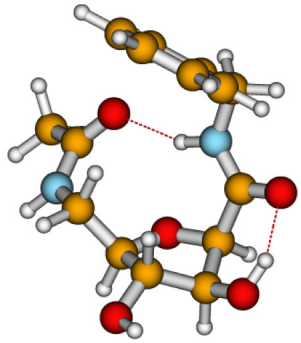
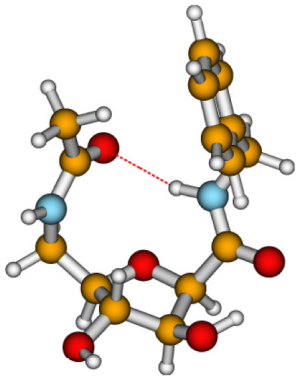
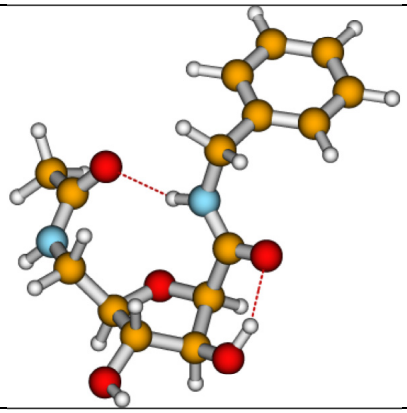
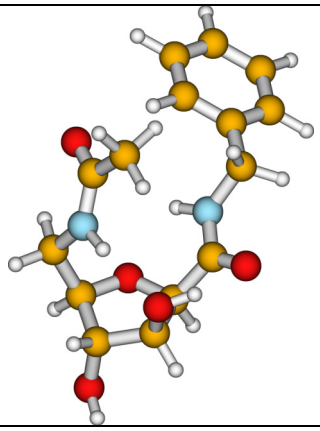
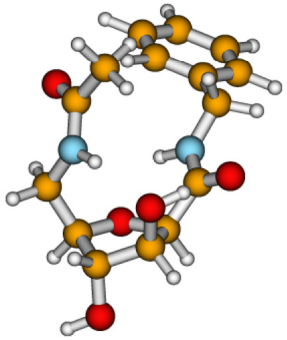
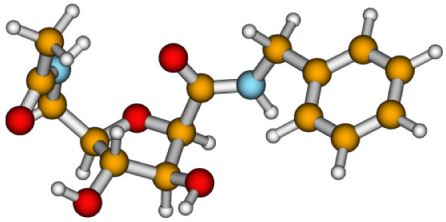
Carbohydrate amino acids: the intrinsic conformational preference for β-turn type structure of a carbopeptoid building block

Rebecca A. Jockusch, Francis O. Talbot, Paul S. Rogers,
Michela I. Simone, George W. J. Fleet and John P. Simons

Electronic Supporting Information

		
Ia: $\Delta E_0 = 0$	Ib: $\Delta E_0 = 3.8$	$\Delta E_0 = 6.2$
		
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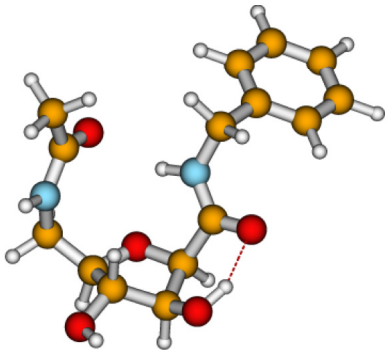
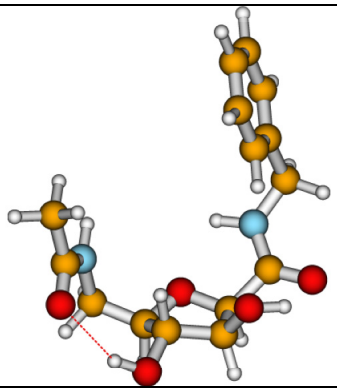
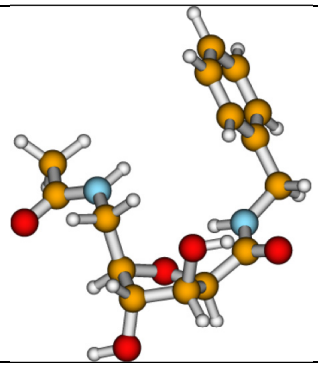
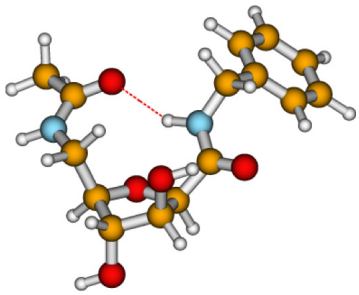
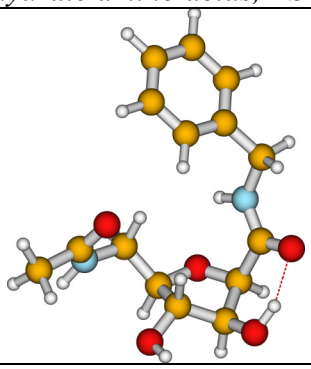
		
