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(54) Title: COMPOUNDS AND THEIR USES

(57) Abstract: Compounds having a mimetic or antagonistic property of an inositol phosphoglycan, and the uses of these compounds are disclosed, together with the use, e.g. to treat a condition ameliorated by administration of an IPG second messenger or an IPG antagonist thereof. In particular, the compounds are based on the 1,6 linkage of a sugar residue and a cyclitol.

Compounds and Their Uses

Field of the Invention

The present invention relates to compounds and their uses, and in particular to compounds which have a mimetic or antagonistic property of an inositol phosphoglycan or a free GPI precursor of an IPG, and the uses of these compounds, e.g. to treat a condition ameliorated by administration of an IPG second messenger or an IPG antagonist thereof.

Background of the Invention

Many of the actions of growth factors or hormones on cells are thought to be mediated by a family of inositol phosphoglycan (IPG) second messengers [13]. It is thought that the source of IPGs is a "free" form of glycosyl phosphatidylinositol (GPI) situated in cell membranes. IPGs are thought to be released by the action of phosphatidylinositol-specific phospholipases following binding of growth factors to receptors on the cell surface. There is evidence that IPGs mediate the action of a large number of growth factors including insulin, nerve growth factor, hepatocyte growth factor, insulin-like growth factor I (IGF-I), fibroblast growth factor, transforming growth factor β, the action of IL-2 on B-cells and T-cells, ACTH signalling of adrenocortical cells, IgE, FSH and hCG stimulation of granulosa cells, thyrotropin stimulation of thyroid cells, cell proliferation in the early developing ear and rat mammary gland.

Partially characterised inositolphosphoglycans (IPGs) have been postulated to mediate the action of a number of growth factors and hormones including insulin and insulin-like growth factor I (IGF-I) [1]. Despite their isolation from several tissues type, the precise chemical structures of these IPGs are, however, still unknown and two main structural groups have been proposed on the basis of the chemical composition [2,3] which display different biological activity and tissue distribution [4]; the family of glucosamine-*myo*-inositol containing IPGs (IPG-A) and the family of *chiro*-inositol-galactosamine containing IPGs (IPG-P).

In an attempt to establish the minimal structural requirements for biological activity, a number of compounds containing some of the basic structural motifs that have been postulated for IPG mediators have been synthesised in the art [5]. These synthetic compounds include *O*-(2-amino-2-deoxy-D-glucopyranosyl)-α(1→6)-*chiro*-inositol 1-phosphate and *O*-(2-amino-2-deoxy-D-glucopyranosyl)-α(1→6)-*myo*-inositol 1-phosphate [6].

US Patent No: 6,004,938 (Hoechst) discloses a group of synthetic inositol glycans having insulin-like action. The compounds are based on 2-6 monsaccharide units linked to an inositol moiety. The examples in the patent all employ *myo*-inositol and are composed of 5 or 6 units apart from two pseudo-trisaccharide compounds G and H. Compounds G and H are HO-PO(H)O-6Man-α(1→4)-GluN-α(1→6)-(L)inositol-1,2(cyclic) phosphate and HO-PO(H)O-6Man-α(1→4)-GluN-α(1→6)-(L)inositol, otherwise known as *O*-(6-hydrogenphosphonate-α-D-mannopyranosyl)-(1→4)-(2-ammonio-2-deoxy-α-D-glucopyranosyl)-(1→6)-L-*myo*-inositol-1,2-cyclic phosphate and *O*-(6-hydrogenphosphonate-α-D-mannopyranosyl)-(1→4)-(2-amino-2-deoxy-α-D-glucopyranosyl)-L-*myo*-inositol. The properties of exemplified compounds are investigated in lipogenesis and glucose transport assays employing rat fat cells.

WO96/14075 (University of Virginia) discloses a generic family of compounds D-hexosamines linked to an inositol via a β1,4-linkage. The inositols can be *myo* or *chiro*-inositol or pinitol, while the hexosamines are glucosamine or galactosamine. However, this application describes the synthesis of just two compounds 4-*O*-(2-deoxy-2-amino-β-D-galactopyranosyl)-D-pinitol and 4-*O*-(2-deoxy-2-amino-β-D-galactopyranosyl)-D-*chiro*-inositol, or in IUPAC notation *O*-(2-amino-2-deoxy-β-D-galactopyranosyl)-(1→4)-D-pinitol and *O*-(2-amino-2-deoxy-β-D-galactopyranosyl)-(1→4)-D-chiro-inositol.

WO99/06421 (University of Virginia) describes synthetic insulin mimetic substances and includes a general formula I showing β1,4-linked disaccharides. However,

despite this the compounds synthesised in this application are exactly the same as those disclosed in the applicant's earlier application, WO96/14075.

A multi-step synthesis of a IPG-P mimetic from glucose has been previously reported in Jaramillo et al [6], which discloses a compound called C4, 1-D-6-*O*-(2-amino-2-deoxy-α-D-glucopyranosyl)-*chiro*-inositol 1-phosphate. A further synthesis of C4 is described in our co-pending International Patent Application PCT/GB99/03715 (Rademacher Group Limited). Zapata et al [16] discloses three other compounds C1-C3 which are:

C1 1-D-4-*O*-(2-amino-2-deoxy-α-D-glucopyranosyl)-*myo*-inositol 1-phosphate.

C2 1-D-6-*O*-(2-amino-2-deoxy-α-D-glucopyranosyl)-*myo*-inositol 1-phosphate.

C3 1-D-6-*O*-(2-amino-2-deoxy-α-D-glucopyranosyl)-*myo*-inositol 1,2 cyclic-phosphate.

C4 1-D-6-*O*-(2-amino-2-deoxy-α-D-glucopyranosyl)-*chiro*-inositol 1-phosphate.

It remains a significant problem in the art to produce synthetic compounds which can mimic one or more of the activities of inositol phosphoglycans or which act as antagonists of IPGs.

Summary of the Invention

Broadly, the present invention relates to IPG mimetic and antagonist compounds and to methods of producing the compounds and to their medical uses. The compounds disclosed herein are useful as synthetic mimetics of IPG-P or IPG-A second messengers and/or growth factors whose action is mediated by IPGs, as synthetic mimetics of GPI precursors of IPGs, or as competitive antagonists of IPGs. In particular, in preferred embodiments, the compounds are based on the 1,6 linkage of a sugar residue and a cyclitol.

Accordingly, in a first aspect, the present invention provides a compound represented

by the general formula:

X-1,6-cyclitol

wherein:

X represents a sugar residue;

the sugar residue is unsubstituted or substituted with between one and four groups, and the cyclitol is unsubstituted or is further substituted with between one and four groups, the group or groups being as defined herein;

with the proviso that the compound is not 1-D-4-*O*-(2-amino-2-deoxy-α-D-glucopyranosyl)-*myo*-inositol 1-phosphate, 1-D-6-*O*-(2-amino-2-deoxy-α-D-glucopyranosyl)-*myo*-inositol 1-phosphate, 1-D-6-*O*-(2-amino-2-deoxy-α-D-glucopyranosyl)-*myo*-inositol 1,2 cyclic-phosphate, 1-D-6-*O*-(2-amino-2-deoxy-α-D-glucopyranosyl)-*chiro*-inositol 1-phosphate, *O*-(6-hydrogenphosphonate-α-D-mannopyranosyl)-(1→4)-(2-ammonio-2-deoxy-α-D-glucopyranosyl)-(1→6)-L-*myo*-inositol-1,2-cyclic phosphate or *O*-(6-hydrogenphosphonate-α-D-mannopyranosyl)-(1→4)-(2-amino-2-deoxy-α-D-glucopyranosyl)-L-*myo*-inositol.

In a further aspect, the present invention provides the present invention provides a compound represented by the general formula:

X-α1,6-cyclitol

wherein:

X represents a sugar residue;

the sugar residue is unsubstituted or substituted with between one and four groups, and the cyclitol is unsubstituted or is further substituted with between one and four groups, the group or groups being as defined herein;

with the proviso that the compound is not 1-D-4-*O*-(2-amino-2-deoxy-α-D-

glucopyranosyl)-*myo*-inositol 1-phosphate, 1-D-6-*O*-(2-amino-2-deoxy-α-D-glucopyranosyl)-*myo*-inositol 1-phosphate, 1-D-6-*O*-(2-amino-2-deoxy-α-D-glucopyranosyl)-*myo*-inositol 1,2 cyclic-phosphate, 1-D-6-*O*-(2-amino-2-deoxy-α-D-glucopyranosyl)-*chiro*-inositol 1-phosphate, *O*-(6-hydrogenphosphonate-α-D-mannopyranosyl)-(1→4)-(2-ammonio-2-deoxy-α-D-glucopyranosyl)-(1→6)-L-*myo*-inositol-1,2-cyclic phosphate or *O*-(6-hydrogenphosphonate-α-D-mannopyranosyl)-(1→4)-(2-amino-2-deoxy-α-D-glucopyranosyl)-L-*myo*-inositol.

In a further aspect, the present invention provides the present invention provides a compound represented by the general formula:

X-β1,6-cyclitol

wherein:

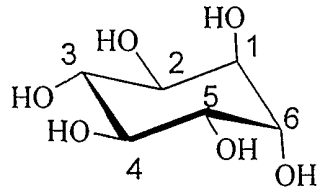
X represents a sugar residue;

the sugar residue is unsubstituted or substituted with between one and four groups, and the cyclitol is unsubstituted or is further substituted with between one and four groups, the group or groups being as defined herein.

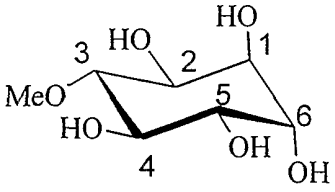
Preferably, the sugar residue is a hexose or a pentose, and may be an aldose or a ketose. The sugar residue can be a member of the D or L series and can include amino sugars, deoxy sugars and their uronic acid derivatives. Preferably, where the sugar residue is a hexose, it is selected from the group consisting of glucose, galactose or mannose, or substituted hexose sugar residues such as an amino sugar residue such as hexosamine, galactosamine or glucosamine, and more preferably D-glucosamine (2-amino-2-deoxy-D-glucose) or D-galactosamine (2-amino-2-deoxy-D-galactose). Preferred pentose sugar residues include arabinose, fucose and ribose. The sugar residue is optionally substituted at one, two, three or four positions, other than the position of linkage to the cyclitol moiety.

The cyclitol moiety is preferably selected from *myo*-inositol, *chiro*-inositol or pinitol (3-*O*-methyl-*chiro*-inositol), in either their D or L forms, and is optionally substituted at one or more of the positions other than the position of linkage to the sugar radical, or in the case of pinitol additionally the 3-position. The sugar radical is optionally substituted at one, two, three or four positions other than at the position of linkage to the inositol moiety or the anomeric position. Where the cyclitol moiety is substituted at the 3-position (e.g. is a pinitol or a related compound), preferably the substituent is C_{1-10} alkyl, and may be a substituted or unsubstituted primary, secondary or tertiary alkyl group. Examples of substituted groups include CF_3, $X(CH_2)_n$-O- (where X is hydrogen, or substituted or unsubstituted alkyl), CHF_2O-. A preferred alkyl group is methyl when the cyclitol is D or L-pinitol (3-*O*-methyl-*chiro*-inositol), and is optionally substituted at one or more of the positions other than the 3-position or the position of linkage to the sugar residue. In further embodiments, the cyclitol may have one or more of the hydroxyl groups through which the substituents described above are removed so that any substituent(s) are linked to the ring carbon atom. The sugar residue is optionally substituted at one, two, three, four or five positions other than at the position of linkage to the inositol moiety. The compounds of the invention may be either α or β linked.

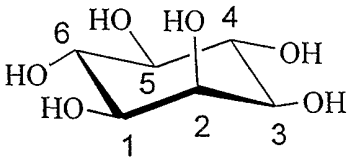
To avoid confusion, the numbering system used herein is clarified with reference to the following structures. Importantly, as the *chiro*-inositol molecule contains a C2 plane of symmetry and positions 1 and 6 are equivalents. Therefore, for instance, compounds containing a **β(1,6)** linkage can be regarded as **β(1,1)** if there are no other substituents to define priority in the numbering system. Monosaccharide residues and oligosaccharides are named and numbered according to the recommendation proposed by the Joint Commission on Biochemical Nomenclature, International Union of Pure and Applied Chemistry and International Union of Biochemistry and Molecular Biology.



chiro-Inositol



Pinitol: 3-*O*-Methyl-*chiro*-inositol



myo-Inositol

In these and other aspects of the invention, preferably the substituent group or groups of the cyclitol moiety and the sugar residue are independently selected from:

(a) phosphoryl groups such as phosphate -O-P(O)$(OH)_2$; thiophosphate -O-P(S)$(OH)_2$; phosphate esters -O-P(O)$(OR)_2$; thiophosphate esters -O-P(S)$(OR)_2$; phosphonate -O-P(O)OHR; thiophosphonate -O-P(S)OHR; substituted phosphonate -O-P(O)OR_1R_2; substituted thiophosphonate -O-P(S)OR_1R_2; -O-P(S)(OH)(SH); cyclic phosphate;

(b) other phosphorus containing compounds such as phosphoramidite -O-P(OR)-NR_1R_2 and phosphoramidate -O-P(O)(OR)-NR_1R_2;

(c) sulphur groups such as -O-S(O)(OH), -SH, -SR, -S(→O)-R, -$S(O)_2$R, RO-$S(O)_2^-$, -O-SO_2NH_2, -O-$SO_2R_1R_2$ or sulphamide -$NHSO_2NH_2$;

(d) amino groups such as -NHR, -NR_1R_2, -NHAc, -NHCOR, -NH-O-COR, -$NHSO_3^-$, -$NHSO_2R$, -$N(SO_2R)_2$, and/or amidino groups such as -NH-C(=NH)NH_2 and/or ureido groups such as -NH-CO-NR_1R_2 or thiouriedo groups such as -NH-C(S)-NH_2;

(e) hydroxy groups and substituted hydroxy groups such as -OR_3, where R_3 is C_{1-10} unsubstituted or substituted alkyl, e.g. CHF_2 or CF_3, alkoxyalkyl, aryloxyalkyl, cycloalkyl, alkenyl (unsubstituted alkyl), alkylene (C_{3-7} cycloalkyl), -OCOR, aryl, heteroaryl, acetal, or where two hydroxyl groups are joined as a ketal;

(f) halogen substituents such as fluorine or chlorine;

(g) hydrogen, e.g. to provide a deoxy sugar;

wherein R, R_1 and R_2 are independently hydrogen or C_{1-10} unsubstituted or substituted alkyl or aryl.

The compounds may be provided as racemic or diasteromeric mixtures, resolved or partially resolved optical isomers, and as pharmaceutically acceptable salts, esters and derivatives as discussed in more detail below.

In a further aspect, the present invention provides a compound represented by the general formula:

X-α1,6-*myo*-inositol

wherein:

X represents a sugar residue;

the sugar residue is unsubstituted or substituted with between one and four groups, and the inositol is unsubstituted or is further substituted with between one and four groups, the group or groups being as defined herein;

with the proviso that the compound is not 1-D-4-*O*-(2-amino-2-deoxy-α-D-glucopyranosyl)-*myo*-inositol 1-phosphate, 1-D-6-*O*-(2-amino-2-deoxy-α-D-glucopyranosyl)-*myo*-inositol 1-phosphate, 1-D-6-*O*-(2-amino-2-deoxy-α-D-glucopyranosyl)-*myo*-inositol 1,2 cyclic-phosphate.

Examples of compounds within this aspect of the invention are RGL1023, RGL1027, RGL1029, RGL1105, RGL1115, RGL1116, RGL1125, RGL1126, RGL1134, RGL1133, RGL1135 and RGL1130.

In a further aspect, the present invention provides a compound represented by the general formula:

X-α1,6-*chiro*-inositol

wherein:

X represents a sugar residue;

the sugar residue is unsubstituted or substituted with between one and four groups, and the inositol is unsubstituted or is further substituted with between one and four groups, the group or groups being as defined herein;

with the proviso that the compound is not 1D-6-O-(2-amino-2-deoxy-α-D-glucopyranosyl)-D-*chiro*-inositol 1-phosphate.

Examples of compounds within this aspect of the invention are RGL1017, RGL1121 and derivatives thereof.

In a further aspect, the present invention provides a compound represented by the general formula:

X-α1,6-pinitol

wherein:

X represents a sugar residue;

the sugar residue is unsubstituted or substituted with between one and four groups, and the pinitol is unsubstituted or is further substituted with between one and four groups, the group or groups being as defined herein.

Examples of compounds within this aspect of the invention are RGL1024 and RGL1025.

In a further aspect, the present invention provides a compound represented by the general formula:

X-β1,6-*myo*-inositol

wherein:

X represents a sugar residue;

the sugar residue is unsubstituted or substituted with between one and four groups, and the inositol is unsubstituted or is further substituted with between one and four groups, the group or groups being as defined herein.

Examples of compounds within this aspect of the invention are RGL1002 and RGL1124.

In a further aspect, the present invention provides a compound represented by the general formula:

X-β1,6-*chiro*-inositol

wherein:

X represents a sugar residue;

the sugar residue is unsubstituted or substituted with between one and four groups, and the inositol is unsubstituted or is further substituted with between one and four groups, the group or groups being as defined herein.

Examples of compounds within this aspect of the invention are RGL1018, RGL1019 and RGL1120 and derivatives thereof.

In a further aspect, the present invention provides a compound represented by the

general formula:

X-β1,6-pinitol

wherein:

X represents a sugar residue;

the sugar residue is unsubstituted or substituted with between one and four groups, and the inositol is unsubstituted or is further substituted with between one and four groups, the group or groups being as defined herein.

Examples of compounds within this aspect of the invention are RGL1015, RGL1119 and derivatives thereof.

In preferred embodiments, the present invention provides a compound, or a substituted form thereof as defined above, selected from the group consisting of:

RGL1023 *O*-(2'-amino-2'-deoxy-6'-phosphate-D-glucopyranosyl)-α(1,6)-D-*myo*-inositol.

RGL1027 *O*-(2'-amino-2'-deoxy-4'-phosphate-D-glucopyranosyl)-α(1,6)-D-*myo*-inositol.

RGL1029 *O*-(2'-amino-2'-deoxy-3'-phosphate-D-glucopyranosyl)-α(1,6)-D-*myo*-inositol.

RGL1017 *O*-(2'-amino-2'-deoxy-D-glucopyranosyl)-α(1,6)-D-*chiro*-inositol.

RGL1024 *O*-(2-amino-2-deoxy-D-glucopyranosyl)-α(1,6)-D-3-*O*-methyl-*chiro*-inositol.

RGL1025 *O*-(2-amino-2deoxy-D-galactopyranosyl)-α(1,6)-D-3-*O*-methyl-*chiro*-inositol.

RGL1018 *O*-(2'-amino-2'-deoxy-D-glucopyranosyl)-β(1,6)-D-*chiro*-inositol.

RGL1019 *O*-(2'-amino-2'-deoxy-D-glucopyranosyl)-α(1,6)-D-*chiro*-inositol-1-phosphate.

RGL1015 *O*-(2-amino-2-deoxy-D-glucopyranosyl)-β(1,6)-3-*O*-methyl-*chiro*-inositol.

RGL1105	1''-D-4'-*O*-(6''-phosphate-α-D-mannopyranosyl)-[1'-D-6-*O*-(2'-amino-2'-deoxy-α-D-glucanopyranosyl)-*myo*-inositol].
RGL1115	1'-D-6-*O*-(2'-amino-2'-deoxy-α-D-glucopyranosyl)-5-*O*-phosphate-*myo*-inositol.
RGL1121	1'-D-1-*O*-(2'-amino-2'-deoxy-α-D-galactopyranosyl)-D-*chiro*-inositol.
RGL1120	1'-D-6-*O*-(2'-amino-2'-deoxy-β-D-glucopyranosyl)-D-*chiro*-inositol.
RGL1129	1'-D-2-*O*-(2'-amino-2'-deoxy-α-D-galactopyranosyl)-D-*chiro*-inositol.
RGL1122	1'-D-5-*O*-(2'-amino-2'-deoxy-α-D-glucopyranosyl)-D-*chiro*-inositol.
RGL1115	1'-D-6-*O*-(2'-amino-2'-deoxy-α-D-glucanopyranosyl)-5-*O*-phosphate-*myo*-inositol.
RGL1116	1'-D-6-*O*-(2'-amino-2'-deoxy-α-D-glucopyranosyl)-D-5-*O*-acetyl-*myo*-inositol.
RGL1117	1'-D-5-*O*-(2'-amino-2'-deoxy-α-D-glucopyranosyl)-D-6-*O*-acetyl-*myo*-inositol.
RGL1119	1'-D-6-*O*-(2'-amino-2'-deoxy-β-D-galactopyranosyl)-3-*O*-methyl-D-*chiro*-inositol.
RGL1124	1'-D-6-O-(2'-amino-2'-deoxy-β-D-glucopyranosyl)-5-O-acetyl-myo-inositol.
RGL1125	1'-D-6-O-(2'-amino-2'-deoxy-α-D-glucopyranosyl)-5-O-butyryl-myo-inositol.
RGL1126	1'-D-6-O-(2'-amino-2'-deoxy-α-D-glucopyranosyl)-5-O-palmityl-myo-inositol.
RGL1134	1'-D-6-*O*-(2'-amino-3'-*O*-benzyl-4'-*O*-phosphate-2'-deoxy-α-D-glucopyranosyl)-3,4,5-tri-*O*-benzyl-*myo*-inositol-1,2-cyclic phosphate.
RGL1133	1'-D-6-*O*-(2'-amino-3'-*O*-benzyl-4',6'-di-*O*-sulphate-2'-deoxy-α-D-glucopyranosyl)-3,4,5-tri-*O*-benzyl-*myo*-inositol-1,2-di-*O*-sulphate.
RGL1135	1'-D-6-*O*-(2'-amino-3'-*O*-benzyl-4',6'-di-*O*-cyclic phosphate-2'-deoxy-α-D-glucopyranosyl)-3,4,5-tri-*O*-benzyl-*myo*-inositol-1,2-cyclic phosphate.

RGL1130 1'-D-6-*O*-(2'-amino-4'-*O*-phosphate-2'-deoxy-α-D-glucopyranosyl)-*myo*-inositol-1,2-cyclic phosphate.
1'-D-6-*O*-(2'-amino-6'-*O*-phosphate-2'-deoxy-α-D-glucopyranosyl)-*myo*-inositol-1,2-cyclic phosphate.

In a further aspect, the present invention provides methods for making the compounds of the invention or their intermediates as set out in the following experimental description and the schemes. In a further related aspect, the present invention further relates to compounds which are the novel intermediates described herein.

In a further aspect, the present invention provides one or more of the above compounds for use in a method of medical treatment. The compounds may be useful as IPG mimetics or IPG antagonists, e.g. as competitive antagonists.

In a further aspect, the present invention provides the use of one or more of the above compounds for the preparation of a medicament for the treatment of a condition ameliorated by the administration of an inositol phosphoglycan (IPG) second messenger or an IPG antagonist. Examples of such conditions are set out in the pharmaceutical uses section below.

In a further aspect, the present invention provides a method of treating a condition in a mammal ameliorated by an inositol phosphoglycan (IPG) second messenger or an IPG antagonist, the method comprising administering to the mammal a therapeutically effective amount of one or more of the above compounds.

Embodiments of the invention will now be described by way of example and not limitation with reference to the accompanying drawings.

Brief Description of the Figures

Scheme 1 shows the coupling of diol **2** with trichloroacetimidate **1** resulting in 6-*O*-glycosylation. Subsequent manipulation of protective groups afforded compound **4**.

Scheme 2 shows the production of compounds RGL1023 and RGL1027 from intermediate **4**.

Scheme 3 shows the production of compound RGL1029 by coupling acceptor **2** with trichloroacetimidate **11**.

Scheme 4 describes the preparation of RGL1019.

Scheme 5 describes the preparation of the precursors for RGL1017 and RGL1018, which are shown in Scheme 6.

Scheme 7 shows the synthesis of building block **7** by bis-protection of the trans-diequatorially oriented hydroxyl groups of D-pinitol (**5**) as cyclohexane 1,2-diacetal and the cis-oriented hydroxyl groups as isopropylidene acetal.

Scheme 8 shows the glycosylation of D-pinitol building block **7** with the 2-azido-2-deoxy-D-glucopyranosyl trichloroacetimidate **8** to give the IPG-like compounds **1** and **2**.

Scheme 9 shows the glycosylation of D-pinitol building block **7** with the 2-azido-2-deoxy-D-galactopyranosyl trichloroacetimidate **13** to give the IPG-like compounds **3** and **4**.

Scheme 10 shows the synthesis of RGL1105.

Scheme 11 shows the synthesis of RGL1115 and RGL1116

Scheme 12 shows the synthesis of RGL1117.

Scheme 13 shows the synthesis of RGL1124.

Scheme 14 shows the synthesis of RGL1125.

Scheme 15 shows the synthesis of RGL1126.

Scheme 16 shows the synthesis of RGL1119.

Scheme 17 shows the synthesis of RGL1134.

Scheme 18 shows the synthesis of RGL1135.

Scheme 19 shows the synthesis of RGL1133.

Scheme 20 show the synthesis of RGL1130.

Figure 1 shows a graph of basal lipogenesis stimulation of exemplary compounds of the invention.

Figure 2 shows a graph of glucose stimulated lipogenesis stimulation of exemplary compounds of the invention.

Figure 3 shows a graph of the PKA inhibition of exemplary compounds of the invention.

Figure 4 shows the results of a G6Pase inhibition assay testing the effect of compound RGL1133 against a known inhibitor, sodium O-vanadate.

Detailed Description

Inositol phosphoglycans (IPGs)

IPG-A mediators modulate the activity of a number of insulin-dependent enzymes such as cAMP dependent protein kinase (inhibits), adenylate cyclase (inhibits) and cAMP phospho-diesterases (stimulates). In contrast, IPG-P mediators modulate the activity of insulin-dependent enzymes such as pyruvate dehydrogenase phosphatase (stimulates) and glycogen synthase phosphatase (stimulates). The A-type mediators mimic the lipogenic activity of insulin on adipocytes, whereas the P-type mediators mimic the glycogenic activity of insulin on muscle. Both A-and P-type mediators are mitogenic when added to fibroblasts in serum free media. The ability of the mediators to stimulate fibroblast proliferation is enhanced if the cells are transfected with the EGF-receptor. A-type mediators can stimulate cell proliferation in the chick cochleovestibular ganglia.

Soluble IPG fractions having A-type and P-type activity have been obtained from a variety of animal tissues including rat tissues (liver, kidney, muscle, brain, adipose, heart) and bovine liver. IPG-A and IPG-P biological activity has also been detected in human liver and placenta, malaria parasitized RBC and mycobacteria. The ability of an anti-inositolglycan antibody to inhibit insulin action on human placental cytotrophoblasts and BC3H1 myocytes or bovine-derived IPG action on rat diaphragm and chick cochleovestibular ganglia suggests cross-species conservation of many structural features. However, it is important to note that although the prior art includes these reports of IPG-A and IPG-P activity in some biological fractions, the purification or characterisation of the agents responsible for the activity is not disclosed.

IPG-A substances are cyclitol-containing carbohydrates, also containing Zn^{2+} ions and phosphate and having the properties of regulating lipogenic activity and inhibiting cAMP dependent protein kinase. They may also inhibit adenylate cyclase, be

mitogenic when added to EGF-transfected fibroblasts in serum free medium, and stimulate lipogenesis in adipocytes.

IPG-P substances are cyclitol-containing carbohydrates, also containing Mn^{2+} and/or Zn^{2+} ions and phosphate and having the properties of regulating glycogen metabolism and activating pyruvate dehydrogenase phosphatase. They may also stimulate the activity of glycogen synthase phosphatase, be mitogenic when added to fibroblasts in serum free medium, and stimulate pyruvate dehydrogenase phosphatase.

Methods for obtaining A-type and P-type mediators are set out in Caro et al, 1997, and in WO98/11116 and WO98/11117. Protocols for determining characteristic IPG biological activities such as PDH activation, PKA inhibition, acetylCoA activation, fructose-1,6-bis-phosphatase activity and lipogenesis are well known in the art or provided in the experimental section below.

Drug Formulation

The compounds of the invention may be derivatised in various ways. As used herein "derivatives" of the compounds includes salts, coordination complexes with metal ions such as Mn^{2+} and Zn^{2+}, esters such as *in vivo* hydrolysable esters, free acids or bases, hydrates, prodrugs or lipids, coupling partners.

Salts of the compounds of the invention are preferably physiologically well tolerated and non toxic. Many examples of salts are known to those skilled in the art. Compounds having acidic groups, such as phosphates or sulfates, can form salts with alkaline or alkaline earth metals such as Na, K, Mg and Ca, and with organic amines such as triethylamine and Tris (2-hydroxyethyl)amine. Salts can be formed between compounds with basic groups, e.g. amines, with inorganic acids such as hydrochloric acid, phosphoric acid or sulfuric acid, or organic acids such as acetic acid, citric acid, benzoic acid, fumaric acid, or tartaric acid. Compounds having both acidic and basic groups can form internal salts.

Esters can be formed between hydroxyl or carboxylic acid groups present in the compound and an appropriate carboxylic acid or alcohol reaction partner, using techniques well known in the art.

Derivatives which as prodrugs of the compounds are convertible *in vivo* or *in vitro* into one of the parent compounds. Typically, at least one of the biological activities of compound will be reduced in the prodrug form of the compound, and can be activated by conversion of the prodrug to release the compound or a metabolite of it. An example of prodrugs are glycolipid derivatives in which one or more lipid moieties are provided as substituents on the sugar residue or the cyclitol moieties, leading to the release of the free form of the compound by cleavage with a phospholipase enzyme. Examples of prodrugs include the use of protecting groups which may be removed *in situ* releasing active compound or serve to inhibit clearance of the drug *in vivo*. Protecting groups are well known in the art and are discussed further below. An example of a suitable protecting group that might be used as a prodrug is the azido group used in the synthesis below, e.g. on the 2-position of the sugar moiety.

Other derivatives include coupling partners of the compounds in which the compounds is linked to a coupling partner, e.g. by being chemically coupled to the compound or physically associated with it. Examples of coupling partners include a label or reporter molecule, a supporting substrate, a carrier or transport molecule, an effector, a drug, an antibody or an inhibitor. Coupling partners can be covalently linked to compounds of the invention via an appropriate functional group on the compound such as a hydroxyl group, a carboxyl group or an amino group. Other derivatives include formulating the compounds with liposomes.

Pharmaceutical Compositions

The compounds described herein or their derivatives can be formulated in pharmaceutical compositions, and administered to patients in a variety of forms, in

particular to treat conditions which are ameliorated by the administration of inositol phosphoglycan second messengers or IPG antagonists such as competitive antagonist.

Pharmaceutical compositions for oral administration may be in tablet, capsule, powder or liquid form. A tablet may include a solid carrier such as gelatin or an adjuvant or an inert diluent. Liquid pharmaceutical compositions generally include a liquid carrier such as water, petroleum, animal or vegetable oils, mineral oil or synthetic oil. Physiological saline solution, or glycols such as ethylene glycol, propylene glycol or polyethylene glycol may be included. Such compositions and preparations generally contain at least 0.1wt% of the compound.

Parental administration includes administration by the following routes: intravenous, cutaneous or subcutaneous, nasal, intramuscular, intraocular, transepithelial, intraperitoneal and topical (including dermal, ocular, rectal, nasal, inhalation and aerosol), and rectal systemic routes. For intravenous, cutaneous or subcutaneous injection, or injection at the site of affliction, the active ingredient will be in the form of a parenterally acceptable aqueous solution which is pyrogen-free and has suitable pH, isotonicity and stability. Those of relevant skill in the art are well able to prepare suitable solutions using, for example, solutions of the compounds or a derivative thereof, e.g. in physiological saline, a dispersion prepared with glycerol, liquid polyethylene glycol or oils.

In addition to one or more of the compounds, optionally in combination with other active ingredient, the compositions can comprise one or more of a pharmaceutically acceptable excipient, carrier, buffer, stabiliser, isotonicizing agent, preservative or anti-oxidant or other materials well known to those skilled in the art. Such materials should be non-toxic and should not interfere with the efficacy of the active ingredient. The precise nature of the carrier or other material may depend on the route of administration, e.g. orally or parentally.

Liquid pharmaceutical compositions are typically formulated to have a pH between about 3.0 and 9.0, more preferably between about 4.5 and 8.5 and still more preferably between about 5.0 and 8.0. The pH of a composition can be maintained by the use of a buffer such as acetate, citrate, phosphate, succinate, Tris or histidine, typically employed in the range from about 1 mM to 50 mM. The pH of compositions can otherwise be adjusted by using physiologically acceptable acids or bases.

Preservatives are generally included in pharmaceutical compositions to retard microbial growth, extending the shelf life of the compositions and allowing multiple use packaging. Examples of preservatives include phenol, meta-cresol, benzyl alcohol, para-hydroxybenzoic acid and its esters, methyl paraben, propyl paraben, benzalconium chloride and benzethonium chloride. Preservatives are typically employed in the range of about 0.1 to 1.0 % (w/v).

Preferably, the pharmaceutically compositions are given to an individual in a "prophylactically effective amount" or a "therapeutically effective amount" (as the case may be, although prophylaxis may be considered therapy), this being sufficient to show benefit to the individual. Typically, this will be to cause a therapeutically useful activity providing benefit to the individual. The actual amount of the compounds administered, and rate and time-course of administration, will depend on the nature and severity of the condition being treated. Prescription of treatment, e.g. decisions on dosage etc, is within the responsibility of general practitioners and other medical doctors, and typically takes account of the disorder to be treated, the condition of the individual patient, the site of delivery, the method of administration and other factors known to practitioners. Examples of the techniques and protocols mentioned above can be found in Remington's Pharmaceutical Sciences, 16th edition, Osol, A. (ed), 1980. By way of example, and the compositions are preferably administered to patients in dosages of between about 0.01 and 100mg of active compound per kg of body weight, and more preferably between about 0.5 and 10mg/kg of body weight .

The composition may further comprise one or more other pharmaceutically active agents, either further compounds of the invention, inositol phosphoglycans, growth factors such as insulin, NGF or other growth factors listed below, or other drugs, e.g. those in use for the treatment of diabetes or other conditions set out below.

Medical Uses

As set out above, IPGs are second messengers for a range of different growth factors, including insulin, nerve growth factor, hepatocyte growth factor, endothelial growth factor, insulin-like growth factor I (IGF-I), fibroblast growth factor, transforming growth factor β, the action of IL-2 on B-cells and T-cells, ACTH signalling of adrenocortical cells, IgE, FSH and hCG stimulation of granulosa cells, thyrotropin stimulation of thyroid cells, cell proliferation in the early developing ear and rat mammary gland. Consequently, IPGs or their antagonists can be used in the treatment or amelioration of disorders mediated by the growth factors or to mimic specific growth factor biological activities.

Examples of conditions which can be treated using IPGs or IPG antagonists include, diabetes, obesity, dyslipidaemia, pre-eclampsia, neurotrophic disorders, hepatic damage and adrenal atrophy.

WO98/10791 discloses that pre-eclampsia is characterised by elevated levels of IPG-P and that it can be treated using an IPG-P antagonist. Compounds of the invention which are IPG-P antagonists, e.g. antagonists which compete with wild-type IPG-P but lack one or more of its activities, could be used in the treatment of pre-eclampsia.

The use of both IPG-P and IPG-A and IPG-A antagonists in the diagnosis and treatment of diabetes is disclosed in WO98/11435. This application discloses that in some forms of diabetes the ratio of P:A-type IPGs is imbalanced and can be corrected by administering a medicament containing an appropriate ratio of IPG-P, IPG-A or antagonist(s) thereof. In particular, it describes the treatment of obese type II diabetes

(NIDDM) patients with a P-type IPG and/or an A-type IPG antagonist and the treatment of IDDM or lean type II diabetes (body mass index < 27) with a mixture of P- and A-type IPGs, typically in a P:A ratio of about 6:1 for males and 4:1 for females. The compounds and compositions of the present invention can be employed in such types of treatment. More particularly, the compounds are likely to be of use in the treatment of various form of diabetes and diabetic complications including diabetes due to insulin resistance, insulin resistance in type I diabetes and brittle diabetes, obese or lean type II diabetes, and of conditions associated with insulin resistance or insulin underproduction, such as neurotrophic disorders or polycystic ovary syndrome, lipodystrophy, age-related memory loss, and post-ischaemic damage secondary to stroke or post-transplant complications.

The compounds of this invention are also likely to be of use in controlling neuron proliferation or neurite outgrowth, either *in vitro* or *in vivo*, e.g. acting as a nerve or neurite growth factor mimetic second messenger. They may thus have applications in the treatment and/or diagnosis of any condition related to neuron proliferation or neurite differentiation. WO99/38516 discloses that IPG-A and synthetic mimetics thereof cause neuron proliferation, mimicking the action of the growth factor IGF-I. In contrast, IPG-P and synthetic mimetics thereof such as compound C4 cause neurite outgrowth. The neurons may be central (brain and spinal cord) neurons, peripheral (sympathetic, parasympathetic, sensory and enteric) neurons, e.g. the compounds used in the regeneration of peripheral nerves, or motor neurons. Treatments may involve the treatment of damage to nerve, spinal cord or central nervous system damage secondary to trauma, or autoimmune or metabolic damage, or post-ischaemic damage secondary to stroke or post-transplant complications, motor neuron disease, neurodegenerative disorders or neuropathy. Damage to the nervous system includes the results of trauma, stroke, surgery, infection (e.g. by viral agents), ischemia, metabolic disease, toxic agents, or a combination of these or similar causes. Motor neuron disease includes conditions involving spinal muscular atrophy, paralysis or amyotrophic lateral sclerosis. Neurodegenerative disorders include Parkinson's

disease, Alzheimer's disease, epilepsy, multiple sclerosis, Huntingdon's chorea and Meniere's disease.

