



(86) Date de dépôt PCT/PCT Filing Date: 2004/06/25

(87) Date publication PCT/PCT Publication Date: 2004/12/29

(45) Date de délivrance/Issue Date: 2013/07/16

(85) Entrée phase nationale/National Entry: 2006/01/27

(86) N° demande PCT/PCT Application No.: CA 2004/000958

(87) N° publication PCT/PCT Publication No.: 2004/113289

(30) Priorité/Priority: 2003/06/25 (US60/482,006)

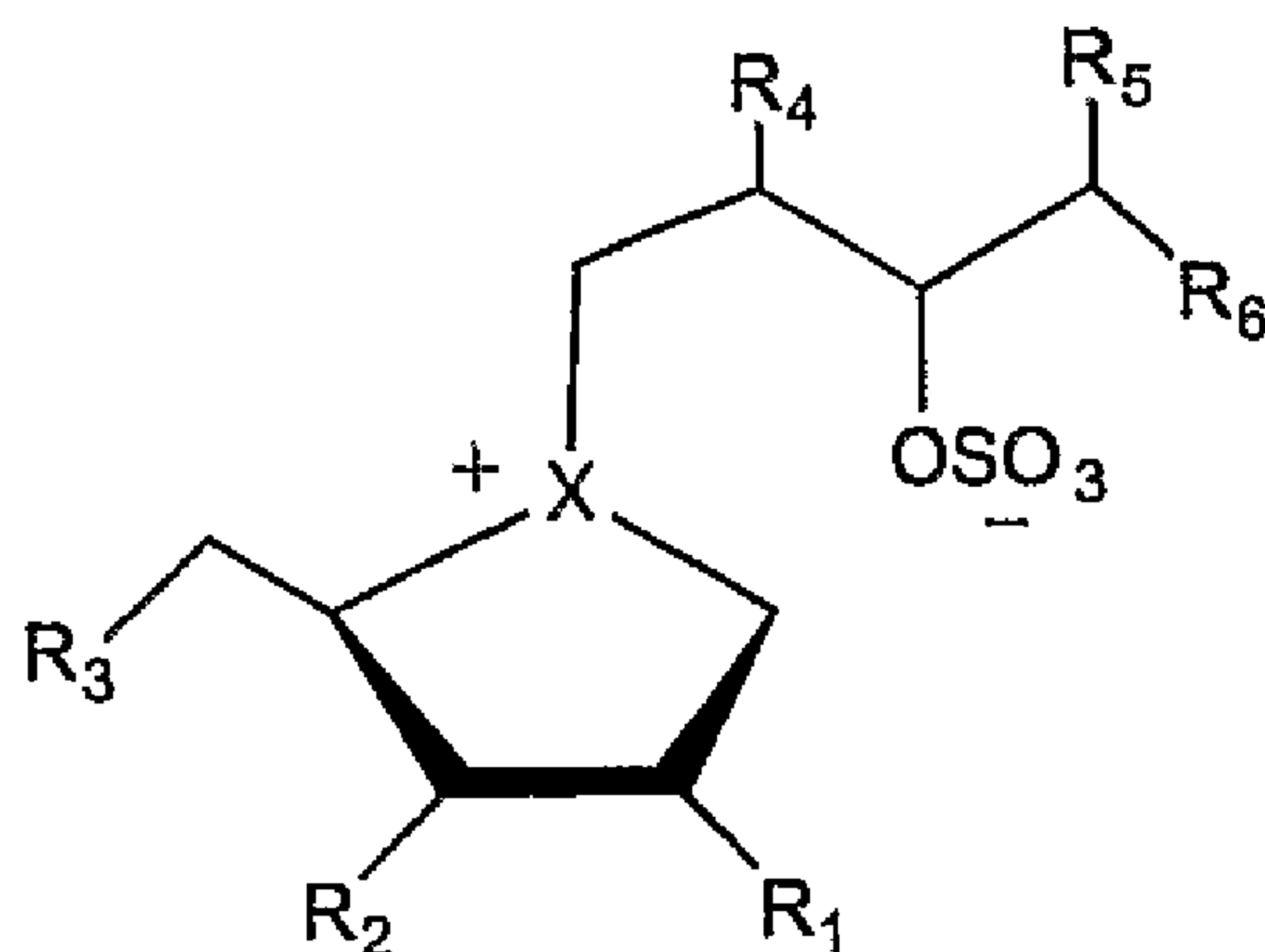
(51) Cl.Int./Int.Cl. *C07D 335/02* (2006.01),
A61K 31/33 (2006.01), *A61K 31/381* (2006.01),
A61P 3/10 (2006.01), *C07D 207/12* (2006.01),
C07D 211/46 (2006.01), *C07D 333/46* (2006.01),
C07D 345/00 (2006.01)

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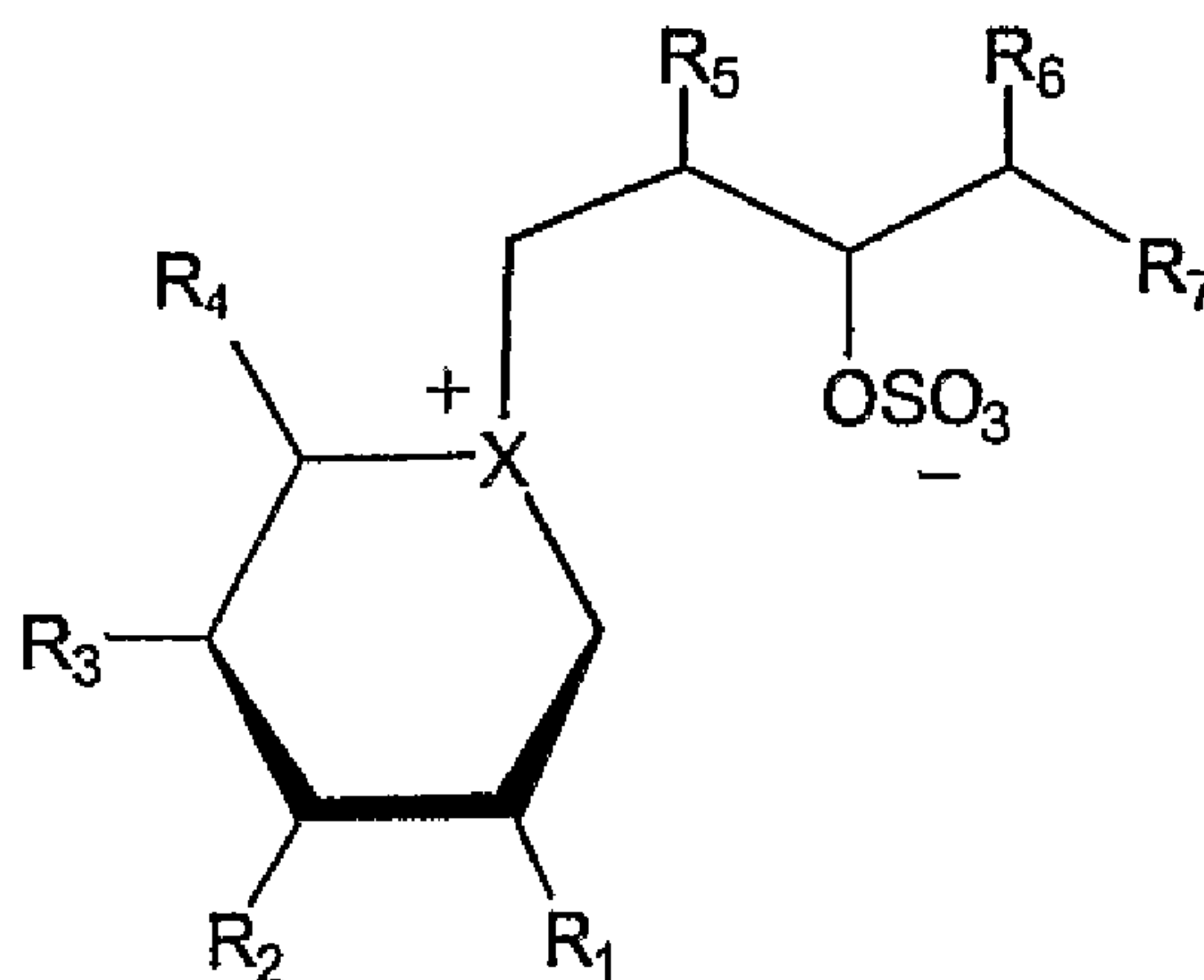
(73) Propriétaire/Owner:

(54) Titre : INHIBITEURS DE LA GLYCOSIDASE ET LEURS PROCEDES DE SYNTHESE

(54) Title: GLYCOSIDASE INHIBITORS AND METHODS OF SYNTHESIZING SAME



(I)



(II)

(57) **Abrégé/Abstract:**

A method for synthesizing Salacinol, its stereoisomers, and analogues, homologues and other derivatives thereof potentially useful as glycosidase inhibitors. The compounds of the invention may have the general formula (I) or (II): The synthetic schemes comprise reacting a cyclic sulfate with a 5-membered ring sugar containing a heteroatom (X). The heteroatom preferably comprises sulfur, selenium, or nitrogen. The cyclic sulfate and ring sugar reagents may be readily prepared from carbohydrate precursors, such as D-glucose, L-glucose, D-xylose and L-xylose. The target compounds are prepared by opening of the cyclic sulfates by nucleophilic attack of the heteroatoms on the 5-membered ring sugars. The resulting heterocyclic compounds have a stable, inner salt structure comprising a heteroatom cation and a sulfate anion. The synthetic schemes yield various stereoisomers of the target compounds in moderate to good yields with limited side-reactions.

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
29 December 2004 (29.12.2004)

PCT

(10) International Publication Number
WO 2004/113289 A3

(51) International Patent Classification⁷: **A61K 31/381**,
C07D 333/46, A61P 3/10, C07D 345/00, A61K 31/33,
31/40, C07D 207/12, A61K 31/452, C07D 211/46, A61K
31/382, C07D 335/02

(21) International Application Number:
PCT/CA2004/000958

(22) International Filing Date: 25 June 2004 (25.06.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/482,006 25 June 2003 (25.06.2003) US

(63) Related by continuation (CON) or continuation-in-part
(CIP) to earlier application:
US 10/226657 (CIP)
Filed on 22 August 2002 (22.08.2002)

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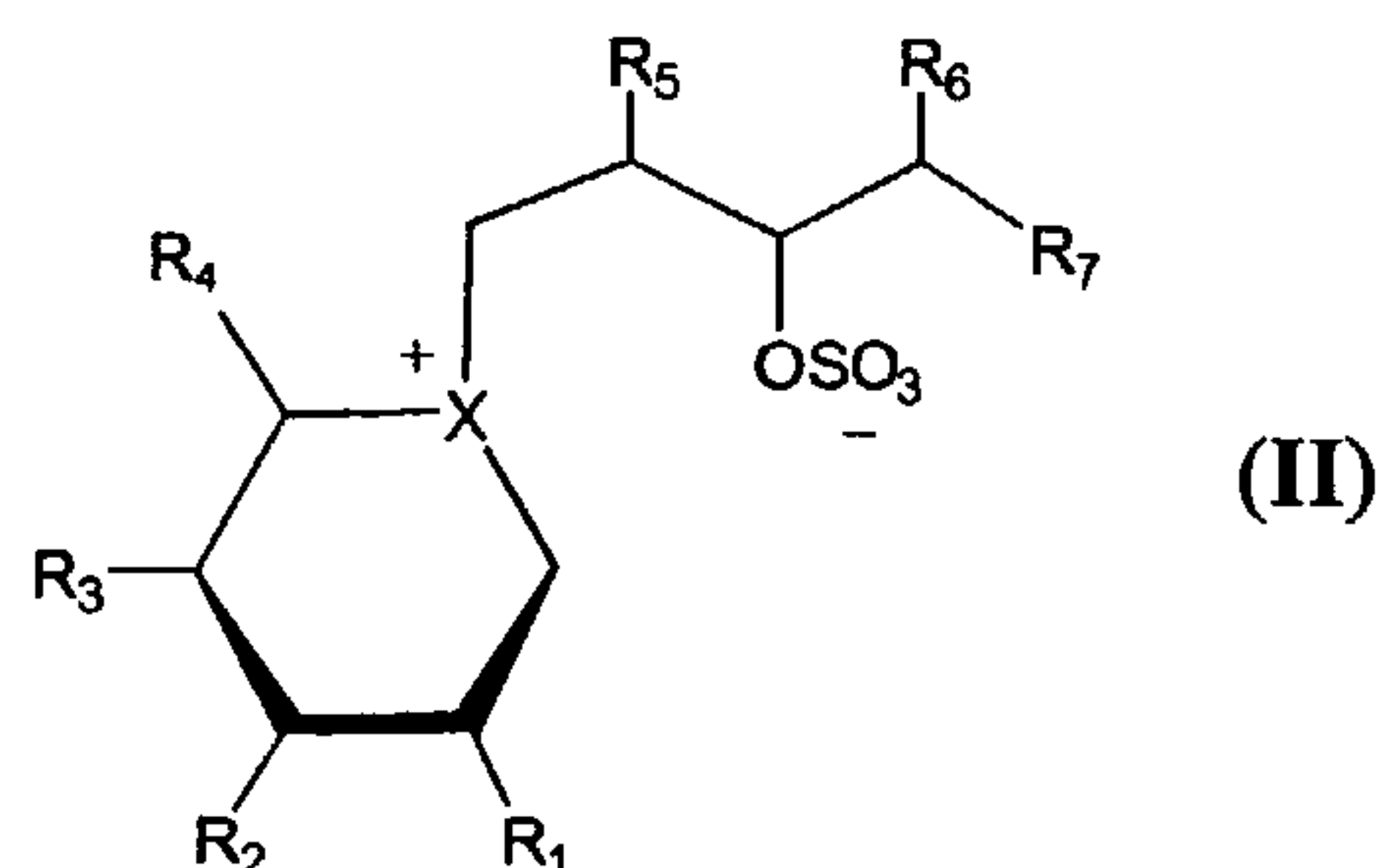
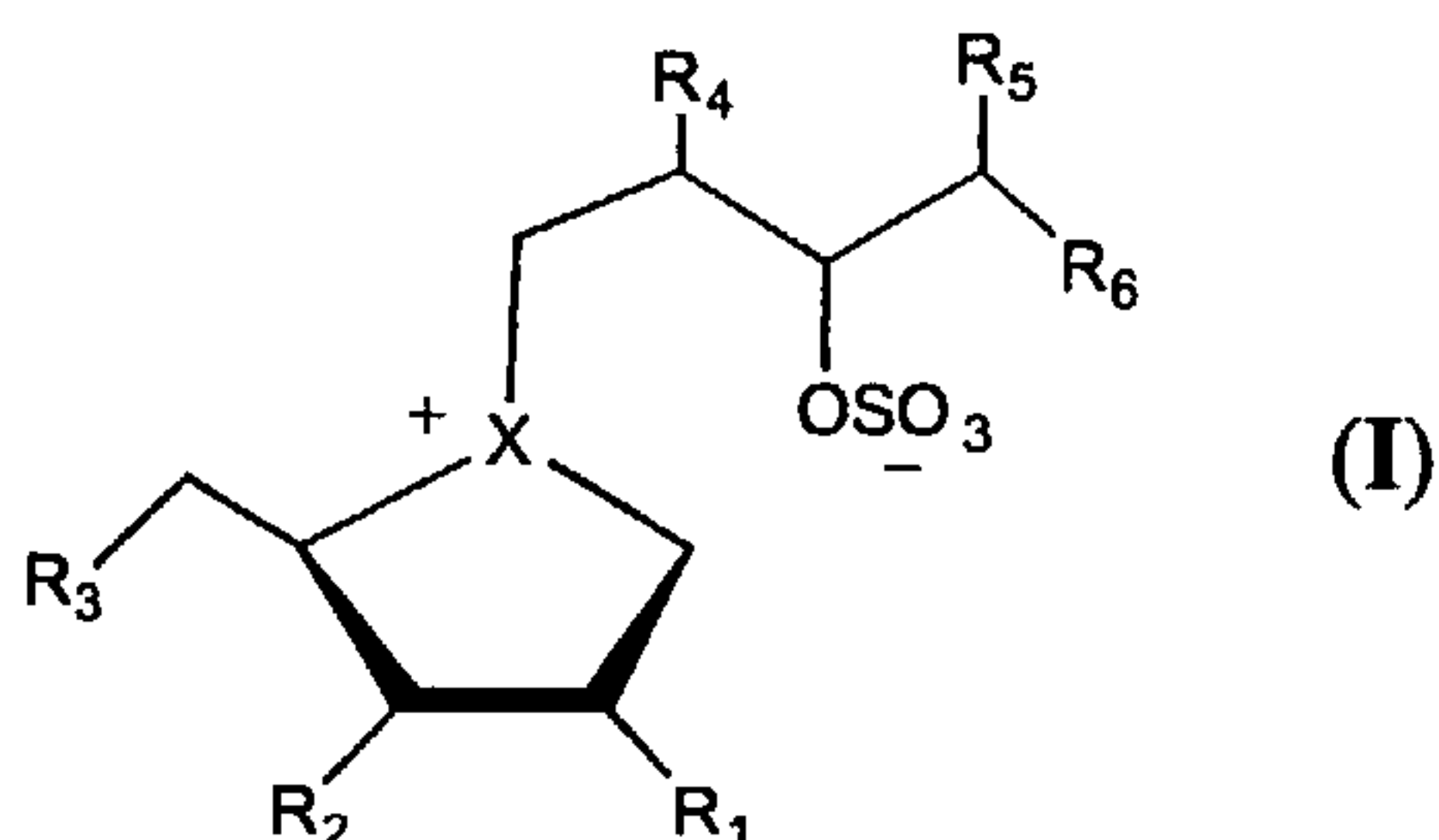
(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,
GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,
KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,
MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG,
PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,
TN, TR, TT, TZ, UA, UG, US (patent), UZ, VC, VN, YU,
ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI,
SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG).

Published:
— with international search report

[Continued on next page]

(54) Title: GLYCOSIDASE INHIBITORS AND METHODS OF SYNTHESIZING SAME



(57) Abstract: A method for synthesizing Salacinol, its stereoisomers, and analogues, homologues and other derivatives thereof potentially useful as glycosidase inhibitors. The compounds of the invention may have the general formula (I) or (II): The synthetic schemes comprise reacting a cyclic sulfate with a 5-membered ring sugar containing a heteroatom (X). The heteroatom preferably comprises sulfur, selenium, or nitrogen. The cyclic sulfate and ring sugar reagents may be readily prepared from carbohydrate precursors, such as D-glucose, L-glucose, D-xylose and L-xylose. The target compounds are prepared by opening of the cyclic sulfates by nucleophilic attack of the heteroatoms on the 5-membered ring sugars. The resulting heterocyclic compounds have a stable, inner salt structure comprising a heteroatom cation and a sulfate anion. The synthetic schemes yield various stereoisomers of the target compounds in moderate to good yields with limited side-reactions.

WO 2004/113289 A3

WO 2004/113289 A3



— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(88) Date of publication of the international search report:

7 April 2005

GLYCOSIDASE INHIBITORS AND METHODS OF SYNTHESIZING SAME

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Technical Field

10 This application relates to methods for synthesizing Salacinol, its stereoisomers, and analogues, homologues and other derivatives thereof potentially useful as glycosidase inhibitors.

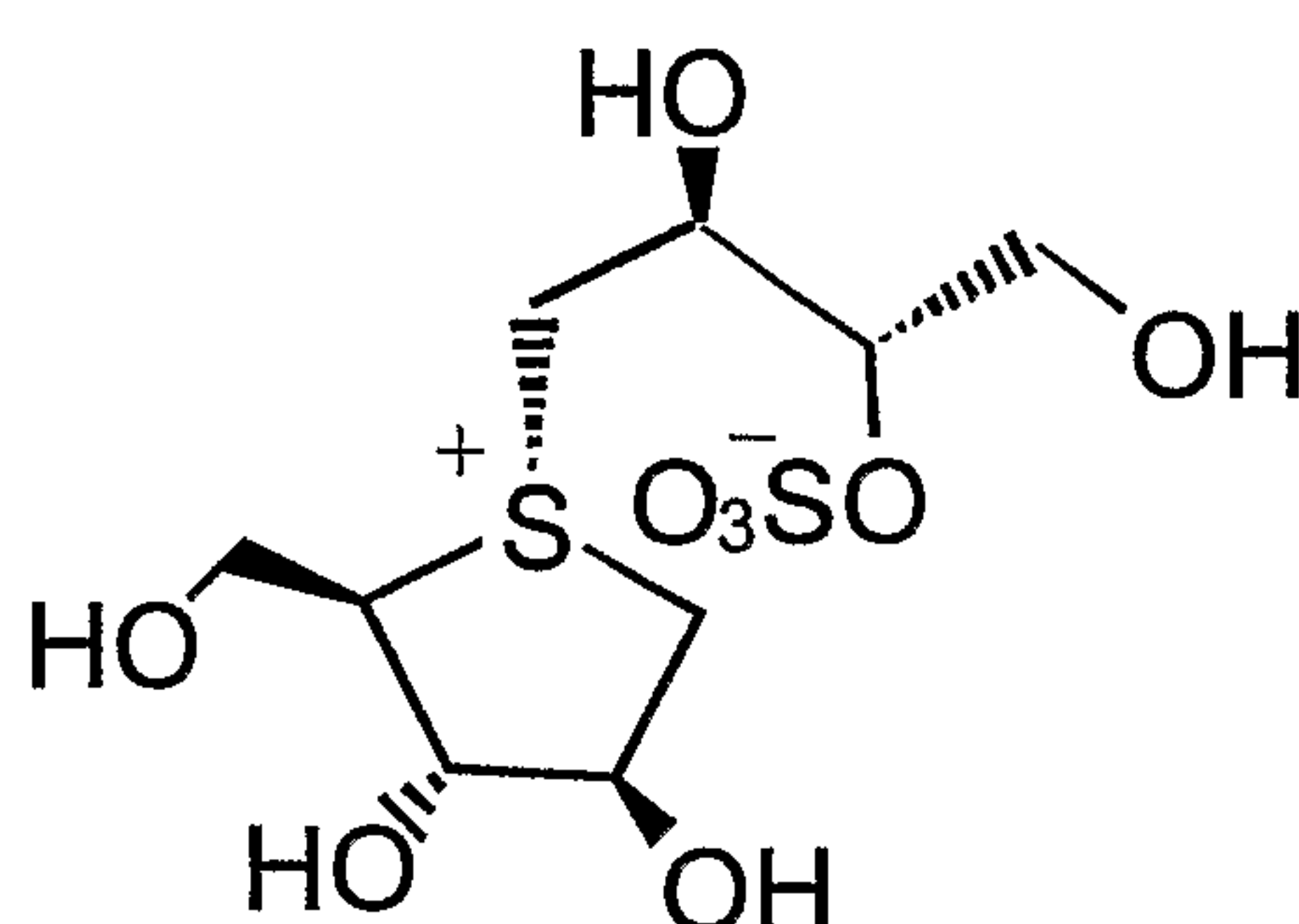
Background

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 In treatment of non-insulin dependent diabetes (NIDD) management of blood glucose levels is critical. One strategy for treating NIDD is to delay digestion of ingested carbohydrates, thereby lowering post-prandial blood glucose concentration. This can be achieved by administering drugs which inhibit the activity
20 of enzymes, such as glucosidases, which mediate the hydrolysis of complex starches to oligosaccharides in the small intestine. For example, carbohydrate analogues, such as Acarbose, reversibly inhibit the function of pancreatic α -amylase and membrane-bound intestinal α -glucoside hydrolase enzymes. In patients suffering from Type II diabetes, such enzyme inhibition results in delayed glucose absorption into the blood
25 and a smoothing or lowering of postprandial hyperglycemia, resulting in improved glycemic control.

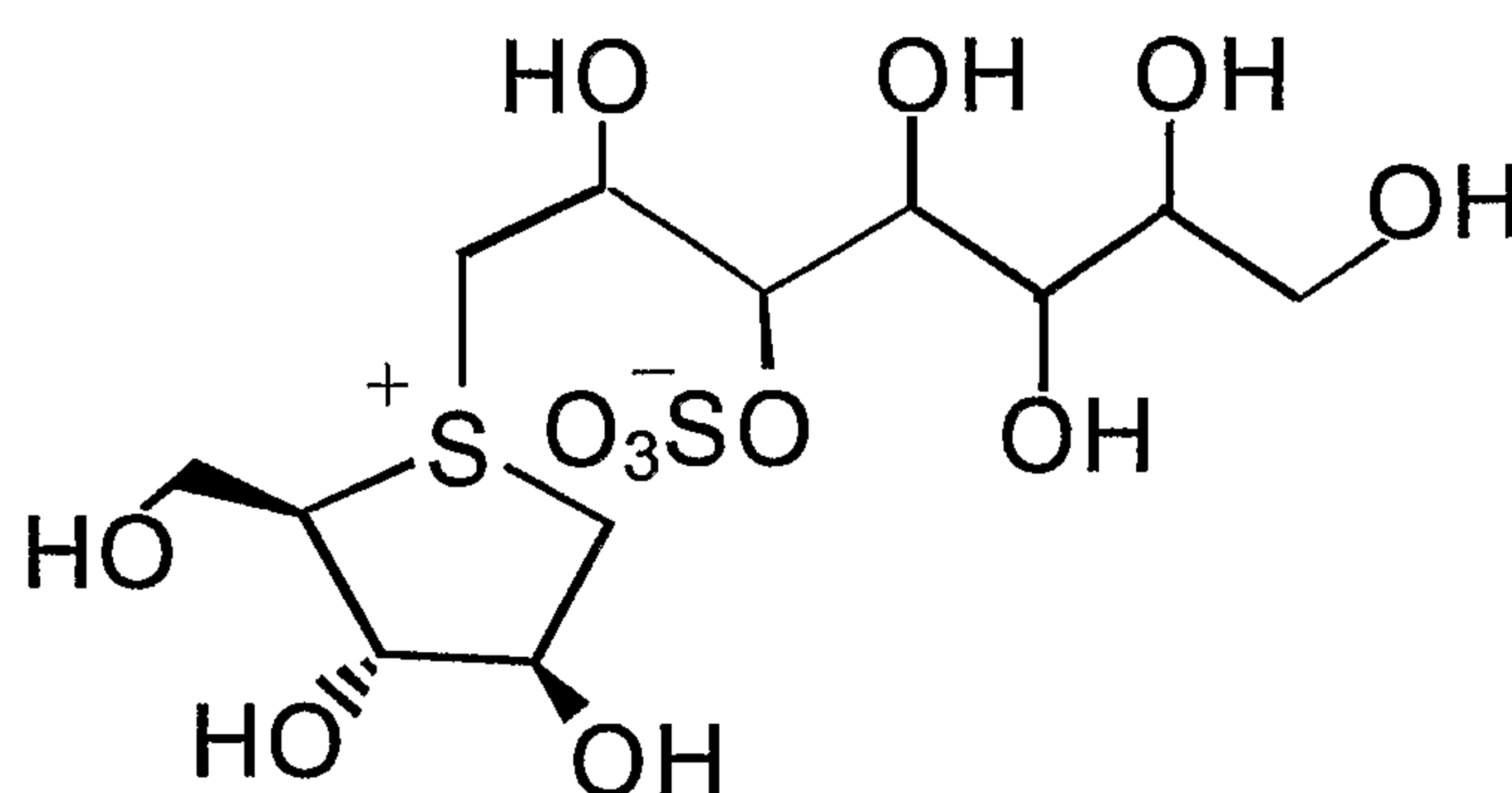
 Some naturally-occurring glucosidase inhibitors have been isolated from *Salacia reticulata*, a plant native to submontane forests in Sri Lanka and parts of
30 India (known as “Kotala himbutu” in Singhalese). *Salacia reticulata* is a woody

climbing plant which has been used in the Ayurvedic system of Indian medicine in the treatment of diabetes. Traditionally, Ayurvedic medicine advised that a person suffering from diabetes should drink water left overnight in a mug carved from Kotala himbutu wood. In an article published in 1997, Yoshikawa et al. reported the isolation of the compound Salacinol from a water-soluble fraction derived from the dried roots and stems of *Salacia reticulata*.¹ Yoshikawa et al. determined the structure of Salacinol, shown below, and demonstrated its efficacy as an α -glucosidase inhibitor.



Salacinol
(C₉H₁₈O₉S₂)

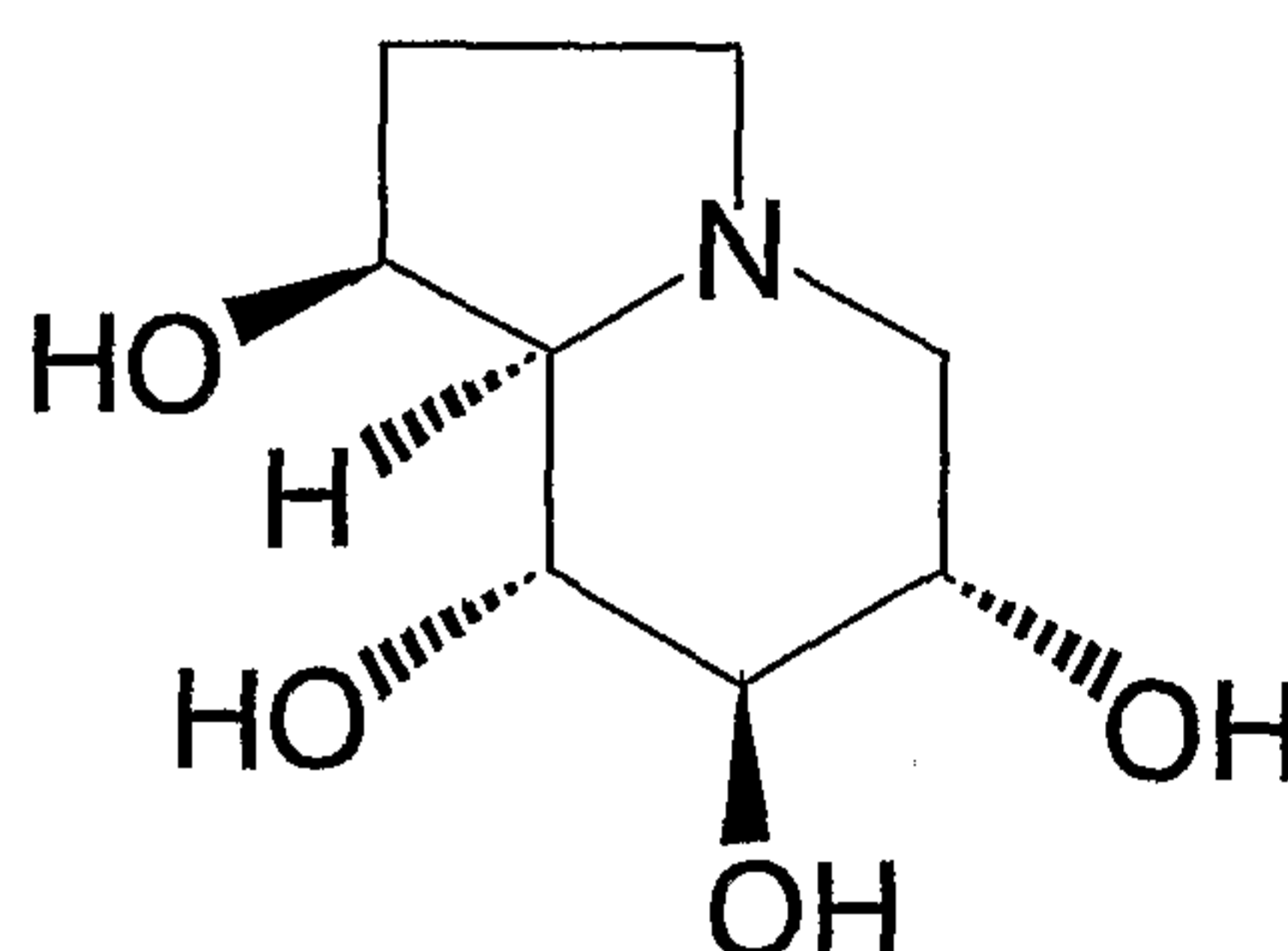
Yoshikawa et al. later reported the isolation from the roots and stems of *Salacia reticulata* of Kotalanol which was also shown to be effective as an α -glucosidase inhibitor.² Like Salicinol, Kotalanol contains a thiosugar sulfonium ion and an internal sulfate providing the counterion:



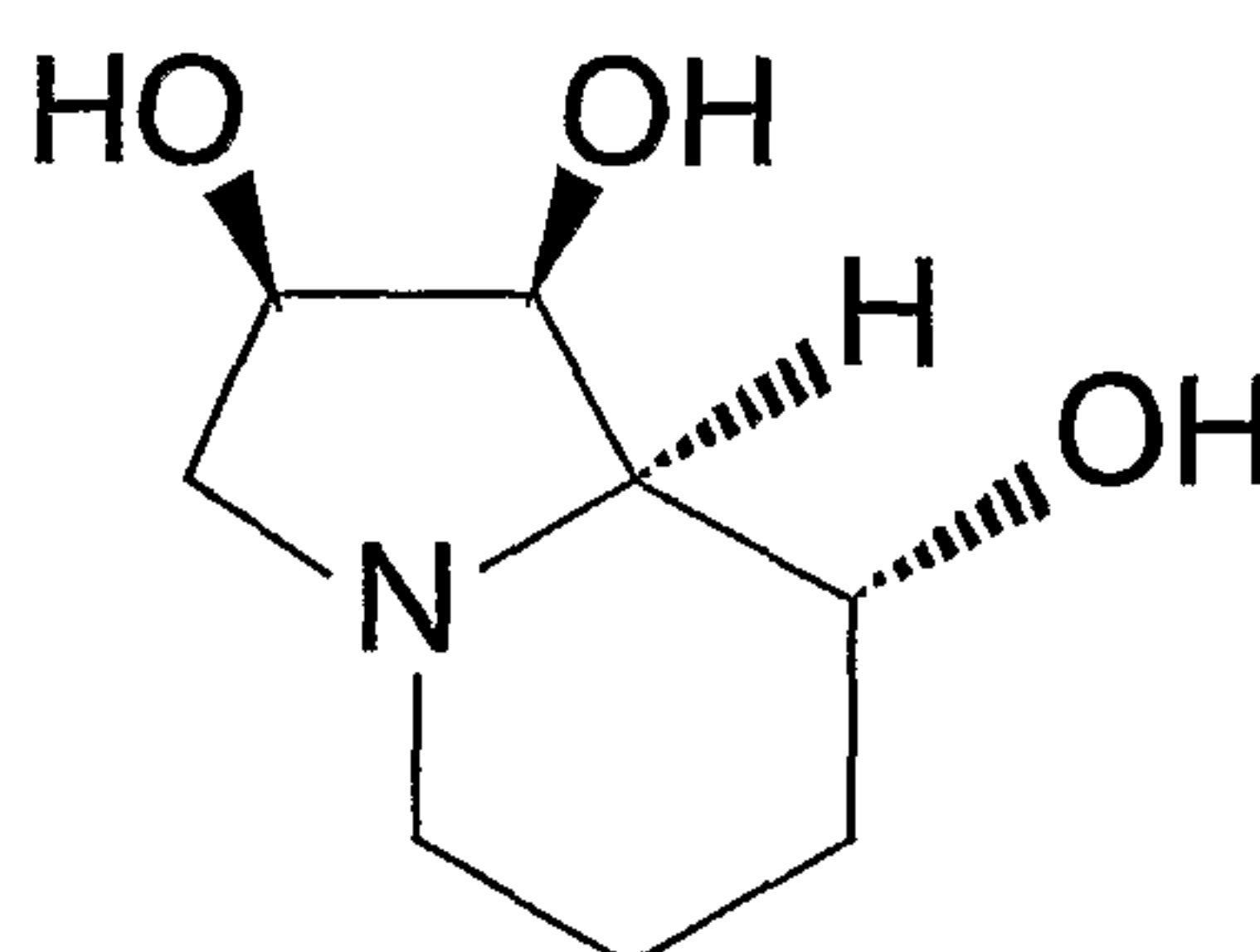
Kotalanol
(C₁₂H₂₄O₁₂S₂)

Kotalanol has been found to show more potent inhibitory activity against sucrase than Salicinol and Acarbose.²

The exact mechanism of action of Salacinol and other glucosidase inhibitors has not yet been elucidated. Some known glycosidase inhibitors, such as the indolizidine alkaloids castanospermine and swainsonine, are known to carry a positive charge at physiological pH.



Castanospermine



Swainsonine

It is believed that the mechanism of action of some known inhibitors may be at least partially explained by the establishment of stabilizing electrostatic interactions between the inhibitor and the enzyme active site carboxylate residues. It is postulated that the compounds of the present invention, which comprise positively charged sulfonium, ammonium, and selenonium ions, could function in a similar manner. It is also possible that Salacinol and other compounds of the same class may act by alteration of a transport mechanism across the intestinal wall rather than by directly binding to glucosidase enzymes.

Salacinol and Kotalanol may potentially have fewer long-term side effects than other existing oral antidiabetic agents. For example, oral administration of Acarbose in the treatment of Type II diabetes results in undesirable gastrointestinal side effects in some patients, most notably increased flatulence, diarrhoea and abdominal pain. As mentioned above, Salacinol has been used as a therapy for diabetes in the Ayurvedic system of traditional medicine for many years with no notable side effects reported. Further, recent animal studies have shown that the oral ingestion of an extractive from a *Salacia reticulata* trunk at a dose of 5,000 mg/kg had no serious acute toxicity or mutagenicity in rats.³

The *Salacia reticulata* plant is, however, in relatively small supply and is not readily available outside of Sri Lanka and India. Accordingly, it would be desirable if Salicinol, Kotalanol and analogues thereof could be produced synthetically.

Carbohydrate processing inhibitors have also been shown to be effective in the treatment of some non-diabetic disorders, such as cancer. While normal cells display characteristic oligosaccharide structures, tumor cells display very complex structures that are usually found in embryonic tissues. It is believed that these complex structures provide signal stimuli for rapid proliferation and metastasis of tumor cells. A possible strategy for therapeutic use of glucosidase inhibitors is to take advantage of the differential rates of normal vs cancer cell growth to inhibit assembly of complex oligosaccharide structures. For example, the indolizidine alkaloid swainsonine, an inhibitor of Golgi α -mannosidase II, reportedly reduces tumor cell metastasis, enhances cellular immune responses, and reduces tumor cell growth in mice.⁴ Swainsonine treatment has led to significant reduction of tumor mass in human patients with advanced malignancies, and is a promising drug therapy for patients suffering from breast, liver, lung and other malignancies.^{5,6}

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The compounds of the present invention may also find application in the treatment of Alzheimer's disease due to their stable, internal salt structure. Alzheimer's is characterized by plaque formation in the brain caused by aggregation

of a peptide, β -amyloid, into fibrils. This is toxic to neuronal cells. One can inhibit this aggregation by using detergent-like molecules. It is believed that the compounds of the present invention, which are amphipathic, may demonstrate this activity.

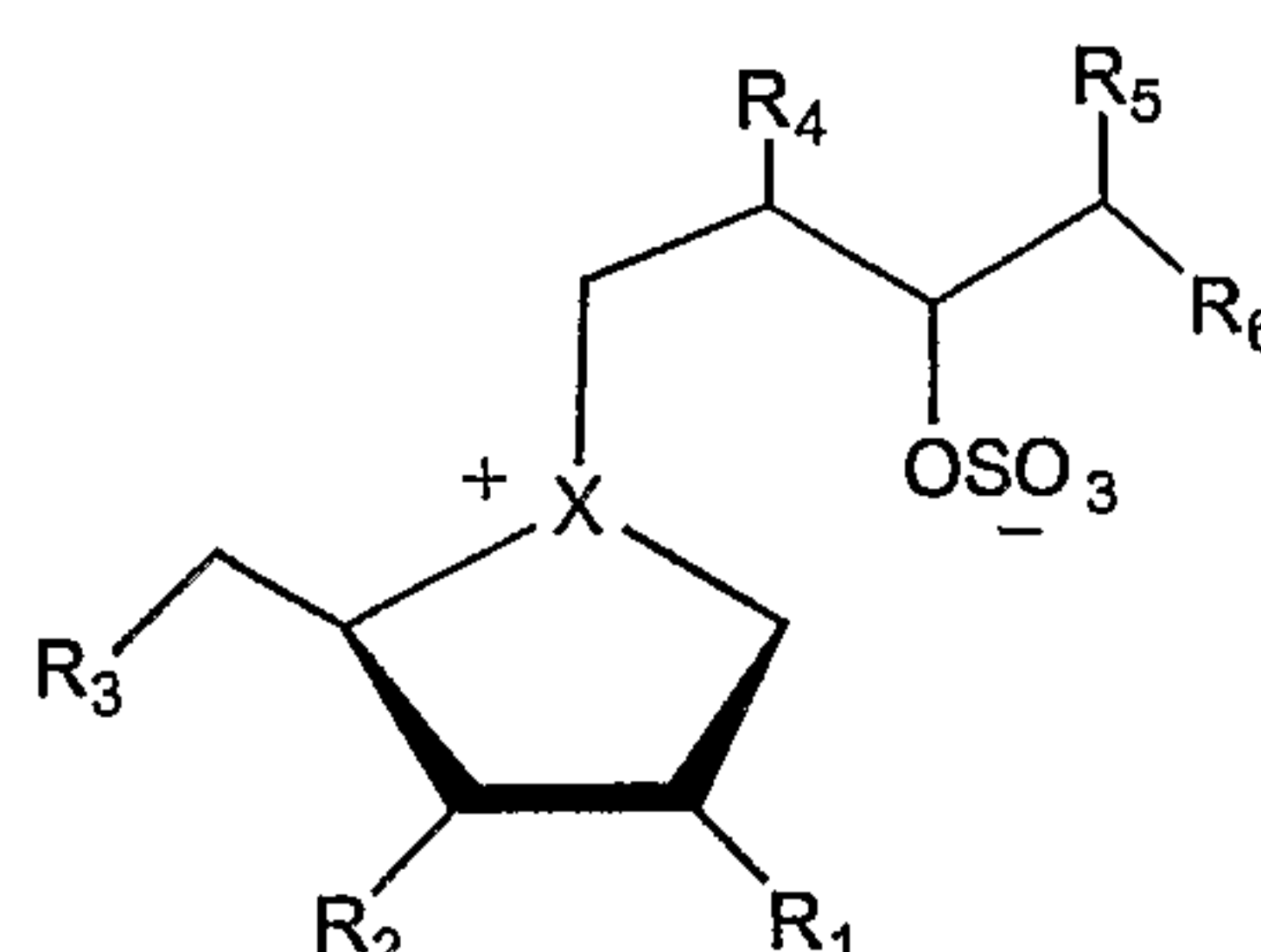
5 The need has therefore arisen for a new class of glycosidase inhibitors which may be synthesized in high yields from readily available starting materials and which have potential use as therapeutics.

Summary of the Invention

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In accordance with the invention, a compound selected from the group consisting of non-naturally occurring compounds represented by the general formula (I), including stereoisomers and pharmaceutically acceptable salts thereof is disclosed,

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(I)

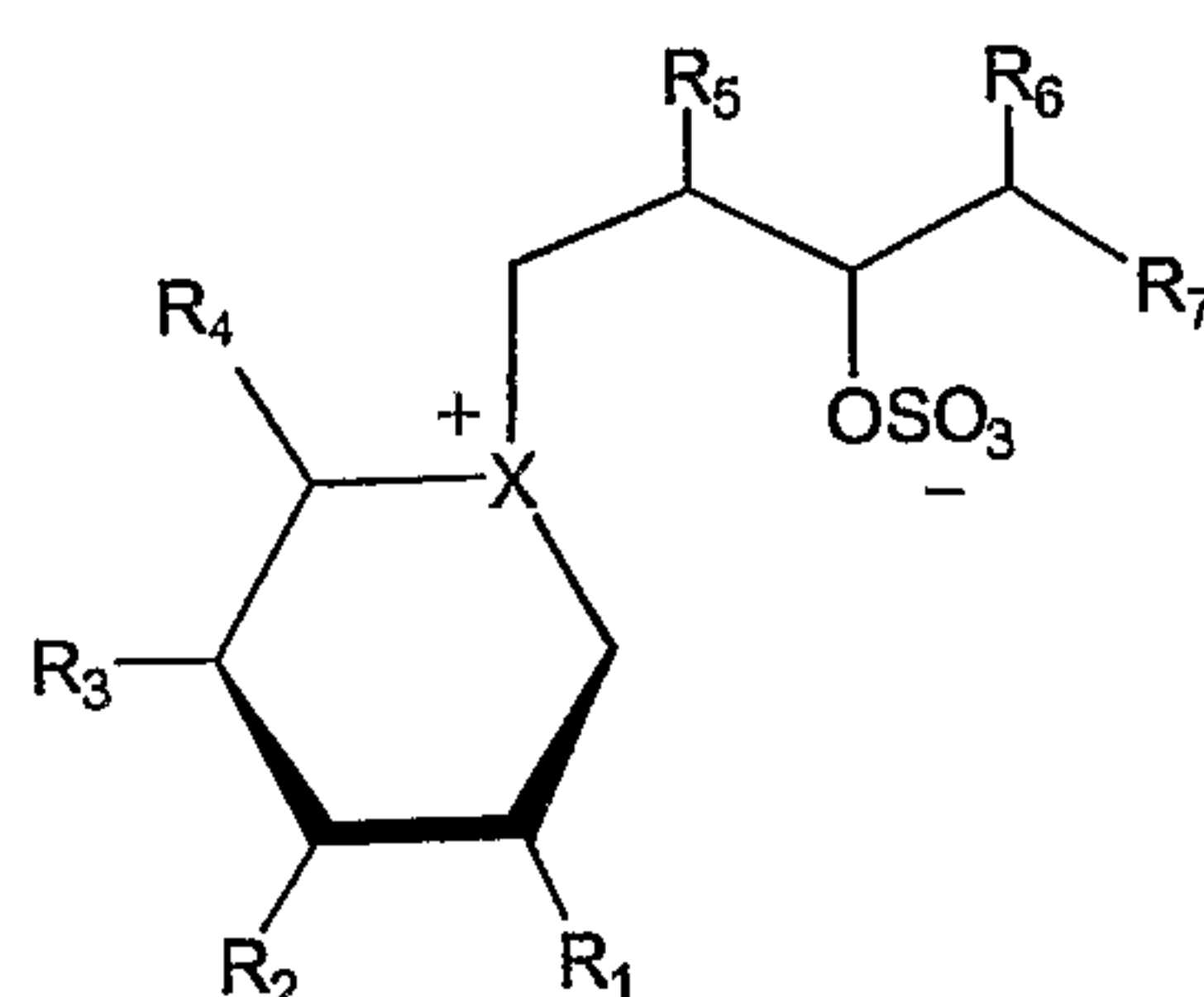
where X is selected from the group consisting of S, Se, and NH. Such compounds include stereoisomers of Salicinol. The target compounds have a stable, internal salt structure comprising heteroatom cation X and a sulfate anion; the substituents may vary without departing from the invention. Preferably, R₁, R₂, R₃, R₄ and R₅ are the same or different and are selected from the group consisting of H, OH, SH, NH₂, halogens and constituents of compounds selected from the group consisting of cyclopropanes, epoxides, aziridines and episulfides; and R₆ is selected from the group consisting of H and optionally substituted straight chain, branched, or cyclic, saturated or unsaturated hydrocarbon radicals, such as alkyl, alkenyl, alkynyl, aryl, and alkoxy substituents containing any suitable functionality. In one embodiment of the

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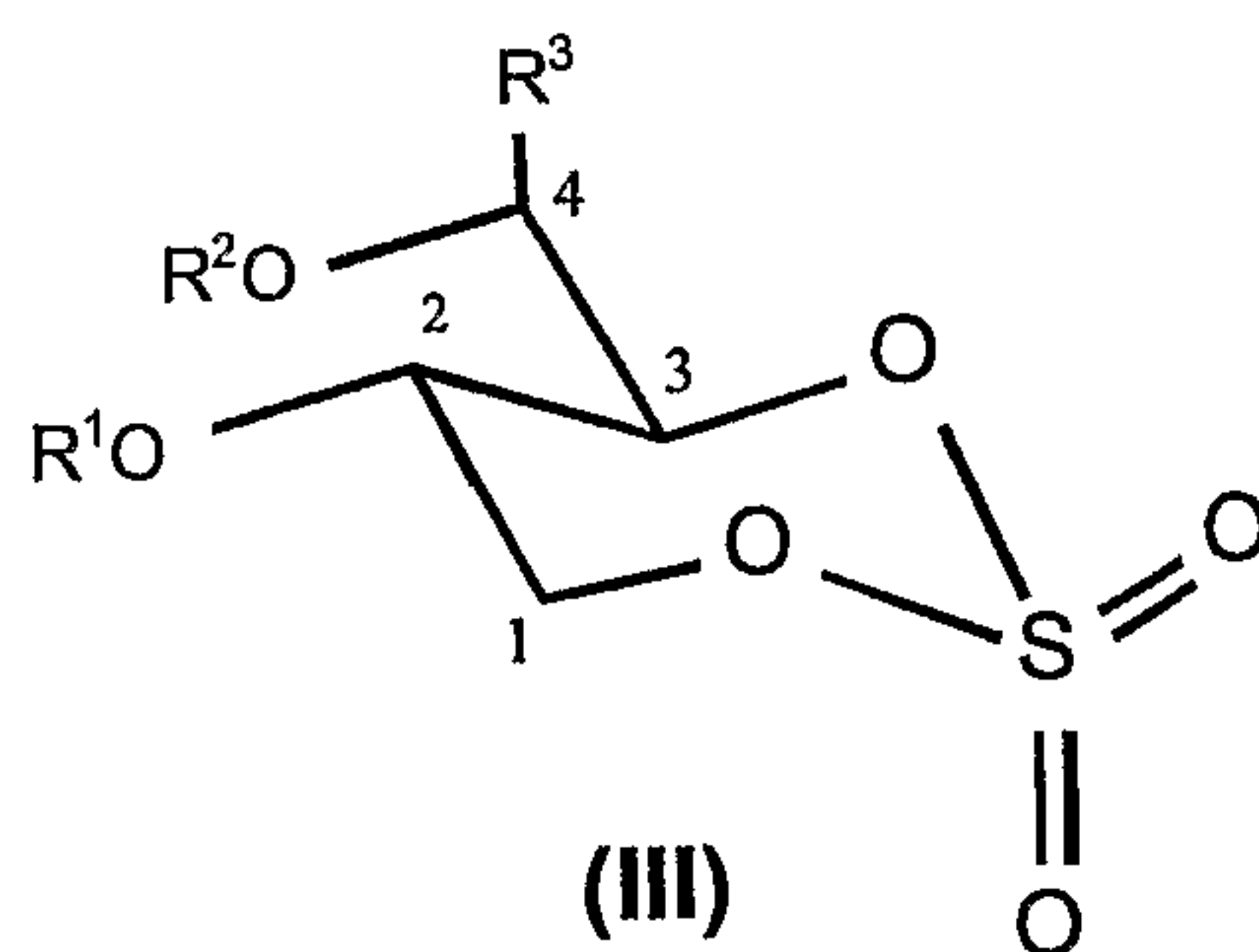
invention R_6 may be a polyhydroxylated, acyclic chain, such as an alditol chain of between 5 and 10 carbons.

