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Methyl 4-*O*-β-L-galactopyranosyl-β-D-glucopyranoside (methyl β-L-lactoside)

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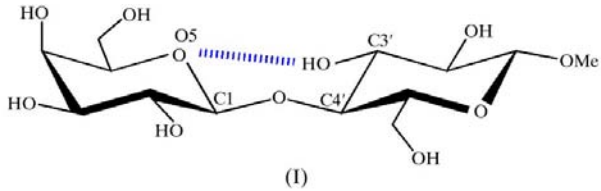
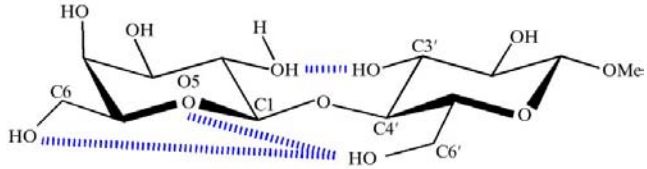
Methyl β-L-lactoside, $C_{13}H_{24}O_{11}$, (II), is described by glycosidic torsion angles φ ($O5_{Gal}-C1_{Gal}-O4_{Glc}-C4_{Glc}$) and ψ ($C1_{Gal}-O1_{Gal}-C4_{Glc}-C5_{Glc}$) of 93.89 (13) and −127.43 (13)°, respectively, where the ring atom numbering conforms to the convention in which C1 is the anomeric C atom and C6 is the exocyclic hydroxymethyl (CH_2OH) C atom in both residues (Gal is galactose and Glc is glucose). Substitution of L-Gal for D-Gal in the biologically relevant disaccharide, methyl β-lactoside [Stenutz, Shang & Serianni (1999). *Acta Cryst.* C**55**, 1719–1721], (I), significantly alters the glycosidic linkage interface. In the crystal structure of (I), one inter-residue (intramolecular) hydrogen bond is observed between atoms $H3O_{Glc}$ and $O5_{Gal}$. In contrast, in the crystal structure of (II), inter-residue hydrogen bonds are observed between atoms $H6O_{Glc}$ and $O5_{Gal}$, $H6O_{Glc}$ and $O6_{Gal}$, and $H3O_{Glc}$ and $O2_{Gal}$, with $H6O_{Glc}$ serving as a donor with two intramolecular acceptors.

Comment

Structural studies of di- and oligosaccharides have focused to a large extent on O-glycosidic linkages observed in nature. For example, crystal structures of β-D-Gal-(1→4)-α- and β-D-$GlcOCH_3$, (I) (Stenutz *et al.*, 1999; Pan *et al.*, 2005), and related β-(1→4) linkages, such as those found in β-D-Glc-(1→4)-β-D-$GlcOCH_3$ (Ham & Williams, 1970) and β-D-GlcNAc-(1→4)-β-D-GlcNAc (Mo & Jensen, 1978), have been investigated, and all contain linkage interfaces between aldopyranosyl rings having the D configuration (Gal is galactose and Glc is glucose). As expected, these disaccharides display common structural motifs dictated by their shared linkage type. For example, β-(1→4) linkages involving D sugars typically show inter-residue hydrogen bonds between atoms H3′O and O5, as shown in the first scheme below for (I). Thus, it may be inferred that efforts aimed at identifying the various structural factors influencing O-glycosidic linkage conformations using natural systems will necessarily reveal only a subset of the possible interface interactions. One way to modulate the linkage interface and the overall molecular topology is to substitute an L sugar for a D sugar while retaining the relative configuration of the substituted residue. This perturbation has been introduced into the structure of β-D-Gal-(1→4)-β-D-$GlcOCH_3$ (methyl β-lactoside; D-LAC), (I), by substituting β-L-Gal at the β-D-Gal residue, yielding β-L-Gal-(1→4)-β-D-$GlcOCH_3$ (methyl β-L-lactoside; L-LAC), (II).