The compounds of the invention may also be useful as hepatocyte growth factor mimetic second messengers, e.g. in the preparation of medicaments for the treatment of hepatic damage caused by infection, alcohol abuse, drug sensitivity, or autoimmunity. The compounds may also be useful as fibroblast growth factor mimetic second messengers or epidermal growth factor mimetic second messengers, e.g. in the preparation of medicaments for the promotion of wound healing following surgery or trauma or tissue damage induced by ischaemia or autoimmunity.

In other embodiments, the compounds of the invention may be useful as adrenal cell growth factor mimetic second messengers or ACTH mimetic second messengers in the preparation of a medicament for the treatment of disease states involving adrenal atrophy.

The compounds of the invention can readily be tested using the assays identified herein to determine their suitability for some or all of the medical uses described above. Thus, even compounds with a relatively low activity in one of the enzymes assays disclosed herein, may be useful by virtue of possessing a different activity, and moreover the pattern of activities can be used to rapidly screen the compounds for suitability in the various medical applications disclosed herein.

Activity	Diabetes I	Diabetes II	Obesity	Alzheimer's	Neurotrophics
PDH Kinase	Inhibit	Inhibit	No Effect	Inhibit	No effect
PDH Phosphatase	Activate	Activate	No effect	No effect	No effect
Acetyl CoA carboxylase I *	Activate	No effect	No effect	No effect	No effect

* found in liver and adipose cytosol.

Methods of Making the Compounds

Based on the disclosure herein, the knowledge in the art and in references [5-11], the skilled person could couple sugar residues and cyclitols together, optionally with one or more substituents. Examples of further compounds of the invention made by analogous syntheses include RGL1115, RGL1121, RGL1120, RGL1129, RGL1122, RGL1116 and RGL1117.

Useful guidance on the synthesis of the exemplified compounds and for introducing the substituents set out herein is provided by the papers by Gigg & Gigg, Khiar & Martin-Lomas [5] and Baeschlin et al [18] and the references cited therein.

Phosphoryl groups such as phosphate, cyclic phosphate or substituted phosphate or cyclic phosphate can be substituted into the compounds of the invention by the phosphate or phosphoramidite method, Bannwath et al, *Helvetica Chemica Acta*, 70:175-186, 1987 and Yu & Fraser-Reid, *Tetrahedron Lett.*, 29:979-982, 1988.

Phosphate protecting groups can also be synthesized according to the methods disclosed in Hoeben-Weyl, Methods of Organic Chemistry, volume 12/1 or 12/2, Teilheimer, Synthetic Methods of Organic Chemistry, Vol 45. Protecting groups for

the OH of sugars include menthoxycarbonyl (MntCO), acetal (in particular, two R groups may together represent a bridging acetal such as *O*-cyclohexylidene, *O*-isopropylidene or *O*-benzylidene), *tert*-butyldimethylsilyl (TBDMS), benzyl (Bn), *tert*-butyldiphenylsilyl (TBDPS). Many protecting groups suitable for use in the syntheses and reactions of saccharides are known and are well documented in standard reference works. The choice depends in part on the route by which the compound is synthesised and/or on the uses to which it is to be put, including the reactions which it is subsequently intended to undergo.

Bioactivity Assays

The compounds of the invention can be tested for one or more the characteristic IPG-P and/or IPG-A activities mentioned above to determine whether they will be suitable for use a IPG mimetics or antagonists. Preferred assays measure the effect of the compounds on PDH phosphatase, PKA or lipogenesis. Protocols for these assays are provided in Caro et al [14]. The compounds can also be tested to determine whether they activate or inhibit other enzymes involved in insulin signalling mechanism, such as glucose-6-phosphatase.

Examples

General Methods.

All reactions were run under an atmosphere of dry argon using oven-dried glassware and freshly distilled and dried solvents. THF and diethyl ether were distilled from sodium benzophenone ketyl. Dichloromethane and acetonitrile were distilled from calcium hydride. TLC was performed on Silica gel GF_{254} (Merck) with detection by charring with phosphomolibdic acid/EtOH. For flash chromatography, Silica Gel (Merck 230-400 mesh) was used. Columns were eluted with positive air pressure. Chromatographic eluents are given as volume to volume ratios (v/v). Routine NMR spectra were recorded with Bruker Avance DPX300 (^{1}H, 300 MHz), Bruker Avance DRX400 (^{1}H, 400 MHz), and Bruker Avance DRX500 (^{1}H, 500 MHz) spectrometers. Chemical shifts are reported in ppm, and coupling constants are reported in Hz.

Spectra were referenced to the residual proton or carbon signals of the solvent. High-resolution mass spectra were recorded on a Kratos MS-80RFA 241-MC apparatus. Optical rotations were determined with a Perkin-Elmer 341 polarimeter. Elemental analyses were performed using a Leco CHNS-932 apparatus. The organic extracts were dried over anhydrous sodium sulfate and concentrated in vacuo.

***Myo*-inositol containing compounds**

The synthesis of compounds RGL 1023, 1027 and 1029 involved the preparation of a glycosyl acceptor with position 6 free for reaction with the corresponding glycosyl donor. Diol **2** was chosen as the *myo*-inositol acceptor [17] as it can be regioselectively glycosylated at position 6. Regio- and stereoselective glycosylation of diol **2** is most conveniently performed using the trichloroacetimidate procedure with 2-azido-2-deoxy glycosyl donors bearing protective group patterns compatible with the further transforamtions required and designed as to provide an acceptable reactivity-selectivity balance in the forthcoming glycosylation reaction. Thus, use of trichloroacetimidate **1** was the glycosyl donor of choice. Coupling of **1** with **2** in diethyl ether at -20°C using TMS triflate as promoter resulted in 6-*O*-glycosylation with good yield. Manipulation of protective groups afforded compound 4, a key intermediate for compounds RGL 1023 and RGL 1027 (Scheme 1). Selective opening of the benzylidene protecting group on positions 4' and 6' of the hexosamine residue afforded **5** and **6** in good yields. These compounds, precursors of phosphorylated species RGL 1023 and RGL 1027, were subjected to treatment with phosphorylating reagent dibenzyloxi(diisopropylamino)phosphine, which afforded the corresponding phosphite derivatives. Oxidation to the phosphate form was achieved *in situ* by reaction with MPBCA in dichloromethane at room temperature for two hours with good yield. Trifluoracetic acid treatment of compounds **7** and **8** in dichloromethane at room temperature for 4 hours afforded diols **9** and **10** with moderate to good yields. Compounds RGL1023 and RGL1027 were obtained after hydrogenolytic debenzylation and concomitant azide reduction of **9** and **10** in buffered medium (Scheme 2).

Synthesis of compound RGL1029 required that the glycosyl donor to be used contained a protecting group in position 3 different from a benzyl group, to be introduced later on in the glycosyl acceptor residue. Thus, trichloroacetimidate **11**, bearing a *p*-methoxy-benzyl group in position 3 was used. Coupling with acceptor **2** in the conditions described above afforded compound **12** in good yield. Trifluoracetic acid hydrolysis and subsequent treatment with benzyl chloride in the presence of NaH in DMF afforded the benzylated derivative **13**, which afforded precursor **14** in good yield after oxidative cleavage of the *p*-methoxy-benzyl group with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in dichloromethane.

Treatment of compound **14** with dibenzyl(diisopropyl)phosphoramidite followed by oxidation of the phosphite group afforded compound 15 (75%). Deprotection of the ketal group on the inositol moiety was achieved by acid hydrolysis to yield compound **16** (65%), which was then subjected to catalytic hydrogenolysis to produce RGL1029 quantitatively.

1'-D-6-*O*-(2'-azido-3'-*O*-benzyl-4',6'-*O*-benzylidene-2'-deoxy-α-D-glucopyranosyl)-1,2-*O*-(L-1,7,7-trimethyl[2.2.1]-bicyclohept-2-ylidene)-3,4-*O*-(1,1,3,3-tetraisopropyldisiloxanyl)-*myo*-inositol (3)

To a solution of trichloroacetimidate 2-azido-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-D-glucopyranoside **1** (1.698 g, 3.217 mmol) and 1-D-1,2-*O*-(L-1,7,7-trimethyl[2.2.1]-bicyclohept-2-ylidene)-3,4-*O*-(1,1,3,3-tetraisopropyldisiloxanyl)-*myo*-inositol **2** (2.51 g, 4.507 mmol) in Et_2O (50 mL) at -20°C, trimethylsilyl trifluromethanesulfonate (29 ml, 0.160 mmol) was added. The mixture was warmed to room temperature over 5 h, quenched by addition of Et_3N (0.5 mL), filtered through celite and concentrated. The residue was purified by flash chromatography (Hexane/EtOAc 95/5 to 75/25) to give three disaccharides : α(1→6) **3** as a white solid (55% yield).

1'-D-6-*O*-(2'-azido-3'-*O*-benzyl-4',6'-*O*-benzylidene-2'-deoxy-α-D-glucopyranosyl)-1,2-*O*-(L-1,7,7-trimethyl[2.2.1]-bicyclohept-2-ylidene)-3,4,5-tri-*O*-benzyl-*myo*-inositol (4)

To a solution of disaccharide α(1→6) **3** (1.60 g, 1.735 mmol) in THF (20 mL) at 0°C, tetrabutyl ammonium fluoride was added (1 M solution in THF, 3.81 mL). After 15 min the solution was concentrated and the residue re-dissolved in DMF (15 mL). The solution was cooled to 0°C and 60 % sodium hydride in mineral oil (312 mg, 7.801 mmol) and benzyl bromide (0.93 mL, 7.801 mmol) was added. After 2 h methanol was added. The mixture was diluted with CH_2Cl_2 (100mL), washed with sat. NaCl (2x100 mL), dried over $MgSO_4$ and concentrated. Flash chromatography of the crude (hexane/AcOEt 95/5) gave product **4** (1.410 g, 1.484 mmol, 85% over two steps).

1'-D-6-*O*-(2'-azido-3',6'-di-*O*-benzyl-2'-deoxy-α-D-glucopyranosyl)-1,2-*O*-(L-1,7,7-trimethyl[2.2.1]-bicyclohept-2-ylidene)-3,4,5-tri-*O*-benzyl-*myo*-inositol (5)

To a solution of disaccharide **4** (1.363 g, 1.431 mmol) in THF (40 mL) sodium cyanoborohydride (1M solution in THF, 21.5 mL) was added. After 15 min at r.t. hydrochloric acid (1M solution in ether) was added until evolution of hydrogen ceased. The mixture was stirred at r.t. for 2 h, diluted with CH_2Cl_2 (60 mL) and washed with sat. $NaHCO_3$ (2x100 mL). The aqueous layer was extracted with CH_2Cl_2 (2x50 mL) and the combined organic layer was dried over $MgSO_4$ and concentrated. Flash chromatography of the crude (hexane/AcOEt 9/1) gave the compound **5** (1.0 g, 1.050 mmol, 73 %).

1'-D-6-*O*-(2'-azido-3',4'-di-*O*-benzyl-2'-deoxy-α-D-glucopyranosyl)-1,2-*O*-(L-1,7,7-trimethyl[2.2.1]-bicyclohept-2-ylidene)-3,4,5-tri-*O*-benzyl-*myo*-inositol (6)

To a solution of disaccharide **4** (460 mg, 0.484 mmol) and borane-dimethylamine complex (115 mg, 1.952 mmol) in CH_2Cl_2 (40 mL) at 0°C, boron trifluoride diethyl etherate (254 mL, 1.963 mmol) was added dropwise. After 30 min, the stirring was continued at r.t. for 1 hour, and then the reaction quenched with sat. $NaHCO_3$ (15 mL). The crude material was diluted with CH_2Cl_2 (60 mL), washed with sat. NaCl

(3x100 mL), dried over $MgSO_4$ and concentrated. Flash chromatography of the crude (hexane/AcOEt 6/1) gave compound **6** (276 mg, 0.290 mmol, 60 %).

1'-D-6-*O*-(2'-azido-3',6'-di-*O*-benzyl-2'-deoxy-4'-dibenzyl-phosphate-α-D-glucopyranosyl)-1,2-*O*-(L-1,7,7-trimethyl[2.2.1]-bicyclohept-2-ylidene)-3,4,5-tri-*O*-benzyl-*myo*-inositol (7)

To a solution of disaccharide **5** (100 mg, 0.105 mmol) and 1-H-tetrazole (30 mg, 0.428 mmol) in anh. CH_2Cl_2 (10 mL) at 0°C, dibenzyl diisipropylphosphoramidite (141 mL, 0.420 mmol) was added dropwise. After the addition was completed, the icebath was removed and the solution stirred for 2 h 30 min. The mixture was cooled to -40°C and a solution of 70% 3-chloroperbenzoic acid (65 mg, 0.264 mmol) in CH_2Cl_2 (4 mL) was added. The mixture was stirred for 2 h 30 min, diluted with CH_2Cl_2 (30 mL), washed with sat. Na_2SO_3 (2x50 mL), sat. $NaHCO_3$ (2x50 mL) and sat. NaCl (2x50 mL), dried over $MgSO_4$ and concentrated. Flash chromatography of the crude mixture (hexane/AcOEt 4/1) gave compound **7** (100 mg, 0.082 mmol, 78%).

1'-D-6-*O*-(2'-azido-3',4'-di-*O*-benzyl-2'-deoxy-6'-dibenzyl-phosphate-α-D-glucopyranosyl)-1,2-*O*-(L-1,7,7-trimethyl[2.2.1]-bicyclohept-2-ylidene)-3,4,5-tri-*O*-benzyl-*myo*-inositol (8)

To a solution of disaccharide **6** (150 mg, 0.157 mmol) and 1-H-tetrazole (44 mg, 0.628 mmol) in CH_2Cl_2 (15 mL) at 0°C, dibenzyl diisipropylphosphoramidite (212 mL, 0.630 mmol) was added dropwise. After the addition was completed, the solution was stirred at r.t. for 3 h. The mixture was cooled to -40°C and a solution of 70% 3-chloroperbenzoic acid (97 mg, 0.393 mmol) in anh. CH_2Cl_2 (5 mL) was added. The mixture was stirred for 45 min, diluted with CH_2Cl_2 (30 mL), washed with sat. $NaHSO_3$ (2x50 mL), sat. $NaHCO_3$ (2x50 mL) and sat. NaCl (2x50 mL), dried over $MgSO_4$ and concentrated. Flash chromatography of the crude mixture (hexane/AcOEt 4/1) gave compound **8** (152 mg, 0.125 mmol, 80%).

1'-D-6-*O*-(2'-azido-3',6'-di-*O*-benzyl-2'-deoxy-4'-dibenzyl-phosphate-α-D-glucopyranosyl)-3,4,5-tri-*O*-benzyl-*myo*-inositol (9)

To a solution of disaccharide **7** (100 mg, 0.082 mmol) in CH_2Cl_2 (10 mL) H_2O (0.09 mL, 5 mmol), and trifluoroacetic acid (0.38 mL, 4.949 mmol) were added and the reaction stirred for 4 h at r.t. The mixture was then diluted with CH_2Cl_2 (40 mL), washed with sat. $NaHCO_3$ (2x50 mL), sat. NaCl (3x50 mL), dried over $MgSO_4$ and concentrated. Flash chromatography of the crude mixture(hexane/AcOEt 1/1 to 1/2 and finally AcOEt 100%) gave compound **9** (60 mg, 0.056 mmol, 68%).

1'-D-6-*O*-(2'-azido-3',4'-di-*O*-benzyl-2'-deoxy-6'-dibenzyl-phosphate-α-D-glucopyranosyl)-3,4,5-tri-*O*-benzyl-*myo*-inositol (10)

To a solution of disaccharide **8** (110 mg, 0.091 mmol) in CH_2Cl_2 (10 mL) H_2O (0.1 mL, 5.551 mmol), and trifluoroacetic acid (0.42 mL, 5.470 mmol) were added and the reaction stirred for 4 h at r.t. The mixture was then diluted with CH_2Cl_2 (40 mL), washed with sat. $NaHCO_3$ (2x50 mL), sat. NaCl (3x50 mL), dried over $MgSO_4$ and concentrated. Flash chromatography of the crude mixture (hexane/AcOEt 1/1 to 1/2 and finally AcOEt 100%) gave compound **10** (84 mg, 0.078 mmol, 86%) as a white solid.

1'-D-6-*O*-(2'-amino-2'-deoxy-4'-phosphate-α-D-glucopyranosyl)-*myo*-inositol (RGL1027)

To a suspension of disaccharide **9** (16 mg, 14.840 mmol) in EtOH (0.6 mL) 10% Pd/C (3.2 mg, 0.003 mmol) was added and the reaction stirred under hydrogen atmosphere at r.t. for 36 h. The solvent was evaporated, the crude suspended in H_2O dest., filtered through celite and the filtrate lyophilized to give **RGL1027** (4.6 mg, 10.919 mmol, 74%). ^{1}H-NMR (D_2O, 500 MHz): δ 5.25 (broad s, 1H, $H_{1'}$), 3.96 (m, 1H, $H_{4'}$), 3.91 (m, 2H, $H_{3'}$+H_2), 3.84 (m, 1H, $H_{5'}$), 3.82 (m, 1H, $H_{6'b}$), 3.61 (m, 3H, $H_{6'a}$+H_1+H_6), 3.52 (t, J= 8.85 Hz, 1H, H_4), 3.41 (broad d, J= 8.85 Hz, 1H, H_3), 3.27 (d, J = 8.85 Hz, 1H, H_5), 3.18 (m, 1H, $H_{2'}$). ^{13}C-NMR (D_2O, 500 MHz): d 97.40 ($C_{1'}$), 80.94 (C_6), 73.03

(C_5), 72.91 (C_4), 72.68 (C_2), 72.25 ($C_{5'}$), 72.08 (C_1), 71.99 ($C_{4'}$), 71.32 (C_3), 70.79 ($C_{3'}$), 60.36 ($C_{6'a}$+$C_{6'b}$), 55.07 ($C_{2'}$).

1'-D-6-*O*-(2'-amino-2'-deoxy-6'-phosphate-α-D-glucopyranosyl)-*myo*-inositol (RGL1023)

To a suspension of disaccharide **10** (16 mg, 14.840 mmol) in a mixture MeOH/H_2O/AcOH 9/1/0.1 (0.5 mL) 10% Pd/C (3.2 mg, 0.003 mmol) was added, and the reaction stirred under hydrogen atmosphere at r.t. for 18 h. The crude was filtered through celite with an aqueous wash and the filtrate lyophilized to give **RGL1023** (5.5 mg, 13.055 mmol, 88%). ^{1}H-NMR (D_2O, 500 MHz): δ 5.23 (broad s, 1H, $H_{1'}$), 4.00 (m, 1H, $H_{5'}$), 3.99 (m, 1H, $H_{6'a}$), 3.90 (broad s, 1H, H_2), 3.78 (m, 1H, $H_{6'b}$), 3.73 (broad t, J= 9.1 Hz, 1H, $H_{3'}$), 3.61 (m, 2H, H_1+H_6), 3.60 (m, 1H, $H_{4'}$), 3.53 (t, J = 9.1 Hz, 1H, H_4), 3.40 (dd, J_1= 2.3 Hz, J_2= 9.1 Hz, 1H, H_3), 3.26 (broad t, J= 8.9 Hz, 1H, H_5), 3.14 (m, 1H, $H_{2'}$). ^{13}C-NMR (D_2O, 500 MHz): d 97.49 ($C_{1'}$), 81.14 (C_6), 73.69 (C_5), 72.90 (C_4), 72.72 (C_2), 72.69 ($C_{5'}$), 72.0 (C_1), 71.27 (C_3), 69.19 ($C_{4'}$), 62.5 ($C_{6'a}$+$C_{6'b}$), 56.65 ($C_{3'}$), 55.0 ($C_{2'}$).

1'-D-6-*O*-(2'-azido-3'-*O*-(*para*)methoxybenzyl-4',6'-*O*-benzylidene-2'-deoxy-α-D-glucopyranosyl)-1,2-*O*-(L-1,7,7-trimethyl[2.2.1]-bicyclohept-2-ylidene)-3,4-*O*-(1,1,3,3-tetraisopropyldisiloxanyl)-*myo*-inositol (12)

To a solution of trichloroacetimidate 2-azido-3-*O*-(*para*)methoxybenzyl-4,6-*O*-benzylidene-2-deoxy-D-glucopyranoside **11** (166 mg, 0.298 mmol) and 1-D-1,2-*O*-(L-1,7,7-trimethyl[2.2.1]-bicyclohept-2-ylidene)-3,4-*O*-(1,1,3,3-tetraisopropyldisiloxanyl)-*myo*-inositol **2** (166 mg, 0.298 mmol) in Et_2O (3 mL) at r.t., trimethylsilyl trifluoromethanesulfonate (1 mL, 5.534 mmol) was added. After 20 minutes, the reaction was quenched by addition of Et_3N (0.1 mL), filtered through celite, concentrated and purified by flash chromatography (hexane/AcOEt 95/5) to give disaccharide **12** (171 mg, 0.180 mmol, 60%).

1'-D-6-*O*-(2'-azido-3'-*O*-*para*methoxybenzyl-4',6'-*O*-benzylidene-2'-deoxy-α-D-glucopyranosyl)-1,2-*O*-(L-1,7,7-trimethyl[2.2.1]-bicyclohept-2-ylidene)-3,4,5-tri-*O*-benzyl-*myo*-inositol (13)

To a solution of disaccharide **12** (120 mg, 0.126 mmol) in THF (1.5 mL) at 0°C, tetrabutylammonium fluoride (1 M solution in THF, 284 mL) was added. The solution was warmed up to r.t. over 1 hour and then concentrated. The residue was re-dissolved in DMF (2 mL), cooled to 0°C and 60% sodium hydride in mineral oil (23 mg, 0.575 mmol) and benzyl bromide (67 mL, 0.563 mmol) were added. After stirring at r.t. overnight under argon atmosphere, the excess of base was destroyed by addition of methanol, the mixture concentrated to dryness, diluted with CH_2Cl_2 (25 mL), washed with sat. NaCl (3x25 mL), dried over $MgSO_4$ and the solvent evaporated to dryness. Flash chromatography of the crude mixture (hexane/AcOEt 9:1) compound **13** (98 mg, 0.100 mmol, 79%).

1'-D-6-*O*-(2'-azido-4',6'-*O*-benzylidene-2'-deoxy-α-D-glucopyranosyl)-1,2-*O*-(L-1,7,7-trimethyl[2.2.1]-bicyclohept-2-ylidene)-3,4,5-tri-*O*-benzyl-*myo*-inositol (14)

To a solution of disaccharide **13** (120 mg, 0.122 mmol) in a CH_2Cl_2/H_2O 9/1 mixture (1.5 mL), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (35 mg, 0.154 mol) was added, and stirred for 30 min at r.t. The reaction was diluted with CH_2Cl_2 (25 mL), filtered over celite, washed with sat. $NaHCO_3$ (2x25 mL), sat. NaCl (25 mL), dried over Na_2SO_4 and concentrated. Flash chromatography of the crude mixture (hexane/AcOEt 6/1) gave dissaccharide **14** (87 mg, 0.101 mmol , 83%).

1'-D-6-*O*-(2'-azido-4',6'-*O*-benzylidene-3'-dibenzyl-phosphate-2'-deoxy-α-D-glucopyranosyl)-1,2-*O*-(L-1,7,7-trimethyl[2.2.1]-bicyclohept-2-ylidene)-3,4,5-tri-*O*-benzyl-*myo*-inositol (15)

To a solution of disaccharide **14** (70 mg, 0.081 mmol) and 1-H-tetrazole (23 mg, 0.328 mmol) in CH_2Cl_2 (7 mL) at 0°C, dibenzyl diisipropylphosphoramidite (110 mL, 0.327 mmol) was added dropwise. After the addition, the solution stirred for 3 h at r.t.. The mixture was then cooled to -40°C and a solution of 70% 3-chloroperbenzoic

acid (50 mg, 0.203 mmol) in CH_2Cl_2 (3 mL) was added. The mixture was stirred for 2 h 30 min, diluted with CH_2Cl_2 (40 mL), washed with sat. $NaHSO_3$ (2x50 mL), sat. $NaHCO_3$ (2x50 mL) and sat. NaCl (2x50 mL), dried over $MgSO_4$ and concentrated. Flash chromatography (hexane/AcOEt 4:1) gave compound **15** (68 mg, 0.061 mmol, 75%).

1'-D-6-*O*-(2'-azido-3'-dibenzyl-phosphate-2'-deoxy-α-D-glucopyranosyl)-3,4,5-tri-*O*-benzyl-*myo*-inositol (16)

To a solution of disaccharide **15** (30 mg, 0.027 mmol) in CH_2Cl_2 (3 mL), H_2O (0.06 mL, 3.330 mmol) and trifluoroacetic acid (249 mL, 3.243 mmol) were added, and the reaction stirred for 18 h at r.t. The mixture was then diluted with CH_2Cl_2 (25 mL), washed with sat. $NaHCO_3$ (2x25 mL), sat. NaCl (3x25 mL), dried over $MgSO_4$ and concentrated. Flash chromatography (hexane/AcOEt 1/3 to AcOEt 100% and finally AcOEt/MeOH 9/1) gave compound **16** (16 mg, 0.018 mmol, 67%).

1'-D-6-*O*-(2'-amino-2'-deoxy-3'-phosphate-α-D-glucopyranosyl)-*myo*-inositol (RGL1029)

To a suspension of disaccharide **16** (8 mg, 8.910 mmol) in a mixture MeOH/H_2O 4/1 (0.3 mL), 10% Pd/C (2.1 mg, 0.002 mmol) was added and stirred under hydrogen atmosphere at r.t. for 18 h. The MeOH was evaporated, the crude suspended in dest. H_2O, filtered through celite and the filtrate lyophilized to give **RGL1029** (3.6 mg, 8.545 mmol, 96%) as a white solid. ^{1}H-NMR (D_2O, 500 MHz): δ 5.30 (broad s, 1H, $H_{1'}$), 4.22 (broad s, 1H, $H_{3'}$), 3.97 (m, 1H, $H_{5'}$), 3.90 (broad s, 1H, H_2), 3.70 (m, 2H, $H_{6'a}$+$H_{6'b}$), 3.66 (broad d, 1H, H_1), 3.60 (broad t, J= 9.1 Hz, 1H, H_6), 3.54 (m, 1H, $H_{4'}$), 3.51 (t, J= 9.1 Hz, H, H_4), 3.41 (dd, J_1= 9.1 Hz, J_2= 4.1 Hz, 1H, H_3), 3.31 (t, J= 9.1 Hz, 1H, H_5), 3.25 (m, 1H, $H_{2'}$). ^{13}C-NMR (D_2O, 500 MHz): d 97.20 ($C_{1'}$), 80.88 (C_6), 73.42 ($C_{3'}$),72.88 (C_5), 72.82 (C_4), 72.76 (C_2), 72.0 ($C_{5'}$), 71.91 (C_1), 71.25 (C_3), 69.52 ($C_{4'}$), 60.25 ($C_{6'a}$+$C_{6'b}$), 54.59 ($C_{2'}$).

***Chiro*-inositol containing compounds**

Compound **3** was obtained when the glycosylation of **1** was carried out using a glycosyl donor such as **2** (Scheme 1). Deallylation of **3** using hydrogen activated [Ir(COD) $(Ph_2MeP)_2$] PF_6 catalytic isomerisation and subsequent NBS-H_2O promoted cleavage yielded **5** that was phosphorylated using the phosphoramidite procedure to give compound **6** in 87% yield. Hydrogenation of **6** in the presence of 10% palladium on charcoal gave **7 (RGL 1019)** in quantitative yield.

The synthesis of D-*chiro*-inositol containing IPG like compounds bearing more complex oligosaccharide structures was envisaged using the trichloroacetimidate derivative **8** (Scheme 2) as glycosyl donor. Using this glycosyl donor, building blocks were also prepared to be used for the synthesis of pseudodisaccharides **RGL 1017** and **RGL1018** (Scheme 3).

Glycosylation of **1** with **8** afforded an α/β mixture of pseudodisaccharides **9** and **10** in 70% overall yield (Scheme 2). These compounds were separated and treated as indicated in Scheme 3. Selective reductive opening of the benzylidene acetals in **9** and **10** with $NaBH_3CN$-HCl afforded the partially protected derivatives **11** and **12** respectively in good yield. Deallylation of **11** gave **13** that after catalytic hydrogenation gave **14** in quantitative yield. A similar route from **12** yielded **16 (RGL1018)** through **15**.

6-*O*-Allyl-1-*O*-(3,4,6-tri-*O*-benzyl-2-azido-2-deoxy-β-D-glucopyranosyl)-2,3,4,5-tetra-*O*-benzyl-D-*chiro*--inositol (3) and 6-*O*-allyl-1-*O*-(3,4,6-tri-*O*-benzyl-2-azido-2-deoxy-α-D-glucopyranosyl), 2,3,4,5-tetra-*O*-benzyl-D-*chiro*--inositol (4)

A mixture of compound **1** (73 mg, 0.125 mmol) and compound **2** (49 mg, 0.078 mmol) was coevaporated two times with toluene and then re-disolved in CH_2Cl_2 and treated with TMSOTf (0.1 M solution in CH_2Cl_2, 50 μL) at -25°C. After 30 min the reaction mixture was allowed to warm during 10 min., then quenched by addition of

Et_3N and evaporated to dryness. The residue was purified by column chromatography [Hexane AcOEt (7:3→3.1)] to give **4** (35 mg, 35%) and **3** (25 mg, 25%) as syrups. Data for **3**: ^1H NMR ($CDCl_3$, 500 MHz): δ 3.29-3.38 (m, 3H, H-2′, H-3′, H-5′), 3.55 (t, 1H, *J* 9.2 Hz, H-4′), 3.63 (d, 2H, H-6′a, H-6′b), 3.79-3.86 (m, 3H), 3.88-3.95 (m, 3H, A11), 4.00 (t, 1H, *J* 3.9, 3.1 Hz), 4.09-4.14 (m, 1H, A11), 4.45-4.55 (m, 4H, H-1′, CH_2Ph), 4.60-4.68 (m, 3H, CH_2Ph), 4.76-4.92 (m, 8H, CH_2Ph), 5.05-5.16 (m, 2H, A11), 5.73-5.81 (m, 1H, A11), 7.14-7.38 (m, 35H, arH). HRFABMS: Calcd. for $C_{64}H_{67}N_3O_{10}Na$ ($M+Na^+$) 1060.472416; Found 1060.476982. Anal. Calcd. for $C_{64}H_{67}N_3O_{10}$: C, 74.04; H, 6.50; N, 4.05. Found: C, 73.54; H, 6.88; N, 4.10.

1-*O*-(2-Azido-2-deoxy-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl)-2,3,4,5,-tetra-*O*-benzyl-D-*chiro*--inositol (5)

A solution of the indium catalyst in anhydrous THF (5.9×10^{-3} M solution, 173 μL) previously treated under a hydrogen atmosphere for 30 minutes was added over a solution of **3** (35 mg, 0.034 mmol) in anhydrous THF (0.4 mL). The mixture was stirred at roon temperature for 1h under Argon and then NBS (9 mg, 0.051 mmol) and distilled water (131 μL) were added and the mixture stirred again for 2h, treated with a saturated solution of sodium hydrogen carbonate (0.3 mL). The reaction mixture was then extracted with AcOEt (2 x 10 mL), washed with saturated sodium chloride solution (2 x 20 mL), dried over $Mg\,SO_4$ and evaporated to dryness. The residue was purified by column chromatography (Hex6- AcOEt 1→ Hex 4- AcOEt 1) to give pure **5** (30 mg, 88%) as a colourless oil. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.4-7.1 (m, 35H, ArH), 4.91-4.76 (m, 8H, AB System), 4.71-4.47 (m, 6H, AB System), 4.53 (d, *J*= 7.0 Hz, 1H, $H_{1'}$), 4.29 (broad t, *J*= 3.5 Hz, 1H, H_1), 4.22 (broad t, *J*= 3.4 Hz, 1H, H_6), 4.0 (t, *J*= 9.5 Hz, 1H, H_4), 3.92 (dd, J_1= 2.8 Hz, J_2= 9.9 Hz, 1H, H_5), 3.85 (dd, J_1= 3.1 Hz, J_2= 9.4 Hz, 1H, H_2), 3.76 (t, *J*= 9.4 Hz, 1H, H_3), 3.66 (m, 2H, $H_{6'a} + H_{6'b}$), 3.60 (m, 1H, $H_{4'}$), 3.35 (m, $H_{2'} + H_{3'}$), 3.31 (dt, J_1= 3.1 Hz, J_2= 9.8 Hz, 1H, $H_{5'}$), 2.44 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 139.04, 138.99, 138.92, 138.09, 137.95, 128.48, 128.47, 128.45, 128.44, 128.35, 128.30, 128.28, 128.17, 128.04, 127.95, 127.92, 127.88, 127.84, 127.76, 127.74, 127.44, 127.30, 102.95 ($C_{1'}$), 82.95, 81.70, 81.30,

80.26, 79.56, 77.52, 76.29, 75.83, 75.76, 75.54, 75.04, 74.90, 73.53, 73.35, 73.07, 68.96, 68.56, 66.81.

6-*O*-(2-Azido-2-deoxy-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl)-2,3,4,5-tetra-*O*-benzyl-1-*O*-(dibenzyloxyphosphoryl)-D-*chiro*--inositol (6)

A solution of **5** (16 mg, 0.016 mmol) in a 1:1 mixture of dichloromethane-acetonitrile (0.4 mL) was treated with *N*, *N*-diisopropyl phosphoramidite (12 μL, 0.036 mmol) and tetrazole (5.1 mg, 0.072 mmol). The mixture was stirred at room temperature for 1.5 hr. and then treated with *tert*-butyl hydroperoxide (30 μL) and the stirring continued for 1h. The solution was then evaporated to dryness and the residue was purified on column chromatography (Hex 7- AcOEt 2) to give **6** as colourless syrup (17.5 mg, 87%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.37-7.10 (m, 45H, ArH), 5.19 (ddd, J_1= 2.9 Hz, J_2= 4.1 Hz, J_3= 7.6 Hz, 1H, H_1), 4.73-4.93 (m, 12H, AB System), 4.66 (d, J= 12.0 Hz, 1H, AB System), 4.54 (m, 4H, AB System), 4.42 (d, 1H, AB System), 4.39 (d, J= 7.9 Hz, 1H, $H_{1'}$), 4.17 (broad t, J= 3.7 Hz, 1H, H_6), 3.92 (m, 2H, H_2 + H_4), 3.79 (dd, J_1= 3.0 Hz, J_2= 9.8 Hz, 1H, H_5), 3.73 (t, J= 9.6 Hz, 1H, H_3), 3.71 (m, 1H, $H_{6'b}$), 3.67 (m, 1H, $H_{3'}$), 3.64 (dd, J_1= 1.8 Hz, J_2= 11.0 Hz, 1H, $H_{6'a}$), 3.36-3.29 (m, 3H, $H_{2'}$ + $H_{4'}$ + $H_{5'}$). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 138.90, 138.64, 138.09, 138.04, 137.98, 137.95, 135.93, 128.59, 128.50, 128.47, 128.43, 128.40, 128.39, 128.37, 128.34, 128.33, 128.29, 128.27, 128.25, 128.20, 128.14, 128.01, 127.99, 127.92, 127.90, 127.84, 127.75, 127.69, 127.62, 127.57, 127.49, 127.46, 127.42, 127.36, 103.32 ($C_{1'}$), 82.81 ($C_{3'}$), 81.39, 80.92, 78.73, 78.21 (C_2, J_{cp}= 42 Hz), 76.03 (C_6, J_{cp}= 3.4 Hz), 75.76, 75.53, 75.07, 75.05, 74.10, 74.06 (C_1, J_{cp}= 5.9 Hz), 73.70, 72.99, 72.67, 69.50 ($POCH_2$ Ar, J_{cp}= 5.9 Hz), 69.11 ($POCH_2$ Ar, J_{cp}= 5.9 Hz), 68.61 ($C_{6'}$), 66.76 ($C_{2'}$). ^{31}P NMR ($CDCl_3$, 202 MHz): δ -2.31.

6-*O*-(2-Ammonio-2-deoxy-β-D-glucopyranosyl)-D-*chiro*--inositol-1-phosphate (7)

To a mixture of **6** (17.5 mg, 13.9 μm) in methanol (1.6 mL) and AcOH/AcONa buffer (1.6 mL) was added 10% Pd/C (21.5 mg). The mixture was stirred under hydrogen for 24h and then filtered over Celite, washed with a 1:1 mixture of EtOH/H_2O and

liophylized. The residue was purified on Sephadex G-10 (10% aqueous EtOH) to afford pure **7 (RGL 1019)** (5 mg, 100%). ^{1}H NMR (D_2O, 500 MHz): δ 4.66 (d, J= 8.2 Hz, 1H, $H_{1'}$), 4.58 (ddd, J_1= 3.0 Hz, J_2= 4.2 Hz, J_3= 8.5 Hz, 1H, H_1), 4.19 (t, J= 3.8 Hz, 1H, H_6), 3.93 (dd, J_1= 9.3 Hz, J_2= 3.3 Hz, 1H, H_5), 3.9 (dd, J_1= 12.7 Hz, J_2= 2.2 Hz, 1H, $H_{6'b}$), 3.71 (dd, J_1= 12.7 Hz, J_2= 5.7 Hz, 1H, $H_{6'a}$), 3.64 (m, 2H, H_2 + H_3), 3.54 (t, J= 9.4 Hz, 1H, H_4), 3.47 (ddd, J_1= 2.2 Hz, J_2= 5.6 Hz, J_3= 9.6 Hz, 1H, $H_{5'}$), 3.45 (t, J= 9.4 Hz, 1H, $H_{3'}$), 3.36 (t, J= 9.6 Hz, 1H, $H_{4'}$), 2.77 (dd, J_1= 9.4 Hz, J_2= 8.2 Hz, 1H, $H_{2'}$). ^{31}P NMR (D_2O, 202 MHz): δ 3.02.

