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A 2-*C*-fructosyl-propanone locked in a 2,7-dioxabicyclo[3.2.1]octane framework☆

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Abstract—Condensation of D-fructose with pentane-2,4-dione in mildly alkaline aqueous solution generates a novel sugar-based scaffold: a 2-*C*-fructosyl-propanone compressed by formation of a cycloacetal into a 2,7-dioxabicyclo[3.2.1]octane framework.
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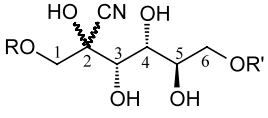
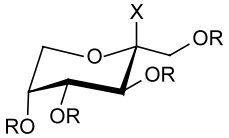
1. Introduction

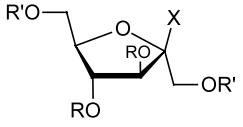
Compared to the plethora of C-glycosides that have been prepared by C-homologation of aldoses, in particular of D-glucose,[2] anomeric C-extensions of ketoses are rare in comparison, some notable examples being 2-C-fructosides **1**–**9** in either pyranoid or furanoid forms. Their modes of preparation involve a large variety of methodologies. Formally, the first anomeric C-extension of D-fructose goes back to Kiliani in 1885,[3] who succeeded in isolating a crystalline product from the exposure of unprotected D-fructose to hydrocyanic acid, which appeared to be a cyanohydrin of open-chain fructose, i.e. **1**, as in water it decomposed gradually to the educts as indicated by the 'odor of hydrocyanic acid after 1–2 h'.[4] This procedure was later applied to fructose-6-phosphate and fructose-1,6-diphosphate, providing the respective cyanohydrins, i.e. **2** and **3**, which could be hydrolysed to the corresponding carboxylic acids that proved to be competitive inhibitors of ribulose-1,6-biphosphate carboxylase.[5] Well defined 2-cyano-β-D-fructopyranosides were readily obtained by BF_3- or TMS-triflate-promoted C-glycosidation with TMS-cyanide of either benzobromofructose →**4**[6] or diacetone-fructose →**5**,[7] whilst the respective 2-carbamido derivatives **6** are obtained on cyanation of D-fructose in the presence of amines.[8] Somewhat unusual C-glycosidation conditions comprise the Grignard reaction of acetobromofructose with phenylmagnesium bromide →**7**[9] or exposure of fructose to hydrogen fluoride in the presence of toluene →**8**,[10] providing only very modest yields. Preparatively more useful proved to be the TMS-triflate-mediated reaction with allyltrimethylsilane: silyl-protected methyl β-D-fructofuranoside yielded either a 2:3 mixture of the 2-*C*-allyl-β- **9** and α-anomers,[11] or, in the case of benzylated methyl α-D-fructofuranoside, the respective α-C-allyl-fructofuranoside essentially quantitatively.[12] Another C-fructofuranoside was effectively prepared by replacement of the nitro group in 2-nitro-α-D-fructofuranose by nitromethane →**10**,[13] whilst structure and configuration of the fructosyl-C-nucleotide from *Cicer arietinum*, supposedly 5-β-D-fructofuranosyl-uracil 1′-phosphate,[14] remains to be established.



1 R = R' = H
2 R = H; R' = PO_3H_2
3 R = R' = PO_3H_2



	X	R
4	CN	Bz
5	CN	CMe_2, Bn
6	CONHR	H
7	C_6H_5	H
8	*p*$CH_3C_6H_4$	H



	X	R	R'
9	$CH_2CH{=}CH_2$	H	H
10	CH_2NO_2	Bn	Bn

☆ Part 30 of the series 'Sugar-Derived Building Blocks'. Part 29. See Ref. 1

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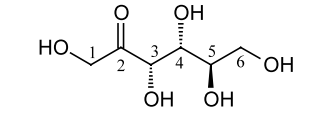
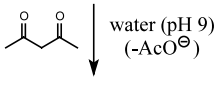
A convenient, preparatively most useful *C*-glycosidation of unprotected aldoses consists in their reaction with *C*-nucleophiles such as Meldrum's acid,[15] barbiturates,[16] or 1,3-diketones such as acetylacetone,[17] all feasible in slightly basic aqueous solution ($NaHCO_3$, pH 9). Applying the high-yielding aldose-*C*-extensions with acetylacetone to 2-ketosugars, e.g. D-fructose, furanoid and/or pyranoid 2-C-fructosyl-propanones of type **4** or **9** ($X=CH_2COCH_3$) would be expected. Yet from an entirely different course of the reaction, a bicyclic product is obtained, having the six-carbon chain of fructose rigidly locked into a dioxabicyclo[3.2.1]octane framework. Its generation and structural elucidation is described herein.

