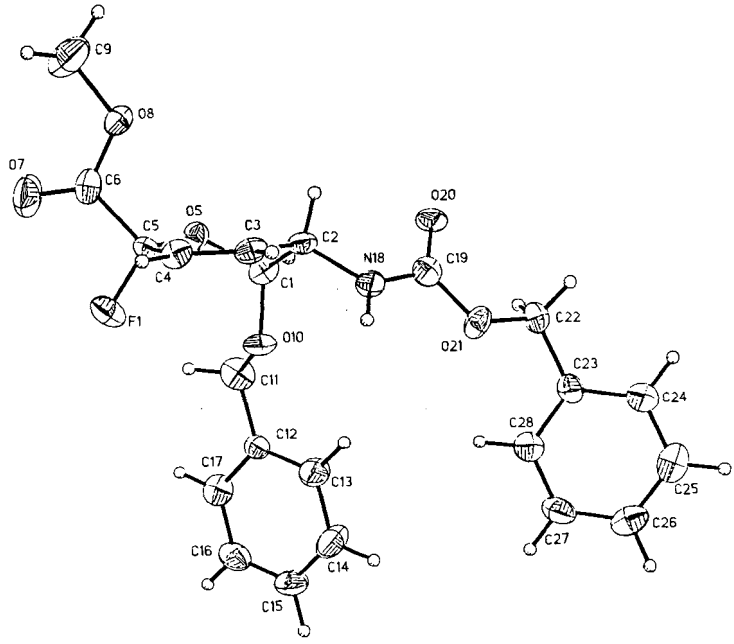


Figure 2: Projection of 8 with 50% probability ellipsoids, indicating numbering of atoms

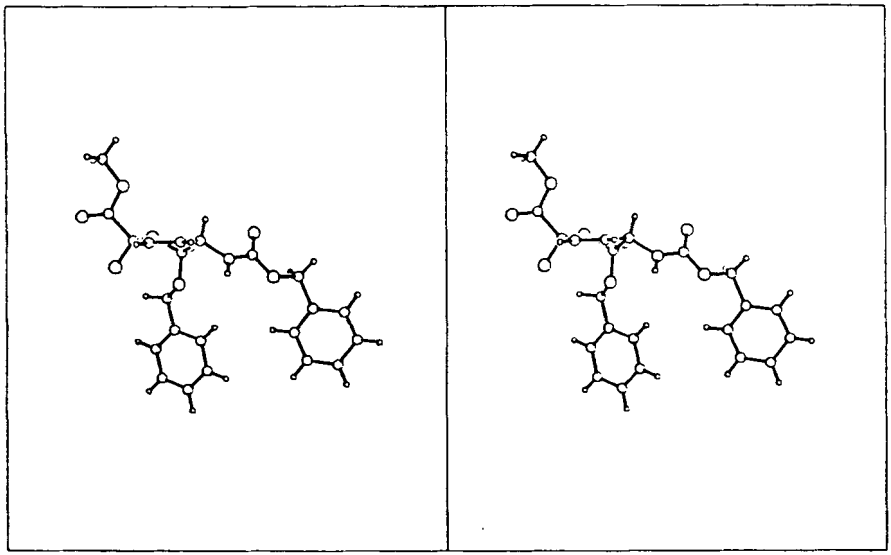


Figure 3: Stereoprojection of 8

with methanolic ammonia[1]. Only traces of 9 were obtained by this route. This reversed CD suggests a mirror-image conformation of the ring.

The coupling constants observed in the ^1H NMR spectra of diastereoisomers 9 ($J_{1,2}$ = 4.4 Hz and $J_{2,3}$ = 2.5 Hz) and 11 ($J_{1,2}$ = 2 Hz and $J_{2,3}$ ≈ 5.5 Hz) suggest also that they adopt different conformations. The observed $J_{2,3}$ values are indicative of a quasi-axial disposition of H-2 in 9 and of a quasi-equatorial disposition[4] of this proton in diastereoisomer 11, and are consistent with the $^0H_1$ (12) and $^1H_0$ (13) conformations as the preponderant half-chair forms of 9 and 11, respectively. The C_1-benzyl and C_5-methoxy substituents in 12 are thus in a favourable axial and quasi-axial position (anomeric effect), respectively, but the C_2-amino substituent in an unfavourable quasi-equatorial position (allylic effect). In contrast, the quasi-axial positions of the C_2-amino and C_5-methoxy groups are favourable in 13, whereas that of the C_1-benzyl group is unfavourable (quasi-equatorial). The coupling values of 8 and 9 are very similar, indicating that both compounds adopt a similar conformation.