1-*O*-(2-Azido-2-deoxy-3-*O*-benzyl-4,6-*O*-benzylidene-α- and-β-D-glucopyranosyl)-6-*O*-allyl-2,3,4,5-tetra-*O*-benzyl-D-*chiro*--inositol (9 and 10)

A mixture of **8** (520 mg, 0.985 mmol) and **1** (382 mg, 0.657 mmol) was dissolved in anhydrous CH_2Cl_2 (6.6 mL) and treated with a solution (2.50 μL) of trimethylsilyl triflate (80 μL) in CH_2Cl_2 (2 mL). The mixture was stirred at room temperature for 1.5 h and then 100 μL of the above solution of TMSOTf was added. After an additional hour with stirring (174 mg, 0.328 mmol) in CH_2Cl_2 (1.5 mL) was added and stirring was continued for 2h. The mixture was the treated with Et_3N, evaporated to dryness and the residue fractionated on column chromatography (Hexane 8: AcoEt 1) to yield **9** (130.5 mg, 49%) and **10** (302 mg, 21%). Data for **9**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.47-7.21 (m, 30H, ArH), 5.79 (ddt, J_1= 5.6 Hz, J_2= 10.5 Hz, J_3= 17.1 Hz, 1H, OCH_2CH=CH_2), 5.51 (s, 1H, CH benzyliden), 5.17 (dd, J_1= 1.5 Hz, J_2= 17.2 Hz, 1H, OCH_2CH=C*H*H), 5.13 (dd, J_1= 1.5 Hz, J_2= 10.4 Hz, 1H, OCH_2CH=CH*H*), 4.97-4.76 (m, 10H, AB System), 4.70 (d, J= 3.8 Hz, 1H, $H_{1'}$), 4.25-4.17 (m, 2H, $H_{5'}$ + O*C*HHCH=CH_2), 3.99 (t, J_1= 9.4 Hz, 1H, $H_{3'}$), 3.97 (m, 1H, O-CH-*H*-CH= CH_2), 3.95 (m, 1H, $H_{6'eq}$), 3.97-3.74 (m, 6H, ChiroIns), 3.64 (t, J_1= 9.3 Hz, 1H, $H_{4'}$), 3.56 (t, J= 10.3 Hz, 1H, $H_{6'ax}$), 3.49 (dd, J_1= 3.7 Hz, J_2= 9.8 Hz, 1H, $H_{2'}$). Data for **10**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.49-7.20 (m, 30H, ArH), 5.74 (ddt, J_1= 5.6 Hz, J_2= 10.4 Hz, J_3= 17.4 Hz, 1H, OCH_2CH= CH_2), 5.54 (s, 1H, CH benzyliden), 5.15 (broad dd, J_1= 17.4 Hz, J_2=1.5 Hz, 1H, OCH_2CH=C*H*H), 5.11 (broad dd, J_1= 10.4 Hz, J_2= 1.5 Hz, 1H, OCH_2CH= CH*H*), 4.49-4.78 (m, 7H, AB System), 4.72 (d, J= 11.7 Hz, 1H, AB

System), 4.62 (d, J= 11.7 Hz, 1H, AB System), 4.60 (d, J= 11.7 Hz, 1H, AB System), 4.54 (d, J= 8.1 Hz, 1H, $H_{1'}$), 4.21 (dd, J_1= 5.1 Hz, J_2= 10.4 Hz, 1H, $H_{6'eq}$), 4.13 (broad dd, J_1= 5.6 Hz, J_2= 13.0 Hz, 1H, OC*H*HCH=CH_2), 3.92-3.74 (m, 6H, ChiroIns), 3.7 (t, J= 10.3 Hz, 1H, $H_{6'ax}$), 3.61 (t, J= 9.3 Hz, 1H, $H_{4'}$), 3.46 (t, J= 9.4 Hz, 1H, $H_{3'}$), 3.28 (t, J= 8.3 Hz, 1H, $H_{2'}$), 3.23 (dt, J_1= 5.1 Hz, J_2= 9.8 Hz, 1H, $H_{5'}$).

1-*O*-(2-Azido-2-deoxy-3,6-di-*O*-benzyl-α-D-glucopyranosyl)-6-*O*-allyl-2,3,4,5-tetra-*O*-benzyl-D-*chiro*--inositol (11)

To a solution of **9** (716 mg, 0.757 mmol) in THF (19 mL) 4Å molecular sieves were added and the mixture stirred for 30 min. Then a 1M solution of sodium cyanoborohydride in THF (15 mL, 15.14 mmol) and a 1M solution of HCl in ether was added until the evolution of gas ceased. The mixture was then treated with saturated aqueous solution of $NaHCO_3$ and the organic layer washed with saturated NaCl, dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (Hexane 4: AcoEt 1) to give **11** (575 mg, 80%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.44-7.23 (m, 30H, Ar-H), 5.82 (ddt, J_1= 5.6 Hz, J_2= 10.4 Hz, J_3= 17.2 Hz, 1H, OCH_2CH=CH_2), 5.21 (broad dd, J_1= 1.6 Hz, J_2= 17.2 Hz, 1H, OCH_2CH=C*H*H), 5.16 (broad dd, J_1= 1.6 Hz, J_2= 10.4 Hz, 1H, OCH_2CH=C*H*H), 4.96-4.65 (m, 10H, AB System), 4.74 (d, J= 3.6 Hz, 1H, $H_{1'}$), 4.44 (d, J= 12.0 Hz, 1H, AB System), 4.32 (d, J= 12.1 Hz, 1H, AB System), 4.22 (broad, dd, J_1= 5.4 Hz, J_2= 13.0 Hz, 1H, OC*H*HCH=CH_2), 4.12 (m, 1H, $H_{5'}$), 4.0 (m, 1H, OCH*H*CH=CH_2), 4.04-3.78 (m, 6H, ChiroIns), 3.76 (m, 2H, $H_{3'}$ + +$H_{4'}$), 3.45 (dd, J_1= 3.6 Hz, J_2= 10.0 Hz, 1H, $H_{2'}$), 3.38 (dd, J_1= 3.5 Hz, J_2=10.4 Hz, 1H, $H_{6'b}$), 3.27(dd, J_1= 4.2 Hz, J_2= 10.4 Hz, 1H, $H_{6'a}$), 2.39 (d, J= 1.6Hz, 1H, $OH_{4'}$).

1-*O*-(2-Azido-2-deoxy-3,6-di-*O*-benzyl-β-D-glucopyranosyl)-6-*O*-allyl-2,3,4,5-tetra-*O*-benzyl-D-*chiro*--inositol (12)

A solution of **10** (290 mg, 0.307 mmol) in anhydrous THF (7.7 mL) was stirred with 4Å molecular sieves for 30 min. Then a 1M solution of sodium cyanoborohydride in THF (5.6 mL) and 1M solution of HCl in ether were added and the mixture stirred

until evolution of gas ceased. The mixture was then treated with saturated aqueous $NaHCO_3$ and the organic layer washed with saturated aqueous NaCl, dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (Hexane 5: AcoEt 1) to give pure **12** (39.2 mg, 95%). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.41-7.21 (m, 30H, Ar-H), 5.76 (ddt, J_1=5.6 Hz, J_2= 10.4 Hz, J_3= 17.2 Hz, 1H, OCH_2CH=CH_2), 5.12 (dd, J_1= 1.6 Hz, J_2= 17.2 Hz, 1H, OCH_2CH=CH*H*), 5.04 (broad dd, J_1= 1.6 Hz, J_2=10.3 Hz, 1H, OCH_2CH=C*H*H), 4.96-4.49 (m, 12H, AB System), 4.48 (d, J= 8.0 Hz, 1H, $H_{1'}$), 4.11 (broad, dd, J_1= 5.4 Hz, J_2=13.0 Hz, 1H, OCH*H*CH=CH_2), 3.99-3.78 (m, 6H, ChiroIns), 3.89 (m, 1H, OC*H*HCH=CH_2), 3.67 (dd, J_1= 4.0 Hz, J_2= 10.3 Hz, 1H, $H_{6'b}$), 3.62 (dd, J_1= 5.2 Hz, J_2= 10.3 Hz, 1H, $H_{6'a}$), 3.51 (dt, J_1= 2.3 Hz, J_2= 9.6 Hz, 1H, $H_{4'}$), 3.29 (m, 1H, $H_{5'}$), 3.25 (t, J=8.0 Hz, $H_{2'}$), 3.16 (t, J_1= 8.8 Hz, 1H, $H_{3'}$), 2.50 (d, J_1= 2.3 Hz, 1H, $OH_{4'}$).

1-*O*-(2-Azido-2-deoxy-3,6-di-*O*-benzyl-α-D-glucopyranosyl)-2,3,4,5-tetra-*O*-benzyl-D-*chiro*--inositol (13)

A solution of the iridium catalyst in anhydrous THF (5.8 x 10^{-13} M solution, 158 µl) previously treated under a hydrogen atmosphere for 30 minutes was added over a solution of **11** (29 mg, 0.030 mmol) in anhydrous THF (0.3 mL). The mixture was then stirred at room temperature for 45 minutes, and cooled to 0°C. NBS (7.7 mg, 0.043 mmol) and water (106 µL), and THF (1.75 mL) were added and the mixture was stirred for 15 min. and treated with a saturated solution of $NaHCO_3$. The mixture was extracted with CH_2Cl_2 and the organic layer dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (Hex 4: AcOEt 1→ Hex 3: AcOEt 1) to give pure **13** (22 mg, 79%). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.41-7.19 (m, 30 H, ArH), 4.94-4.66 (m, 10H, AB System), 4.78 (d, J= 3.6 Hz, 1H, $H_{1'}$), 4.37 (d, J= 12.0 Hz, 1H, AB System), 4.25 (d, J= 12.1 Hz, 1H, AB System), 4.14 (broad t, J= 3.4 Hz, 1H, H_6), 4.08 (m, 1H, $H_{5'}$), 4.04 (broad t, J= 3.6 Hz, 1H, H_1), 3.95 (dd, J_1= 3.2 Hz, J_2= 9.2 Hz, 1H, H_2), 3.86 (dd, J_1= 2.7 Hz, J_2= 9.5 Hz, 1H, H_5), 3.82 (t, J= 9.1 Hz, 1H, H_4), 3.77 (t, J= 9.1 Hz, 1H, H_3), 3.72 (m, 2H, $H_{3'}$ + $H_{4'}$), 3.42 (dd, J_1= 3.6 Hz, J_2=10.0 Hz, 1H, $H_{2'}$), 3.28 (dd, J_1= 3.4 Hz, J_2= 10.3 Hz, 1H, $H_{6'b}$), 3.18 (dd, J_1= 4.3

Hz, J_2=10.3 Hz, 1H, $H_{6'a}$), 2.5 (s, 1H, OH_1), 2.41 (s, 1H, $OH_{4'}$). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 138.83, 138.79, 138.53, 138.15, 138.10, 137.72, 128.57, 128.52, 128.42, 128.36, 128.34, 128.29, 128.19, 128.13, 128.10, 127.98, 127.96, 127.79, 127.71, 127.67, 127.52, 127.43, 127.36, 97.39 ($C_{1'}$), 81.74, 81.20, 80.00, 79.99, 78.38, 76.13, 75.76, 75.23, 73.52, 73.26, 72.99, 72.46, 70.03, 69.13, 67.25, 63.28.

1-*O*-(2-Azido-2-deoxy-3,6-di-*O*-benzyl-β-D-glucopyranosyl)-2,3,4,5-tetra-*O*-benzyl-D-*chiro*--inositol (15)

A solution of the iridium catalyst in anhydrous THF (5.8 x 10^{-3}, 178 µl) previously treated under a hydrogen atmosphere for 30 minutes was added over a solution **12** (32.7 mg, 0.034 mmol) in anhydrous THF (0.3 mL). The mixture was then stirred at room temperature for 45 minutes and cooled to 0 °C. NBS (8.8 mg, 0.049 mmol) water (120 µl) and THF (2 ml) were added and the mixture stirred for 15 min. The reaction mixture was treated with saturated solution of $NaHCO_3$, extracted with CH_2Cl_2 and the organic layer dried and evaporated. The residue was purified by column chromatography (Hex 4: AcOEt 1→ Hexane 3 AcOEt 1) to give pure **15** (22.5 mg, 72%). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.39-7.22 (m, 30 H, ArH), 4.93-4.50 (m, 12H, AB System), 4.53 (d, *J*= 8.1 Hz, 1H, $H_{1'}$), 4.19 (m, 2H, H_6 + H_1), 3.98 (t, *J*= 9.4 Hz, 1H, H_3), 3.90 (dd, J_1=2.6 Hz, J_2= 9.9 Hz, 1H, H_2), 3.80 (dd, J_1= 2.8 Hz, J_2= 9.4 Hz, 1H, H_5), 3.75 (t, *J*= 9.2 Hz, 1H, H_4), 3.65 (m, 2H, $H_{6'b}$ + $H_{6'a}$), 3.54 (dt, J_1= 2.2 Hz, J_2= 9.2 Hz, 1H, H_4), 3.28 (m, 2H, $H_{2'}$ + $H_{5'}$), 3.16 (t, *J*= 9.2 Hz, 1H, $H_{3'}$), 2.54 (d, *J*= 2.2 Hz, 1H, $OH_{4'}$), 2.43 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 139.02, 138.98, 138.93, 138.19, 138.09, 137.69, 128.64, 128.52, 128.44, 128.43, 128.35, 128.29, 128.27, 128.15, 128.12, 128.06, 127.90, 127.87, 127.86, 127.82, 127.67, 127.44, 127.42, 127.31, 102.98 (C_1'), 82.29, 81.69, 81.29, 80.21, 79.56, 76.36, 75.82, 75.76, 75.11, 73.89, 73.71, 73.38, 73.11, 71.68, 70.01, 69.02, 66.20.

6-*O*-(2-Amino-2-deoxy-α-D-glucopyranosyl)-D-*chiro*--inositol (14, RGL 1017)

To a solution of **13** (8 mg, 0.009 mmol) in methanol (2 mL) was added 10% Pd/C (28 mg) and a drop of acetic acid. The mixture was stirred under hydrogen atmosphere for

8 h and then filtered over Celite and liophylized. The residue was purified using a Dowex 50 H^+ resin using methanol, water and 1% ammonium hydroxide to obtain pure **14 (RGL1017)** (2.5 mg, 83%). ^1H NMR (D_2O, 500 MHz): δ 5.0 (d, *J*= 3.6 Hz, 1H, H_1'), 4.12 (t, *J*= 3.6 Hz, 1H, H_6), 4.01 (t, *J*= 3.6 Hz, 1H, H_1), 3.97 (ddd, J_1= 2.5 Hz, J_2= 4.5 Hz, J_3= 9.6 Hz, 1H, $H_{5'}$), 3.82 (dd, J_1= 3.6 Hz, J_2= 9.6 Hz, 1H, H_2), 3.80 (m, 1H, $H_{6'b}$), 3.76 (m, 1H, $H_{6'a}$), 3.70 (dd, J_1= 3.3 Hz, J_2= 9.5 Hz, 1H, H_5), 3.61 (t, *J*= 9.7 Hz, 1H, $H_{3'}$), 3.59 (t, *J*= 8.9 Hz, 1H, H_3), 3.55 (t, *J*= 8.4 Hz, 1H, H_4), 3.40 (t, *J*= 9.6 Hz, 1H, $H_{4'}$), 2.79 (dd, J_1= 9.7 Hz, J_2= 3.6 Hz, $H_{2'}$).

6-*O*-(2-Amino-2-deoxy-β-D-glucopyranosyl)-D-*chiro*--inositol (16, RGL 1018)

To a solution of **15** (4.5 mg, 0.004 mmol) in methanol (1.1 mL) 10% Pd/C (16 mg) and a drop of AcOH were added. The mixture was stirred for 8h under a hydrogen atmosphere and the filtered over Celite, washed with methanol and liophylized. The residue was purified over a Dowex 50 H^+ column using methanol, water and 1% ammonium hydroxide to give pure **16 (RGL 1018)** (1.6 mg, 100%). ^1H NMR (D_2O, 500 MHz): δ 4.57 (d, *J*= 8.2Hz, 1H, $H_{1'}$), 4.26 (t, *J*= 3.6 Hz, 1H, H_1), 4.06 (t, *J*= 3.6 Hz, 1H, H_6), 3.92 (dd, J_1= 2.3 Hz, J_2= 12.4 Hz, 1H, $H_{6'b}$), 3.84 (dd, J_1= 3.2 Hz, J_2= 9.7 Hz, 1H, H_5), 3.77 (dd, J_1= 3.2 Hz, J_2= 9.5 Hz, 1H, H_2), 3.74 (dd, J_1= 12.4 Hz, J_2= 5.6 Hz, 1H, $H_{6'a}$), 3.62 (t, *J*= 9.5 Hz, 1H, H_4), 3.57 (t, *J*= 9.5 Hz, 1H, H_3), 3.47 (m, 1H, $H_{5'}$), 3.41 (t, *J*=9.5 Hz, 1H, $H_{3'}$), 3.37 (t, *J*= 9.3 Hz, 1H, $H_{4'}$), 2.71 (t, *J*= 8.8 Hz, 1H, $H_{2'}$).

Pinitol containing compounds

The synthesis of compounds **1-4** involved the preparation of a glycosyl acceptor with position 6 differentiated to be reactive with the corresponding glycosyl donor. Protection of the pinitol unit as cyclohexane-1,2-diacetal as proposed by Ley [8] was attempted. The selectivity of the reaction of **5** with 1,1,2,2-tetramethoxycyclohexane arises from the stabilising influence of the four anomeric effects in the resulting acetal **6** and the equatorial arrangement of all four sterically demanding alkyl substituents of

the central 1,4-dioxane unit (Scheme 1). Treatment of **6** with 2,2-dimethoxypropane in the presence of TsOH gave **7** in 80% yield.

Glycosylation of **7** with 2-azido-2-deoxy-3,4,6-tri-*O*-benzyl-D-glucopyransol-trichloroacetimidate **8** [9] prepared following a well established procedure[10,6b], in dichloromethane and using TMSOTf as promoter [11] gave a 2:1 mixture of the α (**9**) and β (**10**) linked pseudodisaccharides in 54% yield (Scheme 2). The acetal groups were removed [12] to give **11** and **12** respectively which were subjected to hydrogenolysis to afford finally **1** and **2** in quantitative yield.

Glycosylation of **7** with 2-azido-2-deoxy-3,4,6-tri-*O*-benzyl-D-galactopyranose (**13**) under different conditions gave a mixture of α- and β-linked pseudodisaccharides **14** and **15** in moderate yield (Scheme 3). Removal of the acetal groups and subsequent hydrogenolysis afforded **3** and **4**.

4,5-*O*-(1',2'-dimethoxycyclohexane-1',2'-diyl)-3-O-methyl-D-*chiro*-inositol (6)

3-*O*-methyl-D-*chiro*-inositol (D-pinitol) (283 mg, 1.457 mmol, 1 equiv) was dissolved in methanol (15 mL), then 1,2-cyclohexane diacetal (507 mg, 2.458 mmol, 1.7 equiv), trimethyl orthoformiate (200 mL, 1.752 mmol, 1.2 equiv) and 1-(*S*)-(+)-10-camphorsulfonic acid (24 mg, 0.102 mmol, 0.07 equiv) were added. The reaction mixture was heated at 70°C for 24 h whereupon it was diluted with MeOH and quenched with solid $NaHCO_3$. The residue was concentrated and purified by flash chromatography (Hex/EtOAc 1:15) to give **6** (222 mg, 0.664 mmol, 45%; 89% based on 134 mg of recovered D-pinitol). R_f (Hex/EtOAc 1:20): 0.22; $[\alpha]^{20}_D$ –22.9 (c = 1.05, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): d = 4.12 (Ys, 1H, H_1), 4.10 (s, 2H, H_4, H_5), 4.07 (Ys, 1H, H_6), 3.81 (dt, 1H, $J_{2\text{-}3}$ = 9.0 Hz, $J_{2\text{-}1}$ = 3.6 Hz, $J_{2\text{-}OH}$ = 1.8 Hz, H_2), 3.47 (t, 1H, J = 9.0 Hz, H_3), 3.23 (s, 3H, OCH_3), 3.21 (s, 3H, OCH_3), 2.76 (d, 1H, $J_{OH\text{-}2}$ = 1.8 Hz, OH_2), 2.60 (s, 1H, OH_1), 2.56 (s, 1H, OH_6), 1.86-1.78 (m, 1H, CDA), 1.77-1.66 (m, 3H, CDA), 1.57-1.50 (m, 2H, CDA), 1.42-1.34 (m, 2H, CDA); ^{13}C-NMR ($CDCl_3$, 75 MHz); d = 98.9 (C), 98.0 (C), 80.2 (C_3), 71.5(C_2), 70.8, 70.4, 70.3 (C_1, C_4,

C_6), 68.7 (C_5), 61.1 (OCH_3), 47.0(OCH_3, CDA), 46.8 (OCH_3, CDA), 27.1 (CH_2), 27.0 (CH_2), 21.5 (CH_2), 21.4 (CH_2); HRFABMS Calcd. for $C_{15}H_{26}O_8$: 357.3571 found: 357.1528; MALDI-TOF Calcd. for $C_{15}H_{26}O_8$+Na^+: 357.4, found: 357.5, calcd. for $C_{15}H_{26}O_8$+K^+: 373.5, found: 374.1

4,5-*O*-(1',2'-dimethoxycyclohexane-1',2'-diyl)-3-*O*-methyl-1,2-*O*-isopropyliden-D-*chiro*-inositol (7)

4,5-*O*-(1',2'-dimethoxycyclohexane-1',2'-diyl)-3-*O*-methyl-D-*chiro*-inositol (**6**) (326 mg, 0.975 mmol, 1 equiv) and 2,2-dimethoxypropane (1,321 mL, 1.072 mmol, 1.1 equiv) in acetone (4 mL) were treated with *p*-toluenesulfonic acid monohydrate (9.3 mg, 0.049 mmol, 0.05 equiv). The reaction was stirred for 1h, whereupon it was quenched with solid $NaHCO_3$, the solvent evaporated and the residue purified by flash chromatography (Hex/AcOEt 1:1) to give **7** (292 mg, 0.873 mmol, 81%) as a white solid. R_f(Hex/EtOAc 3:1): 0.71; $[\alpha]^{20}_D$ -18.0 (c = 0.30, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): d = 4.27 (dd, 1H, J_{1-2} = 7.3 Hz, J_{1-6} = 3.2 Hz, H_1), 4.24 (t, 1H, J = 3.2 Hz, H_6), 4.16 (t, 1H, J = 7.3 Hz, H_2), 4.06 (t, 1H, J = 10.2 Hz, H_4), 3.94 (dd, 1H, J_{5-4} = 10.2 Hz, J_{5-6} = 3.2 Hz, H_5), 3.61 (s, 3H, OCH_3), 3.39 (dd, 1H, J_{3-4} = 10.2 Hz, J_{3-2} = 7.3 Hz, H_3), 3.23 (s, 3H, OCH_3, CDA), 3.22 (s, 3H, OCH_3, CDA), 1.86-1.78 (m, 1H, CDA), 1.77-1.66 (m, 3H, CDA),1.52 (s, 3H, CH_3), 1.57-1.51 (m, 2H, CDA), 1.36 (s, 3H, CH_3),1.41-1.33 (m, 2H, CDA); ^{13}C-NMR ($CDCl_3$, 125 MHz): d = 109.0 (C), 98.4 (C, CDA), 97.8 (C, CDA), 82.7 (C_3), 79.6 (C_2), 76.4 (C_1), 68.5 (C_5), 68.3 (C_6), 67,4(C_4), 60.2 (OCH_3), 47.1 (OCH_3, CDA), 46.9 (OCH_3, CDA), 27.0 (CH_3), 27.1 (CH_2), 26.9 (CH_2), 26.0 (CH_3); 21.4 ($2CH_2$); Anal. Calcd. for $C_{18}H_{30}O_8$: C, 57.74%; H, 8.08%; found: 57.46%; H, 7.86%; HRFABMS Calcd. for $C_{18}H_{30}O_8$+Na^+ : 397.1838, found: 397.1854; MALDI-TOF Calcd. for $C_{18}H_{30}O_8$+Na^+ : 397.4, found: 397.3 calcd. for $C_{18}H_{30}O_8$+K^+ : 413.5, found: 413.8

Glycosylation reaction of 7 and 8

To a solution of **8** (809 mg, 1.305 mmol, 1.5 equiv) in CH_2Cl_2 (4 mL), compound **7** (295 mg, 0.788 mmol, 1 equiv) and freshly activated 4 Å molecular sieves were added

and the mixture stirred for 1 h under Argon. Then, TMSOTf (12.6 mL, 0.104 mmol, 0.08 equiv) was added and the reaction mixture stirred for 24 h. The suspension was filtered through celite and the solvent evaporated under vacuum to provide a mixture of two disaccharides (α/β = 2:1) which can be separated by flash chromatography (Hex/EtOAc 4:1) to obtain **9** (235 mg, 0.282 mmol, 36%) and **10** (118 mg, 0.142 mmol, 18%).

2-Azido-2-deoxy-3,4,6-tri-*O*-benzyl-D-glucopyranosyl-α(1→6)-4,5-*O*-(1',2'-dimethoxycyclohexane-1',2'-diyl)-1,2-*O*-isopropyliden-3-*O*-methyl-D-*chiro*-inositol (9)

Rf (Hex/EtOAc 3:1): 0.17; $[\alpha]^{20}_D$ +48.8° (c = 0.25, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): d = 7.43-7.22 (m, 15H, Ph), 4.94 (d, 1H, $J_{1'-2'}$ = 3.2 Hz, $H_{1'}$), 4.83 (d, 1H, J = 13.0 Hz, CHPh), 4.82 (AB syst., 2H, CH_2Ph), 4.58 (d, 1H, J = 12.0 Hz, CHPh), 4.58 (m, 1H, $H_{5'}$), 4.57 (d, 1H, J = 13.0 Hz, CHPh), 4.42 (d, 1H, J= 12.0 Hz, CHPh), 4.25 (t, 1H, J = 6.4 Hz, H_2), 4.18 (t, 1H, J = 2.5 Hz, H_1), 4.16 (t, 1H, J = 2.5 Hz, H_6), 4.11 (t, 1H, J = 10.5 Hz, H_4), 3.96 (t, 1H, J = 10.1 Hz, H_3'), 3.90 (dd, 1H, J_{5-4} = 10.5 Hz, J_{5-6} = 2.5 Hz, H_5), 3.79 (t, 1H, J = 10.1 Hz, $H_{4'}$), 3.71 (dd, 1H, $J_{6a'-6b'}$ = 10.8 Hz, $J_{6a'-5'}$ = 2.4 Hz, $H_{6a'}$), 3.60 (s, 3H, OCH_3), 3.59 (dd, 1H, $J_{6a'-6b'}$ = 10.8 Hz, $J_{6b'-5'}$ = 1.6 Hz, $H_{6b'}$), 3.41 (dd, 1H, J_{3-4} = 10.5 Hz, J_{3-2} = 6.4 Hz, H_3), 3.36 (dd, 1H, $J_{2'-3'}$ = 10.2 Hz, $J_{2'-1'}$ = 3.2 Hz, $H_{2'}$), 3.19 (s, 6H, 2 OCH_3, CDA), 1.83-1.78 (m, 1H, CDA), 1.72-1.61 (m, 3H, CDA), 1.52 (s, 3H, CH_3), 1.55-1.43 (m, 2H, CDA), 1.40-1.30 (m, 2H, CDA), 1.36 (s, 3H, CH_3); MALDI-TOF Calcd. for $C_{45}H_{57}N_3O_{12}+Na^+$: 855.0, found: 854.3, calcd. for $C_{45}H_{57}N_3O_{12}+K^+$: 871.1, found: 870.5

2-Azido-2-deoxy-3,4,6-tri-*O*-benzyl-D-glucopyranosyl-β(1→6)-4,5-*O*-(1',2'-dimethoxycyclohexane-1',2'-diyl)-1,2-*O*-isopropyliden-3-*O*-methyl-D-*chiro*-inositol (10)

R_f(Hex/EtOAc 3:1): 0.20; $[\alpha]^{20}_D$ -8.0° (c = 1.18, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): d 7.40-7.24 (m, 13H, Ph), 7.21-7.13 (m, 2H, Ph), 4.97 (d, 1H, $J_{1'-2'}$ = 8.1 Hz, $H_{1'}$), 4.92 (d, 1H, J = 10.8 Hz, CHPh), 4.82 (d, 1H, J = 10.8 Hz, CHPh), 4.78 (d, 1H,

J = 10.8 Hz, CHPh), 4.62 (d, 1H, J = 10.8 Hz, CHPh), 4.58 (AB syst., 2H, CH_2Ph), 4.49 (t, 1H, J = 2.5 Hz, $H_{6'}$), 4.30 (dd, 1H, J_{1-2} = 5.1 Hz, J_{1-6} = 2.5 Hz, H_1), 4.20 (t, 1H, J = 10.8 Hz, H_4), 4.17 (t, 1H, J = 5.1 Hz, H_2), 3.98 (dd, 1H, J_{5-4} = 10.8 Hz, J_{5-6} = 2.5 Hz, H_5), 3.71-3.57 (m, 3H, $H_{5'}$, $H_{6'}$, $H_{4'}$), 3.61 (s, 3H,OCH_3), 3.47-3.39 (m, 3H, $H_{3'}$, H_3, $H_{6'}$), 3.30 (dd, 1H, J = 8.1 Hz, $H_{2'}$), 3.23 (s, 3H, OCH_3, CDA), 3.18 (s, 3H, OCH_3, CDA), 1.83-1.77 (m, 1H, CDA), 1.80-1.43 (m, 5H, CDA), 1.52 (s, 3H, CH_3), 1.41-1.28 (m, 2H, CDA), 1.33 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$, 125 MHz): d = 138.5 (C), 138.4 (C), 138.3 (C), 128.9 (2CH), 128.8 (2CH), 128.8 (CH), 128.8 (2CH), 128.4 (2CH), 128.3 (2CH), 128.3 (CH), 128.2 (2CH), 128.1 (CH), 109.9 (C), 101.3 ($C_{1'}$), 98.4 (C, CDA), 98.0 (C, CDA), 83.9 ($C_{3'}$),83.6 (C_3),78.1 ($C_{4'}$),76.7 (C_1),76.0 (CH_2),75.9 ($C_{6'}$),75.5 (CH_2),75.4 (CH_2),73.9 (C_6),72.6 ($C_{5'}$),68.8 (C_5),68.7 (C_2),68.1 (C_4), 67.5 ($C_{2'}$), 60.4 (OCH_3),47.4 (OCH_3, CDA),47.3 (OCH_3, CDA),28.4 (CH_3),27.5 (CH_2),27.4 (CH_2),26.3 (CH_3),21.8 ($2CH_2$); HRFABMS Calcd. for $C_{45}H_{57}N_3O_{12}$: 854.3840, found = 854.3872; MALDI-TOF Calcd. for $C_{45}H_{57}N_3O_{12}$+Na^+ : 855.0, found: 854.3, calcd. for $C_{45}H_{57}N_3O_{12}$+K^+ : 871.1, found: 870.4

2-Azido-2-deoxy-3,4,6-tri-*O*-benzyl-D-galactopyranosyl-α(1→6)-4,5-*O*-(1',2'-dimethoxycyclohexane-1',2'-diyl)-1,2-*O*-isopropyliden-3-*O*-methyl-D-*chiro*-inositol (14)

To a solution of **13** (84 mg, 0.14 mmol, 1.3 equiv), **7** (39 mg, 0.10 mmol, 1.0 equiv) in CH_2Cl_2:Hex, 1:3 (2 mL) and freshly activated 4 Å molecular sieves were added and the mixture stirred for 1 h under Argon. Then, TMSOTf (2.43 mL, 0.02 mmol, 0.15 equiv) was added at -40°C and the reaction mixture stirred for 24 h at 0°C. The suspension was filtered through celite and the solvent removed under vacuum to provide the crude material. Flash chromatography (Hex/ EtOAc 4:1) afforded **14** (38 mg, 0.046 mmol, 46%). R_f (Hex/EtOAc 1:1): 0.67; $[\alpha]^{20}_D$ +59.7° (c = 1.44, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) : d = 7.46-7.28, (m, 15H, Ph), 4.98 (d, 1H, J = 3.3 Hz, $H_{1'}$), 4.89 (d, 1H, J = 11.2 Hz, CHPh), 4.78 (d, 1H, J =11.1 Hz, CHPh), 4.69 (m, 1H, $H_{5'}$), 4.67 (d, 1H, J = 11.1 Hz, CHPh), 4.59 (d, 1H, J = 11.2 Hz, CHPh), 4.46, (AB syst., 2H, CH_2Ph),4.28 (t, 1H, J = 6.3 Hz, H_2), 4.20 (m, 2H, H_1, H_6), 4.15 (bs, 1H,

$H_{4'}$), 4.11 (m, 1H, H_4), 4.04 (dd, 1H, $J_{3'-2'}$ = 10.6 Hz, $J_{3'-4'}$ = 2.4 Hz, $H_{3'}$), 3.92 (dd, 1H, J_{4-5} = 10.8 Hz, J_{5-6} = 2.1 Hz, H_5), 3.86 (dd, 1H, $J_{2'-3'}$ = 10.6 Hz, $J_{2'-1'}$ = 3.3 Hz, $H_{2'}$), 3.66-3.60 (m, 1H, $H_{6b'}$), 3.63 (s, 3H, OCH_3), 3.50 (dd, 1H, $J_{6a'-6b'}$ = 8.1 Hz, $J_{6a'-5'}$ = 5.4 Hz, $H_{6a'}$), 3.42 (dd, 1H, J_{3-4} = 10.2 Hz, J_{3-2} = 6.3 Hz, H_3), 3.20 (s, 3H, OCH_3, CDA), 3.18 (s, 3H, OCH_3, CDA), 1.90-1.63 (m, 4H, CDA), 1.54 (s, 3H, CH_3), 1.60-1.33 (m, 4H, CDA),1.40 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 139.0 (C). 138.5 (C), 138.0 (C), 110.2 (C), 98.3 (C, CDA), 98.2 (C, CDA), 97.8 ($C_{1'}$), 83.6 (C_3), 80.6 (C_2), 77.2 ($C_{3'}$), 75.2 (C_6), 75.0 (CH_2), 73.9 ($C_{4'}$), 73.8 (CH_2), 72.8 (C_1), 72.7 (CH_2), 69.9 ($C_{5'}$), 68.4 ($C_{6'}$), 68.1 (C_4), 67.1 (C_5), 60.5 (OCH_3), 60.0 ($C_{2'}$), 47.2 (2OCH_3, CDA), 28.5 (CH_3), 27.4 (CH_2), 27.0 (CH_2), 26.7 (CH_3), 21.9 (2 CH_2); MALDI-TOF Calcd. for $C_{45}H_{57}N_3O_{12}$+Na^+ : 855.0 Found: 854.0 Calcd. for $C_{45}H_{57}N_3O_{12}$+K^+ : 871.1 Found: 870.1

2-Azido-2-deoxy-3,4,6-tri-*O*-benzyl-D-glucopyranosyl-α(1→6)-3-*O*-methyl-D-*chiro*-inositol (11)

Disaccharide (**9**) was dissolved in a mixture of trifluoroacetic acid/water (20:1, 3.7 mL) and stirred at room temperature for 40 min. Then, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and immediately poured into an ice-cold, vigorously stirred solution of saturated aqueous sodium bicarbonate (90 mL). The layers were separated, and the aqueous phase extensively extrated (CH_2Cl_2, 4x 30 ml), dried over Na_2SO_4 and concentrated under vacuum. Purification by flash chromatography (Cl_2CH_2/MeOH, 11:1 and then CH_2Cl_2/MeOH, 15:1) afforded **11** (4 mg, 6.138 mmol, 56%). R_f (Cl_2CH_2/MeOH, 9:1): 0.3; $[\alpha]^{20}_D$ +38.5° (c = 0.19, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): d = 7.34-7.16 (m,15H, Ph), 4.94 (d, 1H, J = 3.5 Hz, H_1), 4.84 (AB syst., 2H, CH_2Ph), 4.79 (d, 1H, J = 11.0 Hz, CHPh), 4.56 (d, 1H, J = 11.0 Hz, CHPh), 4.50 (d, 1H, J = 11.0 Hz, CHPh), 4.47 (d, 1H, J = 11.0 Hz, CHPh), 4.16 (bs, 1H, H_1), 4.12 (m, 1H, $H_{5'}$), 4.04 (bs, 1H, H_6), 3.92 (m, 1H, H_2), 3.87-3.84 (m, 2H, $H_{3'}$, H_5), 3.71 (Yt, 1H, J = 8.0 Hz, H_4), 3.56 (m, 3H, $H_{4'}$, 2$H_{6'}$), 3.63 (s, 3H, OCH_3), 3.44 (dd, 1H, $J_{2'-3'}$ = 10.0 Hz, $J_{1'-2'}$ = 3.5 Hz, $H_{2'}$), 3.37 (Yt, 1H, J = 8.0 Hz, H_3).

