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Note

A surprising C-4 epimerization of 5-deoxy-5-sulfonylated pentofuranosides under Ramberg–Bäcklund reaction conditions

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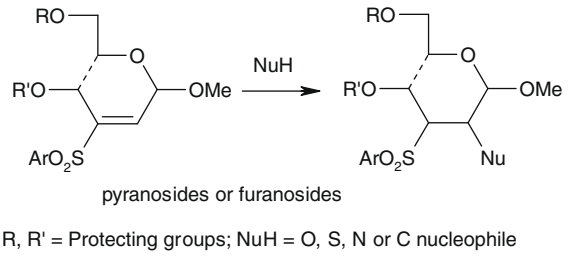
ABSTRACT

Treatment of methyl 5-deoxy-2,3-*O*-isopropylidene-5-(benzylsulfonyl)-β-D-ribofuranoside with CBr_2F_2–KOH/Al_2O_3 afforded the corresponding olefinic sugar. The methyl- and the isopropyl-analogues in contrast underwent epimerization at C-4 to generate the α-L-*lyxo* derivatives.

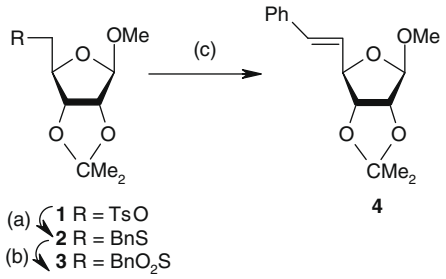
The SO_2-extrusion reaction has been shown to be an efficient tool for the creation of double bonds in various organic molecules[1a] and at the anomeric position of various carbohydrates.[1b] Our interest in the area of sulfonylated carbohydrates obtained after Michael addition of nucleophiles to vinyl sulfone-modified carbohydrates (Scheme 1)[2] prompted us to study the utility of SO_2-extrusion reaction as a method for removing the sulfone group from the Michael adducts. Since the SO_2-extrusion reaction is widely used for the creation of double bonds, we decided to study this reaction for the synthesis of a series of exocyclic olefins at non-anomeric carbons of carbohydrates.

For this study, we selected the furanosyl sulfone **3** as the model for studying the SO_2-extrusion reaction (Scheme 2). Thus, the 5-*O*-tosylated ribofuranoside **1**,[3] on treatment with benzylmercaptan produced the 5-deoxy-5-thio analogue **2**.[4] Compound **2** was oxidized with magnesium monoperoxyphthalate hexahydrate (MMPP) in high yields to the corresponding sulfone **3**. When compound **3** was treated under modified Ramberg–Bäcklund conditions (CBr_2F_2, KOH/Al_2O_3, DCM/^{t}BuOH = 1:1, 0 °C–rt)[5] for 1 h, compound **4** was formed in good yield (73%) of the trans-isomer in high selectivity, which was confirmed from the coupling constant (16 Hz) values of the olefinic protons. It should be noted that this is the first report on the synthesis of compound **4** although the accidental synthesis of the corresponding C-4 epimer is reported in the literature.[6]

After having this encouraging result, we decided to generalize the reaction by treating several carbohydrate-derived sulfones



Scheme 1. Addition of nucleophiles to vinyl sulfone-modified carbohydrates.



Scheme 2. Reagents and conditions: (a) benzylmercaptan, NaOMe, DMF, 5 h, 90 °C, 81%; (b) MMPP, MeOH, 6 h, rt, 97%; (c) CBr_2F_2, DCM, ^{t}BuOH, KOH/Al_2O_3, 0 °C–rt, 1 h, 73%.