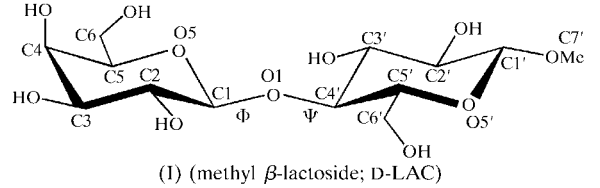


(I)

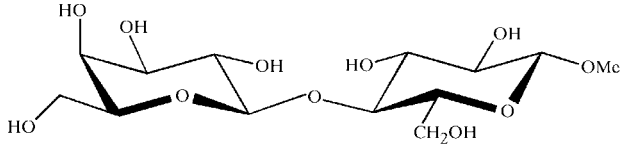


(II)

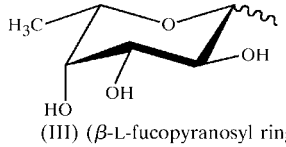
Unlike D-LAC, L-LAC crystallizes in the solvent-free form from methanol (Fig. 1). A comparison of representative molecular parameters for (I) and (II) is shown in Table 2. The bond lengths in (I) and (II) are, on average, similar, although some significant differences exist (*e.g.* C1′—O5′ and C2—O2). The C1—O1—C4′ bond angle is slightly smaller in L-LAC, and this angle is larger than the C1′— O1′—CH_3 glycosidic bond angle in both structures.



(I) (methyl β-lactoside; D-LAC)



(II) (methyl β-L-lactoside; L-LAC)



(III) (β-L-fucopyranosyl ring)

The intra-ring torsion angles C1—C2—C3—C4 and C1′—C2′—C3′—C4′ deviate significantly from the idealized values of 60°. This deviation is smaller for the intra-ring C1—O5—C5—C4 and C1′—O5′—C5′—C4′ torsion angles, suggesting that aldopyranosyl ring distortions result mainly from reduced C—C—C—C torsions. The glycosidic torsion angles φ are very similar in (I) and (II), as indicated by the similar absolute values of the C2—C1—O1—C4′, O5—C1—O1—C4′ and H1—C1—O1—C4′ torsion angles. In both structures, the φ

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torsion angle is consistent with expectations based on stereoelectronic factors (the *exo*-anomeric effect; C2 roughly *anti* to C4′) (Lemieux, 1971; Juaristi & Cuevas, 1995). In contrast, the glycosidic torsion angle ψ differs by ∼34° between (I) and (II). Interestingly, in (II), ψ assumes a nearly eclipsed conformation [−127.43 (13)°] in contrast to the more nearly staggered conformation observed in (I) [−161.3 (2)°], indicating that significant deviations from staggered conformations are possible in glycosidic linkages. This finding contrasts sharply with other mobile exocyclic bonds in saccharides (*e.g.* C5—C6 bonds in aldohexopyranosyl rings) where staggered or nearly staggered rotamers are energetically more stable than the eclipsed or near eclipsed rotamers (Thibaudeau *et al.*, 2004). Hydroxymethyl conformations in the Gal (*gauche–trans*, *gt*) and Glc (*gauche–gauche*, *gg*) residues are the same in both structures.

The change in absolute configuration of the Gal residue affects the linkage interface significantly. In D-LAC, atoms O3′ and O5 are in close proximity (2.764 Å) and an inter-residue hydrogen bond is observed between atoms H3′O and O5 in the crystal structure. In L-LAC, atoms O6′ and O5 are in close proximity [3.0046 (15) Å] and an inter-residue hydrogen bond is observed between atoms H6′O and O5 (see first scheme above). Furthermore, atom O6′ is close to atom O6 [3.0817 (17) Å], atom O3′ is close to atom O2 [3.1357 (17) Å], and two additional hydrogen bonds are observed, with H6′O and H3′O serving as donors. Thus, in (II), atom H6′O participates in two hydrogen bonds with atoms O5 and O6 (a three-center hydrogen-bond system).

