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(72) Inventeurs/Inventors:
SEIFERT, JOACHIM, AU;
SINGH, LATIKA, AU;
RAMSDALE, TRACIE ELIZABETH, AU;
WEST, MICHAEL LEO, AU;
DRINNAN, NICHOLAS BARRY, AU

(73) Propriétaire/Owner:
ALCHEMIA LIMITED, AU

(74) Agent: RIDOUT & MAYBEE LLP

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(54) Title: SYNTHETIC HEPARIN PENTASACCHARIDES

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Preparation of synthetic monosaccharides, disaccharides, trisaccharides, tetrasaccharides and pentasaccharides for use in the preparation of synthetic heparinoids.

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(74) Agent: **CULLEN & CO.**; Level 26, 239 George Street,
Brisbane, Queensland 4000 (AU).

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(71) Applicant (*for all designated States except US*): **AL-CHEMIA PTY LTD** [AU/AU]; 3 Hi-Tech Court,
Brisbane Technology Park, Eight Mile Plains, Queensland
4113 (AU).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **SEIFERT, Joachim**
[DE/AU]; 81 Renoir Crescent, Forest Lake, Queensland
4078 (AU). **SINGH, Latika** [AU/AU]; 81 Renoir Crescent,
Forest Lake, Queensland 4078 (AU). **RAMSDALE, Tra-**
cie, Elizabeth [AU/AU]; 160 Hellawell Road, Sunnybank,
Queensland 4109 (AU). **WEST, Michael, Leo** [AU/AU];
364 Hemmant & Tingalpa Road, Hemmant, Queensland
4074 (AU). **DRINNAN, Nicholas, Barry** [NZ/AU]; 8/23
Chermside Street, Highgate Hill, Queensland 4101 (AU).

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(54) Title: SYNTHETIC HEPARIN PENTASACCHARIDES

(57) Abstract: Preparation of synthetic monosaccharides, disaccharides, trisaccharides, tetrasaccharides and pentasaccharides for
use in the preparation of synthetic heparinoids.



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TITLE**Synthetic Heparin Pentasaccharides**5 **Field of the Invention**

This invention is directed to intermediates, and processes for the chemical synthesis of AT-III binding heparin or heparinoid, pentasaccharides.

10 **Background Art**

Vascular thrombosis is a cardiovascular disease indicated by the partial or total occlusion of a blood vessel by a clot containing blood cells and fibrin. In arteries, it results predominantly from platelet activation and leads to heart attack, angina or stroke, whereas venous thrombosis results in inflammation and pulmonary emboli. The coagulation of blood is the result of a cascade of events employing various enzymes collectively known as activated blood-coagulation factors. Heparin, a powerful anticoagulant has been used since the late 1930's in the treatment of thrombosis. In its original implementation, tolerance problems were noted and so reduced dosage was suggested to reduce bleeding and improve efficacy. In the early 1970's, clinical trials did indeed indicate acceptable tolerance was obtainable whilst still preserving antithrombotic activity. Unfractionated heparin (UFH) is primarily used as an anticoagulant for both therapeutic and surgical indications, and is usually derived from either bovine lung or porcine mucosa. Amongst the modern uses of unfractionated heparin are the management of unstable angina, an adjunct to chemotherapy and anti-inflammatory treatment, and as a modulation agent for growth factors and treatment of haemodynamic disorders.

In the late 1980's, the development of low molecular weight heparins (LMWHs) led to improvements in antithrombotic therapy. LMWHs are derived from UFH by such processes as; chemical degradation, enzymatic depolymerisation and γ -radiation cleavage. This class of heparins has recently been used for treatment of trauma related thrombosis. Of particular interest is the fact that their relative effects on platelets are minimal compared to

heparin, providing an immediate advantage when treating platelet compromised patients. The degree of depolymerisation of UFH can be controlled to obtain LMWH of different lengths. Dosage requirements for the treatment of deep vein thrombosis (DVT) are significantly reduced when
5 employing LMWH as opposed to UFH, although in general the efficacy of both therapeutics seems to be comparable. In addition, LMWH can be effective as an alternative therapeutic for patients who have developed a sensitivity to UFH. Unfortunately, there has recently been a great deal of concern in the use of LMWH due to the perceived potential for cross-species viral
10 contamination as a result of the animal source of the parent UFH.

One way of avoiding the possibility of cross-species contamination, is to prepare heparins by chemical synthesis. This method would also provide the opportunity to develop second generation heparins or heparinoids, that can be tailored to target particular biological events in the blood coagulation
15 cascade.

An investigation to determine the critical structural motif required for an important binding event in a coagulation cascade involving heparin, dates back to the 1970's. Some structural features of heparin were defined, but the binding domains of interest remained essentially undefined. Research
20 conducted by Lindahl and co-workers¹ and separately by Choay and co-workers² eventually led to the determination that a pentasaccharide sequence constituted the critical binding domain for the pro-anticoagulant cofactor, antithrombin III (AT-III). After determination of the critical heparin sugar sequence, complete chemical syntheses were embarked upon to further
25 prove the theories. Complete syntheses of the pentasaccharide binding domain were completed at similar times by Sinay and co-workers³ and by Van Boeckel and co-workers⁴.

Significant difficulties were encountered during both these reported syntheses. The synthesis by Van Boeckel and co-workers provided a method
30 on reasonable scale (156mg's of final product) and with improved yields compared to the Sinay synthesis, but still only provided an overall yield of 0.22%, (compared with 0.053% for the Sinay synthesis). One particular problem encountered during the final deprotection, was the intermolecular reaction of the hemiacetal (the reducing end functionality of the sugar), which

led to the formation dimers and trimers. To reduce the likelihood of this occurring, an α -methyl glycoside of the pentasaccharide was synthesised. The structures of interest are represented in **Figure 1**, wherein **I** represents the hemiacetal form, and **II** represents the α -methylglycoside form.

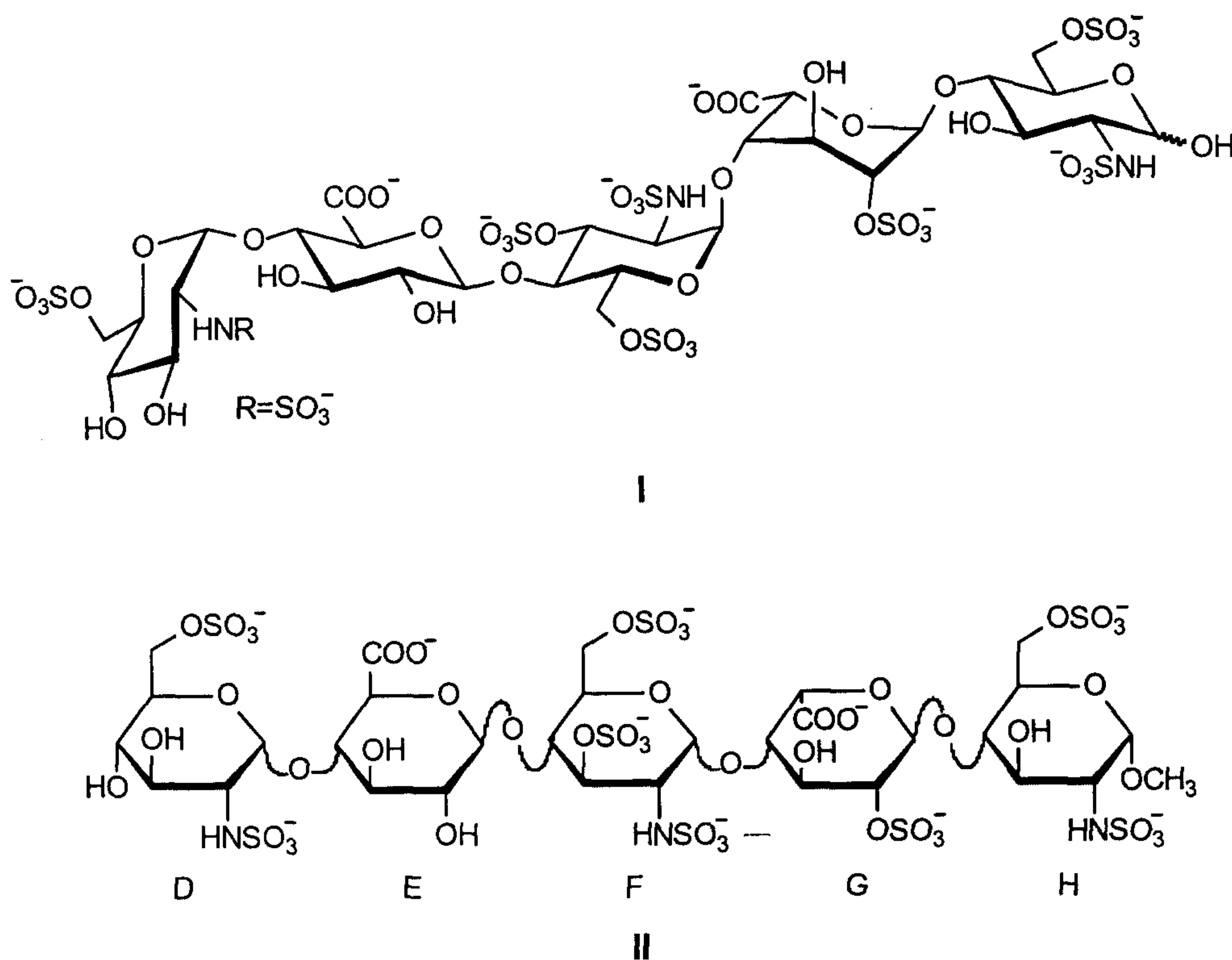


Figure I

As mentioned, studies have determined that the significant biological event in preventing thrombosis is the binding of a pentasaccharide sequence⁵ of heparin, to heparin cofactor antithrombin III (AT-III). As well as pentasaccharide I, the important derivative II has also been prepared by total synthesis⁶. Compound II has recently completed phase III clinical trials for the treatment of deep-vein thrombosis. The following patents display some relevance to the present invention. Patent US 4,401,662 claims composition of matter on the pentasaccharide AT-III binding sequence of heparin as does US 4,496,550. Patents EP 0,084,999 and US 4,818,816 detail synthetic methodologies towards pentasaccharide I, and derivative II.

Object of the Invention

It is an object of the invention to provide a synthetic preparation for heparin pentasaccharides, and intermediates thereof, and to novel
 5 intermediates for heparin pentasaccharides, and to novel heparin pentasaccharides.

The present invention provides composition of matter of intermediates, and a process for the synthesis, of AT-III binding heparins and heparinoids. What this entails is a stepwise synthetic process employing monosaccharide
 10 building blocks.

The nature of the AT-III binding pentasaccharide is such, that under cursory analysis of the individual monomeric units constituting the pentasaccharide, we note that each is distinct from the others. Secondly, we can see that there is an alternating stereospecificity in regard to the glycosidic
 15 linkages (**Fig. 2**).

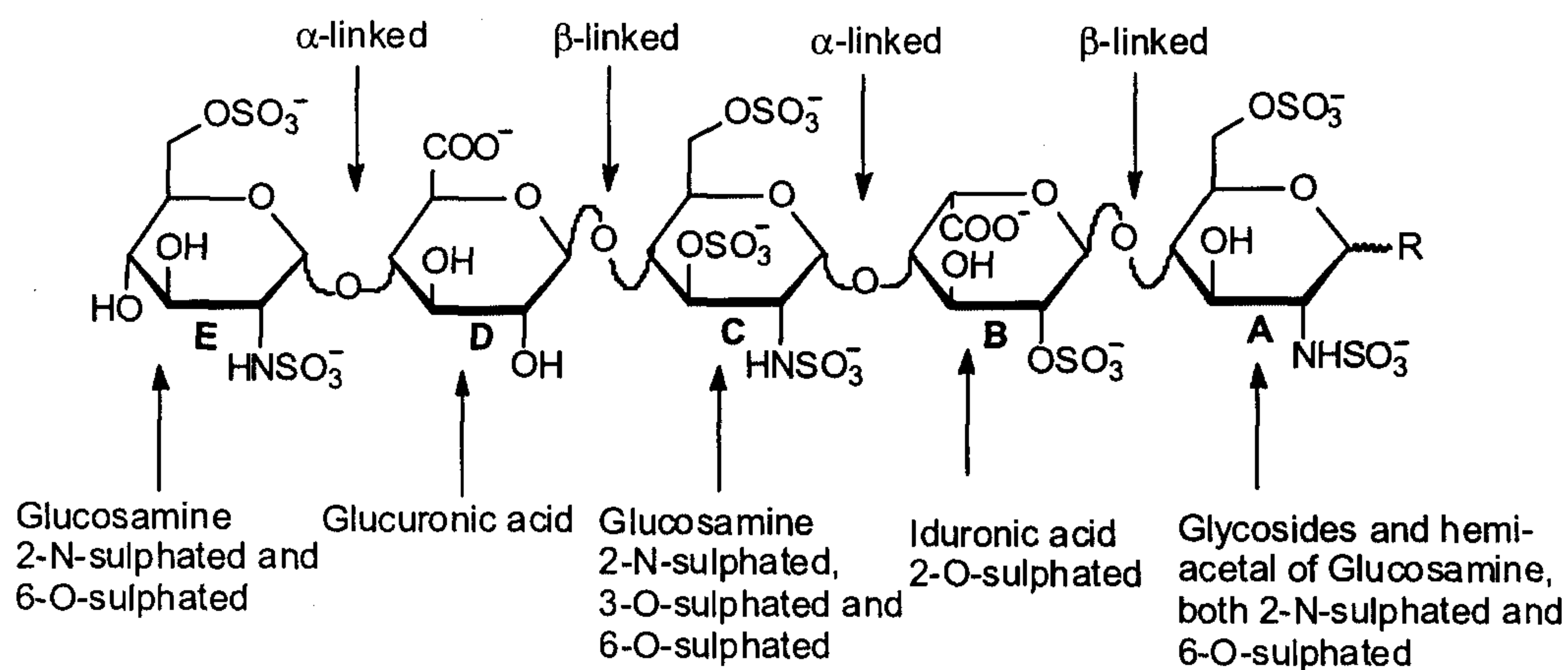


Fig. 2

20

In a synthesis, the difference evident in each block requires that each individual monomer used in the synthesis will need a different protecting group pattern. In light of this, it is essential in the synthesis of the above pentasaccharide that a protecting group strategy is carefully conceived. As
 25 can be seen, the pentasaccharide displays O-sulphation, N-sulphation, there are free hydroxyl groups, and there are stereospecific glycosidic linkages.

Therefore, a protection strategy is required such that (1) sulphation can be effected at the required sites, whilst leaving some hydroxyl groups unsulphated (note that due to the chemical lability of *N*- and *O*-sulphates, sulphation needs to be effected late in the synthesis), (2) a protection strategy is required that assists in effecting the appropriate glycosidic linkage and (3) a protection strategy is required that enables the correct (in terms of regio- and stereoisomerism) glycosidic linkages to be formed. α -Glycosidic linkages are typically generated by the use of what are known as non-participating protecting groups, whilst β -linkages are effected by participating protecting groups. Some *N*- and *O*-participating and non-participating protecting groups are known to the art (the art being considered carbohydrate chemistry). It is also well known to the art that the kind of protecting groups employed can effect the reactivity of the building block. The culmination of these requirements are demonstrated in the exemplary building block in **Fig. 3** below, which displays the kind of characteristics required to effect the synthesis of heparin oligosaccharides.

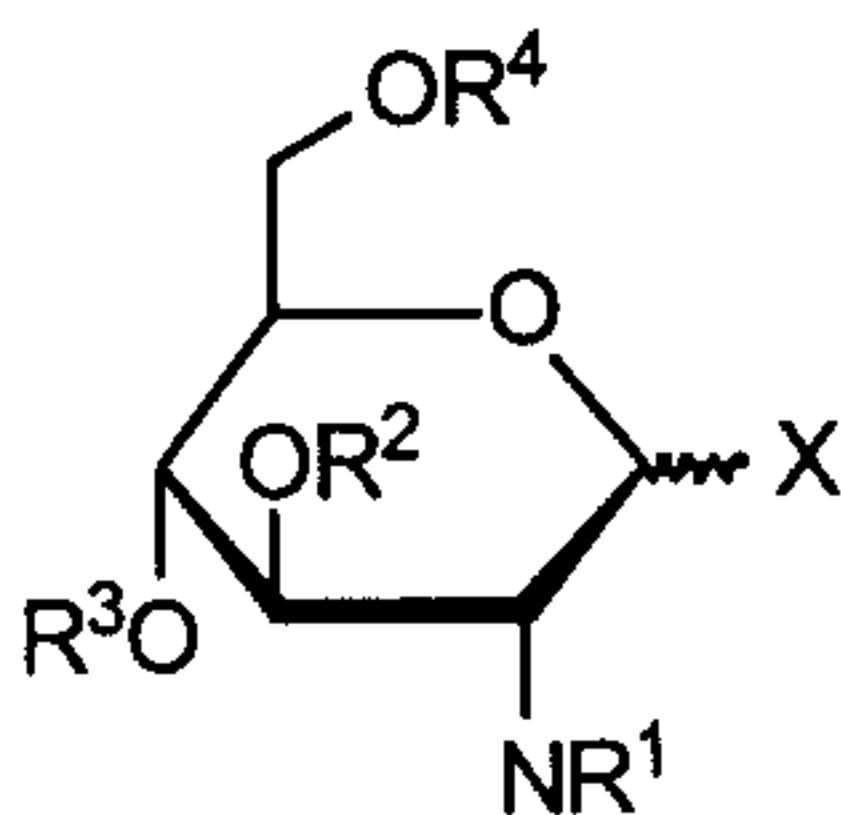


Fig. 3, Exemplary Building Block C

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In exemplary building block **C**, *X* is a leaving group suitable of reacting with another monomer or acceptor, to form an interglycosidic linkage; *R*¹ is a non-participating amino protecting group so as to effect an α -linkage upon activation of *X* followed by coupling to an appropriate acceptor; *R*² and *R*⁴ can be similarly protected to allow for eventual *O*-sulphation, whilst *R*³ is required to be differentially protected so as to allow the formation of an acceptor hydroxyl group to couple this block to the next in the chain. The building blocks in **Fig. 4** exemplify the kind of derivatised monosaccharides required to effect the synthesis of heparin AT-III binding pentasaccharides.

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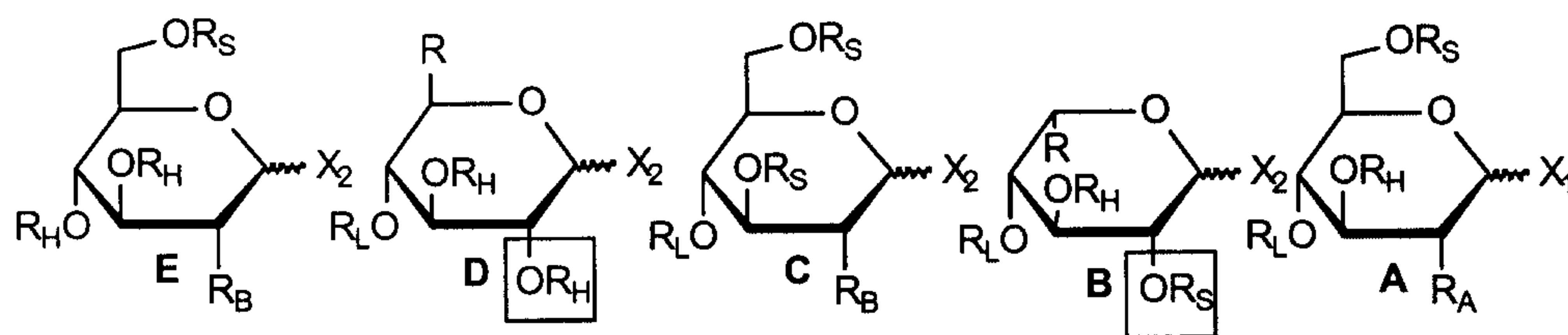


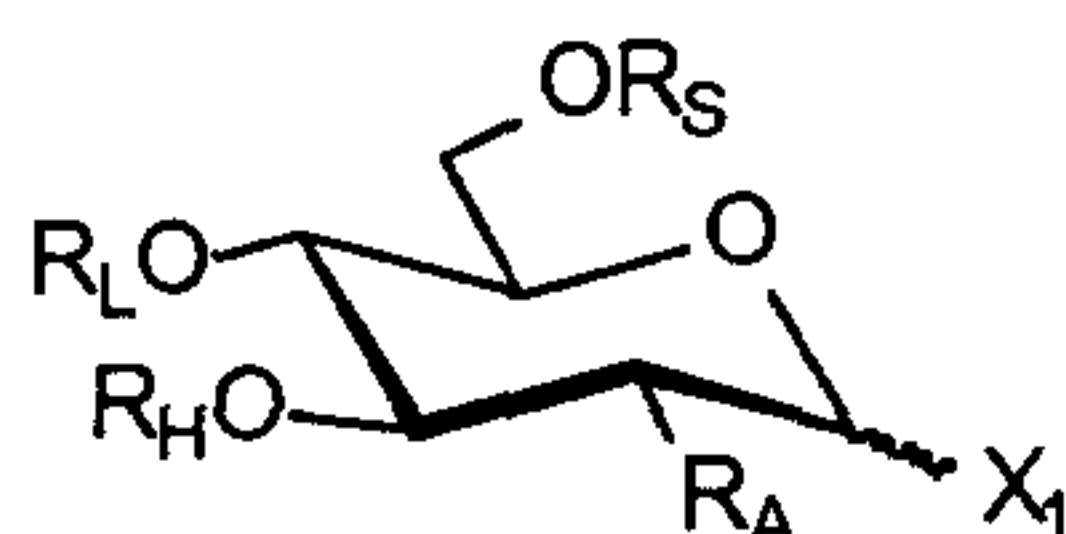
Fig. 4

5 The protecting groups represented by 'R_S' in **Fig. 4** are sites that will eventually require O-sulphation, the protecting groups represented by 'R_H' need to be orthogonal to 'R_S' and represents sites that will eventually become hydroxyl groups. The substituents 'X₁' and 'X₂' represent leaving groups that are activated to react with another suitable protected building block to form a glycosidic linkage, and, in the case of X₁, may also be derivatised as alkyl glycosides or substituted with a group suitable to allow conjugation to a support for drug delivery. The 'R_L' groups are protecting groups orthogonal to both 'R_S' and 'R_H', and represent sites through which chain elongation *via* glycosylation occurs. 'R' is representative of either a protected or latent carboxylate function. The 'R_A' groups are non-participating amino protecting groups that enable α -linkages to be formed while the 'R_B' groups may be either a participating or non-participating amino protecting group. There is another level of complexity to be added to the synthesis in as much as the protecting groups in blocks **D** and **B** that are indicated by the boxes, need to be such that they allow for the formation of a β -glycosidic linkage. This may require a two stage protection at the indicated sites, ie. a protection followed by deprotection and subsequent reprotection with a different protecting group. The initial protection is required to effect the correct stereochemistry in a glycosylation, and second stage protection to allow for the correct sulphation pattern.

As is evident, the pentasaccharide can be constructed in a variety of different ways; blocks B and A can be coupled, blocks E and D can be coupled, block C can be coupled to either, and the resulting dimer and trimer can finally be coupled to form the pentasaccharide. Alternatively, each block can be added sequentially and so on. There are a number of alternative

coupling sequences that can be easily conceived and the choice made in regard to this, in itself, has a marked effect on the synthetic methodologies that will finally be employed, and therefore impacts on the overall success of the synthesis.

- 5 In one aspect the invention provides for a monosaccharide building block in the D-glucopyrano configuration, for the preparation of synthetic heparinoids, said building block of General Formula I,



10

General Formula I (Block A)

- Wherein X_1 includes but is not limited to: hydroxy, alkoxy, aryloxy, benzyloxy, substituted benzyloxy; thioalkyl, thioaryl, halogen, trichloroacetimidoyl, phosphate and related phosphate ester type leaving groups, or other suitable leaving group; a ^tbutyldiphenylsilyloxy or other such substituted silyloxy protecting group; a lipoaminoacid or other such group suitable for conjugation to delivery systems or solid supports; and the stereochemistry may be alpha or beta; other suitable groups will be known to those skilled in the art,

- 20 R_A includes but is not limited to: an azido function, an amine; an *NH*-Dde, *NH*-DTPM, *NH*-Fmoc, *NH*-Boc, *NH*-Cbz, *NH*-Troc, *N*-phthalimido; or, other such suitable protected amino functions known to those skilled in the art, R_H is a benzyl or, substituted benzyl protecting group, allyl, allyloxycarbonyl, or R_{H1} and R_A can combine together to form a cyclic carbamate;

25

- R_L includes but is not limited to: a H atom; a levulinoyl, chloroacetyl, 4-acetoxybenzoyl, 4-acetamidobenzoyl, 4-azidobenzoyl, or other substituted benzoyl type protecting group; a benzyl group, a 4-acetoxybenzyl, 4-acetamidobenzyl or other such suitable substituted benzyl type protecting group; γ -aminobutyryl, 4-*N*-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethylamino]-butyryl, 4-*N*-[1-(1,3-dimethyl-2,4,6(1H,3H,5H)-

30

trioxypyrimidin-5-ylidene)methylamino]-butyryl, 4-*N*-Alloc-butyryl, 4-*N*-Fmoc-butyryl, 4-*N*-Boc-butyryl type protecting groups allyloxycarbonyl, allyl ether, carbonate type protecting groups; or R_L and R_{S1} can combine to form a benzylidene or substituted benzylidene ring.; or, other such suitable protecting

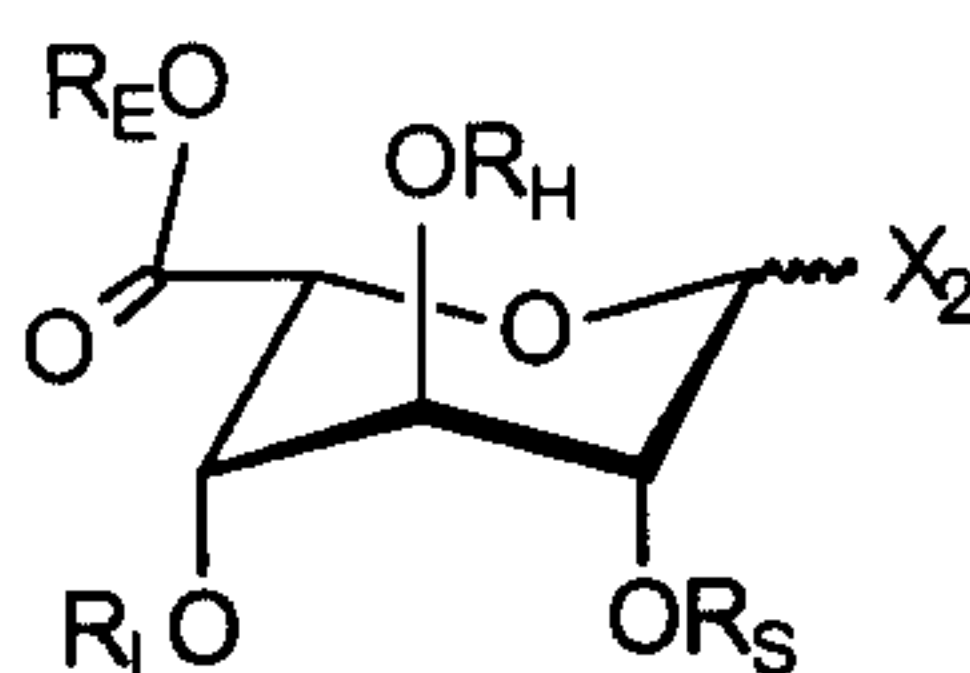
5 groups as known to those skilled in the art, and

R_S includes but is not limited to: 4-methoxyphenyl; substituted benzyl groups; alkylacyl, arylacyl or alkylarylacyl, and substituted alkylacyl, arylacyl or alkylarylacyl protecting groups; carbonate protecting groups, a ^tbutyldiphenylsilyloxy or other such substituted silyloxy protecting group allyl,

10 methoxymethyl, methoxyethyl, benzyloxymethyl;; or, other suitable protecting groups as known to those skilled in the art.

Alternatively R_L and R_S can combine to form a benzylidene or substituted benzylidene ring.

15 In a second aspect the invention provides for a monosaccharide building block in the L-idopyrano conformation, for the preparation of synthetic heparinoids, said building block of General Formula II,



20

General Formula II (Block B)

Wherein X_2 includes but is not limited to: a hydroxyl group; thioalkyl, thioaryl, halogen, trichloroacetimidoyl, phosphate and related phosphate ester type

25 leaving groups, or other suitable leaving group; a ^tbutyldiphenylsilyloxy or other such substituted silyloxy protecting group; and the stereochemistry may be alpha or beta; other suitable groups will be known to those skilled in the art,

R_S is defined as in General Formula I,

30 R_H is defined as in General Formula I,

R_L is defined as in General Formula I, and

R_E includes but is not limited to: methyl, C_2-C_5 alkyl; substituted alkyl; or, benzyl and substituted benzyl groups; other suitable groups will be known to those skilled in the art. Or

R_H is selected from the group consisting of benzyl or substituted benzyl protecting group, allyl, allyloxycarbonyl;

R_S is selected from the group consisting of 4-methoxyphenyl; substituted benzyl groups; alkylacyl, arylacyl or alkylarylacyl, and substituted alkylacyl, arylacyl or alkylarylacyl protecting groups; carbonate protecting groups; a ^tbutyldiphenylsilyloxy or other such substituted silyloxy protecting group allyl, methoxymethyl, methoxyethyl, benzyloxymethyl;

R_E is selected from the group consisting of methyl, C_2-C_5 alkyl; substituted alkyl, C_3-C_5 alkenyl; or, benzyl and substituted benzyl groups;

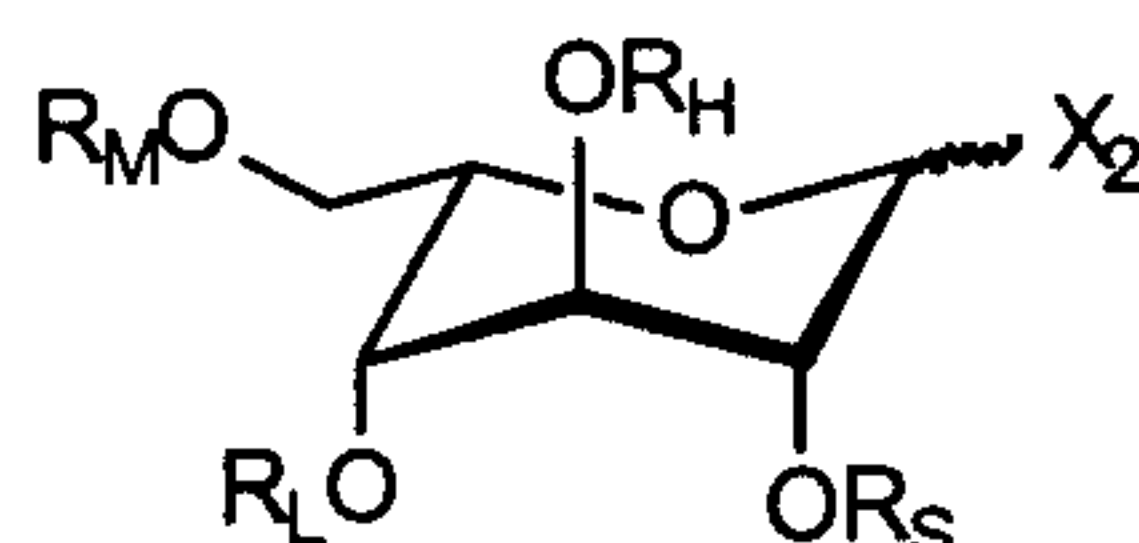
R_L is selected from a H atom; a levulinoyl, chloroacetyl, 4-acetoxybenzoyl, 4-acetamidobenzoyl, 4-azidobenzoyl, or other substituted benzoyl type protecting group; a benzyl group, a 4-acetoxybenzyl, 4-acetamidobenzyl or other such suitable substituted benzyl type protecting group; γ -aminobutyryl, 4-N-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethylamino]-butyryl, 4-N-[1-(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxypyrimidin-5-ylidene)methylamino]-butyryl, 4-N-Alloc-butyryl, 4-N-Fmoc-butyryl, 4-N-Boc-butyryl type protecting groups; allyloxycarbonyl, allyl ether, carbonate type protecting groups;

X_2 is selected from a hydroxyl group; thioalkyl, thioaryl, halogen, imidoyl, phosphate and related phosphate ester type leaving groups, a ^tbutyldiphenylsilyloxy or other such substituted silyloxy protecting group; and the stereochemistry may be alpha or beta.

25

In a third aspect the invention provides for a monosaccharide building block in the L-idopyrano configuration, for the preparation of synthetic heparinoids, said building block of General Formula III,

30



General Formula III (Alternate Block B)

Wherein X_2 is defined as in General Formula II,

5 R_S is defined as in General Formula II,

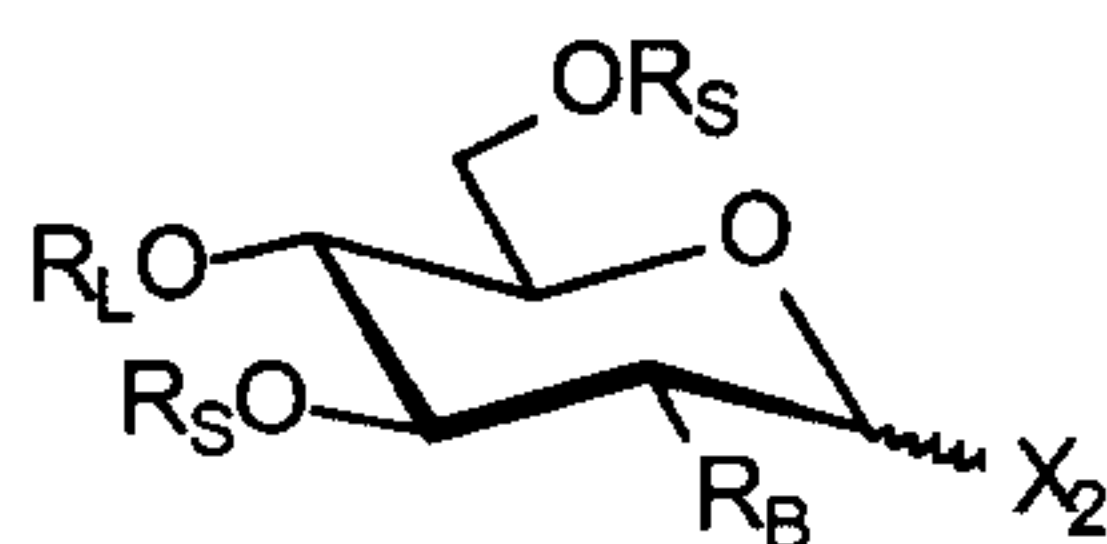
R_H is defined as in General Formula I,

R_L is defined as in General Formula I, and

10 R_M includes but is not limited to a *p*-methoxyphenyl protecting group or other suitable oxidatively labile protecting group; a trityl group; or, other such suitable protecting groups as known to those skilled in the art.

In a fourth aspect the invention provides for a monosaccharide building block in the D-glucopyrano configuration for the preparation of synthetic heparinoids, said building block of General Formula IV,

15



General Formula IV (Block C)

20 Wherein X_2 is defined as in General Formula II,

R_B includes but is not limited to: an azido function, an amine; an *NH*-Dde or *NH*-DTPM group; or other suitably protected amino functions as known to those skilled in the art, or R_S (adjacent R_B) and R_B can combine together to form a cyclic carbamate;

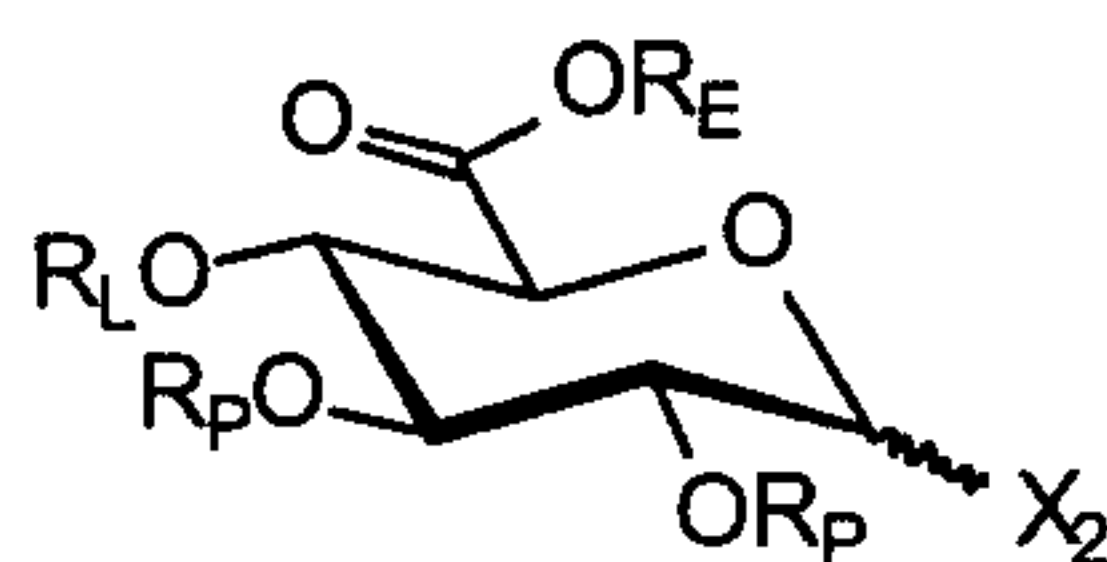
25

R_L is defined as in General Formula I, and

30 R_S (adjacent R_B) is selected from the group consisting of 4-methoxyphenyl; substituted benzyl groups; alkylacyl, arylacyl or alkylarylacyl, and substituted alkylacyl, arylacyl or alkylarylacyl protecting groups; carbonate protecting groups; a *t*-butyldiphenylsilyloxy or other such substituted silyloxy protecting group allyl, methoxymethyl, methoxyethyl, benzyloxymethyl, or R_{S4} and R_B may be combined to form a cyclic carbamate;

R_S (adjacent the oxygen) is selected from the group consisting of 4-methoxyphenyl; substituted benzyl groups; alkylacyl, arylacyl or alkylarylacyl, and substituted alkylacyl, arylacyl or alkylarylacyl protecting groups; carbonate protecting groups; a ^tbutyldiphenylsilyloxy or other such substituted silyloxy protecting group allyl, methoxymethyl, methoxyethyl, benzyloxymethyl;

In a fifth aspect the invention provides for a monosaccharide building block in the D-glucuronate configuration for the preparation of synthetic heparinoids, said building block of General Formula V,



General Formula V (Block D)

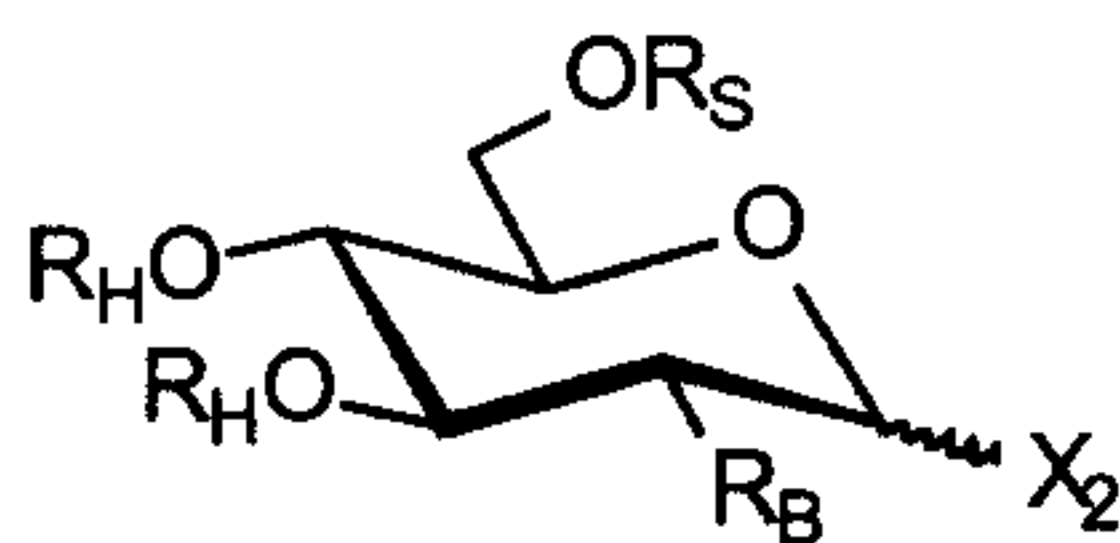
Wherein X_2 is as defined in General Formula II,

R_P includes but is not limited to: 4-methoxyphenyl; substituted benzyl groups; alkylacyl, arylacyl and alkylarylacyl, or substituted alkylacyl, arylacyl and alkylarylacyl protecting groups; carbonate protecting groups; or, other suitable protecting groups as known to those skilled in the art.

R_L is defined as in General Formula I, and

R_E is defined as in General Formula II.

In a sixth aspect the invention provides for a monosaccharide building block in the D-glucopyrano configuration for the preparation of synthetic heparinoids, said building block of General Formula VI,



General Formula VI (Block E)

Wherein X_2 is as defined as in General Formula II,

5 R_B is defined as in General Formula IV,

R_H may be selected independently and are defined as in General Formula I,
and

R_S is defined as in General Formula I

or, wherein

10 R_H (adjacent the ORs moiety) is selected from the group consisting of
benzyl or substituted benzyl protecting group, allyl, allyloxycarbonyl;

R_H (adjacent the R_B moiety) is selected from the group consisting of
benzyl or substituted benzyl protecting group, allyl, allyloxycarbonyl, or this R_H
and R_B independently can combine together to form a cyclic carbamate;

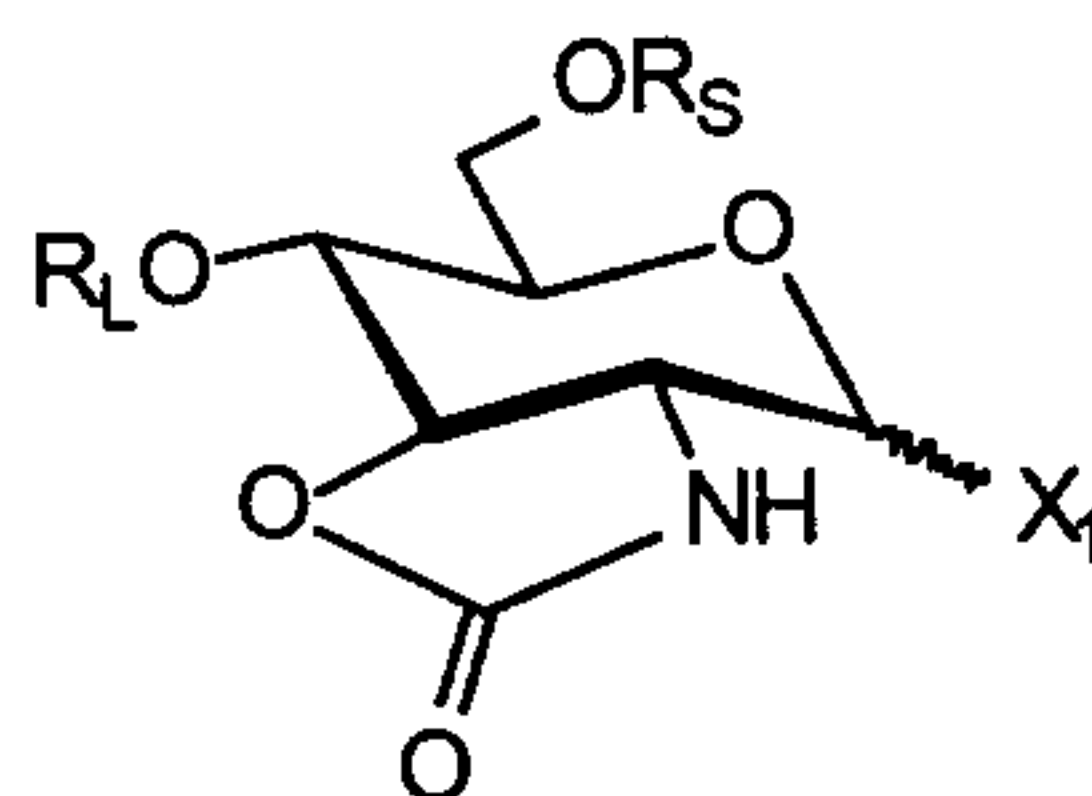
15

R_S is selected from the group consisting of 4-methoxyphenyl;
substituted benzyl groups; alkylacyl, arylacyl or alkylarylacyl; and substituted
alkylacyl, arylacyl or alkylarylacyl protecting groups; carbonate protecting
groups; a *t*-butyldiphenylsilyloxy or other such substituted silyloxy protecting
20 group allyl, methoxymethyl, methoxyethyl, benzyloxymethyl, or R_{S5} and R_H
can be combined to form a cyclic acetal or ketal moiety;

R_B is selected from the group consisting of an azido function, an
amine; an *NH*-Dde or *NH*-DTPM group, or R_H (adjacent the R_B) and R_B can
25 combine together to form a cyclic carbamate;

X_2 is selected from a hydroxyl group; thioalkyl, thioaryl, halogen,
trichloroacetimidoyl, phosphate and related phosphate ester type leaving
groups, a *t*-butyldiphenylsilyloxy or other such substituted silyloxy protecting
30 group; and the stereochemistry may be alpha or beta.

In a seventh aspect the invention provides for a monosaccharide building block in the D-glucopyrano configuration for the preparation of synthetic heparinoids, said building block of General Formula VII,



5

General Formula VII (Common Intermediate for Blocks A, C and E)

Wherein X_1 is defined as in General Formula I,

10 R_L is defined as in General Formula I, and

R_S is defined as in General Formula I.

R_L and R_S may also together combine to form a benzylidene or substituted benzylidene ring or

X_1 is selected from the group consisting of hydroxy, alkoxy, aryloxy,

15 benzyloxy, substituted benzyloxy; thioalkyl, thioaryl, halogen, trichloroacetimidoyl, phosphate and related phosphate ester type leaving groups, a^tbutyldiphenylsilyloxy or other such substituted silyloxy protecting group; a lipoaminoacid or other such group suitable for conjugation to delivery systems or solid supports; and the stereochemistry may be alpha or beta;

20

R_L is selected from a H atom; a levulinoyl, chloroacetyl, 4-acetoxybenzoyl, 4-acetamidobenzoyl, 4-azidobenzoyl, or other substituted benzoyl type protecting group; a benzyl group, a 4-acetoxybenzyl, 4-acetamidobenzyl or other such suitable substituted benzyl type protecting group; γ -aminobutyryl,

25 4-N-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethylamino]-butyryl, 4-N-[1-(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxypyrimidin-5-ylidene)methylamino]-butyryl, 4-N-Alloc-butyryl, 4-N-Fmoc-butyryl, 4-N-Boc-butyryl type protecting groups; allyloxycarbonyl, allyl ether, carbonate type protecting groups.

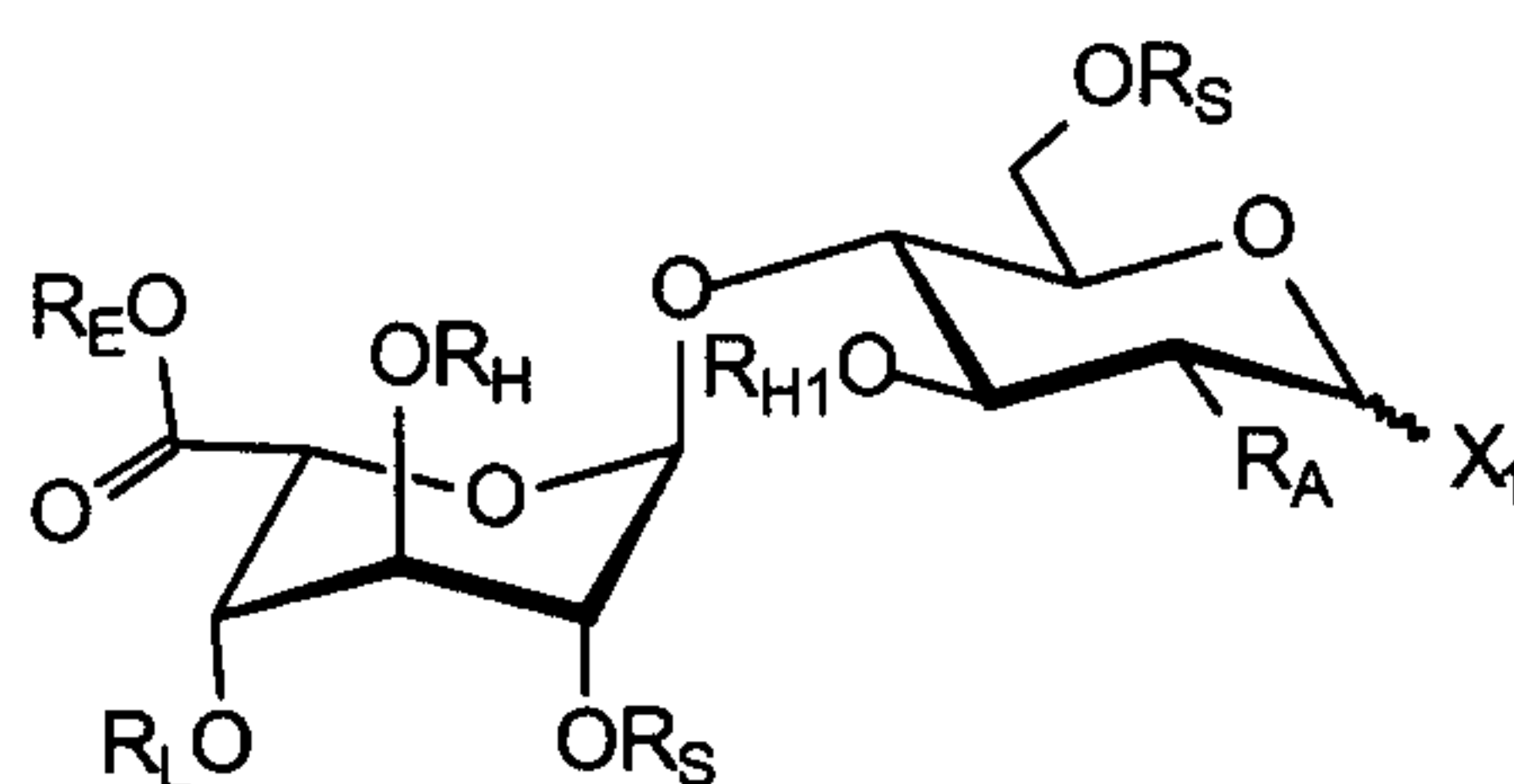
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R_S is selected from the group consisting of 4-methoxyphenyl, 4-methoxybenzyl; substituted benzyl groups; alkylacyl, arylacyl or alkylarylacyl, and substituted alkylacyl, arylacyl or alkylarylacyl protecting groups; carbonate protecting groups; tert-Butyldiphenylsilyl;

5

R_L and R_S may also together combine to form an alkylidene, isopropylidene, benzylidene or substituted benzylidene ring.

- 10 In an eighth aspect the invention provides for a disaccharide building block for the preparation of synthetic heparinoids, said building block of General Formula VIII,



15

General Formula VIII (Block B-A)

Wherein X_1 is defined as in General Formula I,

- R_{H1} is defined as being selected from R_H of General Formula I, with the addition that R_{H1} and R_A can combine together to form a cyclic carbamate,
- 20 R_A is defined as in General Formula I, with the addition that R_{H1} and R_A can combine together to form a cyclic carbamate

R_S is defined as in General Formula I,

R_H is defined as in General Formula I,

- 25 R_L is defined as in General Formula I, and

R_E is defined as in General Formula II or

- X_1 is selected from the group consisting of hydroxy, alkenyloxy, alkoxy, aryloxy, benzyloxy, substituted benzyloxy; thioalkyl, thioaryl, halogen, imidoxy, phosphate and related phosphate ester type leaving groups, a
- 30 t -butyldiphenylsilyloxy or other such substituted silyloxy protecting group; a

lipoaminoacid or other such group suitable for conjugation to delivery systems or solid supports; and the stereochemistry may be alpha or beta;

R_H is selected from the group consisting of benzyl or substituted benzyl protecting group, allyl, allyloxycarbonyl;

R_{H1} is selected from the group consisting of benzyl or substituted benzyl protecting group, allyl, allyloxycarbonyl, or R_{H1} and R_A can combine together to form a cyclic carbamate;

R_A is selected from the group consisting of an azido function, an amine; an *NH*-Dde, *NH*-DTPM, *NH*-Fmoc, *NH*-Boc, *NH*-Troc, *N*-phthalimido, *NH*-Ac, *NH*-Allyloxycarbonyl; or R_{H1} and R_A can combine together to form a cyclic carbamate;

R_S (on block A) is selected from the group consisting of 4-methoxyphenyl; substituted benzyl groups; alkylacyl, arylacyl or alkylarylacyl, and substituted alkylacyl, arylacyl or alkylarylacyl protecting groups; carbonate protecting groups; a *t*-butyldiphenylsilyloxy or other such substituted silyloxy protecting group allyl, methoxymethyl, methoxyethyl, benzyloxymethyl or benzoyl,

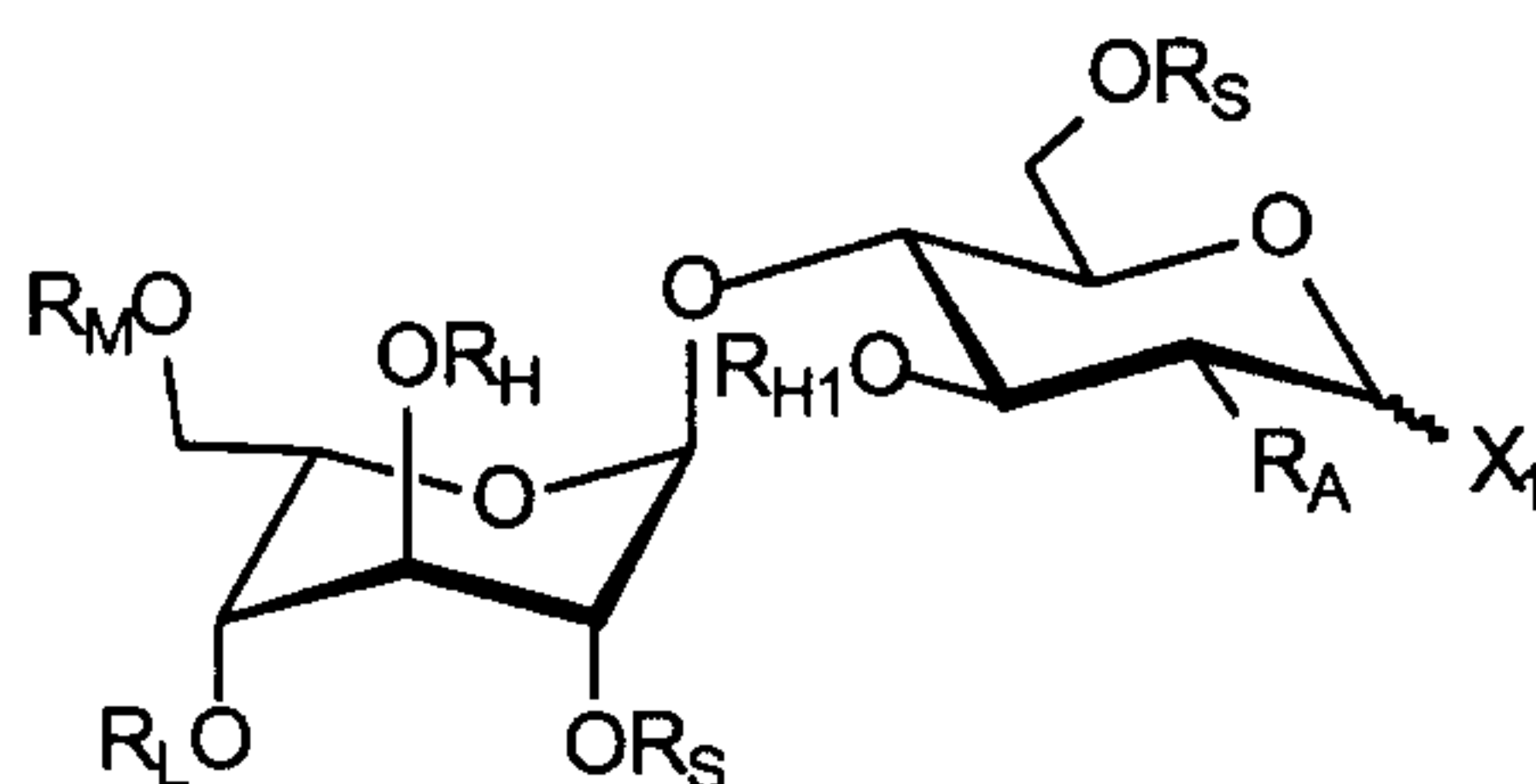
R_S (on block B) is selected from the group consisting of 4-methoxyphenyl; substituted benzyl groups; alkylacyl, arylacyl or alkylarylacyl, and substituted alkylacyl, arylacyl or alkylarylacyl protecting groups; carbonate protecting groups; a *t*-butyldiphenylsilyloxy or other such substituted silyloxy protecting group allyl, methoxymethyl, methoxyethyl, benzyloxymethyl;

R_E is selected from the group consisting of methyl, C_2 - C_5 alkyl; substituted alkyl, C_3 - C_5 alkenyl; or, benzyl and substituted benzyl groups;

R_L is selected from a H atom; a levulinoyl, chloroacetyl, 4-acetoxybenzoyl, 4-acetamidobenzoyl, 4-azidobenzoyl, or other substituted benzoyl type

protecting group; a benzyl group, a 4-acetoxybenzyl, 4-acetamidobenzyl or other such suitable substituted benzyl type protecting group; γ -aminobutyryl, 4-N-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethylamino]-butyryl, 4-N-[1-(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxypyrimidin-5-ylidene)methylamino]-butyryl,
 5 4-N-Alloc-butyryl, 4-N-Fmoc-butyryl, 4-N-Boc-butyryl type protecting groups; allyloxycarbonyl, allyl ether, carbonate type protecting groups.