In another embodiment of the invention, the heterocycle ring may
 5 comprise 6 rather 5 carbons and the compound may be represented by the general formula (II):

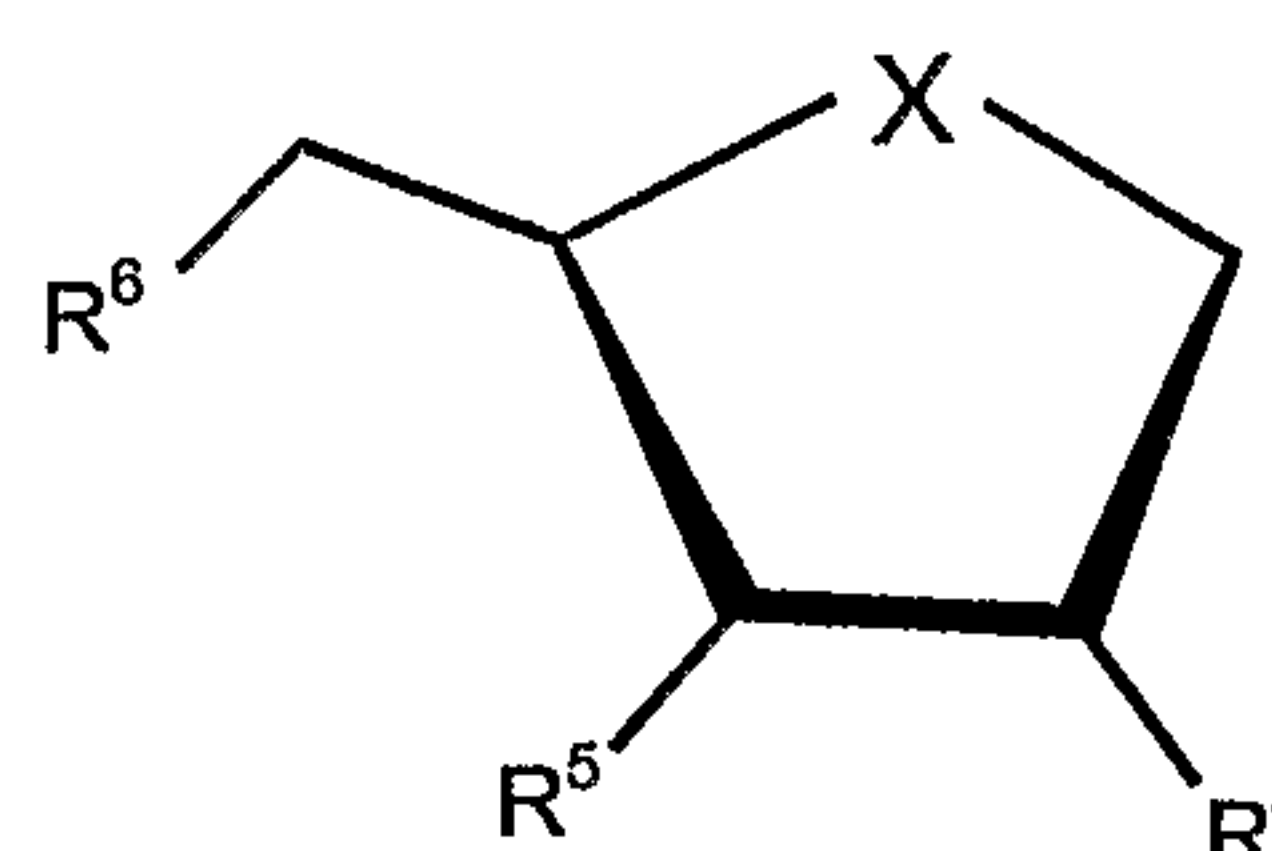


(II)

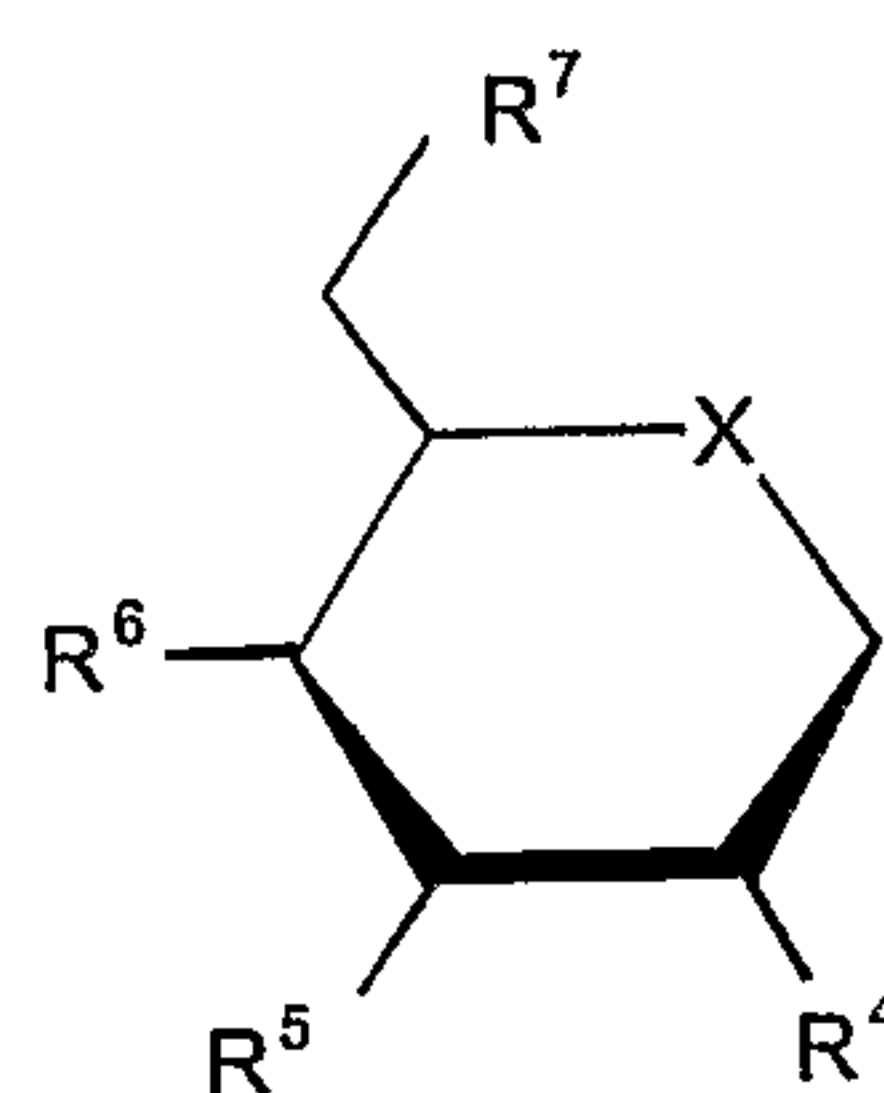
Processes for the production of compounds of the general formula (I)
 and (II) are also disclosed comprising reacting a cyclic sulfate having the general
 15 formula (III) with a 5-membered ring sugar having the general formula (IV) or (V)



(III)



(IV)



(V)

where X is selected from the group consisting of S, Se, and NH; R¹ and R² are selected from the group consisting of H and a protecting group; R³ is selected from the group consisting of H and optionally substituted straight chain, branched, or cyclic, saturated or unsaturated hydrocarbon radicals and their protected derivatives; and R⁴, R⁵ and R⁶ are the same or different and are selected from the group consisting of H, OH, SH, NH₂, halogens and constituents of compounds selected from the group consisting of cyclopropanes, epoxides, aziridines and episulfides and their protected derivatives. Preferably the cyclic sulfate is a 2,4-di-O-protected-D-or L-erythritol-1,3-cyclic sulfate, such as 2,4-O-Benzylidene-D-or L-erythritol-1,3-cyclic sulfate (i.e. R¹ and R² comprise a benzylidene protecting group); R³ is H or a protected polyhydroxylated alkyl chain; and R⁴, R⁵ and R⁶ are selected from the group consisting of OH and a protected OH group, such as OCH₂C₆H₅ or OCH₂C₆H₄OCH₃. The synthetic processes comprise the step of opening the cyclic sulfate (III) by nucleophilic attack of the heteroatom X on the sugar (IV) or (V).

15

The processes for the production of the target compounds may include the use of novel protecting and deprotecting agents, such as *p*-methoxybenzyl, and solvents, such as hexafluoroisopropanol.

20

The application also relates to the use of a compound according to formula (I) or (II) as a glycosidase inhibitor, and to pharmaceutical compositions comprising an effective amount of a compound according to formula (I) or (II), or combinations thereof, together with a pharmaceutically acceptable carrier, and to methods of treating carbohydrate metabolic disorders, such as non-insulin dependent diabetes by administering to a subject in need of such treatment an effective amount of such compounds.

25

Brief Description of the Drawings

In drawings which are intended to illustrate embodiments of the invention and which are not intended to limit the scope of the invention:

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Fig. 1 depicts one dimensional transient NOE difference spectra of compound *S-68b* in D₂O. (a) ¹H NMR spectrum. (b) Spectrum with selective irradiation of the H-

4'b/H-1'a multiplet. (c) Spectrum with selective irradiation of the H-1ax/H-5ax multiplet.

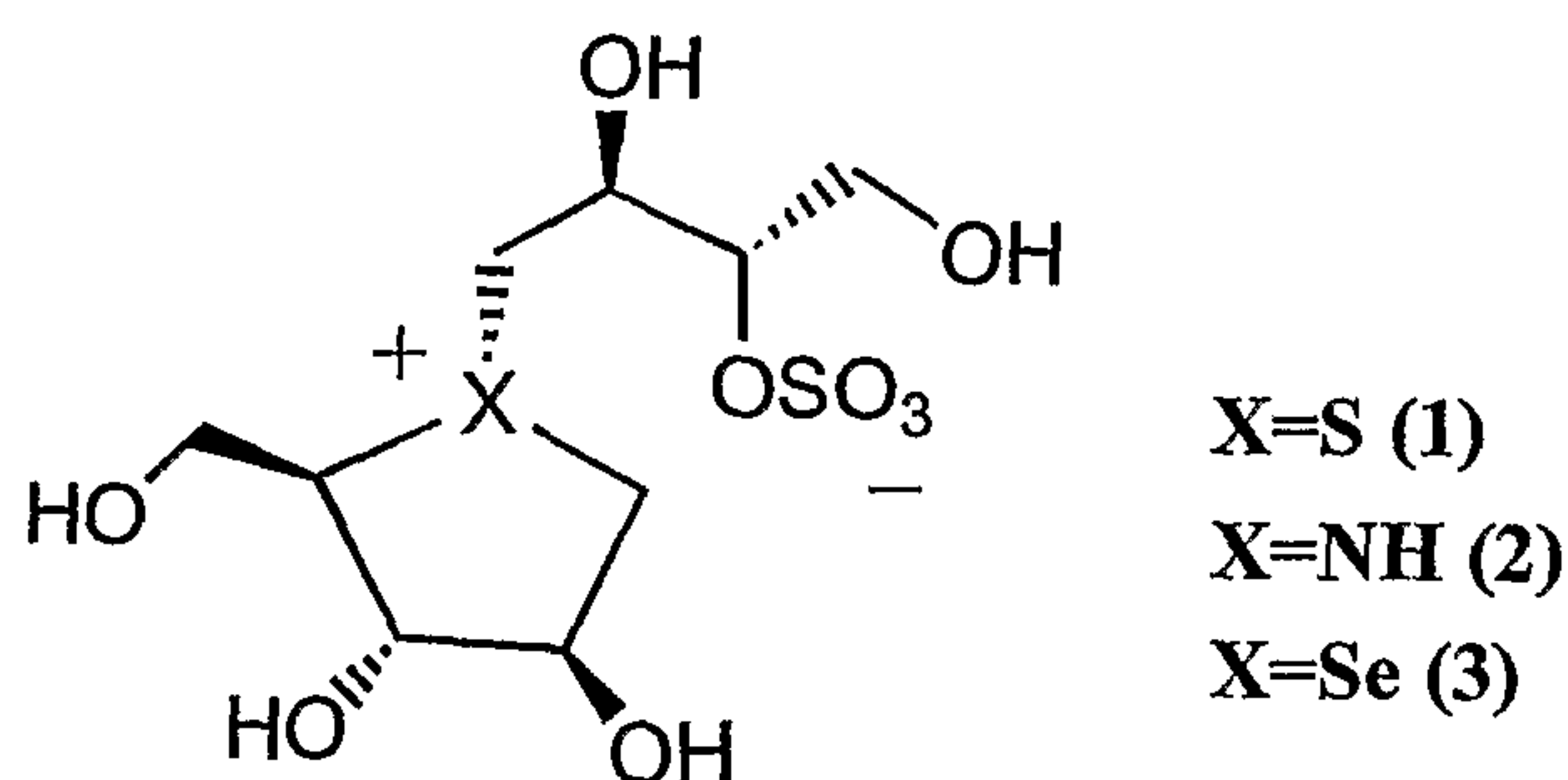
Fig. 2 depicts one dimensional transient NOE difference spectra of compound R-68b in D₂O. (a) ¹H NMR spectrum. (b) Spectrum with selective irradiation of the H-4'b/H-1'b multiplet. (c) Spectrum with selective irradiation of the H-1ax/H-5ax multiplet.

Fig. 3 depicts mean plasma glucose concentrations in rats after treatment with Acarbose, Blintol, and Salacinol. Panel a): Mean plasma glucose time course following a gavage of 1000 mg/kg body weight maltose without drug (Control: ○), or with 25 mg/kg of drug (Blintol: ●, Acarbose: ■, Salacinol: □) n=6 per group, ± standard error. The time zero (basal) sample for each animal was calculated as the mean of the -5 and -15 minute samples. Panel b): Mean Area Under the Curve of the glucose excursion above basal, 0-90 minutes (*: P<0.005, #: P<0.05 versus Control).

Fig.4 depicts mean plasma insulin concentrations in rats after treatment with Acarbose, Blintol, and Salacinol. Panel a): Mean plasma insulin concentration (Control: ○, Blintol: ●, Acarbose: ■, Salacinol: □) n=6 per group, ± standard error. Panel b): Mean Area Under the Curve of the glucose absorption rate (*: P<0.01 versus Control).

Detailed Description of the Invention

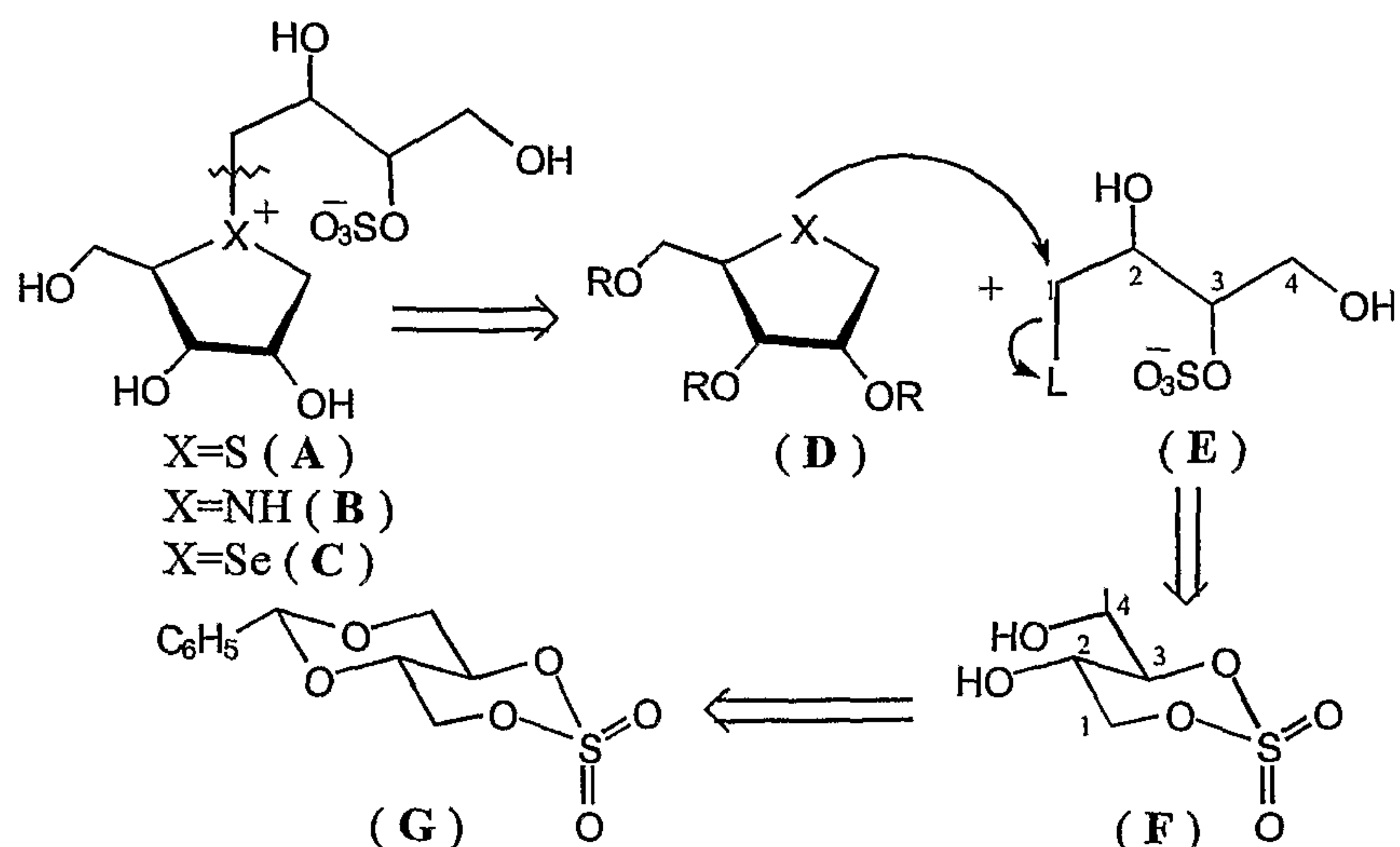
Salacinol is a naturally occurring compound which may be extracted from the roots and stems of *Salacia reticulata*, a plant native to Sri Lanka and India. This application relates to synthetic routes for preparing Salacinol (1), and its nitrogen (2) and selenium (3) analogues shown below.



This application also relates to synthetic routes for preparing compounds (1) to (3) and stereoisomers, analogues, homologues and other derivative thereof. As used in this patent application, stereoisomers includes enantiomers and diastereoisomers. The compounds of the invention (including stereoisomers of Salacinol) comprise a new class of compounds which are not naturally occurring and may find use as glycosidase inhibitors.

1.0 Summary of General Synthetic Scheme

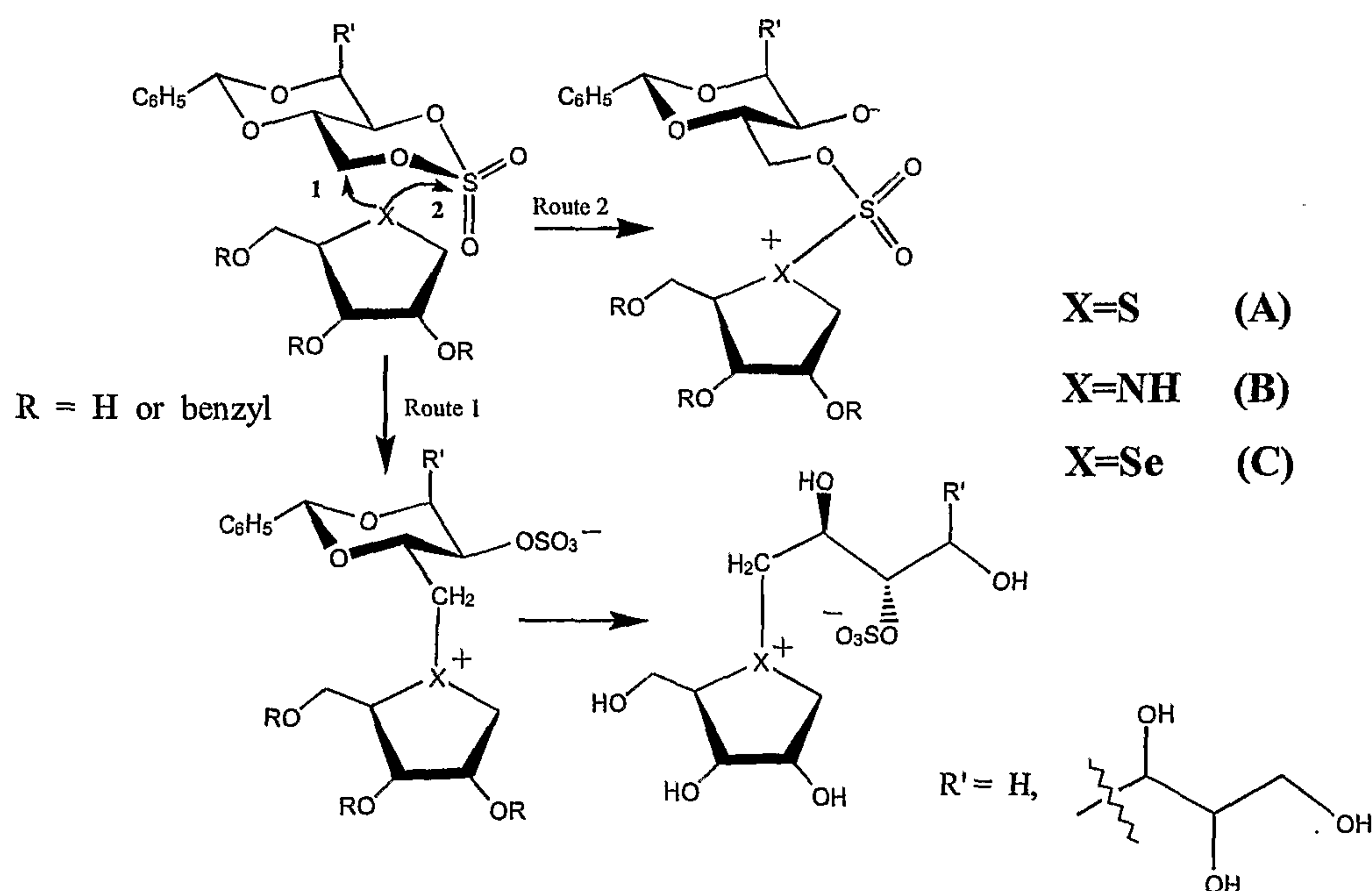
Scheme 1(a) below, shows the general synthetic scheme developed by the inventors for arriving at some of the target compounds. To synthesize different stereoisomers of Salacinol and its nitrogen and selenium analogues (A) - (C), 5-membered-ring sugars are reacted with sulfate-containing compounds in accordance with the invention (in Scheme 1(a) the letters (A), (B), and (C) represent all stereoisomers of Salacinol and its nitrogen and selenium analogues (1), (2) and (3) respectively). The inventors followed a disconnection approach for determining the preferred synthetic route. A reasonable disconnection is one that gives the 5-membered-ring sugars (D) since they can be synthesized easily from readily available carbohydrate precursors. Nucleophilic substitution at C₁ of the sulfate fragment (E) can then yield the target molecules (Scheme 1(a)). A potential problem with this approach is that the leaving group (L) might act later as a base to abstract the acidic hydrogens of the sulfonium salt⁷ and produce unwanted products. Therefore, the cyclic sulfate (F) may be used instead of (E) to obviate the problems associated with leaving group (L). Compound (G) may similarly be used as a cyclic sulfate reagent and is a protected version of (F).



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Scheme 1(a). Disconnection approach for the synthesis of (A) - (C) ($R=H$, $-CH_2C_6H_5$ and L = leaving group).

Scheme 1(b) below shows generally the coupling reactions for
 10 producing the target compounds (A) - (C).



Scheme 1(b). Typical coupling reaction for the synthesis of different stereoisomers (A) - (C)

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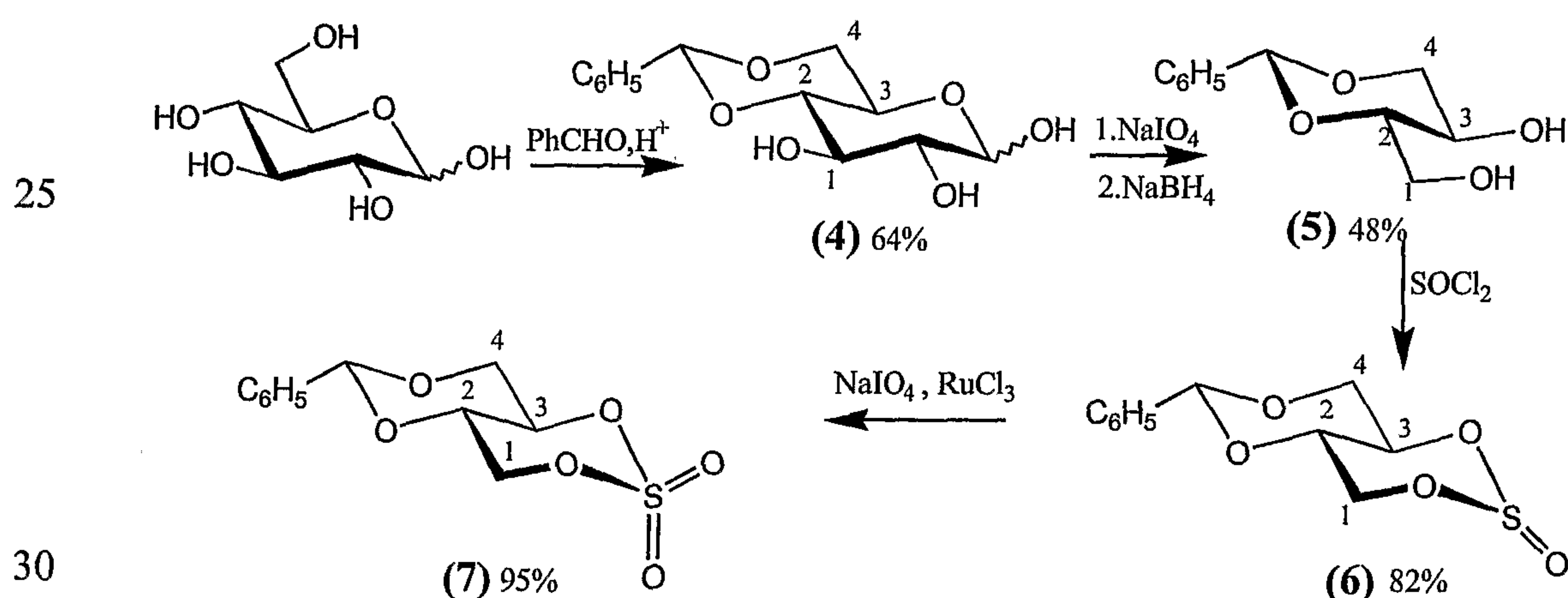
Route 1 of Scheme 1(b) shows the general strategy of reacting a cyclic sulfate with a 5-membered ring sugar to produce an intermediate compound, which may include benzyl or other protecting groups. As described in further detail below, the intermediate compound is then deprotected to yield the target compounds. The inventors have determined that Route 2 of Scheme 1(b), a possible side reaction, does not occur.

2.0 Synthesis of Reagents

Cyclic sulfates and 5-membered-ring sugars were prepared in accordance with the synthetic schemes described below. As will be apparent to a person skilled in the art, other equivalent schemes for producing the reagents of the invention could be substituted.

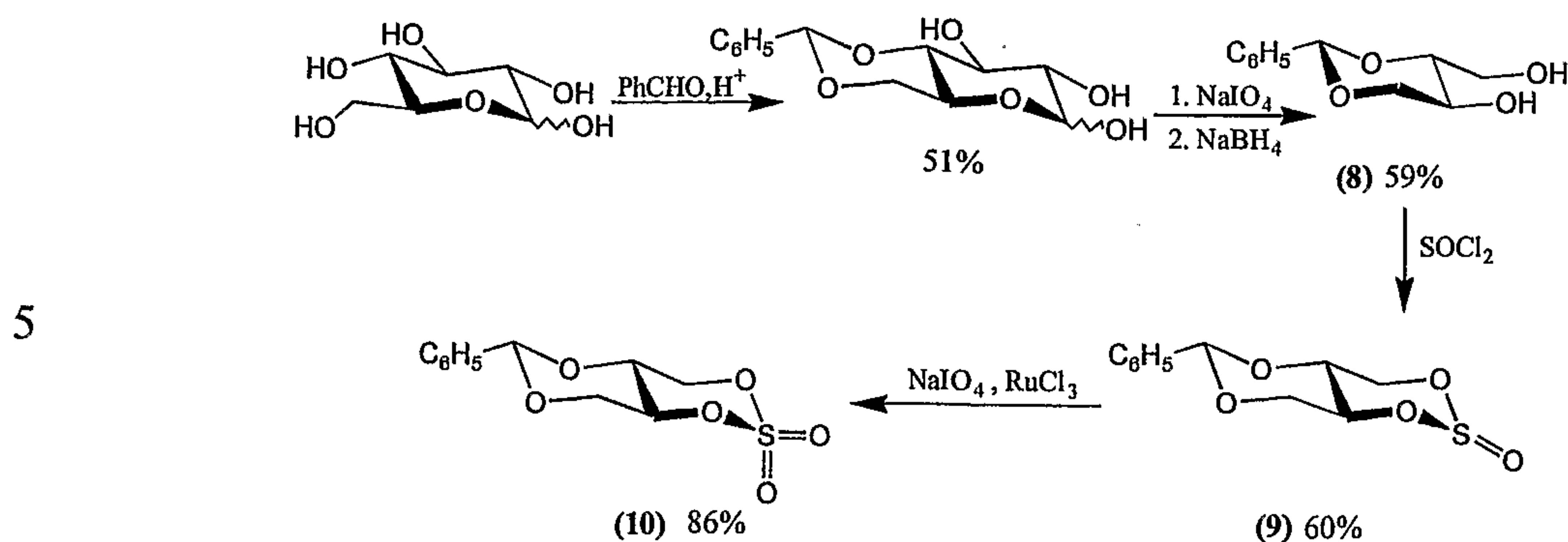
2.1 Cyclic sulfates

Cyclic sulfates were prepared in analogous fashion to the ethylidene acetal.⁸ The cyclic sulfate (7) was synthesized in 4 steps starting from D-glucose (Scheme 2). 2,4-O-Benzylidene-D-erythrithol (5) was synthesized from D-glucose in two steps,^{9,10} and then treated with thionyl chloride to yield the cyclic sulfite (6) which was oxidized to the cyclic sulfate (7) as described by Calvo-Flores et al.⁸



Scheme 2. Synthesis of the cyclic sulfate (7).

The enantiomer (10) was also synthesized using the same route but starting from L-glucose (Scheme 3).

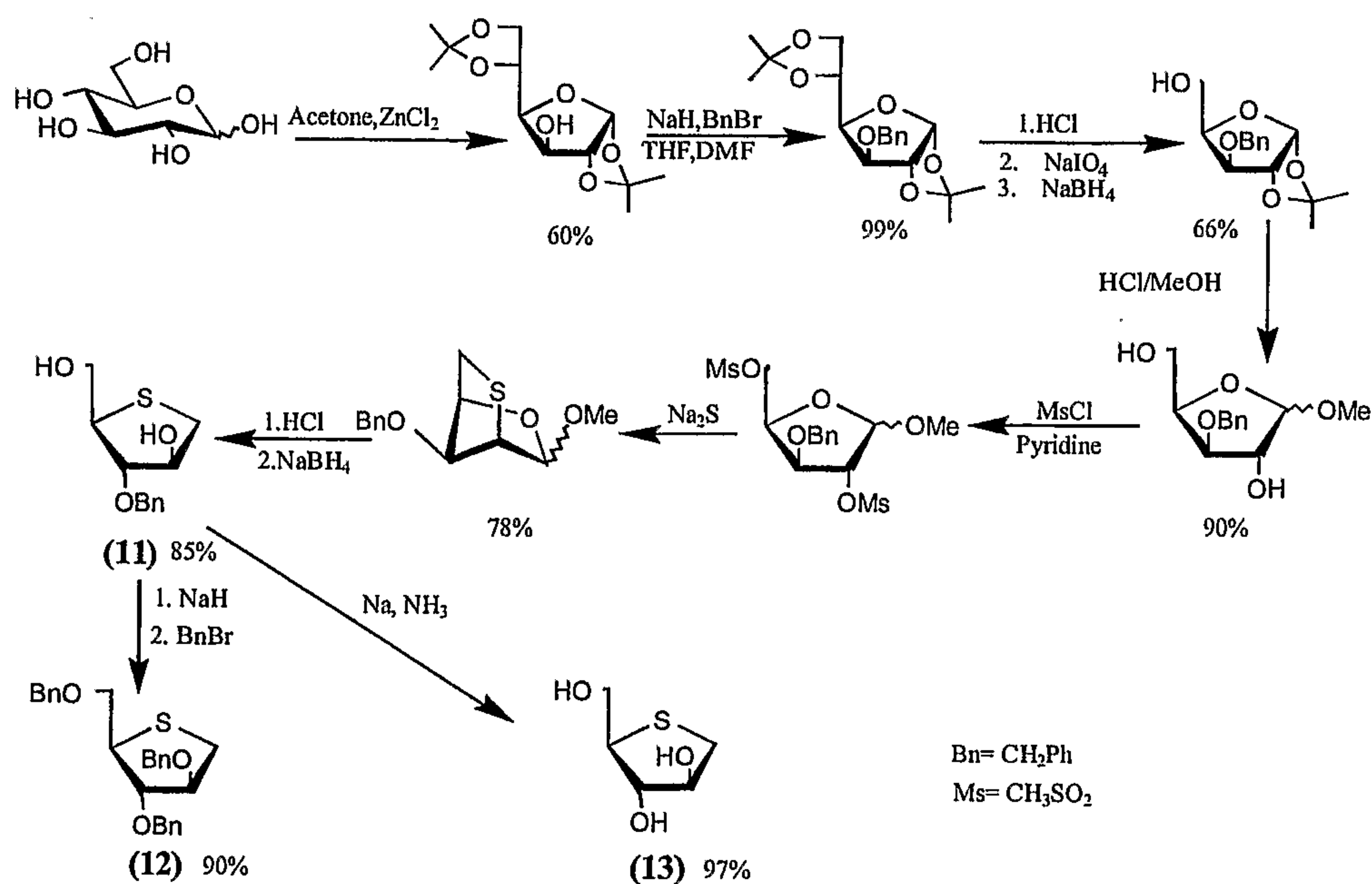


Scheme 3. Synthesis of the cyclic sulfate (10).

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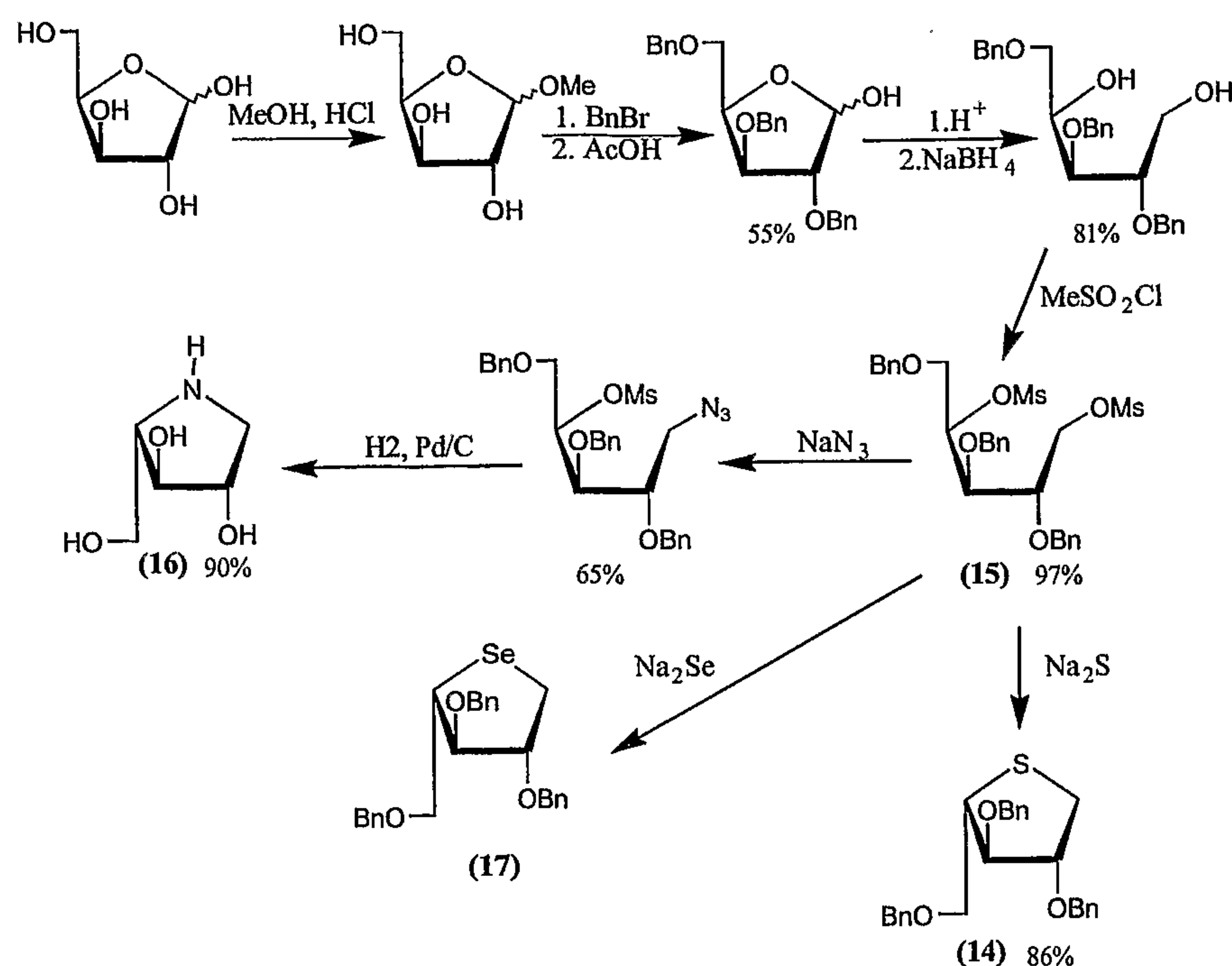
2.2 Synthesis of 5-Membered-ring Heterocycles

In order to synthesize one of the 5-membered-ring sugars (**D**, X=S), 1,4-anhydro-3-*O*-benzyl-4-thio-D-arabinitol (**11**), was synthesized in 9 steps starting from D-glucose (Scheme 4).¹¹ Benzylation of the compound (**11**), using benzyl bromide in DMF yielded 1,4-anhydro-2,3,5-tri-*O*-benzyl-4-thio-D-arabinitol (**12**) in 90% yield. Compound (**11**) was debenzylated to give 1,4-anhydro-4-thio-D-arabinitol (**13**) in 97% yield using a Birch reduction.



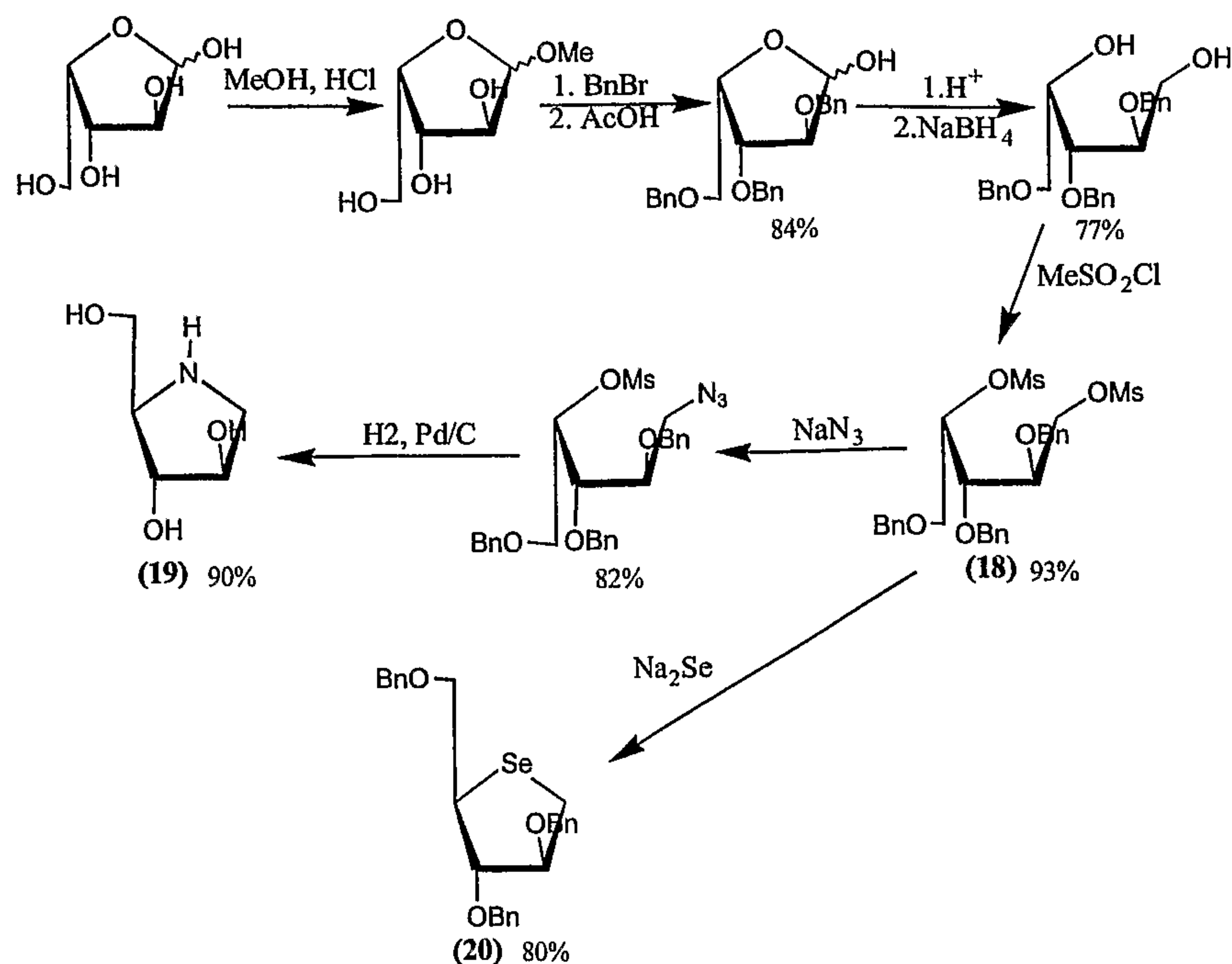
Scheme 4. Synthesis of compounds (**11**) - (**13**).

The L-isomer, 1,4-anhydro-2,3,5-tri-*O*-benzyl-4-thio-L-arabinitol (**14**) was synthesized in 5 steps starting from D-xylose (Scheme 5).¹²



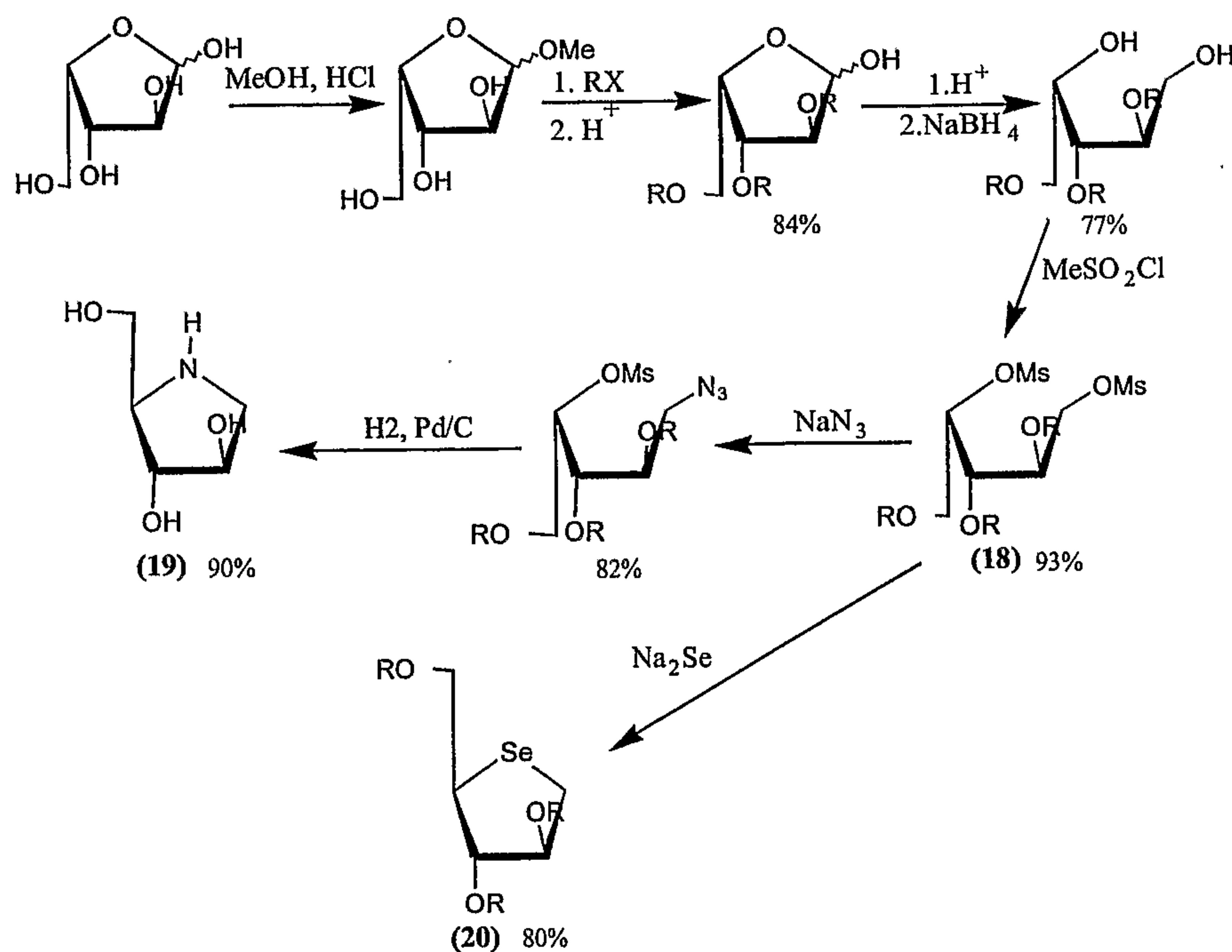
Scheme 5. Synthesis of compounds (14)-(17)

5 1,4-Di-*O*-methanesulfonyl-2,3,5-tri-*O*-benzyl-D-xylitol (15) is also a key intermediate for the synthesis of the aza and seleno sugars (16) and (17). 1,4-Dideoxy-1,4-imino-L-arabinitol (16)¹³ was synthesized in 7 steps starting from D-xylose (Scheme 5). The enantiomer (19)¹³ was synthesized in an analogous way starting from L-xylose (Scheme 6). Compound (19) was also synthesized in 10 steps starting from D-xylose.¹³ 1,4-Anhydro-2,3,5-tri-*O*-benzyl-4-seleno-D-arabinitol (20) was synthesized in 5 steps starting from L-xylose (Scheme 6). To synthesize compound (20), Na₂Se was made in-situ by treatment of selenium metal with sodium in liquid ammonia.



Scheme 6. Synthesis of compounds (19) and (20).

Scheme 6(a) below shows a more generalized scheme for synthesizing compound (20) using other possible protecting groups ($R = \text{COR}, \text{CH}_2\text{C}_6\text{H}_4\text{-OMe}_p$).



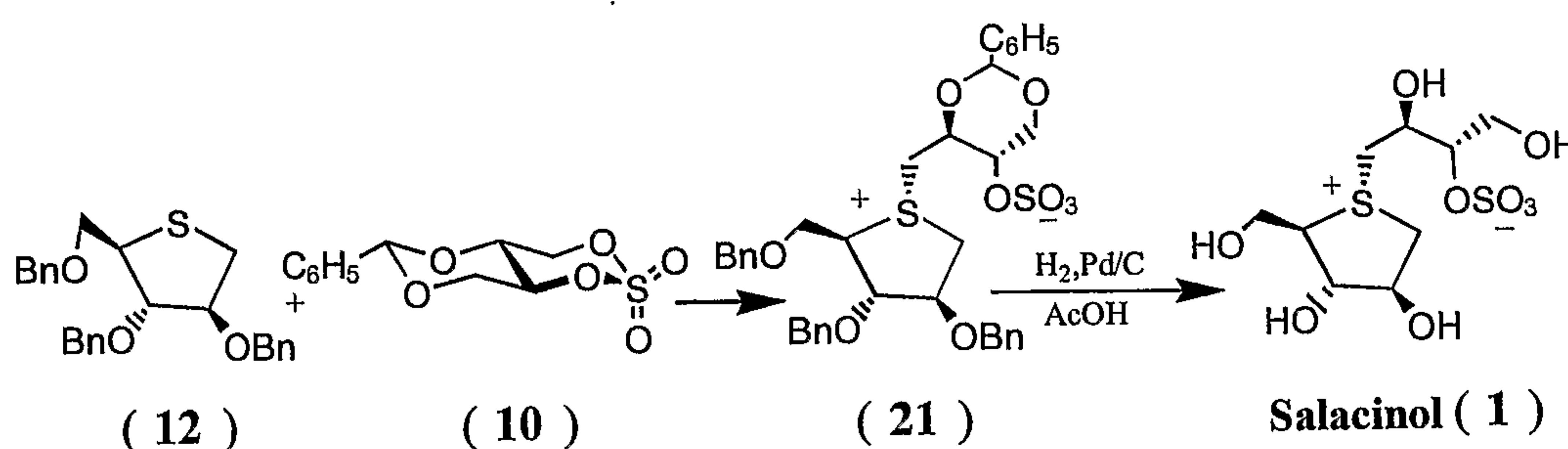
Scheme 6(a). Synthesis of compounds (19) and (20). ($R = \text{COR}, \text{CH}_2\text{C}_6\text{H}_4\text{-OMe}_p$).

3.0 Synthesis of Target Compounds (1) – (3)

The target compounds (1) – (3) were prepared by opening of the cyclic sulfates by nucleophilic attack of the heteroatoms on the 5-membered rings (Scheme 1(b) above). The heteroatom gives rise to a positively charged cation and the cyclic sulfate gives rise to a negatively charged counterion. This internal salt structure may explain the stability of the target compounds toward decomposition by further nucleophilic attack.

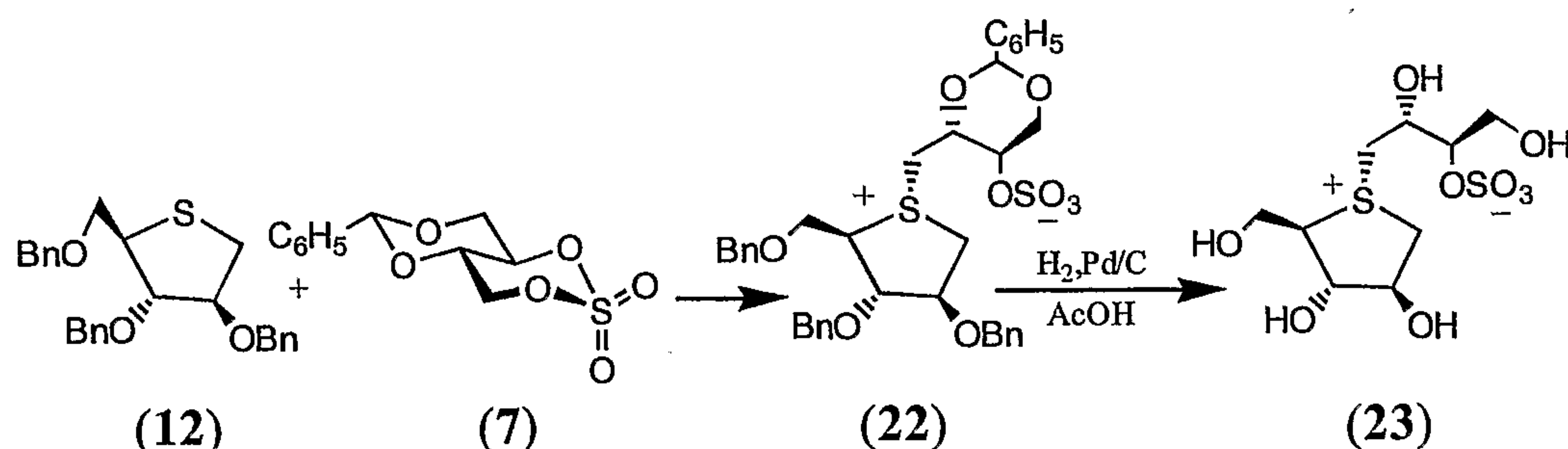
3.1 Synthesis of Salacinol

Salacinol (1) was synthesized by nucleophilic substitution of the protected thio-arabinitol (12) with the cyclic sulfate (10) (1.2 equiv) in dry acetone containing K_2CO_3 , to give the protected intermediate compound (21) in 33% yield. Hydrogenolysis of the benzyl and benzylidene groups in $AcOH:H_2O$, 4:1 afforded Salacinol (1) in 67% yield (Scheme 7).



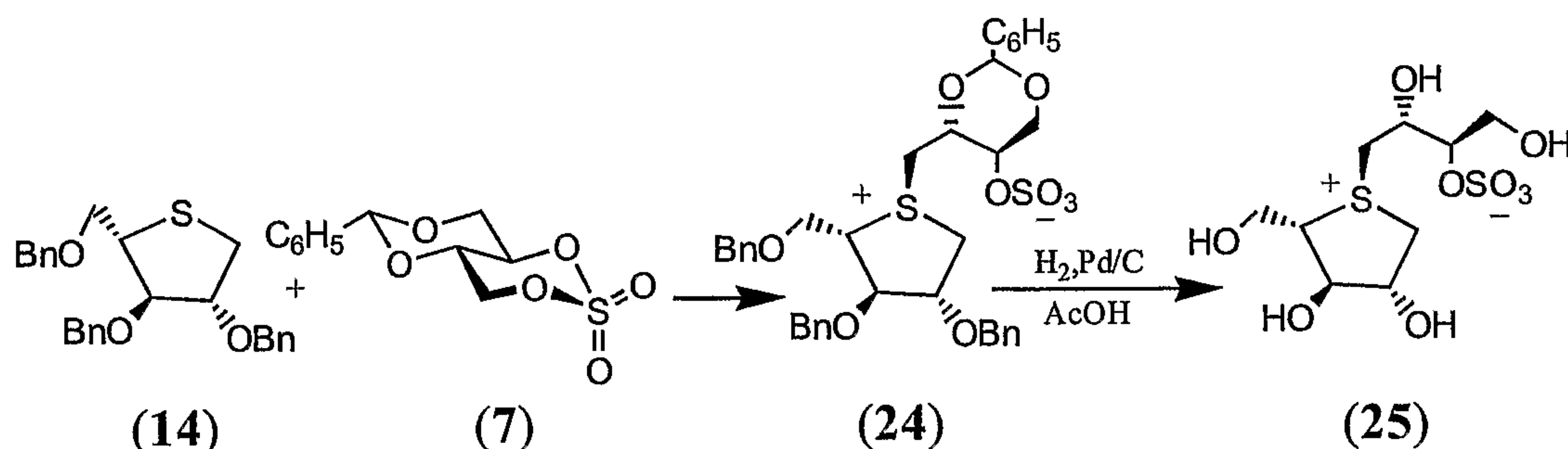
Scheme 7. Synthesis of Salacinol (1)

The same procedure was used to prepare intermediate compound (22) in 79% yield from the enantiomeric cyclic sulfate (7). Deprotection as before gave compound (23) in 59% yield (Scheme 8). Compound (23) is a diastereomer of Salacinol (1).



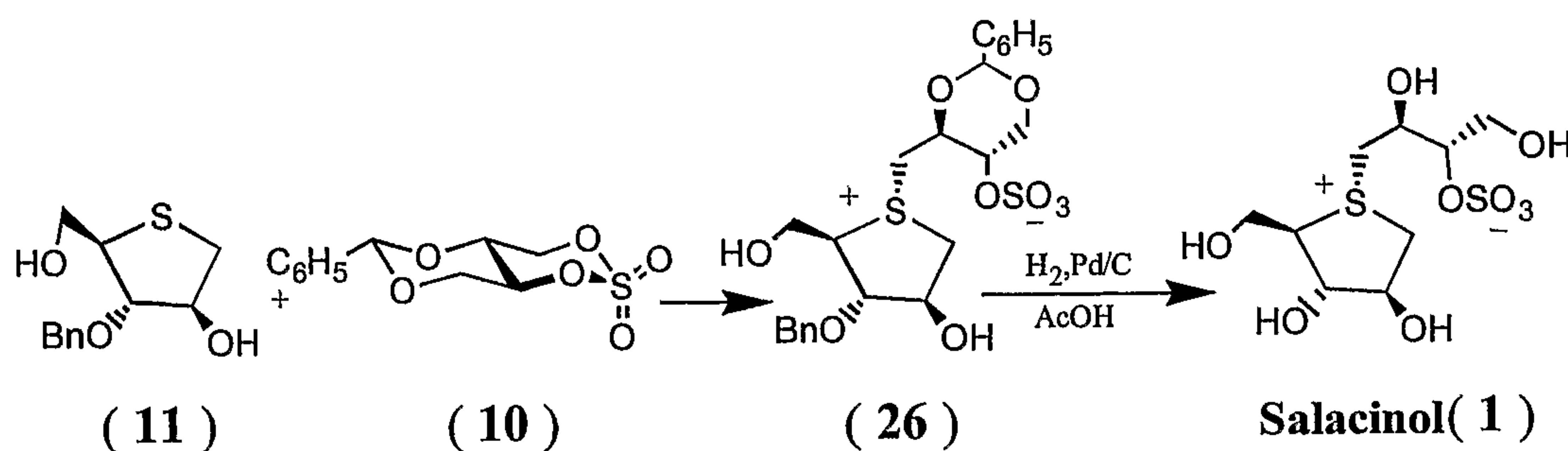
Scheme 8. Synthesis of compound (23)

Compound (24) was prepared in 40% yield from (7) and the enantiomeric thio-ether (14) (Scheme 9). Deprotection in 80% yield gave the enantiomer of Salacinol (25).



Scheme 9. Synthesis of compound (25)

To reduce the number of synthetic steps, the inventors attempted the coupling reactions with the deprotected thio-arabinitols. Thus, the partially deprotected compound (11) was reacted with the cyclic sulfate (10) in acetone, to give compound (26) in 32% yield. Deprotection yielded Salacinol (1) in 36% yield (Scheme 10).

