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Synthesis of new *C*-sulfosugars and *C*-sulfoalditols: Amadori rearrangement of 6-*C*-sulfo-D-fucose

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Abstract—The novel 6-deoxy-6-*C*-sulfo-D-galactose (6-sulfofucose) potassium salt was prepared by oxidation of 1,2,3-tri-*O*-acetyl-6-*S*-acetyl-4-*O*-benzoyl-6-deoxy-α-D-galactopyranose with hydrogen peroxide and potassium acetate in acetic acid. Its cyclohexylammonium salt underwent a spontaneous conversion into 1-cyclohexylamino-1,6-dideoxy-D-tagatofuranose-6-*C*-sulfonic acid **4** through an Amadori rearrangement. 6-Deoxy-6-*C*-sulfo-D-glucose (sulfoquinovose) and 6-deoxy-6-*C*-sulfo-D-galactose were transformed into the corresponding 6-deoxy-6-*C*-sulfoalditols and 1-amino-1,6-dideoxy-6-*C*-sulfoalditols by reduction and reductive amination, respectively. The α anomeric configuration of **4**, crystallised as the monohydrate, was assigned by X-ray crystallographic analysis. A conformation between E_5 and $^4T_5$ for the sugar ring, stabilised by a strong intramolecular hydrogen bond between NH and O-4, was observed.

1. Introduction

Sulfoquinovose is the carbohydrate constituent of the sulfolipid sulfoquinovosyldiacylglycerol (SQDG, 1,2-di-*O*-acyl-3-*O*-(α-D-sulfoquinovosyl)-glyceride), which is present in photosynthetic plants, algae, protozoa, lichen and bacteria,[1] and which has also been isolated from non-photosynthetic bacteria of the genus *Rhizobium*[2] and from the eggs and sperm cells of the sea urchin *Pseudocentrotus depressus*.[3] Sulfoquinovose has been recently identified in the asparagine-linked branched hexasaccharide chains of a hemoprotein isolated from the archaeon *Sulfolobus acidocaldarius*.[4] A sulfofucose derivative (glucosyl-3′,6′-disulfate)-6-sulfofucosyl diacylglycerol was detected in *Phaeophyta* algae,[5] although the proposed structure was not confirmed by NMR.

SQDG and SQMG (sulfoquinovosylmonoacylglycerol) from natural products were reported to be potent mammalian DNA α- and β-polymerases, and terminal deoxynucleotidyl transferase inhibitors.[6–8] These sulfolipids also showed P-selectine receptor inhibition,[9] HIV-RT inhibition,[7,10] AIDS antiviral activity[11] and potent antitumor activities.[12,13] These extensive biological activities led to the synthesis of different SQDGs and SQMGs in order to study the structure–function relationship as DNA polymerase inhibitors and as antitumor agents.[14–19] Anti-HIV activity of synthetic SQDG has also been shown.[20] The β-configuration types of SQDG derivatives, not found in Nature, were potent immunosuppressive agents without cytotoxic side effects, indicating that they could be used clinically for long periods.[21,22]

Several syntheses of the parent sugar sulfoquinovose[23–25] and of sulfoquinovosyl glycerol[24,26] have been described. To our knowledge, no synthesis of 6-deoxy-6-*C*-sulfo-D-galactose (6-sulfofucose) has been reported hitherto; although a preparation of sulfofucosylacylglycerol derivatives has been recently described and proved to be active as DNA polymerase inhibitors.[27]

Continuing our work in *C*-sulfosugar chemistry,[28–32] we present herein the first synthesis of sulfofucose **3** and report the spontaneous conversion of its cyclohexylammonium salt into 6-deoxy-6-sulfo-D-tagatosamine **4** via an Amadori rearrangement. To our knowledge, this is the second report on the synthesis of a *C*-sulfoaminohexulose; a crystalline 1-amino-1,3,4-trideoxy-4-sulfo-2-hexulose was obtained from D-glucosamine and sodium

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bisulfite, via a sulfonated polyhydroxyalkylpyrazine derivative.[33]

We also report the preparation of zwitterionic *C*-sulfoaminopoliols **12** and **13** by reductive amination of sulfofucose **3** and sulfoquinovose **5** with benzylamine, followed by hydrogenolysis of the *N*-benzyl group. These sulfoaminoalditols **12** and **13** can be considered as polyhydroxylated homologues of the natural aminoacid taurine, which has numerous physiological functions,[34,35] such as neurotransmitter,[36] antioxidant,[37] detoxificant,[38] and it is involved in the process of cell volume regulation.[39] Pharmacologically, taurine can be used in the treatment of cardiovascular diseases,[40] hypercholesterolemia,[41] atherosclerotic lesions,[42] hypertension,[43] hepatic disorders,[44] and alcoholism.[45]

2. Results and discussion

Sulfofucose **3** was prepared by oxidation with hydrogen peroxide in glacial acetic acid[29] of **1**. This 6-thiogalactose was obtained from peracetylated 4,6-benzylidene-α-D-galactopyranose following the procedure described by Miljkovic[46] via a 6-bromo derivative. Treatment of a solution of **1** in glacial acetic acid with 34% (w/v) hydrogen peroxide containing potassium acetate, produced 1,2,3-tri-*O*-acetyl-4-*O*-benzoyl-6-deoxy-6-*C*-sulfo-α-D-galactose **2**, which was deacylated with NaOMe. Acidification with Amberlite IR-120(H^+) cation exchange resin and neutralisation with aqueous KOH gave the potassium salt of sulfofucose **3** in 90% overall yield from **1** (Scheme 1). ^{1}H NMR signals of **3** showed an α/β ratio of 34:66.

