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Note

Structural studies on C-2 substitution in a new set of synthetic aminodideoxy sugars: the steric bulk at C-2 influences the puckering of the pyranose ring

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Abstract

Synthesis and single-crystal X-ray structural analyses of selected aminodideoxy sugars with different group substitutions at the C-2 position were carried out. Product formation and X-ray crystallographic determination of the products from C-2 substitution in both α and β anomers were studied. The observed variation in pyranose ring conformations in product compounds is explained in terms of C-2 substitution.

Keywords: α and β Anomers; Amino sugars; C-2 Substitution; Pyranose conformation; Steric hindrance

The most common methods for the synthesis of amino sugars involve the reactions of amines with sugar-derived epoxides, tosylates and ketones, although several other methods that are used to a limited extent are also reported.[1] Nucleophilic addition (Michael addition) at double bonds that are activated by electron-withdrawing groups and are a part of carbohydrate units could serve as a useful methodology for the functionalization of monosaccharides. Several examples of the Michael addition of nitrogen nucleophiles, including amines, to hex-2-enose[2–4] and 3-nitro-hex-2-enopyranosides[5–12] have been reported. During the course of our studies on the synthesis of carbohydrate-modified monovinylsulfone-[13] and bisvinylsulfone-substituted nucleosides,[14] we envisaged that due to the high reactivity of vinyl sulfones towards a wide variety of nucleophiles, vinyl sulfone-modified carbohydrates[15] could be utilized to generate an array of modified aminodeoxy sugars.

Herein we report on the structural investigations of three phenylsulfonyl-modified monosaccharides with amino substitution at C-2. Two of them are a pair of β and α anomers of C-2 isobutylamino-substituted pyranose derivatives, and the third is a β anomer of a C-2 *tert*-butylamino-substituted pyranose. The pyranose ring in the α,β pair assumes a favorable chair conformation, whereas the pyranose ring in the third β anomer is a strained boat conformation. Moreover, the synthetic pathway did not achieve the corresponding C-2 addition in the α anomer. It is possible that the addition of bulky groups at the C-2 position is influenced by the disposition of the methoxy group at C-1; however, further studies will be required to confirm this.

To initiate a systematic study on the reaction patterns of endocyclic monovinylsulfones derived from carbohydrates, the easily accessible anomers, methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-*C*-phenylsulfonyl-α-D-*erythro*-hex-2-enopyranoside (**1α**) and methyl 2,3-dideoxy-4,6-*O*-(phenylmethylene)-3-*C*-phenylsulfonyl-β-D-*erythro*-hex-2-enopyranoside (**1β**) were selected as the first set of candidates. Detailed studies on the addition of primary amines, such as isobutylamine and

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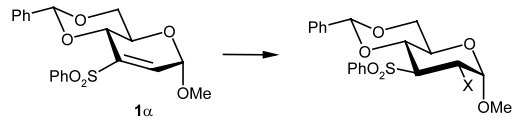
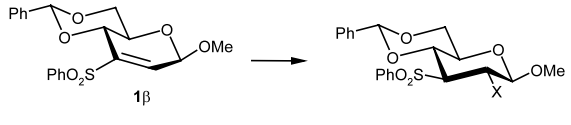


Scheme 1.



Scheme 2.

benzylamine to **1α** have been reported.[16,17] These amines have been added at the C-2 position diastereoselectively to produce single isomers **2αa** and **2αb**, respectively (Scheme 1). Similarly, the anomeric β-vinyl derivative **1β**, upon reaction with isobutylamine and benzylamine, also produced single isomers **2βa** and **2βb**, respectively (Scheme 2).[16,17] The structures of these aminodeoxy sugars have been assigned on the basis of their ^{1}H NMR spectroscopic data. The $J_{1,2}$ values of **2αa** (3.5 Hz)[16] and **2αb** (3.6 Hz)[17] are comparable to those of methyl 2-*N*-alkylamino-4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-α-D-glucopyranosides ($J_{1,2}$ 2.9–3.7 Hz).[8] In case of **2βa** and **2βb**, both of the H-1 signals appeared as doublets with large coupling constant ($J_{1,2}$) values of 6.6 Hz,[16,17] which is in line with the large values reported for methyl 2-*N*-alkylamino-4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-β-D-glucopyranosides (7.7–8.5 Hz).[8]