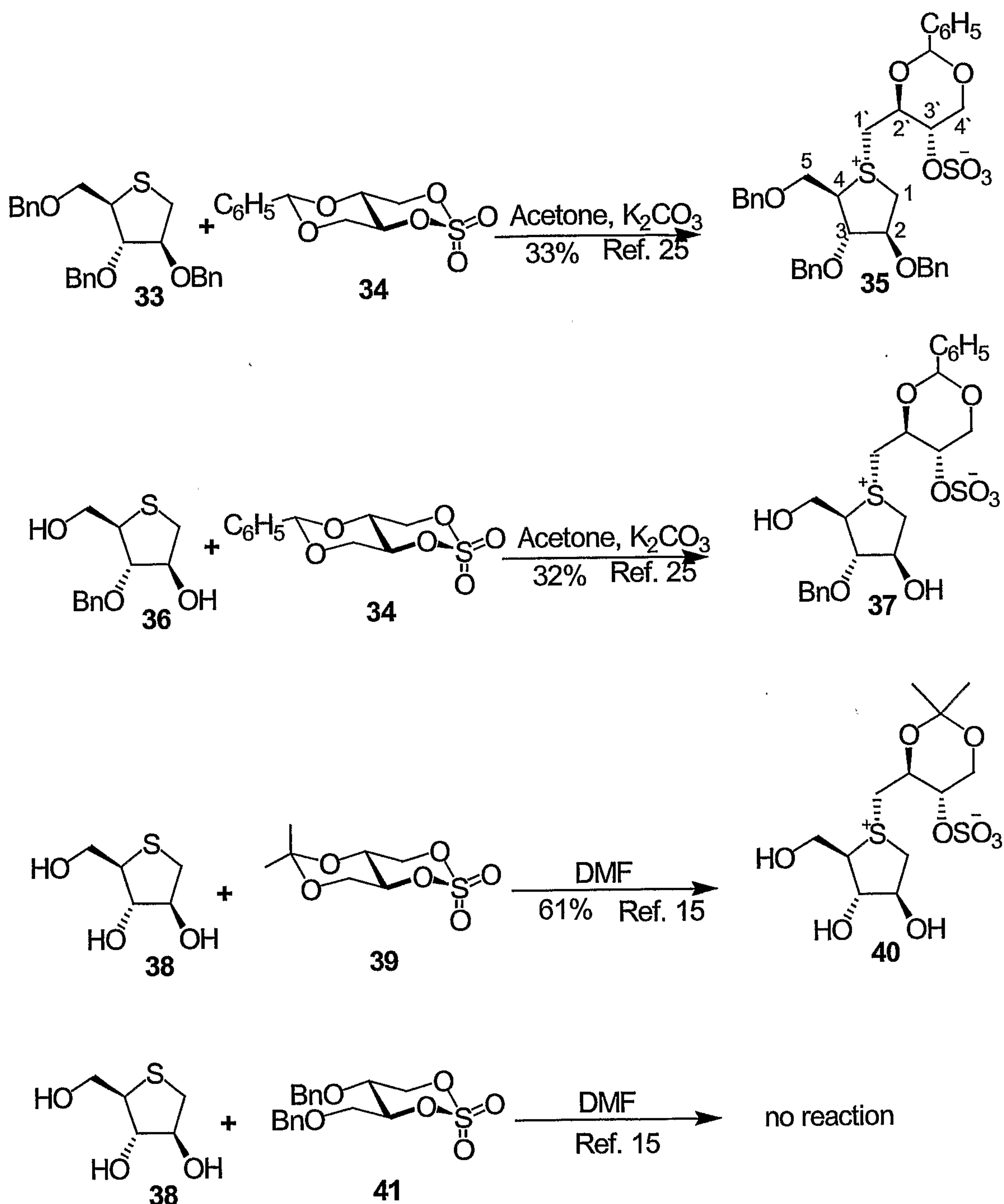


Scheme 10. Synthesis of Salacinol (1)

The fully-deprotected thio-arabinitol (**13**) was not soluble in acetone and the reaction in methanol produced several products.

5 3.1.1 Alternative Synthesis of Salacinol

As described above, a key step in the published syntheses of Salacinol (**1**)^{15,25} is the ring opening reaction of a cyclic sulfate by nucleophilic attack of the ring sulfur atom of 1,4-anhydro-4-thio-D-pentitol (**33**) (Scheme 10a). The alkylation reaction involving these reagents is dependent on the protecting groups on the cyclic sulfate. Thus, the unoptimized reaction of the per-benzylated thioether **33** with the benzylidene-protected cyclic sulfate **34** in acetone, containing potassium carbonate, proceeded in 33% yield (Scheme 10a).²⁵ A similar yield was obtained in the reaction with the monobenzylated thioether **36**.²⁵ Reaction of the unprotected thioether **38** with the isopropylidenated-cyclic sulfate **39** in DMF proceeded in 61% yield to give
10 **40**, although its reaction with the corresponding benzylated-cyclic sulfate **41** did not proceed.¹⁵ The latter derivative **41** is clearly a much less reactive alkylating agent than **39**. Significant decomposition of the cyclic sulfates **39** and **41** at temperatures of 60-70 °C in DMF was also observed.¹⁵ Deprotection of **40** proceeded in 75% yield to afford Salacinol **1** in 46% overall yield.¹⁵
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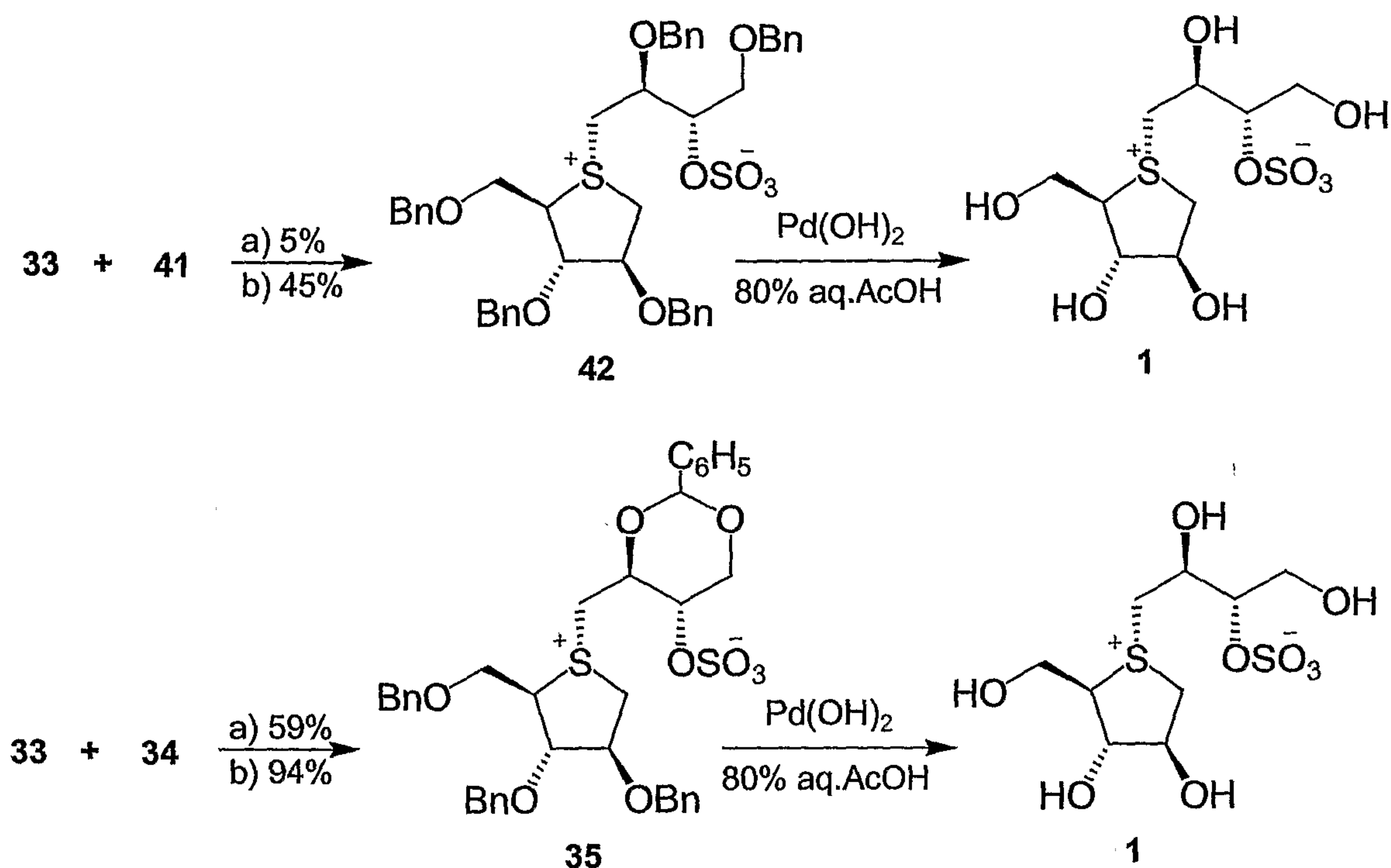


Scheme 10a

The biological importance of Salacinol (1)^{1,2,27} prompted the inventors to investigate a more efficient method for its synthesis. The Hughes-Ingold rules indicate that the S_N2 reaction between a neutral nucleophile, such as 33 or 36, and a neutral electrophile, such as 34, 39 or 41, should show a large increase in rate on increasing solvent polarity. 1,1,1,3,3,3-Hexafluoroisopropanol (HFIP) has a higher

normalized Dimroth-Reichardt solvent polarity parameter, $E_T^N = 1.068$, than water, $E_T^N = 1.00$. In contrast, the E_T^N values for acetone and DMF are only 0.355 and 0.404, respectively. Furthermore, HFIP, bp = 59 °C, is volatile, thus facilitating product purification. Preliminary studies indicated that tetrahydrothiophene reacted cleanly
5 with **34** and **41** in HFIP at 45 °C for 2 days to give the desired alkylation products in >90% yield.

Therefore, a systematic evaluation of the role of solvent in the alkylation reactions of **33** with benzyl- or benzyldiene-protected cyclic sulfates **41** or **34**, respectively was undertaken. The reactions were carried out in acetone and
10 hexafluoroisopropanol (HFIP) concurrently under identical conditions of concentration, temperature, and duration (Scheme 10b). Reaction of the thioether **33** (1 equiv) and the cyclic sulfate **41** (1.2 equiv) in acetone containing K_2CO_3 at 75-80 °C in a sealed tube proceeded very slowly and yielded the desired alkylated product **42** in only 5% yield; the remainder of the starting materials was recovered. Prolonged
15 heating and use of excess cyclic sulfate did not improve the yields. In addition, when excess cyclic sulfate **39** was used, its slow decomposition complicated the purification of the product **42** formed. However, the analogous reaction between **33** and the cyclic sulfate **41** in HFIP yielded the adduct **42** in 45% yield, with recovery of the unreacted starting materials (Scheme 10b). It is noteworthy that the analogous reaction between
20 **33** and the cyclic sulfate **41** in the polar, protic solvent 2-propanol at 83°C for 26 h did not yield any desired product, the starting materials being recovered. It would appear, therefore, that it is the highly polar nature of HFIP that is important in facilitating this reaction.



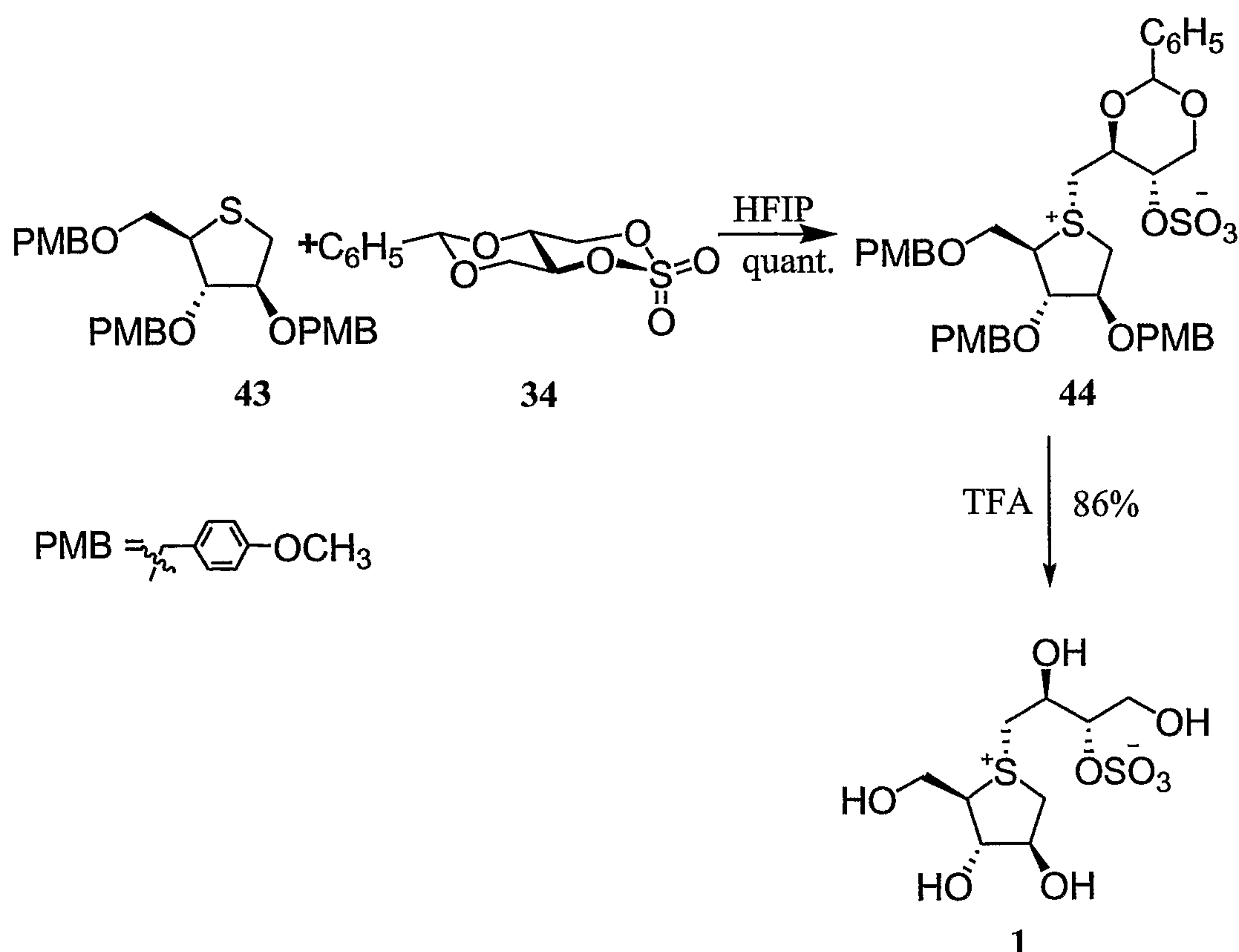
Scheme 10b

Some studies¹⁵ have indicated a far lesser reactivity of the benzylated cyclic sulfate relative to the cyclic sulfate containing an acetal protecting group (Scheme 10a). Thus, the reactions of the benzylidene-protected cyclic sulfate **34** in acetone and HFIP, containing potassium carbonate, under identical conditions of concentration, temperature, and duration were examined next (Scheme 10b). The alkylation reaction of **33** with **34** in acetone proceeded with a dramatic increase in the yield (59%) of the alkylated product **35** relative to the reaction with **41**. The improvement from the unoptimized yield of 33%²⁵ is due to the use of a more concentrated reaction mixture.

More significantly, the desired product **35** was obtained in 94% yield when the reaction was performed in HFIP. Higher temperatures (> 80 °C) and prolonged reaction times led to the decomposition of the cyclic sulfate, although the stability of the cyclic sulfate was greater in the presence of K_2CO_3 . The increased yields in HFIP may be accounted for by better solvation of the transition states for the reactions and of the adducts. The increased reactivity of the cyclic sulfate with the benzylidene protecting group (**34**) may be accounted for by the relief of ring strain accompanying the reaction, unlike in the corresponding reaction of the benzyl-

protected cyclic sulfate **41**. Finally, the reaction of the thioether **38** (not containing protecting groups) with the benzylidene-protected cyclic sulfate **34** in HFIP was examined. At 60 °C, decomposition of the cyclic sulfate was observed, with no significant formation of the desired coupled product. Hydrogenolysis of the protected derivatives **35**²⁵ and **42** afforded Salacinol (**1**), although this step was problematic because of poisoning of the catalyst, and only afforded the product in 65% yield. The stereochemistry of Salacinol (**1**) shown in Scheme 10(b) is an equivalent representation to that shown on page 2 hereof.

In order to obviate the problematic hydrogenolysis step, the inventors next chose to examine the reaction of the thioether containing *p*-methoxybenzyl ether protecting groups with the benzylidene-protected L-erythritol-1,3-cyclic sulfate; the inventors reasoned that the removal of all protecting groups by acid hydrolysis would be facile. Thus, 2,3,5-tri-*O-p*-methoxybenzyl-1,4-anhydro-4-thio-D-arabinitol (**43**), synthesized in 87% yield from **38**, was reacted with the cyclic sulfate **34** in HFIP to afford the sulfonium salt **44** in quantitative yield (Scheme 10c). Deprotection of **44** proceeded smoothly (86%) in aqueous trifluoroacetic acid to afford Salacinol **1** in 75% overall yield. The latter sequence represents, therefore, an efficient synthesis of the biologically important natural product Salacinol **1**.



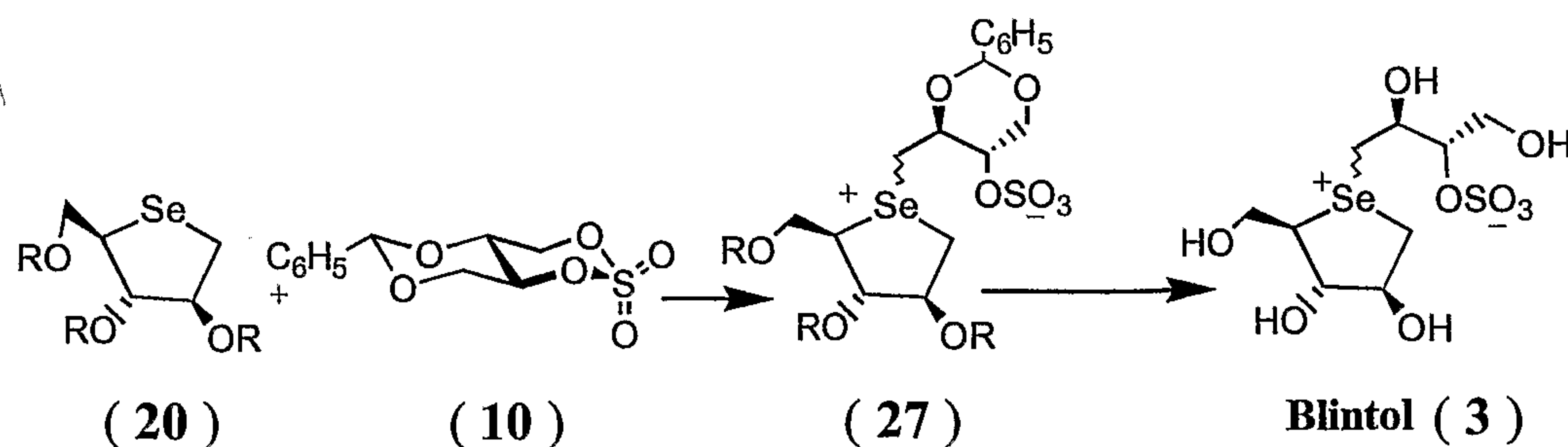
Scheme 10c

The inventors considered the stereochemistry at the stereogenic sulfonium center in **35**, **42**, and **13** and determined that these reactions proceeded stereoselectively irrespective of the solvent used in the reaction. The stereochemistry was confirmed by means of NOESY experiments that showed clear correlations between H-4 and H-1', thus indicating the presence of the isomer with a *trans* relationship between C-5 and C-1'. The barrier to inversion at the sulfonium ion center must be substantial since no evidence for isomerization in these and related derivatives²⁹ has been noted.

3.2 Synthesis of Selenium Analogues

The seleno-analogue intermediate (**27**) ($\text{R}=\text{CH}_2\text{C}_6\text{H}_5$) was made starting from the seleno-arabinitol (**20**) ($\text{R}=\text{CH}_2\text{C}_6\text{H}_5$) and the cyclic sulfate (**10**) in excellent yield 86% (Scheme 11), but NMR spectroscopy showed the presence of two isomers in a ratio of 7:1 that differed in stereochemistry at the stereogenic selenium

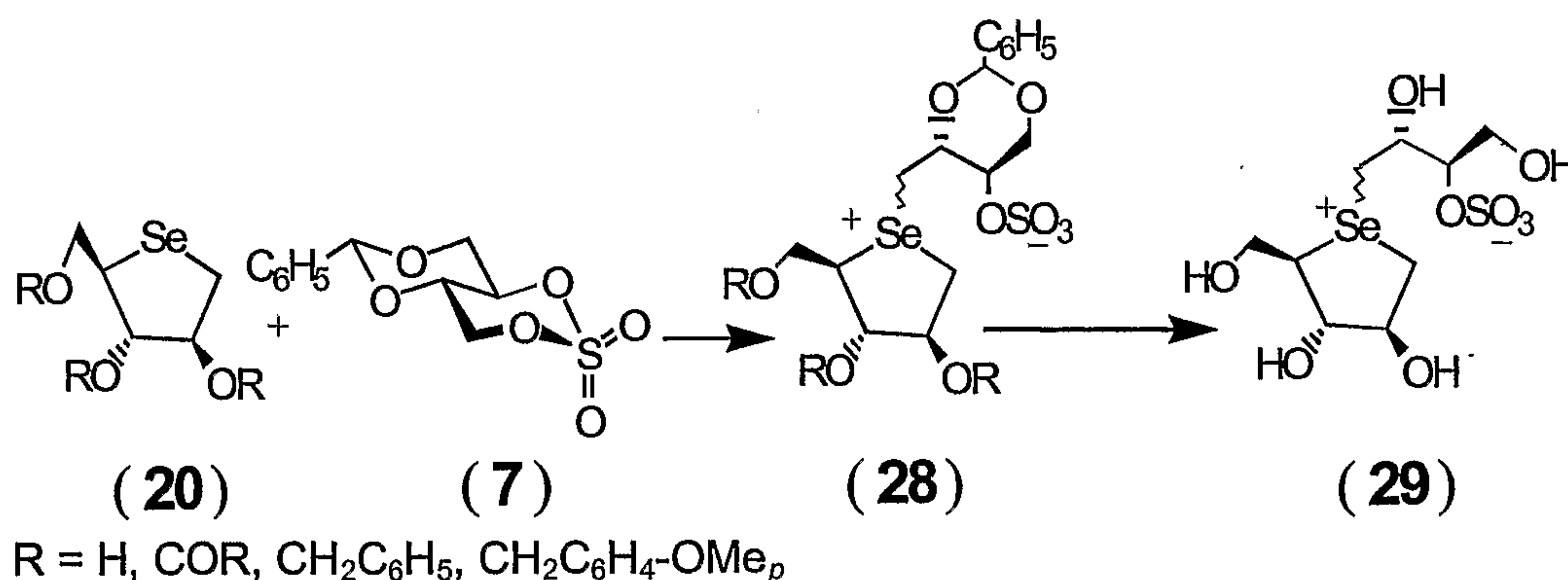
center. The isomers were separable by analytical HPLC. The inventors have assigned the name "Blintol" to the new selenium analogue (3).



$R = \text{H}, \text{COR}, \text{CH}_2\text{C}_6\text{H}_5, \text{CH}_2\text{C}_6\text{H}_4\text{-OMe}_p$

5 **Scheme 11. Synthesis of Blintol (3)**

The seleno-analogue intermediate (28) ($R=\text{CH}_2\text{C}_6\text{H}_5$) was made starting from the seleno-arabinitol (20) ($R=\text{CH}_2\text{C}_6\text{H}_5$) and the cyclic sulfate (7) in excellent yield 97% (Scheme 12); a mixture of two isomers in a ratio of 3:1 that differed in stereochemistry at the stereogenic selenium center was obtained. The isomers were separable by analytical HPLC.

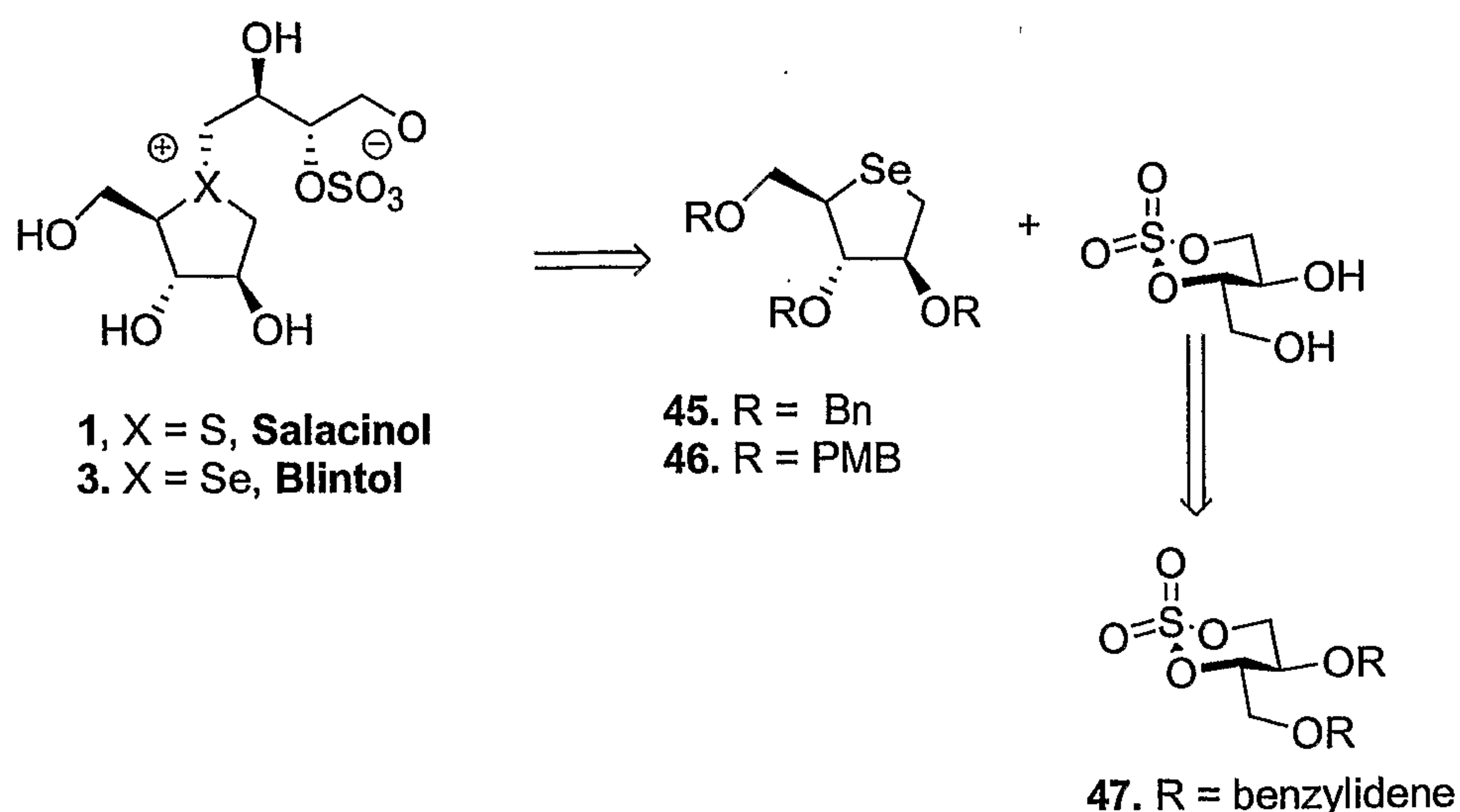


15 **Scheme 12. Synthesis of compound (29)**

Compound (29) is a diastereomer of Blintol (3).

3.2.1 Alternative Route to Synthesis of Blintol

Retrosynthetic analysis indicated that Blintol (**3**) could be obtained by alkylation of anhydroseleno-D-arabinitol (**45**) at the ring heteroatom using an appropriately protected cyclic sulfate (**47**) (Scheme 12a).²⁵



Scheme 12a

5

The previously discussed synthesis of Blintol (**3**) used benzyl ethers as the protecting groups for the hydroxyl groups on the anhydroseleno-D-arabinitol **45**.²⁶ However, the deprotection of the benzyl-protected Blintol (**3**) by hydrogenolysis was problematic due to the poisoning of the palladium catalyst by small amounts of the selenoether **45** formed in the reaction mixture.

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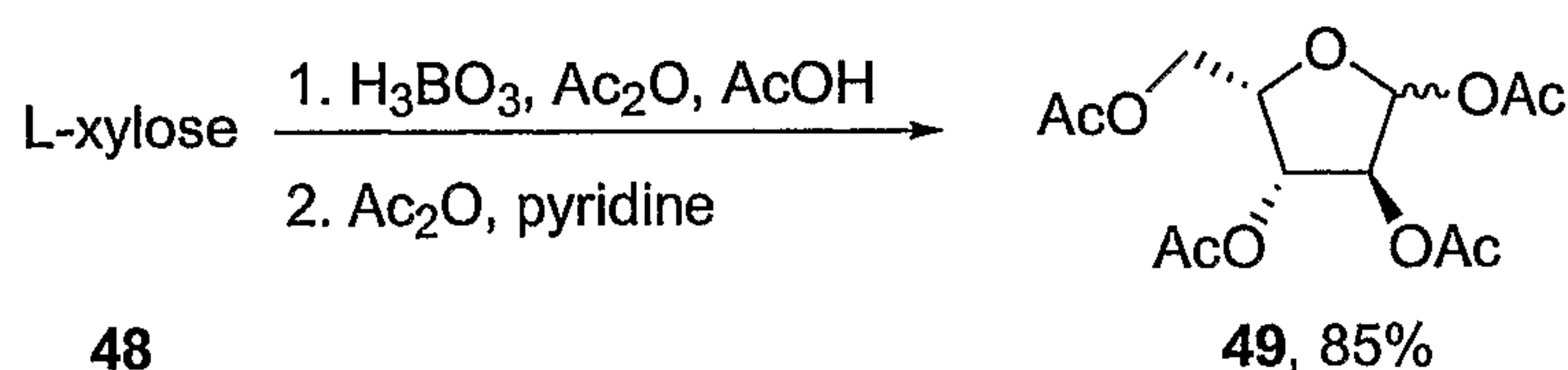
In order to eliminate the problematic hydrogenolysis step, the use of *p*-methoxybenzyl (PMB) protecting groups on the seleno-D-arabinitol, as in the inventors' optimized synthesis of Salacinol (**1**),⁵³ was considered. Thus, the reaction of the *p*-methoxybenzyl-protected selenoether **46** with the benzylidene-protected L-erythritol-1,3-cyclic sulfate (**47**; R = benzylidene) was examined. Since both PMB and benzylidene protecting groups are labile to acidic hydrolysis, the removal of all protecting groups by acid hydrolysis is facile.⁵³

15

The synthesis of the PMB-protected anhydroseleno-D-arabinitol (**45**) from L-xylose (**48**) required the judicious choice of aglycon. Initial attempts to use

the allyl glycosides yielded an inseparable mixture of the desired allyl xylofuranosides and undesired allyl xylopyranosides. Furthermore, the cleavage of the allyl group was judged to be too expensive a process for large-scale synthesis. Nevertheless, the mixture of furanosides and pyranosides was used in the successful synthesis of Blintol (3), their separation being effected at a later stage in the synthetic scheme.

These concerns led the inventors to explore the following strategy: 1) The use of *n*-pentenyl glycosides, first exploited by Fraser-Reid and coworkers;⁵⁴ this group was also reported to be cleaved by NBS without affecting the PMB groups,⁵⁵ and 2) The use of boric acid in the acid-catalyzed acetylation of L-xylose (48) to improve the furanoside to pyranoside ratio.⁵⁶ The latter procedure led to the conversion of L-xylose (48) to 1,2,3,5-tetra-*O*-acetyl-D-xylofuranose (49) in a two-step, one-pot procedure. Analysis of the ¹H and ¹³C NMR spectra indicated that the furanosides 49 were formed exclusively without formation of the undesired pyranoside side products (Scheme 12b).



Scheme 12b

Compound 49 was then treated with 4-penten-1-ol and BF₃ OEt₂ to give the 4-pentenyl 2,3,5-tri-*O*-acetyl-L-xylofuranosides (50).⁵⁷ This compound underwent acidic hydrolysis to cleave the acetyl groups, followed by the reprotection of the three hydroxyl groups with PMB groups, to afford the 4-pentenyl 2,3,5-tri-*O*-*p*-methoxybenzyl-L-xylofuranosides (52). The anomeric hydroxyl group of 52 was then released using NBS in acetonitrile-water to yield the corresponding 2,3,5-tri-*O*-*p*-methoxybenzyl-L-xylofuranose (53) (Scheme 12c).

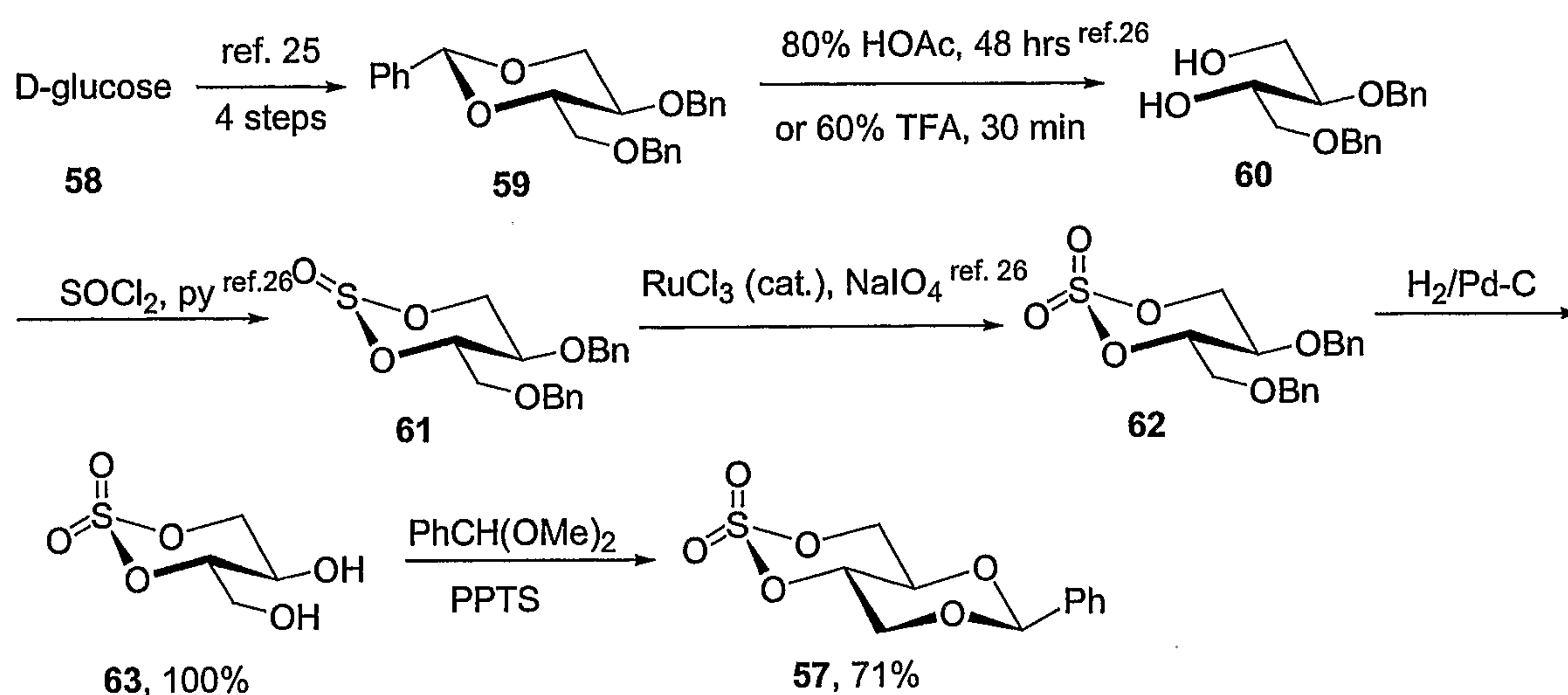


COC1OC(COP(=C(C)C)C)C(COP(=C(C)C)C)C1OP(=C(C)C)C (53)
 $\xrightarrow[\text{MeOH}]{\text{NaBH}_4}$
COC1C(COP(=C(C)C)C)C(COP(=C(C)C)C)C1O (54, 84%)
 $\xrightarrow[\text{DMF}]{\text{MsCl, pyridine}}$
COC1C(COP(=C(C)C)C)C(COS(=O)(=O)C)C1OS(=O)(=O)C (55, 72%)
 $\xrightarrow[\text{EtOH}]{\text{Se, NaBH}_4}$
COC1C(COP(=C(C)C)C)C(C)C1Se (56, 83%)

Scheme 12d

Another factor in the synthesis of Blintol (3) (and the optimized synthesis of Salacinol⁵³) is the availability of 2,4-*O*-benzylidene-L-erythritol-1,3-cyclic sulfate (57). This compound was previously prepared from L-glucose.²⁵ However, due to the high cost of L-glucose and the fact that it was the starting material in a six-step synthetic route, it was desirable to prepare the cyclic sulfate (57) from a less expensive material. As described herein the inventors have successfully prepared the cyclic sulfate 57 from D-glucose (58).

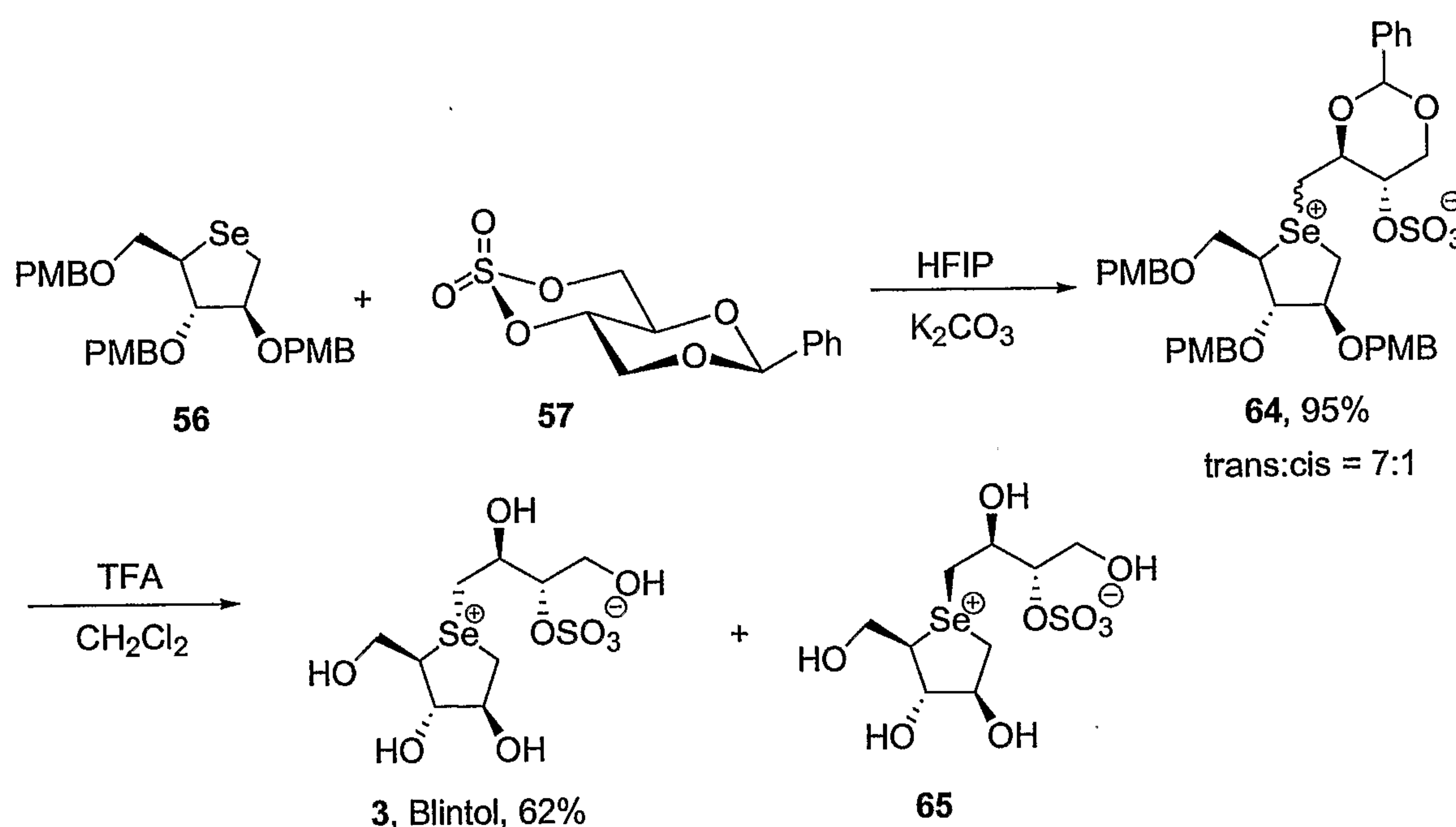
Using the method developed by the inventors,^{25,26} the benzyl-protected cyclic sulfate 62 was prepared from D-glucose (58). It is interesting to note that cleavage of the benzylidene protecting group in compound 59 was achieved with 60% TFA at room temperature for 30 min to afford the corresponding diol 60 in a comparable yield to that obtained with aqueous acetic acid. Since the original method involved refluxing compound 59 in 80% HOAc for 48 h, this modification proved to be more efficient. Compound 62 underwent hydrogenolysis to afford the unprotected cyclic sulfate 63. Installation of the benzylidene acetal using pyridinium *p*-toluenesulfonate (PPTS) as the catalyst was the important step since, under these conditions, the cyclic sulfate was not cleaved. The desired benzylidene-protected cyclic sulfate 57 was obtained in 71% yield (Scheme 12e).



Scheme 12e

The coupling reaction of the anhydroseleno-D-arabinitol **56** with the cyclic sulfate **57** in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) at 60-65 °C proceeded smoothly in 7 h, to give a mixture of the 2,3,5-tri-*O*-*p*-methoxybenzylselenonium salts **64** in 95% yield (Scheme 12f). Analysis of the ^1H and ^{13}C NMR spectra indicated that compound **64** was a 7:1 mixture of isomers at the stereogenic selenium center. The major isomer was assigned to that with a *trans* relationship between C-5 and C-1', by analogy with the results obtained previously.²⁶

The selenonium salts **64** were subsequently deprotected by treatment with trifluoroacetic acid (TFA), and purified by recrystallization to afford pure Blintol (**3**) in 62% yield (Scheme 12f).

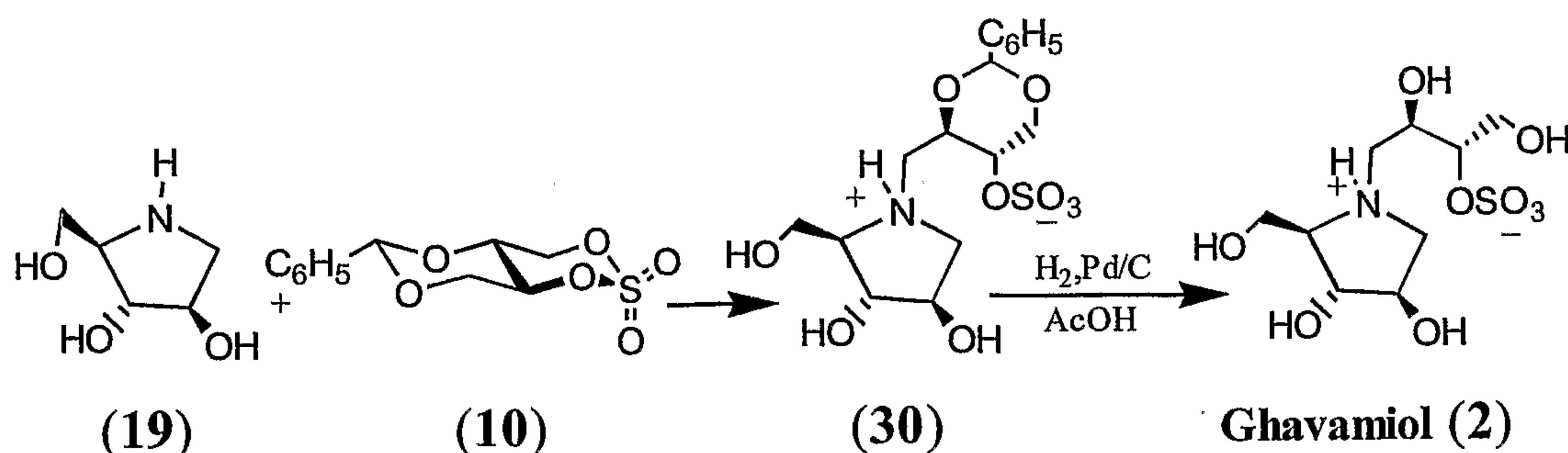


Scheme 12f

3.3 Synthesis of Nitrogen Analogues

The nitrogen analogue intermediate (**30**) was made by the reaction of the deprotected imino-arabinitol (**19**) with the cyclic sulfate (**10**) in a good yield 72% (Scheme 13). Compound (**19**) was not soluble in acetone so the reaction was performed in dry methanol. A side product (19%) which was identified to be the product of methanolysis of the cyclic sulfate was obtained. The inventors have

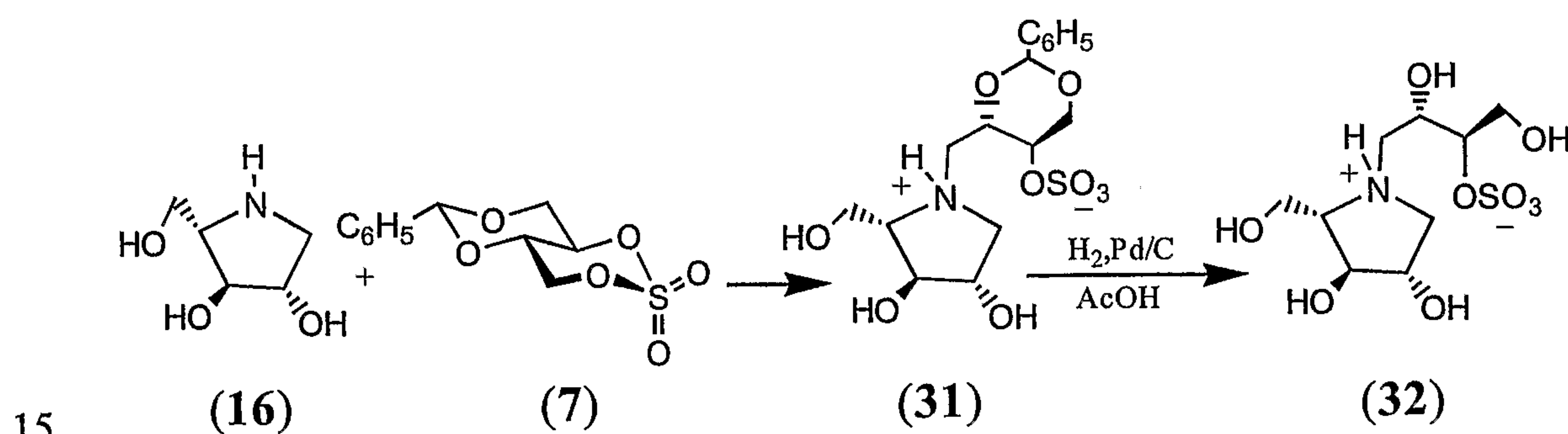
assigned the name "Ghavamiol" to the new nitrogen analogue (2). Compound (30) was deprotected to give Ghavamiol (2) in 64% yield.



5

Scheme 13. Synthesis of Ghavamiol (2)

The enantiomer intermediate (31) was made by the reaction of the deprotected imino-arabinitol (16) with the cyclic sulfate (7) in a good yield 72% (Scheme 14). A side product (21%) which was identified to be the product of methanolysis of the cyclic sulfate was obtained. Compound (31) was deprotected to give compound (32) in 77% yield. Compound (32) is the enantiomer of Ghavamiol (2).



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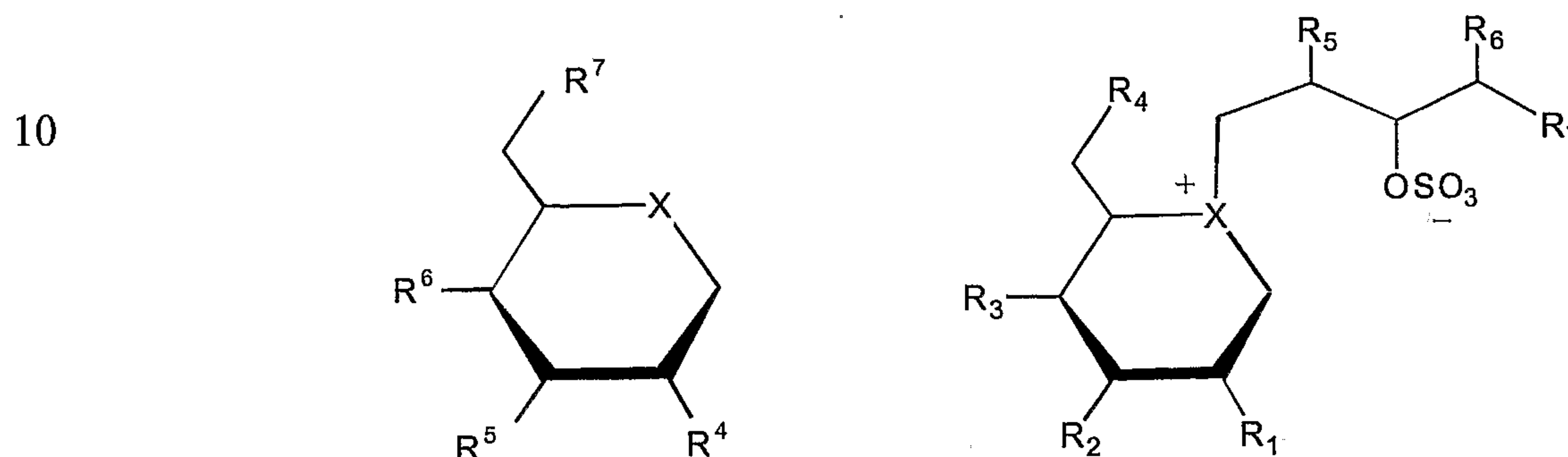
Scheme 14. Synthesis of compound (32)

4.0 Alternative Synthetic Schemes

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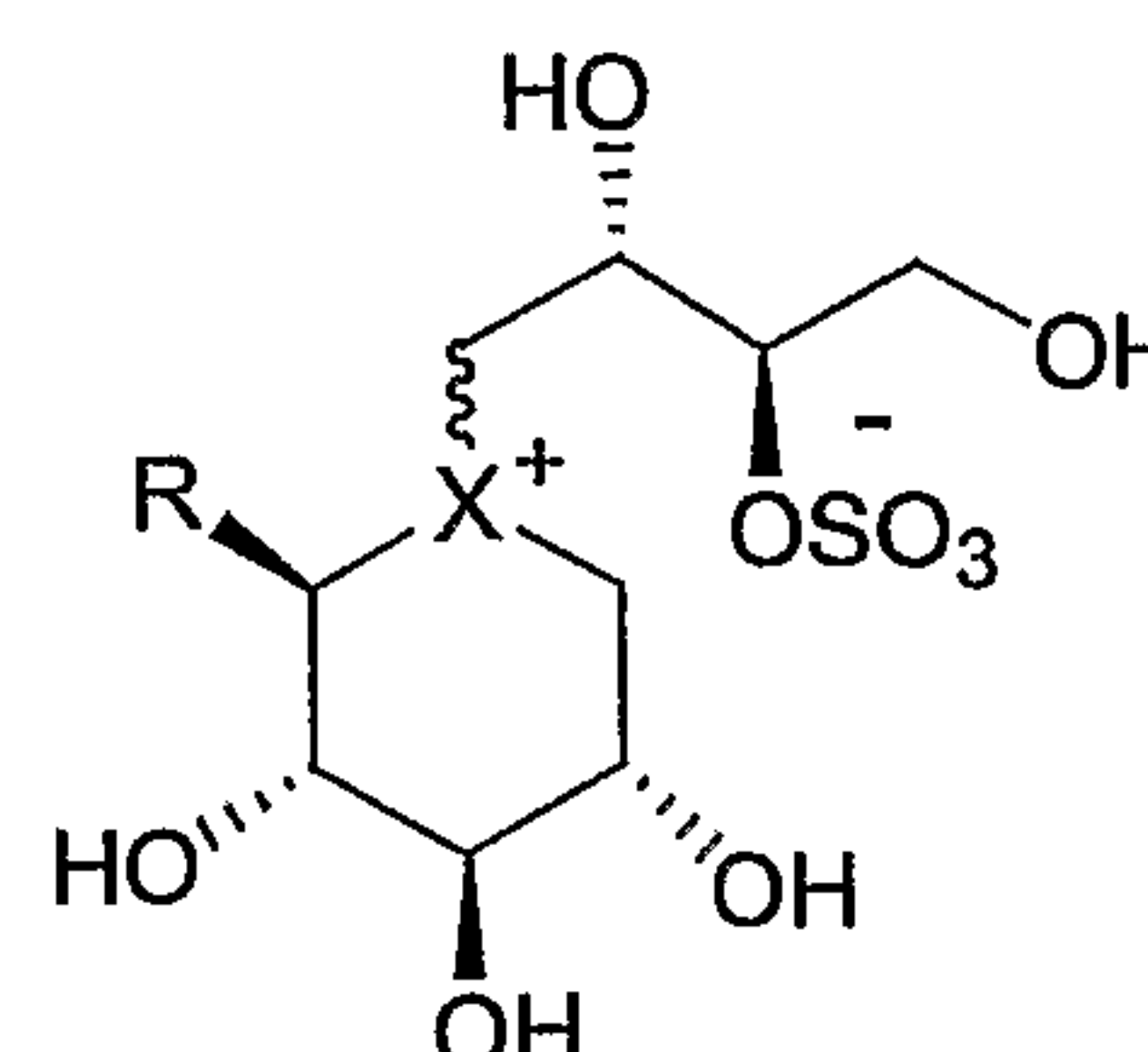
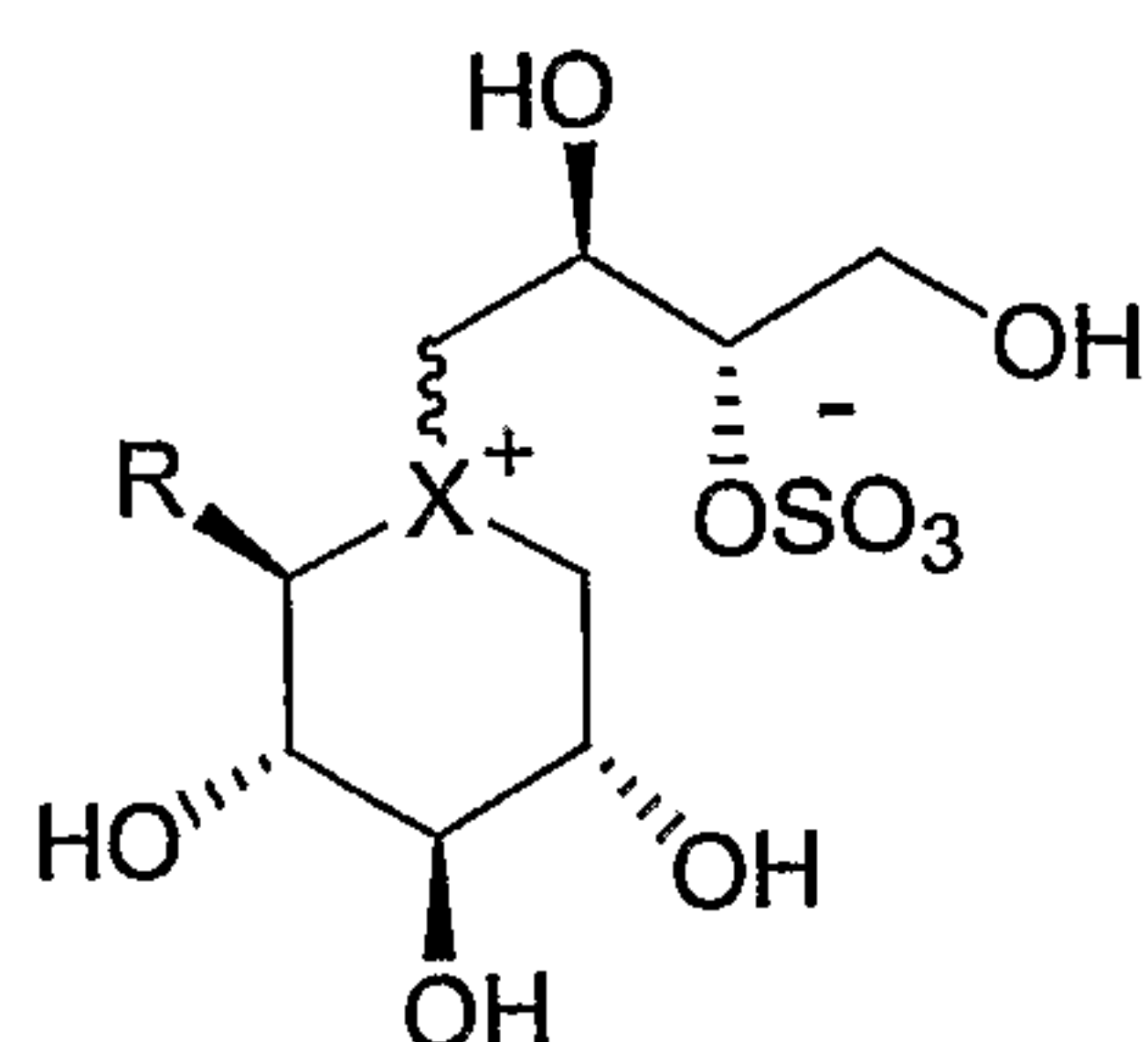
4.1 Six-membered Ring Analogues

In an alternative embodiment of the invention, target compounds having potential application as glycosidase inhibitors may be synthesized in the manner described above using 6-membered rather than 5-membered ring heterocycles as reagents. As in the embodiments described above, the cyclic sulfate (described above) is opened in the coupling reaction due to nucleophilic attack of the heteroatoms (i.e. X=S, Se, NH) on the ring sugars. As will be apparent to a person skilled in the art, the general formulas for the 6-membered sugar reagent and resulting target compound are as shown below.



