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Note

C-Branched pyrrolidines from 2-*C*-acetylmethyl-glycosylazides. Reduction of imines formed by monosaccharide ring opening

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Abstract—Reduction of the protected 2-*C*-acetylmethyl-β-glucopyranosyl azide derivative **1** produced the corresponding β-glucosylamine **3**. Rather than forming a conformationally strained 1,2-trans-fused bicyclic imine, we propose that the β-glycosylamine underwent anomerization to an acyclic imine (**4**) followed by an intramolecular ring closure by the 5-hydroxy group. The resultant 2-*C*-acetylmethyl-α-glucopyranosylamine **5**, which possesses the 1,2-cis-configuration was immediately converted to a bicyclic imine (**2**) in excellent yield. Attempts to selectively reduce the C=N double bond of **2** using sodium borohydride and cyanoborohydride failed to produce bicyclic amine **6**. Instead, compound **6** underwent another ring-opening elimination and further reduction to produce a C-branched pyrrolidine (**8**) in good yield. Catalytic hydrogenation of **1** and **2** also provided the C-branched pyrrolidine (**10**).

Keywords: C-Branched pyrrolidines; Glycosylamine; Glycosylimine; Reductive amination; Epimerization

Heterocyclic structures are ubiquitous features of natural products and these compounds play a prominent role in drug development. For example, one class of nitrogen heterocycles, azasugars, are potent glycosidase inhibitors due to their ability to mimic the oxacarbenium ion transition state in enzymatic catalysis.[1] However, prior to the cleavage of the glycosidic bond that generates the oxacarbenium ion, the initial step in hydrolysis is likely the protonation of the glycosidic oxygen.[2] Therefore, it is conceivable that compounds mimicking a glycosidic oxonium ion may also inhibit enzymatic glycoside hydrolysis. In fact, acarbose, a drug used for the control of diabetes, contains a pseudo-glycosylamine at the nonreducing end. This compound inhibits α-glycosidase (α-amylase) activity by imitating the transition state conformation and by the interaction of the glycosylaminium ion with the catalytic carboxylate residue.[3] Consequently, glycosylamines and pseudo-glycosylamines have been synthesized and tested against various glycosidases.[2,4]

We have been working on the synthesis of aza-C-glycosides and thio-C-glycosides as inhibitors of glycoprocessing enzymes,[5] and also have 2-*C*-acetylmethyl-β-glycosyl azides in hand.[6] The presence of both carbonyl and azido (amino) groups in the same molecule prompted us to investigate a reductive amination reaction sequence to yield a bicyclic glycosylamine as a potential glycosidase inhibitor. Unfortunately, although we were able to obtain a stable bicyclic glycosylimine, the corresponding bicyclic glycosylamine was not obtained because the intermediate underwent a ring-opening elimination that was converted under reductive conditions to a C-branched monocyclic pyrrolidine.

The 2-C-branched glycosyl azide (**1**, Scheme 1) was previously prepared from a 1,2 cyclopropanated sugar, and its β-anomeric configuration was unambiguously assigned based on NMR spectroscopic analysis.[6] Treatment of compound **1** with triphenylphosphine provided

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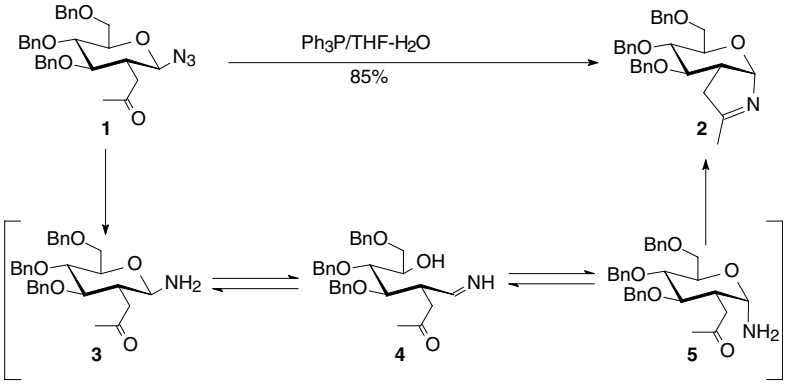
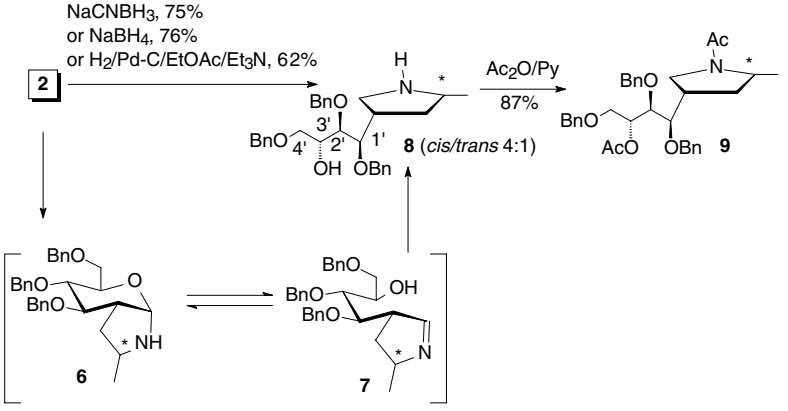