In a ninth aspect the invention provides for a disaccharide building block for
 10 the preparation of synthetic heparinoids, said building block of General Formula IX,



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General Formula IX (Alternate Block B-A)

Wherein X_1 is as defined as in General Formula I,
 R_A is defined as in General Formula XIII,
 20 R_{H1} is defined as in General Formula XIII,
 R_S is defined as in General Formula I,
 R_L is defined as in General Formula I, and
 R_M is defined as in General Formula III
 Or alternatively,
 25 X_1 is selected from the group consisting of hydroxy, alkenyloxy, alkoxy, aryloxy, benzyloxy, substituted benzyloxy; thioalkyl, thioaryl, halogen, imidoyl, phosphate and related phosphate ester type leaving groups, a t -butyldiphenylsilyloxy or other such substituted silyloxy protecting group; a lipoaminoacid or other such group suitable for conjugation to delivery systems
 30 or solid supports; and the stereochemistry may be alpha or beta;

R_A is selected from the group consisting of an azido function, an amine; an *NH*-Dde, *NH*-DTPM, *NH*-Fmoc, *NH*-Boc, *NH*-Troc, *N*-phthalimido, *NH*-Ac, *NH*-Allyloxycarbonyl; or R_{H1} and R_A can combine together to form a
5 cyclic carbamate;

R_S (on block A) is selected from the group consisting of 4-methoxyphenyl; substituted benzyl groups; alkylacyl, arylacyl or alkylarylacyl, and substituted alkylacyl, arylacyl or alkylarylacyl protecting groups; carbonate
10 protecting groups; a *t*-butyldiphenylsilyloxy or other such substituted silyloxy protecting group allyl, methoxymethyl, methoxyethyl, benzyloxymethyl;

R_S (on block B) is selected from the group consisting of 4-methoxyphenyl; substituted benzyl groups; alkylacyl, arylacyl or alkylarylacyl, and substituted alkylacyl, arylacyl or alkylarylacyl protecting groups; carbonate
15 protecting groups; a *t*-butyldiphenylsilyloxy or other such substituted silyloxy protecting group allyl, methoxymethyl, methoxyethyl, benzyloxymethyl;

R_H is selected from the group consisting of benzyl or substituted
20 benzyl protecting group, allyl, allyloxycarbonyl;

R_{H1} is selected from the group consisting of benzyl or substituted benzyl protecting group, allyl, allyloxycarbonyl, or R_{H1} and R_A can combine together to form a cyclic carbamate;
25

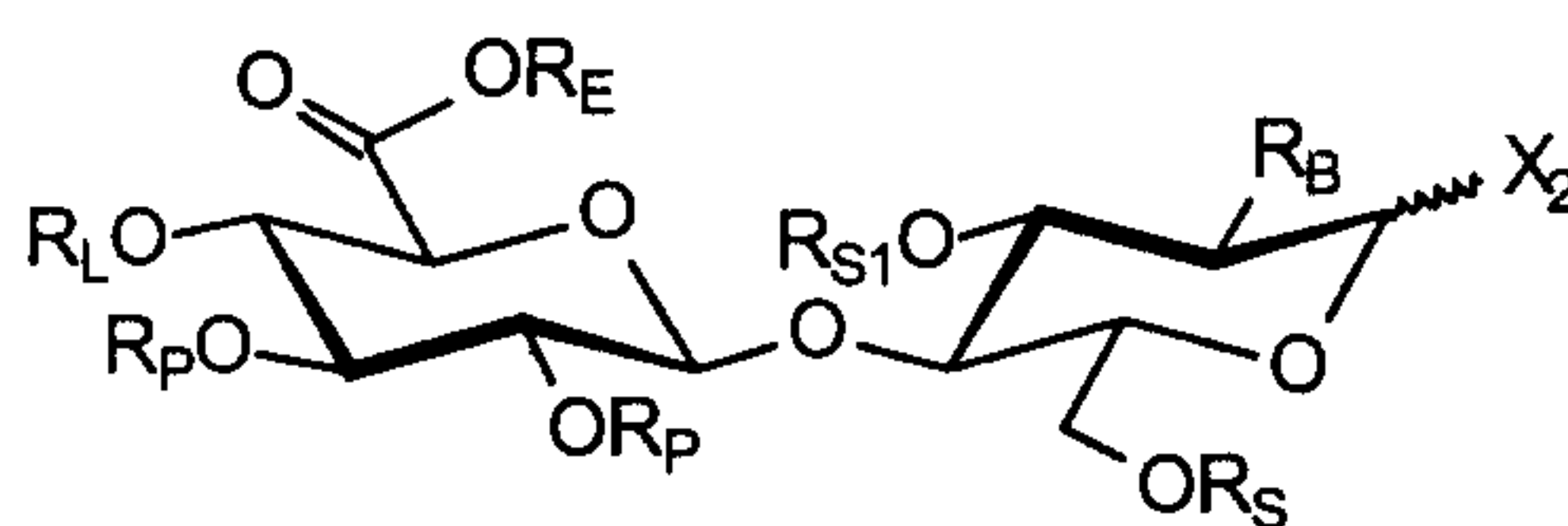
R_M is selected from a *p*-methoxyphenyl or *p*-methoxybenzyl protecting group or other suitable oxidatively labile protecting group; a trityl group;

30 or R_M and R_L are combined together to form an isopropylidene, benzylidene, substituted benzylidene, cyclohexylidene or other acetal or ketal protecting group;

R_L is selected from a H atom; a levulinoyl, chloroacetyl, 4-acetoxybenzoyl, 4-acetamidobenzoyl, 4-azidobenzoyl, or other substituted benzoyl type protecting group; a benzyl group, a 4-acetoxybenzyl, 4-acetamidobenzyl or other such suitable substituted benzyl type protecting group; γ -aminobutyryl, 4-N-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethylamino]-butyryl, 4-N-[1-(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxypyrimidin-5-ylidene)methylamino]-butyryl, 4-N-Alloc-butyryl, 4-N-Fmoc-butyryl, 4-N-Boc-butyryl type protecting groups; allyloxycarbonyl, allyl ether, carbonate type protecting groups.

10

In a tenth aspect the invention provides for a disaccharide building block for the preparation of synthetic heparinoids, said building block of General Formula X,



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General Formula X (Block D-C)

Wherein X_2 is as defined in General Formula II,

20 R_{S1} is defined as being selected from R_S of General Formula I, with the addition that R_{S1} and R_B can combine together to form a cyclic carbamate.

R_B is defined as in General Formula IV, with the addition that R_{S1} and R_B can combine together to form a cyclic carbamate.

R_S is defined as in General Formula I,

25 R_P are defined as in General Formula V,

R_L is defined as in General Formula I, and

R_E is defined as in General Formula II or

X_2 is selected from the group consisting of hydroxy, alkenyloxy, alkoxy, aryloxy, benzyloxy, substituted benzyloxy; thioalkyl, thioaryl, halogen, imidoyl, phosphate and related phosphate ester type leaving groups, a ^tbutyldiphenylsilyloxy or other such substituted silyloxy protecting group; a

30

lipoaminoacid or other such group suitable for conjugation to delivery systems or solid supports; and the stereochemistry may be alpha or beta;

- R_S** is selected from the group consisting of 4-methoxyphenyl; substituted benzyl groups; alkylacyl, arylacyl or alkylarylacyl, and substituted alkylacyl, arylacyl or alkylarylacyl protecting groups; carbonate protecting groups; a ^tbutyldiphenylsilyloxy or other such substituted silyloxy protecting group allyl, methoxymethyl, methoxyethyl, benzyloxymethyl;
- 5
- 10 **R_{S1}** is selected from the group consisting of 4-methoxyphenyl; substituted benzyl groups; alkylacyl, arylacyl or alkylarylacyl, and substituted alkylacyl, arylacyl or alkylarylacyl protecting groups; carbonate protecting groups; a ^tbutyldiphenylsilyloxy or other such substituted silyloxy protecting group allyl, methoxymethyl, methoxyethyl, benzyloxymethyl, or **R_{S1}** and **R_B**
- 15 may be combined to form a cyclic carbamate;

R_E is selected from the group consisting of methyl, C₂-C₅ alkyl; substituted alkyl, C₃-C₅ alkenyl; or, benzyl and substituted benzyl groups;

20

R_B is selected from the group consisting of an azido function, an NH-Dde or NH-DTPM group, or **R_{S4}** and **R_B** can combine together to form a cyclic carbamate;

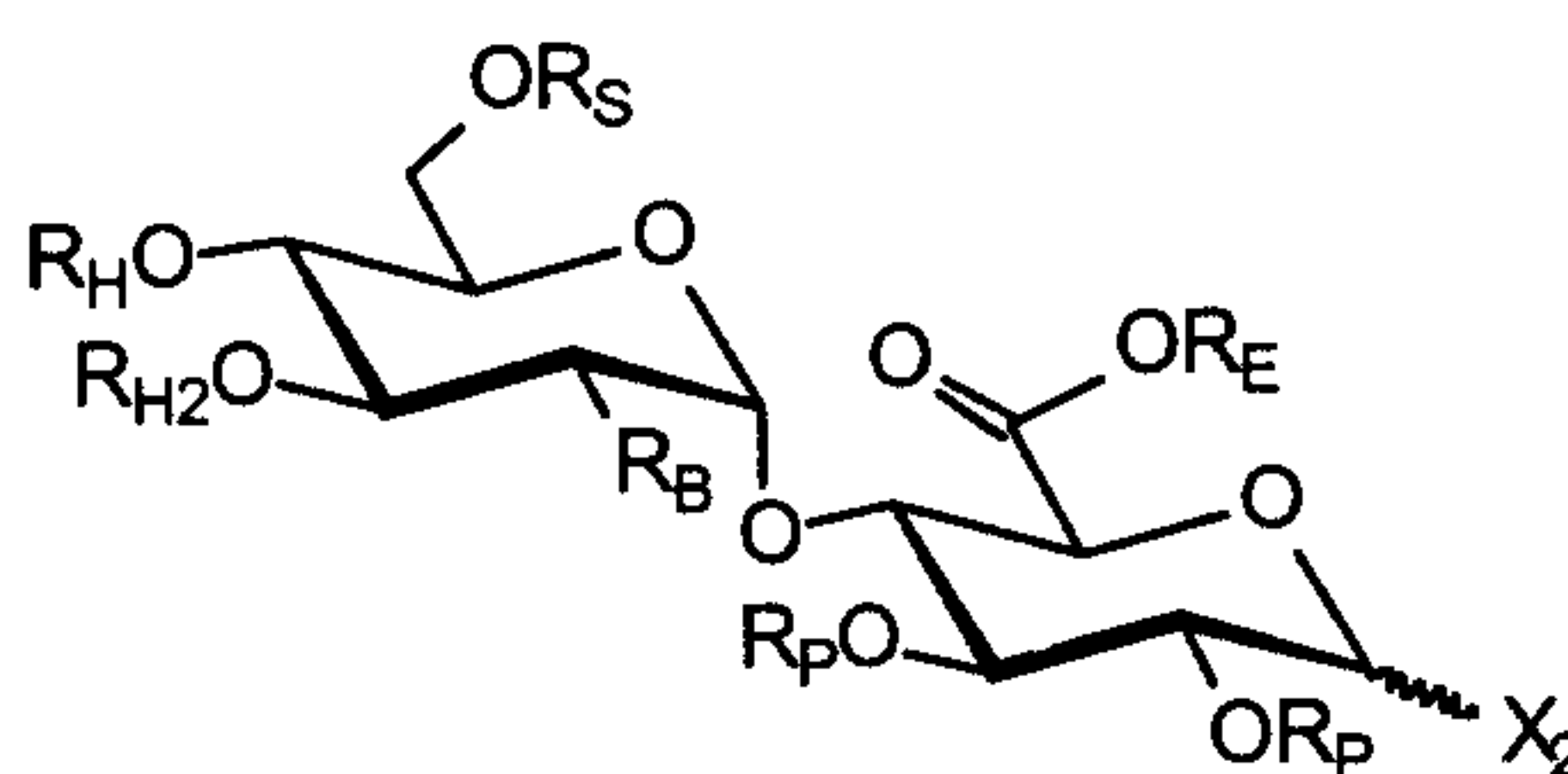
25 **R_P** (adjacent O-RL) is selected from the group consisting of 4-methoxyphenyl; benzyl, substituted benzyl groups; alkylacyl, arylacyl and alkylarylacyl, or substituted alkylacyl, arylacyl and alkylarylacyl protecting groups; carbonate protecting groups;

30 **R_P** (adjacent the link to block C) is selected from the group consisting of hydroxy, 4-methoxyphenyl; benzyl, substituted benzyl groups; alkylacyl, arylacyl and alkylarylacyl, or substituted alkylacyl, arylacyl and

alkylarylacyl protecting groups;, carbonate protecting groups, silyl protecting groups, carbamate protecting groups, C3-C5 alkenyl;

R_L is selected from a H atom; a levulinoyl, chloroacetyl, 4-acetoxybenzoyl, 4-acetamidobenzoyl, 4-azidobenzoyl, or other substituted benzoyl type protecting group; a 4-acetoxybenzyl, 4-acetamidobenzyl or other such suitable substituted benzyl type protecting group; γ -aminobutyryl, 4-N-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethylamino]butyryl, 4-N-[1-(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxypyrimidin-5-ylidene)methylamino]butyryl, 4-N-Alloc-butyl, 4-N-Fmoc-butyl, 4-N-Boc-butyl type protecting groups; allyloxycarbonyl, allyl ether, carbonate type protecting groups.

In an eleventh aspect the invention provides for a disaccharide building block for the preparation of synthetic heparinoids, said building block of General Formula XI,



General Formula XI (Block E-D)

Wherein X_2 is as defined in General Formula II,
 R_P are defined as in General Formula V,
 R_E is defined as in General Formula II,
 R_B is defined as in General Formula IV, with the addition that R_B and R_{H2} can combine to form a cyclic carbamate,
 R_{H2} is defined as being selected from R_H of General Formula I, with the addition that R_B and R_{H2} can combine to form a cyclic carbamate,
 R_H is defined as in General Formula I, and

R_S is defined as in General Formula I or

X_2 is selected from a hydroxyl group; thioalkyl, thioaryl, halogen, trichloroacetimidoyl, phosphate and related phosphate ester type leaving groups, a *t*-butyldiphenylsilyloxy or other such substituted silyloxy protecting group; and the stereochemistry may be alpha or beta;

R_P (adjacent the O link) is selected from the group consisting of 4-methoxyphenyl; benzyl, substituted benzyl groups; alkylacyl, arylacyl and alkylarylacyl, or substituted alkylacyl, arylacyl and alkylarylacyl protecting groups; carbonate protecting groups;

R_P (adjacent X_2) is selected from the group consisting of 4-methoxyphenyl; benzyl, substituted benzyl groups; alkylacyl, arylacyl and alkylarylacyl, or substituted alkylacyl, arylacyl and alkylarylacyl protecting groups; carbonate protecting groups, silyl protecting groups, carbamate protecting groups, C3-C5 alkenyl;

R_E is selected from the group consisting of methyl, C₂-C₅ alkyl; substituted alkyl, C₃-C₅ alkenyl; or, benzyl and substituted benzyl groups;

R_B is selected from the group consisting of an azido function, an amine; an NH-Dde or NH-DTPM group, or R_{H2} and R_{B1} can combine together to form a cyclic carbamate;

R_H is selected from the group consisting of benzyl or substituted benzyl protecting group, allyl, allyloxycarbonyl;

R_{H2} is selected from the group consisting of benzyl or substituted benzyl protecting group, allyl, allyloxycarbonyl, or R_{H2} and R_{B1} independently can combine together to form a cyclic carbamate;

R_S is selected from the group consisting of 4-methoxyphenyl; 4-methoxybenzyl, substituted benzyl groups; alkylacyl, benzoyl arylacyl or alkylarylacyl, and substituted alkylacyl, 4-chlorobenzoyl, arylacyl or

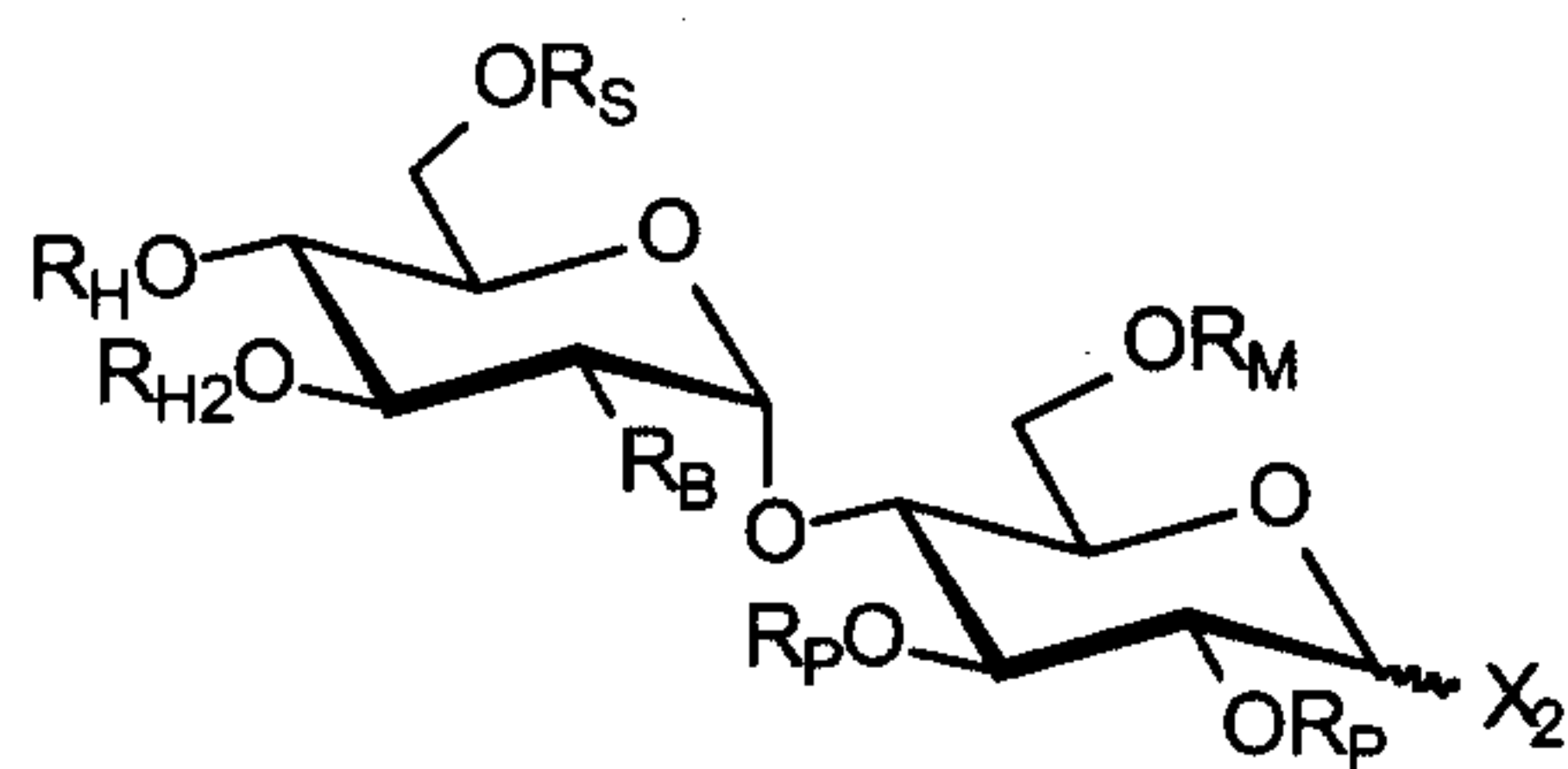
alkylarylacy protecting groups; allyloxycarbonyl, ethoxycarbonyl, tertbutoxycarbonyl, carbonate protecting groups; a ^tbutyldiphenylsilyloxy or other such substituted silyloxy protecting group allyl, methoxymethyl, methoxyethyl, benzyloxymethyl;

5

or R_S and R_H can be combined to form a cyclic acetal or ketal moiety;

In a twelfth aspect the invention provides for a disaccharide building block for the preparation of synthetic heparinoids, said building block of General Formula XII,

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General Formula XII (Alternate Block E-D)

Wherein X₂ is as defined in General Formula II,

R_P are defined as in General Formula V,

R_M is defined as in General Formula III,

20

R_B and R_{H2} are as defined in General Formula XI,

R_H is defined as in General Formula I, and

R_S is defined as in General Formula I or

X₂ is selected from a hydroxyl group; thioalkyl, thioaryl, halogen, trichloroacetimidoyl, phosphate and related phosphate ester type leaving groups, a ^tbutyldiphenylsilyloxy or other such substituted silyloxy protecting group; and the stereochemistry may be alpha or beta;

25

R_P (adjacent the O linking group) is selected from the group consisting of 4-methoxyphenyl; benzyl, substituted benzyl groups; alkylacyl,

arylacyl and alkylarylacyl, or substituted alkylacyl, arylacyl and alkylarylacyl protecting groups; carbonate protecting groups;

R_P (adjacent X) is selected from the group consisting of 4-methoxyphenyl; benzyl, substituted benzyl groups; alkylacyl, arylacyl and alkylarylacyl, or substituted alkylacyl, arylacyl and alkylarylacyl protecting groups; carbonate protecting groups, silyl protecting groups, carbamate protecting groups, C3-C5 alkenyl;

R_B is selected from the group consisting of an azido function, an amine; an *NH*-Dde or *NH*-DTPM group, or **R_{H2}** and **R_{B1}** can combine together to form a cyclic carbamate;

R_H is selected from the group consisting of benzyl or substituted benzyl protecting group, allyl, allyloxycarbonyl;

R_{H2} is selected from the group consisting of benzyl or substituted benzyl protecting group, allyl, allyloxycarbonyl, or **R_{H2}** and **R_{B1}** independently can combine together to form a cyclic carbamate;

20

R_S is selected from the group consisting of 4-methoxyphenyl; 4-methoxybenzyl, substituted benzyl groups; alkylacyl, benzoyl, arylacyl or alkylarylacyl, and substituted alkylacyl, 4-chlorobenzoyl, arylacyl or alkylarylacyl protecting groups; allyloxycarbonyl, ethoxycarbonyl, tertbutoxycarbonyl, carbonate protecting groups; is selected from the group consisting of 4-methoxyphenyl; substituted benzyl groups; alkylacyl, arylacyl or alkylarylacyl, and substituted alkylacyl, arylacyl or alkylarylacyl protecting groups; carbonate protecting groups; a ^tbutyldiphenylsilyloxy or other such substituted silyloxy protecting group allyl, methoxymethyl, methoxyethyl, benzyloxymethyl;

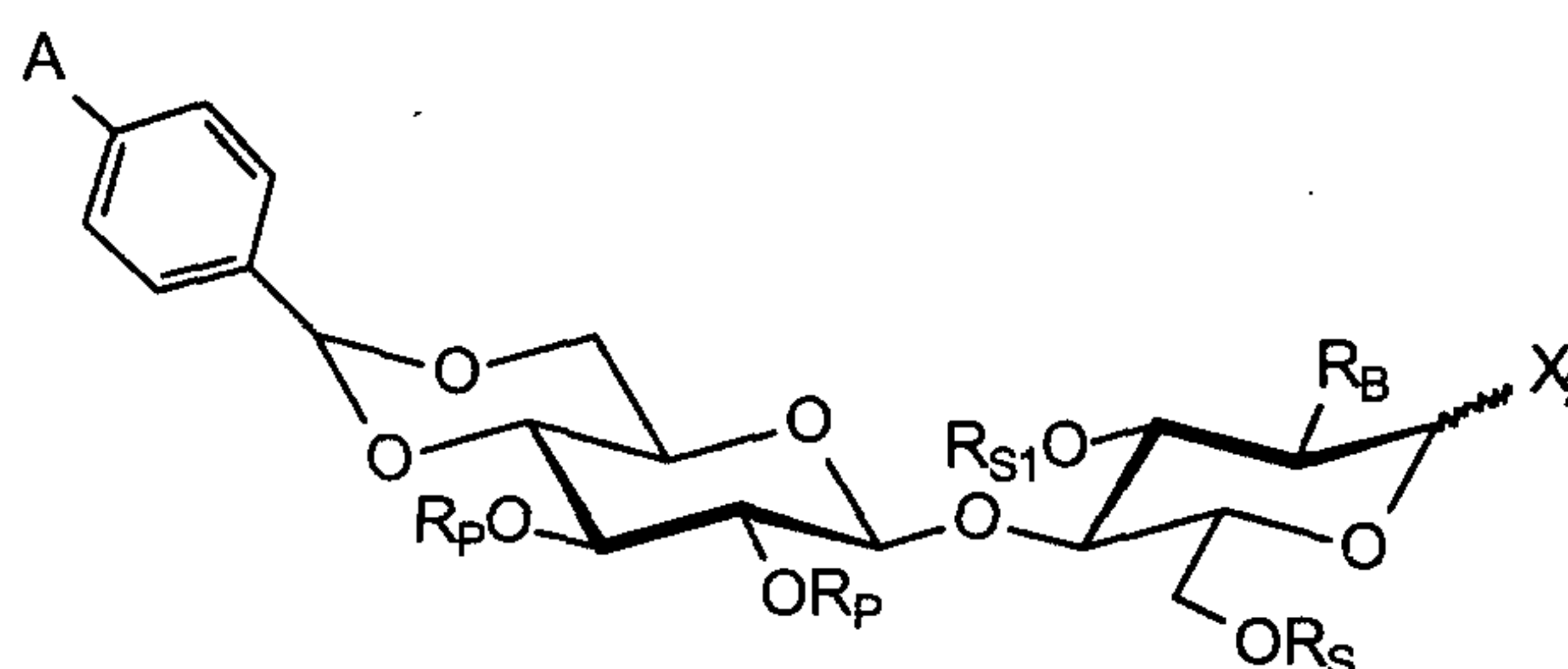
30

Or **R_S** and **R_H** can be combined to form a cyclic acetal or ketal moiety;

RM is selected from the group consisting of a *p*-methoxyphenyl protecting group or other suitable oxidatively labile protecting group; a trityl group.

5

In a thirteenth aspect the invention provides for a disaccharide building block for the preparation of synthetic heparinoids, said building block of General Formula XIII,



10

General Formula XIII (Alternate Block D-C)

Wherein X_2 is defined as in General Formula II,

15 R_B and R_{S1} are defined as in General Formula X,

R_S is defined as in General Formula I,

R_P is defined as in General Formula V, and

A includes but is not limited to; H, Methoxy, Methyl; other suitable substituents will be known to those in the art, or

20 X_2 is selected from a hydroxyl group; thioalkyl, thioaryl, halogen, imidoxy, phosphate and related phosphate ester type leaving groups, a *t*-butyldiphenylsilyloxy or other such substituted silyloxy protecting group; and the stereochemistry may be alpha or beta;

25 R_B is selected from the group consisting of an azido function, an amine; an *NH*-Dde or *NH*-DTPM group, or R_{S4} and R_B can combine together to form a cyclic carbamate;

R_S is selected from the group consisting of 4-methoxyphenyl; substituted benzyl groups; alkylacyl, arylacyl or alkylarylacyl, and substituted alkylacyl, arylacyl or alkylarylacyl protecting groups; carbonate protecting groups; a ^tbutyldiphenylsilyloxy or other such substituted silyloxy protecting group allyl, methoxymethyl, methoxyethyl, benzyloxymethyl;

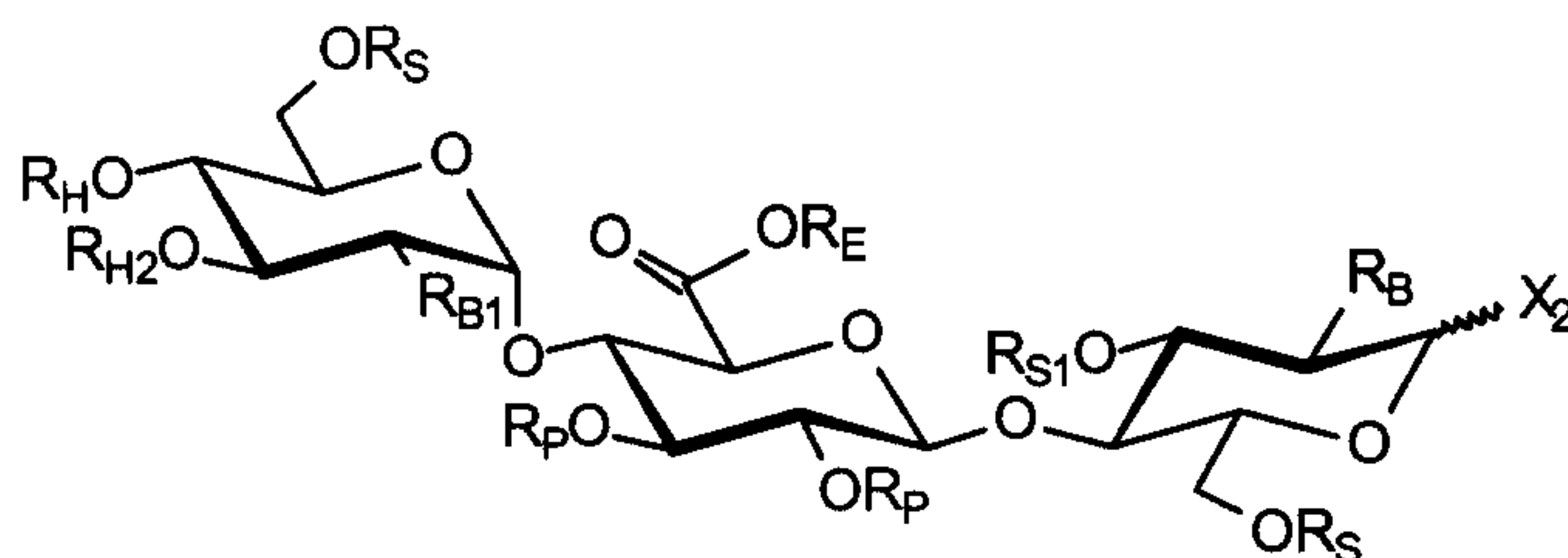
R_{S1} is selected from the group consisting of 4-methoxyphenyl; substituted benzyl groups; alkylacyl, arylacyl or alkylarylacyl, and substituted alkylacyl, arylacyl or alkylarylacyl protecting groups; carbonate protecting groups; a ^tbutyldiphenylsilyloxy or other such substituted silyloxy protecting group allyl, methoxymethyl, methoxyethyl, benzyloxymethyl; or **R_{S4}** and **R_B** may be combined to form a cyclic carbamate;

R_P (adjacent the O linking atom to the benzyl) is selected from the group consisting of 4-methoxyphenyl; benzyl, substituted benzyl groups; alkylacyl, arylacyl and alkylarylacyl, or substituted alkylacyl, arylacyl and alkylarylacyl protecting groups; carbonate protecting groups;

R_P (adjacent the O linking atom to C) is selected from the group consisting of 4-methoxyphenyl; benzyl, substituted benzyl groups; alkylacyl, arylacyl and alkylarylacyl, or substituted alkylacyl, arylacyl and alkylarylacyl protecting groups; carbonate protecting groups, silyl protecting groups, carbamate protecting groups, C3-C5 alkenyl;

A includes but is not limited to; H, Methoxy, Methyl; other suitable substituents will be known to those in the art.

In a fourteenth aspect the invention provides for a trisaccharide building block for the preparation of synthetic heparinoids, said building block of General Formula XIV,



General Formula XIV (Block E-D-C)

- 5 Wherein X_2 is defined as in General Formula II,
 R_B and R_{S1} are defined as in General Formula X,
 R_S is defined as in General Formula I,
 R_P is defined as in General Formula V,
 R_E is defined as in General Formula II,
- 10 R_{B1} is defined as being selected from R_B of General Formula IV, with the
 addition that R_{B1} can combine together with R_{H2} to form a cyclic carbamate,
 R_{H2} is defined as being selected from R_H of General Formula I, with the
 addition that R_{H2} can combine together with R_{B1} to form a cyclic carbamate,
 and
- 15 R_H is defined as in General Formula I or
 X_2 is selected from a hydroxyl group; thioalkyl, thioaryl, halogen,
 trichloroacetimidoyl, phosphate and related phosphate ester type leaving
 groups, a ^tbutyldiphenylsilyloxy or other such substituted silyloxy protecting
 group; and the stereochemistry may be alpha or beta;
- 20 R_P (adjacent block E) is selected from the group consisting of 4-
 methoxyphenyl; benzyl, substituted benzyl groups; alkylacyl, arylacyl and
 alkylarylacyl, or substituted alkylacyl, arylacyl and alkylarylacyl protecting
 groups; carbonate protecting groups;
- 25 R_P (adjacent Block C) is selected from the group consisting of 4-
 methoxyphenyl; benzyl, substituted benzyl groups; alkylacyl, arylacyl and
 alkylarylacyl, or substituted alkylacyl, arylacyl and alkylarylacyl protecting
 groups; carbonate protecting groups, silyl protecting groups, carbamate
- 30 protecting groups, C3-C5 alkenyl;

R_E is selected from the group consisting of methyl, C₂-C₅ alkyl; substituted alkyl, C₃-C₅ alkenyl; or, benzyl and substituted benzyl groups;

- 5 **R_{B1}** is selected from the group consisting of an azido function, an amine; an *NH*-Dde or *NH*-DTPM group, or **R_{H2}** and **R_{B1}** can combine together to form a cyclic carbamate;

R_H is selected from the group consisting of benzyl or substituted benzyl protecting group, allyl, allyloxycarbonyl;

10

R_{H2} is selected from the group consisting of benzyl or substituted benzyl protecting group, allyl, allyloxycarbonyl, or **R_{H2}** and **R_{B1}** independently can combine together to form a cyclic carbamate;

15

- R_S** (on block E) is selected from the group consisting of 4-methoxyphenyl; 4-methoxybenzyl, substituted benzyl groups; alkylacyl, benzoyl, arylacyl or alkylarylacyl, and substituted alkylacyl, 4-chlorobenzoyl, arylacyl or alkylarylacyl protecting groups; allyloxycarbonyl, ethoxycarbonyl, tertbutoxycarbonyl, carbonate protecting groups; is selected from the group
20 consisting of 4-methoxyphenyl; substituted benzyl groups; alkylacyl, arylacyl or alkylarylacyl, and substituted alkylacyl, arylacyl or alkylarylacyl protecting groups; carbonate protecting groups; a ^tbutyldiphenylsilyloxy or other such substituted silyloxy protecting group allyl, methoxymethyl, methoxyethyl,
25 benzyloxymethyl;

or **R_S** and **R_H** can be combined to form a cyclic acetal or ketal moiety;

- 30 **R_S** (on block C and adjacent the ring O) is selected from the group consisting of 4-methoxyphenyl; substituted benzyl groups; alkylacyl, arylacyl or alkylarylacyl, and substituted alkylacyl, arylacyl or alkylarylacyl protecting groups; carbonate protecting groups; a ^tbutyldiphenylsilyloxy or other such

substituted silyloxy protecting group allyl, methoxymethyl, methoxyethyl ,
benzyloxymethyl;

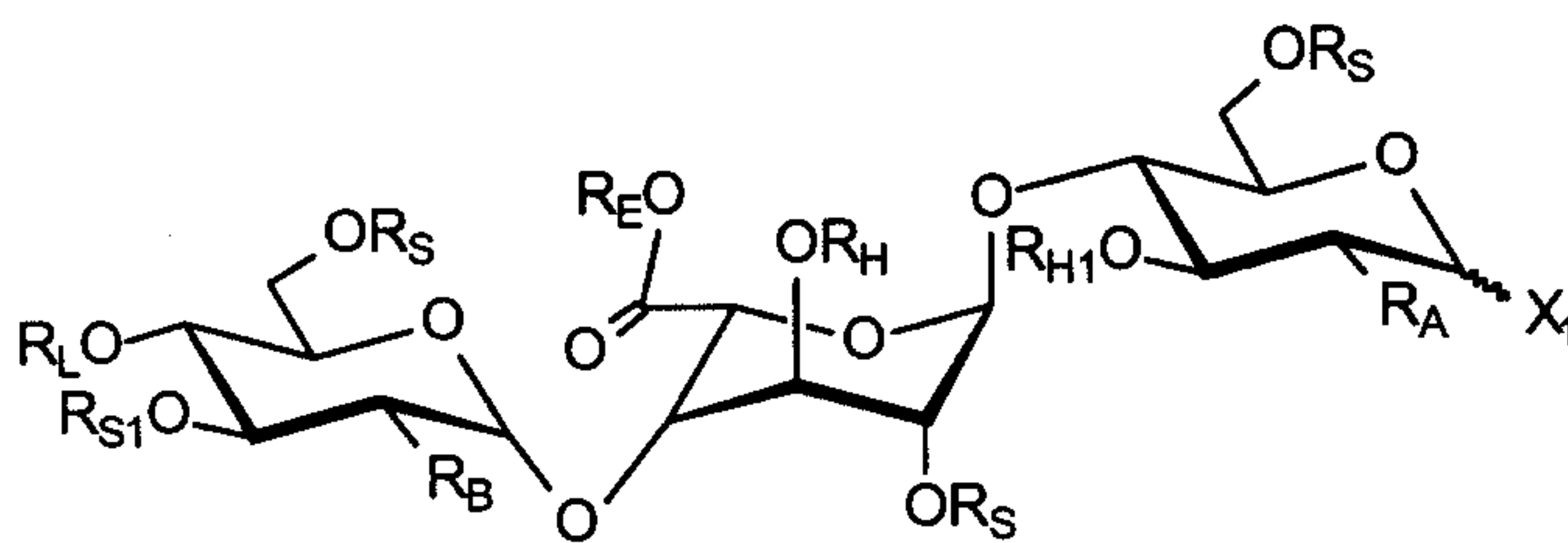
R_S (on block C and adjacent the O linking atom) is selected from
5 the group consisting of 4-methoxyphenyl; substituted benzyl groups; alkylacyl,
arylacyl or alkylarylacyl, and substituted alkylacyl, arylacyl or alkylarylacyl
protecting groups; carbonate protecting groups; a ^tbutyldiphenylsilyloxy or
other such substituted silyloxy protecting group allyl, methoxymethyl,
methoxyethyl, benzyloxymethyl;

10

or R_S and R_B may be combined to form a cyclic carbamate;

R_B is selected from the group consisting of an azido function, an
amine; an NH-Dde or NH-DTPM group, or R_{S4} and R_B can combine together
15 to form a cyclic carbamate;

In a fifteenth aspect the invention provides for a trisaccharide building block
20 for the preparation of synthetic heparinoids, said building block of General
Formula XV,



25

General Formula XV (Block C-B-A)

Wherein X_1 is defined as in General Formula I
 R_A and R_{H1} are defined as in General Formula VIII,
 R_S is defined as in General Formula I,
30 R_H is defined as in General Formula I,

R_E is defined as in General Formula II,

R_B and R_{S1} are defined as in General Formula X, and

R_L is defined as in General Formula I or

X_1 is selected from the group consisting of hydroxy, akenyloxy, alkoxy, aryloxy, benzyloxy, substituted benzyloxy; thioalkyl, thioaryl, halogen, imidoyl, phosphate and related phosphate ester type leaving groups, a ^tbutyldiphenylsilyloxy or other such substituted silyloxy protecting group; a lipoaminoacid or other such group suitable for conjugation to delivery systems or solid supports; and the stereochemistry may be alpha or beta;

10

R_H is selected from the group consisting of benzyl or substituted benzyl protecting group, allyl, allyloxycarbonyl;

R_{H1} is selected from the group consisting of benzyl or substituted benzyl protecting group, allyl, allyloxycarbonyl;

15

R_A is selected from the group consisting of an azido function, an amine; an *NH*-Dde, *NH*-DTPM, *NH*-Fmoc, *NH*-Boc, *NH*-Cbz, *NH*-Troc, *N*-phthalimido, *NH*-Ac, *NH*-Allyloxycarbonyl; or R_H and R_A can combine together to form a cyclic carbamate;

20

R_S (on block A) is selected from the group consisting of 4-methoxyphenyl; substituted benzyl groups; alkylacyl, arylacyl or alkylarylacyl, and substituted alkylacyl, arylacyl or alkylarylacyl protecting groups; carbonate protecting groups; a ^tbutyldiphenylsilyloxy or other such substituted silyloxy protecting group allyl, methoxymethyl, methoxyethyl, benzyloxymethyl;

25

R_S (on block B) is selected from the group consisting of 4-methoxyphenyl; substituted benzyl groups; alkylacyl, arylacyl or alkylarylacyl, and substituted alkylacyl, arylacyl or alkylarylacyl protecting groups; carbonate protecting groups; a ^tbutyldiphenylsilyloxy or other such substituted silyloxy protecting group allyl, methoxymethyl, methoxyethyl, benzyloxymethyl;

30

R_S (on block C) is selected from the group consisting of 4-methoxyphenyl; substituted benzyl groups; alkylacyl, arylacyl or alkylarylacyl, and substituted alkylacyl, arylacyl or alkylarylacyl protecting groups; carbonate protecting groups; a ^tbutyldiphenylsilyloxy or other such substituted silyloxy protecting group allyl, methoxymethyl, methoxyethyl , benzyloxymethyl;

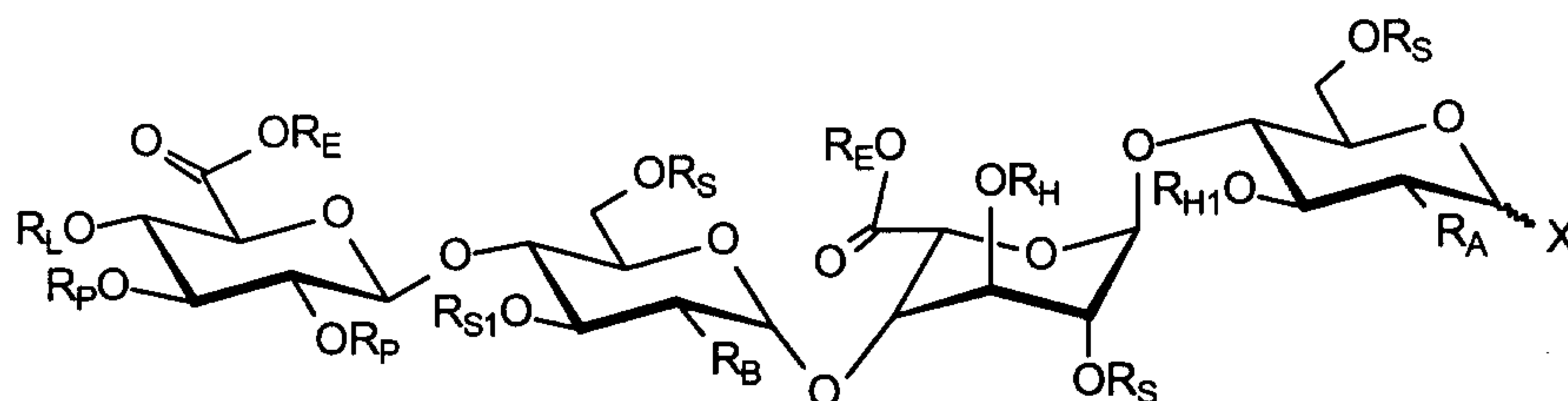
R_{S4} is selected from the group consisting of 4-methoxyphenyl; substituted benzyl groups; alkylacyl, arylacyl or alkylarylacyl, and substituted alkylacyl, arylacyl or alkylarylacyl protecting groups; carbonate protecting groups; a ^tbutyldiphenylsilyloxy or other such substituted silyloxy protecting group allyl, methoxymethyl, methoxyethyl, benzyloxymethyl, or **R_{S4}** and **R_B** may be combined to form a cyclic carbamate;

R_E is selected from the group consisting of methyl, C₂-C₅ alkyl; substituted alkyl, C₃-C₅ alkenyl; or, benzyl and substituted benzyl groups;

R_B is selected from the group consisting of an azido function, an amine; an NH-Dde or NH-DTPM group, or **R_{S4}** and **R_B** can combine together to form a cyclic carbamate;

R_L is selected from a H atom; a levulinoyl, chloroacetyl, 4-acetoxybenzoyl, 4-acetamidobenzoyl, 4-azidobenzoyl, or other substituted benzoyl type protecting group; a benzyl group, a 4-acetoxybenzyl, 4-acetamidobenzyl or other such suitable substituted benzyl type protecting group; γ -aminobutyryl, 4-N-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethylamino]-butyryl, 4-N-[1-(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)methylamino]-butyryl, 4-N-Alloc-butyryl, 4-N-Fmoc-butyryl, 4-N-Boc-butyryl type protecting groups; allyloxycarbonyl, allyl ether, carbonate type protecting groups;

In a sixteenth aspect the invention provides for a tetrasaccharide building block for the preparation of synthetic heparinoids, said building block of General Formula XVI,



5

General Formula XVI (Block D-C-B-A)

Wherein X_1 is defined as in General Formula I

10 R_A and R_{H1} are defined as in General Formula VIII,

R_S is defined as in General Formula I,

R_H is defined as in General Formula I,

R_E is defined as in General Formula II,

R_B and R_{S1} are defined as in General Formula X,

15 R_P is as defined in General Formula V, and

R_L is as defined in General Formula I or

20 X_1 is selected from the group consisting of hydroxy, alkenyloxy, alkoxy, aryloxy, benzyloxy, substituted benzyloxy; thioalkyl, thioaryl, halogen, imidoyl, phosphate and related phosphate ester type leaving groups, a t -butyldiphenylsilyloxy or other such substituted silyloxy protecting group; a lipoaminoacid or other such group suitable for conjugation to delivery systems or solid supports; and the stereochemistry may be alpha or beta,

25 R_H is selected from the group consisting of benzyl or substituted benzyl protecting group, allyl, allyloxycarbonyl;

R_{H1} is selected from the group consisting of benzyl or substituted benzyl protecting group, allyl, allyloxycarbonyl, or R_{H1} and R_A can combine together to form a cyclic carbamate;

30

R_A is selected from the group consisting of an azido function, an amine; an *NH*-Dde, *NH*-DTPM, *NH*-Fmoc, *NH*-Boc, *NH*-Cbz, *NH*-Troc, *N*-phthalimido, *NH*-Ac, *NH*-Allyloxycarbonyl; or **R_{H1}** and **R_A** can combine together to form a cyclic carbamate,

5

R_S (on block A) is selected from the group consisting of 4-methoxyphenyl; substituted benzyl groups; alkylacyl, arylacyl or alkylarylacyl, and substituted alkylacyl, arylacyl or alkylarylacyl protecting groups; carbonate protecting groups; a ^tbutyldiphenylsilyloxy or other such substituted silyloxy protecting group allyl, methoxymethyl, methoxyethyl, benzyloxymethyl,

10

R_S (on block B) is selected from the group consisting of 4-methoxyphenyl; substituted benzyl groups; alkylacyl, arylacyl or alkylarylacyl, and substituted alkylacyl, arylacyl or alkylarylacyl protecting groups; carbonate protecting groups; a ^tbutyldiphenylsilyloxy or other such substituted silyloxy protecting group allyl, methoxymethyl, methoxyethyl, benzyloxymethyl,

15

R_S (on block C and adjacent the ring oxygen) is selected from the group consisting of 4-methoxyphenyl; substituted benzyl groups; alkylacyl, arylacyl or alkylarylacyl, and substituted alkylacyl, arylacyl or alkylarylacyl protecting groups; carbonate protecting groups; a ^tbutyldiphenylsilyloxy or other such substituted silyloxy protecting group allyl, methoxymethyl, methoxyethyl, benzyloxymethyl,

20

25

R_S (on block C and adjacent the linking O) is selected from the group consisting of 4-methoxyphenyl; substituted benzyl groups; alkylacyl, arylacyl or alkylarylacyl, and substituted alkylacyl, arylacyl or alkylarylacyl protecting groups; carbonate protecting groups; a ^tbutyldiphenylsilyloxy or other such substituted silyloxy protecting group allyl, methoxymethyl, methoxyethyl, benzyloxymethyl,

30

or **R_{S4}** and **R_B** may be combined to form a cyclic carbamate,

R_E (on block D) is selected from the group consisting of methyl, C₂-C₅ alkyl; substituted alkyl, C₃-C₅ alkenyl; or, benzyl and substituted benzyl groups;

- 5 **R_E** (on block B) is selected from the group consisting of methyl, C₂-C₅ alkyl; substituted alkyl, C₃-C₅ alkenyl; or, benzyl and substituted benzyl groups,

- R_B** is selected from the group consisting of an azido function, an amine; an NH-Dde or NH-DTPM group, or **R_{S4}** and **R_B** can combine together to form a cyclic carbamate,
- 10

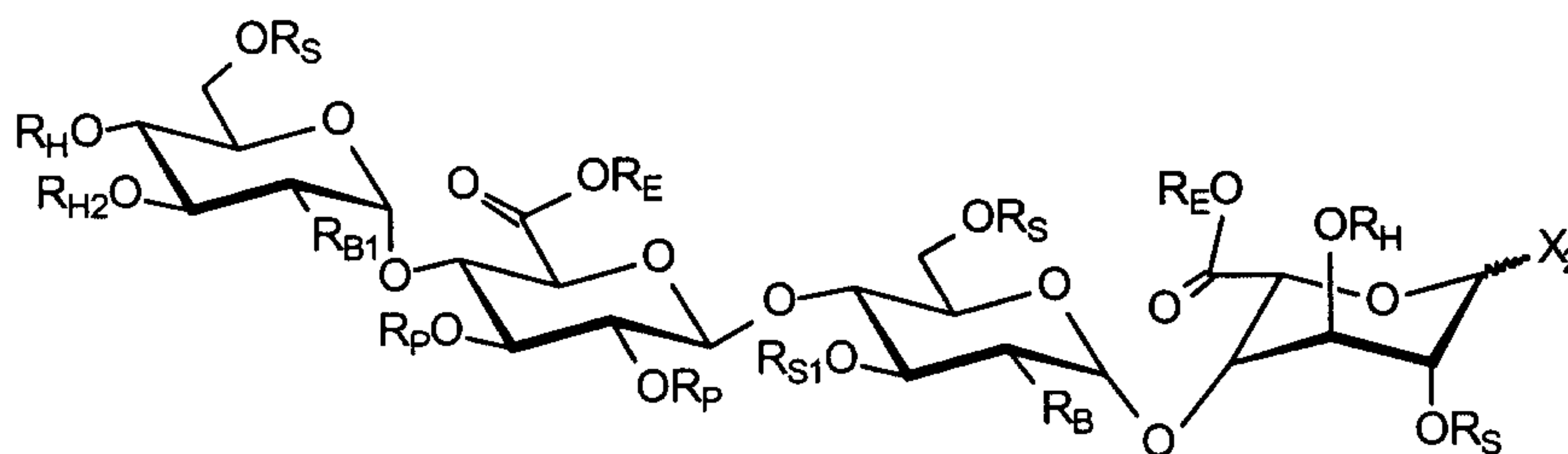
- R_P** (adjacent RL) is selected from the group consisting of 4-methoxyphenyl; benzyl, substituted benzyl groups; alkylacyl, arylacyl and alkylarylacyl, or substituted alkylacyl, arylacyl and alkylarylacyl protecting groups;, carbonate protecting groups;
- 15

- R_P** (on group D and adjacent group C) is selected from the group consisting of 4-methoxyphenyl; benzyl, substituted benzyl groups; alkylacyl, arylacyl and alkylarylacyl, or substituted alkylacyl, arylacyl and alkylarylacyl protecting groups;, carbonate protecting groups, silyl protecting groups, carbamate protecting groups, C₃-C₅ alkenyl;
- 20

- 25 **R_L** is selected from a H atom; a levulinoyl, chloroacetyl, 4-acetoxybenzoyl, 4-acetamidobenzoyl, 4-azidobenzoyl, or other substituted benzoyl type protecting group; a benzyl group, a 4-acetoxybenzyl, 4-acetamidobenzyl or other such suitable substituted benzyl type protecting group; γ -aminobutyryl, 4-N-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethylamino]-butyryl, 4-N-[1-(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)methylamino]-butyryl,
- 30 4-N-Alloc-butyryl, 4-N-Fmoc-butyryl, 4-N-Boc-butyryl type protecting groups; allyloxycarbonyl, allyl ether, carbonate type protecting groups;

In an seventeenth aspect the invention provides for a tetrasaccharide building block for the preparation of synthetic heparinoids, said building block of General Formula XVII,

5



General Formula XVII (Block E-D-C-B)

- 10 Wherein X_2 is defined as in General Formula IV,
 R_H is defined as in General Formula I,
 R_E is defined as in General Formula II,
 R_B and R_{S1} are defined as in General Formula X,
 R_S is defined as in General Formula I,
- 15 R_P is defined as in General Formula V,
 R_L is defined as in General Formula I, and
 R_{B1} and R_{H2} are defined as in General Formula XIV, or
 R_H is selected from the group consisting of benzyl or substituted benzyl protecting group, allyl, allyloxycarbonyl;
- 20 R_{H2} is selected from the group consisting of benzyl or substituted benzyl protecting group, allyl, allyloxycarbonyl, or R_{H2} and R_{B1} independently can combine together to form a cyclic carbamate;
- 25 R_S (on block B) is selected from the group consisting of 4-methoxyphenyl; substituted benzyl groups; alkylacyl, arylacyl or alkylarylacyl, and substituted alkylacyl, arylacyl or alkylarylacyl protecting groups; carbonate protecting groups; a ^tbutyldiphenylsilyloxy or other such substituted silyloxy protecting group allyl, methoxymethyl, methoxyethyl, benzyloxymethyl;

- R_S** (on block C and adjacent the ring O) is selected from the group consisting of 4-methoxyphenyl; substituted benzyl groups; alkylacyl, arylacyl or alkylarylacyl, and substituted alkylacyl, arylacyl or alkylarylacyl protecting groups; carbonate protecting groups; a ^tbutyldiphenylsilyloxy or other such substituted silyloxy protecting group allyl, methoxymethyl, methoxyethyl , benzyloxymethyl;
- 10 **R_S** (on block C and adjacent the O linking atom) is selected from the group consisting of 4-methoxyphenyl; substituted benzyl groups; alkylacyl, arylacyl or alkylarylacyl, and substituted alkylacyl, arylacyl or alkylarylacyl protecting groups; carbonate protecting groups; a ^tbutyldiphenylsilyloxy or other such substituted silyloxy protecting group allyl, methoxymethyl, methoxyethyl, benzyloxymethyl, or this **R_S** and **R_B** may be combined to form a cyclic carbamate,
- 20 **R_S** (on block E) is selected from the group consisting of 4-methoxyphenyl; 4-methoxybenzyl, substituted benzyl groups; alkylacyl, benzoyl, arylacyl or alkylarylacyl, and substituted alkylacyl, 4-chlorobenzoyl, arylacyl or alkylarylacyl protecting groups; allyloxycarbonyl, ethoxycarbonyl, tertbutoxycarbonyl, carbonate protecting groups; is selected from the group consisting of 4-methoxyphenyl; substituted benzyl groups; alkylacyl, arylacyl or alkylarylacyl, and substituted alkylacyl, arylacyl or alkylarylacyl protecting groups; carbonate protecting groups; a ^tbutyldiphenylsilyloxy or other such substituted silyloxy protecting group allyl, methoxymethyl, methoxyethyl, benzyloxymethyl; or this **R_S** and **R_H** can be combined to form a cyclic acetal or ketal moiety;
- 30 **R_E** (on block D) is selected from the group consisting of methyl, C₂-C₅ alkyl; substituted alkyl, C₃-C₅ alkenyl; or, benzyl and substituted benzyl groups;

R_E (on block B) is selected from the group consisting of methyl, C₂-C₅ alkyl; substituted alkyl, C₃-C₅ alkenyl; or, benzyl and substituted benzyl groups;

5 **R_B** is selected from the group consisting of an azido function, an amine; an NH-Dde or NH-DTPM group, or **R_{S4}** and **R_B** can combine together to form a cyclic carbamate;

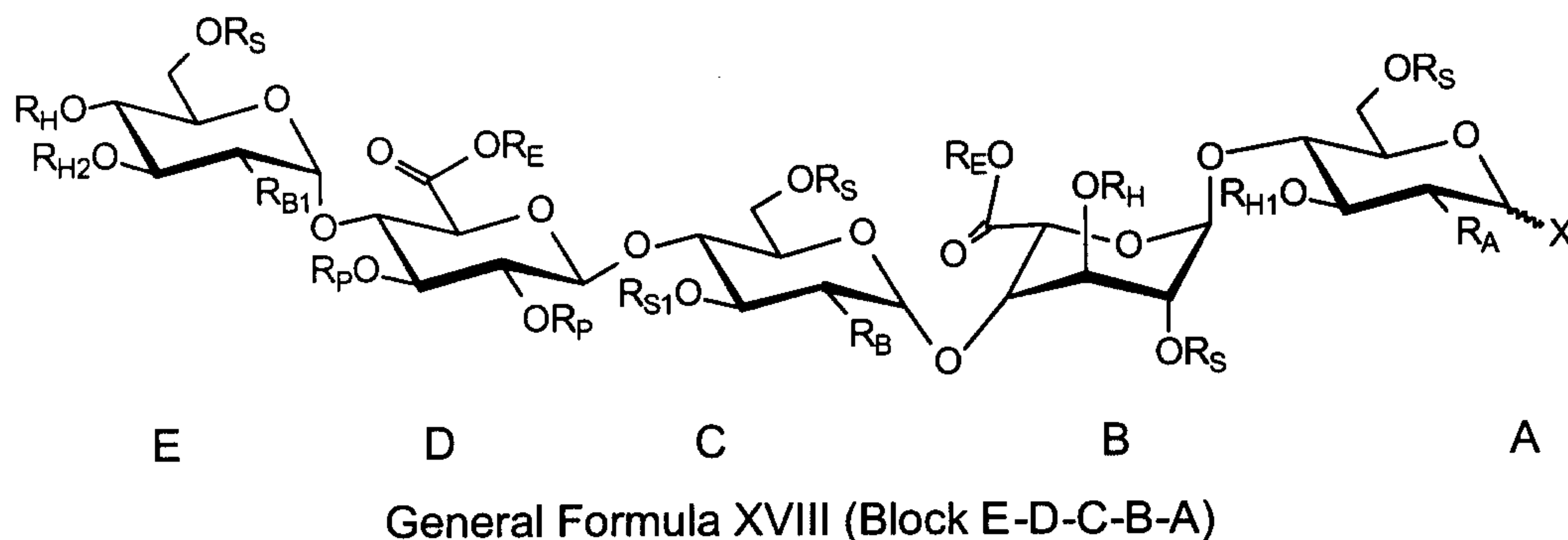
R_{B1} is selected from the group consisting of an azido function, an
10 amine; an NH-Dde or NH-DTPM group, or **R_{H2}** and **R_{B1}** can combine together to form a cyclic carbamate;

R_P (on block D adjacent block E) is selected from the group consisting of 4-methoxyphenyl; benzyl, substituted benzyl groups; alkylacyl,
15 arylacyl and alkylarylacyl, or substituted alkylacyl, arylacyl and alkylarylacyl protecting groups;, carbonate protecting groups;

R_P (on block D adjacent block C) is selected from the group consisting of 4-methoxyphenyl; benzyl, substituted benzyl groups; alkylacyl,
20 arylacyl and alkylarylacyl, or substituted alkylacyl, arylacyl and alkylarylacyl protecting groups;, carbonate protecting groups, silyl protecting groups, carbamate protecting groups, C3-C5 alkenyl;

X₂ is selected from a hydroxyl group; thioalkyl, thioaryl, halogen,
25 trichloroacetimidoyl, phosphate and related phosphate ester type leaving groups, a ^tbutyldiphenylsilyloxy or other such substituted silyloxy protecting group; and the stereochemistry may be alpha or beta

30 In a eighteenth aspect the invention provides for a pentasaccharide building block for the preparation of synthetic heparinoids, said building block of General Formula XVIII,



5 Wherein X_1 is defined as in General Formula I

R_A and R_{H1} are defined as in General Formula VIII, and R_{H1} can also be allyl and alloxycarbonyl or R_A and R_{H1} can combine together to form a cyclic carbamate.