The 6-membered ring target compound shares the same internal salt structure as the 5-membered ring embodiment. The substituent groups may vary as described below without departing from the invention.

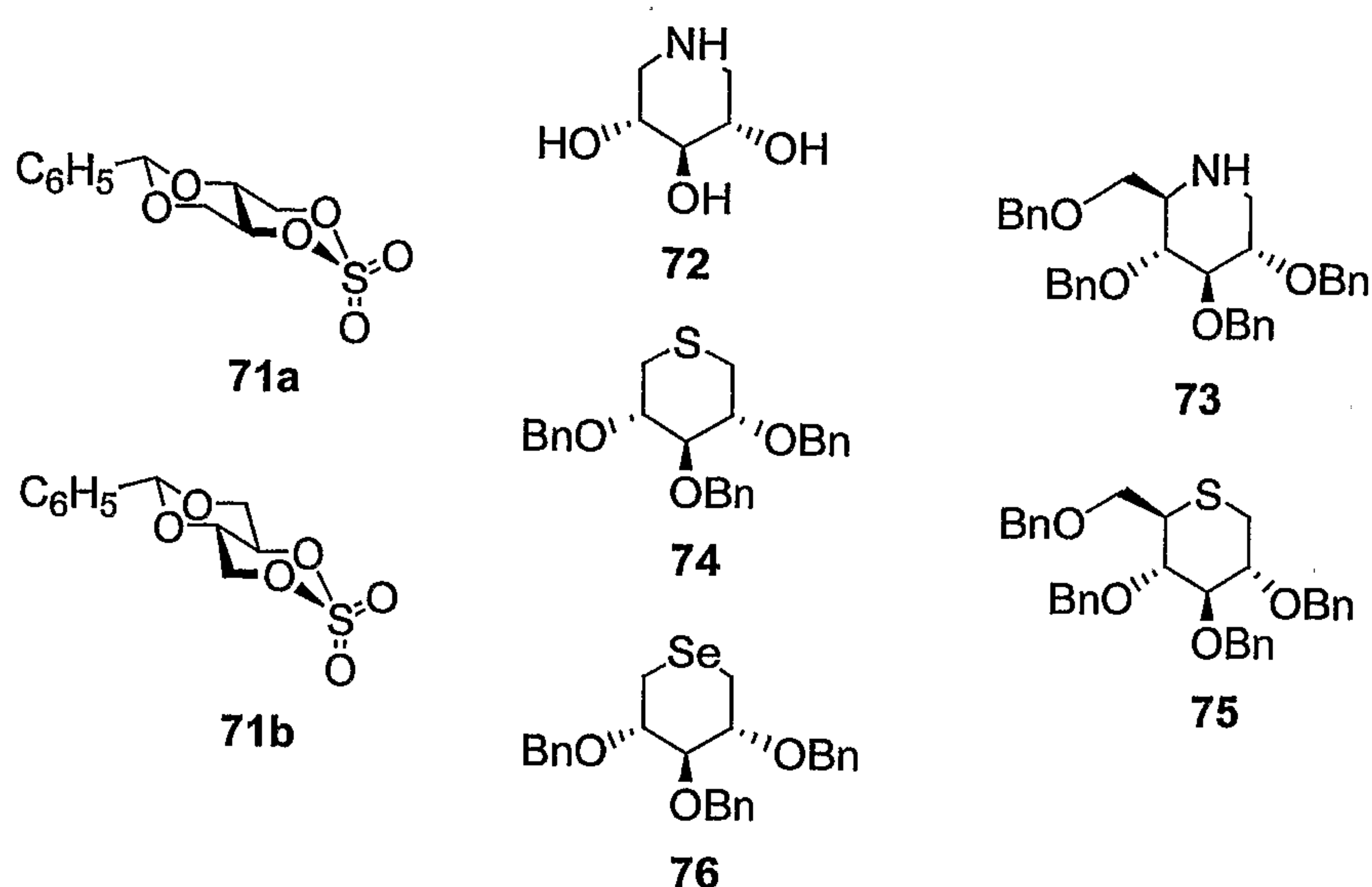
In particular, in order to expand the repertoire of molecules of this class that could serve as glycosidase inhibitors, the inventors proposed to synthesize *N*-alkylated 1,5-dideoxy-1,5-iminoxylitol (**66a**) and deoxynojirimycin (**67a**) having the same L-erythritol-derived, sulfated side-chain as Salacinol. The advantage of having an internal sulfate counterion for the ammonium salt was deemed to be worth pursuing in order to investigate whether such a structural modification would lead to increased *in-vivo* stability and/or membrane permeability. In addition, the internal sulfate salt and polar side-chain may provide cationic inhibitors that bind to glycosidase enzymes without deprotonating the catalytic active-site carboxylic acid and provide additional insight into the structural features that are important for inhibition. The inventors describe herein the syntheses of **66a** and **67a** as well as the corresponding sulfonium and selenonium analogues **68a**, **69a** and **70a**. The inventors report also the syntheses of the corresponding enantiomers or diastereomers **66b** - **70b** resulting from incorporation of a side chain derived from D-erythritol.



66a	X = NH R = H
67a	X = NH R = CH ₂ OH
68a	X = S R = H
69a	X = S R = CH ₂ OH
70a	X = Se R = H

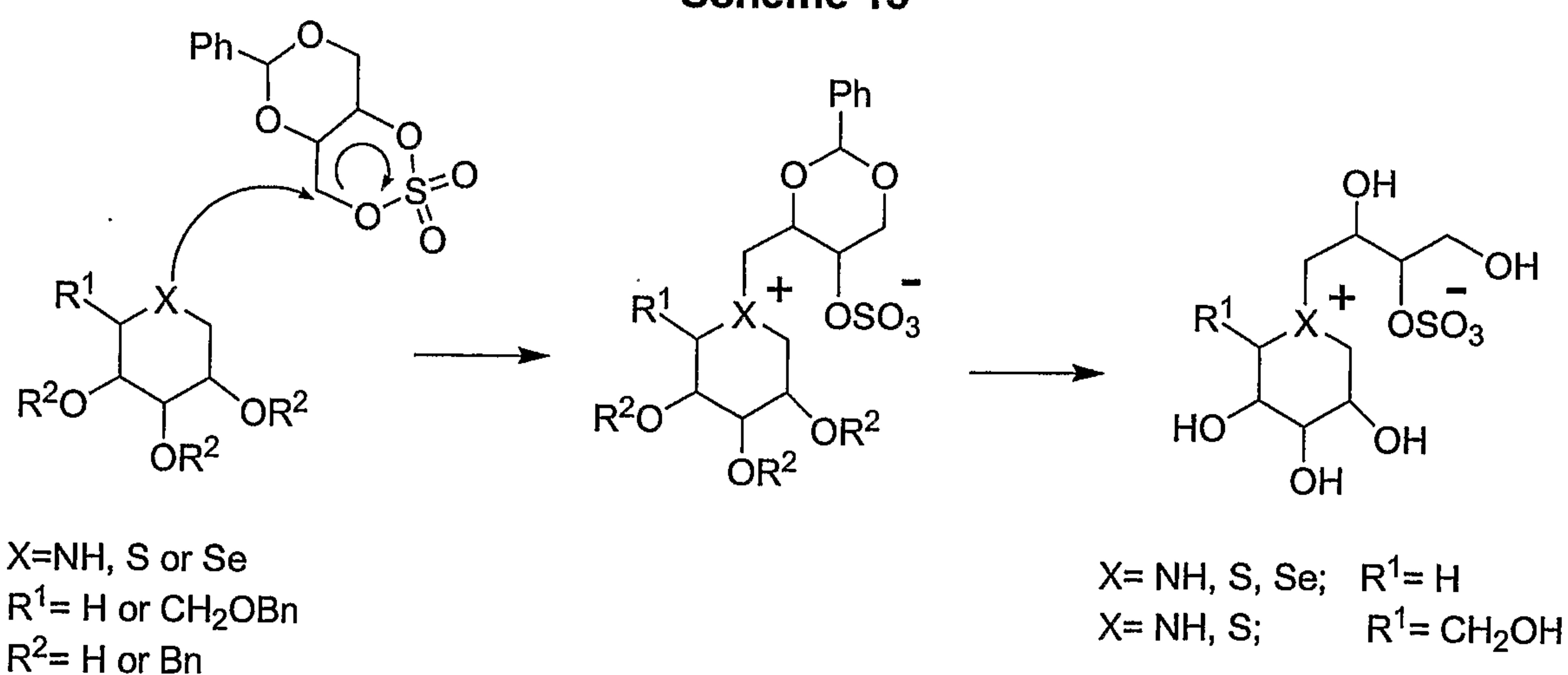
66b	X = NH R = H
67b	X = NH R = CH ₂ OH
68b	X = S R = H
69b	X = S R = CH ₂ OH
70b	X = Se R = H

Each target six-membered ring compound was synthesized in two stereoisomeric forms (a or b) by using either of the enantiomeric forms of the cyclic sulfate **71a** or **71b** as the source of the sulfated alkyl side chain. In the case of compounds **66**, **68**, and **70** these stereoisomers are enantiomers while compounds **67** and **69** were prepared as either of two diastereomers. For the enantiomeric sulfonium salts **68a** and **68b**, *R/S* isomers at the stereogenic sulfonium-ion center were separated and characterized independently. Similar isomers for the sulfonium salts **69** and selenonium salt **70** were not separable by chromatography and the products were characterized as mixtures. In the case of the ammonium salts **66** and **67**, inversion at the nitrogen center, *via* the free amine, was sufficiently fast in solution at room temperature that stereoisomers at the ammonium center were not observed.



The general synthetic strategy (Scheme 15) involved alkylation of the piperidine (72 and 73), tetrahydrothiapyran (74 and 75), or tetrahydroselenapyran (76) heterocycles with either the 2,4-*O*-benzylidene-L-1,3-cyclic sulfate (71a),^{16,53} derived from L-glucose, or its enantiomer (71b),^{16,53} obtained from D-glucose. In general, the reactions with the less-expensive 71b were examined first. These methods are analogous to those described above used by the inventors to synthesize the five-membered ring analogues, Salacinol and its nitrogen or selenium congeners.^{16,25,26,53,72}

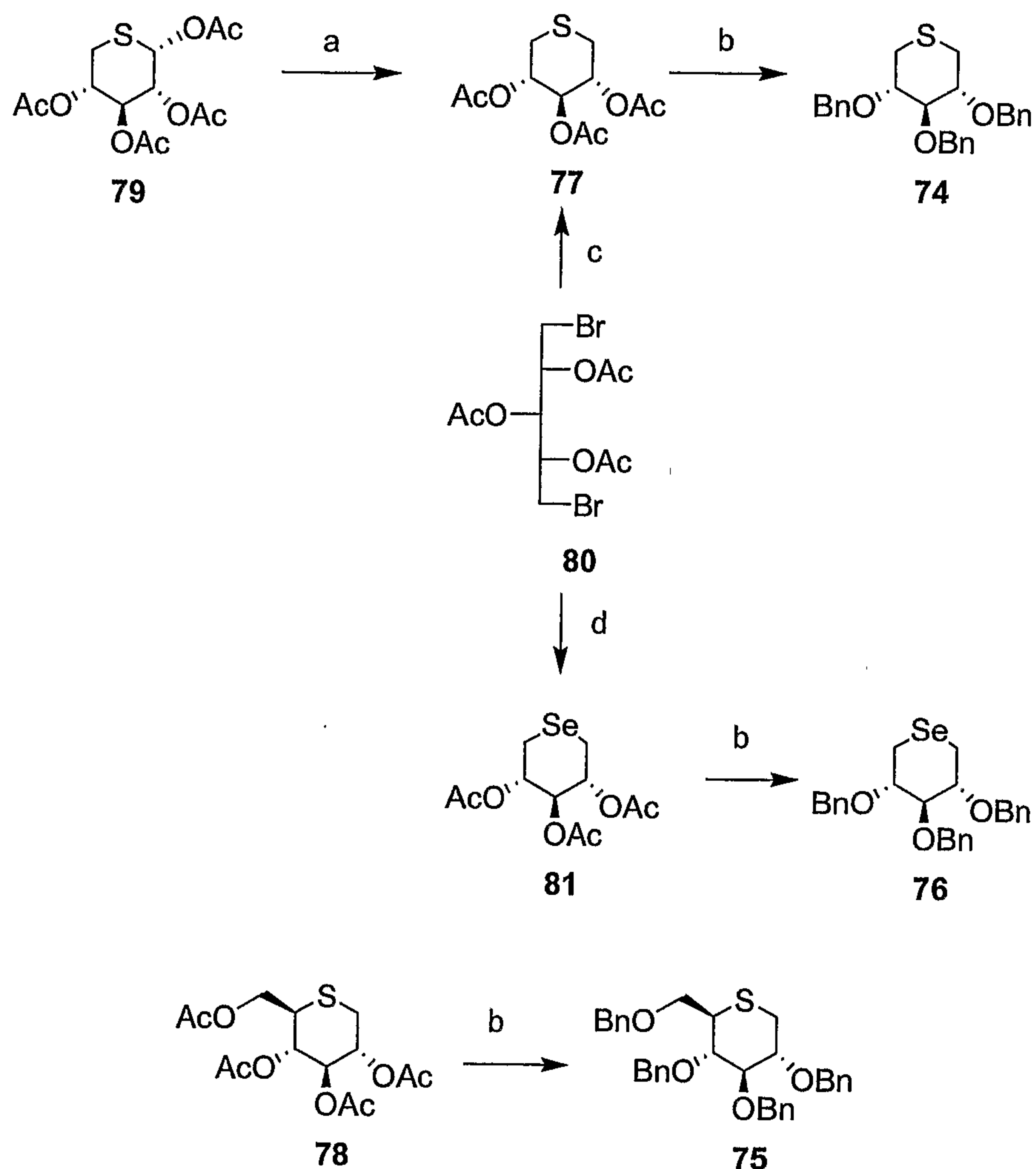
Scheme 15



4.1.1 Preparation of starting materials

In preliminary experiments investigating the reactivity of the cyclic sulfate **71b**, the inventors found that, for complex amine nucleophiles having only secondary alcohols as additional functional groups, protection of hydroxyl groups was unnecessary, but that any primary alcohol functional groups may be alkylated in competition with amines.

Scheme 16



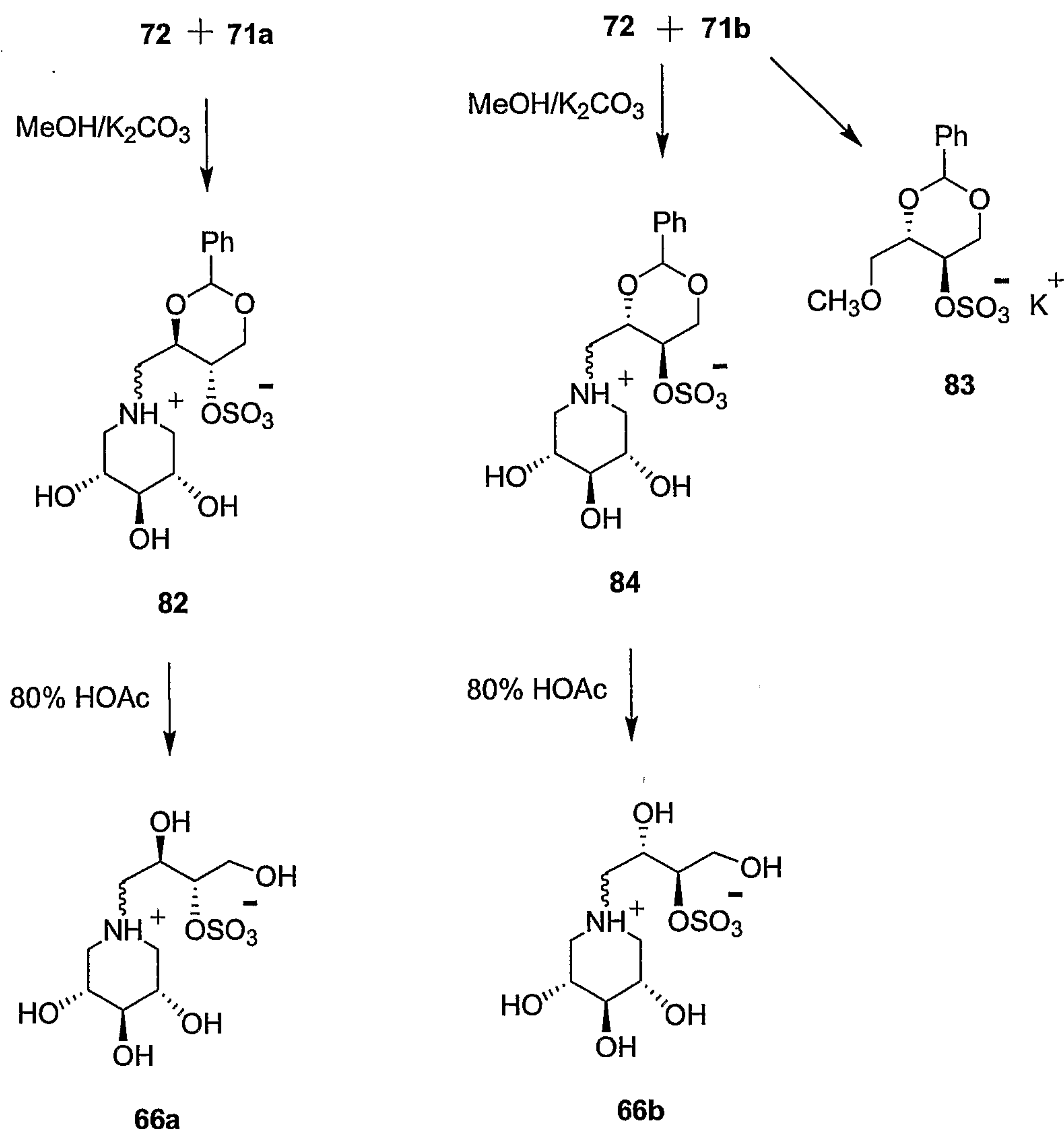
- a. Et_3SiH , HOAc
- b. i) NaOMe/MeOH; ii) BnBr/NaH/DMF
- c. Na_2S /DMF
- d. $\text{NaSeB}(\text{OEt})_3/\text{EtOH}$

Accordingly, the unprotected anhydroxylitol imine (**72**) was prepared by the literature method⁷⁵ while deoxynojirimycin was prepared as its tetra-*O*-benzyl derivative (**73**).⁷³ The tetrahydrothiapyran derivative **74** was prepared (Scheme 16) by deacetylation and benzylation of the known tri-acetate **77**.⁷⁵ The benzylated tetrahydrothiapyran **75** was similarly prepared from the known anhydro-5-thio-D-glucitol tetra-acetate (**78**)²⁸ by protecting group interchange. Compound **77** was obtained, in turn, either by reduction of tetra-*O*-acetyl-5-thio-D-xylopyranose (**79**)³⁹ or, more conveniently, from reaction of acetylated 1,5-dibromoxylitol (**80**) with sodium sulfide.⁷⁵ The selenium heterocycle **81** was prepared by substituting NaSeB(OEt)₃ (obtained in situ⁷⁷ by reduction of Se with NaBH₄/EtOH) for sodium sulfide in the reaction with acetylated 1,5-dibromoxylitol (**80**) (Scheme 16). Subsequent exchange of the acetates for benzyl protecting groups gave the desired tetrahydroselenapyran derivative **76**, whose preparation has been reported by an unrelated method.⁷⁸

4.1.2 Target ammonium compounds

Compound **72** was reacted with the D-cyclic sulfate **71b** in MeOH containing K₂CO₃ (Scheme 17). Isolation of the more polar product gave the ammonium salt **84** in 43% yield. An abundant side-product (**83**) resulting from opening of the cyclic sulfate by the methanol solvent could be isolated from the early chromatographic fractions. A similar reaction with the L-cyclic sulfate **71a** gave somewhat less of this side product and the desired coupled product **82** was obtained in slightly higher yield (56%). The ¹H NMR spectra of compounds **82** and **84** exhibited sharp resonances for methylene groups α to the amine in D₂O (made basic with K₂CO₃), but neutral or acidic D₂O solutions gave downfield shifts and much broader resonances for these methylene resonances. The inventors attribute these observations to exchange, at an intermediate rate relative to the chemical-shift NMR time scale, of the conjugate-acid *R/S* ammonium salts, with nitrogen inversion taking place *via* the free amines that exist in equilibrium with their conjugate acids at acidic pH.

Scheme 17



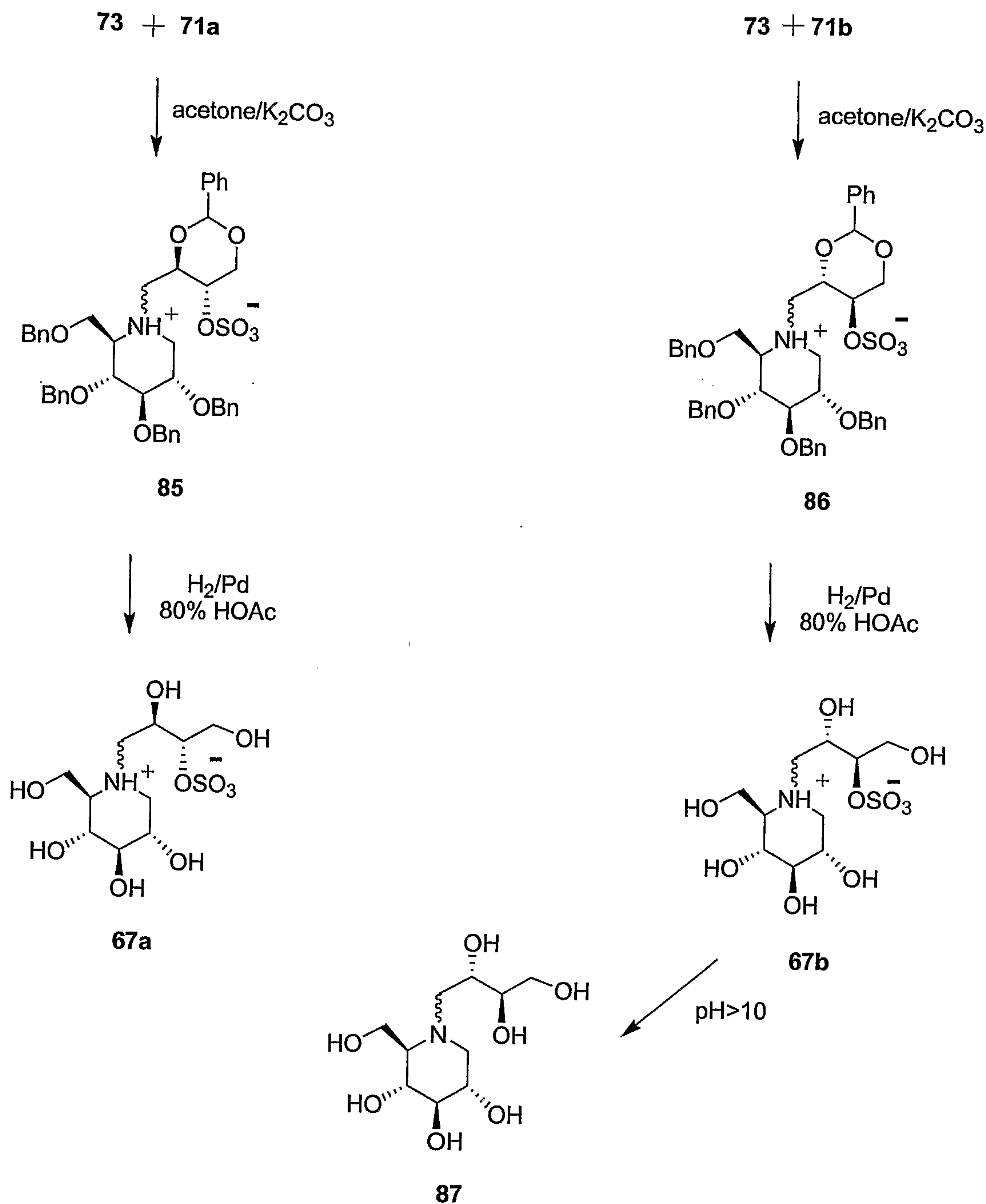
Removal of the benzylidene protecting groups by hydrolysis in aqueous acetic acid gave the target compounds **66a** (73%) and **66b** (72%) after purification by chromatography on silica gel. These ammonium salts gave severely exchange-broadened NMR spectra and were more productively characterized by adding base to the NMR samples to produce the conjugate amine bases. Prolonged treatment with strong base should be avoided, however, due to the possibility of sulfate ester hydrolysis, as noted below. As expected for enantiomers, the NMR data for **66a** and **66b** were virtually identical although small differences in chemical shifts between different samples for both identical and enantiomeric compounds were noted.

These differences were attributed to the concentration and temperature dependence of

the NMR chemical shifts between samples. The tendency of zwitterionic compounds to exist as aggregates in solution is the likely origin of these effects.

The coupled products **85** and **86**, derived from the benzyl-protected deoxynojirimycin, were obtained by reaction of compound **73** with the cyclic sulfates **71a** and **71b** in acetone/ K_2CO_3 in yields of 80% and 65%, respectively (Scheme 18). The ^1H NMR resonances for compounds **85** and **86** were extremely broad in $CDCl_3$ but sharpened in CD_3OD (made basic with NaOD), thus indicating that the coupled products were obtained as an equilibrating mixture of the desired ammonium salts with the corresponding conjugate bases. Simultaneous removal of both the benzyl and benzylidene protecting groups was achieved by hydrogenolysis in aqueous acetic acid to give the target compounds **67a** and **67b**.

Scheme 18



Analysis by ¹H NMR spectroscopy indicated that these products were contaminated by KOAc. Nevertheless, other than a resonance at δ 1.8 in the spectrum that was attributed to the acetate impurity, the target compounds were essentially pure and all resonances in both the ¹H and ¹³C spectra were assigned by two-dimensional techniques. Prolonged storage of the NMR sample of compound **67b** in D₂O/NaOD at pH>10 produced a slow loss of the 3'-sulfate group as evidenced by an upfield shift of the H-3' resonance. After 2 days at ambient temperature the sulfate ester had been

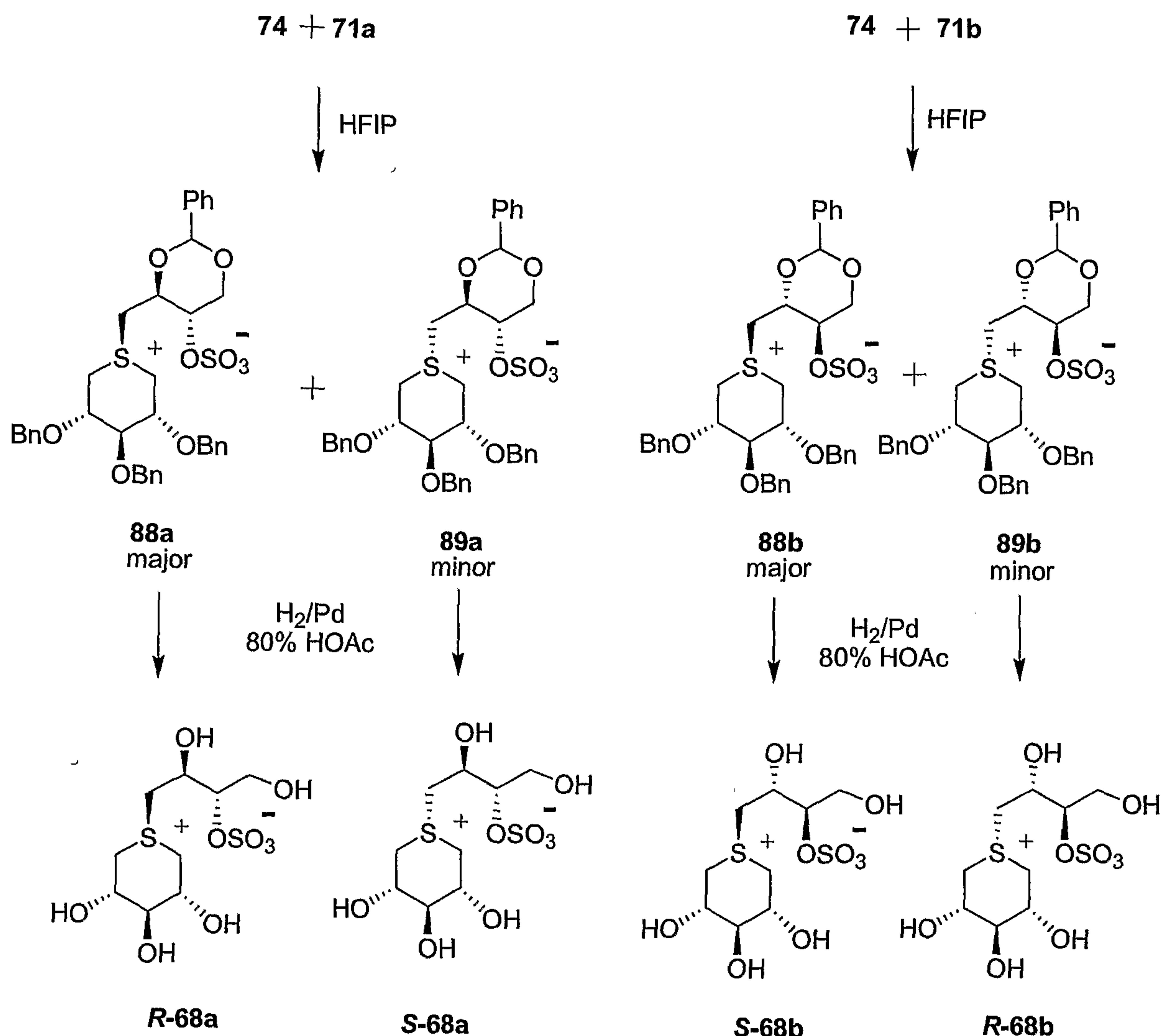
completely hydrolyzed to yield cleanly the tertiary amine compound **87** and inorganic sulfate salts.

The ^1H NMR data for all of the amine compounds in D_2O ($\text{pH} > 8$) indicated that the predominant conformation of the piperidine ring was $^4\text{C}_1$ (carbohydrate numbering) and that this conformational preference did not appear to change upon protonation ($\text{pH} < 3$). Similar conclusions were reached in a previous conformational study of alkylated deoxynojirimycin derivatives.⁷⁴

4.1.3 Target sulfonium compounds

The syntheses of sulfonium salts **68** and **69** (Schemes 19 and 20) were achieved in a similar fashion to those of the ammonium salts. Thus, compound **74** was initially reacted with the D-cyclic sulfate **71b** in acetone at 65°C . Slow formation of two more-polar products was observed by TLC analysis. Isolation of the mixture of products gave **88b** and **89b** in approximately 37% yield. On changing the solvent to 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), the yield improved to 87%. The dramatically beneficial effect of HFIP solvent on the yields for sulfonium salt formation has been noted above. The ratio of the major product **88b** to the minor product **89b** was 2:1. Pure samples of the two components were obtained by chromatography and characterized separately by NMR techniques.

Scheme 19



Initially, 1D ^1H NMR spectra were obtained which revealed that the two compounds were isomers, having the same number of hydrogen atoms. The similarity of the spectra of the two compounds suggested that the compounds differed in stereochemistry only at the stereogenic sulfur atom. COSY spectra permitted the assignment of the proton signals for the tetrahydrothiapyran ring and for the erythritol side chain in both compounds. Notably, it was found that all of the ring proton signals were shifted downfield relative to the parent tetrahydrothiapyran 17. This was anticipated since the positive sulfonium center is electron withdrawing. Furthermore, although it was initially expected that the three benzyloxy groups at C-2, C-3 and C-4 would favor the sterically less-hindered equatorial positions, analysis of vicinal

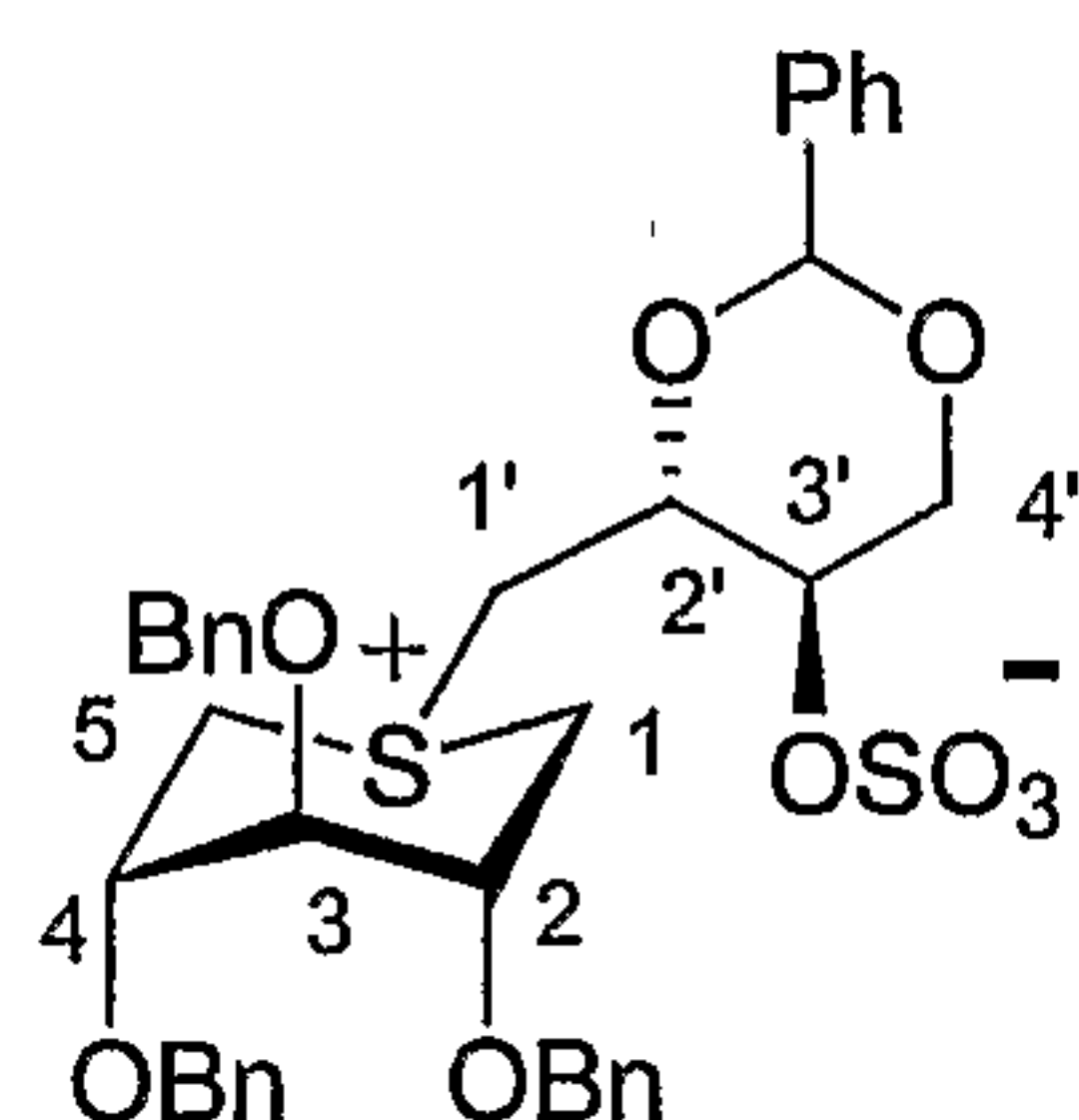
coupling constants showed that $J_{2,3}$ and $J_{3,4} = 3.5\text{-}3.9$ Hz. These values are much smaller than those ($J_{2,3} \approx J_{3,4} \approx 8.9$ Hz) observed for the axial-axial vicinal coupling constants in the precursor 17. Thus, the inventors reasoned that compounds **88b** and **89b** preferred a ${}^1C_4$ conformation, placing the three benzyloxy groups in axial positions and accounting for the small vicinal coupling constants. This conformational preference can be explained by the fact that the axial substituents at C-2 and C-4 provide stabilizing gauche electrostatic interactions of the polar benzyloxy groups with the sulfonium ion center; the group at C-3 can also provide stabilizing electrostatic interactions.²⁸ The results are reminiscent of the inventors' previous work with the sulfonium analogue of castanospermine.²⁸

The configuration at the sulfonium center was next established by means of a NOESY experiment. The NOESY spectrum for the major diastereomer showed H-1b' correlations to H-1ax/H-1eq/H-5ax as well as H-1a' and correlations to H-5eq/H-5ax. This isomer was thus assigned to structure **88b** with the erythritol side chain occupying the equatorial orientation. The absolute configuration at sulfur was thus established as being *S*.

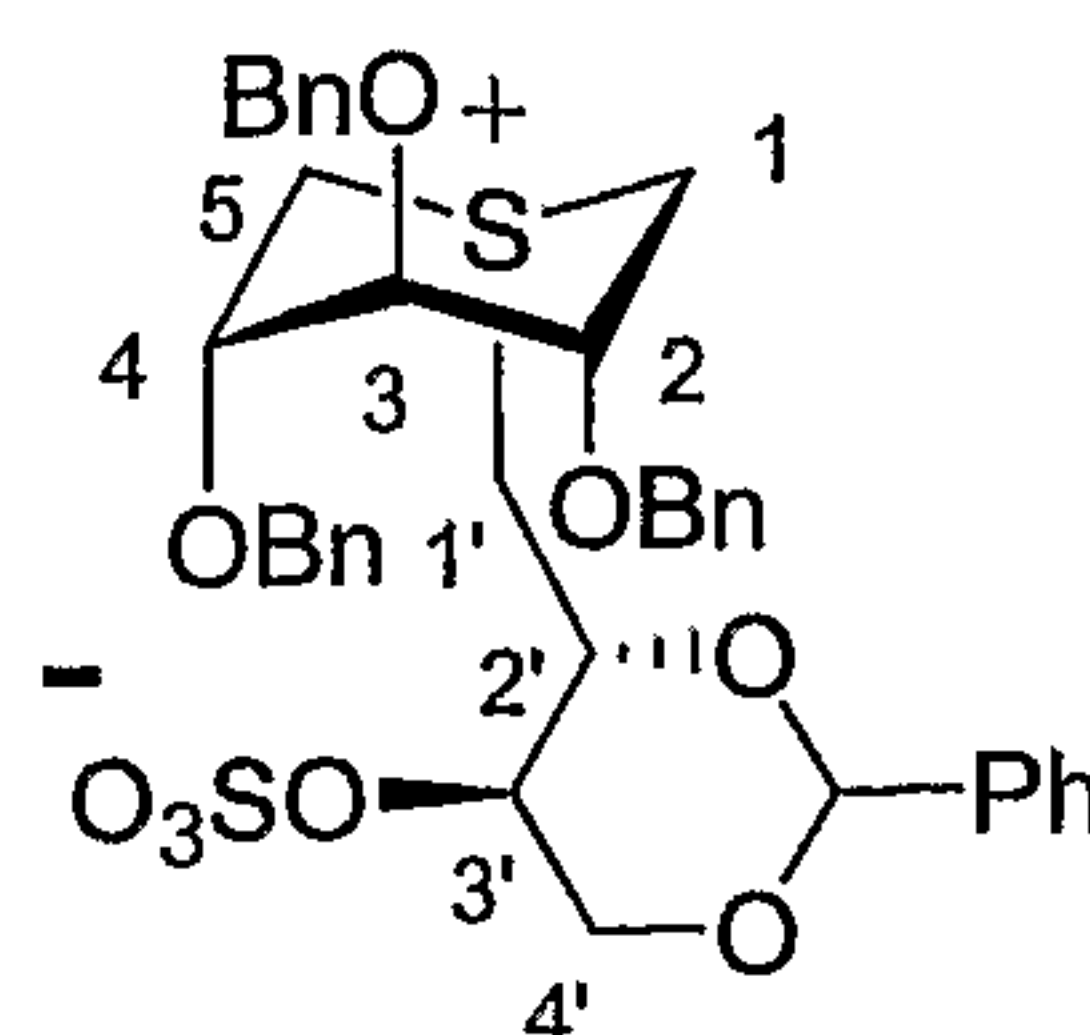
The NOESY spectrum for the minor diastereomer showed a correlation between H-1a' and the isochronous signal assigned to H-1ax/H-1eq, as well as a correlation between H-1b' and H-5eq. No correlation with H-5ax was observed. This isomer was thus assigned to structure **89b**, the diastereomer with the erythritol side chain in an axial orientation. The absolute configuration at sulfur was thus established as being *R*. Each of the diastereomers **88b** and **89b** was deprotected by hydrogenolysis to give sulfonium salts *S*-**68b** and *R*-**68b**, which were obtained in 81 and 95% yields, respectively. Vicinal coupling constants indicated that deprotection was accompanied in both cases by a change in the preponderant ring conformation from ${}^1C_4$ to ${}^4C_1$ (*S*-**68b** $J_{2,3} \approx J_{3,4} \approx 7.2$ Hz, *R*-**68b** $J_{2,3} \approx J_{3,4} \approx 9.0$ Hz). Transient one-dimensional nuclear Overhauser enhancement (NOE) difference experiments confirmed that there was no configurational inversion at the sulfonium center upon removal of the benzyl and benzyldiene protecting groups. Thus, the major isomer *S*-**68b**, upon irradiation of the H-4'b/H-1'a multiplet showed no NOE with the ring axial protons (Fig. 1). Irradiation of H-1ax/H-5ax showed NOEs on the H-1eq/H-5eq/H-3 and H-2/H-4 multiplets only. No NOEs with the erythritol side chain protons were

observed. These experiments provide evidence for the erythritol side chain occupying the axial position at sulfur, on the β -face and opposite to H-1_{ax}., and confirm the *S* configuration at the sulfonium center for the major isomer *S*-**68b**, as was previously assigned for the protected precursor **88b**.

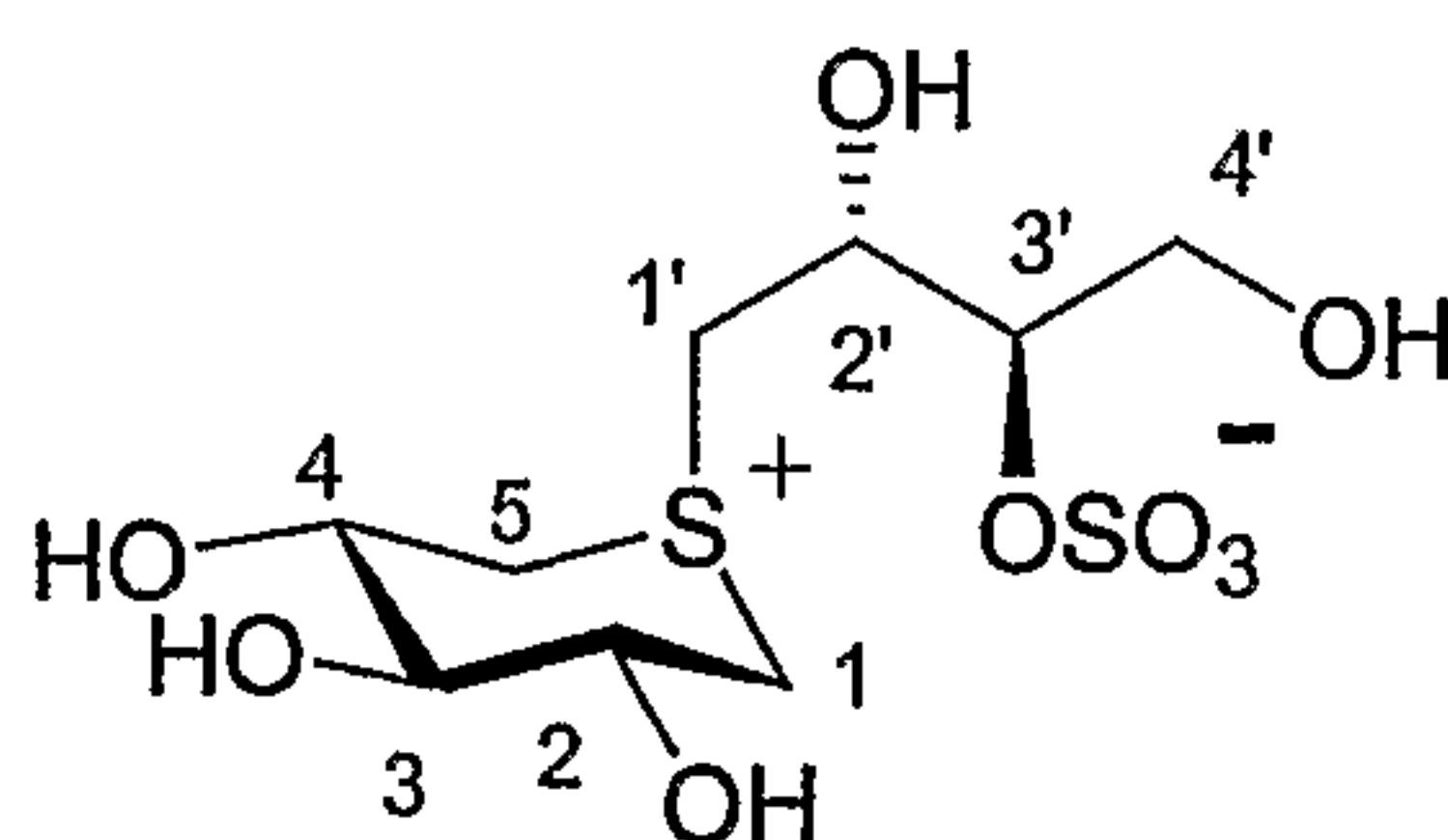
Preferred conformations of **88b**, **89b**, *S*-**68b** and *R*-**68b**



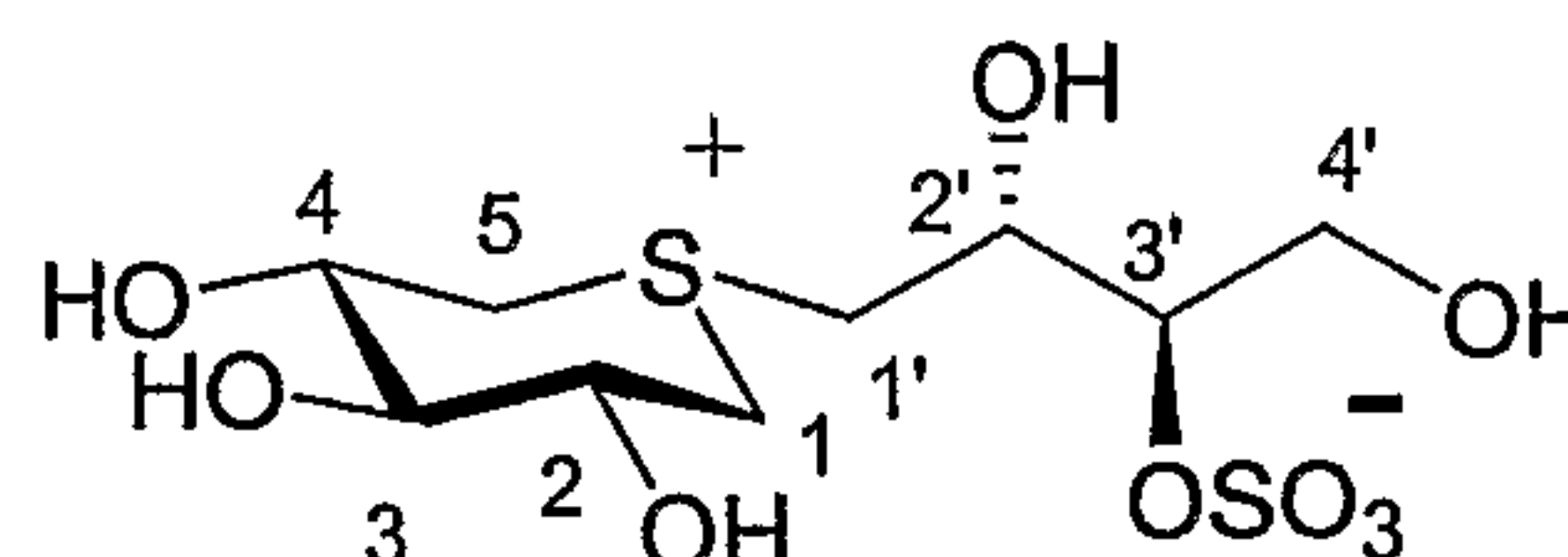
88b



89b



S-**68b**



R-**68b**

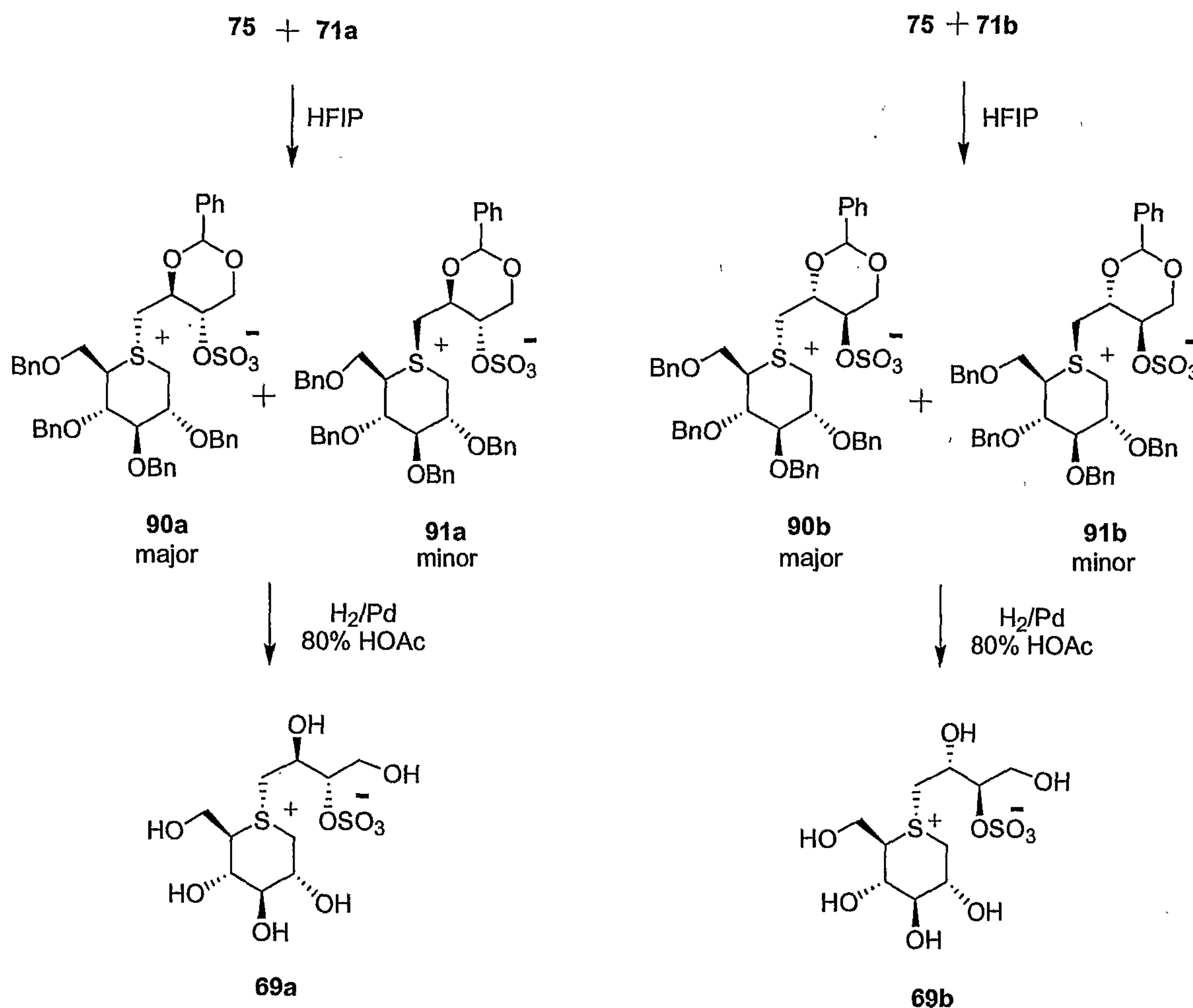
5 The minor isomer *R*-**68b** showed, upon irradiation of the H-4'_b/ H-1'_b multiplet, NOE with the H-1_{ax}/H-5_{ax} protons (Fig. 2). Irradiation of the H-1_{ax}/H-5_{ax} multiplet showed NOEs with the H-4'_b/H-1'_b multiplet as well as to the H-2/H-4/H-4'_a/H-1'_a multiplet, in addition to NOEs to the ring protons. These experiments provide evidence for the erythritol side chain being present on the same face as H-1_{ax}, occupying the α -equatorial position at sulfur, thus confirming the *R* configuration of the minor isomer *R*-**68b** at the sulfonium center, as was previously assigned for the protected precursor **89b**.