$\Delta E_0 = 15.3$	$\Delta E_0 = 15.4$	$\Delta E_0 = 16.2$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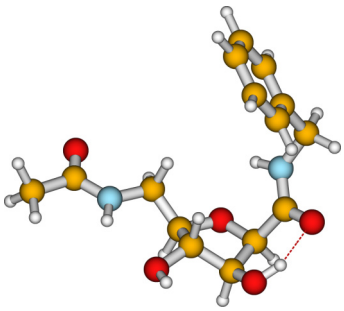
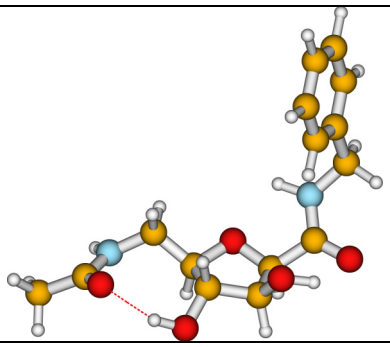
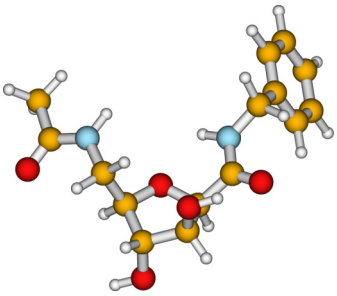
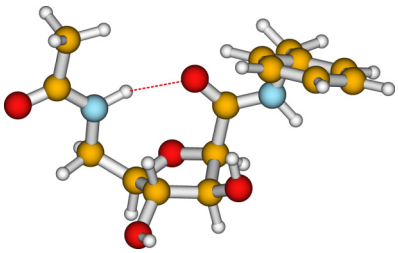
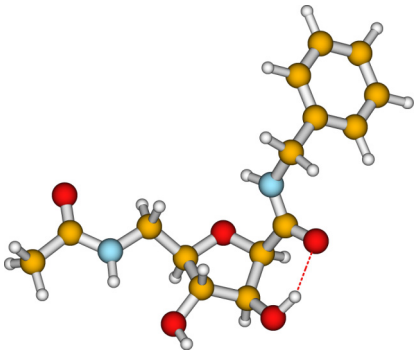
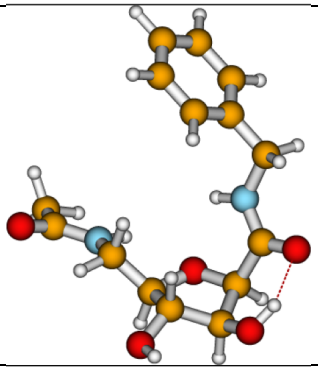
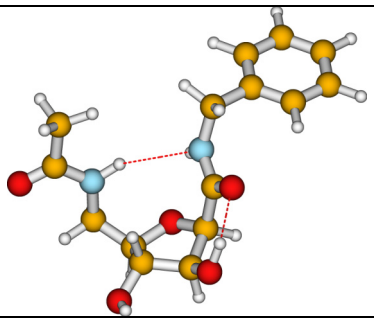
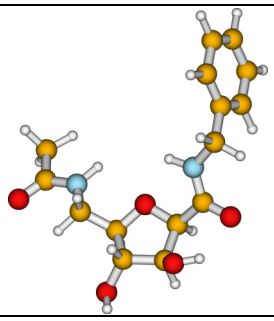
		