R_S is defined as in General Formula I,

10 R_H is defined as in General Formula I, or R_H is selected from the group consisting of benzyl or substituted benzyl protecting group, allyl, allyloxycarbonyl,

R_E is defined as in General Formula II,

R_B and R_{S1} are defined as in General Formula X,

R_P is defined as in General Formula V, and may be benzyl,

15 R_P (adjacent the link from D to C) may also be silyl protecting groups, carbamate protecting groups, C3-C5 alkenyl, and

20 R_{B1} and R_{H2} are defined as in General Formula XIV or R_{H2} is selected from the group consisting of benzyl or substituted benzyl protecting group, allyl, allyloxycarbonyl, or R_{H2} and R_{B1} independently can combine together to form a cyclic carbamate,

25 R_{S1} on block C (R_{S4} in the claims) is selected from the group consisting of 4-methoxyphenyl; substituted benzyl groups; alkylacyl, arylacyl or alkylarylacyl, and substituted alkylacyl, arylacyl or alkylarylacyl protecting groups; carbonate protecting groups; a ^tbutyldiphenylsilyloxy or other such substituted silyloxy protecting group; allyl, methoxymethyl, methoxyethyl, benzyloxymethyl, or R_{S4} and R_B may be combined to form a cyclic carbamate;

R_S on block E C B A, ($R_{S1,2,3,5}$ in the claims) can be a ^tbutyldiphenylsilyloxy or other such substituted silyloxy protecting group; allyl, methoxymethyl, methoxyethyl, benzyloxymethyl,

5

In a nineteenth aspect, the invention provides a method for the preparation of compounds of the eighth aspect, involving the step of reacting a compound of
10 the second or third aspect with a compound of the first or seventh aspect to form a new glycosidic bond.

In a twentieth aspect, the invention provides a method for the preparation of compounds of the eighth aspect, involving the step of selectively removing the
15 protecting group R_M from compounds of the ninth aspect and oxidizing the product of said deprotection.

In a twenty first aspect, the invention provides a method for the preparation of compounds of the tenth aspect, involving the step of reacting a compound of
20 the fifth aspect with a compound of the fourth or seventh aspect to form a new glycosidic bond.

In a twenty second aspect, the invention provides a method for the preparation of compounds of the eleventh aspect, involving the step of
25 reacting a compound of the fifth aspect with a compound of the sixth or seventh aspect to form a new glycosidic bond.

In a twenty third aspect, the invention provides a method for preparation of compounds of the thirteenth aspect involving the reaction of a compound of
30 the fourth or seventh aspect with a suitable donor molecule, to form a new glycosidic bond.

In a twenty fourth aspect, the invention provides a method for the preparation of compounds of the fourteenth aspect involving the step of using any one or

more of the compounds of the fourth, fifth, sixth, seventh, tenth, eleventh, twelfth or thirteenth aspect in a glycosidic bond forming reaction.

5 In a twenty fifth aspect, the invention provides a method for the preparation of compounds of the fifteenth aspect involving the step of using any one or more compounds of the first, second, third, fourth, seventh, eighth and ninth aspects in a glycosidic bond forming reaction.

10 In a twenty sixth aspect, the invention provides a method for the preparation of compounds of the sixteenth aspect involving the step of using any one or more of the compounds of the first, second third, fourth, fifth, seventh, eighth, ninth, tenth, thirteenth or fifteenth aspect in a glycosidic bond forming reaction.

15 In a twenty seventh aspect, the invention provides a method for the preparation of compounds of the seventeenth aspect involving the step of using any one or more of the compounds of the second, third, fourth, fifth, seventh, tenth, eleventh, twelfth, thirteenth or fourteenth aspect in a glycosidic bond forming reaction.

20 In a twenty eighth aspect, the invention provides a method for the preparation of compounds of the eighteenth aspect involving the step of using any one or more of the compounds of the 1,2,3,4,5,7,8,9, 10, 11, 12, 13, 14, or 15, 16 or 17th aspect in a glycosidic bond forming reaction.

25

Brief Description of the Drawings

Figure 1 is an NMR spectrograph of the bis-methyl ester of compound P-33 of the invention.

30

Figure 2 is an NMR spectrogram of compound P-40 of the invention.

Detailed Description of the Invention

Embodiments of the invention representative of the best mode will be described with reference to the following examples. Standard operation
5 protocols (SOPs) are provided for many of the examples.

List of Abbreviations:

AcO: Acetyl,

All: Allyl,

10 **Alloc:** Allyloxycarbonyl,

Bn: Benzyl,

Bz: Benzoyl,

CAN: $(\text{NH}_4)_2\text{Ce}^{\text{IV}}(\text{NO}_3)_6$, ceric ammonium (IV) nitrate,

- ClAc**: Monochloroacetyl,
Cres: p-Tolyl,
DCC: Dicyclohexylcarbodiimide,
Dde: 1-(4,4-dimethyl-2,6-dioxocyclohex-ylidene)ethyl,
5 **DEAD**: Diethyl azodicarboxylate,
DIPEA: Diisopropylethylamine,
DMAP: 4-*N,N*-dimethylaminopyridine,
DMF: *N,N*-Dimethylformamide,
DMTST: Dimethyl (methylthio)sulfoniumtetrafluoromethanesulfonate,
10 **DTPMB** : 2,6-di-*tert*-butyl-4-methylpyridine
DTPM: (1,3-dimethyl-2,4,6 (1H, 3H, 5H)-trioxopyrimidin-5-ylidene) methyl,
Lev: 4-Oxopentanoyl,
MCPBA: 3-chloroperbenzoic acid,
Mes: Methanesulfonyl,
15 **Mp**: 4-Methoxyphenyl,
Mpm: 4-methoxybenzyl,
NBS: *N*-Bromosuccinimide,
NIS: *N*-Iodosuccinimide,
NMP: *N*-Methylpyrrolidone
20 **NPh**: *N*-Phthaloyl
PDC: Pyridiniumdichromate,
Pent: *n*-Pentenyl,

Ph₃P: Triphenylphosphine,
25 **Piv**: Pivaloyl,
TBAF: Tetrabutylammoniumfluoride,
TBDMS: *tert*-Butyldimethylsilyl,
TBDPS: *tert*-Butyldiphenylsilyl,
TCA: Trichloroacetimidyl,
30 **TEMPO**: 2,2,6,6-Tetramethyl-1-piperidinyloxy,
TFA: Trifluoroacetic acid,
TFAA: Trifluoroacetic acid anhydride,
Tf: Trifluoromethanesulfonyl,
TfN₃: Trifluoromethanesulfonyl azide, prepared from NaN₃ and Tf₂O,
35 **TfOH**: Trifluoromethanesulfonic acid,

THF: Tetrahydrofuran,

TMS: Trimethylsilyl,

Tos: *p*-Toluenesulfonyl,

***p*-TosOH:** *p*-Toluenesulfonic acid,

5 **Trit:** Triphenylmethyl.

Standard Operating Procedures

Standard Operating Procedure **1**: Formation of Benzylidene acetals

Standard Operating Procedure **2**: Formation of *p*-Methoxybenzylidene acetals

10 Standard Operating Procedure **3**: Formation of isopropylidene acetals:

Standard Operating Procedure **4**: Dealkyldination (Removal of isopropylidene, benzylidene and *p*-methoxybenzylidene)

Standard Operating Procedure **5**: Regioselective opening of the *p*-methoxybenzylidene acetal to a 6-*O-p*Methoxybenzyl ether

15 Standard Operating Procedure **6**: Regioselective opening of a benzylidene ring to a 4-*O*-benzyl ether

Standard Operating Procedure **7**: Introduction of a benzyl or *p*-methoxybenzyl ether

Standard Operating Procedure **8**: Introduction of a *tert*-butyldiphenylsilyl ether

20 Standard Operating Procedure **9**: Cleavage of a *tert*-Butyl-diphenylsilyl ether

Standard Operating Procedure **10**: Introduction of a *N*-DTPM-group

Standard Operating Procedure **11**: Cleavage of a *N*-DTPM-group

Standard Operating Procedure **12**: Introduction of an azide group via diazo transfer reaction

25 Standard Operating Procedure **13**: Hydrolysis of thioglycosides (NBS)

Standard Operating Procedure **14**: Hydrolysis of thioglycosides (NIS)

Standard Operating Procedure **15**: Chemoselective Oxidation to Uronic acids

Standard Operating Procedure **16**: Methyl ester formation on the Uronic acids

Standard Operating Procedure **17**: Regioselective 6-*O*-Benzoylation

30 Standard Operating Procedure **18**: Common procedure for *O*-Benzoylation

Standard Operating Procedure **19**: Common procedure for *O*-Acetylation

Standard Operating Procedure **20**: PDC-oxidation of alcohols to carboxylic acids

Standard Operating Procedure **21**: Chemoselective 1-*O*-Benzoyl cleavage

- Standard Operating Procedure **22**: Deacylation under Zemplen conditions
- Standard Operating Procedure **23**: Introduction of the 4-Oxopentanoyl (=Levulinoyl) group
- Standard Operating Procedure **24**: Cleavage of the 4-Oxopentanoyl (=Levulinoyl) group
- 5 Standard Operating Procedure **25**: Formation of Trichloroacetimidates
- Standard Operating Procedure **26**: Regioselective introduction of a 6-O-*p*Methoxyphenyl group under Mitsunobu conditions
- Standard Operating Procedure **27**: Cleavage of the *p*-Methoxyphenyl ether
- 10 Standard Operating Procedure **28**: Cleavage of *p*-Methoxybenzyl ethers
- Standard Operating Procedure **29**: Formation of a 2,3-cyclic carbamate
- Standard Operating Procedure **30**: Cleavage of the N-phthaloyl group
- Standard Operating Procedure **31**: Introduction of a thiocresyl ether at the reducing end
- 15 Standard Operating Procedure **32**: Glycosylation with thioglycosides
- a) NIS-promoted glycosylation
- b) DMTST promoted glycosylations:
- Standard Operating Procedure **33**: Glycosylations with trichloroacetimidates
- Standard Operating Procedure **34**: Glycosylations using 2,3-cyclocarbamoyl
- 20 protected *p*Thiocresyl glycosides as glycosyl donors
- Standard Operating Procedure **35**: Introduction of an Alloc-group
- Standard Operating Procedure **36**: Cleavage of an Alloc-group
- Standard Operating Procedure **37**: Lewis acid mediated benzylation
- Standard Operating Procedure **38**: benzylation under mild basic conditions
- 25 Standard Operating Procedure **39**: Ester cleavage under very mild conditions

Standard Operating Procedure 1: Formation of Benzylidene acetals

- The starting material (47.5 mmol) was dissolved in acetonitrile (100 – 200 ml) and reacted with benzaldehyde dimethyl acetal (1.2 equiv.) and a catalytic
- 30 amount of *p*-toluenesulphonic acid monohydrate (0.01-0.1 equiv). The reaction was stirred at 50°C under reduced pressure (350 mbar) until the TLC shows completion. Subsequently, the mixture was neutralized with triethylamine (pH ≈ 9) and concentrated in vacuo. The remaining residue was

dissolved in an organic solvent (e.g. dichloromethane or ethyl acetate) and extracted with H₂O, saturated brine solution, dried over Na₂SO₄ and concentrated. Final purification was achieved either by crystallization or by silica gel chromatography. The typical yields for the product formation varied
5 between 70 and 95 %.

Standard Operating Procedure 2: Formation of *p*-Methoxybenzylidene acetals

The starting material (47.5 mmol) was dissolved in DMF/acetonitrile (1/1, 100
10 – 200 ml) and reacted with *p*-methoxybenzaldehyde dimethyl acetal (1.2 equiv.) and a catalytic amount of *p*-toluenesulphonic acid monohydrate (0.01-0.1 equiv). The reaction was stirred between 50 - 60 °C under reduced pressure (350 mbar) until the TLC shows completion. Subsequently, the mixture was neutralized with triethylamine (pH ≈ 9) and concentrated in
15 vacuo. The remaining residue was dissolved in an organic solvent (e.g. dichloromethane or ethyl acetate) and extracted with H₂O, saturated brine solution, dried over Na₂SO₄ and concentrated. Final purification was achieved either by crystallization or by silica gel chromatography. The typical yields for the product formation varied between 70 and 85 %.

20

Standard Operating Procedure 3: Formation of isopropylidene acetals:

A solution of starting material (10 mmol) and catalytic amounts of camphorsulfonic acid (0.01-0.1 equiv) in 2,2-dimethoxypropane (50 ml) was stirred at 25 °C until completion, neutralized with triethylamine and
25 concentrated. The remaining residue was dissolved in an organic solvent (e.g. dichloromethane or ethyl acetate) and extracted with H₂O and saturated brine solution. The organic layer was dried over Na₂SO₄ and concentrated. Final purification was achieved either by crystallization or by silica gel chromatography. The typical yields for the product formation varied between
30 75 and 93 %.

Standard Operating Procedure 4:

Dealkyldination (Removal of isopropylidene, benzylidene and p-methoxybenzylidene)

A solution of the acetal (31 mmol) in 150 ml dichloromethane was cooled to 0°C and reacted with 80 % aqueous TFA (20.0 ml, cooled to 0°C). After stirring at 0°C until completion, the reaction mixture was neutralized with 30 % NaOH solution and extracted with water and saturated brine solution. The organic layer was dried over Na₂SO₄ and concentrated. Final purification was achieved either by crystallization or by silica gel chromatography. The typical yields for the product formation varied between 70 and 95 %.

Modification using *p*-TosOHxOH₂ in MeOH/CH₃CN for cleavage:

The acetal (16.6 mmol) was dissolved in 100mL of dry acetonitrile and 25 mL MeOH and the solution was reacted with catalytic amounts of *p*-TosOHxOH₂. The reaction mixture was heated at elevated Temperature (between 40 and 60 °C) until completion and then neutralized with Et₃N, concentrated *in vacuo* and purified either by crystallization or by silica gel chromatography. The typical yields for the product formation varied between 70 and 95 %.

Standard Operating Procedure 5: Regioselective opening of the p-methoxybenzyliden acetal to a 6-O-*p*Methoxybenzyl ether

A suspension of the starting sugar (10.2 mmol), molecular sieves 3Å (6.5 g, freshly activated) and Na(CN)BH₃ (3.85 g, 58.2 mmol) in dry DMF (90 ml) was stirred for 1 hr at r.t. and cooled down to 0°C. Subsequently, a solution of TFA (11.2 mL, 143.9 mmol in 51 mL dry DMF) was added dropwise and stirring continued at 50 to 60°C until completion of the reaction. The reaction mixture was cooled to 20°C, diluted with ethyl acetate and extracted with a saturated aqueous NaHCO₃ solution and filtered through a celite pad. The combined organic layers were washed with saturated brine solution, dried over MgSO₄ and concentrated. Final purification was achieved either by crystallization or by silica gel chromatography. The typical yields for the product formation varied between 70 and 90 %.

Standard Operating Procedure 6: Regioselective opening of a benzylidene ring to a 4-O-benzyl ether

A solution of the starting material (3.4 mmol) in 25 mL dichloromethane is cooled to 0°C and to it is added of a solution of BH₃ in THF (1 M, 34 ml) and
5 a solution of Bu₂BOTf in dichloromethane (1 M, 3.7 ml). The reaction is stirred at 0°C till completion and then quenched with 10 ml Et₃N and 10 ml MeOH, concentrated and coevaporated three times with toluene. Final purification was achieved either by crystallization or by silica gel chromatography. The typical yield for the product formation varied between
10 75 and 90 %.

Standard Operating Procedure 7: Introduction of a benzyl or *p*-methoxybenzyl ether

The starting material (40.2 mmol) was dissolved in dry *N,N'*-dimethylformamide (100 mL) at 0°C and reacted with NaH (48.24 mmol, 1.2
15 eq per OH to be benzylated). Then benzyl bromide (1.1 eq per OH to be benzylated) was added dropwise and stirring continued at 0°C until completion. The same conditions were applied for the introduction of an allyl ether (Allylbromide served as allylating reagent).
20 The excess of NaH was neutralized by careful addition of acetic acid, followed by concentration of the reaction mixture *in vacuo*. The residue was dissolved in ethyl acetate and subsequently washed with water, 10 % aqueous HCl solution, saturated aqueous NaHCO₃ solution, saturated brine solution, dried over Na₂SO₄ and concentrated *in vacuo*. Final purification was achieved
25 either by crystallization or by silica gel chromatography. The typical yield for the product formation varied between 70 and 92 %.

The same procedure was followed for the formation of the *p*-methoxybenzyl ether except that *p*-methoxybenzyl chloride was added to the reaction instead of benzyl bromide and the reaction was performed between 50 and 60°C.

30

**Standard Operating Procedure 8:
Introduction of a *tert*-butyldiphenylsilyl ether**

A mixture of the starting material (29.0 mmol) and imidazole (70.1 mmol) was dissolved in 80 mL anhydrous DMF and heated to 55 °C. To the solution was added *tert*-butyldiphenylchlorosilane (8.30 mL, 31.9 mmol) and stirring continued at 55 °C until completion. The reaction mixture was then cooled to 20 °C and quenched with aqueous NaHCO₃ solution. After concentration *in vacuo*, the residue was taken up in ethyl acetate and the organic phase washed successively with water, 10% aqueous citric acid, water, saturated brine solution, dried over Na₂SO₄ and evaporated. Final purification was achieved either by crystallization or by silica gel chromatography. The typical yields for the product formation varied between 85 and 95 %.

Standard Operating Procedure 9: Cleavage of a *tert*-Butyl-diphenylsilyl ether

To a solution of the silyl ether (2.15 mmol) in 2.5 mL dry THF and acetic acid (3.44 mmol) was added 1M TBAF solution in THF (3.22 mL) and stirring continued till completion of the reaction. Subsequently, the reaction mixture was concentrated *in vacuo*. Final purification was achieved either by crystallization or by silica gel chromatography. The typical yields for the product formation varied between 85 and 97 %.

20

Standard Operating Procedure 10: Introduction of a *N*-DTPM-group

To a solution of the starting amine (24.5 mmol) in methanol (60 ml) is added a solution of the DTPM reagent (5.43 g, 25.7 mmol) in methanol (60 ml) at 60 °C. After completion of the reaction, the reaction mixture was concentrated *in vacuo*, taken up in dichloromethane, extracted with water and saturated brine solution, dried over MgSO₄ and evaporated. Final purification was achieved either by crystallization or by silica gel chromatography. The typical yields for the product formation varied between 85 and 97 %.

Standard Operating Procedure 11: Cleavage of a *N*-DTPM-group

The starting material (40.94 mmol) was dissolved in dry DMF (50ml) and reacted with ethylene diamine (20 ml) at room temperature until completion. The reaction mixture was concentrated *in vacuo* and coevaporated with toluene. The residue was suspended in CHCl₃ and filtered through a Celite

pad. The filtrate was evaporated and final purification of the residue was achieved either by crystallization or by silica gel chromatography. The typical yields for the product formation varied between 85 and 92 %.

Standard Operating Procedure 12: Introduction of an azide group via diazo transfer reaction**a) Preparation of a trifluoromethansulfonylazide solution:**

A solution of sodium azide (492mmol) in water (80mL) was prepared under N₂-atmosphere. To this stirred solution was added dichloromethane (100mL) at 0°C, followed by the addition of triflic anhydride (16.5 ml) over 10 min. The mixture was further stirred for 2 hours at 0°C, the organic layer was separated and the aqueous layer was extracted with dichloromethane (2x40 mL). The combined organic layers were washed with saturated, aqueous NaHCO₃ solution (80 mL), water (80 mL) and dried over Na₂SO₄. After filtration, this solution was directly used for the diazotransfer reaction.

b) Diazotransfer reaction:

To a solution of the starting material (26.0 mmol) and 4-*N,N'*-(dimethylamino)pyridine (14.5g) in acetonitrile (100mL) was added dropwise TfN₃-solution (85ml) at room temperature within 10 min. The reaction was stirred till complete conversion of the starting material into the product. The reaction mixture was concentrated *in vacuo* to 30 ml and suspended in chloroform. After filtration through a Celite pad, the filtrate was concentrated and the residue was purified by filtration through a short silica gel pad. The typical yields for the product formation varied between 85 and 95 %.

Standard Operating Procedure 13: Hydrolysis of thioglycosides (NBS)

The starting thioglycoside (33.4 mmol) was suspended in 240 ml Acetone and 18 ml of distilled water and stirred for 45 min at -20°C. After addition of NBS (155 mmol) stirring was continued at -20°C. After completion, the reaction was stopped by addition of NaS₂O₃/NaHCO₃ (20 % aqueous solution , 1/1) and the mixture diluted with ethyl acetate, subsequently washed with water and saturated brine solution. The organic layer was dried over Na₂SO₄ and concentrated *in vacuo*. Final purification was achieved either by crystallization or by silica gel chromatography. The typical yields for the product formation varied between 75 and 90 %.

Standard Operating Procedure 14: Hydrolysis of thioglycosides (NIS)

The starting thioglycoside (33.4 mmol) was suspended in 240 ml Acetone and 18 ml of distilled water and stirred for 45 min at -20°C . After addition of NIS (56.8 mmol) and TMSOTf (2.84 mmol) stirring was continued until completion.

5 The reaction was stopped by addition of NaS_2O_3 / NaHCO_3 (20 % aqueous solution , 1/1), diluted with ethyl acetate and washed with water and saturated brine solution. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. Final purification was achieved either by crystallization (e.g. petroleum spirit/ ethylacetate) or by silica gel chromatography. The typical yields for the

10 product formation varied between 79 and 92 %.

Standard Operating Procedure 15: Chemoselective Oxidation to Uronic acids

A solution of the starting material (20.0 mmol) in dichloromethane (141 ml) was cooled to 0°C and subsequently mixed with TEMPO (0.205 mmol in 12.8

15 ml dichloromethane), Aliquat 336 (N-methyl-N,N-dioctyl-1-octanaminium chloride) (12.8 ml of a 0.08 M solution in dichloromethane) and KBr (2.08 mmol in 4.17 ml H_2O) and stirring continued at 0°C . After 5 mins, a suspension of $\text{Ca}(\text{OCl})_2$ (43.6 mmol) and NaHCO_3 (43.6 mmol) in 135 ml H_2O was

20 added within 15 mins to the reaction mixture and stirring at 0°C was continued till completion. The reaction was concentrated *in vacuo* and freeze dried. The crude residue was used as such for the next reactions.

Standard Operating Procedure 16: Methyl ester formation on the Uronic acids

The crude residue of the oxidation to the uronic acid was dissolved in 50 ml Toluene and 50 ml Methanol and titrated with TMSCHN_2 -solution (2M in hexane) until completion. The reaction mixture was quenched with acetic acid to destroy excess of esterification reagent and evaporated *in vacuo*. Final

30 purification was achieved by silica gel chromatography. The typical yields for the product formation varied between 65 and 80 % over the steps oxidation and esterification.

Standard Operating Procedure 17: Regioselective 6-O-Benzoylation

The starting material (32.04 mmol) was dissolved in dry dichloromethane (50 mL) and dry pyridine (10 mL) and cooled down to - 45°C. Benzoyl chloride (32.04 mmol) was added dropwise and stirring continued at - 45°C till completion. The reaction was concentrated *in vacuo* and coevaporated with toluene three times. The remaining residue was dissolved in dichloromethane and washed with 10% aqueous citric acid solution, saturated aqueous NaHCO₃ solution and saturated brine solution, dried over Na₂SO₄ and evaporated *in vacuo*. Final purification was achieved either by crystallization or by silica gel chromatography. The typical yields for the product formation varied between 75 and 94 %.

Standard Operating Procedure 18: Common procedure for O-Benzoylation

To a solution of the starting material (11.9mmol) and DMAP (13.6mmol) in 1,2-dichloroethane was added dropwise benzoylchloride (1.7g, 12.1mmol). at 0°C. The mixture was then left to stir until completion (dependent on the substrate between 20 to 55°C). Subsequently, the reaction mixture was diluted with dichloromethane and washed with water, 5% NaHSO₄ solution, saturated aqueous NaHCO₃ solution and saturated brine solution. The organic layer was dried over MgSO₄ followed by removal of the solvent *in vacuo* to give a crude residue. Final purification was achieved either by crystallization or by silica gel chromatography. The typical yields for the product formation varied between 80 and 96 %.

Standard Operating Procedure 19: Common procedure for O-Acetylation

To a suspension of the starting material (235 mmol, 3 acetylation sites) in pyridine (350 ml) at 0°C was added dropwise acetic anhydride (175 ml). After completion of the addition, the reaction was allowed to return to room temperature and stirred until completion. The reaction mixture was evaporated to dryness and 3x coevaporated with toluene. The residue was taken up in dichloromethane and washed with 5 % aqueous NaHSO₄-solution, saturated aqueous NaHCO₃-solution, water and saturated brine solution. The organic layer was dried over MgSO₄ and evaporated. Final purification of the residue

was achieved either by crystallization or by silica gel chromatography. The typical yields for the product formation varied between 88 and 98 %.

5 **Standard Operating Procedure 20: PDC-oxidation of alcohols to carboxylic acids**

The starting material (1.15 mol) was dissolved in anhydrous DMF (7.0 ml) and reacted with PDC (11.5 mmol) under stirring at room temperature until complete conversion into the uronic acid. The reaction mixture was subsequently poured into 50 ml water and the whole extracted with diethyl
10 ether. The combined ether layers were washed with 10 % aqueous citric acid solution, filtered through a short silica gel pad, dried over MgSO_4 , evaporated and dried under high vacuum.

Standard Operating Procedure 21: Chemoselective 1-O-Benzoyl cleavage

15 The starting material (36.8 mmol) was dissolved in dry DMF (80 ml) and cooled to 0°C. Subsequently, hydrazine acetate (44.06 mmol) was added and stirring continued until completion. After addition of acetone and acetic acid the reaction mixture was concentrated *in vacuo*. The residue was dissolved in dichloromethane and extracted with 10% aqueous citric acid solution,
20 saturated NaHCO_3 solution, water and saturated brine solution, dried over MgSO_4 , evaporated and dried under high vacuum. Final purification was achieved either by crystallization or by silica gel chromatography. The typical yields for the product formation varied between 72 and 88 %.

25 **Standard Operating Procedure 22: Deacylation under Zemplen conditions**

The starting material (23.7 mmol) was suspended in dry MeOH (70 ml) and stirred for 30 mins at 0 °C. Subsequently, NaOMe (0.1 equiv. / O-Acyl group) was added (positive flush of N_2) and stirring was continued at 0 °C until
30 completion. Finally, the reaction was neutralized with 10 % aqueous HCl and the solvent evaporated. Final purification was achieved either by crystallization or by silica gel chromatography. The typical yield for the product formation varied between 90 and 98 %.

Standard Operating Procedure 23: Introduction of the 4-Oxopentanoyl (=Levulinoyl) group

5 **a) Preparation of the Lev₂O solution:**

To a solution of DCC (31.2 mmol) in 100 mL dichloromethane was added levulinic acid (62.4 mmol) and DIPEA (62.42 mmol). The supernatant was used as such for the levulation reaction.

Reaction

- 10 The above Lev₂O solution was added to a solution of the starting sugar (15.6 mmol) dissolved in 25 mL of dry dichloromethane and stirring was continued until completion. Subsequently, the reaction mixture was filtered through a Celite pad and all combined organic layers were extracted with 10 % aqueous citric acid solution, saturated aqueous brine solution, dried with
- 15 Na₂SO₄ and concentrated. Final purification was achieved either by crystallization or by silica gel chromatography. The typical yields for the product formation varied between 85 and 96 %.

20 **Standard Operating Procedure 24: Cleavage of the 4-Oxopentanoyl (=Levulinoyl) group**

- A solution of the starting sugar (1.28 mmol) and acetic acid (1.35 mL) in pyridine (5.0 mL) was cooled to 0 °C followed by addition of hydrazine hydrate (200 µL). Stirring at 0 °C was continued until completion and the reaction mixture diluted with dichloromethane, subsequently extracted with 10%
- 25 aqueous citric acid, 10 % aqueous NaHCO₃ solution, saturated brine solution, dried over Na₂SO₄, filtered and concentrated. Final purification was achieved either by crystallization or silica gel chromatography. The typical yields for the product formation varied between 80 and 95 %.

30 **Standard Operating Procedure 25: Formation of Trichloroacetimidates**

a) with DBU:

A solution of the starting sugar (1.99 mmol) and trichloroacetonitrile (601 µL, 5.87 mmol) in 5 mL dry dichloromethane was stirred at room temperature for

30 min. The reaction mixture was then cooled to 0°C and DBU (100 µmol) added. Stirring was continued until completion (dependent on the substrate, stirring was performed from 0°C to 20°C). The reaction mixture was concentrated to one half of its volume and directly loaded on a short plug of silica gel and purified via silica gel chromatography. The typical yields for the product formation varied between 78 and 95 %.

b) with K₂CO₃:

A solution of the starting sugar (1.99 mmol) and trichloroacetonitrile (601 µL, 5.87 mmol) in 5 mL dry dichloromethane is stirred at rt for 30 min. The reaction mixture was then cooled down to 0°C and anhydrous K₂CO₃ (19.9 mmol) added. The reaction was stirred at 0°C till completion and then filtered through a celite pad. The filtrate was dried over Na₂SO₄ and evaporated. Final purification was achieved either by crystallization or by silica gel chromatography. The typical yield for the product formation varied between 78 and 95 %.

Standard Operating Procedure 26: Regioselective introduction of a 6-O-*p*-Methoxyphenyl group under Mitsunobu conditions

A solution of the starting sugar (13.52 mmol), 4-methoxyphenol (20.3 mmol) and triphenylphosphine (20.3 mmol) in 85 ml dry dichloromethane was stirred at 0°C for 45 min. After addition of DEAD-reagent (22.9 mmol) at 0°C, the reaction mixture was further stirred at room temperature until completion, filtered through a celite pad, diluted with dichloromethane and extracted with 10 % aqueous NaHCO₃/NaOH solution (1/1), 10 % aqueous citric acid solution and aqueous saturated brine solution. The organic layer was dried over Na₂SO₄ and concentrated. Final purification was achieved by silica gel chromatography. The typical yield for the product formation varied between 70 and 89 %.

Standard Operating Procedure 27: Cleavage of the *p*-Methoxyphenyl ether

The starting material (1.18 mmol) was dissolved in 30 ml acetonitrile and 7.5
5 ml water and cooled to 0°C. Subsequently, CAN (3.83 mmol) was added and
stirring continued at 0°C until completion. The reaction mixture was diluted
with ethyl acetate and extracted with water. The aqueous layer was made
alkaline by addition of solid NaHCO₃ and back extracted with ethyl acetate.
The combined organic layers were extracted with saturated aqueous NaHCO₃
10 solution and saturated brine solution, dried over MgSO₄ and evaporated.
Final purification was achieved by silica gel chromatography. The typical
yields for the product formation varied between 73 and 89 %.

Standard Operating Procedure 28: Cleavage of *p*-Methoxybenzyl ethers

15 The starting material (0.60 mmol) was dissolved in 27 ml acetonitrile and 3.0
ml water and cooled to 0°C. Subsequently, CAN (4.5 equiv.) was added and
stirring continued from 0°C to room temperature until completion. The reaction
mixture was diluted with ethyl acetate and extracted with water. The aqueous
layer was made alkaline by addition of solid NaHCO₃ and back extracted
20 with ethyl acetate. The combined organic layers were extracted with saturated
aqueous NaHCO₃ solution and saturated brine solution, dried over MgSO₄
and evaporated. Final purification was achieved by silica gel chromatography.
The typical yields for the product formation varied between 73 and 85 %.

25 Standard Operating Procedure 29: Formation of a 2,3-cyclic carbamate

To a stirred solution of the starting material (3.56 mmol) in dichloromethane
(100 ml) and 10% aqueous solution of NaHCO₃ (75 ml) was added a solution
of triphosgene (1.25 mmol) in 10 ml dry dichloromethane. The reaction was
stirred at room temperature till completion. The organic phase was washed
30 with water, dried over Na₂SO₄, filtered and concentrated. Final purification
was achieved either by crystallization or silica gel chromatography. The
typical yield for the product formation varied between 75 and 95 %.

Standard Operating Procedure 30: Cleavage of the N-phthaloyl group

The N-phthaloylated starting material (45.9 mmol) was dissolved in *n*-butanol (200 ml) and treated with 1,2-diaminoethane (50 ml) at 100°C. After stirring at 100°C until completion, the reaction mixture was concentrated *in vacuo*,
5 coevaporated with toluene three times and dried under high vacuum. Final purification was achieved by silica gel chromatography. The typical yield for the product formation varied between 78 and 92 %.

**Standard Operating Procedure 31: Introduction of a thiocresyl ether at
10 the reducing end**

A solution of the 1-O-glycosyl acetate (10.48 mmol) and *p*-thiocresol (12.58 mmol) in dry dichloromethane (30ml) was stirred at 0°C and subsequently activated by the addition of boron trifluoride diethylether complex (12.58mmol) over 5 min. Stirring was continued (0°C → 20°C) until completion and the
15 reaction stopped by the addition of triethyl amine (14.0 mmol). The reaction mixture was diluted with dichloromethane and extracted with saturated NaHCO₃-solution, water and saturated brine solution, dried over MgSO₄ and evaporated *in vacuo*. Final purification was achieved by crystallization or silica gel chromatography. The typical yield for the product formation varied
20 between 81 and 92 %.

Standard Operating Procedure 32: Glycosylation with thioglycosides**a) NIS-promoted glycosylation**

A mixture of glycosyl acceptor (1 mmol), thioglycoside (1 mmol) and 1.0 g of
25 freshly activated molecular sieves in 20 ml of a dry solvent (e.g. CH₃CN, CH₂Cl₂, Toluene, Ether) was stirred for 45 min at r.t and cooled down to the reaction temperature. Subsequently, *N*-Iodosuccinimide (1.7 mmol) was added and stirring continued for 20 min at the reaction temperature. After the addition of a Lewis acid as promotor (e.g. TfOH, 85-170 µmol), stirring was
30 continued at the reaction temperature until completion. The reaction mixture was quenched with triethyl amine, filtered through a celite pad and extracted with a 10 % aqueous KHCO₃/Na₂S₂O₃ solution, water and saturated brine solution, dried over MgSO₄ and evaporated. Final purification was achieved

by silica gel column chromatography. The typical yields for the product formation varied between 65 and 85 %.

b) DMTST promoted glycosylations:

5 A mixture of glycosyl acceptor (1 mmol), thioglycoside (1 mmol) and 1.0 g of freshly activated molecular sieves in 20 ml of a dry solvent (e.g. CH₃CN, CH₂Cl₂, Toluene, Ether) was stirred for 45 min at r.t and cooled down to the reaction temperature. Subsequently, DMTST (3-5 equiv.) was added and stirring continued at the reaction temperature until completion. The reaction mixture was quenched with triethyl amine, filtered through a celite pad and
10 extracted with aqueous NaHCO₃-solution, water and saturated brine solution, dried over Na₂SO₄, concentrated *in vacuo* and purified by silica gel column chromatography. The typical yields for the product formation varied between 50 and 85 %.

15 **Standard Operating Procedure 33:**

Glycosylations with trichloroacetimidates

A suspension of the trichloroacetimidate (1.54 mmol), glycosyl acceptor (1.13 mmol) and freshly activated molecular sieves (1.0 g) in an anhydrous solvent (e.g. CH₃CN, CH₂Cl₂, Toluene, Ether, 20 mL) was stirred at rt for 1 h and then
20 cooled to reaction temperature. Subsequently, a catalytic amount of a promotor (e.g. TMSOTf, 0.01-0.1 equiv.) was added and stirring continued at reaction temperature until completion. The reaction was quenched with triethylamine) and filtered through a Celite pad. The combined organic layers were washed with aqueous NaHCO₃-solution and saturated brine solution,
25 dried over Na₂SO₄, concentrated *in vacuo* and purified by silica gel column chromatography. The typical yields for the product formation varied between 50 and 85 %.

Standard Operating Procedure 34:**Glycosylations using 2,3-cyclocarbamoyl protected *p*Thiocresyl glycosides as glycosyl donors**

- 5 PhSCI (0.2 mmol, 2 equiv.) in dry dichloromethane (1 ml) was added dropwise to a mixture of AgOTf (0.2 mmol) in dry dichloromethane (2 ml) at -78°C containing freshly activated molecular sieves 3 Å. After stirring for 15 mins at -78°C , a solution of the thioglycoside (0.1 mmol, 1 equiv.) and DTBMP (0.2 mmol, 2 equiv.) in dry dichloromethane (2 ml) was slowly added. After further
10 stirring for 15 mins at -78°C , the glycosyl acceptor (0.2 mmol, 2 equiv.) in dry dichloromethane (1 ml) was slowly added and stirring continued until completion. The reaction was quenched with saturated aqueous NaHCO_3 solution (1 ml), warmed to rt and diluted with dichloromethane. The organic layer was dried over MgSO_4 , filtered and evaporated. Final purification was
15 achieved by silica gel chromatography. The typical yields for the product formation varied between 60 and 90 %.

Standard Operating Procedure 35: Introduction of an Alloc-group

- A solution of starting material (2 mmol), dry pyridine (5 mmol) and dry THF (5
20 ml) was cooled to 0°C . Subsequently, Allylchloroformate (2.2 mmol) were added dropwise and stirring was continued until completion. The reaction mixture was diluted with dichloromethane and subsequently washed with 10 % aqueous citric acid solution, saturated NaHCO_3 solution, water and saturated brine solution. The organic layer was dried over Na_2SO_4 , filtered
25 and evaporated. Final purification was achieved either by crystallization or by silica gel chromatography. The typical yields for the product formation varied between 80 and 95 %.

Standard Operating Procedure 36: Cleavage of an Alloc-group

- 30 A mixture of the Allyloxycarbonate (1.17 mmol), dimedone (1.33 mmol) and $\text{Pd}(\text{Ph}_3\text{P})_4$ (0.30 mmol) was dissolved in dry THF (60 ml) and stirred under Ar atmosphere until completion of the reaction. The reaction mixture was

concentrated in vacuo and purified by silica gel chromatography. The typical yields for the product formation varied between 78 and 97 %.

Standard Operating Procedure 37: Lewis acid mediated benzylation

5

To a stirred mixture of the starting material (1 mmol) and benzyl trichloroacetimidate in dry hexane/dichloromethane (10 ml, 2/1) was added Lewis acid (0.01-0.05 equiv., e.g. TMSOTf, TfOH) and stirring was continued at rt until completion. The reaction was quenched with triethyl amine and concentrated. Final purification was achieved by silica gel chromatography. The typical yields for the product formation varied between 50 and 92 %.

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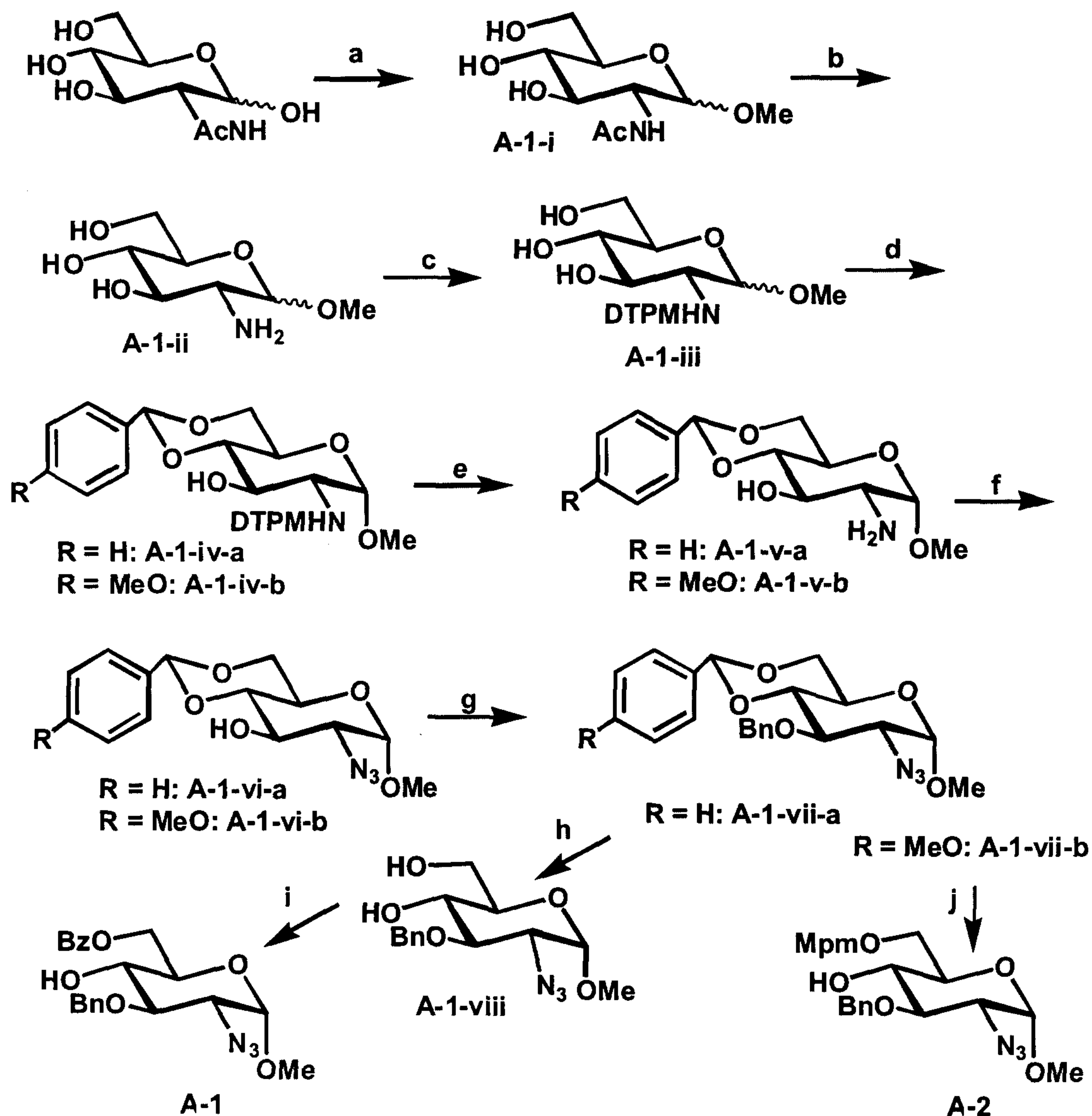
Standard Operating Procedure 38: benzylation under mild basic conditions

The starting material (3.49 mmol) was dissolved in dry DMSO (20 ml) and
5 cooled to 0°C. To the stirred solution were added successively benzyl bromide
(3.5 equiv./OH-group), barium oxide (1.5 equiv./OH-group), catalytic amounts
of TBAI (0.05 equiv./OH-group) and potassium hydroxide (3.5 equiv./ OH-
group). Stirring was continued from 0°C to rt until completion. The reaction
was quenched with methanol, and further stirred for 30 min. After dilution with
10 ether, the organic layer was washed with water and brine solution, dried over
MgSO₄ and concentrated in vacuo. Final purification was achieved by silica
gel chromatography.

**Standard Operating Procedure 39: Ester cleavage under aqueous
15 conditions**

The starting material (0.3mmol ester groups) was dissolved in 11.8 ml of a
mixture of water and THF (3:7), cooled to 0°C and reacted with 1M aqueous
NaOH-solution (5.0 ml). Stirring was continued until completion and the
20 reaction mixture titrated with 10 % aqueous HCl-solution to a pH of 9.5. After
evaporation of the THF, the mixture was freeze dried and the remaining
residue purified by silica gel chromatography to yield the product. The typical
yields for the product formation varied between 85 and 95 %.

25 Example 1: Synthesis of Building Blocks A-1 and A-2 from N-Acetyl
Glucosamine



Example 1: Synthesis of building blocks **A-1** and **A-2** from *N*-Acetyl glucosamine, yields are reported for R=H, conditions; a) Amberlite IR 120 (ion exchange resin) (H^+), MeOH, 60 °C, (70 %); b) 1M NaOH, 120°C; c) 1. SOP 10; 2. Ac_2O , pyridine; 3. NaOMe, MeOH (70 %, 4 steps); d) SOP 1 (91 % for R=H) or SOP 2 for R = OMe; e) SOP 11, (95%); f) SOP 12, (85 %, 2 steps); g) SOP 7, (91%); h) SOP 4, (91 %); i) SOP 17, (82 %); j) SOP 5.

Preparation of A-1-i:

N-Acetyl-2-deoxy- α/β -D-glucopyranoside (8.5 g, 38.4mmol) was suspended in 100 ml dry methanol. Subsequently, 12.0 g Amberlite IR 120 iron exchange resin (H^+ -form) was added and the reaction mixture refluxed for 70 hrs at 65°C. After cooling to 25 °C, the iron exchange resin was removed by filtration and several times extracted with methanol. The combined methanol layers were neutralized with triethyl amine and concentrated *in vacuo*. The crude residue was purified by crystallization to furnish the title compound in 70 % yield (α/β -mixture).

10 Preparation of A-1-iii:

Methyl glycoside **A-1-i** (20.6 mmol) was suspended in 100 ml aqueous NaOH solution (1 M) and stirred under reflux at 120°C until completion. After cooling and neutralization with 10 % aqueous HCl, the mixture was concentrated *in vacuo* and crude **A-1-ii** suspended in 200 ml methanol and reacted with *N*-[(1,3-dimethyl-2,4,6 (1H,3H,5H)-trioxopyrimidin-5-ylidene) methyl]-*N',N''*-dimethylamine (23.6 mmol) at 50°C (pH ~ 9.0) until completion. After evaporation and drying, crude **A-1-iii** was reacted with 150 mL acetylation mixture (pyridine/Ac₂O, 2/1, v/v) until completion, concentrated *in vacuo*, coevaporated with toluene and dried. The residue was suspended in ethyl acetate and extracted with water, 10 % aqueous HCl, saturated, aqueous NaHCO₃ solution and H₂O, dried over Na₂SO₄ and concentrated. The crude residue was dissolved in dry methanol and reacted with a catalytic amount of NaOMe. After completion, the reaction was neutralized with Amberlite IR 120 and filtered. The organic layer was evaporated and dried to furnish the title compound **A-1-iii** in 70 % yield (over 4 steps).

Preparation of A-1-iv-a:

Methyl-2-deoxy-2-*N*-[1-(1,3-dimethyl-2,4,6(1H, 3H, 5H)-trioxopyrimidin-5-ylidene) methyl]- α -D-glucopyranoside **A-1-iii** (16.0 g, 44.5mmol) in acetonitrile (200ml) was reacted with benzaldehyde dimethyl acetal (14.0 ml, 92.3 mmol) and a catalytic amount of *p*-toluenesulphonic acid monohydrate. After 2 hours at 55° C, the mixture was neutralized and evaporated. The remaining residue

was extracted, washed and evaporated. Yield: 18.3 g (92 %), $R_f = 0.20$ (1,2-dichloroethane/ ethylacetate = 7/3).

Preparation of A-1-v-a:

- 5 Methyl-4,6-O-benzylidene-2-deoxy-2-N-[1-(1,3-dimethyl-2,4,6(1H, 3H, 5H)-trioxypyrimidin-5-ylidene) methyl]- α -D-glucopyranoside **A-1-iv-a** (18.30 g, 40.90 mmol) in DMF (50ml) was reacted with ethylenediamine (20ml) at room temperature. After stirring for 35 minutes, the mixture was concentrated. Yield: 10.90 g (94.7 %), $R_f = 0.18$ (chloroform/methanol = 9/1).

10

Preparation of A-1-vi-a:

To a solution of methyl-2-amino-4,6-O-benzylidene-2-deoxy- α -D-glucopyranoside (7.5 g, 26.7 mmol) and 4-*N,N'*-(dimethylamino)pyridine (14.5g) in acetonitrile (100mL) was added TfN_3 -solution (85ml) at room temperature.

- 15 The reaction mixture was concentrated and the residue was purified by filtration through a short silica gel pad. Yield: 7.00 g (85.3 %), $R_f = 0.18$ (chloroform/ methanol = 9/1).

Preparation of A-1-vii-a:

20

Methyl 2-azido-2-deoxy-4,6-benzylidene- α -D-glucopyranoside **A-1-vi-a** (10.87g, 35.40mmol) in *N,N'*-dimethylformamide (50mL) was reacted with NaH (95 %, 0.92g, 36.4 mmol) and benzyl bromide (5.47 ml, 45.9 mmol). After completion, the excess of NaH was quenched, followed by concentration. The residue was extracted, washed and concentrated. Yield: 12.93 g (92.0 %), $R_f = 0.37$ (petroleum spirit/ethyl acetate = 3/1).

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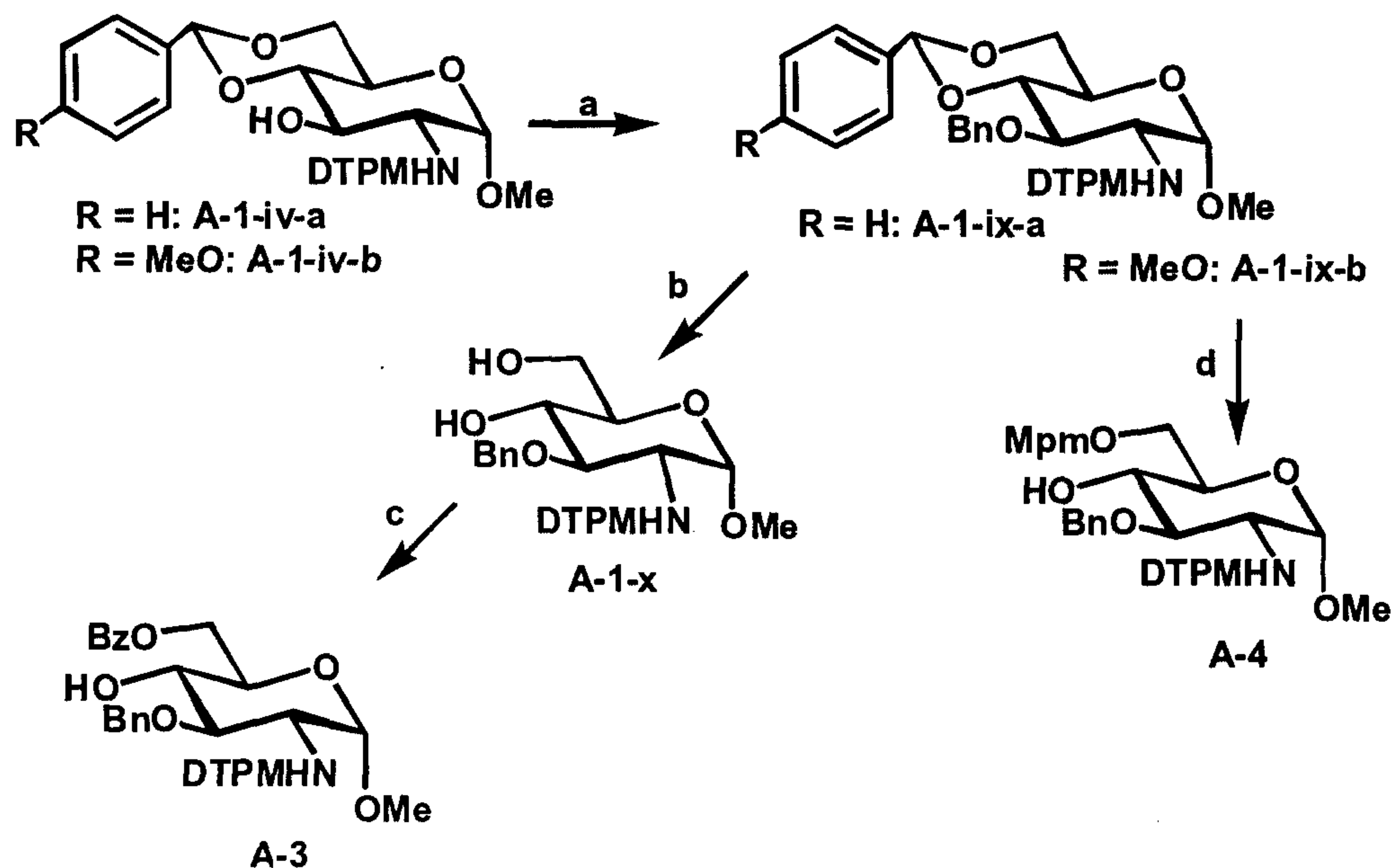
Preparation of A-1:

Methyl-2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranoside (9.87g, 31.9 mmol) in dichloromethane (50 mL) and pyridine (10 mL) was treated with benzoyl chloride (3.72mL, 32.04 mmol) at - 45°C for 2 hours. The reaction was concentrated and the residue extracted, washed and evaporated. Yield: 10.78 g (81.7 %), $R_f = 0.31$ (petroleum spirit/ ethylacetate = 1/1).

30

Compound A-1:

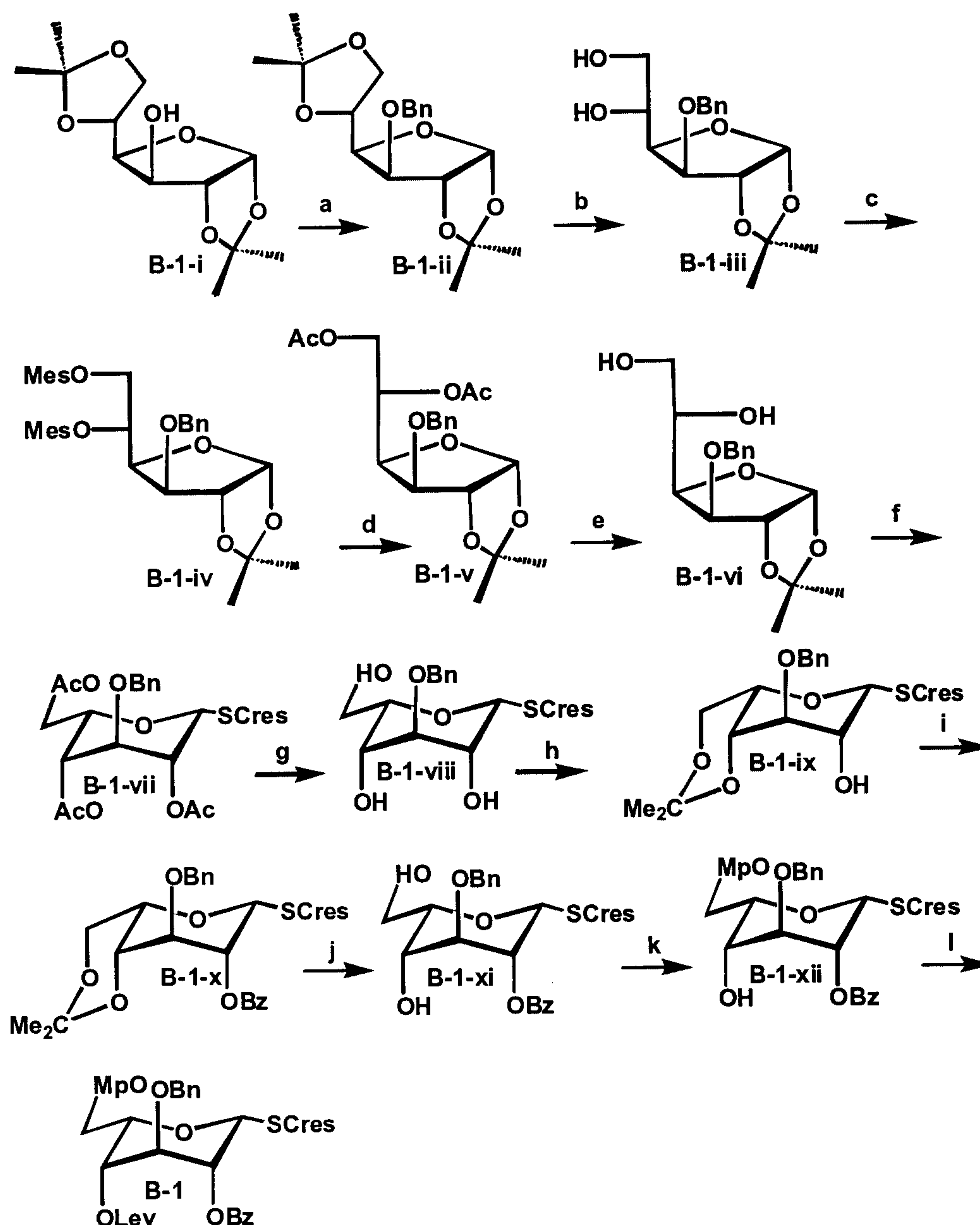
¹H-NMR (400 MHz, CDCl₃): δ = 8.03 (d, 2 H, Aryl), 7.57 (m, 1H, Aryl), 7.45-7.29 (m, 7H, Aryl), 4.93 (d, 1H, J_{gem} = 10.8 Hz, OCH₂), 4.82 (d, 1H, J_{gem} = 10.8 Hz, OCH₂), 4.81 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1 α), 4.73 (dd, 1H, $J_{5,6a}$ = 4.4 Hz, J_{gem} = 12.0 Hz, H-6a), 4.47 (dd, 1H, $J_{5,6b}$ = 2.0 Hz, H-6b), 3.85 (dd, 1H, $J_{3,4}$ = 8.8 Hz, H-3), 3.57 (ddd, 1H, $J_{4,5}$ = 10.0 Hz, H-4), 3.45 (s, 3H, OMe), 3.37 (dd, 1H, $J_{2,3}$ = 10.0 Hz, H-2), 2.80 (bs, 1H, 4-OH).