2-Azido-2-deoxy-3,4,6-tri-*O*-benzyl-D-glucopyranosyl-β(1→6)-3-*O*-methyl-D-*chiro*-inositol (12)

Compound **12** (28 mg, 43.0 mmol, 71%) was obtained *via* the general procedure described above for compound **11**. Purification by flash chromatography (Hex/EtOAc 1:20). R_f(EtOAc): 0.47; ^{1}H NMR ($CDCl_3$, 500 MHz): d = 7.34-7.26 (m, 13H, Ph), 7.19-7.10 (m, 2H, Ph), 4.83 (AB syst., 2H, CH_2Ph), 4.78 (d, 1H, J = 11.0 Hz, CHPh), 4.54 (AB syst., 2H, CH_2Ph), 4.52 (d, 1H, J = 11.0 Hz, CHPh), 4.46 (d, 1H, J = 8.0 Hz, $H_{1'}$), 4.21 (bs, 1H, H_1), 4.10 (bs, 1H, H_6), 3.94-3.90 (m, 2H, H_2, H_5), 3.80 (t, 1H, J = 8.5 Hz, H_4), 3.69-3.59 (m, 2H, $2H_{6'}$), 3.62 (s, 3H, OCH_3), 3.58 (t, 1H, J = 9.5 Hz, $H_{4'}$), 3.47 (t, 1H, J = 9.5 Hz, $H_{3'}$), 3.46-3.36 (m, 3H, $H_{2'}$, $H_{5'}$, H_3), 3.35-3.27 (bs, 1H, OH), 3.27-3.15 (bs, 1H, OH), 3.15-2.94 (2bs, 2H, 2OH).

2-Azido-2-deoxy-3,4,6-tri-*O*-benzyl-D-galactopyranosyl-α(1→6)-3-*O*-methyl-D-*chiro*-inositol (16)

Compound **16** (7 mg, 10.7 mmol, 41%) was obtained *via* the general procedure described above for compound **11**, using purification by flash chromatography (CH_2Cl_2/MeOH, 10:1). R_f (CH_2Cl_2/MeOH 9:1): 0.48; ^{1}H NMR ($CDCl_3$, 500 MHz): d = 7.36-7.21 (m, 15H, Ph), 4.96 (d, 1H, J_{1-2} = 3.5 Hz, $H_{1'}$), 4.85 (d, 1H, J = 11.5 Hz, CHPh), 4.71 (d, 1H, J = 11.0 Hz, CHPh), 4.67 (d, 1H, J = 11.0 Hz, CHPh), 4.49 (d, 1H, J = 11.0 Hz), 4.49 (d, 1H, J = 11.5 Hz, CHPh), 4.40 (d, 1H, J = 11.0 Hz, CHPh), 4.20 (dd, 1H, $J_{4'-5'}$ = 7.5 Hz, $J_{5'-6'}$ = 4.5 Hz, $H_{5'}$), 4.15 (t, 1H, J = 4.0 Hz, H_1), 4.01 (t, 1H, J = 4.0 Hz, H_6), 3.95-3.90 (m, 2H, $H_{2'}$, $H_{4'}$), 3.87 (m, 1H, H_2), 3.84 (dd, $J_{2'-3}$'= 10.5 Hz, $J_{3'-4'}$ = 2.5 Hz, $H_{3'}$), 3.82-3.77 (m, 1H, H_5), 3.65 (t, 1H, J = 8.2 Hz, H_4), 3.62 (s, 3H, OCH_3), 3.58 (dd, 1H, $J_{6a'-6b'}$ = 9.5 Hz, $J_{5'-6a'}$ = 7.5 Hz, $H_{6a'}$), 3,38 (dd, 1H, $J_{6a'-6b'}$ = 9.5 Hz, $J_{5'-6b'}$ = 4.5 Hz, $H_{6b'}$), 3.35 (t, 1H, J = 8.2 Hz, H_3).

2-Amino-2-deoxy-D-glucopyranosyl-α(1→6)-3-*O*-methyl-D-*chiro*-inositol (1)

Compound **11** (3.8 mg, 5.831 mmol, 1.0 equiv) and 10% Pd/C (10 mg, 9.398 mmol) were stirred in methanol under a hydrogen atmosphere for 24 h. The slurry was filtered, washed with water and the filtrate was concentrated and lyophilized to give

the fully deprotected disaccharide **1** (2.6 mg, 7.3 mmol, quantitative). R_f (EtOAc/MeOH/H_2O/AcOH 2:2:1:1): 0.44;$[\alpha]^{20}_D$ +55.2° (c = 0.125, H_2O). ^1H NMR (D_2O, 500 MHz): δ = 5.22 (d, 1H, $H_{1'}$), 4.16 (t, 1H, H_1), 4.19 (t, 1H, H_6), 4.07 (dt, 1H, $H_{5'}$), 3.90 (dd, 1H, H_5), 3.85-3.75 (m, 3H, $H_{4'}$, $H_{6a'}$, $H_{6b'}$), 3.80 (dd, 1H, H_2), 3.70 (t, 1H, $H_{3'}$), 3.64 (s, 3H, OCH_3), 3.52 (t, 1H, H_4), 3.36 (t, 1H, H_3), 3.24 (dd, 1H, $H_{2'}$).

2-Amino-2-deoxy-D-glucopyranosyl-β(1→6)-3-*O*-methyl-D-*chiro*-inositol (2)

Compound **12** (24 mg, 67.54 mmol, 98%) was treated as described above to afford compound **2**. R_f (EtOAc/MeOH/H_2O/AcOH 2:2:1:1): 0.42, ^1H NMR (D_2O, 500 MHz): d = 4.70 (d, 1H, J = 8.5 Hz, $H_{1'}$), 4.32 (Yt, 1H, J = 3.5 Hz, H_1), 4.12 (Yt, 1H, J = 3.5 Hz, H_6), 3.96 (dd, 1H, $J_{6a'-6b'}$ =9.5 Hz, $J_{6a'-5'}$ = 1.7 Hz, $H_{6a'}$), 3.92 (dd, 1H, J_{5-4} = 8.5 Hz, J_{5-6} = 3.5 Hz, H_5), 3.88 (dd, 1H, J_{2-3} = 9.8 Hz, J_{1-2}= 6.6 Hz, H_2), 3.82 (dd, 1H, $J_{6a'-6b'}$ = 9.5 Hz, $J_{5'-6b'}$ = 4.0 Hz, $H_{6b'}$), 3.78 (t, 1H, J = 9.5 Hz, $H_{4'}$), 3.66 (s, 3H, OCH_3), 3.48 (t, 1H, J = 9.8 Hz, $H_{4'}$), 3.57-3.51 (m, 2H, $H_{3'}$, $H_{5'}$), 3.40 (t, 1H, J = 9.8 Hz, H_3), 2.86 (t, 1H, J = 8.5 Hz, $H_{2'}$).

2-Amino-2-deoxy-D-glucopyranosyl-α(1→6)-3-*O*-methyl-D-*chiro*-inositol (14)

Compound **14** (5.3 mg, 14.9 mmol, quantitative) was obtained *via* the general procedure described above for compound **12**. R_f (Cl_2CH_2/MeOH 9/1): 0.071; $[\alpha]^{20}_D$ (c = 0.305, H_2O): +70.1; ^1H NMR (D_2O, 500 MHz): δ = 5.31 (d, 1H, J = 3.5 Hz, $H_{1'}$), 4.29 (t, 1H), 4.19 (Ψt, 1H, H_1), 4.14 (Ψt, 1H, H_6), 4.05 (Ψs, 1H, $H_{4'}$), 3.92 (dd, 1H), 3.77 (d, 3H), 3.72 (t, 1H), 3.65 (s, 3H, OCH_3), 3.62 (m, 1H), 3.52 (dd, 1H, $J_{2'-3'}$ = 11.0 Hz, $J_{1'-2'}$ = 3.5 Hz, $H_{2'}$), 3.37 (t, 1H, J = 10.0 Hz, H_3).

Synthesis of RGL1105

1''-D-4'-*O*-(2'',3'',4''-tri-*O*-benzyl-6''-*tert*butyldimethylsilyl-α-D-mannopyranosyl)-[1'-D-6-*O*-(2'-azido-3',6'-di-*O*-benzyl-2'-deoxy-α-D-glucopyranosyl)-1,2-*O*-(L-1,7,7-trimethyl[2.2.1]-bicyclohept-2-ylidene)-3,4,5-tri-*O*-benzyl-*myo*-inositol] (3)

A mixture of compounds **1** (284 mg, 0.298 mmol) and **2** (340 mg, 0.408 mmol), was dissolved in Toluene and the solvent removed (3x10 mL). To the water-free solid mixture, Et_2O anh. (10 mL) and 4Å powdered molecular sieves was added and allowed to dissolve at room temperature under Argon atmosphere. After 5 min, TMSOTf (12 μL, 0.066 mmol) was added and the reaction allowed to proceed for 90 min. Then, the reaction was quenched with Et_3N (2 mL) and after 5 min stirring, the solvents are removed and the residue purified by column chromatography (SiO_2, hexane/AcOEt 19:1), to obtain **3** (363 mg, 75%). ^1H NMR ($CDCl_3$, 500 MHz): d 7.72-7.58 (m, 5H, ArH), 7.42-7.13 (m, 39H, ArH), 7.07 (m, 5H, ArH), 6.94 (t, J=7.5 Hz, 1H, ArH), 5.58 (d, J=3.0 Hz, 1H, H anom.), 5.261 (d, J=2.9 Hz, 1H, H anom.), 4.95 (d, J=11 Hz, 1H, H benc.), 4.87 (d, J=11 Hz, 1H, H benc.), 4.75-4.63 (m, 7H), 4.62-4.49 (m, 4H), 4.42 (m, 2H), 4.46 (m, 3H), 4,7 (d, J=12.0 Hz, 1H, H benc.), 4.12 (m, 3H), 4.1 (dd, J_1=3Hz, J_2=11.5 Hz, 1H), 3.98-3.91 (m, 3H), 3.78-3.89 (m, 4H), 3.69 (m, 1H), 3.49-3.61 (m, 2H), 3.44 (m, 1 H), 1.99 (m, 2H), 1.74-1.85 (m, 2H), 1.55 (d, J=12.5 Hz, 1H),1.47 (m, 1H), 1.27-1.38 (m, 1H), 1.10 (s, 3H), 0.95 (s, 3H), 0.92 (s, 3H).

1''-D-4'-*O*-(2'',3'',4''-tri-*O*-benzyl-α-D-mannopyranosyl)-[1'-D-6-*O*-(2'-azido-3',6'-di-*O*-benzyl-2'-deoxy-α-D-glucopyranosyl)-1,2-*O*-(L-1,7,7-trimethyl[2.2.1]-bicyclohept-2-ylidene)-3,4,5-tri-*O*-benzyl-*myo*-inositol] (4)

A solution of **3** (290 mg, 0.179 mmol) in THF (15 mL) under Argon atmosphere, was treated with TBAF (1.0 M in THF, 1.8 mL, 1.800 mmol) at 0°C. The reaction mixture was allowed to reach room temperature and kept stirring for 66 h. Then, the solvents were removed, the remaining material redissolved in AcOEt (50 mL), washed with NaCl s.s. (3 x 50 mL), dried over $MgSO_4$ and the solvents evaporated. The residue was purified by column chromatography (SiO_2, hexane/AcOEt 9:1 to 8:1 to 6:1 and finally 4:1), to obtain **4** (206 mg, 83%). ^1H NMR ($CDCl_3$, 500 MHz): 7.25-7.44 (m, 37H, ArH), 7.11-7.20 (m, 3H, ArH), 5.68 (d, *J*=3.5 Hz, 1H, H anom.), 5.32 (d, *J*=2 Hz, 1H, H anom.), 4.95 (m, 1H), 4.55-4.86 (m, 12H), 4.50 (d, *J*=12 Hz, 1H, H benc.), 4.40 (d, *J*=12 Hz, 1H, H benc.),4.34 (m, 1H), 4.20 (d, *J*=12 Hz, 1H, H benc.), 4.10 (m,

3H), 3.82-4.03 (m, 6H), 3.64-3.76 (m, 5H), 3.47-3.58 (m, 2H), 3.41 (dd, J_1=3.5 Hz, J_2=10 Hz, 1H), 2.4 (s,1H, OH), 1.97 (m, 2H), 1.74-1.84 (m, 2H), 1.53 (d, J=13 Hz, 1H), 1.47 (m, 1H), 1.24-1.35 (m, 1H), 1.13 (s, 3H), 0.94 (s, 3H), 0.93 (s, 3H).

1''-D-4'-*O*-(2'',3'',4''-tri-*O*-benzyl-6''-dibenzylphosphate-α-D-mannopyranosyl)-[1'-D-6-*O*-(2'-azido-3',6'-di-*O*-benzyl-2'-deoxy-α-D-glucopyranosyl)-1,2-*O*-(L-1,7,7-trimethyl[2.2.1]-bicyclohept-2-ylidene)-3,4,5-tri-*O*-benzyl-*myo*-inositol] (5)

To a solution of trisaccharide **4** (190 mg, 0.137 mmol) and 1*H*-Tetrazole in anhydrous CH_2Cl_2 (10 mL) under Argon atmosphere and at 0°C, dibenzyl diisipropylphosphoramidite (DBPA, 0.1 mL, 0.298 mmol) was added. The reaction mixture was stirred for 3h, while allowing to reach room temperature. Then, the reaction mixture was cooled to 0°C and a solution of 70% 3-chloroperbenzoic acid (85 mg, 0.345 mmol) in anh. CH_2Cl_2 (5 mL) was added. The mixture was stirred for 1h, diluted with CH_2Cl_2 (25 mL), washed with sat. Na_2SO_3 (2x50 mL), sat. $NaHCO_3$ (2x50 mL) and sat. NaCl (2x50 mL), dried over $MgSO_4$ and concentrated. Flash chromatography of the crude mixture (hexane/AcOEt 9/1, 8/1, 7/1, 6/1, 5/1 and 4/1) gave compound **5** (210 mg, 93%). ^{1}H-NMR ($CDCl_3$, 500 MHz): d 7.13-7.42 (m, 49H, ArH), 7.08 (m, 1H, ArH), 5.66 (d, J=3.5 Hz, 1H, H anom.), 5.28 (d, J=2 Hz, 1H, H anom.), 4.90-5.03 (m, 6H), 4.75-4.81 (m, 4H), 4.72 (d, J=12 Hz, 1H, H benc.), 4.65 (m, 2H), 4.52-4.61 (m, 3H), 4.45 (m, 2H), 4.34 (m, 2H), 4.15-4.29 (m, 3H), 4.03-4.12 (m, 4H), 3.80-3.94 (m, 5H), 3.72 (m, 2H), 3.56 (m, 2H), 3.49 (m, 1H), 3.57 (dd, J_1=3.5 Hz, J_2=10 Hz, 1H), 1.97 (m, 2H), 1.78 (m, 2H), 1.52 (d, J=12.5 Hz, 1H), 1.46 (m, 1H), 1.28 (m, 1H), 1.12 (s, 3H), 0.93 (s, 3H), 0.89 (s, 3H). ^{31}P-NMR ($CDCl_3$, 202 MHz): d -1.72.

1''-D-4'-*O*-(2'',3'',4''-tri-*O*-benzyl-6''-dibenzylphosphate-α-D-mannopyranosyl)-[1'-D-6-*O*-(2'-azido-3',6'-di-*O*-benzyl-2'-deoxy-α-D-glucopyranosyl)-3,4,5-tri-*O*-benzyl-*myo*-inositol] (6)

To a solution of trisaccharide **5** (200 mg, 0.122 mmol) in CH_2Cl_2 (15 mL) H_2O (0.2 mL, 11.1 mmol), and trifluoroacetic acid (0.6 mL, 7.81 mmol) were added and the

reaction stirred for 18 h at r.t. The mixture was then diluted with AcOEt (50 mL), washed with sat. $NaHCO_3$ (2x50 mL), sat. NaCl (3x50 mL), dried over $MgSO_4$ and concentrated. Flash chromatography of the crude mixture (hexane/AcOEt 4/1, 2/1, 1/1 y 1/2) gave compound **6** (142 mg, 77%). ^{1}H-NMR ($CDCl_3$, 500 MHz): d 7.10-7.39 (m, 50H), 5.53 (d, *J*=3.5 Hz, 1H, H anom.), 5.24 (d, *J*=2.5 Hz, 1H, H anom.), 4.87-5.03 (m, 8H), 4.72-4.79 (m, 4H), 4.63 (m, 2H), 4.57 (d, *J*=12Hz, 1H, H benc.), 4.49 (d, *J*=12 Hz, 1H, H benc.), 4.25-4.38 (m, 3H), 4.09-4.26 (m, 4H), 4.01-4.09 (m, 3H), 3.95 (m, 1H), 3.84 (m, 3H), 3.69 (m, 3H), 3.6 (m, 1H), 3.5 (m, 1H), 3.43 (m, 2H), 3.37 (m, 1H), 3.29 (m, 1H), 2.94 (wide s., 1H, OH). ^{31}P-RMN ($CDCl_3$, 202 MHz): d -1.79.

1''-D-4'-*O*-(6''-phosphate-α-D-mannopyranosyl)-[1'-D-6-*O*-(2'-amino-2'-deoxy-α-D-glucopyranosyl)-*myo*-inositol] (RGL 1105)

To a suspension of trisaccharide **6** (115 mg, 0.076 mmol) in a mixture of MeOH/H_2O (5 mL, 9:1) 10% Pd/C (162 mg, 0.152 mmol) was added and the reaction stirred under hydrogen atmosphere at r.t. for 24 h. The solvent was evaporated, the crude suspended in H_2O (10 mL), filtered through celite and the filtrate lyophilized to give **RGL1105** (45 mg, quant.). ^{1}H-RMN (D_2O, 500 MHz): d 5.46 (d, 3.5 Hz, 1H, H anom.), 5.31 (s, 1H, H anom.), 4.0-4.27 (m, 6H), 3.72-3.92 (m, 8H), 3.68 (t, *J*=9.5 Hz, 1H), 3.54 (m, 1H), 3.41 (m, 1H). ^{31}P-RMN (D_2O, 202 MHz): d 0.66.

Synthesis of RGL1115

Synthesis of 1'-D-6-O-(2'-azido-3'-O-benzyl-4',6'-O-benzylidene-2'-deoxy-α-D-glucosopyranosyl)-1,2-O-(L-1,7,7-trimethyl[2.2.1]-bicyclohept-2-ylidene)-3,4-O-(1,1,3,3,-tetraisopropyldisiloxanyl)-5-O-di-benzylphosphate-myo-inositol 12

To a solution of α-1,6 anomer **11** (0.16 mmol) and 1-*H*-tetrazole (0.63 mmol) in anhydrous Cl_2CH_2 (15 ml) at 0 °C (ice bath) was added dropwise dibenzyl diisopropylphosphoramidite (0.63 mmol). After the addition was completed the ice-bath was removed and the mixture left to stir under an inert atmosphere whilst being monitored by TLC analysis (hexane:EtOAc [4:1]). After 72 hours the α-1,6 anomer **11**

starting material had been consumed. A solution of *m*CPBA (0.39 mmol) in anhydrous DCM (5 ml) was added to the reaction vessel and the mixture left to stir for 3 hours at R.T. under an inert atmosphere. The mixture was diluted with DCM (30 ml), washed with sat. Na_2SO_3 (2 x 25 ml), sat. $NaHCO_3$ (2 x 25 ml) and brine (2 x 25 ml). The organic layer was then dried over $MgSO_4$ and concentrated to dryness *in vacuo*. The crude product was purified by column chromatography (hexane:EtOAc [4:1]) to yield phosphate **12** as a pale yellow oil (60 %). δ_H ($CDCl_3$: 360 MHz) 4.6 (2H, dd, PhC$\underline{H}_2$O), 5.3 (1H, d, H1'), 5.4 (1H, s, PhC$\underline{H}$O); δ_P ($CDCl_3$: 146 MHz) 0.2 ($1P^V$).

Synthesis of 1'-D-6-O-(2'-azido-3'-O-benzyl-4',6'-O-benzylidene-2'-deoxy-α-D-glucosopyranosyl)-1,2-O-(L-1,7,7-trimethyl[2.2.1]-bicyclohept-2-ylidene)-5-O-di-benzylphosphate-myo-inositol 13

To a solution of phosphate **12** (0.09 mmol) in anhydrous THF (1.3 ml) at 0°C (ice bath) was added TBAF (1.0 M solution in THF) (0.2 ml) and the reaction left to stir at R.T. under an inert atmosphere. After 45 minutes TLC analysis (hexane:EtOAc [3:2]) indicated that all phosphate **12** starting material had been consumed. The reaction mixture was concentrated to dryness *in vacuo* before being purified by column chromatography (hexane:EtOAc [3:2]) to yield de-silylated saccharide **13** as a pale yellow oil (44 %). δ_H (d4-MeOH: 360 MHz) 5.4 (1H, d, H1'), 5.5 (1H, s, PhC$\underline{H}$O); δ_P (d4-MeOH: 146 MHz) 1.1 ($1P^V$).

Synthesis of 1'-D-6-O-(2'-azido-3'-O-benzyl-2'-deoxy-α-D-glucosopyranosyl)-5-O-di-benzylphosphate-myo-inositol 14

To a solution of de-silylated saccharide **13** (0.04 mmol) in DCM (5.0 ml) was added distilled water (44 ml) then TFA (187 ml) and the mixture stirred at R.T. for 4 hours whilst being monitored by TLC analysis (EtOAc). The reaction mixture was concentrated to dryness *in vacuo* before the crude product was purified by column chromatography (EtOAc [100 %] then EtOAc:MeOH [10:1]) to yield the de-protected

saccharide **14** (89 %) as a pale yellow oil. δ_H (d4-MeOH: 360 MHz) 5.3 (1H, d, H1'); δ_P (d4-MeOH: 146 MHz) 0.9 ($1P^v$).

Synthesis of 1'-D-6-O-(2'-amino-2'-deoxy-α-D-glucosopyranosyl)-5-O-phosphate-myo-inositol 15

To a suspension of de-protected saccharide **14** (0.04 mmol) in a mixture of HPLC grade methanol:distilled water [4:1] (1 ml) was added 10 % wt. Pd/C (10 mg) and the mixture stirred under an atmosphere of hydrogen at R.T. for 72 hours. The methanol was evaporated *in vacuo* before the crude product was suspended in distilled water then filtered through celite. The filtrate was then evaporated to dryness *in vacuo* to yield a yellow oil. ^{1}H-NMR analysis of this oil indicated benzyl groups remained on the pseudo-disaccharide. Consequently, the oil was re-suspended in a mixture of HPLC grade methanol:distilled water [4:1] (1 ml). 10 % wt. Pd/C (10 mg) was added and the mixture stirred under an atmosphere of hydrogen at R.T. for a further 20 hours. The methanol was evaporated *in vacuo*, the crude product suspended in distilled water before being filtered through celite. The filtrate was then evaporated to dryness *in vacuo* to yield de-protected phosphate **15** as a dark yellow oil. ^{1}H-NMR analysis indicated that the product **15** was slightly contaminated with impurities. The product **15** was therefore re-dissolved in distilled water and washed with EtOAc. The aqueous layer was then concentrated to dryness in vacuo to give pure de-protected phosphate **15** (11 mg) as a light brown oil. δ_H (D_2O: 360 MHz) 5.6 (1H, d, H1'); δ_P (D_2O: 146 MHz) 2.4 ($1P^v$).

<u>Synthesis of RGL 1116</u>

Synthesis of 1'-D-6-O-(2'-azido-3'-O-benzyl-4',6'-O-benzylidene-2'-deoxy-a-D-glucosopyranosyl)-1,2-O-(L-1,7,7-trimethyl[2.2.1]-bicyclohept-2-ylidene)-3,4-O-(1,1,3,3,-tetraisopropyldisiloxanyl)-5-O-acetyl-myo-inositol 16

α-1,6 Anomer **11** (0.16 mmol) was dissolved in acetic anhydride (2 ml) before pyridine (4 ml) was added. The reaction mixture was then stirred at R.T. overnight. TLC analysis (hexane:EtOAc [9:1]) of the reaction mixture suggested that only c.a. 50

% of the α-1,6 anomer **11** starting material had been consumed. The reaction was therefore heated to 45 °C for 8 hours at which point TLC analysis (hexane:EtOAc [9:1]) indicated complete consumption of the α-1,6 anomer **11** starting material. The reaction mixture was concentrated to dryness *in vacuo*, using toluene to azeotropically remove the pyridine. The crude product was then purified by column chromatography (hexane:EtOAc [8:1]) to yield acetate **16** (89 %) as a pale yellow oil. δ_H ($CDCl_3$: 360 MHz) 5.1 (2H, dd, PhC$\underline{H}_2$O), 5.3 (1H, dd, H5), 5.7 (1H, d, H1'), 5.8 (1H, s, PhC$\underline{H}$O).

Synthesis of 1'-D-6-O-(2'-azido-3'-O-benzyl-4',6'-O-benzylidene-2'-deoxy-α-D-glucosopyranosyl)-1,2-O-(L-1,7,7-trimethyl[2.2.1]-bicyclohept-2-ylidene)-5-O-acetyl-myo-inositol 18

To a solution of acetate **16** (0.14 mmol) in anhydrous THF (2.0 ml) at 0°C was added TBAF (1.0 M solution in THF) (310 ml) and the reaction left to stir at R.T. under an inert atmosphere. After 1.5 hours TLC analysis (hexane:EtOAc [3:2]) indicated that the acetate **16** starting material had been consumed. The reaction mixture was concentrated to dryness *in vacuo* before being purified by column chromatography (hexane:EtOAc [3:2]) to yield de-silylated acetate **18** as a pale yellow oil (42 %). δ_H ($CDCl_3$: 360 MHz) 4.7 (1H, dd, H5), 4.8 (2H, dd, PhC$\underline{H}_2$O), 5.3 (1H, d, H1'), 5.5 (1H, s, PhC$\underline{H}$O).

Synthesis of 1'-D-6-O-(2'-azido-3'-O-benzyl-2'-deoxy-α-D-glucosopyranosyl)-5-O-acetyl-myo-inositol 20

To a solution of de-silylated acetate **18** (0.06 mmol) in DCM (3.0 ml) was added distilled water (64 ml) then TFA (273 ml) and the mixture stirred at R.T. for 4.5 hours whilst being monitored by TLC analysis (EtOAc:MeOH [10:1]). The reaction mixture was concentrated to dryness *in vacuo* before the crude product was purified by column chromatography (EtOAc (100 %) then EtOAc:MeOH [10:1]) to yield the de-protected acetate **20** (55 %) as an orange oil. δ_H (d4-MeOH: 360 MHz) 4.8 (3H, m, H5 and PhC$\underline{H}_2$O), 5.4 (1H, d, H1').

Synthesis of 1'-D-6-O-(2'-amino-2'-deoxy-α-D-glucosopyranosyl)-5-O-acetyl-myo-inositol 22

To a suspension of de-protected acetate **20** (0.03 mmol) in a mixture of HPLC grade methanol:distilled water [10:1] (1 ml) was added 10 % wt. Pd/C (5 mg) and the mixture stirred under an atmosphere of hydrogen at R.T. for 24 hours. The methanol was evaporated *in vacuo* before the crude product was suspended in distilled water then filtered through celite. The filtrate was then evaporated to dryness *in vacuo* to yield de-protected acetate **22** as a colourless oil (7 mg).

Synthesis of 1'-D-6-O-(2'-azido-3'-O-benzyl-4',6'-O-benzylidene-2'-deoxy-β-D-glucosopyranosyl)-1,2-O-(L-1,7,7-trimethyl[2.2.1]-bicyclohept-2-ylidene)-3,4-O-(1,1,3,3,-tetraisopropyldisiloxanyl)-5-O-acetyl-myo-inositol 17

β-1,6 Anomer **9** (0.12 mmol) was dissolved in acetic anhydride (2 ml) before pyridine (4 ml) was added. The reaction mixture was then stirred at R.T. overnight. TLC analysis (hexane:EtOAc [9:1]) of the reaction mixture suggested that only c.a. 50 % of the β-1,6 anomer **9** starting material had been consumed. The reaction was therefore heated to 45°C for 9 hours at which point TLC analysis (hexane:EtOAc [9:1]) indicated that only a small quantity of the β-1,6 anomer **9** starting material remained unreacted. The reaction mixture was concentrated to dryness *in vacuo*, using toluene azeotropically remove the pyridine. The crude product was then purified by column chromatography (hexane:EtOAc [8:1]) to yield acetate **17** (63 %) as a pale yellow oil. δ_H ($CDCl_3$: 360 MHz) 4.8 (2H, dd, PhC$\underline{H}_2$O), 5.0 (1H, dd, H5), 5.3 (1H, d, H1'), 5.5 (1H, s, PhC$\underline{H}$O).

Synthesis of 1'-D-6-O-(2'-azido-3'-O-benzyl-4',6'-O-benzylidene-2'-deoxy-β-D-glucosopyranosyl)-1,2-O-(L-1,7,7-trimethyl[2.2.1]-bicyclohept-2-ylidene)-5-O-acetyl-myo-inositol 19

To a solution of acetate **17** (0.08 mmol) in anhydrous THF (2.0 ml) at 0°C was added TBAF (1.0 M solution in THF) (165 ml) and the reaction left to stir at R.T. under an inert atmosphere. After 1.5 hours TLC analysis (hexane:EtOAc [3:2]) indicated that

the acetate **17** starting material had been consumed. The reaction mixture was concentrated to dryness *in vacuo* before being purified by column chromatography (hexane:EtOAc [3:2]) to yield de-silylated acetate **19** as a pale yellow oil (53 %). δ_H ($CDCl_3$: 360 MHz) 4.8 (3H, m, $PhC\underline{H}_2O$ and H5), 5.5 (1H, d, H1').

Synthesis of 1'-D-6-O-(2'-azido-3'-O-benzyl-2'-deoxy-β-D-glucosopyranosyl)-5-O-acetyl-myo-inositol 21

To a solution of de-silylated acetate **19** (0.04 mmol) in DCM (3.0 ml) was added distilled water (46 ml) then TFA (200 ml) and the mixture stirred at R.T. for 4.5 hours whilst being monitored by TLC analysis (EtOAc). The reaction mixture was concentrated to dryness *in vacuo* before the crude product was purified by column chromatography (EtOAc (100 %) then EtOAc:MeOH [10:1]) to yield the de-protected acetate **21** (67 %) as an orange oil. δ_H (d4-MeOH: 360 MHz) 4.8 (3H, m, $PhC\underline{H}_2O$ and H5), 5.4 (1H, d, H1').

Synthesis of 1'-D-6-O-(2'-amino-2'-deoxy-β-D-glucosopyranosyl)-5-O-acetyl-myo-inositol 23

To a suspension of de-protected acetate **21** (0.03 mmol) in a mixture of HPLC grade methanol:distilled water [10:1] (1 ml) was added 10 % wt. Pd/C (6 mg) and the mixture stirred under an atmosphere of hydrogen at R.T. for 48 hours. The methanol was evaporated *in vacuo* before the crude product was suspended in distilled water then filtered through celite. The filtrate was then evaporated to dryness *in vacuo* to yield de-protected acetate **23** as a colourless oil (7 mg).

Synthesis of RGL1117

Synthesis of 1'-D-5-O-(2'-azido-3'-O-benzyl-4',6'-O-benzylidene-2'-deoxy-α-D-glucopyranosyl)-1,2-O-(L-1,7,7-trimethyl[2.2.1]-bicyclohept-2-ylidene)-3,4-O-(1,1,3,3,-tetraisopropyldisiloxanyl)-6-O-acetyl-myo-inositol 24

α-1,5 Anomer **10** (0.31 mmol) was dissolved in acetic anhydride (2 ml) before pyridine (4 ml) was added. The reaction mixture was then heated at 45 °C overnight

until TLC analysis (hexane:EtOAc [9:1]) indicated complete consumption of the α-1,5 anomer **10** starting material. The reaction mixture was concentrated to dryness *in vacuo*, using toluene to azeotropically remove the pyridine. The crude product was then purified by column chromatography (hexane:EtOAc [9:1]) to yield acetate **24** (97 %) as a pale yellow oil. δ_H (d4-MeOH: 360 MHz) 4.9 (2H, dd, PhC<u>H</u>$_2$O), 5.3 (1H, dd, H5), 5.8 (2H, m, H1' and PhC<u>H</u>O).

Synthesis of 1'-D-5-O-(2'-azido-3'-O-benzyl-4',6'-O-benzylidene-2'-deoxy-α-D-glucopyranosyl)-1,2-O-(L-1,7,7-trimethyl[2.2.1]-bicyclohept-2-ylidene)-6-O-acetyl-myo-inositol 25

To a solution of acetate **24** (0.30 mmol) in anhydrous THF (4.2 ml) at 0 °C was added TBAF (1.0 M solution in THF) (663 μl) and the reaction left to stir at R.T. under an inert atmosphere. After 1 hour TLC analysis (hexane:EtOAc [3:2]) indicated that the acetate **24** starting material had been consumed. The reaction mixture was concentrated to dryness *in vacuo* before being purified by column chromatography (hexane:EtOAc [3:2]) to yield de-silylated acetate **25** as a pale yellow oil (78 %). δ_H (d4-MeOH: 360 MHz) 4.8 (2H, dd, PhC<u>H</u>$_2$O), 5.1 (1H, dd, H5), 5.5 (1H, d, H1'), 5.6 (1H, s, PhC<u>H</u>O).

Synthesis of 1'-D-5-O-(2'-azido-3'-O-benzyl-2'-deoxy-α-D-glucopyranosyl)-6-O-acetyl-myo-inositol 26

To a solution of de-silylated acetate **25** (0.24 mmol) in DCM (30.0 ml) was added distilled water (260 μl) then TFA (1.1 ml) and the mixture stirred at R.T. for 4 hours whilst being monitored by TLC analysis (EtOAc). The reaction mixture was concentrated to dryness *in vacuo* before the crude product was purified by column chromatography (EtOAc (100 %) then EtOAc:MeOH [10:1]) to yield the de-protected acetate **26** (35 %) as a pale yellow oil. δ_H (d4-MeOH: 360 MHz) 4.8 (2H, dd, PhC<u>H</u>$_2$O), 5.2 (1H, dd, H5), 5.4 (1H, d, H1').

Synthesis of 1'-D-5-O-(2'-amino-2'-deoxy-α-D-glucopyranosyl)-6-O-acetyl-myo-inositol 27 (RGL1117)

To a suspension of de-protected acetate **26** (0.03 mmol) in a mixture of HPLC grade methanol:distilled water:AcOH [10:1:0.1] (1 ml) was added 10 % wt. Pd/C (5 mg) and the mixture stirred under an atmosphere of hydrogen at R.T. for 16 hours. The methanol was evaporated *in vacuo* before the crude product was suspended in distilled water then filtered through celite. The filtrate was then evaporated to dryness *in vacuo* to yield de-protected acetate **27** as a colourless oil (91 %). δ_H (D_2O: 360 MHz) 4.9 (1H, dd, H5), 5.4 (1H, d, H1').

Synthesis of RGL1124

Synthesis of 1'-D-6-O-(2'-azido-3'-O-benzyl-4',6'-O-benzylidene-2'-deoxy-β-D-glucopyranosyl)-1,2-O-(L-1,7,7-trimethyl[2.2.1]-bicyclohept-2-ylidene)-3,4-O-(1,1,3,3,-tetraisopropyldisiloxanyl)-5-O-acetyl-myo-inositol 17

β-1,6 Anomer **9** (0.12 mmol) was dissolved in acetic anhydride (2 ml) before pyridine (4 ml) was added. The reaction mixture was then stirred at R.T. overnight. TLC analysis (hexane:EtOAc [9:1]) of the reaction mixture suggested that only c.a. 50 % of the β-1,6 anomer **9** starting material had been consumed. The reaction was therefore heated to 45 °C for 9 hours at which point TLC analysis (hexane:EtOAc [9:1]) indicated that only a small quantity of the β-1,6 anomer **9** starting material remained unreacted. The reaction mixture was concentrated to dryness *in vacuo*, using toluene to azeotropically remove the pyridine. The crude product was then purified by column chromatography (hexane:EtOAc [8:1]) to yield acetate **17** (63 %) as a pale yellow oil. δ_H ($CDCl_3$: 360 MHz) 4.8 (2H, dd, PhC<u>H</u>$_2$O), 5.0 (1H, dd, H5), 5.3 (1H, d, H1'), 5.5 (1H, s, PhC<u>H</u>O).

Synthesis of 1'-D-6-O-(2'-azido-3'-O-benzyl-4',6'-O-benzylidene-2'-deoxy-β-D-glucopyranosyl)-1,2-O-(L-1,7,7-trimethyl[2.2.1]-bicyclohept-2-ylidene)-5-O-acetyl-myo-inositol 19

To a solution of acetate **17** (0.08 mmol) in anhydrous THF (2.0 ml) at 0 °C was added TBAF (1.0 M solution in THF) (165 µl) and the reaction left to stir at R.T. under an inert atmosphere. After 1.5 hours TLC analysis (hexane:EtOAc [3:2]) indicated that the acetate **17** starting material had been consumed. The reaction mixture was concentrated to dryness *in vacuo* before being purified by column chromatography (hexane:EtOAc [3:2]) to yield de-silylated acetate **19** as a pale yellow oil (53 %). δ_H ($CDCl_3$: 360 MHz) 4.8 (3H, m, $PhC\underline{H}_2O$ and H5), 5.5 (1H, d, H1').