Further chemical transformations of the (hex-4-eno-pyranosid)uronate 7 are underway and will be reported in due course.

EXPERIMENTAL

General. Melting points were determined on a Büchi melting point apparatus and are not corrected. Spectral measurements were performed using the following instruments: ^1H NMR: Bruker HX 270 and WH 400; ^{13}C NMR: Bruker WH 400. Chemical shifts are given in ppm relative to tetramethylsilane (δ = 0 ppm) as internal standard. UV: Uvikon 810 spectrometer (Kontron). CD: modified Jobin-Yvon

Mark II dichrograph. All spectra were measured in dioxane (1 mg/ml); positive and negative maxima are given. Optical rotations: Perkin-Elmer polarimeter Model 141. TLC was performed on precoated plates of silica gel (Kieselgel 60 F_{254}, Merck) and detection was effected by spraying with 10% sulfuric acid and subsequent heating. Column chromatography was carried out on silica gel 60 (0.2-0.5 mm, 35-70 mesh ASTM) of Merck.

Methyl [benzyl 3-O-benzoyl-2-[(benzyloxycarbonyl)-amino]-2-deoxy-α-D-glucopyranosid]uronate (4). To a cold, stirred solution of methyl [benzyl 2-[(benzyloxycarbonyl)-amino]-2-deoxy-α-D-glucopyranosid]uronate (3, 25.8 g, 60 mmol) in dry pyridine (200 ml) was added a solution of benzoyl chloride (7.1 ml, 60 mmol) in toluene (80 ml), dropwise, over 0.5 h. After the addition the mixture was stirred at room temperature for 2 h, poured on ice-water, stirred for 30 min, and extracted with dichloromethane. The dichloromethane extracts were washed with cold dilute hydrochloric acid and water, dried, and evaporated to dryness. The residue was chromatographed on silica gel by using ethyl acetate-hexane as the eluant, to give 23.9 g (74%) oil, $[\alpha]_D^{25}$ = + 98.5° (c 1.0, methanol). Anal. Calcd for $C_{29}H_{29}NO_9$ (535.53): C, 65.04; H, 5.46; N, 2.62. Found: C, 64.93; H, 5.02; N, 2.48.

Methyl [benzyl 3-O-benzoyl-2-[(benzyloxycarbonyl)-amino]-2-deoxy-4-O-(methylsulfonyl)-α-D-glucopyranosid]uronate (5). Methanesulfonyl chloride (6.8 ml, 88 mmol) in toluene (20 ml) was added dropwise to a stirred solution of compound 3 (20.2 g, 37.6 mmol) in dry pyridine (170 ml). After being stirred for 3 h at room temperature, the mixture was poured on ice-water, stirred for 30 min and extracted with dichloromethane. The dichloromethane extracts were washed with cold dilute hydrochloric acid, 10% aqueous sodium hydrogen carbonate, and water, dried, and evaporated to dryness. The residue was recrystallized

from isopropyl ether to give 18.9 g (82%) product, mp 110-111° C, $[\alpha]_D^{25}$ + 94° (c 1.0, chloroform). Anal. Calcd for $C_{30}H_{31}NO_{11}S$ (613.63): C, 58.72; H, 5.09; N, 2.28; S, 5.22. Found: C, 58.54; H, 4.99; N,2.15; S, 5.22.