Example 2: Synthesis of Building Blocks **A-3** and **A-4**

- 5 Example 2: Synthesis of building block **A-3** and **A-4**, conditions: a) SOP 7, (72 % for $R = H$); b) SOP 4, (82 %); c) SOP 17, (84 %); d) SOP 5.

Compound **A-3**:

- ^1H -NMR (400 MHz, $CDCl_3$): δ = 10.16 (dd, 1 H, $J_{NH,2} = 9.4$ Hz, $J_{NH,=CH} = 14.0$ Hz, NH), 8.11 (d, 1H, =C-H), 7.68-7.22 (3m, 8H, Aryl), 4.84 (d, 1H, $J_{1,2} = 3.5$ Hz, H-1 α), 4.83 (dd, 1H, $J_{6a,6b} = 12.3$ Hz, $J_{5,6a} = 3.5$ Hz, H-6a), 4.73 (d, 1H, $J_{gem} = 11.7$ Hz, OCH₂), 4.46 (dd, 1H, $J_{5,6b} = 2.1$ Hz, H-6b), 3.91 (m, 1H, H-5), 3.72 (dd, 1H, $J_{3,4} \approx J_{2,3} = 8.8$ Hz, H-3), 3.57 (ddd, 1H, $J_{4,5} = 9.5$ Hz, H-4), 3.48 (s, 3H, OMe), 3.38 (ddd, 1H, $J_{2,3} = 10.5$ Hz, H-2), 3.32 (s, 3H, NMe), 3.31 (s, 3H, NMe), 3.05 (bs, 1H, 4-OH).
- 10
- 15

Example 3: Synthesis of L-ido configured glycosyl donor **B-1**

- 5 Example 3: Synthesis of Building Block **B-1**, conditions: a) SOP 7, (95%); b) 60% aqueous Acetic acid, 60°C (90%); c) Methanesulfonyl chloride, Pyridine, 0°C-RT (87 %); d) Cesium Acetate, Ac₂O, 120°C (95%); e) SOP 22, (92%); f) 1. 90% TFA, 0°C; 2. Ac₂O, Pyridine; 3. SOP 31, (73%, 3 steps); g) SOP 22, (98%); h) SOP 3, (92%); i) SOP 18, (98%); j) 80% acetic acid, 100°C (98%);
- 10 k) SOP 26, (89%); l) SOP 23, (98%).

Preparation of B-1-iii:

B-1-ii (15.60 mmol) was dissolved in 60 % aqueous acetic acid (50 ml) and stirred at 60 °C until completion. After neutralization with solid NaHCO₃, the mixture was evaporated and co evaporated with toluene. Crude **B-1-iii** was dissolved in CHCl₃/H₂O, the organic layer separated, dried over Na₂SO₄ and evaporated. The remaining residue was purified by a short silica gel chromatography to yield **B-1-iii** in 90 % (4.36 g).

10

Preparation of B-1-iv:

17.72 mmol of **B-1-iii** was dissolved in 25 ml dry pyridine, to which mesyl chloride (methylsulfonyl chloride, 42.5 mmol) was added dropwise at 0°C. The mixture was stirred at 4°C until completion and was subsequently poured into warm water (50°C, 90 ml), cooled and the precipitate isolated by filtration. **B-1-iv** was obtained after drying in 87 % yield (7.19 g).

15

Preparation of B-1-v:

B-1-iv (6.43 mmol) and cesium acetate (64.3 mmol) were suspended in 25 ml acetic anhydride and refluxed at 125 °C until completion. The reaction mixture was concentrated *in vacuo*, co evaporated with toluene and the residue extracted from ethyl acetate/H₂O (1/1). The organic layer was collected and washed with saturated aqueous NaHCO₃ solution and saturated brine solution, dried over Na₂SO₄ and evaporated. Purification was achieved by silica gel chromatography. Yield: 2.68 g (95 %).

25

Preparation of B-1-vii:

B-1-vi (5.61 mmol) was dissolved in aqueous TFA (90 %, 15 ml) and further stirred at 0°C until completion. The reaction mixture was neutralized with aqueous NaOH solution at 0°C, concentrated *in vacuo* and dried. The residue was suspended in 90 ml acetylation mixture (pyridine/acetic anhydride = 2/1) and 50 ml dichloromethane at 0°C and further stirred until completion. After concentration *in vacuo* and co evaporation with toluene, the residue was dissolved in ethyl acetate/H₂O (1/1), the organic layer collected and washed

30

with 10 % aqueous citric acid solution, saturated aqueous NaHCO₃ solution and brine solution, dried over Na₂SO₄ and evaporated. The crude residue and *p*-thiocresol (6.0 mmol) were dissolved in 40 ml anhydrous dichloromethane and cooled to 0°C, reacted with BF₃·OEt₂ (8.41 mmol) and further stirred at rt
5 until completion. The reaction was stopped with saturated NaHCO₃ solution and the organic layer was washed with water, dried over Na₂SO₄ and evaporated. Final purification was achieved by silica gel chromatography to yield **B-1-vii** in 73 % over 3 steps.

10 Preparation of B-1-xi:

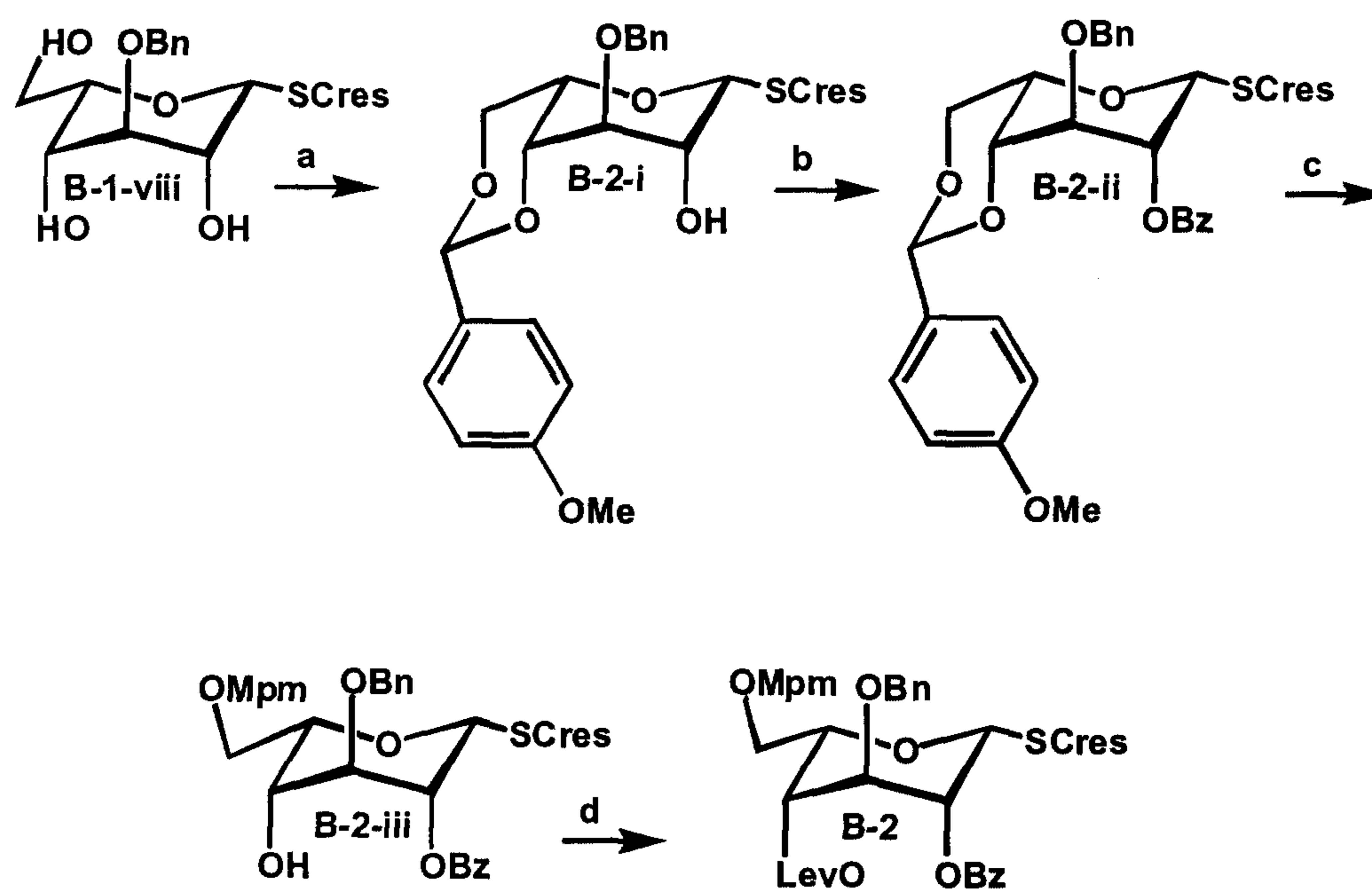
B-1-x (8.0 mmol) was dissolved in 80 % aqueous AcOH and heated at 100°C until completion. The mixture was cooled to rt, neutralized with solid NaHCO₃ and dissolved in ethyl acetate/water (1/1). After removal of the aqueous layer, the organic layer was dried over MgSO₄ and evaporated to dryness furnishing
15 **B-1-xi** in 98 % yield.

Compound B-1:

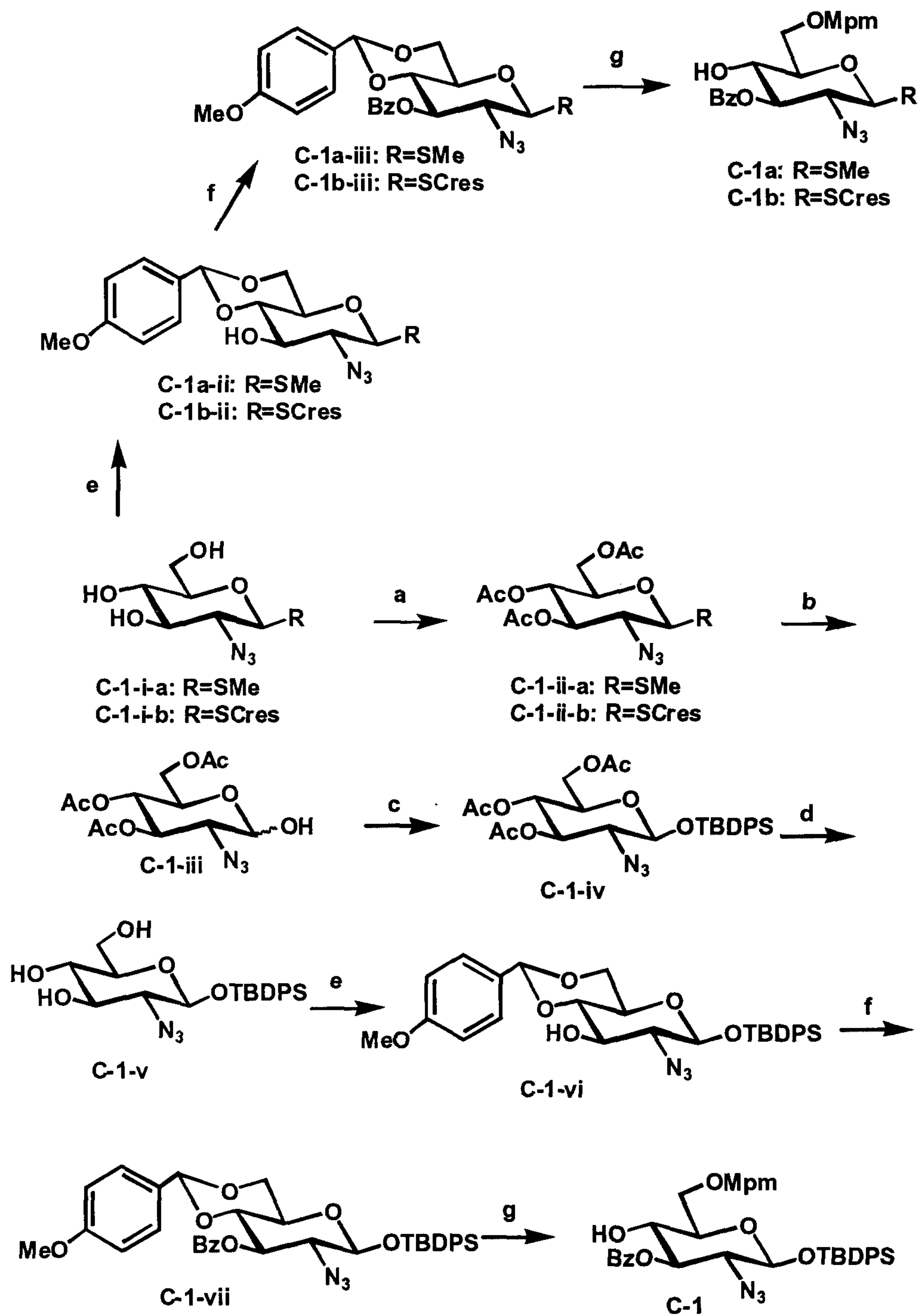
¹H-NMR (400 MHz, CDCl₃): δ = 8.07 (d, 2H, Aryl), 7.57-7.30 (m, 10H, Aryl), 7.10 (d, 2 H, Aryl), 6.88-6.81 (m, 4H, Mp), 5.55 (d, 1H, J_{1,2} < 1.5 Hz, H-1β),
20 5.45 (m, 1H, H-2), 5.26 (ddd, 1H, H-5), 5.13 (m, 1H, H-4), 4.91 (d, 1H, J_{gem} = 12.1 Hz, OCH₂), 4.78 (d, 1H, J_{gem} = 12.1 Hz, OCH₂), 4.16 (dd, 1H, J_{gem} = 9.6 Hz, J_{5,6a} = 7.6 Hz, H-6a), 4.08 (dd, 1H, J_{5,6b} = 5.2 Hz, H-6b), 3.93 (m, 1H, H-3), 3.77 (s, 3H, OCH₃), 2.58-2.36 (m, 4H, (CH₂)₂ Lev), 2.32 (s, 3H, SCH₃), 2.05 (s, 3H, CH₃C=O).

25

Example 4: Synthesis of L-ido configured glycosyl donor B-2.



Example 4: Synthesis of L-ido configured glycosyl donor **B-2**; a) SOP 2; b) SOP 18; c) SOP 5; d) SOP 23.

Example 5: Synthesis of Building Block C-1, C-1a and C-1b

Example 5: Synthesis of Building Blocks **C-1**, **C-1a** and **C-1b**, conditions: a) SOP 19; b) SOP 13, (78 %, 2 steps); c) SOP 8, (91 %); d) SOP 22; e) SOP 2, (85%, 2 steps for **C-1-vi**); f) SOP 18; g) SOP 5, (75 %, 2 steps for **C-1**).

Preparation of **C-1-ii**:

- 5 To methyl 2-azido-2-deoxy-1-thio- β -D-glucopyranoside. (10g, 42.50 mmol) in pyridine (50ml) at 0°C was added acetic anhydride (20g) and the reaction stirred for 1 hour. The reaction mixture was evaporated to dryness and the residue extracted to give the title triacetate (15.23g, quantitative.), R_f =0.7 (CHCl₃/Petroleum ethers, 1 :1).

10 Preparation of **C-1-iii**:

- To a solution of methyl 3,4,6-tri-O-acetyl-2-azido-2-deoxy-1-thio- β -D-glucopyranoside (14.1g, 39 mmol) in wet acetone (200ml) was added NBS (3 equiv.). The resulting mixture was allowed to stir for 2h. The mixture was then quenched, concentrated and the residue purified by silica gel chromatography to give the title hemiacetal as an oil (10.1g, 78%), R_f = 0.5 (EtOAc/Petroleum ether, 1:1).
- 15

Preparation of **C-1-vi**:

- A mixture of 2-azido-2-deoxy- β -D-glucopyranosyl *tert*-butyldiphenylsilane (5.5g, 12.42 mmol), 4-methoxybenzaldehyde dimethylacetal (4.4g, 24mmol), and 4-toluenesulphonic acid (100mg) in acetonitrile/DMF (200ml, 5:3) were heated at 60°C for 1 hour. The reaction mixture was then neutralized and evaporated to give the crude compound as an oil. The residue was purified by silica chromatography to give the product (6.7g, 96%, 85% from C-1-iv); R_f = 0.8 (dichloromethane/Petroleum ethers; 10:2).
- 20

25 Preparation of **C-1-vii**:

- A mixture of DMAP (1.63g, 13.2 mmol) and benzoyl chloride (1.7g, 12.1mmol) and 2-azido-2-deoxy-4,6-O-(4-methoxybenzylidene)- β -D-glucopyranosyl *tert*-butyldiphenylsilane (6.7g, 11.9 mmol) in 1,2-dichloroethane (100mL) was stirred at 60°C for 1h. The reaction mixture was quenched, extracted, washed and concentrated to give a crude residue. The residue was passed through a plug of silica to give the product (5.5g, 69%); R_f = 0.7 (dichloromethane/Petroleum ethers; 4:1).
- 30

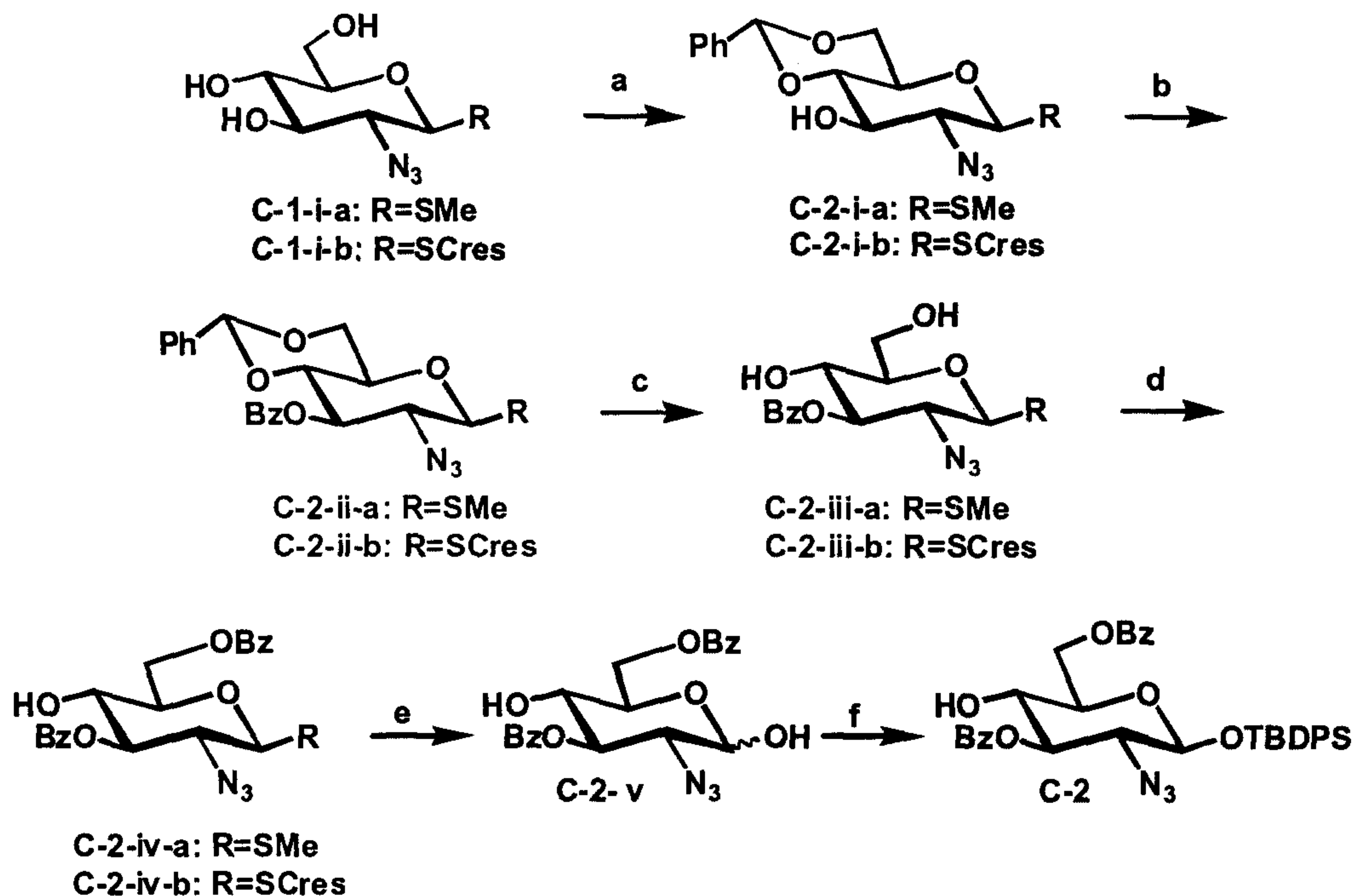
Preparation of **C-1**:

To a mixture of 2-azido-2-deoxy-3-O-benzoyl-4,6-O-(4-methoxybenzylidene)- β -D-glucopyranosyl *tert*-butyldiphenylsilane (10g, 15mmol), sodiumcyanoborohydride (5g, 75.6 mmol) and molecular sieves in DMF (200mL) at 0°C was added trifluoroacetic acid (28g, 247mmol) at 0°C and then left to run overnight at rt. The reaction mixture was quenched, filtered and concentrated and the residue purified by column chromatography to give the title compound (7.0g, 70%), R_f = 0.4 (ethylacetate/petroleum ethers, 3:7).

Compound C-1:

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ = 8.08 (d, 2 H, Aryl), 7.72 (m, 4 H, Aryl), 7.59 (m, 1 H, Aryl), 7.47 (m, 3 H, Aryl), 7.42 (m, 2 H, Aryl), 7.34 (m, 3 H, Aryl), 7.13 (d, 2 H, Mpm) 6.83 (d, 2H, Mpm), 4.96 (dd, 1 H, $J_{2,3} \approx J_{3,4} = 9.7$ Hz, H-3), 4.53 (d, 1 H, $J_{1,2} = 7.6$ Hz, H-1 β), 4.37 (2d, 2 H, OCH_2), 3.83 (ddd, 1 H, H-4), 3.79 (s, 3 H, OCH_3), 3.65 (dd, 1 H, H-2), 3.53 (dd, 1 H, $J_{\text{gem}} = 10.8$ Hz, $J_{5,6a} = 4.1$ Hz, H-6a), 3.46 (dd, 1 H, $J_{5,6b} = 4.1$ Hz, H-6b), 3.12 (m, 1 H, H-5), 3.02 (d, 1 H, $J_{4,\text{OH}} = 3.5$ Hz, 4-OH), 1.12 (s, 9 H, $\text{C}(\text{CH}_3)_3$).

Example 6: Synthesis of Building Block C-2

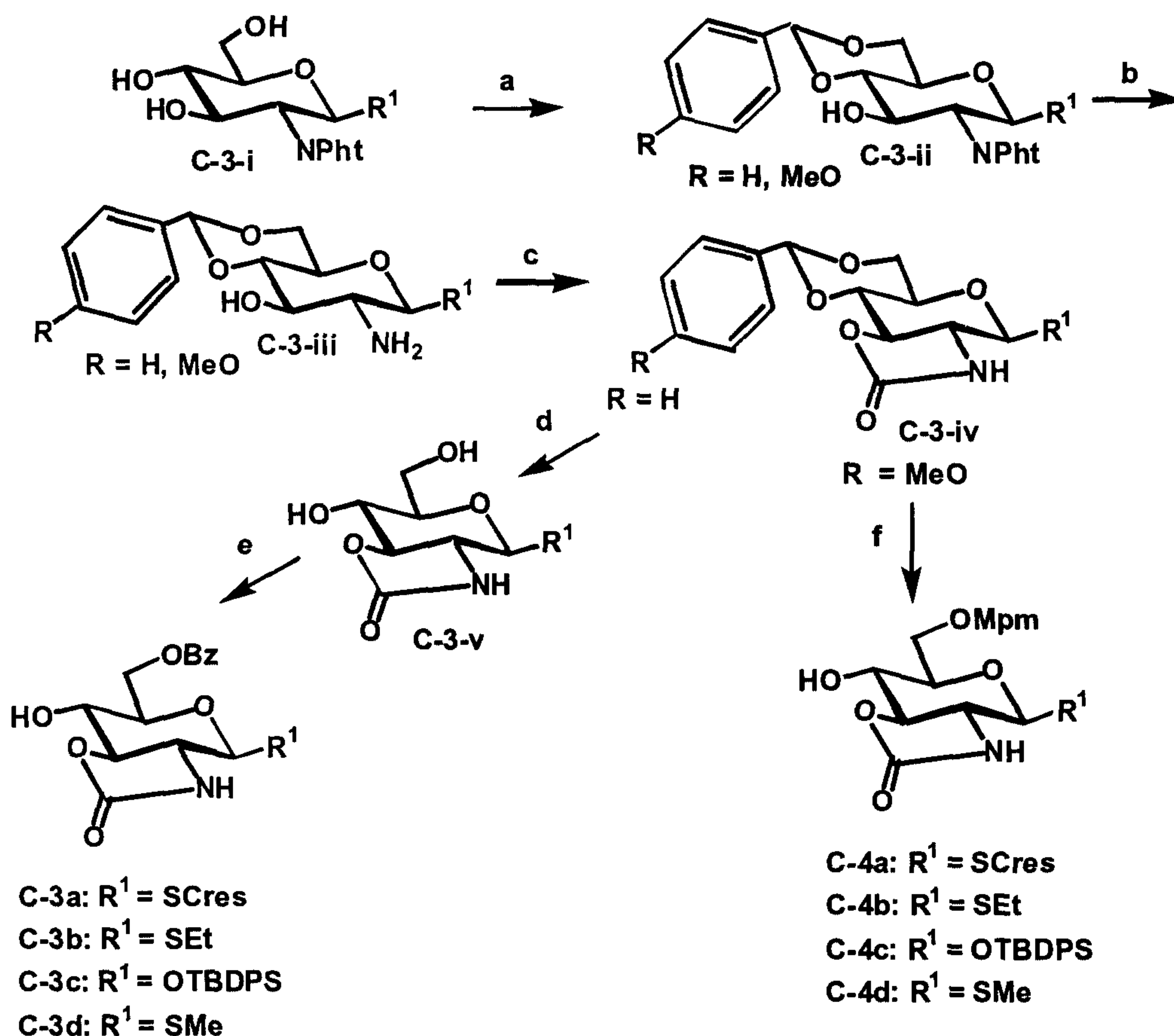


Example 6: Synthesis of Building Block **C-2**, conditions: a) SOP 1, (90% for R=SMe); b) SOP 18, (87% for R=SMe); c) SOP 4, p-TosOH, MeOH, CH₃CN (86% for R=SMe); d) SOP 17, (92% for R=SMe); e) SOP 13, (94%); f) SOP 8, (82%).

5 Compound C-2:

¹H-NMR (400 MHz, CDCl₃): δ = 8.09 (d, 2 H, Aryl), 7.97 (d, 2 H, Aryl), 7.72 (m, 4 H, Aryl), 7.60 (m, 1 H, Aryl), 7.50-7.27 (m, 11 H, Aryl), 4.98 (dd, 1 H, $J_{2,3} \approx J_{3,4} = 9.7$ Hz, H-3), 4.58 (d, 1 H, $J_{1,2} = 7.8$ Hz, H-1 β), 4.51 (dd, 1 H, $J_{\text{gem}} = 11.3$ Hz, $J_{5,6a} = 4.7$ Hz, H-6a), 4.36 (dd, 1 H, $J_{5,6b} = 2.2$ Hz, H-6b), 3.72-3.68 (m, 2 H, H-2, H-4), 3.31 (m, 1 H, H-5), 3.23 (d, 1 H, $J_{4,\text{OH}} = 4.5$ Hz, 4-OH), 1.13 (s, 9 H, C(CH₃)₃).

15 Example 7: Synthesis of several carbamoylated Building Blocks C-3a to C-3d and C-4a to C-4d, containing a 6-O benzoyl or 6-O-p-methoxybenzyl protection

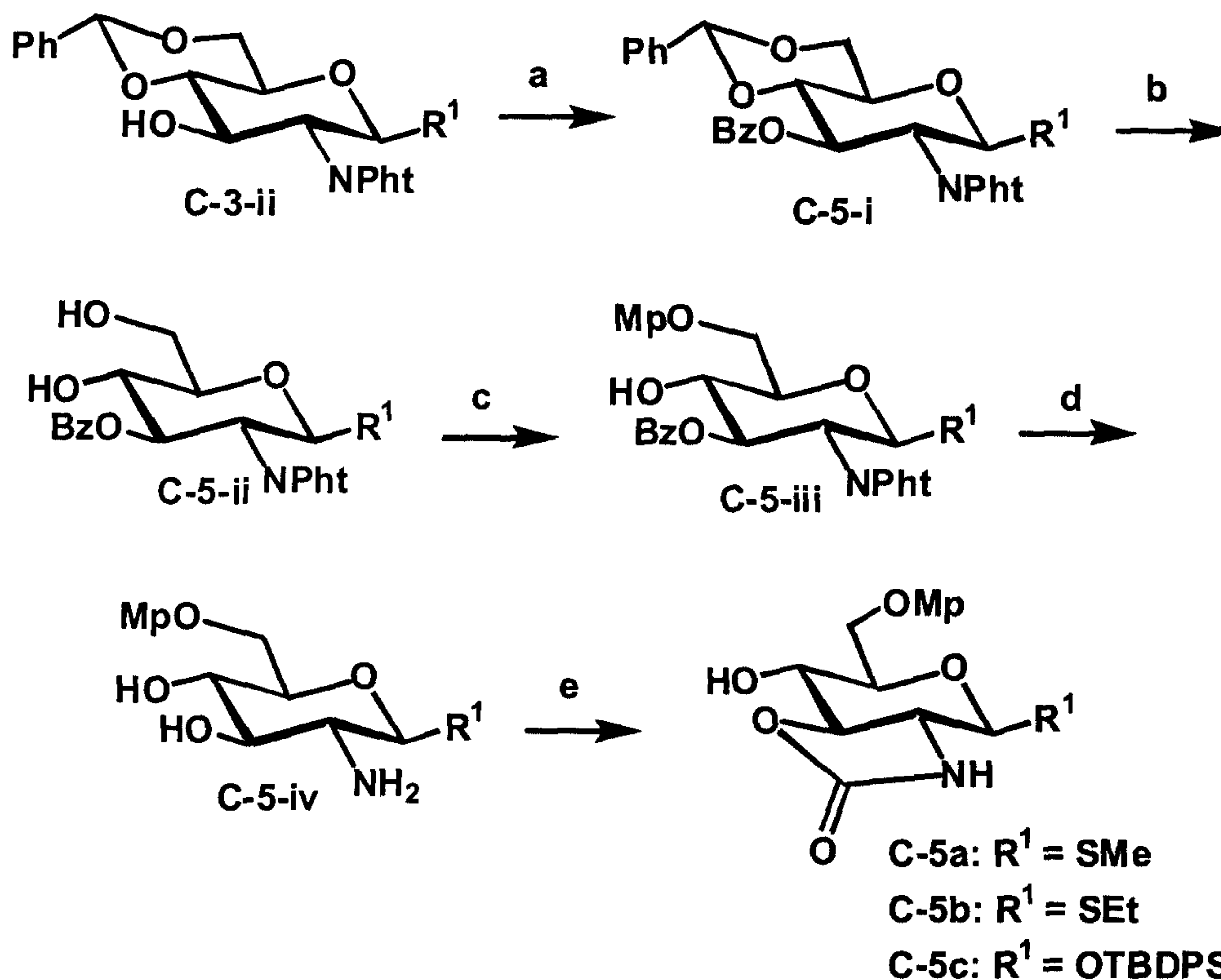


Example 7: Synthesis of several carbamoylated building blocks **C-3a** to **C-3d** and **C-4a** to **C-4d**, containing a 6-O-benzoyl or 6-O-p-methoxybenzyl protection, conditions: a) R = MeO: SOP 2; R = H: SOP 1, (82 %, R¹ = SCres, R = H); b) SOP 30, (87 %, R¹ = SCres, R = H); c) SOP 29, (95 %, R¹ = Scres, R = H); d) SOP 4, (72 %, R¹ = SCres); e) SOP 17, (85 %); f) SOP 5.

Compound **C-3a**:

¹H-NMR (400 MHz, CDCl₃): δ = 8.06 (d, 2 H, Aryl), 7.62 (m, 1 H, Aryl), 7.48 (t, 2 H, Aryl), 7.38 (d, 2 H, Aryl), 6.97 (d, 2 H, Aryl), 5.06 (bs, 1H, NH), 4.79 (dd, 1H, J_{gem} = 12.0 Hz, J_{5,6a} = 3.6 Hz, H-6a), 4.70 (d, 1H, J_{1,2} = 9.2 Hz, H-1 β), 4.63 (dd, 1H, J_{5,6b} = 2.0 Hz, H-6b), 4.18 (dd, 1H, J_{2,3} $\approx$ J_{3,4} = 10.4 Hz, H-3), 3.89 (dd, 1H, J_{4,5} = 9.2 Hz, H-4), 3.72 (m, 1H, H-5), 3.23 (ddd, 1H, H-2), 3.12 (bs, 1H, 4-OH), 2.29 (s, 3H, SCH₃).

Example 8: Synthesis of several 6-OMP and cyclic 2,3-carbamoyl protected building blocks **C-5a** to **C-5c**

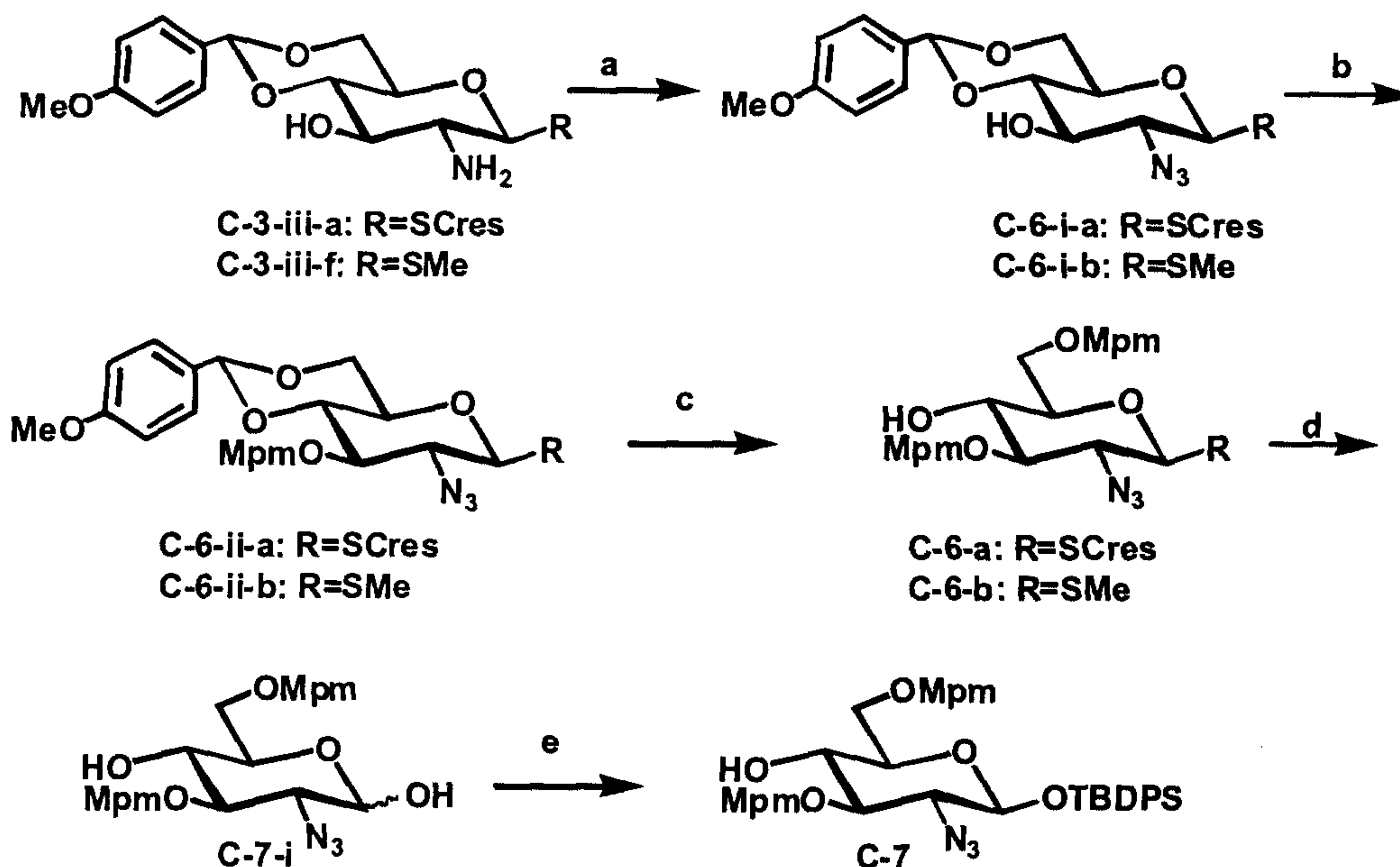


Example 8: Synthesis of several 6-OMp and cyclic 2,3-carbamoyl protected building blocks **C-5a** to **C-5c**, conditions: a) SOP 18, (92 % for $R^1 =$ OTBDPS); b) SOP 4, (82 %); c) SOP 26, (75 % for $R^1 =$ OTBDPS); d) SOP 30, (87 %); e) SOP 29, (95 %).

Compound C-5c:

^1H -NMR (400 MHz, $CDCl_3$): $\delta = 7.69$ (m, 2 H, Aryl), 7.63 (m, 2H, Aryl), 7.46-7.31 (m, 6H, Aryl), 6.82 (bs, 4H, Mp), 5.04 (bs, 1H, NH), 4.78 (d, 1H, $J_{1,2} = 7.6$ Hz, H-1 β), 4.15-4.10 (m, 3H, H's not assigned), 3.97 (dd, 1H, $J = 11.6$ Hz, $J = 9.6$ Hz, H not assigned), 3.78 (s, 3H, OMe), 3.56 (m, 1H, H not assigned), 3.48 (m, 1H, H not assigned), 2.80 (bs, 1H, 4-OH), 1.08 (s, 9H, C-(CH_3) $_3$).

Example 9: Synthesis of Building Blocks C-6-a and C-6-b and C-7



Example 9: Synthesis of building blocks **C-6-a**, **C-6-b** and **C-7**, conditions; a) SOP 12, (83 %); b) SOP 7; c) SOP 5, (75 %, 2steps); d) SOP 14 (82 %); e) SOP 8 (91 %).

Compound **C-6-a**:

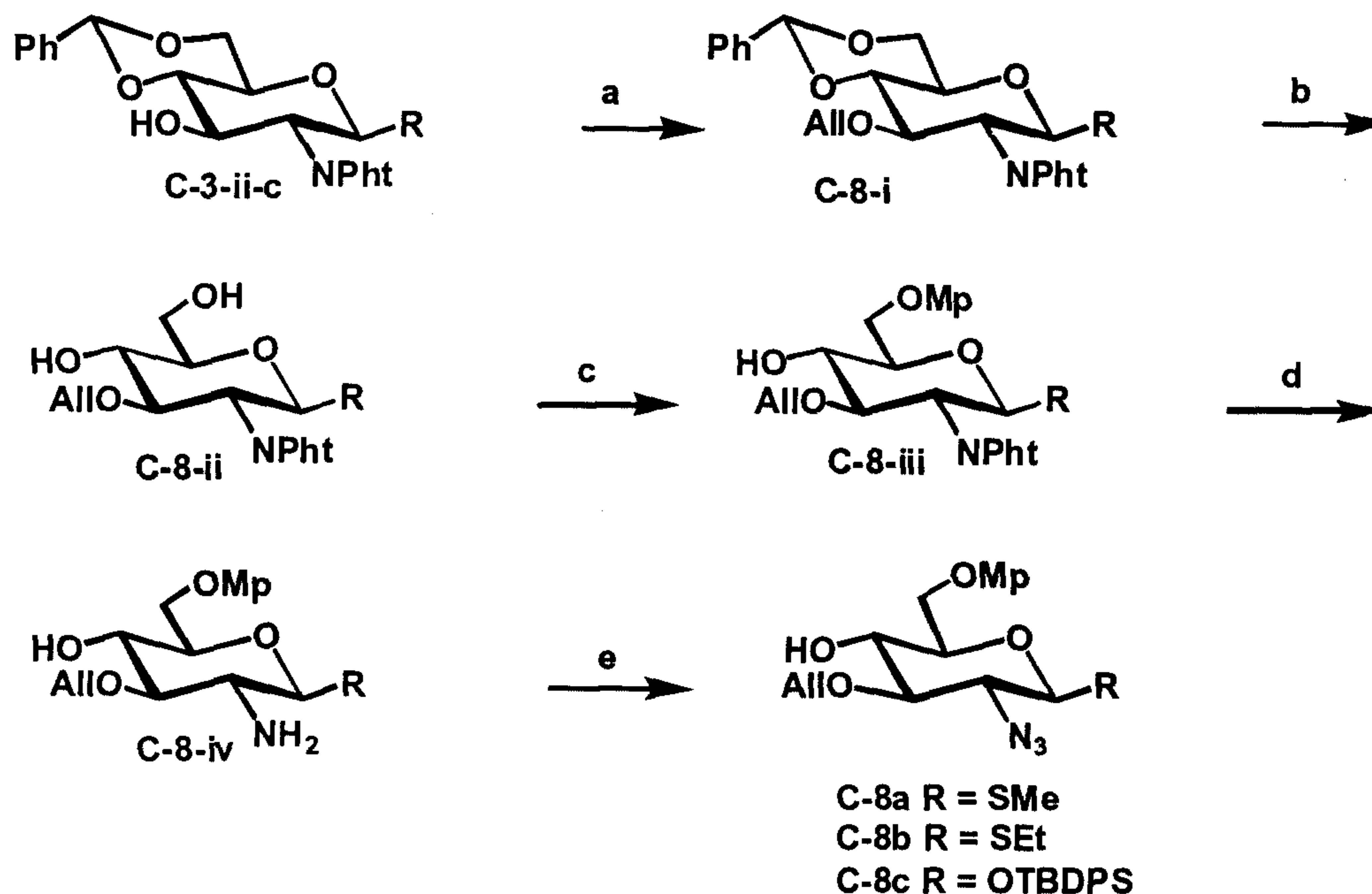
$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ = 7.43 (d, 2 H, Aryl), 7.25 (m, 4 H, Aryl), 7.08 (d, 2 H, Aryl), 6.88 (m, 4 H, Aryl), 4.81 (d, 1 H, $J_{\text{gem}} = 10.8$ Hz, OCH_2), 4.74 (d, 1 H, $J_{\text{gem}} = 10.8$ Hz, OCH_2), 4.53 (d, 1 H, $J_{\text{gem}} = 11.1$ Hz, OCH_2), 4.48 (d, 1 H, $J_{\text{gem}} = 10.8$ Hz, OCH_2), 4.35 (d, 1 H, $J_{1,2} = 10.0$ Hz, H-1 β), 3.82 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 3.76 (dd, 1 H, $J_{\text{gem}} = 10.5$ Hz, $J_{5,6a} = 5.4$ Hz, H-6a), 3.70 (dd, 1 H, $J_{5,6b} = 5.4$ Hz, H-6b), 3.56 (ddd, 1 H, H-4), 3.42 (m, 1 H, H-5), 3.34 (dd, 1 H, $J_{3,4} = 8.8$ Hz, H-3), 3.24 (dd, 1 H, $J_{2,3} = 9.4$ Hz, H-2), 2.72 (d, 1 H, $J_{4,\text{OH}} = 3.5$ Hz, 4-OH), 2.38 (s, 3 H, SCH_3).

Compound **C-7**:

$^1\text{H-NMR}$ (400 MHz, CDCl_3): 7.63 (d, 4 H, Aryl), 7.35-7.21 (m, 8H, Aryl), 7.08 (m, 2 H, Aryl), 6.83-6.78 (m, 4 H, Aryl), 4.72 (d, 1H, $J_{\text{gem}} = 11.0$ Hz, OCH_2), 4.59 (d, 1H, $J_{\text{gem}} = 11.0$ Hz, OCH_2), 4.29 (d, 1 H, $J_{1,2} = 7.8$ Hz, H-1 β), 4.27 (d, 1H, $J_{\text{gem}} = 11.7$ Hz, OCH_2), 4.21 (d, 1H, $J_{\text{gem}} = 11.7$ Hz, OCH_2), 3.72 (s, 3 H, OCH_3), 3.71 (s, 3 H, OCH_3), 3.51 (ddd, 1 H, $J_{3,4} \approx J_{4,5} = 8.6$ Hz, H-4), 3.40-

3.32 (m, 3 H, H-6a, H-6b, H-2), 3.05 (dd, 1 H, $J_{2,3} = 9.8$ Hz, H-3), 2.90 (m, 1 H, H-5), 2.51 (d, 1 H, $J_{4,OH} = 2.2$ Hz, 4-OH), 1.12 (s, 9 H, $C(CH_3)_3$).

5 Example 10: Synthesis of building block C-8a to C-8c



- 10 Example 10: Synthesis of building blocks **C-8a to C-8c**, conditions: a) SOP 7, AlIBr, DMF (65 %, R=OTBDPS); b) SOP 4, (86 %, R=OTBDPS); c) SOP 26, (70 %, R=OTBDPS); d) SOP-30; e) SOP 12, (70 %, 2 steps for R=OTBDPS).

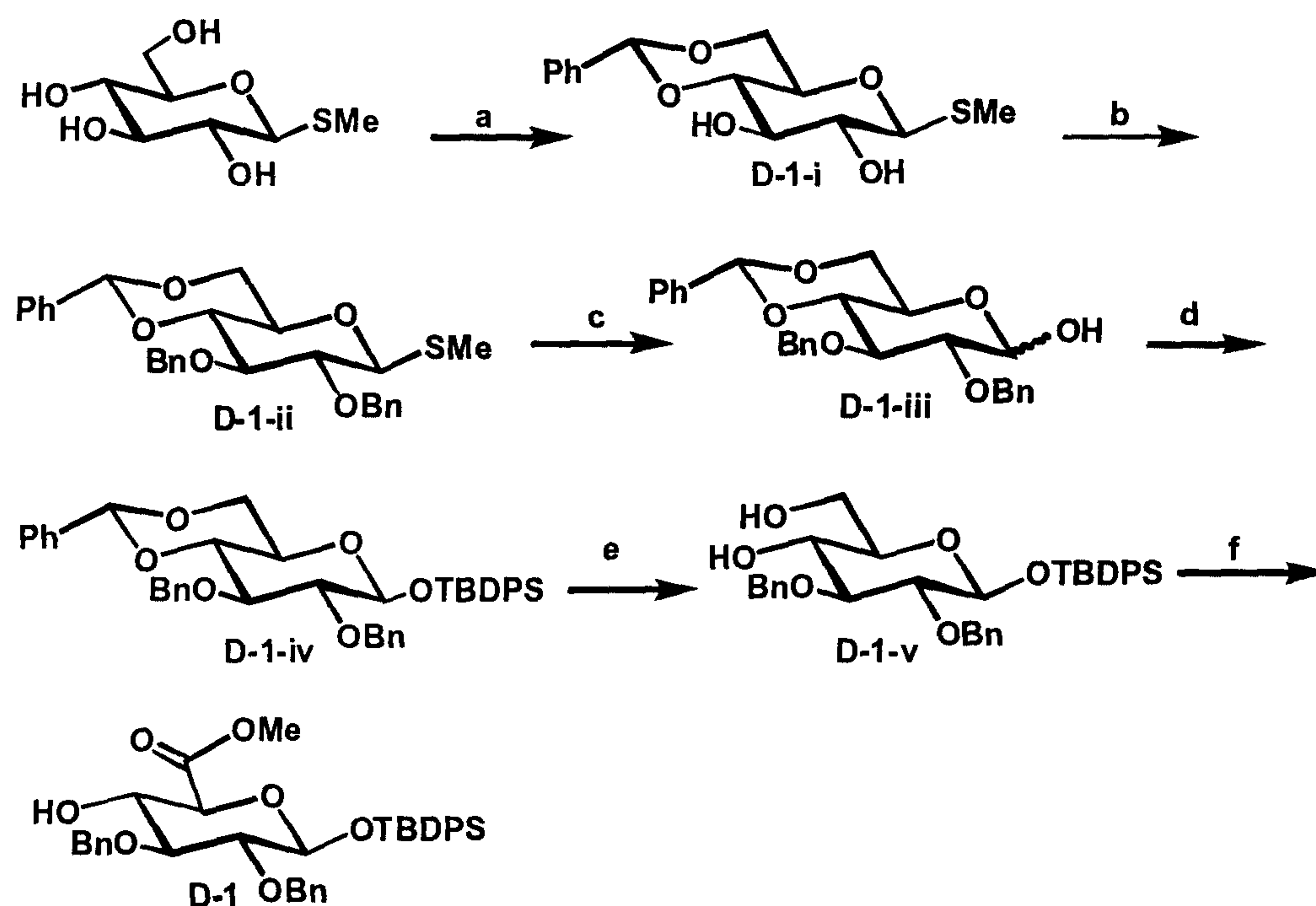
Compound C-8c:

- 15 ^1H -NMR (400 MHz, $CDCl_3$): $\delta = 7.72$ (m, 4 H, Aryl), 7.43-7.16 (m, 6 H, Aryl), 6.76 (m, 4H, Mp), 5.96 (m, 1 H, =CH Allyl), 5.31 (m, 1 H, =CH Allyl), 5.22 (m, 1 H, =CH Allyl), 4.42 (d, 1 H, $J_{1,2} = 7.6$ Hz, H-1 β), 4.39 (m, 1 H, OCH_2 Allyl), 4.23 (m, 1 H, OCH_2 Allyl), 3.97 (dd, 1 H, $J_{gem} = 10.0$ Hz, $J_{5,6a} = 3.6$ Hz, H-6a), 3.92 (dd, 1 H, $J_{5,6b} = 5.2$ Hz, H-6b), 3.77 (s, 3 H, OCH_3), 3.66 (ddd, 1 H, $J_{4,5} \approx$
- 20 $J_{3,4} = 9.4$ Hz, H-4), 3.42 (dd, 1 H, $J = 9.8$ Hz and $J = 7.8$ Hz, H not assigned),

3.22 (m, 1 H, H-5), 3.09 (dd, 1 H, $J = 8.4$ Hz and $J = 9.6$ Hz, H not assigned), 2.48 (d, 1 H, $J_{4,OH} = 2.8$ Hz, 4-OH), 1.12 (s, 9 H, $C(CH_3)_3$).

Example 11: Synthesis of Building Block D-1:

5



Example 11: Synthesis of building block **D-1**; a) SOP 1, (95 %); b) SOP 7, (85 %); c) SOP 13, (92 %); d) SOP 8; e) SOP 4, (70 %, 2 steps); f) 1. SOP 15; 2. SOP 16, (75 %, 2 steps).

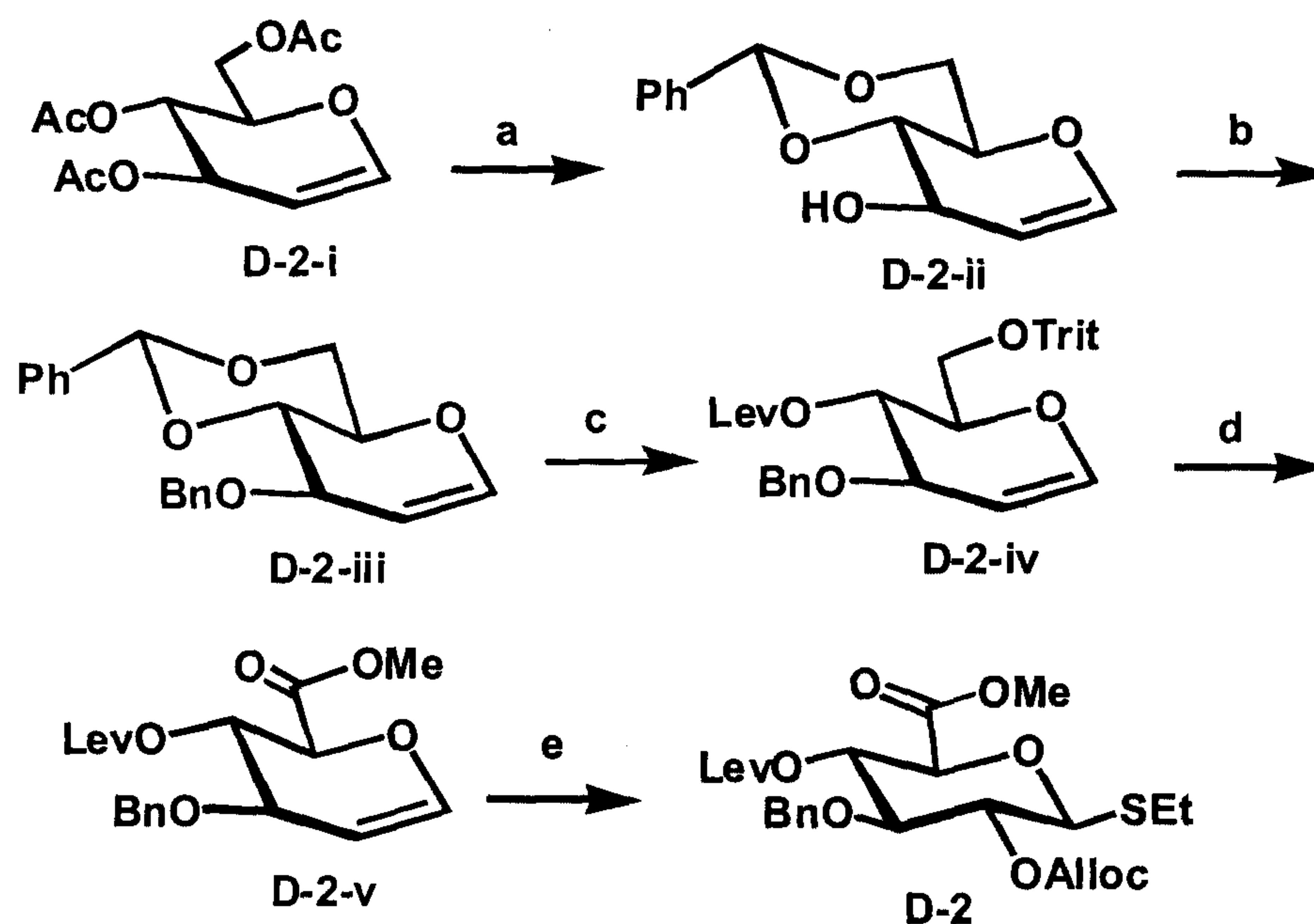
10

Compound D-1:

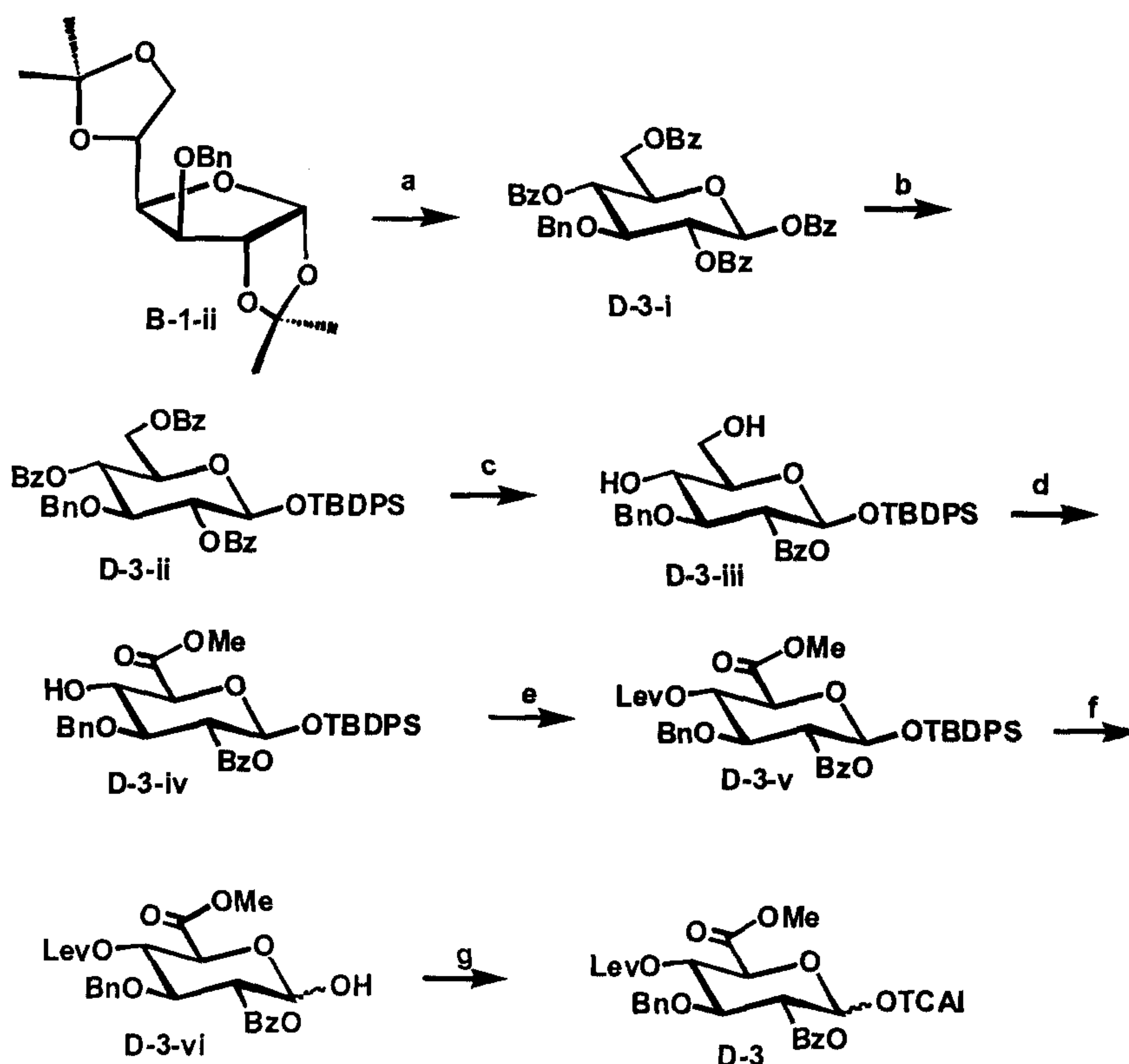
^1H -NMR (400 MHz, $CDCl_3$): $\delta = 7.72$ (m, 4 H, Aryl), 7.41 (m, 2 H, Aryl), 7.32 – 7.25 (m, 14 H, Aryl), 5.04 (d, 1 H, $J_{gem} = 11.0$ Hz, OCH_2), 4.81 (m, 3 H, OCH_2), 4.63 (d, 1 H, $J_{1,2} = 7.4$ Hz, H-1 β), 3.88 (ddd, 1 H, $J_{3,4} \approx J_{4,5} = 9.2$ Hz, H-4), 3.70 (s, 3 H, OCH_3), 3.53 (dd, 1 H, $J = 7.5$ Hz, $J = 9.0$ Hz, H not assigned), 3.47 (d, 1 H, $J_{4,5} = 9.8$ Hz, H-5), 3.42 (dd, 1 H, $J = 8.9$ Hz and $J = 8.9$ Hz, H not assigned), 2.87 (d, 1 H, $J_{4,OH} = 2.4$ Hz, 4-OH), 1.11 (s, 9 H, $C(CH_3)_3$).