Purification of **3** was attempted by crystallisation of the cyclohexylammonium salt, as described for some sulfoquinovosides.[26] Thus, the potassium salt was converted into the free sulfonic acid using Amberlite IR-120(H^+) resin, and then cyclohexylamine was added until to pH 6. Solvent was removed and the residue slowly crystallised (over a month) from H_2O/EtOH at room temperature to give a solid whose ^{1}H and ^{13}C NMR spectra agree with the 6-*C*-sulfo-D-tagatosamine derivative **4**, which was obtained in a 94% yield. We concluded that the cyclohexylammonium salt of sulfofucose **3** underwent an Amadori rearrangement.[47]

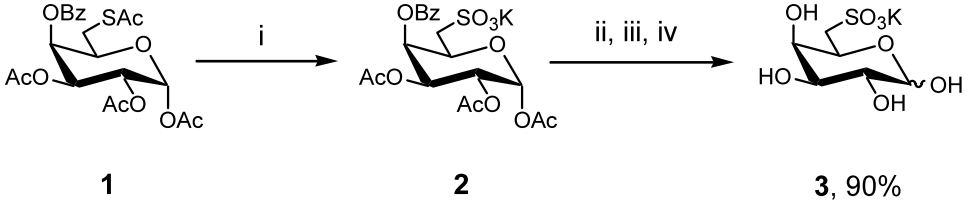
The formation of **4** is outlined in Scheme 2. The open-chain aldehyde form of 6-*C*-sulfo-D-fucose **A** reacts with a minor amount of cyclohexylamine present in the medium to give the imine **B**, which isomerises to the ketose **D** via 1,2-enaminol **C**. Cyclization of **D** to the furanose form **E**, followed by an acid–base equilibrium between the cyclohexylammonium and the secondary amine affords the zwitterion **4**. The crystallisation of **4** acts as driving force displacing the equilibrium totally towards the hexulose. Trying to prepare the cyclohexylammonium salt of sulfoquinovose **5** we did not observe its transformation into the *C*-sulfo-D-fructosamine derivative.

^{13}C NMR spectroscopy (Table 1) was used to confirm the structure of **4**, by comparison with the data reported for D-tagatofuranose,[48] and for the D-tagatofuranose-related bicyclic Amadori compound **7**.[49] The assignment of the signals was made by 2D spectroscopy (H/H-COSY and H/C-COSY). According to integration of the ^{1}H signals, **4** at equilibrium in D_2O consists of α- and β-furanose forms in a ratio of 8:5, whereas the α/β ratio is 2:5 for D-tagatofuranose,[48] 2:8 for D-tagatose 1,6-bisphosphate[50] and ~1:1 for **7**.[49] No signals for the open-chain ketose or its hydrate were detected. The marked increase of the content of the α-anomer for **4** could be explained by favourable electrostatic interactions between opposite charges of the sulfo and the ammonium groups (Fig. 1).

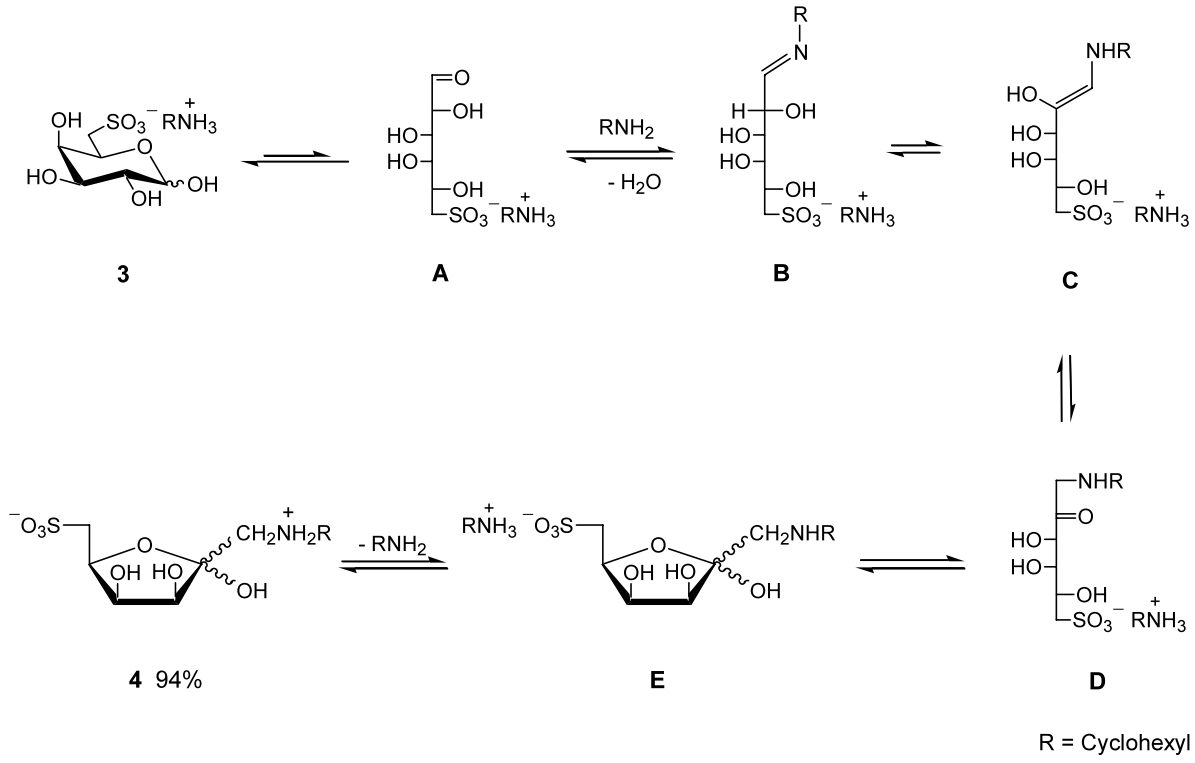
2.1. Solid-state structure

The structure of **4** monohydrate, crystallised as a furanose in the α anomeric configuration, was confirmed by X-ray crystallographic analysis. An ORTEP[51] view of the molecule is shown in Fig. 2. The furanose ring is in a conformation intermediate between E_5 and $^4T_5$. The anomeric effect is observed [C(5)–O(5) = 1.447(4) Å and O(5)–C(2) = 1.436(4) Å]. The length of the three S–O bonds are similar [from 1.436(4) to 1.454(3) Å] indicating that the negative charge on the SO_3^- is delocalised over the three oxygen atoms.[30] The bond angles about the sulfonate group are similar to those found in other sulfoaminosugars.[29,30] The torsion angles around the C-6–S bond agree with the staggered conformation, and the conformation around C-5–C-6 is *trans-gauche* (tg), whereas the found conformation for 6-sulfoquinovose derivatives in the pyranose form was *gauche-trans* (gt).[28,29]

The α-anomeric configuration for **4**, having the bulkier group on C-2 on the crowded side of the ring, is stabilised by a strong intramolecular hydrogen bond N–H-1···O-4 (Table 2). The molecules form a compact



Scheme 1. *Reagents and conditions*: (i) (34% w/v) aq. H_2O_2, AcOH, KOAc (1 equiv.), 40°C, 16 h; (ii) NaOMe, MeOH, rt; (iii) Amberlite IR-120(H^+); (iv) aq. KOH (1 equiv.).