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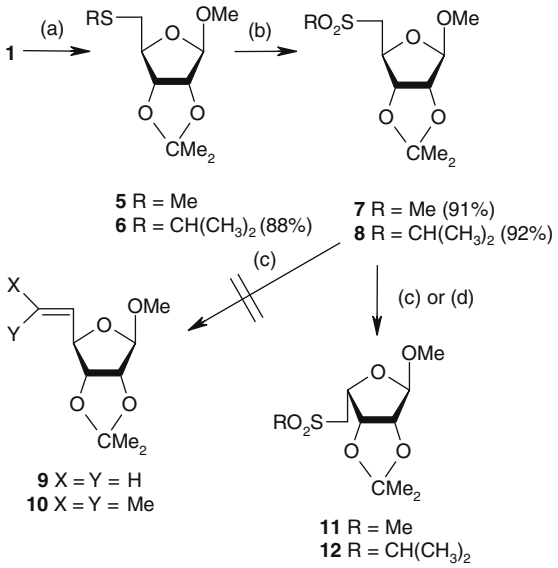


Scheme 3. Reagents and conditions: (a) alkylmercaptan, NaOMe, DMF, 5 h, 90 °C; (b) MMPP, MeOH, 6 h, rt; (c) CBr_2F_2, DCM, ^{t}BuOH, KOH/Al_2O_3, 0 °C–rt, 3 h (for **11**: yield 42%, for **12**: yield 30%); (d) DCM, ^{t}BuOH, KOH/Al_2O_3, 0 °C–rt, 3 h (for **11**: yield 76%, for **12**: yield 65%).

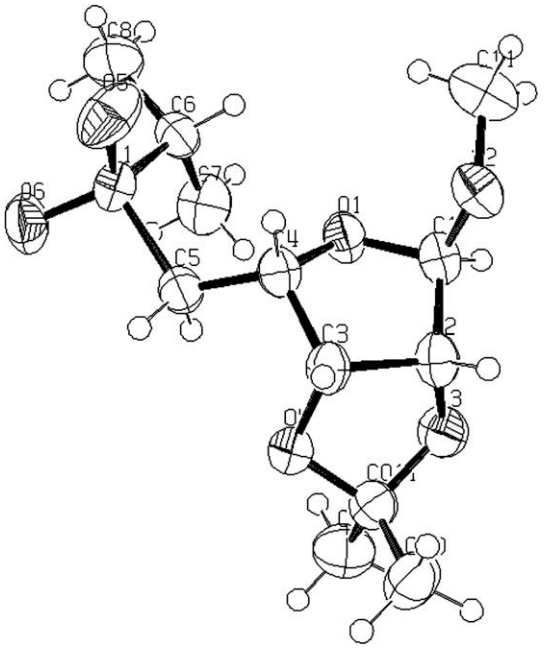
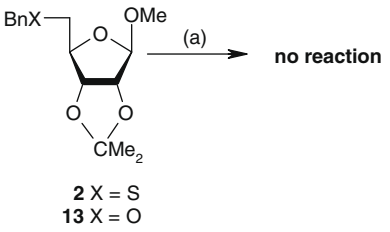


Figure 1. ORTEP diagram of compound **12**.