$\Delta E_0 = 26.5$	$\Delta E_0 = 27.5$	$\Delta E_0 = 29.6$
		
$\Delta E_0 = 31.1$	$\Delta E_0 = 31.5$	$\Delta E_0 = 31.5$
		
$\Delta E_0 = 31.5$	$\Delta E_0 = 35.4$	$\Delta E_0 = 35.5$

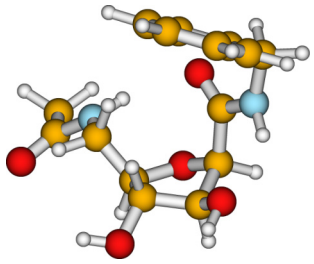
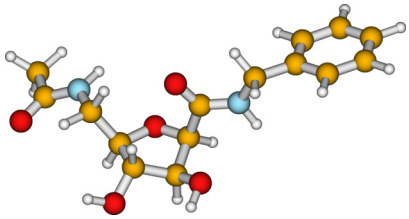
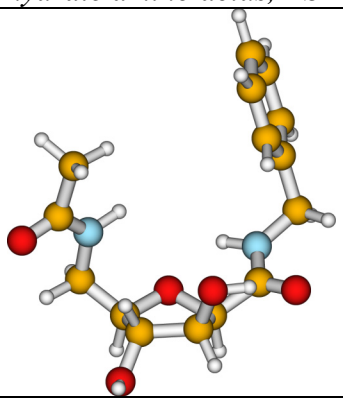
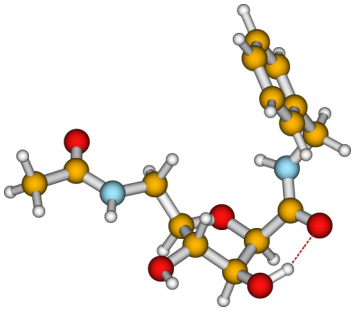
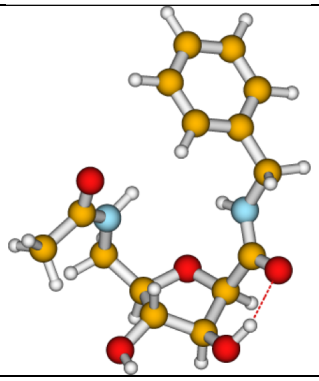
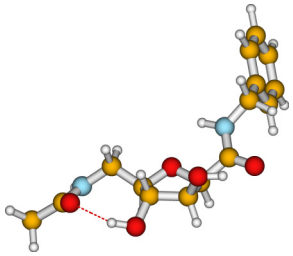
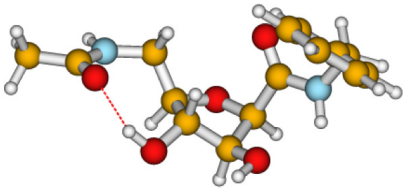
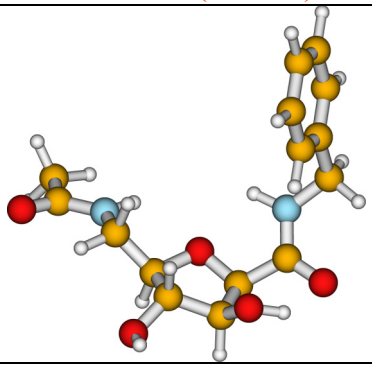
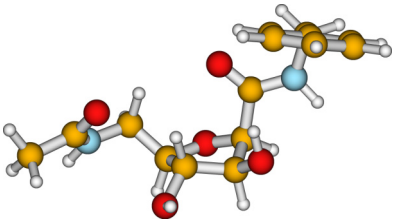
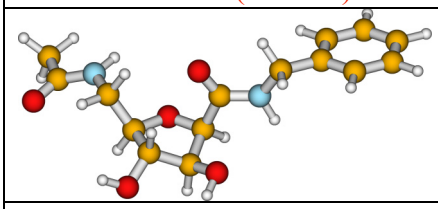
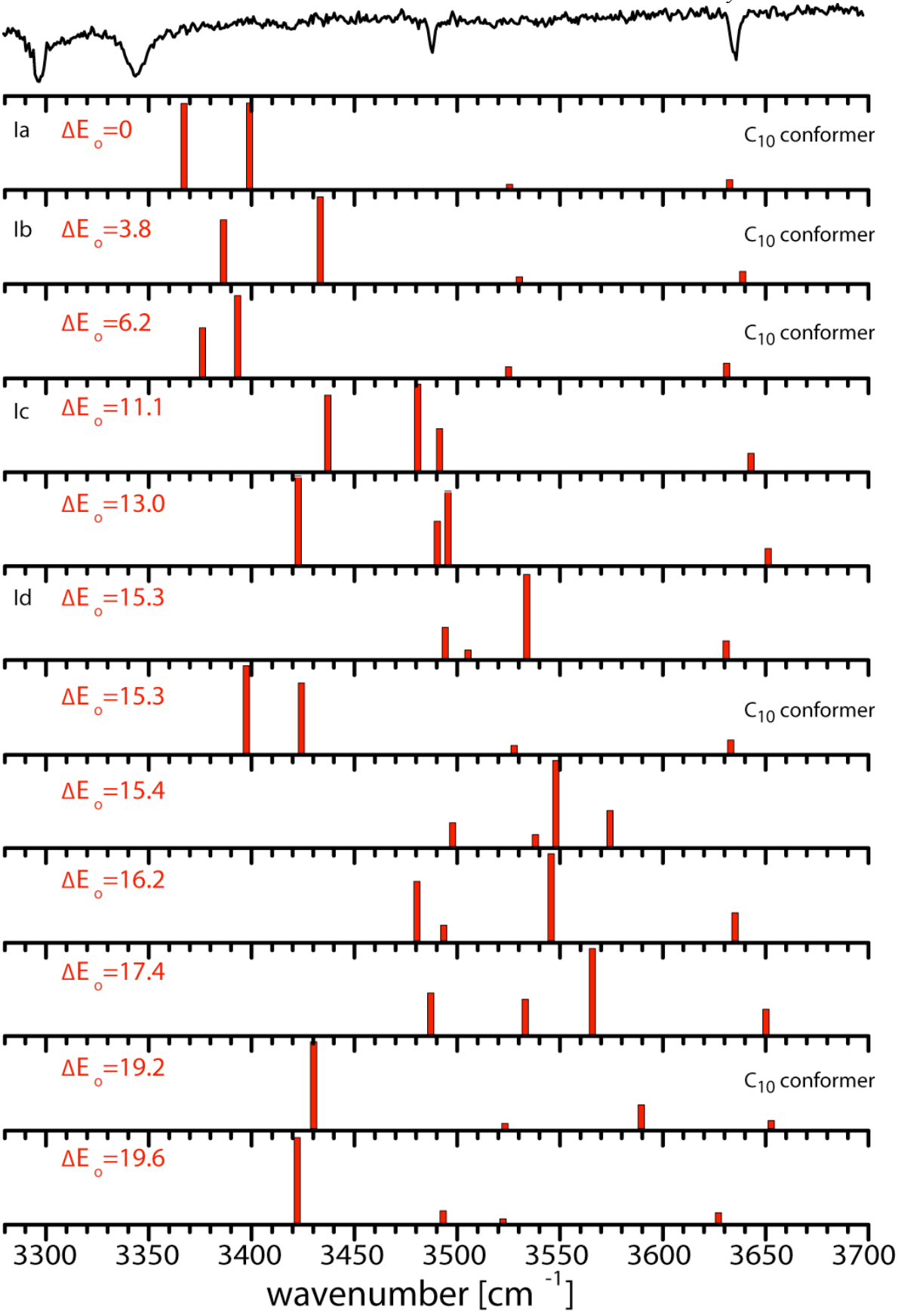
		
$\Delta E_0 = 44.6$	$\Delta E_0 = 46.0$	$\Delta E = 27.6$ (no ZPE)
		
$\Delta E = 28.6$ (no ZPE)	$\Delta E = 29.3$ (no ZPE)	$\Delta E = 33.1$ (no ZPE)
		
$\Delta E = 33.9$ (no ZPE)	$\Delta E = 35.5$ (no ZPE)	$\Delta E = 47.1$ (no ZPE)
		
$\Delta E = 51.0$ (no ZPE)		

Figure S1. Computed structures and relative energies in kJ•mol^{-1} of the unprotected monomer **1**. Geometries are optimized at the B3LYP/6-31+G(d) level and relative energies (ΔE_0 or ΔE) are at the MP2/6-311+G(d)//B3LYP/6-31+G(d) level of theory. The ΔE_0 values include zero-point energy (ZPE) corrections from harmonic frequency calculations at the B3LYP/6-31+G* level of theory.