Scheme 2.

Table 1. ^{13}C NMR data (δ, ppm) for compounds **4** and **6** in D_2O (75.5 MHz)

Compound	Anomer	C-1	C-2	C-3	C-4	C-5	C-6
4	α	58.07	103.17	78.56	72.25	75.56	50.71
	β	58.16	100.15	73.18	71.92	75.86	51.76
6[48]	α	62.64	105.10	76.92	71.43	79.41	60.29
	β	62.86	102.71	70.90	71.27	80.24	61.20

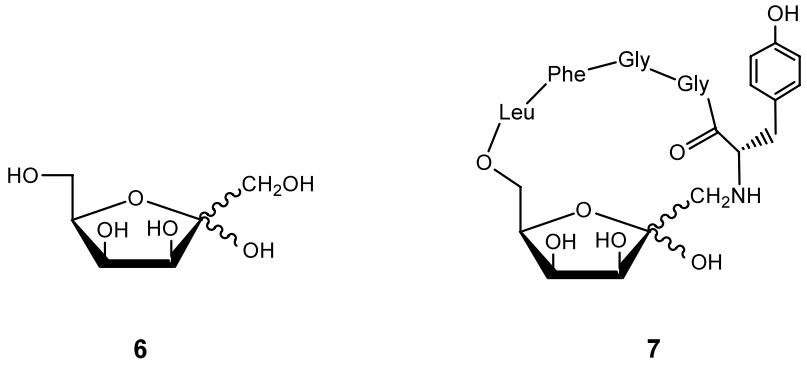


Figure 1.

structure where a water-of-hydration molecule accepts and donates H-bonds to symmetry related pairs of molecules. The molecular packing is shown in Fig. 3. The sulfoamino acid molecules are associated as dimers with the oxygen of the sulfo group of one unit involved as acceptor of the hydrogen bond to the ammonium group of the other unit [N–H-2···O-63(i)], and vice versa. The second oxygen of the sulfo group participates in a cooperative hydrogen bond system (O-2–H···O-3–H···OW–H-1···O-62) involving three sugar molecules and a water molecule. The third oxygen of the sulfo group participates in a short contact interaction with the water molecule (OW–H-2···O-61).

C-Sulfosugars **3** and **5** were used as starting materials for the preparation of 6-*C*-sulfoalditols and 1-amino-6-

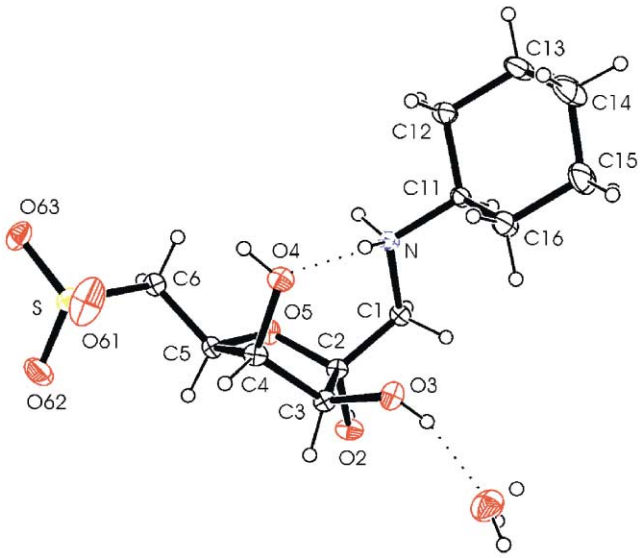


Figure 2. ORTEP view of **4** showing the atomic numbering. The ellipsoids enclose 50% probability.

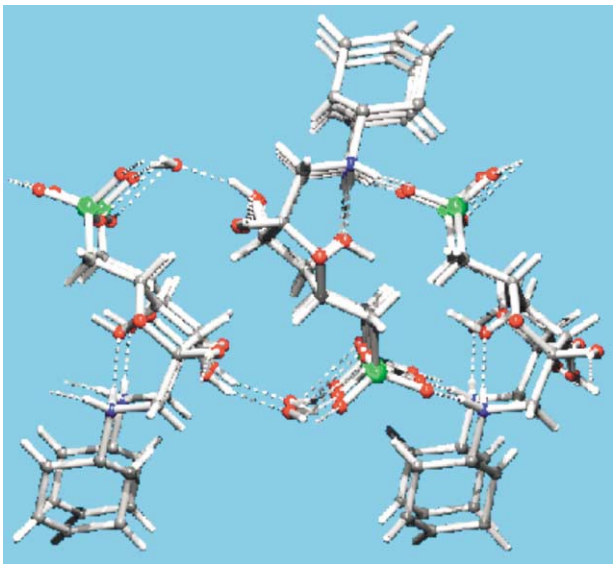


Figure 3. The packing for **4** viewed down the *a* axis. Hydrogen bonds are indicated by dashed lines.

C-sulfoalditols. Thus, treatment of an aqueous solution of **3** with $NaBH_4$ at 5°C, followed by acidification with Amberlite IR-120(H^+) resin and neutralisation with aqueous KOH afforded 6-deoxy-*C*-sulfo-D-galactitol potassium salt **8**, in 93% yield after purification by gel-filtration chromatography. Its isomer of D-*gluco* configuration **9** (94%) was prepared from **5** using the same procedure (Scheme 3).