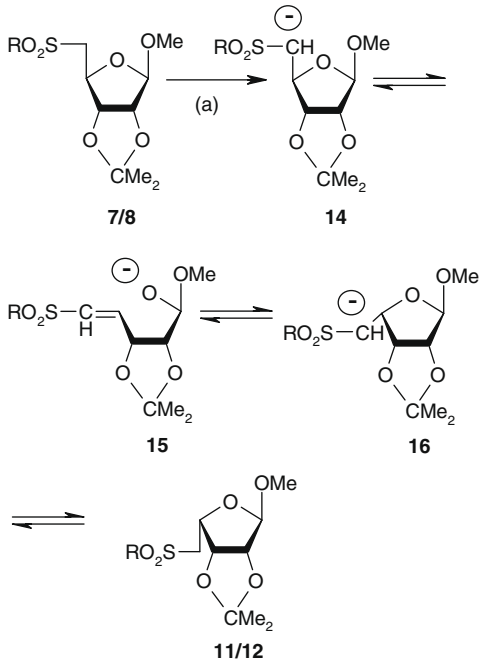
under modified Ramberg–Bäcklund conditions. Thus, the tosylate **1** was converted to the sulfides **5**[4] and **6** using methyl- and isopropylmercaptan respectively (Scheme 3). The sulfides were oxidized to the corresponding sulfones **7** and **8** using MMPP. When compounds **7** and **8** were subjected to modified Ramberg–Bäcklund conditions, we were surprised to note that the expected olefinic compounds **9** and **10** were not formed. Analysis of the NMR data revealed that the major products were structurally close to the starting materials **7** and **8** indicating the possibility of isomerization. The identities of products **11** and **12** were established as follows. The sharp singlets at ~5.0 ppm in starting materials **7/8** and the products **11/12** confirmed the trans-relationship of H-1 and H-2 in these compounds.[6] The only noticeable change was observed for H-4 protons,[6] which shifted approximately from δ 4.71–4.75 (for **7** and **8**) to δ 4.43–4.47 (for **11** and **12**). This change indicated that inversion at C-4 had occurred. However, we looked for an alternative method for the confirmation of the structures of **11** and **12**. The single crystal X-ray diffraction studies of compounds **12** (Fig. 1) confirmed that Ramberg–Bäcklund reaction conditions did convert the β-D-*ribo*-derivative **8** to the α-L-*lyxo* analogue **12** (Scheme 3). By analogy, we concluded that compound **7** also underwent similar isomerization to afford **11** (Scheme 3).

We further treated compounds **7** and **8** with KOH/Al_2O_3 in ^{t}BuOH excluding CBr_2F_2 and isolated compounds **11** and **12**. It should be noted that compounds **11** and **12** were obtained in 42% and 30% yields, respectively, under Ramberg–Bäcklund reaction conditions, but formed in higher yields (76% and 65%, respectively) when CBr_2F_2 was not used as one of the reagents (Scheme 3). The epimerization reaction was therefore one of the several other transformations occurring under Ramberg–Bäcklund reactions. The isomerization in the absence of CBr_2F_2 confirmed the role of a strong base like KOH in the isomerization process. Importantly, a strong organic base like 1,1,3,3-tetramethylguanidine (TMG) failed to isomerize **7** or **8**. In order to gather additional information, the benzyl sulfide derivative **2** and the benzyl-protected ribose analogue **13**[7] were also treated with KOH/Al_2O_3 in ^{t}BuOH (Scheme 4). Both the compounds remained unchanged under these reaction conditions, which was confirmed by NMR data. This experiment established the necessity of having a strong electron-withdrawing group like sulfone at the C-5 position for the epimerization at C-4. Interestingly, when **11** and **12** were treated with KOH/Al_2O_3 in ^{t}BuOH, unreacted starting materials were isolated, proving thereby that the conversion of **7/8** to **11/12** was irreversible. The strain energies of the β-D-*ribo*-derivative **8** and the α-L-*lyxo* analogue **12** were compared using MM2 calculations. Compound **12** was found to be more stable than **8** by 1.75 kcal/mol. The single point energy calculations using DMOL3 also revealed that **12** was more stable than **8**.



Scheme 4. Reagents and conditions: (a) DCM, ^{t}BuOH, KOH/Al_2O_3, 0 °C–rt, 3 h.

It has been reported that the treatment of methyl 2,3-*O*-isopropylidene-β-D-ribofuranosiduronic acid methyl ester with slight excess of NaOMe in MeOH caused an epimerization at C-4.[8] In this case, the acidic proton at C-4 of the uronic acid ester was abstracted by base to give an intermediate carbanion, which was reprotonated to form the α-L-*lyxo* derivative. However, in our case the possibility of abstraction of the H-4 proton was ruled out because it was attached to C-4 and was far removed (β) from the sulfone group at C-5. A comparable scenario was reported when the ylide generated from methyl 5-deoxy-2,3-*O*-isopropylidene-5-(triphenylphosphonio)-β-D-ribofuranoside iodide underwent isomerization to an α-L-*lyxo* derivative through an open chain structure.[6] We believe that the easy halogenation[1a] of the benzyl CH_2 carbon of **3** resulted in the SO_2-extrusion product **4** (Scheme 2). However, under similar reaction conditions, halogenation of carbons on both sides of the SO_2 group in **7** and **8** did not occur efficiently. The acidic C-5 proton was removed by the strong base KOH to generate **14**, which underwent intramolecular ring-opening[6] to generate the



Scheme 5. Reagents and conditions: (a) DCM, ^{t}BuOH, KOH/Al_2O_3, 0 °C–rt, 3 h.