Scheme 1. Formation of 1,2-cis-fused bicyclic imine.

a bicyclic glycosylimine (**2**) in 85% yield. NMR analysis indicated that the stereochemistry at C-1 was inverted. The newly formed bicyclic imine was fused to the pyranoside with 1,2-cis-configuration as evidenced by the observation of a strong NOE between H-1 and H-2 and by the lack of a NOE between H-1 and H-3/H-5. This outcome was not a complete surprise because there is evidence in the literature to support this transformation. It has been documented that mutarotation of glycosylamines may occur under basic, neutral, and acidic conditions.[7] Also, the equilibrium between a glycosylamine and its open-chain imine has provided the basis for the use of the Grignard reaction as a key step in the synthesis of aza-C-glycosides.[8] We propose that because β-glycosylamine **3**, obtained from reduction of azide **1**, was unable to effectively react with the ketone group to form a conformationally strained 1,2-trans fused bicyclic imine, a ring-opening elimination to an acyclic imine (**4**) occurred. This species further equilibrated by way of a ring-closing reaction, to the α-anomer **5** as illustrated in Scheme 1. The 1,2-cis configuration in **5** thus allowed the reaction between the amino and ketone groups to occur to form the bicyclic glycosylimine **2**.

Natural glycosylamine derivatives are often N-substituted with electron-withdrawing groups, such as *N*-acyl in N-glycoproteins and adenine, cytosine, guanine, and thymine in nucleosides. However, stable *N*,*O*-acetals are also found as subunits in natural products such as norzoanthamine[9] and azaspiracid-1.[10] Being aware of the possible rearrangements associated with glycosylamine derivatives, we examined the reduction of compound **2** under different conditions, including treatment with sodium cyanoborohydride, sodium borohydride, and catalytic hydrogenation, which we hoped would lead to the formation of the bicyclic glycosylamine **6** (Scheme 2). Compounds of this kind may be potential glucosaminidase inhibitors due to their structural similarity to the oxazolinium intermediate that forms during enzymatic hydrolysis of 2-acetamido-glycosides.[11]

Treatment of **2** with sodium cyanoborohydride or sodium borohydride did not yield the desired bicyclic glycosylamine. Instead, the major product obtained was a C-branched pyrrolidine **8** (Scheme 2), which was isolated as a mixture of two diastereomers that were inseparable by silica gel chromatography. Thus, we assigned their stereochemistry and estimated the *R*/*S* (or cis/trans) ratio (≈4:1) by NMR spectroscopy. We believe



Scheme 2. A sugar-ring opening reductive amination.

that the bicyclic glycosylamine **6** was formed by initial reduction of imine. Unfortunately, this unstable compound appears to have rearranged in a fashion similar to the conversion of **3** to **4**, via a ring-opening elimination to give a monocyclic imine intermediate (**7**) that was immediately reduced to pyrrolidine **8**. The diastereoselectivity at the 2-position (marked by an asterisk in Scheme 2) was apparently determined in the initial reduction of the C=N bond (from **2** to **6**). As expected, the *R*-configuration (2,4-cis) is favored due to the hydride addition from the less hindered *Si*-face.[12]

We also attempted to obtain an N-acetylated derivative of **6** by subjecting **2** to catalytic hydrogenation in ethyl acetate under basic conditions. We previously observed that reduction of azido groups under such conditions often led to in situ N-acetylation. Unfortunately, after 48 h we obtained only **8** as the major product together with a small amount of polar by-products, presumably from partial de-O-benzylation. To further confirm the proposed structure, **8** was converted to the *N*,*O*-diacetate **9** by treatment of **8** with acetic anhydride and pyridine (Scheme 2).