Methyl [benzyl 2-[(benzyloxycarbonyl)amino]-2,4-dideoxy-ß-L-threo-hex-4-enopyranosid]uronate (6). A solution of 5 (7.5 g, 12.2 mmol) in methanol (120 ml) was treated with methanolic 0.2 N potassium hydroxide (75 ml) at room temperature for 6 h. The mixture was diluted with toluene (600 ml), filtered, and concentrated to an oil. The residue was taken up in dichloromethane, washed with water, dried, and evaporated to dryness. Recrystallization of the residue from isopropyl ether gave 4.2 g (83%) product, mp 86-7° C, $[\alpha]_D^{25}$ + 156.2° (c 1.0, chloroform); UV max (acetonitrile) 236.5 (ε 6420); CD (dioxane): 233 nm ($\Delta\varepsilon$ + 12.3); ^1H NMR ($CDCl_3$, 400 MHz): δ 6.15 (d, H-4, $J_{3,4}$ = 2.5 Hz), 5.23 (d, H-1, $J_{1,2}$ = 2.8 Hz), 5.10 (s, $-COOCH_2-$), ~5.1 (br, -NH-), 4.83 and 4.61 (AB pattern, C_1-OCH_2-, $J_{A,B}$ = 12 Hz), 4.40 (dxdxd, H-3, $J_{2,3}$ ~9 Hz, $J_{3,4}$ = 2.5 Hz, $J_{3,OH}$ = 6 Hz), 3.96 (ca. dxdxd, br, H-2, $J_{2,NH}$ ~9 Hz), 3.80 (s, $-COOCH_3$) and 2.68 (d, C_3-OH); ^{13}C NMR (100.6 MHz, $CDCl_3$) : δ 162.42 (s, $-\underline{C}OOCH_3$), 156.73 (s, -NHCO-), 140.31 (s, C-5), 136.64 and 135.96 (s, substituted aromatic C), 128.51-128.01 (5xd, unsubstituted aromatic C), 113.33 (d, C-4), 97.72 (d, C-1), 70.79 (tr, $-COO\underline{C}H_2-$), 67.27 (tr, $-OCH_2-$), 65,56 (d, C-3), 53.95 (d, C-2) and 52.37 (q, $-OCH_3$). Anal. Calcd for $C_{22}H_{23}NO_7$ (413.43): C, 63.92; H, 5.61; N, 3.39. Found: C, 63.74; H, 5.76; N, 3.32.

Methyl [benzyl 2-[(benzyloxycarbonyl)amino]-3-chloro-2,3,4-trideoxy-ß-L-threo-hex-4-enopyranosid]uronate (7). A solution of 6 (4.1 g, 9.9 mmol) in ethyl acetate (100 ml) containing thionyl chloride (10 ml, 13.8 mmol) was stirred at room temperature for 1 h, and evaporated to dryness. The residue was recrystallized from isopropyl ether to give 3.1 g (73%) product, mp 113-114° C, $[\alpha]_D^{25}$ + 223.8° (c 1.0, chloroform); UV max (acetonitrile) 240.2

(ε 7320); CD (dioxane): 238 nm ($\Delta\varepsilon$ +18.5); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.15 (d, H-4, $J_{3,4}$ ~2.5 Hz), 5.29 (br, $J_{1,2}$ = 1-2 Hz, H-1), 5.11 (s, $-COOCH_2-$), 5.04 (d, -NH-, $J_{2,NH}$ ~8.5 Hz), 4.86 and 4.66 (AB pattern, C_1-OCH_2-, $J_{A,B}$ = 12 Hz), 4.57 (dxd, H-3, $J_{2,3}$ ~8 Hz), 4.24 (dxdxd, H-2) and 3.82 (s, $-COOCH_3$); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 161.83 (s, $-\underline{C}OOCH_3$), 156.02 (s, -NHCO-), 140.88 (s, C-5), 136.42 and 136.19 (s, substituted aromatic C), 128.44 - 127.80 (5xd, unsubstituted aromatic C), 111.25 (d, C-4), 97.20 (d, C-1), 70.84 (tr, $-COO\underline{C}H_2-$), 66.94 (tr, $-OCH_2-$), 54.30 (d, C-2 or C-3), 52.46 (q, $-OCH_3$) and 52.40 (d, C-3 or C-2). Anal. Calcd for $C_{22}H_{22}ClNO_6$ (431.87): C, 61.19; H, 5.13; N 3.24; Cl, 8.21. Found: C, 61.16; H, 5.43; N, 3.24; Cl, 8.24.