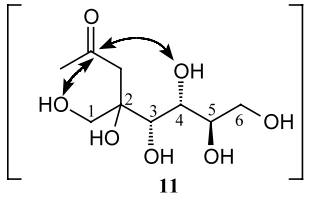
2. Results and discussion

When reacting unprotected D-fructose in aqueous solution with acetylacetone at pH 9 ($NaHCO_3$, 4 h, 85°C), a mixture of condensation products was formed. The minor component, obtained in 5% yield by chromatography was identified as the known[17] β-D-glucosyl-propanone originating from a C-2→C-1-translocation of the carbonyl group of fructose through 1,2-endiolate intermediates (Lobry de Bruyn–Alberda van Ekenstein rearrangement[18]). The major product **12** was isolated either directly by flash chromatography (27%) or upon acetylation (Ac_2O/pyridine) as its well-crystalline tetraacetate **13**.

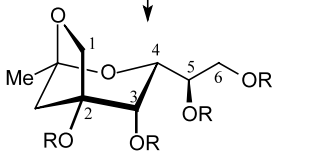


keto-D-Fructose





11

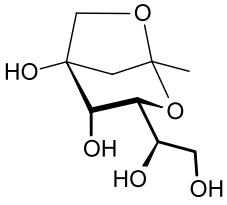


12 R = H
13 R = Ac

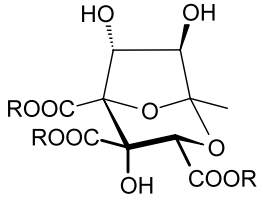
As neither product contained a carbonyl group derivable from a propanone moiety (IR, ^{13}C NMR), and as the ^1H NMR of the peracetate indicated only four acetyl signals, a cycloketal obviously had been formed, in which, based on the chemical shifts of the fructose-derived H-1 and H-4 (cf. Fig. 1), the respective 1-OH and 4-OH groups were involved. In the surprisingly simple ^1H NMR spectrum of the tetraacetate (Fig. 1), all couplings were essentially first order, their detailed analysis leading to either one of two structures: that of a 2,7-dioxabicyclo[3.2.1]octane **13** or a 2,6-dioxabicyclo[3.3.1]octane **14**, with a slight preference for the former **13**, as the long-range coupling of 1.7 Hz was considered to be somewhat better reconcilable with **13** ($J_{4,8}$) than with **14**, where it would result from $J_{5,9}$.

The tetraacetate readily yielded good quality crystals, so an X-ray structure determination could be carried out (cf. Fig. 2), which unequivocally decided for the 2,7-dioxabicyclo[3.2.1]octane skeleton. It reveals a somewhat flattened chair geometry for the pyranoid ring as evidenced by deviation of the ring dihedral angles (Table 1) from the theoretical of 60° by 15° towards either side (i.e. −44.8 and +73.2°), whilst the annelated furanoid ring is in an *E* conformation with C-8 sticking out from the near-plane formed by C1–C7–C6–O5. Notable is also the nearly diaxial disposition of O-4 towards C-6 as evident from their dihedral angle of −168.6°C.

Mechanistically, this one-pot conversion of fructose into the 2-*C*-fructosyl-propanone cycloacetal **12** is envisaged to proceed by attack of an acetoacetonyl anion on the fructose-2-carbonyl and subsequent retroaldol type elimination of an acetyl equivalent: The resulting intermediate **11** then being stabilized by a double cycloketalization of the propanone carbonyl with the fructosyl-oxygens at C-1 and C-4. The only surprising aspect remaining is the ease with which this cycloketalization is effected under mildly alkaline conditions. The overall conversion is reminiscent of elaboration of the zaragozic acid core **15**—a similarly high-oxygenated 2,6-dioxabicyclo[3.2.1]octane scaffold—from related precursors, the bis-cycloketalization though occurring under acidic conditions (2% HCl/MeOH, 18 h, 68°C).[19]