Compound **1α** on treatment with sterically bulky *tert*-butylamine did not produce the expected aminodeoxy sugar **2αc**, and unreacted starting material was recovered from the reaction mixture. The β anomer **1β**, on the other hand, reacted smoothly with the same amine at elevated temperatures to produce a single isomer **2βc** in excellent yield. The structure elucidation of **2βc**, however, turned out to be problematic because the $J_{1,2}$ value of **2βc**, which was assigned to be 2.1 Hz, was well below the $J_{1,2}$ values of its analogues **2βa** and **2βb**. Moreover, the $J_{1,2}$ value of methyl 4,6-*O*-benzylidene-2-*C*-cyano-2,3-dideoxy-3-*C*-nitro-β-D-mannopyranoside was reported as 2.2 Hz,[9] which is comparable to that of **2βc**. Since no other primary amine produced a manno isomer, either with **1α** or **1β**,[16] we decided to subject amino sugar **2βc** to an unambiguous structural analysis by single-crystal X-ray diffraction. We also subjected isobutylamino derivatives **2αa** and **2βa** to the same study to extract information on the effects of amino substituents with different steric bulk on the puckering of the ring and ring conformation.

Crystals of **2αa** and **2βc** contained one molecule each in the asymmetric unit of their unit cell, whereas **2βa** contained two. The difference between the two molecules in the asymmetric unit of **2βa** is mainly due to the differences in mutual orientations of the two phenyl rings in them (shown as angles 53.2(3) and 73.9(3)° for molecule A and B, respectively (Fig. 2(a and b))). When the pyranose rings of the three crystallographically independent molecules of **2αa** and **2βa** were compared, the differences were found to be insignificant in the average of either C–C bond length or

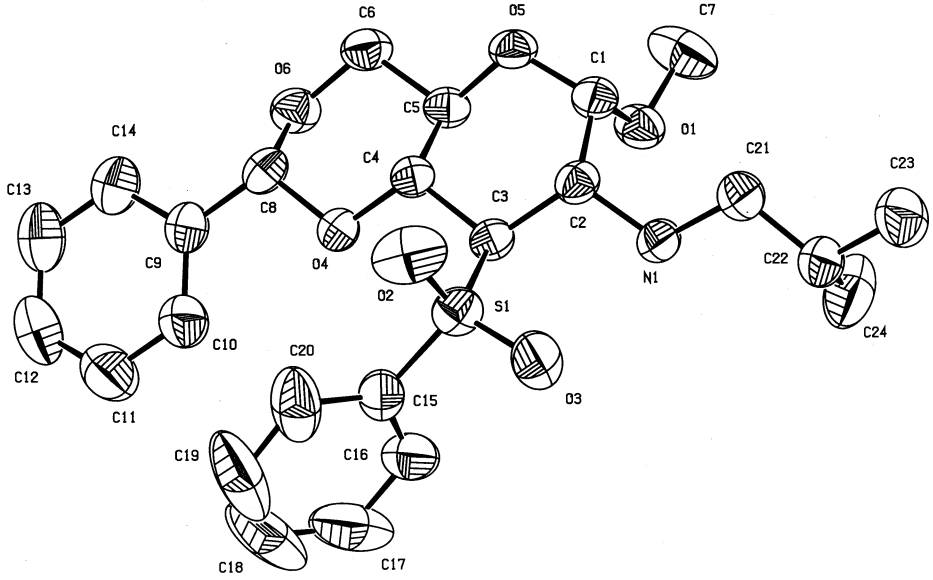


Fig. 1. An ORTEP view of **2αa** showing atom numbering. Displacement ellipsoids are drawn at 50% probability in this figure and in others.