15

Example 12: Synthesis of Building Block **D-2**, a 2-O-Allyloxycarbonyl
 5 protected thioethyl glycoside



Example 12: Synthesis of Building Block **D-2**, conditions: a) 1. SOP 22; 2. SOP 1; b) SOP 7; c) 1. SOP 4; 2. TritCl, Pyridine, (ClCH₂)₂; 3. SOP 23; d) 1. CrO₃, H₂SO₄, Acetone, 0°C, 2. SOP 16; e) 1. Dimethyl dioxirane, Acetone; 2. EtSH, TFAA, CH₂Cl₂, 3. SOP 35.

Example 13: Synthesis of Building Block D-3

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Example 13: Synthesis of Building Block D-3, conditions: a) 1. SOP 4, Amberlite IR 120, H₂O, 80°C; 2. SOP 18, (85 %, 2 steps) b) 1. SOP 21; 2. SOP 8, (70 %, 2 steps); c) SOP 22, (96 %); d) 1. SOP 15; 2. SOP 16, (80 %, 2 steps); e) SOP 23, (92 %); f) SOP 9, (95 %); g) SOP 25a, (91 %).

10

Preparation of D-3-i, step 1:

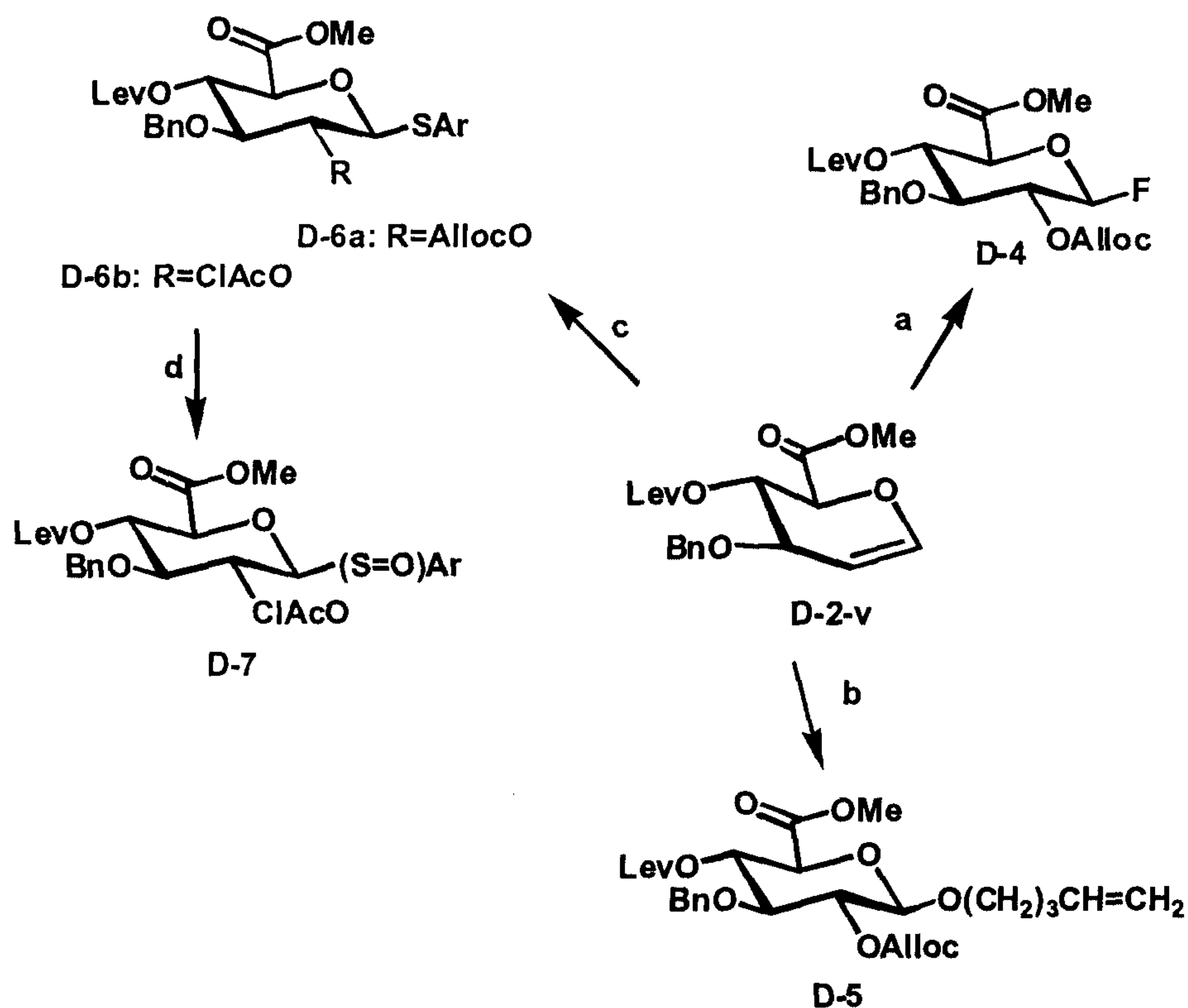
The starting material (57 mmol) and Amberlite IR 120 iron exchange resin (H⁺-form, 20 g) were suspended in water (180 ml) and stirred at 80 °C until completion. The iron exchange resin was removed by filtration and extracted with water. The combined aqueous layers were neutralized with triethyl amine and freeze dried.

15

Compound D-3-v:

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ = 7.95 (m, 2 H, Aryl), 7.68 (m, 2 H, Aryl), 7.58 – 7.12 (m, 16 H, Aryl), 5.47 (dd, $J_{1,2}$ = 7.6 Hz, $J_{2,3}$ = 9.6 Hz, H-2), 5.31 (dd, $J_{3,4}$ = 9.6 Hz, H-4), 4.64 (d, 1H, 7.6 Hz, H-1 β), 4.60 (d, 1H, J_{gem} = 12.0 Hz, OCH_2), 4.55 (d, 1H, J_{gem} = 12.0 Hz, OCH_2), 3.74 (dd, 1H, H-3), 3.70 (s, 3H, OCH_3), 3.63 (d, 1H, $J_{4,5}$ = 9.6 Hz, H-5), 2.68 – 2.16 (m, 4H, $(\text{CH}_2)_2\text{-Lev}$), 2.15 (s, 3H, CH_3), 0.96 (s, 9H, $\text{C}(\text{CH}_3)_3$).

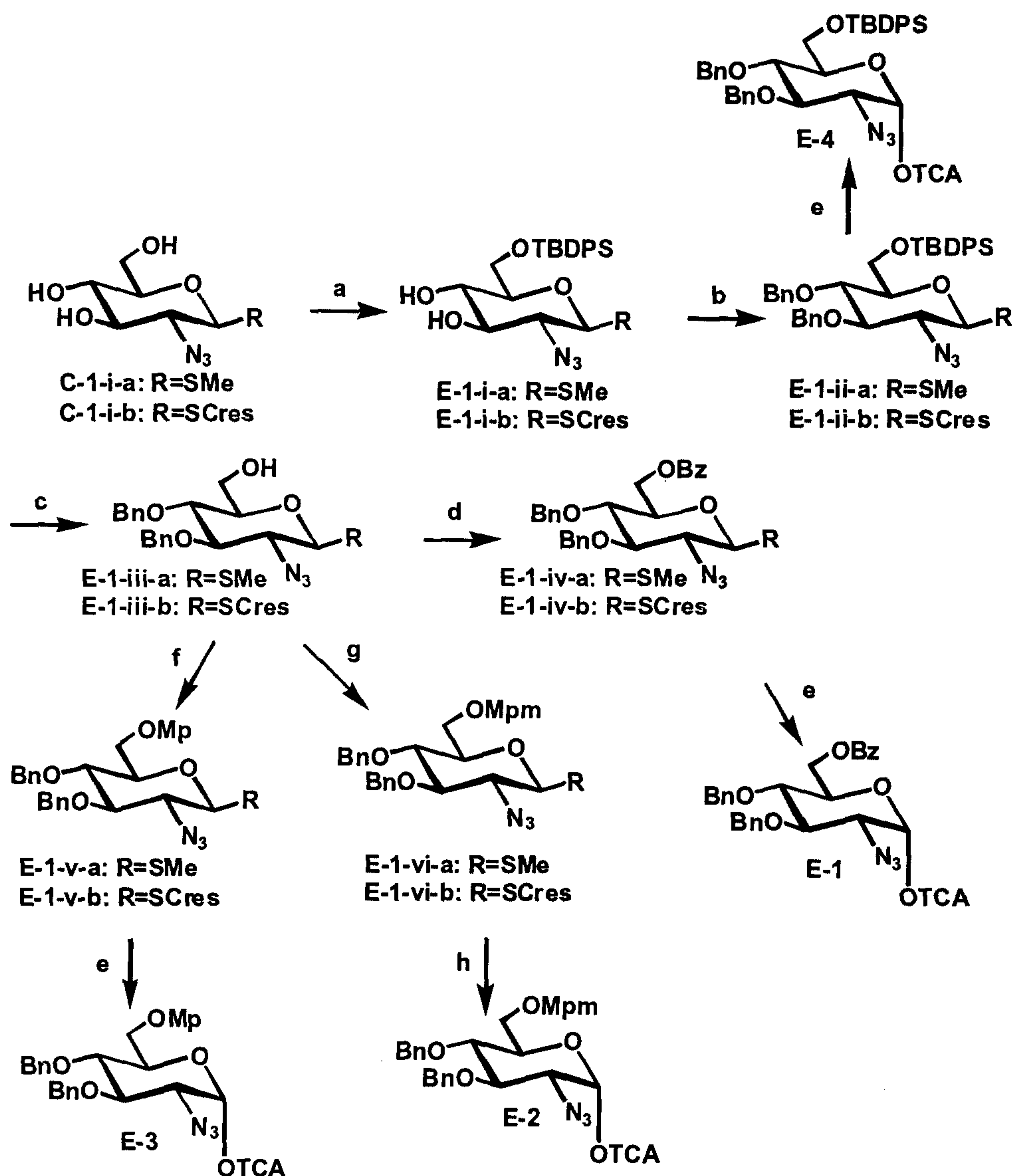
Example 14: Syntheses of a range of block D donor sugars **D-4** to **D-7** from a common intermediate, a 4-O-levulinoyl glucal.



10

Example 14: Syntheses of **D-4** to **D-7** as donor sugars, conditions: a) 1. Dimethyl dioxirane, Acetone; 2. TBAF, THF; 3. SOP 35; b) 1. Dimethyl dioxirane, Acetone; 2. 4-penten-1-ol, ZnCl_2 , CH_2Cl_2 ; 3. SOP 35; c) 1. Dimethyl dioxirane, Acetone; 2. ArSH , TFAA, CH_2Cl_2 , (Ar = Ph, *p*-Tol); 3. SOP 35 or $(\text{ClAc})_2\text{O}$, Pyridine, CH_2Cl_2 (for **D-6b**); d) MCPBA, CH_2Cl_2 (for **D-6b** as substrate).

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Example 15: Synthesis of Building Block **E-1** to **E-4**

- 5 Example 15: Synthesis of Building Block **E-1** to **E-4**, conditions: a) SOP 8; b) SOP 7; c) SOP 9, (84% over 3 steps, R=SMe); d) SOP 18, (82%, R=SMe); e) 1. SOP 13, (75%, for **E-1-iv-a** as starting material); 2. SOP 25b, (88%); f) 1. TosCl, Pyridine; 2. p-MeO-C₆H₄-ONa, NMP, 60°C; g) SOP 7, (78 %, R=SMe); h) 1. SOP 14; 2. SOP 25b, (79 %, 2 steps, R=SMe).

Preparation of **E-1-i-a**:

A mixture of methyl 2-azido-2-deoxy-thio- β -D-glucopyranoside (10g, 42.5mmol) and imidazole (4.9 g, 71.25 mmol) in 20 mL DMF was treated with *tert*-butyldiphenylchlorosilane (11.6mL, 44.63mmol) for 2h. The reaction mixture was concentrated, extracted, washed and dried. yield: 23g (crude light yellow syrup), R_f = 0.74 (CHCl_3 /methanol = 9/1).

Preparation of E-1-ii-a:

The silyl ether from the previous step in 50 mL DMF, was treated with 2.68g of 95% NaH (106.25 mmol) and 12.64 mL (106.25 mmol) of benzyl bromide at 0 °C. After 1h the excess NaH was quenched and the reaction concentrated, extracted, washed and concentrated to afford a yellow syrup yield: 28.5g (crude yellow syrup), R_f = 0.80 (hexane/ethyl acetate = 7/3).

Preparation of E-1-iii-a:

The crude yellow syrup from the above reaction was treated with 36.5 mL AcOH and 106.3 mL (106.25 mmol) of 1M solution of TBAF in THF overnight. The reaction was concentrated and purified by chromatography to afford the title compound. 14.9g (84%, 3 steps) R_f = 0.36 (petroleum spirit/ethyl acetate = 7/3)

Preparation of E-1-iv-a:

Methyl 2-azido-2,3 di-O-benzyl-2-deoxy-thio- β -D-glucopyranoside (14.5 g, 34.9 mmol) in dichloromethane (200 ml) and anhydrous pyridine (8.6 ml, 106.2 mmol) was treated with benzoylchloride (4.93 ml, 42.5 mmol) at 0°C for 1 hour. The reaction mixture was quenched, extracted, washed and evaporated. The residue was purified by silica gel column chromatography to afford the title compound as a white solid.

Yield: 14.9 g (82 %), R_f = 0.82 (Petroleum spirit/Ethyl acetate = 7/3).

Preparation of E-1:

Methyl 2-azido-6-O-benzoyl-2,3di-O-benzyl-2-deoxy-thio- β -D-glucopyranoside (8.68 g, 16.7 mmol) in acetone (50 ml) was treated with *N*-bromosuccinimide (8.92 g, 50.12 mmol) at 0°C for 1 hour. The reaction mixture was then quenched, extracted, washed and evaporated, furnishing a yellow syrup which was purified by chromatography. Yield: 6.13 g (75%), R_f = 0.57 (Petroleum spirit/Ethyl acetate = 7/3). A cooled mixture of 2-azido-6-O-

benzoyl-2,3 di-O-benzyl- 2-deoxy- α/β -D-glucopyranose (5g, 10.2 mmol), K_2CO_3 (7.0 g, 51 mmol) and trichloroacetonitrile (5.1ml, 51 mmol) in 30 ml of dichloromethane was stirred for 2h. The mixture was then filtered through celite and the filtrate was concentrated and purified on a short column of silica gel to obtain the title compound as an amorphous white solid. Yield 5.69 g (88%), R_f = 0.85 (Petroleum spirit/Ethyl acetate = 7/3).

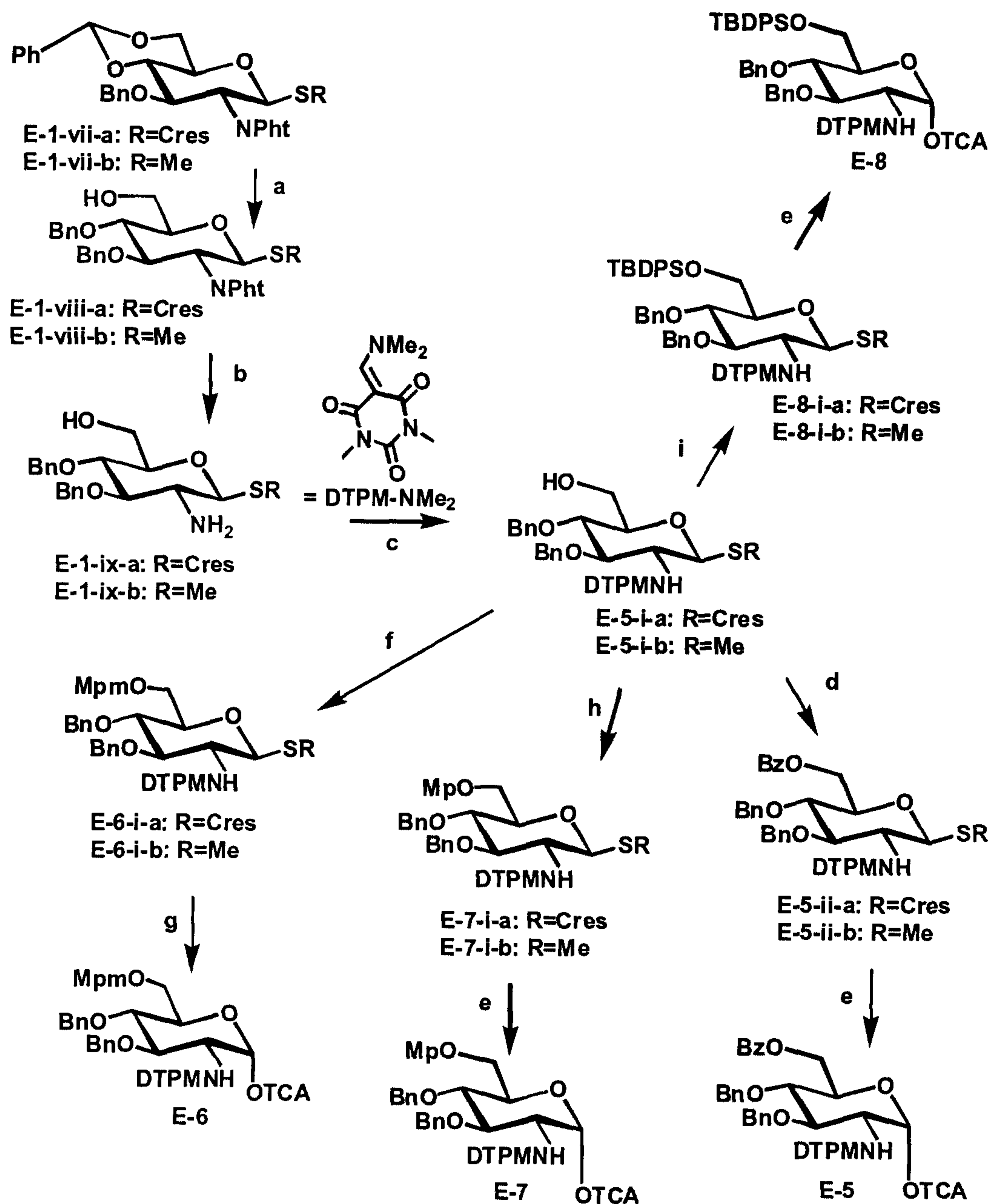
Compound E-1:

^1H -NMR (400 MHz, $CDCl_3$): δ = 8.73 (s, 1 H, C=NH), 8.00 (m, 2 H, Aryl), 7.56 (m, 1 H, Aryl), 7.43-7.25 (m, 12 H, Aryl), 5.66 (d, 1H, J = 8.4 Hz, H-1 β), 4.95 (d, 1H, J_{gem} = 10.8 Hz, OCH_2), 4.87 (d, 2H, J = 10.8 Hz, OCH_2), 4.62 (d, 2H, J_{gem} = 10.8 Hz, OCH_2), 4.58 (dd, 1H, J_{gem} = 12.4 Hz, $J_{5,6a}$ = 2.0 Hz, H-6a), 4.46 (dd, 1H, $J_{5,6b}$ = 3.6 Hz, H-6b), 3.77-3.72 (m, 3H, H-5, 2H not assigned), 3.62 (dd, 1H, J = 8.3 Hz, J = 9.7 Hz, H not assigned).

Compound E-2:

^1H -NMR (400 MHz, $CDCl_3$): δ = 8.70 (s, 1 H, C=NH), 7.38-7.22 (m, 10H, Aryl), 7.13 (m, 2H, Aryl), 6.83 (d, 2H, Mpm), 6.44 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1 α), 4.93 (d, 1H, J_{gem} = 10.5 Hz, OCH_2), 4.89 (d, 1H, J_{gem} = 10.5 Hz, OCH_2), 4.78 (d, 1H, J_{gem} = 10.5 Hz, OCH_2), 4.57 (d, 1H, J_{gem} = 11.7 Hz, OCH_2), 4.51 (d, 1H, J_{gem} = 11.7 Hz, OCH_2), 4.39 (d, 1H, J_{gem} = 11.7 Hz, OCH_2), 4.02 (dd, 1H, $J_{3,4} \approx J_{2,3}$ = 9.5 Hz, H-3), 3.98 (m, 1H, H-5), 3.86 (dd, 1H, $J_{4,5}$ = 9.6 Hz, H-4), 3.76 (dd, 1H, H-2), 3.75 (s, 3H, OCH_3), 3.69 (dd, 1H, $J_{5,6a}$ = 3.5 Hz, J_{gem} = 10.5 Hz, H-6a), 3.63 (dd, 1H, $J_{5,6b}$ = 1.8 Hz, H-6b).

Example 16: Synthesis of Building Blocks E-5 to E-8



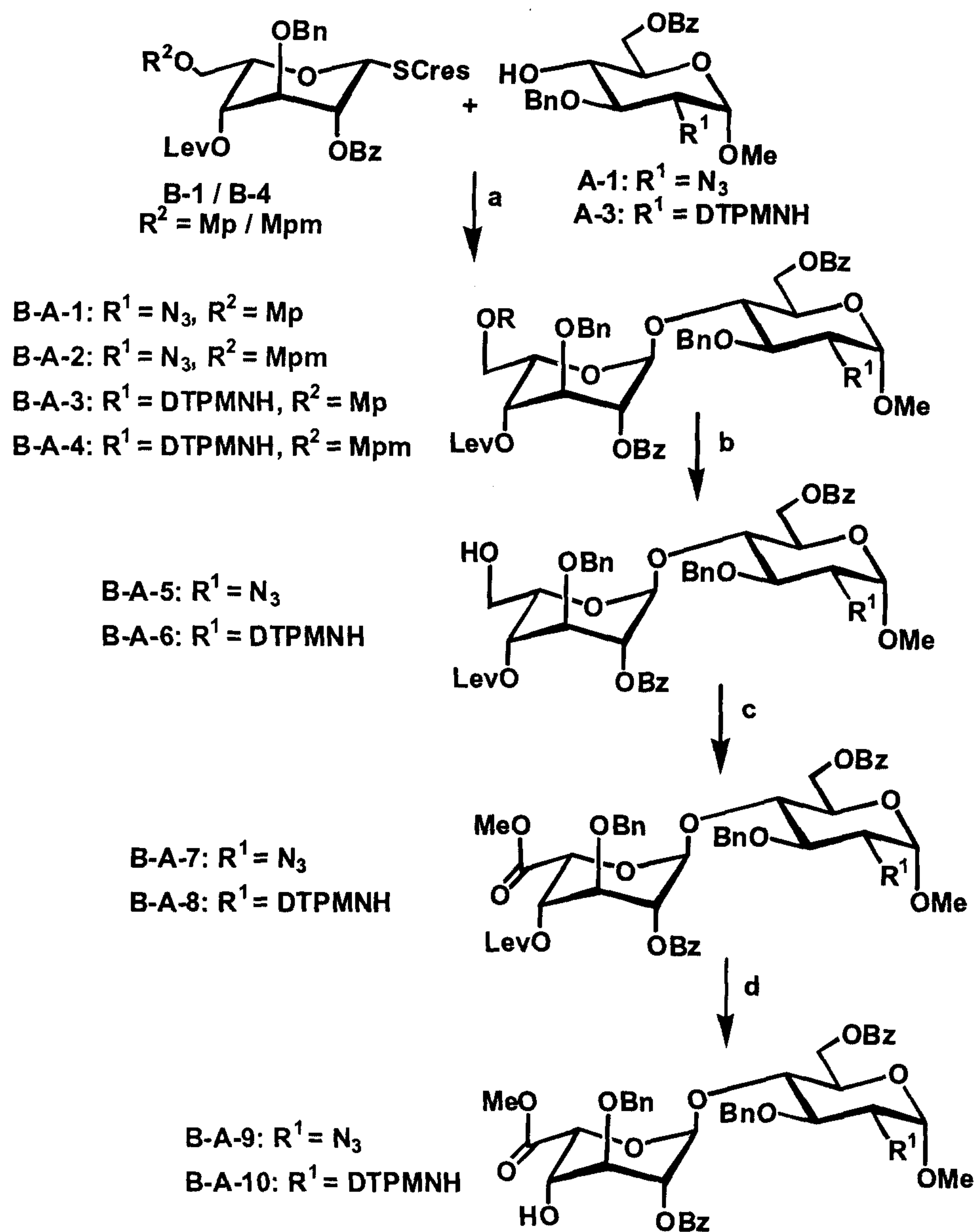
Example 16: Syntheses of Building Blocks **E-5 to E-8**, conditions: a) SOP 6,
 5 (85 %, R=SMe); b) SOP 30, (86 %, R=SMe); c) SOP 10, (88 %, R=SMe); d)
 SOP 18, (92 %, R=SMe); e) 1. SOP 13; 2. SOP 25b, (85 %, 2 steps, R=SMe);
 f) SOP 7; g) 1. SOP 14; 2. SOP 25b; h) 1. TsCl, DMF; 2. p-MeO-C₆H₄-ONa,
 NMP, 60°C; i) SOP 8.

Compound E-5:

¹H-NMR (400 MHz, CDCl₃): δ = 10.20 (dd, 1 H, $J_{\text{NH},\text{C-H}} = 14.0$ Hz, $J_{\text{NH},\text{H-2}} = 9.9$ Hz, NH), 8.80 (s, 1 H, C=NH), 8.16 (d, 1H, =C-H), 7.99 (m, 2H, Aryl) 7.58 (m, 1 H, Aryl), 7.45 (m, 2 H, Aryl), 7.30-7.17 (m, 10H, Aryl), 6.42 (d, 1H, $J_{1,2} = 3.6$ Hz, H-1 α), 4.89 (d, 1H, $J_{\text{gem}} = 8.4$ Hz, OCH₂), 4.68-4.60 (m, 3H, OCH₂), 4.58 (dd, 1H, $J_{5,6a} = 2.0$ Hz, $J_{\text{gem}} = 12.4$ Hz, H-6a), 4.51 (dd, 1 H, $J_{5,6b} = 4.0$ Hz, H-6b), 4.22 (m, 1 H, H-5), 4.03 (dd, 1 H, $J_{3,4} \approx J_{2,3} = 9.6$ Hz, H-3), 3.80 (dd, 1 H, $J_{4,5} = 9.4$ Hz, H-4), 3.70 (ddd, 1 H, H-2), 3.32 (s, 3 H, NCH₃), 3.25 (s, 3 H, NCH₃).

10

Example 17: Preparation of L-iduronic acid containing disaccharides B-A-1 to B-A-10



Example 17: Preparation L-iduronic acid containing disaccharides **B-A-1** to **B-A-10**; a) SOP 32a, (76 %, for **B-A-1**); b) SOP 27, (88 %, for **B-A-5**); c) 1.SOP 20; 2. SOP 16, (84 % for **B-A-7**, 2 steps); d) SOP 24, (94 %, for **B-A-9**).

Formation of disaccharide **B-A-1** (step a)

A suspension of **A-1** (410 mg, 992 μ mol), **B-1** (680 mg, 992 μ mol) and freshly activated molecular sieves 4 Å (1.0 g) in dry CH_2Cl_2 (20 mL) was stirred for 90 min at 0°C. *N*-Iodosuccinimide (405 mg, 1.8 mmol) was added and stirring

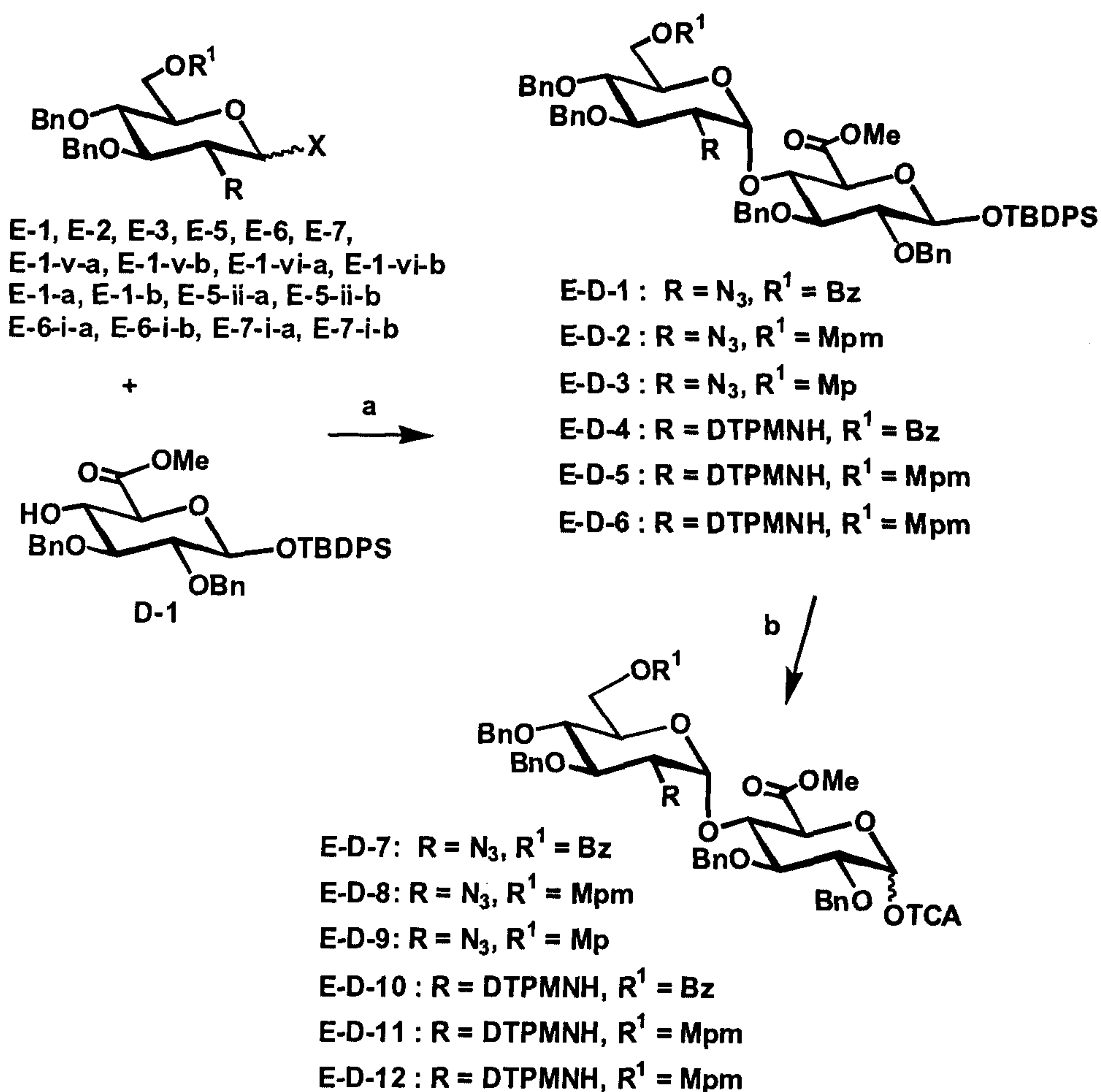
continued for 20 min. After addition of trifluoromethanesulfonic acid (10.6 μ l, 119.7 μ mol), the reaction mixture was further stirred until completion (from 0°C to 25 °C) and quenched with aqueous NaHCO₃-solution (10 %). The mixture was diluted with CH₂Cl₂ and filtered through a celite pad. The filtrate
5 was washed with a 10 % KHCO₃/Na₂S₂O₃ solution, water and saturated brine solution, dried over MgSO₄ and evaporated. Final purification was achieved by silica gel column chromatography. Yield: 730 mg (76 %).

Formation of disaccharide **B-A-7**(step c)

10 Disaccharide **B-A-5** (1.00 g, 1.15 mol) was dissolved in anhydrous DMF (7.0 ml) and reacted with pyridinium dichromate (4.33 g, 11.5 mmol) under stirring at room temperature until complete conversion into the uronic acid. The reaction mixture was subsequently poured into 50 ml water and the whole extracted with diethyl ether. The combined ether layers were washed with 10
15 % aqueous citric acid solution, filtered through a short silica gel pad, dried over MgSO₄, evaporated and dried under high vacuum. The crude residue was dissolved in Toluene (3 ml) and methanol (3 ml) and titrated with TMSCHN₂ solution (2M in hexane) until completion. The excess of TMSCHN₂ was destroyed by addition of acetic acid and the mixture evaporated. Final
20 purification was achieved via silica gel chromatography. Yield: 871 mg (84 %).

Compound **B-A-9**:

¹H-NMR (400 MHz, CDCl₃): δ = 8.03 (m, 2H, Aryl), 7.91 (m, 2H, Aryl), 7.53 (m, 2H, Aryl), 7.42-7.23 (m, 14H, Aryl), 5.37 (d, 1H, $J_{1,2} < 1.5$ Hz, H-1' α), 5.21
25 (m, 1H, H-2'), 4.97 (d, 1H, $J_{4,5} = 2.3$ Hz, H-5'), 4.84 (d, 2H, $J_{gem} = 10.8$ Hz, OCH₂), 4.81 (d, 1H, $J_{gem} = 10.8$ Hz, OCH₂), 4.80 (d, 1H, $J_{1,2} = 3.6$ Hz, H-1 α), 4.77 (1H, $J_{5,6a} = 1.8$ Hz, H-6a), 4.70 (m, 2H, OCH₂), 4.47 (dd, 1H, $J_{5,6b} = 4.2$ Hz, $J_{gem} = 12.3$ Hz, H-6b), 4.05-3.97 (m, 3H, H-4', H-4, H-5), 3.91-3.87 (m, 2H, H-3', H-3), 3.49 (s, 3H, OCH₃), 3.44 (m, 1H, H-2), 3.43 (s, 3H, OCH₃).
30 Selected ¹³C-NMR (100 MHz, CDCl₃): δ = 98.73 C-1 ($J_{CH} = 172.5$ Hz), 98.35 C-1' ($J_{CH} = 171.8$ Hz).

Example 18: Syntheses of Building Blocks E-D-1 to E-D-12

Example 18 : Syntheses of disaccharides **E-D-1** to **E-D-12**, conditions: a) SOP
 5 32 a/b for X = SMe/ Sres or SOP 33 for X = OTCA, (88 % for **E-D-1** via **E-1**,
 84% for **E-D-4** via **E-5**, as α/β mixtures), b) 1. SOP 9; 2. SOP 25a, (90 % for
E-D-7 over 2 steps).

Preparation of **E-D-1**: Methyl (2-azido-6-O-benzoyl-3,4-di-O-benzyl-2-deoxy- α -
 10 D-glucopyranosyl)-(1 $\rightarrow$ 4)-tert-butyldiphenylsilyl 2,3-di-O-benzyl- β -D-
 glucopyranosid)uronate

A mixture of 2-azido-6-O-benzoyl-2,3 di-O-benzyl- 2-deoxy- α/β -D-
 glucopyranosyl trichloroacetimidate (2.5 g, 3.94 mmol), and methyl (tert-
 15 butyldiphenylsilyl 2,3-di-O-benzyl- β -D-glucopyranoside) uronate (1.6 g, 2.55

mmol) and molecular sieves 4A (2.5 g) in 50 ml diethyl ether was treated with TBDMSOTf (180 μ l, 788.76 μ mol) at -20°C for 1h. The reaction was quenched filtered, concentrated and the residue purified by silica gel column chromatography to obtain the desired disaccharide 2.48 g, 88%. R_f = 0.67 (toluene/ethyl acetate 9/1)

Compound E-D-1:

E-D-1 was formed according to SOP 33 with ether as solvent at -30°C and TBDMSOTf as promotor in 86 % yield (α/β -mixture).

¹H-NMR (400 MHz, CDCl₃): δ = 8.00 (m, 2H, Aryl), 7.68 (m, 4H, Aryl), 7.56 (m, 1H, Aryl), 7.42 (m, 4H, Aryl), 7.36-7.17 (m, 24H, Aryl), 5.47 (d, 1H, $J_{1,2}$ = 3.8 Hz, H-1' α), 5.02 (d, 1H, J_{gem} = 11.4 Hz, OCH₂), 4.97 (d, 1H, J_{gem} = 11.0 Hz, OCH₂), 4.84 (m, 4H, OCH₂), 4.75 (d, 1H, J_{gem} = 11.4 Hz, OCH₂), 4.66 (d, 1H, $J_{1,2}$ = 7.5 Hz, H-1 β), 4.57 (d, 1H, J_{gem} = 10.9 Hz, OCH₂), 4.45 (m, 2H, H-6'a, H-6'b), 4.15 (dd, J = 8.8 Hz and J = 9.6 Hz), 3.86 (m, 1H), 3.65 (s, 3H, OCH₃), 3.68-3.58 (m, 3H), 3.55 (d, 1H, $J_{4,5}$ = 10.0 Hz, H-5), 3.31 (dd, 1H, $J_{2,3}$ = 10.2 Hz, H-2'), 1.12 (s, 9H, C(CH₃)₃).

Compound E-D-4:

E-D-4 was formed according to SOP 33 with ether as solvent at -30°C and TBDMSOTf as promotor in 84 % yield (α/β -mixture).

Selected ¹H-NMR (400 MHz, CDCl₃): δ = 10.02 (dd, 1 H, $J_{NH,=CH}$ = 14.4 Hz, $J_{NH,H2}$ = 9.6 Hz, N-H), 8.02 (m, 2 H, Aryl), 7.79 (d, 1H, =C-H), 7.72-6.93 (m, 33 H, Aryl), 5.60 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1' α), 4.49 (d, 1H, $J_{1,2}$ = 7.8 Hz, H-1 β), 3.66 (s, 3 H, OCH₃), 3.29 (s, 3 H, NCH₃), 3.28 (s, 3 H, NCH₃), 1.14 (s, 9 H, C(CH₃)₃).

Preparation of **E-D-7**: *Methyl (2-azido-6-O-benzoyl-3,4-di-O-benzyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-2,3-di-O-benzyl- β -D-glucopyranosyl trichloroacetimidyl)uronate*

A solution of methyl (2-azido-6-O-benzoyl-3,4-di-O-benzyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-*tert*-butyldiphenylsilyl 2,3-di-O-benzyl- β -D-glucopyranoside)

uronate (2.09 g, 1.90 mmol) in acetic acid (1.74 ml, 30.45 mmol) and 1 M solution of tetrabutylammoniumfluoride (7.6 ml, 7.61 mmol) was stirred at room temperature overnight. The reaction mixture was then concentrated and the residual syrup was purified by silica gel column chromatography to obtain the desired hemiacetal. Yield: 1.57 g (95.8%), R_f = 0.21 (toluene/ethyl acetate 9/1).

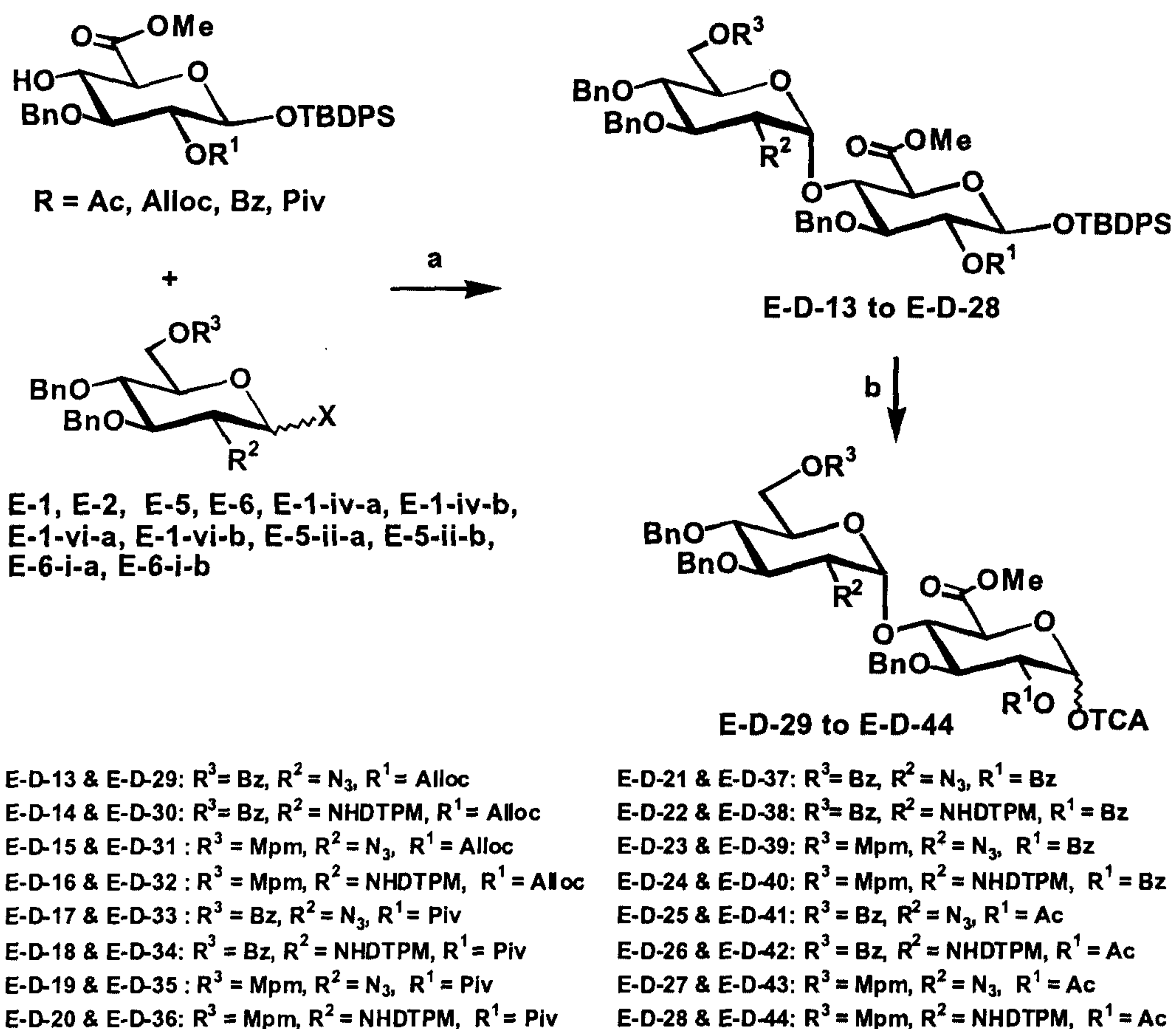
A mixture of methyl (2-azido-6-O-benzoyl-3,4-di-O-benzyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-2,3-di-O-benzyl- β -D-glucopyranosyl)uronate (594 mg, 690.70 μ mol), trichloroacetonitrile (280 μ l, 2.74 mmol) and DBU (31 μ l, 209.3 μ mol) in 8.0 ml dichloromethane was stirred at 0°C for 1 h. The mixture was then concentrated and purified on a short column of silica gel to obtain the title compound as an amorphous white solid. Yield: 662 mg (95.3 %), R_f = 0.46 (toluene/ethyl acetate 9/1).

15 Compound E-D-7:

Selected $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ = 8.68 (s, 1H, C=NH), 8.00 (m, 2H, Aryl), 7.56 (m, 2H, Aryl), 7.43-7.23 (m, 22H, Aryl), 6.48 (d, 1H, $J_{1,2}$ = 4.3 Hz, H-1 α), 5.59 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1' α), 5.03 (1H, J_{gem} = 10.8 Hz, OCH_2), 4.93-4.83 (m, 4H, OCH_2), 4.70 (d, 1H, J_{gem} = 12.0 Hz, OCH_2), 4.64 (d, 1H, J_{gem} = 12.0 Hz, OCH_2), 4.60 (d, 1H, J_{gem} = 11.2 Hz, OCH_2), 4.47 (m, 2H, H-6'a, H-6'b), 4.42 (m, 1H, not assigned), 4.15 (m, 2H, not assigned), 3.97 (dd, 1H, J = 8.2 Hz and J = 10.2 Hz, not assigned), 3.80 (m, 1H, not assigned), 3.76 (m, 3H, OCH_3), 3.72-3.64 (m, 2H, not assigned), 3.30 (dd, 1H, $J_{2,3}$ = 10.4 Hz, H-2').

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Example 19: Syntheses of disaccharides E-D-13 to E-D-44



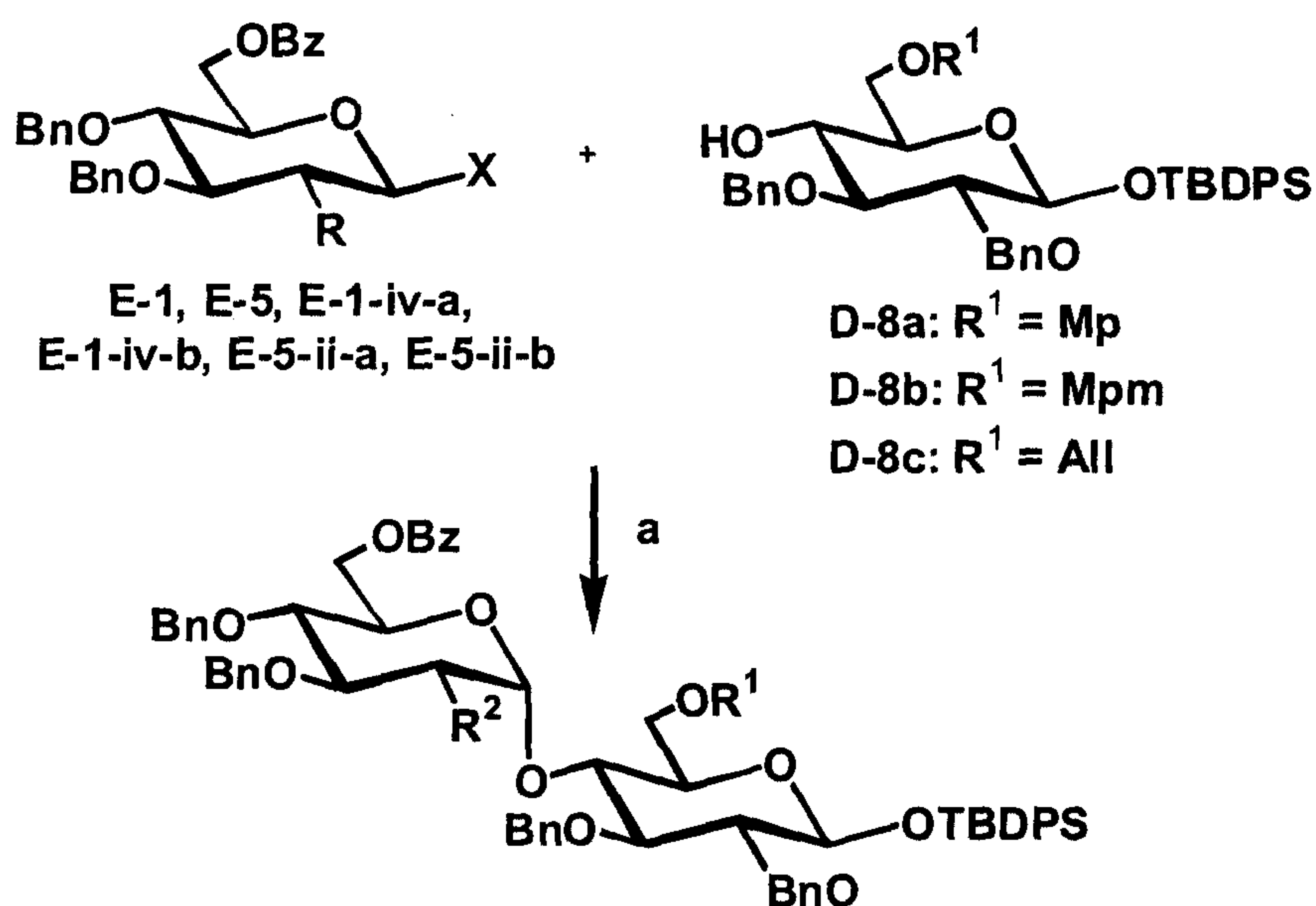
Example 19: Syntheses of disaccharides **E-D-13** to **E-D-44**, conditions: a)

- 5 SOP 32 a/b for $X = \text{SMe/ Scres}$ or SOP 33 for $X = \text{OTCA}$ (70 % for **E-D-23**, α/β mixture); b) 1. SOP 9; 2. SOP 25a.

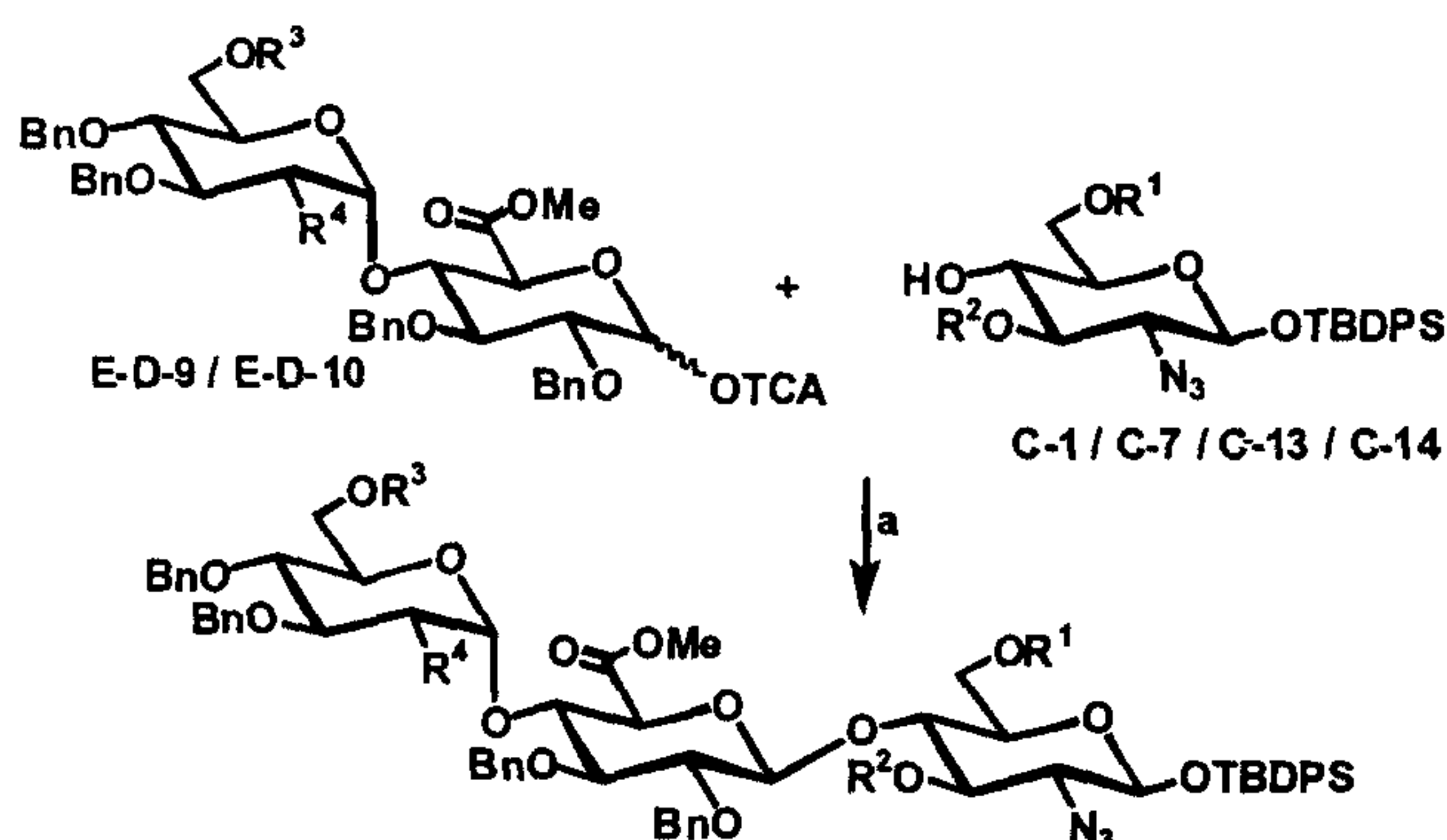
Compound E-D-27:

E-D-27 was formed according to SOP 33 with ether as solvent at -20°C and TBDMSOTf as promotor in 70 % yield (α/β -mixture).

- 5 Selected $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ = 7.58 (m, 2H, Aryl), 7.54 (m, 2H, Aryl), 7.36 – 7.00 (m, 23 H, Aryl), 6.73 (m, 2H, Aryl), 5.37 (d, 1H, $J_{1,2}$ = 3.9 Hz, H-1' α), 5.12 (dd, 1H, $J_{2,3}$ = 8.8 Hz, H-2), 4.63 (d, 1H, J_{gem} = 11.2 Hz, OCH_2), 4.58 (d, 1H, J_{gem} = 11.2 Hz, OCH_2), 4.48 (d, 1H, $J_{1,2}$ = 7.3 Hz, H-1 β), 3.66 (s, 3 H, OCH_3), 3.55 (s, 3 H, OCH_3), 3.34 (m, 1H), 3.22 (dd, 1H, J = 3.4 Hz, J = 10.7 Hz), 1.81 (s, 3 H, OAc), 0.98 (s, 9H, $\text{C}(\text{CH}_3)_3$).
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Example 20 : Synthesis of alternative E-D-disaccharides E-D-45 to E-D-50

Example 20 : Synthesis of alternative E-D-disaccharides **E-D-45** to **E-D-50**, conditions: a) SOP 32a/b for X = SMe/SCres or SOP 33 for X = OTCA, diethyl ether, TBDMS-OTf, -20 deg. C (75 % for **E-D-45** as α/β -mixture).