Methyl [benzyl 2-[(benzyloxycarbonyl)amino]-2,3,4-trideoxy-5-fluoro-α-D-erythro-hex-3-enopyranosid]uronate (8). A solution of 7 (1.2 g, 2.8 mmol) in acetonitrile (30 ml) containing silver fluoride (3 g, 24 mmol) was stirred at room temperature for 12 h in the dark, filtered, and concentrated under reduced pressure. Chromatography of the residue on silica gel (elution with toluene-ether, 9:1) gave 0.94 g (81%) product, mp 130-131°C (from isopropyl ether), $[\alpha]_D^{25}$ + 0.9° (c 1.0, chloroform). CD (dioxane) : 217 nm ($\Delta\varepsilon$ -15.3); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.01 (d, H-3 or H-4, $J_{3,4}$ = 10-11 Hz), 5.98 (d, H-4 or H-3), 5.19 (d, H-1, $J_{1,2}$ = 4.2 Hz), 5.12 (d, -NH-, $J_{2,NH}$ ~9 Hz), 5.11 (s, $-COOCH_2-$), 4.96 and 4.54 (AB pattern, C_1-OCH_2-, $J_{A,B}$ = 11.2 Hz), 4.70 (dxdxd, H-2, $J_{2,3} \leqslant 2$ Hz) and 3.86 (s, $-COOCH_3$); (270 MHz, benzene-d_6): δ 5.75 (~d, H-3 or H-4, $J_{3,4}$ = 10 Hz), 5.46 (~d, H-4 or H-3, $J_{3,F} \leqslant 1$ Hz), 5.01 (s, $-COOCH_2-$), 4.88 (d, H-1, $J_{1,2}$ = 3.5 Hz), 4.83 and 4.15 (AB pattern, C_1-OCH_2-, $J_{A,B}$ = 11.5 Hz), 4.75 (br, H-2 and -NH-, $J_{2,F} \leqslant 1$ Hz) and 3.26 (s, $-COOCH_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 165.96 (d, $-\underline{C}OOCH_3$, $^2J_{C,F}$ = 37.4 Hz), 155.79 (s, -NHCO-),136.42 and 136.09 (s, substituted aromatic C), 132.09 (d, C-3, $^3J_{C,F}$ = 8.4 Hz), 128.54 - 128.12 (5xd, unsubstituted aromatic C), 122.62 (d, C-4,

$^2J_{C,F}$ = 27.5 Hz), 97.26 (d, C-5, $^1J_{C,F}$ = 224.3 Hz), 94.61 (d, C-1), 70.13 (tr, -COOCH$_2$-), 67.12 (tr, -OCH$_2$-), 53.31 (q, -OCH$_3$) and 46.91 (d, C-2). Anal. Calcd for $C_{22}H_{22}FNO_6$ (415.42): C, 63.61; H, 5.34; N, 3.57; F, 4.57. Found: C, 63.36; H, 5.46; N, 3.37; F, 4.71.

Benzyl 2-[(benzyloxycarbonyl)amino]-2,3,4-trideoxy-5-C-methoxy-α-D-erythro-hex-3-enopyranosiduronamide (9). Compound 8 (0.30 g, 0.72 mmol) was stirred in saturated methanolic ammonia (20 ml) for 15 min at room temperature. The solid material was then filtered off, washed with methanol, and recrystallized from methanol to give 0.20 g (67%) product, mp 185°C dec, $[\alpha]_D^{25}$ -6.8° (c 0.8, chloroform). CD (dioxane): 236 nm ($\Delta\varepsilon$ -18.9) and 206 ($\Delta\varepsilon$ -13.5); ^{1}H NMR (270 MHz, $CDCl_3$): δ 6.62 and 5.55 (br, -CONH$_2$), 5.99 (dxd, H-3 or H-4, $J_{3,4}$ = 11 Hz, $J_{3,2}$ or $J_{4,2}$ = 2.5 Hz), 5.91 (dxd, H-4 or H-3, $J_{2,4}$ or $J_{2,3}$ ~2 and additional long range coupling), 5.19 (d, H-1, $J_{1,2}$ = 4.4 Hz), 5.13 (d, -NH-, $J_{2,NH}$ ~10 Hz), 5.09 (s, -COOCH$_2$-), 4.91 and 4.57 (AB pattern, C_1-OCH$_2$-, $J_{A,B}$ = 12 Hz), ~4.56 (m, H-2) and 3.45 (s, -COOCH$_3$). Anal. Calcd for $C_{22}H_{24}N_2O_6$ (412.44): C, 64.07; H, 5.87; N, 6.79. Found: C, 63.97; H, 5.94; N, 6.71.