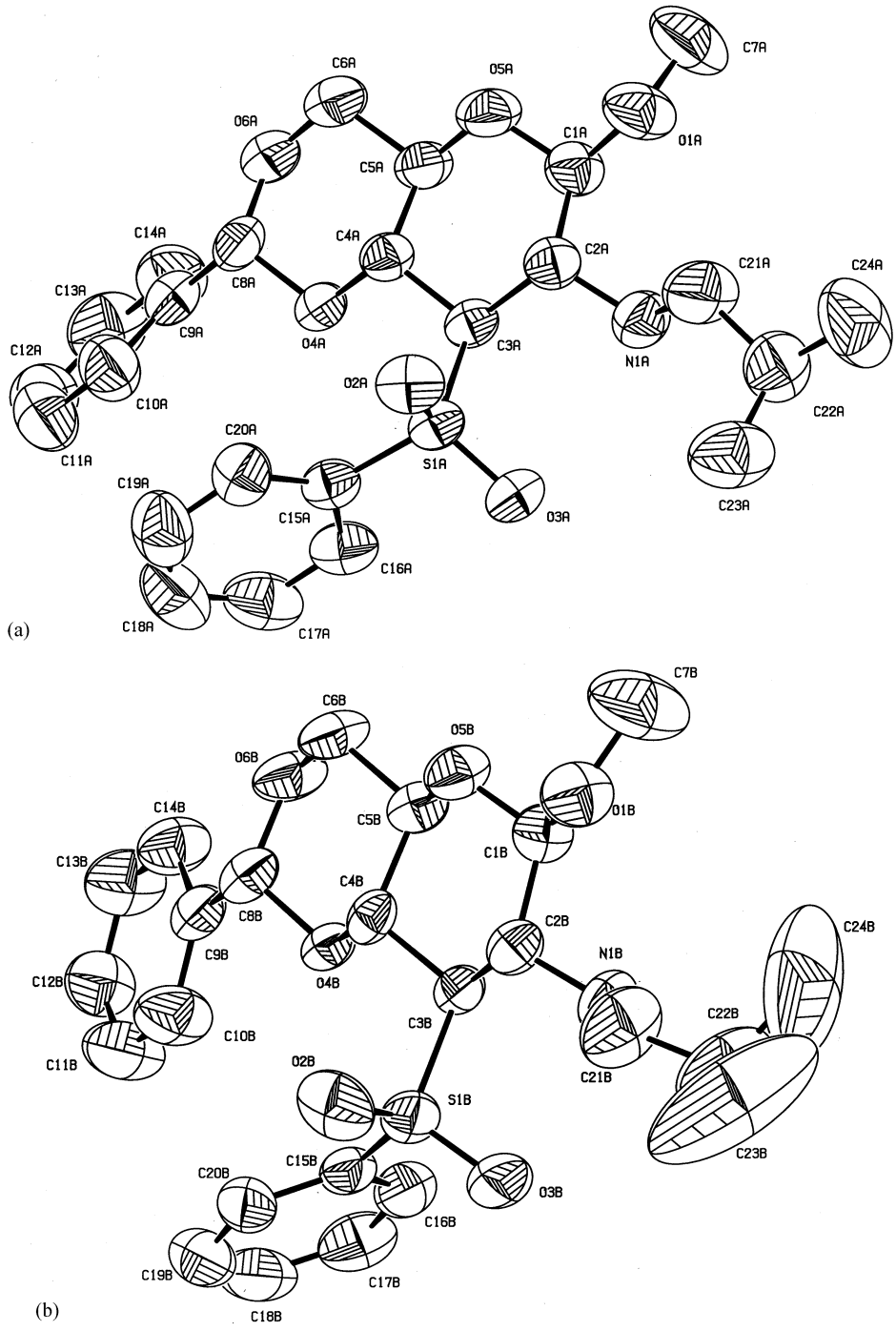


Fig. 2. (a) An ORTEP view of Molecule A in the asymmetric unit of **2βa**. (b) An ORTEP view of Molecule B in the asymmetric unit of **2βa**.

angles around the ring carbon atoms. In case of **2βc**, the average values of the pyranose ring carbon angles and O-5 angle had comparatively higher values. The pyranose ring conformation of **2αa** (Fig. 1) is similar to that reported for the structure of **2αb**.[18] Similarly the sugar puckering of **2βc** (Fig. 3) closely resembles that of the one reported for **2βb**.[18] However, the pyranose ring of **2βa** in its structure is in the chair conformation. In all these structures the addition of the amino group at C-2 is at the equatorial position. Thus in the β anomers the vinyl sulfone, amino and methoxy groups at the C-3,-2, and -1 positions are all equatorial. Even then, in cases where bulkier groups are present at C-2, such as in **2βa** and **2βc**, the pyranose ring assumes a boat conformation to facilitate positioning the methoxy group of C-1 away from the amino group of C-2. The

observation of increasing values (magnitudes) of conformational angles O-1–C-1–C-2–N-1 in the order **2βa → 2βb → 2βc** in their respective β anomeric structures (Table 1)[18] confirms this argument. However, in the case of α anomers, the mechanism by which to increase this particular conformational angle is limited due to the axial positioning of methoxy group at C-1. Thus a bulkier group, greater than a critical size, could not be accommodated at the C-2 position in the α anomer, in the absence of a mechanism to release the resultant strain due to steric hindrance. This could be an explanation for the non-formation of **2αc** when the synthesis was started with **1α**, whereas product formation of **2βc** took place in the synthesis starting from **1β**.