Ia
ΔE o=0
C10 conformer
Ib
ΔE o=3.8
C10 conformer
ΔE o=6.2
C10 conformer
Ic
ΔE o=11.1
ΔE o=13.0
Id
ΔE o=15.3
ΔE o=15.3
C10 conformer
ΔE o=15.4
ΔE o=16.2
ΔE o=17.4
ΔE o=19.2
C10 conformer
ΔE o=19.6
3300
3350
3400
3450
3500
3550
3600
3650
3700
wavenumber [cm -1]

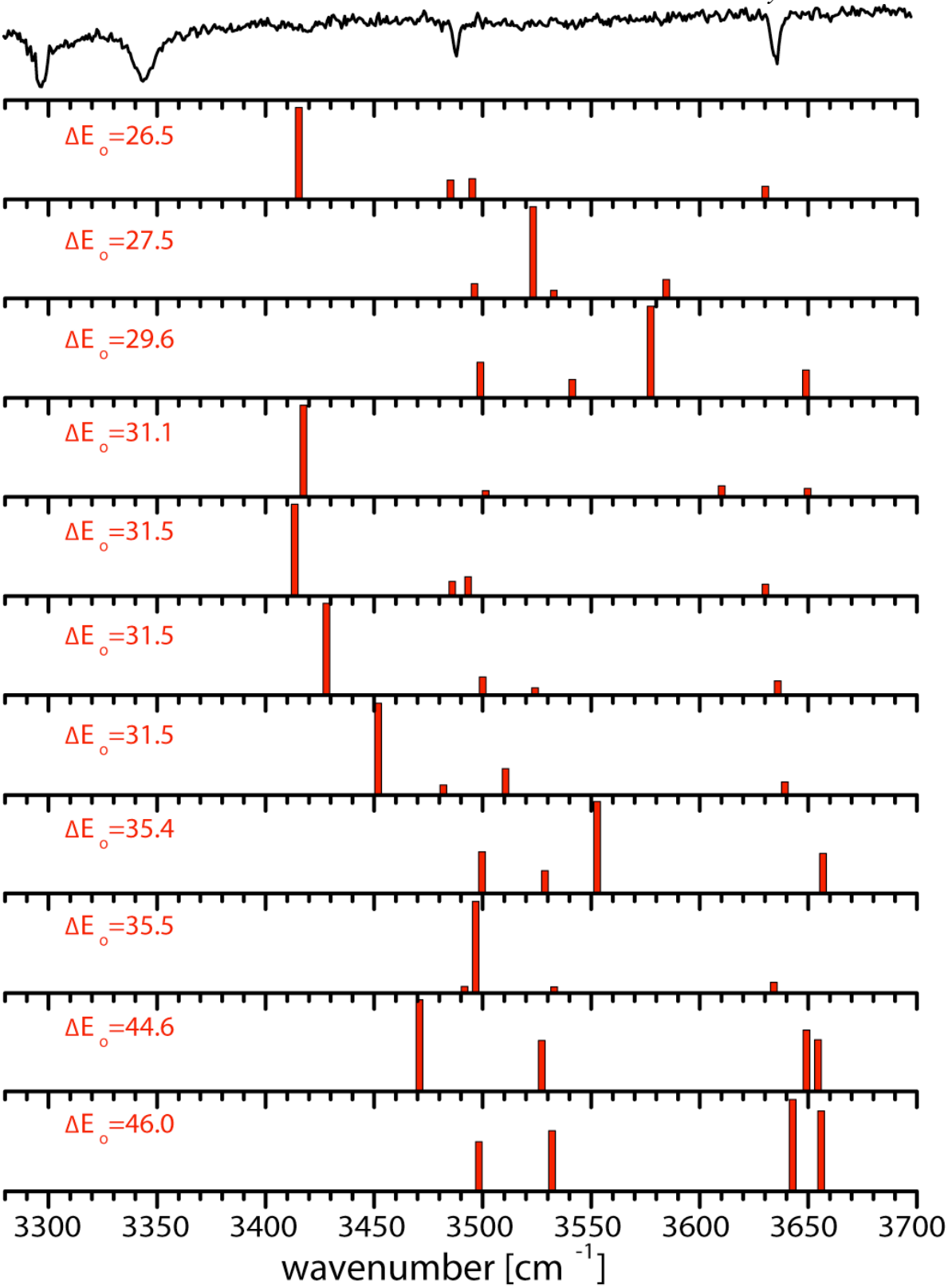


Figure S2. Experimental IRID spectrum of the unprotected monomer **1** compared to calculated infrared spectra for the structures illustrated in Figure S1. Frequencies are calculated at the B3LYP/6-31+G* level of theory and scaled by 0.9734.