Methyl [benzyl 2-[(benzyloxycarbonyl)amino]-2-deoxy-3,4-di-O-(methylsulfonyl)-α-D-glucopyranosid]uronate (1). Compound 3 was treated with methanesulfonyl chloride exactly as described for 5 to give, after recrystallization from ethyl acetate-hexane, 74% product, mp 141-142°C, $[\alpha]_D^{25}$ = + 99.4° (c 1.0, chloroform); ^{1}H NMR (270 MHz, $CDCl_3$): δ 5.04 (d, H-1, $J_{1,2}$ = 3.3 Hz), 4.73 and 4.53 (AB pattern, C_1-OCH$_2$-, $J_{A,B}$ = 12 Hz), 4.36 (~d, H-5, J = 9.3 Hz), 4.20 (dxdxd, H-2, $J_{2,3}$ $J_{2,NH}$ ~10 Hz), 3.83 (s, -COOCH$_3$), 3.11 and 2.91 (s, -SO$_2$CH$_3$). Anal. Calcd for $C_{24}H_{29}NO_{12}S_2$ (587.61): C, 49.06; H, 4.97; N, 2.38; S, 10.91. Found: C, 49.08; H, 5.11; N, 2.21; S, 10.92.

Benzyl 2-[(benzyloxycarbonyl)amino]-2,3,4-trideoxy-5-C-methoxy-ß-L-threo-hex-3-enopyranosiduronamide (11). A solution of 1 (3.0 g, 5.1 mmol) in saturated methanolic

X-Ray Crystal Structure Analysis of 8

Crystal Data

Formula: $C_{22}H_{22}F\ N\ O_6$
Molecular Weight: 415.42 F(000) = 872
Melting Point : 130-131°C
Crystallisation Solvent: Isopropylether
Space Group and Cell Dimensions:
Orthorhombic: $P2_12_12_1$, a = 4.929(1), b = 9.897(1), c = 41.483(5)Å
Density: D = 1.36mg.m^{-3}, Z = 4.
μ (Cu-K-alpha) = 0.85mm^{-1}, absorption effects ignored.

Data collection

Crystal size: 0.05 x 0.1 x 0.18mm^3
Temperature: 170°K
Wavelength: 1.5418Å
Scan mode: theta/2theta
Scan speed: 1.4°/min minimum speed: strong reflections measured at up to 10°/min.
Scan width: 3.0°
Theta min/Theta max: 0/55.75
Peak:Background ratio: 5:1, Intensity from profile analysis.
Total data measured: 1621 excluding standards
Total data observed: 1046
Rejection criterion: I>2.5*sigma(I)
Number of parameters: 278
Weights: $w = 1/(\sigma^2|F_o| + 0.001 * |F_o|^2)$

Data were collected on a Nicolet R3m four-circle diffractometer fitted with a graphite monochromator and the LT1 cooling apparatus.

Structure Determination and Refinement

The structure was determined by direct methods using 48 starting phase permutations. Refinement proceeded smoothly to convergence at R = 0.0451 with anisotropic refinement of all non-hydrogen atoms. The position of the hydrogen atom attached to the N atom was found from a difference map. The remaining hydrogen atom co-ordinates were calculated using known geometries. All calculations were carried out with the SHELXTL[7] package of the R3m System.

The structural parameters are outlined in Tables 1 to 6.

ammonia (50 ml) was stirred at room temperature for 17 h, filtered, and concentrated under reduced pressure. Examination of the crude product by TLC (chloroform-methanol 19:1) then revealed the presence of a major product (11, R_f 0.4) and a trace of 9 (R_f 0.37). An analytical sample of 11 was obtained by column chromatography on silica gel with chloroform-ethanol 99:1; mp