Michael acceptor **15** (Scheme 5). Intramolecular cyclization of **15** generated the carbanion **16**, which was protonated to afford α-L-*lyxo* derivatives **11** and **12** (Scheme 5). Formation of the final product is expected to be controlled by the stereochemical and electronic environment.[8]

In conclusion, we have identified a β-D-*ribo* to α-L-*lyxo* isomerization for the first time under Ramberg–Bäcklund reaction conditions. Although the desired olefin was formed in the case of benzyl sulfone derivative, the methyl- and isopropyl sulfones underwent epimerization at C-4. We may conclude that the Ramberg–Bäcklund SO_2-extrusion reaction using CBr_2F_2–KOH/Al_2O_3 is not an efficient reagent system for the creation of double bond at the C-5 site of 5-deoxy-2,3-*O*-isopropylidene-5-(alkylsulfonyl)-β-D-ribofuranosides.

1. Experimental

2.1. General methods

Melting points were determined in open-end capillary tubes, and are uncorrected. Carbohydrates and other fine chemicals were obtained from commercial suppliers and are used without purification. Solvents were dried and distilled following the standard procedures. TLC was carried out on precoated plates (Merck Silica Gel 60, F_{254}), and the spots were visualized with UV light or by charring the plates dipped in 5% H_2SO_4/MeOH soln. Column chromatography was performed on silica gel (60–120 or 230–400 mesh). ^{1}H and ^{13}C NMR spectra for most of the compounds were recorded at 200/400 and 50.3/100 MHz, respectively, in $CDCl_3$ unless stated otherwise. Optical rotations were recorded at 589 nm.

2.2. Methyl 5-benzylsulfonyl-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranoside 3

To a well-stirred soln of **2** (0.45 g, 1.45 mmol) in dry MeOH (40 mL) was added MMPP (3.6 g, 7.25 mmol), and the mixture was stirred under N_2. After 6 h, MeOH was evaporated to dryness under diminished pressure and the residue was dissolved in satd. $NaHCO_3$ soln (30 mL). The soln was washed with EtOAc (3 × 10 mL). The combined organic layers were dried over anhyd Na_2SO_4, filtered and the filtrate was concentrated under diminished pressure to get a residue which was purified over silica gel (1:4 EtOAc–petroleum ether) to the sulfone **3** (0.482 g, 97%). White solid. Mp: 86 °C. $[\alpha]_D^{29.2}$ −31.6 (*c* 0.16, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.30 (s, 3H), 1.48 (s, 3H), 3.07–3.14 (m, 1H), 3.20–3.29 (m, 1H), 3.32 (s, 3H), 4.25–4.36 (m, 2H), 4.58 (d, *J* = 6.0 Hz, 1H), 4.70 (t, *J* = 6.8 Hz, 1H), 4.75 (d, *J* = 5.6 Hz, 1H), 5.02 (s, 1H), 7.42 (br s, 5H). ^{13}C NMR ($CDCl_3$): δ 24.9, 26.3, 55.3 (CH_2), 55.5, 60.5 (CH_2), 80.4, 83.8, 84.7, 110.1, 112.9, 127.3, 128.9, 129.1, 130.8. Anal. Calcd for $C_{16}H_{22}O_6S$: C, 56.12; H, 6.48. Found: C, 56.45; H, 6.50.