12



15

In conclusion, we have uncovered a simple, one-pot transformation of D-fructose into a *C*-fructoside cycloketal embodying the novel scaffolding of a 2,7-dioxabicyclo[3.2.1]octane skeleton—to our knowledge the first such structure in the carbohydrate field. The conditions involved in this transformation—aqueous solution, $NaHCO_3$, 85°C—may legitimately be referred

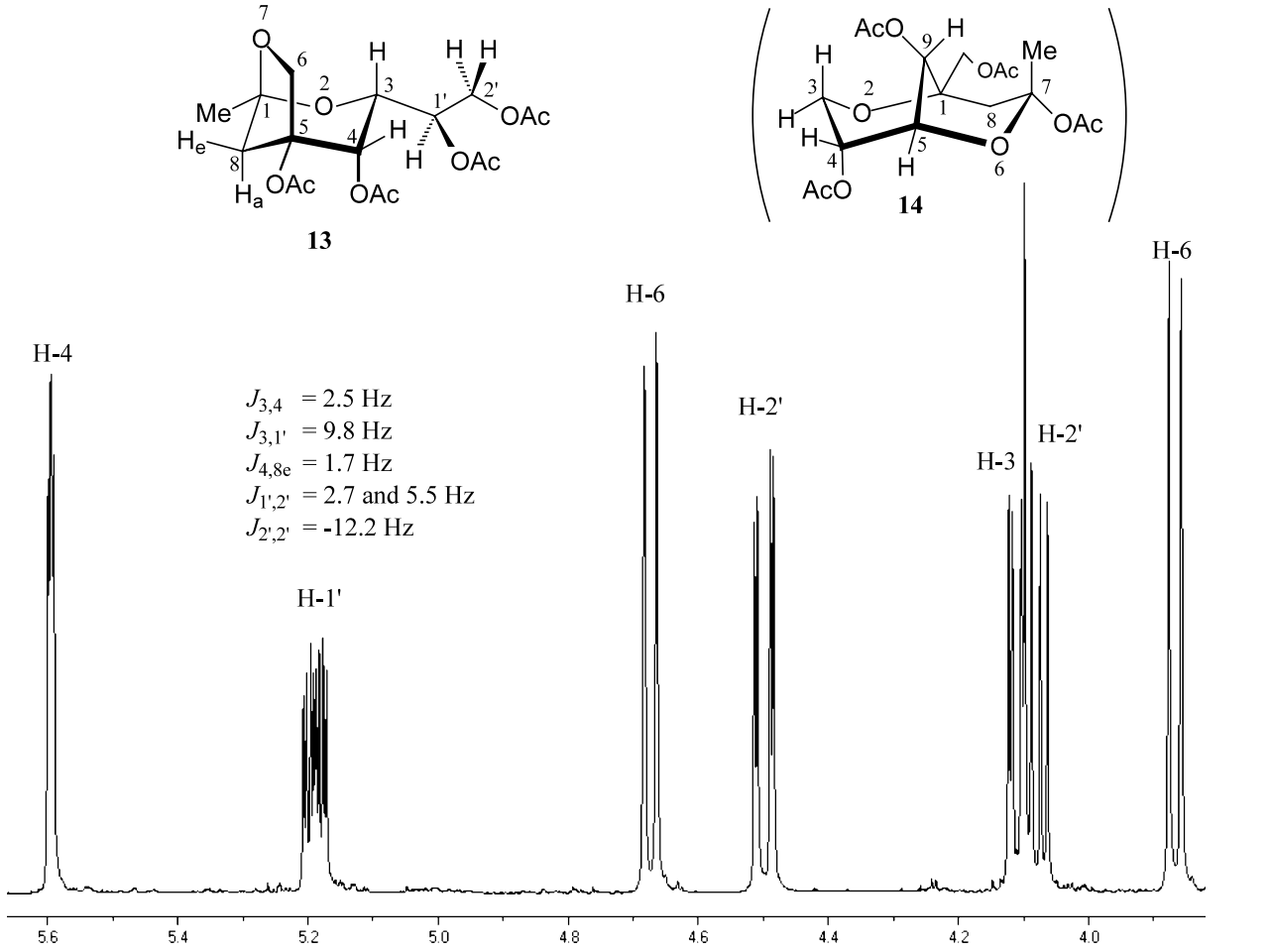


Figure 1. ^{1}H NMR spectrum of **13** (500 MHz, $CDCl_3$). A notable feature is the long-range coupling between 4-H and 8-H_e revealing their essentially perfect W-arrangement.