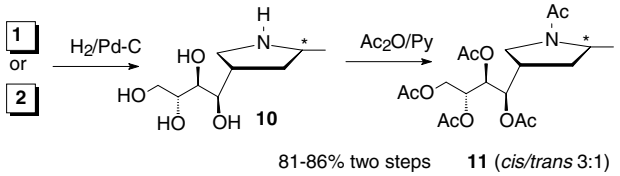
Based on the proposed mechanism illustrated in Schemes 1 and 2, we were able to simplify the synthesis of the C-branched pyrrolidine by subjecting **1** or **2** to catalytic hydrogenation thus affording **10** (Scheme 3). To facilitate the purification of the pyrrolidine, compound **10** was further acetylated to give **11**.

In summary, we describe here a procedure for the synthesis of C-branched pyrrolidines from 2-C-branched glycosylamines under various reductive conditions. The transformation is achieved either by a direct reduction of the 2-C-branched glycosylazide or by way of an indirect stepwise approach through a stable, isolable glycosylimine. The key conversion involves a ring-opening elimination followed by imine reduction to the monocyclic pyrrolidine.

1. Experimental

1.1. General methods

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or CD_3OD at 400 and 100 MHz, respectively, with a Varian instrument at 293 K. Chemical shifts are given in parts per million downfield from the signal of internal Me_4Si and were assigned on the basis of 2D ^{1}H COSY and ^{1}H–^{13}C chemical-shift correlated experiments. All chemicals were purchased from Aldrich Chemical Co. and used without further purification.



Scheme 3. C-Branched pyrrolidine formation by hydrogenation.

1.2. 3,4,6-Tri-*O*-benzyl-[1-*N*,2-*C*-(isopropylimino)]-1,2-di-deoxy-α-glucopyranosylimine (2)

A solution of **1** (50 mg, 0.097 mmol) and triphenylphosphine (40 mg, 0.152 mmol) in THF (10 mL) with a drop of H_2O was stirred at rt for 24 h. The solvent was evaporated to a residue, which was purified by chromatography (1:1, hexane/EtOAc→100:1, EtOAc/CH_3OH) to give compound **2** (38.8 mg, 85%) as a syrup: $[\alpha]_D$ +33.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ_H 1.91 (d, 3H, –CH_3, $J = 1.6$ Hz), 2.20 (d, 1H, –CH_2–, $J = 16.0$ Hz), 2.37–2.48 (m, 2H, H-2, –CH_2–), 3.16 (dd, 1H, H-3, $J = 8.4$, 8.4 Hz), 3.59 (ddd, 1H, H-5, $J = 9.6$, 2.8, 2.8 Hz), 3.74 (dd, 1H, H-4, $J = 9.6$, 8.4 Hz), 3.76 (dd, 1H, H-6, $J = 10.8$, 4.0 Hz), 3.85 (dd, 1H, H-6′, $J = 10.8$, 2.8 Hz), 4.55 (d, 1H, CH_2Ph, $J = 12.0$ Hz), 4.62 (d, 1H, CH_2Ph, $J = 11.6$ Hz), 4.63 (d, 1H, CH_2Ph, $J = 10.8$ Hz), 4.69 (d, 1H, CH_2Ph, $J = 12.0$ Hz), 4.76 (d, 1H, CH_2Ph, $J = 10.8$ Hz), 4.84 (d, 1H, CH_2Ph, $J = 11.6$ Hz), 5.43 (m, 1H, H-1), 7.18–7.37 (m, 15H, 3 × Ph); ^{13}C NMR ($CDCl_3$): δ_C 20.8 (*C*H_3), 43.4 (–CH_2–), 44.2 (C-2), 69.0 (C-6), 73.0 (C-5), 73.9 (–*C*H_2Ph), 74.6 (2 × –*C*H_2Ph), 78.3 (C-4), 81.8 (C-3), 99.2 (C-1), 127.8, 127.9, 128.1, 128.2, 128.5, 128.6 (2), 128.7, 138.2, 138.4, 138.7 (3 × Ph), 176.5 (–C=N–); FABMS: *m*/*z* calcd for $C_{30}H_{34}O_4N$ $[M+H]^+$: 472.2488. Found: 472.2483.