Synthesis of 1'-D-6-O-(2'-azido-3'-O-benzyl-2'-deoxy-β-D-glucopyranosyl)-5-O-acetyl-myo-inositol 21

To a solution of de-silylated acetate **19** (0.04 mmol) in DCM (3.0 ml) was added distilled water (46 µl) then TFA (200 µl) and the mixture stirred at R.T. for 4.5 hours whilst being monitored by TLC analysis (EtOAc). The reaction mixture was concentrated to dryness *in vacuo* before the crude product was purified by column chromatography (EtOAc (100 %) then EtOAc:MeOH [10:1]) to yield the de-protected acetate **21** (67 %) as an orange oil. δ_H (d4-MeOH: 360 MHz) 4.8 (3H, m, $PhC\underline{H}_2O$ and H5), 5.4 (1H, d, H1').

Synthesis of 1'-D-6-O-(2'-amino-2'-deoxy-β-D-glucopyranosyl)-5-O-acetyl-myo-inositol 23 (RGL 1124)

To a suspension of de-protected acetate **21** (0.03 mmol) in a mixture of HPLC grade methanol:distilled water [10:1] (1 ml) was added 10 % wt. Pd/C (6 mg) and the mixture stirred under an atmosphere of hydrogen at R.T. for 48 hours.

The methanol was evaporated *in vacuo* before the crude product was suspended in distilled water then filtered through celite. The filtrate was then evaporated to dryness *in vacuo* to yield de-protected acetate **23** as a colourless oil (7 mg).

Synthesis of RGL1125

Synthesis of 1'-D-6-O-(2'-azido-3'-O-benzyl-4',6'-O-benzylidene-2'-deoxy-α-D-

glucopyranosyl)-1,2-O-(L-1,7,7-trimethyl[2.2.1]-bicyclohept-2-ylidene)-3,4-O-(1,1,3,3,-tetraisopropyldisiloxanyl)-5-O-butyryl-myo-inositol 28

α-1,6 Anomer **11** (0.22 mmol) was dissolved in pyridine (1.5 ml) before butyric anhydride (71 μl) was added. The reaction mixture was then heated at 45 °C overnight at which point TLC analysis (hexane:EtOAc [10:1]) indicated only slight consumption of the α-1,6 anomer **11** starting material. Butyric anhydride (284 μl) was subsequently added and the reaction mixture stirred at 55 °C for 18 hours. TLC analysis (hexane:EtOAc [10:1]) indicated that approximately 30 % of the α-1,6 anomer **11** starting material had been consumed at this stage. A further amount of butyric anhydride was then added (to take the concentration to 15 molar equivalents) and the mixture heated at 80 °C overnight. TLC analysis (hexane:EtOAc [10:1]) indicated that approximately 50 % of the α-1,6 anomer **11** starting material remained. Therefore, the reaction mixture was heated to 110 °C for 6 hours until it was determined by TLC analysis (hexane:EtOAc [10:1]) that approximately 30 % of the α-1,6 anomer **11** starting material remained. Butyric anhydride (5 equivalents) and pyridine (1.5 ml) were added and the reaction mixture heated at 110 °C overnight. TLC analysis (hexane:EtOAc [10:1]) then indicated that the α-1,6 anomer **11** starting material had been consumed. The reaction mixture was concentrated to dryness *in vacuo*, using toluene to azeotropically remove the pyridine. The crude product was then purified by column chromatography (hexane:EtOAc [9:1]) to yield butyrate **28** as a yellow oil. The product **28** was observed by ^{1}H-NMR to be contaminated with butyric anhydride. Further purification *via* column chromatography (hexane:EtOAc [9:1]) was attempted but the 213 mg of isolated butyrate **28** still retained a slight contamination of butyric anhydride. δ_H ($CDCl_3$: 360 MHz) 4.9 (PhC$\underline{H}_2$O), 5.1 (H5), 5.7 (H1'), 5.8 (PhC$\underline{H}$O).

Synthesis of 1'-D-6-O-(2'-azido-3'-O-benzyl-4',6'-O-benzylidene-2'-deoxy-α-D-glucopyranosyl)-1,2-O-(L-1,7,7-trimethyl[2.2.1]-bicyclohept-2-ylidene)-5-O-butyryl-myo-inositol 29

To a solution of butyrate **28** (0.22 mmol) in anhydrous THF (3.0 ml) at 0 °C was added TBAF (1.0 M solution in THF) (480 µl) and the reaction left to stir at R.T. under an inert atmosphere. After 1 hour TLC analysis (hexane:EtOAc [3:2]) indicated that the butyrate **28** starting material had been consumed. The reaction mixture was concentrated to dryness *in vacuo* before being purified by column chromatography (hexane:EtOAc [3:2]) to yield de-silylated butyrate **29** as a pale yellow oil (160 mg) [slight butyric anhydride impurity present in product **29**]. δ_H ($CDCl_3$: 360 MHz) 4.7 (2H, m, $PhC\underline{H}_2O$), 5.0 (1H, m, H5), 5.4 (1H, d, H1'), 5.5 (1H, s, $PhC\underline{H}O$).

Synthesis of 1'-D-6-O-(2'-azido-3'-O-benzyl-2'-deoxy-α-D-glucopyranosyl)-5-O-butyryl-myo-inositol 30

To a solution of de-silylated butyrate **29** (0.22 mmol) in DCM (15.0 ml) was added distilled water (240 µl) then TFA (1.0 ml) and the mixture stirred at R.T. After 20 hours TLC analysis (EtOAc) indicated consumption of butyrate **29** starting material. The reaction mixture was then concentrated to dryness *in vacuo* before the crude product was purified by column chromatography (EtOAc (100 %) then EtOAc:MeOH [10:1]) to yield the de-protected butyrate **30** (20 mg).

Synthesis of 1'-D-6-O-(2'-amino-2'-deoxy-α-D-glucopyranosyl)-5-O-butyryl-myo-inositol 31 (RGL 1125)

To a suspension of de-protected butyrate **30** (0.04 mmol) in a mixture of HPLC grade methanol:distilled water:AcOH [10:1:0.1] (1.5 ml) was added 10 % wt. Pd/C (8 mg) and the mixture stirred under an atmosphere of hydrogen at R.T. for 60 hours. The methanol was evaporated *in vacuo* before the crude product was suspended in distilled water then filtered through celite. The filtrate was then evaporated to dryness *in vacuo* to yield de-protected butyrate **31** as a colourless oil (14 mg).

Synthesis of RGL 1126

Synthesis of 1'-D-6-O-(2'-azido-3'-O-benzyl-4',6'-O-benzylidene-2'-deoxy-α-D-glucopyranosyl)-1,2-O-(L-1,7,7-trimethyl[2.2.1]-bicyclohept-2-ylidene)-3,4-O-(1,1,3,3,-tetraisopropyldisiloxanyl)-5-O-palmityl-myo-inositol 32

α-1,6 Anomer **11** (0.14 mmol) was dissolved in pyridine (2.5 ml) before palmitic anhydride (2.1 mmol) was added. The reaction mixture was then heated to reflux for 80 hours until TLC analysis (hexane:EtOAc [10:1]) indicated that the α-1,6 anomer **11** starting material had been consumed. The reaction mixture was concentrated to dryness *in vacuo*, using toluene to azeotropically remove the pyridine. The crude product was then purified by column chromatography (hexane:EtOAc [9:1]) [using a wide column to ensure separation of the large excess of palmitic anhydride] to yield palmitate **32** as a pale yellow oil (87 %). δ_H ($CDCl_3$: 360 MHz) 4.7 (2H, m, PhC<u>H</u>$_2$O), 4.9 (1H, m, H5), 5.4 (1H, d, H1'), 5.5 (1H, s, PhC<u>H</u>O).

Synthesis of 1'-D-6-O-(2'-azido-3'-O-benzyl-4',6'-O-benzylidene-2'-deoxy-α-D-glucopyranosyl)-1,2-O-(L-1,7,7-trimethyl[2.2.1]-bicyclohept-2-ylidene)-5-O-palmityl-myo-inositol 33

To a solution of palmitate **32** (0.12 mmol) in anhydrous THF (1.7 ml) at 0 °C was added TBAF (1.0 M solution in THF) (280 μl) and the reaction left to stir at R.T. under an inert atmosphere. After 1 hour TLC analysis (hexane:EtOAc [3:2]) indicated that the palmitate **32** starting material had been consumed. The reaction mixture was concentrated to dryness *in vacuo* before being purified by column chromatography (hexane:EtOAc [3:2]) to yield de-silylated palmitate **33** as a pale yellow oil (92 %). δ_H ($CDCl_3$: 360 MHz) 4.7 (2H, m, PhC<u>H</u>$_2$O), 5.2 (1H, d, H1'), 5.4 (1H, s, PhC<u>H</u>O).

Synthesis of 1'-D-6-O-(2'-azido-3'-O-benzyl-2'-deoxy-α-D-glucopyranosyl)-5-O-palmityl-myo-inositol 34

To a solution of de-silylated palmitate **33** (0.11 mmol) in DCM (9.0 ml) was added distilled water (150 μl) then TFA (630 μl) and the mixture stirred at R.T. After 18 hours TLC analysis (EtOAc) indicated consumption of palmitate **33** starting material.

The reaction mixture was then concentrated to dryness *in vacuo* before the crude product was purified by column chromatography (EtOAc (100 %) then EtOAc:MeOH [10:1]) to yield the de-protected palmitate **34** (25 %).

Synthesis of 1'-D-6-O-(2'-amino-2'-deoxy-α-D-glucopyranosyl)-5-O-palmityl-myo-inositol 35 (RGL 1126)

To a suspension of de-protected palmitate **34** (0.25 mmol) in a mixture of HPLC grade methanol:distilled water:AcOH [10:1:0.1] (1.5 ml) was added 10 % wt. Pd/C (6 mg) and the mixture stirred under an atmosphere of hydrogen at R.T. for 60 hours. The methanol was evaporated *in vacuo* before the crude product was suspended in distilled water and filtered through celite. The filtrate was then evaporated to dryness *in vacuo* to yield a colourless oil (7 mg).

Synthesis of RGL1119

2-Deoxy-3,4,6-tri-*O*-acetyl-2-trichloroacetamide-D-galactopyranosyl-β-(1→6)-1,2-diisopropylidene-3,4-(1',2'-dimethoxycyclohexane-1',2'-diyl)-3-*O*-methyl-D-*chiro*-inositol (3)

A 10 mL round-bottomed flash was charged with donor **1** (81 mg, 0.14 mmol, 1.6 eq.), acceptor **2** (32 mg, 0.08 mmol, 1.0 eq), freshly 4 Å molecular sieves and CH_2Cl_2 (2 mL) and the mixture was stirred for 1 h under Argon. Then TfOTMS was added (3.1 mL, 0.02 mmol, 0.2 eq) at 0°C and the reaction mixture was stirred for 5 h. The suspension was filtered through a short pad of celite and the solvent removed to provide the crude material. Flash chromatography (Hex/EtOAc 2:1) afforded **9b** (42 mg, 0.054 mmol, 63%). Rf (Hex/EtOAc 1:3): 0.52; $[\alpha]_D^{20}$-27.5 (c = 1.19, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) : δ = 6.59 (d, 1H, $J_{NH\text{-}H2'}$= 9.0 Hz, NH), 5.35 (d, 1H, J = 2.8 Hz, $H_{4'}$), 5.28 (d, 1H, J = 8.0 Hz, $H_{1'}$), 5.16 (dd, 1H, $J_{H3'\text{-}H2'}$= 11.0 Hz, $J_{H3'\text{-}H4'}$=2.8 Hz, $H_{3'}$), 4.46 (s, 1H, H_6), 4.26 (m, 1H, H_1),4.20-4.10 (m, 3H, $H_{2'}$, $H_{6a'}$, $H_{6b'}$), 4.07 (t, 1H, J = 6.0 Hz, H_2), 4.02 (t, 1H, J = 10.0 Hz, H_4), 3.95 (m, 1H, H_5), 3.85 (m, 1H, $H_{5'}$), 3.53 (s, 3H, OCH_3), 3.33 (t, 1H, J = 10.0 Hz, H_3), 3.22 (s, 3H, OCH_3, CDA), 3.20 (s, 3H, OCH_3, CDA), 2.16 (s, 3H, CH_3CO), 2.02 (s, 3H, CH_3CO), 1.98 (s, 3H, CH_3CO),

1.72-1.60 (m, 4H, $2CH_2$), 1.52-1.48 (m, 2H, CH_2), 1.51 (s, 1H, CH_3), 1.36-1.31 (m, 2H, CH_2), 1.34 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) : δ = 170.7 ($CH_3\underline{C}O$), 170.3 ($CH_3\underline{C}O$), 170.2 ($CH_3\underline{C}O$), 162.2 ($CCl_3\underline{C}O$),109.6 ($\underline{C}Cl_3CO$), 99.4 ($C_{1'}$), 97.9 (C, CDA), 97.8 (C, CDA), 92.2 (C), 83.5 (C_3), 79.6 (C_2), 76.0 (C_1), 72.2 (C_6), 71.2 ($C_{5'}$), 70.1 ($C_{3'}$), 68.2 (C_5), 67.7(C_4), 66.8 ($C_{4'}$), 61.4 ($C_{6'}$), 59.8 (OCH_3), 53.1 ($C_{2'}$), 47.3 (OCH_3, CDA), 46.9 (OCH_3, CDA), 28.5 ($2CH_2$), 27.2 (CH_3), 27.0 (CH_3), 26.2 ($2CH_2$), 21.4 ($\underline{C}H_3CO$), 20.7 ($\underline{C}H_3CO$), 20.6 ($\underline{C}H_3CO$).

2-Deoxy-2-trichloroacetamido-3,4,6-tri-*O*-acetyl-D-galactopyranosyl-β-(1→6)-3-*O*-methyl-D-*chiro*-inositol(4)

Pseudodisaccharide **3** (36 mg, 0.05 mmol, 1.0 eq) was dissolved in a mixture of trifluoroacetic acid/water (15:1, 3.2 mL) and stirred for 3 h at room temperature. The solvent was removed under vacuum and the crude was purified by flash chromatography to provide **4** (22 mg, 0.03 mmol, 75%) as a white solid. Rf (Cl_2CH_2/MeOH 7:1): 0.15; $[\alpha]_D^{20}$ -1.7 (c = 0.72, MeOH); ^1H NMR (MeOD, 500 MHz) : δ = 5.36 (d, 1H, $J_{H4'-H5'}$= 3.5 Hz, $H_{4'}$), 5.24 (dd, 1H, $J_{H3'-H2'}$= 11.1 Hz, $J_{H3'-H4'}$=3.5 Hz $H_{4'}$), 5.01 (d, 1H, J = 8.5 Hz, $H_{1'}$), 4.16 (m, 2H, $H_{6a'}$, $H_{6b'}$), 4.08 (dd, 1H, $J_{H2'-H3'}$= 11.2 Hz, $J_{H2'-H1'}$= 8.5 Hz, $H_{2'}$), 4.05-4.02 (m, 2H, $H_{5'}$, H_6), 3.98 (t, 1H, J= 3.0 Hz, H_1), 3.79 (dd, 1H, J_{H5-H4}= 9.5 Hz, J_{H5-H6}= 3.0 Hz, H_5), 3.70 (dd, 1H, J_{H2-H3}= 9.7 Hz, J_{H2-H1}= 3.0 Hz, H_2), 3.58 (m, 1H, H_4), 3.56 (s, 3H. OCH_3), 3.22 (t, 1H, J = 9.7 Hz, H_3), 2.16 (s, 3H, $\underline{C}H_3CO$), 2.05 (s, 3H, CH_3CO), 1.93 (s, 3H, CH_3CO); ^{13}C NMR (MeOD, 125 MHz) : δ = 170.8 ($CH_3\underline{C}O$), 170.6 ($CH_3\underline{C}O$), 170.1 ($CH_3\underline{C}O$), 163.2 ($Cl_3C\underline{C}O$), 101.3 ($C_{1'}$), 92.5 ($Cl_3\underline{C}CO$), 83.3 (C_3), 79.1 (C_6), 72.4 (C_4), 71.4 (C_1), 71.0 (C_5), 70.6 ($C_{5'}$), 70.4 (C_2), 70.3 ($C_{3'}$), 66.9 ($C_{4'}$), 61.3 ($C_{6'}$), 58.9 (OCH_3), 52.5 ($C_{2'}$), 19.2, 19.1, 19.0 ($3\underline{C}H_3CO$); anal. calcd. for $C_{21}H_{30}NO_{14}Cl_3$: C, 40.24%; H, 4.82%; N, 2.23%; found: 38.89%; H, 5.17%; N, 1.94%.

2-amino-2-deoxy-D-galactopyranosyl-β-(1→6)-3-*O*-methyl-D-*chiro*-inositol (5, RGL 1119)

Compound **4** (6 mg, 10 mmol) and $Ba(OH)_2$ (8 mg, 0.094 mmol, 4.8 eq.) was stirred in water/EtOH 1:1 (4 mL) for 1 h at 90°C, whereupon the solvent was removed under vacuum. Cold water was added to the residue and filtered through a paper filter to eliminate $Ba(OH)_2$.. The filtrate was removed under vacuum and the residue was redissolved in the minimum amount of MeOH and loaded onto a Varian CBA (carboxylic acid) cartridge (3 cm^3/500 mg) preequilibrated with MeOH. After elution with some lengths of MeOH to remove barium salts, pseudodisaccharide was neutralized loading it directly onto a Varian PSA (ethylenediamine-N-propyl) cartridge preequilibrated with MeOH to give **RGL 1119** (3 mg, 8 mmol, 79%). R_f (EtOAc/MeOH/H_2O/AcOH 2:2:1:1): 0.29; $[\alpha]_D^{20}$ +8.1 (c = 0.28, H_2O); ^1H NMR (D_2O, 500 MHz): δ = 4.32 (d, 1H, J = 9.0 Hz, $H_{1'}$), 4.15 (bt, 1H, J = 3.5 Hz, H_6), 3.90 (bt, 1H, J = 3.5 Hz, H_1), 3.75-3.71 (m, 3H, H_5, H_2, $H_{4'}$), 3.68-3.53 (m, 4H, $H_{6a'}$, $H_{6b'}$, $H_{5'}$, H_4), 3.47 (s,3H, OCH_3), 3.42 (dd, 1H, $J_{H3'-H2'}$= 10.0 Hz, $J_{H3'-H4'}$= 3.5 Hz, $H_{3'}$), 3.21 (t, 1H, J = 9.5 Hz, H_3), 2.74 (t, 1H, J = 9.0 Hz $H_{2'}$); ^{13}C NMR ($CDCl_3$, 125 MHz) : δ = 100.8 ($C_{1'}$), 83.5 (C_3), 82.2 (C_1), 75.9 (C_4), 73.9 ($C_{3'}$), 73.1 ($C_{5'}$), 71.3 (C_6), 70.8 (C_2), 70.0 (C_5), 68.2 ($C_{4'}$), 62.4 ($C_{6'}$), 53.7 ($C_{2'}$). CI HRMS calcd. for $C_{13}H_{25}NO_{10}$ (M^++H): 356.1556, found: 356.1548.

Synthesis of RGL 1134

1'-D-6-*O*-(2'-azido-3'-*O*-benzyl-2'-deoxy-α-D-glucopyranosyl)-3,4,5-tri-*O*-benzyl-*myo*-inositol (2)

To a mixture of the disaccharide **1** (0.72 g, 0.75 mmol) in DCM (45 ml) was added water (0.82 ml, 0.82 g, 45.6 mmol) and trifluoroacetic acid (5.18 g, 3.5 mmol, 45.4 mmol) at room temperature for 1.25 h. The mixture was diluted with DCM (100 ml) and washed with $NaHCO_3$ (3 x 50 ml) and brine (1 x 50 ml). The solvent was dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a crude oil (0.84 g). The tetrol **2** (0.37 g, 67%) was isolated after flash chromatography (silica, 60→80→100% ethyl acetate/hexanes).

1'-D-6-*O*-(2'-azido-3'-*O*-benzyl-6'-*O*-DMT-2'-deoxy-α-D-glucopyranosyl)-3,4,5-tri-*O*-benzyl-*myo*-inositol (3)

The tetrol **2** (110 mg, 0.15 mmol) was co-evaporated with pyridine (2 x 1 ml) and dissolved in pyridine (2 ml). To the solution was added DMTCl (78 mg, 1.5 eq) and the reaction stirred for 16 h. The solvent was removed *in vacuo* and the residue dissolved in DCM (30 ml). The solution was washed with $NaHCO_3$ (sat, 2 x 20 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residual pyridine was removed by co-evaporation with toluene. The product (100 mg, 97 μmol) was isolated by flash chromatography (silica, 10%→50% ethyl acetate/hexanes).

1'-D-6-*O*-(2'-azido-3'-*O*-benzyl-4'-*O*-phosphate-6'-*O*-DMT-2'-deoxy-α-D-glucopyranosyl)-3,4,5-tri-*O*-benzyl-*myo*-inositol-1,2-cyclic phosphate, sodium salt (4)

Methyldichlorophosphate (30 μl, 0.29 mmol, 3 eq) was added to pyridine (630 μl) with stirring under an atmosphere of nitrogen at room temperature. After 30 min the triol **3** (100 mg, 0.10 mmol) in pyridine (100 μl) was added and the reaction stirred for a further 4 h. The reaction was diluted with DCM (10 ml) and quenched by addition of $NaHCO_3$ solution. The resulting emulsion was separated by the addition of brine and the aqueous phase extracted with DCM (1 x 10 ml). The combined organic solvents were dried (Na_2SO_4), filtered and concentrated *in vacuo* to yield the required product **4** (17 mg, 13.8 μmol, 14%, R_f 0.04 20% ethyl acetate/hexanes).

1'-D-6-*O*-(2'-azido-3'-*O*-benzyl-4'-*O*-phosphate-2'-deoxy-α-D-glucopyranosyl)-3,4,5-tri-*O*-benzyl-*myo*-inositol-1,2-cyclic phosphate, sodium salt (5)

To a stirred solution of compound **4** (17 mg, 13.4 μmol) in DCM (2 ml) was added a solution of TFA in DCM (2 %, 2 ml) at 0°C. TLC indicated the reaction proceeded to completion in *ca.* 1 min. The reaction was quenched by addition of $NaHCO_3$ (sat. 5 ml), diluted with DCM (10 ml). The phases were separated and the organic phase dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (silica, 1:1 ethyl acetate/hexanes→ethyl acetate) to yield the

product as a colourless solid (10 mg, 10.8 μmol, 81%). ^{1}H-NMR (250 MHz), δ (ppm): 7.25 (m, 20 H); 5.3 (d, 1 H, H-1'); 5.0 (d, 1 H); 4.7 (m); 7.6 (*b*s, 1 H); 3.9 (m, 2 H); 3.64 (m); 3.3 (m); 2.62 (s, 1 H); 2.22 (d, 1 H).

1'-D-6-*O*-(2'-amino-3'-*O*-benzyl-4'-*O*-phosphate-2'-deoxy-α-D-glucopyranosyl)-3,4,5-tri-*O*-benzyl-*myo*-inositol-1,2-cyclic phosphate, sodium salt (6, RGL 1134)

Pd/C (10%, 5 mg) was added to a solution of compound **5** (10 mg, 10.8 μmol) in methanol/THF/H_2O (1:1:1, 3 ml) and stirred at room temperature overnight under an atmosphere of hydrogen. The mixture was filtered through celite and the celite washed with methanol (2 x 5 ml) and water (2 x 5 ml). The solution was concentrated *in vacuo* to yield a colourless solid. Residual celite was removed by filtration through cotton wool and the crude product **RGL 1134** (12 mg) was isolated after evaporation *in vacuo*. ^{1}H-NMR (250 MHz), δ (ppm): 7.4 (m, 20 H); 5.38 (d, 1 H, H-1'); 5.0 (d, 1 H); 4.8 (m); 4.18 (*b*s, 1 H); 3.9 (m, 2 H); 3.8 (*b*d, 1 H); 3.6 (m, 2 H); 3.22 (m, 4 H); 2.65 (m, 1 H).

Synthesis of RGL1135

1'-D-6-*O*-(2'-azido-3'-*O*-benzyl-4',6'-di-*O*-cyclic phosphate-2'-deoxy-α-D-glucopyranosyl)-3,4,5-tri-*O*-benzyl-*myo*-inositol-1,2-cyclic phosphate, triethylammonium salt (2)

Methyldichlorophosphate (30 μl, 0.29 mmol, 3 eq) was added to pyridine (630 μl) with stirring under an atmosphere of nitrogen at room temperature. After 30 min compound **1** (100 mg, 0.14 mmol) in pyridine (100 μl) was added and the reaction stirred for a further 4 h. The reaction was diluted with DCM (10 ml) and quenched by addition of $NaHCO_3$ solution. The resulting emulsion was separated by the addition of brine and the aqueous phase extracted with DCM (1 x 10 ml). The combined organic solvents were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude material was purified by preparative TLC (methanol/DCM/Et_3N 10:90:1) to yield compound **2** (11 mg, 7.5%).

1'-D-6-*O*-(2'-amino-3'-*O*-benzyl-4',6'-di-*O*-cyclic phosphate-2'-deoxy-α-D-glucopyranosyl)-3,4,5-tri-*O*-benzyl-*myo*-inositol-1,2-cyclic phosphate, triethylammonium salt (3, RGL 1135)

Compound **2** (11 mg, 10.4 μmol) in THF/ethanol/water (1:1:1, 3 ml) was stirred at room temperature for 22 h under an atmosphere of hydrogen. The mixture was filtered through celite and washed with methanol. The solvent was removed *in vacuo* to yield **RGL 1135** (8 mg, 71%). ^{1}H-NMR (250 MHz), δ (ppm): 7.25 (m, 20 H); 5.6 (d, 1 H, H-1'); 5.0 (d, 1 H); 4.8 (m); 4.4 (m); 4.2 (m); 4.0 (m); 3.7 (m); 3.45 (m, 1 H); 3.25 (dd, 1 H); 3.1 (c); 2.1 (s, 1 H); 1.3 (t).

Synthesis of RGL 1133

1'-D-6-*O*-(2'-azido-3'-*O*-benzyl-4',6'-di-*O*-sulphate-2'-deoxy-α-D-glucopyranosyl)-3,4,5-tri-*O*-benzyl-*myo*-inositol-1,2-di-*O*-sulphate, sodium salt (2).

A mixture of the tetrol **1** (88 mg, 0.12 mmol), sulfur trioxide-trimethylamine complex (0.32 g, 2.30 mmol, 20 eq) in DMF was heated for 16 h at 50°C. The DMF was removed *in vacuo* and the residue dissolved in MeOH/water (9:1, 5 ml). Portions (1 ml) were taken for prep. TLC (R_f 0.2, 4:1 EtOH/0.88 ammonia solution). Each 1 ml portion yielded *ca.* 15 mg (11 % per pTLC). The ammonium salts were dissolved in MeOH/water (9:1) and passed through Dowex (Na^+) to give a quantitative return of the sodium salt after concentration *in vacuo*, re-dissolution in water and lyophilisation. ^{1}H-NMR (250 MHz), δ (ppm): 7.35 (m 20 H); 5.85 (d, 1 H), 5.55 (s, 1 H); 5.15 (d, 1 H), 4.8 (m), 4.25 (m); 3.95 (c, 2 H); 3.48 (m, 3 H); 3.25 (m); 2.95. IR (cm^{-1}): 3460.44; 2111.27; 1633.18; 1496.32; 1453.97; 1213.66; 1123.57; 1047.01; 1016.31; 922.85; 802.42; 747.37; 696.33; 582.86

1'-D-6-*O*-(2'-amino-3'-*O*-benzyl-4',6'-di-*O*-sulphate-2'-deoxy-α-D-glucopyranosyl)-3,4,5-tri-*O*-benzyl-*myo*-inositol-1,2-di-*O*-sulphate, sodium salt (3)

A mixture of the tetrasulfate **2** (17 mg, 15 μmol), Pd/C (10%, 13 mg), ammonium acetate (5 mg) in THF/ethanol/water (1:1:1, 3 ml) was stirred at room temperature for 22 h. The mixture was filtered through celite and the celite washed with methanol. The solvent was removed *in vacuo* and the residue dissolved in water. Compound **3, RGL 1133** (14 mg, 84 %) was isolated after freeze drying. ^{1}H-NMR (250 MHz), δ (ppm): 7.4, (m, 20 H); 5.5, (s, 1 H); 5.18 (s, 1 H); 4.8 (m, 8 H), 4.1 (m, 6 H); 3.6 (m, 7 H). IR (cm^{-1}): 2924.62; 1573.89; 1496.74; 1453.79; 1214.25; 1130.12; 1048.06; 996.84; 925.29; 802.77; 748.57; 696.19; 579.54.

Synthesis of RGL 1130

1'-D-6-*O*-(2'-azido-3',6'-di-*O*-benzyl-2'-deoxy-α-D-glucopyranosyl)-1,2-*O*-(L-1,7,7-trimethyl[2.2.1]-bicyclohept-2-ylidene)-3,4,5-tri-*O*-benzyl-*myo*-inositol and 1'-D-6-*O*-(2'-azido-3',4'-di-*O*-benzyl-2'-deoxy-α-D-glucopyranosyl)-1,2-*O*-(L-1,7,7-trimethyl[2.2.1]-bicyclohept-2-ylidene)-3,4,5-tri-*O*-benzyl-*myo*-inositol (2)

Compound **1** (150 mg, 0.16 mmol) was dissolved in dry THF (3.75 ml) and sodium cyanoborohydride (2.07 ml, 1 M in THF) was added. The mixture was stirred at room temperature for 15 min and hydrogen chloride (*ca.* 1.8 ml, 1 M in diethyl ether) added until gas evolution ceased. The turbid mixture was stirred for a further 1.5 h. The mixture was diluted with DCM (10 ml) and washed with $NaHCO_3$ (sat, 2 x 25 ml). The aqueous phase was extracted with DCM (2 x 20 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting yellow material was purified by column chromatography (silica, 15%→20% ethyl acetate/hexanes) yielding the desired product (110 mg, 73%, 1:1 mixture of 4' and 6' ethers).

1'-D-6-*O*-(2'-azido-3',6'-di-*O*-benzyl-4'-*O*-(dibenzyl)phosphate-2'-deoxy-α-D-glucopyranosyl)-1,2-*O*-(L-1,7,7-trimethyl[2.2.1]-bicyclohept-2-ylidene)-3,4,5-tri-*O*-benzyl-*myo*-inositol and 1'-D-6-*O*-(2'-azido-3',4'-di-*O*-benzyl-6'-*O*-(dibenzyl)phosphate 2'-deoxy-α-D-glucopyranosyl)-1,2-*O*-(L-1,7,7-trimethyl[2.2.1]-bicyclohept-2-ylidene)-3,4,5-tri-*O*-benzyl-*myo*-inositol (3)

To a solution of the disaccharides **2** (100 mg, 0.1 mmol) and tetrazole (38 mg, 0.55 mol) in dry DCM (10 ml) at 0°C was added dibenzyl diisopropylphosphramidite (140µl). After 2.5 h, the mixture was cooled to -40 °C and *m*CPBA (60 mg) in DCM (4 ml) was added. The reaction mixture was warmed to room temperature and stirred for 2.5 h. The mixture was diluted with DCM (20 ml), washed with sodium metabisulfite (2 x 10 ml), $NaHCO_3$ (sat. 2 x 10 ml) and brine (2 x 10 ml). The solution was dried ($MgSO_4$) and concentrated *in vacuo*. The mixture of products (100 mg, 78%) was isolated after column chromatography (silica, 20% ethyl acetate/hexanes).

1'-D-6-*O*-(2'-azido-3',6'-di-*O*-benzyl-4'-*O*-(dibenzyl)phosphate-2'-deoxy-α-D-glucopyranosyl)-3,4,5-tri-*O*-benzyl-*myo*-inositol and 1'-D-6-*O*-(2'-azido-3',4'-di-*O*-benzyl-6'-*O*-(dibenzyl)phosphate 2'-deoxy-α-D-glucopyranosyl)-3,4,5-tri-*O*-benzyl-*myo*-inositol (4)

To a mixture of Compounds **3** (110 mg, 89.6 µmol) in DCM (45 ml) was added water (approx. 1 ml) and TFA (3.5 ml) at room temperature and kept stirring for 2 h. The mixture was diluted with DCM (100 ml) and washed with $NaHCO_3$ (3 x 50 ml) and brine (50 ml). The solvent was dried ($MgSO_4$), filtered and concentrated to yield compounds **4** (80 mg, 82%), which were isolated after column chromatography (silica, 50%→60% ethyl acetate/hexanes).

1'-D-6-*O*-(2'-amino-4'-*O*-phosphate-2'-deoxy-α-D-glucopyranosyl)-*myo*-inositol-1,2-cyclic phosphate and 1'-D-6-*O*-(2'-amino-6'-*O*-phosphate-2'-deoxy-α-D-glucopyranosyl)-*myo*-inositol-1,2-cyclic phosphate (5, RGL 1130)

Dichloromethylphosphate (40 µl) was added to pyridine (700 µl) and stirred for 30 min. Compounds **4** (80 mg, 73.1 µmol) were dissolved in a minimum of pyridine and added to the dichloromethylphosphate solution and stirred for 2.5 h. $NaHCO_3$ (sat. 2 ml) was added and the solvent removed *in vacuo*. The residue was taken up in water (10 ml) and acidified (pH 1) with dilute HCl. The aqueous solution was extracted with ethyl acetate (2 x 50 ml), dried ($MgSO_4$) and concentrated under reduced

pressure. The oil was dissolved in THF/EtOH/water (1:1:1, 15 ml) and the resulting solution was degassed and flushed with nitrogen. Pd/C (10 %, 150 mg) and ammonium acetate (40 mg) were added and the reaction placed under an atmosphere of hydrogen. The mixture was stirred for 24 h and the reaction mixture filtered through celite and the celite was washed with water and ethanol. The solvent was removed *in vacuo* and the residue co-evaporated with ethanol (2 x) and toluene (3 x) to give compound **5, RGL 1130** as a crude solid (30 mg). ^{1}H-NMR (500 MHz), δ (ppm): 5.38 (*bs*); 4.7 (m); 4.5 (dt); 4.17-3.17 (m); 2.7 (s); 2.4-2.28 (m); 2.23-2.03 (m); 1.13-1.19 (m).

Assay Data

PDH activation:	**100μM**
RGL1023	14%
RGL1027	132%
RGL1029	361%
RGL1015	38%
RGL1024	65%
RGL1025	17%

PKA inhibition:

	0.1μM	**1.0μM**	**10μM**
RGL1027	18%		10%
RGL1029	59%		33%
RGL1018	19%		-
RGL1019	32%		31%
RGL1015	14%	15%	12%
RGL1024	17%	34%	2%
RGL1025	48%	-13%	

Figure 4 shows the result of an assay measuring the effect of compound RGL1133 in inhibiting glucose 6-phosphatase, as compared to an known inhibitor, sodium O-vanadate. The results show that RGL1133 is a good inhibitor of G6Pase activity and would be useful for decreasing hepatic glucose output in diabetic subjects. This suggests that this compound would be useful in the treatment of both type I and type II diabetes.

References:

The references mentioned herein are all expressly incorporated by reference.

[1](a) Varela-Nieto et al, *Comp. Biochem. Physiol.*,. 115B:223-241, 1996; (b) Strälfors, *Bioassays*, 19:327-335, 1997; (c) Field, *Glycobiology*, 7:161-168, 1997; d) Jones & Varela-Nieto, *Int. J. Biochem. Cell Biol.*, 30:313-326, 1998.

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WO98/11116 and WO98/11117 (Rademacher Group Limited).

WO98/11435 and WO98/10791 (Rademacher Group Limited).

WO99/38516 (Rademacher Group Limited).

Claims:

1. A compound represented by the general formula:

X-1,6-cyclitol

wherein:

X represents a sugar residue;

the sugar residue is unsubstituted or substituted with between one and four groups, and the cyclitol is unsubstituted or is further substituted with between one and four groups, the group or groups being independently selected from;

(a) phosphoryl groups such as phosphate -O-P(O)$(OH)_2$; thiophosphate -O-P(S)$(OH)_2$; phosphate esters -O-P(O)$(OR)_2$; thiophosphate esters -O-P(S)$(OR)_2$; phosphonate -O-P(O)OHR; thiophosphonate -O-P(S)OHR; substituted phosphonate -O-P(O)OR_1R_2; substituted thiophosphonate -O-P(S)OR_1R_2; -O-P(S)(OH)(SH); cyclic phosphate;

(b) other phosphorus containing compounds such as phosphoramidite -O-P(OR)-NR_1R_2 and phosphoramidate -O-P(O)(OR)-NR_1R_2;

(c) sulphur groups such as -O-S(O)(OH), -SH, -SR, -S(→O)-R, -$S(O)_2$R, RO-$S(O)_2^-$, -O-SO_2NH_2, -O-$SO_2R_1R_2$ or sulphamide -$NHSO_2NH_2$;

(d) amino groups such as -NHR, -NR_1R_2, -NHAc, -NHCOR, -NH-O-COR, -$NHSO_3^-$, -$NHSO_2$R, -$N(SO_2R)_2$, and/or amidino groups such as -NH-C(=NH)NH_2 and/or ureido groups such as -NH-CO-NR_1R_2 or thiouriedo groups such as -NH-C(S)-NH_2;

(e) hydroxy groups and substituted hydroxy groups such as -OR_3, where R_3 is C_{1-10} unsubstituted or substituted alkyl, e.g. CHF_2 or CF_3, alkoxyalkyl, aryloxyalkyl, cycloalkyl, alkenyl (unsubstituted alkyl), alkylene (C_{3-7} cycloalkyl), -OCOR, aryl, heteroaryl, acetal, or where two hydroxyl groups are joined as a ketal;

(f) halogen substituents such as fluorine or chlorine;

(g) hydrogen, e.g. to provide a deoxy sugar;

wherein R, R_1 and R_2 are independently hydrogen or C_{1-10} unsubstituted or substituted alkyl or aryl;

or a derivative thereof;

with the proviso that the compound is not 1-D-4-*O*-(2-amino-2-deoxy-α-D-glucopyranosyl)-*myo*-inositol 1-phosphate, 1-D-6-*O*-(2-amino-2-deoxy-α-D-glucopyranosyl)-*myo*-inositol 1-phosphate, 1-D-6-*O*-(2-amino-2-deoxy-α-D-glucopyranosyl)-*myo*-inositol 1,2 cyclic-phosphate, 1-D-6-*O*-(2-amino-2-deoxy-α-D-glucopyranosyl)-*chiro*-inositol 1-phosphate, *O*-(6-hydrogenphosphonate-α-D-mannopyranosyl)-(1→4)-(2-ammonio-2-deoxy-α-D-glucopyranosyl)-(1→6)-L-*myo*-inositol-1,2-cyclic phosphate or *O*-(6-hydrogenphosphonate-α-D-mannopyranosyl)-(1→4)-(2-amino-2-deoxy-α-D-glucopyranosyl)-L-*myo*-inositol.