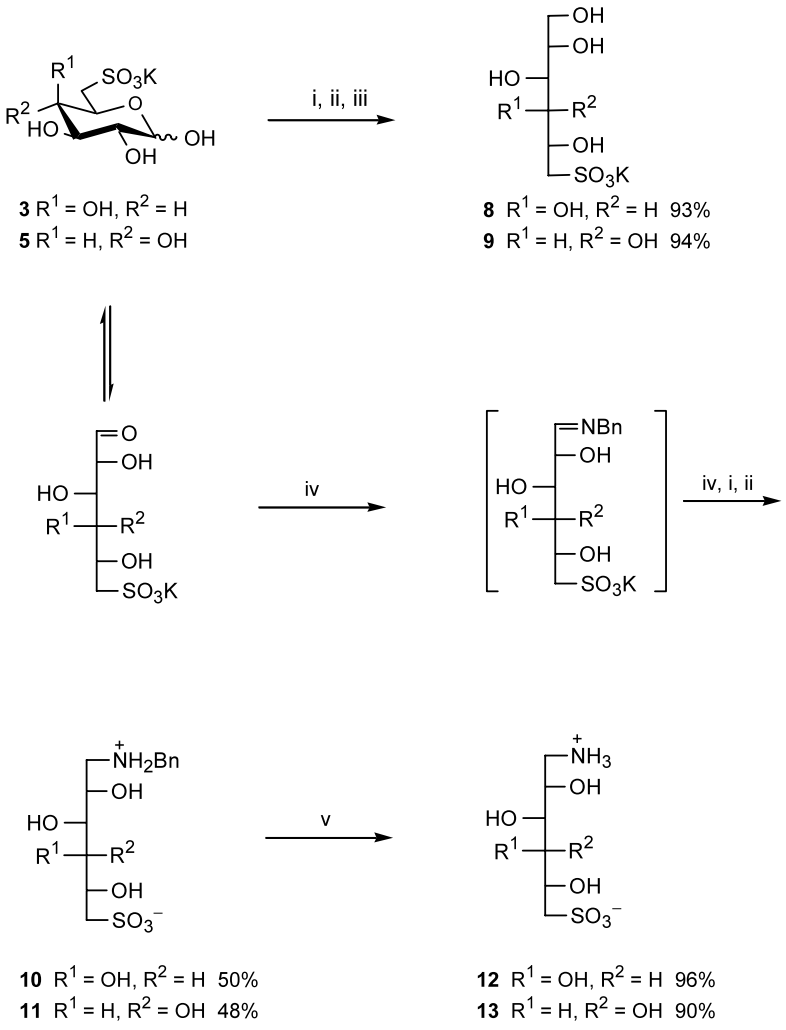
A number of methods for the synthesis of 1-aminoalditols by reductive amination of reducing sugars has previously been reported.[52] We carried out the synthesis of 1-amino-6-*C*-sulfoalditols **12** and **13** by the reductive amination method with benzylamine previously used for the synthesis of galactamine[53] and of 1-aminoalditols derived from disaccharides.[52] Reaction of **3** with an excess of benzylamine at 60°C to form the imine intermediate, followed by reduction with $NaBH_4$ at 5°C and finally treatment with Amberlite IR-120(H^+) resin gave the zwitterionic 1-benzylamino-1-deoxy derivative **10** in 50% overall yield after recrystallisation from MeOH–H_2O. Reaction of **5** under the same conditions gave the D-*gluco* isomer **11** in 48% yield (Scheme 3). Acidification to pH 1 with the resin followed by co-evaporation with methanol was needed to cleave the boron complexes formed during the reduction and to remove the boric acid as its trimethylester. The second step was the catalytic hydrogenolysis of the *N*-benzyl group to give the *N*-deprotected compounds **12** and **13**. Treatment of an aqueous solution of **10** and **11** with atmospheric hydrogen in the presence of 10% Pd/C at room temperature for 12 h gave **12** and **13** in 96 and 90% yield, respectively, after recrystallisation from MeOH–H_2O.

The conformations of compounds **9**–**12** in D_2O solutions at room temperature were studied by ^1H NMR spectroscopy. Compound **8** was not included due to the extensive signal overlapping observed in the ^1H NMR spectrum. In the D-*galacto* series, the $^3J_{H,H}$ values (Table 3) for **12** indicate a zig-zag planar conformation P[54] in equilibrium with the conformations ${}_1G^+$ and ${}_5G^-$ (Fig. 4) associated with the chain-end flexibility; whereas for compound **10** the chain end bearing the *N*-benzyl group is mainly in the extended form ($J_{1a,2}$ 9.8 Hz, $J_{1b,2}$ 3.1 Hz). The symbolism ${}_nG^-$ denotes a sickle conformation obtained by a 120° clockwise rotation of the remote atom along the C_n–C_{n+1} bond.

Table 2. Geometry of the hydrogen-bonding system and short contacts for **4**

Donor–H···acceptor	Acceptor symmetry code[a]	D···A (Å)	D–H (Å)	H···A (Å)	D–H···A (°)
O-3···OW	(0)[b]	2.652(5)	0.82	1.86	161
N–H-1···O-4	(0)[b]	2.773(4)	0.90	1.93	156
N–H-2···O-63	(i)	2.753(5)	0.90	1.90	158
O-2···O-3	(ii)	2.700(4)	0.82	1.91	161
OW–H-1···O-62	(iii)	2.776(7)	0.85	2.03	146
OW–H-2···O-61	(iv)	3.048(8)	0.86	2.60	114

[a] Symmetry code: (0) *x*, *y*, *z*; (i) *x*−1/2, −*y*+1/2, −*z*+1; (ii) *x*−1, *y*, *z*; (iii) *x*+1/2, −*y*+3/2, −*z*+1; (iv) *x*−1/2, −*y*+3/2, −*z*+1.
[b] Intramolecular hydrogen bonds.



Scheme 3. *Reagents and conditions*: (i) $NaBH_4$, H_2O, 5°C, 12 h; (ii) Amberlite IR-120(H^+), pH 1; (iii) aq. KOH (1 equiv.); (iv) $BnNH_2/H_2O$, 60°C, 4 h; (v) H_2, 10% Pd(C), H_2O, rt, 12 h.

Table 3. Coupling constants (J, Hz) for compounds **8**–**13** in D_2O (500 MHz)

	$J_{1a,2}$	$J_{1b,2}$	$J_{1a,1b}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$
Glucitol[54]	4.3	6.6		5.4	2.5	7.7	3.3	6.2	
9	3.5	5.8	11.8	5.7	2.4	7.5	1.9	9.4	14.6
10	9.8	3.1	13.0	1.5	9.5	1.3	5.1	7.2	14.4
11	3.4	9.6	12.9	4.8	2.9	7.2	2.1	9.2	14.6
12	7.7	5.0	–	1.6	9.5	1.4	5.1	7.2	–
13	3.3	9.4	13.1	4.8	2.9	7.2	2.1	9.1	14.6

In the D-*gluco* series (**9**, **11**, **13**, and D-glucitol[55]) the vicinal coupling constants indicate an increased conformational mobility compared with D-*galacto* isomers, due to the unfavourable 1,3-parallel interaction between OH-2 and OH-4 present in the *P* rotamer. The rather large values observed for $J_{2,3}$ (4.8–5.7 Hz) support the participation of the rotamer ${}_2G^-$. Zwitterionic compounds **11**, **13** show the two chain ends in extended arrangements, whereas **9** presents the expected flexibility around C-1–C-2 bond (${}_1G^+$ rotamer, Fig. 5), and D-glucitol shows that flexibility for both ends.