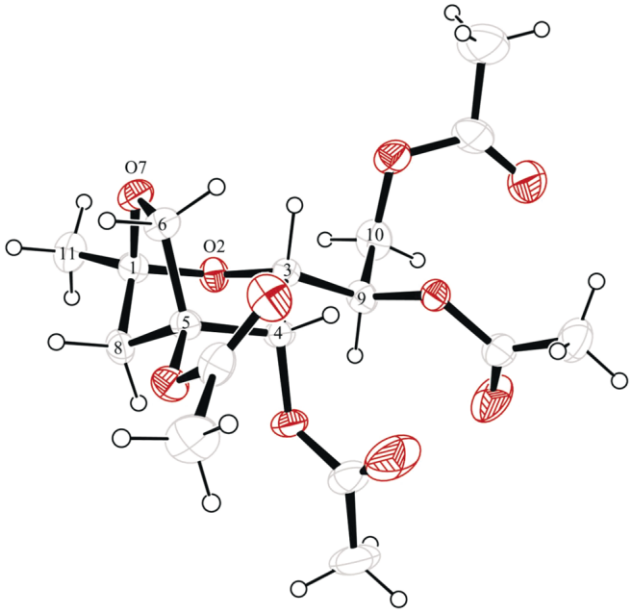


Figure 2. Perspective view of the molecular structure of **13**.

Table 1. Selected torsional angles (°) for **13**

Pyranoid ring	
C1–O2–C3–C4	47.7
O2–C3–C4–C5	−44.8
C3–C4–C5–C8	59.7
C4–C5–C8–C1	−71.6
C5–C8–C1–O2	73.2
C8–C1–O2–C3	−64.4
Furanoid ring	
C1–O7–C6–C5	6.0
O7–C6–C5–C8	−32.8
C6–C5–C8–C1	45.0
C5–C8–C1–O7	−43.3
C8–C1–O7–C6	23.6
Ring substituents	
C9–C3–C4–O4	−46.3
O4–C4–C5–O5	61.9
O4–C4–C5–C6	−168.6
O7–C1–O2–C3	49.4
C11–C1–O2–C3	167.9

to as green and/or sustainable in accord with approved principles,[20] the moderate yield obtained (27%) being tolerable inasmuch as D-fructose is the second most abundant natural sugar and ton-scale accessible.[21] As the product is a heavily functionalised bicyclic intermediate, it has the potential of various further preparative manipulations towards enantiopure building blocks, whereas configurationally different frameworks of this type are apt to be accessible from other ketoses such as L-sorbose or D-psicose, on which we expect to report in due course.

3. Experimental

Melting points were determined on a Büchi SMP-20 apparatus and are uncorrected. Optical rotations were measured on a Perkin–Elmer 241 polarimeter at 20°C using a cell of 1 dm path length. Mass spectra were recorded on Varian MAT 311 and MAT 212 spectrometers. Microanalyses were determined on a Perkin–Elmer 240 elemental analyzer. Analytical thin layer chromatography (TLC) was performed on precoated Merck plastic sheets (0.2 mm silica gel 60 F_{254}) with detection by UV (254 nm) and/or spraying with H_2SO_4 (50%) and heating. Column and flash chromatography was carried out on Fluka silica gel 60 (70–230 mesh) using the specified eluents. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE 500 spectrometer.

