(54) Title: COMBINATORIAL LIBRARIES OF MONOSACCHARIDES

(57) Abstract: The present invention provides a monosaccharide compound of general formula I as shown in the specification. The invention also provides processes for the preparation of the compound of formula I and methods of screening for antibacterial or antibiotic compounds involving the compound of formula I.
FIELD OF THE INVENTION

This invention relates to monosaccharide compounds, methods for their preparation and their use in producing combinatorial libraries of potentially biologically active mono- or oligosaccharide compounds.

The compounds of the invention are variously functionalized, with a view to varying lipid solubility, size, function and other properties, with the particular aim of the discovery of novel drug or drug-like compounds, or compounds with useful properties. The invention provides intermediates, processes and synthetic strategies for the solution or solid phase synthesis of various amides of $\alpha$- and $\beta$-$D$-glucosamine and $\beta$-galactosamine, their PEG-glycosides and other glycosides, with various functionality about the sugar ring, including the addition of aromaticity, and the placement of amino acid and peptide units or their isosteres.

These compounds are structural mimetics of the substrates of enzymes in the muramyl pathway in peptidoglycan biosynthesis. It is expected that compounds of the type proposed, or analogues thereof, will act as inhibitors of the formation of the peptidoglycan layers that protect bacterial cell membranes or as inhibitors of other bacterial enzymes. Thus compounds of this type are attractive targets for the discovery of new antibiotics and antibacterials.

BACKGROUND OF THE INVENTION

Since the discovery of penicillin in 1928 the apparent ability of the ever-growing numbers of available antibiotics to treat infections and disease has, until recently, caused a high degree of complacency about the threat of bacterial resistance. This complacency has created a situation where antibiotics are over-prescribed in both hospitals and in the community, and used
extensively in animal feeds. The alarming speed with which bacteria have become resistant to microbial agents has meant that there is a very real danger that infections, which were until recently completely controllable, will pose serious threats to human health.

All unicellular bacteria contain a cell wall which is associated with a diverse range of functions, although the major one is that of protecting the cell from lysing under high internal osmotic pressures. The cell wall is composed of peptidoglycan, a rigid mesh of β-1,4-linked carbohydrate polymers covalently cross-linked by peptide chains. The peptidoglycan synthetic pathway is not present in mammalian systems, suggesting that the side-effects associated with such inhibitors could be minimized. Thus the bacterial peptidoglycan biosynthetic pathway presents an opportunity for the development of novel antibacterial agents.

There is a great deal of interest in the substrates of the muramyl pathway and their analogues, and in the synthesis of related compounds that may result in new therapeutics. Tanner and co-workers have recently prepared compounds that inhibit the MurD and MurE enzymes of the muramyl pathway. These non-carbohydrate compounds have the sugar and lactate moieties of a muramic acid-like compound replaced with a five carbon linker unit (Zeng, B., Wong, K.K., Pompliano, D.L., Reddy, S., and Tanner, M.E., JOC 1998 63(26) 10081-5; Tanner, M.E., Vaganay, S., van Heijenoort, J., and Blanot, D., JOC 1996 61(5) 1756-60), and are prepared by standard organic chemistry techniques. They are linear, flexible organic compounds with substituents that resemble those of UDP-MurNAc-pentapeptide (the "Park Nucleotide" (Park, J. J. Biol. Chem. 1952, 194, 877)). One of those compounds in particular was found to be a relatively potent inhibitor of MurE (Zeng, B., Wong, K.K., Pompliano, D.L., Reddy, S., and Tanner, M.E. JOC 1998 63(26) 10081-5).

In other studies on an analogous phosphinate inhibitor of MurD, it was found that retaining the MurNAc
sugar residue, instead of replacing it with a carbon linker unit, increases the potency of the inhibitor by almost two orders of magnitude (Gegnas, L. D., Waddell, S. T., Chabin, R. M., Reddy, S., Wong, K. K., Bioorg. Med. Chem. Lett. 1998 8 1643). This suggests that building a library of monosaccharide analogues of the substrates of the muramyl pathway is an attractive proposition for the generation of new therapeutics which target that system.

One approach to the synthesis of such compounds is to make use of biosynthetic techniques, such as that used in preparing labelled versions or analogues of MurNAc from GlcNac by implementing the MurA and MurB enzymes themselves (Lees, W.J., Benson, T.E., Hogle, J.M., and Walsh. C.T., Biochemistry 1996, 35(5), 1342-1351).

Chemical methods require protected building blocks, and some well-established chemistry has been implemented, using GlcNac to yield the benzyl glycoside of N-acetyl-4,6-benzyldenemuramic acid (Jeanloz, R. W., Walker, E., Sinaï, P., Carbohydr. Res. 1968, 6, 184). One challenge to the synthesis of such compounds is the alkylation of the C-3 position of the carbohydrate residue. In the natural muramyl system, the MurA and MurB enzymes add what is ultimately a lactate moiety to the C-3 position.

The addition of a lactate moiety at C-3 has been achieved chemically in a process in which the required materials were generated through the intermediate preparation of a nitroalkene sugar (Vega-Perez, et al. Tetrahedron 1999, 55, 9641-9650). An alternative approach is the alkylation of the C-3 hydroxyl with the α-bromide of an appropriately protected propiolic acid to generate the required compound (Iglesias-Guerra, F., Candela, J.I., Bautista, J., Alcudia, F., and Vega-Perez, J.M., Carb.Res. 1999, 316, 71-84).

Having compounds with a lactate moiety, or similar acid, in place at C-3 allowed the addition of amino acids to build the required pentapeptide substituent. This molecule was subsequently converted to the natural

Combinatorial chemistry and parallel synthesis have become the methods of choice for the rapid synthesis of a large number of related compounds simultaneously, and this approach has been used to produce libraries of compounds to be screened for biological activity. Sometimes such libraries are focussed to test for activity of the compounds so generated towards a particular biological agent or organism, although often large libraries are also prepared in a random fashion. Either way, the intended end result of combinatorial chemistry is the rapid discovery and optimization of leads for the development of new pharmaceuticals.

Despite the obvious advantages of a combinatorial approach to the preparation of compounds for drug discovery, this technique is underexplored in the field of carbohydrate chemistry. This is primarily because of the well-known difficulties associated with the synthesis of carbohydrate compounds. For that reason carbohydrate libraries prepared in the past have tended to be relatively simple. For example, Hindsgaul et al have produced a library of monosaccharide compounds by a combinatorial approach (Ole Hindsgaul US Patent 5780603); however, the variation in the compounds was limited to the glycosidic bond. A glycopeptide library in which mannose residues were decorated with various amino acids has been described, but these were conjugated to the sugar solely through the C-6 position (Tennant-Eyles, R.J., and Fairbanks, A.J., Tetrahedron Asymmetry. 1999, 10, 391-401).

Access to greater variation has been attempted by making used of libraries of carbohydrate mimetics
(Byrgesen, E., Nielsen, J., Willert, M., and Bols, M., Tetrahedron Lett. 1997, 38, 5697-5700 and Lohse, A., Jensen, K.B., and Bols, M., Tetrahedron Lett., 1999, 40, 3033-3036). However, one approach which successfully added greater diversity to monosaccharides was that of Goebel and Ugi (Tetrahedron Lett., 1995, 36(34), 6043-6046) who generated a small library of alkylated glucals by subjecting protected glucals to electrophilic attack and then subsequent reactions. Unfortunately this method is limited by the fact that each starting glucal may give rise to a number of isomeric products.

For these reasons there is particular interest in libraries of aminoglycosides and amino sugars for drug discovery. Some work on such compounds has been published, with Silva and co-workers preparing impressive disaccharide libraries containing glucosamine (Silva, D.J., Wang, H., Allanson, N.M., Jain, R.K., and Sofia, M.J., JOC 1999, 64(16), 5926-5929). However, this library still suffers from the limitation that the variation is limited solely to acylations of the amino group.

More variation, and in fact a three-dimensional diversity, was obtained in the preparation of amino sugars by Sofia and co-workers (Sofia, M.J., Hunter, R., Chan, T.Y., Vaughan, A., Dulina, R., Wang, H., and Gange, D., JOC 1998, 63(9), 2802-2803). This allowed chemical diversity at three combinatorial sites on the sugar residue. Other workers have prepared a library of compounds with four (Wunberg, T., Kallus, C., Opatz, T., Henke, S., Schmidt, W., and Kunz, H., Angew. Chem. Int. Ed. 1998, 37(18), 2503-2505), and five (Kallus, C., Opatz, T., Wunberg, T., Schmidt, W., Henke, S., and Kunz, H., Tetrahedron Lett. 1999, 40, 7783-7786) such sites of functionalization, although these compounds were not amino-sugars.

It will be clearly understood that, although a number of prior art publications are referred to herein, this reference does not constitute an admission that any of
these documents forms part of the common general knowledge in the art, in Australia or in any other country.

Hitherto, there have been few attempts to synthesise analogues of the muramyl substrates, particularly those which contain modifications at the anomeric position or at the C-2 nitrogen. The natural substrate and all of the muramyl enzyme intermediates contain exclusively the α-glycosidic diphosphate. Our modelling and design studies with the crystal structure of the Mur D enzyme suggest that both the α or β anomeric configuration of many of the compounds proposed in this invention can fit into the active site of this enzyme. We believe that this is the first time that β-glycosides which contain no phosphate groups have been prepared as potential inhibitors of the muramyl enzyme system.

Many of the traditional methods of carbohydrate synthesis have proved to be unsuitable to a combinatorial approach, particularly because modern high-throughput synthetic systems require that procedures to be readily automatable. The compounds and processes described herein are particularly suited to the solid and solution phase combinatorial synthesis of carbohydrate-based libraries, and are amenable to automation. The methods of the invention yield common intermediates which are suitably functionalized to provide diversity in the structure of the compounds so generated. In this way the technology described can produce many and varied compounds around the basic structure shown in formula I. Using this method, it is possible to introduce varied functionality in order to modulate both the biological activity and pharmacological properties of the compounds generated.

Thus the compounds and methods disclosed herein provide the ability to produce random or focussed combinatorial-type libraries not only for the discovery of new antibacterial agents, but also for the discovery of other novel drug or drug-like compounds, or compounds with other useful properties.
SUMMARY OF THE INVENTION

According to the present invention there is provided a monosaccharide compound of general formula I

\[
\begin{align*}
\text{R}_3 & \quad \text{O} \\
\text{R}_4 & \quad \text{O} \\
\text{R}_5 & \quad \text{O} \\
\text{R} & \quad \text{O} \\
\text{NR}_1\text{R}_2' & \\
\text{OR}_3 & \\
\end{align*}
\]

in which the monosaccharide ring is of the glucosamine or galactosamine configuration;

\(\text{R}_4\) and \(\text{R}_3\) are hydrogen or together form an optionally substituted benzylidene acetal in which the optional substituent is chosen from halo, azido, alkoxy, nitro or alkyl;

\(\text{R}_3\) is hydrogen; optionally substituted glycolate or optionally substituted lactate or derivatives thereof; or a carboxylic acid mimic;

\(\text{R}_1\) is optionally substituted acyl, optionally substituted benzoyl, optionally substituted biphenylcarbonyl, heteroaryl acyl, optionally substituted bicycloacyl, optionally substituted bicycloheteroacyl, sulfonamide, urea or carbamates;

\(\text{R}_2'\) is hydrogen;

\(\text{R}_1\) and \(\text{R}_2'\) together form succinimide, maleimide or optionally substituted phthalimide,

\(\text{R}\) is \(\text{N}_3\), \(\text{O-Y}\),

\[
\text{NH} \quad Y' \\
\text{X} \quad \text{or}-\text{NH-SO}_2\cdot Y''
\]
in which \( Y \) is

\[
\begin{align*}
\text{(Z\(^m\))} & \quad \text{(Z\(^m\))} \\
\end{align*}
\]

5

\[
\begin{align*}
\text{O} & \quad Z' \\
\end{align*}
\]

10

\[
\begin{align*}
\text{O} & \quad \text{O} \quad Z' \\
\end{align*}
\]

15

\[
\begin{align*}
\text{Z''} & \quad \text{Z''} \\
\text{OH} & \quad \text{OH} \\
\text{OH} & \quad \text{OH} \\
\end{align*}
\]

in which \( Z \) is positioned on one or both of the aromatic rings of the bicyclic structures and is independently selected from OH, SH, CF\(_3\), alkyl, alkenyl, alkynyl, NO\(_2\), halo, SO\(_2\)H, NH\(_2\), CO\(_2\)H, azido, nitroso, alkoxy, aryloxy, SO\(_2\)NH\(_2\), amidine and guanidinium;

\( q \) is 0 or 1;

\( m \) is an integer of 0 to 3;

\( Z' \) is halo, optionally substituted S-aryl, optionally substituted S-heteroaryl, optionally substituted aryl or optionally substituted heteroaryl;

\( Z'' \) is an optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl;

\( X \) is O, NH or S;
Y' is optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkyl, optionally substituted arylalkyl, optionally substituted heteroaryl alkyl,

in which Z''' is O, NH or S;
R₆ is H, CONH₂ or COOH;
n is an integer of 0 to 4;
R₇ is optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl or optionally substituted heteroarylalkyl
R₈ is H, OH, NH₂, alkyl, alkenyl or alkynyl;
R₉ is H, OH, NH₂, or NHCO-R₁₀ in which R₁₀ is an optionally substituted alkyl;
R₁₁ is an optionally substituted alkylene, optionally substituted cycloalkyl, optionally substituted heterocycle, optionally substituted aryl or optionally substituted heteroaryl; and
Y''' is optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkyl, optionally substituted arylalkyl or optionally substituted heteroaryl alkyl,
derivatives thereof, tautomers thereof and/or isomers thereof.
The term "derivatives" is used herein in its broadest sense to include protected forms and synthetic precursors of compounds of the present invention, for example, azide is a protected form/precursor of amine, nitrile is a protected form/precursor of amine, carboxylic acid and amide.