Recent NMR investigations of (I) indicate the presence of hydrogen bonding between atoms H3′O and O5 in a water/acetone solvent at 253 K, based on the behavior of $^3J_{HCOH}$ and $^3J_{CCOH}$ values (Zhao *et al.*, 2006). NMR studies of (I) in aqueous solution indicate a mixture of *gg* and *gt* hydroxymethyl rotamers in the Glc residue based on an analysis of $^3J_{HH}$ values (Hayes *et al.*, 1982). If hydrogen bonding between atoms O6′ and O5 of (II) exists in water/acetone solvent, not only might the $^3J_{HCOH}$ and $^3J_{CCOH}$ values involving atom H6′O be affected, but also the distribution of *gg* and *gt* rotamers in the Glc residue, with a shift towards the *gg* state expected. Furthermore, comparisons of trans-glycoside *J*-couplings in D-LAC and L-LAC may establish whether ψ is shifted in solution in a manner similar to that observed in the crystal. The results of these NMR investigations will be reported elsewhere.

The crystal structure is a three-dimensional hydrogen-bonded network composed of two-dimensional sheets that are staggered to form columns in a three-dimensional lattice. In the sheets, which are formed from a 6,3-network parallel to (100), each molecule is connected to three additional molecules *via* two, two and three hydrogen bonds, respectively. Additional hydrogen bonding connects each molecule to three complementary molecules through two, one and one hydrogen bond, extending the structure into alternating columns parallel to the *a* axis. While there is no hydrogen bonding between molecules of a given column, hydrogen bonds exist

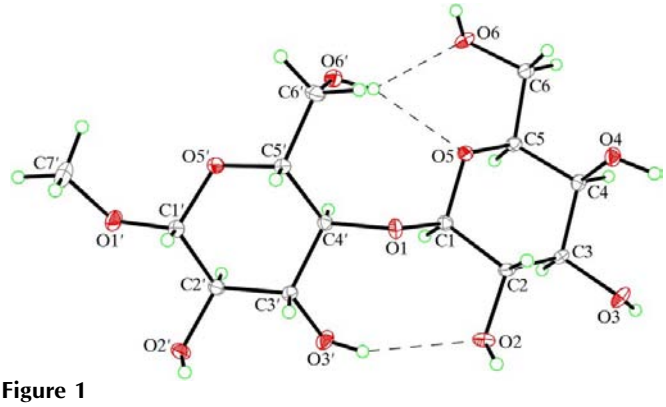

Figure 1
The crystal structure of (II), showing the close proximity of atoms O6′, O6 and O5, and atoms O3′ and O2.

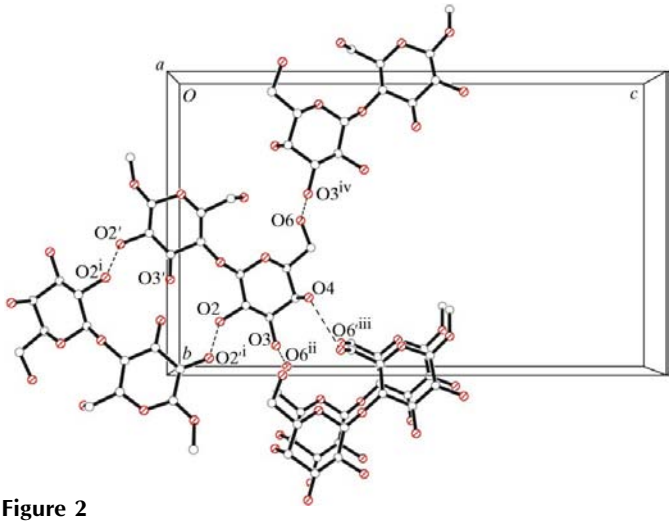

Figure 2
The hydrogen-bonding network generated from one molecule of (II). Hydrogen bonds are shown as dashed lines and H atoms have been omitted. The symmetry codes are as given in Table 1.