15 The synthesis of the sulfonium salts from the L-cyclic sulfate **71a** was examined next (Scheme 19). Compound **74** was reacted with **71a** at 70°C in HFIP solvent to give two products **88a** and **89a** in a 5:2 ratio (84% yield). The major diastereoisomer **88a**, in which the erythritol side chain is cis to the C-3 benzyloxy

group, was separated from the minor diastereoisomer **89a**, with the erythritol side chain trans to the C-3 benzyloxy group. The ^1H NMR spectra were virtually identical to those of the enantiomers **88b** and **89b** except for small variations due to concentration, as noted above. Each of the diastereomers **88a** and **89a** was
5 deprotected *via* hydrogenolysis to give the target compounds *R*-**68a** and *S*-**68a**.

Entry into the 5-thio-D-glucitol analogues began by treatment of 1,5-anhydro-2,3,4,6-tetra-*O*-benzyl-5-thio-D-glucitol **75** with the D-cyclic sulfate **71b**. The reaction afforded an inseparable mixture of compounds **90b** and **91b** with an approximate 2:1 isomer ratio in 70% yield (Scheme 20). As in the xylitol series, the
10 protected glucitol derivative **90b** displayed an unusual $^1\text{C}_4$ conformational preference, as indicated by the coupling constants. This places the three benzyloxy groups at C-2, C-3 and C-4 as well as the benzyloxymethyl group at C-5 in an axial orientation.

Scheme 20



The stereochemistry at the stereogenic sulfonium center for the major isomer **90b** was established by means of a NOESY experiment. A strong NOESY correlation was observed between the H-1b' proton and the H-5 proton, thus confirming that the benzylidene-protected erythritol side chain was *cis* to H-5. NOEs to H-1ax and to H-6a/H-6b were not observed. Thus, the absolute configuration at the sulfonium center in the major isomer was *S*. Alkylation of the sulfur must occur preferentially from the α -face of 1,5-anhydro-2,3,4,6-tetra-*O*-benzyl-5-thio-D-glucitol **75** due to shielding of the β -face by the adjacent C-5 benzyloxymethyl group.

The mixture consisting of compounds **90b** and **91b** was then subjected to hydrogenolysis to give primarily 1,5-dideoxy-1,5-[[*(2R, 3R)*-2,4-dihydroxy-3-(sulfooxy)-butyl]-episulfoniumylidene]-D-glucitol inner salt *S*-**69b** in 81% yield

(Scheme 20). Treatment of 1,5-anhydro-2,3,4,6-tetra-*O*-benzyl-5-thio-D-glucitol (**75**) with the L-cyclic sulfate **71a** afforded an inseparable mixture of compounds **90a** and **91a** with an approximate 3:1 isomer ratio in 68% yield (Scheme 20). Whereas the achiral anhydro xylitol compound **74** generated enantiomers upon reaction with the enantiomeric D- and L- cyclic sulfates, this was not the case for the chiral compound **75**. For this reaction, the products **90a** and **90b** are diastereomers rather than enantiomers.

The stereochemistry at the stereogenic sulfonium center for the major isomer **90a** was again established by means of a NOESY experiment. A strong NOE correlation was observed between the H-1'a proton and H-5. In addition, there was also an NOE correlation between H-2' and H-5, confirming that the benzyldiene protected erythritol side chain was on the same side as H-5. NOEs to H-1ax and to H-6a/H-6b were not observed. Thus, the absolute configuration at the sulfonium center for compound **90a** was *R*; that is, the same stereochemistry at sulfur previously found for the diastereoisomer **90b**. (Note: The change in *R/S* configuration between **90a** and **90b** due to sequence rules does not imply a change in stereochemistry at sulfur in this case). Therefore, independent of the configuration (**71a** or **71b**) of the cyclic sulfate reagent, in both cases, alkylation at sulfur occurred preferentially from the least hindered β -face of compound **75**.

The mixture containing **90a** and **91a** was then subjected to hydrogenolysis to give primarily 1,5-dideoxy-1,5-[[*(2R,3R)*-2,4-dihydroxy-3-(sulfooxy)-butyl]-*R*-episulfonium-ylidene]-D-glucitol inner salt *R*-**69a** in 67 % yield (Scheme 20).

Upon removal of the protecting groups, compounds *R*-**69a** and *S*-**69b** adopted a $^4C_1$ conformation, as indicated by the vicinal proton coupling constants. This places all of the ring substituents in an equatorial orientation, as observed for the xylitol series.

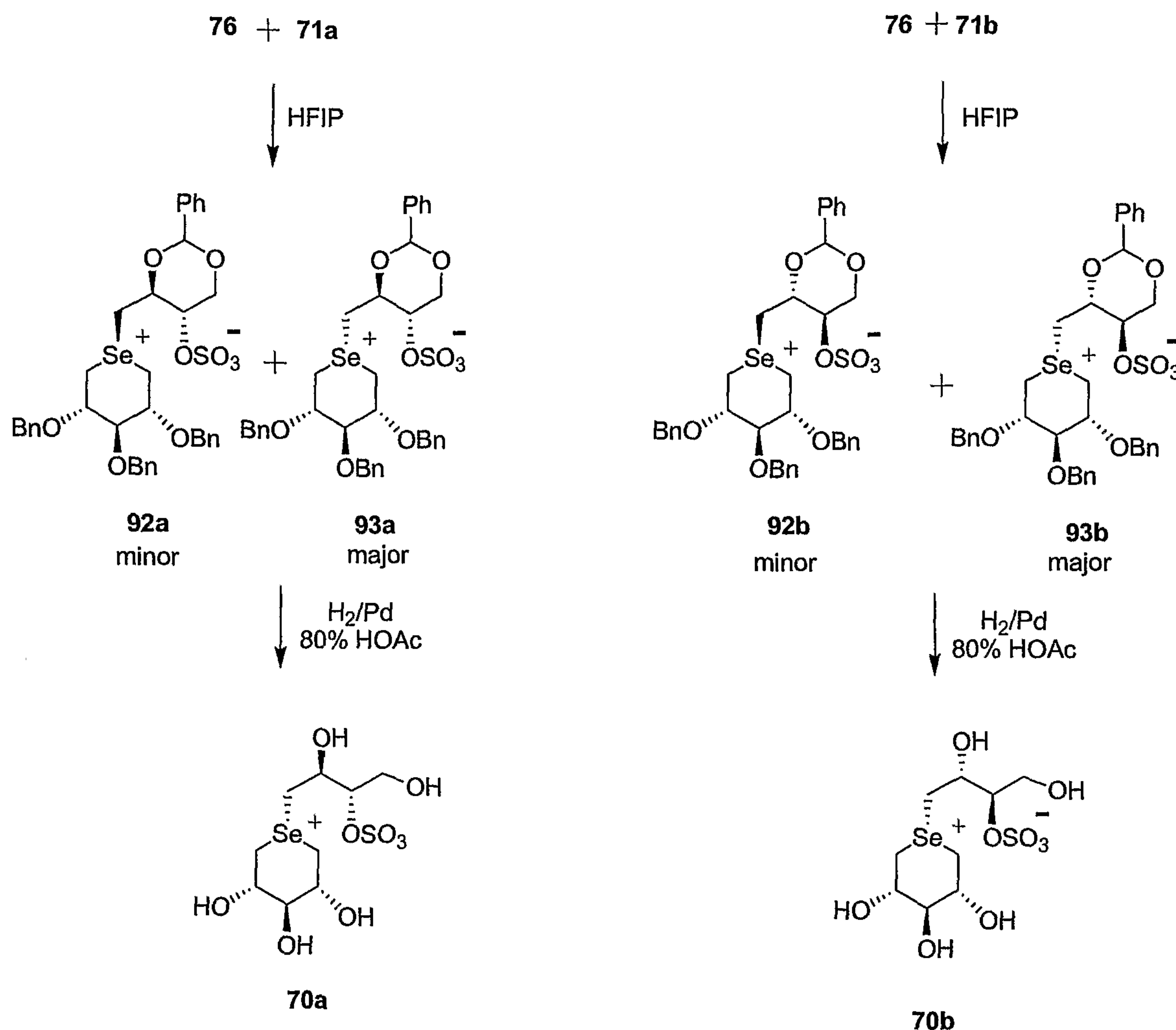
4.1.4 Target selenonium compounds

The tetrahydroselenapyran **76** was coupled to the D-cyclic sulfate **71b** in HFIP solvent and afforded an inseparable mixture of two compounds, **92b** and **93b**

in a 1:4 ratio in 96% yield (Scheme 21). These two compounds are diastereoisomers at the stereogenic selenium center. Alkylation can occur on selenium to give, as with sulfur, the benzylidene protected erythritol side chain either cis to the C-3 benzyloxy group or trans to the C-3 benzyloxy group. It was found by comparison of the NMR data to those of the sulfonium analogues **88b/89b**, and by analysis of the NOESY spectrum (see below), that the major product, **93b**, was that in which the benzylidene-protected erythritol side chain was trans to the benzyloxy group at C-3. The minor product, **92b**, was that in which the benzylidene protected erythritol side chain was cis to the C-3 benzyloxy group. Curiously, the ratio was opposite to the results obtained with the tetrahydrothiapyran products **88b** and **89b** for which the major isomer was the cis isomer. The predominant conformations observed in both compounds **92b** and **93b** were, as with the corresponding thio analogues, those which placed all three benzyloxy groups in an axial arrangement, thus favoring $^1C_4$ conformations, as evidenced by the coupling constants. The major isomer **93b** in its preferred $^1C_4$ conformation places the selenonium alkyl group in the axial position. The longer C-Se bonds in compounds **92b/93b** compared to the thio analogues must result in less severe gauche steric interactions between the selenonium alkyl group and C-2 and C-4.

The mixture consisting of compounds **92b** and **93b** was then deprotected *via* hydrogenolysis to give mostly one diastereoisomer of **70b**, in 39 % yield (Scheme 21). The low yield was due to catalyst poisoning by decomposition products and the reaction could not be brought to completion. This major compound was characterized by NMR techniques and found to be 1,5-dideoxy-1,5-[[*(2R,3R)*-2,4-dihydroxy-3-(sulfooxy)-butyl]-*R*-episelenoniumylidene]-xylitol inner salt *R*-**70b**.

Scheme 21



Reaction of the selenoether **76** with the L-cyclic sulfate **71a** was also performed. The product was an inseparable mixture of two diastereoisomers at the stereogenic selenium center, **92a** and **93a**, in a 1:3 ratio. (Scheme 21).

5 The configuration at the stereogenic selenonium centers for the enantiomers **93a** and **93b** was confirmed by means of NOESY experiments performed on the mixtures of the compounds containing their minor diastereomers. The major isomer in each case was found to be that in which the erythritol side chain occupied the axial position in the preferred ${}^1C_4$ conformation. This was evidenced by

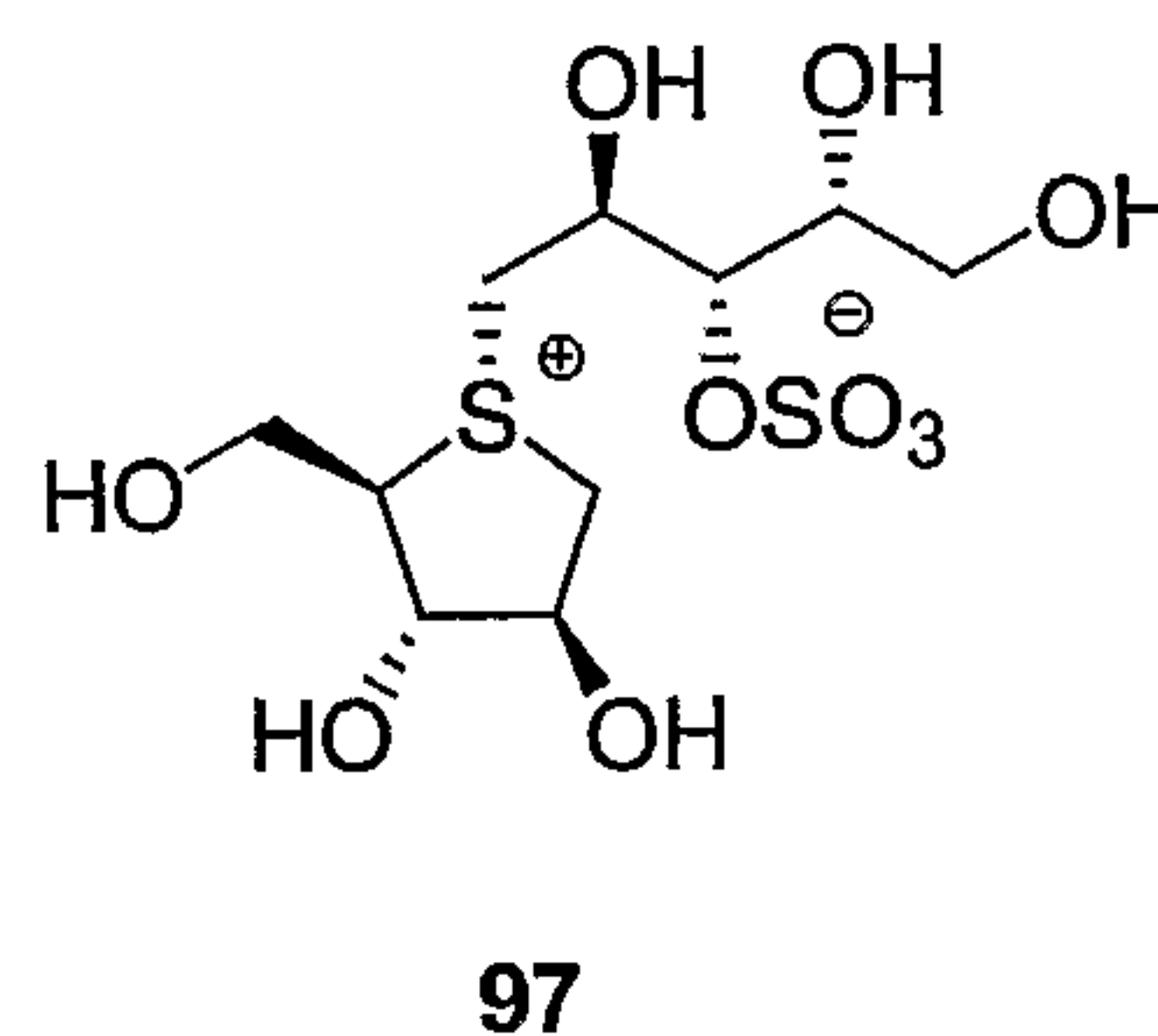
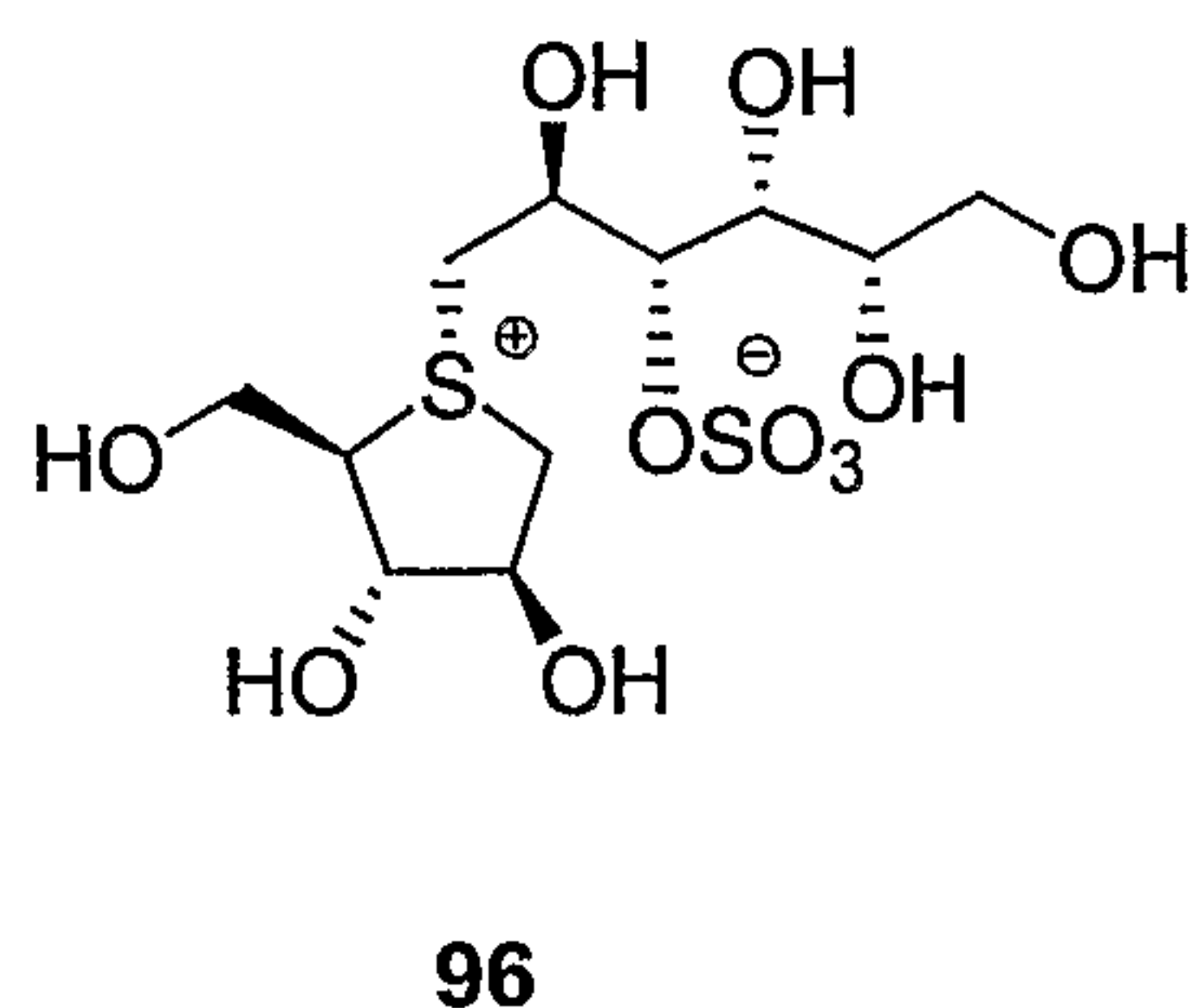
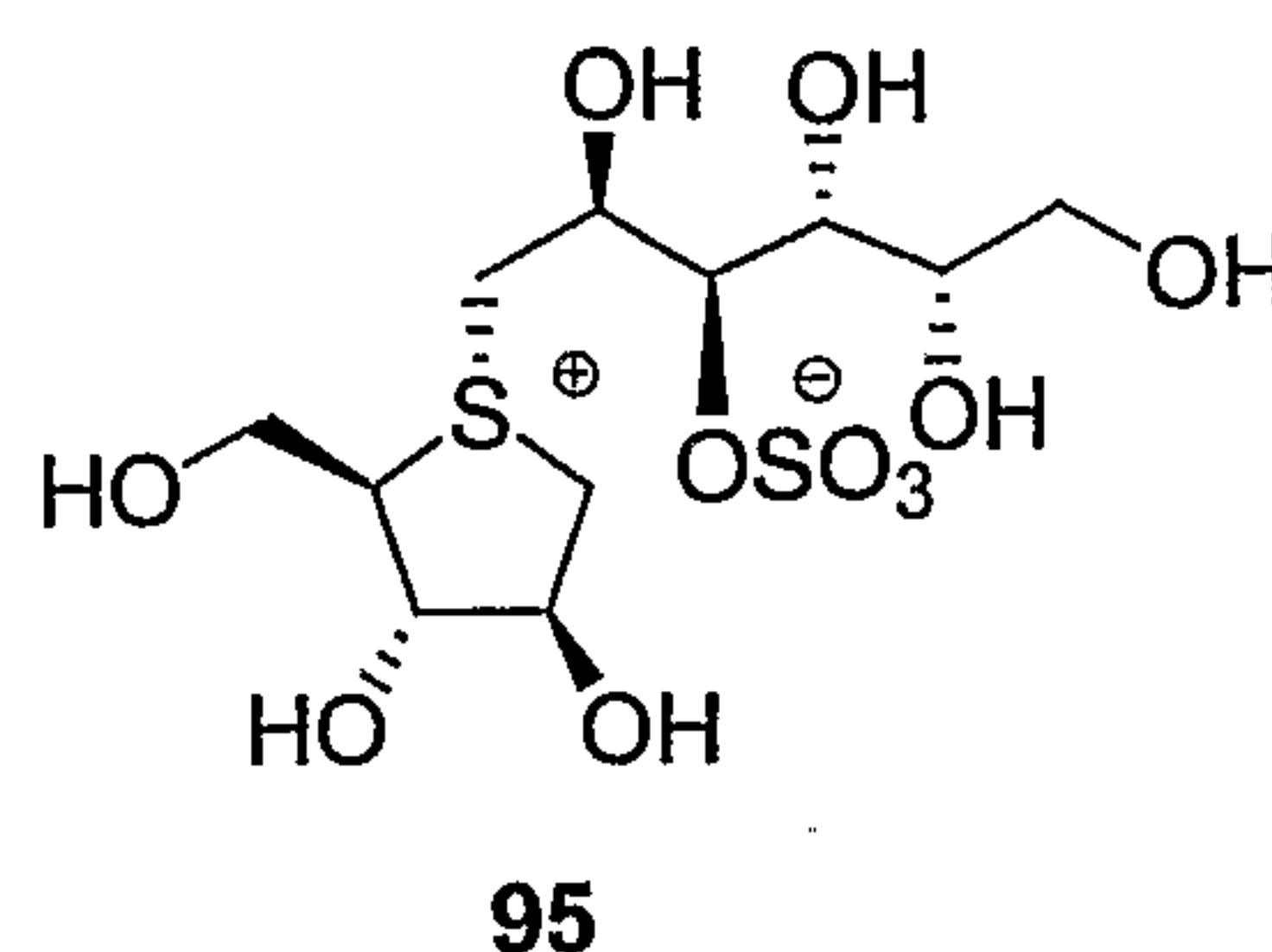
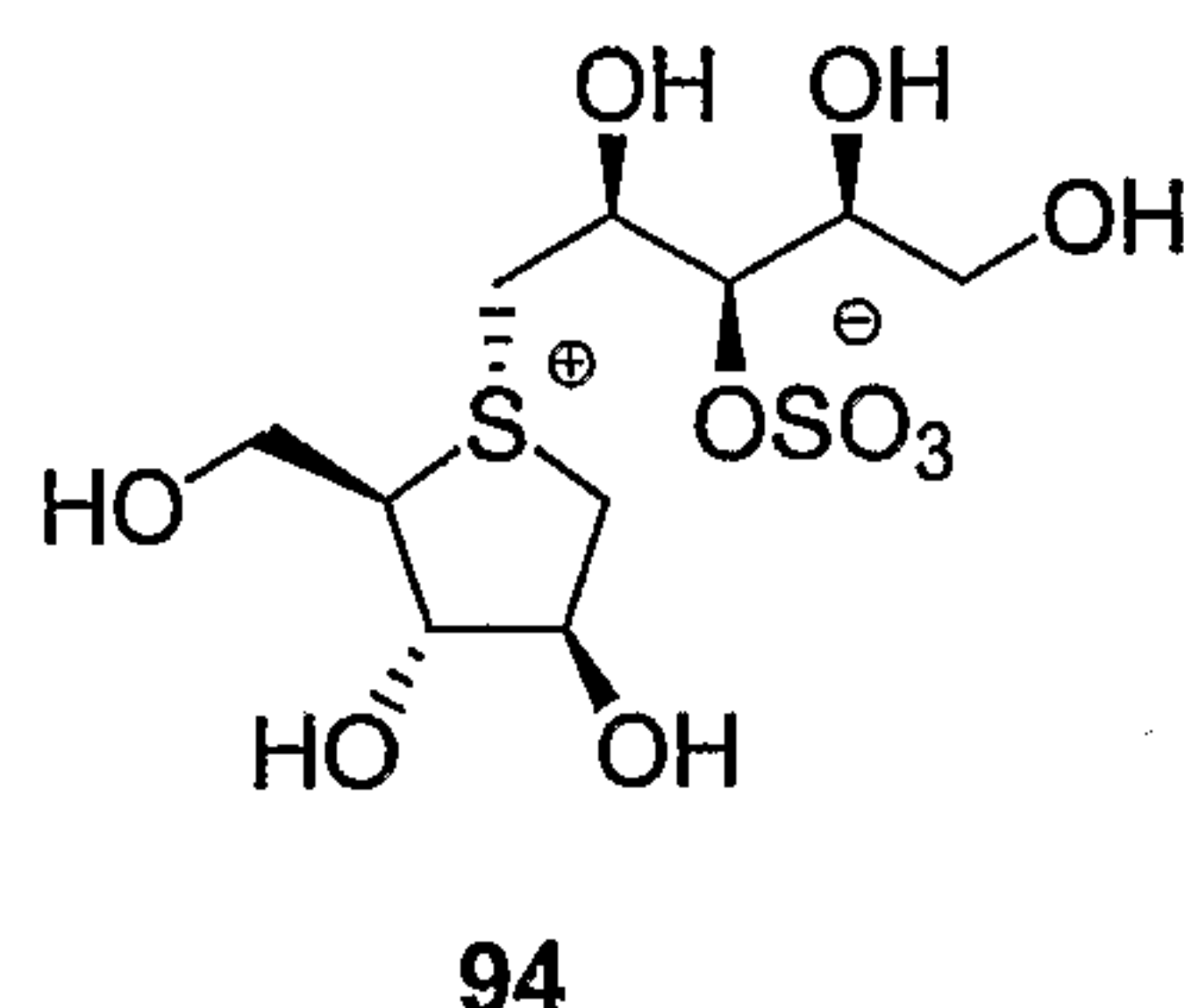
10 correlations between H-1b' and H-5eq as well as correlations between H-1'a and H-1eq. An axial preference would imply correlations between H-1'a/H-1'b and H-5eq,

and H-1'a/H-1'b and H-1eq only, since free rotation about the C-1'-Se bond would not permit the H-1'a and H-1'b protons to interact with the axial C-1 and C-5 protons as these are on the opposite side of the selenoether ring. Therefore, NOEs would not be expected between H-1'a/H-1'b and H-1ax/H-1eq. On the other hand, an equatorial preference would imply correlations between H-1'a/H-1'b to H-1ax and H-5ax as well as possibly to H-1eq and H-5eq. Thus, for compound **93b** the absolute configuration at the selenium center is *R* and that for the enantiomeric **93a** is *S*. In both cases, the erythritol side chain is cis to the benzyloxy groups at C-2 and C-4 and trans to the C-3 benzyloxy group.

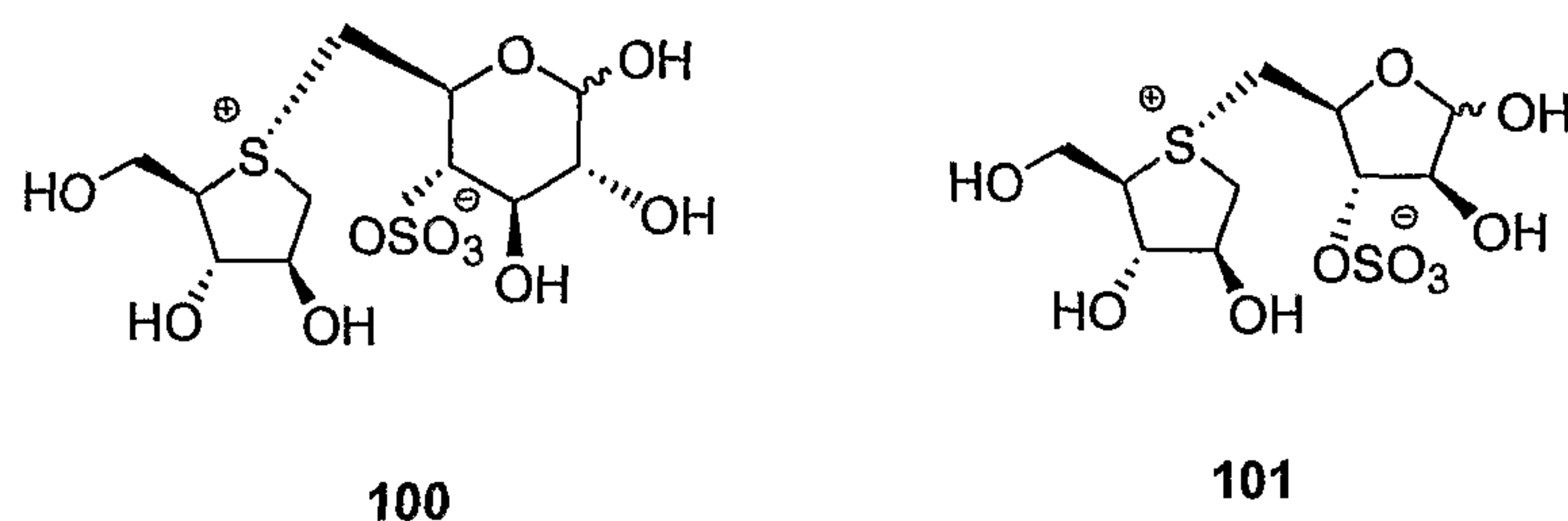
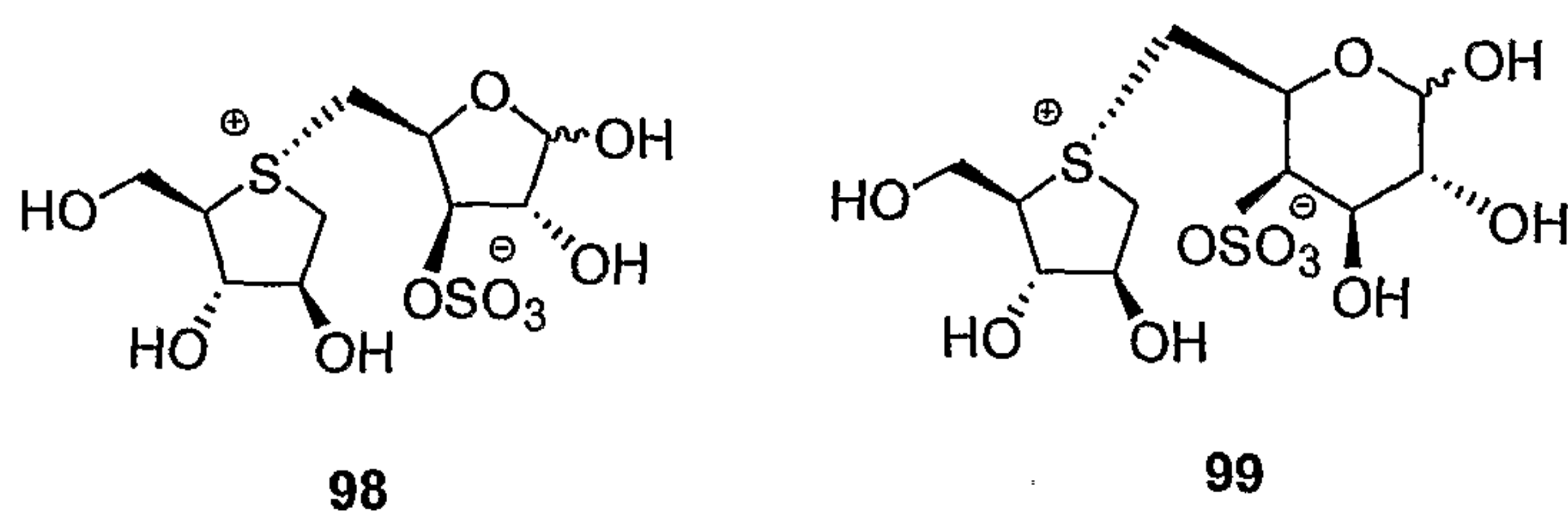
The mixture consisting of **92a** and **93a** was then deprotected by hydrogenolysis to afford mostly one diastereoisomer of **70a** in 25% yield (Scheme 21). The major compound was characterized by NMR techniques and found to be the desired 1,5-dideoxy-1,5-[[*(2S,3S)*-2,4-dihydroxy-3-(sulfooxy)-butyl]-*S*-episelenoniumylidene]-xylitol inner salt **S-70a**, the enantiomer of compound *R*-**70b**.

4.2 Chain Extended Homologues of Salacinol

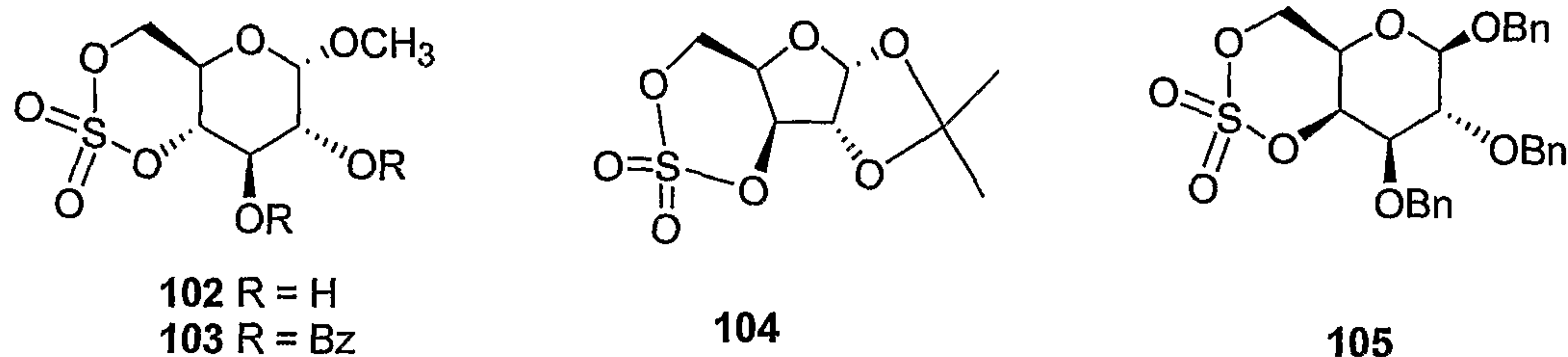
The synthesis of Salacinol and some of its enantio- and diastereoisomers is described above. In addition, the inventors have developed a strategy for synthesizing Salacinol homologues having an extended alditol side chain. In one embodiment, the side chain may have 5 or 6 carbons. Four Salacinol homologues **94** - **97** are shown below.



In principle, the desired compounds could be obtained from the sulfonium-sulfate disaccharide analogues **98** – **101**; such analogues are representatives of a new class of carbohydrate derivatives and may have interesting properties in and of themselves. They are disaccharide analogues in which a permanent positive charge resides on the non-reducing ring and linkage heteroatom simultaneously. As such, they may be mimics of the partial positive charge that is generated on analogous atoms at the transition state stage of enzyme catalyzed glycoside hydrolysis.



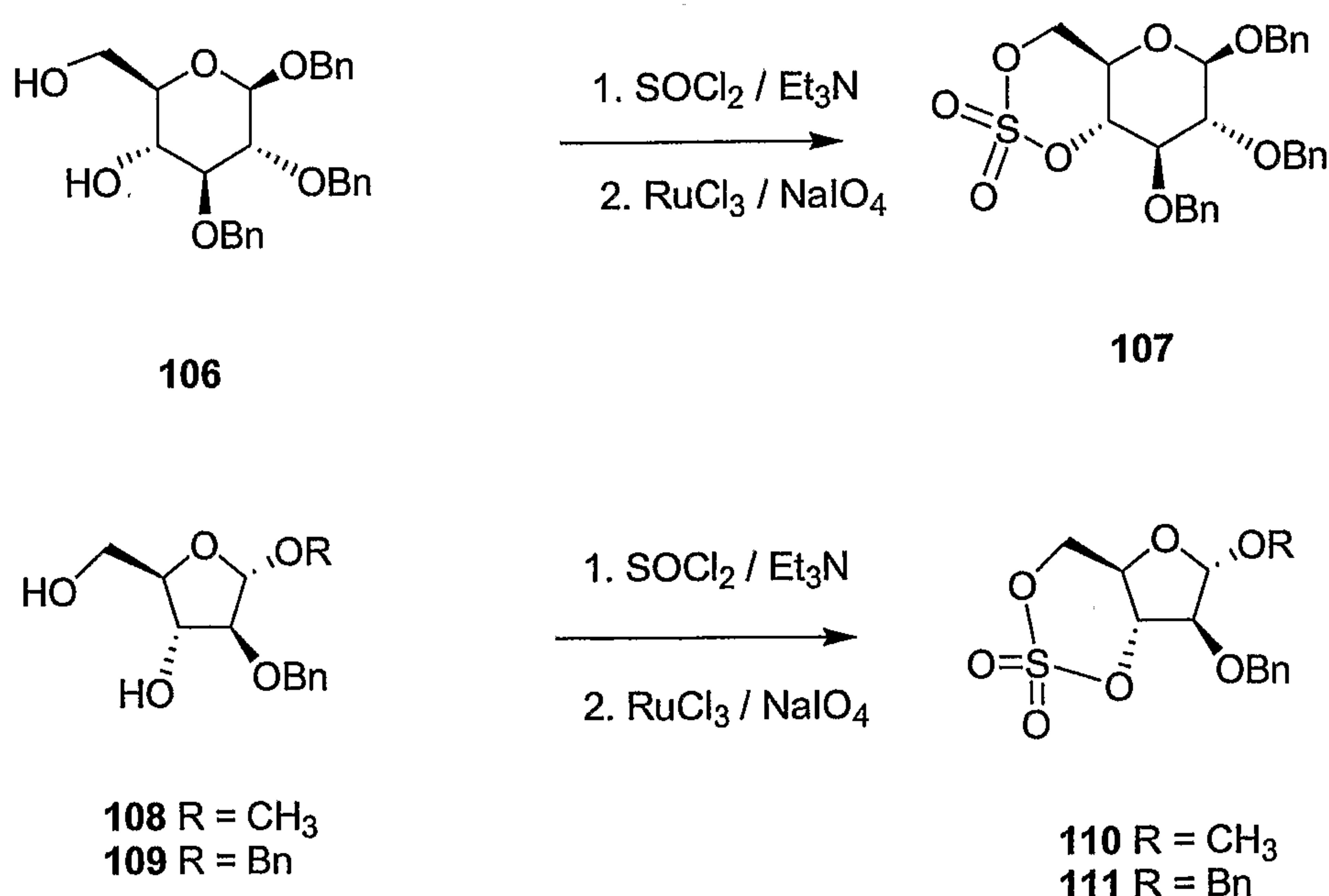
The inventors' synthetic strategy was similar to that used to the inventors' advantage for related structures as described above. This involves opening of a 1,3-cyclic sulfate ring by nucleophilic attack of a sulfide. In this case the target structures were chosen partly due to the availability of appropriate cyclic sulfate derivatives. A literature survey, searching for 1,3-cyclic sulfates of carbohydrate derivatives, returned the glucopyranoside 4,6-*O*-cyclic sulfates **102**³⁷ and **103**³⁸ as well as the xylose derivative **104**³⁹ and the galactose derivative **105**.⁴⁰



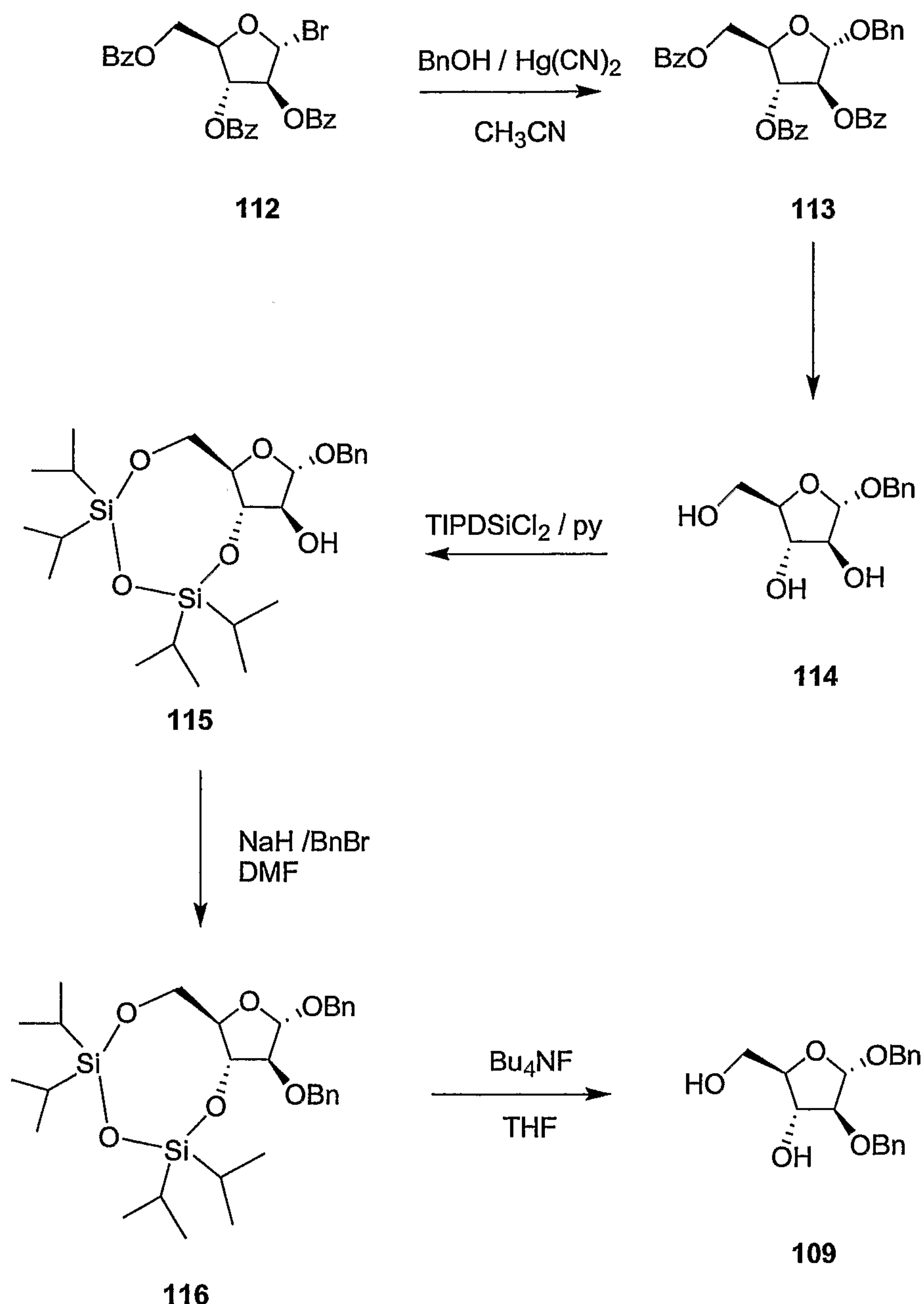
These derivatives have been shown to react with oxygen, nitrogen or sulfur nucleophiles selectively at the primary carbon. The methyl pyranosides **102** and **103** were rejected due to the probable harsh conditions necessary for hydrolysis of the glycoside bond during the deprotection of the proposed, and possibly sensitive, sulfonium intermediates. Compounds **104** and **105** were deemed to be more suitable and could be prepared by the literature methods. Three other cyclic sulfates could be prepared by new methods. Benzyl glucopyranoside 4,6-cyclic sulfate **107** could be prepared by the Sharpless method⁸¹ from known benzyl glucopyranoside **106**⁴¹ and similar treatment of the methyl or benzyl arabinofuranosides **108**⁴² and **109** would yield cyclic sulfates **110** and **111** (Scheme 22).

Schemes for the synthesis of the target chain-extended homologue compounds are shown in the schemes that follow and the testing of the general strategy is described for the reaction of the cyclic sulfate **105**.

Scheme 22



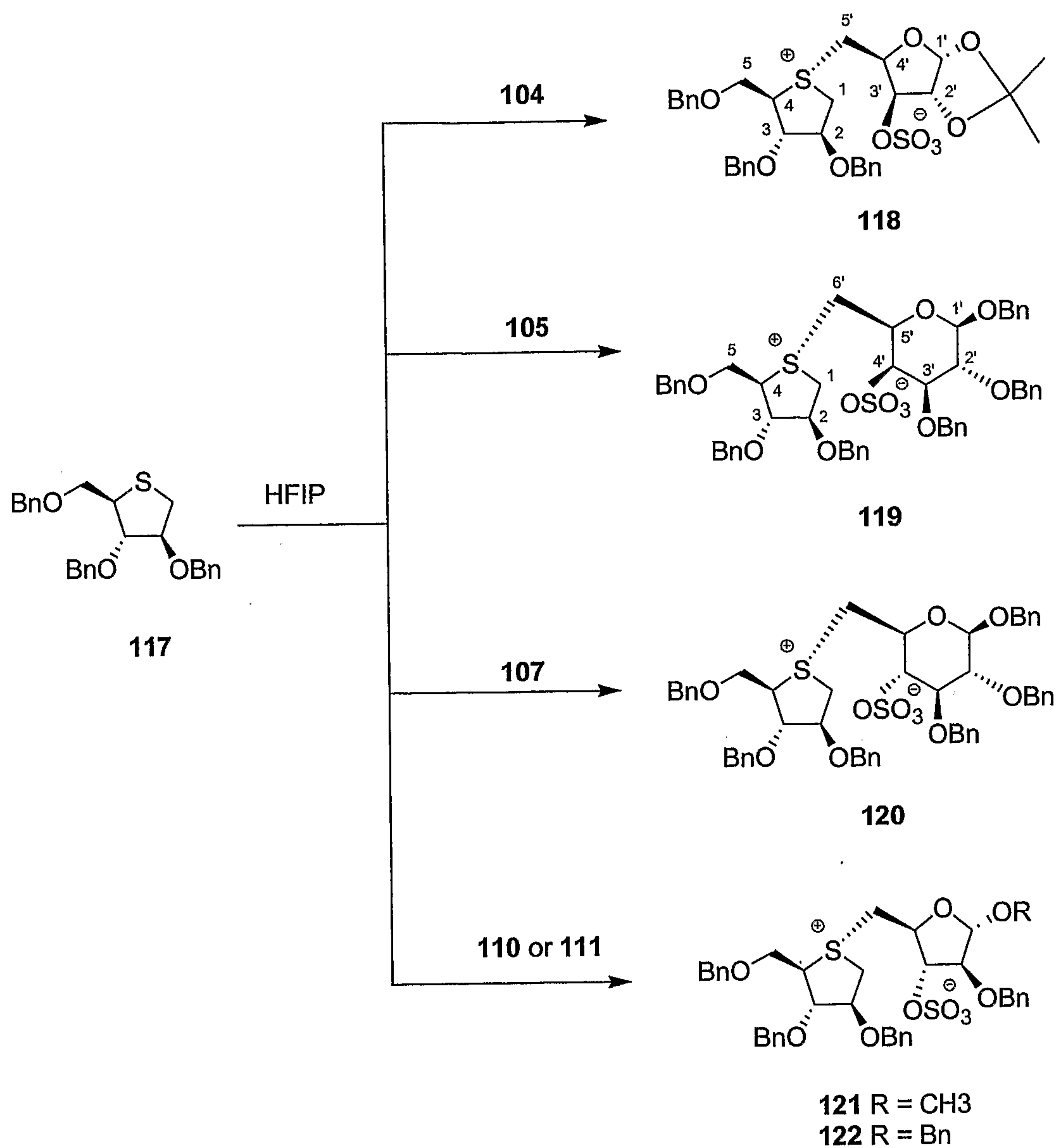
Scheme 23



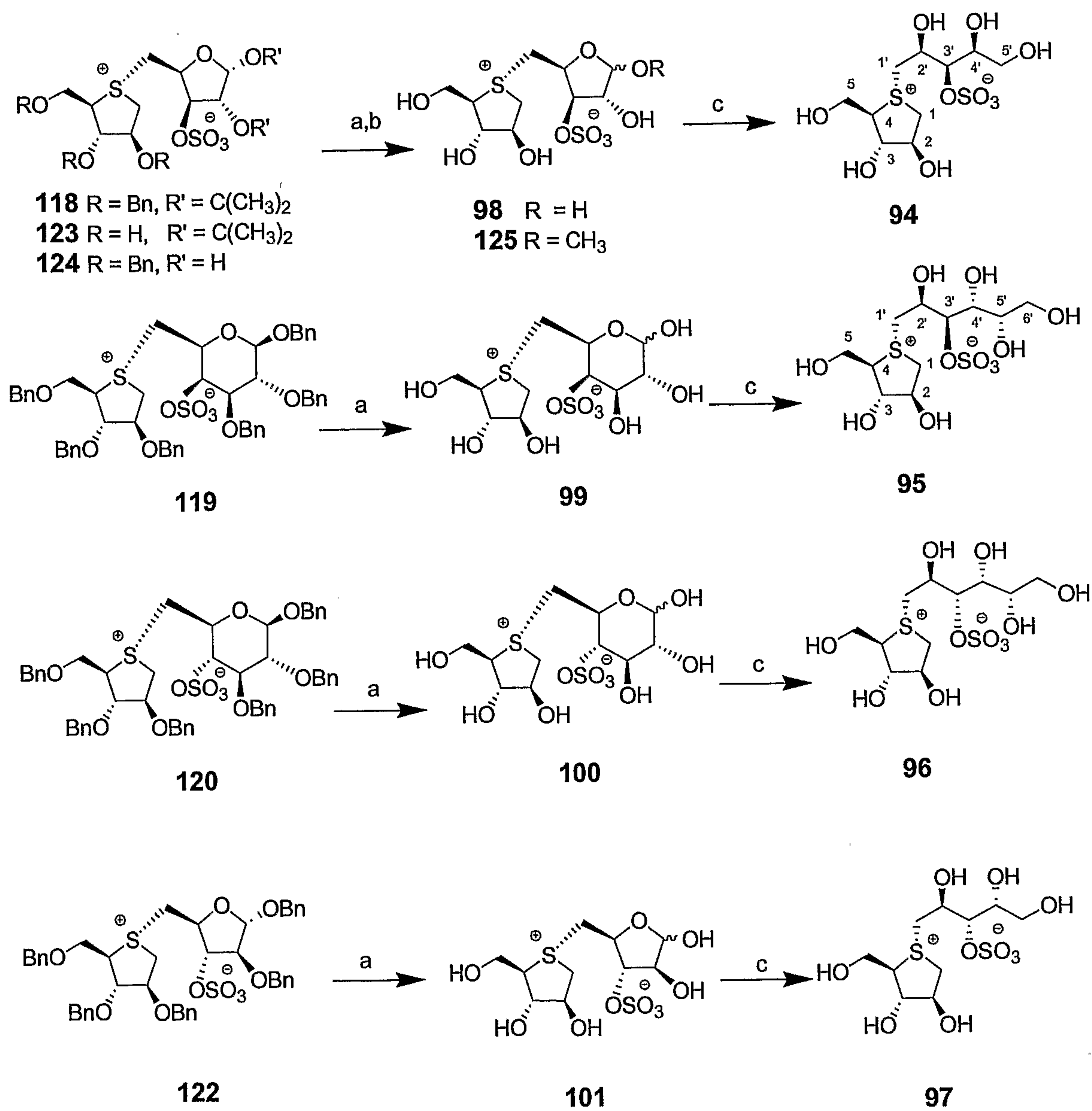
Sulfide 117 was available from earlier work²⁵ and could be prepared more conveniently by a method analogous to that developed for the corresponding selenium derivative.²⁶ Compound 117 was reacted with cyclic sulfate 105 to give protected sulfonium sulfate compound 119 (Scheme 24). The solvent was the unusual solvent 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) which the inventors have found to offer significant advantages in reactions to form sulfonium salts as mentioned above. Compound 119 was deprotected by hydrogenolysis with H₂ over a Pd catalyst to give

hemiacetal derivative **99** as a mixture of anomers. Reduction of the mixture with sodium borohydride yielded compound **95**, a chain extended analogue of Salacinol.

Scheme 24



Scheme 25



5.0 Examples

The following examples will further illustrate the invention in greater detail although it will be appreciated that the invention is not limited to the specific examples.

5 5.1 Experimental Methods

Optical rotations were measured at 20° C. ¹H and ¹³C NMR spectra were recorded at 400.13 and 100.6 MHz for proton and carbon respectively. All assignments were confirmed with the aid of two-dimensional ¹H, ¹H (COSYDFTP) or ¹H, ¹³C (INVBTP) experiments using standard Bruker pulse programs. MALDI-TOF mass spectra were obtained for samples dispersed in a 2,5-dihydroxybenzoic acid matrix using a Perseptive Biosystems Voyager-DE instrument. Silica gel for chromatography was Merck kieselgel 60. High resolution mass spectra were LSIMS (Fab), run on a Kratos Concept H double focussing mass spectrometer at 10000 RP.

15 5.2 Preparation of Intermediates

5.2.1 Example 1 - Preparation of Cyclic Sulfate (7) (Scheme 2)

Step 1 – 2,4-O-Benzylidene-D-erythritol (5).

Compound (5) was prepared from 4,6-O-benzylidene-D-glucose (4) according to standard procedures.^{9,10} Compound (5) has been mentioned by MacDonald et al.,¹⁰ without characterization, which is therefore dealt with here. Mp 138-139°C ; [α]_D – 44° (c 1.0, MeOH) ; ¹H NMR (CD₃OD): δ 7.53-7.28 (5H, m, Ar), 5.53 (1H, s, H-5), 4.2 (1H, dd, *J* = 10.1, 3.6 Hz, H-4a), 3.92 (1H, dd, *J* = 12.1, 1.7 Hz, H-1a), 3.74 (1H, dd, *J* = 12.1, 5.7 Hz, H-1b), 3.67-3.55 (3H, m, H-3, H-2, H-4b); ¹³C NMR (100.6 MHz, CD₃OD): δ 139.52 (C_{ipso}), 129.77 (C_{para}), 128.99, 127.49 (4C_{ortho+meta}), 102.36 (C-5), 84.22 (C-3), 72.21 (C-4), 62.76 (C-1), 62.59 (C-2); MALDI-TOF MS: *m/e* 211 (M⁺ + H), 233 (M⁺ + Na). Anal. Calcd for C₁₁H₁₄O₄: C, 62.83; H, 6.72. Found: C, 62.96; H, 6.55.

Step 2 – 2,4-O-Benzylidene-D-erythritol-1,3-cyclic sulfite (6).