3.1. 3*R*-[1′*R*,2′-Di-hydroxyethyl]-1*S*-methyl-2,7-dioxabicyclo[3.2.1]octane-4*S*,5*S*-diol 12

To a solution of D-fructose (2.5 g, 13.9 mmol) in water (50 mL) were added sodium bicarbonate (3.2 g, 38 mmol) and pentane-2,4-dione (3.6 g, 36 mmol), and the mixture was stirred at 85°C for 15 h. The solution was allowed to cool, washed with EtOAc (3×20 mL), followed by neutralization with Dowex resin (50X8, H^+ form). After evaporation to dryness the remaining D-fructose was separated from the products by elution from a silica gel column (EtOAc/MeOH/water, 15:4:1). The eluates were combined—fructose remains on the column—taken to dryness in vacuo and subjected to flash chromatography on silica gel (EtOAc/*i*PrOH/H_2O, 8:1:1). The fractions eluted first, having R_f=0.27 (TLC in EtOAc/MeOH, 20:3) were free from the solvent in vacuo to yield 825 mg (27%) of **12** as a colorless solid; $[\alpha]_D^{20}$=−27.4 (*c* 1.0, MeOH); ^{1}H NMR (500 MHz, d_4-MeOH): δ 1.37 (s, 3H, C*H*$_3$), 1.71 (dd, 1H, 8-H$_e$), 2.30 (d, 1H, 8-H$_a$), 3.57, 3.75 (2 dd, 1H each, 2′-H$_2$), 3.65 (m, 2H, 6-H, 3-H), 3.87 (d, 1H, 6-H), 3.86 (m, 2H, 4-H, 1′-H); $J_{6,6}$=8.0, $J_{4,8e}$=1.4, $J_{8,8}$=10.7, $J_{1',2'}$=3.4 and 6.1, $J_{2',2'}$=11.4 Hz. ^{13}C NMR (125 MHz, d_4-MeOH): δ 24.2 (*C*H$_3$), 42.2 (C-8), 64.8 (C-2′), 71.7, 72.0 (C-4, C-1′), 74.0 (C-3), 75.1 (C-6), 79.4 (C-5), 108.3 (C-1). MS (ESI): *m*/*z* 243.1 [M+Na]$^+$. Anal. calcd for $C_9H_{16}O_6$ (220.22): C, 49.08; H, 7.32. Found: C, 49.01; H, 7.24.

The fractions eluted next contained the minor product, **1′-*C*-(β-D-glucopyranosyl)-2′-propanone** formed by reaction of pentane-2,4-dione with the small amounts of D-glucose generated through from D-fructose isomerization under the basic reaction conditions: 0.18 g (6%) of a colorless syrup of $[\alpha]_D^{20}$=−3.2 (*c* 1.2, MeOH); lit.[22]: $[\alpha]_D$=−3.0 (*c* 1.3, MeOH). ^{1}H NMR data in D_2O (500 MHz) matched those reported.[22]

3.2. 4*S*,5*S*-Bis-acetoxy-3*R*-[1′*R*,2′-bis-acetoxyethyl]-1*S*-methyl-2,7-dioxabicyclo[3.2.1]octane 13

To a solution of D-fructose (2.5 g, 13.9 mmol) in water (50 mL) was added sodium bicarbonate (3.2 g, 38 mmol) and pentane-2,4-dione (3.6 g, 36 mmol), and the mixture was stirred at 85°C for 15 h, followed upon cooling down by washing with EtOAc (3×20 mL) and neutralization by stirring with Dowex resin (50X8, H^+ form). After evaporation to dryness the remaining D-fructose was separated from the products by elution from a silica gel column (EtOAc/MeOH/water, 17:3:1). The product fractions were combined, taken to dryness and then dissolved in pyridine (50 mL) and treated with Ac_2O (10 mL) for 15 h. The solvent was removed in vacuo and the residue dissolved in CH_2Cl_2 (50 mL), washed with 2N HCl (2×20 mL) and $NaHCO_3$ (2×20 mL), dried ($MgSO_4$), and evaporated to dryness. The residue was purified on a silica gel column (toluene/EtOAc, 4:1) to yield in vacuo on evaporation of the first fractions with R_f=0.44 (TLC in toluene/EtOAc, 2:1) a syrup which crystallized on trituration with EtOH: 1.22 g (23%) of **13**; mp 95–97°C; $[\alpha]_D^{20}$=+1.1 (*c* 1.0, $CHCl_3$); $[\alpha]_{365}^{20}$=+5.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.48 (s, 3H, C*H*$_3$), 1.90 (dd, 1H, 8-H$_e$), 1.96, 1.98, 2.06, 2.08 (4 s, 1H each, 4 AcCH$_3$), 2.40 (d, 1H, 8-H$_a$), 3.87, 4.68 (2 d, 1H each, 6-H$_2$), 4.08, 4.50 (2 dd, 1H each, 2′-H$_2$), 4.11 (dd, 1H, 3-H), 5.18 (ddd, 1H, 1′-H), 5.59 (d, 1H, 4-H); $J_{3,4}$=2.5, $J_{6,6}$=9.4, $J_{4,8e}$=1.7, $J_{8,8}$=11.0, $J_{3,1'}$=9.8, $J_{1',2'}$=2.7 and 5.5, $J_{2',2'}$=12.2 Hz. ^{13}C NMR (125 MHz, $CDCl_3$): δ 18.9, 19.0 (4 Ac*C*H$_3$), 21.4 (*C*H$_3$), 38.9 (C-8), 61.0 (C-2′), 65.5 (C-4), 66.5 (C-1′), 67.8 (C-3), 70.6 (C-6), 80.7 (C-5), 103.4 (C-1), 168.1, 168.3, 168.6, 168.9 (AcCO). MS (ESI): *m*/*z* 411.2 [M+Na]$^+$. Anal. calcd for $C_{17}H_{24}O_{10}$ (388.36): C, 52.57; H, 6.23. Found: C, 52.13; H, 6.12.