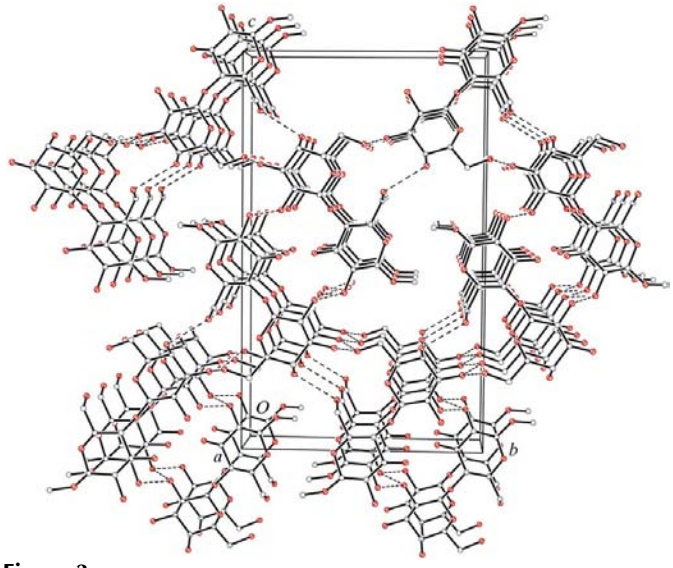

Figure 3
A view of the crystal packing of (II) along the *a* axis. Hydrogen bonds are shown as dashed lines and H atoms have been omitted.

between molecules of neighboring columns. These alternating columns are slipped with respect to each other by a $\frac{1}{2}$ translation along the *a* axis. Details of the hydrogen bonding are given in Table 1 and a representative view is shown in Fig. 2. A view emphasizing the columnar packing is shown in Fig. 3.

Intermolecular hydrogen-bonding patterns observed for (II) are very similar, but not identical, to those found for natural disaccharides (Pan *et al.*, 2005). Thus, atoms O1′, O5′ and O1 do not participate as hydrogen-bond acceptors. All hydroxy H atoms are involved in hydrogen bonding, and most hydroxy O atoms participate in either zero (O4) or one (O2′, O6′, O2, O3 and O6) hydrogen bond as acceptors.

The glycosidic linkage in (II) is a structural mimic of linkages involving the biologically important β-L-fucopyranosyl ring, (III), and the crystal structure of methyl β-L-fucopyranosyl-(1→3)-α-D-glucopyranoside trihydrate has been reported recently (Färnbäck *et al.*, 2003). In di- and oligosaccharides containing (III), however, potential interresidue hydrogen bonding is more restricted than for L-Gal, since the L-Fuc ring lacks a hydroxy group at atom C6.

In addition to its modified glycosidic linkage interface, L-LAC displays an overall contact surface very different from that of D-LAC. An identical but mirror-image contact surface (and linkage interface) would be generated in the alternate L-LAC structure composed of D-Gal and L-Glc residues. Because both the linkage interface and surface topology are affected by L-sugar substitution, this derivatization may prove generally useful in the design of saccharide-based biological agents or pharmaceuticals having novel binding properties or functions.

Experimental

Compound (II) was prepared by coupling 2,3,4,6-tetra-*O*-acetyl-α-L-galactopyranosyl trichloroacetimidate, (IV) (600 mg, 1.21 mmol), with methyl 2,3,6-tri-*O*-benzyl-β-D-glucopyranoside, (V) (500 mg, 1.08 mmol), in the presence of silver trifluoromethanesulfonate (350 mg, 1.4 mmol) in dichloromethane (20 ml) at 253 K. When the reaction was complete (2 h), the product was deprotected at room temperature with 10% Pd/C (400 mg) in EtOAc (20 ml), followed by addition of a 0.1 *M* methanol solution of $NaOCH_3$ (15 ml). Compound (IV) was prepared by standard methods (Schmidt *et al.*, 1984) and (V) was prepared by reacting methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranoside (450 mg, 0.97 mmol) in tetrahydrofuran (30 ml) with $NaBH_3CN$ (0.85 g, 13.7 mmol), immediately followed by the addition of 1 *N* HCl in Et_2O (14 ml). Purification of (II) was achieved by chromatography on silica gel using methanol/dichloromethane (1:4 *v*/*v*) as the solvent. Crystals were grown from a methanol solution by slow evaporation at 277 K.