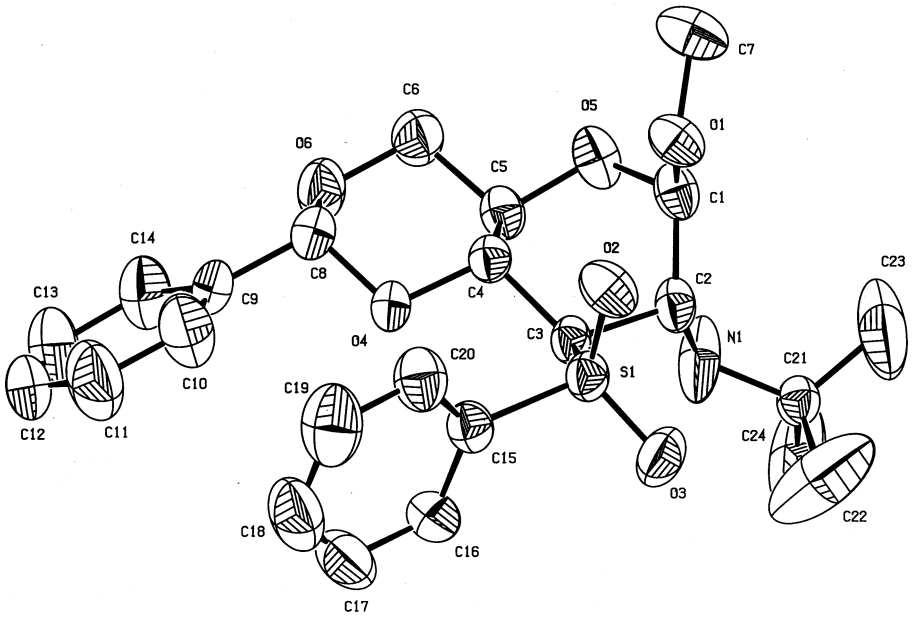


Fig. 3. An ORTEP view of **2βc**.

Table 1
Selected conformational angles in the three structures, **2αa**, **2βa**, and **2βc** [a]

Conformation angle	(**2αa**)	(**2βa**) Molecule A	(**2βa**) Molecule B	(**2βc**)
C-5–O-5–C-1–C-2	**−57.8(3)**	**−65.6(5)**	**−61.9(5)**	**32.9(4)**
O-5–C-1–C-2–C-3	**−42.0(3)**	**−47.9(5)**	**−49.6(4)**	**16.1(3)**
C-5–O-5–C-1–O-1	65.8(3)	174.8(4)	179.6(4)	−90.4(3)
O-5–C-1–O-1–C-7	73.1(3)	−78.5(7)	−79.9(7)	−62.0(4)
O-1–C-1–C-2–N-1	43.0(3)	−61.8(6)	−65.2(5)	−166.4(3)
O-5–C-1–C-2–N-1	167.4(2)	179.5(4)	176.7(4)	68.3(3)
C-1–C-2–C-3–C-4	**44.0(3)**	**56.1(5)**	**52.7(5)**	**−56.2(3)**
N-1–C-2–C-3–S-1	74.6(3)	64.7(4)	67.7(4)	126.0(3)
C-15–S-1–C-3–C-4	73.9(2)	48.1(3)	60.6(3)	61.4(3)
C-2–C-3–C-4–O-4	172.6(2)	169.1(3)	172.7(3)	156.0(2)
C-2–C-3–C-4–C-5	**52.2(3)**	**50.0(5)**	**54.8(4)**	**39.5(3)**
C-1–O-5–C-5–C-6	−171.9(2)	−175.0(5)	−174.1(4)	147.2(3)
C-1–O-5–C-5–C-4	**69.1(3)**	**66.1(5)**	**66.5(5)**	**27.5(4)**
O-6–C-6–C-5–O-5	−173.6(2)	−178.8(4)	−175.1(4)	−178.0(3)
O-6–C-6–C-5–C-4	−55.1(3)	−58.6(6)	−55.9(5)	−56.6(4)
O-4–C-4–C-5–O-5	173.7(2)	−179.9(4)	176.7(3)	176.6(3)
C-3–C-4–C-5–O-5	**−65.6(3)**	**−59.0(5)**	**−63.1(4)**	**−66.0(3)**
O-4–C-4–C-5–C-6	54.6(3)	60.2(5)	57.2(4)	58.1(3)
C-3–C-4–C-5–C-6	175.2(2)	−178.9(4)	177.4(4)	175.6(3)
C-1–C-2–N-1–C-21	62.5(3)	86.4(6)	102.0(6)	101.2(5)
C-3–C-2–N-1–C-21	−172.7(2)	−151.6(5)	−135.9(6)	−134.7(4)
C-2–N-1–C-21–C-22	177.9(3)	166.8(6)	−170.9(7)	