1.3. 2*R*/*S*-Methyl-4*S*-(1′*R*,2′*S*,4′-tri-benzyloxy-3′*R*-hydroxy-butyl)-pyrrolidine (8)

Method A: To a solution of compound **2** (60 mg, 0.127 mmol) in CH_3OH (6 mL) under N_2 at rt was added $NaBH_4$ (15 mg, 0.39 mmol) in portions. The mixture was stirred for 16 h, and was diluted with EtOAc and washed with H_2O and HOAc until neutral and then concentrated to give a crude product. Purification by chromatography (10:1, *i*-PrOH/1 M aq NH_4OAc) afforded compound **8** (46 mg, 76%) as a syrup. FABMS: *m*/*z* calcd for $C_{30}H_{38}O_4N$ $[M+H]^+$: 476.2801. Found: 476.2771. Compound **8**-*cis*: ^{1}H NMR (CD_3OD): δ_H 1.33 (d, 3H, –CH_3, $J = 6.0$ Hz), 1.50 (ddd, 1H, H-3a, $J = 11.6$, 11.2, 11.2 Hz), 2.28 (m, 1H, H-3b), 2.75 (m, 1H, H-4), 2.95 (dd, 1H, H-5a, $J = 9.6$, 9.6 Hz), 3.12 (dd, 1H, H-5b, $J = 9.6$, 9.6 Hz), 3.51 (m, 1H, H-2), 3.59–3.71 (m, 4H, H-3′, H-4′a, H-4′b, H-1′), 3.93 (m, 1H, H-2′), 4.51–4.63 (m, 5H, 2.5 × CH_2Ph), 4.75 (d, 1H, CH_2Ph, $J = 11.6$ Hz), 7.23–7.34 (m, 15H, 3 × Ph); ^{13}C NMR (CD_3OD): δ_C 16.2 (*C*H_3), 35.5 (C-3), 40.6 (C-4), 46.3 (C-5), 56.0 (C-2), 70.7 (C-2′), 71.3 (C-4′),

73.3 (–CH_2Ph), 73.8 (–CH_2Ph), 74.2 (–CH_2Ph), 79.6 (C-1′), 80.1 (C-3′), 127.6, 127.7, 128.0, 128.2, 128.3, 138.3, 138.4 (3 × Ph). Compound **8**-*trans*: ^{1}H NMR (CD_3OD): δ_H 1.26 (d, 3H, –CH_3, $J = 6.4$ Hz), 1.70 (m, 1H, H-3a), 2.15 (m, 1H, H-3b), 2.73–2.78 (m, 2H, H-4, H-5a), 3.18 (m, 1H, H-5b), 3.53–3.70 (m, 5H, H-2, H-3′, H-4′a, H-4′b, H-1′), 3.92 (m, 1H, H-2′), 7.23–7.34 (m, 15H, 3 × Ph); ^{13}C NMR (CD_3OD): δ_C 16.5 (CH_3), 33.4 (C-3), 39.0 (C-4), 46.3 (C-5), 55.6 (C-2), 70.8 (C-2′), 71.3 (C-4′), 73.3 (–CH_2Ph), 73.9 (–CH_2Ph), 74.3 (–CH_2Ph), 79.4 (C-1′), 80.2 (C-3′), 127.6, 127.7, 128.0, 128.2, 128.3, 138.3, 138.4 (3 × Ph).

Method B: To a solution of **2** (30 mg, 0.064 mmol) in CH_3OH (3 mL) under N_2 at rt was added $NaCNBH_3$ (10 mg, 0.16 mmol) in portions. The mixture was stirred for 16 h and then worked up as described above and the product was purified by column chromatography (10:1, *i*-PrOH/1 M aq NH_4OAc) gave **8** (22.8 mg, 75%) as a syrup.