TABLE 1. Atom coordinates ($x10^4$) and temperature factors (A $x10^3$)

atom	x	y	z	U
F(1)	10915(7)	2493(4)	2113(1)	43(1)*
C(1)	7052(13)	2129(6)	1543(1)	28(2)*
C(2)	7242(14)	3381(6)	1326(1)	26(2)*
C(3)	9382(13)	4324(6)	1456(1)	27(2)*
C(4)	10183(13)	4284(5)	1760(1)	27(2)*
C(5)	8892(13)	3327(6)	1994(1)	26(2)*
O(5)	6786(8)	2555(4)	1873(1)	26(1)*
C(6)	7786(15)	4069(6)	2291(1)	30(2)*
O(7)	8478(11)	3847(5)	2560(1)	56(2)*
O(8)	5880(9)	4955(4)	2205(1)	40(2)*
C(9)	4646(18)	5691(8)	2471(2)	62(3)*
O(10)	9335(8)	1346(4)	1487(1)	29(1)*
C(11)	9209(14)	23(5)	1634(1)	35(2)*
C(12)	11266(13)	-874(6)	1474(1)	25(2)*
C(13)	11960(15)	-706(6)	1157(1)	39(2)*
C(14)	13834(15)	-1567(6)	1015(1)	48(3)*
C(15)	14973(15)	-2609(6)	1191(1)	41(2)*
C(16)	14291(14)	-2770(6)	1508(1)	38(2)*
C(17)	12436(14)	-1916(6)	1648(1)	34(2)*
N(18)	7818(10)	3009(5)	996(1)	28(2)*
C(19)	5942(13)	2471(5)	804(1)	30(2)*
O(20)	3510(9)	2446(5)	868(1)	32(2)*
O(21)	7028(9)	1987(4)	536(1)	33(1)*
C(22)	5246(13)	1278(6)	319(1)	35(2)*
C(23)	6985(13)	434(6)	100(1)	28(2)*
C(24)	6738(14)	498(6)	-229(1)	34(2)*
C(25)	8391(15)	-275(6)	-427(1)	40(2)*
C(26)	10352(15)	-1106(6)	-290(2)	40(2)*
C(27)	10557(14)	-1189(6)	35(2)	39(2)*
C(28)	8934(13)	-440(6)	231(1)	34(2)*

* Equivalent isotropic U defined as one third of the trace of the orthogonalised U_{ij} tensor

TABLE 2. Bond lengths (Å)

F(1)-C(5)	1.386(7)	C(1)-C(2)	1.533(8)
C(1)-O(5)	1.440(6)	C(1)-O(10)	1.386(7)
C(2)-C(3)	1.508(8)	C(2)-N(18)	1.448(7)
C(3)-C(4)	1.323(8)	C(4)-C(5)	1.496(8)
C(5)-O(5)	1.383(7)	C(5)-C(6)	1.535(8)
C(6)-O(7)	1.188(7)	C(6)-O(8)	1.335(8)
O(8)-C(9)	1.455(9)	O(10)-C(11)	1.445(6)
C(11)-C(12)	1.501(8)	C(12)-C(13)	1.371(8)
C(12)-C(17)	1.385(8)	C(13)-C(14)	1.388(9)
C(14)-C(15)	1.383(9)	C(15)-C(16)	1.367(8)
C(16)-C(17)	1.374(9)	N(18)-C(19)	1.329(8)
C(19)-O(20)	1.228(8)	C(19)-O(21)	1.324(7)
O(21)-C(22)	1.441(7)	C(22)-C(23)	1.504(8)
C(23)-C(24)	1.368(8)	C(23)-C(28)	1.403(9)
C(24)-C(25)	1.387(9)	C(25)-C(26)	1.391(10)
C(26)-C(27)	1.353(9)	C(27)-C(28)	1.360(9)

TABLE 3. Bond angles (deg.)