2. The compound of claim 1, wherein the sugar reside and cyclitol moiety are α linked.

3. The compound of claim 1 wherein the sugar reside and cyclitol moiety are β linked.

4. The compound of any one of claims 1 to 3, wherein the cyclitol is selected from *myo*-inositol, *chiro*-inositol or pinitol.

5. The compound of any one of the preceding claims, wherein the sugar residue is a hexose or a pentose, or substituted forms thereof.

6. The compound of claim 5, wherein the sugar residue is a hexose selected from the group consisting of glucose, galactose or mannose.

7. The compound of claim 5, wherein the sugar residue is a hexosamine.

8. The compound of claim 7, wherein the hexosamine is galactosamine or glucosamine.

9. The compound of any one of the preceding claims, wherein the cyclitol is a D or L-enantionmer.

10. The compound which is selected from the group consisting of:

RGL1023 *O*-(2'-amino-2'-deoxy-6'-phosphate-D-glucopyranosyl)-α(1,6)-D-*myo*-inositol;

RGL1027 *O*-(2'-amino-2'-deoxy-4'-phosphate-D-glucopyranosyl)-α(1,6)-D-*myo*-inositol;

RGL1029 *O*-(2'-amino-2'-deoxy-3'-phosphate-D-glucopyranosyl)-α(1,6)-D-*myo*-inositol;

RGL1017 *O*-(2'-amino-2'-deoxy-D-glucopyranosyl)-α(1,6)-D-*chiro*-inositol;

RGL1024 *O*-(2-amino-2-deoxy-D-glucopyranosyl)-α(1,6)-D-3-*O*-methyl-*chiro*-inositol;

RGL1025 *O*-(2-amino-2deoxy-D-galactopyranosyl)-α(1,6)-D-3-*O*-methyl-*chiro*-inositol;

RGL1018 *O*-(2'-amino-2'-deoxy-D-glucopyranosyl)-β(1,6)-D-*chiro*-inositol;

RGL1019 *O*-(2'-amino-2'-deoxy-D-glucopyranosyl)-α(1,6)-D-*chiro*-inositol-1-phosphate;

RGL1015 *O*-(2-amino-2-deoxy-D-glucopyranosyl)-β(1,6)-3-*O*-methyl-*chiro*-inositol;

RGL1105 1''-D-4'-*O*-(6''-phosphate-α-D-mannopyranosyl)-[1'-D-6-*O*-(2'-amino-2'-deoxy-α-D-glucanopyranosyl)-*myo*-inositol];

RGL1115 1'-D-6-*O*-(2'-amino-2'-deoxy-α-D-glucopyranosyl)-5-*O*-phosphate-*myo*-inositol;

RGL1121 1'-D-1-*O*-(2'-amino-2'-deoxy-α-D-galactopyranosyl)-D-*chiro*-inositol;

RGL1120 1'-D-6-*O*-(2'-amino-2'-deoxy-β-D-glucopyranosyl)-D-*chiro*-inositol;

RGL1129 1'-D-2-*O*-(2'-amino-2'-deoxy-α-D-galactopyranosyl)-D-*chiro*-inositol;

RGL1122 1'-D-5-*O*-(2'-amino-2'-deoxy-α-D-glucopyranosyl)-D-*chiro*-inositol;

RGL1115 1'-D-6-*O*-(2'-amino-2'-deoxy-α-D-glucanopyranosyl)-5-*O*-phosphate-*myo*-inositol;

RGL1116 1'-D-6-*O*-(2'-amino-2'-deoxy-α-D-glucopyranosyl)-D-5-*O*-acetyl-*myo*-inositol;

RGL1117 1'-D-5-*O*-(2'-amino-2'-deoxy-α-D-glucopyranosyl)-D-6-*O*-acetyl-*myo*-inositol;

RGL1119 1'-D-6-*O*-(2'-amino-2'-deoxy-β-D-galactopyranosyl)-3-*O*-methyl-D-*chiro*-inositol;

RGL1124 1'-D-6-O-(2'-amino-2'-deoxy-β-D-glucopyranosyl)-5-O-acetyl-myo-inositol;

RGL1125 1'-D-6-O-(2'-amino-2'-deoxy-α-D-glucopyranosyl)-5-O-butyryl-myo-inositol;

RGL1126 1'-D-6-O-(2'-amino-2'-deoxy-α-D-glucopyranosyl)-5-O-palmityl-myo-inositol;

RGL1134 1'-D-6-*O*-(2'-amino-3'-*O*-benzyl-4'-*O*-phosphate-2'-deoxy-α-D-glucopyranosyl)-3,4,5-tri-*O*-benzyl-*myo*-inositol-1,2-cyclic phosphate;

RGL1133 1'-D-6-*O*-(2'-amino-3'-*O*-benzyl-4',6'-di-*O*-sulphate-2'-deoxy-α-D-glucopyranosyl)-3,4,5-tri-*O*-benzyl-*myo*-inositol-1,2-di-*O*-sulphate;

RGL1135 1'-D-6-*O*-(2'-amino-3'-*O*-benzyl-4',6'-di-*O*-cyclic phosphate-2'-deoxy-α-D-glucopyranosyl)-3,4,5-tri-*O*-benzyl-*myo*-inositol-1,2-cyclic phosphate;

RGL1130 1'-D-6-*O*-(2'-amino-4'-*O*-phosphate-2'-deoxy-α-D-glucopyranosyl)-*myo*-inositol-1,2-cyclic phosphate;

1'-D-6-*O*-(2'-amino-6'-*O*-phosphate-2'-deoxy-α-D-glucopyranosyl)-*myo*-inositol-1,2-cyclic phosphate;

or a substituted form or derivative thereof.

11. A compound represented by the general formula:

X-α1,6-cyclitol

wherein:

X represents a sugar residue;

the sugar residue is unsubstituted or substituted with between one and four groups, and the cyclitol is unsubstituted or is further substituted with between one and four groups, the group or groups being independently selected from:

(a) phosphoryl groups such as phosphate -O-P(O)$(OH)_2$; thiophosphate -O-P(S)$(OH)_2$; phosphate esters -O-P(O)$(OR)_2$; thiophosphate esters -O-P(S)$(OR)_2$; phosphonate -O-P(O)OHR; thiophosphonate -O-P(S)OHR; substituted phosphonate -O-P(O)OR_1R_2; substituted thiophosphonate -O-P(S)OR_1R_2; -O-P(S)(OH)(SH); cyclic phosphate;

(b) other phosphorus containing compounds such as phosphoramidite -O-P(OR)-NR_1R_2 and phosphoramidate -O-P(O)(OR)-NR_1R_2;

(c) sulphur groups such as -O-S(O)(OH), -SH, -SR, -S(→O)-R, -$S(O)_2$R, RO-$S(O)_2^-$, -O-SO_2NH_2, -O-$SO_2R_1R_2$ or sulphamide -$NHSO_2NH_2$;

(d) amino groups such as -NHR, -NR_1R_2, -NHAc, -NHCOR, -NH-O-COR, -$NHSO_3^-$, -$NHSO_2$R, -$N(SO_2R)_2$, and/or amidino groups such as -NH-C(=NH)NH_2 and/or ureido groups such as -NH-CO-NR_1R_2 or thiouriedo groups such as -NH-C(S)-NH_2;

(e) hydroxy groups and substituted hydroxy groups such as -OR_3, where R_3 is C_{1-10} unsubstituted or substituted alkyl, e.g. CHF_2 or CF_3, alkoxyalkyl, aryloxyalkyl, cycloalkyl, alkenyl (unsubstituted alkyl), alkylene (C_{3-7} cycloalkyl), -OCOR, aryl, heteroaryl, acetal, or where two hydroxyl groups are joined as a ketal;

(f) halogen substituents such as fluorine or chlorine;

(g) hydrogen, e.g. to provide a deoxy sugar;

wherein R, R_1 and R_2 are independently hydrogen or C_{1-10} unsubstituted or substituted alkyl or aryl;

or a derivative thereof;

with the proviso that the compound is not 1-D-4-*O*-(2-amino-2-deoxy-α-D-glucopyranosyl)-*myo*-inositol 1-phosphate, 1-D-6-*O*-(2-amino-2-deoxy-α-D-glucopyranosyl)-*myo*-inositol 1-phosphate, 1-D-6-*O*-(2-amino-2-deoxy-α-D-glucopyranosyl)-*myo*-inositol 1,2 cyclic-phosphate, 1-D-6-*O*-(2-amino-2-deoxy-α-D-

glucopyranosyl)-*chiro*-inositol 1-phosphate, *O*-(6-hydrogenphosphonate-α-D-mannopyranosyl)-(1→4)-(2-ammonio-2-deoxy-α-D-glucopyranosyl)-(1→6)-L-*myo*-inositol-1,2-cyclic phosphate or *O*-(6-hydrogenphosphonate-α-D-mannopyranosyl)-(1→4)-(2-amino-2-deoxy-α-D-glucopyranosyl)-L-*myo*-inositol.

12. A compound represented by the general formula:

X-β1,6-cyclitol

wherein:

X represents a sugar residue;

the sugar residue is unsubstituted or substituted with between one and four groups, and the cyclitol is unsubstituted or is further substituted with between one and four groups, the group or groups being independently selected from:

(a) phosphoryl groups such as phosphate -O-P(O)$(OH)_2$; thiophosphate -O-P(S)$(OH)_2$; phosphate esters -O-P(O)$(OR)_2$; thiophosphate esters -O-P(S)$(OR)_2$; phosphonate -O-P(O)OHR; thiophosphonate -O-P(S)OHR; substituted phosphonate -O-P(O)OR_1R_2; substituted thiophosphonate -O-P(S)OR_1R_2; -O-P(S)(OH)(SH); cyclic phosphate -O-P(O)$(OR)_2$;

(b) other phosphorus containing compounds such as phosphoramidite -O-P(OR)-NR_1R_2 and phosphoramidate -O-P(O)(O^-)-NR_1R_2;

(c) sulphur groups such as -O-S(O)$(OH)_2$, -SH, -SR, -S(→O)-R, -S$(O)_2$R, RO-S$(O)_2^-$, -O-SO_2NH_2, -O-$SO_2R_1R_2$ or sulphamide -$NHSO_2NH_2$;

(d) amino groups such as -NHR, -NR_1R_2, -NHAc, -NHCOR, -NH-O-COR, -$NHSO_3^-$, -$NHSO_2$R, -N(SO_2R), and/or amidino groups such as -NH-C(=NH)NH_2 and/or ureido groups such as -NH-CO-NR_1R_2 or thiouriedo groups such as -NH-C(S)-NH_2;

(e) hydroxy groups and substituted hydroxy groups such as -OR_3, where R_3 is C_{1-10} unsubstituted or substituted alkyl, e.g. CHF_2 or CF_3, alkoxyalkyl, aryloxyalkyl,

cycloalkyl, alkenyl (unsubstituted alkyl), alkylene (C_{3-7} cycloalkyl), -OCOR, aryl, heteroaryl, acetal, or where two hydroxyl groups are joined as a ketal;

(f) halogen substituents such as fluorine or chlorine;

(g) hydrogen, e.g. to provide a deoxy sugar.

wherein R, R_1 and R_2 are independently hydrogen or C_{1-10} unsubstituted or substituted alkyl or aryl;

or a derivative thereof.

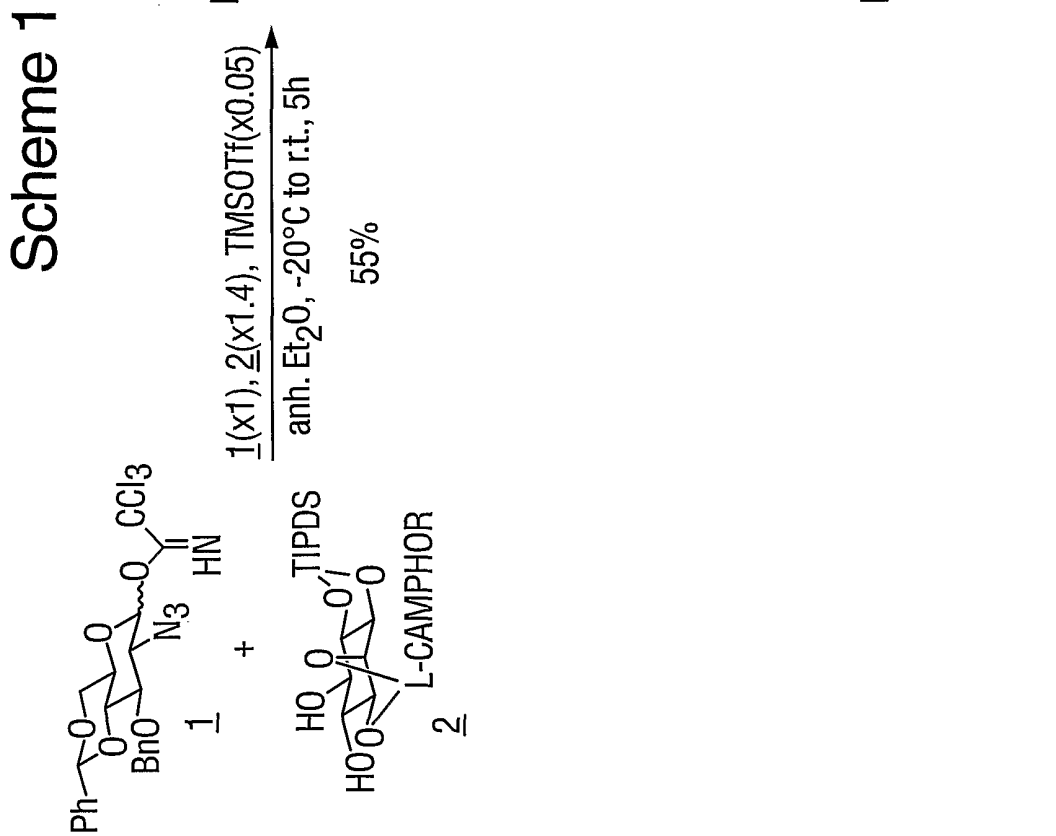
13. A composition comprising a compound of any one of the preceding claims, in combination with a pharmaceutically acceptable carrier.

14. A method of treating a condition in a mammal ameliorated by an inositol phosphoglycan (IPG) second messenger or an IPG antagonist, the method comprising administering to the mammal a therapeutically effective amount of a compound of any one of claims 1 to 12.

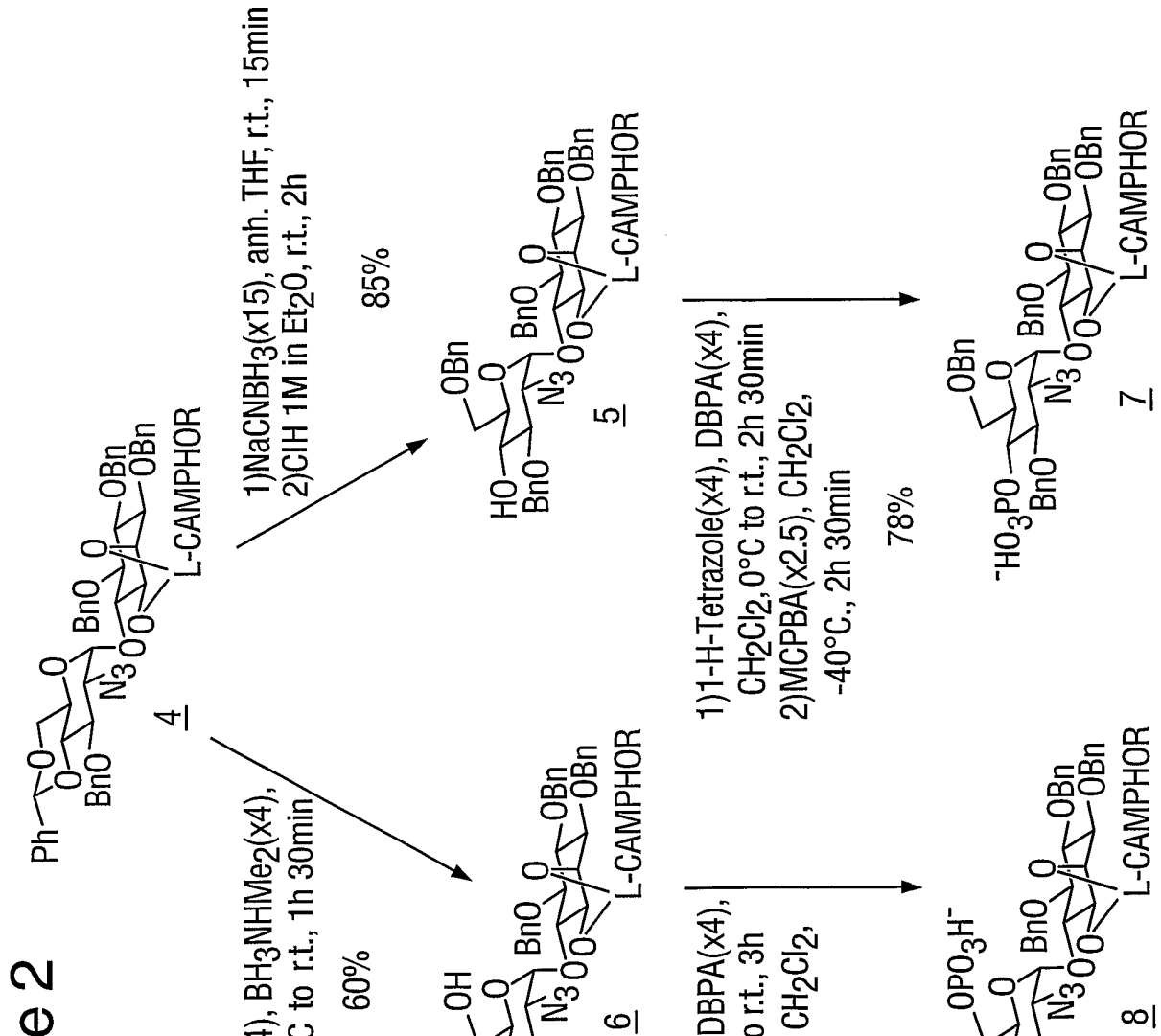
15. A compound of any one of claims 1 to 12 for use in a method of medical treatment.

16. Use of a compound of any one of claims 1 to 12 for the preparation of a medicament for the treatment of a condition ameliorated by the administration of an inositol phosphoglycan (IPG) second messenger or an IPG antagonist.

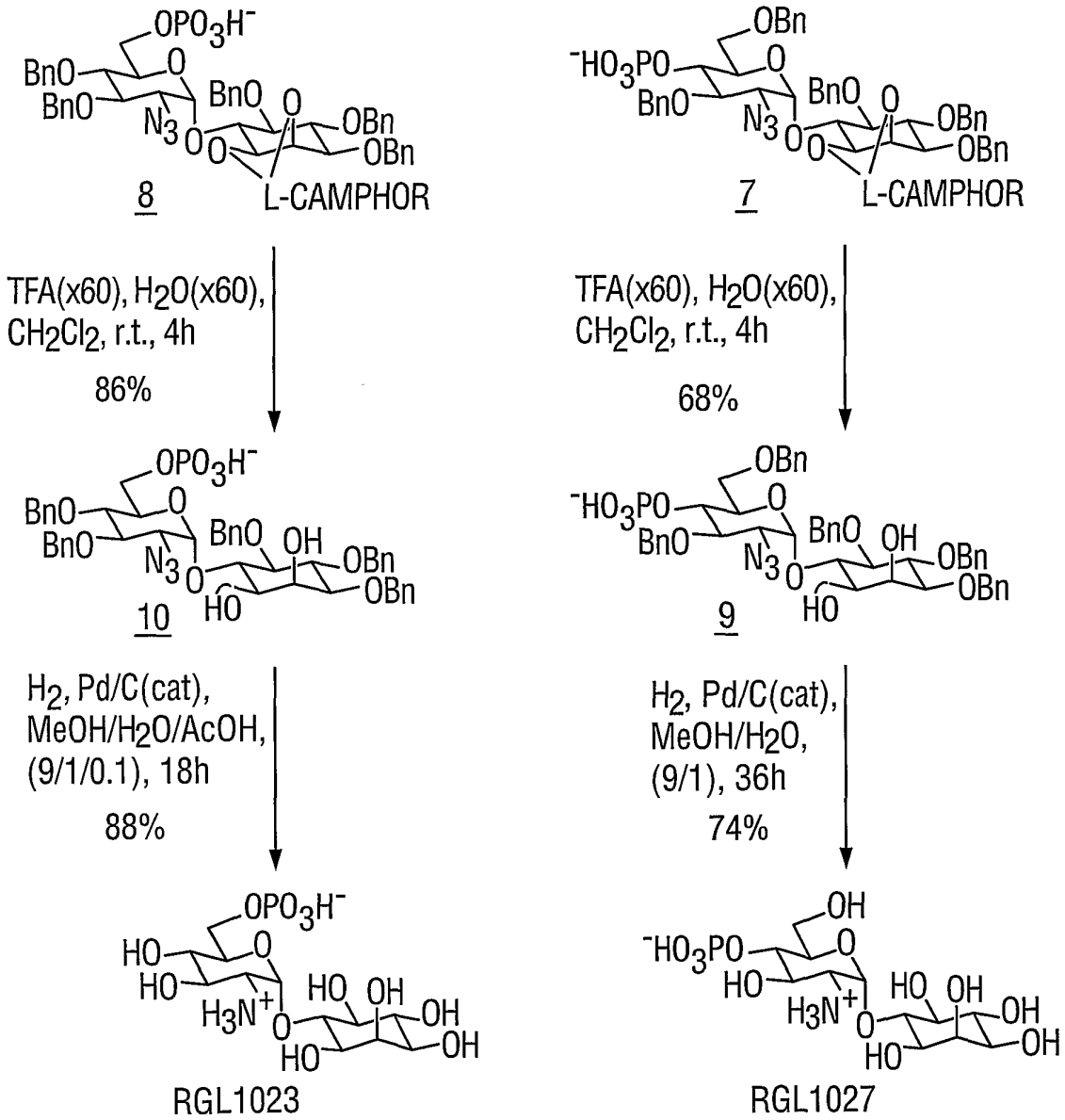
Scheme 1

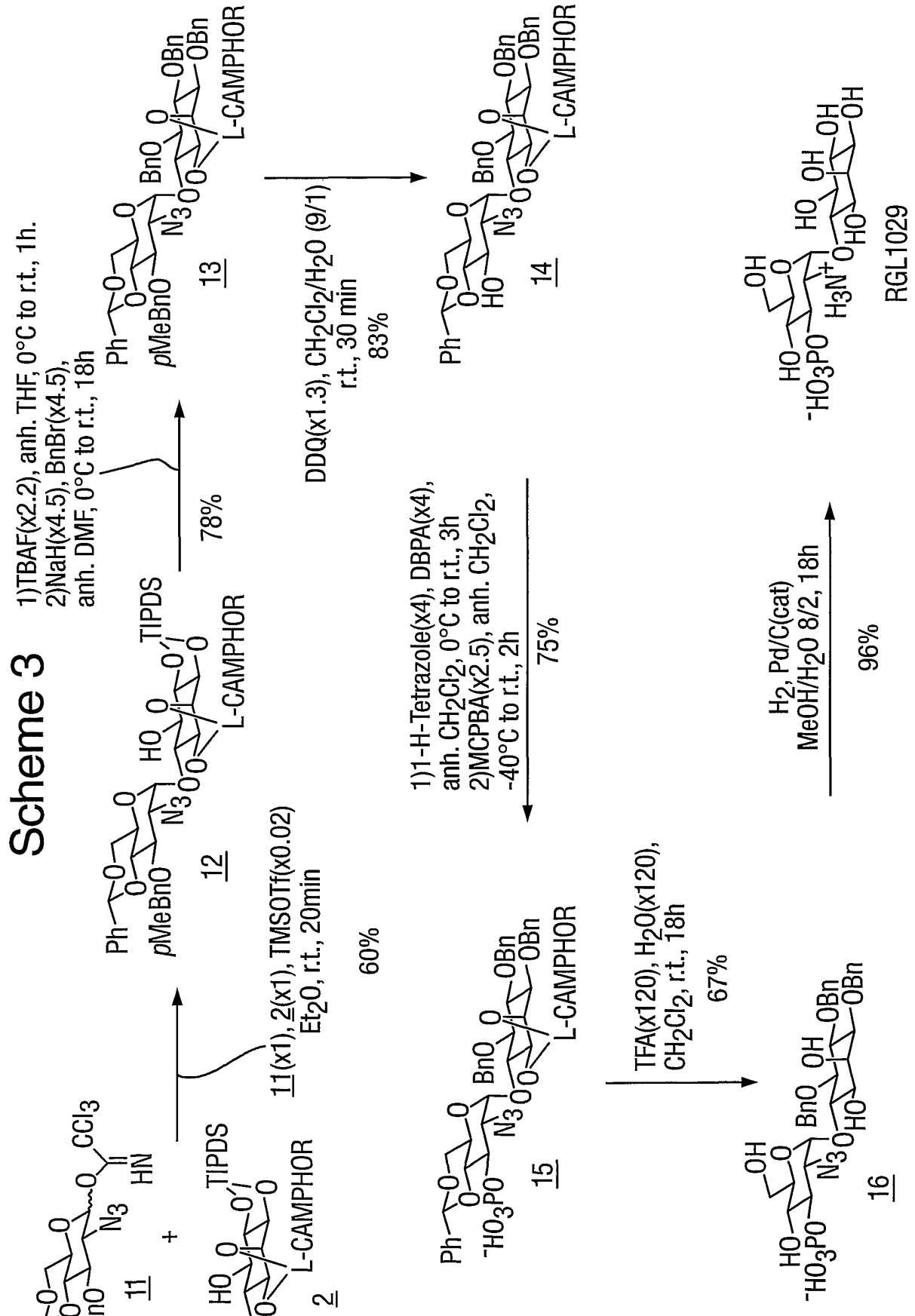

1
2
1(x1), 2(x1.4), TMSOTf(x0.05)
anh. Et2O, -20°C to r.t., 5h
55%
3
1)TBAF(x2.2), anh. THF, 0°C, 15min
2)NaH(x4.5), BnBr(x4.5), anh. DMF,
0°C to r.t., 2h
85%
4
L-CAMPHOR
TIPDS

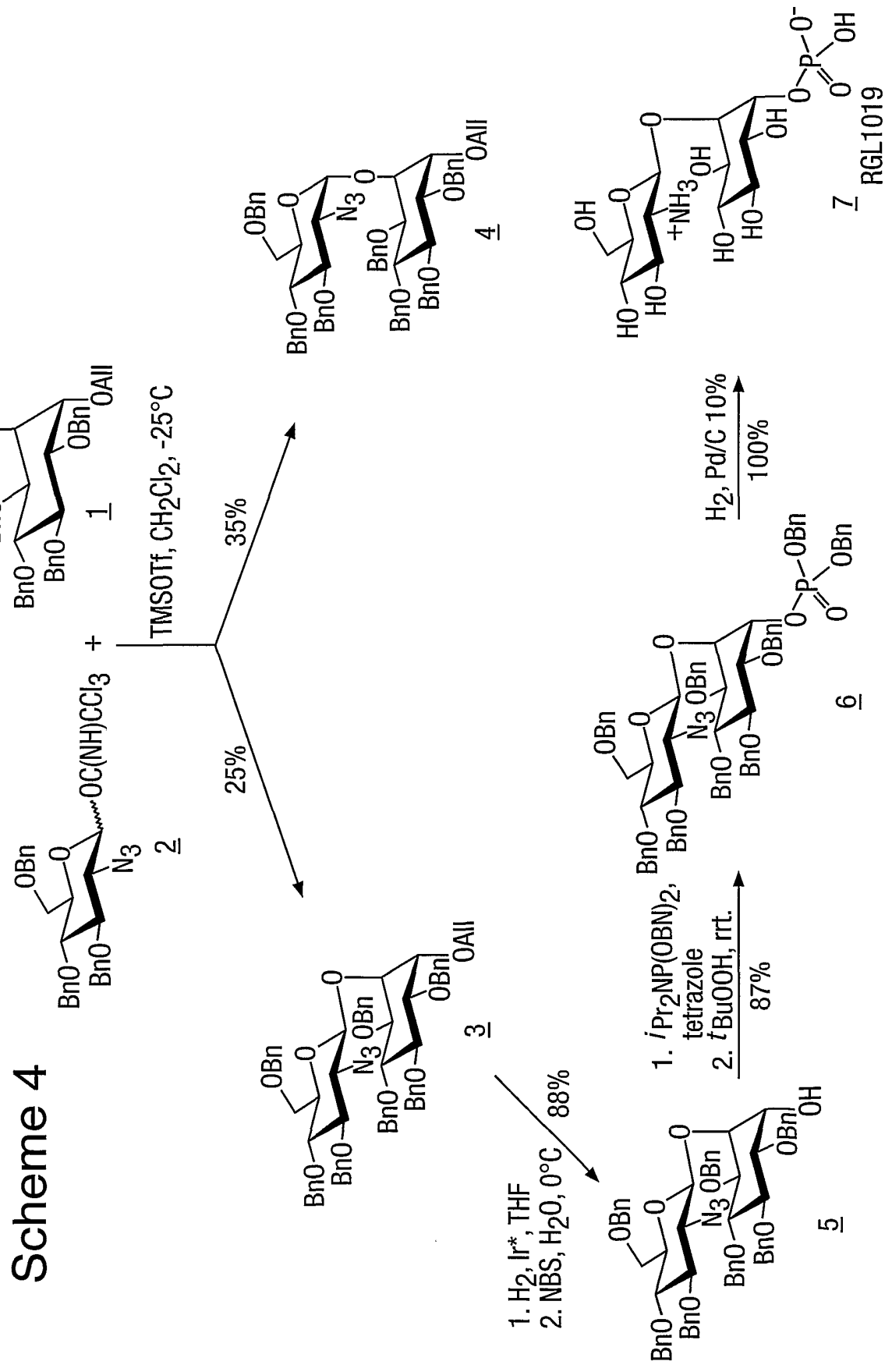
Scheme 2


Ph
BnO
O
N3
OBn
L-CAMPHOR
4
1)NaCNBH3(x15), anh. THF, r.t., 15min
2)ClH 1M in Et2O, r.t., 2h
85%
HO
5
BF3Et2O(x4), BH3NHMe2(x4),
anh. CH2Cl2, 0°C to r.t., 1h 30min
60%
OH
6
1)1-H-Tetrazole(x4), DBPA(x4),
anh. CH2Cl2, 0°C to r.t., 3h
2)MCPBA(x2.5),anh. CH2Cl2,
-40°C to, 45 min
80%
1)1-H-Tetrazole(x4), DBPA(x4),
CH2Cl2, 0°C to r.t., 2h 30min
2)MCPBA(x2.5), CH2Cl2,
-40°C., 2h 30min
78%
-HO3PO
7
OPO3H-
8

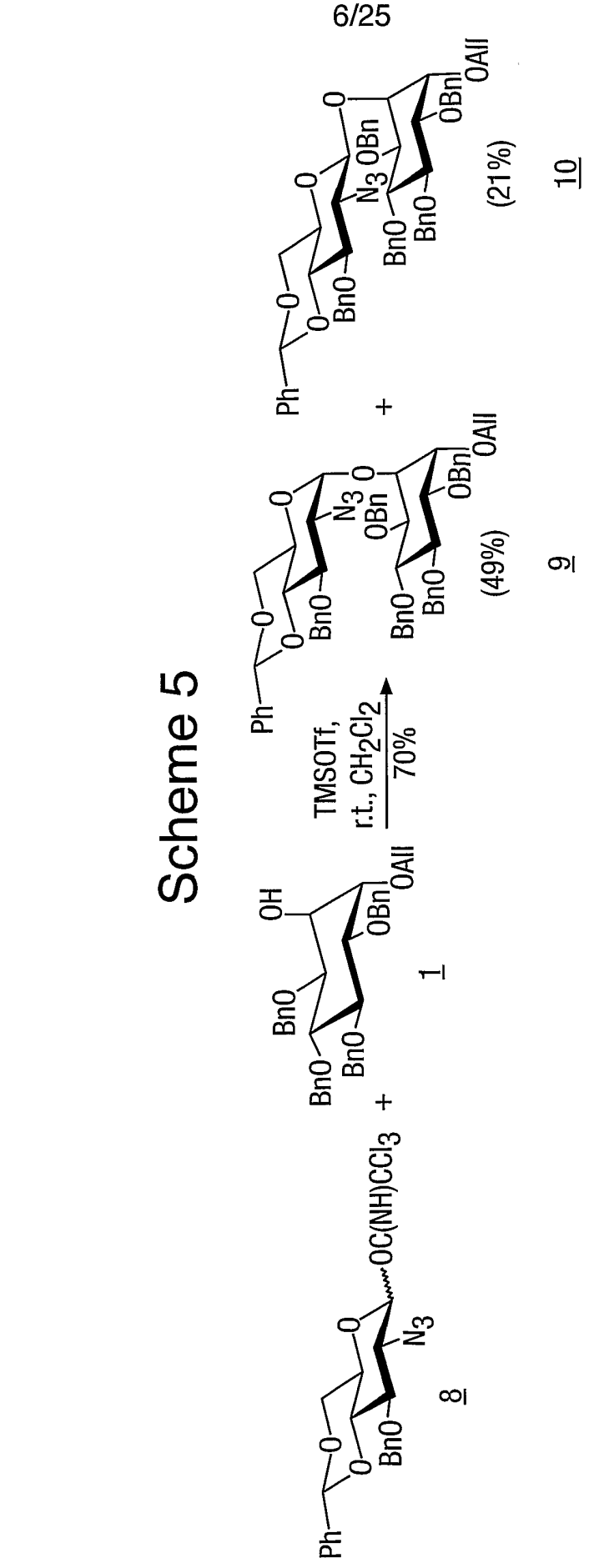
Scheme 2(cont.)