Method C: A solution of **2** (28 mg, 0.06 mmol) in EtOAc (3 mL) and Et_3N (0.2 mL) containing Pd/C (10%, 28 mg) was stirred under H_2 at atmospheric pressure and rt for 18 h. Work-up as described above and purification by chromatography (10:1, *i*-PrOH/1 M aq NH_4OAc) afforded **8** (17.5 mg, 62%) as a syrup.

1.4. *N*-Acetyl-2*R*/*S*-methyl-4*S*-(3′*R*-acetyloxy-1′*R*,2′*S*,4-tri-benzyloxy-butyl)-pyrrolidine (9)

A solution of **8** (30 mg, 0.063 mmol) in Ac_2O (1.2 mL) and pyridine (1.8 mL) was stirred at rt for 16 h. The mixture was diluted with ice H_2O and extracted with EtOAc. The organic phase was dried and concentrated. Purification by column chromatography (1:1→6:1, EtOAc/hexane) afforded compound **9** (30.6 mg, 87%) as a syrup. FABMS: *m*/*z* calcd for $C_{34}H_{42}O_6N$ $[M+H]^+$: 560.3012. Found: 560.2997. Compound **9**-*cis*: ^{1}H NMR ($CDCl_3$): δ_H 1.25 (d, 3H, –CH_3, $J = 6.4$ Hz), 1.47 (m, 1H, H-3a), 1.87 (*s*, 3H, –$COCH_3$), 2.02 (*s*, 3H, –$COCH_3$), 2.27–2.36 (m, 2H, H-3b, H-4), 3.02 (m, 1H, H-5a), 3.15 (dd, 1H, H-5b, $J = 10.0$, 7.6 Hz), 3.51 (m, 1H, H-1′), 3.72–3.78 (m, 2H, H-2′, H-4′a), 3.86 (dd, 1H, H-4′b, $J = 10.4$, 4.4 Hz), 3.94 (m, 1H, H-2), 4.43 (d, 1H, CH_2Ph, $J = 10.4$ Hz), 4.52 (*s*, 2H, CH_2Ph), 4.61 (d, 1H, CH_2Ph, $J = 11.2$ Hz), 4.68 (d, 1H, CH_2Ph, $J = 11.2$ Hz), 4.73 (d, 1H, CH_2Ph, $J = 10.4$ Hz), 5.21 (m, 1H, H-3′), 7.23–7.31 (m, 15H, 3 × Ph); ^{13}C NMR ($CDCl_3$): δ_C 21.4 (CH_3), 21.5 (COCH_3), 23.6 (COCH_3), 35.6 (C-3), 40.1 (C-4), 50.0 (C-5), 53.1 (C-2), 68.3 (C-4′), 73.0 (C-3′), 73.6 (–CH_2Ph), 74.6 (–CH_2Ph), 74.7 (–CH_2Ph), 79.6 (C-1′), 80.2 (C-2′), 127.9, 128.0, 128.1, 128.2, 128.3, 128.6, 128.7, 138.0, 138.2, 138.3 (3 × Ph), 168.9, 170.5 (2 × $COCH_3$). Compound **9**-*trans*: ^{1}H NMR ($CDCl_3$): δ_H 1.24 (d, 3H, –CH_3, $J = 6.0$ Hz), 1.62 (m, 1H, H-3a), 2.00 (*s*, 3H, –$COCH_3$), 2.06 (*s*, 3H, –$COCH_3$), 2.31–2.42 (m, 2H, H-4, H-3b), 3.05 (m, 1H, H-5a), 3.52 (m, 1H, H-1′), 3.74–3.95 (m, 4H, H-2′, H-4′a, H-4′b, H-2), 4.02 (dd, 1H, H-5b, $J = 11.6$, 7.2 Hz), 4.46 (d, 1H, CH_2Ph, $J = 10.8$ Hz), 4.51 (*s*, 2H, CH_2Ph), 4.62–4.69 (m, 2H, CH_2Ph), 4.72 (d, 1H, CH_2Ph, $J = 10.4$ Hz), 5.21 (m, 1H, H-8), 7.23–7.31 (m, 15H, 3 × Ph); ^{13}C NMR ($CDCl_3$): δ_C 20.8 (CH_3), 21.4 (COCH_3), 21.8 (COCH_3), 36.2 (C-3), 39.4 (C-4), 47.5 (C-5), 53.6 (C-2), 68.2 (C-4′), 73.3 (C-3′), 73.4 (–CH_2Ph), 74.9 (–CH_2Ph), 75.0 (–CH_2Ph), 79.6 (C-1′), 80.9 (C-2′), 127.9, 128.0, 128.1, 128.2, 128.3, 128.6, 128.7, 138.0, 138.2, 138.3 (3 × Ph), 169.4, 170.7 (2 × $COCH_3$).