A solution of the diol (**5**) (4.5g, 21 mmol) and Et₃N (11mL, 4equiv) in dry CH₂Cl₂ (90mL) was added dropwise to a solution of SOCl₂ (2.4mL, 1.5equiv) in dry CH₂Cl₂ (60mL), with stirring in an ice-bath under an N₂ atmosphere. Stirring was continued at 0°C, until TLC (hex:EtOAc, 4:1) showed complete disappearance of the starting material. The mixture was diluted with CH₂Cl₂ (150mL) and washed with H₂O (150mL) and brine (150mL). The organic solution was dried (Na₂SO₄) and concentrated on a rotary evaporator. The product was purified by flash chromatography [hex:EtOAc, 4:1 + 0.1% Et₃N] to give a mixture of two diastereomers (4.5g, 82%). One of the isomers was selectively recrystallized from EtOAc:hex. Mp 137-139°C; [α]_D +32° (c 1.0, CH₂Cl₂); ¹H NMR (CD₂Cl₂): δ 7.48-7.36 (5H, m, Ar), 5.68 (1H, s, H-5), 5.04 (1H, ddd, *J* = 10.4, 9.5, 5.0 Hz, H-3), 4.80 (1H, dd, *J* = 10.4, 10.4 Hz, H-1a), 4.24 (1H, dd, *J* = 10.5, 5.0 Hz, H-4e), 4.18 (1H, ddd, *J* = 10.4, 9.5, 4.8 Hz, H-2), 4.06 (1H, dd, *J* = 10.4, 4.8 Hz, H-1e), 3.89 (1H, dd, *J* = 10.5, 10.4 Hz, H-4a); ¹³C NMR (100.6 MHz, CD₂Cl₂): δ 137.14 (C_{ipso}), 129.74 (C_{para}), 128.65, 126.50 (4C_{ortho+meta}), 102.72 (C-5), 73.56 (C-2), 68.16 (C-4), 63.90 (C-3), 60.18 (C-1). Anal. Calcd for C₁₁H₁₂O₅S: C, 51.55; H, 4.72. Found: C, 51.80; H, 4.66.

Step 3 – 2,4-*O*-Benzylidene-D-erythritol-1,3-cyclic sulfate (7**).**

The cyclic sulfite (**6**) (3.5g, 14mmol) was dissolved in a mixture of MeCN (50mL) and CCl₄ (50mL), and NaIO₄ (4.1g, 1.5equiv) and RuCl₃·H₂O (50mg) were added followed by H₂O (50mL). The mixture was stirred vigorously at rt until TLC (hex:EtOAc,4:1) showed complete disappearance of the starting material. The mixture was diluted with Et₂O (200mL) and washed with H₂O (200mL) and brine (200mL). The organic solution was dried (Na₂SO₄) and concentrated on a rotary evaporator. The product was purified by flash chromatography [hex:EtOAc, 4:1 + 0.1% Et₃N] to yield a white solid (3.5g, 95%). A portion of the product was recrystallized from EtOAc:hex. Mp 115-125°C (dec); [α]_D +4° (c 1.0, CHCl₃); ¹H NMR (CD₂Cl₂): δ 7.48-7.37 (5H, m, Ar), 5.65 (1H, s, H-5), 4.86 (1H, ddd, *J* = 10.2, 9.8, 5.0 Hz, H-3), 4.76 (1H, dd, *J* = 10.7, 10.5 Hz, H-1a), 4.65 (1H, dd, *J* = 10.5, 5.0 Hz, H-1e), 4.44 (1H, dd, *J* = 10.5, 5.0 Hz, H-4e), 4.25 (1H, ddd, *J* = 10.7, 9.8, 5.0 Hz, H-2), 3.97 (1H, dd, *J* = 10.5, 10.2 Hz, H-4a); ¹³C NMR (100.6 MHz, CD₂Cl₂): δ 136.32 (C_{ipso}), 130.03 (C_{para}), 128.74, 126.52 (4C_{ortho+meta}), 102.98 (C-5), 75.74 (C-3),

73.19 (C-1), 71.68 (C-2), 67.64 (C-4); MALDI-TOF MS: m/e 273 ($M^+ + H$), Anal. Calcd for $C_{11}H_{12}O_6S$: C, 48.52; H, 4.45. Found: C, 48.43; H, 4.39.

5.2.2 Example 2 - Preparation of thio-arabinitol (Scheme 4)

5

1,4-Anhydro-2,3,5-tri-*O*-benzyl-4-thio-D-arabinitol(12).

A mixture of 1,4-anhydro-3-*O*-benzyl-4-thio-D-arabinitol (1.0g, 4.2mmol) and 60% NaH (0.85g, 5equiv) in DMF (20mL) was stirred in an ice-bath for 1h. A solution of benzyl bromide (1.9mL, 3.8equiv) in DMF (5mL) was added and the solution was
 10 stirred at rt for 3h. The mixture was added to ice-water (150mL) and extracted with Et_2O (150mL). The organic solution was dried (Na_2SO_4) and concentrated. The product was purified by flash chromatography [hex:EtOAc, 4:1] to give a syrup (1.6g, 90%). $[\alpha]_D +5^\circ$ (c 1.6, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.38-7.23 (15H, m, Ar), 4.64-4.45 (6H, m, CH_2Ph), 4.19 (1H, dd, $J = 8.9, 4.6$ Hz, H-2), 4.11 (1H, dd, $J = 7.2, 3.8$
 15 Hz, H-3), 3.69 (1H, dd, $J = 8.8, 7.6$ Hz, H-5a), 3.57 (1H, ddd, $J = 7.5, 6.4, 3.6$ Hz, H-4), 3.50 (1H, dd, $J = 8.9, 6.3$ Hz, H-5b), 3.08 (1H, dd, $J = 11.4, 5.1$ Hz, H-1a), 2.91 (1H, dd, $J = 11.4, 4.6$ Hz, H-1b). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 138.16, 138.06, 137.88 (3 C_{ipso}), 128.40-127.59 (15 C_{Ar}), 85.08 (C-3), 85.04 (C-2), 73.01 (CH_2Ph), 72.34 (C-5), 71.85, 71.50 (2 CH_2Ph), 48.99 (C-4), 33.10 (C-1). Anal.
 20 Calcd for $C_{26}H_{28}O_3S$: C, 74.25; H, 6.72. Found: C, 74.18; H, 6.53.

5.2.3 Example 3 - Preparation of seleno-arabinitol (Scheme 6)

1,4-Anhydro-2,3,5-tri-*O*-benzyl-4-seleno-D-arabinitol (20).

25 Selenium metal (1.1g, 14mmol) was added to liquid NH_3 (60mL) in a $-50^\circ C$ bath and small pieces of Na (0.71g) were added until a blue color appeared. A small portion of selenium (20mg) was added to remove the blue color. NH_3 was removed by warming on a water bath and DMF was added and removed under high vacuum to remove the rest of NH_3 . A solution of the mesylated compound (18) (7.4g, 12.7mmol) in DMF
 30 (100mL) was added and the mixture was stirred under N_2 in a $70^\circ C$ bath for 3 h. The mixture was cooled and the solvent was removed on high vacuum. The product was partitioned between CH_2Cl_2 (150mL) and water (50mL), and the organic solution was washed with water (50mL) and brine (50mL) and dried ($MgSO_4$). The product was

purified by flash chromatography (hex:EtOAc, 3:1) to give a yellow oil (4.74g, 80%).
 $[\alpha]_D^{+22}$ (c 1.3, CHCl₃); ¹H NMR (CDCl₃): δ 7.22-7.48 (15H, m, Ar), 4.67, 4.61
 (2H, 2d, *J* = 11.8 Hz, CH₂Ph), 4.56, 4.48 (2H, 2d, *J* = 12.1 Hz, CH₂Ph), 4.53, 4.50
 (2H, 2d, CH₂Ph), 4.22 (1H, dd, *J* = 10.1, 5.1 Hz, H-2), 4.07 (1H, dd, *J* = 4.6, 4.6 Hz,
 5 H-3), 3.85 (1H, dd, *J* = 9.2, 7.6 Hz, H-5a), 3.77 (1H, ddd, *J* = 7.5, 6.9, 4.5 Hz, H-4),
 3.53 (1H, dd, *J* = 9.1, 6.8 Hz, H-5b), 3.11 (1H, dd, *J* = 10.4, 5.1 Hz, H-1a), 2.96 (1H,
 dd, *J* = 10.4, 5.3 Hz, H-1b). ¹³C NMR (100.6 MHz, CDCl₃): δ 138.24, 138.21, 138.06
 (3C_{ipso}), 128.40-127.60 (15C_{Ar}), 85.93 (C-2), 85.63 (C-3), 72.96 (C-5, CH₂Ph),
 72.14, 71.50 (2CH₂Ph), 42.59 (C-4), 23.96 (C-1). Anal. Calcd for C₂₆H₂₈O₃Se: C,
 10 66.65; H, 6.03. Found: C, 66.49; H, 6.05.

5.2.4 Example 4 - General procedure for the synthesis of the protected sulfonium,
 selenonium and ammonium sulfates (21), (22), (24), (26), (27), (28), (30), (31)
 (Schemes 7 – 14).

15

The thio, aza or selenosugar (3mmol) and the cyclic sulfate (1.2equiv) were dissolved
 in dry acetone (in the case of (21), (22), (24), (26), (27) and (28)) or dry methanol (in
 the case of (30) and (31)) (0.5mL) and anhydrous K₂CO₃ (7mg) was added. The
 mixture was stirred in a Carius tube in an oil-bath (75°C) overnight. The solvent was
 20 removed under reduced pressure and the product was purified by column
 chromatography.

**1-((1',4'-Anhydro-2',3',5'-tri-*O*-benzyl-4'-thio-D-arabinitol)-4'-S-yl)-2,4-*O*-
 benzylidene-1-deoxy-L-erythritol-3-sulfate (21).**

25 Column chromatography [CHCl₃:MeOH, 10:1 + 0.1% Et₃N] of the crude product
 gave an amorphous solid (33%). $[\alpha]_D^{-11.9}$ (c 1.7, CH₂Cl₂); ¹H NMR (CD₂Cl₂): δ
 7.49-7.12 (20H, m, Ar), 5.54 (1H, s, H-5), 4.59 (1H, ddd, *J* = 9.9, 5.4, 4.5 Hz, H-3),
 4.55-4.33 (8H, m, 4CH₂Ph, H-2', H-4a, H-1a, H-3'), 4.29 (1H, dt, *J* = 9.5, 3.0 Hz, H-
 2), 4.25 and 4.15 (2H, 2d, *J* = 11.9 Hz, CH₂Ph), 4.04 (1H, m, H-1'a) 4.02-3.95 (2H,
 30 m, H-4', H-1b), 3.78 (1H, dd, *J* = 10.7, 10.7 Hz, H-4b), 3.74 (1H, dd, *J* = 13.6, 3.8 Hz,
 H-1'b), 3.62 (1H, dd, *J* = 9.9, 8.6 Hz, H-5'a), 3.54 (1H, dd, *J* = 9.9, 7.2 Hz, H-5'b);
¹³C NMR (100.6 MHz, CD₂Cl₂): δ 137.34, 137.24, 136.56, 136.39 (4C_{ipso}), 129.73-

126.62 (20C_{Ar}), 101.95 (C-5), 83.75 (C-3'), 82.82 (C-2'), 76.80 (C-2), 73.73, 72.84, 72.52 (3CH₂Ph), 69.54 (C-4), 67.01 (C-5'), 66.48 (C-3), 65.27 (C-4'), 49.67 (C-1), 48.28 (C-1'); MALDI-TOF MS: m/e 693 (M⁺ + H). Anal. Calcd for C₃₇H₄₀O₉S₂: C, 64.14; H, 5.82. Found: C, 63.88; H, 5.83.

5 **1-((1',4'-Anhydro-2',3',5'-tri-*O*-benzyl-4'-thio-D-arabinitol)-4'-S-yl)-2,4-*O*-benzylidene-1-deoxy-D-erythritol-3-sulfate (22).**

Column chromatography [CHCl₃:MeOH, 10:1 + 0.1% Et₃N] of the crude product gave an amorphous solid (79%). [α]_D -46.9° (c 0.65, CH₂Cl₂); ¹H NMR (CD₂Cl₂): δ 7.43-7.10 (20H, m, Ar), 5.49 (1H, s, H-5), 4.62-4.34 (11H, m, CH₂Ph, H-3, H-4a, H-2', H-1a, H-3'), 4.30-4.21 (2H, m, H-2, H-4'), 3.96 (1H, dd, *J* = 9.7, 6.2 Hz, H-5'a), 3.90 (1H, dd, *J* = 13.3, 3.4 Hz, H-1b), 3.82 (1H, dd, *J* = 9.8, 9.8 Hz, H-5'b), 3.79-3.71 (2H, m, H-1'a, H-4b), 3.51 (1H, dd, *J* = 13.2, 3.9 Hz, H-1'b); ¹³C NMR (100.6 MHz, CD₂Cl₂): δ 137.62, 137.27, 136.48, 136.29 (4C_{ipso}), 129.80-126.56 (20C_{Ar}), 102.16 (C-5), 84.25 (C-3'), 82.56 (C-2'), 77.07 (C-2), 74.02, 72.74 (3CH₂Ph), 69.75 (C-4), 67.19 (C-5'), 66.82 (C-3), 65.76 (C-4'), 50.41 (C-1), 49.60 (C-1'); MALDI-TOF MS: m/e 693 (M⁺ + H). Anal. Calcd for C₃₇H₄₀O₉S₂: C, 64.14; H, 5.82. Found: C, 64.16; H, 5.73.

20 **1-((1',4'-Anhydro-2',3',5'-tri-*O*-benzyl-4'-thio-L-arabinitol)-4'-S-yl)-2,4-*O*-benzylidene-1-deoxy-D-erythritol-3-sulfate (24).**

Column chromatography [CHCl₃:MeOH, 10:1 + 0.1% Et₃N] of the crude product gave an amorphous solid (40%). [α]_D +14.3° (c 1.4, CH₂Cl₂); ¹H NMR (CD₂Cl₂): δ 7.49-7.12 (20H, m, Ar), 5.55 (1H, s, H-5), 4.60 (1H, ddd, *J* = 9.8, 5.5, 4.5 Hz, H-3), 4.55-4.44 (5H, m, 3CH₂Ph, H-2', H-4a), 4.42 (1H, dd, *J* = 13.3, 2.3 Hz, H-1a), 4.39-4.34 (2H, m, CH₂Ph, H-3'), 4.28 (1H, dt, *J* = 9.8, 2.9 Hz, H-2), 4.24 and 4.14 (2H, 2d, *J* = 11.9 Hz, CH₂Ph), 4.10 (1H, d, *J* = 13.4 Hz, H-1'a), 3.98-3.90 (2H, m, H-4', H-1b), 3.78 (1H, dd, *J* = 10.5, 10.5 Hz, H-4b), 3.67 (1H, dd, *J* = 13.4, 3.8 Hz, H-1'b), 3.62 (1H, dd, *J* = 9.9, 8.7 Hz, H-5'a), 3.53 (1H, dd, *J* = 9.9, 7.2 Hz, H-5'b); ¹³C NMR (100.6 MHz, CD₂Cl₂): δ 137.32, 137.26, 136.48, 136.25 (4C_{ipso}), 129.79-126.64 (20C_{Ar}), 102.06 (C-5), 83.96 (C-3'), 82.74 (C-2'), 76.93 (C-2), 73.81, 72.97, 72.57

(3CH₂Ph), 69.59 (C-4), 67.07 (C-5'), 66.36 (C-3), 66.31 (C-4'), 49.96 (C-1), 48.52 (C-1'). Anal. Calcd for C₃₇H₄₀O₉S₂: C, 64.14; H, 5.82. Found: C, 64.13; H, 5.74.

1-((1',4'-Anhydro-3'-O-benzyl-4'-thio-D-arabinitol)-4'-S-yl)-2,4-O-benzylidene-1-deoxy-L-erythritol-3-sulfate (26).

Column chromatography [CHCl₃:MeOH, 10:1 + 0.1% Et₃N] of the crude product gave an amorphous solid (32%); ¹H NMR (CD₂Cl₂): δ 7.49-7.26 (10H, m, Ar), 6.22 (1H, d, *J* = 4.4 Hz, 2'-OH), 5.54 (1H, s, H-5), 4.96 (1H, br-s, H-2'), 4.64 (1H, d, *J* = 11.6 Hz, CH₂Ph), 4.64-4.62 (1H, m, 5'-OH), 4.56 (1H, d, *J* = 11.6 Hz, CH₂Ph), 4.54-4.48 (1H, m, H-3), 4.46 (1H, dd, *J* = 10.5, 5.4 Hz, H-4a), 4.33-4.25 (3H, m, H-3', H-2, H-1'a), 4.12 (1H, dd, *J* = 13.5, 2.6 Hz, H-1a), 4.12-4.09 (1H, m, H-4'), 4.01 (1H, dd, *J* = 13.5, 3.4 Hz, H-1b), 3.92-3.82 (2H, m, H-5'a, H-5'b), 3.78 (1H, dd, *J* = 10.5, 10.1 Hz, H-4b), 3.67 (1H, dd, *J* = 13.5, 3.9 Hz, H-1'b); ¹³C NMR (100.6 MHz, CD₂Cl₂): δ 136.92, 136.73 (2C_{ipso}), 129.97-126.61 (10C_{Ar}), 102.32 (C-5), 88.45 (C-3'), 76.61 (C-2), 76.22 (C-2'), 72.96 (CH₂Ph), 71.24 (C-4'), 69.27 (C-4), 66.96 (C-3), 60.51 (C-5'), 52.43 (C-1'), 48.30 (C-1); MALDI-TOF MS: *m/e* 513 (M⁺ + H). Anal. Calcd for C₂₃H₂₈O₉S₂: C, 53.89; H, 5.51. Found: C, 53.64; H, 5.34.

1-((1',4'-Anhydro-2',3',5'-tri-O-benzyl-4'-seleno-D-arabinitol)-4'-Se-yl)-2,4-O-benzylidene-1-deoxy-L-erythritol-3-sulfate (27).

Column chromatography [CHCl₃:MeOH, 15:1] of the crude product gave an amorphous solid (86%). NMR showed the presence of two isomers (7:1) at the stereogenic selenium center which were separated on analytical HPLC [acetonitrile/H₂O]. Anal. Calcd for C₃₇H₄₀O₉SSe: C, 59.99; H, 5.45. Found: C, 59.91; H, 5.44.

1-((1',4'-Anhydro-2',3',5'-tri-O-benzyl-4'-seleno-D-arabinitol)-4'-Se-yl)-2,4-O-benzylidene-1-deoxy-D-erythritol-3-sulfate (28).

Column chromatography [CHCl₃:MeOH, 15:1] of the crude product gave an amorphous solid (96%). NMR showed the presence of two isomers (3:1) at the stereogenic selenium center which were separated on analytical HPLC

[acetonitrile/H₂O]. Anal. Calcd for C₃₇H₄₀O₉SSe: C, 59.99; H, 5.45. Found: C, 59.91; H, 5.37.

1-((1',4'-Dideoxy-1',4'-imino-D-arabinitol)-4'-N-yl)-2,4-O-benzylidene-1-deoxy-L-erythritol-3-sulfate (30).

A mixture of 1,4-Dideoxy-1,4-imino-D-arabinitol (**19**) (100mg, 0.7mmol) and 2,4-O-benzylidene-L-erythritol-1,3-cyclic sulfate (**10**) (235mg, 1.2equiv) were dissolved in dry MeOH (0.5mL) and anhydrous K₂CO₃ (15mg) was added. The mixture was stirred in a Caries tube in an oil-bath (75°C) overnight. The solvent was removed under reduced pressure and column chromatography [CH₂Cl₂:MeOH, 4.5:1] of the crude product gave an amorphous solid (219mg, 72%). ¹H NMR (CD₃OD): δ 7.53-7.30 (5H, m, Ar), 5.61 (1H, s, H-5), 4.53 (1H, dd, *J* = 11.1, 5.2 Hz, H-4a), 4.25 (1H, m, H-2), 4.20 (1H, ddd, *J* = 9.8, 5.2, 4.4 Hz, H-3), 4.11 (1H, br-s, H-2'), 3.99-3.84 (4H, m, H-1a, H-3', H-5'a, H-5'b), 3.82 (1H, dd, *J* = 10.7, 9.8 Hz H-4b) 3.58 (1H, m, H-1'a), 3.55-3.42 (2H, m, H-1'b, H-4'), 3.38 (1H, m, H-1b); ¹³C NMR (100.6 MHz, CD₃OD): δ 138.72 (C_{ipso}), 130.12 (C_{para}), 129.21, 127.39 (4C_{ortho+meta}), 102.33 (C-5), 78.01 (C-4', C-3', C-2), 76.31 (C-2'), 70.29 (C-4), 69.02 (C-3), 62.64 (C-1'), 60.51 (C-5'), 58.46 (C-1); MALDI-TOF MS: *m/e* 428 (M⁺ + Na), 406 (M⁺ + H); HRMS. Calcd for C₁₆H₂₃O₉SN (M + H): 406.1179. Found: 406.1192.

20

1-((1',4'-Dideoxy-1',4'-imino-L-arabinitol)-4'-N-yl)-2,4-O-benzylidene-1-deoxy-D-erythritol-3-sulfate (31).

A mixture of 1,4-Dideoxy-1,4-imino-L-arabinitol (**16**) (80mg, 0.6mmol) and 2,4-O-benzylidene-D-erythritol-1,3-cyclic sulfate (**7**) (190mg, 1.2equiv) were dissolved in dry MeOH (0.5mL) and anhydrous K₂CO₃ (10mg) was added. The mixture was stirred in a Caries tube in an oil-bath (75°C) overnight. The solvent was removed under reduced pressure and column chromatography [CH₂Cl₂:MeOH, 5:1] of the crude product gave an amorphous solid (175mg, 72%). ¹H NMR (CD₃OD): δ 7.52-7.31 (5H, m, Ar), 5.62 (1H, s, H-5), 4.53 (1H, dd, *J* = 10.9, 5.2 Hz, H-4a), 4.28 (1H, m, H-2), 4.20 (1H, ddd, *J* = 9.7, 5.1, 4.6 Hz, H-3), 4.14 (1H, br-s, H-2'), 4.03 (1H, m, H-1a), 3.98-3.84 (3H, m, H-3', H-5'a, H-5'b), 3.81 (1H, dd, *J* = 10.9, 10 Hz H-4b) 3.63 (1H, m, H-1'a), 3.55-3.42 (2H, m, H-1'b, H-4'), 3.38 (1H, m, H-1b); ¹³C NMR

30

(100.6 MHz, CD₃OD): δ 138.66 (C_{ipso}), 130.15 (C_{para}), 129.23, 127.40 (4C_{ortho+meta}), 102.34 (C-5), 77.81 (C-4'), 77.52 (C-3', C-2), 76.19 (C-2'), 70.27 (C-4), 68.92 (C-3), 62.68 (C-1'), 60.41 (C-5'), 58.61 (C-1); MALDI-TOF MS: m/e 428 (M⁺ + Na), 406 (M⁺ + H).

5

5.2.4.1 Example 4.1 – General procedure for the alternative synthesis of Salacinol (1) (Schemes 10(a) to 10(c)).

2,3,5-Tri-*O*-benzyl-1,4-dideoxy-1,4-[[*(2S,3S)*-2,4-di-(benzyloxy)-3-sulfoxy]butyl]-episulfoniumylidene]-D-arabinitol Inner Salt (42).

- 10 A mixture of the thioether **33**²⁵ (270 mg, 0.64 mmol) and 2,4-Di-*O*-benzyl-1,3-cyclic sulfate (**41**)^{15,26} (280 mg, 0.77 mmol) in either acetone or HFIP (0.5 mL), containing anhydrous K₂CO₃ (16 mg, 0.10 mmol) was stirred in a sealed tube in an oil-bath (75-80 °C) for 14h. The solvent was removed under reduced pressure and the residue was purified by column chromatography using (CH₂Cl₂:MeOH, 10:1) as eluant to give the
- 15 *title compound 42*, as an amorphous solid (29 mg, 5%) in acetone and (229 mg, 45%) in HFIP. R_f 0.40 (CH₂Cl₂:MeOH, 10:1); [α]_D - 26° (c 1.3, CHCl₃); ¹H NMR (CDCl₃): δ 7.38-7.05 (25H, m, Ar), 4.67 and 4.45 (2H, 2d, J_{A,B} = 11.8 Hz, CH₂Ph), 4.60 and 4.45 (2H, 2d, J_{A,B} = 9.5 Hz, CH₂Ph), 4.59 and 4.44 (2H, 2d, J_{A,B} = 11.2 Hz, CH₂Ph), 4.58 (1H, dt, J_{2',3'} = 5.0 Hz, H-3'), 4.42 and 4.28 (2H, 2d, J_{A,B} = 11.0 Hz, CH₂Ph), 4.36 (1H, m, H-2), 4.32 (1H, ddd, J = 1.7, 4.1, 6.3 Hz, H-2'), 4.30 and 4.20 (2H, 2d, J_{A,B} = 11.7 Hz, CH₂Ph), 4.23 (1H, m, H-3), 4.13 (1H, dd, J_{1'a,1'b} = 13.4, J_{1'a,2'} = 2.0 Hz, H-1'a), 4.05 (1H, d, J_{2,3} = 13.3 Hz, H-1a), 4.00 (1H, dd, J_{4'a,4'b} = 11.1, J_{3',4'a} = 2.7 Hz, H-4'a), 3.86 (1H, dd, J_{3',4'b} = 2.4, J_{4'a,4'b} = 11.3 Hz, H-4'b), 3.71 (1H, brt, J = 9.2 Hz, H-4), 3.69 (1H, dd, J_{1'b,2'} = 3.8, J_{1'b,1'a} = 9.2 Hz, H-1'b), 3.60 (1H, dd, J_{1a,1b} = 13.5, J_{1b,2} = 3.8 Hz, H-1b), 3.51 (1H, dd, J_{5a,5b} = 13.6, J_{4,5a} = 9.7 Hz, H-5a), 3.49 (1H, dd, J_{4,5b} = 9.7 Hz, H-5b); ¹³C NMR (CDCl₃): δ 137.97, 136.77, 136.71, 136.05 and 135.77 (5×C_{ipso} Ph), 128.81-127.66 (25C, Ph), 83.14 (C-3), 81.65 (C-2), 74.59 (C-3'), 73.81, 73.53, 3.39, 72.12, 71.84 (5×CH₂Ph), 73.10 (C-2'), 68.79 (C-4'), 66.62 (C-5), 65.53 (C-4), 50.89 (C-1'), 48.07 (C-1). MALDI-TOF MS: m/e 785.41 (M⁺+H),
- 25 808.32 (M⁺+Na). Anal. Calcd for C₄₄H₄₈O₉S₂: C, 67.32; H, 6.16. Found: C, 67.36; H, 6.10.
- 30

2,3,5-Tri-*O*-benzyl-1,4-dideoxy-1,4-[[*(2S,3S)*-2,4-*O*-benzylidene-3-(sulfooxy)butyl]-episulfoniumylidene]-D-arabinitol (35).

A mixture of the thioether 33²⁵ (260 mg, 0.62 mmol) and 2,4-Di-*O*-benzylidene-1,3-cyclic sulfate (34)²⁵ (200 mg, 0.74 mmol) in either acetone or HFIP (0.5 ml) containing K₂CO₃ (13 mg, 0.09 mmol) was treated as described above to yield the *title compound* 35²⁵ as an amorphous solid (252 mg, 59% in acetone) and (406 mg, 94% in HFIP).

1,4-Anhydro-2,3,5-tri-*O*-(*p*-methoxybenzyl)-4-thio-D-arabinitol (43).

To an ice cold mixture of 1,4-anhydro-4-thio-D-arabinitol 38²⁵ (0.98 g, 6.52 mmol) and 60% NaH (1.56 g, 39.15 mmol, 6 equiv.) in THF (15 mL), a solution of *p*-methoxybenzyl chloride (4.59 g, 29.34 mmol, 4.5 equiv.) in THF (10 mL) was added over 30 min. The reaction mixture was allowed to attain room temperature and further stirred for 1h before heating to 55 °C for 12h. The reaction mixture was cooled and poured in to ice-water (150 mL) and extracted with Et₂O (150 mL). The organic solution was dried (Na₂SO₄) and concentrated. The product was purified by column chromatography [hexanes:EtOAc, 7:3] to give a colorless syrup (2.96 g, 87%). $[\alpha]_D + 6^\circ$ (*c* 1, CHCl₃); ¹H NMR (CDCl₃): δ 7.20-6.80 (12H, m, Ar), 4.55 (2H, s, CH₂Ph), 4.48 and 4.45 (2H, 2d, *J*_{A,B} = 11.7 Hz, CH₂Ph), 4.42 and 4.39 (2H, 2d, *J*_{A,B} = 12.0 Hz, CH₂Ph), 4.13 (1H, dd, *J*_{1a,2} = 4.6 , *J*_{2,3} = 9.1 Hz, H-2), 4.05 (1H, dd, *J*_{2,3} = *J*_{3,4} = 3.7 Hz, H-3), 3.81 (3H, s, OCH₃), 3.79 (3H, s, OCH₃), 3.76 (3H, s, OCH₃), 3.64 (1H, dd, *J*_{5a,5b} = 8.9, *J*_{4,5a} = 7.5 Hz, H-5a), 3.50 (1H, ddd, *J*_{4,5b} = 6.3 Hz, H-4), 3.45 (1H, dd, H-5b), 3.04 (1H, dd, *J*_{1a,1b} = 11.4, *J*_{1a,2} = 5.2 Hz, H-1a), 2.85 (1H, dd, H-1b). ¹³C NMR (CDCl₃): δ 159.24, 159.16 (3C_{para}), 130.31, 130.19, 130.01 (3C_{ipso}), 129.48, 129.28, 129.22 (6 C_{ortho}), 113.80, 113.74 (6 C_{meta}), 84.77 (C-3), 84.70 (C-2), 72.66, 71.49, 71.20 (3×CH₂Ph), 72.15 (C-5), 55.24 (3×OCH₃), 48.96 (C-4), 33.07 (C-1). Anal. Calcd for C₂₉H₃₄O₆S: C, 68.21; H, 6.71. Found: C, 67.99; H, 6.69.

2,3,5-Tri-*O*-*p*-Methoxybenzyl-1,4-dideoxy-1,4-[[*(2S,3S)*-2,4-benzylidenedioxy-3-(sulfooxy)butyl]-episulfoniumylidene]-D-arabinitol Inner Salt (44).

A mixture of the thioether 43 (1.50 g, 2.94 mmol), and the cyclic sulfate 34 (0.96 g, 1.2 equiv) in HFIP (2.5 mL) containing anhydrous K₂CO₃ (30 mg) was stirred in a

sealed tube in an oil-bath (55°C) overnight. TLC analysis (CH₂Cl₂:MeOH, 10:1) showed that the thioether **43** was completely consumed. The solvent was removed under reduced pressure and the product was purified by column chromatography (gradient of CH₂Cl₂ to CH₂Cl₂:MeOH, 10:1) to give compound **13** (2.3 g, 100%) as a colorless foam. $[\alpha]_D -10.5^\circ$ (*c* 1.1, CH₂Cl₂); ¹H NMR (CD₂Cl₂): δ 7.51-6.81 (17H, m, Ph), 5.53 (1H, s, C₆H₅CH), 4.57 (1H, ddd, $J_{2',3'} = J_{3',4'ax} = 10.0$, $J_{3',4'eq} = 5.5$ Hz, H-3'), 4.49 (1H, dd, $J_{4'ax,4'eq} = 10.8$ Hz, H-4'eq), 4.44 (2H, s, CH₂Ph), 4.42-4.39 (1H, m, H-2), 4.39 and 4.29 (2H, 2d, $J_{A,B} = 11.4$ Hz, CH₂Ph), 4.33 (1H, dd, $J_{1'a,1'b} = 13.4$, $J_{1'a,2'} = 2.6$ Hz, H-1'a), 4.29-4.26 (1H, m, H-3), 4.26 (1H, ddd, H-2'), 4.19 and 4.09 (2H, 2d, $J_{A,B} = 11.5$ Hz, CH₂Ph), 4.03 (1H, br d, $J_{1a,2} < 1$ Hz, H-1a), 3.96-3.89 (2H, m, H-4, H-1'b), 3.80 (3H, s, OCH₃), 3.79 (3H, s, OCH₃), 3.78 (3H, s, OCH₃), 3.77 (1H, dd, H-4'ax), 3.63 (1H, dd, $J_{1a,1b} = 13.3$, $J_{1b,2} = 3.8$ Hz, H-1b), 3.58 (1H, dd, $J_{5a,5b} = 9.9$, $J_{4,5a} = 8.5$ Hz, H-5a), 3.49 (1H, dd, $J_{4,5b} = 7.3$ Hz, H-5b); ¹³C NMR (CD₂Cl₂): δ 160.30, 160.23, 159.97, 137.20 and 130.27-126.61 (21×C, Ph), 114.45, 114.36 and 114.18 (3×C_{ipso}, OMBn), 101.96 (PHCH), 83.29 (C-3), 82.37 (C-2), 76.76 (C-2'), 73.36, 72.43, and 72.14 (3×CH₂Ph), 69.50 (C-4'), 66.71 (C-5), 66.55 (C-4), 66.45 (C-3'), 55.61 (3C, 3×OCH₃), 49.55 (C-1'), 48.48 (C-1). Anal. Calcd for C₄₀H₄₆O₁₂S₂: C, 61.36; H, 5.92. Found: C, 61.13; H, 6.00.

1,4-Dideoxy-1,4-[[[(2S,3S)-2,4-dihydroxy-3-(sulfooxy)butyl]-episulfoniumylidene]-D-arabinitol Inner Salt (1). Compound **13** (2.30 g, 2.94 mmol) was dissolved in trifluoroacetic acid (24 mL) and while stirring, water (2.4 mL) was added. The mixture was stirred at room temperature for 0.5 h. The solvent was removed under reduced pressure and the gummy residue was washed with CH₂Cl₂ (3 × 20 mL). Water (15 mL) was added to dissolve the crude product, and then evaporated under reduced pressure to remove the traces of acid left. Salacinol **1** (0.67 g, 68%) was crystallized from MeOH. The mother liquor was concentrated and purified by column chromatography (EtOAc:MeOH:H₂O, 7:3:1) to give more Salacinol **1** as a white solid (0.18 g, 18%).

5.2.5 Example 5 - General procedure for the deprotection of the protected sulfonium sulfates (Schemes 7 - 10) and ammonium sulfates (Schemes 13 - 14)

The protected compound was dissolved in AcOH:H₂O, 4:1 (3mL) and stirred with Pd-C (80mg) under H₂ (52 psi). After 60h the reaction mixture was filtered through a pad of Celite, which was consequently washed with MeOH. The combined filtrates were concentrated and the residue was purified by column chromatography.

5

1-((1',4'-Anhydro-4'-thio-D-arabinitol)-4'-S-yl)-1-deoxy-L-erythritol-3-sulfate (1).

Column chromatography [CHCl₃:MeOH:H₂O, 7:3:1] of the crude product gave an amorphous solid (67%). $[\alpha]_D +2.1^\circ$ (c 0.48, MeOH); ¹H NMR (pyridine-d₅): δ 5.25 (1H, ddd, $J = 7.4, 3.8, 3.6$ Hz, H-3), 5.14-5.09 (2H, m, H-3', H-2'), 5.00 (1H, m, H-2), 4.78 (1H, dd, $J = 13.0, 4.9$ Hz H-1a), 4.70 (1H, m, H-4'), 4.63 (1H, dd, $J = 13.0, 4.0$ Hz H-1b), 4.61 (1H, dd, $J = 11.8, 3.7$ Hz H-4a) 4.53 (2H, m, H-5'a, H-5'b), 4.38 (1H, dd, $J = 11.8, 3.8$ Hz H-4b), 4.32 (2H, br-s, H-1'a, H-1'b); ¹³C NMR (100.6 MHz, pyridine-d₅): δ 79.14 (C-3), 79.06 (C-3'), 78.18 (C-2'), 72.30 (C-4'), 67.44 (C-2), 62.05 (C-4), 59.98 (C-5'), 52.46 (C-1), 50.35 (C-1'). HRMS. Calcd for C₉H₁₈O₉S₂ (M + H): 335.0471. Found: 335.0481.

1-((1',4'-Anhydro-4'-thio-D-arabinitol)-4'-S-yl)-1-deoxy-D-erythritol-3-sulfate (23).

Column chromatography [CHCl₃:MeOH:H₂O, 7:3:1] of the crude product gave an amorphous solid (59%). $[\alpha]_D -35.6^\circ$ (c 0.86, MeOH); ¹H NMR (pyridine-d₅): δ 5.19 (1H, ddd, $J = 8.0, 4.1, 3.6$ Hz, H-3), 5.17-5.12 (2H, m, H-2', H-3'), 5.00 (1H, ddd, $J = 8.0, 5.3, 4.1$ Hz, H-2), 4.83 (1H, dd, $J = 13.0, 5.1$ Hz H-1a), 4.78 (1H, m, H-4'), 4.65 (1H, dd, $J = 11.9, 3.8$ Hz H-4a), 4.64-4.57 (2H, m, H-5'a, H-5'b), 4.53 (1H, dd, $J = 13.0, 4.1$ Hz H-1b), 4.40 (1H, dd, $J = 11.9, 3.8$ Hz H-4b), 4.29 (1H, dd, $J = 12.7, 3.9$ Hz H-1'a), 4.17 (1H, dd, $J = 12.7, 2.6$ Hz H-1'b); ¹³C NMR (100.6 MHz, pyridine-d₅): δ 79.46 (C-3), 79.38 (C-3'), 78.94 (C-2'), 71.94 (C-4'), 67.52 (C-2), 62.02 (C-4), 60.26 (C-5'), 52.64 (C-1), 51.01 (C-1'). HRMS. Calcd for C₉H₁₈O₉S₂ (M + H): 335.0471. Found: 335.0486.

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1-((1',4'-Anhydro-4'-thio-L-arabinitol)-4'-S-yl)-1-deoxy-D-erythritol-3-sulfate (25).

Column chromatography [CHCl_3 :MeOH:H₂O, 7:3:1] of the crude product gave an amorphous solid (80%). $[\alpha]_D +1.1^\circ$ (c 1.5, MeOH); ^1H NMR (pyridine- d_5): δ 5.23 (1H, ddd, $J = 7.4, 3.8, 3.7$ Hz, H-3), 5.11(1H, m, H-3'), 5.10 (1H, m, H-2'), 4.98 (1H,m, H-2), 4.76 (1H, dd, $J = 11.7, 3.7$ Hz H-1a), 4.70 (1H, m, H-4'), 4.63 (1H, dd, $J = 11.7, 3.8$ Hz H-1b), 4.60 (1H, dd, $J = 11.8, 3.7$ Hz H-4a)4.51 (2H, m, H-5'a, H-5'b),4.35 (1H, dd, $J = 11.8, 4.0$ Hz H-4b), 4.31 (2H, m, H-1'a, H-1'b); ^{13}C NMR (100.6 MHz, pyridine- d_5): δ 79.38 (C-3, C-2'), 78.41 (C-3'), 72.51 (C-4'), 67.63 (C-2), 62.23 (C-4), 60.21 (C-5'), 52.60 (C-1), 50.57 (C-1'). HRMS. Calcd for $\text{C}_9\text{H}_{18}\text{O}_9\text{S}_2$ (M + H): 335.0471. Found: 335.0466.

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1-((1',4'-Dideoxy-1',4'-imino-D-arabinitol)-4'-N-yl)-1-deoxy-L-erythritol-3-sulfate (2).

Column chromatography [CHCl_3 :MeOH:H₂O, 7:3:1] of the crude product gave an amorphous solid (64%). ^1H NMR (CD_3OD): δ 4.26-4.20 (2H, m H-2, H-3), 4.15 (1H, m, H-2'), 3.98 (1H,br-s, H-3'), 3.94-3.87 (3H,m, H-5'a, H-5b', H-4a), 3.81 (1H, dd, $J = 12.0, 3.5$ Hz H-4b), 3.74-3.62 (2H, m, H-1a, H-1'a), 3.49-3.42 (1H, m, H-1'b),3.40-3.35 (1H, m, H-4'), 3.15 (1H, m, H-1b); ^{13}C NMR (100.6 MHz, CD_3OD): δ 81.17 (C-3), 78.27 (C-3'),77.86 (C-4'), 76.19 (C-2'), 68.07 (C-2), 62.57 (C-1'), 61.67(C-4), 60.72 (C-1, C-5'). HRMS. Calcd for $\text{C}_9\text{H}_{18}\text{O}_9\text{SN}$ (M + H): 318.0859. Found: 318.0863.

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1-((1',4'-Dideoxy-1',4'-imino-L-arabinitol)-4'-N-yl)-1-deoxy-D-erythritol-3-sulfate (32).

Column chromatography [CHCl_3 :MeOH:H₂O, 7:3:1] of the crude product gave an amorphous solid (77%). ^1H NMR (CD_3OD): δ 4.25 (1H, m H-2), 4.23(1H, m, H-3), 4.16 (1H, br-s, H-2'), 3.99 (1H,br-s, H-3'), 3.94-3.87 (3H,m, H-5'a, H-5b', H-4a), 3.81 (1H, dd, $J = 12.1, 3.6$ Hz H-4b), 3.77-3.64 (2H, m, H-1a, H-1'a), 3.55-3.39 (2H, m, H-1'b, H-4'), 3.22 (1H, m, H-1b); ^{13}C NMR (100.6 MHz, CD_3OD): δ 81.18 (C-3), 78.23 (C-3', C-4'), 76.10 (C-2'), 68.05 (C-2), 62.66 (C-1'), 61.88(C-4), 60.49 (C-1, C-5'). HRMS. Calcd for $\text{C}_9\text{H}_{18}\text{O}_9\text{SN}$ (M + H): 318.0859. Found: 318.0856.

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5.2.6 Example 6 - General procedure for the alternative synthesis of Blintol (3)
(Schemes 12a-12f).

1,2,3,5-Tetra-*O*-acetyl-L-xylofuranose (49)

L-Xylose (5.00 g, 33.3 mmol), boric acid (4.50 g, 73.2 mmol), and glacial acetic acid
5 (100 mL) were added into a 250 mL round bottom flask. The mixture was stirred at
80 °C until L-xylose and boric acid were dissolved in acetic acid. Acetic anhydride
(50 mL) was added and the reaction mixture was stirred at 75 °C for 4 h. Analysis by
TLC (EtOAc: MeOH: H₂O, 10:3:1) showed that the L-xylose had been completely
consumed. MeOH was then added to the reaction mixture, and the reaction mixture
10 was concentrated to give a dark, orange-brown syrup. To this syrup, acetic anhydride
(50 mL) and pyridine (50 mL) were added and the reaction mixture was stirred at
room temperature for 4 h. The orange-brown mixture was pour into crushed ice and
was extracted with Et₂O (100 mL). The organic layer was washed with saturated
aqueous NaHCO₃ (50 mL), aqueous HCl, water, and saturated NaCl, dried over
15 MgSO₄ and concentrated to a yellow syrup. Purification by column chromatography
on silica gel (Hexane:EtOAc, 2:1) yielded the tetra-*O*-acetylxylofuranose **49** (9.01 g,
85 %) as a colorless syrup (α : β ratio 1:23). Data for the β (major) isomer.

¹H NMR (CDCl₃): δ 6.08 (1H, s, H-1), 5.35 (1H, dd, $J_{2,3}$ = 1.7, $J_{3,4}$ = 5.6 Hz, H-3),
5.18 (1H, d, $J_{1,2}$ < 1 Hz, H-2), 4.62 (1H, dd, $J_{4,5a}$ < 1, $J_{4,5b}$ = 12.1 Hz, H-4), 4.22 (2H,
20 m, H-5a, H-5b), 2.10, 2.09, 2.08, and 2.04 (12H, 4 s, COCH₃). ¹³C NMR (CDCl₃): δ
170.71, 169.69, 169.52, 169.43 (4 x C=O, OAc), 99.01 (C-1), 80.03 (C-2), 79.58 (C-
3), 74.43 (C-4), 62.54 (C-5), 21.33, 20.97, 20.82, 20.68 (4 x CH₃, OAc). Anal. Calcd
for C₁₃H₁₈O₉: C, 49.06; H, 5.70. Found: C, 48.93; H, 5.84.

4-Pentenyl-2,3,5-tri-*O*-acetyl-L-xylofuranoside (50)

25 Tetra-*O*-acetylxylofuranose **49** (5.00 g, 17.7 mmol), CH₂Cl₂ (100 mL), 4-penten-1-ol
(9.1 mL, 88 mmol), and crushed molecular sieves (4Å, 2 g) were added to a 250 mL
round bottom flask and cooled to 0 °C. Boron trifluoride (11 mL, 88 mmol) was
added to the reaction mixture and the mixture was stirred at 0 °C for 2 h. The
temperature was raised to room temperature and the mixture was stirred for 1 h.
30 Analysis by TLC (Hexane: EtOAc, 2:1) showed that the majority of the starting

material had been consumed. The reaction mixture was poured into ice/ NaHCO_3 mixture, extracted with Et_2O (100 mL), and dried over MgSO_4 . The reaction mixture was concentrated to a dark, orange-brown syrup. Purification by column chromatography on silica gel (Hexane: EtOAc , 2:1) yielded the pentenyl glycosides **50** (3.28 g, 60 %) as a colorless syrup (α : β ratio 1:23).

Data for the β (major) isomer. ^1H NMR (CDCl_3): δ 5.78 (1H, dddd, $J_{4',5b'} = 23.6$, $J_{4',5a'} = 17.1$, $J_{3a',4'} = 3.6$, $J_{3b',4'} = 13.3$ Hz, H-4'), 5.30 (1H, dd, $J_{2,3} = 1.5$, $J_{3,4} = 6.0$ Hz, H-3), 5.07 (1H, s, $J_{1,2} < 1$ Hz, H-2), 4.99 (1H, 2 ddd, $J_{3'a,5'a} = 1.7$, $J_{3'b,5'a} = 1.7$, $J_{5'b,5'a} = 3.5$ Hz, H-5a'), 4.94 (1H, s, H-1), 4.93 (1H, m, H-5'b), 4.55 (1H, ddd, $J_{4,5a} = 5.3$, $J_{4,5b} = 7.3$ Hz, H-4), 4.24 (1H, dd, $J_{5a,5b} = 11.5$, H-5a), 4.18 (1H, dd, H-5b), 3.69 (1H, ddd, $J_{1'a,2'a} = 6.7$, $J_{1'a,2'b} = 6.7$, $J_{1'a,1'b} = 13.3$ Hz, H-1'a), 3.40 (1H, ddd, $J_{1'b,2'a} = 6.4$, $J_{1'b,2'b} = 6.4$ Hz, H-1'b), 2.07 (6H, s, 2 x COCH_3), 2.04 (3H, s, COCH_3), 2.04 (2H, m, H-3'a, H-3'b), 1.65 (2H, m, H-2'a, H-2'b). ^{13}C NMR (CDCl_3): δ 170.72, 170.11, and 169.74 (3 x C=O, OAc), 138.22 (C-4'), 115.13 (C-5'), 106.08 (C-1), 80.92 (C-2), 78.17 (C-4), 75.11 (C-3), 67.77 (C-1'), 63.42 (C-5), 30.34 (C-3'), 28.78 (C-2'), 20.99, 20.93, and 20.81 (3 x CH_3 , OAc). Anal. Calcd for $\text{C}_{16}\text{H}_{24}\text{O}_8$: C, 55.81; H, 7.02. Found: C, 55.99; H, 7.19.

4-Pentenyl-L-xylofuranoside (**51**)

The pentenyl glycoside **50** (3.28 g, 9.52 mmol) was dissolved into MeOH (50 mL) in a 250 mL round bottom flask. NaOMe in MeOH (0.02 M) was added to the reaction mixture and the mixture was stirred at room temperature for 1 h. Analysis by TLC (CH_2Cl_2 : MeOH, 10:1) showed the starting material had been consumed. Rexyn[®] 101 (H) resin was added to the reaction mixture to adjust the PH to 7. The reaction mixture was then filtered and the filtrate was concentrated to give a light brown syrup. Purification by column chromatography on silica gel (CH_2Cl_2 : MeOH, 10:1) yielded the pentenyl glycosides **51** (1.97 g, 95 %) as a colorless syrup (α : β ratio 1:23).

Data for the β (major) isomer. ^1H NMR (CD_3OD): δ 5.75 (1H, m, H-4'), 5.03 (1H, m, H-5'a), 4.96 (1H, m, H-5'b), 4.86 (1H, s, $J_{1,2} < 1$ Hz, H-1), 4.24 (1H, ddd, $J_{4,5a} = 5.0$, $J_{4,5b} = 6.6$, $J_{3,4} = 5.1$ Hz, H-4), 4.08 (1H, dd, $J_{2,3} = 2.0$, H-3), 4.03 (1H, br.s, H-2), 3.83 (1H, dd, $J_{5a,5b} = 11.6$, H-5a), 3.79 (1H, m, H-1'a), 3.74 (1H, m, H-5b), 3.43 (1H, m, H-

1'b), 2.17 (2H, m, H-3'a, H-3'b), 1.68 (2H, m, H-2'a, H-2'b). ^{13}C NMR (CD_3OD): δ 138.23 (C-4'), 114.17 (C-5'), 109.62 (C-1), 82.71 (C-4), 81.01 (C-2), 76.31 (C-3), 67.42 (C-1'), 61.49 (C-5), 32.20 (C-3'), 28.78 (C-2'). Anal. Calcd for $\text{C}_{10}\text{H}_{18}\text{O}_5$: C, 55.03; H, 8.31. Found: C, 55.30; H, 8.44.

5 4-Pentenyl-2,3,5-tri-*O-p*-methoxybenzyl-L-xylofuranoside (52)

In a 250 mL flask NaH (4.38 g, 0.11 mol) and DMF (80 mL) were added and cooled to 0 °C. The pentenyl glycoside **51** (3.00 g, 13.7 mmol) was dissolved in DMF (10 mL) and the solution was added dropwise to the NaH/DMF mixture. After the addition, the reaction mixture was stirred at 0 °C for 2 h. The temperature was then raised to room temperature and the mixture was stirred for 1 h. *p*-Methoxybenzyl chloride (15 mL, 0.11 mol) dissolved in DMF (10 mL) was then added dropwise to the reaction mixture. The mixture was stirred at room temperature for 2 h after the addition. The reaction mixture was quenched with ice water, extracted with Et_2O (100 mL), washed with H_2O (8 × 20 mL portions), and dried over MgSO_4 . The mixture was concentrated to give a orange-brown syrup. Purification by column chromatography on silica gel (Hexane:EtOAc, 4:1) yielded the pentenyl glycosides **52** (7.30 g, 92 %) as a colorless syrup (α : β ratio 1:23).

Data for the β (major) isomer. ^1H NMR (CDCl_3): δ 7.25-6.85 (12H, m, Ar), 5.83 (1H, dddd, $J_{4',5b'} = 6.6$, $J_{4',5a'} = 16.9$, $J_{3'a,4'} = 6.8$, $J_{3'b,4'} = 10.4$ Hz, H-4'), 5.03 (1H, dddd, $J_{3'a,5'a} = 1.7$, $J_{3'b,5'a} = 5.5$, $J_{5'b,5'a} = 3.5$ Hz, H-5a'), 4.98 (1H, br.s, $J_{1,2} = 1.8$ Hz, H-1), 4.97 (1H, m, H-5'b), 4.49 (6H, m, 3 x CH_2Ph), 4.41 (1H, m, H-4), 4.02 (1H, dd, $J_{2,3} = 2.3$, $J_{3,4} = 5.8$ Hz, H-3), 3.97 (1H, br.t, H-2), 3.81 (6H, s, 2 x OCH_3), 3.80 (3H, s, OCH_3), 3.76 (1H, m, H-1'a), 3.72 (1H, dd, $J_{4,5a} = 4.7$, $J_{5a,5b} = 10.3$ Hz, H-5a), 3.67 (1H, dd, $J_{4,5b} = 7.3$ Hz, H-5b), 3.42 (1H, m, H-1'b), 2.12 (2H, m, H-3'a, H-3'b), 1.68 (2H, m, H-2'a, H-2'b). ^{13}C NMR (CDCl_3): δ 159.60-113.91 (12 C_{Ar}), 138.51 (C-4'), 114.03 (C-5'), 107.38 (C-1), 87.02 (C-2), 81.83 (C-3), 80.04 (C-4), 73.32, 71.93, 71.81 (3 x CH_2Ph), 69.78 (C-5), 67.94 (C-1'), 55.52 (OCH_3), 30.61 (C-3'), 28.98 (C-2'). Anal. Calcd for $\text{C}_{34}\text{H}_{42}\text{O}_8$: C, 70.57; H, 7.32. Found: C, 70.44; H, 7.48.

2,3,5-Tri-*O-p*-methoxybenzyl-L-xylofuranose (53)

In a 500 mL round bottom flask pentenyl glycosides **52** (7.00 g, 12.1 mmol) were dissolved in CH₃CN (180 mL). H₂O (20 mL) was added and the mixture was cooled to 0 °C. *N*-Bromosuccinimide (5.38 g, 30.2 mmol) was added to the reaction mixture and the reaction mixture was stirred at 0 °C for 1 h. Analysis by TLC (Hexane:
5 EtOAc, 2:1) showed that the starting material had been completely consumed. Na₂S₂O₃ 5H₂O (15 g, 60 mmol) dissolved in H₂O (60 mL) was then added and the mixture was stirred for 20 min. The mixture was then concentrated to give a dark orange syrup. The syrup was dissolved in EtOAc (150 mL), washed with H₂O, saturated NaCl, and dried over MgSO₄. The mixture was then concentrated to give a
10 dark brown syrup. Purification by column chromatography on silica gel (Hexane:EtOAc, 1:1) yielded the *p*-methoxybenzyl xylofuranoses **53** (5.52 g, 90 %) as a colorless syrup (α : β ratio 1:2).

Data for the β (major) isomer. ¹H NMR (CDCl₃): δ 7.25-6.80 (12H, m, Ar), 5.20 (1H, br.s, $J_{1,2}$ = 1.8 Hz, H-1), 4.55 - 4.40 (6H, m, 3 x CH₂Ph), 4.34 (1H, ddd, $J_{4,5b}$ = 5.0, $J_{4,5a}$ = 4.1, $J_{3,4}$ = 5.4 Hz, H-4), 4.05 (1H, dd, $J_{2,3}$ = 2.8 Hz, H-3), 3.95 (1H, br.d, $J_{1,2}$ < 1 Hz H-2), 3.82, 3.81, 3.80 (9H, 3 x s, 3 x OCH₃), 3.68 (2H, m, H-5a, H-5b). ¹³C NMR (CDCl₃): δ 159.60-113.50 (12 C_{Ar}), 101.68 (C-1), 86.24 (C-2), 80.91 (C-3), 79.83 (C-4), 73.32, 72.33, 71.48 (3 x CH₂Ph), 68.31 (C-5), 55.22 (OCH₃). Anal. Calcd for C₂₉H₃₄O₈: C, 68.22; H, 6.71. Found: C, 68.17; H, 6.65.