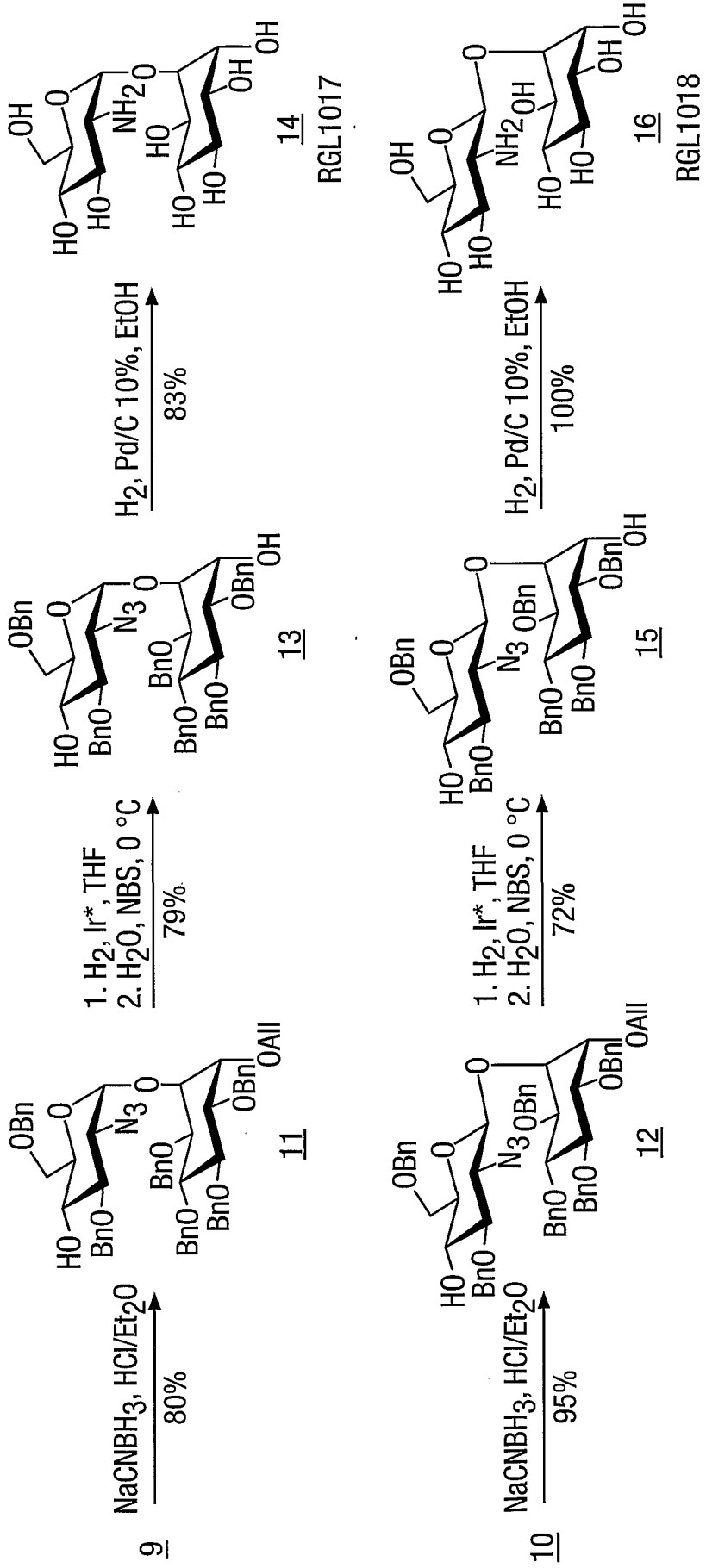

Scheme 3
1)TBAF(x2.2), anh. THF, 0°C to r.t., 1h.
2)NaH(x4.5), BnBr(x4.5),
anh. DMF, 0°C to r.t., 18h
11(x1), 2(x1), TMSOTf(x0.02)
Et2O, r.t., 20min
60%
78%
DDQ(x1.3), CH2Cl2/H2O (9/1)
r.t., 30 min
83%
1)1-H-Tetrazole(x4), DBPA(x4),
anh. CH2Cl2, 0°C to r.t., 3h
2)MCPBA(x2.5), anh. CH2Cl2,
-40°C to r.t., 2h
75%
TFA(x120), H2O(x120),
CH2Cl2, r.t., 18h
67%
H2, Pd/C(cat)
MeOH/H2O 8/2, 18h
96%
11
2
12
13
14
15
16
RGL1029


Scheme 4
TMSOTf, CH_2Cl_2, -25°C
35%
25%
1. H_2, Ir*, THF
2. NBS, H_2O, 0°C
88%
1. $iPr_2NP(OBN)_2$, tetrazole
2. $tBuOOH$, rrt.
87%
H_2, Pd/C 10%
100%
RGL1019

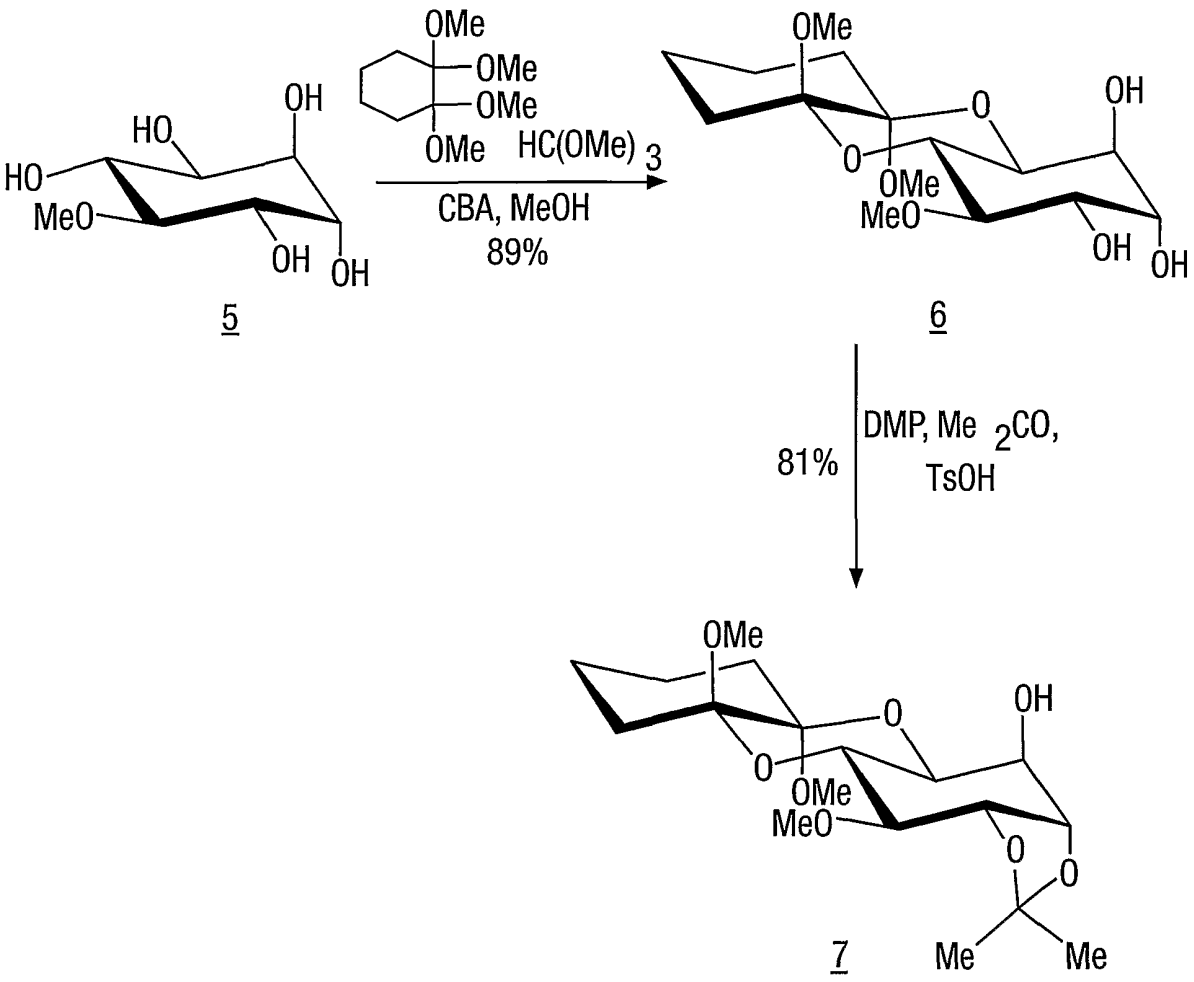
Scheme 5


Ph
BnO
O
OC(NH)CCl3
N3
8
+
OH
OBn
OAll
1
TMSOTf,
r.t., CH2Cl2
70%
(49%)
9
(21%)
10

Scheme 6

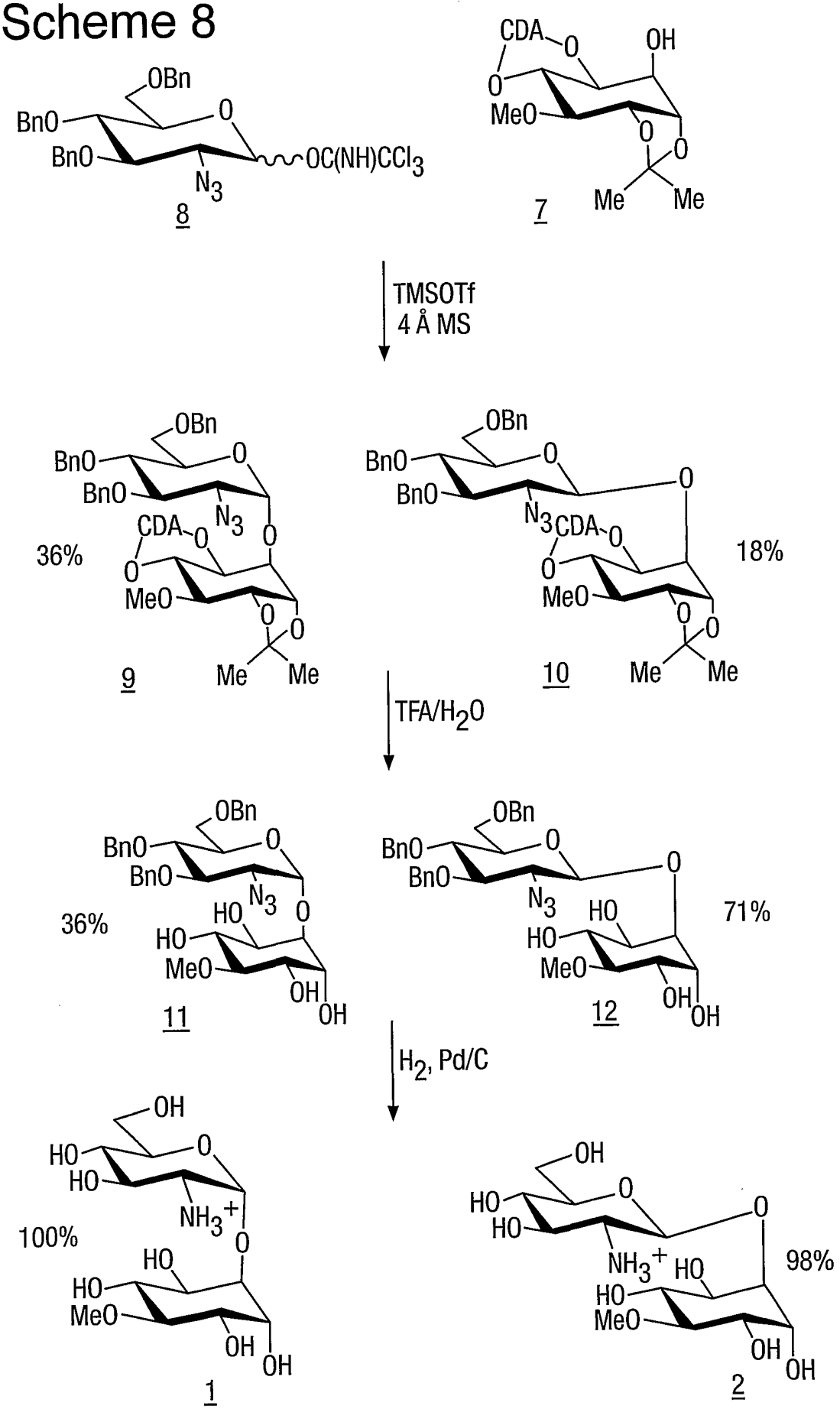

NaCNBH3, HCl/Et2O
80%
1. H2, Ir*, THF
2. H2O, NBS, 0 °C
79%
H2, Pd/C 10%, EtOH
83%
RGL1017
NaCNBH3, HCl/Et2O
95%
1. H2, Ir*, THF
2. H2O, NBS, 0 °C
72%
H2, Pd/C 10%, EtOH
100%
RGL1018

Scheme 7

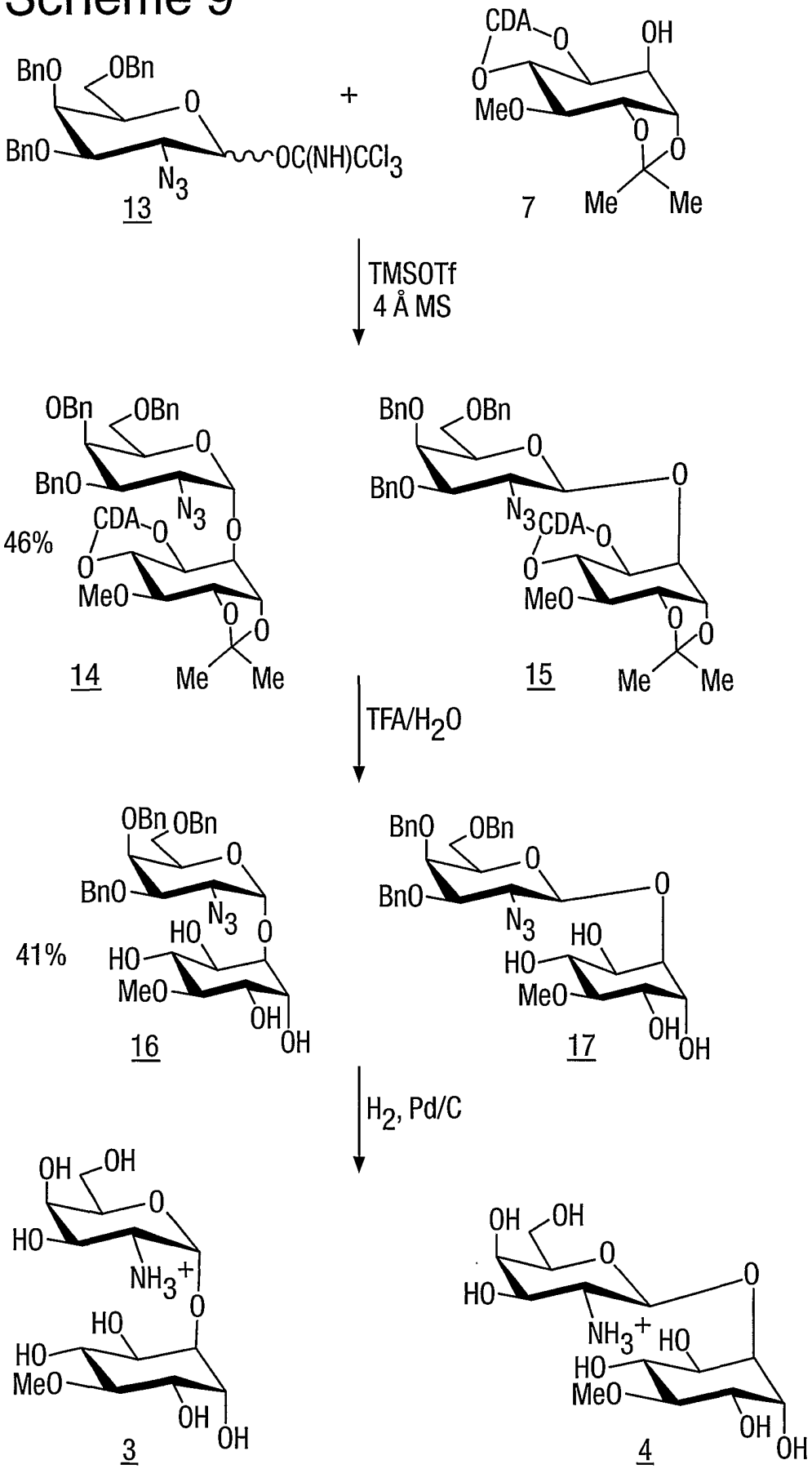

OMe
OMe
OMe
OMe
HC(OMe)3
CBA, MeOH
89%
HO
HO
MeO
OH
OH
OH
OMe
O
O
OMe
MeO
OH
OH
81%
DMP, Me2CO,
TsOH
Me
Me

5 6 7

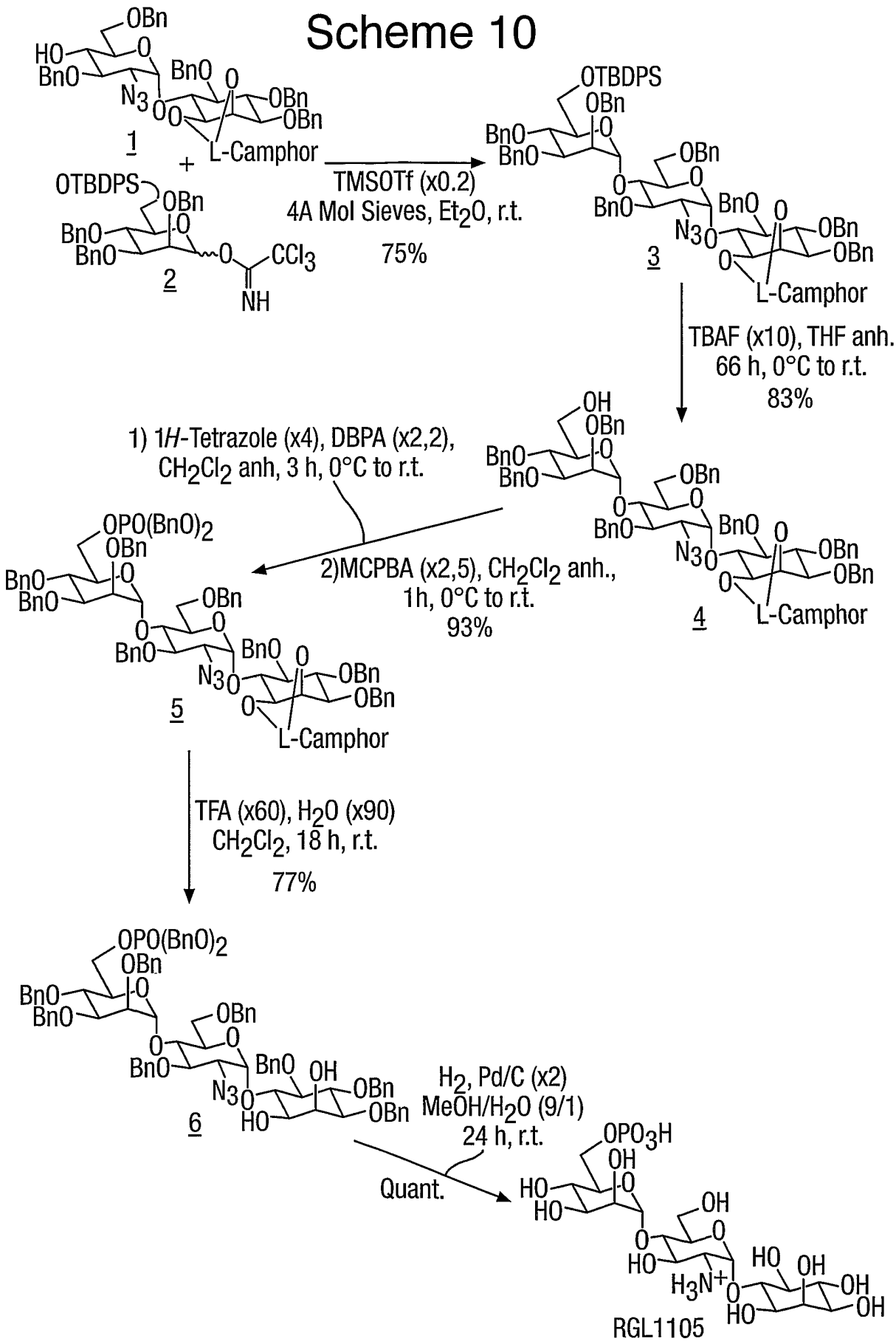
Scheme 8


OBn
BnO
BnO
O
N3
OC(NH)CCl3
8
CDA
O
OH
MeO
Me
Me
7
TMSOTf
4 Å MS
36%
18%
9
10
TFA/H2O
36%
71%
11
12
H2, Pd/C
100%
98%
1
2

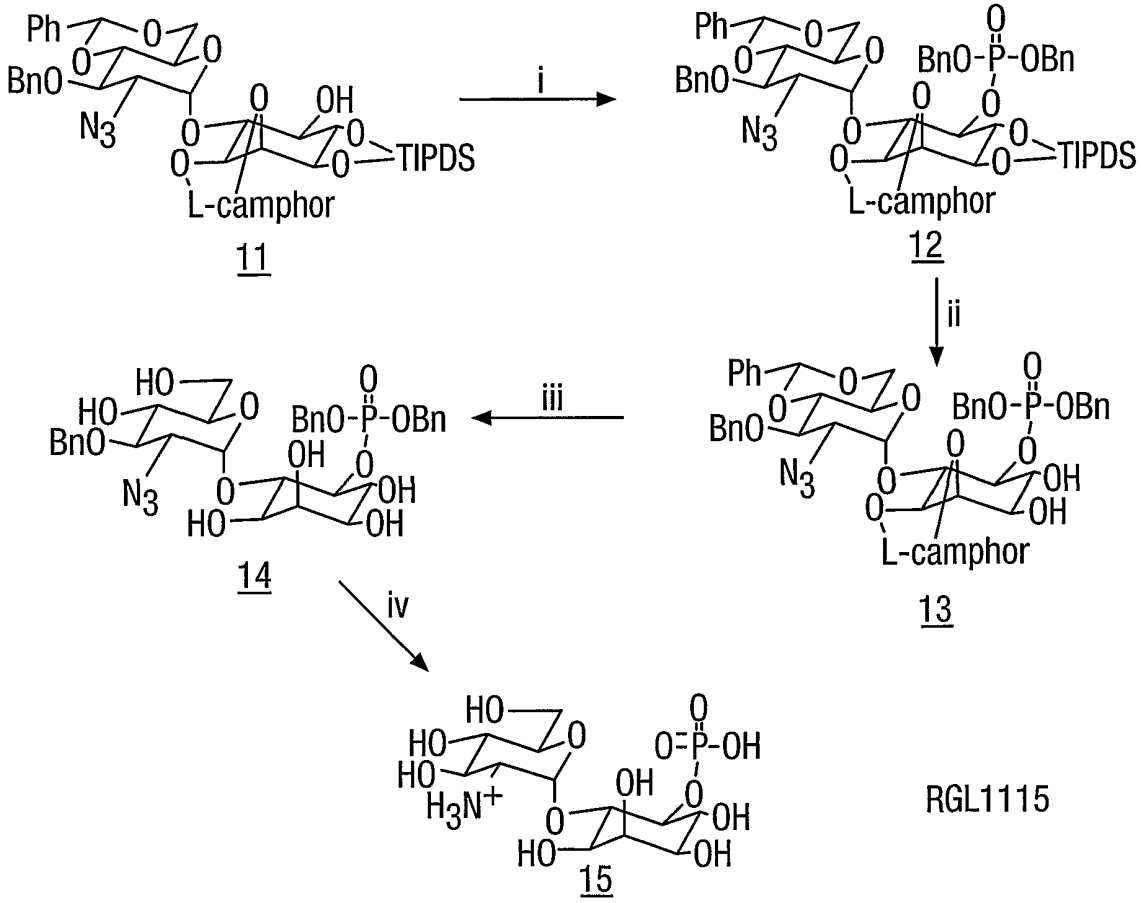
Scheme 9


BnO
OBn
O
BnO
N3
OC(NH)CCl3
13
+
CDA
O
OH
O
MeO
O
O
Me
Me
7
TMSOTf
4 Å MS
OBn
OBn
O
BnO
N3
CDA
O
O
MeO
O
O
Me
Me
46%
14
BnO
OBn
O
BnO
N3
O
CDA
O
O
MeO
O
O
Me
Me
15
TFA/H2O
OBn
OBn
O
BnO
N3
O
HO
HO
MeO
OH
OH
41%
16
BnO
OBn
O
BnO
N3
O
HO
HO
MeO
OH
OH
17
H2, Pd/C
OH
OH
O
HO
NH3+
O
HO
HO
MeO
OH
OH
3
OH
OH
O
HO
NH3+
O
HO
HO
MeO
OH
OH
4

Scheme 10

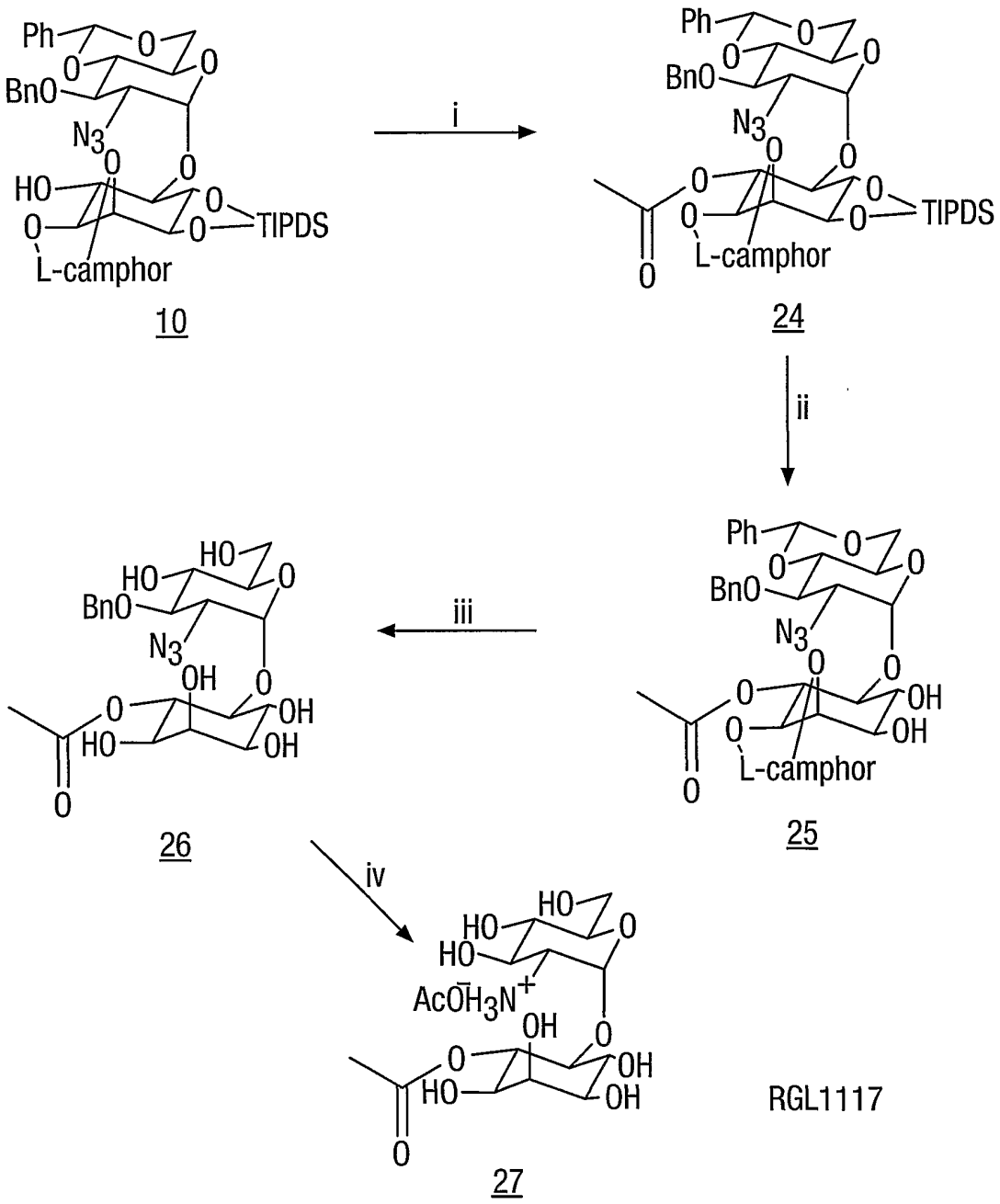

1
+
L-Camphor
2
TMSOTf (x0.2)
4A Mol Sieves, Et2O, r.t.
75%
3
TBAF (x10), THF anh.
66 h, 0°C to r.t.
83%
4
1) 1H-Tetrazole (x4), DBPA (x2,2),
CH2Cl2 anh, 3 h, 0°C to r.t.
2)MCPBA (x2,5), CH2Cl2 anh.,
1h, 0°C to r.t.
93%
5
TFA (x60), H2O (x90)
CH2Cl2, 18 h, r.t.
77%
6
H2, Pd/C (x2)
MeOH/H2O (9/1)
24 h, r.t.
Quant.
RGL1105

Scheme 11



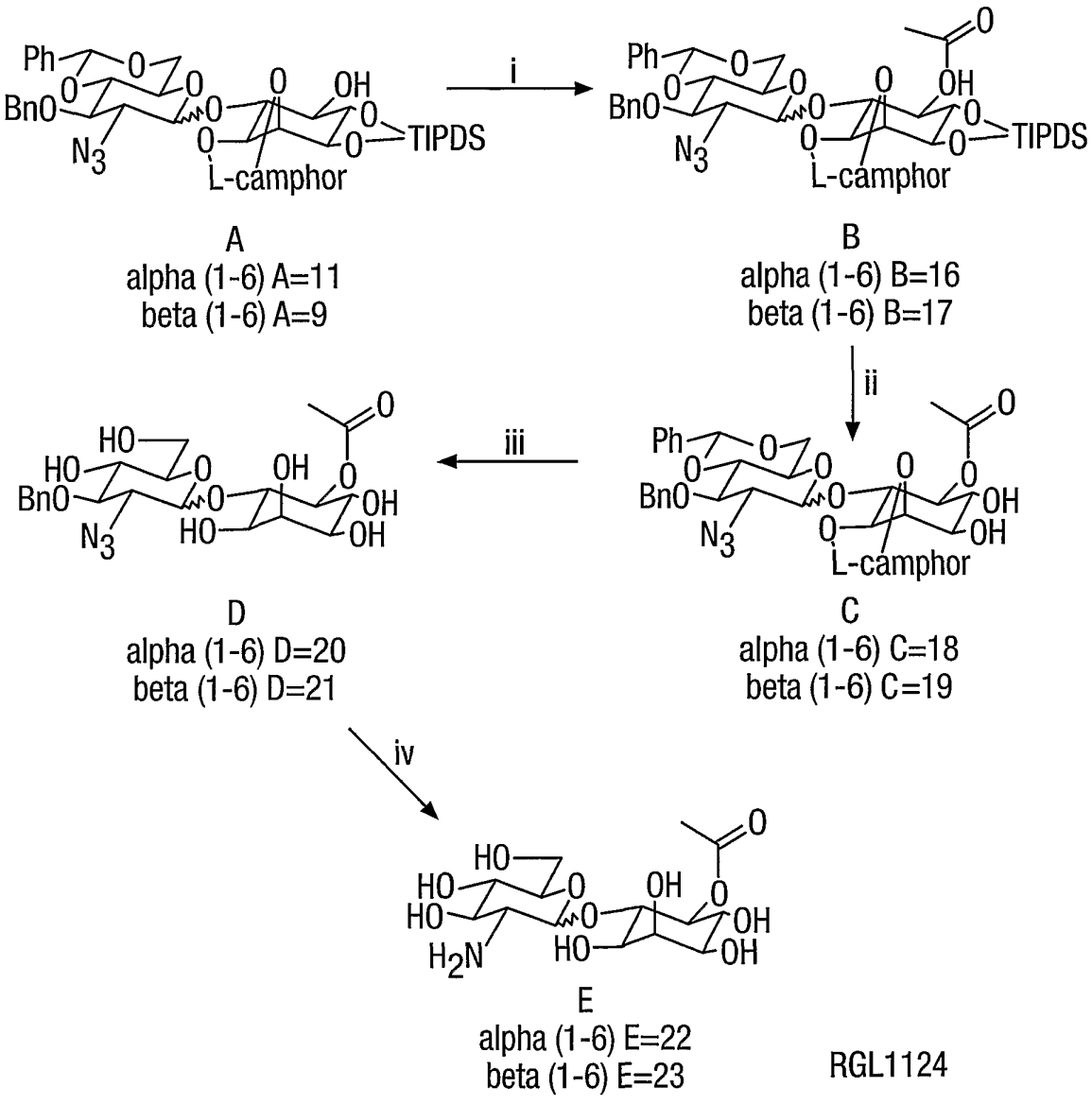
Reagents and conditions: i) dibenzyl diisopropylphosphoramidite, tetrazole, anhydrous DCM, R.T., 72 hrs, then *m*CPBA, anhydrous DCM, r.t., 3 hrs. ii) TBAF [1.0 M solution in THF], THF, 0°C, 1 hr.iii) TFA, DCM, water, R.T., 4 hrs. iv) H_2, Pd/C (10 % wt.), HPLC grade MeOH:distilled water (4:1).

Scheme 12



Reagents and conditions: i) Ac_2O, pyridine, R.T. then 45°C, 24 hrs. ii) TBAF [1.0 M solution in THF], THF, 0°C 1 hr. iii) TFA, DCM, water, R.T., 4 hrs. iv) H_2, Pd/C (10% wt.), HPLC grade MeOH:distilled water:AcOH (4:1:0.1)

Scheme 13



A
alpha (1-6) A=11
beta (1-6) A=9

B
alpha (1-6) B=16
beta (1-6) B=17

C
alpha (1-6) C=18
beta (1-6) C=19

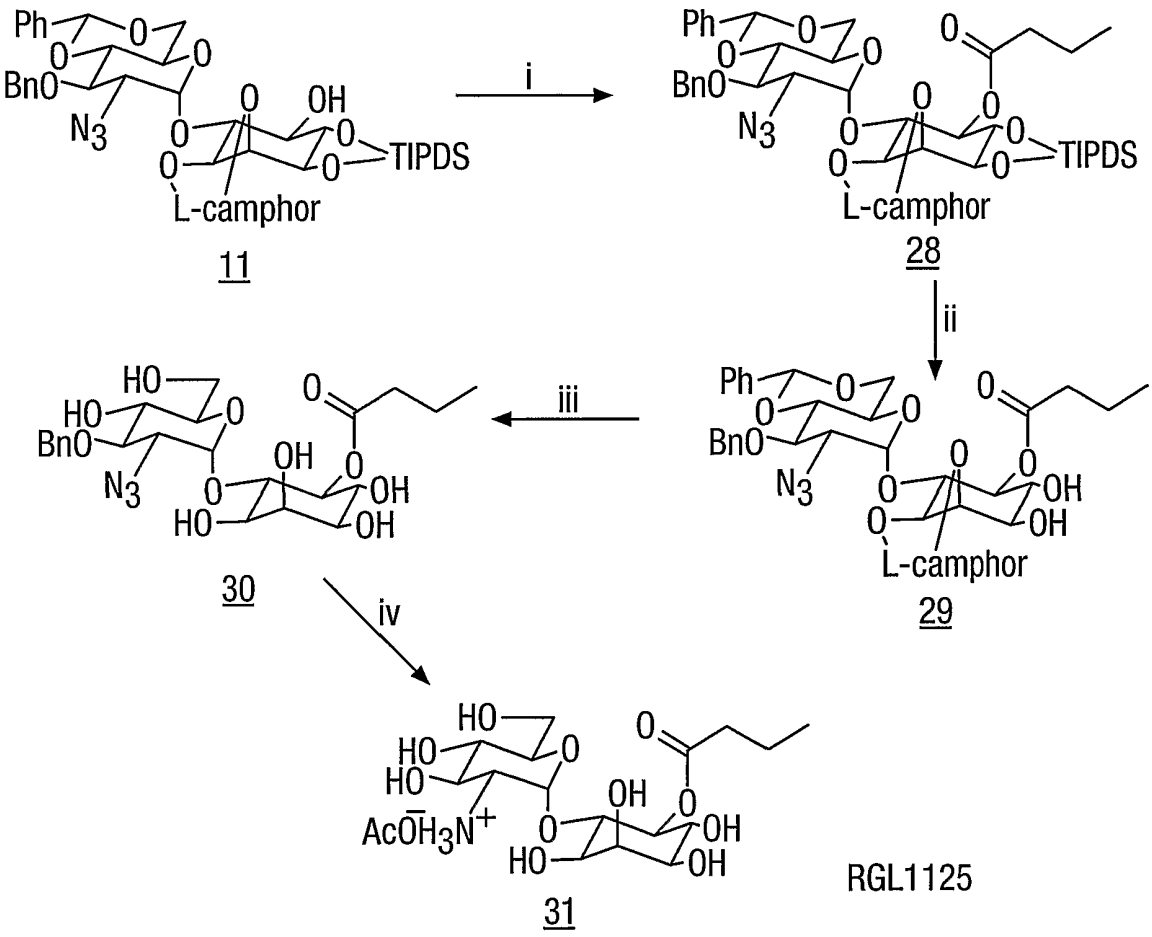
D
alpha (1-6) D=20
beta (1-6) D=21

E
alpha (1-6) E=22
beta (1-6) E=23

RGL1124

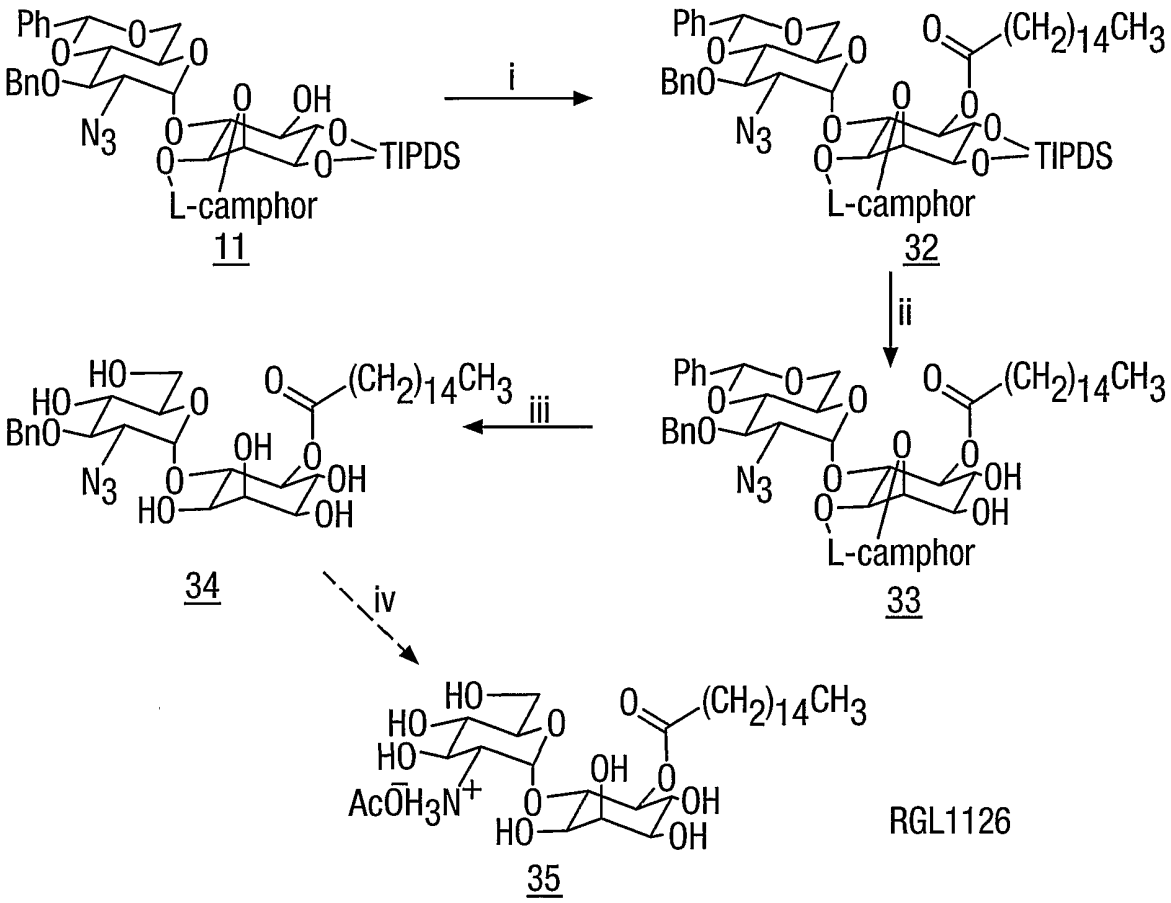
Reagents and conditions: i) Ac_2O, pyridine, R.T. then 50°C, 24 hrs. ii) TBAF [1.0 M solution in THF], THF, 0°C, 1 hr. iii) TFA, DCM, water, R.T., 4 hrs. iv) H_2, Pd/C (10% wt.), MeOH:water (4:1).