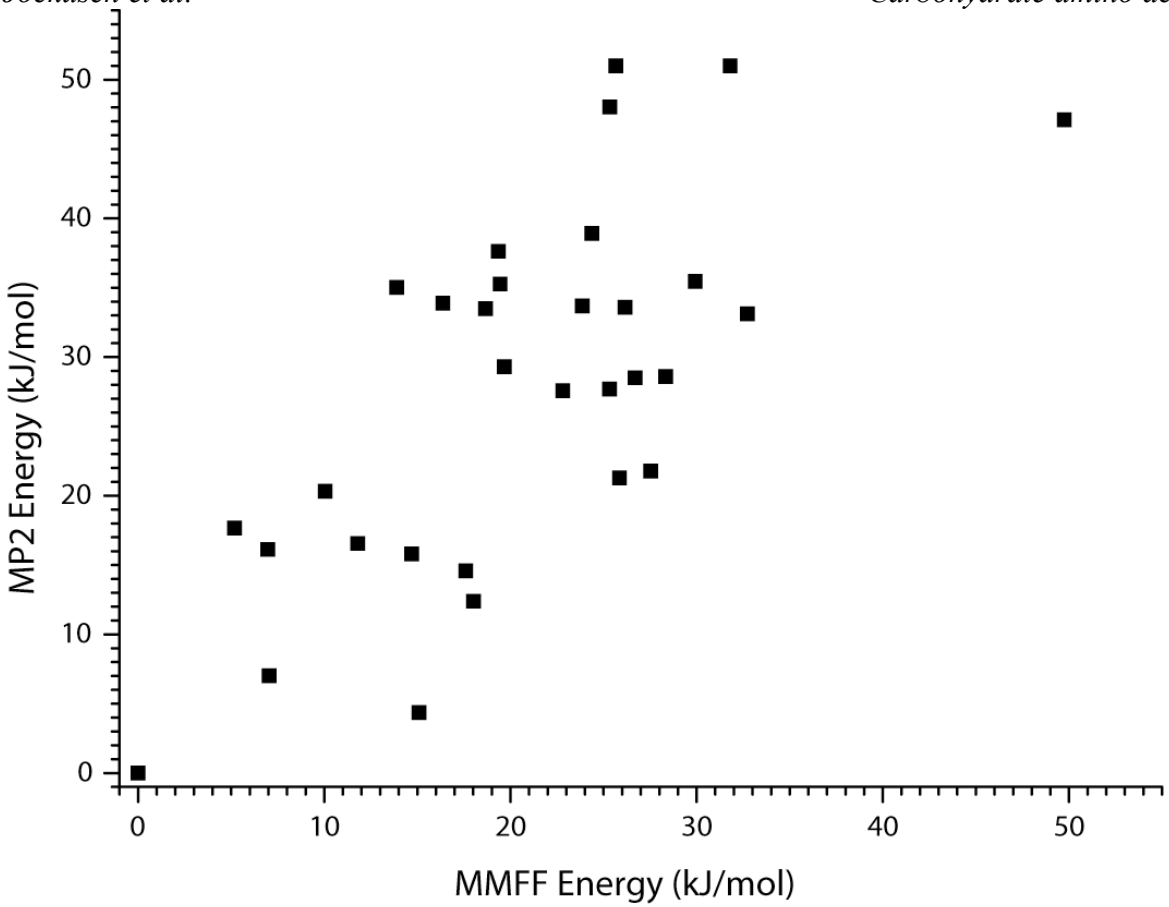
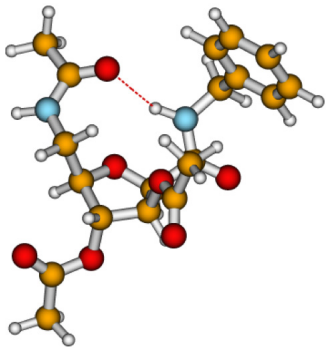
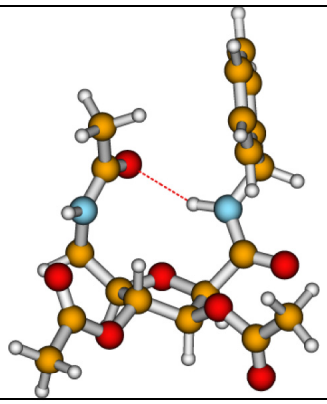
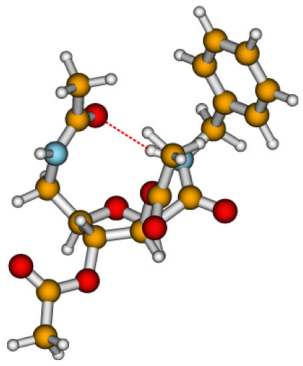
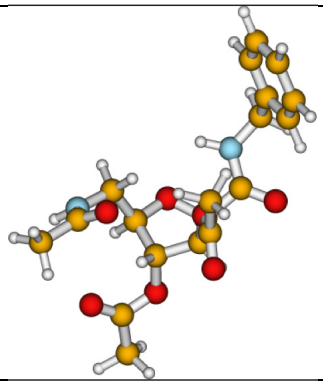
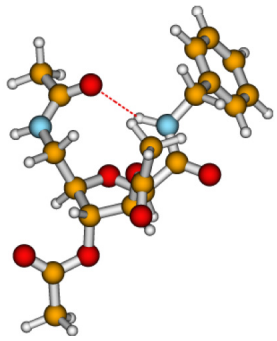
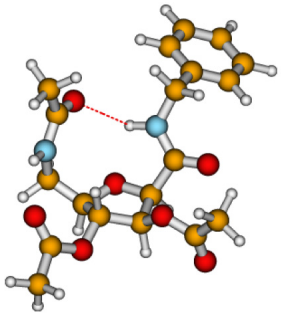
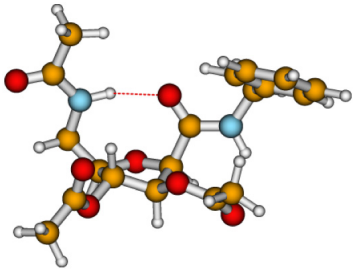
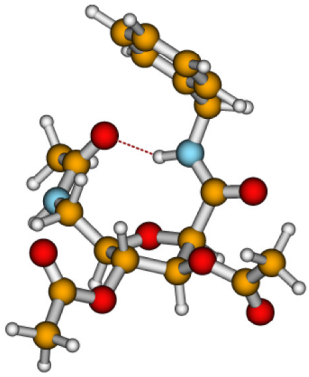
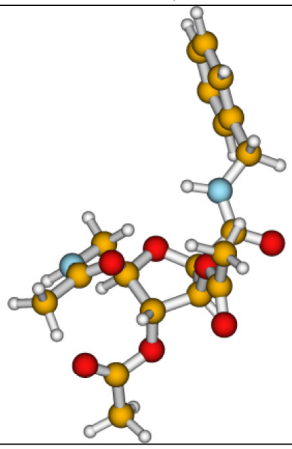
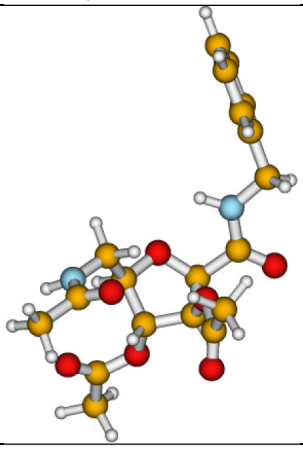
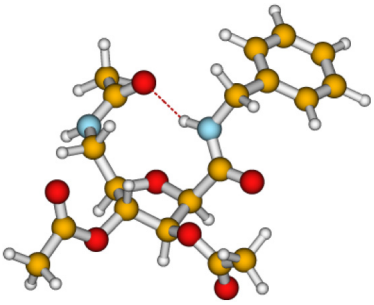
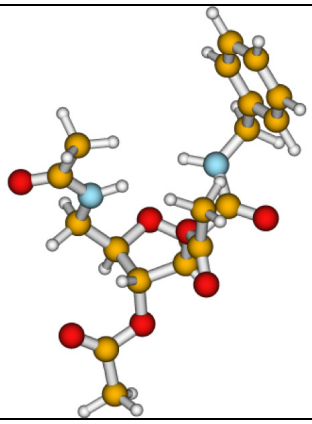
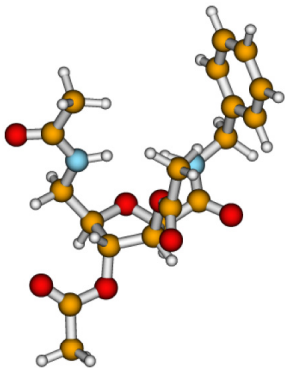
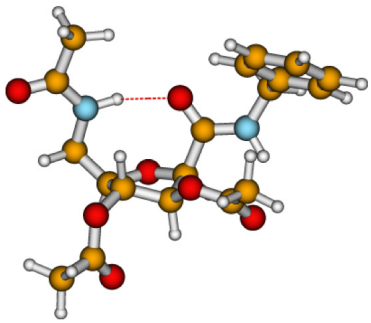