3. Conclusion

Cyclohexylammonium salt of 6-*C*-sulfofucose **3**, prepared by oxidation of a peracylated 6-thiogalactose derivative **1**, undergoes a spontaneous Amadori rearrangement to yield the highly crystalline 6-deoxy-6-*C*-sulfotagosamine **4**. X-Ray analysis of **4** reveals its α-furanose form in solid state, stabilised by an extensive system of hydrogen bonds. Zwitterionic 1-amino-1,6-dideoxy-6-*C*-sulfoalditols **12** and **13** can be prepared by reductive amination with benzylamine of 6-*C*-sulfofu-

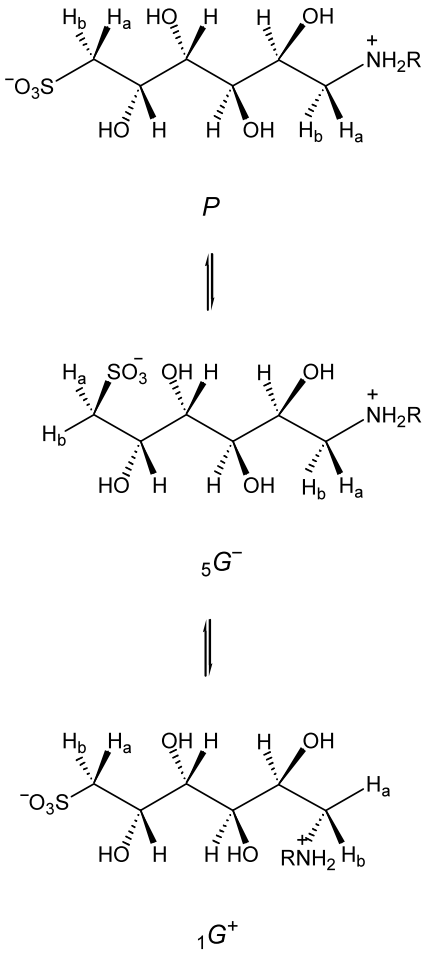


Figure 4. Conformational equilibrium of D-galactitol derivatives **10** (R = Bn) and **12** (R = H).

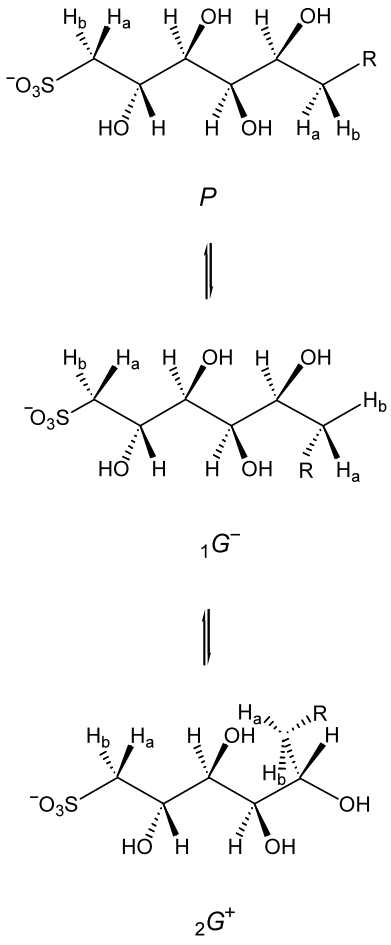


Figure 5. Conformational equilibrium of D-glucitol derivatives **9** (R = OH), **11** (R = NH_2Bn^+), and **13** (R = NH_3^+).

cose **3** and 6-*C*-sulfoquinovose **5**, and subsequent catalytic hydrogenation.

4. Experimental

Melting points were determined on an Electrothermal apparatus and are uncorrected. Optical rotations were measured at 22°C with a Perkin–Elmer 241 polarimeter, and IR spectra (KBr disks) were obtained with an FT-IR Bomem MB-120 spectrophotometer. ^{1}H (300 and 500 MHz) and ^{13}C (75.5 and 125.7 MHz) NMR spectra were recorded on Bruker AMX-300 and AMX-500 spectrometers for solutions in D_2O (internal DOH at 4.75 ppm and internal 1,4-dioxane at 67.4 ppm). The assignments of ^{1}H and ^{13}C signals were confirmed by homonuclear COSY and heteronuclear 2D correlated spectra, respectively. Mass spectra were recorded on Kratos MS 80 RFA and Micromass AutoSpeQ mass spectrometers. TLC was performed on aluminium pre-coated sheets (E. Merck silica gel 60 F_{254}); spots were visualised by UV light and by charring with 10% H_2SO_4 in EtOH. Gel-filtration chromatography was performed on a 47×3.5 cm column, using Biogel P2 as stationary phase and 1:1 MeOH–H_2O as eluent. Microanalyses were performed at 'Instituto de Investigaciones Químicas de la Cartuja', Seville, Spain.

4.1. Potassium 6-deoxy-D-galactopyranose-6-*C*-sulfonate 3

To a solution of 1,2,3-tri-*O*-acetyl-6-*S*-acetyl-4-*O*-benzoyl-6-deoxy-α-D-galactopyranose **1**[46] (1.38 g, 2.96 mmol) in glacial acetic acid (15 mL) was added potassium acetate (0.29 g, 2.96 mmol) and 34% hydrogen peroxide (2.8 mL, 35.6 mmol). The mixture was heated at 40°C for 16 h and the resulting solution was concentrated to dryness, coevaporating several times with water to afford crude **2**. The residue was dried overnight in vacuum over P_2O_5, then dissolved in dry methanol (20 mL) and 0.1 M NaOMe was added up to pH 9–10. After 6 h at room temperature, the solution was diluted with water and taken to pH 0–1 using Amberlite IR-120(H^+) cation exchange resin. Resin was filtered off and washed, and the combined filtrate and washings were taken to pH 7 using aqueous 0.1 M KOH. The solution was concentrated to dryness and the residue was lyophilised to afford **3** as a yellowish foam (757 mg, 90%). An analytical sample was obtained by gel-filtration chromatography. R_f 0.30 (^{i}PrOH/MeOH/H_2O, 3:2:1); $[\alpha]_D$ +43 (*c* 1.1, H_2O); ^{1}H NMR (300 MHz, D_2O): δ 5.15 (d, 1H, $J_{1,2}$ = 3.8 Hz, H-1α), 4.52 (d, 1H, $J_{1,2}$ = 7.9 Hz, H-1β), 4.39 (dddd, 1H, $J_{1,5}$ = 0.5 Hz, $J_{4,5}$ = 1.2 Hz, $J_{5,6a}$ = 4.7 Hz, $J_{5,6b}$ = 7.3