20 **2,3,5-Tri-*O*-*p*-methoxybenzyl-L-xylitol (54)**

The *p*-methoxybenzyl xylofuranoses **53** (5.50 g, 10.8 mmol) were dissolved in THF (10 mL) and MeOH (50 mL) was then added. NaBH₄ was added portionwise to the reaction mixture at room temperature until the TLC analysis (Hexane:EtOAc, 1:1) showed that the starting material had been consumed. The mixture was concentrated
25 to give a light yellow solid. This solid was dissolved in EtOAc (150 mL), washed with water, saturated aqueous NaCl, dried over MgSO₄, and concentrated to give a light yellow syrup. Purification by column chromatography on silica gel (Hexane:EtOAc, 1:1) yielded the *p*-methoxybenzyl xylitol **54** as a colorless syrup (4.62 g, 84 %).

$[\alpha]_D +7.25$ (c 2.8, CHCl_3). ^1H NMR (CDCl_3): δ 7.20-6.80 (12H, m, Ar), 4.58, 4.43 (2H, 2d, $J_{A,B} = 11.2$ Hz, CH_2Ph), 4.54 (2H, 2d, $J_{A,B} = 11.2$ Hz, CH_2Ph), 4.44, 4.39 (2H, 2d, $J_{A,B} = 11.7$ Hz, CH_2Ph), 4.02 (1H, ddd, $J_{2,3} = 1.9$, $J_{1a,2} = 6.4$, $J_{1b,2} = 6.2$ Hz, H-2), 3.80 (9H, s, 3 x OCH_3), 3.75 (2H, m, H-4, H-5a), 3.66 (1H, dd, $J_{3,4} = 6.4$ Hz, H-3), 3.63 (1H, m, H-5b), 3.46 (1H, dd, $J_{1a,1b} = 9.4$ Hz, H-1a), 3.37 (1H, dd, H-1b). ^{13}C NMR (CDCl_3): δ 159.60-113.50 (12 C_{Ar}), 78.32 (C-3), 77.01 (C-5), 73.88, 73.08, 72.10 (3 x CH_2Ph), 71.23 (C-1), 68.79 (C-2), 60.81 (C-4), 55.53 (OCH_3). Anal. Calcd for $\text{C}_{29}\text{H}_{36}\text{O}_8$: C, 67.95; H, 7.08. Found: C, 67.85; H, 7.12.

2,3,5-Tri-*O-p*-methoxybenzyl-1,4-di-*O*-methanesulfonyl-L-xylitol (55)

In a 250 mL round bottom flask, methanesulfonyl chloride (5.3 mL, 68 mmol), pyridine (6 mL, 68 mmol), and CH_2Cl_2 (50 mL) were cooled to 0 °C. The *p*-methoxybenzyl xylitol (**54**, 3.50 g, 6.84 mmol) in CH_2Cl_2 (50 mL) was then added dropwise to the methanesulfonyl chloride/pyridine mixture. After the addition was completed, the temperature was raised to room temperature and the mixture was stirred for 3 h. The reaction mixture was then poured onto crushed ice, extracted with EtOAc (150 mL), washed with water, saturated aqueous NaCl, dried over MgSO_4 , and was concentrated to give a light yellow syrup. Purification by column chromatography on silica gel (Hexane:EtOAc, 1:1) yielded the methanesulfonyl xylitol **55** as a colorless syrup (3.28 g, 72 %).

$[\alpha]_D -16.2$ (c 5.6, CHCl_3). ^1H NMR (CDCl_3): δ 7.20-6.80 (12H, m, Ar), 4.92 (1H, ddd, $J_{2,3} = 9.2$, $J_{1a,2} = 3.6$, $J_{1b,2} = 6.1$ Hz, H-2), 4.60, 4.43 (2H, 2d, $J_{A,B} = 11.3$ Hz, CH_2Ph), 4.57 (2H, 2d, $J_{A,B} = 11.3$ Hz, CH_2Ph), 4.41, 4.33 (2H, 2d, $J_{A,B} = 11.1$ Hz, CH_2Ph), 4.36 (1H, dd, $J_{4,5a} = 5.6$, $J_{5a,5b} = 11.0$ Hz, H-5a), 4.31 (1H, dd, $J_{4,5b} = 4.2$ Hz, H-5b), 3.83 (1H, m, H-4), 3.80, 3.79, 3.78 (9H, 3s, 3 x OCH_3), 3.78 (1H, m, H-3), 3.56 (1H, dd, $J_{1a,1b} = 11.2$ Hz, H-1a), 3.54 (1H, dd, H-1b), 2.99, 2.92 (6H, 2 s, 2 x OSO_2CH_3). ^{13}C NMR (CDCl_3): δ 159.60-113.50 (12 C_{Ar}), 80.32 (C-2), 75.63 (C-3), 75.24 (C-4), 74.11, 72.83, 72.69 (3 x CH_2Ph), 68.43 (C-5), 68.41 (C-1), 55.12 (OCH_3), 38.5, 37.1 (2 x OSO_2CH_3). Anal. Calcd for $\text{C}_{31}\text{H}_{40}\text{O}_{12}\text{S}_2$: C, 55.67; H, 6.03. Found: C, 55.45; H, 6.13.

1,4-Anhydro-2,3,5-tri-*O-p*-methoxybenzyl-4-seleno-D-arabinitol (56)

In a 250 mL round bottom flask, selenium metal (0.61 g, 7.7 mmol) and 95% EtOH (50 mL) were added. NaBH₄ was then added portionwise at room temperature until the color of the reaction mixture changed from black to white. The dimesylate **55** (3.28 g, 4.91 mmol) dissolved into THF (10 mL) was then added to the reaction mixture and the mixture was heated and stirred at 60 °C for 12 h. The mixture was then concentrated to give a dark orange-red syrup. This solid was dissolved into Et₂O (100 mL), washed with water, saturated aqueous NaCl, dried over MgSO₄, and was concentrated to give a light yellow syrup. Purification by column chromatography on silica gel (Hexane:EtOAc, 4:1) yielded the selenoarabinitol **56** as a colorless syrup (2.27 g, 83 %).

$[\alpha]_D +17.83$ (c 1.5, CHCl₃). ¹H NMR (CDCl₃): δ 7.20-6.80 (12H, m, Ar), 4.58, 4.52 (2H, 2d, $J_{A,B} = 11.4$ Hz, CH₂Ph), 4.48, 4.44 (2H, 2d, $J_{A,B} = 11.6$ Hz, CH₂Ph), 4.45, 4.42 (2H, 2d, $J_{A,B} = 11.7$ Hz, CH₂Ph), 4.16 (1H, ddd, $J_{2,3} = 5.2$, $J_{1a,2} = 5.1$, $J_{1b,2} = 5.4$ Hz, H-2), 4.00 (1H, dd, $J_{3,4} = 4.8$ Hz, H-3), 3.81 (1H, m, H-5a), 3.81 (6H, s, 2 x OCH₃), 3.80 (3H, s, OCH₃), 3.72 (1H, m, H-4), 3.48 (1H, dd, $J_{4,5b} = 7.2$, $J_{5a,5b} = 9.3$ Hz, H-5b), 3.06 (1H, dd, H-1a), 2.92 (1H, dd, H-1b). ¹³C NMR (CDCl₃): δ 159.20-113.50 (12 C_{Ar}), 85.73 (C-2), 85.33 (C-3), 72.89 (C-5), 72.83, 72.01, 71.42 (3 x CH₂Ph), 55.22 (OCH₃), 42.38 (C-4), 23.91 (C-1). Anal. Calcd for C₂₉H₃₄O₆Se: C, 62.47; H, 6.15. Found: C, 62.39; H, 6.25.

20 **2,4-O-Benzylidene-L-erythritol-1,3-cyclic sulfate (57)**

The cyclic sulfate **62**, prepared according to literature procedures,²⁵ (13.5 g, 37.0 mmol) was dissolved in EtOAc (120 mL) in a 500 mL round bottom flask. Pd on activated carbon (200 mg, 10 % palladium) was added to the solution and H₂ was bubbled through the solution with stirring at room temperature for 48 h. Periodic analysis by TLC (Hexane: EtOAc, 1:1) showed that the reaction proceeded smoothly until the cyclic sulfate **62** had been consumed. The Pd was removed by filtration and the solvent was evaporated to yield the deprotected cyclic sulfate **63** as a white solid (6.82 g, quantitative yield). The cyclic sulfate **63** was used directly without further purification. The cyclic sulfate **63** and pyridinium *p*-toluenesulfonate (500 mg) were dissolved in CH₂Cl₂ (20 mL) in a 250 mL round bottom flask and PhCH(OMe)₂ (37 mL, 0.26 mol) was added. The solution was heated to 60 °C on a rotary evaporator

under vacuum for 1 h. Analysis by TLC (Hexane: EtOAc, 1:1) showed that the cyclic sulfate **57** had been consumed. The mixture was dissolved in EtOAc (100 mL), washed with saturated aqueous NaCl (20 mL), dried over MgSO₄, and was concentrated to give a colorless syrup. Purification by column chromatography on silica gel (Hexane:EtOAc, 1:1) yielded the cyclic sulfate **57** as a white solid (7.14 g, 71 %). This material was identical in all respects to that obtained previously²⁵ using L-glucose.

1,3-Di-*O*-benzyl-D-erythritol (60) – Alternative Procedure

In a 250 mL flask, 2,4-*O*-Benzylidene-1,3-di-*O*-benzyl-D-erythritol (**59**, 36.6 g, 93.7 mmol) and 50% aqueous TFA solution (100 mL) were added. The reaction mixture was stirred at room temperature for 0.5 h. Analysis by TLC (Hexane: EtOAc, 2:1) showed the starting material had been consumed. The reaction mixture was cooled to 0 °C and 50% aqueous KOH solution (50 mL) was added. The reaction mixture was stirred at 0 °C for additional 0.5 h, extracted with EtOAc (200 mL), and dried over Na₂SO₄. The mixture was concentrated to give a brown syrup. Purification by column chromatography on silica gel (Hexane: EtOAc, 1:1) yielded the erythritol **60** (17.6 g, 60%) as a colorless syrup. This material was identical in all respects to that obtained previously²⁶ using aqueous acetic acid.

2,3,5-Tri-*O*-*p*-Methoxybenzyl-1,4-dideoxy-1,4-[[[(2*S*,3*S*)-2,4-benzylidenedioxy-3-(sulfooxy)butyl]-episelenoniumylidene]-D-arabinitol Inner Salt (64)

The seleno-D-arabinitol **56** (3.11 g, 5.59 mmol), the cyclic sulfate **57** (1.33 g, 4.88 mmol) and K₂CO₃ (160 mg, 1.16 mmol) were added to 1,1,1,3,3,3-hexafluoro-2-propanol (8.0 mL) and the mixture was stirred in a sealed tube with heating at 60-65 °C for 7 h. Periodic analysis by TLC (EtOAc: MeOH, 10:1) showed that the reaction proceeded smoothly until the selenoether had been consumed leaving some cyclic sulfate unreacted. The mixture was cooled and filtered through Celite with the aid of CH₂Cl₂. The solvents were removed and the residue was purified by column chromatography (gradient of EtOAc to EtOAc: MeOH, 10:1). The selenonium salt **64** (3.85 g, 95 % based on selenoether **14**) was obtained as a colorless foam. Analysis of the ¹H and ¹³C NMR spectra indicated that compound **64** was produced as a 7:1 mixture of isomers at the stereogenic selenium center. The major isomer was assigned

to be the isomer with a trans relationship between C-5 and C-1' by analogy to the results obtained previously for the corresponding benzyl-protected selenonium salt. For *trans* **64**: ^1H NMR (600 MHz, CD_2Cl_2) δ 7.45-6.80 (17H, m, Ar), 5.58 (1H, s, $\text{C}_6\text{H}_5\text{CH}$), 4.51 (1H, dd, $J_{2',3'} = J_{3',4'\text{ax}} = 9.7$, $J_{3',4'\text{eq}} = 5.3$ Hz, H-3'), 4.48 (1H, br s, H-2), 4.46 (1H, dd, $J_{4'\text{ax},4'\text{eq}} = 10.5$ Hz, H-4'eq), 4.41, 4.33 (2H, 2d, $J_{\text{A,B}} = 11.1$ Hz, CH_2Ph), 4.57 (2H, 2d, $J_{\text{A,B}} = 11.3$ Hz, CH_2Ph), 4.43 and 4.40 (2H, 2d, $J_{\text{A,B}} = 12.0$ Hz, CH_2Ph), 4.39 and 4.26 (2H, 2d, $J_{\text{A,B}} = 11.4$ Hz, CH_2Ph), 4.32 (1H, dd, $J_{1'\text{a},2'} = 2.2$ Hz, H-1'a), 4.27 (1H, br d, $J_{2,3} = 2.0$ Hz, H-3), 4.25 and 4.19 (2H, 2d, $J_{\text{A,B}} = 10.8$ Hz, CH_2Ph), 4.21 (1H, ddd, H-2'), 4.04 (1H, br d, $J_{1,2} < 1$ Hz, H-1a), 4.03 (1H, br dd, $J_{3,4} < 1$ Hz, H-4), 3.90 (1H, dd, $J_{1'\text{a},1'\text{b}} = 12.2$, $J_{1'\text{b},2'} = 3.6$ Hz, H-4), 3.78 (3H, s, OCH_3), 3.77 (1H, dd, H-4'ax), 3.77 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.55 (1H, dd, $J_{1\text{a},1\text{b}} = 12.8$, $J_{1\text{b},2} = 2.9$ Hz, H-1b), 3.54 (1H, dd, $J_{5\text{a},5\text{b}} = 9.7$, $J_{4,5\text{a}} = 6.7$ Hz, H-5a), 3.48 (1H, dd, $J_{4,5\text{b}} = 9.4$ Hz, H-5b); ^{13}C NMR (150 MHz, CDCl_2): δ

160.34, 160.09, 136.58 and 130.14 – 126.51 (21 C_{Ar}), 114.56, 114.47 and 114.70 (3 x C_{ipso} , OMBn), 102.17 (PHCH), 84.31 (C-3), 83.00 (C-2), 77.30 (C-2'), 73.37, 72.49, and 72.10 (3 x CH_2Ph), 69.67 (C-4'), 67.75 (C-3'), 66.80 (2 x C, C-4, C-5), 55.67 (3 x C, 3 x OCH_3), 48.73 (C-1'), 46.69 (C-1). Anal. Calcd for $\text{C}_{40}\text{H}_{46}\text{O}_{12}\text{SSe}$: C, 57.90; H, 5.59. Found: C, 57.87; H, 5.57.

1,4-Dideoxy-1,4-[[*(2S,3S)*-2,4-dihydroxy-3-(sulfooxy)butyl]episelenoniumylidene]-D-arabinitol Inner Salt (Blintol, 3)

The selenonium salts **64** (3.80 g, 4.58 mmol) were dissolved in cold trifluoroacetic acid (40 mL) to give a purple solution. Water (4.0 mL) was added and the reaction mixture was kept at room temperature for 0.5 h. The solvents were removed on a rotary evaporator and the residue was triturated with CH_2Cl_2 (4×50 mL), with each portion of solvent being decanted from the insoluble gummy product. The crude product was dissolved in water (50 mL) and filtered to remove a small amount of insoluble material. The aqueous filtrate was concentrated to a syrupy residue (1.84 g). Analysis by NMR spectroscopy indicated that the product was an isomeric mixture (7:1) of **3** with its stereoisomer at the selenium center. Recrystallization from MeOH gave pure **3** (1.09 g, 62%) in two crops. This material was identical in all respects to that obtained previously²⁶ using hydrogenolysis to remove the benzyl protecting

groups. Purification of the mother liquor fractions by column chromatography (EtOAc: MeOH: H₂O, 6:3:1) gave a 3:2 mixture of **3** with its isomer (0.25g, 14%) as a syrup.

5.2.7 Example 7 Synthesis of Six-membered Ring Analogues (Schemes 15 to 21)

5 General.

Optical rotations were measured at 23°C. Analytical thin-layer chromatography (TLC) was performed on aluminum plates precoated with Merck silica gel 60F-254 as the adsorbent. The developed plates were air-dried, exposed to UV light and/or sprayed with a solution containing 1% Ce(SO₄)₂ and 1.5% molybdic acid in 10% aq H₂SO₄ and heated. Compounds were purified by flash chromatography on Kieselgel 60 (230-400 mesh). Rexyn 101 was obtained from Fischer. ¹H and ¹³C NMR spectra were recorded on: Bruker AMX-400 NMR spectrometer at 400.13 MHz, Bruker AMX-600 NMR spectrometer at 600.13 MHz and Varian INOVA 500 NMR spectrometer at 499.97 MHz for ¹H. Chemical shifts are given in ppm downfield from TMS for those measured in CDCl₃, CD₃OD and CD₂Cl₂ and from 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) for those spectra measured in D₂O. Chemical shifts and coupling constants were obtained from a first-order analysis of the spectra. Assignments were fully supported by two-dimensional ¹H,¹H (COSY), ¹H,¹H (NOESY) and ¹H,¹³C (HMQC) experiments using standard Bruker or Varian pulse programs. Processing of the spectra was performed with standard UXNMR and WINNMR software (Bruker) or MestReC software (Varian).

The 1D- transient NOE experiments were performed by inverting the signal of interest with a 80 ms Gaussian selective pulse which was constructed from 1024 steps. Spectra were collected in difference mode by alternating the phase of the receiver gain during on- and off-resonance. The digitized signal was stored in a 32 K data set using a sweep width of 10 ppm, an acquisition time of 2.72 s, 128 scans, and 8 dummy scans. Processing of the spectra was accomplished by zero filling to 64 K followed by an exponential multiplication using a line width of 1 Hz. NOESY spectra were obtained with a mixing time of 500 or 800 ms.

MALDI mass spectra were obtained on a PerSeptive Biosystems, Voyager DE time-of-flight spectrometer for samples dispersed in a 2,5-dihydroxybenzoic acid matrix. High resolution mass spectra were liquid secondary ion mass spectrometry (LSIMS), run on a Kratos Concept double focussing mass spectrometer at 10 000 RP, using a glycerin matrix or, in the case of compound **88a**, with *meta*-NO₂-benzyl alcohol as the matrix. Solvents were distilled before use and were dried, as necessary. Solvents were evaporated under reduced pressure and below 50°C.

1,5-Anhydro-2,3,4-tri-*O*-benzyl-5-thioxylitol (74).

(a) Acetate Methanolysis: A mixture of 1,5-anhydro-2,3,4-tri-*O*-acetyl-5-thioxylitol **77** (0.125 g, 0.453 mmol) and 1M NaOMe in MeOH (0.6 mL, 0.6 mmol) in dry MeOH (10 mL) was stirred under N₂ overnight. The mixture was neutralized with excess Rexyn 101. The resin was removed by filtration and the organic phase was concentrated to give 1,5-anhydro-5-thioxylitol as a solid (59.6 mg, 88%). Mp 137-140°C; ¹H NMR (D₂O): δ 3.65 (2H, m, $J_{1eq,2} = J_{4,5eq} = 4.5$ Hz, $J_{1ax,2} = J_{4,5ax} = 10.9$ Hz, H-2 and H-4), 3.15 (1H, t, $J_{2,3} = J_{3,4} = 9.1$ Hz, H-3), 2.66 (2H, m, H-5eq and H-1eq), 2.56 (2H, dd, $J_{5ax,5eq} = J_{1ax,1eq} = 13.6$ Hz, H-5ax and H-1ax); ¹³C NMR (D₂O): δ 81.20 (C-3), 75.75 (2C, C-2 and C-4), 34.86 (2C, C-1 and C-5). Anal. Calcd for C₅H₁₀O₃S: C, 39.99; H, 6.71. Found: C, 39.68; H, 6.91.

(b) Benzylation: A mixture of 1,5-anhydro-5-thioxylitol (0.520 g, 3.47 mmol) and 60% NaH (0.744 g, 5 equiv) in DMF (50 mL) was stirred in an ice-bath for 1 h. A solution of BnBr (1.4 mL, 4 equiv) was added and the solution was stirred at RT overnight. The mixture was quenched with MeOH (8 mL), H₂O (100 mL) was added, and the solution was extracted with Et₂O (3 x 150 mL). The organic solution was dried over Na₂SO₄, concentrated, and the residue was purified by flash chromatography [hexanes:EtOAc, 20:1] to give **74** as a white solid (0.928 g, 64%). Mp 46-49°C; ¹H NMR (CDCl₃): δ 7.36-7.24 (15H, m, Ar), 4.83 (2H, s, CH₂Ph), 4.69 (2H, d, $J_{A,B} = 11.4$ Hz, CH₂Ph), 4.65 (2H, d, $J_{A,B} = 11.6$ Hz, CH₂Ph), 3.63 (2H, m, $J_{1eq,2} = J_{4,5eq} = 4.2$ Hz, $J_{1ax,2} = J_{4,5ax} = 11.0$ Hz, H-4 and H-2), 3.31 (1H, t, $J_{2,3} = J_{3,4} = 8.9$ Hz, H-3), 2.72 (2H, m, H-5eq and H-1eq), 2.47 (2H, dd, $J_{5ax,5eq} = J_{1ax,1eq} = 13.4$ Hz, H-5ax and H-1ax); ¹³C NMR (CDCl₃): δ 138.9, 138.37 (3C_{ipso}), 128.42-127.51 (15C, Ar), 86.76 (C-3), 82.26 (2C, C-2 and C-4), 76.33 (CH₂Ph), 73.02 (2 CH₂Ph),

31.49 (2C, C-1 and C-5). Anal. Calcd for $C_{26}H_{28}O_3S$: C, 74.25; H, 6.71. Found: C, 74.16; H, 6.91.

1,5-Anhydro-2,3,4,6-tetra-*O*-benzyl-5-thio-D-glucitol (75).

(a) Acetate Methanolysis: To a solution of 1,5-anhydro-2,3,4,6-tetra-*O*-acetyl-5-thio-D-glucitol **78** (0.310 g, 0.89 mmol) in dry MeOH (20 mL) was added 1M NaOMe/MeOH (4 mL, 4 equiv), and the mixture was stirred under N_2 overnight. The mixture was neutralized with excess Rexyn 101 ion-exchange resin, the resin was removed by filtration, and the organic phase was concentrated. The residue was purified by flash chromatography [$CHCl_3$:MeOH, 5:2] to give 1,5-anhydro-5-thio-D-glucitol as a white solid (0.125 g, 78%). Mp 110-115°C; $[\alpha]_D = +27.4$ (c 1.2, MeOH); ^1H NMR (D_2O): δ 3.90 (1H, dd, $J_{5,6a} = 3.2$ Hz, $J_{6b,6a} = 11.9$ Hz, H-6a), 3.75 (1H, dd, $J_{5,6b} = 6.4$ Hz, H-6b), 3.64 (1H, m, H-2), 3.48 (1H, dd, $J_{4,5} = 10.2$ Hz, H-4), 3.19 (1H, t, $J_{2,3} = J_{3,4} = 9.1$ Hz, H-3), 2.88 (1H, m, H-5), 2.71 (1H, dd, $J_{1eq,2} = 4.6$ Hz, $J_{1eq,1ax} = 13.3$ Hz, H-1eq), 2.62 (1H, dd, $J_{1ax,2} = 11.0$ Hz, H-1ax).

(b) Benzylation: To a stirred solution of 1,5-anhydro-5-thio-D-glucitol (0.194 g, 1.08 mmol) in dry DMF (60 mL) was added NaH (0.5 g, 12.5 mmol) and then BnBr (0.7 mL, 5.9 mmol), and the mixture was stirred overnight. Excess NaH was destroyed by the addition of MeOH. The organic phase was concentrated under reduced pressure. To the residue was added H_2O (200 mL) and this was extracted with CH_2Cl_2 (5 x 100 mL). The organic phase was dried over Na_2SO_4 and concentrated. The product was purified by flash chromatography [hexanes:EtOAc, 20:1] to give a syrup that was recrystallized from EtOAc/hexanes to give compound **75** as a white solid (0.276 g, 58%). Mp 56-59°C; $[\alpha]_D = +15.1$ (c 1.1, $CHCl_3$). The ^1H NMR spectrum was consistent with the literature data.⁷⁹

1,5-Anhydro-2,3,4-tri-*O*-acetyl-5-selenoxylitol (81).

To a stirred suspension of selenium (1.48 g, 18.7 mmol) in anhydrous EtOH (40 mL) at 0°C was added $NaBH_4$ (0.9 g, 23.8 mmol). An almost colorless solution resulted. The ice bath was removed and 2,3,5-tri-*O*-acetyl-1,5-dibromo-1,5-dideoxy-xylitol **80** (4.87 g, 12.0 mmol) was added, and the mixture was stirred at RT overnight. H_2O (200 mL) was added and the mixture was extracted with Et_2O (5 x 100 mL). The

solids were removed by filtration, the solution was concentrated, and the residue was purified by flash chromatography [hexanes:EtOAc, 1:1] to give **81** as yellow crystals (2.22 g, 57%). Mp 106-111°C; ¹H NMR (CDCl₃): δ 5.11 (2H, ddd, $J_{1eq,2} = J_{4,5eq} = 4.5$ Hz, $J_{1ax,2} = J_{4,5ax} = 10.8$ Hz, H-2, H-4), 4.96 (1H, t, $J_{2,3} = J_{3,4} = 9.7$ Hz, H-3), 2.74 (2H, dd, H-1eq, H-5eq), 2.67 (2H, t, $J_{5ax,5eq} = J_{1ax,1eq} = 12.0$ Hz, H-1ax, H-5ax), 2.00 (3H, s, OAc), 1.99 (6H, s, OAc); ¹³C NMR (CDCl₃): δ 169.79 and 169.65 (3C=O), 73.98 (C-3), 73.78 (2C, C-2 and C-4), 21.02 (2 OAc), 20.80 (2C, C-1 and C-5), 20.56 (OAc). Anal. Calcd for C₁₁H₁₆O₆Se: C, 40.88; H, 4.99. Found: C, 40.76; H, 5.02.

1,5-Anhydro-2,3,4-tri-*O*-benzyl-5-selenoxylitol (76).

- (a) Acetate Methanolysis: A mixture of 1,5-anhydro-2,3,4-tri-*O*-acetyl-5-selenoxylitol **81** (2.22 g, 6.87 mmol) and 1M NaOMe in MeOH (10 mL, 10 mmol) in dry MeOH (60 mL) was stirred under a N₂ atmosphere overnight. The mixture was neutralized with excess Rexyn 101, the resin was removed by filtration, and the organic phase was concentrated to give 1,5-anhydro-selenoxylitol as tan crystals (1.19 g, 88%). Mp 98-105°C; ¹H NMR (D₂O): δ 3.75 (2H, m, $J_{1eq,2} = J_{4,5eq} = 4.6$ Hz, $J_{1ax,2} = J_{4,5ax} = 10.8$ Hz, H-2, H-4), 3.11 (1H, t, $J_{2,3} = J_{3,4} = 9.2$ Hz, H-3), 2.66 (2H, t, $J_{5ax,5eq} = J_{1ax,1eq} = 11.8$ Hz, H-5ax, H-1ax), 2.60 (2H, dd, H-1eq, H-5eq); ¹³C NMR (D₂O): δ 81.40 (C-3), 76.62 (2C, C-2 and C-4), 25.65 (2C, C-1 and C-5). Anal. Calcd for C₅H₁₀O₃Se: C, 30.47; H, 5.11. Found: C, 30.29; H, 5.21.
- (b) Benzylation: To 1,5-anhydro-5-selenoxylitol **81** (0.289 g, 1.47 mmol) in dry DMF (20 mL) was added 60% NaH (0.516 g, 6 equiv) while stirring in an ice bath. The ice bath was removed and BnBr (0.9 mL, 4 equiv) was added. The mixture was stirred under N₂ overnight. The reaction was then quenched with MeOH (5 mL), H₂O (100 mL) was added, and the mixture was extracted with Et₂O (3 x 50 mL). The organic solution was dried over Na₂SO₄ and concentrated. The product was purified by flash chromatography [hexanes:EtOAc, 20:1] to give the title compound **76** as a white solid (0.505 g, 74%). Mp 56-60°C; ¹H NMR (CDCl₃): δ 7.32-7.24 (15H, m, ArH), 4.81 (2H, s, CH₂Ph), 4.70 (2H, d, $J_{A,B} = 11.6$ Hz, CH₂Ph), 4.66 (2H, d, $J_{A,B} = 11.5$ Hz, CH₂Ph), 3.73 (2H, m, $J_{1eq,2} = J_{4,5eq} = 4.2$ Hz, $J_{1ax,2} = J_{4,5ax} = 11.2$ Hz, H-2, H-4), 3.27 (1H, t, $J_{2,3} = J_{3,4} = 8.9$ Hz, H-3), 2.69 (2H, dd, $J_{5ax,5eq} = J_{1ax,1eq} = 12.0$ Hz, H-5eq, H-1eq), 2.58 (2H, t, H-5ax, H-1ax); ¹³C NMR (CDCl₃): 138.89 (C_{ipso}), 138.44 (2C_{ipso}),

128.39-127.46 (15C, Ar), 86.98 (C-3), 83.17 (2C, C-2 and C-4), 76.34 (CH₂Ph), 72.97 (2 CH₂Ph), 22.11 (2C, C-1 and C-5). Anal. Calcd for C₂₆H₂₈O₃Se: C, 66.80; H, 6.04. Found: C, 66.88; H, 6.22.

1,5-Dideoxy-1,5-[[*N*-(2*R*,3*R*)-2,4-*O*-benzylidene-2,4-dihydroxy-3-(sulfooxy)-butyl]iminoonium]-xylitol (84).

1,5-Dideoxy-1,5-iminoxylitol **72** (0.161 g, 1.21 mmol) and 2,4-*O*-benzylidene-D-erythritol-1,3-cyclic sulfate **71b** (0.360 g, 1.32 mmol) were dissolved in reagent grade MeOH (2 mL). Anhydrous K₂CO₃ (0.015 g, 0.11 mmol) was added and the mixture was stirred in a sealed tube at 65°C for 3.5 h, at which point TLC showed that the cyclic sulfate had been consumed. The solvent was removed and the residue was purified by column chromatography (EtOAc:MeOH:H₂O, 8:2:1) to give the product **84** as a yellow oil (0.209 g, 43%): [α]_D −50 (*c* 0.48, H₂O); NMR data in Tables 1 and 3.

1,5-Dideoxy-1,5-[[*N*-(2*R*,3*R*)-2,4-dihydroxy-3-(sulfooxy)-butyl]iminoonium]-xylitol (66b).

Aqueous 60% HOAc (25 mL) was added to compound **84** (0.209 g, 0.515 mmol) and the mixture was stirred while warming in an open flask for 20 h at 70°C. The mixture was cooled and concentrated and the crude product was purified by column chromatography (EtOAc:MeOH:H₂O, 6:4:1) to give compound **66b** (0.118 g, 72%) as a colorless, hard foam: [α]_D −9 (*c* 0.57, H₂O); NMR data in Tables 2 and 4; MALDI MS *m/e* 339.99 (M⁺ + Na), 238.12 (M⁺ + H - SO₃).

1,5-Dideoxy-1,5-[[*N*-(2*S*,3*S*)-2,4-*O*-benzylidene-2,4-dihydroxy-3-(sulfooxy)-butyl]iminoonium]-xylitol (82).

1,5-Dideoxy-1,5-iminoxylitol **72** (0.158 g, 1.19 mmol) and 2,4-*O*-benzylidene-L-erythritol-1,3-cyclic sulfate **71a** (0.347 g, 1.27 mmol) were dissolved in reagent grade MeOH (2 mL). Anhydrous K₂CO₃ (0.018 g, 0.15 mmol) was added and the mixture was stirred in a sealed tube at 65°C for 4 h. The solvent was removed and the residue was purified by column chromatography (EtOAc:MeOH:H₂O, 8:2:1) to give the product **82** as a yellow oil (0.273 g, 56%). [α]_D +55 (*c* 0.65, H₂O); ¹H and ¹³C NMR

data were virtually identical with those of the enantiomer **84** (see Tables 1 and 3); MALDI MS m/e 428.09 ($M^+ + Na$), 406.11 ($M^+ + H$), 326.15 ($M^+ + H - SO_3$).

1,5-Dideoxy-1,5-[[*N*-(2*S*,3*S*)-2,4-dihydroxy-3-(sulfooxy)-butyl]iminoonium]-xylitol (66a).

- 5 Aqueous 60% HOAc (25 mL) was added to compound **82** (0.273 g, 0.673 mmol) and the mixture was stirred while warming in an open flask for 14 h at 75°C. The mixture was cooled and concentrated and the crude product was purified by column chromatography (EtOAc:MeOH:H₂O, 6:4:1) to give compound **66a** (0.156 g, 73%) as a colorless, hard foam. $[\alpha]_D +11$ (c 0.56, H₂O); ¹H and ¹³C NMR data were virtually
10 identical to those of the enantiomer **66b** (see Tables 2 and 4); MALDI MS m/e 399.99 ($M^+ + Na$), 318.28 ($M^+ + H$), 238.12 ($M^+ + H - SO_3$).

2,3,4,6-Tetra-*O*-benzyl-1,5-dideoxy-1,5-[[*N*-(2*R*,3*R*)-2,4-*O*-benzylidene-2,4-dihydroxy-3-(sulfooxy)-butyl]iminoonium]-D-glucitol (86).

- Tri-*O*-benzyldeoxynojirimycin **73** (0.241 g, 0.460 mmol) and 2,4-*O*-benzylidene-D-
15 erythritol-1,3-cyclic sulfate **71b** (0.143 g, 0.525 mmol) were dissolved in reagent grade acetone (2 mL). Anhydrous K₂CO₃ (0.020 g, 0.15 mmol) was added and the mixture was stirred in a sealed tube at 70°C for 20 h. The solvent was removed and the residue was purified by column chromatography (CHCl₃: MeOH, 5:1) to give the product **86** as a colorless gum (0.240 g, 65%). $[\alpha]_D -5.4$ (c 0.9, CHCl₃); NMR data in
20 Tables 1 and 3.

1,5-Dideoxy-1,5-[[*N*-(2*R*,*RS*)-2,4-dihydroxy-3-(sulfooxy)-butyl]iminoonium]-D-glucitol (67b).

- Compound **86** (0.209 g, 0.263 mmol) was dissolved in 80% aqueous acetic acid (20 mL) and the solution was stirred with 10% Pd/C catalyst (0.42 g) under 1 atm of H₂
25 for 20 h. The catalyst was removed by filtration through a small plug of silica gel, and washed with water (50 mL). The filtrate was evaporated and the gummy residue was freed of acetic acid by dissolving in water and re-concentrating (2 × 50mL). The crude product was purified by column chromatography (EtOAc: MeOH: H₂O, 6:3:1)

to give compound **67b** (0.096 g, containing 0.56 equiv. or 13% by weight of KOAc by ^1H NMR, 91% after correcting for acetate content). NMR data in Tables 2 and 4.

2,3,4,6-Tetra-*O*-benzyl-1,5-dideoxy-1,5-[[*N*-(2*S*,3*S*)-2,4-*O*-benzylidene-2,4-dihydroxy-3-(sulfooxy)-butyl]iminoonium]-D-glucitol (85).

- 5 Tri-*O*-benzyldeoxynojirimycin **73** (0.223 g, 0.426 mmol) and 2,4-*O*-benzylidene-L-erythritol-1,3-cyclic sulfate **71a** (0.123 g, 0.4535 mmol) were dissolved in reagent grade acetone (2 mL). Anhydrous K_2CO_3 (0.020 g, 0.15 mmol) was added and the mixture was stirred in a sealed tube at 70°C for 20 h. The solvent was removed and the residue was purified by column chromatography (CHCl_3 : MeOH, 5:1) to give the
10 product **85** as a colorless amorphous solid (0.271 g, 80%): $[\alpha]_{\text{D}} +36$ (*c* 0.8, CHCl_3); NMR data in Tables 1 and 3.

1,5-Dideoxy-1,5-[[*N*-(2*R*,3*R*)-2,4-dihydroxy-3-(sulfooxy)-butyl]iminoonium]-D-glucitol (67a).

- Compound **85** (0.205 g, 0.263 mmol) was dissolved in 80% aqueous acetic acid (20
15 mL) and the solution was stirred with 10%Pd/C catalyst (0.41 g) under 1 atm of H_2 for 20h. The catalyst was removed by filtration through a small plug of silica gel, and washed with water (50 mL). The filtrate was evaporated and the gummy residue was freed of acetic acid by dissolving in water and re-concentrating ($2 \times 50\text{mL}$). The crude product was purified by column chromatography (EtOAc: MeOH: H_2O , 6:3:1)
20 to give compound **67a** (0.094 g, containing 0.77 equiv. or 18% by weight of KOAc by ^1H NMR, 89% after correcting for acetate content). See Tables 2 and 4 for ^1H and ^{13}C NMR data.

- 2,3,4-Tri-*O*-benzyl-1,5-dideoxy-1,5-[[*(2R,3R)*-2,4-*O*-benzylidene-2,4-dihydroxy-3-(sulfooxy)butyl]-(*S*)-episulfoniumylidene]-xylitol inner salt (88b) and 2,3,4-tri-*O*-
25 benzyl-1,5-dideoxy-1,5-[[*(2R,3R)*-2,4-*O*-benzylidene-2,4-dihydroxy-3-(sulfooxy)butyl]-(*R*)-episulfoniumylidene]-xylitol inner salt (89b).**

To 1,1,1,3,3,3-hexafluoro-2-propanol (0.5 mL) were added 2,4-*O*-benzylidene-D-erythritol-1,3-cyclic-sulfate **71b** (0.565 g, 2.08 mmol), 1,5-anhydro-2,3,4-tri-*O*-benzyl-5-thioxylitol **7** (0.677 g, 1.61 mmol) and anhydrous K_2CO_3 (70 mg). The

mixture was stirred in a sealed tube in a 70°C oil bath overnight, after which an extra 40 mg of anhydrous K₂CO₃ was added. The solvents were removed and the residue was chromatographed [CHCl₃:MeOH, 10:1] to give **88b** and **89b** in a 2:1 ratio (0.975 g, 87%).

- 5 Major isomer **88b**: mp 186-189°C; [α]_D +2.1 (*c* 1.2, CH₂Cl₂); NMR data in Tables 1 and 3; HRMS Calcd for C₃₇H₄₀O₉S₂ (M + H): 693.2192. Found: 693.2209. Anal. Calcd for C₃₇H₄₀O₉S₂: C, 64.14; H, 5.82. Found: C, 64.39; H, 5.94.

Minor isomer **89b**: mp 169-172°C; [α]_D -49.1 (*c* 0.8, CH₂Cl₂); NMR data in Tables 1 and 3; Anal. Calcd for C₃₇H₄₀O₉S₂: C, 64.14; H, 5.82. Found: C, 63.84; H, 5.96.

- 10 **1,5-Dideoxy-1,5-[[*(2R,3R)*-2,4-dihydroxy-3-(sulfooxy)butyl]-(*S*)-episulfoniumylidene]-xylitol inner salt (*S*-68b).**

- To compound **88b** (0.33 g, 0.48 mmol) dissolved in 80% AcOH (12 mL) was added Pd(OH)₂ (0.2 g). The mixture was stirred under H₂ (110 psi) for 48 h and then filtered through Celite with MeOH. The solvent was evaporated and the residue was purified
15 by column chromatography [EtOAc:MeOH:H₂O, 7:3:1]. Compound *S*-**68b** was obtained as a syrup (0.13 g, 81%); [α]_D -21.8 (*c* 1.1, H₂O); NMR data in Tables 2 and 4; HRMS Calcd for C₉H₁₉O₉S₂ (M + H): 335.0470. Found: 335.0454. Anal. Calcd for C₉H₁₈O₉S₂: C, 32.33; H, 5.43. Found: C, 32.03; H, 5.59.

- 20 **1,5-Dideoxy-1,5-[[*(2R,3R)*-2,4-dihydroxy-3-(sulfooxy)butyl]-(*R*)-episulfoniumylidene]-xylitol inner salt (*R*-68b).**

- Compound **89b** (0.249 g, 0.36 mmol) was deprotected by hydrogenolysis using the procedure described above for *S*-**68b** to give the title compound as a syrup (0.13 g, 95%); [α]_D -16.2 (*c* 0.9, H₂O); NMR data in Tables 2 and 4; HRMS Calcd for C₉H₁₉O₉S₂ (M + H): 335.0470. Found: 335.0478. Anal. Calcd for C₉H₁₈O₉S₂: C,
25 32.33; H, 5.43. Found: C, 31.88; H, 5.21.

2,3,4-Tri-*O*-benzyl-1,5-dideoxy-1,5-[[*(2S,3S)*-2,4-*O*-benzylidene-2,4-dihydroxy-3-(sulfooxy) butyl]- (*R*)-episulfoniumylidene]-xylitol inner salt (88a**) and 2,3,4-tri-*O*-benzyl-1,5-dideoxy-1,5-[[*(2S,3S)*-2,4-*O*-benzylidene-2,4-dihydroxy-3-(sulfooxy) butyl]-(*S*)-episulfoniumylidene]-xylitol inner salt (**89a**).**

To 1,1,1,3,3,3-hexafluoro-2-propanol (0.5 mL) were added 2,4-*O*-benzylidene-L-erythritol-1,3-cyclic-sulfate **71a** (0.265 g, 0.97 mmol), 1,5-anhydro-2,3,4-tri-*O*-benzyl-5-thioxylitol **74** (0.328 g, 0.78 mmol) and anhydrous K₂CO₃ (24 mg). The mixture was stirred in a sealed tube in a 70°C oil bath for 5 days. The solvent was evaporated and the residue was purified by column chromatography [CHCl₃:MeOH, 10:1] to give **88a** and **89a** in a 5:2 ratio as a white solid (0.465 g, 86%). Pure samples were obtained by rechromatography.

Major isomer **88a**: Mp 175-180°C; [α]_D -3.7 (*c* 0.9, CH₂Cl₂); ¹H and ¹³C NMR data were virtually identical to those of the enantiomer **88b**. Anal. Calcd for C₃₇H₄₀O₉S₂: C, 64.14; H, 5.82; Found: C, 63.81; H, 5.68.

Minor isomer **89a**: Mp 163-170°C; [α]_D +41.8 (*c* 1.1, CH₂Cl₂); ¹H and ¹³C NMR data were virtually identical to those of the enantiomer **89b**. Anal. Calcd for C₃₇H₄₀O₉S₂: C, 64.14; H, 5.82. Found: C, 64.42; H, 5.75.

1,5-Dideoxy-1,5-[[*(2S,3S)*-2,4-dihydroxy-3-(sulfooxy)butyl]-(*R*)-episulfoniumylidene]-xylitol inner salt (*R*-68a).

To compound **88a** (0.304 g, 0.44 mmol) dissolved in 80% AcOH (10 mL) was added Pd/C (0.5 g). The mixture was stirred under 120 psi H₂ for 96 h. The mixture was filtered through Celite with MeOH, and the solvent removed. The residue was then redissolved in 80% AcOH (10 mL). To the solution was added Pd(OH)₂ (0.2 g) and the solution was stirred under 120 psi H₂ for 48 h. The mixture was filtered through Celite with MeOH, the solvent evaporated, and the residue was purified by column chromatography [EtOAc:MeOH:H₂O, 7:3:1] to give the title compound as a syrup (0.08 g, 55%); [α]_D +21.7 (*c* 0.8, H₂O). ¹H and ¹³C NMR data were virtually identical to those of the enantiomer *S*-**68b** (see Tables 1 and 3). HRMS Calcd for C₉H₁₈O₉S₂Na (M + Na): 357.0290. Found: 357.0284.

1,5-Dideoxy-1,5-[[*(2S,3S)*-2,4-dihydroxy-3-(sulfooxy)butyl]-(*S*)-episulfoniumylidene]-xylitol inner salt (*S*-68a).

Compound **89a** (0.240 g, 0.35 mmol) was deprotected by hydrogenolysis using the procedure described above for *S*-**68b** to give the title compound as a syrup (0.08 g,

67%); $[\alpha]_D +19.5$ (c 0.7, H_2O). ^1H and ^{13}C NMR data were virtually identical to the enantiomer *R*-**68b** (see Tables 2 and 4) HRMS Calcd for $C_9H_{19}O_9S_2$ ($M + H$): 335.0470. Found: 335.0477.

2,3,4,6-Tetra-*O*-benzyl-1,5-dideoxy-1,5-[[*(2R,3R)*-2,4-*O*-benzylidene-2,4-dihydroxy-3-(sulfooxy) butyl]-(*S/R*)-episulfoniumylidene]-D-glucitol inner salts (90b) and (91b).

To 1,1,1,3,3,3-hexafluoro-2-propanol (0.5 mL) were added 2,4-*O*-benzylidene-D-erythritol-1,3-cyclic-sulfate **71b** (0.115 g, 0.42 mmol), 1,5-anhydro-2,3,4,6-tetra-*O*-benzyl-5-thio-D-glucitol **75** (0.174 g, 0.32 mmol) and anhydrous K_2CO_3 (30 mg). The mixture was stirred in a sealed tube in a 70°C oil bath for 5 days. The solvent was removed and the residue was purified by column chromatography [$CHCl_3$:MeOH, 10:1] to give an inseparable mixture of **90b** and **91b** in a 2:1 ratio as a white solid (0.182 g, 70%); $[\alpha]_D = +2.1$ (c 1.3, CH_2Cl_2). Major isomer **90b**: See Tables 1 and 2 for ^1H and ^{13}C NMR data. Anal. Calcd for $C_{45}H_{48}O_{10}S_2$: C, 66.48 ; H, 5.96. Found: C, 66.36; H, 6.08.

1,5-Dideoxy-1,5-[[*(2R,3R)*-2,4-dihydroxy-3-(sulfooxy)butyl]-(*S*)-episulfoniumylidene]-D-glucitol inner salt (69b).

To a mixture of compounds **90b** and **91b** (0.1639 g, 0.20 mmol) dissolved in 80% AcOH (10 mL) was added $Pd(OH)_2$ (0.17 g). The mixture was stirred under 120 psi H_2 for 48 h. The mixture was filtered through Celite with MeOH, the solvent was removed, and the residue was purified by column chromatography [EtOAc:MeOH: H_2O , 7:3:1]. Compound **69b** was obtained as a syrup (0.06 g, 81%); $[\alpha]_D = -20.4$ (c 0.8, H_2O). See Tables 2 and 4 for ^1H and ^{13}C NMR data. HRMS. Calcd for $C_{10}H_{21}O_{10}S_2$ ($M + H$): 365.0576 Found: 365.0574.

2,3,4,6-Tetra-*O*-benzyl-1,5-dideoxy-1,5-[[*(2S,3S)*-2,4-*O*-benzylidene-2,4-dihydroxy-3-(sulfooxy) butyl]-(*R/S*)-episulfoniumylidene]-D-glucitol inner salts (90a) and (91a).

To 1,1,1,3,3,3-hexafluoro-2-propanol (0.5 mL) were added 2,4-*O*-benzylidene-L-erythritol-1,3-cyclic-sulfate **71a** (0.148 g, 0.54 mmol), 1,5-anhydro-2,3,4,6-tetra-*O*-

benzyl-5-thio-D-glucitol **75** (0.240 g, 0.44 mmol) and anhydrous K₂CO₃ (33 mg). The mixture was stirred in a sealed tube in a 69-70°C oil bath for 84 h. The solvent was evaporated and the residue was purified by column chromatography [CHCl₃:MeOH, 10:1] to give an inseparable 3:1 mixture of **90a** and **91a** as a white solid (0.25g, 68%); $[\alpha]_D = +48.8$ (*c* 1.6, CH₂Cl₂). Major isomer **90a**: See Tables 1 and 2 for ¹H and ¹³C NMR data. Anal. Calcd for C₄₅H₄₈O₁₀S₂: C, 66.48; H, 5.95. Found: C, 66.19; H, 6.07.

1,5-Dideoxy-1,5-[[*(2S,3S)*-2,4-dihydroxy-3-(sulfooxy)butyl]-(*R*)-episulfoniumylidene]-D-glucitol inner salt (69a**).**

To a mixture of compounds **90a** and **91a** (0.180 g, 0.22 mmol) dissolved in 80% AcOH (10 mL) was added Pd(OH)₂ (0.20 g), and the mixture was stirred under 120 psi H₂ for 6 days. The mixture was filtered through Celite with MeOH, the solvent was removed and the residue was purified by column chromatography [EtOAc:MeOH:H₂O, 7:3:1]. Compound **69a** was obtained as a syrup (0.05g, 67%); $[\alpha]_D = +10.3$ (*c* 0.6, H₂O). See Tables 2 and 4 for ¹H and ¹³C NMR data. HRMS Calcd for C₁₀H₂₁O₁₀S₂ (M + H): 365.0576. Found: 365.0577.

2,3,4-Tri-*O*-benzyl-1,5-dideoxy-1,5-[[*(2R,3R)*-2,4-*O*-benzylidene-2,4-dihydroxy-3-(sulfooxy)butyl]-(*S/R*)-episelenoniumylidene]-xylitol inner salt (92b** and **93b**).**

To 1,1,1,3,3,3-hexafluoro-2-propanol (0.5 mL) were added 2,4-*O*-benzylidene-D-erythritol-1,3-cyclic-sulfate **71b** (0.272 g, 1.00 mmol), 1,5-anhydro-2,3,4-tri-*O*-benzyl-5-selenoxylitol **76** (0.362 g, 0.78 mmol) and anhydrous K₂CO₃ (50 mg). The mixture was stirred in a sealed tube in a 70°C oil bath for 48 h. The solvent was concentrated and the residue was purified by column chromatography [CHCl₃:MeOH, 10:1] to give an inseparable mixture of **92b** and **93b** in a 1:4 ratio (0.20 g, 96%). $[\alpha]_D -45.7$ (*c* 1.1, CH₂Cl₂). For the major isomer **36b**: See Tables 1 and 2 for ¹H and ¹³C NMR data. Anal. Calcd for C₃₇H₄₀O₉SSe: C, 59.99; H, 5.45. Found: C, 59.73; H, 5.36.

1,5-Dideoxy-1,5-[[*(2R,3R)*-2,4-dihydroxy-3-(sulfooxy)butyl]-(*R*)-episelenoniumylidene]-xylitol inner salt (70b**).**

To the mixture of compounds **92b** and **93b** (0.295 g, 0.40 mmol) dissolved in 80% AcOH (10 mL) was added Pd(OH)₂ (0.29 g), and the mixture was stirred under 120 psi H₂ for 5 days. TLC revealed one major product and two minor products. The mixture was filtered through Celite™, concentrated, and the residue was purified by
 5 column chromatography [EtOAc:MeOH:H₂O, 7:3:1] to give the major product, compound **70b** as a syrup (0.06 g, 39%); [α]_D -16.6 (*c* 0.9, H₂O). See Tables 2 and 4 for ¹H and ¹³C NMR data. HRMS Calcd for C₉H₁₉O₉SSe (M + H): 382.9915. Found: 382.9916. Anal. Calcd for C₉H₁₈O₉SSe: C, 28.35 ; H, 4.76. Found: C, 28.44; H, 4.71.

2,3,4-Tri-*O*-benzyl-1,5-dideoxy-1,5-[[*(2S,3S)*-2,4-*O*-benzylidene-2,4-dihydroxy-3-
 10 **(sulfooxy)butyl]-(*R/S*)-episelenoniumylidene]-xylitol inner salts (**92a** and **93a**).**

To 1,1,1,3,3,3-hexafluoro-2-propanol (0.5 mL) were added 2,4-*O*-benzylidene-L-erythritol-1,3-cyclic-sulfate **71a** (0.226 g, 0.83 mmol), 1,5-anhydro-2,3,4-tri-*O*-benzyl-5-selenoxylitol **76** (0.308 g, 0.66 mmol) and anhydrous K₂CO₃ (20 mg). The mixture was stirred in a sealed tube in a 70°C oil bath for 72 h. The solvent was removed and
 15 the residue was purified by column chromatography [CHCl₃:MeOH, 10:1] to give an inseparable 1:3 mixture of **92a** and **93a** as a white solid (0.42 g, 85%). [α]_D -44.0 (*c* 0.9, CH₂Cl₂). For the major isomer **93a**, the ¹H and ¹³C NMR data were virtually identical to those of the enantiomer (compound **93b**, see Tables 1 and 2) except for small chemical shift differences due to concentration effects. Anal. Calcd for
 20 C₃₇H₄₀O₉SSe: C, 59.99; H, 5.45. Found: C, 59.85; H, 5.58.

1,5-Dideoxy-1,5-[[*(2S,3S)*-2,4-dihydroxy-3-(sulfooxy)butyl]-(*S*)-episelenoniumylidene]-xylitol inner salt (70a**).**

To a mixture of compounds **92a** and **93a** (0.406 g, 0.55 mmol) dissolved in 80% AcOH (10 mL) was added Pd(OH)₂ (0.50 g), and the mixture was stirred under 120
 25 psi H₂ for 8 days. TLC revealed one major product and two minor products. The mixture was filtered through Celite with MeOH, the solvent was removed, and the residue was purified by column chromatography [EtOAc/MeOH/H₂O, 7:3:1]. Compound **70a** was obtained as a syrup (0.05 g, 25%); [α]_D +14.1 (*c* 0.4, H₂O). For compound **70a**, the ¹H and ¹³C NMR data were virtually identical to the enantiomer
 30 (compound **70b**, see Tables 1 and 2) except for small chemical shift differences due to

concentration effects. HRMS Calcd for $C_9H_{18}O_9SSeNa$ (M + Na): 404.9734. Found: 404.9735. Anal. Calcd for $C_9H_{18}O_9SSe$: C, 28.35; H, 4.76. Found: C, 28.56; H, 4.54.

Table 1. ¹H NMR Data for Compounds **84**, **85**, **86**, **88b**, **89b**, **90a**, **90b** and **93b**.