Figure S3. Computed relative energies for unique conformers of the unprotected monomer **1**. Relative energies on the x-axis are from minimizations using the MMFFs force field. These conformers were then geometry optimized at the B3LYP/6-31+G(d) level of theory and single point energies calculated at the MP2/6-311+G(d) level of theory (see Methods section of the main text). The MP2 single point energies (ΔE, which do not include zero-point energy) are plotted on the y-axis.

		
IIa: $\Delta E_0 = 0$, $\Delta E = 0.2$	IIb: $\Delta E_0 = 1.6$, $\Delta E = 0$	$\Delta E_0 = 3.9$, $\Delta E = 3.3$

		
IIc:ΔE_0 = 10.6, ΔE = 10.8	ΔE_0 = 13.8, ΔE = 14.2	ΔE_0 = 14.0, ΔE = 12.7
		
IId: ΔE_0 = 14.5, ΔE = 14.1	a, ΔE = 17.1	ΔE_0 = 19.6, ΔE = 18.7
		
a, ΔE = 19.5	a, ΔE = 19.8	a, ΔE = 21.0
		
a, ΔE = 21.8	a, ΔE = 22.0	a, ΔE = 24.7

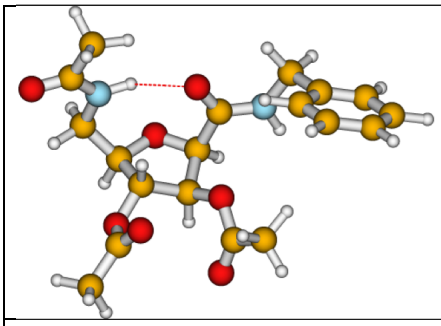
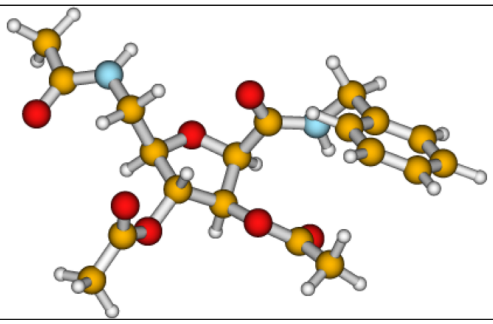
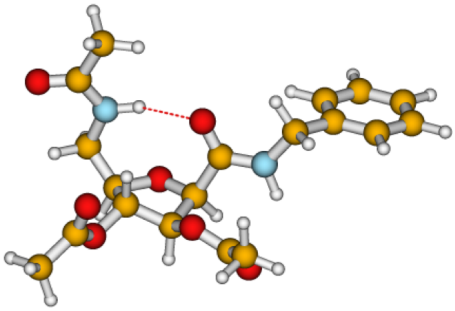
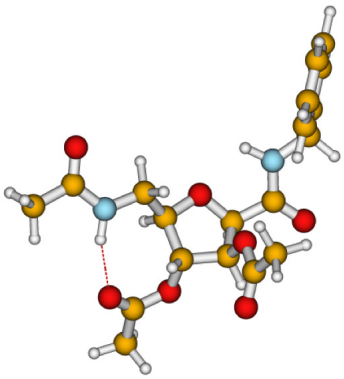
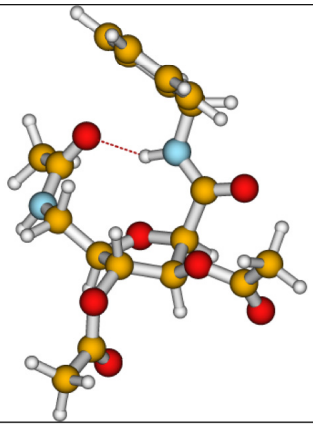
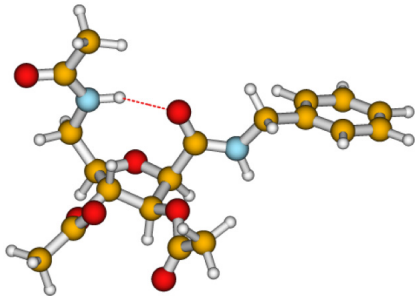
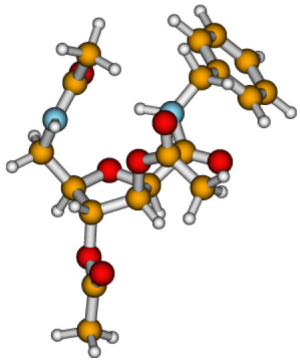
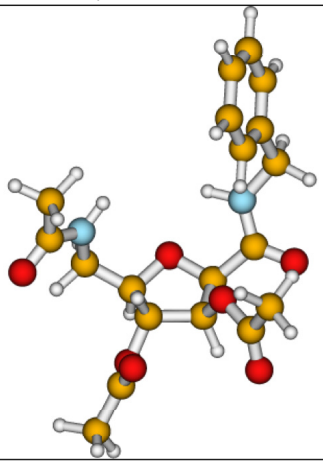
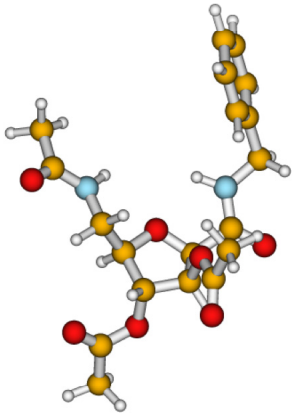
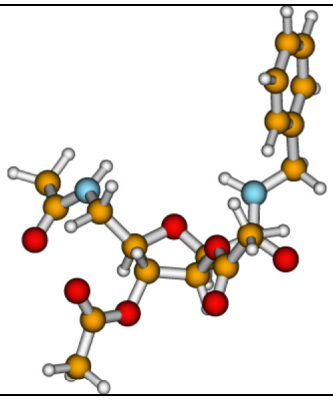
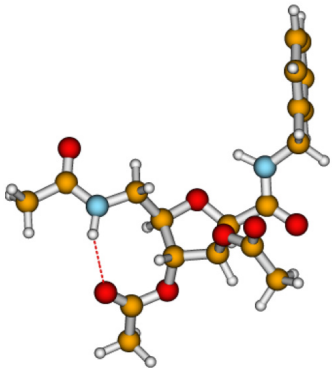
		
a, ΔE = 25.6	a, ΔE = 26.2	a, ΔE = 30.8
		
a, ΔE = 31.4	a, ΔE = 31.6	a, ΔE = 31.7
		
ΔE_0 = 32.2, ΔE = 32.0	a, ΔE = 33.5	a, ΔE = 38.2
		
a, ΔE = 41.5	ΔE_0 = 61.2, ΔE = 62.0	

Figure S4. Computed structures and relative energies in kJ•mol^{-1} of the protected monomer **2**. Geometries are optimized at the B3LYP/6-31+G(d) level and relative energies (ΔE_0, ΔE) are at the MP2/6-311+G(d)//B3LYP/6-31+G(d) level of theory and do and do not include zero-point energy level corrections, respectively, from harmonic frequency calculations at the B3LYP/6-31+G* level of theory.

a: frequency calculation not done

Details of synthesis