Crystal data

$C_{13}H_{24}O_{11}$
M_r = 356.32
Orthorhombic, $P2_12_12_1$
a = 4.7087 (4) Å
b = 14.1428 (12) Å
c = 23.2401 (19) Å
V = 1547.7 (2) Å^3
Z = 4
D_x = 1.529 Mg m^{-3}
Mo *Kα* radiation
Cell parameters from 4991 reflections
θ = 2.9–31.3°
μ = 0.14 mm^{-1}
T = 100 (2) K
Needle, colorless
0.35 × 0.07 × 0.05 mm

Data collection

Bruker X8-APEXII CCD diffractometer
φ and ω scans
13853 measured reflections
2964 independent reflections
2644 reflections with $I > 2\sigma(I)$
R_{int} = 0.031
θ_{max} = 31.5°
h = −6 → 4
k = −16 → 20
l = −30 → 34

Table 1
Hydrogen-bond geometry (Å, °).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O2—H2O···O2′^{i}	0.83 (3)	1.97 (3)	2.8042 (19)	175 (2)
O3—H3O···O6^{ii}	0.74 (3)	1.93 (3)	2.6580 (19)	167 (2)
O4—H4O···O6′^{iii}	0.82 (2)	2.03 (2)	2.8475 (16)	174 (2)
O6—H6O···O3^{iv}	0.79 (3)	1.91 (3)	2.6713 (19)	163 (2)
O2′—H2′O···O2^{i}	0.80 (3)	2.03 (3)	2.8263 (19)	169 (2)
O3′—H3′O···O2	0.78 (3)	2.42 (2)	3.1357 (17)	153 (2)
O3′—H3′O···O3′^{i}	0.78 (3)	2.43 (3)	2.9719 (19)	128 (2)
O6′—H6′O···O5	0.76 (3)	2.30 (3)	3.0046 (15)	157 (2)
O6′—H6′O···O6	0.76 (3)	2.52 (2)	3.0817 (17)	133 (2)

Symmetry codes: (i) $x+\frac{1}{2}, -y+\frac{3}{2}, -z$; (ii) $-x+1, y+\frac{1}{2}, -z+\frac{1}{2}$; (iii) $-x+2, y+\frac{1}{2}, -z+\frac{1}{2}$; (iv) $-x+2, y-\frac{1}{2}, -z+\frac{1}{2}$.

Table 2
Comparison of structural parameters in (I) and (II).

Parameter	(I)	(II)
Bond lengths (Å)		
C1—C2	1.527 (3)	1.528 (2)
C1′—C2′	1.516 (3)	1.534 (2)
C1—O5	1.425 (3)	1.4293 (17)
C1′—O5′	1.413 (3)	1.4352 (18)
C1—O1	1.387 (3)	1.3988 (18)
C1′—O1′	1.384 (3)	1.3821 (18)
C4′—O1	1.437 (3)	1.4390 (17)
C2—O2	1.414 (3)	1.4313 (17)
C4—O4	1.423 (3)	1.4268 (18)
C6—O6	1.426 (3)	1.4392 (18)
C2′—O2′	1.418 (3)	1.4252 (17)
C5—C6	1.511 (3)	1.516 (2)
C5′—C6′	1.508 (3)	1.519 (2)
O3′···O5	2.764	–
O(CH$_3$OH)···O6′	2.727	–
O6′···O5	–	3.0046 (15)
O6′···O6	–	3.0817 (17)
O3′···O2	–	3.1357 (17)
Bond angles (°)		
C1—O1—C4′	116.2 (2)	114.60 (12)
C1′—O1′—CH$_3$	113.7 (2)	112.56 (13)
O3′—H3′O···O5	140.9	–
O—H(CH$_3$OH)···O6′	164.4	–
O6′—H6′O···O5	–	157
O6′—H6′O···O6	–	133
O3′—H3′O···O2	–	153
Torsion angles (°)		
C1—C2—C3—C4	−54.8 (2)	53.35 (16)
C1′—C2′—C3′—C4′	−44.2 (3)	−52.15 (16)
C1—O5—C5—C4	65.0 (2)	−62.68 (15)
C1′—O5′—C5′—C4′	67.6 (2)	66.04 (15)
C2—C1—O1—C4′ (φ)	153.8 (2)	−146.19 (12)
C2′—C1′—O1′—CH$_3$ (φ′)	164.2 (2)	167.74 (13)
C1—O1—C4′—C3′ (ψ)	78.4 (2)	111.14 (13)
C1—O1—C4′—C5′ (ψ)	−161.3 (2)	−127.43 (13)
O5—C1—O1—C4′ (φ)	−88.4 (2)	93.89 (13)
O5′—C1′—O1′—CH$_3$(φ′)	−77.4 (3)	−73.32 (16)
H1—C1—O1—C4′ (φ)	31.9	−25.6
C1—O1—C4′—H4′ (ψ)	−43.7	−7.3
O5—C5—C6—O6 (ω)	57.3 (2) (*gt*)	−58.02 (16) (*gt*)
O5′—C5′—C6′—O6′ (ω′)	−54.6 (2) (*gg*)	−69.22 (16) (*gg*)