[a] The six endocyclic conformation angles of the pyranosyl ring are in bold face type.

Table 2
X-ray crystallographic data and structure refinement for **2αa**, **2βa** and **2βc**

Compound	(**2αa**)	(**2βa**)	(**2βc**)
Color/shape	colorless/rectangular block	colorless/regular block	white/needle
Empirical formula	$C_{24}H_{31}NO_6S$	$C_{24}H_{31}NO_6S$	$C_{24}H_{31}NO_6S$
Formula weight	461.56	461.56	461.56
Temperature (°C)	20 ± 2	20 ± 2	20 ± 2
Crystal system	monoclinic	triclinic	triclinic
Space group	$P2_1$	$P1$	$P1$
Unit cell dimensions			
a (Å)	11.297 (2)	9.476 (3)	8.123 (5)
b (Å)	8.534 (2)	10.010 (3)	12.485 (6)
c (Å)	13.405 (4)	13.935 (3)	5.9460 (11)
α (°)	90.0	72.47 (2)	92.95(3)
β (°)	114.71 (2)	85.66 (2)	94.96 (4)
γ (°)	90.0	70.98 (2)	84.23(5)
V (Å^3)	1174.0 (5)	1191.2 (6)	597.2(5)
Z	2	2	1
D_{calcd} (g cm^{-3})	1.306	1.287	1.283
Absorption coefficient (mm^{-1})	0.177	0.175	0.174
Diffractometer	CAD-4	CAD-4	AFC-7S
Radiation ($\lambda = 0.71069$ Å)	Mo K_α	Mo K_α	Mo K_α
$F(000)$	492	492	246
Crystal size (mm)	$0.56 \times 0.34 \times 0.20$	$0.80 \times 0.70 \times 0.45$	$0.80 \times 0.20 \times 0.12$
2θ Range for data collection (°)	0–50	0–50	0–65
Index ranges	$0 \le h \le 13$, $0 \le k \le 10$, $-15 \le l \le 14$	$0 \le h \le 11$, $-11 \le k \le 11$, $-16 \le l \le 16$	$0 \le h \le 12$, $-18 \le k \le 18$, $-8 \le l \le 8$
Reflections collected	2324	4474	4574
Independent/observed reflections	2207 (2123 with $I > 2\sigma$)	4386 (4223 with $I > 2\sigma$)	4313 (2814 with $I > 2\sigma$)
Absorption correction	0	0	0
Refinement method	full-matrix least squares on F^2	full-matrix least squares on F^2	full-matrix least squares on F^2
Computing	SHELXL-93	SHELXL-93	SHELXL-93
Data/restraints/parameters	2207/1/293	4386/3/583	4313/3/293
Goodness-of-fit on F^2	1.061	1.095	1.131
Function minimized	$\Sigma\, w(F_o^2 - F_c^2)^2$	$\Sigma\, w(F_o^2 - F_c^2)^2$	$\Sigma\, w(F_o^2 - F_c^2)^2$
Final weighted R (wR)	0.1020 for all 2207 reflections	0.1540 for all 4386 reflections	0.1372 for all 4313 reflections
Final crystallographic R	0.0373 for 2123 [$I > 2\sigma(I)$]	0.0563 for 4386 [$I > 2\sigma(I)$]	0.0494 for 4313 [$I > 2\sigma(I)$]
Large difference peak and hole (e Å^{-3})	0.287/−0.235	0.395/−0.261	0.620/−0.389
Flack parameter[19]	0.09(10)	−0.01(10)	0.08(9)