All commercial reagents were used as supplied. Tetrahydrofuran and *N,N*-dimethylformamide were purchased dry from the Aldrich chemical company in sure-seal bottles. Methanol and pyridine were purchased dry from the Fluka chemical company in sure-seal bottles over molecular sieves. All other solvents were used as supplied (Analytical or HPLC grade), without prior purification. Reactions were performed under an atmosphere of nitrogen or argon, unless stated otherwise. Thin layer chromatography (t.l.c.) was performed on aluminium sheets coated with 60 F_{254} silica. Sheets were visualised using a spray of 0.2% w/v cerium (IV) sulphate and 5% ammonium molybdate in 2 M sulphuric acid. Flash chromatography was performed on Sorbsil C60 40/60 silica. Melting points were recorded on a Kofler hot block and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a path length of 1 dm. Concentrations are quoted in g 100 ml^{-1}. Elemental analyses were performed by the microanalysis service of the Inorganic Chemistry Laboratory, Oxford. Infrared spectra were recorded on a Perkin-Elmer 1750 IR Fourier Transform spectrophotometer using thin films on NaCl plates (thin film). Only the characteristic peaks are quoted. Low resolution mass spectra (*m/z*) were recorded on VG MassLab 20–250, Micromass BIOQ-II, Micromass Platform 1, Micromass TofSpec 2E, or Micromass Autospec 500 OAT spectrometers and high resolution mass spectra (HRMS *m/z*) on a Micromass Autospec 500 OAT spectrometer. Techniques used were electrospray (ESI), chemical ionization (CI NH_3), or atmospheric pressure chemical ionization (APCI). Nuclear magnetic resonance (NMR) spectra were recorded on Bruker AMX 500 (^{1}H: 500 MHz and ^{13}C: 125.7 MHz) and Bruker DPX 400 and DQX 400 spectrometers (^{1}H: 400 MHz and ^{13}C: 100.6 MHz) in the deuterated solvent stated. All chemical shifts (δ) are quoted in ppm and coupling constants (*J*) in Hz. Residual signals from the solvents were used as an internal reference. The azido ester 6 was prepared as previously described.[i,ii]