Hz, H-5α), 3.97 (ddd, 1H, $J_{4,5}=0.9$ Hz, $J_{5,6a}=4.9$ Hz, $J_{5,6b}=6.8$ Hz, H-5β), 3.89 (dd, 1H, $J_{3,4}=3.3$ Hz, H-4α), 3.86 (dd, 1H, $J_{3,4}=3.4$ Hz, H-4β), 3.81 (dd, 1H, $J_{2,3}=10.3$ Hz, H-3α), 3.69 (dd, 1H, H-2α), 3.60 (dd, 1H, $J_{2,3}=10.0$ Hz, H-3β), 3.38 (dd, 1H, H-2β), 3.17 (dd, 1H, $J_{6a,6b}=14.6$ Hz, H-6aβ), 3.12 (dd, 1H, $J_{6a,6b}=14.6$ Hz, H-6aα), 3.09 (dd, 1H, H-6bβ), 3.05 (dd, 1H, H-6bα); ^{13}C NMR (75.5 MHz, D_2O): δ 96.53 (C-1β), 92.40 (C-1α), 72.75 (C-3β), 71.60 (C-2β), 71.18 (C-5β), 71.12 (C-4α), 70.50 (C-4β), 69.20 (C-3α), 68.12 (C-2α), 66.66 (C-5α), 52.19 (C-6α), 52.04 (C-6β); IR: ν_{max} 3370 (OH), 1187 and 1048 (SO_2) cm^{-1}; FAB-MS: m/z 305 [100, $(M+Na)^+$]; HRFAB-MS calcd for $C_6H_{11}Na_2O_8S$ $(M-K+2Na)^+$ 288.9970, found 288.9982.

4.2. 1-Cyclohexylamino-1,6-dideoxy-α-D-tagatofuranose-6-*C*-sulfonic acid 4

To a solution of **3** (262 mg, 0.93 mmol) in water (5 mL) was added Amberlite IR-120(H^+) cation exchange resin up to pH 0–1. The resin was filtered off and washed, and the combined filtrate and washings were taken to pH 6 using cyclohexylamine (ca. 0.11 mL). The solution was concentrated to dryness coevaporating several times with absolute ethanol, and the resulting residue was slowly crystallised from H_2O/EtOH 1:1 (8 mL) to afford a first crop of **4**. Mother liquors were concentrated to dryness and the residue was crystallised from H_2O/EtOH 1:3 (4 mL) to give a second crop of **4**. Total yield: 300 mg (94%); R_f 0.50 (^{i}PrOH/MeOH/H_2O, 3:2:1); mp 224–226°C; $[\alpha]_D$ +31 (*c* 0.6, H_2O); ^{1}H NMR (300 MHz, D_2O): δ 4.57 (m, 1H, H-5α), 4.40–4.33 (m, 3 H, H-4α, H-3α, H-5β), 4.25 (dd, 1H, $J_{3,4}=4.6$ Hz, $J_{4,5}=3.6$ Hz, H-4β), 4.12 (d, 1H, H-3β), 3.31–3.10 (m, 8H, H-1aα, H-1aβ, H-1bα, H-1bβ, H-6aα, H-6aβ, H-6bα, H-6bβ), 2.04–1.11 (m, 22H, cyclohexyl); ^{13}C NMR (75.5 MHz, D_2O): Table 1 and 28.84, 28.73, 28.68, 24.58, 24.17, 23.97 (cyclohexyl); IR: ν_{max} 3468, 3333, 3079 (NH_2^+, OH), 1164 and 1053 (SO_2) cm^{-1}; FAB-MS: m/z 326 [100, $(M+H)^+$]. Anal. calcd for $C_{12}H_{23}NO_7S$: C, 44.30; H, 7.12; N, 4.30. Found: C, 44.27; H, 6.82; N, 4.62.

4.3. General procedure for the synthesis of potassium 6-deoxy-D-alditol-6-*C*-sulfonates 8 and 9

To a solution of 6-deoxy-6-*C*-sulfo-D-aldopyranose (100 mg, 0.35 mmol) in water (1 mL) cooled at 0°C was added a solution of $NaBH_4$ (15 mg, 0.40 mmol) in water (0.5 mL). After 12 h at 5°C, Amberlite IR-120(H^+) cation exchange resin was added up to pH 0–1. The resin was filtered off and washed, and the combined filtrate and washings were concentrated to dryness, coevaporating several times with methanol. The residue was dissolved in water and the solution was neutralised using aqueous 0.1 M KOH and lyophilised to give crude products that were purified by gel-filtration chromatography. The following compounds were prepared in this manner.

4.3.1. Potassium 6-deoxy-D-galactitol-6-*C*-sulfonate 8. Yield: 93 mg (93%); R_f 0.48 (^{i}PrOH/MeOH/H_2O, 3:1:1); $[\alpha]_D$ −3 (*c* 1.1, H_2O); ^{1}H NMR (300 MHz, D_2O): δ 4.38 (bt, 1H, H-5), 3.94 (bt, 1H, H-2), 3.66 (m, 4H, H-1a, H-1b, H-3, H-4), 3.16 (d, 2H, $1/2(J_{5,6a}+J_{5,6b})=6.2$ Hz, H-6a, H-6b); ^{13}C NMR (75.5 MHz, D_2O): δ 71.70 (C-4), 70.31 (C-2), 69.50 (C-3), 66.45 (C-5), 63.37 (C-1), 54.70 (C-6); IR: ν_{max} 3355 (OH), 1219 and 1050 (SO_2) cm^{-1}; FAB-MS: m/z 269 [100, $(M-K+Na+H)^+$], 291 [50, $(M-K+2Na)^+$], 307 [54, $(M+Na)^+$]; HRFAB-MS calcd for $C_6H_{13}KNaO_8S$ $[M+Na]^+$ 306.9866, found 306.9867.