2.3. Methyl (*E*)-5,6-dideoxy-2,3-*O*-isopropylidene-6-phenyl-β-D-ribo-hex-5-enofuranoside 4

CBr_2F_2 (1 ml) was dropwise added to a vigorously stirred mixture of the sulfone **3** (0.2 g, 0.58 mmol), alumina-supported KOH (2 g),[5] ^{t}BuOH (20 ml) and DCM (10 ml) kept at 5–10 °C. The reaction mixture was stirred at room temperature for an additional 5 h, after which the solid catalyst was removed by suction filtration through Celite bed. The filtrate was evaporated to dryness. The filter cake was washed thoroughly with DCM and the washes were combined with the residue from the first filtrate. The resultant organic soln was washed with brine and water, dried and evaporated. The residue was purified on silica gel (1:4 EtOAc–petroleum ether) resulting in **4** (0.118 g, 73%). Hydroscopic solid. $[\alpha]_D^{29.2}$ −40.3 (*c* 0.13, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.32 (s, 3H), 1.51 (s, 3H), 3.38 (s, 3H), 4.53–4.63 (m, 2H), 4.70–4.75 (m, 1H), 4.95 (s, 1H), 6.35 (dd, *J* = 8, 16 Hz, 1H), 6.72 (d, *J* = 16 Hz, 1H), 7.24–7.36 (m, 3H), 7.42–7.46 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 24.9, 26.1, 54.7, 80.9, 81.6, 85.3, 107.2, 112.6 (C), 123.2, 126.7, 127.9, 128.4, 134.3, 136.4. Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.55; H, 7.30. Found: C, 70.04; H, 7.46.

2.4. Methyl 5-deoxy-2,3-*O*-isopropylidene-5-isopropylthio-β-D-ribofuranoside 6

A mixture of isopropylmercaptan (0.26 mL, 2.79 mmol) and NaOMe (0.226 mg, 4.19 mmol) in DMF (10 mL) was stirred for 30 min. Compound **1** (0.5 g, 0.39 mmol) was added and the mixture was heated at 90 °C with stirring under N_2. After 4–5 h, the reaction mixture was poured into satd soln of $NaHCO_3$ (60 mL) and the product was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over anhyd Na_2SO_4, filtered and the filtrate was concentrated under diminished pressure. The residue was purified over silica gel (1:4 EtOAc–petroleum ether to obtain the sulfide **6** (0.32 g, 88%). Glassy liquid. $[\alpha]_D^{29.2}$ −74.0 (*c* 0.45, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.27 (m, 6H), 1.32 (s, 3H), 1.48 (s, 3H), 2.51–2.62 (m, 1H), 2.76–2.80 (m, 1H), 2.94–3.02 (m, 1H), 3.34 (s, 3H), 4.21–4.25 (m, 1H), 4.59 (d, *J* = 6 Hz, 1H), 4.70 (d, *J* = 5.6 Hz, 1H), 4.96 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 23.3, 23.4, 24.8, 26.3, 34.0 (CH_2), 34.7, 54.9, 83.3, 85.2, 86.1, 109.5, 112.3 (C). HRESIMS: calcd for $C_{12}H_{22}O_4SNa$ $[M+Na]^+$: 285.1137; found: 285.1142.

2.5. Methyl 5-deoxy-2,3-*O*-isopropylidene-5-methylsulfonyl-β-D-ribofuranoside 7

Compound **5** (0.28 g, 1.19 mmol) was converted to **7** (0.29 g, 91%) following the general procedure described above for the synthesis of compound **3**. White solid. Mp: 62 °C. $[\alpha]_D^{29.2}$ −21.1 (*c* 0.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.32 (s, 3H), 1.48 (s, 3H), 3.01 (s, 3H), 3.14–3.19 (m, 1H), 3.38–3.44 (m, 4H), 4.62 (d, *J* = 5.6 Hz, 1H), 4.71–4.75 (m, 2H), 5.01 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 24.9, 26.3, 41.9, 55.8, 58.9 (CH_2), 81.2, 83.8, 84.6, 110.4, 113.0 (C). HRESIMS: calcd for $C_{10}H_{18}O_6SNa$ $[M+Na]^+$: 289.0722; found: 289.0729.