Benzyl 2,5-anhydro-6-azido-6-deoxy-D-gluconamide 7

Benzylamine (0.13 ml, 1.19 mmol) was added to a stirred solution of the azido ester 6 (110 mg, 0.51 mmol) in methanol (2 ml). After 24h, t.l.c. (ethyl acetate:cyclohexane, 3:1) indicated the formation of a major product (R_f 0.30) and the remnants of some starting material (R_f 0.25). The solution was concentrated *in vacuo* and purified by flash column chromatography (ethyl acetate : cyclohexane, 3:1) to afford benzyl 2,5-anhydro-6-azido-6-deoxy-D-gluconamide 7 (84 mg, 57%) as a white crystalline solid. Found: C, 53.57; H, 5.74; N, 19.03; $C_{13}H_{16}N_4O_4$ requires: C, 53.42; H, 5.52; N, 19.17. m.p. 108-110°C. $[\alpha]_D^{23}$ +74.8 (*c*, 1.24 in methanol). ν_{max} (KBr disc) 3402, 3315, 3127 (b, NH & OH), 2082 (s, N_3), 1648 (s, amide I), 1553 (s, amide II). δ_H (400 MHz, CD_3CN) 3.50 (dd, 1H, $J_{6,6'}$ 12.8, $J_{6,5}$ 4.8 Hz, H-6), 3.60 (dd, 1H, $J_{6',6}$ 12.8, $J_{6',6}$ 6.8 Hz, H-6'), 3.95-4.00 (m, 2H, H-4 and H-5), 4.22 (a-dt, 1H, *J* 4.3, *J* 1.5 Hz, H-3), 4.39 (dd, 1H, J_{CH} 15.6, J_{NH} 6.0 Hz, C*H*Ph), 4.48 (dd, 1H, J_{CH} 15.6, J_{NH} 6.8 Hz, C*H'*Ph), 7.27 (m, 2H, Ar-*H*), 7.33 (m, 3H, Ar-*H*). δ_C (100.6 MHz, CD_3CN) 42.4 (CH_2Ph), 52.8 (C-6), 78.2 (C-3), 78.8 (C-4), 82.8 (C-2), 85.6 (C-5), 127.3 (*p*-Ar-*C*H), 127.6, 128.8 (2 x *o*-Ar-*C*H and 2 x *m*-Ar-*C*H), 139.5 (Ar–*C*), 169.3 (C-1). *m/z* (ES+) 293 (M+H$^+$, 100%).

Benzyl 6-*N*-acetamido-2,5-anhydro-6-deoxy-3,4-di-*O*-acetyl-D-gluconamide 2

Palladium (10% on activated carbon, 20 mg) was added to a stirred solution of the azide **7** (100 mg, 0.35 mmol) in 1,4-dioxane and water (2:1, 5 ml). The apparatus was purged with argon, flushed with hydrogen and left stirring under an atmosphere of hydrogen. After 90 min, t.l.c. (ethyl acetate) indicated the complete conversion of starting material (R_f 0.3) to a major product (R_f 0.0). The reaction

was purged with nitrogen, filtered through Celite (eluent 1,4-dioxane) and concentrated *in vacuo* to afford the corresponding amine which was treated without further purification with acetic anhydride (1 ml) in pyridine (1 ml) stirred at 0°C. The reaction mixture was allowed to warm to room temperature and after 21 h, t.l.c. (ethyl acetate) indicated the formation of a major product (R_f 0.2). The reaction mixture was concentrated *in vacuo* (co-evaporated with toluene) and the residue purified by flash column chromatography (ethyl acetate) to afford fully acetylated derivative **2** (96 mg, 74% over two steps) as a white foam. Found: C, 57.70; H, 6.25; N, 7.05; $C_{19}H_{24}N_2O_7$ requires: C, 58.16; H, 6.16; N, 7.14. HRMS (ES+) found: 393.1658; $C_{19}H_{25}N_2O_7$ ($M+H^+$) requires: 393.1662. $[\alpha]_D^{24}$ –11.5 (*c*, 0.72 in chloroform). ν_{max} (chloroform, 2 mM) 3450, 3429 (s, sharp, NH), 3315 (br, NH); (KBr disc) 3392 (br, NH), 1750 (s, 2 x C=O), 1662 (s, 2 x amide I), 1544 (s, 2 x amide II) cm^{-1}. δ_H (500 MHz, $CDCl_3$) 1.90, 2.16 (2 x s, 2 x 3H, 2 x OCOC*H*$_3$), 2.01 (s, 3H, NHCOC*H*$_3$), 3.46 (a-dt, 1H, $J_{6,6'}$

Complete Reference 17:
Gaussian 03 (Revision B.03), Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez C.; Pople, J. A. Gaussian, Inc., Pittsburgh PA, 2003.

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[ii] Smith, M.D.; Claridge, T.D.W.; Sansom M.S.P.; Fleet G.W.J., *Org. Biomol. Chem.* **2003**, *1*, 3647-3655.