4.3.2. Potassium 6-deoxy-D-glucitol-6-*C*-sulfonate 9. Yield: 94 mg (94%); R_f 0.39 (^{i}PrOH/MeOH/H_2O, 3:1:1); $[\alpha]_D$ +6 (*c* 1.0, H_2O); ^{1}H NMR (300 MHz, D_2O): δ 4.15 (ddd, 1H, $J_{4,5}=7.5$ Hz, $J_{5,6a}=1.9$ Hz, $J_{5,6b}=9.4$ Hz, H-5), 3.84 (dd, 1H, $J_{2,3}=5.7$ Hz, $J_{3,4}=2.4$ Hz, H-3), 3.80 (m, 1H, $J_{1a,2}=3.5$ Hz, $J_{1b,2}=5.8$ Hz, H-2), 3.71 (dd, 1H, $J_{1a,1b}=11.8$ Hz, H-1a), 3.60 (dd, 1H, H-6b), 3.59 (dd, 1H, H-4), 3.33 (dd, 1H, $J_{6a,\ 6b}=14.6$ Hz, H-6a), 3.00 (dd, 1H, H-6b); ^{13}C NMR (75.5 MHz, D_2O): δ 73.12 (C-4), 72.94 (C-2), 69.57 (C-3), 67.87 (C-5), 62.56 (C-1), 53.97 (C-6); IR: ν_{max} 3317 (OH), 1204 and 1045 (SO_2) cm^{-1}; FAB-MS: m/z 269 [64, $(M-K+Na+H)^+$], 291 [100, $(M-K+2Na)^+$], 307 [20, $(M+Na)^+$]; HRFAB-MS calcd for $C_6H_{13}KNaO_8S$ $[M+Na]^+$ 306.9866, found 306.9865.

4.4. General procedure for the synthesis of 1-benzylamino-1,6-dideoxy-D-alditol-6-*C*-sulfonic acids 10, 11

To a solution of 6-deoxy-6-*C*-sulfo-D-aldopyranose (300 mg, 1.06 mmol) in water (3 mL) was added benzylamine (0.58 mL, 5.31 mmol), and the mixture was stirred at 60°C for 4 h. The resulting solution was cooled at 0°C and $NaBH_4$ (80 mg, 2.11 mmol) was added. The reaction was left at 5°C overnight and Amberlite IR-120(H^+) cation exchange resin was added up to pH 0–1. The resin was filtered off and washed, and the combined filtrate and washings were concentrated to dryness, coevaporating several times with methanol. The residue was washed with hot methanol (3 mL) to afford the crude products that were recrystallised from H_2O/MeOH. The following compounds were prepared in this manner.

4.4.1. 1-Benzylamino-1,6-dideoxy-D-galactitol-6-*C*-sulfonic acid 10. Yield: 179 mg (50%); R_f 0.63 (^{i}PrOH/MeOH/H_2O, 2:1:1); mp 216–218°C (from H_2O/MeOH, 2:1); $[\alpha]_D$ −19 (*c* 1.0, H_2O); ^{1}H NMR (500 MHz, D_2O): δ 7.54 (s, 5H, Aromatic), 4.41 (ddd, 1H, $J_{4,5}=1.3$ Hz, $J_{5,6a}=5.1$ Hz, $J_{5,6b}=7.2$ Hz, H-5), 4.35 (s, 2H, CH_2Ph), 4.28 (ddd, 1H, $J_{1a,2}=9.8$ Hz, $J_{1b,2}=3.1$ Hz, $J_{2,3}=1.5$ Hz, H-2), 3.73 (dd, 1H, $J_{3,4}=9.5$ Hz, H-4), 3.64 (dd, 1H, H-3), 3.32 (dd, 1H, $J_{1a,1b}=13.0$ Hz, H-1a), 3.25 (dd, 1H, H-1b), 3.22 (dd, 1H, $J_{6a,6b}=14.4$ Hz, H-6a), 3.19 (dd, 1H, H-6b); ^{13}C NMR (125.5 MHz, D_2O): δ 131.81, 131.12, 130.95, 130.53 (aromatics), 72.63 (C-4), 71.66 (C-3), 67.36 (C-5), 66.94 (C-2), 55.63 (C-1), 52.37 (*C*H_2Ph), 51.13 (C-1); ν_{max} 3406, 3270 (OH), 2936, 2801 (NH_2^+), 1201 and 1050 (SO_2) cm^{-1}; FAB-MS: m/z 336 [100, $(M+H)^+$]. Anal. calcd for $C_{13}H_{21}NO_7S$: C, 46.55; H, 6.31; N, 4.18; S, 9.56. Found: C, 46.28; H, 6.35; N, 4.28; S, 9.99.

4.4.2. 1-Benzylamino-1,6-dideoxy-D-glucitol-6-*C*-sulfonic acid 11. Yield: 172 mg (48%); R_f 0.64 (^{i}PrOH/MeOH/H_2O, 2:1:1); mp 266–268°C (from H_2O/MeOH, 2:1); $[\alpha]_D$ −10.3 (*c* 1.2, H_2O); ^{1}H NMR (500 MHz, D_2O): δ 4.12 (ddd, 1H, $J_{4,5}=7.2$, $J_{5,6a}=2.1$, $J_{5,6b}=9.2$ Hz, H-5), 4.06 (ddd, 1H, $J_{1a,2}=3.4$, $J_{1b,2}=9.6$, $J_{2,3}=4.8$ Hz, H-2), 3.76 (dd, 1H, $J_{3,4}=2.9$ Hz, H-3), 3.56 (dd, 1H, H-4), 3.28 (dd, 1H, $J_{6a,6b}=14.6$ Hz, H-6a), 3.21 (dd, 1H, $J_{1a,1b}=12.9$ Hz, H-1a), 3.15 (dd, 1H, H-1b), 2.97 (dd, 1H, H-6b); ^{13}C NMR (125.5 MHz, D_2O): δ 131.74, 131.14, 130.98, 130.55 (aromatics), 73.81 (C-4), 71.64 (C-3), 69.13 (C-2), 69.03 (C-5), 54.92 (C-6), 52.34 (*C*H_2Ph), 50.13 (C-1); ν_{max} 3477, 3403 (OH), 3011, 2790, 2634 (NH_2^+), 1171 and 1048 (SO_2) cm^{-1}; FAB-MS: *m*/*z* 336 [100, (M+H)$^+$], 670 [16, (2M+H)$^+$]. Anal. calcd for $C_{13}H_{21}NO_7S$: C, 46.55; H, 6.31; N, 4.18; S, 9.56. Found: C, 46.42; H, 6.12; N, 4.19; S, 9.45.