2.6. Methyl 5-deoxy-2,3-*O*-isopropylidene-5-isopropylsulfonyl-β-D-ribofuranoside 8

Compound **6** (0.5 g, 1.9 mmol) was converted to **8** (0.51 g, 92%) following the procedure described for the synthesis of **3**. White solid. Mp: 67 °C. $[\alpha]_D^{29.2}$ −72.0 (*c* 0.12, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.32 (s, 3H), 1.40 (s, 3H), 1.41 (s, 3H), 1.48 (s, 3H), 3.07–3.12 (m, 1H), 3.17–3.24 (m, 1H), 3.33–3.38 (m, 4 H), 4.62 (d, *J* = 6 Hz, 1H), 4.75 (t, *J* = 6.8 Hz, 1H), 4.83 (d, *J* = 5.6 Hz, 1H), 4.99 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 14.4, 15.7, 24.9, 26.3, 53.1 (CH_2), 53.7, 55.5, 80.6, 83.9, 84.7, 110.2, 112.9. HRESIMS: calcd for $C_{12}H_{22}O_6SNa$ $[M+Na]^+$: 317.1035; found: 317.1047.

2.7. Methyl 5-deoxy-2,3-*O*-isopropylidene-5-methylsulfonyl-α-L-lyxofuranoside 11

The mixture of the sulfone **7** (0.1 g, 0.37 mmol), alumina-supported KOH (2 g),[5] ^{t}BuOH (20 ml) and DCM (10 ml) was stirred vigorously at room temperature for 3 h. Then the solid catalyst was removed by suction filtration through Celite bed. The filtrate was evaporated to dryness. The filter cake was washed thoroughly with DCM and the washes were combined with the residue from the first filtrate. The resultant organic soln was washed with brine and water, dried and evaporated. The residue was purified on silica gel (1:4 EtOAc–petroleum ether) to 11 (0.076 g, 76%). Glassy liquid. $[\alpha]_D^{29.2}$ −72.9 (*c* 0.75, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.30 (s, 3H), 1.45 (s, 3H), 3.04 (s, 3H), 3.23–3.27 (m, 1H), 3.33 (s, 3H), 3.40–3.47 (m, 1H), 4.43–4.47 (m, 1H), 4.58 (d, *J* = 6 Hz, 1H), 4.71–4.73 (m, 1H), 4.92 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 24.6, 25.9, 42.5, 54.7, 54.8 (CH_2), 74.2, 80.2, 84.4, 107.0, 112.8. HRESIMS: calcd for $C_{10}H_{18}O_6SNa$ $[M+Na]^+$: 289.0722; found: 289.0718.

2.8. Methyl 5-deoxy-2,3-*O*-isopropylidene-5-isopropylsulfonyl-α-L-lyxofuranoside 12

Compound **8** (0.1 g, 0.34 mmol) was converted to **12** (0.065 g, 65%) following the procedure described for the synthesis of **11**. White solid. Mp: 72 °C. $[\alpha]_D^{29.2}$ −36.5 (*c* 0.15, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.31 (s, 3H), 1.39 (s, 3H), 1.43 (s, 3H), 1.44 (s, 3H), 3.14–3.24 (m, 1H), 3.26–3.37 (m, 4H), 3.42–3.54 (m, 1H), 4.43–4.48 (m, 1H), 4.57 (d, *J* = 5.8 Hz, 1H), 4.70–4.73 (m, 1H), 4.90 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 13.9, 16.1, 24.7, 25.9, 49.4 (CH_2), 53.7, 54.6, 73.8, 80.2, 84.5, 106.9, 112.7. HRMS $[ES^+, (M+Na)^+]$ calcd for $C_{12}H_{22}O_6SNa$: 317.1035; obsd, 317.1030.

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Supplementary data

Complete crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 688742. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB21EZ, UK (fax: +44-1223-336033, e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk), and spectra of **3–4**, **6–8**, **11–12** all new compounds. Full ^1H NMR and ^{13}C NMR are available online. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2008.08.010.

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