Scheme 14



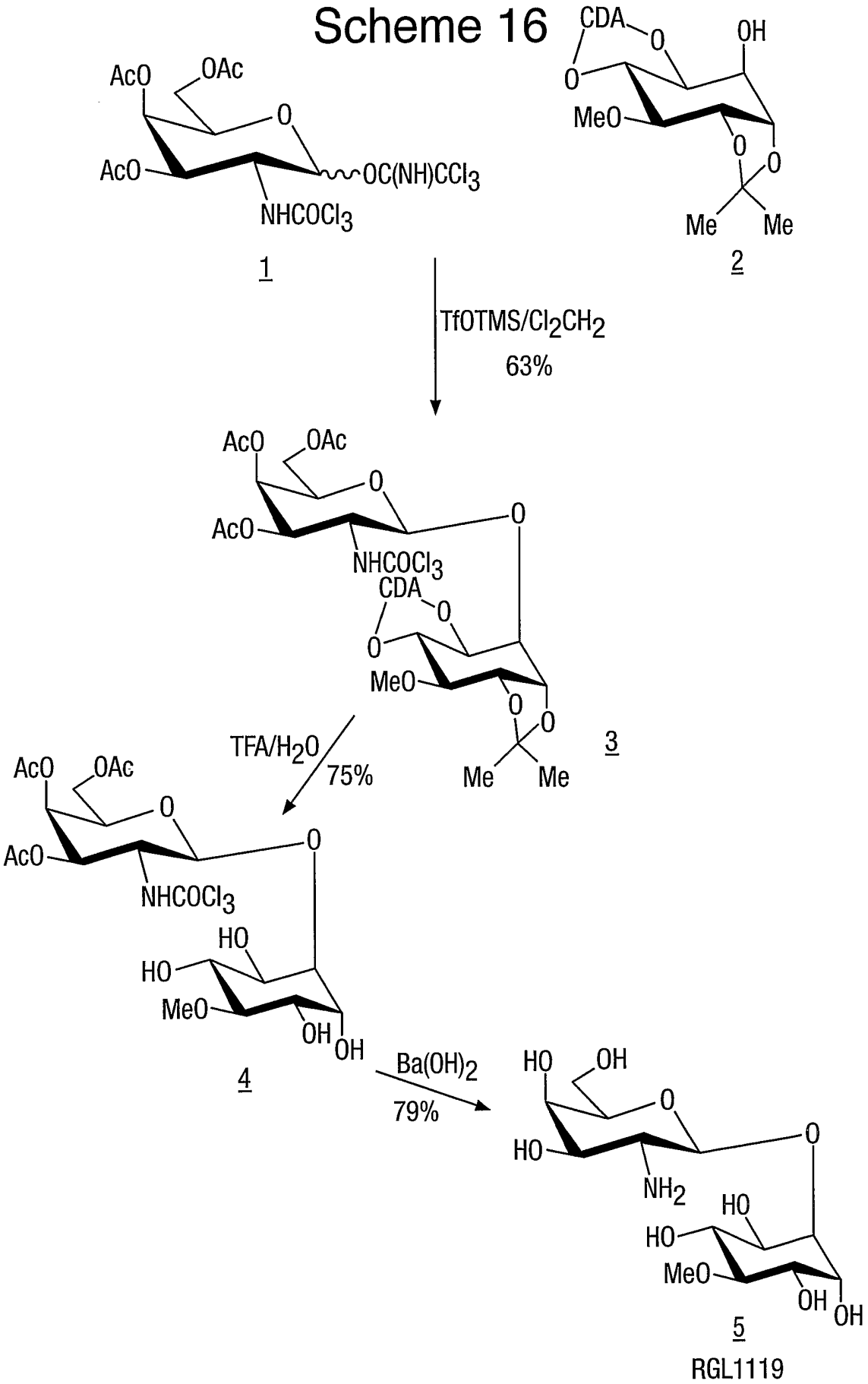
Reagents and conditions: i) Bu_2O, pyridine, 110°C, 80 hrs. ii) TBAF [1.0 M solution in THF], THF, 0°C, 1 hr. iii) TFA, DCM, water, R.T., 20 hrs. iv) H_2, Pd/C (10% wt.), HPLC grade MeOH:distilled water:AcOH (4:1:0.1).

Scheme 15

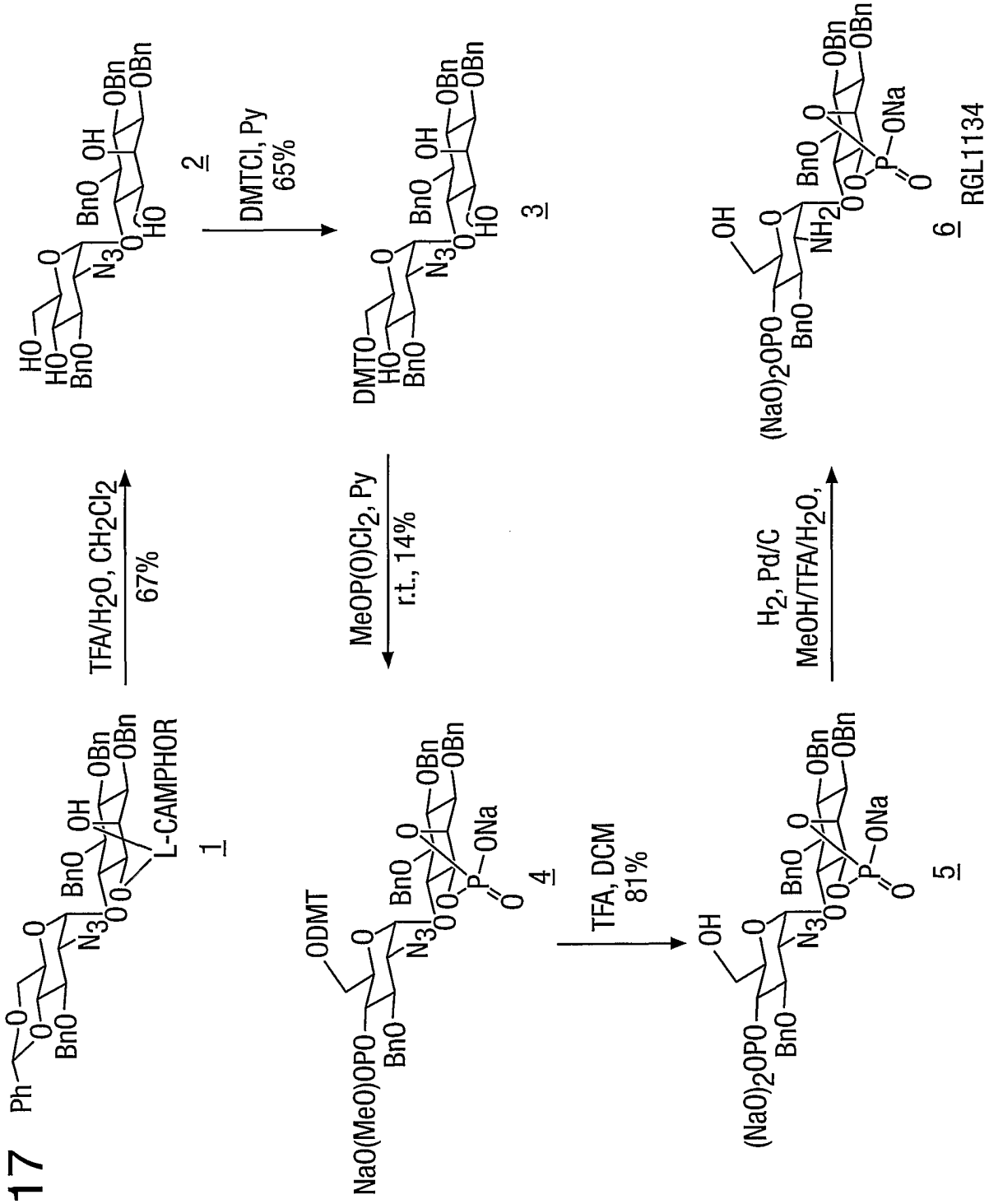


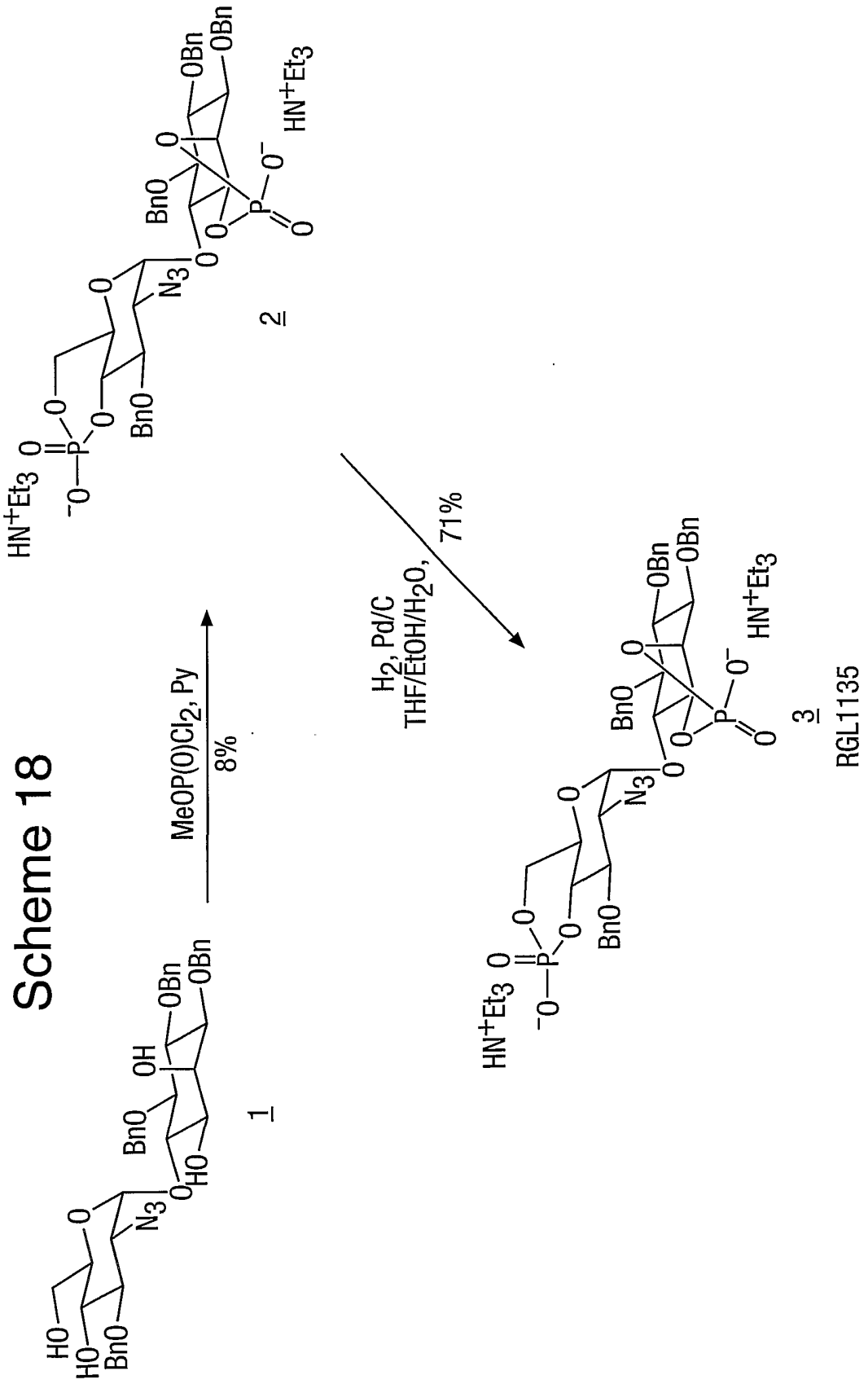
Reagents and conditions: i) palmitic anhydride, pyridine, reflux, 80 hrs. ii) TBAF [1.0 M solution in THF], THF, 0°C, 1 hr. iii) TFA, DCM, water, R.T., 20 hrs. iv) H_2, Pd/C (10% wt), HPLC grade MeOH:distilled water:AcOH (4:1:0.1).

Scheme 16

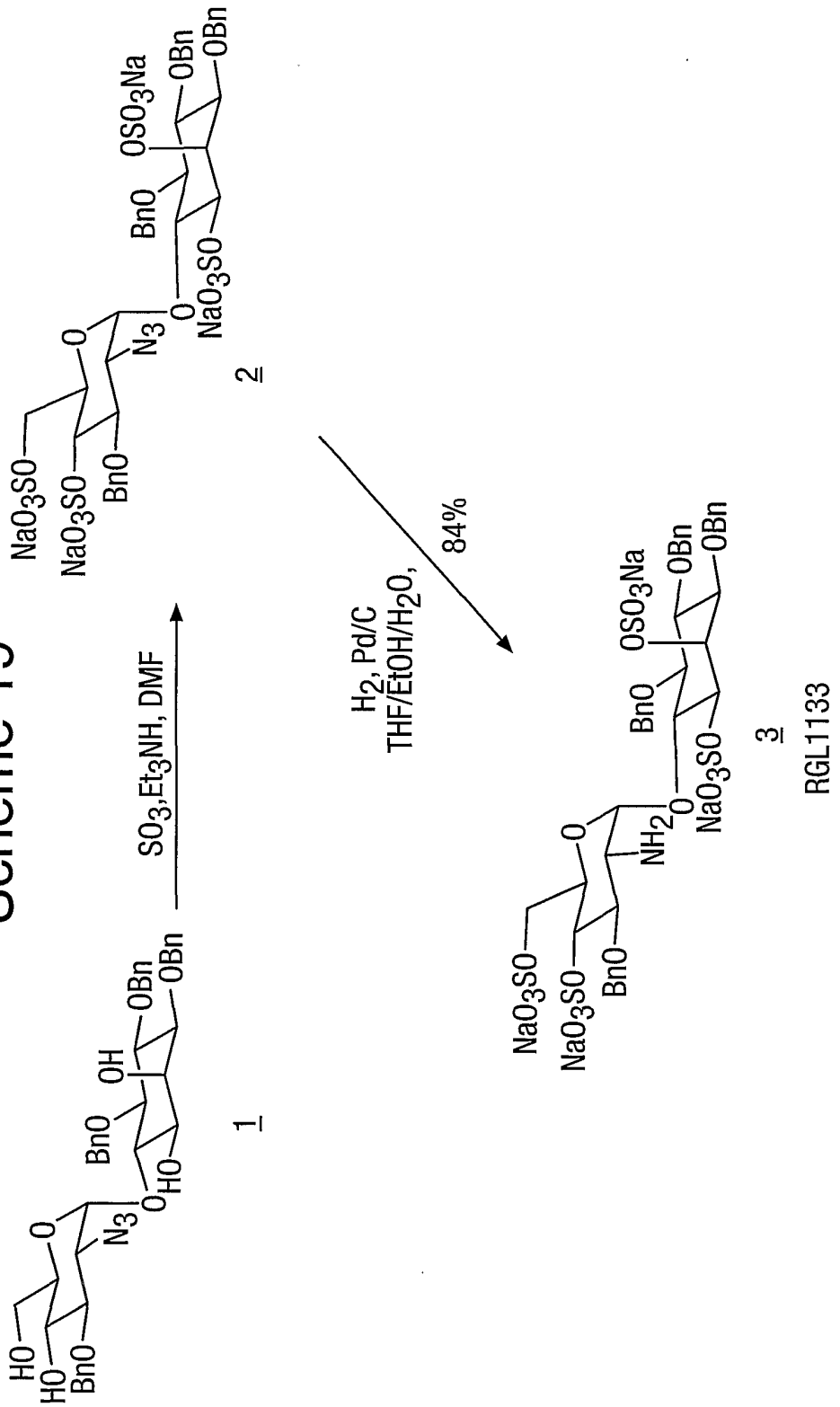

AcO
OAc
O
AcO
OC(NH)CCl3
NHCOCl3
1
CDA
O
OH
O
MeO
O
O
Me
Me
2
TfOTMS/Cl2CH2
63%
AcO
OAc
O
AcO
O
NHCOCl3
CDA
O
O
MeO
O
O
Me
Me
3
TFA/H2O
75%
AcO
OAc
O
AcO
O
NHCOCl3
HO
HO
MeO
OH
OH
4
Ba(OH)2
79%
HO
OH
O
HO
O
NH2
HO
HO
MeO
OH
OH
5
RGL1119

Scheme 17


Ph
BnO
OBn
OH
N3
L-CAMPHOR
1
TFA/H2O, CH2Cl2
67%
HO
HO
BnO
2
DMTCl, Py
65%
DMTO
3
MeOP(O)Cl2, Py
r.t., 14%
ODMT
NaO(MeO)OPO
ONa
4
TFA, DCM
81%
5
H2, Pd/C
MeOH/TFA/H2O,
NH2
(NaO)2OPO
6
RGL1134


Scheme 18
MeOP(O)Cl2, Py
8%
H2, Pd/C
THF/EtOH/H2O,
71%
1
2
3
RGL1135

Scheme 19



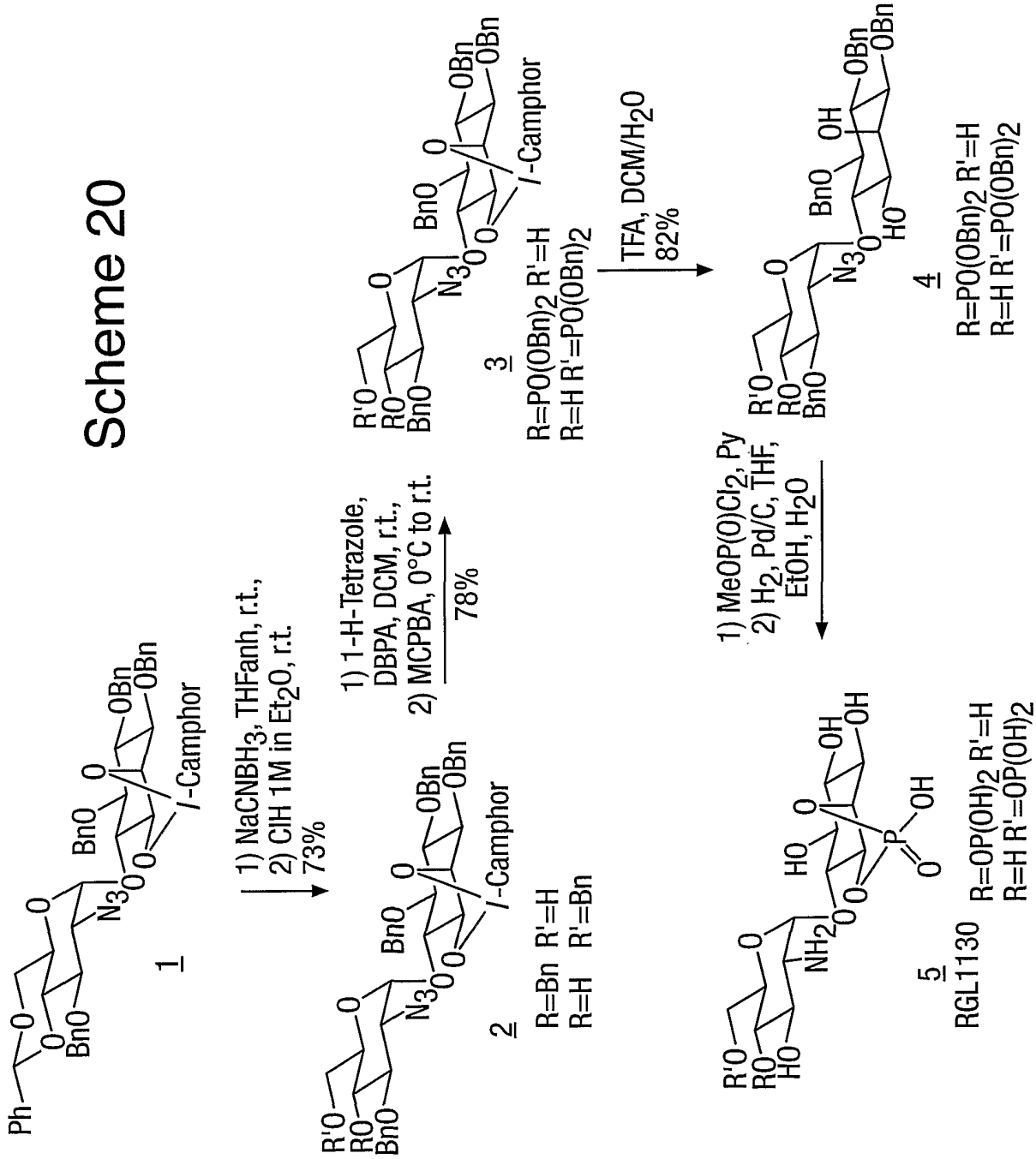

Scheme 20
1) NaCNBH3, THFanh, r.t.,
2) ClH 1M in Et2O, r.t.
73%
1) 1-H-Tetrazole,
DBPA, DCM, r.t.,
2) MCPBA, 0°C to r.t.
78%
TFA, DCM/H2O
82%
1) MeOP(O)Cl2, Py
2) H2, Pd/C, THF,
EtOH, H2O
1
2
R=Bn R'=H
R=H R'=Bn
3
R=PO(OBn)2 R'=H
R=H R'=PO(OBn)2
4
R=PO(OBn)2 R'=H
R=H R'=PO(OBn)2
5
RGL1130
R=OP(OH)2 R'=H
R=H R'=OP(OH)2

Fig.1.

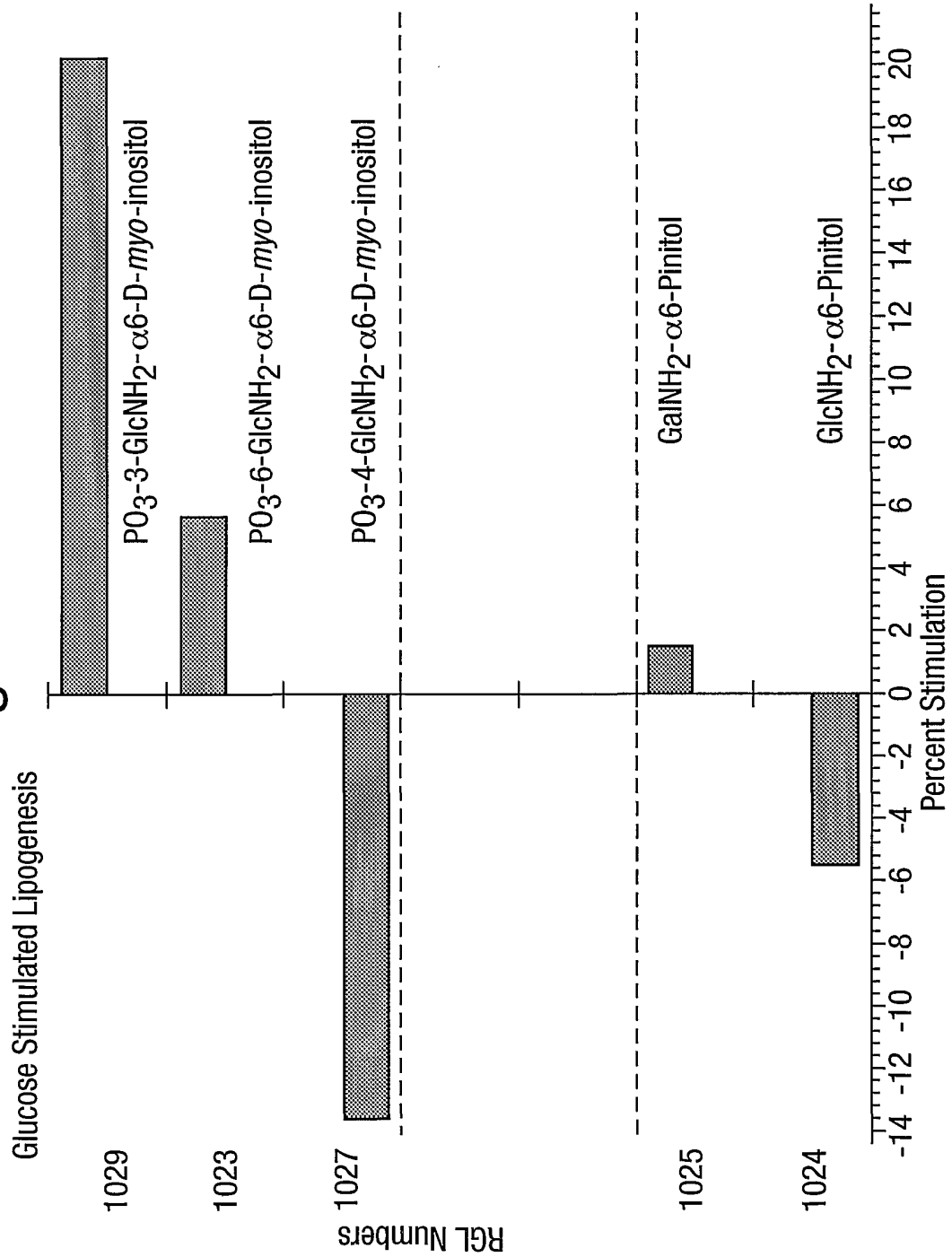

Glucose Stimulated Lipogenesis
PO3-3-GlcNH2-α6-D-myo-inositol
PO3-6-GlcNH2-α6-D-myo-inositol
PO3-4-GlcNH2-α6-D-myo-inositol
GalNH2-α6-Pinitol
GlcNH2-α6-Pinitol
1029
1023
1027
1025
1024
RGL Numbers
-14 -12 -10 -8 -6 -4 -2 0 2 4 6 8 10 12 14 16 18 20
Percent Stimulation

Fig.2.

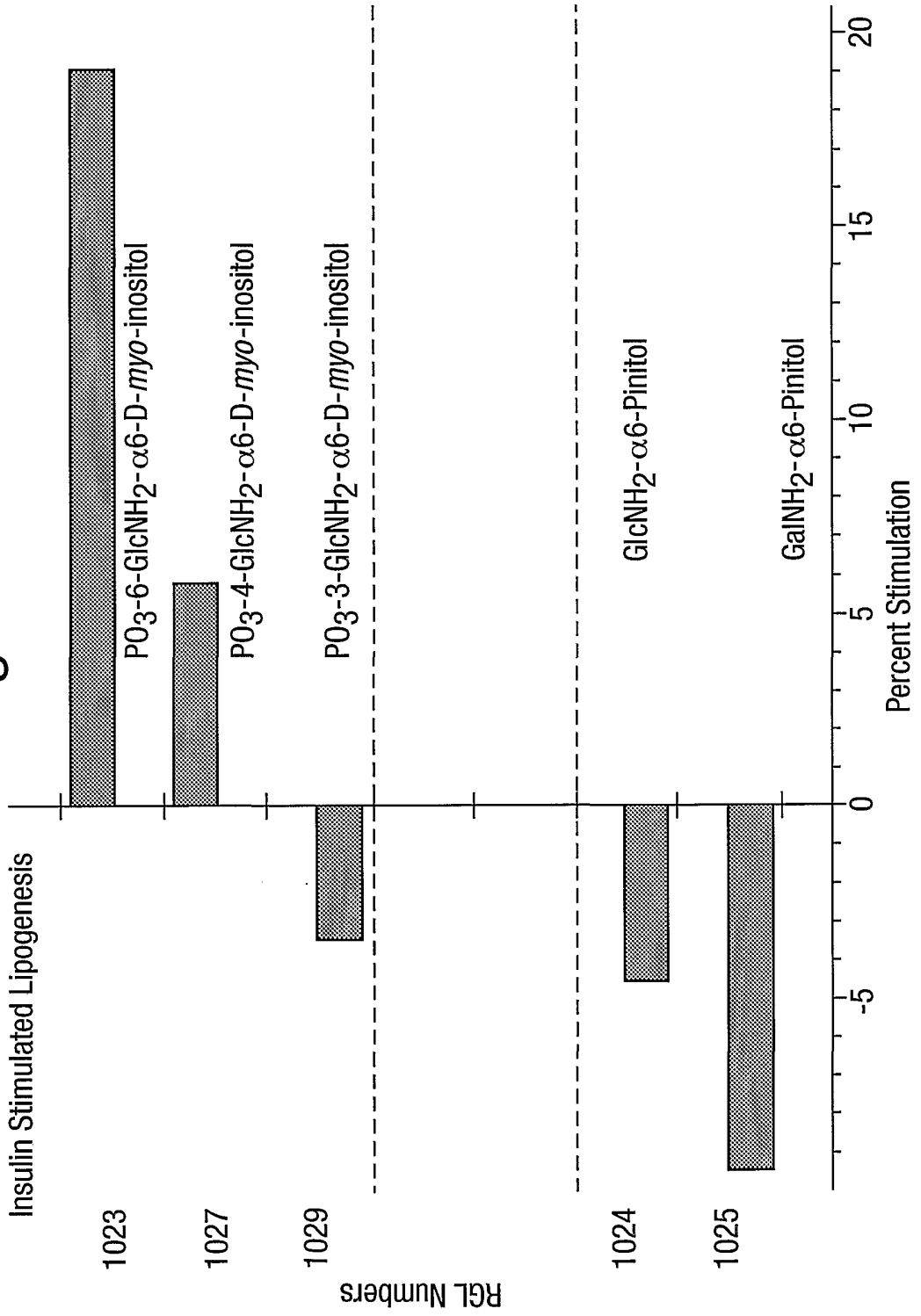

Insulin Stimulated Lipogenesis
1023
1027
1029
1024
1025
RGL Numbers
PO3-6-GlcNH2-α6-D-myo-inositol
PO3-4-GlcNH2-α6-D-myo-inositol
PO3-3-GlcNH2-α6-D-myo-inositol
GlcNH2-α6-Pinitol
GalNH2-α6-Pinitol
-5
0
5
10
15
20
Percent Stimulation

Fig.3.

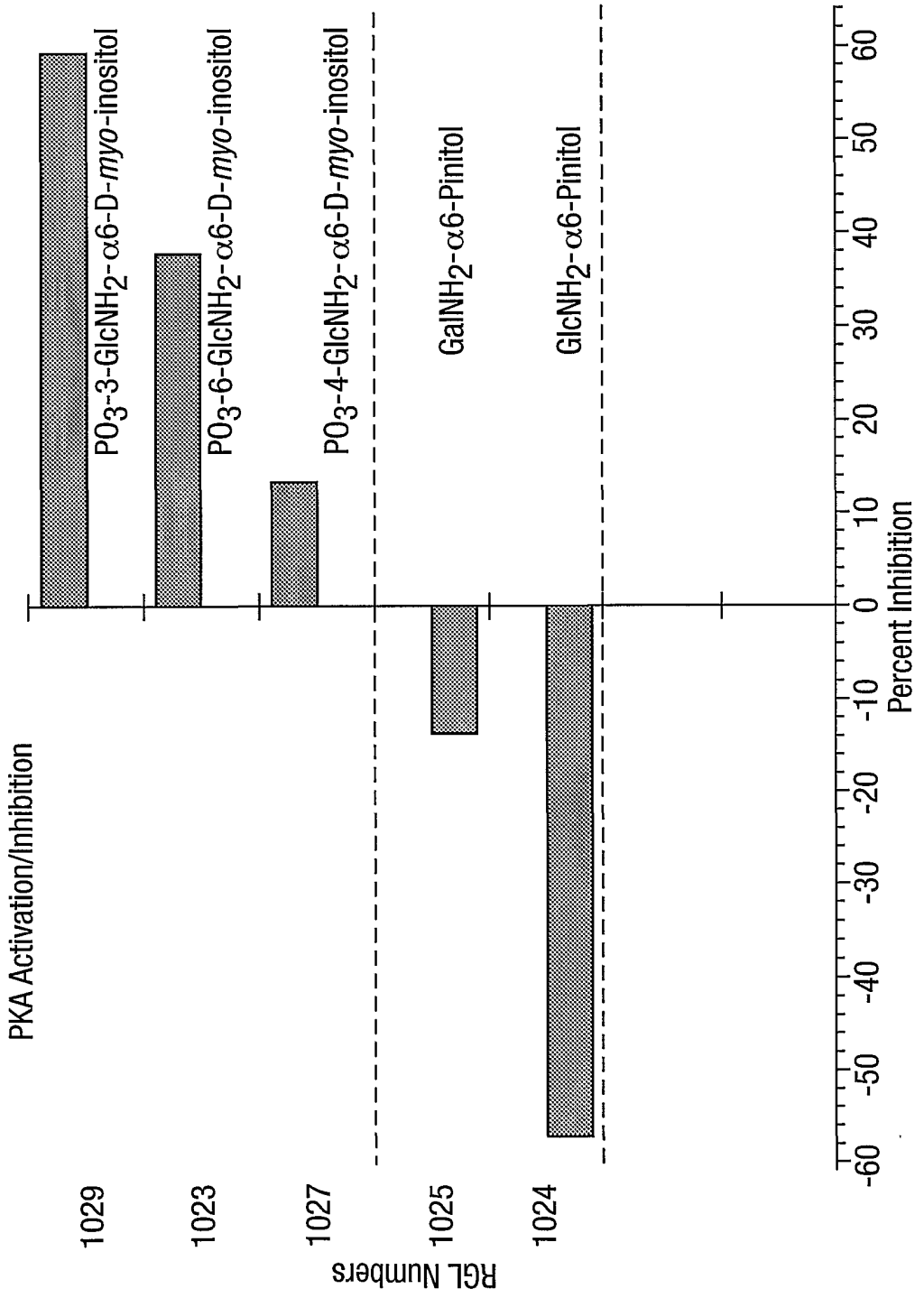
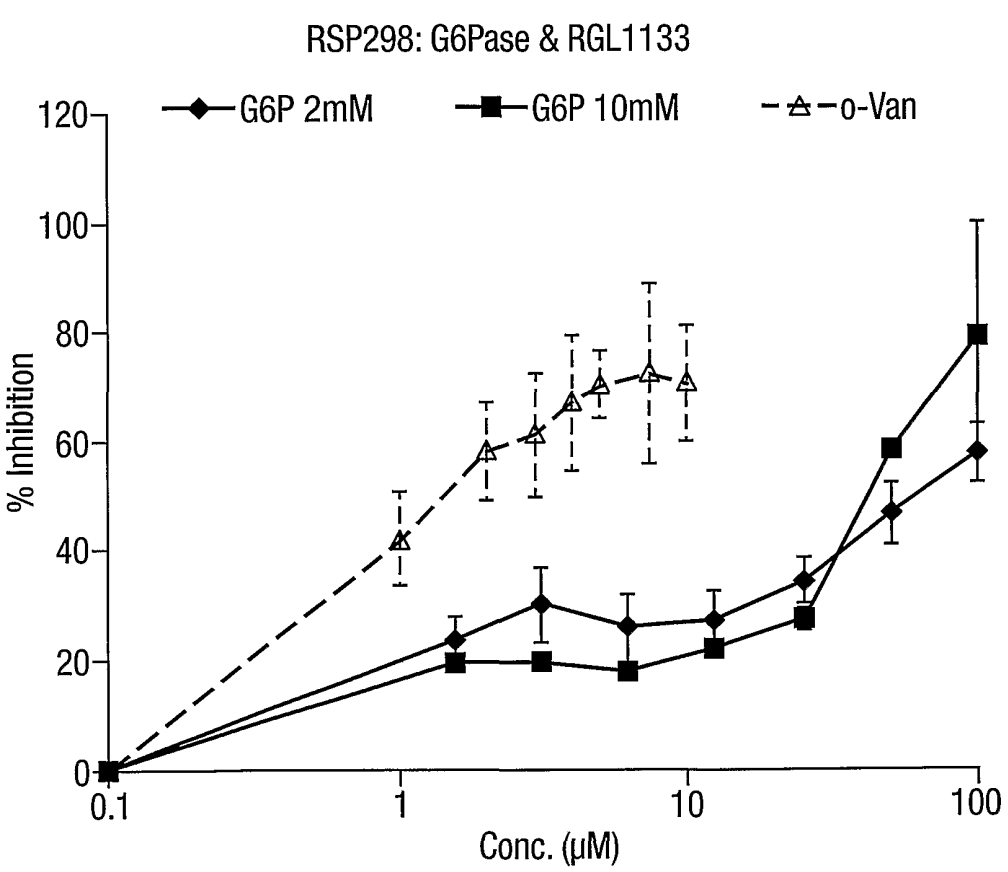

PKA Activation/Inhibition
PO3-3-GlcNH2-α6-D-myo-inositol
PO3-6-GlcNH2-α6-D-myo-inositol
PO3-4-GlcNH2-α6-D-myo-inositol
GalNH2-α6-Pinitol
GlcNH2-α6-Pinitol
1029
1023
1027
1025
1024
RGL Numbers
-60 -50 -40 -30 -20 -10 0 10 20 30 40 50 60
Percent Inhibition

Fig.4.


RSP298: G6Pase & RGL1133
G6P 2mM
G6P 10mM
o-Van
% Inhibition
120
100
80
60
40
20
0
0.1
1
10
100
Conc. (µM)