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0559P)^2 + 0.1003P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)] = 0.033$	$(\Delta/\sigma)_{max} = 0.002$
$wR(F^2) = 0.088$	$\Delta\rho_{max} = 0.45$ e Å^{-3}
$S = 1.04$	$\Delta\rho_{min} = -0.21$ e Å^{-3}
2964 reflections	
246 parameters	
H atoms: see below	

Hydroxy H atoms were located in a difference electron-density map and freely refined in subsequent cycles of least-squares refinement, including an isotropic displacement parameter. All other H atoms were placed at calculated positions and allowed to ride on their parent atoms. Displacement parameters for these H atoms were set at 1.2 times U_{eq} of the parent atom (1.5 times for methyl H atoms). 2143 Friedel pairs were merged in the final stages of refinement, and the Flack (1983) parameter is thus meaningless. The absolute configuration was assumed from the synthesis.

Data collection: *APEX2* (Bruker, 2004); cell refinement: *APEX2* and *SAINT* (Bruker, 2004); data reduction: *SAINT* and *XPREP* (Sheldrick, 2003); program(s) used to solve structure: *XS* (Sheldrick, 2001); program(s) used to refine structure: *XL* (Sheldrick, 2001); molecular graphics: *XP* (Sheldrick, 1998); software used to prepare material for publication: *XCIF* (Sheldrick, 2001) and *enCIFer* (Allen *et al.*, 2004).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: JZ1778). Services for accessing these data are described at the back of the journal.

References

Allen, F. H., Johnson, O., Shields, G. P., Smith, B. R. & Towler, M. (2004). *J. Appl. Cryst.* **37**, 335–338.
Bruker (2004). *APEX2* and *SAINT*. Bruker AXS Inc., Madison, Wisconsin, USA.
Färnbäck, M., Eriksson, L. & Widmalm, G. (2003). *Acta Cryst.* C**59**, o171–o173.
Flack, H. D. (1983). *Acta Cryst.* A**39**, 876–881.
Ham, J. T. & Williams, D. G. (1970). *Acta Cryst.* B**26**, 1373–1383.
Hayes, M. L., Serianni, A. S. & Barker, R. (1982). *Carbohydr. Res.* **100**, 87–101.
Juaristi, E. & Cuevas, G. (1995). *The Anomeric Effect.* Boca Raton, Florida, USA: CRC Press.
Lemieux, R. U. (1971). *Pure Appl. Chem.* **25**, 527–548.
Mo, F. & Jensen, L. H. (1978). *Acta Cryst.* B**34**, 1562–1569.
Pan, Q., Noll, B. C. & Serianni, A. S. (2005). *Acta Cryst.* C**61**, o674–o677.
Schmidt, R. R., Michel, J. & Roose, M. (1984). *Liebigs Ann. Chem.* pp. 1343–1357.
Sheldrick, G. M. (1998). *XP*. Bruker AXS Inc., Madison, Wisconsin, USA.
Sheldrick, G. M. (2001). *XCIF*, *XL* and *XS*. Bruker AXS Inc., Madison, Wisconsin, USA.
Sheldrick, G. M. (2003). *XPREP*. Bruker AXS Inc., Madison, Wisconsin, USA.
Stenutz, R., Shang, M. & Serianni, A. S. (1999). *Acta Cryst.* C**55**, 1719–1721.
Thibaudeau, C. Stenutz, R., Hertz, B., Klepach, T., Zhao, S., Wu, Q., Carmichael, I. & Serianni, A. S. (2004). *J. Am. Chem. Soc.* **126**, 15668–15685.
Zhao, H., Pan, Q., Zhang, W., Carmichael, I. & Serianni, A. S. (2006). *J. Am. Chem. Soc.* Submitted.