C(2)-C(1)-O(5)	109.1(4)	C(2)-C(1)-O(10)	107.7(5)
O(5)-C(1)-O(10)	113.3(4)	C(1)-C(2)-C(3)	109.4(5)
C(1)-C(2)-N(18)	111.2(4)	C(3)-C(2)-N(18)	111.0(5)
C(2)-C(3)-C(4)	122.1(5)	C(3)-C(4)-C(5)	120.6(5)
F(1)-C(5)-C(4)	107.6(5)	F(1)-C(5)-O(5)	109.8(5)
C(4)-C(5)-O(5)	115.8(4)	F(1)-C(5)-C(6)	104.7(4)
C(4)-C(5)-C(6)	111.6(5)	O(5)-C(5)-C(6)	106.8(5)
C(1)-O(5)-C(5)	116.0(4)	C(5)-C(6)-O(7)	124.4(6)
C(5)-C(6)-O(8)	110.3(5)	O(7)-C(6)-O(8)	125.3(6)
C(6)-O(8)-C(9)	114.7(5)	C(1)-O(10)-C(11)	113.7(4)
O(10)-C(11)-C(12)	108.7(5)	C(11)-C(12)-C(13)	121.3(5)
C(11)-C(12)-C(17)	119.5(5)	C(13)-C(12)-C(17)	119.2(6)
C(12)-C(13)-C(14)	120.0(6)	C(13)-C(14)-C(15)	120.2(6)
C(14)-C(15)-C(16)	119.7(6)	C(15)-C(16)-C(17)	120.0(6)
C(12)-C(17)-C(16)	120.9(5)	C(2)-N(18)-C(19)	122.0(5)
N(18)-C(19)-O(20)	123.9(5)	N(18)-C(19)-O(21)	111.4(5)
O(20)-C(19)-O(21)	124.7(5)	C(19)-O(21)-C(22)	117.1(5)
O(21)-C(22)-C(23)	107.6(5)	C(22)-C(23)-C(24)	121.7(5)
C(22)-C(23)-C(28)	119.9(5)	C(24)-C(23)-C(28)	118.4(6)
C(23)-C(24)-C(25)	120.8(6)	C(24)-C(25)-C(26)	119.5(6)
C(25)-C(26)-C(27)	119.7(6)	C(26)-C(27)-C(28)	121.2(6)
C(23)-C(28)-C(27)	120.5(6)		

TABLE 4. Anisotropic temperature factors (A x10^3)

atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
F(1)	36(2)	44(2)	47(2)	8(2)	-8(2)	11(2)
C(1)	28(4)	25(4)	32(3)	-2(3)	6(3)	-5(3)
C(2)	23(4)	28(4)	28(3)	1(3)	7(3)	6(3)
C(3)	28(4)	22(3)	31(3)	0(3)	10(3)	0(3)
C(4)	27(4)	21(3)	32(3)	-3(3)	3(3)	-5(4)
C(5)	18(4)	36(4)	24(3)	-2(3)	-1(3)	8(4)
O(5)	26(3)	28(2)	25(2)	-3(2)	-0(2)	-4(2)
C(6)	35(5)	26(4)	29(4)	-2(3)	-3(3)	-15(4)
O(7)	76(4)	65(3)	26(2)	-1(2)	-8(3)	5(4)
O(8)	38(3)	51(3)	32(2)	-17(2)	-1(2)	9(3)
C(9)	61(6)	62(5)	64(5)	-29(4)	11(5)	-3(5)
O(10)	26(3)	22(2)	39(2)	1(2)	8(2)	6(2)
C(11)	40(5)	15(3)	49(4)	9(3)	-0(4)	-8(4)
C(12)	25(4)	21(3)	29(3)	-3(3)	-2(3)	-0(3)
C(13)	52(5)	31(4)	34(4)	1(3)	1(4)	13(4)
C(14)	71(6)	43(4)	29(3)	-1(3)	11(4)	14(5)
C(15)	41(5)	35(4)	45(4)	-4(3)	4(4)	14(4)
C(16)	40(4)	24(4)	49(4)	1(3)	-7(4)	7(4)
C(17)	41(5)	23(3)	37(3)	-0(3)	0(4)	-7(4)
N(18)	15(3)	40(3)	29(3)	-3(3)	4(3)	-2(3)
C(19)	42(4)	19(3)	29(3)	8(3)	2(3)	3(4)
O(20)	16(3)	40(3)	38(2)	-2(2)	5(2)	3(3)
O(21)	32(3)	39(3)	26(2)	-13(2)	0(2)	-10(3)
C(22)	31(4)	43(4)	30(3)	-5(3)	-9(3)	0(4)
C(23)	22(4)	32(4)	30(3)	-1(3)	-6(3)	-7(3)
C(24)	33(4)	28(4)	40(4)	3(3)	0(4)	-2(4)
C(25)	51(5)	33(4)	35(4)	1(3)	5(4)	-19(4)
C(26)	36(5)	33(4)	50(4)	-14(4)	9(4)	-8(4)
C(27)	33(4)	33(4)	51(4)	-8(3)	-11(4)	9(4)
C(28)	35(5)	31(4)	35(3)	3(3)	1(4)	-1(4)