Example 21: Synthesis of trisaccharides E-D-C-1 to E-D-C-16

E-D-C-1 : $R^1 = \text{Mpm}, R^2 = \text{Mpm}, R^3 = \text{Mpm}, R^4 = \text{NHDTMP}$
 E-D-C-2 : $R^1 = \text{Mp}, R^2 = \text{Mpm}, R^3 = \text{Mpm}, R^4 = \text{NHDTMP}$
 E-D-C-3 : $R^1 = \text{Mpm}, R^2 = \text{Mpm}, R^3 = \text{Bz}, R^4 = \text{NHDTMP}$
 E-D-C-4 : $R^1 = \text{Mp}, R^2 = \text{Mpm}, R^3 = \text{Bz}, R^4 = \text{NHDTMP}$
 E-D-C-5 : $R^1 = \text{Mpm}, R^2 = \text{Bz}, R^3 = \text{Mpm}, R^4 = \text{NHDTMP}$
 E-D-C-6 : $R^1 = \text{Mp}, R^2 = \text{Bz}, R^3 = \text{Mpm}, R^4 = \text{NHDTMP}$
 E-D-C-7 : $R^1 = \text{Mpm}, R^2 = \text{Bz}, R^3 = \text{Bz}, R^4 = \text{NHDTMP}$
 E-D-C-8 : $R^1 = \text{Mp}, R^2 = \text{Bz}, R^3 = \text{Bz}, R^4 = \text{NHDTMP}$

E-D-C-9 : $R^1 = \text{Mpm}, R^2 = \text{Mpm}, R^3 = \text{Mpm}, R^4 = \text{N}_3$
 E-D-C-10 : $R^1 = \text{Mp}, R^2 = \text{Mpm}, R^3 = \text{Mpm}, R^4 = \text{N}_3$
 E-D-C-11 : $R^1 = \text{Mpm}, R^2 = \text{Mpm}, R^3 = \text{Bz}, R^4 = \text{N}_3$
 E-D-C-12 : $R^1 = \text{Mp}, R^2 = \text{Mpm}, R^3 = \text{Bz}, R^4 = \text{N}_3$
 E-D-C-13 : $R^1 = \text{Mpm}, R^2 = \text{Bz}, R^3 = \text{Mpm}, R^4 = \text{N}_3$
 E-D-C-14 : $R^1 = \text{Mp}, R^2 = \text{Bz}, R^3 = \text{Mpm}, R^4 = \text{N}_3$
 E-D-C-15 : $R^1 = \text{Mpm}, R^2 = \text{Bz}, R^3 = \text{Bz}, R^4 = \text{N}_3$
 E-D-C-16 : $R^1 = \text{Mp}, R^2 = \text{Bz}, R^3 = \text{Bz}, R^4 = \text{N}_3$

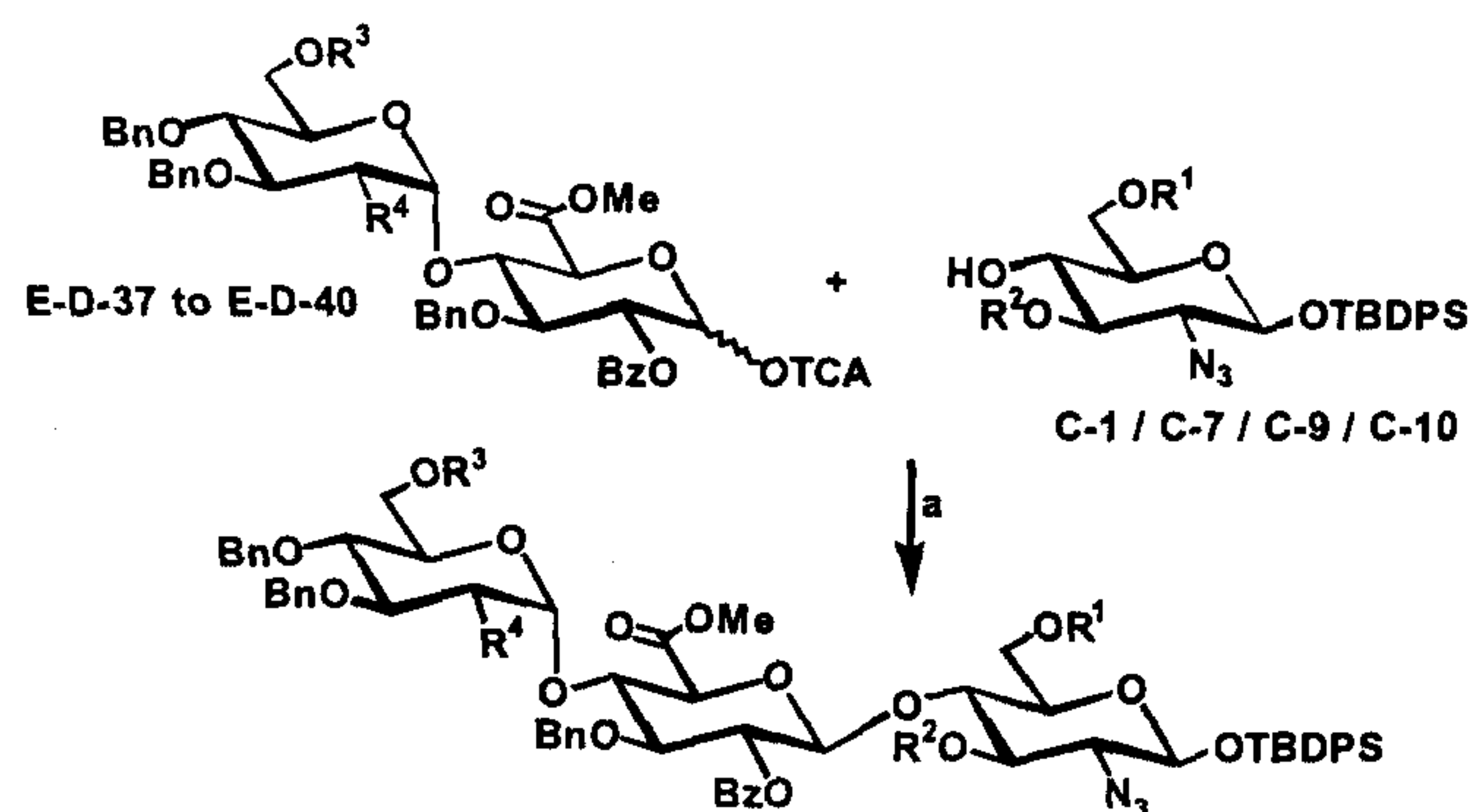
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Example 21: Synthesis of trisaccharide **E-D-C-1** to **E-D-C-16**, conditions: a)
 SOP 33, (70 % for **E-D-C 15** as an α/β mixture).

Compound E-D-C-15:

E-D-C-15 was formed according to SOP 33 with dichloromethane as solvent
 at 0 to 20°C and TBDMSOTf as promotor in 70 % yield (α/β -mixture).

$^1\text{H-NMR}$ (400 MHz, CDCl_3): $\delta = 7.93$ (m, 2H, Aryl), 7.87 (m, 2H, Aryl), 7.66 (m, 2H, Aryl), 7.61 (m, 2H, Aryl), 7.46 (m, 2H, Aryl), 7.38-6.99 (m, 32 H, Aryl), 6.79 (m, 2H, Aryl), 5.27 (d, 1 H, $J_{1,2} = 3.8$ Hz, H-1'' α), 4.99 (dd, 1 H, $J_{3,4} \approx J_{2,3} = 9.5$ Hz, H-3), 4.80-4.69 (m, 6 H, OCH_2), 4.52 (m, 3 H, OCH_2), 4.40 (d, 1H, $J_{1,2} = 8.0$ Hz, H-1 β), 4.38-4.32 (m, 2 H, not assigned), 4.29 (d, 1 H, $J_{1,2} = 7.5$ Hz, H-1' β), 4.15 (m, 1 H, $J_{\text{gem}} = 12.0$ Hz, OCH_2), 4.02 (dd, 1 H, $J_{4,5} = 9.6$ Hz, H-4), 3.80 (2 dd, 2 H, H-3'', H-4'), 3.71, (s, 3 H, OCH_3), 3.67 (m, 1 H, not assigned), 3.61-3.53 (m, 2 H, H-5', H-2'), 3.46 (dd, 1 H, $J_{\text{gem}} = 11.2$ Hz, $J_{5,6a} = 2.4$ Hz, H-6a), 3.41 (dd, 1H, $J_{2,3} \approx J_{3,4} = 9.0$ Hz, H-3'), 3.27 (s, 3 H, OCH_3), 3.21 (dd, 1 H, $J_{2,3} = 10.0$ Hz, H-2''), 3.14 (dd, 1 H, H-2'), 3.00 (dd, 1 H, $J_{5,6b} < 2.0$ Hz, H-6b), 2.75 (m, 1 H, H-5) 1.05 (s, 9H, $\text{C}(\text{CH}_3)_3$).

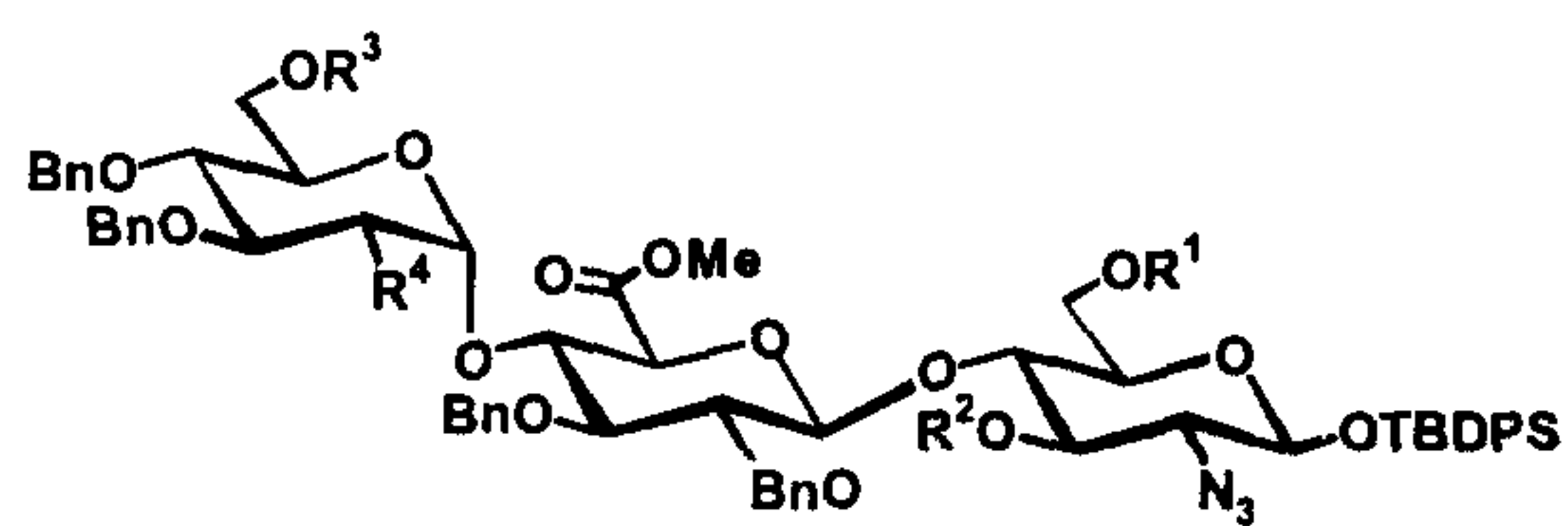
Example 22: Synthesis of trisaccharides E-D-C-17 to E-D-C-32

E-D-C-17 : $R^1 = \text{Mpm}, R^2 = \text{Mpm}, R^3 = \text{Mpm}, R^4 = \text{NHDTMP}$
 E-D-C-18 : $R^1 = \text{Mp}, R^2 = \text{Mpm}, R^3 = \text{Mpm}, R^4 = \text{NHDTMP}$
 E-D-C-19 : $R^1 = \text{Mpm}, R^2 = \text{Mpm}, R^3 = \text{Bz}, R^4 = \text{NHDTMP}$
 E-D-C-20 : $R^1 = \text{Mp}, R^2 = \text{Mpm}, R^3 = \text{Bz}, R^4 = \text{NHDTMP}$
 E-D-C-21 : $R^1 = \text{Mpm}, R^2 = \text{Bz}, R^3 = \text{Mpm}, R^4 = \text{NHDTMP}$
 E-D-C-22 : $R^1 = \text{Mp}, R^2 = \text{Bz}, R^3 = \text{Mpm}, R^4 = \text{NHDTMP}$
 E-D-C-23 : $R^1 = \text{Mpm}, R^2 = \text{Bz}, R^3 = \text{Bz}, R^4 = \text{NHDTMP}$
 E-D-C-24 : $R^1 = \text{Mp}, R^2 = \text{Bz}, R^3 = \text{Bz}, R^4 = \text{NHDTMP}$

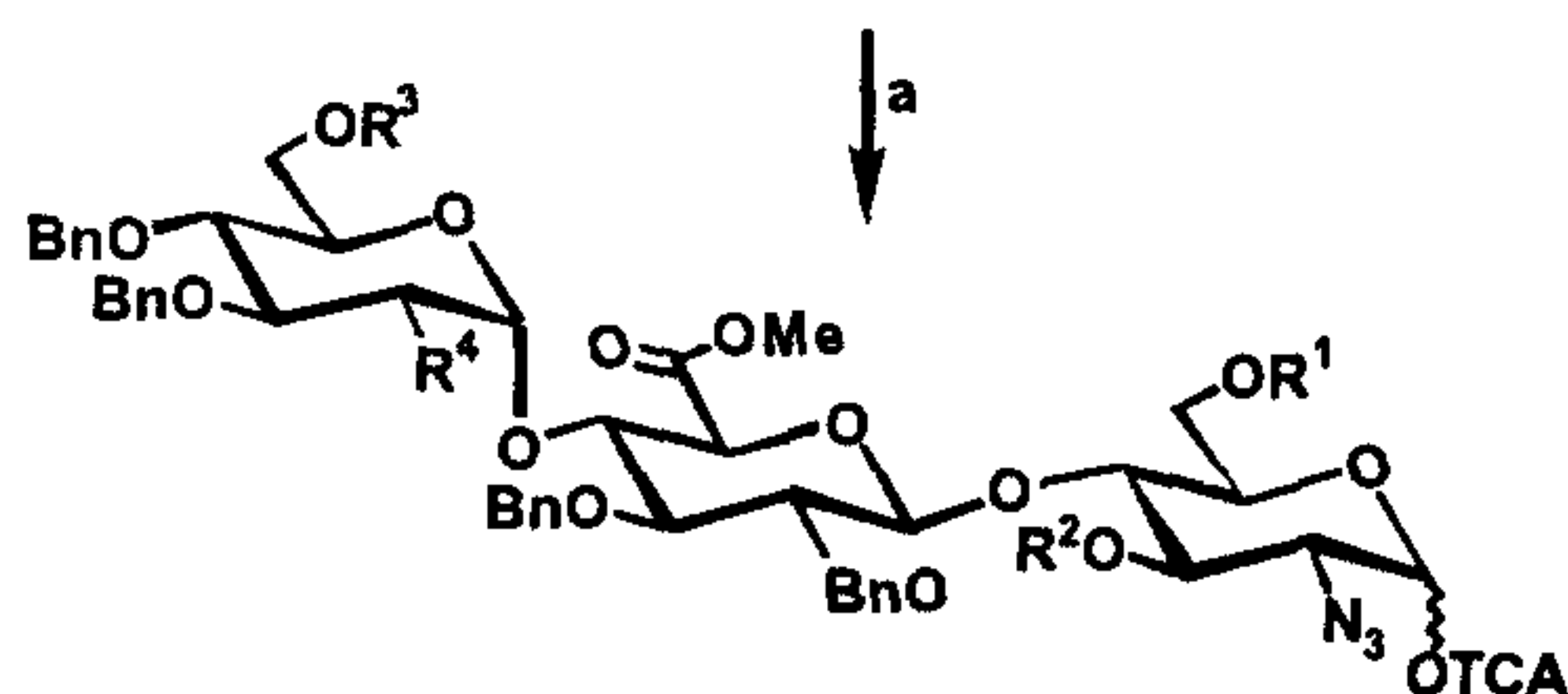
E-D-C-25 : $R^1 = \text{Mpm}, R^2 = \text{Mpm}, R^3 = \text{Mpm}, R^4 = \text{N}_3$
 E-D-C-26 : $R^1 = \text{Mp}, R^2 = \text{Mpm}, R^3 = \text{Mpm}, R^4 = \text{N}_3$
 E-D-C-27 : $R^1 = \text{Mpm}, R^2 = \text{Mpm}, R^3 = \text{Bz}, R^4 = \text{N}_3$
 E-D-C-28 : $R^1 = \text{Mp}, R^2 = \text{Mpm}, R^3 = \text{Bz}, R^4 = \text{N}_3$
 E-D-C-29 : $R^1 = \text{Mpm}, R^2 = \text{Bz}, R^3 = \text{Mpm}, R^4 = \text{N}_3$
 E-D-C-30 : $R^1 = \text{Mp}, R^2 = \text{Bz}, R^3 = \text{Mpm}, R^4 = \text{N}_3$
 E-D-C-31 : $R^1 = \text{Mpm}, R^2 = \text{Bz}, R^3 = \text{Bz}, R^4 = \text{N}_3$
 E-D-C-32 : $R^1 = \text{Mp}, R^2 = \text{Bz}, R^3 = \text{Bz}, R^4 = \text{N}_3$

- 5 Example 22: Synthesis of trisaccharide **E-D-C-17** to **E-D-C-32**, conditions: a) SOP 33.

Example 23: Formation of trisaccharidic Trichloroacetimidates E-D-C-33 to E-D-C-48



E-D-C-1 to E-D-C-16

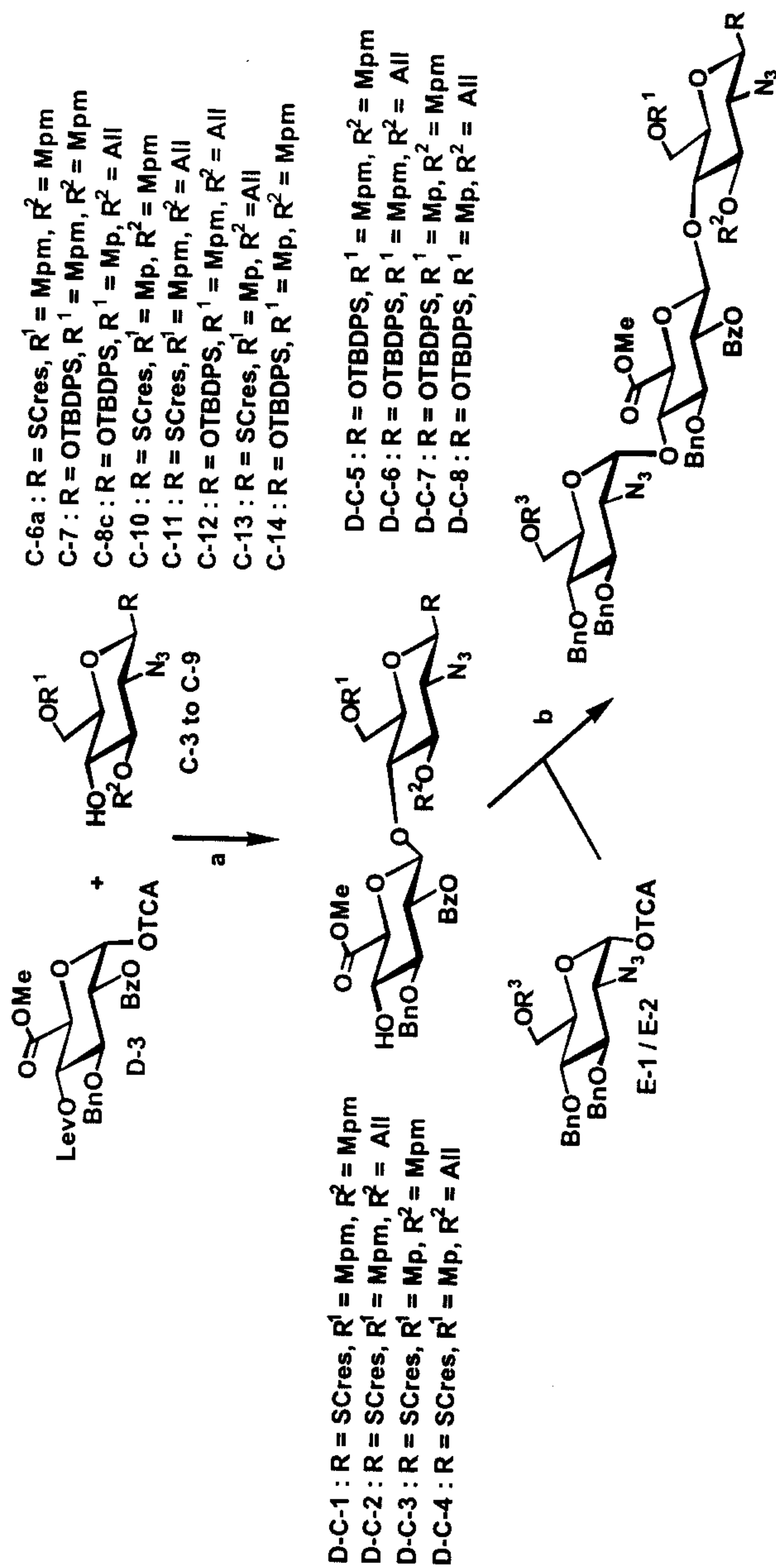


E-D-C-33 : $R^1 = \text{Mpm}$, $R^2 = \text{Mpm}$, $R^3 = \text{Mpm}$, $R^4 = \text{NHDTMP}$
 E-D-C-34 : $R^1 = \text{Mp}$, $R^2 = \text{Mpm}$, $R^3 = \text{Mpm}$, $R^4 = \text{NHDTMP}$
 E-D-C-35 : $R^1 = \text{Mpm}$, $R^2 = \text{Mpm}$, $R^3 = \text{Bz}$, $R^4 = \text{NHDTMP}$
 E-D-C-36 : $R^1 = \text{Mp}$, $R^2 = \text{Mpm}$, $R^3 = \text{Bz}$, $R^4 = \text{NHDTMP}$
 E-D-C-37 : $R^1 = \text{Mpm}$, $R^2 = \text{Bz}$, $R^3 = \text{Mpm}$, $R^4 = \text{NHDTMP}$
 E-D-C-38 : $R^1 = \text{Mp}$, $R^2 = \text{Bz}$, $R^3 = \text{Mpm}$, $R^4 = \text{NHDTMP}$
 E-D-C-39 : $R^1 = \text{Mpm}$, $R^2 = \text{Bz}$, $R^3 = \text{Bz}$, $R^4 = \text{NHDTMP}$
 E-D-C-40 : $R^1 = \text{Mp}$, $R^2 = \text{Bz}$, $R^3 = \text{Bz}$, $R^4 = \text{NHDTMP}$

E-D-C-41 : $R^1 = \text{Mpm}$, $R^2 = \text{Mpm}$, $R^3 = \text{Mpm}$, $R^4 = \text{N}_3$
 E-D-C-42 : $R^1 = \text{Mp}$, $R^2 = \text{Mpm}$, $R^3 = \text{Mpm}$, $R^4 = \text{N}_3$
 E-D-C-43 : $R^1 = \text{Mpm}$, $R^2 = \text{Mpm}$, $R^3 = \text{Bz}$, $R^4 = \text{N}_3$
 E-D-C-44 : $R^1 = \text{Mp}$, $R^2 = \text{Mpm}$, $R^3 = \text{Bz}$, $R^4 = \text{N}_3$
 E-D-C-45 : $R^1 = \text{Mpm}$, $R^2 = \text{Bz}$, $R^3 = \text{Mpm}$, $R^4 = \text{N}_3$
 E-D-C-46 : $R^1 = \text{Mp}$, $R^2 = \text{Bz}$, $R^3 = \text{Mpm}$, $R^4 = \text{N}_3$
 E-D-C-47 : $R^1 = \text{Mpm}$, $R^2 = \text{Bz}$, $R^3 = \text{Bz}$, $R^4 = \text{N}_3$
 E-D-C-48 : $R^1 = \text{Mp}$, $R^2 = \text{Bz}$, $R^3 = \text{Bz}$, $R^4 = \text{N}_3$

- 5 Example 23: Formation of trisaccharidic Trichloroacetimidates **E-D-C-33** to **E-D-C-48**, conditions: a) 1. SOP 9; 2. SOP 25, (82% over 2 steps for **E-D-C-47**)

Example 24: Syntheses of trisaccharides **E-D-C-9** to **E-D-C-12** and **E-D-C-49** to **E-D-C-60**



Example 24: Syntheses of trisaccharides **E-D-C-9** to **E-D-C-12** and **E-D-C-49** to **E-D-C-60**, conditions: a) 1. SOP 33; 2. SOP 24; b) SOP 33. (for **D-C-5**: 70 %, 2 steps); b) SOP 33, (78 % for **E-D-C-9** as an α/β mixture).

Compound D-C-5:

D-C-5 was formed according to SOP 33 with ether as solvent at -20°C and TMSOTf as promotor, followed by SOP 24 in 70 % yield (over 2 steps as α/β -mixture).

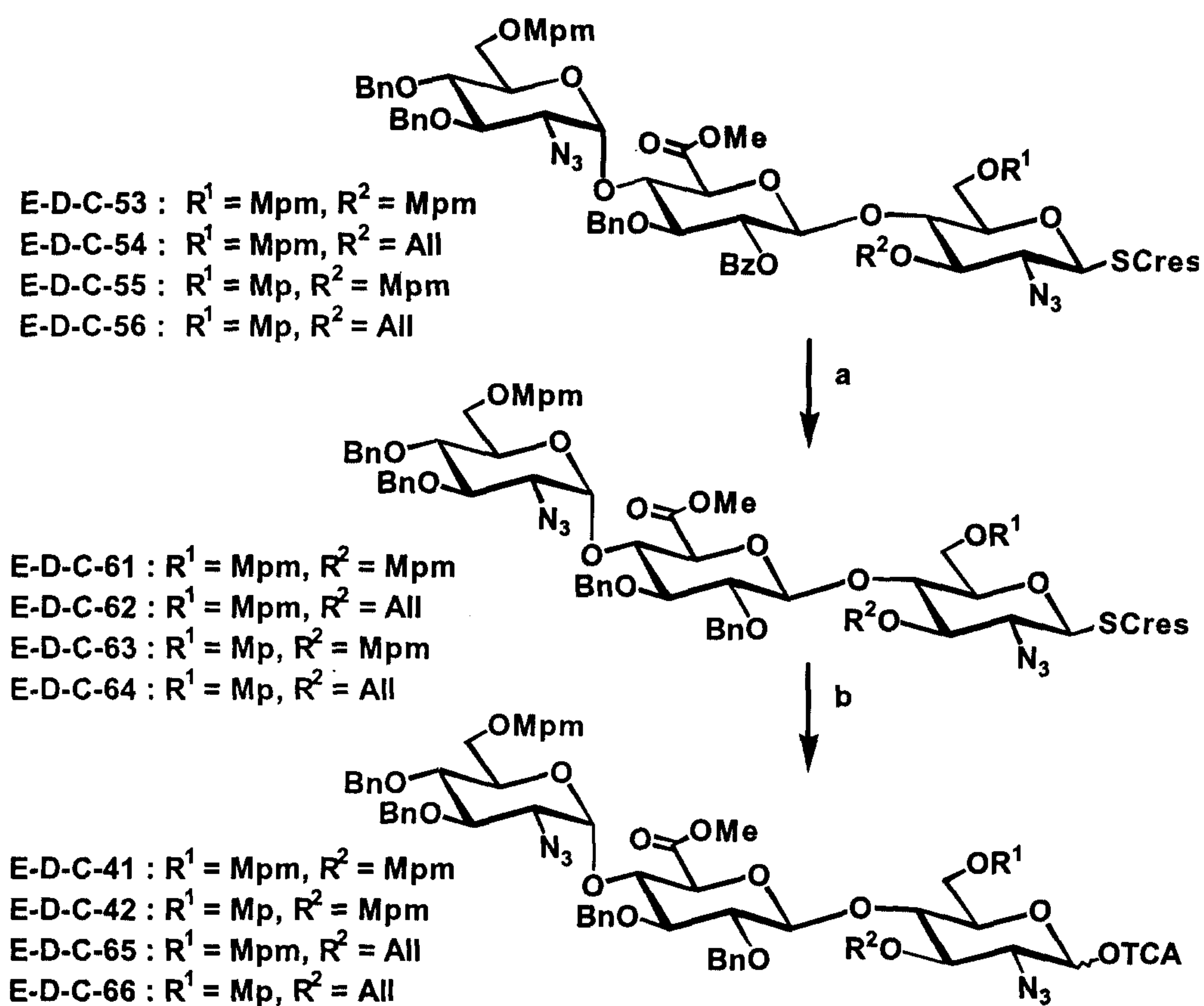
- 5 Selected $^1\text{H-NMR}$ (400 MHz in CDCl_3): δ = 7.88 (m, 2H, Ar), 7.67- 7.58 (m, 5H, Ar), 7.42 (m, 2H, Ar), 7.37-7.12 (m, 16H, Aryl), 6.84 (m, 3H, Ar), 5.14 (dd, 1H, $J_{1,2}$ = 8.2 Hz, $J_{2,3}$ = 9.5 Hz, H-2'), 4.90 (d, 1H, J_{gem} = 10.7 Hz, OCH_2), 4.73 (d, 1H, J_{gem} = 11.5 Hz, OCH_2), 4.65 (d, 1H, $J_{1,2}$ = 8.2 Hz, H-1' β), 4.63 – 4.58 (m, 2H, OCH_2), 4.51 (d, 1H, J_{gem} = 12.0 Hz, OCH_2), 4.20 (d, 1H, $J_{1,2}$ = 7.9 Hz, H-1 β), 4.05 (d, 1H, J_{gem} = 11.9 Hz, OCH_2), 4.02 – 3.95 (m, 2H, not assigned), 3.81 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.71 (d, 1H, $J_{4,5}$ = 9.9 Hz, H-5'), 3.67 (s, 3H, OCH_3), 3.47 - 3.40 (m, 3H, not assigned), 3.21 (dd, 1 H, J = 9.0 Hz, J = 9.8 Hz, not assigned), 3.00 (dd, 1 H, $J_{5,6b}$ = 1.4 Hz, J_{gem} = 10.5 Hz, H-6b), 2.63 (m, 1 H, H-5), 2.35 (bs, 1 H, 4-OH), 1.07 (s, 9H, $\text{C}(\text{CH}_3)_3$).

15 **Compound E-D-C-9:**

E-D-C-9 was formed according to SOP 33 with ether as solvent at -20°C and TBDMSOTf as promotor in 78 % yield (α/β -mixture).

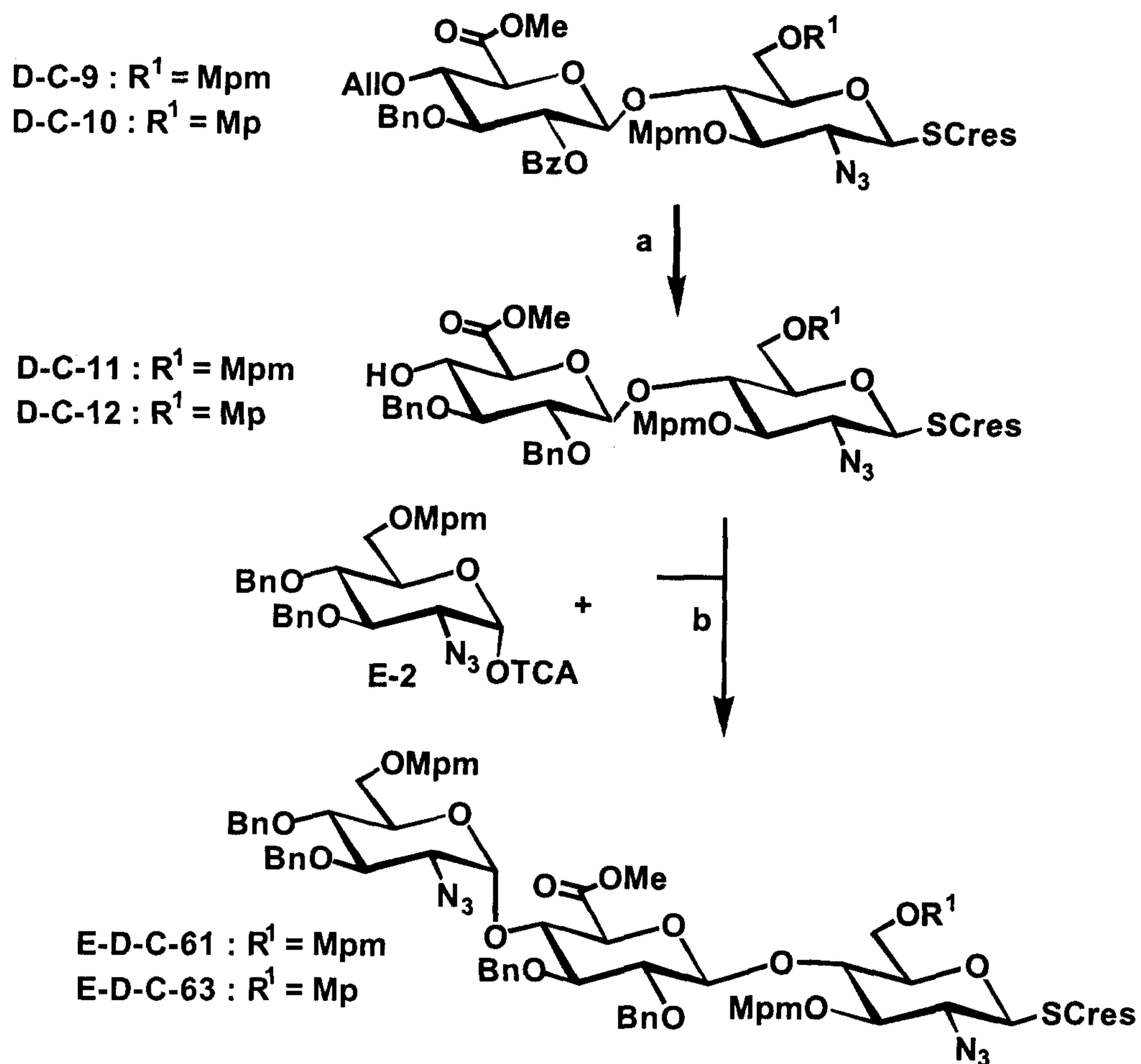
- Selected $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ = 7.77 (m, 2H, Aryl), 7.59, 7.54 (2m, 2 x 2H, Aryl), 7.35 – 7.00 (m, 30 H, Aryl), 6.88 (m, 2H, Aryl), 6.82 (m, 2H, Aryl), 6.73 (m, 2H, Aryl), 5.41 (d, 1 H, $J_{1,2}$ = 3.5 Hz, H-1'' α), 5.19 (dd, 1 H, $J_{2,3} \approx J_{1,2}$ = 9.6 Hz, H-2'), 4.85 - 4.78 (m, 4 H, OCH_2), 4.67 (m, 2H, OCH_2), 4.65 (d, 1H, $J_{1,2}$ = 8.5 Hz, H-1 β , not assigned), 4.38 (d, 1 H, J_{gem} = 11.1 Hz, OCH_2), 4.29 (d, 1 H, J_{gem} = 11.7 Hz, OCH_2), 4.17 (dd, 1H, not assigned), 4.11 (d, 1H, $J_{1,2}$ = 7.9 Hz, H-1 β not assigned), 4.03 (d, 1 H, J_{gem} = 12.0 Hz, OCH_2), 3.90 - 3.76 (m, 3H, not assigned), 3.730, 3.727 (2s, 2 x 3H, OCH_3), 3.65 (s, 3H, OCH_3), 3.54 (s, 3H, OCH_3), 2.89 (dd, 1 H, J_{gem} = 10.5 Hz, $J_{5,6b} < 2.0$ Hz, H-6b), 2.52 (m, 1H, H-5), 1.02 (s, 9 H, $\text{C}(\text{CH}_3)_3$).

30 **Example 25: Synthesis of trisaccharides E-D-C-41, E-D-C-42 and E-D-C-61 to E-D-C-66**



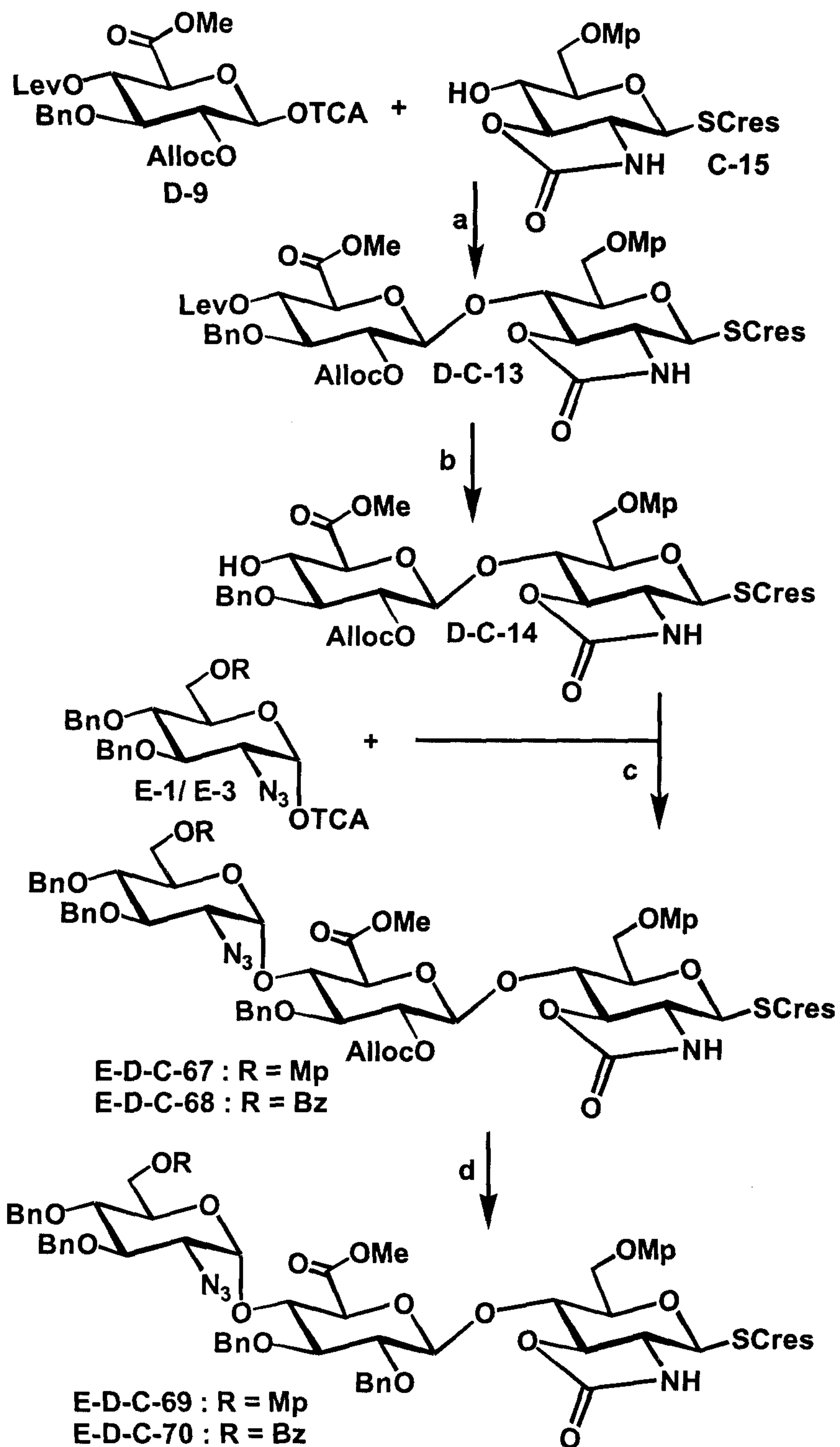
Example 25: Synthesis of trisaccharides **E-D-C-41**, **E-D-C-42** and **E-D-C-61** to **E-D-C-66**, conditions: a) 1. SOP 39; 2. SOP 38; 3. SOP 16; b) 1. SOP 14; 2. SOP 25a.

Example 26: An alternative route to the trisaccharides **E-D-C-61** and **E-D-C-63**



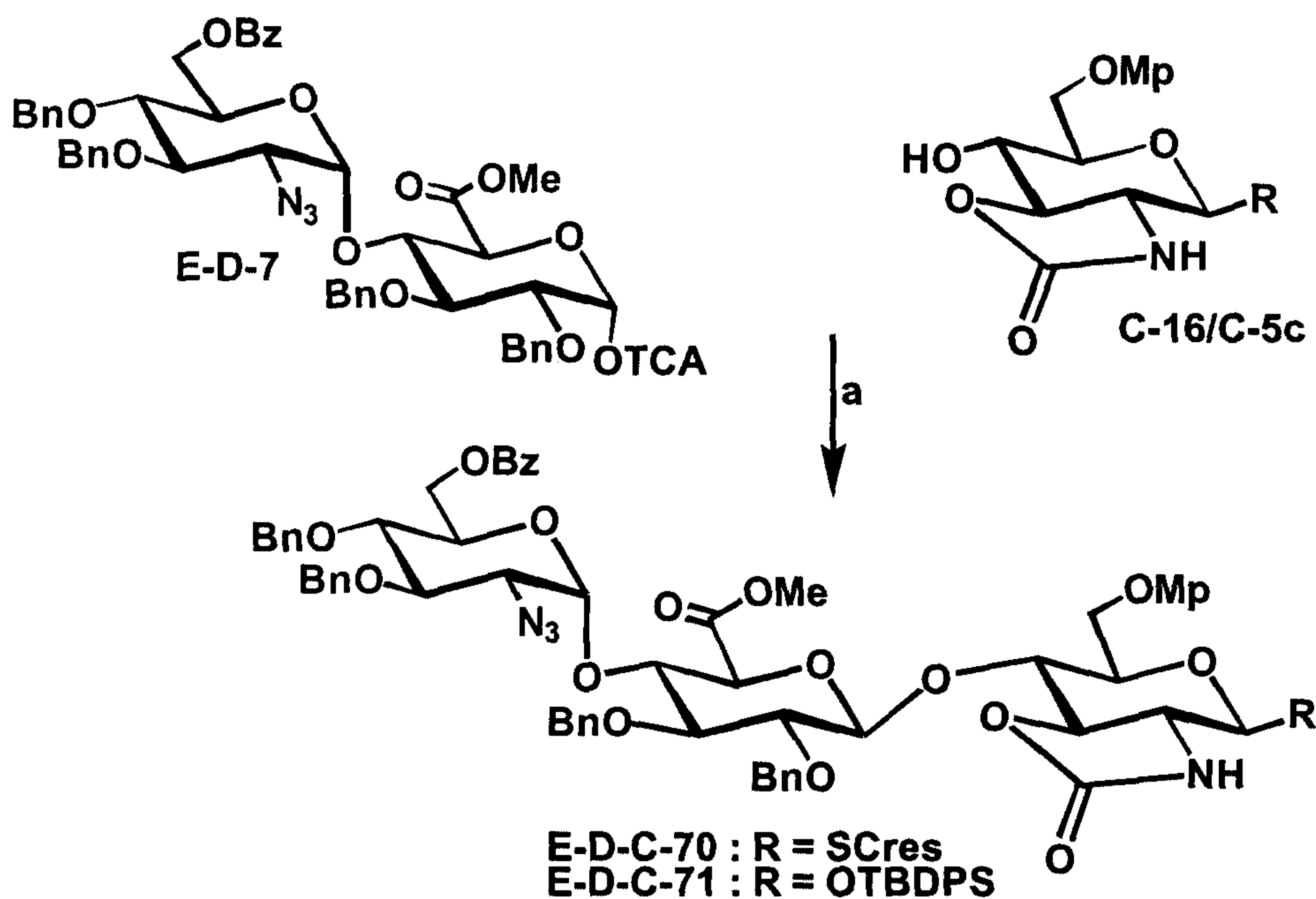
Example 26: An alternative route to the trisaccharides **E-D-C-61** and **E-D-C-63**, conditions: a) 1. SOP 39; 2. SOP 38; 3. SOP 16; 4. Pd(Ph₃P)₄, p-TolSO₂Na, THF, MeOH; b) SOP 33.

Example 27: Syntheses of blocks **E-D-C-67** to **E-D-C-70**



Example 27 : Syntheses of trisaccharides **E-D-C-67** to **E-D-C-70**, conditions:

a) SOP 33; b) SOP 24; c) SOP 33; d) 1. SOP 36; 2. SOP 37.

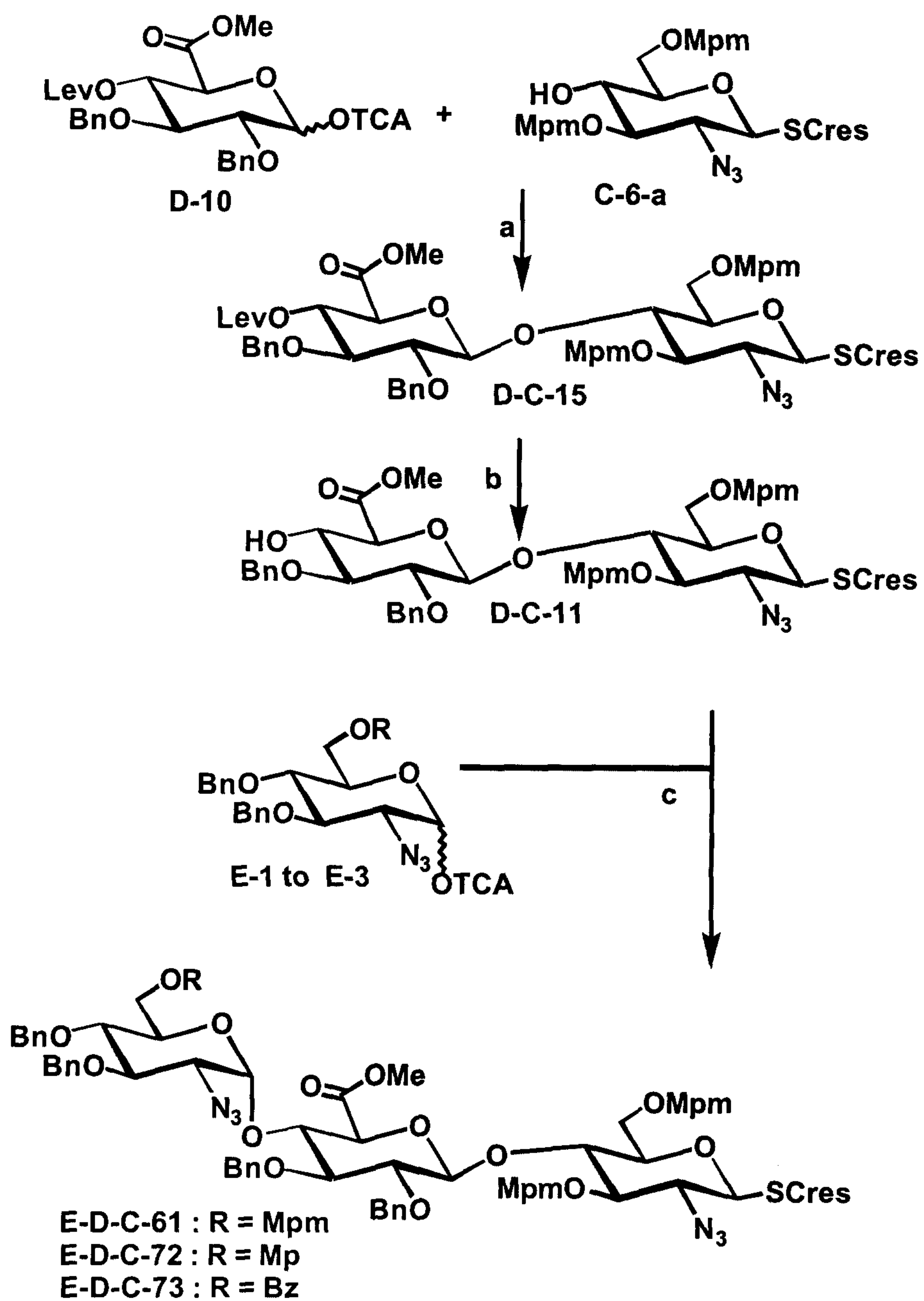
Example 28: Synthesis of trisaccharides E-D-C-70 and E-D-C-71

- 5 Example 28: Synthesis of trisaccharides **E-D-C-70** and **E-D-C-71**, conditions:
 a) SOP 33, (55% for **E-D-C-71**, α/β mixture).

Compound E-D-C-71:

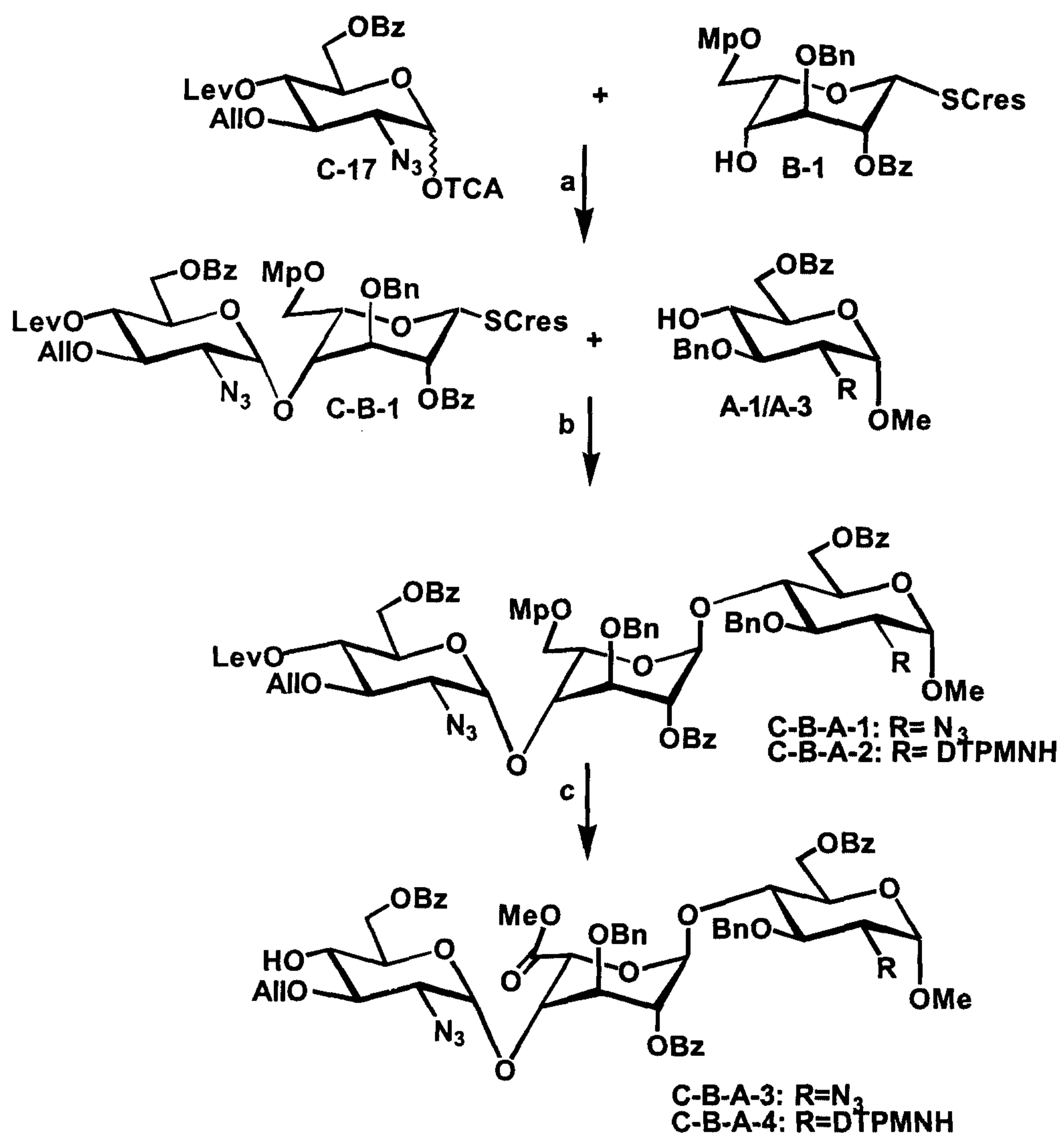
- 10 **E-D-C-71** was formed according to SOP 33 with dichloromethane as solvent at 40°C and TBDMSOTf as promotor in 55 % yield (as α/β -mixture).
- Selected $^1\text{H-NMR}$ (400 MHz, CDCl_3): $\delta = 7.91$ (m, 2H, Aryl), 7.61 (m, 2H, Aryl), 7.55 (m, 2H, Aryl), 7.50 – 7.02 (m, 29 H, Aryl), 6.65 (m, 4H, Mp), 5.38 (d, 1 H, $J_{1,2} = 3.9$ Hz, H-1'' α), 5.22 (bs, 1 H, NH), 4.67 (d, 1H, $J_{1,2} = 7.4$ Hz, H-1 β , not assigned), 4.50 (d, 1H, $J_{1,2} = 7.8$ Hz, H-1 β , not assigned), 3.92 (d, 1 H, $J_{4,5} = 9.8$ Hz, H-5'), 3.698 (s, 3 H, OCH_3), 3.693 (s, 3 H, OCH_3), 1.03 (s, 9 H, $\text{C}(\text{CH}_3)_3$).
- 15 $M_{\text{found}} = 1408.52$ ($M + \text{H}_2\text{O}$) $^+$, $M_{\text{calc}} = 1390.54$ (M) $^+$.

Example 29: Syntheses of trisaccharides E-D-C-61, E-D-C-72 and E-D-C-73

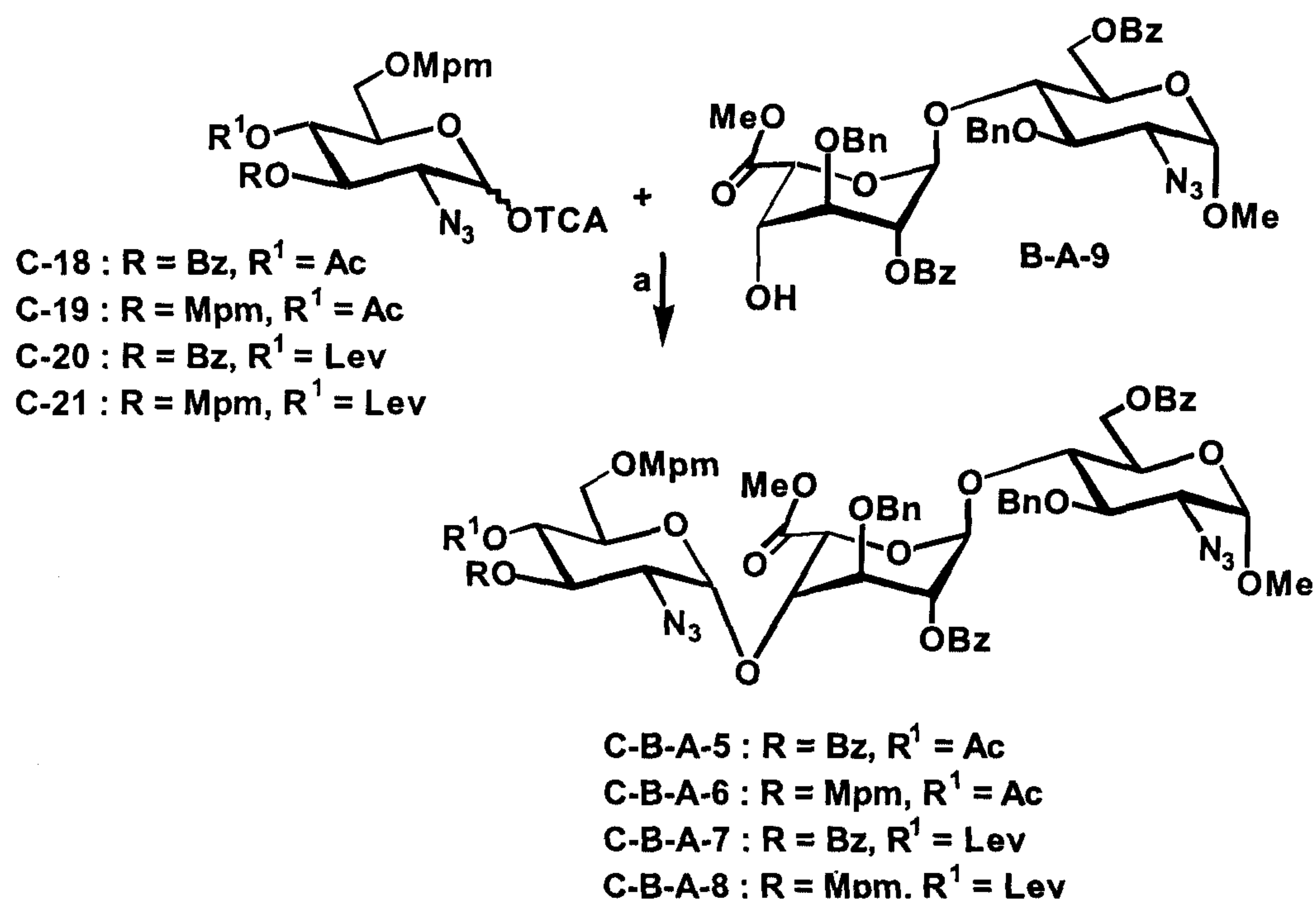


Example 29: Syntheses of trisaccharides **E-D-C-72** to **E-D-C-73** and **E-D-C-61**, conditions: a) SOP 33; b) SOP 24; c) SOP 33.

Example 30: Syntheses of trisaccharides **C-B-A-1** to **C-B-A-4**



Example 30: Syntheses of trisaccharides **C-B-A-1** to **C-B-A-4**, conditions: a) SOP 33; b) SOP 32a; c) 1. SOP 27; 2. SOP 20; 3. SOP 16; 4. SOP 24.

Example 31: Synthesis of trisaccharides C-B-A-5 to C-B-A-8

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Example 31: Synthesis of trisaccharides **C-B-A-5** and **C-B-A-8**, conditions: a) SOP 33, (50% for **C-B-A-5**, α/β mixture).