The term "tautomer" is used herein in its broadest sense to include compounds of formula I which are capable of existing in a state of equilibrium between two isomeric forms. Such compounds may differ in the bond connecting two atoms or groups and the position of these atoms or groups in the compound.

The term "isomer" is used herein in its broadest sense and includes structural, geometric and stereo isomers. As the compound of formula I may have one or more chiral centres, its is capable of existing in enantiomeric forms. The anomeric centre of the monosaccharide ring may also be of either the α or β configuration.

The term "halo" denotes fluorine, chlorine, bromine or iodine, preferably fluorine, chlorine or bromine.

The term "alkyl" used either alone or in compound words such as "optionally substituted alkyl", "optionally substituted cycloalkyl", "arylalkyl" or "heteroarylalkyl", denotes straight chain, branched or cyclic alkyl, preferably C1-6 alkyl or cycloalkyl. Examples of straight chain and branched alkyl include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, amyl, isoamyl, sec-amyl, 1,2-dimethylpropyl, 1,1-dimethylpropyl, hexyl, 4-methylpentyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 1,2,2-trimethylpropyl, 1,1,2-trimethylpropyl, heptyl, 5-methylhexyl, 1-methylhexyl, 2,2-dimethylpentyl, 3,3-
dimethylpenty1, 4,4-dimethylpenty1, 1,2-dimethylpentyl, 1,3-dimethylpentyl, 1,4-dimethylpentyl, 1,2,3-trimethylbutyl, 1,1,2-trimethylbutyl, 1,1,3-trimethylbutyl, octyl, 6-methylhepty1, 1-methylhepty1, 1,1,3,3-tetramethylbutyl, nonyl, 1-_, 2-_, 3-_, 4-_, 5-_, 6- or 7-methyloctyl, 1-_, 2-_, 3-_, 4- or 5-ethylhepty1, 1-_, 2- or 3-propylhexyl, decyl, 1-_, 2-_, 3-_, 4-_, 5-_, 6-_, 7- or 8-methylnonyl, 1-_, 2-_, 3-_, 4-_, 5- or 6-ethyloctyl, 1-_, 2-_, 3- or 4-propylheptyl, undecyl 1-_, 2-_, 3-_, 4-_, 5-_, 6-_, 7-_, 8- or 9-methyldecyl, 1-_, 2-_, 3-_, 4-_, 5-_, 6- or 7-ethylnonyl, 1-_, 2-_, 3-_, 4- or 5-propyloctyl, 1-_, 2- or 3-butylheptyl, 1-pentylhexyl, dodecyl, 1-_, 2-_, 3-_, 4-_, 5-_, 6-_, 7-_, 8- or 10-methylundecyl, 1-_, 2-_, 3-_, 4-_, 5-_, 6-_, 7- or 8-ethyldecyl, 1-_, 2-_, 3-_, 4-_, 5- or 6-propylnonyl, 1-_, 2-_, 3- or 4-butylctyl, 1-2 pentylheptyl and the like. Examples of cyclic alkyl include mono- or polycyclic alkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl and the like.

The term "alkylene" used either alone or in compound words such as "optionally substituted alkenyl" denotes the same groups as "alkyl" defined above except that an additional hydrogen has been removed to form a divalent radical. It will be understood that the optional substituent may be attached to or form part of the alkenyl chain.

The term "alkenyl" used either alone or in compound words such as "optionally substituted alkenyl" denotes groups formed from straight chain, branched or cyclic alkenes including ethylenically mono-, di- or polyunsaturated alkyl or cycloalkyl groups as defined above, preferably C₂₆-alkenyl. Examples of alkenyl include vinyl, allyl, 1-methylvinyl, butenyl, iso-butenyl, 3-methyl-2-butenyl, 1-pentenyl, cyclopentenyl, 1-methyl-cyclopentenyl, 1-hexenyl, 3-hexenyl, cyclohexenyl, 1-heptenyl, 3-heptenyl, 1-octenyl, cyclooctenyl, 1-nonenyl, 2-nonenyl, 3-nonenyl, 1-decenyl, 3-decenyl, 1,3-butadienyl, 1,4-pentadienyl, 1,3-
cyclopentadienyl, 1,3-hexadienyl, 1,4-hexadienyl, 1,3-
cyclohexadienyl, 1,4-cyclohexadienyl, 1,3-cycloheptadienyl,
1,3,5-cycloheptatrienyl and 1,3,5,7-cyclooctatetraenyl.

The term "alkynyl" used either alone or in
compound words, such as "optionally substituted alkynyl"
denotes groups formed from straight chain, branched, or
mono- or poly- or cyclic alkynes, preferably C₃-₆ alkynyl.
Examples of alkynyl include ethynyl, 1-propynyl, 1- and 2-
butynyl, 2-methyl-2-propynyl, 2-pentynyl, 3-pentynyl, 4-
pentynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl, 10-
undecynyl, 4-ethyl-1-octyn-3-yl, 7-dodecynyl, 9-dodecynyl,
10-dodecynyl, 3-methyl-1-dodecyn-3-yl, 2-tridecynyl, 11-
tridecynyl, 3-tetradecynyl, 7-hexadecynyl, 3-octadecynyl
and the like.

The term "alkoxy" used either alone or in
compound words such as "optionally substituted alkoxy"
denotes straight chain or branched alkoxy, preferably
C₁₋₇ alkoxy. Examples of alkoxy include methoxy, ethoxy, n-
propoxyloxy, isopropoxyloxy and the different butoxy isomers.

The term "aryloxy" used either alone or in
compound words such as "optionally substituted aryloxy"
denotes aromatic, heteroaromatic, arylalkoxy or heteroaryl
alkoxy, preferably C₆₋₁₃ aryloxy. Examples of aryloxy
include phenoxy, benzylxylo, 1-naphthoxy, and 2-naphthoxy.

The term "acyl" used either alone or in compound
words such as "optionally substituted acyl" or
"heteroarylacyl" denotes carbamoyl, aliphatic acyl group
and acyl group containing an aromatic ring, which is
referred to as aromatic acyl or a heterocyclic ring which
is referred to as heterocyclic acyl. Examples of acyl
include carbamoyl; straight chain or branched alkanoyl such
as formyl, acetyl, propanoyl, butanoyl, 2-methylpropanoyl,
pentanoyl, 2,2-dimethylpropanoyl, hexanoyl, heptanoyl,
octanoyl, nonanoyl, decanoyl, undecanoyl, dodecanoyl,
tridecanoyl, tetradecanoyl, pentadecanoyl, hexadecanoyl,
heptadecanoyl, octadecanoyl, nonadecanoyl, and icosanoyl;
alkoxycarbonyl such as methoxycarbonyl, ethoxycarbonyl, t-
butoxycarbonyl, t-pentyloxy carbonyl and heptyloxy carbonyl; cycloalkyl carbonyl such as cyclopropylcarbonyl
cyclobutylcarbonyl, cyclopentylcarbonyl and
cyclohexylcarbonyl; alkylsulfonyle such as methylsulfonyle
and ethylsulfonyle; alkoxy sulfonyle such as methoxy sulfonyle
and ethoxy sulfonyle; aroyl such as benzoyle, toluoyl and
naphthoyl; aralkanoyl such as phenylalkanoyl (e.g.
phenylacetyle, phenylpropanoyl, phenylbutanoyl,
phenylisobutyrl, phenylpentanoyl and phenylhexanoyl) and
naphthylalkanoyl (e.g. naphthylacetyl, naphthlpropanoyl and
naphthylbutanoyl); aralkenoyl such as phenylalkenoyl (e.g.
phenylpropenoyl, phenylbutenoyl, phenylmethacryl,
phenylpentenoyl and phenylhexenoyl and naphthylalkenoyl
(e.g. naphthylpropenoyl, naphthylbutenoyl and
naphthylpentenoyl); aralkoxy carbonyl such as
phenylalkoxy carbonyl (e.g. benzyloxy carbonyl);
aryloxy carbonyl such as phenoxy carbonyl and
naphthoxy carbonyl; aryloxy alkanoyl such as phenoxyacetyle
and phenoxy propionoyl; aryl carbamoyl such as
phenyl carbamoyl; aryli thiocarbamoyl such as
phenylthiocarbamoyl; arylglyoxyloyl such as
phenylglyoxyloyl and naphthylglyoxyloyl; arylsulfonyle such
as phenylsulfonyle and naphthylsulfonyle;
heterocyclic carbonyl; heterocyclic alkanoyl such as
thienyl acetyle, thi enylpropanoyl, thi enylbutanoyl,
thi enylpentanoyl, thi enylhexanoyl, thiazolyl acetyle,
thiadiazolyl acetyle and tetrazolyl acetyle;
heterocyclic alkenoyl such as heterocyclic propenoyl,
heterocyclic butenoyl, heterocyclic pentenoyl and
heterocyclic hexenoyl; and heterocyclic glyoxyloyl such as
thiazole glyoxyloyl and thieny glyoxyloyl.

The term "aryl" used either alone or in compound
words such as "optionally substituted aryl", "arylalkyl" or
"heteroaryl" denotes single, polynuclear, conjugated and
fused residues of aromatic hydrocarbons or aromatic
heterocyclic ring systems. Examples of aryl include
phenyl, biphenyl, terphenyl, quaterphenyl, phenoxy phenyl,
naphthyl, tetrahydronaphthyl, anthracenyl, dihydroanthracenyl, benzanthracenyl, dibenzanthracenyl, phenanthrenyl, fluorenyl, pyrenyl, indenyl, azulenyl, chrysenyl, pyridyl, 4-phenylpyridyl, 3-phenylpyridyl, thienyl, furyl, pyrrol, pyrrolyl, furanyl, imidazolyl, pyrrolydiny1, pyridinyl, piperidinyl, indolyl, pyridazinyl, pyrazolyl, pyrazinyl, thiazolyl, pyrimidinyl, quinolinyl, isoquinolinyl, benzofuranyl, benzothienyl, purinyl, quinazolinyl, phenazinyl, acridinyl, benzoxazolyl, benzothiazolyl and the like. Preferably, the aromatic heterocyclic ring system contains 1 to 4 heteroatoms independently selected from N, O and S and containing up to 9 carbon atoms in the ring.

The term "heterocycle" used either alone or in compound words as "optionally substituted heterocycle" denotes monocyclic or polycyclic heterocycl1 groups containing at least one heteroatom atom selected from nitrogen, sulphur and oxygen. Suitable heterocyclic groups include N-containing heterocyclic groups, such as, unsaturated 3 to 6 membered heteromonocyclic groups containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl or tetrazolyl; saturated to 3 to 6-membered heteromonocyclic groups containing 1 to 4 nitrogen atoms, such as, pyrroldinyl, imidazolidinyl, piperidino or piperazinyl; unsaturated condensed heterocyclic groups containing 1 to 5 nitrogen atoms, such as, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl or tetrazolopyridazinyl;
saturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, such as, pyranyl or furyl; unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulphur atoms, such as, thieryl; unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, such as, oxazolyl, isoxazolyl or oxadiazolyl;
saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, such as, morpholinyl;
unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, such as, benzoazolyl or benzoazadiolyl;
unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulphur atoms and 1 to 3 nitrogen atoms, such as, thiazolyl or thiaazolyl;
saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulphur atoms and 1 to 3 nitrogen atoms, such as, thiazolidinyl; and
unsaturated condensed heterocyclic group containing 1 to 2 sulphur atoms and 1 to 3 nitrogen atoms, such as, benzothiazolyl or benzothiaazolyl.

In this specification "optionally substituted" means that a group may or may not be further substituted with one or more groups selected from alkyl, alkenyl, alkynyl, aryl, halo, haloalkyl, haloalkenyl, haloalkynyl, haloaryl, hydroxy, alkoxy, alkenyloxy, aryloxy, carboxy, benzyloxy, haloalkoxy, haloalkenyloxy, haloaryloxy, nitro, nitroalkyl, nitroalkenyl, nitroalkynyl, nitroaryl, nitroheterocyclyl, nitroso, azido, amidine, guanidium, amino, alkylamino, alkenylamino, alkynylamino, ary lamino, benzylamino, acylamino, acyl, alkenylacyl, alkynylacyl, arylacyl, acylamino, acyloxy, aldehyde, alkylsulphonyl, arylsulphonyl, sulphonylamino, alkylsulphonylamino, arylsulphonylamino, alky lsulphonyloxy, arylsulphonyloxy, heterocyclyl, heterocycloxy, heterocyclylamino, haloheterocyclyl, alkylsulphenyl, arylsulphenyl, carboxalkoxy, carboxaryloxy, mercapto, sulfonic acid, alkythio, arylthio, acylthio and peptidomimetics.

Preferred optional substituents include OH, SH, CF₃, alkyl, alkenyl, alkynyl, NO₂, halo, SO₂H, NH₂, CO₂H, azido, nitroso, alkoxy, aryloxy, SO₂NH₂, amidine, guandinium or peptidomimetics.
A preferred compound of formula I has the formula

\[
{\text{R}_3\text{O}} \qquad \text{O} \quad \text{O} - \text{Y} \\
{\text{R}_4\text{O}} \qquad \text{NR}_1\text{R}_2 \\
\text{OR}_3
\]

Ia

in which the monosaccharide ring is of the glucosamine or galactosamine configuration and the anomic centre may be either the \(\alpha\) or \(\beta\) configuration;

- \(\text{R}_3\), \(\text{R}_4\) and \(\text{R}_3\) are as defined in formula I above;
- \(\text{R}_2\) is hydrogen;
- \(\text{R}_1\) is
  - (i) \(\text{C}_{2-8}\) acyl which may be branched or linear and optionally substituted with one or more \(\text{OH}, \text{SH}, \text{CF}_3, \text{NO}_2, \text{halo}, \text{SO}_2\text{H}, \text{NH}_2, \text{CO}_2\text{H}, \text{azido, nitroso, alkoxy, aryloxy, SO}_2\text{NH}_2, \text{amidine or guanidinium;}
  - (ii) a benzoyl group which may be optionally substituted with one or more \(\text{OH}, \text{SH}, \text{CF}_3, \text{alkyl, alkenyl, alkynyl, NO}_2, \text{halo, SO}_2\text{H, NH}_2, \text{CO}_2\text{H, azido, nitroso, alkoxy, SO}_2\text{NH}_2, \text{amidine or guanidinium;}
  - (iii) a biphenylcarbonyl group which may be optionally substituted on either one or both of the aromatic rings with one or more of \(\text{OH}, \text{SH}, \text{CF}_3, \text{alkyl, alkenyl, alkynyl, NO}_2, \text{halo, SO}_2\text{H, NH}_2, \text{CO}_2\text{H, azido, nitroso, alkoxy, SO}_2\text{NH}_2, \text{amidine or guanidinium; or}
  - (iv) a heteroaryl acyl, sulfonamide, urea or carbamate;

- \(\text{R}_1\) and \(\text{R}_2\) together form optionally substituted succinimide, optionally substituted maleimide or optionally substituted phthalimide;

- \(\text{Y}\) is as defined in formula I above in which the optional substituents for \(\text{Z}'\) or \(\text{Z}''\) are at least one of \(\text{OH}, \text{SH}, \text{CF}_3, \text{alkyl, alkenyl, alkynyl, NO}_2, \text{halo, SO}_2\text{H, NH}_2, \)}
CO₂H, azido, nitroso, alkoxy, aryloxy, SO₂NH₂, amidine or guanidinium.

Preferably, the glycolate or lactate or derivatives thereof are optionally substituted with at least one amino acid or peptidomimetic.


Non-limiting examples of carboxylic acid mimetics and other suitable substituents for R₃ are:

\[
\begin{align*}
A & \quad \text{OA'} \\
B & \quad \text{O} \\
\end{align*}
\]

\[
\begin{align*}
A' & \quad \text{OA'} \\
B & \quad \text{O} \\
\end{align*}
\]

\[
\begin{align*}
A & \quad \text{F} \\
B & \quad \text{U} \\
\end{align*}
\]

\[
\begin{align*}
A & \quad \text{NHpeptide} \\
B & \quad \text{O} \\
\end{align*}
\]

\[
\begin{align*}
A & \quad \text{SO₃H} \\
B & \quad \text{O} \\
\end{align*}
\]

\[
\begin{align*}
A & \quad \text{SO₂NHU} \\
B & \quad \text{O} \\
\end{align*}
\]

\[
\begin{align*}
A & \quad \text{U} \\
B & \quad \text{O} \\
\end{align*}
\]

\[
\begin{align*}
A & \quad \text{(n) W} \\
B & \quad \text{O} \\
\end{align*}
\]

in which A and B are independently hydrogen, alkyl, trihaloalkyl or halo;
A' is hydrogen or alkyl;
A'' is hydroxy, optionally substituted amine or oxyaryl;
U is hydrogen, aryl, heteroaryl, alkyl, alkenyl or alkynyl each of which may be optionally substituted with one or more of OH, SH, CF₃, alkyl, alkenyl, alkynyl, NO₂, halo, SO₂H, NH₂, CO₂H, azido, nitroso, alkoxy, SO₂NH₂, amidine or guanidinium; and
- 18 -

W is hydrogen or an acidic or acid mimetic, such as, for example, OH, SH, CF₃, NO₂, halo, SO₂H, CO₂H, azido, nitroso, alkoxy, aryloxy, SO₂NH₂, or forms a carbocyclic or heterocyclic ring.

Another preferred compound of formula I has the formula Ib

\[
\begin{align*}
\text{R}_3 \text{O} & \text{O} \text{N}\text{R}_1' \\
\text{R}_4 \text{O} & \text{N}\text{R}_1 \text{R}_2 \\
\text{OR}_3 &
\end{align*}
\]

in which the monosaccharide ring substitution is of the glucosamine or galactosamine configuration and the anomeric centre may be of the \(\alpha\) or \(\beta\) configuration;

\(\text{R}_3, \text{R}_4\) and \(\text{R}_3\) are as defined in formula I above;

\(\text{R}_2\) and \(\text{R}_1\) are as defined in formula Ia above;

\(\text{R}_1'\) is \(\text{N}_2\) or

\[
\text{X} \text{Y}'
\]

in which

\(\text{X}\) is \(\text{O, NH or S}\); and

\(\text{Y}'\) is as defined in formula I above in which \(\text{R}_7\) may be optionally substituted with at least one of OH, SH, CF₃, alkyl, alkenyl, alkynyl, NO₂, halo, SO₂H, NH₂, CO₂H, azido, nitroso, alkoxy, SO₂NH₂, amidine or guanidinium.

A further preferred compound of formula I has the formula Ic

\[
\begin{align*}
\text{R}_3 \text{O} & \text{O} \text{N}\text{NH} \text{SO} \text{Y}'' \\
\text{R}_4 \text{O} & \text{N}\text{R}_1 \text{NR}_2 \\
\text{OR}_3 &
\end{align*}
\]

Ic
in which the monosaccharide ring substitution is of the glucosamine or galactosamine configuration and the anomeric center may be of the α or β configuration;

in which $R_5$, $R_4$ and $R_3$ are as defined in formula I above;

$R_2$ and $R_1$ are as defined in formula Ia above;

$Y''$ is as defined in formula I above and may be optionally substituted with one or more OH, SH, CF₃, alkyl, alkenyl, alkynyl, NO₂, halo, SO₂H, NH₂, CO₂H, azido, nitroso, alkoxy, SO₂NH₂, amidine or guanidinium.

The present invention also provides a method for the preparation of a compound of general formula I, comprising the step of glycosylating an intermediate compound of formula IV,

![IV](image)

in which $L$ is a leaving group and $L'$ is a protecting groups with an alcohol or phenol acceptor.

The leaving group may be of any suitable known type, such as, for example, those leaving groups disclosed in J. March, "Advanced Organic Chemistry: Reactions, Mechanisms and Structure," 4th Edition, pp 352-357, John Wiley & Sons, New York, 1992 which is incorporated herein by reference.

Preferably, the leaving group is acetate, thiomethyl, trichloroacetimidyl or halogen, more preferably bromine or chlorine.

Suitable protecting groups include those disclosed in Greene, T.W., "Protective Groups in Organic Synthesis", John Wiley & Sons, New York, 1981, such as optionally substituted silyl, optionally substituted alkyl, optionally substituted acyl or optionally substituted heteroacyl, for
example, azide or 4,4-dimethyl-2,6-dioxocyclohex-1-y-idene (Dde), butyldimethylsilyl, butyldiphenylsilyl, benzylidene, 4-methoxybenzylidene, benzoate, acetate, chloroacetate, 9-fluorenymethylcarbamate, benzyloxy carbamate, isopropylidene and 4-methoxyphenyl.

Examples of suitable alcohols include methanol, ethanol, propanol, iso-propanol, benzyl alcohol, 2′,2′-chloroethoxyethanol, 2′′,2′,2-chloroethoxyethoxyethanol, 2-napthylmethanol, 1-napthylmethanol, allyl alcohol, 5-penteneol, 4-buteneol, 5-butanol, sec-butanol and n-butanol.

Examples of suitable "phenol acceptor" include 4-nitrophenol, phenol, resorcinol, phloroglucinol, 4-chlorophenol, catechol and 4-allylphenol.

The present invention further provides a method for the preparation of a compound of formula I, in particular formula Ib or Ic, comprising the step of acylating an intermediate compound of general formula V

\[
\begin{align*}
\text{V} & \\
& \begin{array}{c}
\text{L''} \\
\end{array}
\end{align*}
\]

in which L'' is hydrogen, NO₂, halo, azido or alkoxy.

The compounds of the present invention are useful in screening for biological activity, particularly use of compounds of the formulae Ia, Ib and Ic for screening for anti-bacterial or antibiotic activity. In particular,
compounds of the invention are useful in screening for inhibitory activity against one or more enzymes of the muramyl cascade.

Thus, according to a further aspect of the present invention there is provided a method of screening for antibacterial or antibiotic compounds comprising the steps of:

(a) forming a combinatorial library comprising a compound of the formula I defined above; and

(b) testing the combinatorial library for antibacterial or antibiotic activity.

According to a still further aspect of the present invention there is provided an antibacterial or antibiotic compound identified using the method defined above.

In a particularly preferred embodiment for this purpose, the compound of formula Ia has structure A

![Structure A]

in which R₅' and R₄' are hydrogen or together form a benzylidene-type acetal;

R₃' is a lactate or lactate mimetic which may be optionally substituted with short peptides or peptidomimetics such as those found in the muramyl enzyme products;

R₁' is an acetyl group as in the naturally-occurring system; or

NHCOR₁' may be other amides, sulfonamides, urea and the like; and

YA is a structural or functional mimic of uridine diphosphate or a simple diphosphate.
Analogous compounds to Structure A of the formulae Ib and Ic of the invention are also contemplated as preferred embodiments for this purpose.

For the purposes of this specification it will be clearly understood that the word "comprising" means "including but not limited to", and that the word "comprises" has a corresponding meaning.

BRIEF DESCRIPTION OF THE FIGURES

Figures 1 to 3 show HPLC and mass spectra for representative compounds produced following General Step 9. Figure 1: 1-(2'-(2'-(4'''-chlorophenylthio)ethoxy)ethyl]-2-deoxy-2-benzoylamino-β-D-glucose. HPLC and mass spectrum. Figure 2: 1-(2'-(2'-(m-trifluoromethylphenylthio)ethoxy)ethoxy)ethyl]-2-deoxy-2-acetylamino-β-D-glucose. HPLC and mass spectrum. Figure 3: 1-(2'-(2'-(2''-(m,p-dichlorophenylthio)ethoxy)ethoxy)ethyl]-2-deoxy-2-(3',3',3' trimethylpropionylamino)-β-D-glucose. HPLC and mass spectrum.

Figure 4a shows a ¹Hnmr spectrum and Figure 4b shows a mass spectrum for a protected tripeptide product produced according to General step 10. 1-(2'-(2'-(2''-chloroethoxy)ethoxy)ethyl]-2-deoxy-2-benzoylamino-4,6-O-benzylidene-3-O-methylcarbonyl-[(α-O-benzyl)-γ-glutamyl]- (N⁶-(2'chlorobenzylcarbamoyl)-lysiny1)-(O-benzylalany1)]-β-D-glucopyranoside.

DETAILED DESCRIPTION OF THE INVENTION

The invention will now be described in detail by way of reference only to the following non-limiting examples and to the drawings.

Abbreviations used herein are as follows:

AN Acetonitrile
MeCN Acetonitrile
Ether  Diethyl Ether
DCM  methylene chloride; dichloromethane
MeOH  methanol
EtOAc  Ethyl Acetate
DMF  N,N-dimethylformamide
HBTU  O-benzotriazol-1-yl-N,N,N',N''-tetramethylyuronium hexafluorophosphate
TBAF  tetrabutylammonium fluoride
Dde  4,4-dimethyl-2,6-dioxocyclohex-1-ylidene
BOP  Benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate
PyBOP  Benzotriazol-1-yloxy-tris(pyrrolidyl)phosphonium hexafluorophosphate
HATU  O-(7-Azabenzotriazol-1-yl)-N,N,N',N''-tetramethylyuronium hexafluorophosphate
Fmoc  9-Fluorenylmethylcarbamate
Boc  t-Butylcarbamate

20 **Experimental Support**

Exemplary compounds of the invention were prepared as set out in the following synthetic schemes 1 to 3 and detailed in the general procedures.

All final compounds were purified by liquid chromatography-mass spectrometry (LC-MS), using a micromass LCZ electrospray mass spectrometer as detector. Proton NMR results are included for representative compounds.
Scheme 1

\[ y = \text{benzyl, naphthylmethyl, 2'}-\text{chloroethoxyethyl, 2''-chloroethoxyethoxyethyl.} \]
\[ R_1 = \text{methyl, phenyl, 1'butyl, 1'butyrmethylene, biphenyl.} \]
2-deoxy-2-[(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)-ethylamino]-α-D-glucopyranose (1)

Glucosamine hydrochloride (50g, 231mmol) was suspended in anhydrous methanol (500ml), then 2-acetyl-dimedone sodium salt (47.3g, 231mmol) was added. The reaction mixture was stirred at room temperature for 10 minutes, then 2-acetyl-dimedone (21.1g, 115.9mmol) was added. The reaction mixture was stirred under reflux for 2.5 hours and monitored by tlc. At the completion of the reaction (TLC: MeCN-H₂O, 10:2), the reaction mixture was cooled to room temperature and filtered. The filtrate was evaporated and the resulting solid residue was washed on a funnel with ether (3 x 500 ml) and dried to give crude product (75g, 94%). No further purification was required for the next reaction.

1,2,4,6-tetra-O-acetyl-2-deoxy-2-[(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)-ethylamino]-α-D-glucopyranose (2)

Crude 2-Deoxy-2-[(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)-ethylamino]-α,β-D-glucopyranose (75g, 218.6mmol) was dissolved in pyridine (320ml) and acetic anhydride (165ml) was added dropwise keeping the temperature below 30°C. The reaction mixture was stirred overnight then solvents evaporated. Toluene (2 x 100ml) was evaporated off the residue. The residue was taken up in CH₂Cl₂ (550ml), washed with 5% HCl solution (280ml), water (3 x 11), saturated NaHCO₃ (11), then dried over magnesium sulphate and the solvents evaporated. The product was crystallised from MeOH (250ml), filtered, washed with cold MeOH (-40°C) on the funnel. The solid was dried to give 1,2,4,6-tetra-O-Acetyl-2-deoxy-2-Deoxy-2-[(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)-ethylamino]-α-D-glucopyranose (95g, 85%).
3,4,6-tri-O-Acetyl-2-deoxy-2-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)-ethylamino]-α-D-glucopyranosyl bromide (3)

1,2,4,6-tetra-O-Acetyl-2-deoxy-2-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)-ethylamino]-α-D-glucopyranose (150g, 293.5 mmol) was dissolved in dry CH₂Cl₂ (300 ml) and hydrogen bromide in acetic acid (400 ml, 30%) was added. The reaction mixture was stirred at room temperature for 2 hours, then diluted with cold CH₂Cl₂ (-15°C, 2 l) and washed with cold water (0°C, 3 times 2l), saturated NaHCO₃ (2 l). The organic phase was dried over MgSO₄ and evaporated in vacuo at 30°C. The resulting white solid residue was suspended in ether (1 l) and filtered. The solid was dried under vacuum giving 3,4,6-O-acetyl-2-deoxy-2-[1-(4,4-dimethyl-2,6-dioxocyclohexa-1-ylidene)-ethylamino]-α-D-glucopyranosyl bromide (150g, 95%).

Rf 0.62 (EtOAc / Hexane 2:1); MS (electrospray) C₂₂H₂₃BrNO₉ (532.1/534.0) m/z (%) 533.38/535.38 [M + H]⁺ (100).

General Step 1: Reaction of (3) with acceptor alcohols

A mixture of 3,4,6-tri-O-acetyl-2-deoxy-2-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)-ethylamino]-β-D-glucopyranosyl bromide (3) (1 equivalent), the acceptor alcohol (1.5 equivalents) and activated [4Å] molecular sieves (equal mass as bromide (3)) were stirred in 1,2-dichloroethane (10 ml per gram of (3)) under a nitrogen atmosphere at -78°C in a flask that had been covered to preclude ambient light. Silver triflate (1.45 equivalents) was added and the mixture allowed to warm to room temperature. This reaction was then stirred at room temperature for 1 hour, diluted with CH₂Cl₂ (20 ml per gram of (3)) and filtered through a plug of Celite. The eluent was then washed with saturated NaHCO₃ (3 times 10 ml per gram of (3)), dried (MgSO₄) and the solvent removed in vacuo to yield an anomeric mixture of the glycosylated compounds.
Acceptor A = 2-(2-(2-Chloroethoxy)ethoxy)ethanol, amount of (3) used 21 gm, yield 4A 20.57 gm (84%)
MS (electrospray) C_{28}H_{42}ClNO_{12} (619.3/621.2) m/z (%) 620.32/622.4 [M + H]^+ (100).

Acceptor B = 2-(2-Chloroethoxy)ethanol, amount of (3) used = 35 gm, yield 4B 37 gm 97%

Acceptor C = 2-napthylmethanol, amount of (3) used 34.5 gm, yield 4C 25.75 gm (66%)
MS (electrospray) C_{33}H_{38}NO_{10} (609) m/z (%) 610[M + H]^+ (100).

Acceptor D = Benzyl alcohol

Amount of (3) used 2.24 gm, yield 4D 2.35 gm

**General Step 2: Deacylation of glycosylation products 4**

Products of general step 1 (1 eq) were dissolved in methanol (4 ml per gram of substrate) and sodium metal (10 mg per gram of substrate dissolved in methanol) was added. The reaction vessel was fitted with a calcium chloride guard tube and the mixture stirred at room temperature for 30 minutes with monitoring by t.l.c (EtOAc / Hexane 2:1).

When the reaction was complete Amberlite IR-120 (H) cation exchange resin was added to the mixture until slightly acidic (pH 5 - 6). The resin was filtered off and the solvent removed in vacuo. The residue was further purified by passing through a short column of silica gel and eluting with (acetonitrile / water 10:1). Solvents were removed to yield the desired triols 5A, 5B, and 5C

5A) Substrate 41.30 grams yield 30.98 grams (94%)
MS (electrospray) C_{22}H_{36}ClNO_{4} (493.2, 495.1) m/z (%) 494, 496 [M + H]^+ (30); (516.1, 518.2) m/z (%) 516, 518 [M + Na]^+ (100).

5B) amount of substrate 4B 37 gm, Yield 28.5 gm 97%
amount of substrate 4C 25.70 gm , Yield 18.24 gm (89%)
MS (electrospray) C_{27}H_{33}NO_{7} (483) m/z (%) 484 [M + H]^+ (100); (507) m/z (%) 507 [M + Na]^+ (35).

General Step 3: Benzyldiene acetal formation

Product from general step 2 (5A, 5B or 5C) 1 equivalent was dissolved in dry acetonitrile (7.5 mL per gram of
substrate), benzaldehyde dimethyl acetal (2 equivalents) and para-toluenesulfonic acid monohydrate (2 mg per gram of
substrate) were added. The flask was fitted with a calcium chloride guard tube and the mixture stirred at 60°C for 14
hours, after which triethylamine (1 ml) was added and the solvent removed in vacuo. The residue was taken into
CH_{2}Cl_{2} (20 ml per gram of substrate) and washed with brine (3 times 5 ml per gram of substrate), dried (MgSO_{4}) and the
residue triturated with ether/petrol. The solvent was then removed in vacuo to yield the desired acetals as a white
solid. The product was used without further purification in the next step.

General Step 4: Removal of Dde

The product of general step 3 (6A to 6C) was dissolved in a mixture of methanol and aqueous ammonia (28%) 1:1 (20 ml
per gram of substrate) and warmed to 60°C for 14 hours. The solvents were removed in vacuo and the residue purified by
column chromatography (gradient acetonitrile to
acetonitrile methanol 1:1) to yield both the α and β
anomers as pure components.

amount of substrate Crude 5A 76.5 gm ,
Yield 7Aα 20.6 gm (38%)
yields are over 3 steps.
MS (electrospray) C_{19}H_{23}C1NO (417,419) m/z (%) 418,420[M +H]^+ (100), 250 (70).
Yield 7Aβ 12.6 gm (23%)
MS (electrospray) C₁₉H₂₈ClNO₃ (417, 419) m/z (%) 418, 420 [M + H]⁺ (100).

amount of substrate pure 5B 34.1 gm ,
Yield 7Bα 8.16 gm 34%
Yield 7Bβ 14.86 gm 62%

amount of substrate crude 5C 20.30 gm ,
Yield 7Cα 1.2 gm
yields are over 3 steps.
¹H NMR (500 MHz, CD₃OD) δ 7.30–8.10 (14H m aromatics + NH₂),
5.55 (1H s Ph-[CH]), ?? 5.20 (1H d J=12 napthyl CH₉), 5.00
(1H d J=12 napthyl CH₈), 4.95 (1H d J=4 H-1), 4.25 (1H dd
J=5,10 H-4), 3.90-4.00 (1H m H-5), 3.75-3.80 (2H m H-6),
3.50 (1H t J=9.5 H-3), 2.80-2.85 (1H m H-2).
Yield 7Cβ 6.58 gm
MS (electrospray) C₂₄H₂₅NO₅ (407) m/z (%) 408 [M + H]⁺ (100).
¹H NMR (500 MHz, CD₃OD) δ 7.35–8.15 (14H m aromatics + NH₂),
5.55 (1H s Ph-CH), 5.40 (1H d J=12 napthyl CH₉), 5.05 (1H d
J=12 napthyl CH₈), 4.45 (1H d J=8 H-1), 4.40 (1H dd J=5,10
(1H m H-5), 2.80-2.90 (1H m H-2).

General Step 5: Selective acylation of free amine

The products of general step 4 (7Aα, 7Aβ, 7Bα, 7Bβ, 7Cα, and 7Cβ) were dissolved in dry methanol (10 ml per gram of
substrate) (dry dichloromethane may be substituted for
methanol) and the solution stirred at room temperature.
Where available the symmetrical anhydride of the acylating
agent was added (1.05 equivalents). In the case of the
biphenylcarbonyl, ⁵Butylacetetyl and ⁵Butylcarbonyl acyl
groups the acid chloride was used. In many cases the
product began to precipitate after 5 minutes and the
product was collected after 30 minutes by filtration. The
solid was washed with a small amount of cold methanol. In
cases where the product did not precipitate, the product was partitioned between dichloromethane and sodium hydrogen carbonate solution. The organic layer being dried and evaporated to yield the desired product. The yields are summarized in Table 1.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>NMR data / yields for general step 5 of Scheme 1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7Aα yield</td>
</tr>
<tr>
<td>1) Acetyl</td>
<td>74%</td>
</tr>
<tr>
<td>2) Benzoyl</td>
<td>69%</td>
</tr>
<tr>
<td>3) Biphenylcarbonyl</td>
<td>80%</td>
</tr>
<tr>
<td>4) Butylcarbonyl</td>
<td>74%</td>
</tr>
<tr>
<td>5) Butylacetyl</td>
<td>68%</td>
</tr>
</tbody>
</table>

|         | 7Bα yield | 7Bβ yield | 7Bα H-1 shift | 7Bβ H-1 shift |
| 1) Acetyl | 44% | 86% | 4.72 d J=4.0 | 4.77 d J=8.4 |
| 2) Benzoyl | 66% | 75% | Not recorded | 3.86 d J=7.7 |
| 3) Biphenylcarbonyl | 87% | 86% | Not recorded | 3.88 d J=7.8 |
| 4) Butylcarbonyl | 85% | 69% | Not recorded | 4.87 d J=8.3 |
| 5) Butylacetyl | 76% | 77% | 4.56 d J=3.0 | 4.79 d J=8.4 |
| 6) 2-nitrophenacetyl | Not done | 83% | Not done | Not recorded |

|         | 7Cα yield | 7Cβ yield | 7Cα H-1 shift | 7Cβ H-1 shift |
| 1) Acetyl | 61% | 87% | 5.10 d J=3.0 | 4.85 d J=8.0 |
| 2) Benzoyl | 75% | 89% | Not recorded | 4.90 d J=8.0 |
| 3) Biphenylcarbonyl | 87% | 82% | 5.25 d J=4.0 | 4.90 d J=8.0 |
| 4) Butylcarbonyl | 58% | 83% | Not recorded | 4.90 d J=8.0 |
| 5) Butylacetyl | 68% | 80% | Not recorded | 4.85 d J=8.2 |
Expected masses were observed for each compound and 1H NMR spectra were recorded for selected compounds.

5 **General Step 6: Alkylation of C-3 hydroxyl**

The products of general step 5 (8αα, 8αβ, 8βα, 8ββ, 8αα, and 8ββ) with their appropriate acyl groups on nitrogen as indicated in the tables above (1 equivalent) were dried under high vacuum and added to a stirred suspension of 95% Sodium Hydride (2 equivalents) in dry N,N-dimethylformamide at 0°C under nitrogen. The mixture was stirred for 30 minutes, then the alkylation agent (methyl bromoacetate: 2 equivalents) was added and the reaction mixture allowed to warm to room temperature. The reaction was monitored by LC-MS for disappearance of starting alcohol. Typically reactions proceeded over 3 hours; however in some instances, the mixture was stirred overnight. The reaction mixture was worked up by cooling the mixture to 0°C and quenching unreacted sodium hydride with methanol. Solvents were removed in vacuo, and the residue taken up in dichloromethane and extracted with 10% citric acid, saturated sodium chloride then dried over anhydrous magnesium sulphate and concentrated.

In cognate preparations 'Butyl bromoacetate and benzyl bromoacetate have been used as the alkylation agent. 1H NMR spectra were recorded for 10 example products of this reaction. In each case a characteristic methyl singlet at δ 3.45 was observed corresponding to the methyl ester group. The location and coupling constant of the anemic proton remained essentially unchanged.

Exemplary yield and Mass spec data are shown in the Table 2.
Table 2
MS data / yields for general step 6 of Scheme 2

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield</th>
<th>M+H (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9Cβ acetate</td>
<td>76%</td>
<td>522 (100)</td>
</tr>
<tr>
<td>9Cβ benzoate</td>
<td>66%</td>
<td>584 (100)</td>
</tr>
<tr>
<td>9Cβ biphenylformate</td>
<td>82%</td>
<td>660 (100)</td>
</tr>
<tr>
<td>9Cβ t-Butylformate</td>
<td>78%</td>
<td>564 (100)</td>
</tr>
<tr>
<td>9Cβ t-Butylacetate</td>
<td>87%</td>
<td>578 (100)</td>
</tr>
<tr>
<td>9Aβ acetate</td>
<td>90%</td>
<td>532 (50)</td>
</tr>
<tr>
<td>9Aβ benzoate</td>
<td>78%</td>
<td>594 (100)</td>
</tr>
<tr>
<td>9Aβ biphenylformate</td>
<td>59%</td>
<td>670 (100)</td>
</tr>
<tr>
<td>9Aβ t-Butylformate</td>
<td>84%</td>
<td></td>
</tr>
<tr>
<td>9Aβ t-Butylacetate</td>
<td>77%</td>
<td></td>
</tr>
<tr>
<td>9Bβ acetate</td>
<td>88%</td>
<td></td>
</tr>
<tr>
<td>9Bβ benzoate</td>
<td>53%</td>
<td></td>
</tr>
<tr>
<td>9Bβ biphenylformate</td>
<td>81%</td>
<td></td>
</tr>
<tr>
<td>9Bβ t-Butylformate</td>
<td>Not recorded</td>
<td></td>
</tr>
<tr>
<td>9Bβ t-Butylacetate</td>
<td>Not recorded</td>
<td></td>
</tr>
<tr>
<td>9Cα acetate</td>
<td>77%</td>
<td>522 (100)</td>
</tr>
<tr>
<td>9Cα benzoate</td>
<td>62%</td>
<td>584 (100)</td>
</tr>
<tr>
<td>9Cα biphenylformate</td>
<td>63%</td>
<td>660 (100)</td>
</tr>
<tr>
<td>9Cα t-Butylformate</td>
<td>98%</td>
<td>564 (100)</td>
</tr>
<tr>
<td>9Cα t-Butylacetate</td>
<td>44%</td>
<td>578 (100)</td>
</tr>
<tr>
<td>9Aα acetate</td>
<td>74%</td>
<td>532 (50)</td>
</tr>
<tr>
<td>9Aα benzoate</td>
<td>87%</td>
<td>594 (100)</td>
</tr>
<tr>
<td>9Aα biphenylformate</td>
<td>79%</td>
<td>670 (100)</td>
</tr>
<tr>
<td>9Aα t-Butylformate</td>
<td>68%</td>
<td></td>
</tr>
<tr>
<td>9Aα t-Butylacetate</td>
<td>74%</td>
<td></td>
</tr>
<tr>
<td>9Bα acetate</td>
<td>Not recorded</td>
<td></td>
</tr>
<tr>
<td>9Bα benzoate</td>
<td>93%</td>
<td>550 (80)</td>
</tr>
<tr>
<td>9Bα biphenylformate</td>
<td>Not recorded</td>
<td>626 (100)</td>
</tr>
<tr>
<td>9Bα t-Butylformate</td>
<td>55%</td>
<td>530 (70)</td>
</tr>
<tr>
<td>9Bα t-Butylacetate</td>
<td>89%</td>
<td>544 (95)</td>
</tr>
</tbody>
</table>
Scheme 2

\[ R_2 = \text{methyl, benzyl, } t\text{-butyl} \]

\[ R_1 \text{ is as defined in scheme 1 above} \]

\[ Y \text{ is as defined in scheme 1 above} \]

\[ Z = -S-(4\text{-methoxy})\text{phenyl}; \quad -S-(4\text{-methyl})\text{phenyl}; \quad -S-(4\text{-chloro})\text{phenyl}; \quad -S-(3,4\text{-dichloro})\text{phenyl}; \quad -S-(3\text{-trifluoromethyl})\text{phenyl} \]
General Step 7: Ester hydrolysis

The products of general step 6 (9α, 9β, 9αβ, 9ββ, 9αβ, and 9ββ) with their appropriate acyl groups on nitrogen as indicated in the tables above were hydrolysed by treatment of a solution of the ester in tetrahydrofuran/methanol (3:2, approx 10 mL per gram of substrate) with aqueous sodium hydroxide (1M, 2 equivalents). Removal of the solvents in vacuo yielded the sodium salt of the corresponding acid and sodium hydroxide as crude product (10αα, 10αβ, 10βα, 10ββ, 10αβ, and 10ββ) with their appropriate acyl groups on nitrogen.

General Step 8: Thiol displacement of halide

The substrate was dissolved in N,N-dimethylformamide and treated with the appropriate thiol (1.3 equivalents) which was pre-evaporated from 1.3 equivalents of sodium methoxide. 1.3 equivalents of sodium iodide was added to the solution and the mixture stirred overnight at room temperature under nitrogen. After this time, the solvents were removed in vacuo and the crude preparation passed through a plug of silica gel with ethyl acetate eluent, to yield essentially pure product. Exemplary products are shown in Table 3. M+H ion and relative intensity are shown. Yields, where shown, are purified yields.
<table>
<thead>
<tr>
<th>Substrate</th>
<th>4-methyl thiophenol</th>
<th>4-methoxy thiophenol</th>
<th>4-chloro thiophenol</th>
<th>3,4-dichloro thiophenol</th>
<th>3-tri fluoromethyl thiophenol</th>
</tr>
</thead>
<tbody>
<tr>
<td>10Aβ benzoate</td>
<td>668 (80)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10Aβ acetate</td>
<td>606 (80)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10Aβ biphenyl formate</td>
<td>744 (100)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10Aβ acetate</td>
<td>562 (70)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10Aβ biphenyl formate</td>
<td>700 (50)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10Aβ benzoate</td>
<td>623 (65)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8Aβ acetate</td>
<td>549 (10%) 53% yield</td>
<td>565 (10%) 91% yield</td>
<td>569 (15%) 89% yield</td>
<td>603 (3%) 64% yield</td>
<td>603 (3%) 80% yield</td>
</tr>
<tr>
<td>8Aβ benzoate</td>
<td>611 (6%) 34% yield</td>
<td>627 (5%) 29% yield</td>
<td>631 (8%) 39% yield</td>
<td>665 (4%) 42% yield</td>
<td>665 (3%) 40% yield</td>
</tr>
<tr>
<td>8Aβ 1′Butyl formate</td>
<td>591 (10%) 67% yield</td>
<td>607 (10%) 89% yield</td>
<td>611 (5%) 78% yield</td>
<td>646 (12%) 89% yield</td>
<td>645 (15%) 74% yield</td>
</tr>
<tr>
<td>8Aβ 1′Butyl acetate</td>
<td>605 (9%) 30% yield</td>
<td>621 (16%) 43% yield</td>
<td>625 (3%) 77% yield</td>
<td>659 (12%) 39% yield</td>
<td>659 (13%) 30% yield</td>
</tr>
<tr>
<td>8Aα acetate</td>
<td>549 (15%) 71% yield</td>
<td>565 (10%) 96% yield</td>
<td>569 (17%) 93% yield</td>
<td>603 (12%) 56% yield</td>
<td>603 (7%) 86% yield</td>
</tr>
<tr>
<td>8Aα benzoate</td>
<td>611 (7%) 33% yield</td>
<td>627 (1%) 28% yield</td>
<td>631 (2%) 23% yield</td>
<td>665 (1%) 35% yield</td>
<td>665 (1%) 26% yield</td>
</tr>
<tr>
<td>8Aα biphenyl formate</td>
<td>Not prepared</td>
<td>Not prepared</td>
<td>Not prepared</td>
<td>Not prepared</td>
<td>Not prepared</td>
</tr>
<tr>
<td>8Aα 1′Butyl formate</td>
<td>591 (11%) 45% yield</td>
<td>607 (17%) 46% yield</td>
<td>611 (15%) 46% yield</td>
<td>646 (13%) 47% yield</td>
<td>645 (27%) 47% yield</td>
</tr>
<tr>
<td>8Aα 1′Butyl acetate</td>
<td>605 (17%) 20% yield</td>
<td>621 (26%) 43% yield</td>
<td>625 (11%) 35% yield</td>
<td>659 (10%) 41% yield</td>
<td>659 (21%) 41% yield</td>
</tr>
</tbody>
</table>
General Step 9: Benzyldene cleavage

The benzyldene compounds were taken up in methanol and acetonitrile, (100 mg of compound in 1 mL of acetonitrile and 2 ml methanol) and treated with amberlite IRA (H⁺ form) at 45°C for 12 hours. After this time the resin was removed by filtration and the solvents evaporated in vacuo. The products were purified by reverse phase HPLC with mass based detection.

Exemplary ¹H NMR data:

R = acetate: 7.35-8.05, m, 7H (Aromatics); 5.35, d, J=12.0, 1H (benzyl); 4.95, d, J=12.0, 1H (benzyl); 4.55, d, J=8, 1H (H-1); 3.15-4.05, m, 8H; 1.80, s, 3H (acetate CH₃).
R = benzoate: 7.10-8.35, m, 12H (Aromatics); 5.20, d, J=12.0, 1H (benzylic); 5.00, d, J=12.0, 1H (benzylic); 4.65, d, J=8, 1H (H-1); 3.20-4.20, m, 8H.

R = biphenylcarbonyl: 7.10-8.30, m, 16H (Aromatics); 5.25, d, J=12.0, 1H (benzylic); 5.00, d, J=12.0, 1H (benzylic); 4.70, d, J=8, 1H (H-1); 3.20-3.90, m, 8H.

R = tert-butylcarbonyl: 7.30-8.10, m, 7H (Aromatics); 5.25, d, J=12.0, 1H (benzylic); 5.00, d, J=12.0, 1H (benzylic); 4.65, d, J=8, 1H (H-1); 3.20-4.15, m, 8H; 0.95, s, 9H (tert-butyl 3×CH₃).

Exemplary HPLC and mass spectral data products are shown in the attached figures.

Figure 1 LC-MS data for

Figure 2 LC-MS data for
Figure 3 LC-MS data for

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} \\
\text{Cl} & \quad \text{S} \\
\text{O} & \quad \text{O} \\
\text{OH} & \quad \text{O} \\
\text{O} & \quad \text{NH} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{Cl} & 
\end{align*}
\]

**General Step 10: Coupling of groups to the C-3 acid moiety**

Acid substrates (10) are dissolved in N,N-dimethylformamide and activated with HBTU in the presence of triethylamine. Peptides with one free amine, amino acids with one free amine or other nucleophilic amines are added in excess and the mixture stirred for 2 hours. After this time the solvents are removed in vacuo and the crude material chromatographed on silica gel to yield the desired product.

In a specific example, substrate 10Aβ benzoate was reacted with the tripeptide α-O-benzyl-γ-glutamyl-ω-(2-chlorobenzylcarbamoyl)-lysiny1-O-benzyl-alanine to yield the desired protected product. HPLC and mass spectral data are shown in Figure 4.
In this instance the benzyl and o-chloro-benzylloxycarbonyl protecting groups were removed by hydrogenolysis in methanol with 10% palladium on charcoal as catalyst (1% w/w Pd; 40 psi, 2 hours). The benzylidene was subsequently removed as described in general step 9. In a cognate experiment in which alanine t-buty1 ester was used, the t-buty1 protecting group and the benzylidene were removed by general step 9. It is expected that BOC amine protecting groups will be similarly amenable to this latter deprotection strategy.
Scheme 3

17 \( R_3 = -\text{CH}_2\text{-COO} \text{Me} \)
18 \( R_3 = -\text{CH}_2\text{-COOH} \)
19, 20, 21 \( R_3 = -\text{CH}_2\text{-CONH-OBn} \); \( -\text{CH}_2\text{-CONH-CH(3)-COOBn} \)
or 17, 18, 19, 20, 21 R₃ = is 2-nitrophenyl; benzyl; 4-methylbenzyl; 4-chlorobenzyl; 4-methoxybenzyl; 4-phenylbenzyl; 1-napthylmethyl; 2-napthylmethyl.

R₁ is as defined in scheme 1 + Dde; 4-methylphenyl.

Y is shown in the following list:
1-Deoxy-1-azido-3,4,6-tri-O-acetyl-2-deoxy-2-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)-ethylamino]-α-D-glucopyranose (14):

3,4,6-tri-O-Acetyl-2-deoxy-2-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)-ethylamino]-α-D-glucopyranosyl bromide (3) (60g, 0.112 mol) is suspended in acetonitrile (280mL) and trimethylsilylazide (TMS-N₃) (29.9 μL, 0.224 mol) is added dropwise followed by the dropwise addition of tetrabutylammonium fluoride (1M TBAF in tetrahydrofuran) (225 mL, 0.225 mol). The reaction is stirred for 16 hr protected from light. The solvents are removed under reduced pressure, and the residue is preabsorbed on silica (150g) and the product eluted with ethyl acetate / petroleum ether (1:1) (2 L). The solvents are evaporated and the crude residue used directly in the next step.

Alternative preparation of 1-Deoxy-1-azido-3,4,6-tri-O-acetyl-2-deoxy-2-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)-ethylamino]-α-D-glucopyranose (14):
3,4,6-tri-O-Acetyl-2-deoxy-2-[1-(4,4-dimethyl-2,6-
dioxocyclohex-1-ylidene)-ethylamino]-α-D-glucopyranosyl bromide (3) (150g, 0.282 mol) is suspended in ethyl acetate (3000mL) and a solution of 10% aqueous sodium hydrogen carbonate (1500 mL) containing sodium azide (22 g, 0.338 mol) is added. Tetrabutylammonium hydrogen sulfate (28.7g, 30 mol%) was added and the biphasic mixture stirred vigorously for 16h. The organic layer was then separated, extracted and dried, then the solvent removed at reduced pressure. The residue was chromatographed as above to yield the desired product (105g, 75%).

^1H NMR (500 MHz, CDCl₃) δ 13.90 (d, J=9.6, 1H), 5.22 (t, J=9.6, 1H), 5.11 (t, J=9.7, 1H), 4.90 (d, J=8.9, 1H), 4.36 (dd, J=4.5, 12.5, 1H), 4.17 (dd, J=12.4, 1.7, 1H), 3.81-3.91 (m, 2H), 2.60 (s, 3H), 2.42 (s, 2H), 2.36 (s, 2H), 2.11, (s, 3H), 2.04 (s, 3H), 1.03 (s, 3H)
m/z 495 (M+H).

1-Deoxy-1-azido-2-deoxy-2-amino-4,6-benzylidene-α-D-glucopyranose (15a):
The crude product 14 is taken up in methanol (450 mL) and sodium metal (2.5g, 0.112 mol) added carefully. The reaction vessel is guarded from the light and stirred for 45 minutes. The reaction is neutralized to pH 6 with Amberlite IR 120(H) resin. The resin is filtered and solvents evaporated under reduced pressure at rt. The residue is adsorbed on silica (150 g) and the product washed out with acetonitrile/water (1:1) (1L). Solvents are evaporated under reduced pressure (at rt). Remaining water is removed by adding acetonitrile and evaporating under reduced pressure. The crude reaction product is suspended in acetonitrile (dry, 450 mL) and benzaldehyde dimethyl acetal (34.3g, 0.225mol) and para-toluenesulfonic acid monohydrate (0.4g, 0.225mol) were added. The reaction mixture is heated to 80°C for 2 hours, then triethylamine (1 equivalent) added and solvents evaporated under reduced pressure. The residue is adsorbed on silica (150g) and the
silica washed with petroleum ether (500 mL). The product is eluted with ethyl acetate/petroleum ether (2/3). After evaporation of the solvents 42.73 g of crude product are obtained (83% yield from the bromo sugar 3). The product is then suspended in MeOH (475 mL) and hydrazine hydrate (13.6 g, 0.25 mol) added at 0°C. The solution is stirred for 10 minutes and then another 90 minutes at rt. The volume is reduced under vacuum to half, ethyl acetate (200 mL) is added and the organic solution washed with brine. The organic layer is dried on magnesium sulfate and evaporated to dryness. The residue is adsorbed on silica (100 g) and eluted with ethyl acetate/petroleum ether (3/2) (400 mL) then with ethyl acetate (400 mL) and finally with acetonitrile / ethyl acetate (1/5). The product is separated as a white solid (20.31 g, 74%)

1H NMR (500 MHz, CDCl₃) δ 7.32 – 7.53 (5H m aromatics), 5.54 (1H, s, Ph-CH) 4.53 (1H, d, J=8.8, H-1), 4.3-4.4 (1H, m), 3.7-3.8 (1H, m), 3.4-3.6 (3H, m), 2.71 (1H, t, J=9, H-3), 1.62 (2H, br).

Cognate preparation of 1-Deoxy-1-azido-2-deoxy-2-amino-4,6-p-methoxybenzylidene-α-D-glucopyranose (15b):
This compound was prepared in an analogous manner to 15a except that 4-methoxybenzaldehyde dimethyl acetal was used in place of benzaldehyde dimethyl acetal.

1H NMR (500 MHz, CDCl₃) δ 7.41 (d, J=10, 2H), 6.89 (d, J=10, 2H), 5.51 (1H, s) 4.54 (d, J=8.8, 1H), 4.35 (dd, J=4.2, 10.5, 1H), 3.80 (s, 1H), 3.74-3.90 (m, 1H), 3.57 – 3.63 (m, 1H), 3.50 -3.55 (m, 2H), 2.71(1H, t, J=9.1, 1H, m/z 323.18 (M+H)

General step 5 to N-acylate (16a):
Example :1-Deoxy-1-azido-2-deoxy-2-N-(acetyl)-amino-4,6-benzylidene-α-D-glucopyranose: the product is isolated in 97% yield (2.22g, 6.6 mmol).

1H NMR (500 MHz, CDCl₃) δ 7.26-7.52 (5H, m, aromatics), 5.56 (1H, s, Ph-CH), 4.83 (1H, d, J=9.3), 4.75 (1H, d,
J=4.5), 4.3-4.4 (1H, m), 3.9-4 (1H,m), 3.7-3.8(1H, m), 3.6-
3.7 (1H, m), 3.5 -3.6 (2H, m), 2.0 (3H)

**General step 5 to N-acylate (16b):**

**Example: 1-Deoxy-1-azido-2-deoxy-2-N-(acetyl)-amino-4,6-p-
methoxybenzylidene-α-D-glucopyranose:**

Was prepared by general method 5 utilising the symmetric
anhydride (acetic anhydride).

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.41 (d, J=8.5, 2H), 6.90 (d,
J=7, 2H), 5.51 (1H, S) 5.01 (d, J=9.5,1H), 4.36 (dd, J=5,
10.5, 1H), 4.18 (t, J=10.0 1H), 3.81 (s, 3H), 3.78 (t,
J=10.0 1H), 3.59 (dd, J=5, 9.5, 1H),3.54 (dd, J=9, 19, 1H),
3.46(dd, J=8.5,18, 1H), 2.07 (s, 3H).

m/z 365.3 (M+H)

**Example: 1-Deoxy-1-azido-2-deoxy-2-N-(benzoyl)-amino-4,6-p-
methoxybenzylidene-α-D-glucopyranose:**

Was prepared by general method 5 utilising the acid
chloride (benzoyl chloride).

M/z 427.3 (M+H)

**Example: 1-Deoxy-1-azido-2-deoxy-2-N-(t-butylcarbonyl)-amino-4,6-p-
methoxybenzylidene-α-D-glucopyranose:**

Was prepared by general method 5 utilising the acid
chloride (2,2,2-trimethylacetyl chloride).

M/z 407.4 (M+H)

**General step 6 to prepare (17a):**

**Example: 1-Deoxy-1-azido-2-deoxy-2-N-(acetyl)-amino-4,6-
benzylidene-3-(methyl acetate)-α-D-glucopyranose:** Methyl
bromoacetate was employed as the alkylating agent. The
target product was isolated in 74% yield (1.97gr). $^1$H NMR
(500 MHz, CDCl$_3$) δ 7.32-7.47 (5H, m, aromatics), 6.73 (1H,
d, J=6.6), 5.55 (1H, s), 4.75 (1H, d, J=9.1), 4.3-4.5 (3H,
m), 3.6-3.9 (7H,m), 3.5-3.6(1H, m), 2.1 (3H, s).

**General step 6 to prepare (17b):**
Example: 1-Deoxy-1-azido-2-deoxy-2-N-(acetyl)-amino-4,6-p-methoxybenzylidene-3-(methyl acetate)-α-D-glucopyranose: Methyl bromoacetate was employed as the alkylating agent. The target product was isolated in 85% yield.

M/z 437.36 (M+H)

Example: 1-Deoxy-1-azido-2-deoxy-2-N-(benzoyl)-amino-4,6-p-methoxybenzylidene-3-(methyl acetate)-α-D-glucopyranose: Methyl bromoacetate was employed as the alkylating agent. The target product was isolated in 85% yield.

M/z 499.4 (M+H)

Example: 1-Deoxy-1-azido-2-deoxy-2-N-(butylacetetyl)-amino-4,6-p-methoxybenzylidene-3-(methyl acetate)-α-D-glucopyranose: Methyl bromoacetate was employed as the alkylating agent. The target product was isolated in 85% yield.

M/z 479.4 (M+H)

Example: Preparation of further C-3 alkylated compounds: The appropriate alkyl halide was employed in place of methyl bromoacetate as the alkylating agent. The target product was isolated and yields are shown in parentheses.
Table 4
MS data / yields for general step 6 Scheme 3 compounds 17b

Table of building blocks, MH+ values in ESMS and yields between brackets.

<table>
<thead>
<tr>
<th>R3 ↓ \ R1→</th>
<th>Dde</th>
<th>CH3-CO</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>609</td>
<td>485 (61%)</td>
<td>547 (40%)</td>
<td>623 (68%)</td>
</tr>
<tr>
<td></td>
<td>577</td>
<td>455 (84%)</td>
<td>517 (80%)</td>
<td>593 (100%)</td>
</tr>
<tr>
<td>Me–</td>
<td>591</td>
<td>469 (51%)</td>
<td>531 (55%)</td>
<td>607 (63%)</td>
</tr>
<tr>
<td>Cl–</td>
<td>611</td>
<td>489 (87%)</td>
<td>551 (89%)</td>
<td>627 (97%)</td>
</tr>
<tr>
<td>MeO–</td>
<td>607</td>
<td>485 (50%)</td>
<td>547 (80%)</td>
<td>623 (95%)</td>
</tr>
<tr>
<td></td>
<td>653</td>
<td>531 (75%)</td>
<td>593 (78%)</td>
<td>669 (91%)</td>
</tr>
<tr>
<td></td>
<td>627</td>
<td>505 (80%)</td>
<td>567 (86%)</td>
<td>643 (100%)</td>
</tr>
<tr>
<td></td>
<td>627</td>
<td>505 (100%)</td>
<td>567 (77%)</td>
<td>643 (86%)</td>
</tr>
</tbody>
</table>

General step 10 to prepare (19b): Where R₃ is other than - CH2-COOME, this step is omitted.

Example: The products of hydrolysis of 17b were coupled according to general step 10 with L-alanine-O-benzyl ester to yield compounds of general formula 19b.
N-acetylated compound m/z 584.4 (M+H)
N-benzoylated compound m/z 646.5 (M+H)
In a cognate preparation, hydroxylamine-O-benzyl ether was coupled to the products of hydrolysis of 17b.

**General step 11: reduction of the azide with Pd/C or with dithiol to prepare (20a and 20b)**

1. With Pd/C: starting material (0.74 mmol) is dissolved in dichloromethane (10 mL), catalyst (Pd/C, 150 mg) is added and the solution degassed. The reaction mixture is hydrogenated (H₂ at 1 atm) for 1 hour, then filtered and solvent evaporated under reduced pressure. The crude 1-amino glycoside is employed without further purification.

   **Example:** 1*-Deoxy-1-amino-2-deoxy-2-N-(acetyl)-amino-4,6-benzylidene-3-(methyl acetate)-α-D-glucopyranose: product was isolated in quantitative yield. ¹H NMR (500 MHz, CDCl₃) δ 7.33-7.50 (5H, m, aromatics), 5.56 (1H, s), 4.47 - 4.55 (1H, m), 4.27-4.46 (2H, m), 4.15 (1H, d, J=9), 3.60-3.83 (7H, m), 3.37-3.44 (1H, m), 2.08 (3H, s).

2. With dithiol: starting material (0.12 mmol) is dissolved in chloroform/methanol (1/1) (1.2 mL), dithiotreitol (57 mg, 3 equiv) is added and the solution degassed using a nitrogen stream. The reaction mixture is stirred under nitrogen for 10 hours. The reaction mixture is diluted with chloroform washed with water and brine, dried with magnesium sulfate and solvent evaporated. The crude 1-amino glycoside is employed without further purification for the generation for the isocyanate.

**General step 12: formation of a urea bond 21a and 21b**

The Y substituents are introduced by reacting of in situ generated isocyanate (from the 1-aminopyranose 20a or 20b) with the amino functionality of the Y group.

The 1-isocyanato pyranose is first generated by treating the 1-aminopyranose 20 with one equivalent of one of the following reagents: phosgene, triphosgene, 1,1’-carbonyldiimidazole, or N,N’-disuccinimidyl carbonate. Suitable solvents for this purpose are dichloromethane,
dimethylformamide or chloroform. The Y group is then added directly (1 equivalent) to the crude isocyanate mixture and the reaction is left stirring for 16 hours. 1 equivalent of diisopropylethylamine is added if the reaction is not complete after this time. The reaction is worked up by evaporating the solvents, adding dichloromethane and filtering the precipitated product.

The Y groups are prepared using commonly used amide bond forming procedures or urea bond forming procedures from commercially available precursors. Examples of suitable amide bond forming reagents include HBTU, BOP, HATU, and PyBOP. The urea bond in some of the Y groups are generated through the reaction of an isocyanate and an amine using well known procedures. The isocyanates are generated as above for the sugar isocyanate.

Y group reagents for general step 12 are in table 5:

![Chemical structures]

Table 5
Where Y = benzylamine  m/z 514.52 M+H RT 8.55 minutes

| 1H nmr: (CDCl3) | 1.83 (s, 3H) | 3.45 (s, 3H) | 3.30-4.30 (m 10H) | 4.92 (dd, J=10Hz, 1Hz, 1H) | 5.60 (s, 1H), 6.45 (d J=10Hz, 1H), 6.85 (t, J=6 Hz, 1H) | 7.20-7.45 (m 10H), 8.20 (d J=9 Hz, 1H). |

General step 13 : formation of an amide bond 21a and 21b
The Y substituents are introduced through an amide bond forming reaction between the 1-amino pyranose 20 and
the carboxylic acid functionality on the Y group. The amine (20) (0.2 mmol) is suspended in anhydrous DMF (1.2 mL) and a solution of the appropriate acid (0.95 equiv), HBTU (87 mg, 1.15 equiv), diisopropylamine (62 mg, 83 µL, 2.4 equiv) in DMF (0.8 mL) was added. The mixture was stirred for 16 hours and the solution then diluted with chloroform (10 mL), extracted with 10% citric acid solution, dried and solvents removed to yield the desired amides (21) in yields varying from 40% to 90%.

Y group reagents (carboxylic acids) for general step 13 are shown in table 6:
<p>| | | | | |</p>
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**Table 6**
Scheme 4

R<sup>1</sup> is as defined in scheme 3
R<sub>3</sub> is acetyl; 4-chlorobenzoyl
Y is as defined in scheme 3

10 **Acyl protection of compounds 16a and 16b to form 22a and 22b. General step 14**

Compound 16 (0.27 mmol) was dissolved in DMF (1.4 ml) and diisopropylethylamine (71 mg, 96 μl, 2 equiv) added.

Acetic anhydride (56 mg, 52 μl, 2 equiv) was added followed by a catalytic amount of DMAP. The mixture was stirred for 16 h, water added and stirring continued for a further 30 min. The mixture was diluted with chloroform, washed with 10% citric acid, NaHCO<sub>3</sub> solution, brine, dried (MgSO<sub>4</sub>) and evaporated to give the desired compound as a white solid (85 - 95%).

In a cognate preparation 4-chlorobenzoyl chloride was used in place of acetic anhydride.

**Example: 1-Deoxy-1-azido-2-deoxy-2-N-(acetyl)-amino-3-p-chlorobenzoyl-4,6-p-methoxybenzylidene-α-D-glucopyranose**

<sup>1</sup>H nmr (d<sub>6</sub>-DMSO, 500 MHz)

1.91 (s, 3 H), 3.71 (dt, J = 7, 10 Hz, 1 H), 3.76 (s, 3 H), 3.84 (t, J = 10 Hz, 1 H), 3.92 (t, J = 9.5 Hz, 1 H), 4.12
Compounds of the type 21a, 21b, 24a and 24b were further elaborated by deprotection of ester groups as exemplified by general procedure 7 followed by cleavage of the benzylidene protecting groups according to general procedure 9 to yield the final compounds as exemplified by table 7.

Compounds were analysed by HPLC/MS with evaporative light scattering detection. Retention times and peak purities for the peaks corresponding to the desired compound as detected by mass spectrometry are shown. NA denotes prepared but not analysed. Codes for Y are as shown in table 6 above.

**Table 7**

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## Preparation of sulfonamide derivative 25.

![chemical structure of compound 25](image)

Compound 19a (40 mg) in which R1 is methyl and R3 is -CH$_2$COOMe was dissolved in dichloromethane (1 mL), to which was added triethylamine (13 mg, 1.2 equiv) followed by p-toluenesulfonyl chloride (24 mg, 1.2 equiv). The reaction was stirred at room temperature for 18 hours, diluted with dichloromethane and extracted with 10% citric acid, saturated sodium hydrogen carbonate and brine, dried over magnesium sulfate and the solvents removed in vacuo to yield 25 (figure 5) (33 mg, 59%).

**Solid phase approach:**

The groups may be attached to a solid support via an ester linking bond ($R_6$ or $R_7$ = resin-CH$_2$-CO-). These resin
bound groups are prepared by linking alpha amino, alpha-hydroxy, or alphathiohydroxy acids to a commercially available hydroxy or chloromethylated resin. Suitable examples include but are not limiteds to tentagel-OH, hydroxymethyl polystyrene, Novasyn TG-hydroxy resin, or chloromethylated polystyrene.

Exemplary compounds were synthesized on solid support as described by the following reaction scheme 5:

![Reaction scheme 5](image)

**Scheme 5**

Example solid phase strategy

**Solid Phase Step 1: Attachment to hydroxy-resin**

Novasyn TG-hydroxy resin (purchased from Novabiochem) (1 g, 0.37 mmol/gr) is mixed with DMF (6mL), left standing for 30 min. and then filtered off. Fmoc-L-Lysine(Boc)-OH (940 mg, 2 mmol) is dissolved in dichloromethane (4 mL) at 0°C and dicyclohexylcarbodiimide (206 mg, 1 mmol) is added at once. After 20 minutes the DCM is evaporated, DMF (3 mL)
added and the solution is added to the filtered resin. Dimethylaminopyridine (5 mg, 0.04 mmol) is added to the mixture and the reaction is left for 60 minutes. The resin is filtered and washed with DMF (3 x 6 mL), MeOH/DCM (1:1) (3 x 6mL), and finally DCM (3 x 6 mL). The resin is further dried by air.

**Solid Phase Step 2: Removal of the Boc group**

The resin (1.1 g) is treated with a solution of trifluoroacetic acid (3 mL) in DCM (3mL) for 2 minutes. The resin is then filtered and washed with DCM (5x 6mL).

**Solid Phase Step 3**

DCM (6mL) is added to the resin (1.1 g) followed by diisopropylethylamine (0.65 mL, 3.7 mmol) and triphosgene (90 mg, 0.25 mmol). After 10 minutes the solvent is filtered and the resin washed with DCM (3 x 6 mL). Aniline (186 mg, 2 mmol) is dissolved in DCM (4 mL) and the solution added to the resin. After 30 minutes the resin is filtered, washed with DCM (4x 4mL) and air dried.

**Solid Phase Step 4**

The resin (1.1 g) is treated with piperidine/DMF (1:1) (5 mL) for 5 minutes. The resin is filtered and washed with DMF (3 x 6 mL), MeOH/DCM (1:1) (3 x 6mL), and finally DCM (3 x 6 mL). DCM (6mL) is added to the resin followed by diisopropylethylamine (0.65 mL, 3.7 mmol) and triphosgene (90 mg, 0.25 mmol). After 10 minutes the solvent is filtered and the resin washed with DCM (3 x 6 mL). 4,6-Benzylidene-2-deoxy-2-N-acetamido-1-deoxy-1-amino-alpha-D-muramic acid (155 mg, 0.4 mmol) is dissolved in DMF (4 mL) and the solution added to the resin. After 12 hours the resin is filtered and washed with DMF (3 x 6 mL), MeOH/DCM (1:1) (3 x 6mL), and finally DCM (3 x 6 mL). The resin is further dried by air.
Solid Phase Step 5

A solution of aqueous NaOH (1M, 0.2 mL) and MeOH (2mL) is added to the resin and the reaction left for 40 min. The resin is filtered and washed with MeOH (3 x 6mL). The filtrates are combined, neutralized with 0.1M HCl and solvent evaporated.

The target product was detected by LCMS at m/z 658 (M+H), Molecular Weight calc. For C_{31}H_{35}N_{5}O_{11} : 657 g/mol.

It will be apparent to the person skilled in the art that while the invention has been described in some detail for the purposes of clarity and understanding, various modifications and alterations to the embodiments and methods described herein may be made without departing from the scope of the inventive concept disclosed in this specification.

References cited herein are listed on the following pages, and are incorporated herein by this reference.
REFERENCES


CLAIMS:

1. A monosaccharide compound of general formula I

\[
\begin{array}{c}
\text{R}_5^0 \\
\text{R}_4 \text{O} \\
\text{R}_3 \text{O} \\
\text{N}\text{R}_1 \text{R}_2' \\
\text{OR}_3 \\
\end{array}
\]

I

in which the monosaccharide ring is of the glucosamine or galactosamine configuration;

\(\text{R}_4\) and \(\text{R}_5\) are hydrogen or together form an optionally substituted benzylidene acetal in which the optional substituent is chosen from halo, azido, alkoxy, nitro or alkyl;

\(\text{R}_3\) is hydrogen; optionally substituted glycolate or optionally substituted lactate or derivatives thereof; or a carboxylic acid mimic;

\(\text{R}_1\) is optionally substituted acyl, optionally substituted benzoyl, optionally substituted biphenylcarbonyl, heteroaryl acyl, optionally substituted bicycloacetyl, optionally substituted bicycloheteroacetyl, sulfonamide, urea or carbamates;

\(\text{R}_2'\) is hydrogen;

\(\text{R}_1\) and \(\text{R}_2'\) together form succinimide, maleimide or optionally substituted phthalimide;

\(\text{R}\) is \(\text{N}_3\), \(\text{O}-\text{Y},\)

\[
\begin{array}{c}
\text{NH} \\
\text{X} \\
\text{Y}' \\
\end{array}
\]

or \(-\text{NH-SO}_2\text{-Y}''\)
in which \( Y \) is 

\[
\begin{align*}
\text{[Chemical Structures]}
\end{align*}
\]

in which \( Z \) is positioned on one or both of the aromatic rings of the bicyclic structures and is independently selected from \( \text{OH, SH, CF}_3, \text{alkyl, alkenyl, alkynyl, NO}_2, \text{halo, SO}_3\text{H, NH}_2, \text{CO}_2\text{H, azido, nitroso, alkoxy, SO}_2\text{NH}_2, \text{amidine and guanidinium;} \)

\( n \) is 0 or 1

\( m \) is an integer of 0 to 3;

\( Z' \) is halo, optionally substituted \( S \)-aryl, optionally substituted \( S \)-heteroaryl, optionally substituted aryl or optionally substituted heteroaryl; \( Z'' \) is optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl;

\( X \) is \( 0, \text{NH or S} \);
Y' is optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkyl, optionally substituted arylalkyl, optionally substituted heteroaryl alkyl,

\[
\begin{align*}
\text{in which } Z'' & = \text{O, NH or S;} \\
R_6 & = \text{H, CONH}_2 \text{ or COOH} ; \\
n & = \text{an integer of 0 to 4} ; \\
R_7 & = \text{optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl or optionally substituted heteroarylalkyl} \\
R_8 & = \text{H, OH, NH}_2, \text{ alkyl, alkenyl or alkynyl;} \\
R_9 & = \text{H, OH, NH}_2, \text{ or NHCO-R}_{10} \text{ in which } R_{10} \text{ is an} \\
& \text{optionally substituted alkyl;} \\
R_{11} & = \text{an optionally substituted alkylene, optionally substituted cycloalkyl, optionally substituted} \\
& \text{heterocycle, optionally substituted aryl or optionally substituted heteroaryl; and} \\
Y'' & = \text{optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkyl,} \\
& \text{optionally substituted arylalkyl or optionally substituted heteroaryl alkyl,}
\end{align*}
\]
derivatives thereof, tautomers thereof and/or isomers thereof.

2. A compound according to claim 1 in which the
optional substituents are selected from at least one of
OH, SH, CF₃, alkyl, alkenyl, alkynyl, NO₂, halo, SO₃H, NH₂,
CO₂H, azido, nitroso, alkoxy, SO₂NH₂, amidine, guanidinium
and peptidomimetics.

3. A compound according to claim 1 or claim 2 which
has the formula Iα

```
R₅O    O-Y    O
 R₄O    NR₁R₂
  OR₃
```

Iα

in which the monosaccharide ring is of the
glucosamine or galactosamine configuration and the
anomeric centre is either the α or β configuration;
R₅, R₄ and R₃ are as defined in claim 1;
R₂ is hydrogen;
R₁ is
(i) C₂₋₈ acyl which is optionally substituted with
one or more OH, SH, CF₃, NO₂, halo, SO₃H, NH₂, CO₂H, azido,
nitroso, alkoxy, aryloxy, SO₂NH₂, amidine or guanidinium;
(ii) a benzoyl group which is optionally substituted
with one or more OH, SH, CF₃, alkyl, alkenyl, alkynyl, NO₂,
halo, SO₃H, NH₂, CO₂H, azido, nitroso, alkoxy, SO₂NH₂,
amidine or guanidinium;
(iii) a biphenylcarbonyl group which is optionally
substituted on either one or both of the aromatic rings
with one or more of OH, SH, CF₃, alkyl, alkenyl, alkynyl,
NO₂, halo, SO₃H, NH₂, CO₂H, azido, nitroso, alkoxy, SO₂NH₂,
amidine or guanidinium; or
(iv) a heteroaryl acyl, sulfonamide, urea or carbamate;

R₁ and R₂ together form optionally substituted succinimide, optionally substituted maleimide or optionally substituted phthalimide;

Y is as defined in claim 1 in which the optional substituents for Z' or Z'' are at least one of OH, SH, CF₃, alkyl, alkenyl, alkynyl, NO₂, halo, SO₃H, NH₂, CO₂H, azido, nitroso, alkoxy, aryloxy, SO₂NH₂, amidine or guanidinium.

4. A compound according to claim 1 or claim 2 which has the formula Ib

\[
\begin{array}{c}
\text{R}_5 \text{O} \\
\text{R}_4 \text{O} \\
\text{OR}_3 \\
\text{NR}_1 \text{R}_2 \\
\text{NR}_1' \\
\end{array}
\]

in which the monosaccharide ring substitution is of the glucosamine or galactosamine configuration and the anomeric centre is either of the α or β configuration;

R₅, R₄ and R₃ are as defined in claim 1;
R₂ and R₁ are as defined in claim 3;
R₁' is N₂ or

\[
\begin{array}{c}
\text{Y}' \\
\text{X} \\
\end{array}
\]

in which
X is O, NH or S; and
Y' is as defined in claim 1 in which R₇ is optionally substituted with at least one of OH, SH, CF₃, alkyl, alkenyl, alkynyl, NO₂, halo, SO₃H, NH₂, CO₂H, azido, nitroso, alkoxy, SO₂NH₂, amidine or guanidinium.
5. A compound according to claim 1 or claim 2 which has the formula Ic

\[
\begin{align*}
R_3 &\text{O} & \text{O} & \text{NH} & \text{SO} & \text{Y''} \\
R_4 &\text{O} & \text{NR}_1 & \text{NR}_2 & \text{OR}_3
\end{align*}
\]

in which the monosaccharide ring substitution is of the glucosamine or galactosamine configuration and the anomeric center is either the α or β configuration;
in which R₅, R₄ and R₃ are as defined in claim 1;
R₂ and R₁ are as defined in claim 3;
Y'' is as defined in claim 1 and is optionally substituted with one or more OH, SH, CF₃, alkyl, alkenyl, alkynyl, NO₂, halo, SO₂H, NH₂, CO₂H, azido, nitroso, alkoxy, SO₂NH₂, amidine or guanidinium.

6. A compound according to any one of the preceding claims in which the glycolate or lactate or derivatives thereof are substituted with at least one amino acid or peptidomimetic.
7. A compound according to any one of the preceding claims in which the carboxylic acid mimetic is

\[
\begin{align*}
\text{A} & \quad \text{B} \quad \text{O} \\
\text{A} & \quad \text{B} \quad \text{CH}_3 \\
\text{A} & \quad \text{B} \quad \text{NH} \\
\text{A} & \quad \text{B} \quad \text{U}
\end{align*}
\]

in which A and B are independently hydrogen, alkyl, trihaloalkyl or halo;
A' is hydrogen or alkyl;
A'' is hydroxy, optionally substituted carboxy or oxyaryl;
U is hydrogen, aryl, heteroaryl, alkyl, alkenyl or alkynyl each of which are optionally substituted with one or more of OH, SH, CF$_3$, alkyl, alkenyl, alkynyl, NO$_2$, halo, SO$_3$H, NH$_2$, CO$_2$H, azido, nitroso, alkoxy, SO$_2$NH$_2$, amidine or guanidinium; and
W is hydrogen or an acidic or acid mimic or forms a carbocyclic or heterocyclic ring.

8. A compound according to any one of the preceding claims in which the acidic or acid mimic is OH, SH, CF$_3$, NO$_2$, halo, SO$_3$H, CO$_2$H, azido, nitroso, alkoxy or SO$_2$NH$_2$. 

9. A method for the preparation of a compound of general formula I as defined in any one of the preceding claims, comprising the step of glycosylating an intermediate compound of formula IV,

\[
\text{IV}
\]

in which L is a leaving group and L' is a protecting groups with an alcohol or phenol acceptor.

10. A method for the preparation of a compound of formulae Ib or Ic, comprising the step of acylating an intermediate compound of general formula V

\[
\text{V}
\]

in which L'' is hydrogen, NO₂, halo, azido or alkoxy.
11. A method of screening for antibacterial or antibiotic compounds comprising the steps of:
   (a) forming a combinatorial library comprising a compound of the formula I as defined in any one of claims
      1 to 8; and
   (b) testing the combinatorial library for antibacterial or antibiotic activity.

12. An antibacterial or antibiotic compound identified using the method defined in claim 11.
Figure 4b mass spectrum
### INTERNATIONAL SEARCH REPORT

**A. CLASSIFICATION OF SUBJECT MATTER**

Int. Cl.: C07H 15/18, 15/12, 9/04, 5/06, 15/26, 13/12; A61K 31/7008; A61P 31/04

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN File Registry and CA, Substructure search and key words "antibacter? or muramyl or combinatorial or library"

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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Further documents are listed in the continuation of Box C

See patent family annex

* Special categories of cited documents:
  
  "A" document defining the general state of the art which is not considered to be of particular relevance
  "E" earlier application or patent but published on or after the international filing date
  "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  "O" document referring to an oral disclosure, use, exhibition or other means
  "P" document published prior to the international filing date but later than the priority date claimed
  "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
  "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
document member of the same patent family

Date of the actual completion of the international search 27 December 2001

Date of mailing of the international search report 7 JAN 2002

Name and mailing address of the ISA/AU

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Form PCT/ISA/210 (second sheet) (July 1998)
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<td>WO 01/51499 A (ALCHEMIA PTY LTD), 19 July 2001. See compounds 30 and 31.</td>
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### Box I  Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. □ Claims Nos: 
   - because they relate to subject matter not required to be searched by this Authority, namely:

2. [X] Claims Nos: 1-12 (all in part) 
   - because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
     An economical search could not be carried out for the present compounds. Moreover, a fairly conservative substructure search of these compounds resulted in too large a number of Chemical Abstracts to be economically displayed. The present search report cites only a small selection of the answers that anticipate the present claims.

3. □ Claims Nos:
   - because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

### Box II  Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. □ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. □ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. □ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. □ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

□ The additional search fees were accompanied by the applicant's protest.

□ No protest accompanied the payment of additional search fees.
This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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END OF ANNEX