1.5. *N*-Acetyl-2*R*/*S*-methyl-4*S*-(1′*R*,2′*S*,3′*R*,4-tetra-acetyloxy-butyl)-pyrrolidine (11)

A solution of compound **1** (108 mg, 0.21 mmol) in CH_3OH (8 mL) containing Pd/C (10%, 60 mg) was stirred in the presence of H_2 at atmospheric pressure and rt for 18 h. The catalyst was filtered, and the solvent was evaporated to give crude **10**, which was dissolved in Ac_2O (1.8 mL) and pyridine (2.7 mL). The mixture was stirred at rt for 8 h and poured into ice H_2O and extracted with EtOAc. The organic phase was washed with H_2O and aq $NaHCO_3$ until neutral, and then dried and concentrated to a crude product, which was passed through a silica gel column (1:1→6:1, EtOAc/hexane) to afford compound **11** (73 mg, 84%) as a syrup. FABMS: *m*/*z* calcd for $C_{19}H_{30}O_9N$ $[M+H]^+$: 416.1921. Found: 416.1906. Compound **11**-*cis*: ^{1}H NMR ($CDCl_3$): δ_H 1.28 (d, 3H, –CH_3, $J = 6.0$ Hz), 1.40 (ddd, 1H, H-3, $J = 11.6$, 10.8, 10.8 Hz), 2.10–2.28 (m, 2H, H-3, H-4), 3.15 (dd, 1H, H-5a, $J = 10.4$, 10.4 Hz), 3.70 (dd, 1H, H-5b, $J = 10.4$, 7.6 Hz), 3.98 (m, 1H, H-2), 4.13 (dd, 1H, H-4′a, $J = 12.4$, 4.8 Hz), 4.22 (dd, 1H, H-4′b, $J = 12.4$, 2.4 Hz), 5.05 (m, 1H, H-3), 5.21–5.28 (m, 2H, H-1′, H-2′); ^{13}C NMR ($CDCl_3$): δ_C 20.6 (CH_3), 20.9 (2), 21.1 (2), 23.6 (5 × –COCH_3), 36.8 (C-3), 39.4 (C-4), 50.0 (C-5), 53.2 (C-2), 62.0 (C-4′), 68.3 (C-3′), 69.9 (C-2′), 71.4 (C-1′), 169.3, 170.1, 170.2, 170.6, 170.8 (5 × –CO–). Compound **11**-*trans*: ^{1}H NMR ($CDCl_3$): δ_H 1.27 (d, 3H, –CH_3, $J = 6.0$ Hz), 1.53 (m, 1H, H-3), 2.22–2.28 (m, 2H, H-3, H-4), 2.92 (m, 1H, H-5a), 3.88 (m, 1H, H-2), 4.10–4.18 (m, 3H, H-5b, H-4′a, H-4′b), 5.04 (m, 1H, H-3′), 5.16–5.26 (m, 2H, H-1′, H-2′) ppm; ^{13}C NMR ($CDCl_3$): δ_C 20.6 (CH_3), 20.9 (2), 21.1, 21.9, 22.7 (5 × –COCH_3), 37.5 (C-3), 38.1 (C-4), 47.6 (C-5), 53.5 (C-2), 61.8 (C-4′), 68.5 (C-3′), 70.0 (C-2′), 71.5 (C-1′), 169.4, 169.7, 170.2, 170.7, 170.9 (5 × –CO–) ppm.

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Supplementary data

NMR spectra (^{1}H, ^{13}C, HSQC, NOESY) for compounds **2**, **8**, **9**, and **11**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2006.07.005.

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