4.5. General procedure for the synthesis of 1-amino-1,6-dideoxy-D-alditol-6-*C*-sulfonic acids 12 and 13

A solution of 1-benzylamino-1,6-dideoxy-D-alditol-6-*C*-sulfonic acid (100 mg, 0.29 mmol) in water (3 mL) was hydrogenated at atmospheric pressure by stirring with 10% Pd(C) catalyst for 12 h at rt. After filtration of the mixture through a thin Celite pad, the solution is concentrated to dryness to afford the crude products that were recrystallised from H_2O/MeOH. The following compounds were prepared in this manner.

4.5.1. 1-Amino-1,6-dideoxy-D-galactitol-6-*C*-sulfonic acid 12. Yield: 68 mg (96%); R_f 0.13 (^{i}PrOH/MeOH/H_2O, 2:1:1); mp 245–247°C (H_2O/MeOH, 1:1); $[\alpha]_D$ −13 (*c* 1.0, H_2O); ^{1}H NMR (500 MHz, D_2O): δ 4.38 (ddd, 1H, $J_{4,5}=1.4$ Hz, $J_{5,6a}=5.1$ Hz, $J_{5,6b}=7.2$ Hz, H-5), 4.17 (dd, 1H, $J_{1a,2}=7.7$ Hz, $J_{1b,2}=5.0$ Hz, $J_{2,3}=1.6$ Hz, H-2), 3.70 (dd, 1H, $J_{3,4}=9.5$ Hz, H-4), 3.64 (dd, 1H, H-3), 3.17 (m, 4H, H-1a, H-1b, H-6a, H-6b); ^{13}C NMR (125.5 MHz, D_2O): δ 72.71 (C-4), 71.79 (C-3), 67.72 (C-2), 67.41 (C-5), 55.67 (C-6), 44.01 (C-1); ν_{max} 3428, 3166, 3102 (NH_2^+, OH), 1172 and 1037 (SO_2) cm^{-1}; FAB-MS: *m*/*z* 246 [100, (M+H)$^+$)]. Anal. calcd for $C_6H_{15}NO_7S{\cdot}H_2O$: C, 27.38; H, 6.51; N, 5.32; S, 12.18. Found: C, 27.80; H, 6.61; N, 5.19; S, 12.73.

4.5.2. 1-Amino-1,6-dideoxy-D-glucitol-6-*C*-sulfonic acid 13. Yield: 64 mg (90%); R_f 0.13 (^{i}PrOH/MeOH/H_2O, 2:1:1); mp 216–218°C (H_2O/MeOH, 1:1); $[\alpha]_D$ −5 (*c* 1.0, H_2O); ^{1}H NMR (500 MHz, D_2O): δ 4.15 (ddd, 1H, $J_{4,5}=7.2$ Hz, $J_{5,6a}=2.1$ Hz, $J_{5,6b}=9.1$ Hz, H-5), 4.01 (ddd, 1H, $J_{1a,2}=3.3$ Hz, $J_{1b,2}=9.4$ Hz, $J_{2,3}=4.8$ Hz, H-2), 3.82 (dd, 1H, $J_{3,4}=2.9$ Hz, H-3), 3.62 (dd, 1H, H-4), 3.31 (dd, 1H, $J_{6a,6b}=14.6$ Hz, H-6a), 3.20 (dd, 1H, $J_{1a,1b}=13.1$ Hz, H-1a), 3.08 (dd, 1H, H-1b), 3.01 (dd, 1H, H-6b); ^{13}C NMR (125.5 MHz, D_2O): δ 74.04 (C-4), 71.68 (C-3), 69.96 (C-2), 69.04 (C-5), 54.91 (C-6), 43.03 (C-1); ν_{max} 3475, 3390, 3281, 3158 (NH_2^+, OH), 1172 and 1041 (SO_2) cm^{-1}; FAB-MS: *m*/*z* 246 [100, (M+H)$^+$], 491 [12, (2M+H)$^+$]. Anal. calcd for $C_6H_{15}NO_7S$: C, 29.38; H, 6.16; N, 5.71; S, 13.07. Found: C, 29.13; H, 6.11; N, 5.52; S, 13.34.

4.6. Crystallographic analysis of compound 4

4.6.1. Experimental conditions for the crystal structure determination of 4. Molecular formula, $C_{12}H_{23}NO_7S{\cdot}H_2O$; molecular weight, 343.391; crystal system, orthorhombic; space group, $P2_12_12_1$; unit-cell dimensions, $a=5.653(2)$, $b=10.331(1)$, $c=26.056(3)$ Å; unit-cell volume, V, 1521.5(5) Å^3; formula units per unit cell, Z 4; calculated density, D_{calcd}, 1.50 g cm^{-3}. Radiation, Mo$K\alpha$; wavelength, 0.71069 Å; $F(000)$ value, 736; absorption coefficient, μ, 0.254 mm^{-1}; temperature, T, 293 K; crystal shape, prismatic; crystal size, 0.20×0.40×0.40 mm; diffractometer, Enraf-Nonius CAD-4; determination of unit cell, least squares; number of reflections used, 25; θ range, 7–14°; intensity data collection, $w/2\theta$ scan mode; maximum θ, 25°; range of h, k, and l, −7 to 0, −1 to 14 and 0 to 36; standard reflections; (−2 2 4), (−1 1 9) and (−1 −1 11); internal agreement, R_{int} 0.006; number of measured reflections 2567; number of significant reflections, 2110; criterion for significance, $I>2\sigma(I)$; number of refined parameters, 199; final R, 0.05; final $\omega R(F^2)$, 0.18, goodness-of-fit S 1.058.

Corrections were made for Lorentz polarisation effects, but not for extinction and absorption. This effect was not taken into account because the crystal absorption with Mo radiation was practically negligible. The structure was solved by direct methods using SIR[56] to locate all non-hydrogen atoms, and refinement based on F^2 using SHELXL97.[57] All H-atoms were included fixed in the later refinement placed in geometrically calculated positions. Atomic scattering factors were taken from the International Tables for X-Ray Crystallography.[58] The geometrical analysis was performed using PARST.[59]

Crystallographic data (excluding structure factors) for this structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 196071. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-11223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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