The anisotropic temperature factor exponent takes the form:

$-2\pi^2(h^2a^*U_{11} + k^2b^*U_{22} + \ldots + 2hka^*b^*U_{ij})$

TABLE 5. Hydrogen coordinates (x10^4) and temperature factors (A x10^3)

atom	x	y	z	U
H(1)	5484	1589	1495	42(4)
H(2)	5522	3836	1327	42(4)
H(3)	10188	4974	1314	42(4)
H(4)	11607	4874	1832	42(4)
H(9a)	3151	6196	2384	42(4)
H(9b)	5869	6293	2579	42(4)
H(9c)	3980	5030	2621	42(4)
H(11a)	9604	93	1860	42(4)
H(11b)	7427	-350	1605	42(4)
H(13)	11151	7	1033	42(4)
H(14)	14339	-1439	793	42(4)
H(15)	16238	-3216	1091	42(4)
H(16)	15108	-3479	1633	42(4)
H(17)	11946	-2044	1870	42(4)
H(18)	9284(108)	2932(49)	958(11)	42(4)
H(22a)	4036	708	439	42(4)
H(22b)	4211	1913	195	42(4)
H(24)	5407	1086	-323	42(4)
H(25)	8180	-237	-657	42(4)
H(26)	11555	-1618	-425	42(4)
H(27)	11871	-1787	129	42(4)
H(28)	9125	-509	460	42(4)

TABLE 6. Torsion angles (deg.)

O(5)-C(1)-C(2)-C(3)	50.5(6)
C(2)-C(1)-O(5)-C(5)	-60.1(6)
C(1)-C(2)-C(3)-C(4)	-21.7(8)
C(2)-C(3)-C(4)-C(5)	-2.7(9)
C(3)-C(4)-C(5)-O(5)	-2.5(8)
C(4)-C(5)-O(5)-C(1)	35.4(7)

163-164°C (from ethanol), $[\alpha]_D^{25}$ + 50.7° (c 0.15, chloroform). CD (dioxane) : 203 ($\Delta\varepsilon$ - 18.8) and 233 nm ($\Delta\varepsilon$ + 14.0); ^{1}H NMR (400 MHz, $CDCl_3$) : δ 6.61 and 5.62 (br, $-CONH_2$), 6.10 (dxd, H-3, $J_{2,3}$ = 5 Hz, $J_{3,4}$ = 10 Hz), 6.02 (dxd, H-4, $J_{2,4}$ = 1 Hz), 5.16 (d, H-1, $J_{1,2}$ = 2.0 Hz), 5.12 (~s, $-COOCH_2-$), 5.10 (br, -NH-), 4.80 and 4.73 (AB pattern, C_1-OCH_2-, $J_{A,B}$ = 12 Hz), 4.32 (m, H-2) and 3.34 (s, $-OCH_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 169.93 (s, -NHCO-), 156.28 (s, $-CONH_2$), 137.10 and 136.34 (s, substituted aromatic C), 129.03 - 127.43 (5xd, unsubstituted aromatic C), 98.14 (s, C-5), 95.33 (d, C-1), 70.63 (tr, $-COOCH_2-$), 67.10 (tr, $-OCH_2-$), 51.20 (q, $-OCH_3$) and 46.10 (d, C-2). Anal. Calcd for $C_{22}H_{24}N_2O_6$ (412.44): C, 64.07; H, 5.87; N, 6.79. Found: C, 63.98; H, 5.86; N, 6.75.

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REFERENCES

1. J. Kiss and W. Arnold, Helv., 64, 1566 (1981).

2. K. Heyns and H. Paulsen, Ber., 88, 188 (1955).

3. J. Kiss and F. Burckhardt, Helv., 52, 2622 (1969).

4. R. J. Ferrier and G. H. Sankey, J. Chem. Soc.(C), 2345 (1966).

5. R. Blattner, R. J. Ferrier and P. C. Tyler, J. Chem. Soc. Perkin I, 1535 (1980).

6. J. C. P. Schwarz, J. C. S. Chem. Comm., 505 (1973).

7. G. M. Sheldrick, University of Goettingen, FRG, SHELXTL 3.0 (1981).