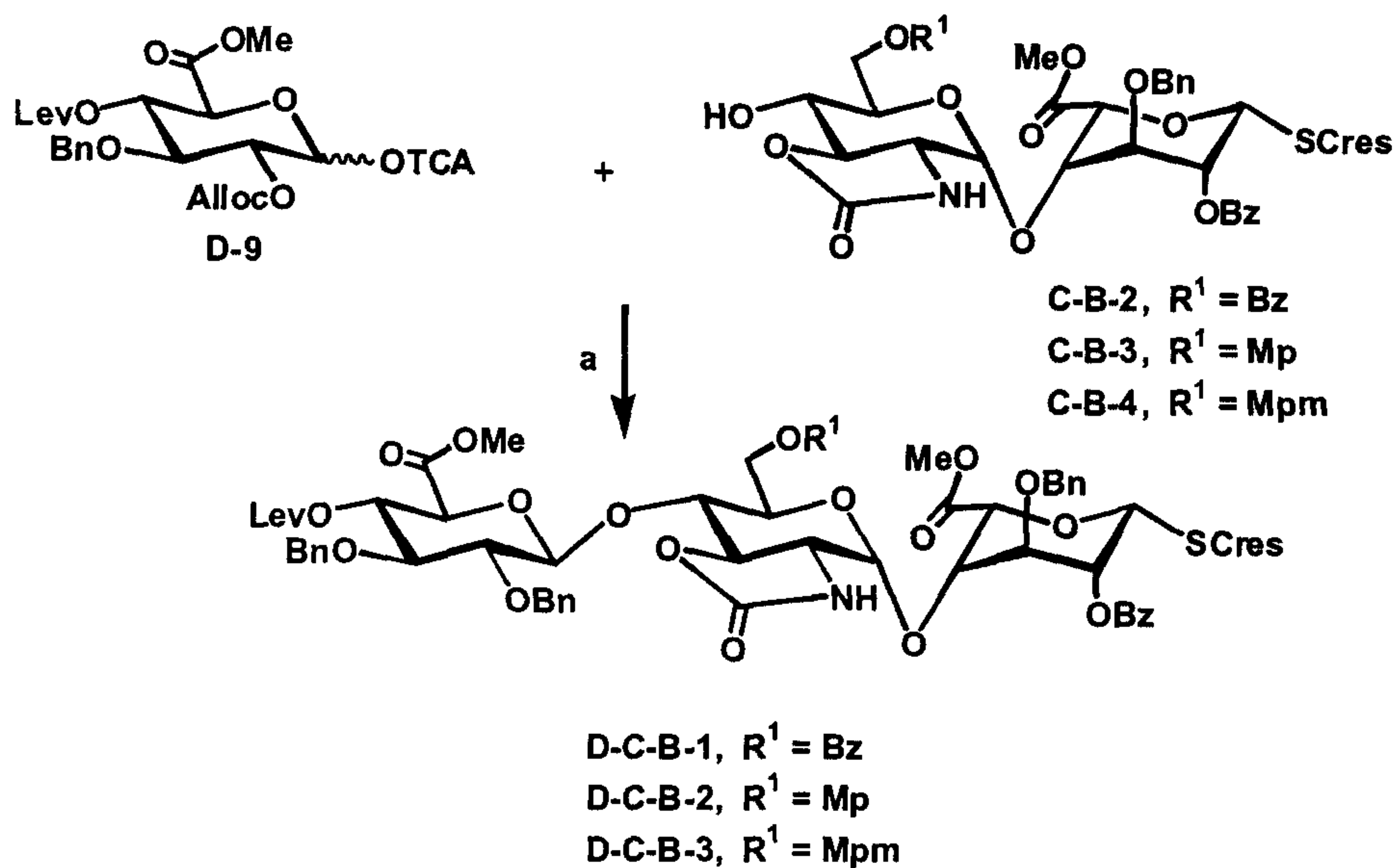
Compound C-B-A-5:

- 10 **C-B-A-5** was formed according to SOP 33 with ether as solvent at -20°C and TBDMSOTf as promotor in 50 % yield (as α/β -mixture).

$M_{\text{found}} = 1269.65 (M+H+H_2O)^+$, $M_{\text{calc}} = 1250.43 (M^+)$.

Example 32: Syntheses of D-C-B trisaccharides D-C-B-1 to D-C-B-3.

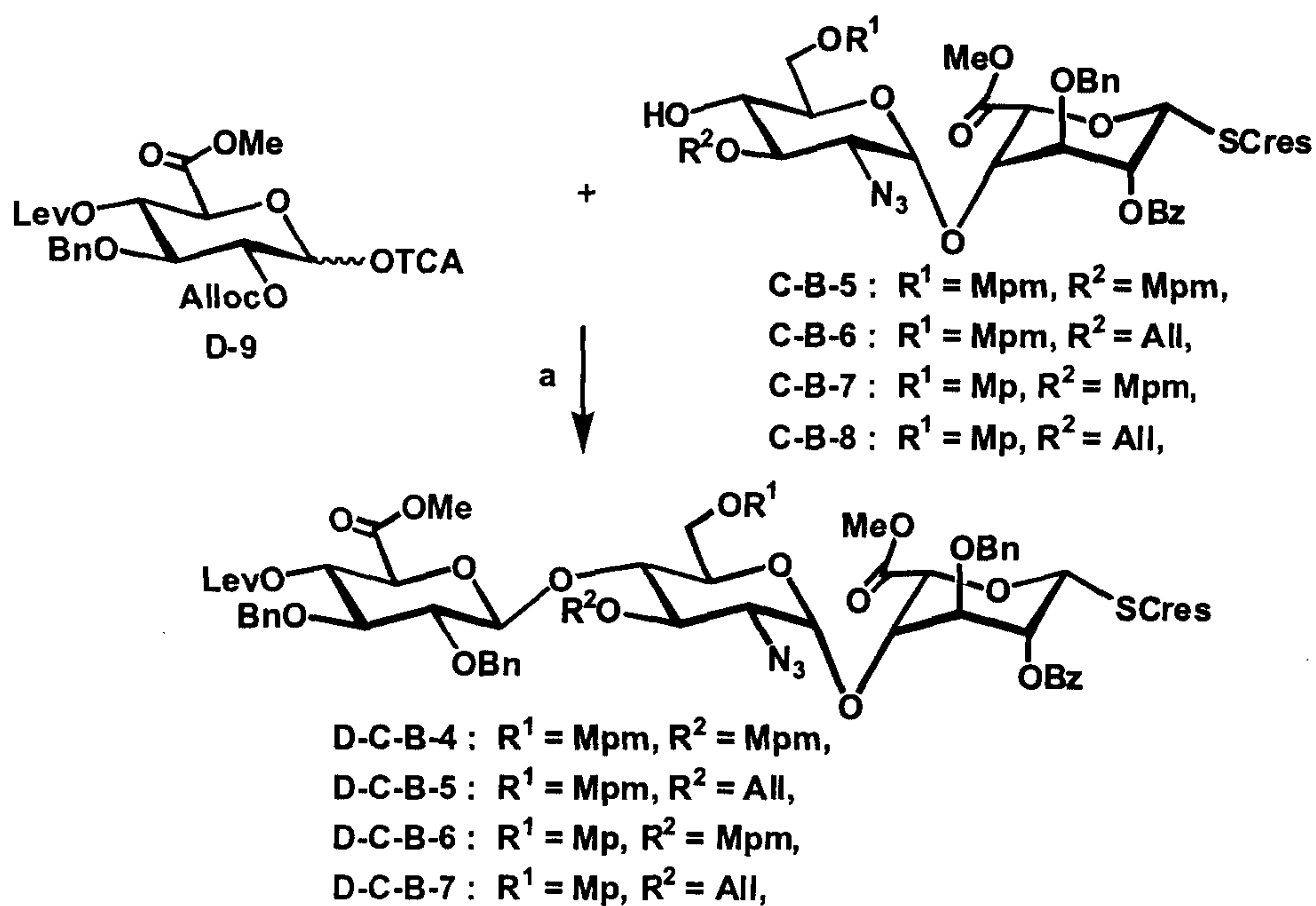
15



Example 32: Syntheses of D-C-B-trisaccharides **D-C-B-1** to **D-C-B-3**, conditions: a) 1. SOP 33; 2. SOP 36; 3. SOP 37.

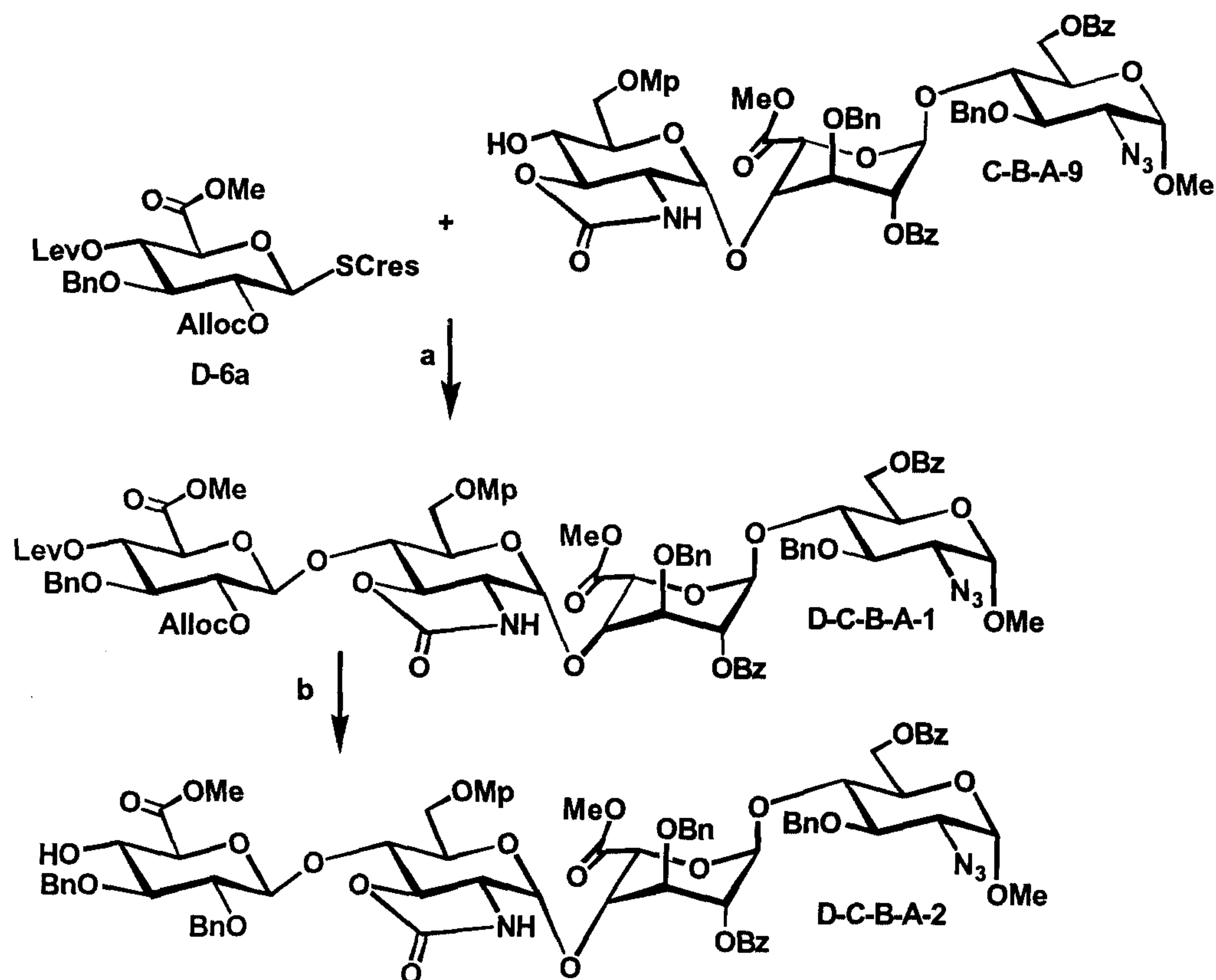
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Example 33: Syntheses of D-C-B trisaccharides **D-C-B-4** to **D-C-B-7**.



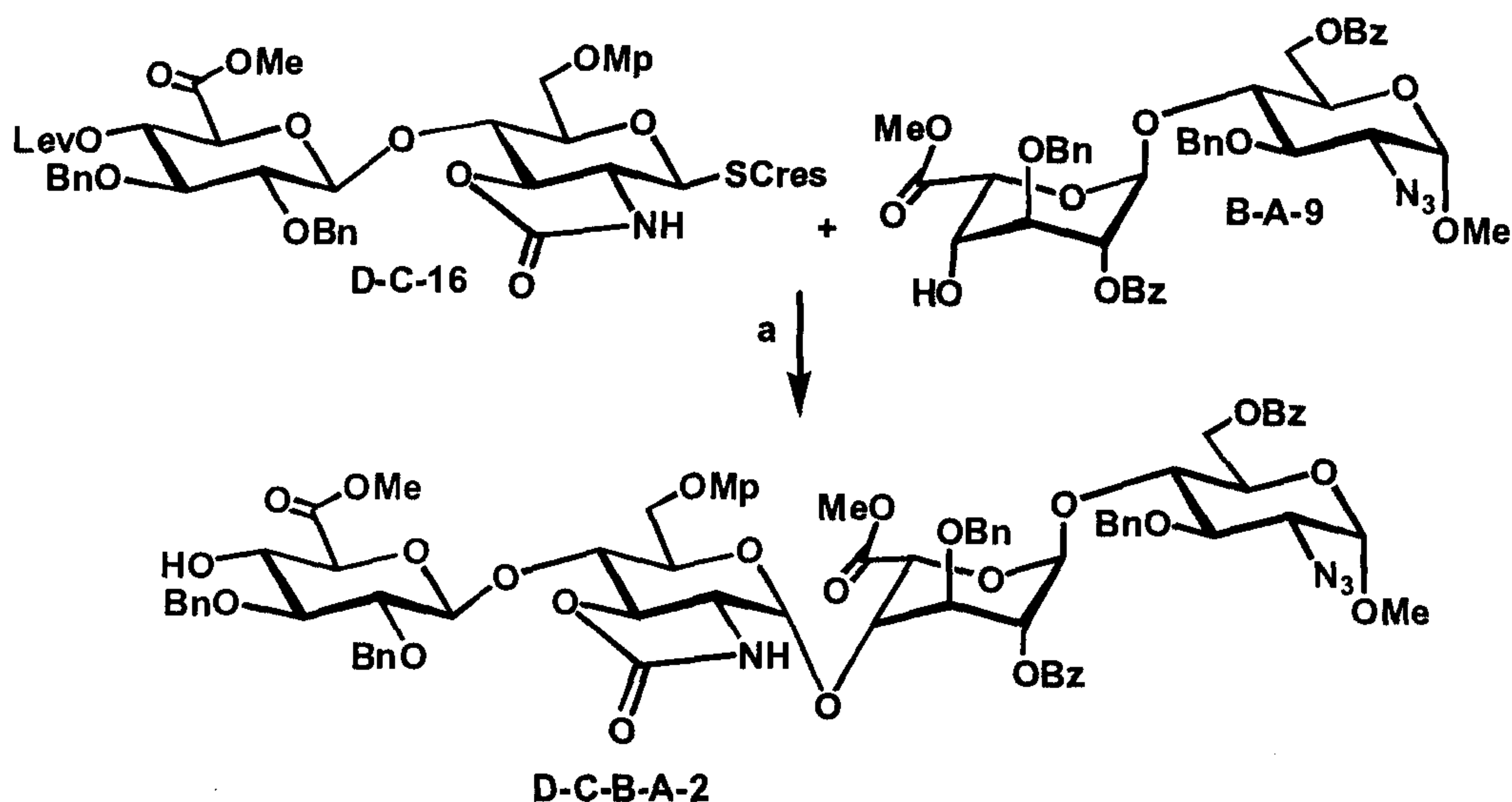
10

Example 33: Syntheses of D-C-B-trisaccharides **D-C-B-4** to **D-C-B-7**,
conditions: a) 1. SOP 33; 2. SOP 36; 3. SOP 37.

Example 34: Syntheses of tetrasaccharides D-C-B-A-1 to D-C-B-A-2

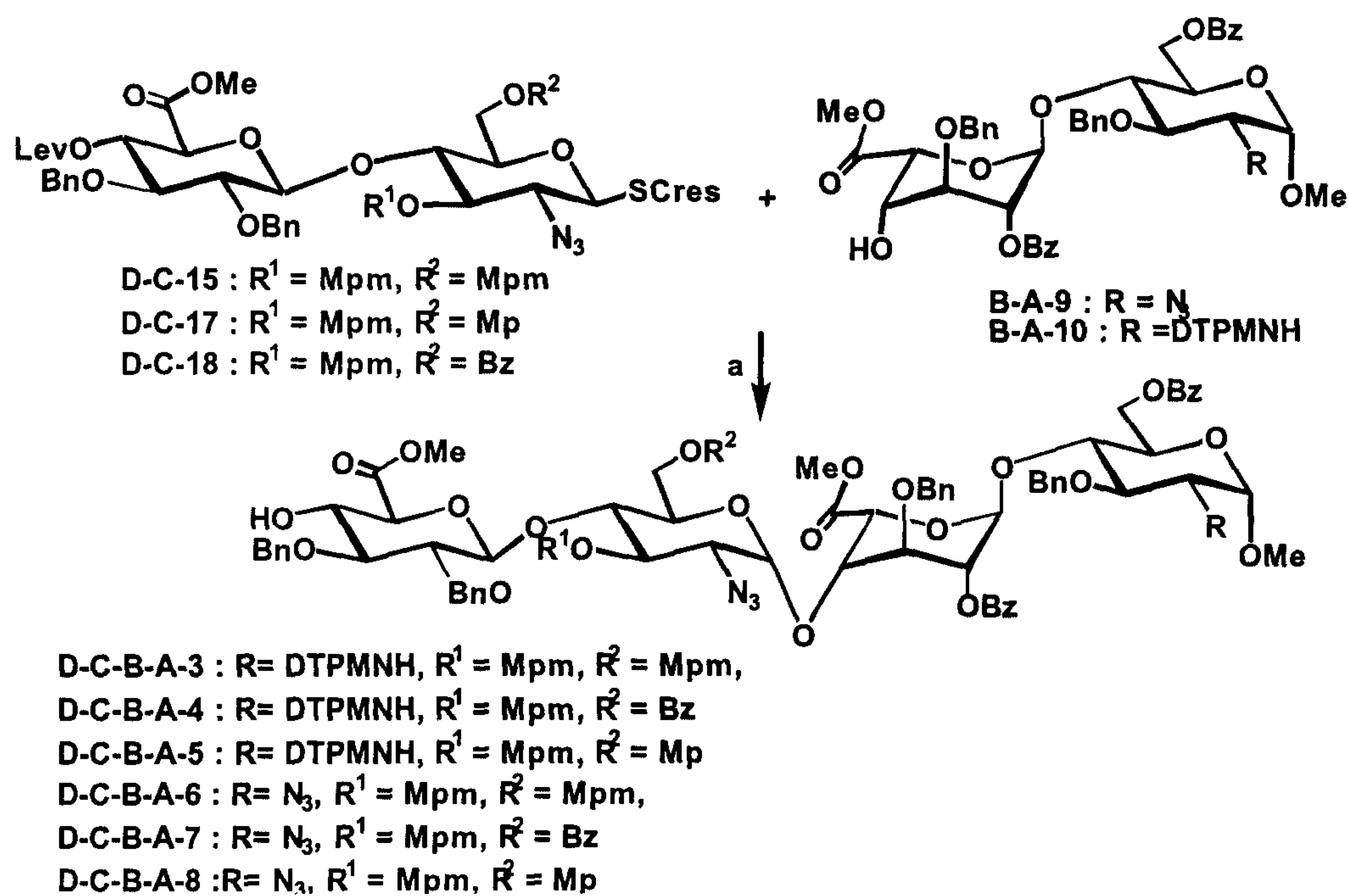
- 5 Example 34: Syntheses of tetrasaccharides **D-C-B-A-1** and **D-C-B-A-2**, conditions: a) SOP 32a; b) 1. SOP 36; 2. SOP 37; 3. SOP 24.

Example 35: Alternative syntheses of tetrasaccharides D-C-B-A-2



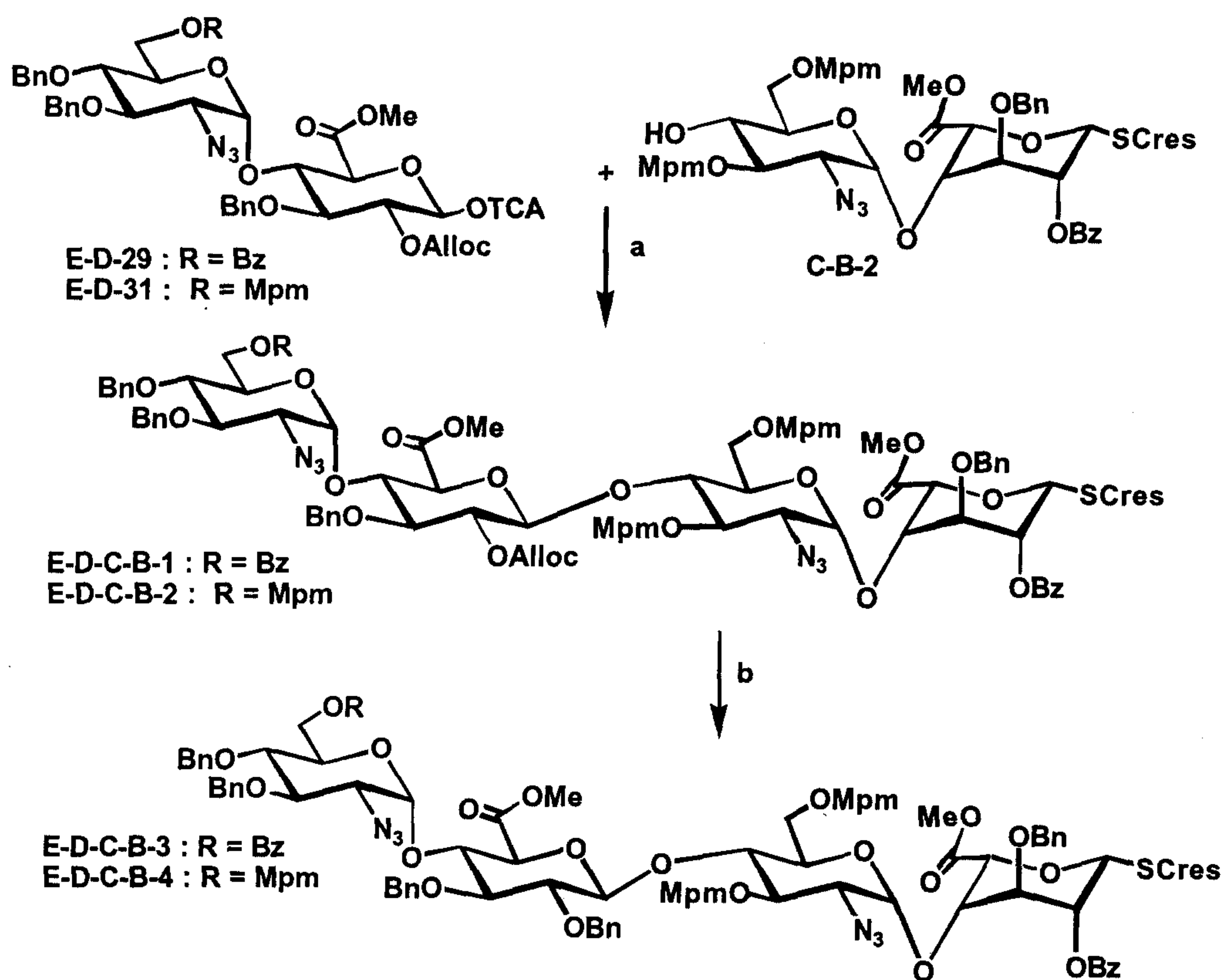
Example 35: Alternative synthesis of tetrasaccharide **D-C-B-A-2**, conditions:
a) 1. SOP 34; 2. SOP 24.

5 Example 36: Syntheses of tetrasaccharides **D-C-B-A-3** to **D-C-B-A-8**



Example 36: Syntheses of tetrasaccharides **D-C-B-A-3** to **D-C-B-A-8**,
conditions: a) 1 SOP 32b; 2. SOP 24.

Example 37: Syntheses of tetrasaccharides **E-D-C-B-1** to **E-D-C-B-4**

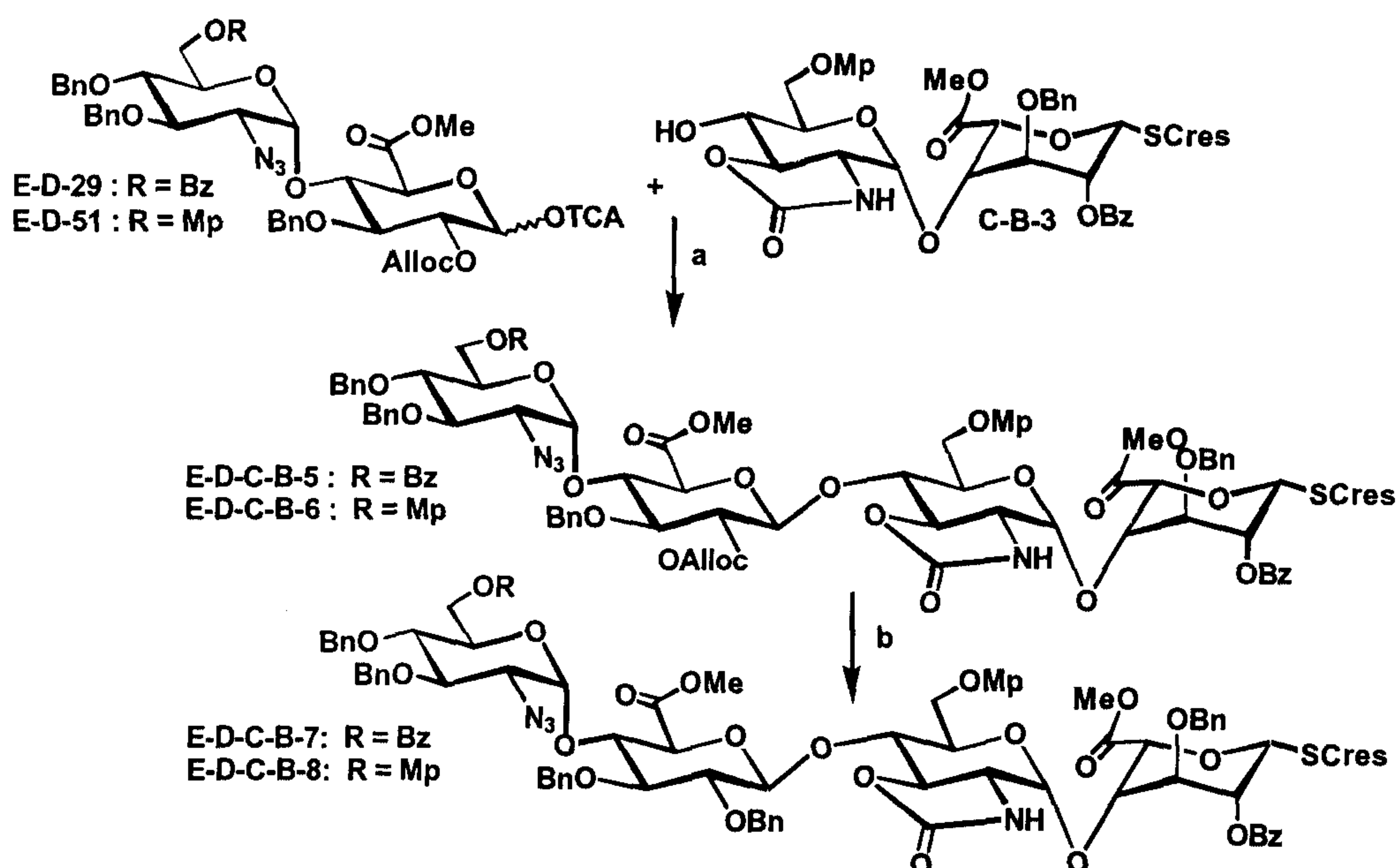


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Example 37: Syntheses of tetrasaccharides **E-D-C-B-1** to **E-D-C-B-4**, conditions: a) SOP 33; b) 1. SOP 36; 2. SOP 37.

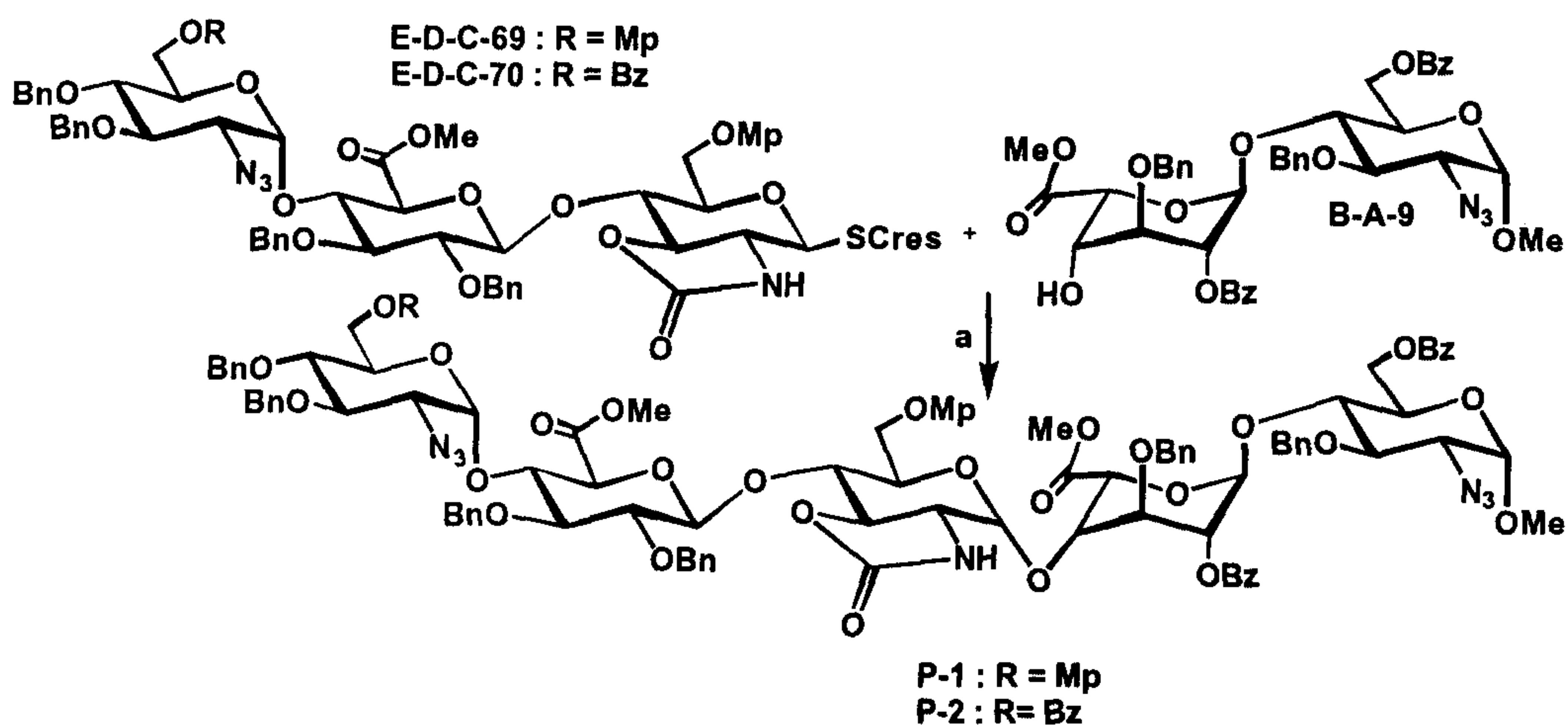
Example 38: Syntheses of blocks **E-D-C-B-5** to **E-D-C-B-8**

10



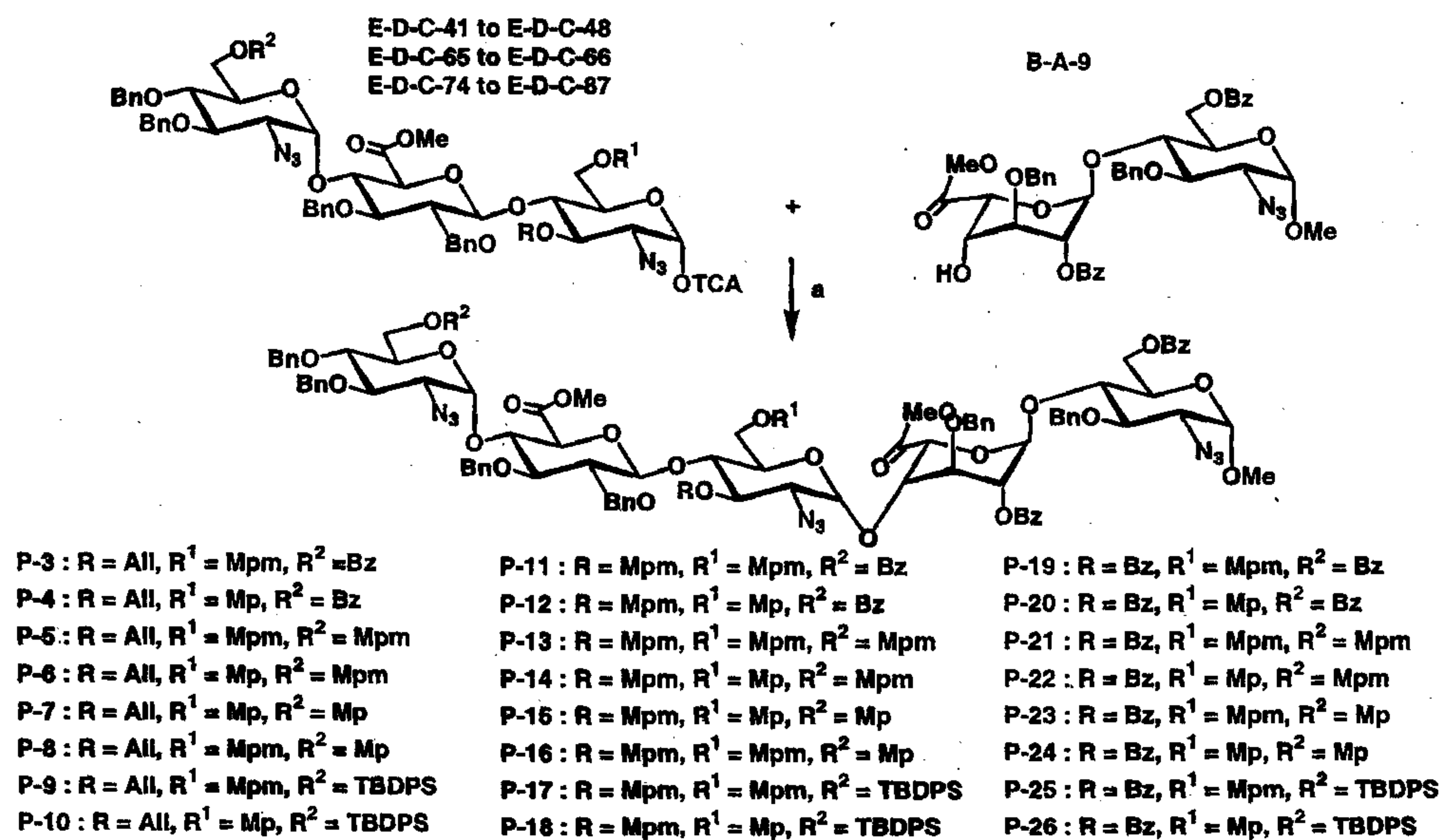
Example 38: Syntheses of tetrasaccharides **E-D-C-B-5** to **E-D-C-B-8**, conditions: a) SOP 33; b) 1. SOP 36; 2. SOP 37.

5 Example 39 : Syntheses of E-D-C-B-A pentasaccharides **P-1** and **P-2**



Example 39: Syntheses of E-D-C-B-A pentasaccharides **P-1** and **P-2**, conditions: a) SOP 34.

Example 40: Synthesis of E-D-C-B-A pentasaccharides **P-3** to **P-26**



Example 40: Synthesis of E-D-C-B-A pentasaccharide **P-3** to **P-26**, conditions:

a) SOP 33 (75 % for **P-19** as an α/β mixture).

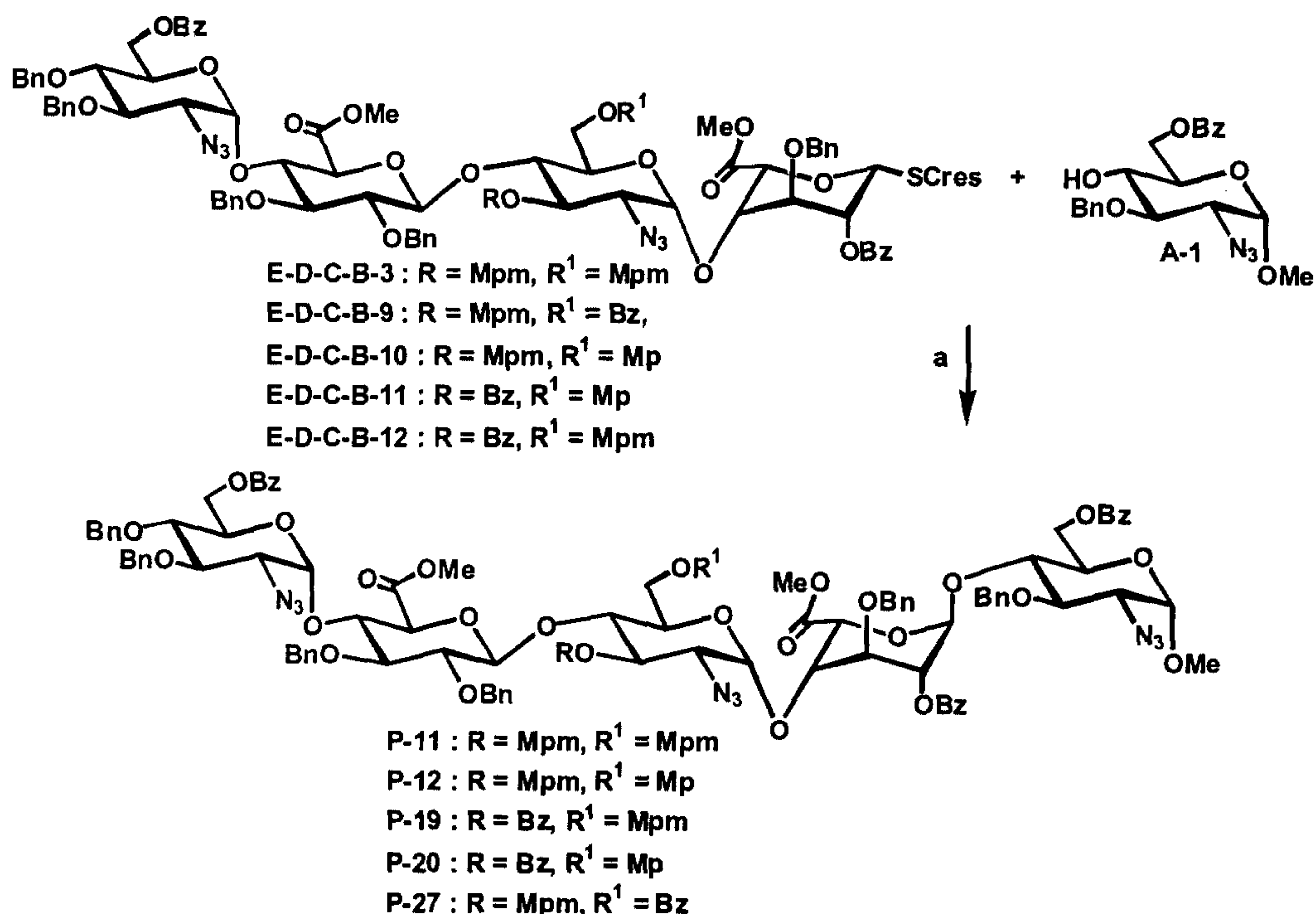
5 Compound **P-19**:

P-19 was formed according to SOP 33 with dichloromethane as solvent at -20°C and TMSOTf as promotor;

$M_{\text{found}} = 2068.76 (M+H+H_2O)^+$, $M_{\text{calc}} = 2049.74 (M^+)$.

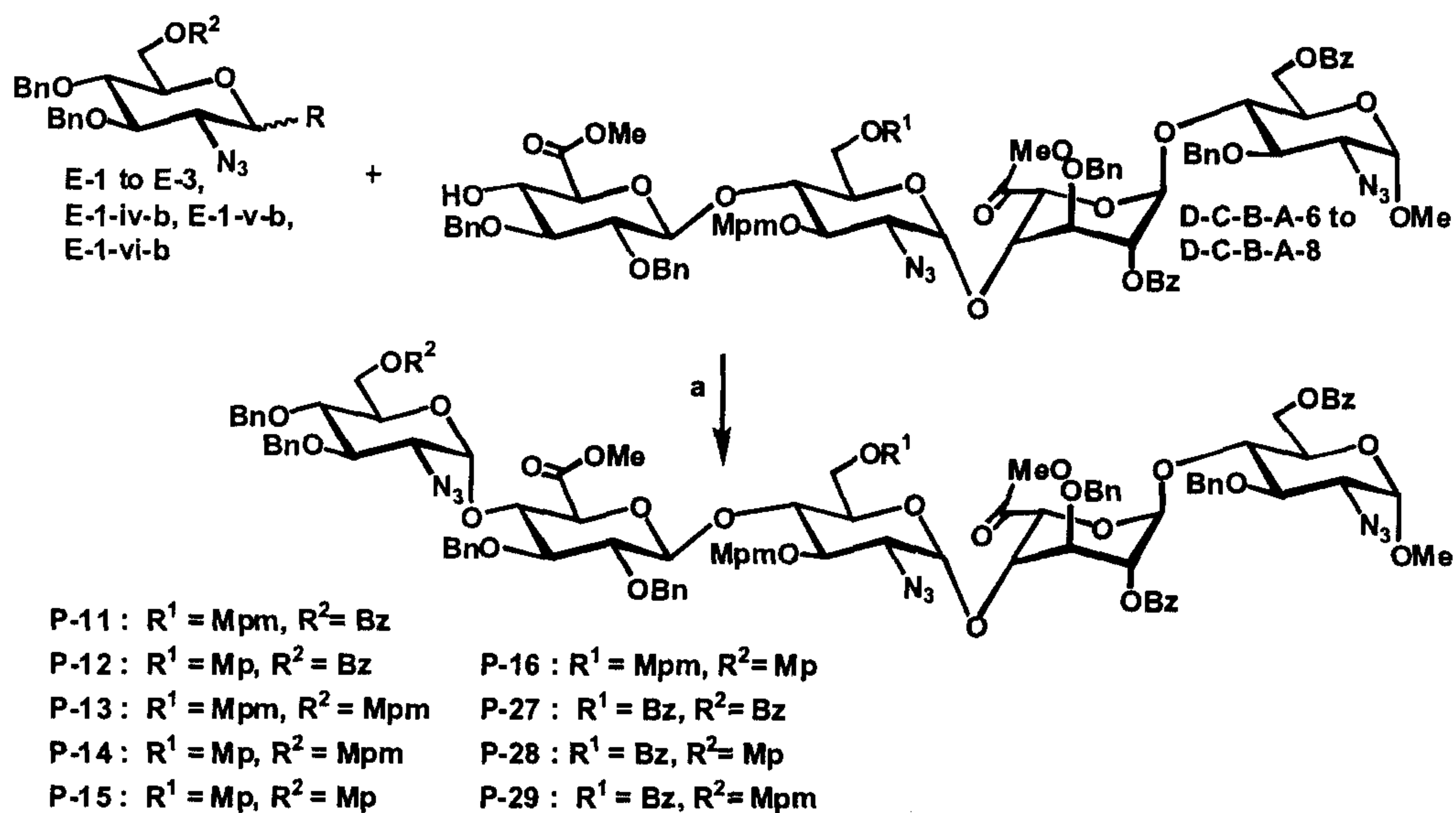
10

Example 41: Alternative syntheses of E-D-C-B-A pentasaccharides **P-11**, **P-12**, **P-19**, **P-20** and **P-27**

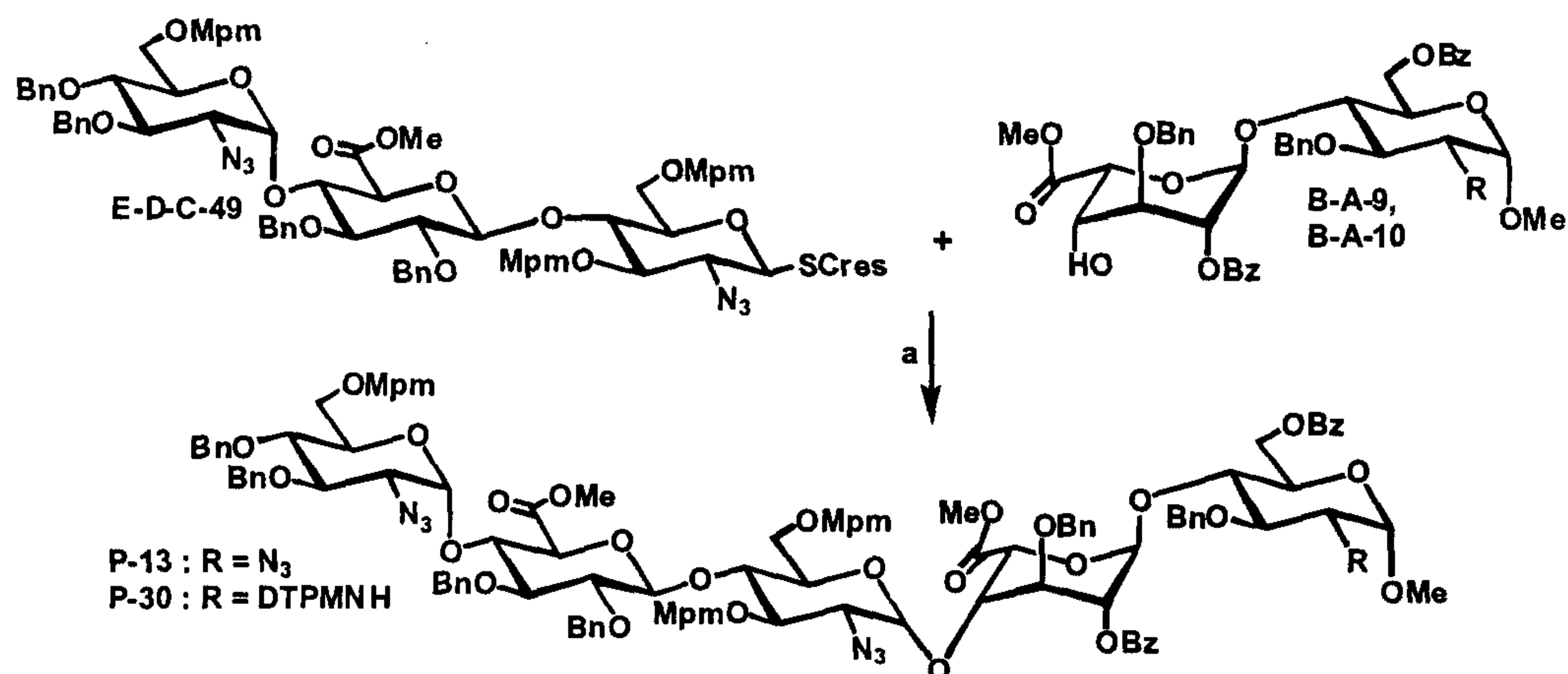


Example 41: Alternative syntheses of E-D-C-B-A pentasaccharides **P-11**, **P-12**, **P-19**, **P-20** and **P-27**, conditions: a) SOP 32a.

5 Example 42: Alternative syntheses of some E-D-C-B-A pentasaccharides

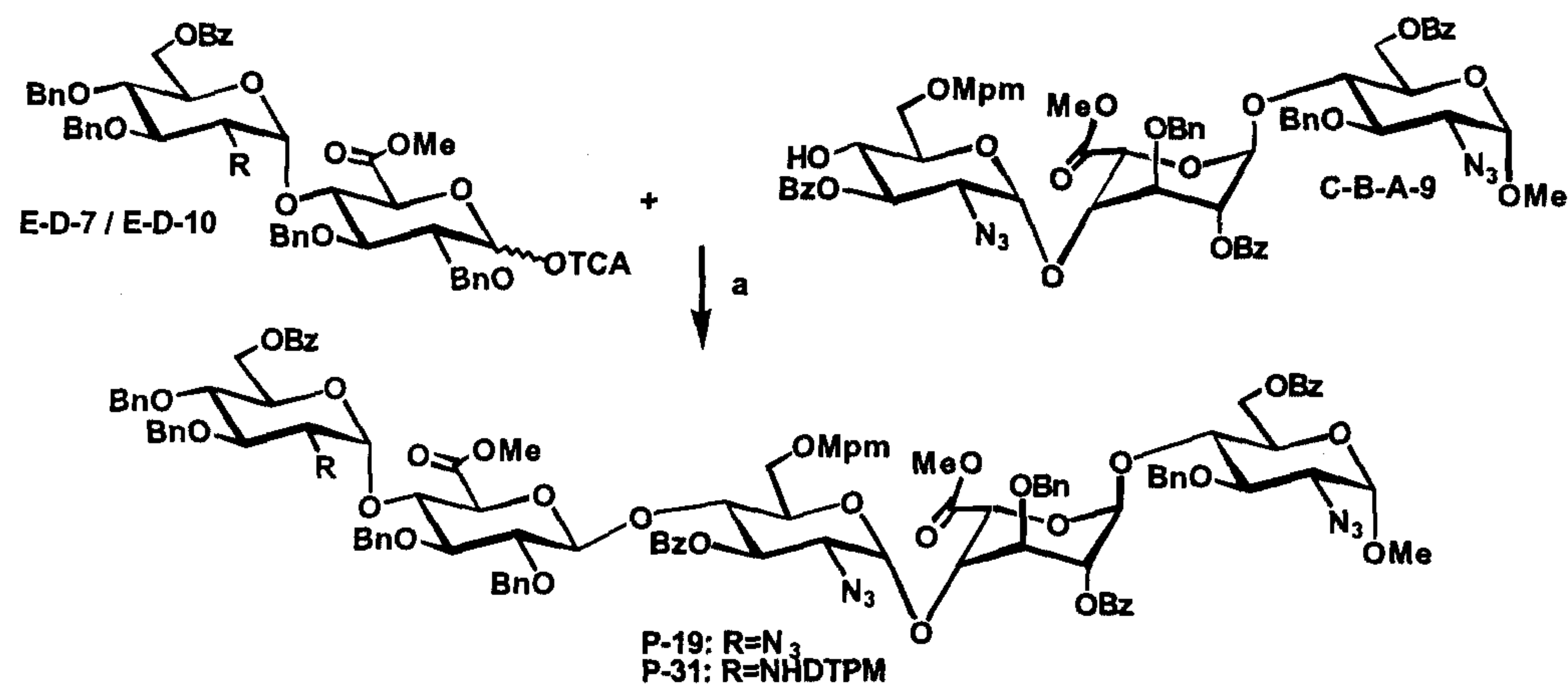


10 Example 42: Alternative syntheses of some E-D-C-B-A pentasaccharides, conditions: a) SOP 32a (for R = SCres) or SOP 33 (for R = OTCA).

Example 43: Synthesis of pentasaccharide P-13 and P-30

5

Example 43: Formation of pentasaccharides **P-13** and **P-30**, conditions: a)
SOP 32a.

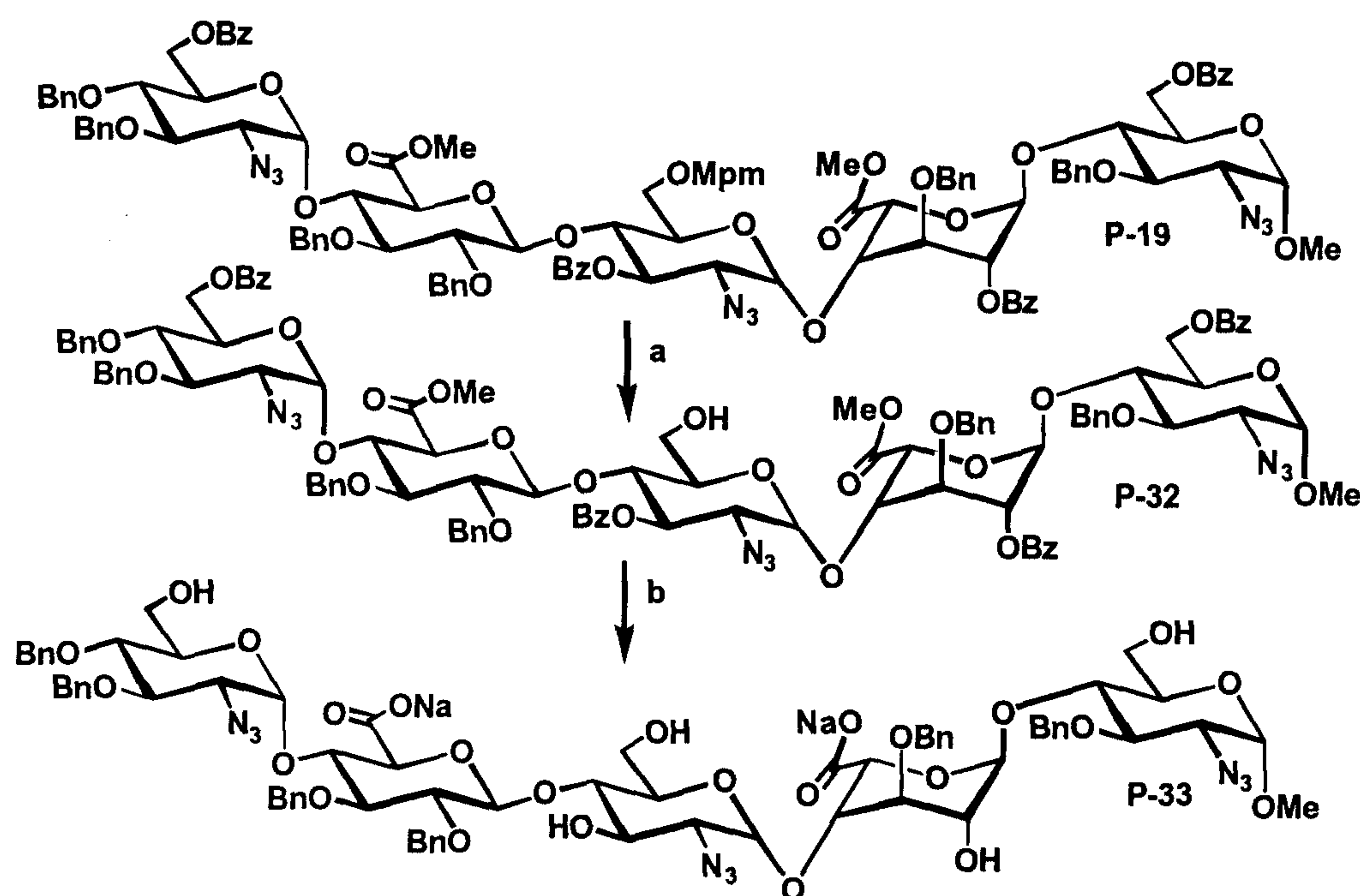
Example 44: Formation of pentasaccharide P-19 and P-31**Example 44: Formation of pentasaccharide P-19 and P-31**

15 conditions: a) SOP 33

Example preparation of **P19** :

A mixture of O-(2-azido-6-O-benzoyl-3,4-di-O-benzyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(methyl 2,3-di-O-benzyl- β -D-glucopyranosyluronate)-(1 $\rightarrow$ 4)-2-azido-3-O-benzoyl-2-deoxy-6-O-*p*-methoxybenzyl- α -D-glucopyranosyltrichloroacetimidate (30.0 mg, 21.2 μ mol) and methyl (methyl 2-O-benzoyl-3-O-benzyl- α -L-idupyransyluronate)-(1 $\rightarrow$ 4)-2-azido-3-O-benzyl-6-O-benzoyl-2-deoxy- α -D-glucopyranoside (15.4 mg 19.3 μ mol) and 100 mg of molecular sieves 4Å in 1.5 ml dry dichloromethane was treated with TBDMSOTf (0.97 μ l, 4.24 μ mol) at -20°C for 20 hours. The reaction was quenched, filtered and concentrated. Further purification of the title compound was achieved by silica gel chromatography Yield: 15.83 mg (40%), R_f = 0.30 (toluene/ethyl acetate = 9/1).

Example 45: Partial deprotection of pentasaccharide P-19



Example 45: Partial deprotection of pentasaccharide P-19, conditions: a) SOP 28, 84%; b) SOP 39, 86%.

Compound P-33:

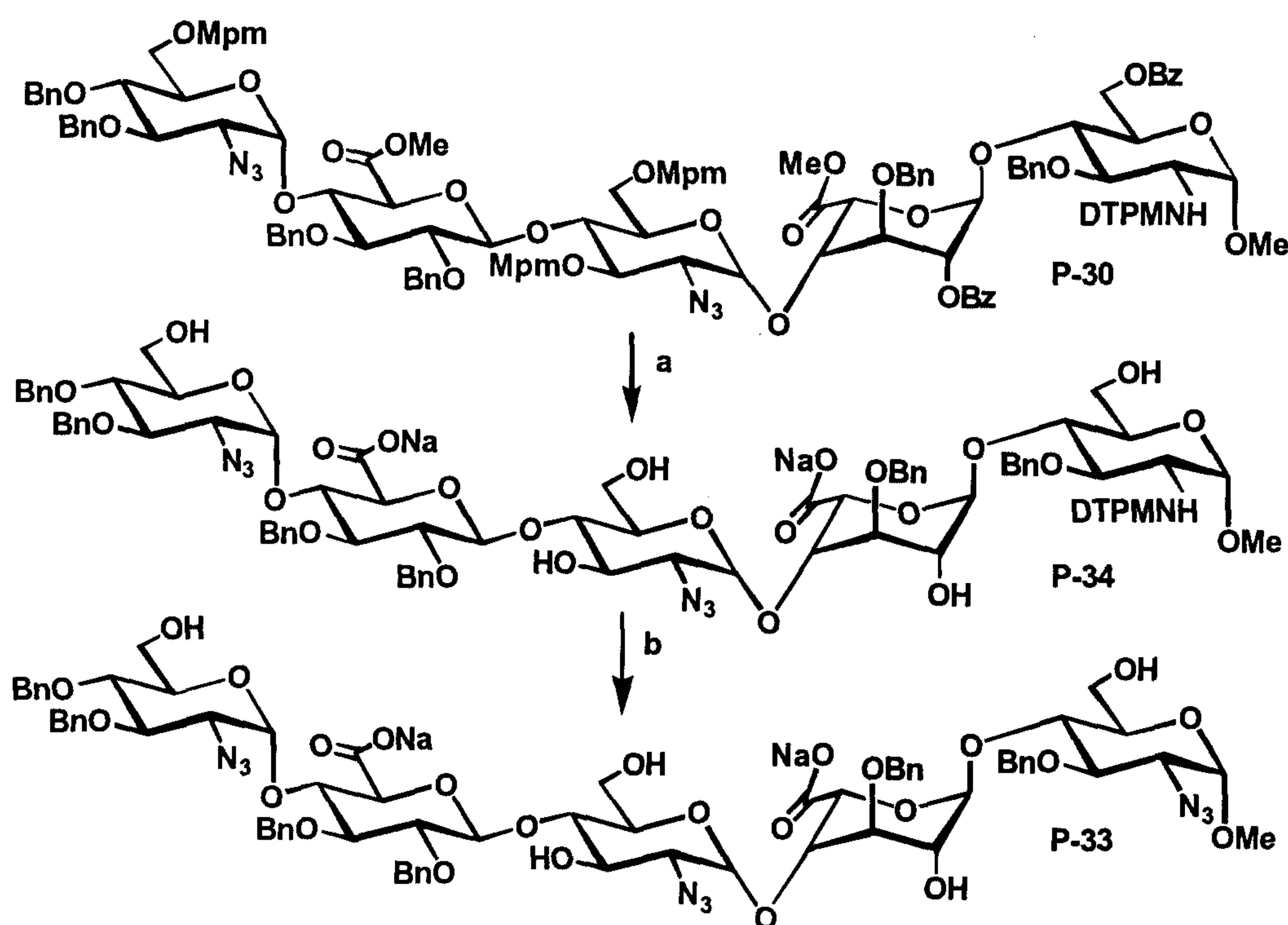
$M_{\text{found}} = 1503.5 (M-N_2+2H)^+$, $M_{\text{calc}} = 1529.51 (M^+)$.