The fraction eluted next (R_f=0.28 on TLC with toluene/EtOAc, 2:1), crystallized upon removal of the solvents in vacuo: 270 mg (5%) of a product of mp 102–103°C and $[\alpha]_D^{20}$=+8.9 (*c* 1.0, $CHCl_3$), which on the basis of these as well as its ^{1}H and ^{13}C NMR data[17b] proved to be **1′-*C*-(1,3,4,5-tetra-*O*-acetyl-β-D-glucopyranosyl)-2′-propanone**, formed by reaction of pentane-2,4-dione with the small amounts of D-glucose generated through isomerization of D-fructose under the basic reaction conditions.

Tetraacetate **13** was also obtained in 95% yield by acetylation of **12** with 2:1 pyridine/Ac_2O for 12 h at ambient temperature, workup by evaporation to dryness in vacuo and crystallization from EtOH.

3.3. X-Ray structure determination of 13

X-Ray data collection was carried out with an Oxford Diffraction Xcalibur™ Single Crystal X-ray Diffraction with Sapphire CCD Detector, graphite monochromized Mo Kα radiation from a sealed X-ray tube, λ(Mo-Kα)= 0.71073 Å. Data treatment and reduction was

carried out with CrysAlis CCD and CrysAlis RED (Oxford Diffraction Ltd., 2003). The structures were solved with direct methods using program SHELXS 97 and were refined on F^2 using program SHELXL 97.[23] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were inserted in idealized positions and rode on the atoms to which they were bonded.

Crystal data for **13** at $T=299$ K: $C_{17}H_{24}O_{10}$, $M_r=388.36$, colorless crystals of 0.75×0.16×0.06 mm obtained from ethanol, orthorhombic, space group $P2_12_12_1$, $a=6.8120(10)$, $b=8.7122(8)$, $c=32.896(3)$ Å, $\alpha=\beta=\gamma=90°$, $V=1952.3(4)$ Å^3, $Z=4$, $D_x=1.321$ Mg/m^3, $\mu=0.110$ mm^{-1}, $T=299(2)$ K. 12718 reflections with $\theta=4.23$ to 26.37° were measured, and merged to 2319 unique reflections, $R_{int}=0.1046$. Final refinement: 265 parameters, $R_1=\Sigma\|F_o|-|F_c\|/\Sigma|F_o|=0.0869$, $wR_2=[\Sigma(w(F_o^2-F_c^2)^2)/\Sigma(w(F_o^2)]^{1/2}=0.1714$, and $S=1.097$ for all reflections; $R_1=0.0667$ for the 1785 observed data [$I>2\sigma(I)$].[24]

Acknowledgements

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24. Supplementary crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 210251 Copies of the data can be obtained, free of charge, via www.ccdc.cam.ac.uk/conts/retrieving.html or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk.