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(54) Title: COLLECTION OF ACTIVATED GLYCOSIDE COMPOUNDS AND THEIR BIOLOGICAL USE			
(57) Abstract The present invention relates to the field of combinatorial carbohydrate chemistry and involves the modification of organic molecules and/or the synthesis of large numbers of products comprising carbohydrate and/or glycomimetic entities. More specifically, the present invention relates to activated carbon glycosides useful for the modification of organic molecules by incorporation of carbohydrate units, providing the synthesis of large numbers of products having novel chemical characteristics. The present invention further relates to methods for the generation of chemical compounds comprising carbon glycosides. Methods are disclosed to provide large arrays of molecules and to identify species that act as agonists or antagonists of various biological, chemical, and other activities.			

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DESCRIPTION**Collection of activated glycoside compounds and their biological use**I. Field of the Invention

The present invention relates to the field of combinatorial carbohydrate chemistry and involves the modification of organic molecules and/or the synthesis of arrays of products comprising carbohydrate and/or glycomimetic entities. More specifically, the present invention relates to tools and methods for generating chemical compounds comprising carbohydrate and/or glycomimetic units and the compounds so generated. The invention also relates to libraries of such compounds and their use for the identification of molecular species which act as agonists or antagonists of various biological, chemical, and other activities.

II. Background of the Invention

An improved understanding of the molecular basis underlying the physiological/biological processes involved in the development of diseases facilitates the development of assays to directly screen for agonists and antagonists of biomolecules involved in pathological disorders. With such assays, large arrays of molecules may be easily tested for the desired effects. Consequently, there is a substantial interest in devising simple methods for synthesizing large arrays of randomly generated compounds.

Conventional approaches for pharmaceutical drug discovery and drug development involve the synthesis of small molecules to identify potential drug candidates and subsequent "hand-crafted" molecular modifications to the candidate drugs to optimize their effects. The route to the target molecule, or advanced intermediate, involved the elucidation of its structure/activity relationships and the rational alteration of the functional groups on the molecule, which frequently require complicated

synthetic transformations. As result, usually only one or a few compounds suitable for screening could be produced.

However, since the introduction of solid phase synthesis, the researcher's tools and options to create
5 molecular diverse libraries of compounds have changed significantly and new methods have been developed for the generation of large arrays of novel compounds. Thousands, in some cases millions of different molecules can be created by using automated or manual techniques.
10 Typically, these techniques comprise successive steps, each of which involves chemical modification of the pre-existing molecule, e.g., by addition of a unit to a growing sequence or by modification of a functional group, especially where the modification involves the addition of
15 complex naturally-occurring units, such as amino acids, nucleotides, sugars, lipids, or heterocyclic compounds. In these instances one may be able to create a large diversity of compounds. These synthesis strategies, which generate families or libraries of compounds, are generally
20 referred to as "combinatorial chemistry" or "combinatorial synthesis" strategies.

Combinatorial chemistry strategies have particular promise for identifying new therapeutics. See generally, Gordon et al., 1994, J. Med. Chem. 37:1385-401; and Gallop
25 et al., 1994, J. Med. Chem. 37:1233-51. For example, combinatorial libraries have been used to identify nucleic acids (Latham et al., 1994, Nucl. Acids Res. 22:2817-2822), to identify RNA ligands to reverse transcriptase (Chen & Gold, 1994, Biochemistry 33:8746-56), and to
30 identify catalytic antibodies specific to a particular reaction transition state (Posner et al., 1994, Trends. Biochem. Sci. 19:145-50).

The diversity of libraries generated using combinatorial strategies is impressive. For example,
35 these methods have been used to generate a library containing four trillion decapeptides (Pinilla et al., 1994, Biochem. J. 301:847-53), 1,4-benzodiazepines

libraries (Bunin et al., 1994, Proc. Natl. Acad. Sci. 91:4708-12, U.S. Patent No. 5,288,514 issued Feb. 22, 1994), libraries containing multiple small ligands tied together in the same molecules (Wallace et al., 1994, Pept. Res. 7:27-31), libraries of small organics (Chen et al., 1994, J. Am. Chem. Soc. 116:2661-2662), libraries of peptidosteroidal receptors (Boyce & Nestler, 1994, J. Am. Chem. Soc. 116:7955-7956), and peptide libraries containing non-natural amino acids (Kerr et al., 1993, J. Am. Chem. Soc. 115:2529-31).

However, inherent in the aforementioned approaches for the production of a large number of diverse compounds, in which each step involves a significant number of different choices, typically each individual compound will be present in a minute amount. As a consequence of the limited amount of any particular compound available in a library, while the physiological characteristic of a particular compound (e.g., its physiological activity) may be determinable, it is usually impossible to identify the chemical structure of this specific compound present. To date, three general strategies for the generation of large numbers of diverse compounds facilitating the identification of the desired compound (the "hit") have emerged, referenced as "spatially-addressable," "split-bead" and recombinant strategies. See, generally, Gordon et al., *supra*, and Gallop et al., *supra*.

One example of a spatially-addressable strategy involves the generation of peptide libraries on immobilized pins that fit the dimensions of standard microtitre plates. See, PCT Publication Nos. 91/17271 and 91/19818, Geysen et al., 1993, BioMed. Chem. Lett. 3:391-404), U.S. Patent No. 5,288,514 issued Feb. 22, 1994 and Bunin et al., 1994, Proc. Natl. Acad. Sci. 91:4708-12). The structures of the individual library members can be decoded by analyzing the pin location in conjunction with the sequence of reaction steps used during the synthesis.

Another related spatially-addressable strategy involves solid-phase synthesis of polymers in individual reaction vessels in which the individual vessels are arranged into a single reaction unit. Each reaction vessel is spatially defined by a two-dimensional matrix. Thus, the structures of individual library members can be decoded by analyzing the sequence of reactions to which each reaction unit was subjected.

A third spatially-addressable strategy employs "tea bags" which hold a synthesis resin. The reaction sequence to which each tea bag is subject is recorded, determining the structure of the oligomer synthesized in each tea bag. See, e.g., Lam et al., 1991, Nature 354:82-84; Houghten et al., 1991, Nature 354:84-86; Houghten, 1985, Proc. Natl. Acad. Sci. 82:5131-5135; and Jung et al., 1992, Angew. Chem. Int. Ed. Engl. 31:367-383.

However, the use of a spatially addressable approach has at least one significant drawback: since members of spatially addressable libraries must be synthesized in spatially segregated arrays, only relatively small libraries can be constructed. The position of each reaction vessel in a spatially-addressable library is defined by an XY coordinate pair such that the entire library is defined by a two-dimensional matrix. As the size of the library increases the dimensions of the two-dimensional matrix increases. In addition, as the number of different transformation events used to construct the library increases linearly, the library size increases exponentially.

Thus, while generating the complete set of linear tetramers comprised of four different inputs requires only a 16x16 matrix ($4^4=256$ library members), generating a complete set of linear octamers composed of four different inputs requires a 256x256 matrix ($4^8=65,536$ library members), and generating a complete set of linear tetramers composed of twenty different inputs requires a 400x400 matrix ($20^4=160,000$ library members). Therefore,

not only does the physical size of the library matrix quickly become unwieldy (constructing the complete set of linear tetrameres composed of twenty different inputs using spatially-addressable techniques requires 1667 microtitre plates), delivering reagents to each reaction vessel in the matrix requires either tedious, time-consuming manual manipulations, or complex, expensive automated equipment.

A second general strategy that has emerged involves the use of "split-bead" combinatorial synthesis strategies. See, e.g., Furka et al., 1991, Int. J. Pept. Protein Res. 37:487-493. Generally, synthesis supports are apportioned into aliquots. Each aliquot is then exposed to a monomer and the beads are pooled. The beads are then mixed, reapportioned into aliquots, and exposed to a second monomer. This process is repeated until the desired library is generated.

Since the polymers generated with the "split-bead" method are not spatially-addressable, the structures of the individual library members cannot be elucidated by analyzing the reaction histogram. Rather, the structures of the compounds comprising the library are determined by analyzing the polymers directly. Thus, one limitation of the split-bead approach is the requirement of a separate step to analyze the polymer composition. While sequencing techniques are available for peptides and nucleic acids, sequences of polymers of other compositions, such as, for example carbohydrates, organics, peptide nucleic acids or mixed polymers, may not be easily determinable. Thus, the split-bead technique is limited to either readily available compounds that are synthesized by a limited number of synthesis steps, or to the use of peptides and nucleic acids as building units.

Recently, variations on the "split-bead" scheme that obviate the need to sequence the library member directly have been proposed. These methods, also known as "co-synthesis" techniques, utilize chemicals to tag the

growing polymers with a unique identification tag (marker). See, e.g., PCT Publication No. WO 94/08051, April 14, 1994; Nestler et al., 1994, J. Org. Chem. 59:4723-4724; PCT Publication No. WO 93/06121, April 1, 1993; Needels et al., 1993, Proc. Natl. Acad. Sci. 90:10700-10704; Kerr et al., 1993, J. Amer. Chem. Soc. 115:2529-2531; and Brenner & Lerner, 1992, Proc. Natl. Acad. Sci. 89:5381-5383. Encoding library members with chemical detachable "tags" provide for the construction or co-synthesis of unique identifiers of the chemical structures of the individual library members with the library members. See PCT/US93/093145.

However, the application of co-synthesis strategies is limited. For example, the tagging structures may be incompatible with synthetic organic chemistry reagents and conditions. Additional limitations are a result of the necessity for compatible protecting groups that allow the alternating co-synthesis of tag and library members. Also, assay confusion may arise from the tags selectively binding to the assay receptor.

A third general approach involves recombinant methods for preparing collections of oligomers. See, e.g., PCT Publication No. 91/17271; PCT Publication No. 91/19818; Scott, "Discovering Peptide Ligands Using Epitope Libraries," TIBS 17:241-245 (1992); Cwirla et al., "Peptides on Phage: A Vast Library of Peptides for Identifying Ligands," Proc. Natl. Acad. Sci. 87:6378-6382 (1990); Devlin et al., "Random Peptide Libraries: A Source of Specific Protein Binding Molecules," Science 249:404-406 (1990); and Scott & Smith, "Searching for Peptide Ligands with an Epitope Library," Science 249:386-390 (1990). Using these methods, one can identify each oligomer in the library by determining the coding sequences in the recombinant organism or phage. However, since the library members are generated *in vivo*, recombinant methods are limited to polymers whose synthesis is mediated in the cell. Thus, these methods typically have

been restricted to constructing peptide and oligonucleotide libraries.

In another recent development, the techniques of photolithography, chemistry and biology have been combined to create large collections of oligomers and other compounds on the surface of a substrate. This technique is known as "VLSIPS™". See, for example, U.S. Patent No. 5,143,854; PCT Publication No. 90/15070; PCT Publication No. 92/10092, 25, 1992; Fodor et al., 1991, Science 251:767-773; Pease et al., 1994, Proc. Natl. Acad. Sci. 91:5022-5026; and Jacobs & Fodor, 1994, Trends. Biotechnology 12:19-26. However, although the VLSIPS™ method overcomes the problem of library size limitation through miniaturization, it requires specialized photoblocking chemistry and expensive, specialized synthesis and assay equipment. Thus, VLSIPS™ is not readily or economically adaptable to emerging solid phase chemistries and assay methodologies.

At present, carbohydrates are almost untapped in the field of combinatorial chemistry. Since many physiological interactions of biological molecules, e.g., between receptors and ligands, are defined by specific glycosylation patterns, glycosylated drugs are expected to offer a major impact for the targeted inhibition or activation of biomolecules (see, for example, Yamazaki et al., 1992, Intl. J. Biochem. 24:99-104; Borman et al., 1992, C&EN, December 7, 1992:25-28; Petitou, 1993, Trends in Receptor Research, ed: Claassen, Elsevier Science Publishers B.V.).

For example, selectins are cell adhesion molecules that interact with cell surface carbohydrates, such as sLe^x. Current scientific evidence suggests that selectin receptors play an important role in the trafficking of leukocytes to tissues. Selectins also have been shown to be upregulated during injury, eosinophil and neutrophil migration and activation. Many immunoinflammatory disorders are, in part, the result of leukocytes present

at the site of the relevant tissues. Carbohydrate-protein interactions such as E-, L- or P-Selectin/sLe^x interactions are involved in a variety of inflammatory related diseases such as dermal inflammation, asthma, and lung inflammation. Furthermore, selectins are involved in cell adhesion during cancer metastasis. In fact, numerous tumor types, e.g., urinary bladder carcinoma, and colonic and pancreatic tumors, exhibit high expression levels of sLe^x as these tumors progress through metastatic stages of malignancy.

Thus, agents designed to inhibit the early events associated with adhesion, specifically the carbohydrate/protein interaction mediated by selectins, are expected to be useful in preventing and treating the high number of severe diseases related to adhesion of cells, including cancer, arthritis and other types of inflammatory diseases. Therefore, glycosylated drugs may be a powerful tool for the targeted inhibition of protein/carbohydrate interaction involved in numerous biological interactions.

For example, sLe^x containing oligosaccharides have previously been shown to inhibit selectin receptors. Moreover, ex vivo potency of glycoconjugates of digitoxigenin is increased by altering the nature of the monosaccharide unit at the C-3 position of the core-structure (Brown et al., 1995, Tetrahedron Letters 36:1117-1120)).

Other examples of biologically relevant carbohydrate-protein interactions can be found in, for example, Platt et al., 1994, Journal of Biological Chemistry 269:27108-14; Hinman et al., 1993, Cancer Research 53:3336-42; Paul et al., 1992, Analytical Biochemistry 204:265-72; Keukens et al., 1992, Biochemica et Biophysica Acta 1110:127-136; Varga-Defterdarovic et al., 1992, Int. H. Peptide Protein Res. 39:12-17; Yamazaki et al., *supra*; Giorgianni et al., 1992, Cancer Chemother Pharmacol 29:290-96; Ciarrocchi et al., 1991, Anticancer Research 11:1317-1322; Mingeot-Leclercq, 1991, J. Med. Chem. 34:1476-82;

Gabius et al., 1990, Anticancer Research 10:1005-12; From et al., 1990, Molecular and Cellular Biochemistry 94:157-65; Bodley et al., 1989, Cancer Research 49:5969-5978; Thiele et al., 1989, Eur. J. Immunol. 19:1161-64; Chu et al., 1989, Journal of Medicinal Chemistry 32:612-17; Torres et al., 1988, Int. J. Peptide Protein Res. 31:474-80; Montecucco et al., 1988, Nucleic Acids Research 16:3907-18; Konishi et al., 1986, The Journal of Antibiotics 39:784-91; Ozaki et al., 1985, Eur. J. Biochem. 152:475-80; Musser, Fügedi, and Anderson, 1995, Burger's Medicinal Chemistry and Drug Discovery 1:902-47.

One reason that the integration of carbohydrates in combinatorial chemistry has so far been left behind appears to be inherent in the chemistry of carbohydrates. That is, the O-glycosidic bond is known to be hydrolytically unstable and cleavable by enzymes. Recently, the generation of carbohydrate libraries comprising at least six different sugar-containing molecules has been reported (PCT Patent Application, WO 95/03315, published February 1995). However, the teaching disclosed therein does not solve the problem of instability of the O-glycosidic bonds, which may decrease the applicability and thus the expected commercial value of compounds provided by such libraries. In addition, the compounds of the libraries provided in WO95/03315 consist exclusively of sugar moieties. That disclosure also does not provide for the combination of carbohydrates with moieties of different chemical nature, like steroids or peptides, which appears to be particularly desirable in light of the significance such molecules (i.e., glycosylated peptides) appear to play in biological systems.

Though the integration of carbohydrates in compounds generated by combinatorial chemical strategies, i.e., the generation of arrays of glycosylated compounds, would be highly desirable, due to the difficulties inherent in carbohydrate chemistry and thus the unpredictable nature

of creating carbohydrate related libraries, carbohydrates thus far have not been exploited in combinatorial chemical approaches.

III. SUMMARY OF THE INVENTION

5 The development of novel and improved methods for the modification of chemical compounds and/or the synthesis of complex combinatorial chemical libraries is highly desirable. Of particular need are strategies that allow the integration and exploitation of carbohydrates for such
10 approaches.

 The present invention provides relatively inexpensive and facile tools and methods for the generation of a theoretically infinite array of novel compounds comprising carbohydrate units. Furthermore, the invention provides
15 methods for simple elucidation of the molecular nature of an active compound of interest by deconvolution of the crude array of molecules.

 One aspect of the present invention is to provide "activated" carbon glycosides useful as tools for the
20 incorporation of carbohydrate or glycomimetic units in chemical compounds and members of combinatorial libraries comprising suitable functional groups. The "activated" glycosides of the present invention comprise at least one carbohydrate unit attached, via a spacer/linker unit
25 containing at least one carbon atom, to a suitable derivatized functional group. Generally, the "activated" glycosides of the present invention comprise the following general formula:



30 wherein:

X is a carbohydrate unit or modified carbohydrate unit;

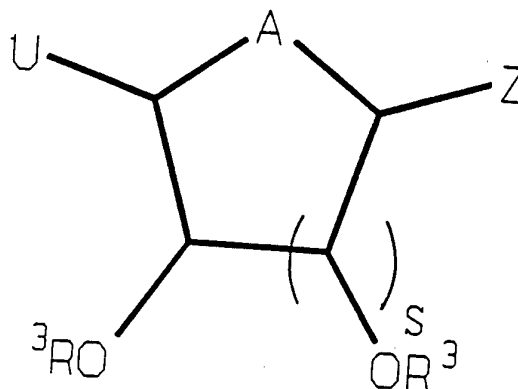
Z is an activated functional group attached, via a spacer/linker unit containing at least one carbon atom, to
35 an X at the anomeric position which is not oxygen but instead carbon; and

11

m is a positive integer.

In a more specific embodiment, the "activated" glycoside $[(X)_m - Z]$ provided by the present invention is characterized by the following formula:

5



wherein:

Z is $-\text{CH}_2\text{WCH}_2\text{T}$, $-\text{CCCH}_2\text{T}$, $=\text{C}=\text{CHCH}_2\text{T}$, $-\text{ArCH}_2\text{T}$, $-\text{ArV}$, or $-(\text{CH}_2)_n\text{V}$;

W is $\text{C}=\text{O}$, $\text{C}=\text{CR}_2^1$, CR^1CR_3^1 , $\text{CR}^1-\text{CR}_2^1\text{OR}^1$, $\text{COR}^1-\text{CR}_2^1\text{OR}^1$, CR_2^1 ,
10 $\text{CR}^2-\text{CR}_2^2\text{OR}^3$, or $\text{CR}^2-\text{CR}^2\text{R}_2^1$;

T is O^-M^1 , M^2 , SR^1 , $\text{S}(\text{O})\text{R}^1$, SO_2R^1 , $\text{P}(\text{O})\text{OR}_2^1$, COD, $\text{OC}(\text{NH})\text{CCl}_3$, or NR_2^1 ;

V is O^-M^1 , SR^1 , $\text{S}(\text{O})\text{R}^1$, SO_2R^1 , $\text{P}(\text{O})\text{OR}_2^1$, COD, NR_2^1 ;

n is a positive integer, preferably between 1-10;

15 M^1 is a Na^+ , K^+ , Mg^{++} , Cu^+ , or Cu^{++} ion;

M^2 is a Li^+ , Mg^{++} , Ca^{++} ion;

R^1 is H, CH_3 , or lower alkyl;

R^2 is OR^1 , NR_2^1 , or SR^1 ;

20 R^3 is R^1 , protecting group, SO_3M^1 , C-carbohydrate (linear or branched) or O-carbohydrate (linear or branched);

s is 1, 2, or 3;

Protecting Groups include methyl-, benzyl-, MOM, MEM, MPM, and tBDMS;

25 U is CH_2OR^1 , CH_2O -protecting group, $\text{CH}_2\text{OSO}_3\text{M}^1$, $\text{CH}_2\text{SO}_3\text{M}^1$, CH_2OR^3 , or COD;

A is O, S, $\text{NR}_2^1\text{CR}_2^1$, or NR^1 ;

D is OR^1 , NR_2^1 , or $O^{\cdot}M^1$; and

Lower Alkyl is C_1 to C_{10} , branched or unbranched.

In an alternate embodiment of the present invention:

- 5 Z is CH_2-W-CH_2E , $-CCCH_2E$, $=C=CH_2E$, $-ArCH_2E$, $-ArE$, $-ArG$, or $-(CH_2)_nG$;
 W is $C=O$, $C=CR_2^1$, $CR^1CR_3^1$, $CR^1-CR_2^1OR^1$, $COR^1-CR_2^1OR^1$, CR_2^1 , $CR^2-CR_2^2OR^3$, or $CR^2-CR^2R_2^1$;
 E is OH, Cl, Br, I, OMs, OTf, OTs, OAc, or
 10 $OC(NH)CCl_3$;
 G is OH, Cl, Br, I, OMs, OTf, OTs, OAc, or COD;
 n is a positive integer, preferably between 1-10;
 M^1 is a Na^+ , K^+ , Mg^{++} , or Ca^{++} ion;
 R^1 is H, or lower alkyl;
 15 R^2 is OR^1 , NR_2^1 , or SR^1 ;
 R^3 is R^1 , protecting group, SO_3M^1 , C-carbohydrate (linear or branched) or O-carbohydrate (linear or branched);
 s is 1, 2, or 3;
 20 Protecting Groups include methyl-, benzyl-, benzoyl-, acetyl-, MOM, MEM, MPM, tBDMS, and TMS;
 U is CH_2OR^1 , CH_2O -protecting group, $CH_2OSO_3M^1$, $CH_2SO_3M^1$, CH_2OR^3 , or COD;
 A is O, S, $NR_2^1CR_2^1$, or NR^1 ;
 25 D is OR^1 , NR_2^1 , or $O^{\cdot}M^1$; and
 Lower Alkyl is C_1 to C_{10} , branched or unbranched.

Another aspect of the present invention is to provide methods for the generation of a synthetic library comprising a plurality of compounds wherein each compound
 30 is composed of one or a plurality of monomers and at least one monomer is a carbohydrate. More specifically, the methods provided comprise reacting one or a plurality of activated carbon glycosides (defined as $(X)_m - Z$, see, above), in a Z-primed reaction with one or a plurality of
 35 monomeric, homo/hetero-oligomeric, or homo/hetero-

polymeric entities of any chemical nature, including organic molecules, inorganic molecules, and solid synthesis supports.

The libraries generated by the methods of the present invention may comprise an array of molecules with a diverse core structure, a diverse carbohydrate moiety or both. The carbohydrate moieties employed for the generation of such libraries include monomers, dimers, trimers, and oligomers, branched or unbranched, linked to a suitable functional group of a chemical moiety comprising such functional group. Suitable functional groups include, but are not limited to, phenolic, hydroxyl, carboxyl, thiol, amido, and amino groups. In the case a moiety has more than one such suitable functional group, one or more such functional groups may be protected by suitable protecting groups during the coupling reaction. Such protecting groups include for example benzyl or alkyl groups. After the coupling reaction, the protecting groups may be selectively removed.

The plurality of different library members may be synthesized either in liquid phase or, alternately, linked to a solid synthesis support or by a combination of both techniques. After synthesis, the library members may be cleaved from the synthesis support.

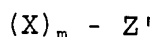
The members of such libraries may be linked to a chemical identifier tag which identifies the structure of the library member (see e.g., PCT Patent Application WO 94/08051, published April 14, 1994). The linkage between the library member and identifier tag may comprise a linker between the identifier tag and the library member, or, alternately, a linker between the identifier tag and a solid synthesis support.

The generation of such libraries may involve the modification of existing chemical compound libraries, providing the incorporation of carbohydrate(s) into existing and new combinatorial libraries, bio-oligomers

and organic substrates. Syntheses may involve a plethora of stages, each stage having numerous choices, in which large numbers of products having varying compositions are obtained by direct modification of an existing
5 combinatorial natural product or chemical library of compounds. Alternately, such libraries may be obtained by employing combinatorial chemistry with modified carbohydrates, including monomers, dimers, trimers, oligomers branched and unbranched.

10 Another aspect of the invention is to provide methods for deconvoluting an array of compounds. More specifically, the methods comprise: (1) synthesis of a plurality of compounds wherein each said compound is composed of one or a plurality of monomers and at least
15 one monomer is a heteroatom glycoside in a combinatorial reaction wherein a plurality of "A"s (defined as $(X)_m - Z$, see, above) is reacted with a plurality of "B"s (defined as one or a plurality of monomeric, homo/hetero-oligomeric, or homo/hetero-polymeric entities of any
20 chemical nature, including organic molecules, inorganic molecules, solid synthesis supports, see, above), (2) screening for the desired biological, chemical or other effect, (3) repeating step (2) with a smaller plurality of "A"s and/or "B"s, (4) repeating steps (2) and (3) until an
25 active compound is synthesized and/or identified.

Still another aspect of the invention is to provide an array of novel chemical compounds comprising at least one carbohydrate unit, attached via a spacer/linker unit to a suitable derivatized functional group. The subject
30 invention provides novel chemical compounds comprising the formula:



wherein:

35 X is a carbohydrate unit or modified carbohydrate unit;

Z' is the reaction product of "Z" and "B"; and

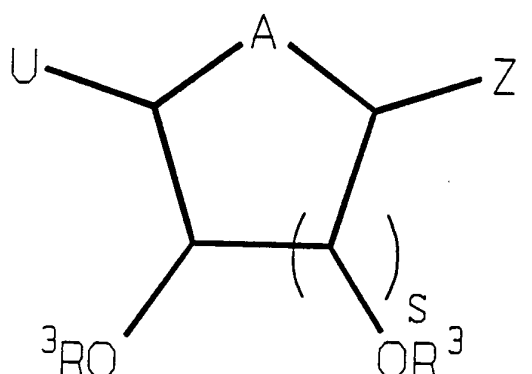
15

B is one or a plurality of monomeric, homo/hetero-oligomeric, or homo/hetero-polymeric entities of any chemical nature, including organic molecules, inorganic molecules, solid synthesis supports.

5 Z is an activated functional group attached, via a spacer/linker unit containing at least one carbon atom, to a X at the anomeric position which is not oxygen but instead carbon;

m is a positive integer.

10 In a more specific embodiment, the array of compounds generated by the tools and methods of the present invention comprises the following formula:



wherein:

15 Z' is the reaction product of "Z" and "B";

B is one or a plurality of monomeric, homo/hetero-oligomeric, or homo/hetero-polymeric entities of any chemical nature, including organic molecules, inorganic molecules, solid synthesis supports; and

20 the other variables (i.e Z, W, T, etc.) are as defined above.

IV. GLOSSARY

The following terms are intended to have the following general definitions as each are used herein:

25 Carbohydrate: As used herein "carbohydrate" is a chemical moiety comprising the general composition $(CH_2O)_n$,

where n is an integer of three or more, including, but not limited to glucose, galactose, fucose, fructose, saccharose, mannose, arabinose, xylose, sorbose, lactose, and derivatives, homo-/hetero-oligomers, homo-/hetero-
5 polymers thereof, including but not limited to compounds which have other elemental compositions, such as aldonic acids, uronic acids, deoxysugars, or which contain additional elements or moieties, such as amino sugars, mucopolysaccharides wherein n is typically 4, 5, 6, 7
10 atoms. The oxygen atom in the carbohydrate may be replaced by a heteroatom such as nitrogen, sulfur, carbon etc. A carbohydrate as used herein is understood to include chemical structures wherein the "H" of any hydroxy groups is replaced by any chemically compatible moiety
15 "R", which can be any monomer, oligomer or polymer in the meaning as used herein.

Carbohydrate Unit: As used herein, a "carbohydrate unit" is a monomer comprising a monosaccharide.

Carbon Glycoside: As used herein, a "carbon
20 glycoside" is a carbohydrate derivative wherein the anomeric position does not have an oxygen but rather a carbon atom (see, heteroatom glycoside).

Chemical Abbreviations: The following chemical abbreviations, as set forth below at TABLE I, are used
25 herein:

TABLE I
CHEMICAL ABBREVIATIONS

CHEMICAL ABBREVIATIONS	
Ac	acetyl
9-BBN	9-borabicyclo[3.3.1]nonane
Bn	benzyl
Bz	benzoyl
CBn	p-chlorobenzyl
DHP	dihydropyran
DME	dimethoxyethane
DMF	N,N-dimethylformamide
Et	ethyl
Me	methyl
Ms	methanesulfonyl
sLe ^x	Sialyl Lewis ^x
TBAF	tetrabutylammonium fluoride
TBS or TBDMS	t-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TMS	trimethylsilyl
TsOH	p-toluenesulfonic acid
TTN	thallium trinitrate
Ts	tosyl

Functional Group: As used herein, a "functional group" comprises an atom or a group of atoms, and the associated chemical bonds acting as a unit, that has about the same type of chemical reactivity whenever it occurs in different compounds.

Heteroatom Glycoside: As used herein, a "heteroatom glycoside" is a carbohydrate wherein the oxygen at the anomeric position is replaced by a carbon atom.

Identifier Tag: An "identifier tag" is any detectable attribute that provides a means to elucidate the structure of an individual oligomer in a labeled synthetic oligomer library. For example, an identifier tag can be used to identify the resulting products in the synthesis of a labeled synthetic oligomer library.

Linker: A linker is that which joins or connects separate parts. A "linker" is a moiety, molecule, or group of molecules attached to a synthesis support or substrate and spacing a synthesized polymer or oligomer
5 from the synthesis support or substrate. A "linker" also can be a moiety, molecule, or group of molecules attached to a substrate and spacing a synthesis support from the substrate.

A linker may be bi-functional, wherein said linker has
10 a functional group at one end capable of attaching to a monomer, oligomer, synthesis support or substrate, a series of spacer residues, and a functional group at the end capable of attaching to a monomer, oligomer, synthesis support or substrate. The functional groups may be
15 identical or distinct.

Monomer: As used herein, a "monomer" is any atom or molecule capable of forming at least one chemical bond. Thus, a "monomer" is any member of the set of atoms or molecules of any chemical nature, including inorganic and
20 organic molecules that can be joined together as single units in a multiple of sequential or concerted chemical or enzymatic reaction steps to form an oligomer or polymer. Monomers may have one or a plurality of functional groups, which functional groups may be, but need not be,
25 identical.

The set of monomers useful in the present invention includes, but is not restricted to, alkyl and aryl amines, alkyl and aryl mercaptans, alkyl and aryl ketones, alkyl and aryl carboxylic acids, alkyl and aryl esters, alkyl
30 and aryl ethers, alkyl and aryl sulfoxides, alkyl and aryl sulfones, alkyl and aryl sulfonamides, phenols, alkyl alcohols, alkyl and aryl alkenes, alkyl and aryl lactams, alkyl and aryl lactones, alkyl and aryl di- and polyenes, alkyl and aryl alkynes, alkyl and aryl unsaturated
35 ketones, aldehydes, 1,6-anhydrocarbohydrates, sulfoxides, sulfones, heteroatomic compounds containing one or more of

the atoms of: nitrogen, sulfur, phosphorous, oxygen, and other polyfunctional molecules containing one or more of the above functional groups, L-amino acids, D-amino acids, deoxyribonucleosides, deoxyribonucleotides, ribonucleosides, ribonucleotides, sugars, benzodiazepines, β -lactams, hydantoins, quinones, hydroquinones, terpenes, and the like.

Monosaccharide: As used herein, a "monosaccharide" is any carbohydrate monomer or derivative thereof.

Named Reactions: As used herein, "Named Reactions" are chemical reactions which are chemical standard reactions known by the skilled artisan, including but not limited to the Alper Reaction, Barbier Reaction, Claisen-Ireland Reaction, Cope Rearrangement, Delepine Amine synthesis, Gewald Heterocycle Synthesis, Hiyama-Heathcock Stereoselective Allylation, Stork Radical Cyclization, Trost Cyclopentanation, Weidenhagen Imidazole Synthesis. See, in general, Hassner and Stumer, 1994. See also, "Organic Syntheses Based on Named Reactions and Unnamed Reactions", Tetrahedron Organic Chemistry Series, eds. Baldwin and Magnus, Pergamon, Great Britain.

Oligomer or Polymer: As used herein, an "oligomer" or "polymer" is any chemical structure that comprises a plurality of monomers of the same or diverse chemical nature, including, for example, amides, esters, thioethers, ketones, ethers, sulfoxides, sulfonamides, sulfones, phosphates, alcohols, aldehydes, alkenes, alkynes, aromatics, polyaromatics, heterocyclic compounds containing one or more of the atoms of: nitrogen, sulfur, oxygen, and phosphorous, and the like, chemical entities having a common core structure such as, for example, terpenes, steroids, β -lactams, benzodiazepines, xanthates, indoles, indolones, lactones, lactams, hydantoins, quinones, hydroquinones, and the like, chains of repeating

monomer units such as polysaccharides, phospholipids, polyurethanes, polyesters, polycarbonates, poly ureas, polyamides, polyethyleneimines, poly arylene sulfides, polyimides, polyacetates, polypeptides, polynucleotides, and the like, or other oligomers or polymers as will be readily apparent to one skilled in the art upon review of this disclosure. Thus, an "oligomer" and "polymer" may be linear, branched, cyclic, or assume various other forms as will be apparent to those skilled in the art.

10 *Oligosaccharide or Polysaccharide:* As used herein, an "oligosaccharide" or "polysaccharide" refers to carbohydrates, including carbon glycosides, comprising a plurality of monosaccharides.

15 *Protecting Groups:* The moiety of the present invention may have groups protecting one or several inherent functional groups. Suitable "protecting groups" will depend on the functionality and particular chemistry used to construct the library. Examples of suitable functional protecting groups will be readily apparent to skilled artisans, and are described, for example, in 20 Greene and Wutz, Protecting Groups in Organic Synthesis, 2d ed., John Wiley & Sons, NY (1991), which is incorporated herein by reference.

25 *Spacer/Linker Unit.* As used herein and according to the invention, the compounds of the invention comprise a spacer/linker unit which joins or connects a carbohydrate or glycomimetic entity to a second entity. The spacer/linker unit is generally attached to a carbon atom at the anomeric position of the carbohydrate or 30 glycomimetic entity, and contains at least one carbon atom. Preferably, the spacer/linker unit is an aliphatic or an aromatic entity.

The spacer/linker unit may be of such chemical nature that it is cleaved or decomposed in a physiological environment.

Synthetic Chemical Library: A "synthetic chemical library" is a collection of random and semi-random synthetic molecules wherein each member of such library is produced by chemical or enzymatic synthesis.

Synthesis Support: A "synthesis support" is a material having a rigid or semi-rigid surface and having functional groups or linkers. A synthesis support may be capable of being derivatized with functional groups or linkers that are suitable for carrying out synthesis reactions.

Preferably, such materials will take the form of small beads, pellets, disks, capillaries, hollow fibers, needles, solid fibers, cellulose beads, pore-glass beads, silica gels, polystyrene beads optionally cross-linked with polyethylene glycol divinylbenzene, grafted co-poly beads, poly-acrylamide beads, latex beads, dimethylacrylamide beads optionally cross-linked with N,N'-bis-acryloyl ethylene diamine, glass particles coated with a hydrophobic polymer, or other convenient forms.

A "synthesis support" may be constructed such that it is capable of retaining identifier tags.

Synthetic: A compound is "synthetic" when produced by *in vitro* chemical or enzymatic synthesis.

Transformation Event or Reaction: As used herein, a "transformation event" or "reaction" is any event that results in a change of chemical structure of a monomer, an oligomer or polymer. A "transformation event" or "reaction" may be mediated by physical, chemical, enzymatic, biological or other means, or a combination of means, including but not limited to, photo, chemical,

enzymatic or biologically mediated isomerization or cleavage, photo, chemical, enzymatic or biologically mediated side group or functional group addition, removal or modification, changes in temperature, changes in pressure, and the like. Thus, "transformation event" or "reaction" includes, but is not limited to, events that result in an increase in molecular weight of a monomer, an oligomer or polymer, such as, for example, addition of one or a plurality of monomers, addition of solvent or gas, or coordination of metal or other inorganic substrates such as, for example, zeolites. A "transformation event" or "reaction" may also result in a decrease in molecular weight of an oligomer or polymer, such as, for example, de-hydrogenation of an alcohol to form an alkene or enzymatic hydrolysis of an ester or amide. "Transformation events" or "reaction" also include events that result in no net change in molecular weight of a monomer, an oligomer or polymer, such as, for example, stereochemistry changes at one or a plurality of a chiral centers, Claissen rearrangement, Ireland rearrangement, or Cope rearrangement and other events as will become apparent to those skilled in the art upon review of this disclosure.

V. DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to the field of combinatorial carbohydrate chemistry and is directed to tools and methods for generating compounds comprising at least one carbohydrate or glycomimetic entity and the compounds so generated. The present invention is based, in part, on the novel use of carbon glycosides as modifiers of organic chemical compounds, thereby incorporating carbohydrate/glycomimetic units into pre-existing molecules and, for example, preexisting libraries of synthetic compounds. Employing the tools and methods disclosed herein, theoretically infinite numbers of novel molecules comprising carbohydrate units may be generated.

As such, the subject invention provides for the generation of large arrays of compounds comprising carbohydrate/glycomimetic entities for the identification of novel molecular species which may act as agonists or
5 antagonists of various biological, chemical or other activities.

A. Novel Compounds Comprising Carbohydrate And/Or Glycomimetic Entities

Carbohydrates are critical in the operation of
10 fundamental biological processes of cellular recognition. More and more detailed knowledge that has accumulated on carbohydrate-containing complex molecules reveals that carbohydrates play a significant role in physiological interactions and recognition. For example, the
15 recognition and binding between receptors and their ligands are defined by specific glycosylation patterns. The significance of sugars in the modulation of physiological processes compels the conclusion that carbohydrates are expected to have a promising impact in
20 the field of drug discovery and development. Moreover, the theoretically infinite number of readily available carbohydrates would facilitate the generation of a theoretically unlimited array of novel compounds, involving only few transformations. For example, using
25 only six sugars in the pyranose form results in 128 disaccharides. Laine, 1994, Glycobiology 4:759-767. In the case of peptides, in contrast, 20 amino acids are necessary to arrive at $20^2=400$ different dipeptides. Baum, 1994, Chemical & Engineering News 20-26.

30 The calculation provided in TABLE II illustrates the tremendously high diversity inherent in carbohydrate chemistry.

TABLE II
35 CALCULATION OF ALL POSSIBLE OLIGOSACCHARIDE ISOMERS OF A HEXASACCHARIDE

	Oligosaccharide	Hexose	Linear/Isomers ^{*)}
	Monosaccharide	1	2
	Disaccharide	2	128
	Trisaccharide	3	6,144
5	Tetrasaccharide	4	393,216
	Pentasaccharide	5	31,457,280
	Hexasaccharide	6	3,019,898,880

^{*)} Linear isomers of D-hexoses wherein each hexose unit is not used more than once (Lane, *supra*).

10 In addition to their high diversity, carbohydrates are versatile and can be attached to a wide variety of pre-existing compounds as will be specified hereinbelow. As such, carbohydrate units could be applied to modify specific chemical compounds, lead molecules, pre-existing
15 combinatorial libraries, or could be employed for the generation of novel combinatorial libraries. Finally, most carbohydrates are facile to obtain in large scale (multi gram to kilogram level) and relatively inexpensive.

For all these reasons it can be expected that the
20 integration and exploitation of carbohydrates in the field of combinatorial chemistry for the generation of drugs would be of promising impact. So far, however, problems inherent in the carbohydrate chemistry, i.e. the instability of the O-glycosidic bond, have averted the
25 integration of carbohydrates in the platform of combinatorial chemistry.

The present invention avoids and overcomes the obstacles inherent in carbohydrate chemistry, i.e., the instability of the O-glycosidic bond, by employing carbon
30 glycosidic bonds for the attachment to various chemical compounds. The carbon glycosidic bond, preferably a C-C linkage, portends to be hydrolytically and biologically much more stable than the O-glycosidic bond. Carbon glycosides are as versatile as "normal" carbohydrates, and
35 can be attached easily to a high diversity of chemical moieties comprising suitable functional groups, including

amino acids, peptides, nucleic acids, sugars, steroids, lipids, alcohols, and the like.

A carbon-glycoside results when the oxygen of the anomeric carbon of a glycoside is replaced by a carbon atom. For example, when the oxygen linkage is a disaccharide is replaced by a methylene group, a carbon glycoside is formed. As discussed above, such carbon glycoside is no longer cleavable by hydrolysis and tends to be enzymatically stable, which is well known in the art. In fact, carbon glycosides have been used for enzymatic and metabolic studies. See, Lalegerie et al., 1982, Biochemie 64:977; Shulman et al., 1974, Carbohydr. Res. 33:229; Chmielewski et al., 1981, *ibid.* 97. However, carbon glycosides have not been employed for the generation of novel molecules and combinatorial chemical libraries to generate molecular species that act as agonists or antagonists of various biological, chemical, and other desired activities.

Several physiologically active natural products are known which natively comprise such carbon-glycosidic linkages. Kawasaki et al., 1986, Tetrahedron Lett. 27:2145 and references therein. For example showdomycin (Nishimura et al., 1964, Antibiot. Ser. A. 17:148) has been shown to possess strong activity against *Streptococcus hemolyticus* and is also found to inhibit Ehrlich ascites tumors in mice. Vineomycin, an aryl carbon glycoside (Imamura et al., 1981, J. Antibiot. 34:1517), exhibits strong antitumor activity, which is also true for ravidomycin and gilvoarcin V (Hirayama et al., 1981, Bull. Chem. Soc. Jpn. 54:1338). Thus, carbon glycosides, as it is true for carbohydrates, comprise biological and physiological activity. Thus, one would expect that carbon glycosides may resemble the biological feature of "normal" carbohydrates and comprise promising candidates of novel compounds active as antagonists or agonists of biomolecules. In fact, recently compounds comprising carbon glycosides have been developed as breast

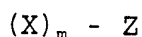
cancer chemopreventive drugs (PCT Patent Application, WO 94/11030, published May, 1994).

The use of carbon glycosides as chemical modifiers successfully integrates small, medium and large sized molecules with novel glycomimetics and carbohydrates as a source of new drug leads and new drug candidates. The methods disclosed herein encompass the preparation of novel molecules and chemical libraries for screening and drug discovery using novel glycosides, including monomers, dimers, trimers, oligomers, branched or unbranched etc. Within the invention are tools and methods for the generation of novel compounds and combinatorial libraries, in which the products contain at least one modified carbohydrate and the compounds so generated.

B. Generation of "Activated" Carbon Glycoside Building Blocks

In one aspect, the present invention "activated" glycosides which are useful as tools for the generation of compounds comprising at least one carbohydrate and/or glycomimetic entity.

The "activated" carbon glycosides provided by the present invention comprise the following general formula:



wherein:

X is a carbohydrate unit(s) or modified carbohydrate unit(s);

Z is an activated functional group attached, via a spacer/linker unit containing at least one carbon atom, to a X at the anomeric position which is not oxygen but rather a carbon;

m is a positive integer;

with the proviso that at least one X does not have an oxygen at its anomeric position.

The carbohydrate of the invention compounds may be a monosaccharide, disaccharide, oligosaccharide or polysaccharide, and either branched or unbranched. The carbohydrate units may be five membered ring structures, six membered ring structures, or both. The hydrogen of any hydroxy-group may be replaced by any compatible moiety, linker, or solid synthesis support. The molecular weight of the carbohydrate moiety (X_m) may less or equal to the molecular weight of a monosaccharide (about 180), or several hundred thousand daltons, as for example cellulose and other complex sugars.

In more specific embodiments, the activated functional group Z may comprise one of the following:

Z is $-\text{CH}_2\text{WCH}_2\text{T}$, $-\text{CCCH}_2\text{T}$, $=\text{C}=\text{CHCH}_2\text{T}$, $-\text{ArCH}_2\text{T}$, $-\text{ArV}$, or $-(\text{CH}_2)_n\text{V}$;

W is $\text{C}=\text{O}$, $\text{C}=\text{CR}_2^1$, CR^1CR_3^1 , $\text{CR}^1-\text{CR}_2^1\text{OR}^1$, $\text{COR}^1-\text{CR}_2^1\text{OR}^1$, CR_2^1 , $\text{CR}^2-\text{CR}_2^2\text{OR}^3$, or $\text{CR}^2-\text{CR}^2\text{R}_2^1$;

T is O^-M^1 , M^2 , SR^1 , $\text{S}(\text{O})\text{R}^1$, SO_2R^1 , $\text{P}(\text{O})\text{OR}_2^1$, COD, $\text{OC}(\text{NH})\text{CCl}_3$, or NR_2^1 ;

V is O^-M^1 , SR^1 , $\text{S}(\text{O})\text{R}^1$, SO_2R^1 , $\text{P}(\text{O})\text{OR}_2^1$, COD, NR_2^1 ;

n is a positive integer, preferably between 1-10;

M^1 is a Na^+ , K^+ , Mg^{++} , Cu^+ , or Cu^{++} ion;

M^2 is a Li^+ , Mg^{++} , Ca^{++} ion;

R^1 is H, CH_3 , or lower alkyl;

R^2 is OR^1 , NR_2^1 , or SR^1 ;

R^3 is R^1 , protecting group, SO_3M^1 , C-carbohydrate (linear or branched) or O-carbohydrate (linear or branched);

s is 1, 2, or 3;

Protecting Groups include methyl-, benzyl-, MOM, MEM, MPM, and tBDMS;

U is CH_2OR^1 , CH_2O -protecting group, $\text{CH}_2\text{OSO}_3\text{M}^1$, $\text{CH}_2\text{SO}_3\text{M}^1$, CH_2OR^3 , or COD;

A is O, S, $\text{NR}_2^1\text{CR}_2^1$, or NR^1 ;

D is OR^1 , NR_2^1 , or O^-M^1 ; and

Lower Alkyl is C_1 to C_{10} , branched or unbranched.

In an alternate embodiment of the present invention:

Z is $\text{CH}_2\text{-W-CH}_2\text{E}$, $\text{-CCCH}_2\text{E}$, $\text{=C=CH}_2\text{E}$, $\text{-ArCH}_2\text{E}$, -ArE , -ArG , or $\text{-(CH}_2\text{)}_n\text{G}$;

W is C=O , C=CR_2^1 , CR^1CR_3^1 , $\text{CR}^1\text{-CR}_2^1\text{OR}^1$, $\text{COR}^1\text{-CR}_2^1\text{OR}^1$, CR_2^1 ,
 5 $\text{CR}^2\text{-CR}_2^2\text{OR}^3$, or $\text{CR}^2\text{-CR}^2\text{R}_2^1$;

E is OH, Cl, Br, I, OMs, OTf, OTs, OAc, or OC(NH)CCl_3 ;

G is OH, Cl, Br, I, OMs, OTf, OTs, OAc, or COD;

n is a positive integer, preferably between 1-10;

10 M^1 is a Na^+ , K^+ , Mg^{++} , or Ca^{++} ion;

R^1 is H, or lower alkyl;

R^2 is OR^1 , NR_2^1 , or SR^1 ;

R^3 is R^1 , protecting group, SO_3M^1 , C-carbohydrate
 (linear or branched) or O-carbohydrate (linear or
 15 branched);

s is 1, 2, or 3;

Protecting Groups include methyl-, benzyl-, benzoyl-,
 acetyl-, MOM, MEM, MPM, tBDMS, and TMS;

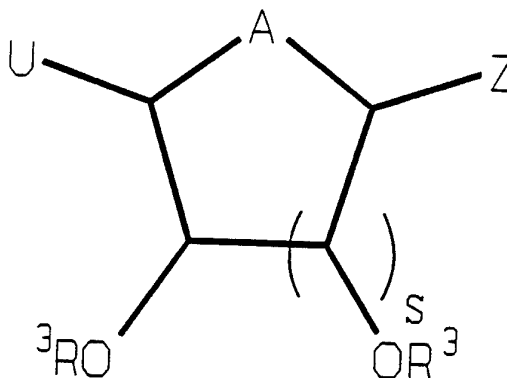
U is CH_2OR^1 , $\text{CH}_2\text{O-protecting group}$, $\text{CH}_2\text{OSO}_3\text{M}^1$,
 20 $\text{CH}_2\text{SO}_3\text{M}^1$, CH_2OR^3 , or COD;

A is O, S, $\text{NR}_2^1\text{CR}_2^1$, or NR^1 ;

D is OR^1 , NR_2^1 , or O-M^1 ; and

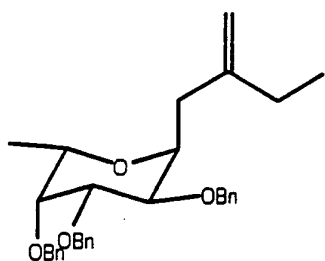
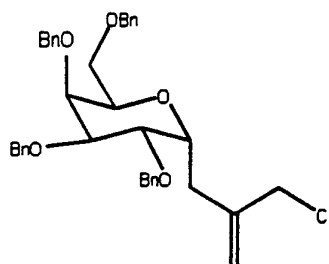
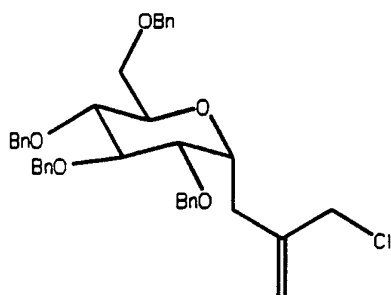
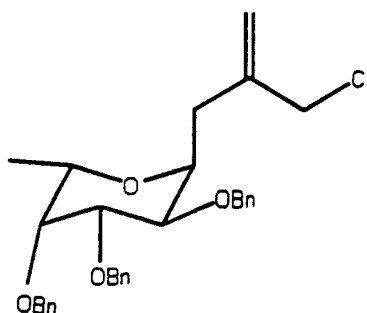
Lower Alkyl is C_1 to C_{10} , branched or unbranched.

25 In one specific embodiments of the invention, the
 "activated" carbon glycoside comprises the following
 general structural formula:

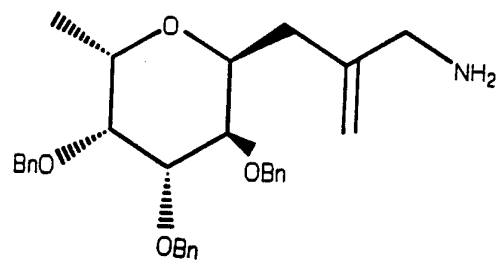
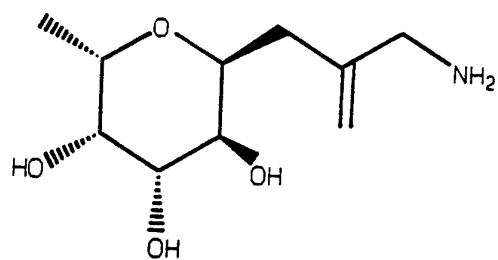
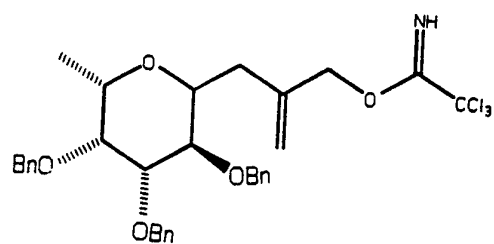
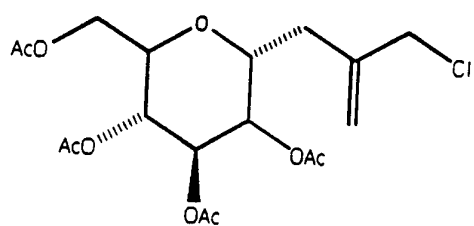
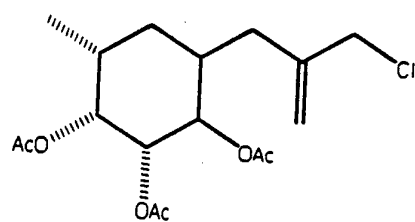


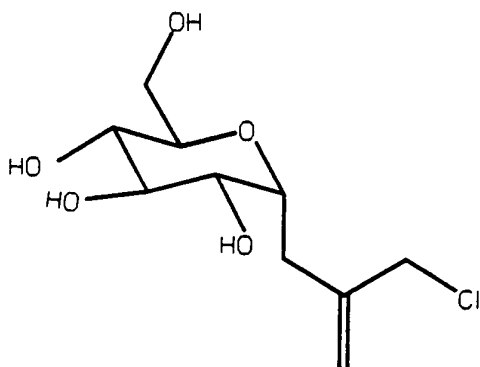
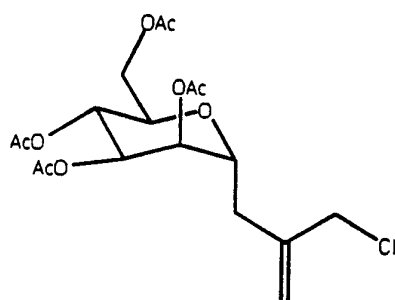
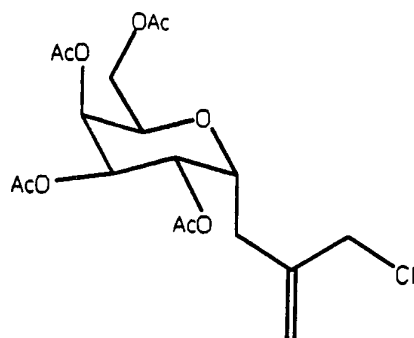
wherein the variables (Z, A, U, etc.) are defined above.

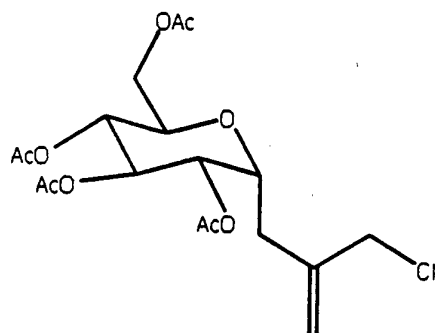
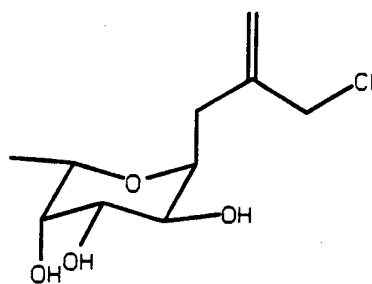
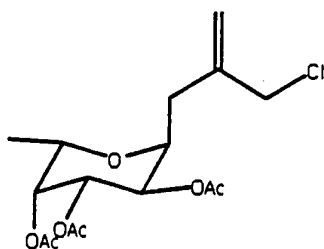
In the most preferred embodiments of the invention, the "activated" carbon glycoside comprises the following formulas. Although the α -form is shown in the examples, 5 the invention includes the β -configuration of the bond.



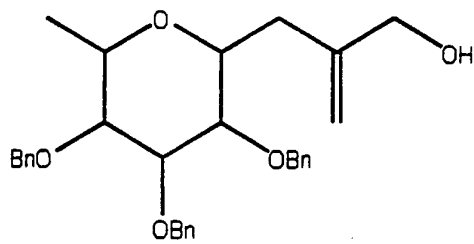
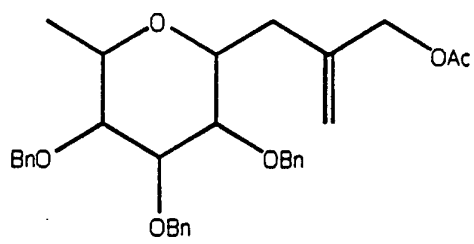
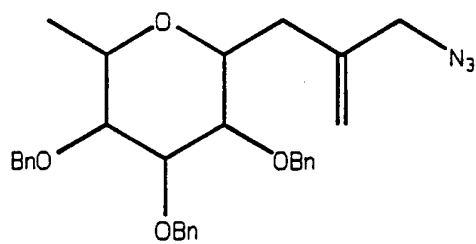
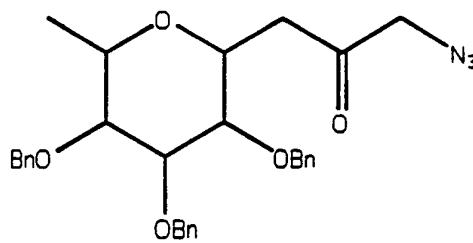
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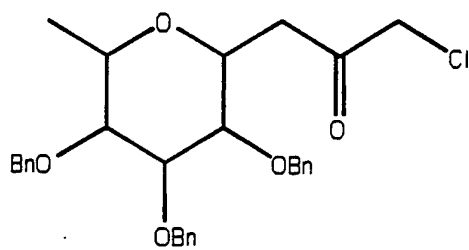
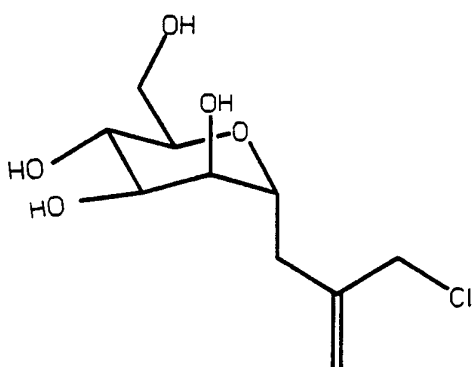
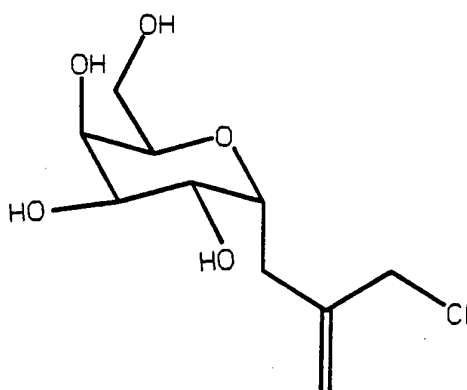






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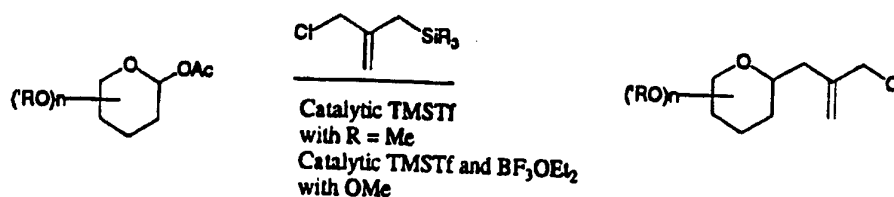




A vast array of methods for carbon-carbon bond formation at the anomeric carbon are known in the art. The most common method for carbon-carbon bond formation at the anomeric carbon involves nucleophilic attack on this electrophilic center. A wide variety of electrophilic sugars have been employed, such as glycosyl halides, imidates, glycals, lactones, thioglycosides, as well as oxygen-protected glycosides such as p-nitrobenzoates. The carbon nucleophiles that have been used include silyl enol ethers, alkenes, allylsilanes, allylstannanes, homoenolates, and organometallics such as Grignard reagents, organolithiums, cuprates, and aluminates.

Further, procedures to synthesize carbon-glycosides based on metals (palladium, manganese, rhodium, and cobalt) have been developed. Concerted reactions such as [4+2] cycloadditions and sigmatropic rearrangements also have been employed to generate carbon glycosides. The field of free radical chemistry also has been extended to this area; the special merits of free radical methods are mild reaction conditions and tolerance of a wide range of functional groups. The subject of carbon-glycoside synthesis has been reviewed by Hanessian and Pernet, 1976, Adv. Chem. Biochem. 33:111; Suhadoluid, 1970, Nucleosid. Antibiotics Wiley-Interscience: New York; and Daves and Cheng, 1976, Prog. Med. Chem. 13:303; Inch, 1984, Tetrahedron 40:3161; Hacksell and Daves, 1985, Prog. Med. Chem. 22:1; and Buchanan, 1983, Prog. Chem. Org. Natl. Prod. 44:243.

The following scheme shows the general chemical reaction underlying the generation of activated carbon glycosides useful for the generation of novel compounds and combinatorial libraries provided by the present invention:



R' denotes a protecting group for the carbohydrate

The typical procedure to make carbon-carbon bonds at the anomeric carbon involves nucleophilic attack on the electrophilic center. A wide variety of electrophilic sugars have been employed, such as reducing sugars (or lactols), alkyl glycosides, anomeric esters, anomeric trichloroacetimidates, and glycosyl halides. The carbon nucleophiles have been used include silyl enol ethers, olefins, allyl-, propargylsilanes, cyanides, homoenolates, and organometallics such as Grignard reagents, organolithiums, cuprates, and aluminates. These reactions can be used to modify the anomeric position. Protecting groups typically used when modifying the anomeric position of carbohydrates should be apparent to the skilled artisan. In addition, a plurality of functional groups may be employed. The C-atom of the carbohydrate used for the formation of the carbon glycosidic bond can be modified by differential protection of functional groups, as it will be apparent to those skilled in the art. Techniques and methods for the protection of functional groups can be found, among other places, in Greene and Wutz, *supra*.

An array of different reaction types have been employed for the generation of carbon glycosides (Postema, 1992, *Tetrahedron* **48**:8545; Postema, C-Glycoside Synthesis, 1995, CRC Press, Ann Arbor, Michigan). For example, concerted reactions, such as the sigmatropic rearrangement or cycloadditions as the Diels-Alder Reaction can be used for the formation of carbon glycosides. Also, the Wittig Reaction has extensively been applied to carbon glycoside

synthesis, which can be pursued by reaction of anomeric phosphoranes. Other approaches for the synthesis of carbon glycosides encompass, among others, palladium mediated reactions, free radical reactions, and reactions
5 relying on the electrophilic activity of the anomeric center of sugar molecules. These methods are readily known by the skilled artisan.

Reagents effective for the preparation of carbon glycosides include allyltrimethylsilane (Herscovici and
10 Antonakis, 1992, Nat. Prod. Chem. 10:337; Postema, 1992, Tetrahedron 48:8545; Daves, 1990, Acc. Chem. Res. 23:201; Hacksell, 1985, Progress in Medical Chemistry 22:1; Hanessian and Pernet, 1976, Adv. Chem. Biochem. 33:111; Carbohydrate Chemistry, Specialist Periodical Reports,
15 Royal Chemical Society, 1968-1990, p. 1-24); preparation of allyl silanes: Anderson and Fuchs, 1987, Synthetic Commun. 17:621) and an array of carbon nucleophiles available from commercial sources. Additional examples include, trimethylsilyl enol ethers, allyltrimethylsilane,
20 E- and Z-crotyltrialkylsilanes, organoaluminum reagents, trialkylstannanes, propargylic trialkylstannanes, [1-(acetoxymethyl)-2-propenyl]trimethylsilane, [1-(acetoxymethyl)-2-methyl-2-propenyl]-trimethylsilane, and ethyl-2-propenyltrimethylsilane-1-carbonate. All are efficient
25 carbon nucleophiles in the field of carbon glycosidation reactions (Panek and Sparks, 1989, J. Org. Chem. 54:2034, and references therein). The use of a [1-(acetoxymethyl)-2-methyl-2-propenyl]-trimethylsilane agent provides access to terminally oxygen substituted propenyl groups.

30 Although carbon glycosides can be produced in a few synthetic transformations, these compounds do not necessarily form suitable carbon glycosides which could easily be used as alkylating agents for the preparation of novel carbohydrate mimics. In one aspect, the present
35 invention provides novel carbohydrate analogues for the preparation of carbohydrate mimetics. Using the present invention, libraries of glycomimetics of complex

carbohydrates such as, but not limited, to Sialyl Lewis^x (sLe^x) tetrasaccharide can be prepared (Rao et al., 1994, The Journal of Biological Chemistry 269:1963; Allanson et al., 1994, Tetrahedron Asymmetry 5:2061). One of the
5 advantages of having an allylic halide as an alkylating agent is it would not be prone to E-2 elimination reactions (see, among other places, Lowry and Richardson, Mechanisms and Theory in Organic Chemistry, Second edition, 1981, Harper & Row, New York, p. 530). Among the
10 distinct advantages of this type of novel carbon glycoside is in the plethora of new chemical entities created by virtue of the invention.

For example, several terminally substituted halogen carbon glycosides are efficiently obtained from reaction
15 of 2-chloromethyl-3-trimethylsilyl-1-propene or 2-chloromethyl-3-trimethoxysilyl-1-propene with an activated carbohydrate when the reaction is catalyzed by Lewis acid. Thereby, the allylsilanes can undergo a stereochemically controlled axial addition to the pyranose oxonium ions
20 produced by Lewis acid catalysis and anomeric acetates. Benzyl protected carbohydrates result in a stereoselective and efficient route to α -C-glycosides, incorporating an allylic chloride. The use of the per-O-acetylated carbohydrates offers added versatility by avoiding the
25 hydrogenolysis step required for O-benzyl protected sugars. Nashed and Anderson, 1982, J. Amer. Chem. Soc. 104:7282; Panek and Sparks, 1989, J. Org. Chem. 54:2034. 2-chloromethyl-3-trimethylsilyl-1-propene and 2-chloromethyl-3-trimethoxysilyl-1-propene reagents react
30 with benzyl protected carbohydrates with equal efficiency while per-O-acetylated carbohydrates show better results with the 2-chloromethyl-3-trimethylsilyl-1-propene reagent. Examples for the carbon glycoside synthesis as employed by the subject invention are provided by the
35 instant disclosure, *infra*. Both the α - and the β -configuration are part of the invention.

C. Generation of Compounds Comprising C-Carbohydrate And/Or Glycomimetic Entities

The tools and methods of the present invention are focused towards the incorporation of carbohydrate and/or glycomimetic entities into existing and novel organic compounds, bio-oligomers, and combinatorial chemical libraries. Carbon glycosides, including monomers, dimers, trimers, oligomers, polymers, branched and unbranched, can be used as modifiers of biological activity, lifetime, efficacy, and the like.

In general terms, the tools of the present invention, the "activated" glycosides, are used for the generation of novel compounds and synthetic libraries comprising a plurality of compounds wherein each compound is composed of one or a plurality of monomers and at least one monomer is a carbohydrate or a glycomimetic. One or a plurality of the activated carbon glycosides (defined as $(X)_m - Z$, see, above) is reacted in a Z-primed reaction with one or a plurality of "B", defined as a monomeric, homo/hetero-oligomeric, or homo/hetero-polymeric entity of any chemical nature, including organic molecules, inorganic molecules, and solid synthesis supports. The arrays of compounds so generated are referred to as $[(X)_m - Z']$.

The carbohydrate moieties employed for the generation of such libraries include monomers, dimers, trimers, oligomers, branched or unbranched, linked to a suitable functional group of a chemical moiety comprising such functional group. Suitable functional groups include, but are not limited to, phenolic, hydroxyl, carboxyl, thiol, amido, and amino groups. In the case a moiety has more than one such suitable functional group, one or more such functional groups may be protected by suitable protecting groups during the coupling reaction. Such protecting groups include lower methyl-, benzyl-, benzoyl-, acetyl-, MOM, MEM, MPM, tBDMS, or TMS groups. After the coupling reaction, the protecting groups may be selectively removed.

The plurality of different library members may be synthesized either in liquid phase or, alternately, linked to a solid synthesis support or possibly using a combination of both techniques. After synthesis, the library members may be cleaved from the synthesis support. If the arrays of novel compounds are synthesized on a solid support, the solid support may be linked to the "B" entity or be included in the "B" entity using a suitable linker (see, *infra*), or, alternately the solid support can be included in $[(X)_m - Z]$. The solid support may be or may not be removed after or during synthesis reactions.

The members of such libraries may be linked to a chemical identifier tag which identifies the structure of the library member (see e.g., PCT Patent Application WO 94/08051, published April 14, 1994). The linkage between the library member and identifier tag may comprise a linker between the identifier tag and the library member, or, alternately, a linker between the identifier tag and a solid synthesis support.

The generation of such libraries may involve the modification of existing chemical compound libraries, providing the incorporation of carbohydrate(s) into existing and new combinatorial libraries, bio-oligomers and organic substrates. Syntheses may involve a plethora of stages, each stage having numerous choices in which large numbers of products having varying compositions are obtained by direct modification of an existing combinatorial natural product or chemical library of compounds. Alternately, such libraries may be obtained by employing combinatorial chemistry with carbohydrates or glycomimetics, including monomers, dimers, trimers, oligomers branched and unbranched. As such, the subject invention can be applied to three general strategies for the generation of novel compounds and large combinatorial libraries:

(1) a chosen compound can be subjected to chemical modification using an array of different carbon glycosides or a carbon glycoside library; or

(2) a mixture of organic molecules, e.g., a pre-existing chemical library, can be subjected to chemical modification using a single carbon glycoside reagent; or

(3) a mixture of organic molecules or a pre-existing library can be subjected to chemical modification using an array of different carbon glycosides.

10 In all three cases, every organic molecule comprising at least one suitable functional group can be employed as a substrate to react with the activated carbon glycosides/heteroatom glycosides of the present invention. Suitable functional groups that would react with the carbon
15 glycoside reagent include, but not are limited to, thiols, amines, phenols, carboxylates, carbohydrates, heparin derivatives, steroids, nucleic acids, tetrazoles, peptides, aromatics, pyridines, pyrazines, terpens, alkaloids, and the like. Other examples will be apparent
20 to the skilled artisan. The reactions can be performed either in solution phase, or the substrate may be attached to a solid support.

Approach (1), wherein an organic molecule of defined chemical structure is reacted with an array of diverse
25 carbon glycoside reagents, is particularly useful for the chemical modification of molecules with known or unknown biological, physiological, chemical, or any other activity in order to achieve improvement in a desired characteristic of the compound, such as life time,
30 stability, efficacy, activity, and the like. Depending upon the number of reactive functional groups inherent in the substrate and the complexity of different carbohydrate reagents used for the reaction, the number of reaction products will vary. For example, when the substrate has
35 one reactive functional group and ten different carbon glycosides are used, the number of reaction products is expected to be ten (10). When the number of reactive

functional groups is two, and ten different carbon glycosides are used, the complexity of products is expected to be 120. In general terms, when the number of reactive functional groups is defined as n, and the number
5 of carbon glycosides used is C, the complexity of products can be mathematically determined as:

$$\text{Number of Products} = (C + 1)^n - 1$$

Further variation of the present invention can be achieved by the use of unprotected or partially protected
10 carbon glycoside reagents, which will result in the formation of branched or unbranched molecules consisting of a plurality of monomer units in one concerted reaction. An additional variation can be accomplished by the use of both α - and β -isomers of carbon glycosides in one
15 reaction. Other modifications will become apparent to the skilled artisan upon the foregoing description.

In a preferred embodiments of the invention Penicillin-O has been modified with the approach provided, i.e., suitably functionalized carbon glycoside(s) have
20 been reacted with a suitably modified Penicillin-O precursor. As a result, novel Penicillin-O derivatives are provided by the present invention.

In another preferred embodiment of the invention, Vitamin E has been subjected to reaction with carbon
25 glycosides, resulting in a novel derivate of the natural form of Vitamin E.

In still another preferred embodiment of the invention, estrone has been modified by chemical reaction with carbon glycosides as provided, resulting in novel
30 estrone derivatives.

In still another preferred embodiment of the invention, castanospermine has been subjected to reaction with carbon glycosides as provided, resulting in novel derivated of castanospermine.

Further preferred embodiments of the invention demonstrating the workability of the approach provided can be found in the example section of the present disclosure.

In approach (2), a mixture of diverse organic molecules is reacted with one defined and particular carbon glycoside reagent (α , β , or both). This method is particularly useful for applying further variation to pre-existing combinatorial chemical libraries. All different kinds of pre-existing libraries can be used, as long as the library members comprise one or a plurality of functional groups that would react with the activated carbon glycosides of this invention. Examples of such functional groups have been described above. For the reaction, the substrate molecules may be linked to a solid synthesis support, or, alternately, the reaction may be performed in solution, or as a mixture of both. The skilled artisan will be able to determine the suitable conditions for each individual case.

Modification with carbon glycosides will generally be compatible with most of the pre-existing combinatorial libraries which have emerged in recent years (for example: Lam *et al.*, WO 92/00091, PCT/US91/04666; Still *et al.*, WO 94/08051, PCT/US93/09345; Gordon *et al.*, *supra*; Gallop *et al.*, *supra*), resulting in the generation of novel combinatorial libraries and novel compounds. For example, spatially-addressable libraries, split-bead libraries, and libraries generated using recombinant strategies may be derivatized with carbon glycosides. Also libraries wherein the members contain identifier tags for the identification of the molecular nature of library members may be used, whenever the chemical nature of the identifier tag is compatible, *i.e.*, not reactive, with activated carbon glycosides. The skilled artisan will be able to determine compatibility for each individual instance.

In a preferred embodiment of the invention, a peptide library is subjected to modification with carbon

glycosides as provided by the subject disclosure. For example, the carbohydrate unit may react with the hydroxyl group of tyrosine or serine. In preferred embodiments, the phenolic hydroxyl group is used as reactive functional group. The tyrosine residues can be either pre-functionalized prior to a random library generation, or, alternately, be appended to the library during generation, or, alternately, appended to the library post generation. Both solid phase or solution methodologies can be used.

10 In another preferred embodiment of the invention, a novel di-amino acid library is generated by derivatization of the phenolic hydroxyl group of the amino acid tyrosine with a carbon glycoside, followed by attachment to a solid support. A second amino acid is then attached, whereby
15 any natural or unnatural amino acid can be used.

Approach (3), wherein a mixture of organic molecules is reacted with an array of different carbon glycosides reagents or carbon glycoside libraries, provides the largest diversity of novel compounds. In fact, given the
20 unlimited diversity of carbohydrates that can be modified to be suitable reactive "activated" carbon glycoside reagents, and given the abundance and diversity in chemical nature of the pre-existing organic molecules suitable to react with such carbon glycoside reagents, the
25 potential of this approach is, simply put, tremendous and the number and chemical diversity of novel compounds which can be generated is infinite.

A whole array of compatible pre-existing combinatorial libraries, *see, supra*, is available and can be randomly
30 reacted with suitable functionalized carbon glycosides. This approach results in highly randomized libraries of theoretically unlimited size. For example, in a specific embodiment of the invention peptide libraries are reacted with such arrays of carbon glycosides, or carbon glycoside
35 libraries, resulting in unlimited numbers of novel compounds. The skilled artisan will appreciate the power and potential of this approach.

Protection Groups. The monomers of the present invention, i.e., the carbohydrates used for the formation of carbon glycosides, and/or the substrates may have groups protecting part of the functional groups within the monomer. Suitable protecting groups will depend on the functionality and particular chemistry used to generate the novel compound or combinatorial chemical library. Examples for suitable functional protecting groups will be readily apparent to the skilled artisan, and can be found, among other places, in Greene and Wutz, 1991, Protecting Groups in Organic Synthesis, 2d ed., John Wiley & Sons, NY. Most preferred protecting groups of the present invention comprise benzyl- and acetyl-groups.

Coupling Reactions. The carbon glycoside reagent can be functionalized to be used in a plethora of chemical reactions in order to form unique compounds. Suitable functionalized carbon glycosides can be attached, for example, to phenolic, hydroxyl, carboxyl, thiol, amino, amido, and/or equivalent functionality under mild conditions.

The coupling reactions can be performed to form novel compounds under standard conditions typically used for allyl chlorides, bromides, iodides, acetates, alcohols, Grignards, Cope rearrangements, Claisen rearrangements allylic couplings, as they are readily known by the skilled artisan and as are described in various examples provided hereinbelow to form novel glycomimetics and unique compounds. Many named standard reaction conditions using allylic halides parallel the use of carbon glycosides containing allylic halide functionality to prepare novel compounds and functional groups, including but not limited to the Alper Reaction, Barbier Reaction, Claisen-Ireland Reaction, Cope Rearrangement, Delepine Amine synthesis, Gewald Heterocycle Synthesis, Hiyama-Heathcock Stereoselective Allylation, Stork Radical

Cyclization, Trost Cyclopentanation, Weidenhagen Imidazole Synthesis. See, in general, Hassner and Stumer, 1994, "Organic Syntheses Based on Named Reactions and Unnamed Reactions", Tetrahedron Organic Chemistry Series, eds.

5 Baldwin and Magnus, Pergamon, Great Britain.

The skilled artisan will appreciate that the methods of the present invention can be used to incorporate carbohydrate units (monomers, dimers, trimers, oligomers, branched and unbranched) in virtually any compatible
10 chemical composition, including, but not limited to ketones, amides, esters, thioesters, ethers, sulfones, sulfonamides, sulfoxides, nucleic acids, amino acids, sugars, aromatics, alcohols, aldehydes, alkenes, alkynes, polyaromatics, heterocyclic compounds, terpenes, steroids,
15 β -lactams, xanthans, indoles, indolones, lactams, benzodiazepines, quinones, hydroquinones, hydantoins, oligo- and polymers thereof, such as peptides, heparin, cyclodextrines, and the like. Other chemical compositions suitable to be subjected to modification with carbon
20 glycosides will be readily apparent to those skilled in the art.

In the case a substrate comprises more than one suitable functional group to react with the functionalized carbon glycosides of the present invention, these
25 functionalities need not be identical.

The present invention can either utilize solid phase synthesis strategies, solution phase chemistries, or both. Techniques for solid phase synthesis of peptides are described, for example, in Atherton and Sheppard, Solid
30 Phase Peptide Synthesis: A Practical Approach, IRL Press at Oxford University Press, Oxford, England (1989); for oligonucleotides in, for example, Gait, Oligonucleotide Synthesis: A Practical Approach, IRL Press at Oxford University Press, Oxford, England (1984). Techniques for
35 solution and solid phase multiple component combinatorial array syntheses strategies also have been described.

Other synthetic strategies that may be employed by the present invention are described in, for example, Bunin et al., 1994, Proc. Natl. Acad. Sci. 91:4708-12, and U.S. Patent No. 5,288,514, issued Feb. 22, 1994; and Chen et al., 1994, J. Am. Chem. Soc. 116:2661-2662.

Thus, as those of skill in the art will appreciate, the methods of the present invention may be used with virtually any synthesis strategy, be it chemical, biological or otherwise, that is now known or will be later developed, to generate libraries of oligomers or polymers comprising carbohydrate units.

Synthesis Supports: Attachment and Detachment. In certain cases the synthetic protocol may require that one provide for a plurality of different reactions involving different reactants resulting in a plurality of different intermediates at each stage of the synthesis. While other techniques are available, this synthesis can be achieved by employing small definable solid substrates, commercially available as beads, which can be readily mixed, separated, and serve as a solid substrate for the sequential synthesis. The solid substrates may be solid, porous, deformable or hard, and have any convenient structure and shape. In some instances, magnetic or fluorescent beads may be useful. The beads will generally be at least 10-2000 μm , usually at least 20-500 μm , more usually at least 50-250 μm in diameter.

Depending upon the nature of the synthetic procedure or the assay of the final product, one or another bead may be more or less desirable. While beads are especially convenient, other solid supports may also find use, such as capillaries, hollow fibers, needles, solid fibers, etc., where the size of the solid support allows for the desired variation in reaction histories.

Depending upon the nature of the synthesis, the beads may be functionalized in a variety of ways to allow for attachment of the initial reactant. These may be linked

through linkages such as an ester bond, amide bond, amine bond, ether bond, or through a carbon atom, depending upon whether one wishes to be able to remove the product from the bead. The bead may be, for example, linked to a hydroxy group of the carbohydrate unit or any other suitable functional group of the activated carbon glycoside reagent $[(X)_m - Z]$, or, alternately, to a suitable functional group of the substrate "B", which may be of any chemical nature.

Conveniently, the bond to the bead may be permanent, but a linker between the bead and the product may be provided which is cleavable. Suitable linkages are well established in the art, and the skilled artisan will know which to employ for a particular chemical reaction scheme. Furthermore, two or more different linkages may be employed to allow for differential release of tags and/or products.

Depending upon the nature of the linking group bound to the particle, reactive functionalities on the bead may not be necessary where the manner of linking allows for insertion into single or double bonds, such as is available with carbenes and nitrenes or other highly-reactive species. In this case, the cleavable linkage will be provided in the linking group which joins the product or the tag to the bead.

Desirably, when the product is permanently attached, the link to the bead will be extended, so that the bead will not sterically interfere with the binding of the product during screening. Various links may be employed, particular hydrophilic links, such as polyethyleneoxy, saccharide, polyol, esters, amides, combinations thereof, and the like.

Functionalities present on the bead may include hydroxy, carboxy, iminoaldehyde, amino, thio, active halogen (Cl or Br) or pseudohalogen (e.g., $-CF_3$, $-CN$, etc.), carbonyl, silyl, tosyl, mesylates, brosylates, triflates or the like. In the case the carbon glycoside reagents

are reacted with pre-existing compounds comprising identifier tags, in selecting the functionality, some consideration should be given to the fact that the identifiers will usually also become bound to the bead.

5 Consideration will include whether the same or a different functionality should be associated with the product and the identifier, as well as whether the two functionalities will be compatible with the product or identifier attachment and tag detachment stages, as appropriate.

10 Different linking groups may be employed for the product, so that a specific quantity of the product may be selectively released. In some instances the particle may have protected functionalities which may be partially or wholly deprotected prior to each stage, and in the latter

15 case, reprotected. For example, amino acids may be protected with a carbobenzoxy group as in polypeptide synthesis, hydroxy with a benzyl ether, etc.

Where detachment of the product is desired, there are numerous functionalities and reactants which may be used.

20 Conveniently, ethers may be used, where substituted benzyl ether or derivatives thereof, e.g., benzhydryl ether, indanyl ether, etc. may be cleaved by acidic or mild reductive conditions. Alternatively, one may employ β -elimination, where a mild base may serve to release the

25 product. Acetals, including the thio analogs thereof, may be employed, where mild acid, particularly in the presence of a capturing carbonyl compound, may serve. By combining formaldehyde, HCl and an alcohol moiety, an α -chloroether is formed. This may then be coupled with an hydroxy

30 functionality on the bead to form the acetal. Various photolabile linkages may be employed, such as o-nitrobenzyl, 7-nitroindanyl, 2-nitrobenzhydryl ethers or esters, etc. Esters and amides may serve as linkers, where half-acid esters or amides are formed, particularly

35 with cyclic anhydrides, followed by reaction with hydroxyl or amino functionalities on the bead, using a coupling agent such as a carbodiimide. Peptides may be used as

linkers, where the sequence is subject to enzymatic hydrolysis, particularly where the enzyme recognizes a specific sequence. Carbonates and carbamates may be prepared using carbonic acid derivatives, e.g., phosgene, carbonyl diimidazole, etc. and a mild base. The link may be cleaved using acid, base or a strong reductant, e.g., LiAlH_4 , particularly for the carbonate esters. The versatility of the various systems that have been developed allows for broad variation in the conditions for attachment of products and identifiers and differential detachment of products and tags, as desired.

Linker. In cases in which synthesis reactions are performed on solid supports, the choice of linker will be part of the synthetic strategy, since the linking group may result in a residual functionality on the product. It will usually be feasible to further modify the product after detachment from the bead. In designing the synthetic strategy, one can use a functionality to be retained in the product as the point of attachment for the linking group. Alternatively, when permitted by the nature of the product, one could use a cleavage or detachment method that the linking functionality, e.g., an arylthioether or silyl with a metal hydride or acid.

Since in many cases the synthetic strategy will be able to include a functionalized site for linking, the functionality can be taken advantage of in choosing the linking group. In some instances it may be desirable to have different functionalities at the site of linking the product to the support, which may necessitate using different modes of linking, which modes must accommodate either the same detachment method or different detachment methods which may be carried out concurrently or consecutively, e.g., irradiation with light and acid hydrolysis.

The materials upon which the combinatorial syntheses of this invention are performed are referred to herein

interchangeably as beads, solid surfaces, (solid) substrates, particles, supports, etc. These terms are intended to include:

- 5 a) solid supports such as beads, pellets, disks, capillaries, hollow fibers, needles, solid fibers, cellulose beads, pore-glass beads, silica gels, polystyrene beads optionally crosslinked with divinylbenzene, grafted co-poly beads, polyacrylamide beads, latex beads, dimethylacrylamide
10 beads optionally cross-linked with N,N'-bis-acryloyl ethylene diamine, glass particles coated with a hydrophobic polymer, etc., i.e., a material having a rigid or semirigid surface; and
- 15 b) soluble supports such as low molecular weight non-cross-linked polystyrene.

The methods of this invention permit the variation in reaction at each stage, depending upon the choice of agents and conditions involved. Thus, for amino acids, one may have up to twenty (20) involved using the common
20 naturally-encoded amino acids and a much wider choice, if one wishes to use other amino acids, such as D-amino acids, amino acids having the amino group at other than the α -position, amino acids having different substituents on the side chain or substituents on the amino group, and
25 the like.

For sugars and lipids, a very large number of different compounds exist, which compounds may be further increased by various substitutions. All of these compounds may be used in the present synthesis. For
30 individual organic compounds the choice may be astronomically large. In addition, one may have mimetic analogs, where ureas, urethanes, carbonylmethylene groups, and the like may substitute for the peptide linkage; various organic and inorganic groups may substitute for
35 the phosphate linkage; and nitrogen or sulfur may substitute for oxygen in an ether linkage or vice versa.

The synthetic strategies will vary with the nature of the group of products one wishes to produce. Thus, the strategy must take into consideration the ability to stage-wise change the nature of the product, while
5 allowing for retention of the results of the previous stages and anticipating needs for the future stages. Where the various units are of the same family, such as nucleotides, amino acids and sugars, the synthetic strategies are relatively well-established and frequently
10 conventional chemistry will be available. Thus, for nucleotides, phosphoramidite or phosphite chemistries may be employed; for oligopeptides, Fmoc or Boc chemistries may be employed where conventional protective groups are used; for sugars, the strategies may be less conventional,
15 but a large number of protective groups, reactive functionalities, and conditions have been established for the synthesis of polysaccharides. For other types of chemistries, one will look to the nature of the individual unit and either synthetic opportunities will be known or
20 will be devised, as appropriate.

In some instances, one may wish to have the same or different blocks introduced at the same or different stages. For example, one may wish to have a common peptide functional unit, e.g., the fibronectin binding
25 unit (RGDS), a polysaccharide, an oligosaccharide, such as sLe^x, or an organic group, e.g., a lactam, lactone, benzene ring, olefin, glycol, thioether, etc., introduced during the synthesis. In this manner one may achieve a molecular context into which the variation is introduced. These
30 situations may involve only a few stages having the plurality of choices, where a large number of products are produced in relation to a particular functional entity. This strategy could have particular application where one is interested in a large number of derivatives related to
35 a core molecule or unit known to have a characteristic of interest.

In developing synthetic strategies, one can provide for batch synthesis of a few compounds which would be prepared during the course of the combinatorial synthesis. By taking extreme examples, for example, syntheses which might involve steric hindrance, charge and/or dipole interactions, alternative reaction pathways, or the like, one can optimize conditions to provide for enhanced yields of compounds which might not otherwise be formed or be formed only in low yield. In this manner, one may allow for a variety of reaction conditions during the combinatorial synthesis, involving differences in solvent, temperatures, times, concentrations, and the like. Furthermore, one may use the batch syntheses, which will provide much higher concentrations of particular products than the combinatorial synthesis, to develop assays to characterize the activity of the compounds.

D. Screening Methods

Generally, currently available screening strategies can be applied to the combinatorial methodologies of the present invention. The three general strategies presently preferred by the skilled artisan are "Discrete Molecule Synthesis", "Encoded Mixture Synthesis", and "Deconvolution Techniques", and variations thereof.

Discrete Molecule Synthesis, for example, involves the synthesis of individual compounds in solution or on solid supports around a biased or general "Structure Activity Relationship" (SAR) by automated synthesis or by traditional chemistry means. During this arrayed, "spatially addressable" synthesis, building blocks are reacted systemically in individual reaction wells or positions to form separated "discrete molecules" comprising at least one carbohydrate unit. Active compounds are defined by their location on the grid, for example a 96 well plate or an array of reaction vessels, depending on the size and nature of the reaction.

Alternatively, compounds may be synthesized on solid support, and the assays are performed stagewise using individual particles or groups of particles or combinations thereof. For example, after carrying out the combinatorial syntheses, groups of about 50 to 10,000 particles may be segregated in separate vessels. In each vessel, a portion of the product bound to the particle is released. The fractional release may be as a result of differential linking of the product to the particle or by using a limited amount of reagent, condition or the like, so that the average number of product molecules released per particle is less than the total number of product molecules per particle. One would then have a mixture of products in a small volume. The mixture could then be used in an assay for binding, where the binding event could be inhibition of a known binding ligand binding to a receptor, activation or inhibition of a metabolic process of a cell, or the like.

Various assay conditions may be used for the detection of binding activity as will be known by the skilled artisan. Once a group is shown to be active, the individual particles may then be screened, by the same or a different assay. One could of course, have a three- or four-stage procedure, in which large groups are divided up into smaller groups, etc. and finally single particles are screened. In each case, portions of the products on the particles would be released and the resulting mixture used in an appropriate assay. The assays could be the same or different, the more sophisticated and time consuming assays being used in the later or last stage.

The strategy of "Encoded Mixture Synthesis" may be applicable to the libraries synthesized with the tools and methods provided by the instant invention. Chemically inert identifier tags, such as peptides, nucleotides or the like, are used to identify each synthesized compound in a mixture. This method is of particular interest when the methods and tools of the present invention are

used to incorporate carbohydrate units in the compounds of a pre-existing library with identifier tags (e.g., PCT Publication No. WO 94/08051, April 14, 1994; Nestler et al., 1994, J. Org. Chem. 59:4723-4724; PCT Publication No. 5 WO 93/06121, April 1, 1993; Needels et al., 1993, Proc. Natl. Acad. Sci. 90:10700-10704; Kerr et al., 1993, J. Amer. Chem. Soc. 115:2529-2531; and Brenner & Lerner, 1992, Proc. Natl. Acad. Sci. 89:5381-5383). The skilled artisan will know which libraries and which identifier 10 tags are compatible with the chemistry of the tools and methods provided by the present invention.

The major disadvantage of all the above methods is that the search rate is fairly limited (see, for further discussion, Section II of this disclosure). As the 15 present invention provides for the generation of theoretically unlimited arrays of novel compounds, all of the above structure elucidation strategies would restrict the power of this invention - to provide for a high, or even unlimited throughput of novel compounds. Thus, to 20 begin to tap the true power of the methods and compounds disclosed, the compounds must be screened in mixtures, or pools, which can subsequently be "deconvoluted".

Generally, the idea of the "Deconvolution" strategy is to produce a complex array of new compounds and 25 "deconvolute" its complexity by fractionation, retesting, purification and structure elucidation. A limitation of this strategy is that as the number of compound in a library increases, usually each individual compound will be present only in minute amounts. This fact is 30 especially true when the library members are synthesized on solid supports. However, known techniques of structure elucidation and product segregation require certain amounts of substance. Thus, the accurate determination of the structure of individual compounds is 35 often impossible. The chemistry provided by the present invention does not suffer this limitation: individual compounds can be synthesized in theoretically unlimited

amounts, enabling the researcher to eventually elucidate the structure of the compound of interest by readily available standard techniques, as for example mass spectrometry or NMR.

5 More specifically, a deconvolution strategy applied to the libraries of compounds of the present invention for the screening and identification of the desired active compound, i.e., the "hit," may be as follows: In a first step, a series of compound mixtures are synthesized
10 combinatorially and the different pools are tested for a desired biological, physiological, chemical or other activity. Only a pool identified to exhibit the desired activity is further pursued. In the next synthesis round, the reaction mixture of the "active" pool is divided in a
15 subset of pools, the "active" pool again is identified, and so on. In every synthesis round, the complexity of the individual pools is narrowed down and a specific structural feature is fixed to eventually arrive, after a number of rounds, at the specific active compound.

20 For example, $[(X)_m - Z]$ carbon glycoside sublibraries may be generated, wherein each X comprises a distinct disaccharide, oligosaccharides or polysaccharides, formally analogous to the strategy used to develop peptide libraries. For example, libraries of carbohydrates, as
25 for example provided by the PCT Patent Application WO 95/03315, published February, 1995, or arrays of oligomeric/polymeric carbon glycosides may be used for the generation of the activated carbon glycoside reagent (the carbon glycoside "sublibrary"). Subsequently, such
30 "sublibraries" comprising pools of activated carbon glycosides can be reacted with "B", wherein B comprises a monomer, oligomer, or polymer of any chemical nature, as described above.

In the simplest case, "B" may be a lead compound of
35 known chemical nature and defined structure. The reaction product pools resulting from each sublibrary reacted with "B" are tested for the desired biological, chemical, or

other effect employing a suitable assay, and those pools showing the desired activity are further pursued. Subsequently, selective protection and deprotection schemes allow the generation of $[(X)_m - Z]$ sublibraries
5 representing pools of smaller diversity. Particular features are stepwise fixed, until the carbon glycoside reagent moiety and as such the chemical nature of the active compound (the "hit") is identified (as the chemical nature of "B" was known in this case!).

10 Alternatively, the $[(X)_m - Z]$ "sublibraries" can be reacted with arrays of different substrate molecules. For example, "B" may simply comprise a pre-existing synthetic library, e.g., a peptide library. "B" also may comprise a biased, pre-existing library representing a particular
15 class of organic compounds, such as triterpenes, aromatic phenols, antibiotics, rutin, retinase acids, steroids, and the like, for attachment of the initial $[(X)_m - Z]$ s. Or, to encompass the highest chemical diversity, "B" may comprise any random array of compounds of any different
20 chemical nature, for example crude fractions of natural products, synthetic products or the like.

Whereas the chemical nature of the carbon glycoside moiety can be determined ("deconvoluted") as described above, the structure of "B" has to be deconvoluted and
25 elucidated separately by suitable means. In the case "B" is a pre-existing library, the structure of "B" may be identified by methods suitable for the identification of "B"-library members. For example, the "B" library members may comprise identifier tags to determine the structure of
30 the "B" moiety of the active compound. In other cases the structure of the active compound may be elucidated by classical means, such as NMR or mass spectrometry. The skilled artisan will determine suitable means to identify the chemical nature of the desired $[(X)_m - Z']$ in any
35 particular case.

E. Assay Methods

To determine the characteristic of interest in the product, a wide variety of assays and techniques may be employed.

5 If one is interested in binding an invention compound to a particular biomolecule such as a receptor, the receptor may be a single molecule, a molecule associated with a microsome or cell, or the like. Where agonist activity is of interest, one may wish to use an intact
10 organism or cell, where the response to the binding of the subject product may be measured. In cases in which the compounds are synthesized on solid supports, it may be desirable to detach the product from the support bead, particularly where physiological activity by transduction
15 of a signal is of interest.

 Various devices are available for detecting cellular response, such as microphysiometer, available from Molecular Devices, Redwood City, CA. If binding is of interest, one may use a labeled receptor, in which the
20 label is a fluorescer, enzyme, radioisotope, or the like, and one can detect the binding of the receptor to the bead. Alternatively, one may provide for an antibody to the receptor, where the antibody is labeled, which may allow for amplification of the signal and avoid changing
25 the receptor of interest, which might affect its binding to the product of interest. Binding may also be determined by displacement of a ligand bound to the receptor, where the ligand is labeled with a detectable label.

30 In some instances, one may be able to carry out a two-stage screen, whereby one first uses binding as an initial screen, following by biological activity with a viable cell in a second screen. By employing recombinant techniques, one can greatly vary the genetic capability of
35 cells. One can then produce exogenous genes or exogenous transcriptional regulatory sequences, so that binding to a surface membrane protein will result in an observable

signal, e.g., an intracellular signal. For example, one may introduce a leuco dye into the cell, where an enzyme which transforms the leuco dye to a colored product, particularly a fluorescent product, becomes expressed upon
5 appropriate binding to a surface membrane, e.g., β -galactosidase and digalactosidylfluorescein. In this matter, by associating a particular cell or cells with a particular particle or soluble compound, the fluorescent nature of the cell may be determined using a FACS, so that
10 particles carrying active compounds or soluble compounds may be identified.

One may also provide for spatial arrays, in which the particles or soluble compounds may be distributed over a honeycomb plate, with each well in the honeycomb having 0
15 or 1 particle or soluble compound.

The subject array of compounds may be used to find chemicals with certain catalytic properties. For this purpose, the array of compounds may be embedded in a semisolid matrix surrounded by diffusible test substrates.
20 If the catalytic activity can be detected locally by processes that do not disturb the matrix, for example, by changes in the absorption of light or by the detection of fluorescence due to a cleaved substrate, the beads in the zone of catalytic activity can be isolated and their
25 labels decoded, or, where the compounds are in solution, deconvolution strategies as described above may be employed.

Instead of catalytic activity, compounds with inhibitory or activating activity can be developed.
30 Compounds may be sought that inhibit or activate an enzyme or block a binding reaction. To detect compounds that inhibit an enzyme, it is advantageous to enable them to diffuse into a semisolid matrix or onto a filter where this inhibition, activation or blocking can be observed.
35 Thus, in cases where the compounds are synthesized on solid support, it might be desirable to release the products from the beads prior to the screening procedure.

Of particular interest is finding products that have biological activity. In some applications it is desirable to find a product that has an effect on living cells, such as inhibition of microbial growth, inhibition of viral growth, inhibition of gene expression or activation of gene expression. In cases in which compounds are synthesized and available in solution, cells are simply exposed to arrays of such compounds, and active molecules of the desired effect are identified by deconvolution strategies as described. Screening of the compounds on beads can be readily achieved, for example, by embedding the beads in a semisolid medium and the library of product molecules released from the beads (while the beads are retained) enabling the compounds to diffuse into the surrounding medium. The effects, such as plaques with a bacterial lawn, can be observed. Zones of growth inhibition or growth activation or effects on gene expression can then be visualized and the beads at the center of the zone picked and analyzed.

In cases where the compounds are linked to a solid particle, one assay scheme will involve gels in which the molecule or system, e.g., cell, to be acted upon may be embedded substantially homogeneously in the gel. Various gelling agents may be used such as polyacrylamide, agarose, gelatin, etc. The particles may then be spread over the gel so as to have hydrolytic activity, and a substrate is present in the gel which would provide a fluorescent product. One would then screen the gel for fluorescence and mechanically select the particles associated with the fluorescent signal. One could have cells embedded in the gel, in effect creating a cellular lawn. The particles would be spread out as indicated above. Of course, one could place a grid over the gel defining areas of one or no particle. If cytotoxicity were the criterion, one could release the product, incubate for a sufficient time, followed by spreading a

vital dye over the gel. Those cells which absorbed the dye or did not absorb the dye could then be distinguished.

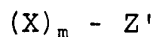
As indicated above, cells can be genetically engineered so as to indicate when a signal has been transduced. There are many receptors for which the genes are known whose expression is activated. By inserting an exogenous gene into a site where the gene is under the transcriptional control of the promoter responsive to such receptor, an enzyme can be produced which provides a detectable signal, e.g., a fluorescent signal. The compound associated with the fluorescent cell(s) may then be analyzed by one of the strategies described.

In a specific embodiment of the invention, an ELISA assay has been developed to test compounds of the invention for selectin binding and inhibition. For example, ELISA plates may be coated with sLe^x-hexa-ceramide or control glycolipids and the target compound's effect on subsequent binding of E-Selectin, L-Selectin or P-Selectin IgG chimera may be evaluated.

20 F. Compounds Comprising Carbon Glycosides

In a further aspect, the invention is directed to an array of chemical compounds comprising at least one carbohydrate unit, attached, via a spacer/linker unit, to a suitably derivatized functional group of an entity of any chemical nature.

The subject invention provides novel chemical compounds comprising the formula:



wherein:

30 X is a carbohydrate unit or modified carbohydrate unit;

Z' is the reaction product of "Z" and "B";

B is one or a plurality of monomeric, homo/hetero-oligomeric, or homo/hetero-polymeric entities of any chemical nature, including organic molecules, inorganic molecules, solid synthesis supports.

Z is an activated functional group attached, via a spacer/linker unit containing at least one carbon atom, to a X at the anomeric position which is oxygen;

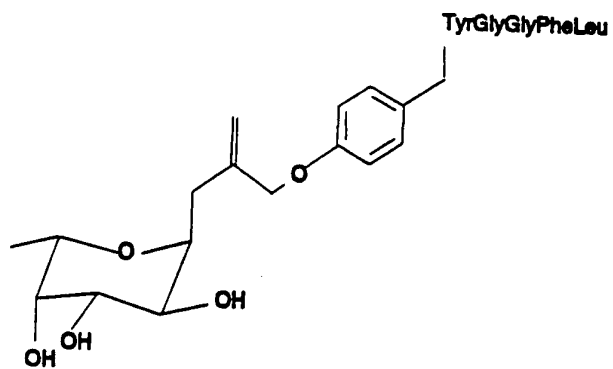
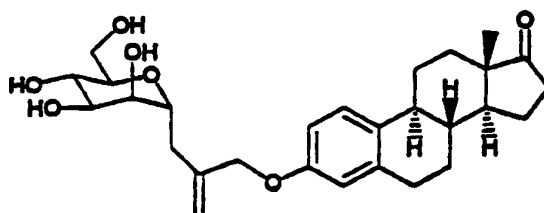
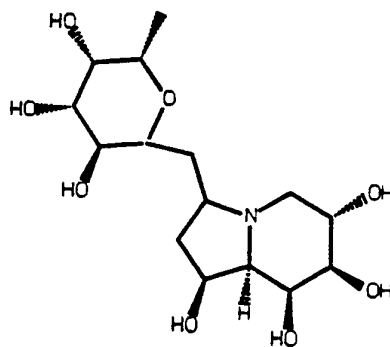
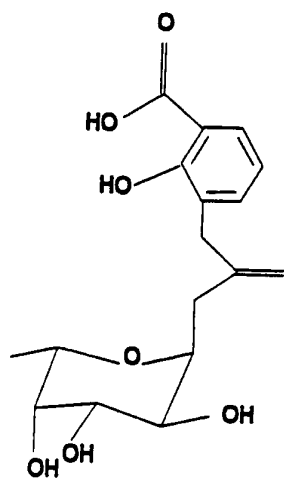
m is a positive integer.

5 The carbohydrate of the compound may be a monosaccharide, disaccharide, oligosaccharide or polysaccharide, either branched or unbranched. The carbohydrate units may comprise five membered ring structures, six membered ring structures, or both. The
10 hydrogen of any hydroxy-group may be replaced by any compatible moiety, linker, or solid synthesis support. The molecular weight of the carbohydrate moiety (X_m) may be as less as the molecular weight of a monosaccharide (about 180), or as much as several hundred thousand, as for
15 example cellulose or other very complex sugars may have.

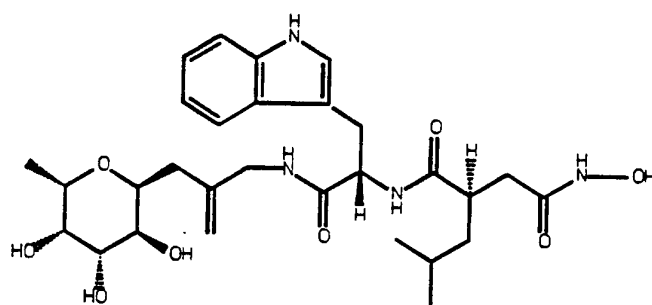
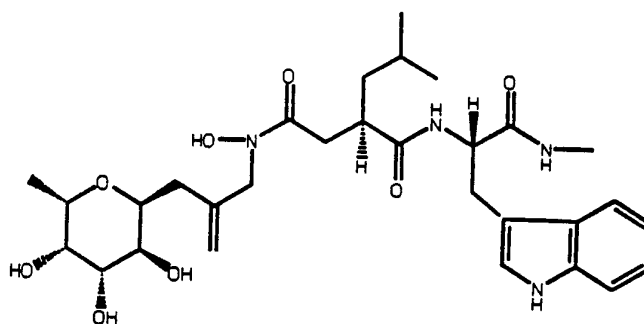
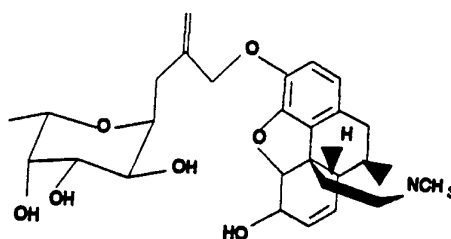
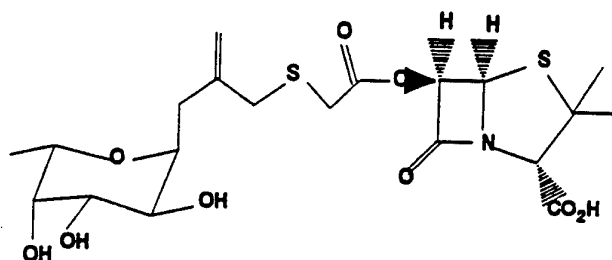
"B" comprises any monomeric, homo/hetero-oligomeric, or homo/hetero-polymeric entities of any chemical nature, including organic molecules, inorganic molecules, solid synthesis supports. For example, "B" can be any
20 monomeric, homo/hetero-oligomeric, or homo/hetero-polymeric molecule comprising ketones, amides, esters, thioesters, ethers, sulfones, sulfonamides, sulfoxides, nucleic acids, amino acids, sugars, aromatics, alcohols, aldehydes, alkenes, alkynes, polyaromatics, heterocyclic
25 compounds, terpenes, steroids, β -lactames, xanthans, indoles, indolones, lactams, benzodiazepines, quinones, hydroquinones, hydantoins, oligo- and polymers thereof, such as peptides, heparin, cyclodextrines, and the like.

In more specific embodiments, the activated functional
30 group Z may comprise one of the structures defined in section B above.

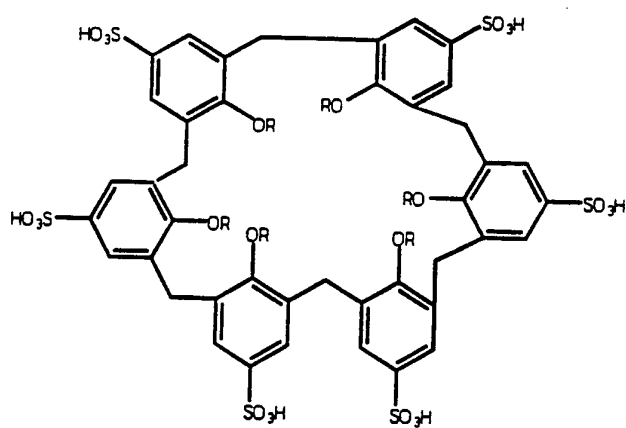
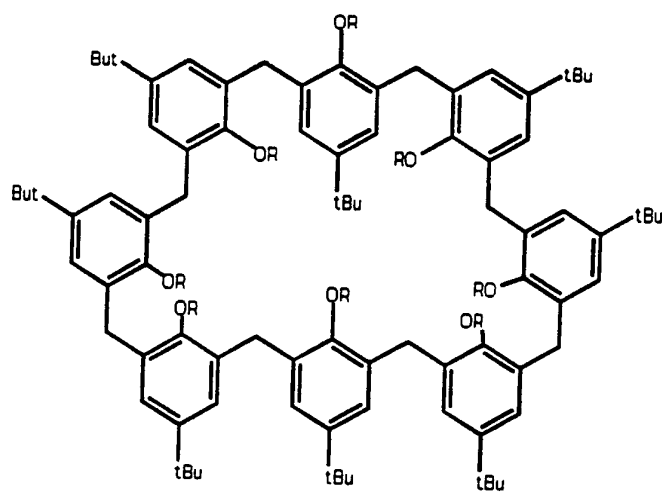
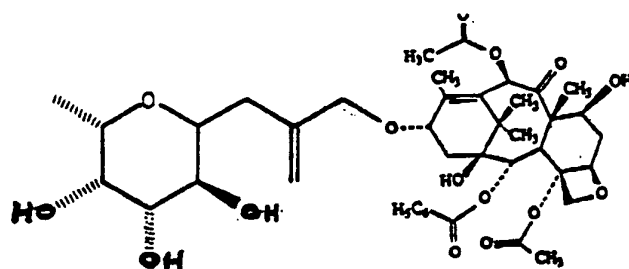
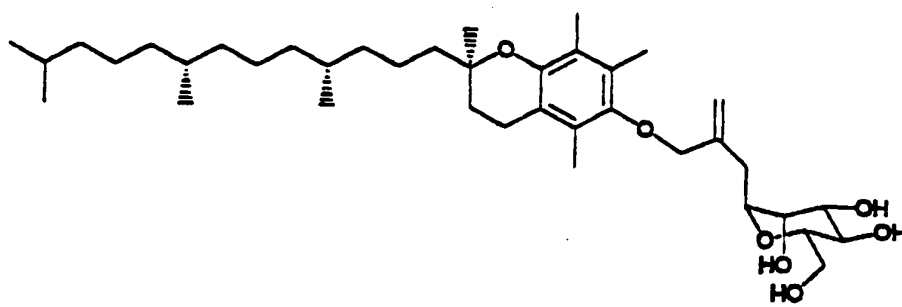
In the most preferred embodiments of the invention, the "activated" glycoside comprises one of the following formula. Although the α -form is shown in the examples the
35 invention includes the β -configuration of the bond.



64



65



The foregoing specific embodiments of the invention are unique compounds which have been generated according to the teachings of this invention. However, these embodiments are only examples and intended to serve as
5 illustrations and are not understood to limit the scope of this invention. In addition to the above compounds and their pharmaceutically acceptable salts, the invention is further directed, where applicable, to solvated as well as unsolvated forms of the compounds (e.g., hydrated forms)
10 that can be generated employing the tools disclosed.

The chemical formulae referred herein may exhibit the phenomon of tautomerism. As the formula drawings within this specification can only represent one of the possible tautomeric forms, it should be understood that the
15 invention encompasses any tautomeric form which can be generated by employing the tools disclosed and is not limited to any one tautomeric form utilized within the formulae drawings.

The compounds described above may be prepared by any
20 process known to be applicable to the preparation of chemically-related compounds. Suitable processes are illustrated by the following representative examples. It should be noted that these examples are not intended to limit the scope of the subject invention.

25 Some of the compounds described herein contain one or more centers of asymmetry and may thus give rise to enantiomers, diastereoisomers, and other stereoisomeric forms. The present invention is meant to include all such possible stereoisomers as well as their racemic and
30 optically pure forms. Optically active (R) and (S) isomers may be prepared using chiral synthons, chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic double bonds, it is intended to include both E and Z geometric
35 isomers.

G. Use of Compounds Modified with Carbon Glycosides

The use of the carbon glycoside modified compounds may be the agonistic or antagonistic modulation of any biological, chemical, physiological or other activity. In the case the instant methods are used for the modulation of pre-existing bioactive molecules, they may simply provide improved drugs or natural products, for example, antibiotics not susceptible to resistance mechanisms, improved cytostatica and cytotoxica, improved antiviral agents, higher stability of an active compound, and the like. Novel compounds generated and identified by the methods provided may be useful for the treatment of pathological disorders such as cancer and metastasis, inflammation, viral or bacterial infections, and the like, further for the modulation of physiological effects such as cell adhesion, cell proliferation, enzymatic activity, and the like.

A wide variety of drug analogues may be produced, such as analogs of antihypertensive agents, β -blockers, antiulcer drugs, antifungal agents, anti-proliferative drugs, anxiolytics, analgesics, antibiotics, vitamins, antiinflammatories, abortifacient, antihistamines, antitussives, sedatives, and the like.

In a specific embodiment of the invention, the compounds are inhibitors of members of the selectin family. Selections are a class of cell adhesion molecules which interact with cell surface carbohydrates, such as sLe^x. Selectins are involved in cell adhesion, e.g., of the transendothelial migration of leukocytes. Thus, in specific embodiments, compounds comprised within the subject invention may be used as drugs for the treatment of diseases related to inappropriate cell adhesion, for example asthma, arthritis, and other inflammatory diseases, further numerous types of cancer and cancer metastasis.

The pharmaceutical compositions of compounds provided by the present invention may be manufactured in a manner

that is itself known, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes. Pharmaceutical compositions may
5 be formulated in conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations that can be used pharmaceutically. Proper formulation is dependent upon
10 the route of administration chosen.

For injection, the agents of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline
15 buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

For oral administration, the compounds can be
20 formulated readily by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like,
25 for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or
30 dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose,
35 hydroxypropylmethyl- cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as

the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, 5 which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for 10 identification or to characterize different combinations of active compound doses.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, 15 such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active 20 compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for such administration.

25 For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

For administration by inhalation, the compounds for use according to the present invention are conveniently 30 delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a 35 pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, e.g., gelatin for use in an inhaler or

insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

5 The compounds may be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions
10 or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the active
15 compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl
20 oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents
25 which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

30 The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described previously,
35 the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously

or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or
5 as sparingly soluble derivatives, for example, as a sparingly soluble salt.

A pharmaceutical carrier for the hydrophobic compounds of the invention is a cosolvent system comprising benzyl alcohol, a nonpolar surfactant, a water-miscible organic
10 polymer, and an aqueous phase. The cosolvent system may be the VPD co-solvent system. VPD is a solution of 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant polysorbate 80, and 65% w/v polyethylene glycol 300, made up to volume in absolute ethanol. The VPD co-solvent
15 system (VPD:5W) consists of VPD diluted 1:1 with a 5% dextrose in water solution. This co-solvent system dissolves hydrophobic compounds well, and itself produces low toxicity upon systemic administration. Naturally, the proportions of a co-solvent system may be varied
20 considerably without destroying its solubility and toxicity characteristics. Furthermore, the identity of the co-solvent components may be varied: for example, other low-toxicity nonpolar surfactants may be used instead of polysorbate 80; the fraction size of
25 polyethylene glycol may be varied; other biocompatible polymers may replace polyethylene glycol, e.g., polyvinyl pyrrolidone; and other sugars or polysaccharides may substitute for dextrose.

Alternatively, other delivery systems for hydrophobic
30 pharmaceutical compounds may be employed. Liposomes and emulsions are well known examples of delivery vehicles or carriers for hydrophobic drugs. Certain organic solvents such as dimethylsulfoxide also may be employed, although usually at the cost of greater toxicity. Additionally,
35 the compounds may be delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent.

Various of sustained-release materials have been established and are well known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein stabilization may be employed.

The pharmaceutical compositions also may comprise suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients include but are not limited to calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

Some of the compounds of the invention may be provided as salts with pharmaceutically compatible counterions. Pharmaceutically compatible salts may be formed with many acids, including but not limited to hydrochloric, sulfuric, acetic, lactic, tartaric, malic, succinic, etc. Salts tend to be more soluble in aqueous or other protonic solvents that are the corresponding free base forms.

Pharmaceutical compositions suitable for use of the compounds provided by the present invention include compositions wherein the active ingredients are contained in an effective amount to achieve its intended purpose. More specifically, a therapeutically effective amount means an amount effective to prevent development of or to alleviate the existing symptoms of the subject being treated. Determination of the effective amounts for effecting desired biological, chemical or other effects is well within the capability of those skilled in the art.

VI. EXPERIMENTAL SECTION

A. Materials and Methods

1. Materials

Reagents were purchased from commercial suppliers such as Pfanstiehl Laboratories, Aldrich Chemical Company or

Lancaster Synthesis Ltd. and were used without further purification unless otherwise indicated. Tetra-hydrofuran (THF) and dimethylformamide (DMF) were purchased from Aldrich in sure seal bottles and used as received. All
5 solvents were purified by using standard methods readily known to those skilled in the art unless otherwise indicated.

2. General Protocol

The reactions set forth below were done generally
10 under a positive pressure of nitrogen or with a drying tube, at ambient temperature (unless otherwise stated), in anhydrous solvents, and the reaction flasks were fitted with rubber septa for the introduction of substrates and reagents via syringe. Glassware was oven dried and/or
15 heat dried. Analytical thin layer chromatography (tic) was performed on glass-backed silica gel 60 F 254 plates Analtech (0.25 mm) and eluted with the appropriate solvent ratios (v/v) and are denoted where appropriate. The reactions were assayed by TLC and terminated as judged by
20 the consumption of starting material.

Visualization of the TLC plates was done with a *p*-anisaldehyde spray reagent or phosphomolybdic acid reagent (Aldrich Chemical 20% wt in ethanol) and activated with heat.

25 Work-ups were typically done by doubling the reaction volume with the reaction solvent or extraction solvent and then washing with the indicated aqueous solutions using 25% by volume of the extraction volume unless otherwise indicated.

30 Product solutions were dried over anhydrous Na_2SO_4 prior to filtration and evaporation of the solvents under reduced pressure on a rotary evaporator and noted as solvents removed *in vacua*.

Flash column chromatography (Still et al, 1978, A.J. Org. Chem. 43:2923) was done using Baker grade flash
35

silica gel (47-61 μ m) and a silica gel: crude material ratio of about 20:1 to 50:1 unless otherwise stated.

Hydrogenolysis can be done at the pressure indicated in the examples, or at ambient pressure.

5 ¹H-NMR spectra were recorded on a Varian 300 instrument operating at 300 MHz and ¹³C-NMR spectra were recorded on a Varian 300 instrument operating at 75 MHz. NMR spectra were obtained as CDCl₃ solutions (reported in ppm), using chloroform as the reference standard (7.25 ppm and
10 77.00 ppm) or DC₃OD (3.4 and 4.8 ppm and 49.3 ppm) or internally tetramethylsilane (0.00 ppm) when appropriate. When peak multiplicities are reported, the following abbreviations are used: s (singlet), d (doublet), t (triplet), m (multiplet), br (broadened), dd (doublet of
15 doublets), dt (doublet of triplets). Coupling constants, when given, are reported in Hertz.

Infrared spectra were recorded on a Perkin-Elmer FT-IR Spectrometer as neat oils, or a CDCl₃ solutions, and are reported in wave numbers (cm⁻¹).

20 The mass spectra were obtained using LSIMS. All melting points are uncorrected. Microanalyses were carried out by Galbraith Laboratories, Inc., Knoxville, TN.

25 3. Synthesis of "Activated" Carbon Glycoside Building Blocks

A preferred method for the synthesis of terminally substituted halogen carbon glycosides comprises a chemical reaction of 2-chloromethyl-3-trimethylsilyl-1-propene (SAF Bulk Chemicals), or 2-chloromethyl-3-trimethoxysilyl-1-
30 propene by Gelest Inc. (U.S. Patent No. 3,696,138), with an activated carbohydrate and a Lewis acid, whereby the allylsilanes undergo addition to the pyranose oxonium ions produced by Lewis acid catalysis for example with anomeric acetates. Nashed and Anderson, 1982, Amer. Chem. Soc.
35 104:7282; Panek and Sparks, 1989, J. Org. Chem. 54:2034. Other electro-philic sugars can be employed as stated

earlier (Postema, 1995, *supra*). It will be apparent to those skilled in the art, that other functional groups at the C-1 position also can be used to convert the anomeric hydroxyl functionality into an appropriate leaving group to form the oxonium ion. 2-chloromethyl-3-trimethylsilyl-1-propene and 2-chloro-methyl-3-trimethoxysilyl-1-propene exhibit about the same efficiency on the benzyl protected carbohydrates, while at least under the specific reaction conditions employed the per-O-acetylated carbohydrates used the 2-chloromethyl-3-trimethylsilyl-1-propene reagent.

3.1. The Carbon Glycoside Formation with Benzyl Protected Sugar

a. 2-Chloromethyl-3-(tri-O-benzyl- α -L-C-fucopyranoside)-1-propene

To a stirred solution of 500 g 2,3,4-tri-O-benzyl-L-fucopyranose (1) (1.15 mole) (Pfanstiehl, Inc.) in 500 ml 1,2-dichloroethane or 550 ml THF, 240 ml acetic anhydride, 135 ml pyridine was added, and the mixture stirred at room temperature for 22 hours. Subsequently, the reaction was diluted with ethyl acetate, washed with water, saturated sodium bicarbonate and again with water. The solvents were removed *in vacuo* and azeotrophed with toluene. The white solid was placed on a vacuum line, which afforded 542 g (99%) of 1-O-Acetyl-2,3,4-tri-O-benzyl-L-fucopyranose (1) as a colorless crystalline solid in a mixture of anomeric acetates, mp=86-87.5°C.

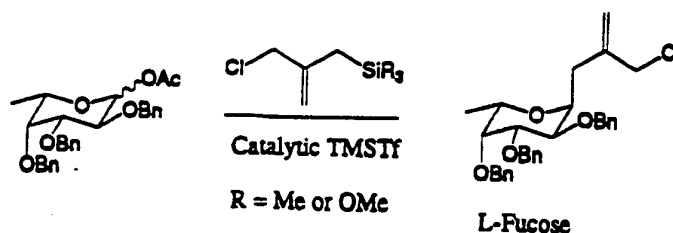
564.35 g 1-O-Acetyl-2,3,4-tri-O-benzyl-L-fuco-pyranose (1) (1.19 mole, 1.00 eq.) and 214.6 ml 2-chloromethyl-3-trimethylsilyl-1-propene (1.19 mole, 1.00 eq.) were dissolved in 1.2 l acetonitrile (HPLC grade) and cooled to approximately 0°C using an ice-water bath. Subsequently, 11.46 ml trimethylsilyltrifluoromethane sulfonate (59.28 mmoles, 0.05 eq.) was carefully added, the ice-water bath was allowed to melt and the reaction slowly warmed to room temperature (18 hours). Completion of the transformation

from starting material to product was indicated by tlc. The reaction was terminated by pouring the reaction contents onto 1 l of ice-water, followed by adjustment to room temperature. The resulting mixture was extracted with 1 l ethyl acetate and the organic phase then washed with 1.0 N aqueous sodium hydroxide and brine. The organic phase was dried over anhydrous magnesium sulfate, filtered, and the solvent was removed in vacuo, which afforded 600.5 g of 2-Chloromethyl-3-(tri-O-benzyl- α -L-C-fucopyranoside)-1-propene (2) as a light yellow solid. The product was purified either by crystallization in methanol at 0°C, or by column chromatography using Baker grade flash silica gel (47-61mm) (ratio of 20 to 1), followed by elution with 5 to 10% ethyl acetate in hexanes giving a white solid (98%), mp 47-49°C.

In low scale reactions, the α - to β - ratios of the C-glycosidation reaction was > 10:1 in favor of the α -fucose derivative (Cha, et al., 1982, J. Am. Chem. Soc. 104:4976). The higher the reaction scale, the less β isomer could be observed, at scales in the multi-gram levels, sometimes only trace amounts are seen.

The results of this study are complementary to related C-glycoside formation reactions for pyranosides using an allylic silane and an activated glycal. In another preferred embodiment, the Finkelstein exchange of the chloride for iodide (97% yield) or bromide (95% yield) was performed under standard conditions such as NaI in refluxing acetone or LiBr in refluxing THF, the proceeding of the reaction was monitored by tlc or NMR techniques. Under certain conditions, bromide appears to be more stable than the corresponding iodide and seems to result in higher yielding alkylations.

The C-glycoside forming reaction with a benzyl protected sugar, in this preferred embodiment 1-O-acetyl-2,3,4-tri-O-benzyl-L-fucopyranoside (1), is reflected the following scheme:



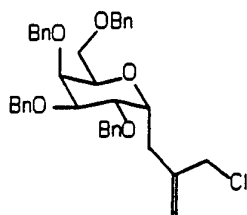
Examples for typical scales of this reaction: Starting material Acetate/2-chloromethyl-3-trimethylsilyl-1-propene (310 g/118 ml), Product obtained (331 g);
 5 Acetate/2-chloromethyl-3-trimethylsilyl-1-propene (380 g/144 ml), Product obtained (400 g).

An alternate procedure starting from the anomeric hydroxyl can be performed as follows: To a solution of 20 g tri-O-benzyl-L-fucopyranose (46.03 mmole, 1.00 mmole equiv.) in 200 ml anhydrous acetonitrile 30.0 g 2-chloromethyl-3-trimethylsilyl-1-propene (184.34 mmole, 4.00 mmole equiv.) was added at 0°C. 10.24 g trimethylsilane trifluoromethane sulfonic acid (46.03 mmol, 1.00 mmole equiv.) was added dropwise in 30 ml anhydrous
 15 acetonitrile (overall reaction concentration 0.2M) and the reaction contents stirred at 0°C for 30 minutes. After 30 minutes, the reaction was diluted with 230 ml ethyl acetate and terminated by pouring the contents slowly into aqueous saturated sodium bicarbonate. The heterogeneous
 20 layers were separated and the organic phase was washed twice with portions of water, 1.0 M hydrochloric acid and brine. The crude product was dried over anhydrous sodium sulfate, filtered and plugged through a small pad of silica gel. The solvent was removed in vacuo which
 25 afforded an oil that was chromatographed on Baker grade flash silica gel (47-61mm; ratio of 50 to 1) and eluted with 5 to 10% ethyl acetate in hexanes. Concentration in vacuo afforded 20.01 g of 2-chloromethyl-3-(tri-O-benzyl- α -L-C-fucopyranoside)-1-propene (85%). MW=507, $[\alpha]_D$:
 30 -27.37, C=0.95 in CHCl_3 . A second product was obtained as a result of these conditions, that was the α -L-2,3,4-tri-O-benzylfucopyranose- α -L-2,3,4-tri-O-benzyl-fucopyranose.
 The product gave the following analytical data:

Reaction yield: 91%, mp=47-49°C. $^1\text{H-NMR}$ (CDCl_3) δ , 7.20-7.50(m, 15H, aromatics), 5.2 (d, $J=47.9$ Hz, 2H, terminal vinyl), 4.50-4.90 (complex multiplet, 6H, benzylic), 4.25 (p, 1H, H-1), 4.10 (s, 2H, $-\text{CH}_2\text{Cl}$), 3.90 (m, 1H), 3.75 (s, 1H), 2.50 (m, 2H), 1.25 (d, 3H). $^{13}\text{C-NMR}$ (CDCl_3) δ 142.68 alkene (e), 138.62 aromatic (e), 138.39 aromatic (e), 138.11 aromatic (e), 128.17 aromatic (o), 127.86 aromatic (o), 127.45 aromatic (o), 127.34 aromatic (o), 116.28 alkene (e), 76.58 (o), 75.95 (o), 73.24 (e), 72.97 (e), 68.33 (o), 48.23 $-\text{CH}_2\text{Cl}$ (e), 30.30 allylic (e), 15.38 fucose methyl (o). Mass Spec. (LSIMS with mNBA) 505.1/507.3. Analytical Calculated for $\text{C}_{31}\text{H}_{35}\text{ClO}_4$: C, 73.43; H, 6.96. Found: C, 73.16; H, 7.12.

b. 2-Chloromethyl-3-(tetra-O-benzyl- α -L-C-glucopyranocide)-1-propene

In another preferred embodiment, 1-O-acetyl-2,3,4,6-tetra-O-benzyl-D-glucopyranose was subjected to the same reaction conditions as have been described for L-fucopyranoside, resulting in the α -C-glycosides of glucose (3) (91%, mp=79-81°C), as reflected in the following scheme:



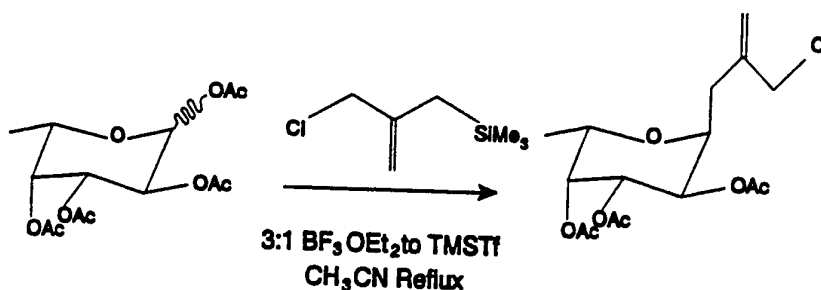
In general, the reagent ratios for the remaining per-O-acetylated carbohydrates were for example: 1,2,3,4,6-penta-O-acetyl-D-galactopyranoside (1.00 mmole equiv.) and 2-chloromethyl-3-trimethylsilyl-1-propene (2.00 mmole equiv.) were dissolved in acetonitrile (1.3M). Boron trifluoride etherate (2.00 mmole equiv.) and trimethylsilyltrifluoromethane sulfonate (0.40 mmole equiv.) were carefully added neat at room temperature. The reaction was refluxed for 6 hours and worked up as described. TLC 30% ethyl acetate in hexanes.

The glucose product (3) gave the following analytical data:

Reaction yield: 91%, mp=79-81°C. $^1\text{H-NMR}$ (CDCl_3) δ , 7.10-7.40 (20H), 5.1 (d, $J=41.3$ Hz, 2H, terminal vinyl), 4.96 (d, 10.87 Hz, 1H), 4.82 (d, 10.87 Hz, 1H), 4.82, (d, $J=10.56$ Hz, 1H), 4.63 (d, $J=12.15$ Hz, 1H), 4.44 (d, $J=12.15$ Hz, 1H), 4.45 (d, $J=10.56$ Hz, 1H), 4.67 (q, $J=11.6$ Hz, 2H), 4.24 (p, $J=5.07$ Hz, 1H, H-1), 4.12 (s, 2H), 3.68 (m, 6H, ring), 2.65 (m, 2H). $^{13}\text{C-NMR}$ (CDCl_3) δ 142.32 alkene (e), 138.68 (e), 138.08 (e), 137.93 (e), 128.5 (o), 128.0 (o), 127.8 (o), 127.5 (o), 116.95 alkene (e), 82.31 ring (o), 79.85 ring (o), 77.91 ring (o), 75.56 (e), 75.16 (e), 73.46 (e), 73.19 (e), 72.80 ring (o), 71.31 ring (o), 68.79 CH_2 ring (e), 48.15 CH_2Cl allylic (e), 27.98 allylic (e). Mass Spec. (LSIMS with mNBA and NaOAc) 635.2 (MNa^+). Analytical Calculated for $\text{C}_{38}\text{H}_{41}\text{ClO}_5$; C, 74.43; H, 6.74. Found: C, 74.62; H, 6.92.

c. 1-O-Acetyl-2,3,4,6-tetra-O-benzyl-D-galactopyranose

In another preferred embodiment, 1-O-acetyl-2,3,4,6-tetra-O-benzyl-D-galactopyranose was subjected to the same reaction conditions as have been described for L-fucopyranoside, resulting in the α -C-glycosides of galactose (4) (84%, oil), as reflected in the following scheme:



The product gave the following analytical data:

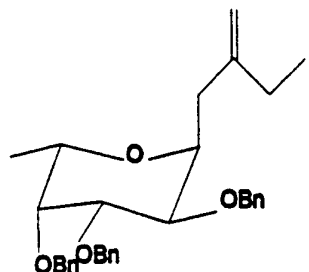
Reaction yield: 84%, and the compound isolated as an oil. $^1\text{H-NMR}$ (CDCl_3) δ , 7.25 (m, 20H), 5.16 (d, $J=37.54$ Hz,

2H), 4.85-4.50 (overlapping benzylic patterns, 6H), 4.26 (p, 3.85 Hz, 1H, H-1), 4.16 (s, 2H), 4.09 (m, 2H), 3.88 (m, 2H), 3.79 (dd, J=4.88 Hz, 1H), 2.59 (m, 2H). ¹³C-NMR (CDCL₃) δ 143.32 alkene (e), 139.21 (e), 139.09 (e), 138.90 (e), 138.83 (e), 128.5 (o), 128.0 (o), 127.8 (o), 127.5 (o), 117.22 alkene (e), 77.32 ring (o), 74.89 ring (o), 74.00 (e), 73.88 (e), 73.83 (e), 73.69 (e), 72.72 (o), 68.19 (e), 49.09 (e), 28.98 allylic (e). Mass Spec. (LSIMS with mNBA and NaOAc) 635.3 (MNa⁺). Analytical
10 Calculated for C₃₈H₄₁ClO₅: C, 74.43; H, 6.74. Found: C, 74.31; H, 6.87.

d. 2-Iodomethyl-3-(2,3,4-tri-O-benzyl-α-L-Cfucopyranoside)-1-propene

331g 2-chloromethyl-3-(tri-O-benzyl-α-L-C-fucopyranoside)-1-propene (653 mmole, 1 mmole equiv.) was
15 added to a stirred suspension of 480 g NaI (3222 mmole, 5 mmole equiv.) in 3 l acetone; the reaction was heated to reflux for 3 hours and then allowed to cool to room temperature. Completion of the reaction was monitored by
20 tlc assay. The tlc conditions used were 10% ethyl acetate in hexanes (v/v), the completion reaction was indicated when the product R_f was slightly higher than starting material. The reaction contents were poured into cold water and extracted with EtOAc. The organic layer was
25 washed twice with saturated cold sodium thiosulfate, saturated NaHCO₃, and with water. The product was dried over anhydrous sodium sulfate and filtered to remove the drying agent. The solvent was removed in vacuo which afforded a light yellow waxy solid. The product was
30 dissolved in THF and then concentrated in vacuo twice at low temperatures to remove any residual solvents not desired for the next step to afford 380g 2-Iodomethyl-3-(tri-O-benzyl-α-L-C-fucopyranoside)-1-propene (5) (97%). This material should be protected from heat and light, and
35 used immediately. A typical scale for this reaction: 331g starting material, resulting in a yield of 380 g product.

The product is reflected in the following scheme:



e. 2,3,4-Tri-O-benzyl- α -L-C-Fucopyranoside allyl bromide reagent

5 To a stirred suspension of 42.72 g LiBr (493 mmole, 5 mmole equiv.) in 197 ml THF 50.0 g 2-chloromethyl-3-(tri-O-benzyl- α -L-C-fucopyranoside)-1-propene (98.6 mmole, 1 mmole equiv.) was added and the reaction was heated to reflux for 3 hours, and then allowed to cool to room
10 temperature. The reaction was complete as assayed by TLC (product Rf slightly higher than starting material). The TLC conditions used were 10% ethyl acetate in hexanes (v/v). The reaction contents were concentrated to half of the original volume of THF, poured into cold water and
15 then extracted with EtOAc. The organic layer was washed twice with water, 1.0M HCl and again with water. The product was dried over anhydrous sodium sulfate and filtered to remove the drying agent. The solvent was removed in vacuo which afforded a light yellow solid. The
20 product was dissolved in methanol and then concentrated in vacuo at low temperatures twice to remove any residual solvents. The product was dissolved in 150 ml warm methanol and cooled to 0°C overnight. Filtration of the solids resulted in 40.8 grams as a white crystalline
25 solid. Concentration of the mother liquors to half of the original volume and again cooling to 0°C overnight gave an additional 10.87 grams of a white crystalline solid. Combined recovery yielded 51.67 g of 2-bromomethyl-3-

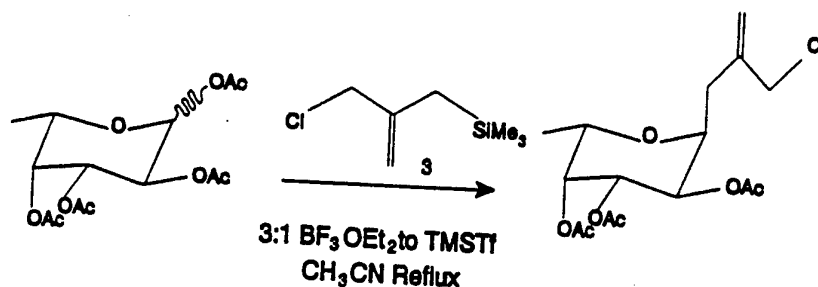
(2,3,4-tri-O-benzyl- α -L-C-fucopyranoside)-1-propene;
mp=51.5-53°C, (95%).

The product gave the following analytical data:

$^1\text{H-NMR}$ (CDCl_3) δ , 7.20-7.50 (m, 15H, aromatics), 5.2
5 (d, $J=61.5$ Hz, 2H, terminal vinyl), 4.50-4.90 (complex
multiplet, 6H, benzylic), 4.25 (p, $J=4.22$ Hz, 1H, H-1),
4.04 (d, $J=3.1$ Hz, 2H, $-\text{CH}_2\text{Br}$), 3.90 (m, 1H), 3.75 (s, 1H),
2.50 (m, 2H), 1.25 (d, 3H). $^{13}\text{C-NMR}$ (CDCl_3) δ 1423.11 alkene
(e), 138.77 aromatic (e), 138.53 aromatic (e), 138.26
10 aromatic (e), 128.17 aromatic (o), 127.86 aromatic (o),
127.45 aromatic (o), 127.34 aromatic (o), 117.00 alkene
(e), 76.69 (o), 76.16 (o), 73.46 (e), 73.11 (e), 69.9 (o),
68.46 (o), 37.03 $-\text{CH}_2\text{Br}$ (e), 30.54 allylic (e), 15.61
fucose methyl (o). Analytical Calculated for $\text{C}_{31}\text{H}_{35}\text{BrO}_4$: C,
15 67.51; H, 6.40. Found: C, 67.81; H, 6.56.

In general, the reagent ratios for the remaining per-
O-acetylated carbohydrates were for example: 1,2,3,4,6-
penta-O-acetyl-D-galactopyranoside (1.00 mmole equiv.) and
2-chloromethyl-3-trimethylsilyl-1-propene (2.00 mmole
20 equiv.) were dissolved in acetonitrile (1.3M). Boron
trifluoride etherate (2.00 mmole equiv.) and
trimethylsilyltrifluoromethane sulfonate (0.400 mmole
equiv.) were carefully added neat at room temperature.
The reaction was refluxed for 6 hours and worked up as
25 described. TLC 30% ethyl acetate in hexane.

3.2. The Carbon Glycoside Formation with Acetyl Protected Sugar



a. 2-Chloromethyl-3-(tri-O-acetyl- α -L-C-fucopyranoside)-1-propene:

50.0 g 1,2,3,4-tetra-O-acetyl-L-fucopyranose (5) (150.5 mmole, 1.00 mmole equiv.) and 36.7 g (40.9 ml) 2-chloromethyl-3-trimethylsilyl-1-propene (225.7 mmole, 2.00 mmole equiv.) were dissolved in 116 ml acetonitrile; subsequently, 74.8 g boron trifluoride etherate (526.8 mmole, 3.50 mmole equiv.) and 13.4 g (11.6 ml) trimethylsilyltrifluoromethane sulfonate (60.2 mmole, 0.40 mmole equiv.) were carefully added. After the addition of the Lewis acids (preferentially trimethylsilyltrifluoromethanesulfonate and boron trifluoride etherate), the reaction was slowly warmed to reflux and maintained at reflux for 6 hours. The reaction was terminated by cooling to room temperature, pouring the reaction contents on 100 ml of water, followed by extraction of the crude α -C-glycoside with ethyl acetate. The heterogeneous layers were separated and the organic phase was washed with portions of water, saturated sodium bicarbonate, 1.0 M hydrochloric acid and brine. The crude extract was dried over anhydrous sodium sulfate, filtered, and the solvent was removed in vacuo to afford an oil that was purified by column chromatography on Baker grade flash silica gel (47-61mm) (ratio of 20 to 1), eluted with 10% ethyl acetate in hexanes. Concentration in vacuo afforded 46.4 g of 2-chloromethyl-3-(2,3,4-tri-O-acetyl- α -L-C-fucopyranoside)-1-propene (85%, oil).

Under these reaction conditions, the 1,2,3,4-tetra-O-acetyl-L-fucopyranoside reaction mixture turned a dark brown to black color, tlc monitoring showed the transformation from starting material to the α -C-glycoside proceeded as expected. Two compounds, distinguishable by tlc, were isolated by column chromatography on silica gel by elution with 10% ethyl acetate in hexane. As determined by NMR analysis, the major compound was the 2,3,4-tri-O-acetyl- α -C-L-fucopyranoside (85%), a minor compound was a small amount of starting material, and the

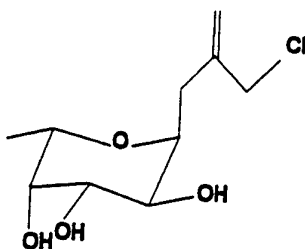
baseline material observed by tlc probably representing a third unidentified molecule.

The product gave the following analytical data:

Reaction yield: 85%, and the compound isolated as an oil. $^1\text{H-NMR}$ (CDCl_3) δ , 5.3 (m, 1H), 5.2 (m, 2H), 5.2 (s, 1H), 5.05 (s, 1H), 4.38 (m, $J=3.48$ Hz, 1H, H-1), 4.09 (s, 2H), 3.95 (dq, $J=1.71$ Hz and 4.70 Hz, 1H), 2.6 (dd, $J=11.39$ Hz, 1H), 2.4 (dd, $J=3.42$ Hz, 1H), 2.15 (s, 3H), 2.05 (s, 3H), 1.98 (s, 3H), 1.09 (d, $J=6.41$ Hz, 3H). $^{13}\text{C-NMR}$ (CDCl_3) δ 171.03 acetyl (e), 170.66 acetyl (e), 170.38 acetyl (e), 142.06 alkene (e), 117.72 alkene (e), 71.66 ring (o), 71.19 ring (o), 68.94 ring (o), 68.40 ring (o), 66.33 ring (o), 48.51 allylic (chloride side) (e), 29.50 allylic (e), 20.77 (o), 20.71 (o), 20.64 (o), 16.53 L-fucose methyl group (o). IR 2985, 1746, 1646 cm^{-1} . Mass Spec. (LSIMS with mNBA and NaOAc) 385.1 (MNa^+), 363.2 (MH^+). Analytical Calculated for $\text{C}_{16}\text{H}_{23}\text{ClO}_7$: C, 52.97; H, 6.39. Found: C, 52.66; H, 6.40.

Deprotection of Fucose:

The deprotection of the fucose reagent was done in methanol with a catalytic amount of sodium metal added to the stirring methanol. The reaction was terminated by the careful addition of 1.0M HCl until the pH was approximately 2. The solvent was removed *in vacuo*. The deprotected fucose derivative is reflected in the following schemes:

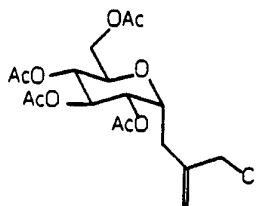


The product gave the following analytical data: The reaction was quantitative, mp=185-186-5°C. ¹H-NMR (CDCl₃) δ, 5.02 (d, J=42.8, 2H, terminal vinyl), 4.01 allylic -CH₂Cl (s, 2H), 3.89 (p, J=3.91 Hz, 1H, H-1), 3.69 (m, 2H, H-2 & 5), 3.45 (m, 2H, H-3 & 4), 2.36 (m, 2H, allylic), 0.97 (d, J=6.47 Hz, 3H). ¹³C-NMR (CD₃OD) δ 145.35 alkene (e), 117.18 alkene (e), 75.35 ring (o), 72.84 ring (o), 72.34 ring (o), 69.88 ring (o), 69.15 ring (o), 49.34 -CH₂Cl (e), 29.50 allylic (e), 17.05 L-fucose methyl (o). Mass Spec. (LSIMS with Gly) 237.1 (MH⁺). Analytical Calculated for C₁₀H₁₇ClO₄: C, 50.74; H, 7.24. Found: C, 50.63; H, 7.43.

b. 2-Chloromethyl-3-(tetra-O-acetyl-
α-L-C-glucopyranoside)1-propene

The reaction conditions used for the α-C-glycosidation of 1,2,3,4-tetra-O-acetyl-L-fucopyranoside were applied to 1,2,3,4,6-penta-O-acetyl-D-glucopyranose 14, 1,2,3,4,6-penta-O-acetyl-D-galactopyranose yielding the expected α-C-glycosides of α-C-glucose 17 (20%).

NMR analysis of the α-C-glycoside carbon shifts (CDCl₃) for the added C-3 unit in the acetyl protected sugars showed a chemical shift around δ 48 for the -CH₂Cl allylic carbon and δ 28 for the allylic carbon which forms the C-glycoside at the C-1 carbohydrate position, and the alkene shifts were around δ 142 and δ 117. The carbon shifts for the allylic chloride side chain in the benzylated sugars and in the acetyl protected sugars were comparable. The α-carbon glycoside derivated of glucose (6) is shown in the following scheme:



(6)

The product gave the following analytical data:

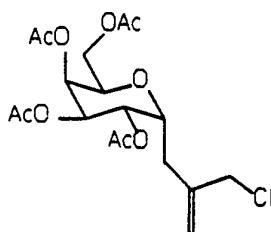
Reaction yield: 20%, and the compound isolated as an oil. ¹H-NMR (CDCl₃) δ, 5.26 (t, J=9.10 Hz, 1H, H-3), 5.10 (d, J=45.12 Hz, 2H, terminal vinyl), 5.02 (m, 1H, H-2), 5 4.90 (t, J=8.97 Hz, 1H, H-4), 4.33 (m, 1H, H-1), is 4.13 (dd, J=5.44 Hz, 1H, H-6), 3.98 (dd, J=2.62 Hz, 1H, H-6), 4.05 (s, 2H, -CH₂Cl), 3.86 (m, 1H, H-5), 2.61 (dd, J=11.54 Hz, 1H), 2.38 (dd, J=3.17 Hz, 1H), 1.99 (s, 3H, acetyl), 1.98 (s, 3H, acetyl), 1.96 (s, 3H, acetyl), 1.95 (s, 3H, 10 acetyl). ¹³C-NMR (CDCl₃) δ 172.03 acetyl (e), 171.54 acetyl (e), 171.04 acetyl (e), 170.99 acetyl (e), 142.33 alkene (e), 118.96 alkene (e), 72.55 ring (o), 71.57 ring (o), 71.43 ring (o), 70.49 ring (o), 70.13 ring (o), 63.63 C-6 ring (e), 49.29 CH₂Cl (e), 30.15 allylic (e), 22.11 acetyl 15 groups (o), 22.06 acetyl groups. IR 2958, 1729, 1646 cm⁻¹.

c. 2-Chloromethyl-3-tetra-O-acetyl-α-L-C-galactopyranoside)-1-propene

The reaction conditions used for the α-C-glycosidation of 1,2,3,4-tetra-O-acetyl-L-fucopyranoside were applied to 20 the 1,2,3,4,6-penta-O-acetyl-D-galactopyranose yielding the expected α-C-glycosides of α-C-galactose 18 (74%). 1,2,3,4,6-penta-O-Acetyl-D-galactopyranoside (1.00 mmole equiv.) and 2-chloromethyl-3-trimethylsilyl-1-propene (2.00 mmole equiv.) were dissolved in acetonitrile (1.3m). Boron 25 trifluoride etherate (2.00 mmole equiv.) and trimethylsilyltrifluoromethane sulfonate (0.40 mmole equiv.) were carefully added neat at room temperature. The reaction was refluxed for 6 hours and worked up as described; tlc: 30% ethyl acetate in hexanes.

30 NMR analysis of the α-C-glycoside carbon shifts (CDCl₃) for the added C-3 unit in the acetyl protected sugars showed a chemical shift around δ 48 for the -CH₂Cl allylic carbon and δ 28 for the allylic carbon which forms the C-glycoside at the C-1 carbohydrate position, and the alkene 35 shifts were around δ 142 and δ 117. The carbon shifts for the allylic chloride side chain in the benzylated sugars

and in the acetyl protected sugars were comparable. The α -carbon glycoside derivated of galactose (7) is shown in the following scheme:



(7)

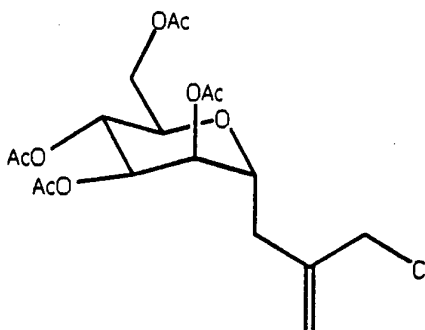
- 5 The product gave the following analytical data:
 Reaction yield: 74%, mp=80-82°C. $^1\text{H-NMR}$ (CDCl_3) δ ,
 5.31 (br, 1H), 5.16 (m, 2H), 5.05 (d, $J=47.17$ Hz, 2H,
 terminal vinyl), 4.33 (m, $J=3.54$, 1H, H-1), 4.1-3.9 (m,
 3H), 4.02 (s, 2H), 2.52 (dd, $J=11.41$, 1H), 2.28 (dd,
 10 $J=2.75$, 1H), 2.01 (s, 3H, acetyl), 1.98 (s, 3H, acetyl),
 1.91 (s, 6H, acetyl). $^{13}\text{C-NMR}$ (CDCl_3) δ 170.18 acetyl (e),
 169.81 acetyl (e), 169.67 acetyl (e), 169.53 acetyl (e),
 141.04 alkene (c), 117.17 alkene (e), 70.64 ring (o),
 68.09 ring (o), 67.79 ring (o), 67.55 ring (o), 67.42 ring
 15 (o), 62.32 C-6 ring (e), 47.65 $-\text{CH}_2\text{Cl}$ (e), 28.86 allylic
 (e), 20.53 acetyl group (o), 20.47 acetyl group (o), 20.41
 acetyl group (o). IR 2958, 1729, 1646 cm^{-1} . Mass Spec.
 (LSIMS with mNBA and NaOAc) 443.1 (MNa^+), 421.2 (MH^+).
 Analytical Calculated for $\text{C}_{18}\text{H}_{25}\text{ClO}_9$: C, 51.37; H, 5.99.
 20 Found: C, 51.47; H, 6.15.

d. 2-Chloromethyl-3-tetra-O-acetyl-
 α -L-Cmannosopyranoside)-1-propene

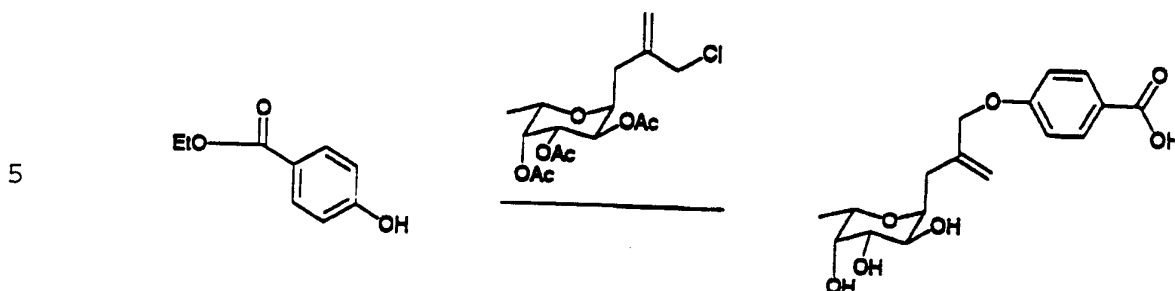
The reaction conditions used for the α -C-glycosida-
 tion of 1,2,3,4-tetra-O-acetyl-L-fucopyranoside were
 25 applied to 1,2,3,4,6-penta-O-acetyl-D-mannopyranose
 yielding the expected α -C-glycoside of α -C-mannose (80%).

NMR analysis of the α -C-glycoside carbon shifts (CDCl_3)
 for the added C-3 unit in the acetyl protected sugars

showed a chemical shift around δ 48 for the $-\text{CH}_2\text{Cl}$ allylic carbon and δ 28 for the allylic carbon which forms the C-glycoside at the C-1 carbohydrate position, and the alkene shifts were around δ 142 and δ 117. The carbon shifts for the allylic chloride side chain in the benzylated sugars and in the acetyl protected sugars were comparable. The α -carbon glycoside derivated of mannose (8) is shown in the following scheme:



- 10 The product gave the following analytical data:
 Reaction yield: 80%, (compound isolated as an oil).
 $^1\text{H-NMR}$ (CDCl_3) δ 5.13 (m, 3H), 5.12 (d, $J=41.76$ Hz, 2H, terminal vinyl), 4.20 (q, $J=6.41$ Hz, 1H, H-1), 4.05 (m, 2H), 4.04 (d, $J=1.65$ Hz, 2H), 3.85 (m, $J=2.69$ Hz, 1H),
 15 2.60 (dd, $J=10.32$ Hz, 1H), 2.39 (dd, $J=4.52$ Hz, 1H), 2.03 (s, 3H, acetyl), 1.98 (s, 3H, acetyl), 1.93 (s, 3H, acetyl). $^{13}\text{C-NMR}$ (CDCl_3) δ 170.28 acetyl (e), 169.89 acetyl (e), 169.66 acetyl (e), 169.37 acetyl (e), 140.43 alkene (e), 117.61 alkene (e), 73.06 ring (o), 70.52 ring (o), 70.07 ring (o), 68.47 ring (o), 66.52 ring (o), 62.04 CH_2 (e), 47.47 $-\text{CH}_2\text{Cl}$ (e), 31.95 allylic (e), 20.67 acetyl CH_3 (o), 20.50 acetyl CH_3 (o), 20.47 acetyl CH_3 (o), 20.43 acetyl CH_3 (o). IR 2958, 1729, 1646 cm^{-1} . Mass Spec. (LSIMS with mNBA and NaOAc) 443.0 (MNa^+), 421.3 (MH^+).

B. Example: Reaction Examples1. Reaction in Solution Phasea. Para-(C-2,3,4-tri-O-acetyl- α -C-L-fucopyranose)ethylbenzoate

To a stirred solution of 0.5 g para-hydroxy ethylbenzoate (3.01 mmole, 1.00 mmole equiv.) in 6.0 ml DMF 2.94 g cesium carbonate (9.03 mmole, 3.00 mmole equiv.) and 1.64 g C-fucoside reagent (4.52 mmole, 1.50 mmole equiv.) were added and the reaction was stirred at room temperature for 12 hours. The reaction was complete as assayed by tlc at 30% ethyl acetate in hexanes (v/v) as assay conditions. The reaction contents were diluted with ethyl acetate and then poured into cold water. The organic layer was washed twice with water and then brine, the product was dried over anhydrous sodium sulfate and filtered to remove the drying agent. The solvent was removed in vacuo which afforded a light yellow, waxy solid, that was chromatographed on Baker grade flash silica gel (47-61mm) (ratio of 20 to 1) and eluted with 5 or 10% ethyl acetate in hexaries. Concentration in vacuo afforded the product as a light yellow oil (1.33 g, 90%).

b. Para-(C-2,3,4-tri-O-hydroxyl- α -C-L-fucopyranose) methylbenzoate

25 To a solution of 1.0 g para-(C-tri-O-acetyl- α -C-L-fucopyranose) ethylbenzoate (2.03 mmole, 1.00 mmole equiv.) in 10 ml methanol, 3.31 g cesium carbonate (10.15

mmole, 5.00 mmole equiv.) and 5 ml water were added and the contents stirred for 48 hours. The reaction was quenched with 1.0 M HCl until the pH was approximately 1, and the product extracted with chloroform. The organic
5 layer was washed with water, the product dried over anhydrous sodium sulfate and filtered to remove the drying agent. The solvent was removed in vacuo which afforded a white solid. The white solid was the de-acetylated methyl ester (0.70 g, 97%).

10 c. Para-(C-2,3,4-tri-O-hydroxyl- α -C-L-fucopyranose) benzoic acid

To a solution of the 0.50 g methyl ester (1.42 mmole, 1.00 mmole equiv.) in 6 ml THF (6 mL), 1.19 g cesium hydroxide (7.10 mmole, 5.00 mmole equiv.) and 1 ml water
15 were added, and the reaction was stirred at room temperature for 12 hours, then quenched using 1.0 M HCl until the pH was approximately 1. The product was extracted with chloroform, dried over anhydrous sodium sulfate and filtered to remove the drying agent. The
20 solvent was removed in vacua which afforded white solid (0.432 g, 90%).

2. Alkylation and Deprotection on Solid Phase

The following is a preferred protocol for alkylation and deprotection of the carbohydrate reagent on a solid
25 support.

For alkylation, a para-methylene hydroxy resin (2.00 g, which contains 0.70 mmole alcohol per gram of resin, 1.40 mmole, 1.00 mmole equiv.) was placed in a flask. 25 ml DMF (0.06 M) was added and the resin/DMF mixture was
30 stirred for 1 hour, just enough to cover the resin after it swells. 0.387 g para-hydroxy benzoic acid (2.80 mmole, 2.00 mmole equiv.) was added to the stirring resin in a minimum of DMF, followed by addition of 1.89 g HOBT (14.0 mmole, 10.00 mmole equiv.), 0.171 g DMAP (1.40 mmole, 1.00
35 mmole equiv.) and 2.89 g DCC (14.0 mmole, 1000 mmole

equiv.). The reaction contents were stirred for an additional 4 hours at room temperature, subsequently the reaction was quenched by filtering off the resin on a sintered glass funnel (fine mesh) and washing the resin
5 with DMF, methanol, acetone, water, 1.0 M HCl, water, acetone and then ethyl acetate. The resin was allowed to air dry on the fritted funnel. Completion of the reaction was monitored by tlc assay, which did not show any remains of the starting materials. 2 grams of the derivatized
10 resin could be recovered.

For deprotection, 2.00 g derivatized resin (1.40 mmole, 1.00 mmole equiv.) was suspended in 20 ml DMF and gently stirred for 30 minutes. 1.02 g carbon-fucoside reagent (2.80 mmole, 2.00 mmole equiv.) was dissolved in
15 a minimum of DMF along with 1.03 g TBAI (2.80 mmole, 2.00 mmole equiv.), then added to the stirring resin. The reaction contents, turning to a brown color, were stirred at room temperature for 6 hours. Then the reaction was terminated by addition of 20 ml methanol with an
20 additional stirring of 2 hours. Completion of the reaction was monitored by tlc assay, which confirmed the formation of deacetylated methyl ester. Then 2.28 g cesium hydroxide (7.00 mmole, 5.00 mmole equiv.) in 10 ml water were added, and after 2 hours, the reaction quenched
25 with 1.0 M HCl until the pH was approximately 1. The resin was removed by filtering through a sintered glass funnel and the filtrate was collected and the solvents were removed *in vacuo*. The crude product was extracted with chloroform with the aid of small amounts of methanol,
30 and the extraction layer washed with water and the solvents were removed *in vacuo*. The product was the same as that produced earlier (0.280 g, 59% based on initial resin moles).

C. Example: Generation of Random Libraries with Constant Core Structure and Variation in Carbon Glycosides

In one specific embodiment of this invention, the core
5 structure remains constant, whereas the amounts/ratios and
classes of the carbon glycoside reagent(s) are varied.

For example, an aromatic core structure comprising a
single aromatic phenol is mixed with acetyl protected
fucoside and galactoside reagents in a 2 to 1 ratio,
10 respectively. The substrate is dissolved in DMF, followed
by the addition of a 2 to 5 mmole equivalent of cesium
carbonate and the two carbon glycoside reagents.
Statistically, an approximate ratio of equal amounts
fucoside and galactoside adducts can be expected. The
15 number of reaction products can simply be varied by the
use of a higher complexity of carbon glycosides, for
example three carbon glycoside reagents will account for
three products, or in general terms, x carbon glycosides
will account for x reaction products.

20 Further variation can be achieved by employing the
chemical reaction with substrates which contain more than
one aromatic phenol hydroxyl group. Mathematically, the
number of resulting adducts is then expected to be the
product of the number of reactive groups and the number of
25 different carbohydrate reagents used, and additionally,
the type and the ratio of carbohydrate reagents employed
will have influence on the result of the reaction. A
variation of the theme can be accomplished by the use of,
for example, carboxylic acids and unprotected carbon
30 glycoside reagents, further variation is achieved where
both the alpha and beta glycosides are used. Other
modifications will be obvious to those of the ordinary
skill in the art. This example is not intended to omit
other functionalities which could react with the carbon
35 glycoside reagent, such as, for example, thiols, amines,
phenols, carboxylates, carbohydrates, heparin derivatives,
polymeric species, etc.

The method described can be employed either with substrates attached to a solid phase support or, alternately, in solution phase.

5 D. Example: Generation of Random Libraries with Variation in the Core Structure and Constant Carbon Glycosides

This method retains a single carbohydrate reagent (alpha, beta or both) for the reaction and will vary the core structure used for the reaction.

10 A random library of peptides is created using a tyrosine, which has been pre-functionalized prior to a random library generation or, alternatively, appended to the library during generation or after the library generation. Employing solid phase or solution
15 methodologies, di-amino acid libraries may be generated using any one of the 20 natural amino acids or other (unnatural) D-, and L- amino acids. The tyrosine is derivatized with the carbon glycoside at the phenolic hydroxyl and attached to a solid support, followed by
20 attachment of the second amino acid. Further variation is achieved in the cases where both the alpha and beta glycosides are employed.

25 E. Example: Generation of Random Libraries with Variation in the Core Structure and Variation in the Carbon Glycoside

This method can be a combination of methods 1 and 2 above. This method generates a large and highly randomized library. Again, the use of both the alpha and beta glycosides further expands the number of variations.

30 F. Example: Generation of Compounds:
 General Reaction and General Experimental Procedures:

The skilled artisan will appreciate and understand the following general experimentals as they are used in the art to prepare novel compounds from the invention. The

mmole equivalent refers to the reaction substrate to be functionalized by the reaction with the carbon glycoside reagent per position to be alkylated. Additional functional group transformations can be accomplished by the skilled artisan using standard reaction conditions. For example, the transformation of allylic halides into allylic amines can be via the allylic azide with reduction of the azide to the amine with triphenyl-phosphine in water. The amine is then available for amide bond formation.

Alkylation conditions using Sodium Hydride and an Aliphatic Alcohol

To a mechanically stirred solution of sodium hydride (3.00 mmole equiv. Note: the sodium hydride is washed three times with hexanes prior to use.) in THF (slurry) at ambient temperature is added an aliphatic alcohol (1.00 mmole equiv.) dropwise in a minimum amount of anhydrous tetrahydrofuran. The tributylammonium iodide (0.10 mmole equiv.) is added and the reaction contents are stirred at room temperature (slight warming to above room temperature is sometimes needed for the initiation of the reaction) for 60 minutes in order to minimize the rate of gas evolution. The reaction contents are warmed for a period of 2 hours; carefully watching for the evolution of hydrogen. The reaction contents are stirred using a mechanical stirrer while being gently refluxed for a period of 1.5 hours. A benzyl protected carbon glycoside reagent (1.50 mmole equiv.) is slowly added dropwise in anhydrous tetrahydrofuran (total reaction concentration of 0.2 to 0.5 M) over a period of 1-2 hours and stirred for 4 hours. [An aliquot of the reaction contents is removed and quenched into 1.0M HCl and extracted with ethyl acetate; the tlc conditions used are 5% methanol in chloroform (v/v).] The reaction is then diluted with toluene and terminated by the careful addition of 50% methanol in toluene at 0°C to consume the residual sodium hydride, followed by acidification of 1.0M hydrochloric

acid until the pH is ~2. The reaction contents are diluted with ethyl acetate. The heterogeneous layers are separated and the organic phase is washed twice with portions of 1.0M hydrochloric acid, saturated sodium
5 thiosulfate and brine. The product can be purified by column chromatography using Baker grade flash silica gel (47-61 mm) and a suitable solvent system. For example, 10% ethyl acetate in hexanes and then with 30% ethyl acetate in hexanes. The silica gel is eluted with
10 methanol and checked by tlc for any product material. The solvents are removed *in vacuo* and the product dried under vacuum. The desired product is recovered.

General alkylation conditions using Cesium Carbonate as a mild base for the alkylation of thiols, amines, carboxylic acids and the like
15

To a stirred solution of thiols, phenols, amines, carboxylic acids and the like (1.00 mmole equiv.) in DMF or acetone (0.5M) is added cesium carbonate (3.00 mmole equiv.) and the Carbon-glycoside reagent (1.50 mmole
20 equiv.). The reaction is stirred at room temperature for 12 hours and the reaction is assayed by tlc. The tlc conditions used are 30% ethyl acetate in hexanes (v/v). The reaction contents are diluted with ethyl acetate and then poured into cold water. The organic layer is washed
25 twice with water and then brine. The product is dried over anhydrous sodium sulfate and filtered to remove the drying agent. The solvent is removed *in vacuo*. The product can be purified by column chromatography using Baker grade flash silica gel (47-61mm) and a suitable
30 solvent system. For example, 10% ethyl acetate in hexanes and then with 30% ethyl acetate in hexanes. The silica gel is eluted with methanol and checked by tlc for any product material. The solvents are removed *in vacuo* and the product dried under vacuum. The desired product is
35 recovered.

Removal of the acetyl protecting groups from the acetylated carbon glycosides

To a solution of the acetyl protected compounds (1.00 mmole equiv.) in methanol (0.5M) is added cesium carbonate
5 or sodium methoxide (5.00 mmole equiv.) and water (catalytic) and the contents stirred for 48 hours. The reaction is quenched with 1.0M HCl until the pH is approximately 1. The product is extracted with an appropriate extraction solvent such as chloroform and the
10 organic layer is washed with water. The product is dried over anhydrous sodium sulfate and filtered to remove the drying agent. The product can be purified by column chromatography using Baker grade flash silica gel (47-61mm) and a suitable solvent system. For example, 10%
15 ethyl acetate in hexanes and then with 30% ethyl acetate in hexanes. The silica gel is eluted with methanol and checked by tlc for any product material. The solvents are removed *in vacuo* and the product dried under vacuum. The desired product is recovered.

20 Example: Alkylation on Resin. This specific example serves as a general example for similar compounds. A para-methylene hydroxy resin (2.00 g, which contains 0.70 mmole alcohol per gram of resin, 1.40 mmole, 1.00 mmole equiv.) is placed in a flask and 25 mL of DMF is added
25 (0.06M) and the resin in DMF is stirred for 1 hour (this is just enough to cover the resin after it swells). para-Hydroxy benzoic acid (0.387 g, 2.80 mmole, 2.00 mmole equiv.) is added in a minimum of DMF to the stirring. The reaction contents are stirred for 4 hours are room
30 temperature. The reaction is quenched by filtering off the resin on a sintered glass funnel (fine mesh) and washing the resin with DMF, methanol, acetone, water, 1.0M HCl, water, acetone and then ethyl acetate. The resin is allowed to air dry on the fritted funnel. Removing a
35 small sample of the resin and suspending it in methanol and checking the suspension by tlc did not show any of the

starting materials. Recovery is 2 grams of the derivatized resin.

The derivatized resin (2.00 g, 1.40 mmole, 1.00 mmole equiv.) is suspended in DMF (20 mL) and gently stirred for 5 30 minutes. The carbon-fucoside reagent (1.02g, 2.80 mmole, 2.00 mmole equiv.) is dissolved in a minimum of DMF along with TBAI (1.03 g, 2.80 mmole, 2.00 mmole equiv.) and added to the stirring resin. The reaction contents turned a brown color. The reaction contents are stirred 10 at room temperature for 6 hours. The reaction is terminated by the addition of methanol (20 mL) with an additional stirring of 2 hours. TLC indicated that the de-acetylated methyl ester is formed. Then cesium hydroxide (2.28 g, 7.00 mmole, 5.00 mmole equiv.) is added 15 in 10 mL of water. After 2 hours, the reaction is quenched with 1.0 M HCl until the pH is approximately 1. The resin is removed by filtering through a sintered glass funnel and the filtrate is collected and then solvents are removed *in vacuo*. The crude product is extracted with 20 chloroform with the aid of small amounts of methanol. The extraction layer is washed with water and the solvents are removed *in vacuo*. The product is the same as that produced earlier (0.280 g, 59% based on initial resin mmoles).

25 Bishydroxylation of the olefin via Oxidation with osmium tetroxide. To a stirred solution of the olefin, (1.00 mmole equiv.) in 1% water in acetone (0.5M) at 0°C is added osmium tetroxide pre-dissolved in acetone (0.01 mmole equiv.) and N-methylmorpholine-N-oxide (2.00 mmole 30 equiv.) is carefully added as a solid. The reaction contents are stirred at 0°C and the cooling bath (water/ice) is allowed to melt. The reaction is allowed to stir at ambient temperature for 18 hours or until the reaction is complete via analysis by tlc. The reaction 35 can be assayed by TLC or an aliquot of the reaction acetate. The aliquot is checked by ¹H-NMR in CDCl₃. The

reaction is terminated by the careful addition of sodium bisulfite (contains a mixture of NaHSO_3 and $\text{Na}_2\text{S}_2\text{O}_5$), stirred for 1 hour at room temperature and then water. An extraction solvent such as chloroform is added and the
5 heterogeneous layers are separated and the organic phase is washed with 1.0M hydrochloric acid, water and brine. The washed product is dried over anhydrous sodium sulfate and filtered. The product can be purified by column chromatography using Baker grade flash silica gel (47-
10 61mm) and a suitable solvent system. For example, 10% ethyl acetate in hexanes and then with 30% ethyl acetate in hexanes. The silica gel is eluted with methanol and checked by tlc for any product material. The solvents are removed *in vacuo* and the product dried under vacuum the
15 desired product is recovered.

Oxidation of the alkene to the ketone via catalytic oxidation with osmium tetroxide sodium periodate. To a stirred solution of the olefin, (1.00 mmole equiv.) in 1% water in acetone (0.5M) at 0°C is added osmium tetroxide
20 predissolved in acetone (0.01 mmole equiv.) and sodium periodate (2.00 mmole equiv.) is carefully added as a solid. The reaction contents are stirred at 0°C and the cooling bath (water/ice) is allowed to melt and the reaction allowed to stir at ambient temperature for 18
25 hours or until the reaction is complete via analysis by tlc. The reaction can be assayed by TLC or an aliquot of the reaction contents is removed, quenched into aqueous sodium metasilicate and extracted with ethyl acetate. The aliquot is checked by $^1\text{H-NMR}$ in CDCl_3 . The reaction is
30 terminated by the careful addition of sodium bisulfite (contains a mixture of NaHSO_3 and $\text{Na}_2\text{S}_2\text{O}_5$), stirred for 1 hour at room temperature and then water. An extraction solvent such as chloroform is added, followed by hydrochloric acid, water and brine. The washed product is
35 dried over anhydrous sodium sulfate and filtered. The product can be purified by column chromatography using

Baker grade flash silica gel (47-61mm) and a suitable solvent system. For example, 10% ethyl acetate in hexanes and then with 30% ethyl acetate in hexanes. The silica gel is eluted with methanol and checked by tlc for any product material. The solvents are removed *in vacuo* and the product dried under vacuum. The desired product is recovered.

Catalytic hydrogenation for the removal of benzyl protecting groups. For a compound containing benzyl protecting groups, 1.00 mmole equiv. is dissolved in an appropriate hydrogenation solvent suitable for the compound to be deprotected. For example, the solvent could be methanol with a catalytic amount of acetic acid or ethyl acetate and methanol 5% or 10% palladium on carbon (1 g for every 50 grams of starting material with the catalyst wetted with 50-100 mL of toluene under argon) is evacuated and hydrogen gas is added and the process repeated three times. The reaction is shaken or stirred for several hours until the deprotection is complete. The reaction is terminated by filtering the contents through Celite to remove the catalyst and the catalyst is washed with 30% methanol in chloroform. Concentration *in vacuo* afforded the desired compound. The product can be purified by column chromatography using Baker grade fresh silica gel (47-61mm) and a suitable solvent system. For example, 10% ethyl acetate in hexanes and then with 30% ethyl acetate in hexanes. The silica gel is eluted with methanol and checked by tlc for any product material. The solvents are removed *in vacuo* and the product dried under vacuum. The desired product is recovered.

Sulfation of hydroxyl functionalities. To a solution of the alcohol(s) groups to be sulfated from the products of the invention (1.00 mmole equiv.) in anhydrous dimethylformamide (0.2M) at ambient temperature was added sulfur trioxide pyridine complex of the sulfur trioxide pyridine complex polymer bound [Graf, W. chem. Ind. 1987, 232] (10 mmole equiv.). The reaction contents were

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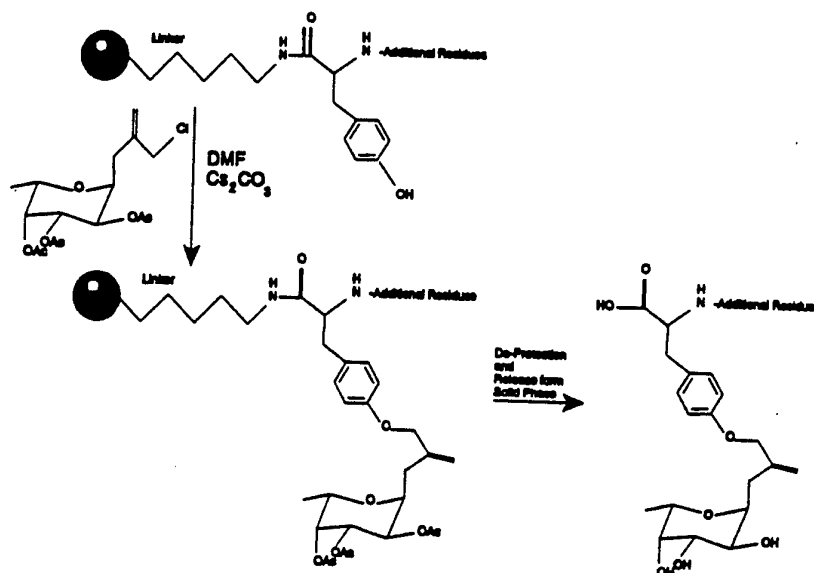
stirred at ambient temperature for 8 hours. The reaction was quenched using sodium carbonate and removing the solvents by lyophilization and the resulting material was subjected to sodium ion exchange resin for the exchange of residual ionic salts for sodium ions. Concentration *in vacuo* affords the sulfated materials.

The experimental procedures described can be applied to make and modify the following exemplified novel products (Example G, H, I, J, K, L, O, P, Q, R, S, T, U).

10 G. Example: Generation of New Peptide Libraries

The reaction of carbon-glycosides with peptides, in this preferred embodiment with the hydroxy-group of tyrosine can be employed for the generation of novel peptide libraries.

15

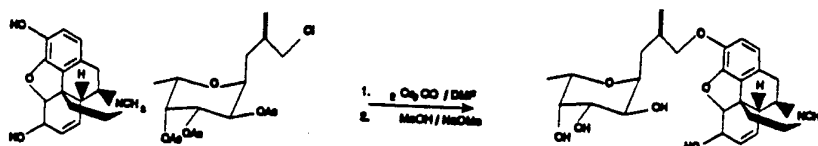


The reagent(s) can be attached to the peptide at nearly any stage of the synthesis, e.g. the reagent can be added during or after the peptide's synthesis using general procedures for aromatic systems, or, alternatively as being attached to a premodified amino acid.

H. Example: Modification of Natural Products

Reaction with carbon glycosides can be used for the generation of novel compounds by modification of aromatic systems of known pharmaceutically active compounds.

5



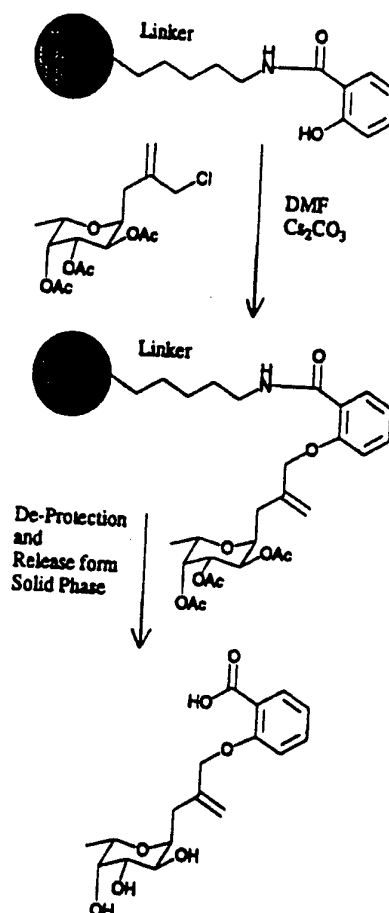
The alkylation of the aromatic hydroxyl was performed under the same reaction conditions as generally employed for alkylations, which can be found, among other places, in R.C. Larock, *Comprehensive Organic Transformations*, ISBN 0-89573-710-8, 1989, VCH Publishers, Inc. 220 East 23rd Street, Suite 909, New York, NY 10010. Alkylation at the allylic alcohol can be achieved by protecting the aromatic hydroxyl group, followed by alkylation of the allylic alcohol. Protection of aromatic hydroxyl group is referenced in Green, *supra*.

I. Example: Generation of New Aromatic Systems

Reaction of aromatic molecules with carbon glycosides under suitable conditions can be used for the generation of novel aromatic molecules, as it is exemplified in the following scheme:

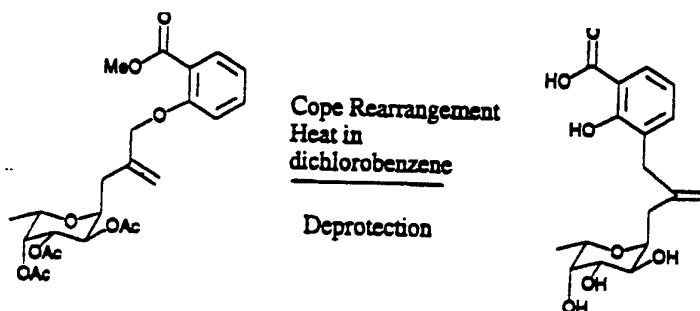
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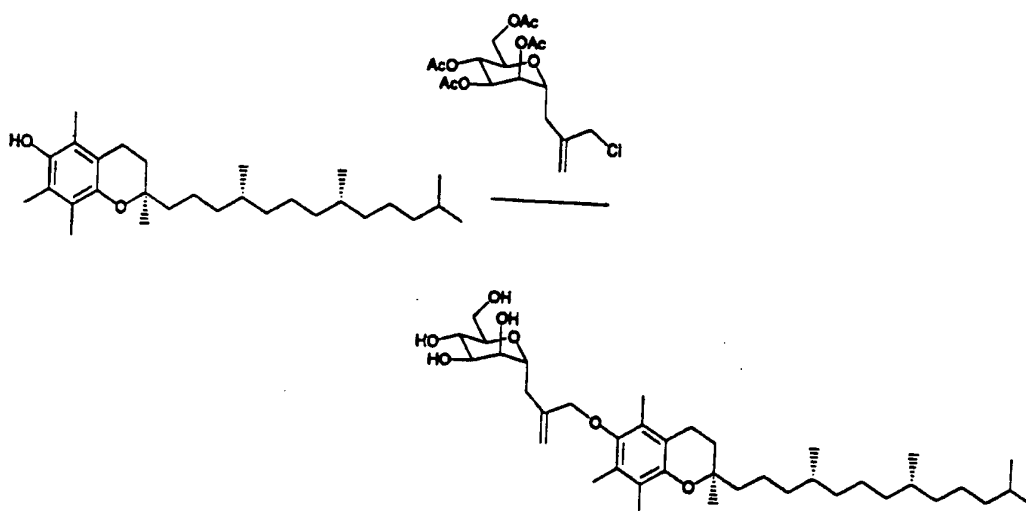
J. Example: Modification of Aromatic Systems

In another preferred embodiment, the aromatic hydroxyl group of methyl salicylate is alkylated under standard conditions. The Cope rearrangement can be performed in 1,2-dichlorobenzene at 180-220°C. These are typical conditions employed by one skilled in the art, resulting in novel compounds of the invention. See, "Organic Syntheses Based on Named Reactions and Unnamed Reactions",
 10 Tetrahedron Organic Chemistry Series, eds. Baldwin and Magnus, Pergamon, Great Britain.



K. Example: Derivatization of Natural Products

In another preferred embodiment, novel structural analogues of Vitamin E and other natural products are synthesized by reaction with carbon glycosides. Shown here is an example using an mannose-derived carbon glycoside reagent.



2.34 g carbon mannoside reagent (5.57 mmole, 1.20 mmole equiv.), 3.43 g tetra-butyl ammonium iodide (9.28 mmole, 2.00 mmole equiv.), and finally 3.02 g cesium carbonate (9.28 mmole, 2.00 mmole equiv.) were added to a solution of 2.00 g Vitamin E (4.64 mmole, 1.00 mmole equiv.) in 9 ml DMF (0.5 M). The reaction contents, which turned brown upon addition of the reagents, were protected from light and stirred at room temperature for 12 hours. Completion of the reaction was monitored by tlc assay (condition: 30% ethyl acetate in hexanes (v/v)). The reaction contents were diluted with ethyl acetate, then poured into cold water; the organic layer was washed twice with water, thrice with 1.0 M HCl and once with brine. The product was dried over anhydrous sodium sulfate and filtered to remove the drying agent. The solvent was removed in vacuo affording a light brown oil which was chromatographed on Baker grade flash silica gel (47-62mm) (ratio of 20 to 1) and eluted with 10% ethyl acetate in

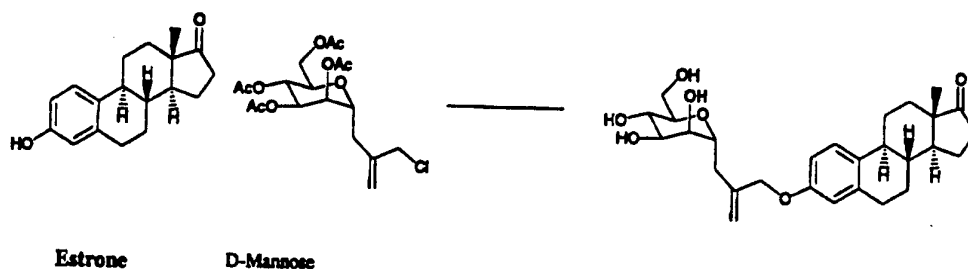
hexanes, followed by 30% ethyl acetate in hexanes. Concentration *in vacuo* afforded the product as a light yellow oil (3.14 g, 83 %).

Vitamin E Derivate Deprotection:

5 To a solution of 2.00 g derivatized Vitamin E (2.45 mmole, 2.00 mmole equiv.) in 245 ml methanol (0.01 M), 1.60 g cesium carbonate (4.90 mmole, 2.00 mmole equiv.) was added and the contents stirred for 12 hours. The reaction was quenched with 1.0 M HCl until the pH was
10 approximately 1, then the product is extracted with chloroform and the organic layer was washed with water. The product was dried over anhydrous sodium sulfate and filtered to remove the drying agent. The solvent was removed *in vacuo* which afforded 1.44 grams (91%) of the
15 deacetylated product.

L. Example: Generation of Estrone Derivatives

In another preferred embodiment, novel structural analogues of estrone and other natural products are synthesized by reaction with carbon glycosides. Shown
20 here is an example using an mannose-derived carbon glycoside reagent.



2.34 g carbon mannoside reagent (5.57 mmole, 1.20 mmole equiv.), 3.43 g tetrabutyl ammonium iodide (9.28 mmole, 2.00 mmole equiv.), and finally 3.02 g cesium carbonate (9.28 mmole, 2.00 mmole equiv.) were added to a
25 solution of 1.25 g estrone (4.64 mmole, 1.00 mmole equiv.)

in 9 ml DMF (0.5 M). The reaction contents, which turned brown upon addition of the reagents, were protected from light. The reaction was complete after stirring at room temperature for 12 hours, as confirmed by tlc assay (condition: 30% ethyl acetate in hexanes (v/v)). The reaction contents were diluted with ethyl acetate, then poured into cold water; the organic layer was washed twice with water, thrice with 1.0 M HCl and finally once with brine. The product was dried over anhydrous sodium sulfate and filtered to remove the drying agent. Finally, the solvent was removed in vacuo which afforded a light brown oil which was chromatographed on Baker grade flash silica gel (47-61mm) (ratio of 20 to 1) and eluted with 30% ethyl acetate in hexanes. In vacuo concentration afforded the product as a light yellow oil (3.0 g, 98%).

Estrone Derivative Deprotection:

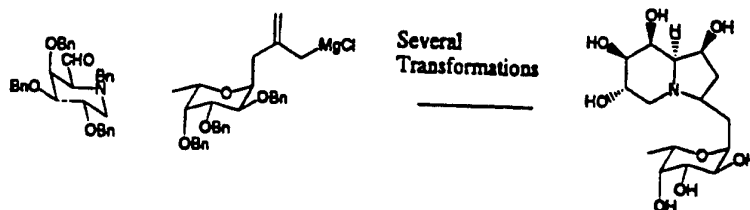
1.89 g cesium carbonate (5.80 mmole, 2.00 mmole equiv.) was added to a solution of 1.90 g derivatized Estrone (2.90 mmole, 1.00 mmole equiv.) in 200 ml methanol (0.01 M) and the contents stirred for 12 hours. The reaction was quenched with 1.0 M HCl until the pH was approximately 1, the product extracted with chloroform and the organic layer was washed with water. After drying over anhydrous sodium sulfate the product was filtered to remove the drying agent. Finally, the solvent was removed in vacuo which afforded 1.26 grams deacetylated product (89%). Analytical calculated for $C_{28}H_{38}O_7$: C, 69, 11; H, 7.87. Found: C, 68.93; H, 8.08.

M. Example: Generation of Castanospermine Derivative

Derivatives of castanospermidine were prepared as essentially described in Hamana et al., 1988, J. Amer. Chem. Soc. 110:312-313. Briefly, Grignard reagent of benzylated fucose (see, item 3.1.a) is prepared under standard synthetic conditions using magnesium turnings. This reaction provides a novel Grignard Reagent suitable

for reacting with, for example, aldehydes, ketons, esters, etc. In contrast to the chemistry described in this reference, castanosperinidine was prepared using Grignard instead of allyl Grignard, employing similar chemistry.

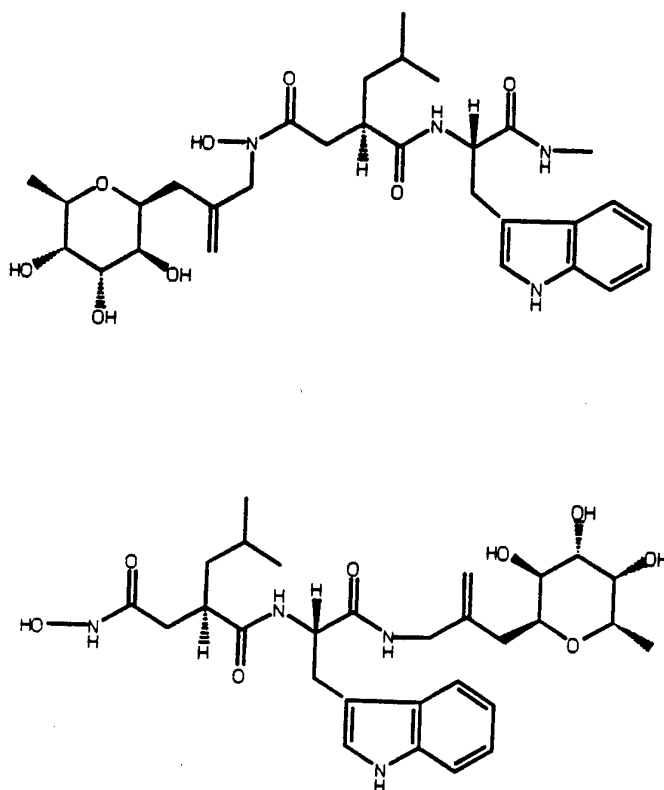
5



N. Modification of Peptides/Peptide Libraries

In another preferred embodiment, derivatives of matrix metallo protease inhibitors (MMPI) have been generated by reaction with carbonglycosides.

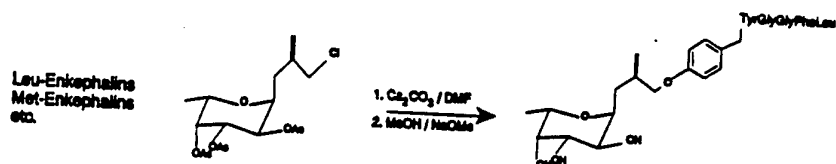
10



O. Example: Modification of Peptide-Libraries

An array of structural analogues of existing peptides and peptide libraries may be synthesized by modification with carbon glycosides.

5



For experimental procedures and conditions, see, item F.

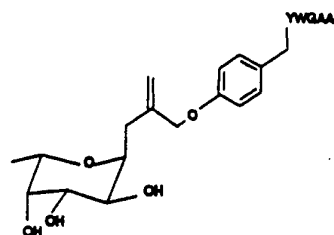
P. Example: Generation of Random Peptide Libraries

Random peptide libraries comprising an array of randomly modified peptides are generated by reaction of amino acid residues at different positions with carbon glycosides.

10

YWGAAl
YXGAAl
YWXAAl
YWGXAAl
YWGAXI
YWGAAX

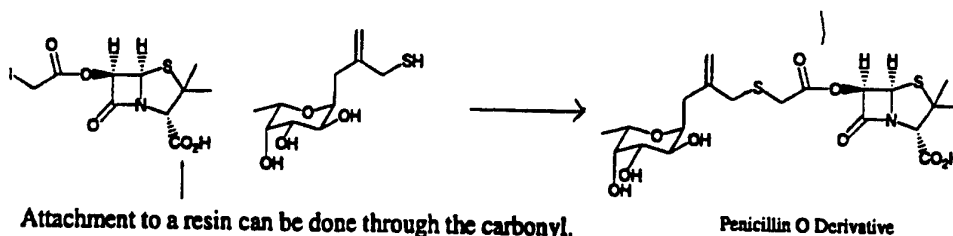
Wherein
X = Modified
with glycoside.



For experimental procedures and conditions, see, item F.

Q. Example: Modification of Antibiotics

Improved derivatives of antibiotics, as for example
5 penicillin O, are generated by reaction with carbon
glycosides.



The thiol compound can be prepared from the allylic
chloride carbon glycoside reagent and sodium sulfide. A
10 general reference on functional group transformations can
be found, among other places, in R. C. Larock, Comprehen-
sive Organic Transformations, ISBN 0-89573-710-8, 1989,
VCH Publishers, Inc. 220 East 23rd Street, Suite 909, New
York, NY 10010.

15 R. Example: Transformation of Organic
Molecules by Multistep Reaction with Carbon
Glycosides

Multistep reaction with carbon glycosides allows the
generation of an infinite array of novel organic
20 compounds.

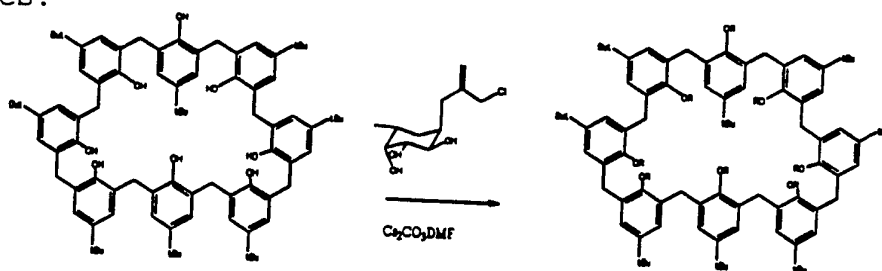
A general reference on applicable transformations can
be found, among other places, in Hamana, et al., 1988 J.
Amer. Chem. Soc., 110:312-31.

Generally, the formation of Grignards can be found,
25 among other places, in R.C. Larock, Comprehensive Organic
Transformations, ISBN 0-89573-710-8, 1989, VCH Publishers,
Inc. 220 East 23rd Street, Suite 909, New York, NY 10010.

S. Example: Fucoidan Mimics (4-tetra-Butylcalix[8]arene)

In another preferred embodiment, derivatives of fucoidans are generated by reaction with carbon

5 glycosides:



Where at least one R is a carbon glycoside.

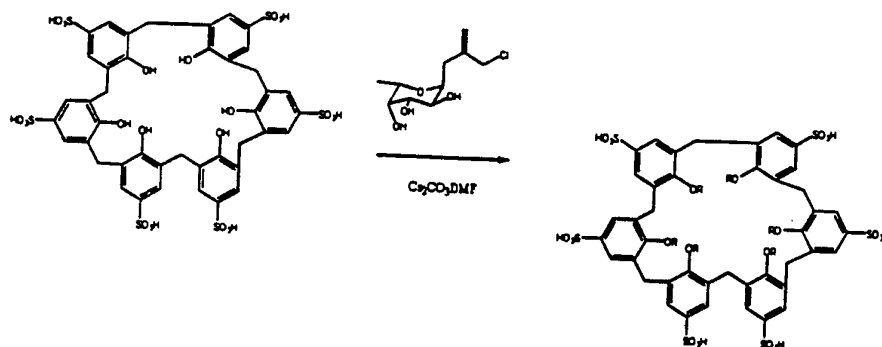
For experimental procedures and conditions, see, item F.

T. Example: Fucoidan Mimics (4-Sulfonic calix[6]arene)

10

In another preferred embodiment, derivatives of fucoidans are generated by reaction with carbon

glycosides:



15

Where at least one R is a carbon glycoside.

For experimental procedures and conditions, see, item

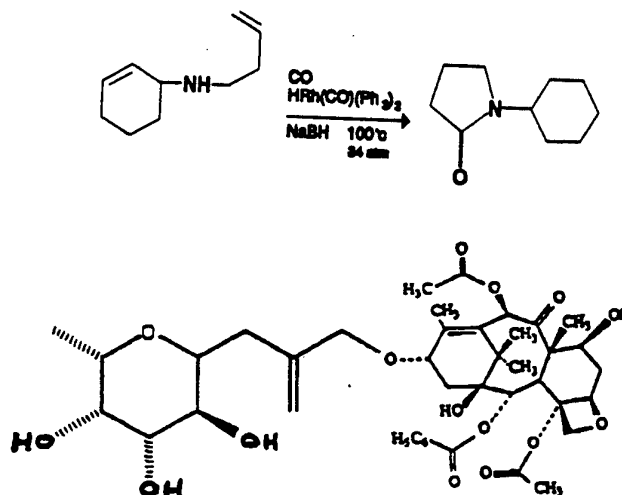
F.

U. Example: Modification of Natural Products

Derivates of natural products are generated by

20 modification with carbon glycosides:

110



The present invention is not to be limited in scope by the exemplified embodiments which are intended as illustrations of single aspects of the invention, and any
5 chemical compound or method which are equivalent are within the scope of the invention. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and the
10 accompanying reaction schemes. Such modifications are intended to fall within the scope of the appended claims.

All references cited herein are hereby incorporated by reference in their entirety.

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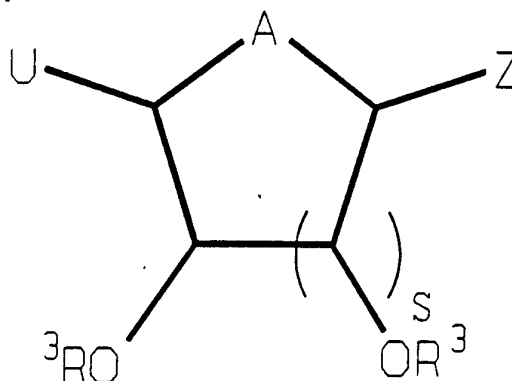
CLAIMSWHAT IS CLAIMED IS:

1. A compound comprising the formula:
5 $(X)_m - Z$
wherein:
X is a carbohydrate unit or modified carbohydrate unit;
Z is an activated functional group attached, via a
10 spacer/linker unit containing at least one carbon atom, to
an X at the anomeric position which is carbon;
m is a positive integer, preferably between 1-100.
2. The compound of Claim 1 wherein m is 1.
3. The compound of Claim 1 wherein m is in the range
15 between 2 and 14.
4. The compound of Claim 1 wherein m is greater 15.
5. The compound of Claim 1 wherein X is a five or a
six membered ring.
6. The compound of Claim 1 wherein $(X)_m$ has a
20 molecular weight of less than 400.
7. The compound of Claim 1 wherein $(X)_m$ has a
molecular weight in the range between 400 and 40,000.
8. The compound of Claim 1 wherein $(X)_m$ has a
molecular weight of more than 40,000.
- 25 9. The compound of Claim 1 wherein Z is selected
from the group consisting of $-\text{CH}_2(\text{C}=\text{CH}_2)\text{CH}_2\text{T}$, $-\text{CH}_2(\text{C}=\text{O})\text{CH}_2\text{T}$,
 $=\text{C}=\text{CHCH}_2\text{T}$, $-\text{ArCH}_2\text{T}$, and T is selected from the group
consisting of ONa, OK, NH_2 , SH, $\text{S}(\text{O})\text{H}$, SO_3H , $\text{P}(\text{O})\text{OEt}_2$, CO_2H ,

112

O-C(NH)CCl₃, OH, NH₂, N₃, SH, SQ Ph, Cl, Br, I, OMs, OTf, OTs, OAc, O-C(NH)CCl₃.

10. A chemical compound having the formula:



5 wherein:

Z is -CH₂WCH₂T, -CCCH₂T, =C=CHCH₂T, -ArCH₂T, -ArV, or - (CH₂)_nV;

W is C=O, C=CR₂¹, CR¹CR₃¹, CR¹-CR₂¹OR¹, COR¹-CR₂¹OR¹, CR₂¹, CR₂²-CR₂³OR³, or CR₂²-CR₂²R₂¹;

10 T is O-M¹, M², SR¹, S(O)R¹, SO₂R¹, P(O)OR₂¹, COD, OC(NH)CCl₃, or NR₂¹;

V is O-M¹, SR¹, S(O)R¹, SO₂R¹, P(O)OR₂¹, COD, NR₂¹;

n is a positive integer, preferably between 1-10;

M¹ is a Na⁺, K⁺, Mg⁺⁺, Cu⁺, or Cu⁺⁺ ion;

15 M² is a Li⁺, Mg⁺⁺, Ca⁺⁺ ion;

R¹ is H, CH₃, or lower alkyl;

R₂² is OR¹, NR₂¹, or SR¹;

R₃³ is R¹, protecting group, SO₃M¹, C-carbohydrate (linear or branched) or O-carbohydrate (linear or
20 branched);

s is 1, 2, or 3;

Protecting Groups include methyl-, benzyl-, MOM, MEM, MPM, and tBDMS;

U is CH₂OR¹, CH₂O-protecting group, CH₂OSO₃M¹,
25 CH₂SO₃M¹, CH₂OR₃³, or COD;

A is O, S, NR₂¹CR₂¹, or NR¹;

D is OR¹, NR₂¹, or O-M¹; and

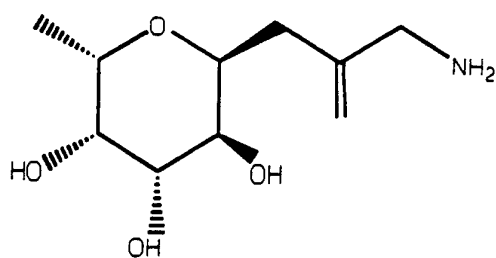
Lower Alkyl is C₁ to C₁₀, branched or unbranched; or

- Z is $\text{CH}_2\text{-W-CH}_2\text{E}$, $\text{-CCCH}_2\text{E}$, $\text{=C=CH}_2\text{E}$, $\text{-ArCH}_2\text{E}$, -ArE , ArG , or $\text{-(CH}_2\text{)}_n\text{G}$;
- W is C=O , C=CR_2^1 , CR^1CR_3^1 , $\text{CR}^1\text{-CR}_2^1\text{OR}^1$, $\text{COR}^1\text{-CR}_2^1\text{OR}^1$, CR_2^1 , $\text{CR}^2\text{-CR}_2^2\text{OR}^3$, or $\text{CR}^2\text{-CR}^2\text{R}_2^1$;
- 5 E is OH, Cl, Br, I, OMs, OTf, OTs, OAc, or OC(NH)CCl_3 ;
- G is OH, Cl, Br, I, OMs, OTf, OTs, OAc, or COD;
- n is a positive integer, preferably between 1-10;
- M^1 is a Na^+ , K^+ , Mg^{++} , or Ca^{++} ion;
- 10 R^1 is H, or lower alkyl;
- R^2 is OR^1 , NR_2^1 , or SR^1 ;
- R^3 is R^1 , protecting group, SO_3M^1 , C-carbohydrate (linear or branched) or O-carbohydrate (linear or branched);
- 15 s is 1, 2, or 3;
- Protecting Groups include methyl-, benzyl-, benzoyl-, acetyl-, MOM, MEM, MPM, tBDMS, and TMS;
- U is CH_2OR^1 , $\text{CH}_2\text{O-protecting group}$, $\text{CH}_2\text{OSO}_3\text{M}^1$, $\text{CH}_2\text{SO}_3\text{M}^1$, CH_2OR^3 , or COD;
- 20 A is O, S, $\text{NR}_2^1\text{CR}_2^1$, or NR^1 ;
- D is OR^1 , NR_2^1 , or O-M^1 ; and
- Lower Alkyl is C_1 to C_{10} , branched or unbranched.

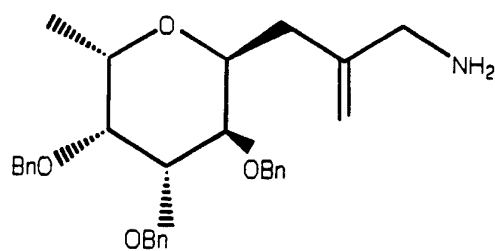
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11. A compound having a formula selected from the group consisting of:

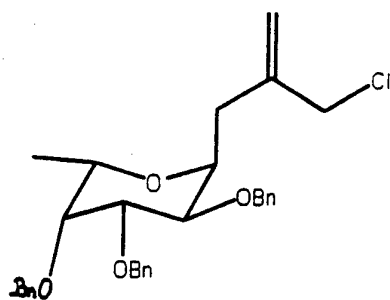
A.



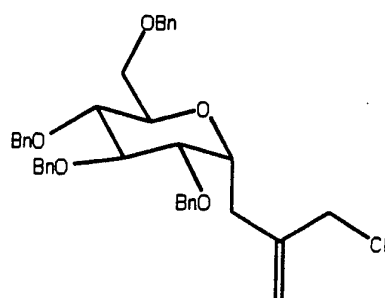
B.



C.

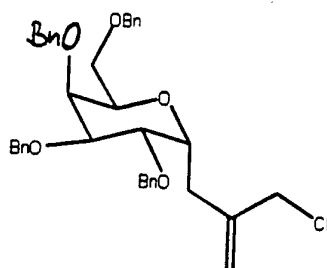


D.

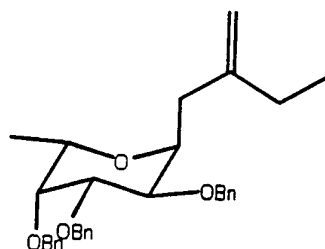


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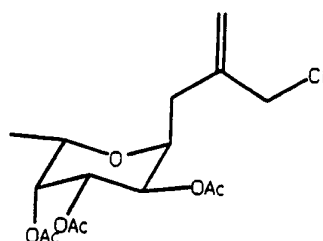
E.



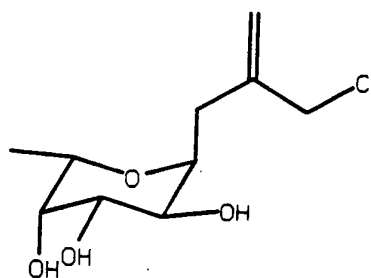
F.



G.

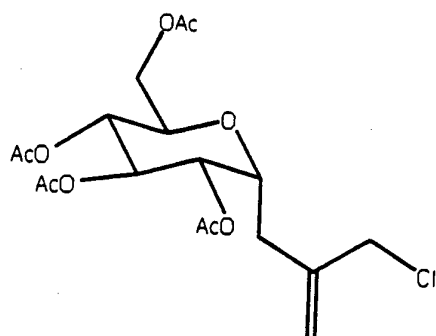


H.

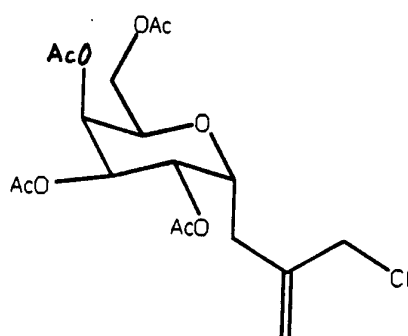


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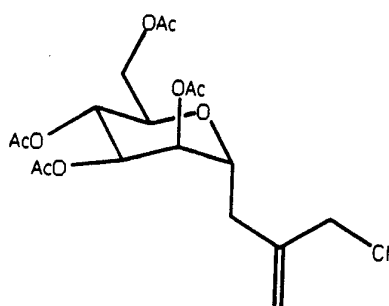
I.



J.

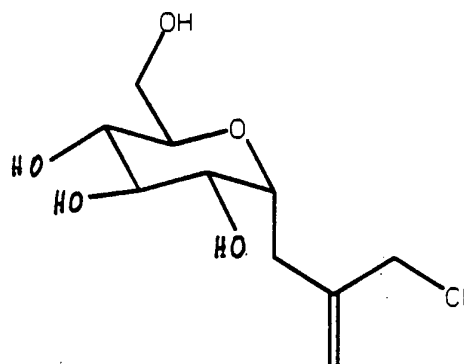


K.

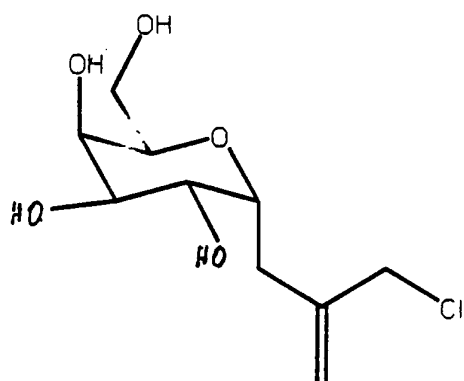


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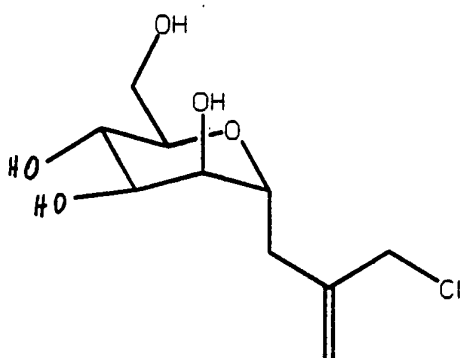
L.



M.

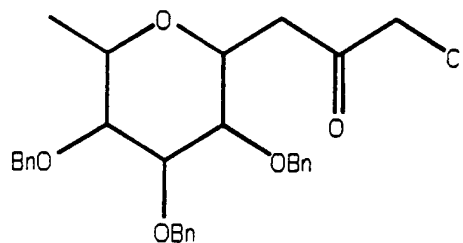


N.

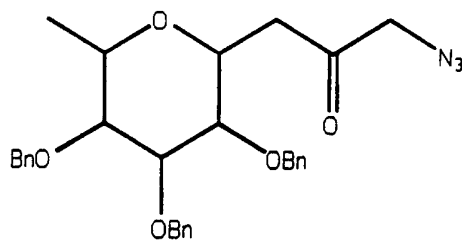


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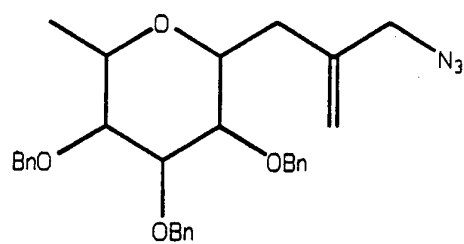
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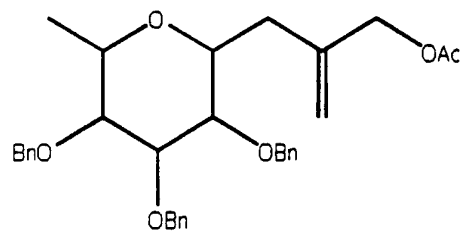
P.



Q.

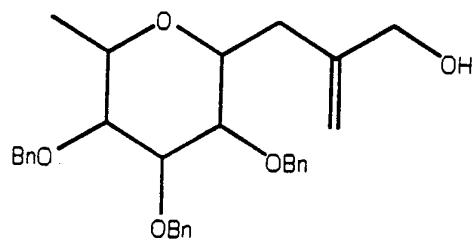


R.

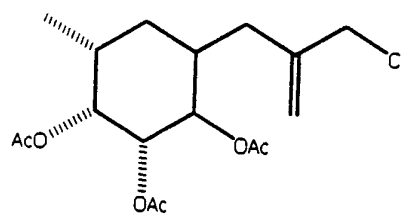


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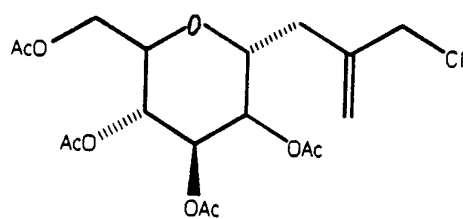
S.



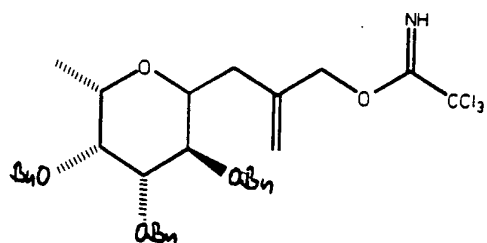
T.



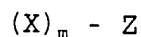
U.



V.



12. A method of preparing a synthetic library of carbon glycoside compounds comprising a plurality of compounds wherein each said compound is composed of one or a plurality of monomers and at least one monomer is a carbohydrate, said method comprising reacting one or a plurality of



wherein:

X is a carbohydrate unit or modified carbohydrate unit;

Z is an activated functional group attached, via spacer/linker unit containing at least one carbon atom, to a X at the anomeric position which is a carbon atom;

m is a positive integer;

in a Z-primed reaction with one or a plurality of "B", wherein "B" is a monomeric, homo-/hetero-oligomeric, homo-/heteropolymeric molecule of any chemical nature.

13. A method of preparing a synthetic library comprising a plurality of compounds wherein each said compound is composed of one or a plurality of monomers and at least one monomer is a carbohydrate, said method comprising reacting one or a plurality of the compounds of claim 10 in a Z-primed reaction with one or a plurality of "B", wherein "B" is a monomeric, homo-/hetero-oligomeric, homo-/heteropolymeric molecule of any chemical nature.

14. The method of Claim 13 wherein B is an organic chemical compound.

15. The method of Claim 13 wherein B is selected from the group consisting of a peptide library, a polymer, an aromatic phenol, or Cope rearrangement thereof.

16. The method of Claim 13 wherein B is selected from the group consisting of a peptide, a vitamin, an estrone and an antibiotic.

17. The method of Claim 12 wherein each library member is linked to a synthesis support, and the linkage between said library member and said synthesis support comprises a linker between said library member and said synthesis support.

18. The method of Claim 17 wherein B is an organic chemical compound.

19. The method of Claim 17 wherein B is selected from the group consisting of a peptide library, polymer, an aromatic phenol or Cope rearrangement thereof.

20. The method of Claim 17 wherein B is a synthetic chemical library comprising identifier tags which identifier tags identify the molecular structure of each library member.

21. The method of Claim 17 wherein B is a peptide, a vitamin, an estrone or an antibiotic.

22. The method of Claim 15 wherein each library member is linked to a synthesis support, and the linkage between said library member and said synthesis support comprises a linker between said library member and said synthesis support.

23. The method of Claim 17, wherein functional groups of said monomers are selectively protected by protection groups.

24. The method of Claim 17, wherein functional groups of said monomers are selectively protected by protection groups, wherein said protection groups are selected from the group consisting of methyl-, benzyl-, benzoyl-, acetyl-, MOM, MEM, MPM, tBDMS and TMS.

25. The methods of Claim 17, wherein functional groups of said monomers are selectively protected by protection groups, wherein said protection groups are selected from the group consisting of methyl-, benzyl-, benzoyl-, acetyl-, MOM, MEM, MPM, tBDMS and TMS wherein said protection groups are removed as part of the synthesis reaction.

26. The method of Claim 22, wherein functional groups of said monomers are selectively protected by protection groups.

27. The method of Claim 22, wherein functional groups of said monomers are selectively protected by protection groups, wherein said protection groups are selected from the group consisting of methyl-, benzyl-, benzoyl-, acetyl-, MOM, MEM, MPM, tBDMS, TMS.

28. The methods of Claim 22, wherein functional groups of said monomers are selectively protected by protection groups, wherein said protection groups are selected from the group consisting of methyl-, benzyl-, benzoyl-, acetyl-, MOM, MEM, MPM, tBDMS, TMS wherein said protection groups are removed as part of the synthesis reaction.

29. A method for deconvoluting an array of compounds comprising:

a. synthesis of pools of compounds according to Claim 13, wherein each pool is synthesized using a defined set of $[(X)_m - Z]$ and "B"s;

b. identifying pools of compounds having a desired biological, chemical or other effect;

c. repeating step a. using smaller subsets of $[(X)_m - Z]$ and/or "B"s wherein said subsets are derived from the sets used to synthesize the pools identified in b.; and

d. repeating b. and c. until single active compound is synthesized and/or identified.

30. A pharmaceutical composition comprising the formula:

5 $(X)_m - Z'$

wherein:

X is a carbohydrate unit or modified carbohydrate unit;

Z' is the reaction product of "Z" and "B";

10 B is one or a plurality of monomeric, homo/hetero-oligomeric, or homo/hetero-polymeric entities of any chemical nature, including organic molecules, inorganic molecules, solid synthesis supports;

Z is an activated functional group attached, via a spacer/linker unit containing at least one carbon atom, to
15 a X at the anomeric position which is carbon; and

m is a positive integer; with proviso that at least one X does not have an oxygen at its anomeric position; and pharmaceutically acceptable salts thereof.

20 31. A pharmaceutical compound comprising:
at least one compound of claim 10;
and pharmaceutically acceptable salts thereof.

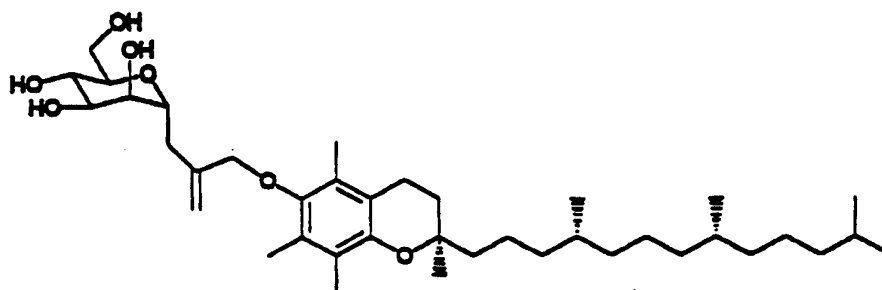
32. The compound of Claim 31 wherein Z' is selected from the group consisting of $-\text{CH}_2(\text{C}=\text{CH}_2)\text{CH}_2\text{T}$, $-\text{CH}_2(\text{C}=\text{O})\text{CH}_2\text{T}$,
25 and $-\text{ArCH}_2\text{T}$ and T is an organic molecule.

33. The compound of Claim 31 wherein Z' is selected from the group consisting of $-\text{CH}_2(\text{C}=\text{CH}_2)\text{CH}_2\text{T}$, $-\text{CH}_2(\text{C}=\text{O})\text{CH}_2\text{T}$, or $-\text{ArCH}_2\text{T}$ and T is selected from the group consisting of a peptide, a vitamin, an estrone or an antibiotic.

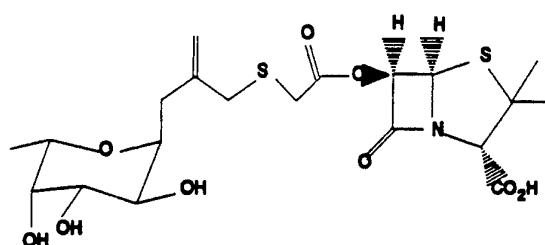
30 34. A chemical compound selected from the group consisting of:

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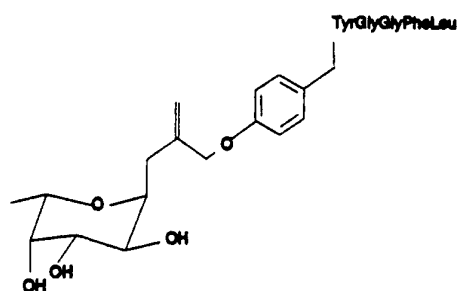
A.



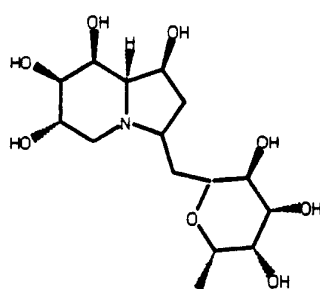
B.



C.

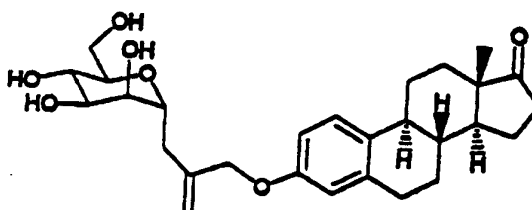


D.

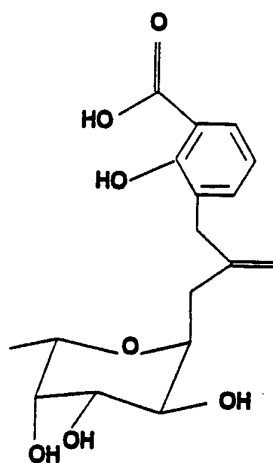


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E.

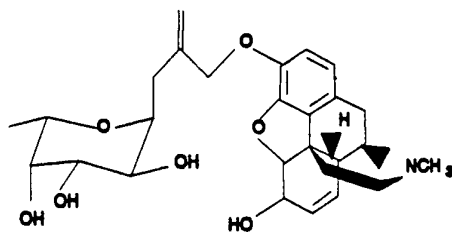


F.

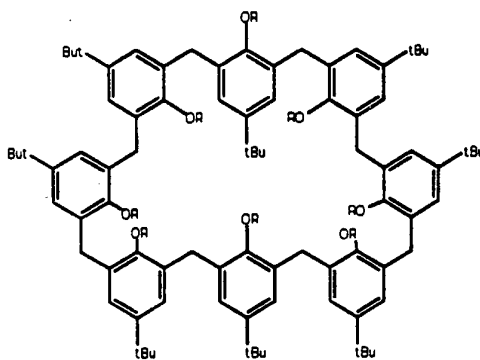


126

G.



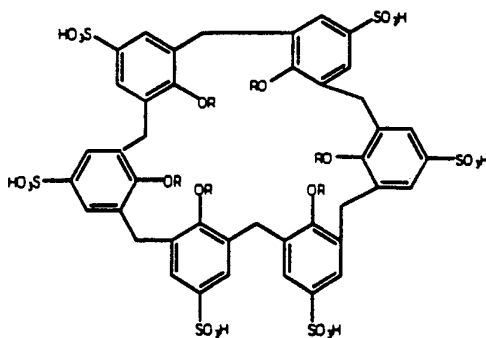
H.



Wherein at least one R is a carbon glycoside

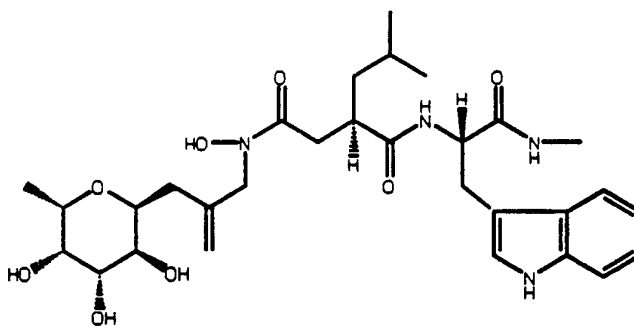
127

I.



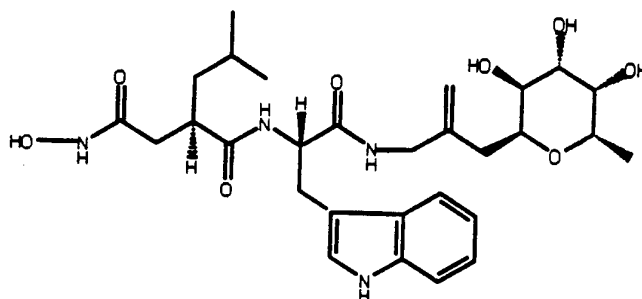
Wherein at least one R is a carbon glycoside

J.

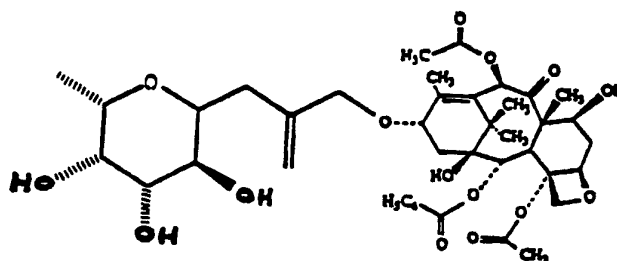


128

K.



L.



INTERNATIONAL SEARCH REPORT

Intern: 1 Application No

PCT/US 96/06522

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D309/10 C07D407/12 C07D499/00 C07D405/12

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)

IPC 6 C07D

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 practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,95 04526 (GLYCOMED) 16 February 1995 see the whole document ---	1,11,12, 17,18, 30-32
A	TETRAHEDRON LETTERS, vol. 25, no. 22, 1984, OXFORD GB, pages 2383-2385, XP002010792 AKIRA HOSOMI: "HIGHLY STEREOSELECTIVE C-ALLYLATION OF GLYCOPYRANOSIDES WITH ALLYL SILANES" see page 2383 - page 2385 -----	1,10,12

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in 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 document 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

"X" 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

13 August 1996

Date of mailing of the international search report

21. 08. 96

Name and mailing address of the ISA

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Authorized officer

Francois, J

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 96/ 06522

Box I Observations where certain claims were found unsearchable (Continuation of item 1 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. ☐ Claims Nos.:
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:
The definition of the compounds X^m-Z is very general and encompasses a very broad range of different chemical groups. A complete search is not possible on economic grounds (Capt. II, 2.1, Guidelines E.P.O., Part B). The search has been based on the activated glycosides and their application.
Claims searched incompletely: 1-10,12,17,18,30,31
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 2 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.

INTERNATIONAL SEARCH REPORT

Internal	Application No
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PCT/US 96/06522

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9504526	16-02-95	AU-B- 7520594	28-02-95
		CA-A- 2169291	16-02-95
		EP-A- 0714291	05-06-96