1. Experimental

General methods.—Melting points were determined in open-end capillary tubes and are uncorrected. All chemicals were obtained from commercial suppliers and were used without purification. TLC was carried out on precoated plates (E. Merck, Silica Gel 60, F_{254}), and the spots were visualized with UV light. Column chromatography was performed on silica gel (Silica Gel 60, 230–400 mesh). ^{1}H NMR spectra were recorded at 200 and 300 MHz in $CDCl_3$ using the residual $CHCl_3$ as standard, and ^{13}C NMR spectra were recorded at 50.3 and 75 MHz in $CDCl_3$ using the triplet centered at δ 77.0 as the standard. The optical rotation was recorded at 589 nm. Methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-*C*-phenylsulfonyl-2-isobutylamino-α and β-D-glucopyranoside (**2αa**) and (**2βa**), respectively, were prepared according to the reported procedure.[16]

*Methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-*C*-phenylsulfonyl-2-*tert*-butylamino-β-*D*-glucopyranoside* (**2βc**).—A solution of **1β** (0.15 g, 0.386 mmol) in neat *tert*-butylamine (3 mL) was heated under reflux for 6 h, at the end of which time the amine was evaporated under reduced pressure. The resulting residue was dissolved in EtOAc (25 mL), and the solution was washed with water (3×5 mL). The EtOAc layer was separated,

dried over anhyd Na_2SO_4, and filtered. The filtrate was concentrated to dryness under reduced pressure to afford a white solid that was crystallized from MeOH to afford white crystalline **2βc** (0.37 g, 96%); mp 168–169 °C; $[\alpha]_D^{31}$ −74.8° (*c* 0.107, $CHCl_3$). ^1H NMR ($CDCl_3$, ^1H–^1H COSY): δ 1.15 (s, 9 H, $C(CH_3)_3$), 3.42 (s, 3 H, OCH_3), 3.57 (dd, *J* 1.5, 8.8 Hz, 1 H, H-3), 3.66 (t, *J* 7.5 Hz, 1 H, H-6_{ax}), 3.90 (dt, *J* 4.0, 10.0 Hz, 1 H, H-5), 4.09 (dd, *J* 2.4 Hz, 1 H, H-2), 4.33 (dd, *J* 4.9, 10.3 Hz, 1 H, H-6_{eq}), 4.58 (d, $J_{1,2}$ 2.4 Hz, 1 H, H-1), 4.73 (t, *J* 9.5 Hz, 1 H, H-4), 5.49 (s, 1 H, Ph-C*H*), 7.18–7.43 (m, 8 H, Ar), 7.88 (m, 2 H, Ar). ^{13}C NMR ($CDCl_3$): δ 29.3, 51.1, 51.5, 54.5, 62.7, 69.7 (CH_2), 71.5, 74.9, 100.7, 101.9, 125.7, 127.6, 128.3, 132.7, 136.5, 141.4. Anal. Calcd for $C_{24}H_{30}NO_6S$: C, 62.58; H, 6.56; N, 3.04; S, 6.96. Found: C, 62.38; H, 6.11; N, 2.74; S, 6.95.

Crystallographic data.—Crystallographic data were collected with either an Enraf–Nonius CAD-4 or AFC-7S diffractometer as indicated (Table 2). H-atoms were located using geometrical considerations and a difference Fourier map. They were treated as riding on the heavier atoms to which they were attached. For compounds **2αa** and **2βa**, data collection and cell refinement: CAD-4-PC software,[20] data reduction: NRCVAX DATRD2;[21] for compound **2βc** data collection, cell refinement and data reduction: MSC/AFC DIFFRACTOMETER CONTROL software.[22] For all the compounds, programs to solve structure: SHELXS86;[23] program(s) used to refine structure: SHELXL93;[24] molecular graphics: PLATON.[25]

2. Supplementary material

Full crystallographic details, excluding structure factors, have been deposited (184373, 184374 and 184375) with the Cambridge Crystallographic Data Centre. These data may be obtained, on request, from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Tel.: +44-1223-336408; fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk; www: http://www.ccdc.cam.ac.uk).

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