To ease the structural proof, a small part of **P-33** was transformed into the bis methyl uronate derivative and characterized via NMR-spectroscopy. Characteristic ^1H -NMR-spectral regions are shown in figure 1.

5 $M_{\text{found}} = 1514.62 (M+H)^+$, $M_{\text{calc}} = 1513.58 (M^+)$.

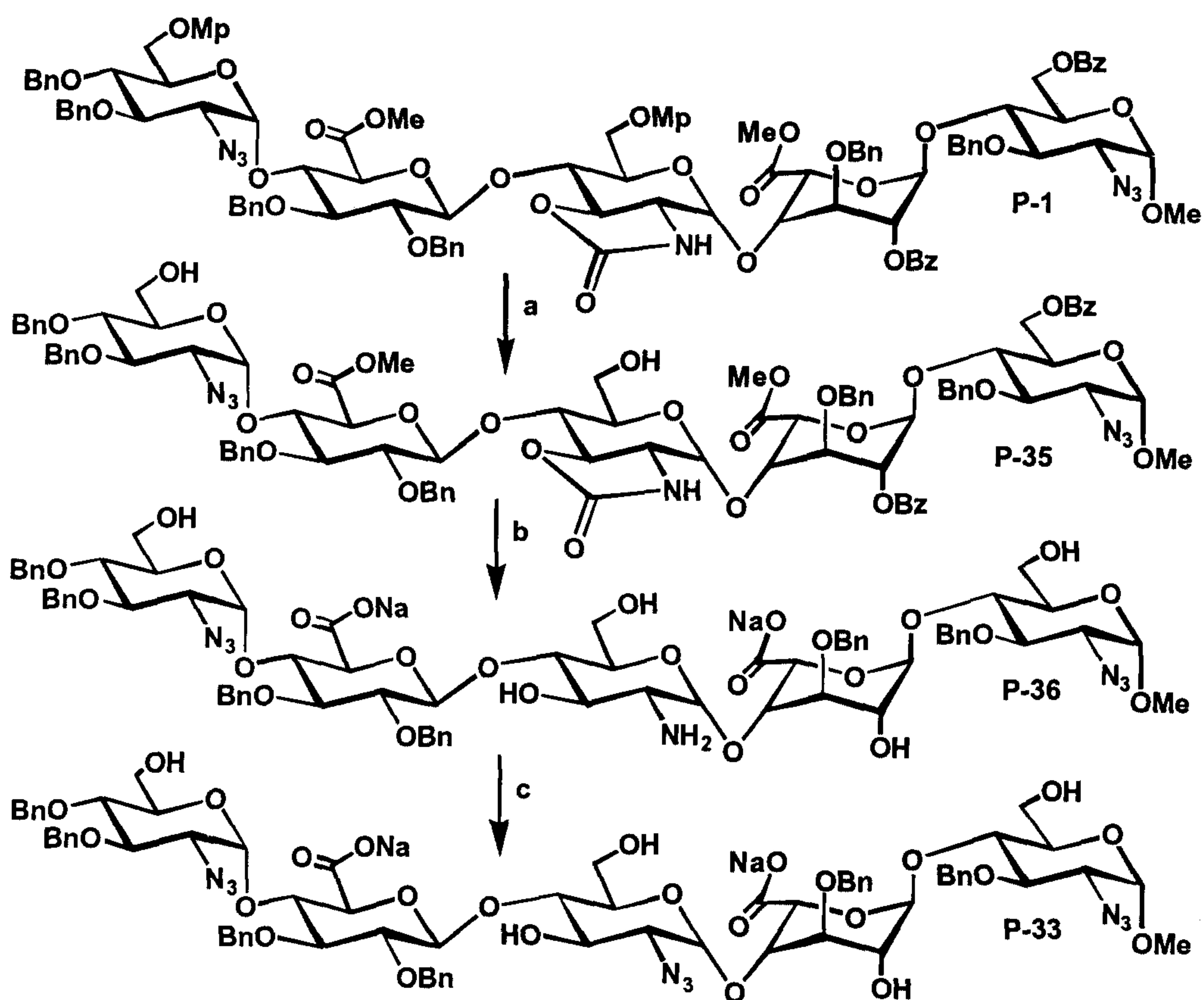
Example 46: Partial deprotection of pentasaccharide **P-30**, containing a

10 DTPM-group as amino protection



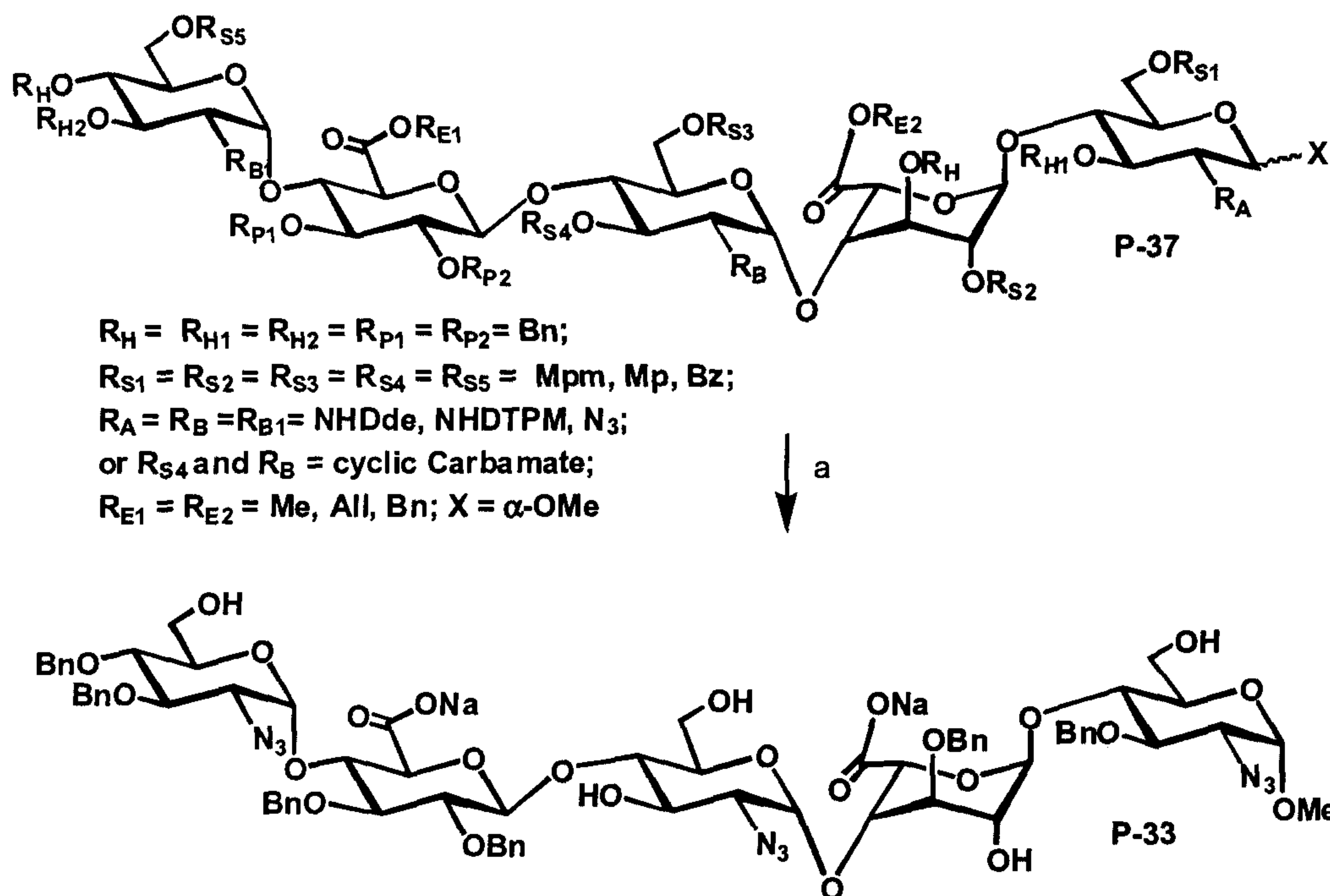
15 Example 46: Partial deprotection of pentasaccharide **P-30**, containing a DTPM-group as amino protection, conditions: a) 1. SOP 28; 2. SOP 39; b) 1. SOP 11 with MeNH₂ as primary amine and MeOH as solvent; 2. SOP 12.

20 Example 47: Partial deprotection of pentasaccharide **P-1**, containing a cyclic carbamate as amino protection



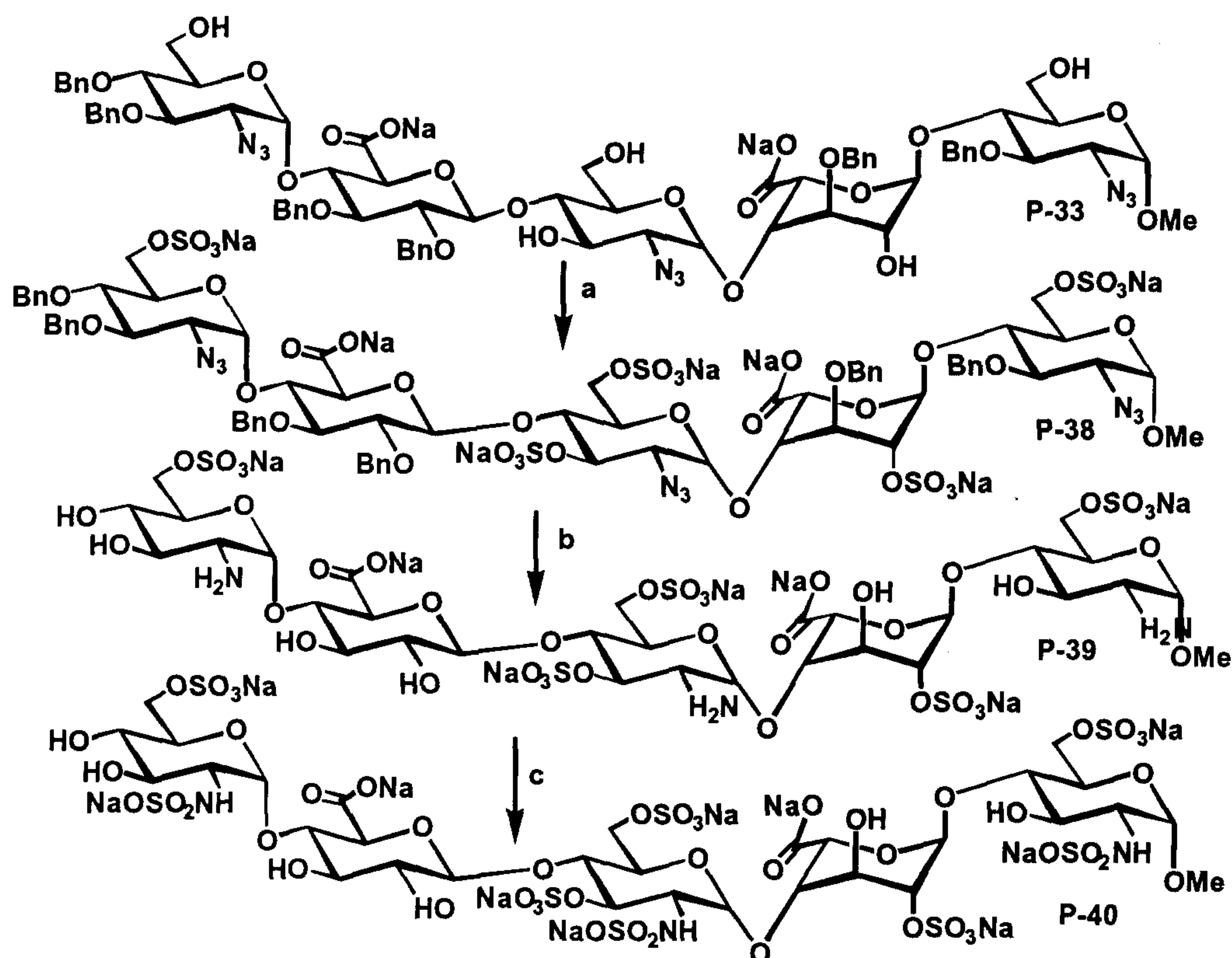
Example 47: Partial deprotection of pentasaccharide **P-1**, containing a cyclic
 5 carbamate as amino protection, conditions: a) SOP 27; b) SOP 39; c) SOP
 12.

Example 48: Deprotection protocol for pentasaccharides **P-37** of claim 4



Example 48: Deprotection protocol for pentasaccharides **P-37** of claim 4,
 conditions: a) 1. SOP 27 and 28; 2. SOP 39; 3. SOP 11 with MeNH_2 as
 5 primary amine and MeOH as solvent; 4. SOP 12.

Example 49: Transformation of pentasaccharide **P-33** into the O-and N-
 sulfated pentasaccharide **P-35**



Example 49: Transformation of pentasaccharide **P-33** into the O- and N-sulfated pentasaccharide **P-40**, conditions: a) SO_3xNMe_3 , DMF, 50°C ; b) H_2 (70 psi), Pd/C, H_2O ; c) $\text{SO}_3\text{xPyridine}$, H_2O , pH = 9.5. The transformation of **P-33** into **P-40** has been performed according to literature: Petitou et al., *Carbohydr. Res.* **1987**, 167, 67-75.

The ^1H -NMR (400 MHz, D_2O) of **P-40** is shown in figure 6.

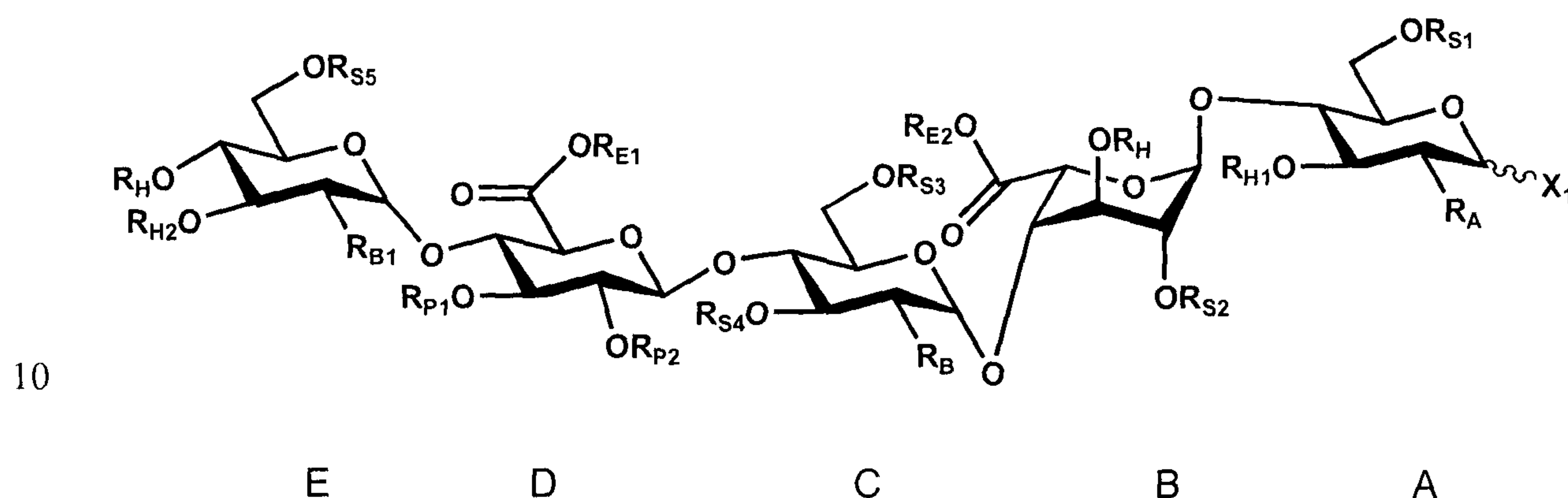
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- ³ Pierre Sinay, Jean-Claude Jacquinet, *Carbohydrate Research*, 132, (1984), C5-C9.
- ⁴ C.A.A. van Boeckel, T. Beetz, J.N. Vos, A.J.M. de Jong, S.F. van Aelst, R.H. van den Bosch, J.M.R. Mertens and F.A. van der Vlugt., *J. Carbohydrate Chemistry*, 4(3), 1985, 293-321.
- ⁵ J. Choay, M. Petitou, J.C. Lormeau, P. Sinay, J. Fareed, *Ann. NY Acad. Sci.*, **1981**, 370, 644-649.
- ⁶ J. Choay et al., *Biochem. Biophys. Res. Commun.*, **1983**, 116, 492-499.

Claims

5

1. A pentasaccharide building block for the preparation of synthetic heparinoids, said building block being of General Formula Ia,



General Formula Ia (Block E-D-C-B-A)

15

wherein the configuration of the monosaccharidic units and the stereochemistry of the internal linkages is defined as D-gluco-alpha-1,4-D-glucurono-beta-1,4-D-Gluco-alpha-1,4-L-idurono-alpha1,4-D-gluco, and the substituents are defined as;

20

X_1 is hydroxy, C_2 to C_{10} alkoxy, aryloxy; thioalkyl, thioaryl, imidoyl, or tert-butyldiphenylsilyloxy; and the stereochemistry may be alpha or beta; or an alpha methoxy group;

25

R_H , R_{H1} and R_{H2} is benzyl;

R_A , R_B and R_{B1} is independently an azido function, an *NH*-Dde, or *NH*-DTPM;

R_{E1} and R_{E2} are methyl;

R_{P1} and R_{P2} are benzyl;

5

R_{S1}, R_{S2} and R_{S5} are independently benzoyl or acetyl groups;

R_{S3} and R_{S4} are independently 4-methoxyphenyl; substituted benzyl groups; substituted alkylacyl groups; a tert-butyldiphenylsilyl, tert-butyldimethylsilyl or
10 trimethylsiloxyethyl group; or allyl.

2. The pentasaccharide building block of claim 1,

wherein:

15 **R_{S1}, R_{S2} and R_{S5}** are benzoyl groups.

3. The pentasaccharide building block of claim 1,

wherein:

20 **R_{S1}, R_{S2} and R_{S5}** are acetyl groups and

R_{S3} and R_{S4} are independently 4-methoxyphenyl; or substituted benzyl groups.

4. The pentasaccharide building block of claim 1,

25

wherein:

X₁ is alpha methoxy and;

30 **R_A, R_B and R_{B1}** are azido groups.

5. The pentasaccharide building block of claim 1, wherein **X₁** is C₂ to C₅ alkoxy.

6. The pentasaccharide building block of claim 1, wherein R_A is azido.

5 7. The pentasaccharide building block of claim 4, wherein R_{S3} is 4-methoxybenzyl.

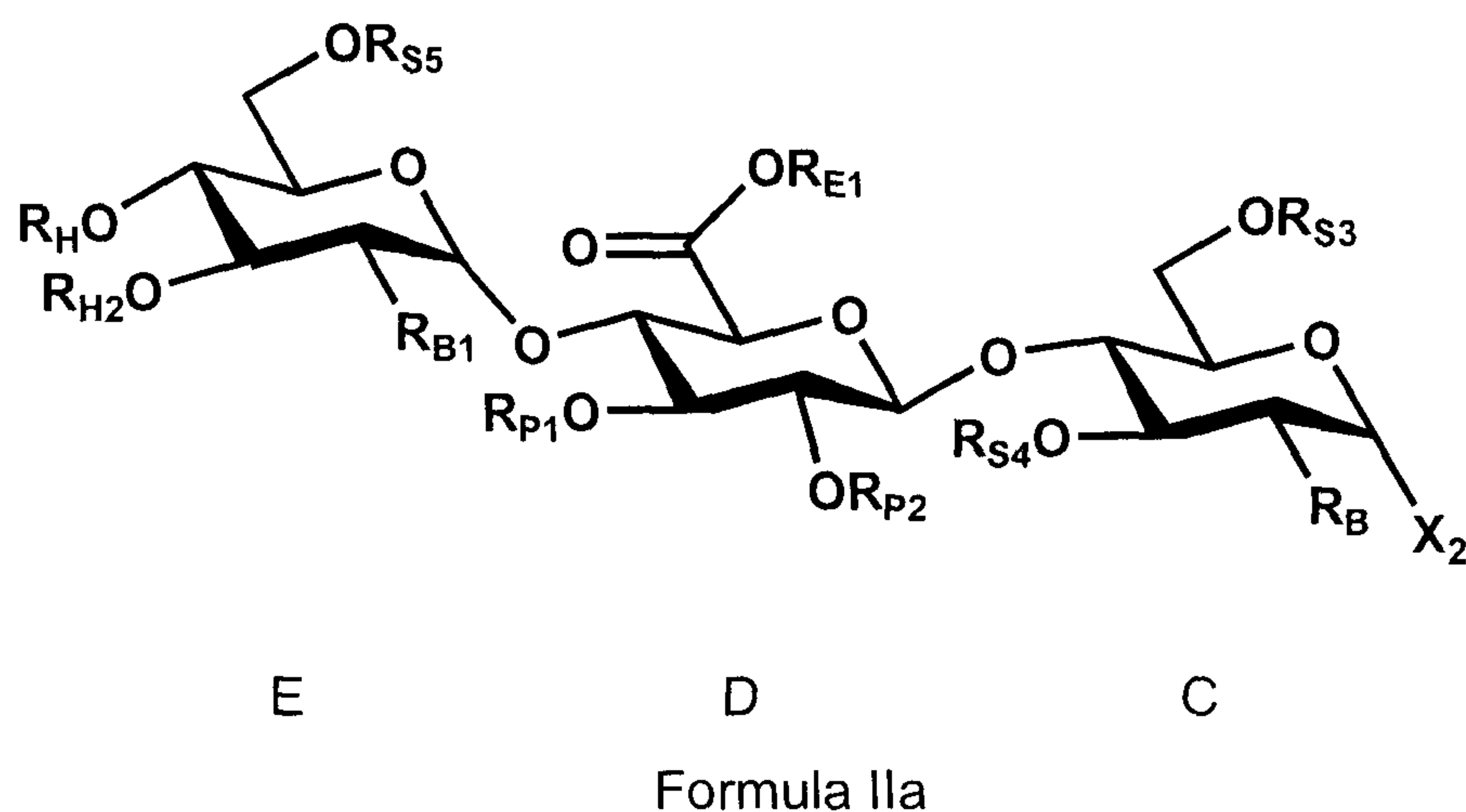
8. The pentasaccharide building block of claim 4, wherein R_{S3} , and R_{S4} are 4-methoxybenzyl.

10

9. The pentasaccharide building block of claim 1, wherein R_{B1} is azido.

15

10. A method of synthesizing the pentasaccharide of claim 1 comprising the steps of forming a trisaccharide EDC of formula IIa,



20

25 wherein:

X_2 is thioalkyl, thioaryl, halogen, trichloroacetimidoyl, or n-pentenyl and the stereochemistry may be alpha or beta;

R_H and R_{H2} are benzyl;

R_{S3} and R_{S4} are independently 4-methoxyphenyl; substituted benzyl groups; substituted alkylacyl, tert-butyldiphenylsilyl, tert-butyldimethylsilyl or
5 trimethylsiloxyethyl group, or allyl;

R_{S5} is benzoyl or acetyl;

R_{E1} is methyl;

10

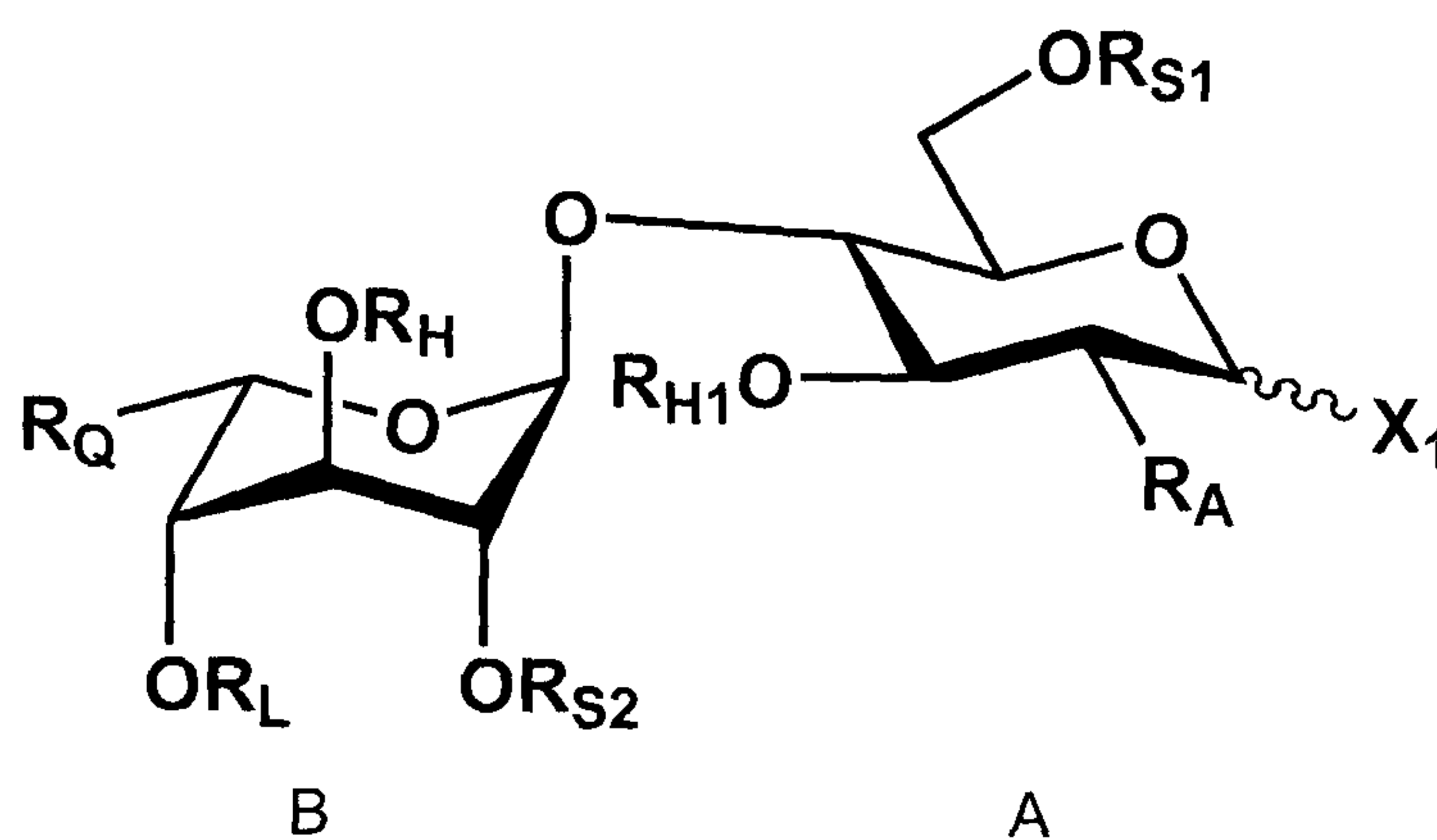
R_B and R_{B1} are independently an azido function, *NH*-Dde or *NH*-DTPM group;

R_{P1} is benzyl;

15

R_{P2} is benzyl;

and forming a disaccharide BA of formula IIIa



20

Formula IIIa

25 wherein:

X_1 is alkoxy, alkenyloxy, aryloxy, substituted benzyloxy; thioalkyl, thioaryl, or a tert-butyldiphenylsilyloxy group; and the stereochemistry may be alpha or beta;

5

R_{H1} is benzyl;

R_A is an azido function, *NH*-Dde, or *NH*-DTPM;

R_{S1} and R_{S2} are independantly benzoyl or acetyl;

10

R_Q is either a) $-(C=O)-OR_{E2}$ wherein R_{E2} is methyl;

or b) $-(CH_2)-OR_M$ wherein R_M is *p*-methoxyphenyl, *p*-methoxybenzyl, a trityl group, allyl, or levulinoyl;

15

R_L is H;

and linking the trisaccharide to the disaccharide to form the pentasaccharide.

11. A method of claim 10, wherein:

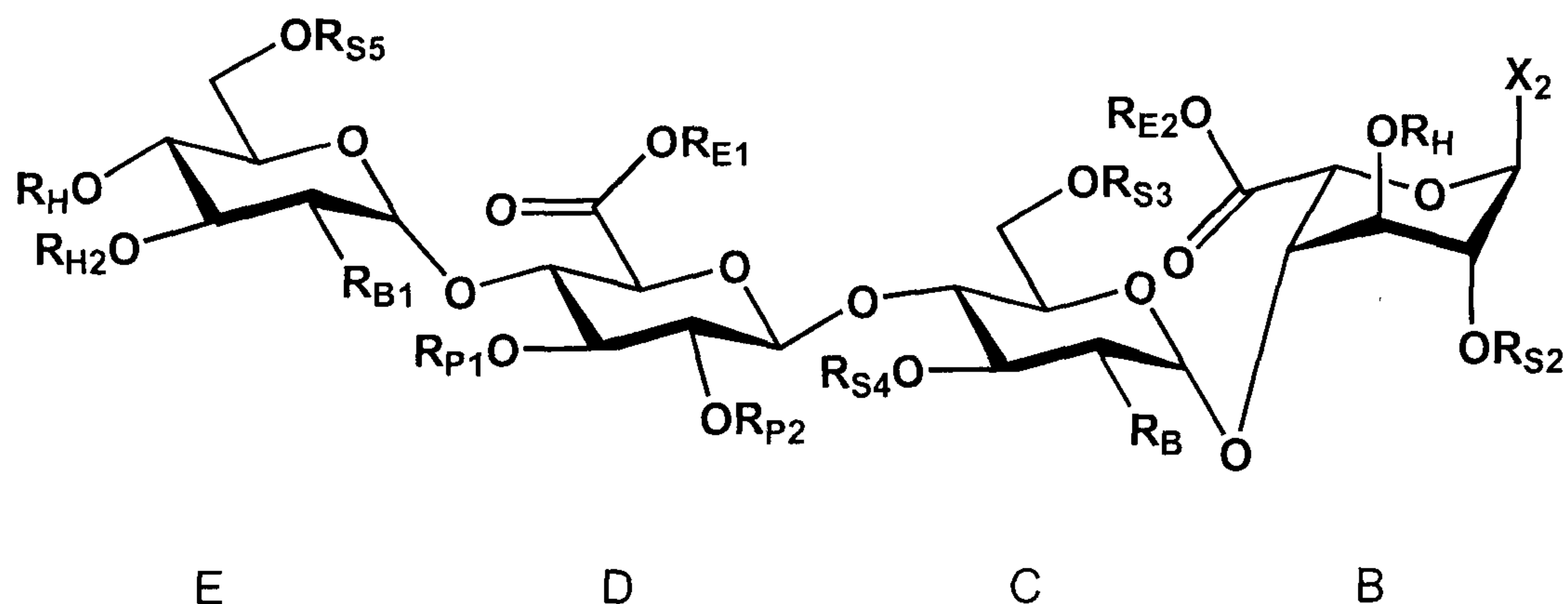
20

X_2 is thiomethyl, thiocresyl or trichloroacetimidoyl, and the stereochemistry may be alpha or beta,

R_Q is $-(C=O)-OR_{E2}$ wherein R_{E2} is methyl.

25

12. A method of synthesizing the pentasaccharide as defined in claim 1, comprising the step of synthesizing a tetrasaccharide EDCB (formula IV),



Formula IV

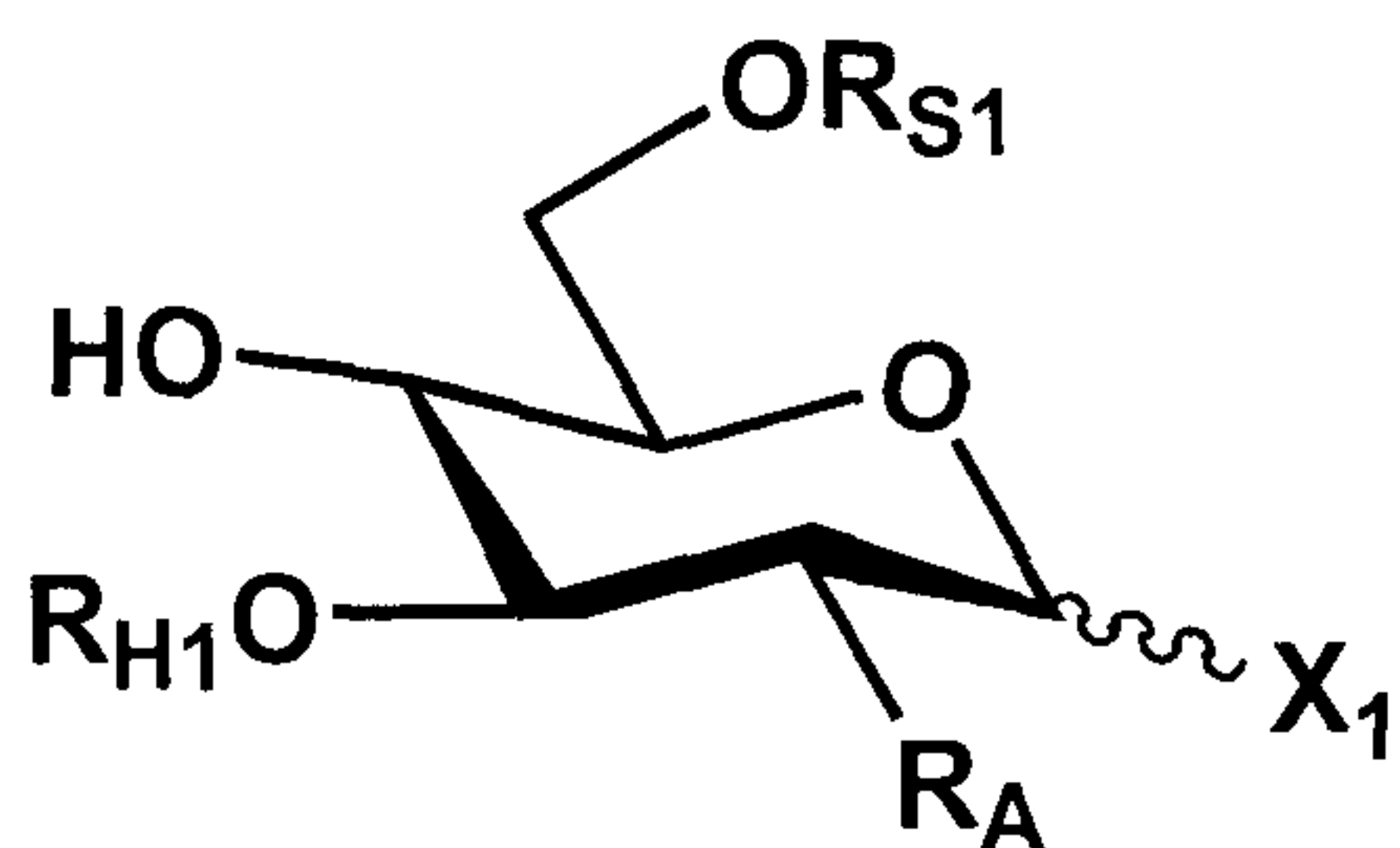
5

wherein:

X_2 is selected from a thioalkyl, thioaryl, halogen, trichloroacetimidoyl, phosphate and related phosphate ester type leaving groups, and the stereochemistry may be alpha or beta;

10

and linking the tetrasaccharide to a monosaccharide of formula V



A

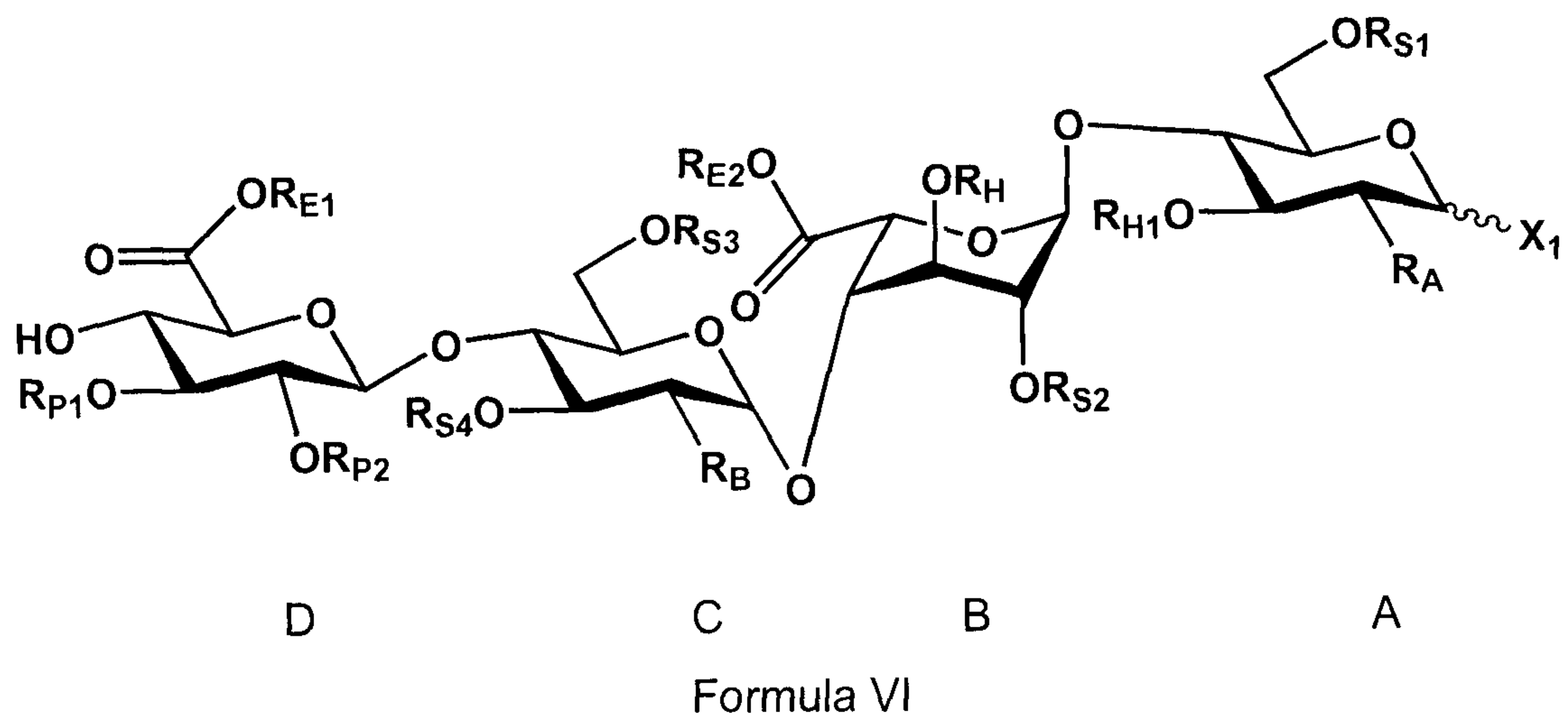
Formula V

15

wherein, X_1 , R_H , R_{H1} , R_{H2} , R_A , R_B , R_{B1} , R_{E1} , R_{E2} , R_{P1} , R_{P2} , R_{S1} , R_{S2} , R_{S3} , R_{S4} and R_{S5} are as defined in claim 1.

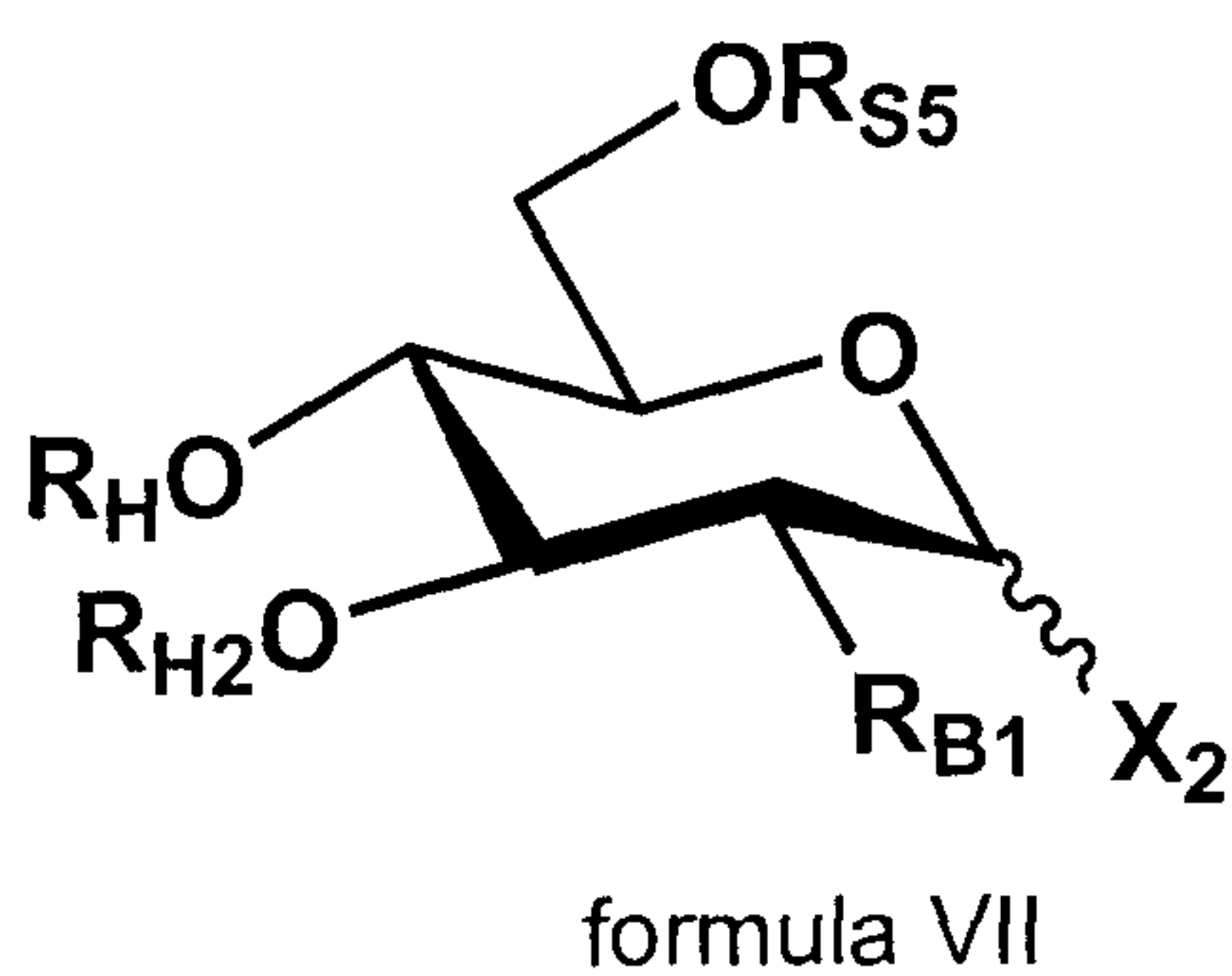
20

13. A method of synthesizing the pentasaccharide as defined in claim 1 comprising synthesizing a tetrasaccharide DCBA of formula VI



5

and linking the tetrasaccharide to a monosaccharide of formula VII



10

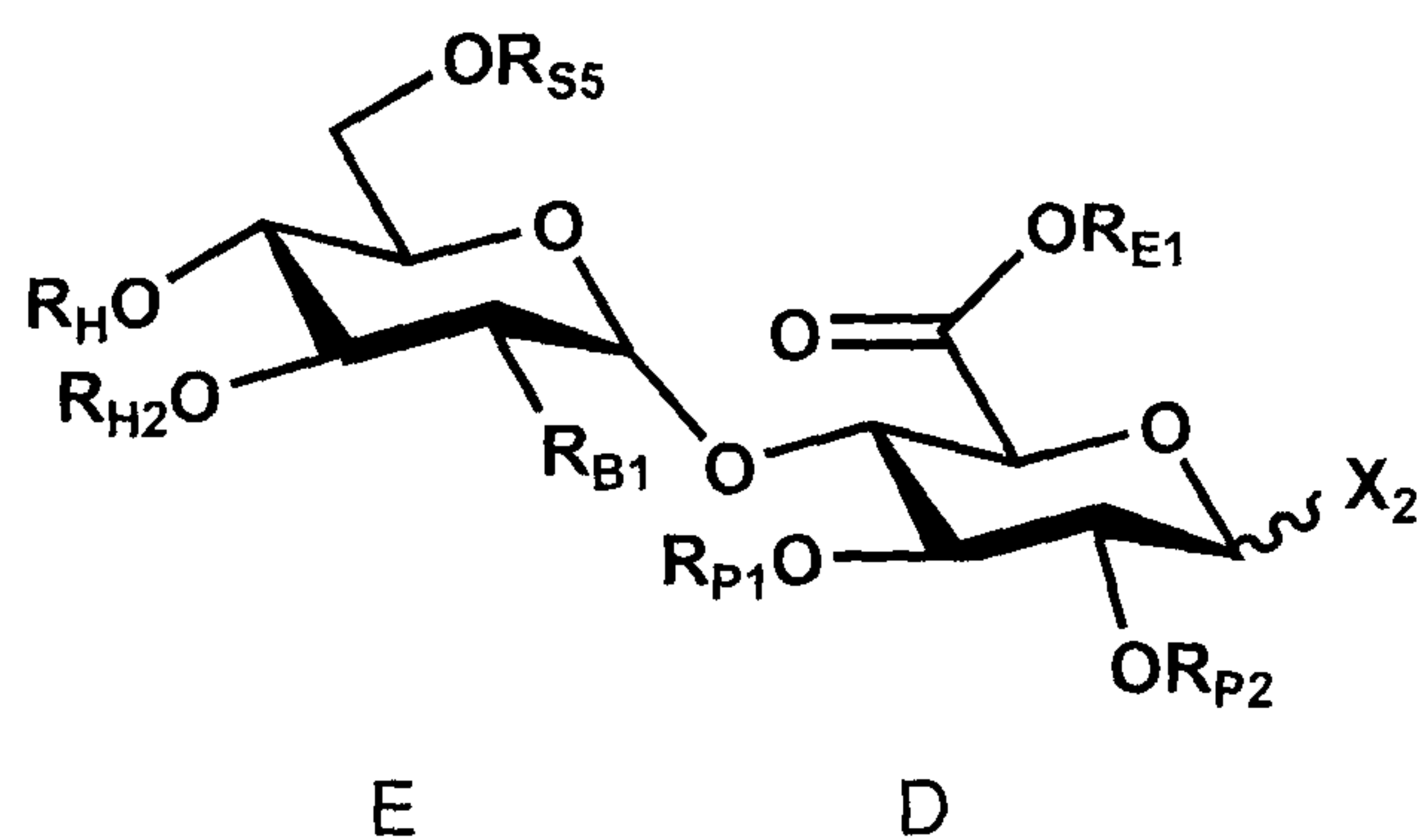
wherein

X_2 is selected from a thioalkyl, thioaryl, trichloroacetimidoyl; and the stereochemistry may be alpha or beta; and

15 wherein, X_1 , R_H , R_{H1} , R_{H2} , R_A , R_B , R_{B1} , R_{E1} , R_{E2} , R_{P1} , R_{P2} , R_{S1} , R_{S2} , R_{S3} , R_{S4} and R_{S5} are as defined in claim 1.

14. A method of synthesizing the pentasaccharide as defined in claim 1 comprising the steps of forming a disaccharide ED of formula VIII,

20



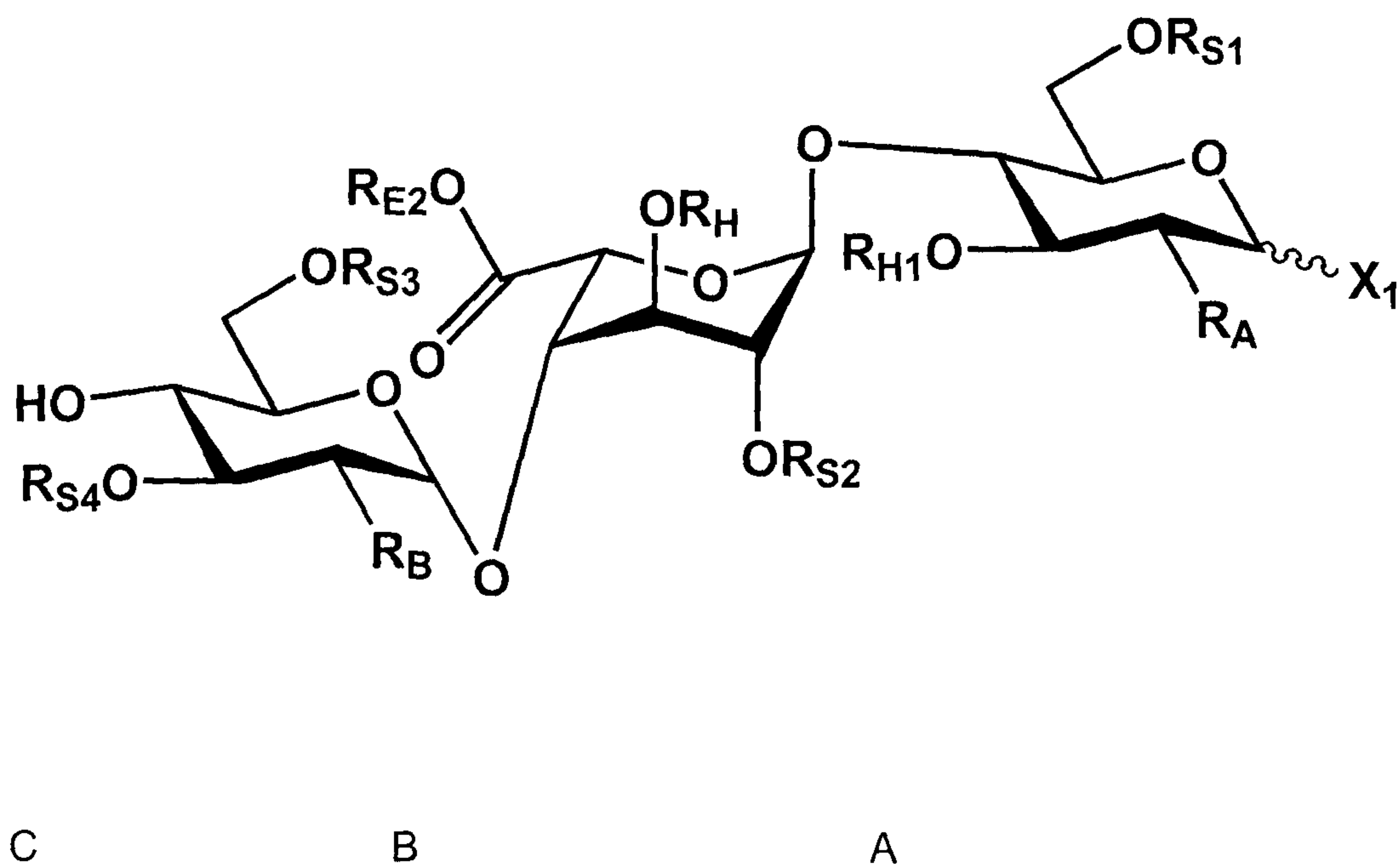
Formula VIII

5 wherein:

X_2 is selected from thioalkyl, thioaryl, halogen, trichloroacetimidoyl, phosphate and related phosphate ester type leaving groups, and the stereochemistry may be alpha or beta;

10

and forming a trisaccharide CBA of formula IX



Formula IX

20 wherein, X_1 , R_H , R_{H1} , R_{H2} , R_A , R_B , R_{B1} , R_{E1} , R_{E2} , R_{P1} , R_{P2} , R_{S1} , R_{S2} , R_{S3} , R_{S4} and R_{S5} are as defined in claim 1,

and linking the disaccharide to the trisacharide.

15. The method as defined in any one of claims 12 to 14 wherein:

5 **R_{S1}, R_{S2} and R_{S5}** are benzoyl groups.

16. The method as defined in any one of claims 12 to 14 wherein:

wherein:

10 **R_{S1}, R_{S2} and R_{S5}** are acetyl groups and
R_{S3} and R_{S4} are independently 4-methoxyphenyl; or substituted benzyl
 groups.

17. The method as defined in any one of claims 12 to 14 wherein:

15 wherein:

X₁ is alpha methoxy and;
R_A, R_B and R_{B1} are azido groups.

18. The method as defined in any one of claims 12 to 14 wherein

20 **X₁** is C₂ to C₅ alkoxy.

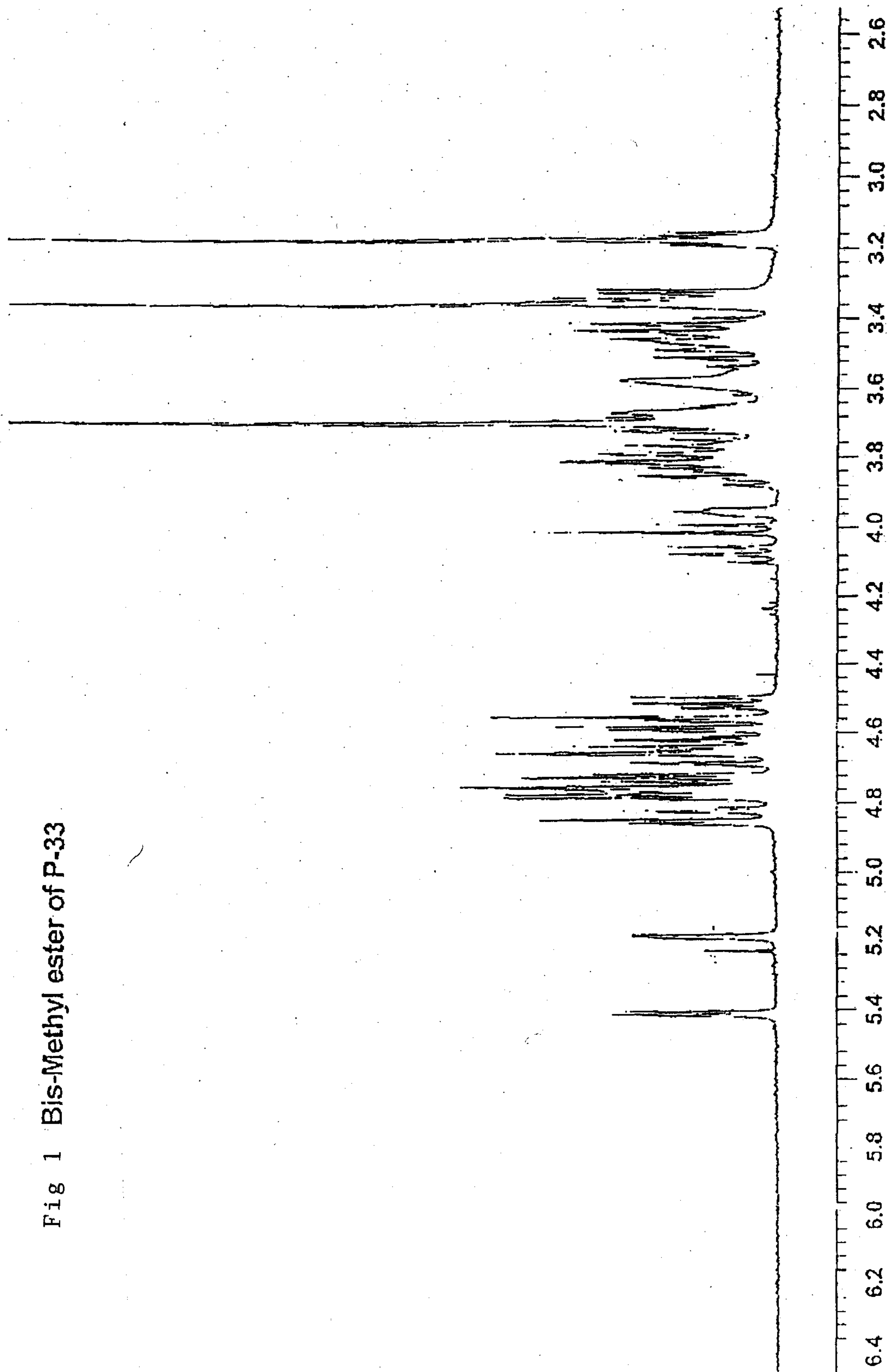
19. The method as defined in any one of claims 12 to 14 wherein
R_A is azido.

25 **20.** The method as defined in any one of claims 12 to 14 wherein
R_{S3} is 4-methoxybenzyl.

21. The method as defined in any one of claims 12 to 14 wherein
R_{S3}, and R_{S4} are 4-methoxybenzyl.

120A

Fig 1 Bis-Methyl ester of P-33



120B

Fig 2 P40