Compound	84 ^{a*}	85 ^b	86 ^c	88b ^{d*}	89b ^{e*}	90a ^f	90b ^g	93b ^{h*}
H-1eq (<i>J</i> _{1eq,2} , <i>J</i> _{1eq,5eq})	3.18-3.13 (m) (nd, nd)	3.47 (dd) (4.9, ~0)	3.33 (dd) (4.8, ~0)	3.59 (ddd) (4.4, 2.4)	3.38 (d) (2.9, ~0)	3.82 (dd) (4.5, ~01)	3.40 (dd) (4.5, ~0)	3.36 (dd) (3.2, ~0)
H-1ax (<i>J</i> _{1ax,1eq} , <i>J</i> _{1ax,2})	2.32 (dd) (9.1, 9.1)	2.34 (dd) (11.5, 11.0)	2.58 (dd) (11.1, 10.6)	3.38 (dd) (12.5, 2.1)	3.38 (d) (nd, 2.9)	3.57 (dd) (14.9, 2.7)	3.31 (dd) (14.7, 3.2)	3.18 (dd) (13.3, 4.0)
H-2 (<i>J</i> _{2,3} , <i>J</i> _{2,4})	3.61-3.53 (m) (10.9, nd)	3.62 (ddd) (9.0, ~0)	3.58 (ddd) (9.0, ~0)	3.89 (dddd) (3.6, 1.8)	3.84 (ddd) (~2, ~0)	4.20 (ddd) (4.3, ~0)	3.92 (ddd) (4.5, ~0)	3.86 (ddd) (4.2, ~0)
H-3 (<i>J</i> _{3,4})	3.22 (dd) (10.9)	3.38 (dd) (9.0)	3.39 (dd) (9.0)	3.79 (dd) (3.6)	3.92 (dd) (<1)	3.87 (dd) (4.3)	3.85 (dd) (4.5)	3.91 (dd) (4.2)
H-4 (<i>J</i> _{4,5eq} , <i>J</i> _{4,5ax})	3.61-3.53 (m) (nd, 9.1)	3.55 (ddd) (na, 9.5)	3.54 (dd) (na, 9.5)	4.05 (dddd) (4.1, 1.9)	4.02 (ddd) (3.5, 2.6)	3.79 (dd) (4.3, na)	4.02 (dd) (5.1, na)	3.98 (ddd) (4.5, 2.9)
H-5eq	3.18-3.13 (m)	na	na	3.93 (ddd)	3.76 (dd)	3.90 (ddd)	4.09 (ddd)	3.56 (ddd)
H-5ax (<i>J</i> _{5eq,5ax})	2.32 (dd) (9.1)	2.40 (ddd) (na)	2.55 (ddd) (na)	3.54 (dd) (12.6)	3.64 (dd) (15.1)	na	na	3.66(dd) (13.4)
H-6a (<i>J</i> _{6a,6b} , <i>J</i> _{5,6a})	na	3.90 (dd) (10.7, 2.2)	3.85 (dd) (10.2, 2.4)	na	na	3.72(dd) (11.1, 7.3)	4.03(dd) (10.5, 5.7)	na
H-6b (<i>J</i> _{5,6b})	na	3.68 (dd) (1.6)	3.78 (dd) (2.0)	na	na	3.63(dd) (5.1)	3.95(dd) (5.3)	na
H-1'a (<i>J</i> _{1'a,1'b} , <i>J</i> _{1'a,2'})	3.12 (d) (14.2, <1)	3.56 (d) (15.1, <1)	3.67 (d) (15.6, <1)	4.28 (dd) (13.5, 3.1)	4.99 (dd) (14.2, 3.7)	4.67 (dd) (13.9, 3.7)	4.70 (dd) (13.9, 4.1)	4.82 (dd) (12.8, 4.0)
H-1'b (<i>J</i> _{1'b,2'})	2.83 (dd) (8.3)	2.78 (dd) (8.0)	2.93 (dd) (7.9)	3.67 (dd) (3.9)	4.27 (dd) (1.5)	4.32 (dd) (1.8)	4.32 (dd) (1.9)	4.30 (dd) (1.7)
H-2' (<i>J</i> _{2',3'})	4.14 (dd) (9.7)	4.05 (dd) (10.0)	4.07 (dd) (9.7)	4.32 (ddd) (10.0)	4.21 (ddd) (10.1)	4.21 (ddd) (9.7)	4.22 (ddd) (9.6)	4.18 (ddd) (9.6)
H-3' (<i>J</i> _{3',4'eq})	4.21 (ddd) (5.2)	4.11 (ddd) (5.4)	4.16 (ddd) (5.3)	4.62 (ddd) (5.4)	4.66 (ddd) (5.5)	4.66 (ddd) (5.5)	4.62 (ddd) (5.5)	4.54 (ddd) (5.3)
H-4'eq (<i>J</i> _{4'eq,4'ax})	4.50 (dd) (11.0)	4.55 (dd) (10.6)	4.60 (dd) (11.0)	4.49 (dd) (10.9)	4.47 (dd) (10.8)	4.50 (dd) (10.5)	4.51 (dd) (10.7)	4.45 (dd) (10.6)
H-4'ax (<i>J</i> _{3',4'ax})	3.89 (dd) (9.8)	3.77 (dd) (9.8)	3.82 (dd) (9.7)	3.77 (dd) (10.3)	3.74 (dd) (10.1)	3.74 (dd) (10.9)	3.74 (dd) (10.2)	3.76 (dd) (10.1)

Footnotes for Table 1

^a 500 MHz, pH=8, D₂O. Others: 7.51-7.43 (5H, m, Ar), 5.72 (1H, s, benzylidene CH).

5 ^b 500 MHz, pH=10, CD₃OD. Others: 7.44-7.03 (25H, m, Ar), 5.55 (1H, s, benzylidene CH), 4.89 and 4.73 (2H, 2d, J_{A,B} = 11.2 Hz, CH₂Ar), 4.75 and 4.41 (2H, 2d, J_{A,B} = 11.0 Hz, CH₂Ar), 4.62 and 4.55 (2H, 2d, J_{A,B} = 11.5 Hz, CH₂Ar), 4.57 and 4.43 (2H, 2d, J_{A,B} = 12.2 Hz, CH₂Ar).

10 ^c 500 MHz, pH=10, CD₃OD. Others: 7.50-7.00 (25H, m, Ar), 5.61 (1H, s, benzylidene CH), 4.88 and 4.74 (2H, 2d, J_{A,B} = 11.3 Hz, CH₂Ar), 4.74 and 4.38 (2H, 2d, J_{A,B} = 10.8 Hz, CH₂Ar), 4.70 and 4.46 (2H, 2d, J_{A,B} = 11.7 Hz, CH₂Ar), 4.62 and 4.57 (2H, 2d, J_{A,B} = 11.9 Hz, CH₂Ar).

15 ^d 600 MHz, CD₂Cl₂. Others: 7.45-7.10 (20H, m, Ar), 5.55 (1H, s, benzylidene CH), 4.69 and 4.49 (2H, 2d, J_{A,B} = 11.5 Hz, CH₂Ar), 4.49 and 4.43 (2H, 2d, J_{A,B} = 11.8 Hz, CH₂Ar), 4.46 and 4.44 (2H, 2d, J_{A,B} = 11.6 Hz, CH₂Ar).

15 ^e 600 MHz, CD₂Cl₂. Others: 7.45-7.05 (20H, m, Ar), 5.52 (1H, s, benzylidene CH), 4.64 and 4.58 (2H, 2d, J_{A,B} = 11.4 Hz, CH₂Ar), 4.49 and 4.46 (2H, 2d, J_{A,B} = 11.9 Hz, CH₂Ar), 4.40 (2H, s, CH₂Ar).

20 ^f 500 MHz, CD₂Cl₂. Others: 7.46-7.01 (25H, m, Ar), 5.52 (1H, s, benzylidene CH), 4.65 and 4.54 (2H, 2d, J_{A,B} = 11.5 Hz, CH₂Ar), 4.46 and 4.41 (2H, 2d, J_{A,B} = 11.7 Hz, CH₂Ar), 4.46 and 4.43 (2H, 2d, J_{A,B} = 11.4 Hz, CH₂Ar), 4.32 and 4.29 (2H, 2d, J_{A,B} = 11.9 Hz, CH₂Ar).

25 ^g 400 MHz, CD₂Cl₂. Others: 7.44-7.06 (25H, m, Ar), 5.52 (1H, s, benzylidene CH), 4.66 and 4.50 (2H, 2d, J_{A,B} = 11.6 Hz, CH₂Ar), 4.61 and 4.55 (2H, 2d, J_{A,B} = 11.4 Hz, CH₂Ar), 4.48 and 4.44 (2H, 2d, J_{A,B} = 11.7 Hz, CH₂Ar), 4.40 (2H, s, CH₂Ar).

25 ^h 600 MHz, CD₂Cl₂. Others: 7.40-7.10 (20H, m, Ar), 5.55 (1H, s, benzylidene CH), 4.63 and 4.57 (2H, 2d, J_{A,B} = 11.4 Hz, CH₂Ar), 4.50 and 4.47 (2H, 2d, J_{A,B} = 11.8 Hz, CH₂Ar), 4.47 and 4.42 (2H, 2d, J_{A,B} = 11.8 Hz, CH₂Ar).

30 *Assignments for diastereotopic H-1/H-5 and H-2/H-4 pairs may be reversed.
na = not applicable, n.d. = not determined

Table 2. ^{13}C NMR Data for Compounds **84**, **85**, **86**, **88b**, **89b**, **90a**, **90b** and **93b**.

Compound	84 ^{a*}	85 ^b	86 ^c	88b ^{d*}	89b ^{e*}	90a ^f	90b ^g	93b ^{h*}
C-1	57.89	56.62	56.96	42.08	32.90	32.49	34.69	30.17
C-2	69.92	79.27	79.48	71.61	70.99	72.52	73.49	72.16
C-3	78.72	88.10	88.17	70.94	70.31	73.84	76.87	72.48
C-4	69.92	79.71	79.70	71.72	70.72	73.16	73.66	72.08
C-5	58.07	66.55	64.35	39.24	33.41	52.36	53.46	30.73
C-6	na	66.16	66.05	na	na	65.89	65.33	na
C-1'	57.77	54.19	53.95	46.00	43.31	44.94	45.38	43.37
C-2'	77.78	79.81	77.28	76.75	77.44	77.10	77.23	77.47
C-3'	69.18	69.53	69.34	66.88	65.73	65.80	66.63	67.41
C-4'	69.06	70.56	70.61	69.51	69.51	69.50	69.59	69.51

Footnotes for Table 2

- 5 ^a125 MHz, D₂O. Others: 136.85 (*C*_{ipso}, Ar), 130.34, 129.28, 126.66 (5C, Ar), 101.44 (benzylidene CH)
- ^b125 MHz, CD₃OD. Others: 140.32, 139.82, 139.76 and 139.36 (2C) (5 × *C*_{ipso}, Ar), 129.93 - 127.27 (25C, Ar), 101.97 (benzylidene CH), 76.19 (2C), 74.34 and 73.23 (4 × CH₂Ar).
- 10 ^c125 MHz, CD₃OD. Others: 140.35, 139.88, 139.71, 139.506 and 139.41 (5 × *C*_{ipso}, Ar), 130.12 - 127.27 (25C, Ar), 101.69 (benzylidene CH), 76.23 (2C), 74.25 and 73.34 (4 × CH₂Ar).
- ^d100 MHz, CD₂Cl₂. Others: 137.35, 136.96, 136.92 and 136.85 (4 × *C*_{ipso}, Ar), 128.84 - 126.54 (20C, Ar), 102.07 (benzylidene CH), 73.68, 72.17 and 72.00 (3 × CH₂Ar).
- 15 ^e100 MHz, CD₂Cl₂. Others: 137.38, 137.11, 137.00 and 136.80 (4 × *C*_{ipso}, Ar), 129.80 - 126.48 (20C, Ar), 102.19 (benzylidene CH), 73.59, 72.64 and 72.10 (3 × CH₂Ar).
- ^f100 MHz, CD₂Cl₂. Others: 137.18, 137.07, 137.00, 136.85 and 136.75 (5 × *C*_{ipso}, Ar), 129.71 - 126.65 (25C, Ar), 102.11 (benzylidene CH), 73.70, 73.51, 73.40 and 71.85 (4 × CH₂Ar).
- 20 ^g100 MHz, CD₂Cl₂. Others: 137.54, 137.44, 137.35, 137.17 and 136.85 (5 × *C*_{ipso}, Ar), 129.80 - 126.54 (25C, Ar), 101.95 (benzylidene CH), 74.48, 74.13, 73.99 and 72.35 (4 × CH₂Ar).

^h100 MHz, CD₂Cl₂. Others: 137.39, 137.29, 137.13 and 137.09 (4 × C_{ipso}, Ar), 129.74- 126.49 (25C, Ar), 102.04 (benzylidene CH), 73.37, 72.83 and 72.255 (3 × CH₂Ar).

* Assignments for diastereotopic C-1/C-5 and C-2/C-4 pairs may be reversed.

Table 3. ¹H NMR Data Compounds **66b**, **67a**, **67b**, *S*-**68b**, *R*-**68b**, **69a**, **69b** and **70b**.

Compound	66b ^{a*}	67a ^b	67b ^c	<i>S</i> - 68b ^{d*}	<i>R</i> - 68b ^{e*}	69a ^f	69b ^g	70b ^{h*}
H-1eq (<i>J</i> _{1eq,2})	3.08 (dd) (4.8)	3.57 (br d) (4.8)	3.16 (dd) (4.9)	3.70 (dd) (3.5)	3.38-3.72 (m) (3.8)	3.85 (dd) (3.6)	3.89 (dd) (3.9)	3.36 (dd) (3.2, <1)
H-1ax (<i>J</i> _{1ax,1eq} , <i>J</i> _{1ax,2})	2.18 (dd) (11.0, 11.0)	2.93 (br dd) (11.8, 10.8)	2.49 (dd) (11.7, 11.1)	3.54 (dd) (13.9, 7.2)	3.36 (d) (11.8, 11.8)	3.52 (dd) (11.5, 11.5)	3.45 (dd) (11.5, 11.5)	3.18 (dd) (13.3, 4.0)
H-2 (<i>J</i> _{2,3})	3.58 (ddd) (9.2)	3.80 (ddd) (9.4)	3.55 (ddd) (9.3)	4.29 (ddd) (7.2)	4.01-3.93 (m) (9.0)	3.91 (ddd) (8.5)	3.97 (ddd) (9.1)	3.86 (ddd) (4.2, <1)
H-3 (<i>J</i> _{3,4})	3.20 (dd) (9.2)	3.47 (dd) (9.4)	3.30 (dd) (9.5)	3.75 (dd) (7.2)	3.51 (dd) (9.0)	3.51 (dd) (8.5)	3.54 (dd) (9.1)	3.91 (dd) (4.2)
H-4 (<i>J</i> _{4,5eq} , <i>J</i> _{4,5ax})	3.55 (ddd) (4.7, 11.0)	3.62 (dd) (na, 9.8)	3.44 (dd) (na, 9.5)	4.28 (ddd) (3.5, 7.2)	4.01-3.93 (m) (3.5, 11.8)	3.80 (dd) (na, 10.5)	3.86 (dd) (na, 10.8)	3.98 (ddd) (2.9, 4.5)
H-5eq (<i>J</i> _{5eq,6a})	3.073 (dd) na	na	na	3.71 (ddd) (na)	3.38-3.72 (m) (na)	na	na	3.66 (ddd) (na)
H-5ax (<i>J</i> _{5eq,5ax})	2.13 (dd) (11.0)	3.07 (br m) (na,)	2.37 (ddd) (na,)	3.55 (dd) (13.8)	3.36 (dd) (11.8)	3.75 (ddd) (na)	3.76 (ddd) (na)	3.56 (dd) (13.4)
H-6a (<i>J</i> _{6a,6b} , <i>J</i> _{5,6a})	na	4.08 (dd) (12.7, 2.9)	3.93 (dd) (12.6, 2.4)	na	na	4.21 (dd) (12.8, 3.7)	4.21 (dd) (13.2, 3.8)	na
H-6b (<i>J</i> _{5,6b})	na	4.03 (dd) (2.8)	3.86 (dd) (2.4)	na	na	4.12 (dd) (2.8)	4.11 (dd) (2.6)	na
H-1'a (<i>J</i> _{1'a,1'b} , <i>J</i> _{1'a,2'})	2.78 (dd) (13.7, 2.8)	3.57 (br d) (14.1, 2.2)	2.92 (d) (13.5, 2.6)	3.86 (dd) (14.4, 3.6)	3.93 (dd) (12.8, 3.7)	4.15 (dd) (13.9, 3.4)	3.98 (dd) (13.3, 6.3)	4.82 (dd) (12.8, 4.0)
H-1'b (<i>J</i> _{1'b,2'})	2.57 (dd) (8.8)	3.15 (br dd) (9.3)	2.88 (dd) (8.7)	3.74 (dd) (7.6)	3.83 (dd) (7.5)	3.70 (dd) (8.5)	3.85 (dd) (3.2)	4.30 (dd) (1.7)
H-2' (<i>J</i> _{2',3'})	4.12 (ddd) (5.7)	4.35 (ddd) (6.8)	4.19 (ddd) (6.0)	4.45 (ddd) (7.5)	4.41 (ddd) (7.5)	4.40 (ddd) (7.1)	4.39 (ddd) (6.3)	4.18 (ddd) (9.6)
H-3' (<i>J</i> _{3',4'a})	4.23 (ddd) (3.5)	4.29 (ddd) (3.4)	4.24 (ddd) (3.4)	4.39 (ddd) (3.6)	4.32 (ddd) (3.4)	4.27 (ddd) (3.6)	4.35 (ddd) (2.7)	4.54 (ddd) (5.3)
H-4'a (<i>J</i> _{4'a,4'b})	3.87 (dd) (12.6)	3.97 (dd) (12.7)	3.91 (dd) (12.2)	3.99 (dd) (12.9)	4.94 (dd) (12.6)	3.96 (dd) (12.5)	3.97 (dd) (12.6)	4.45 (dd) (10.6)
H-4'b (<i>J</i> _{3',4'b})	3.80 (dd) (4.6)	3.88 (dd) (3.8)	3.85 (dd) (4.3)	3.88 (dd) (3.3)	3.84 (dd) (3.4)	3.84 (dd) (3.5)	3.84 (dd) (3.4)	3.76 (dd) (10.1)

Footnotes for Table 3

^a 500 MHz, pH=10, D₂O.^b 500 MHz, pH=8, Temp.=25°C, D₂O.^c 500 MHz, pH=8, Temp.=40°C, D₂O.5 ^d 600 MHz, D₂O.^e 600 MHz, D₂O.^f 500 MHz, D₂O.^g 400 MHz, D₂O.^h 600 MHz, D₂O.

10 *Assignments for diastereotopic H-1/H-5 and H-2/H-4 pairs may be reversed.

na = not applicable, n.d. = not determined

Table 4. ^{13}C NMR Data Compounds **66b**, **67a**, **67b**, *S*-**68b**, *R*-**68b**, **69a**, **69b** and **70b**.

Compound	66b ^{a*}	67a ^b	67b ^b	<i>S</i> - 68b ^{c*}	<i>R</i> - 68b ^{c*}	69a ^c	69b ^c	70b ^{c*}
C-1	58.19	55.85	56.48	41.25	43.24	43.62	41.76	39.29
C-2	69.96	67.67	78.62	69.09	69.85	69.69	69.64	70.64
C-3	78.77	77.60	78.14	74.05	78.10	78.57	78.58	78.42
C-4	70.00	79.04	69.68	69.05	69.81	70.95	70.91	70.64
C-5	57.64	66.90	66.29	41.01	43.13	61.19	60.88	39.10
C-6	na	56.57	56.91	na	na	58.69	58.63	na
C-1'	59.38	54.65	54.98	45.44	50.39	49.41	49.01	50.20
C-2'	67.82	66.90	65.99	67.97	69.09	68.54	67.04	68.02
C-3'	81.92	81.15	81.55	82.29	62.33	83.15	83.03	83.03
C-4'	60.20	60.03	60.16	62.01	62.04	62.10	62.11	62.30

Footnotes for Table 4

^a 125 MHz, pH=10, D₂O.

^b 125 MHz, pH=8, D₂O.

^c 100 MHz D₂O.

* Assignments for diastereotopic C-1/C-5 and C-2/C-4 pairs may be reversed.

na = not applicable

5.2.8 Example 8 Synthesis of Chain-Extended Homologues of Salacinol (Schemes 22 to 25)

General procedure

A mixture of sulfide **117** and cyclic sulfate **105** in HFIP (1.0 - 3.0 mL / mmol of sulfide **117**) was placed in a sealed reaction vessel and warmed with stirring for the indicated time at the temperature given below. The progress of the reaction was followed by TLC analysis of aliquots (developing solvent CHCl₃:MeOH, 10:1). When the limiting starting compound had been essentially consumed, the mixture was

cooled; then diluted with CH₂Cl₂ and evaporated to a syrupy residue. Purification by column chromatography (CHCl₃ to CHCl₃:MeOH, 10:1) gave the purified sulfonium salt **119**.

Benzyl 2,3-Di-O-benzyl-4-O-sulfoxy-6-deoxy-6-[2,3,5-tri-O-benzyl-1,4-dideoxy-1,4-episulfoniumylidene-D-arabinitol]-β-D-galactopyranose Inner Salt (119).

Reaction of sulfide **117** (431 mg, 1.02 mmol) with cyclic sulfate **105** (588 mg, 1.15 mmol) in HFIP (3.0 mL) for 42 h at 70°C gave compound **119** as a colorless gummy solid (571 mg, 60%). $[\alpha]_D -7.6^\circ$ (c 1.1, CHCl₃). See Tables 5 and 6 for NMR data. MALDI MS m/e 955.39 (M⁺ + Na), 853.42 (M⁺ + H - SO₃). Anal. Calcd for C₅₃H₅₆O₁₁S₂: C, 68.22; H, 6.05. Found: C, 68.48; H, 6.09.

1,4-Dideoxy-1,4-[[2R,3R,4R,5S-2,4,5,6-tetrahydroxy-3-(sulfoxy)hexyl]episulfonium-ylidene]-D-arabinitol (95).

The protected sulfonium salt **119** (460 mg, 0.493 mmol) was dissolved in MeOH (50 mL) and stirred at rt with 10% Pd/C catalyst (580 mg) under 1 atm. of H₂ for 24 h. Analysis by TLC (EtOAc:MeOH:H₂O, 6:3:1) showed formation of a single product (rf 0.10). The catalyst was removed by filtration, using additional MeOH, through Celite and the filtrate was evaporated to give the crude hemiacetal compound 4-O-sulfoxy-6-deoxy-6-[1,4-dideoxy-1,4-episulfoniumylidene-D-arabinitol]-α/β-D-galactopyranose inner salt (**99**, α:β = 1:1) as a colorless foam (184 mg, 95%). See Tables 7 and 8 for NMR data of **99**. MALDI MS m/e 414.89 (M⁺ + Na), 392.93 (M⁺ + H), 312.93 (M⁺ + H - SO₃).

Reduction of hemiacetal **99** (430 mg, 1.10 mmol) with NaBH₄ as described above for compound **98** gave sulfonium sulfate **95** (232 mg, 54%) as a colorless glass. $[\alpha]_D +18^\circ$ (c 0.72, MeOH). See Tables 9 and 10 for NMR data of **95**. MALDI MS m/e 416.94 (M⁺ + Na), 315.03 (M⁺ + H - SO₃); HRMS. Calcd for C₁₁H₂₂O₁₁S₂Na (M+Na): 417.0501. Found: 417.0498.

Table 5 ^1H NMR Data for Compound 119

Compound	119 ^a
H-1a ($J_{1a,1b}$, $J_{1a,2}$)	4.07 (br d) (13.3, <1)
H-1b ($J_{1b,2}$)	3.59 (dd) (3.7)
H-2 ($J_{2,3}$)	4.27 (br d) (~2)
H-3 ($J_{3,4}$)	4.32 (br s) (<1)
H-4 ($J_{4,5a}$)	3.91 (dd) (6.3)
H-5a ($J_{5a,5b}$)	3.80 (dd) (9.6)
H-5b ($J_{4,5b}$)	3.63 (t) (9.8)
H-1' ($J_{1',2'}$)	4.45 (d) (7.6)
H-2' ($J_{2',3'}$)	3.80 (dd) (9.6)
H-3' ($J_{3',4'}$)	3.55 (dd) (3.4)
H-4' ($J_{4',5'a}$)	5.00 (dd) (1.2)
H-5'a ($J_{5'a,5'b}$)	—
H-5'b ($J_{4',5'b}$)	—
H-5' ($J_{5',6'a}$)	3.99 (br m) (2.3)
H-6'a ($J_{6'a,6'b}$)	4.35 (dd) (13.0)
H-5'b ($J_{5',6'b}$)	3.94 (dd) (5.6)

Footnote for Table 5

- 5 ^a Others: 7.45-7.02 (30H, m, Ar), 5.03 and 4.56 (2H, 2d, $J_{A,B}$ = 12.0 Hz, CH₂Ar), 4.78 and 4.55 (2H, 2d, $J_{A,B}$ = 12.2 Hz, CH₂Ar), 4.76 and 4.71 (2H, 2d, $J_{A,B}$ = 11.3 Hz, CH₂Ar), 4.54 and 4.52 (2H, 2d, $J_{A,B}$ = 12.2 Hz, CH₂Ar), 4.33 and 4.20 (2H, 2d, $J_{A,B}$ = 11.8 Hz, CH₂Ar), 4.25 and 4.19 (2H, 2d, $J_{A,B}$ = 12.0 Hz, CH₂Ar).

Table 6 ^{13}C NMR Data for Compounds **119**

Compound	119 ^a
C-1	47.65
C-2	81.94
C-3	83.16
C-4	65.81
C-5	66.72
C-1'	103.20
C-2'	77.52
C-3'	78.28
C-4'	72.98
C-5'	69.21
C-6'	50.09

Footnote for Table 6

5

^a Others: 138.61, 138.55, 137.25, 136.86, 136.22 and 135.83 ($6 \times \text{C}_{ipso}$, Ar), 128.87 - 127.15 (30C, Ar), 75.37, 73.51, 72.34, 71.68, 71.59 and 71.36 ($6 \times \text{CH}_2\text{Ar}$).

Table 7 ^1H NMR Data for Compounds **99 α** and **99 β**

Compound	99α ^a	99β ^a
H-1a (J _{1a,1b} , J _{1a,2})	3.87 (m) (n.d., 3.9)	3.87 (m) (n.d., 3.9)
H-1b (J _{1b,2})	3.87 (m) (3.9)	3.87 (m) (3.9)
H-2 (J _{2,3})	4.73 (ddd) (3.9)	4.73 (ddd) (3.7)
H-3 (J _{3,4})	4.44 (dd) (3.7)	4.44 (dd) (3.7)
H-4 (J _{4,5a})	4.06 (dd) (5.0)	4.08 (dd) (5.0)
H-5a (J _{5a,5b})	4.11 (dd) (11.8)	4.13 (dd) (12.2)
H-5b (J _{4,5b})	3.95 (dd) (n.d.)	3.96 (dd) (n.d.)
H-1' (J _{1',2'})	5.32 (d) (3.9)	4.65 (d) (7.9)
H-2' (J _{2',3'})	3.83 (dd) (10.4)	3.52 (dd) (10.1)
H-3' (J _{3',4'})	4.02 (dd) (3.3)	3.81 (dd) (3.3)
H-4' (J _{4',5'a})	4.74 (d) (<1)	4.68 (dd) (0.9)
H-5'a (J _{5'a,5'b})	—	—
H-5'b (J _{4',5'b})	—	—
H-5' (J _{5'6'a})	4.67 (m) (n.d.)	4.30 (ddd) (7.6.)
H-6'a (J _{6'a,6'b})	3.95 (dd) (n.d.)	3.97 (dd) (12.2.)
H-5'b (J _{5',6'b})	3.92 (dd) (n.d.)	3.94 (dd) (4.0.)

Footnotes for Table 7

5

n.d. not determined, ^a Temperature 313 K, D₂O,

Table 8 ^{13}C NMR Data for Compounds **99 α** and **99 β**

Compound	99α ^b	99β ^b
C-1	49.27	49.27
C-2	78.35 ⁱ	78.29 ⁱ
C-3	79.26	79.06
C-4	71.43	71.26
C-5	60.62	60.62
C-1'	94.07	98.17
C-2'	69.35	72.85
C-3'	69.17	72.85
C-4'	79.63	78.65
C-5'	66.88	60.91
C-6'	48.73	48.30

Footnotes for Table 8

5

^a Temperature 308 K, D₂O, ^b Temperature 313K, D₂O,
^{e f g h i j k l m n} Assignments may be interchanged for resonances with the same
superscript letter.

Table 9 ¹H NMR Data for Compound 95

Compound	95 ^a
H-1a (<i>J</i> _{1a,1b} , <i>J</i> _{1a,2})	3.92 (d) (n.d., 3.6)
H-1b (<i>J</i> _{1b,2})	3.92 (d) (3.6)
H-2 (<i>J</i> _{2,3})	4.78 (dt) (3.6)
H-3 (<i>J</i> _{3,4})	4.47 (dd) (2.9)
H-4 (<i>J</i> _{4,5a})	4.11 (ddd) (4.8)
H-5a (<i>J</i> _{5a,5b})	4.16 (dd) (11.2)
H-5b (<i>J</i> _{4,5b})	3.91 (dd) (8.1)
H-1a' (<i>J</i> _{1'a,1'b} , <i>J</i> _{1'a',2'})	3.99 (dd) (13.3, 9.8)
H-1'b (<i>J</i> _{1'b,2'})	3.92 (dd) (3.6)
H-2' (<i>J</i> _{2',3'})	4.63 (ddd) (1.3)
H-3' (<i>J</i> _{3',4'a})	4.45 (dd) (9.2)
H-4' (<i>J</i> _{4',5a'})	3.98 (dd) (1.0)
H-4'b (<i>J</i> _{4'a,4'b} , <i>J</i> _{3',4'b})	—
H-5'a (<i>J</i> _{5'a,5'b})	—
H-5'b (<i>J</i> _{4',5'b})	—
H-5' (<i>J</i> _{5',6'a})	4.03 (t) (6.6)
H-6'a (<i>J</i> _{6'a,6'b})	3.71 (d) (n.d.)
H-6'b (<i>J</i> _{5',6'b})	3.71 (d) (6.6)

Footnotes for Table 9

5

n.d. not determined ^a Temperature 318K, D2O

Table 10 ^{13}C NMR Data for Compound **95**

Compound	95^a
C-1	48.49
C-2	77.58
C-3	78.32
C-4	70.40
C-5	59.85
C-1'	51.15
C-2'	66.58
C-3'	78.89
C-4'	769.36
C-5'	70.12
C-6'	63.40

Footnotes for Table 10

^a Temperature 318K, D₂O

5.3 Example 9 - Enzyme Inhibition Assays

10 5.3.1 *In Vitro* Inhibition Assays of Non-Human Glycosidase Enzymes

Various isomers of Salacinol, Blintol, Ghavamiol, and Acarbose were tested for their inhibition of three glycosidase enzymes, namely glucoamylase G2,^{19,20} porcine pancreatic α -amylase (PPA), and barley α -amylase (AMY1).²³ The results are summarized in Table 11. Glucoamylase G2 was weakly inhibited by Salacinol (**1**) (K_i = 1.7 mM) whereas a stereoisomer of Blintol was a better inhibitor of this enzyme, with a K_i value of 0.72 mM. Salacinol (**1**) inhibited AMY1 and PPA, with K_i values of 15 $\pm$ 1 and 10 $\pm$ 2 μ M, respectively. Other compounds did not significantly

inhibit either AMY1 or PPA. It would appear then that Salacinol (1) and analogues of Salacinol (1) show discrimination for certain glycosidase enzymes, and are promising candidates for selective inhibition of a wider panel of enzymes that includes human small intestinal maltase-glucoamylase¹⁷ and human pancreatic α -amylase.¹⁸

5 The glucoamylase G2 form from *Aspergillus niger* was purified from a commercial enzyme (Novo Nordisk, Bagsvaerd, Denmark) as described.^{19, 20} The initial rates of glucoamylase G2-catalyzed hydrolysis of maltose was tested with 1 mM maltose as substrate in 0.1 M sodium acetate pH 4.5 at 45 °C using an enzyme concentration of 7.0×10^{-8} M and five inhibitor concentrations in the range 1 μ M - 5
10 mM. The effect of the inhibition on rates of substrate hydrolysis were compared for the different compounds. The glucose released was analyzed in aliquots removed at appropriate time intervals using a glucose oxidase assay adapted to microtiter plate reading and using a total reaction volume for the enzyme reaction mixtures of 150 or 300 μ L.²¹ The K_i values were calculated assuming competitive inhibition from $1/v =$
15 $(1/V_{max}) + [(K_m)/(V_{max}[S]K_i)][I]$, where v is the rate measured in the presence or absence of inhibitor, $[I]$ and $[S]$ the concentrations of inhibitor and substrate, K_m 1.6 mM and k_{cat} 11.3 s^{-1} , using ENZFITTER.²²

 Porcine pancreatic α -amylase (PPA) and bovine serum albumin (BSA) were purchased from Sigma. Amylose EX-1 (DP17; average degree of
20 polymerization 17) was purchased from Hayashibara Chemical Laboratories (Okayama, Japan). Recombinant barley α -amylase isozyme 1 (AMY1) was produced and purified as described.²³ An aliquot of the porcine pancreatic α -amylase (PPA) crystalline suspension (in ammonium sulfate) was dialyzed extensively against the assay buffer without BSA. The enzyme concentration was determined by aid of
25 amino acid analysis as determined using an LKB model Alpha Plus amino acid analyzer. The inhibition of AMY1 (3×10^{-9} M) and PPA (9×10^{-9} M) activity towards DP17 amylose was measured at 37 °C in 20 mM sodium acetate, pH 5.5, 5 mM CaCl_2 , 0.005 % BSA (for AMY1) and 20 mM sodium phosphate, pH 6.9, 10 mM NaCl, 0.1 mM CaCl_2 , 0.005 % BSA (for PPA). Six different final inhibitor
30 concentrations were used in the range 1 μ M - 5 mM. The inhibitor was pre-incubated with enzyme for 5 min at 37 °C before addition of substrate. Initial rates were

determined by measuring reducing sugar by the copper-bicinchoninate method as described.^{23,24} The K_i values were calculated assuming competitive inhibition, as described above for the case of glucoamylase, and a K_m of 0.57 mg/ml and k_{cat} of 165 s⁻¹ for AMY1 and 1 mg/ml and 1200 s⁻¹ for PPA, as determined in the substrate concentration range 0.03 - 10 mg/ml using ENZFITTER.²² For the K_i determinations, [S] = 0.7 mg/mL amylose DP 17 for the AMY1 binding and [S] = 2.5 mg/mL amylose DP 17 for the PPA binding.

5.3.2 In Vitro Inhibition Assays of Human Glycosidase Enzymes

The *in vitro* inhibitory activities of Salacinol, Blintol, Ghavamiol, and Acarbose were tested against human glycosidase enzymes as described below.

5.3.2.1 Enzyme Assays with Maltase Glucoamylase (MGA)

Since recombinant MGA enzyme has not been expressed successfully, the assay for MGA activity measured effects on cell extracts. In the assays, COS cells transfected with MGA5' (maltase subunit clone 10) construct were used. Activity measurements were performed with cell extracts containing MGA. Maltose hydrolysis was monitored by measurement of the glucose released by a glucose oxidase colorimetric assay. Inhibition of this hydrolysis was measured as a reduction in OD reading. Since the assay deals with cell extracts, a standard inhibitor, e.g. Salacinol, is always included in each new assay of a putative inhibitor.

In practice, an OD reading in the absence of the inhibitor was recorded, followed by a reading in the presence of the inhibitor. The percent reduction in OD reading upon administering a candidate inhibitor (see Table 11) was then correlated with a percent inhibition for a given concentration. For example: 1) at 200 nM (0.2 μ M), Blintol inhibits 50% of MGA activity whereas Salacinol inhibits 50% of MGA activity at 2500 nM (2.5 μ M); 2) Whereas Salacinol at 5 μ M concentration inhibits 60% of the breakdown of maltose, Acarbose only inhibits 4% of the activity.

5.3.2.2 Enzyme Assays with Human Pancreatic α -Amylase (HPA)

These assays were performed with purified enzyme. The ability of candidate inhibitors to inhibit the hydrolysis of 2,4-Dinitrophenyl maltotrioside was monitored by UV-visible spectroscopy of the released 2,4-dinitrophenol.

5 5.3.2.3 Summary of *In Vitro* Biological Activity

- 1) It appears that Acarbose acts principally by inhibiting human pancreatic α -amylase (HPA) and the breakdown of starch. Salacinol inhibits both HPA and MGA and Blintol appears to only MGA.
- 10 2) The selenium analogue of Salacinol, Blintol, shows inhibition of MGA at lower concentrations than Salacinol. More significantly, Blintol does not appear to inhibit HPA. Salacinol, on the other hand, inhibits both HPA and MGA, and Acarbose inhibits only HPA in these experimental assays.
- 15 3) Using similar monitoring of OD readings as in the MGA assay, the maltase activity in biopsies with live intestinal cells was monitored. At 5 μ M concentration, Blintol inhibits 50% of maltase activity whereas Salacinol inhibits only 13% of the activity.

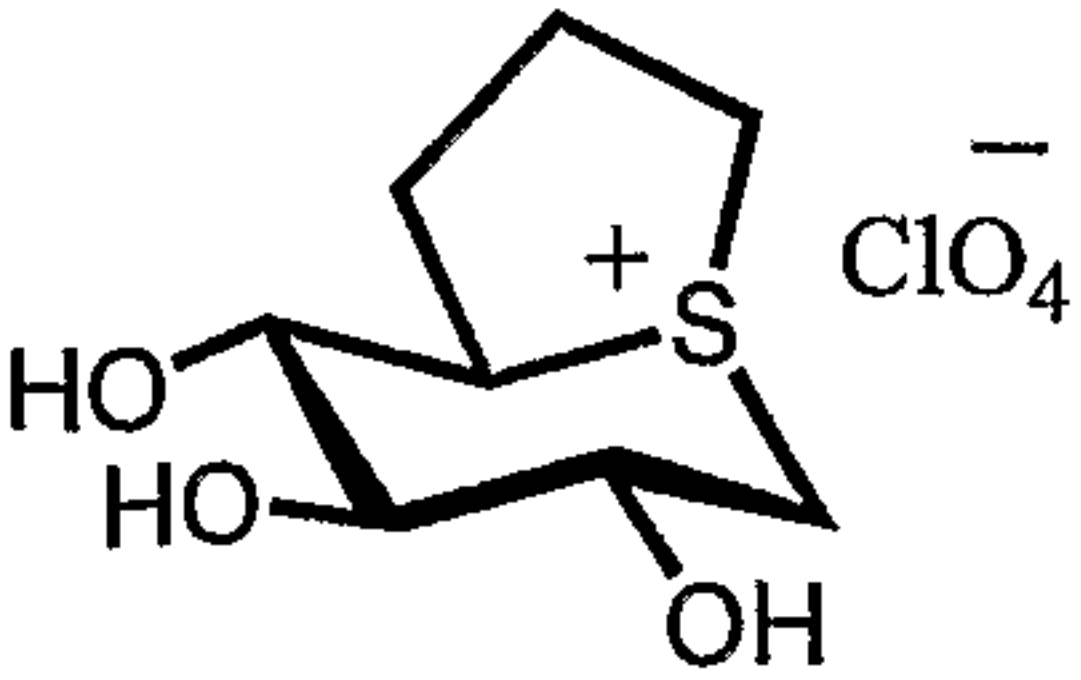
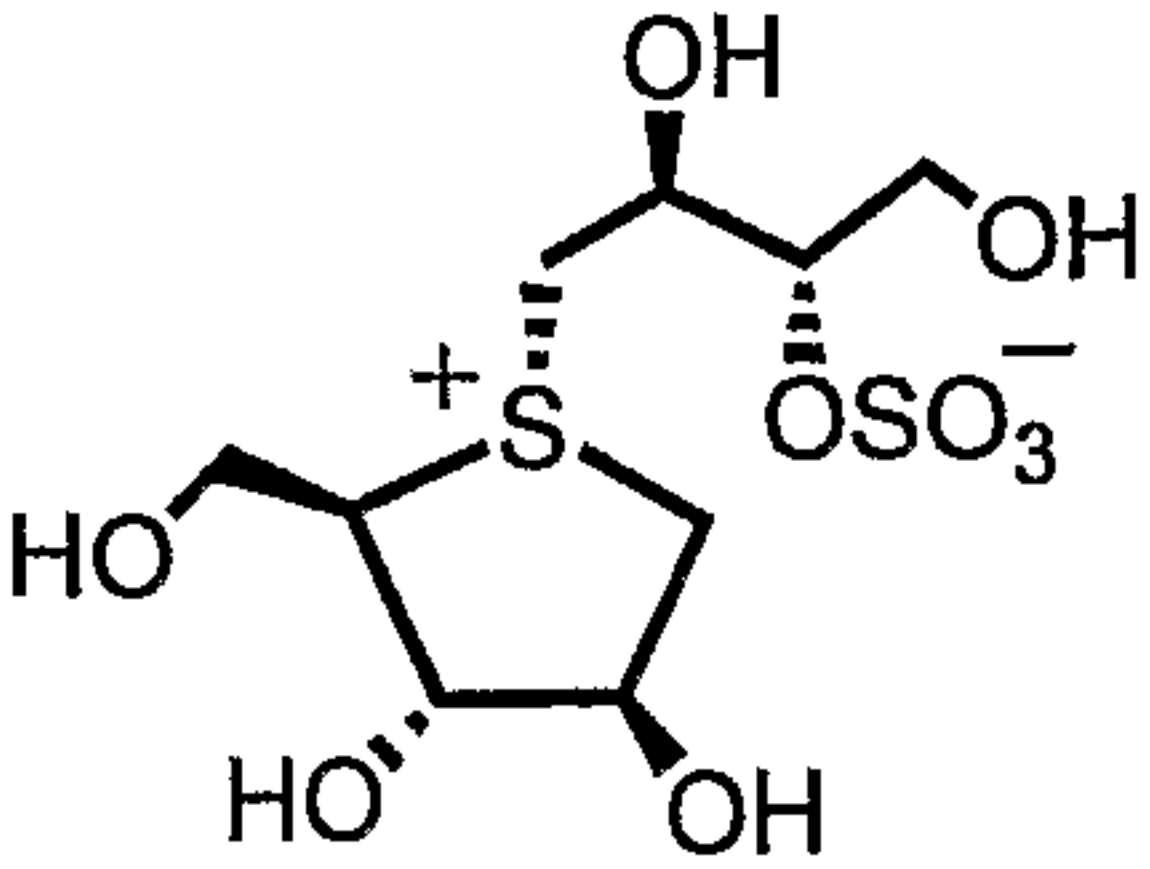
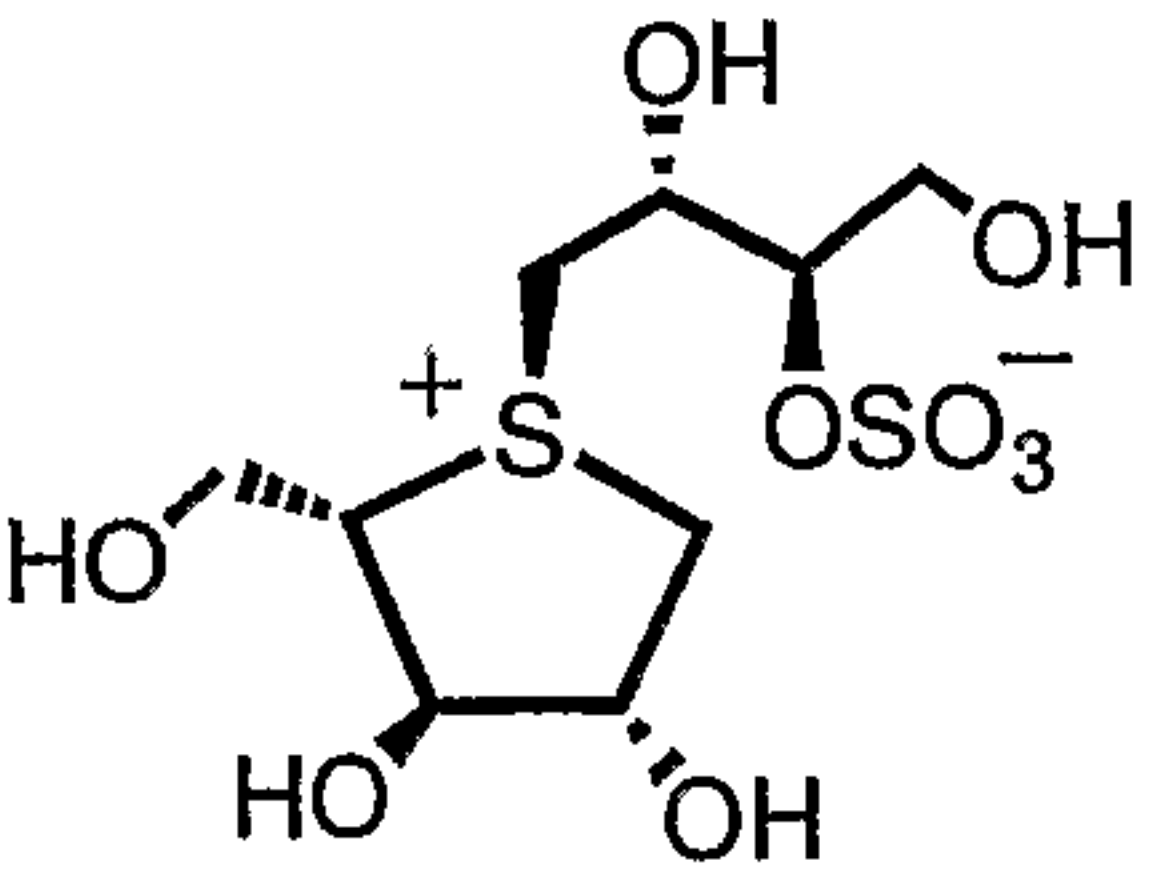
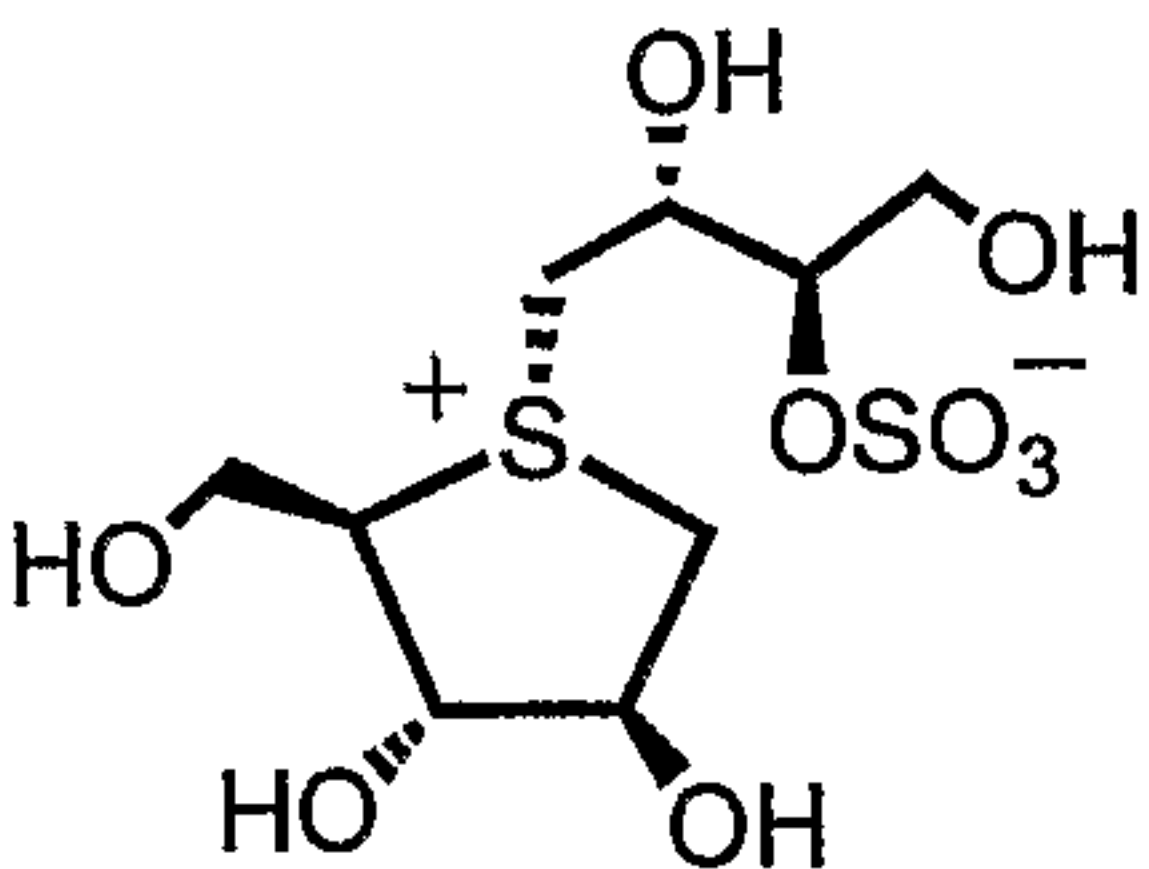
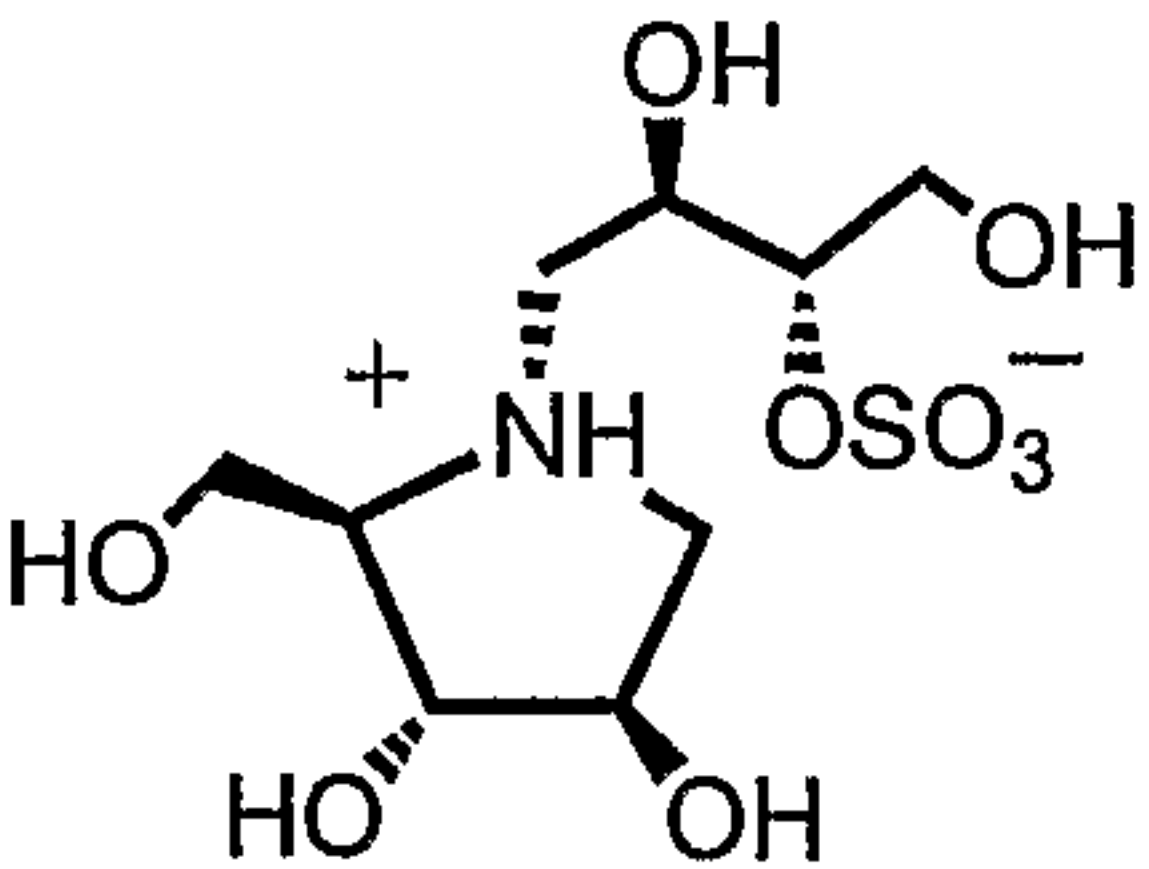
Compound	K _i (mM)				
	AMY1 ^a	PPA ^b	HPA ^c	GA ^d	MGA ^e
	>5	>5	—	1.32	—
 AG-1	0.015	0.01	0.075	1.71	μM
 AG-2	>5	>5	n.a.	2.17	n.a.
 AG-3	>5	>5	n.a.	1.06	mM
 AG-4	>5	>5	n.a.	>2.5	mM

Table 11: Summary of Activity of Salacinol Derivatives Against Human Glycosidases

^aAMY1 = Barley α-amylase

^bPPA = Porcine pancreatic α-amylase

5 ^cHPA = Human pancreatic α-amylase

^dGA = Glucoamylase

^eMGA = Human intestinal maltase glucoamylase

n.a. = not active

- = not tested

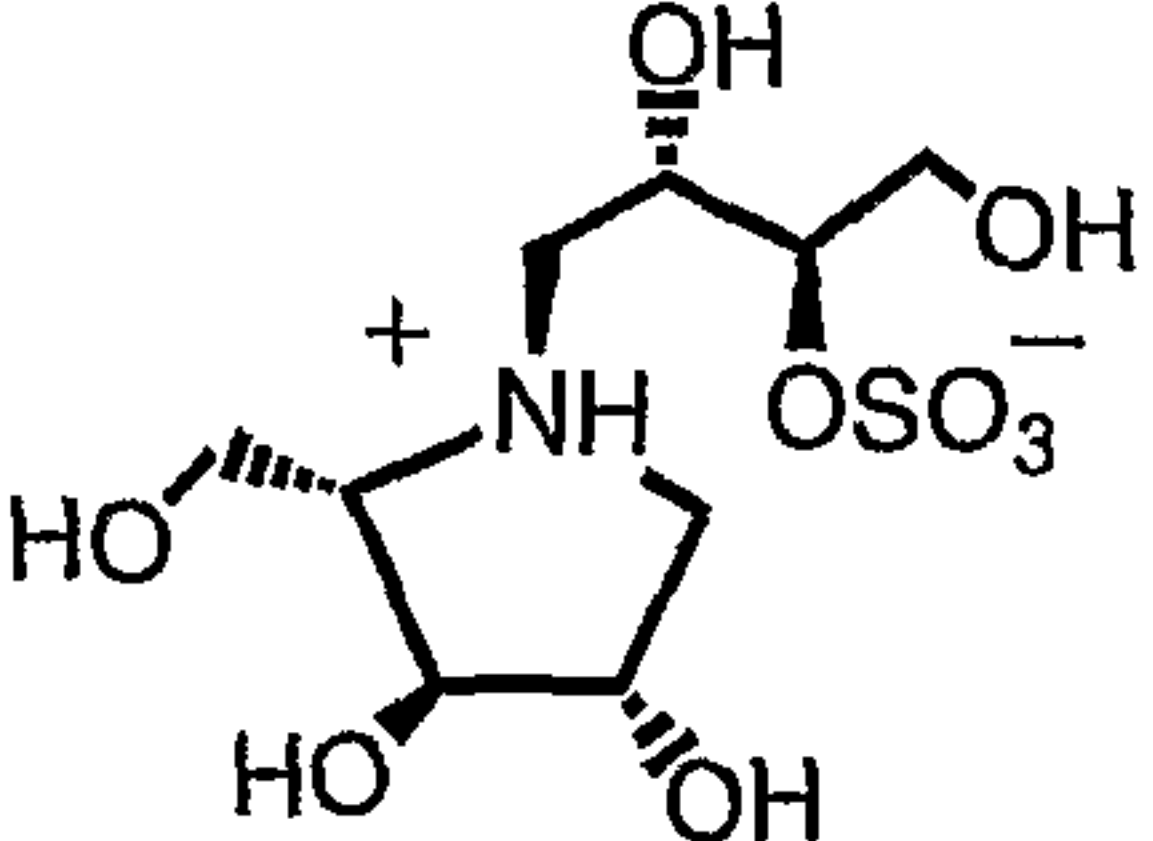
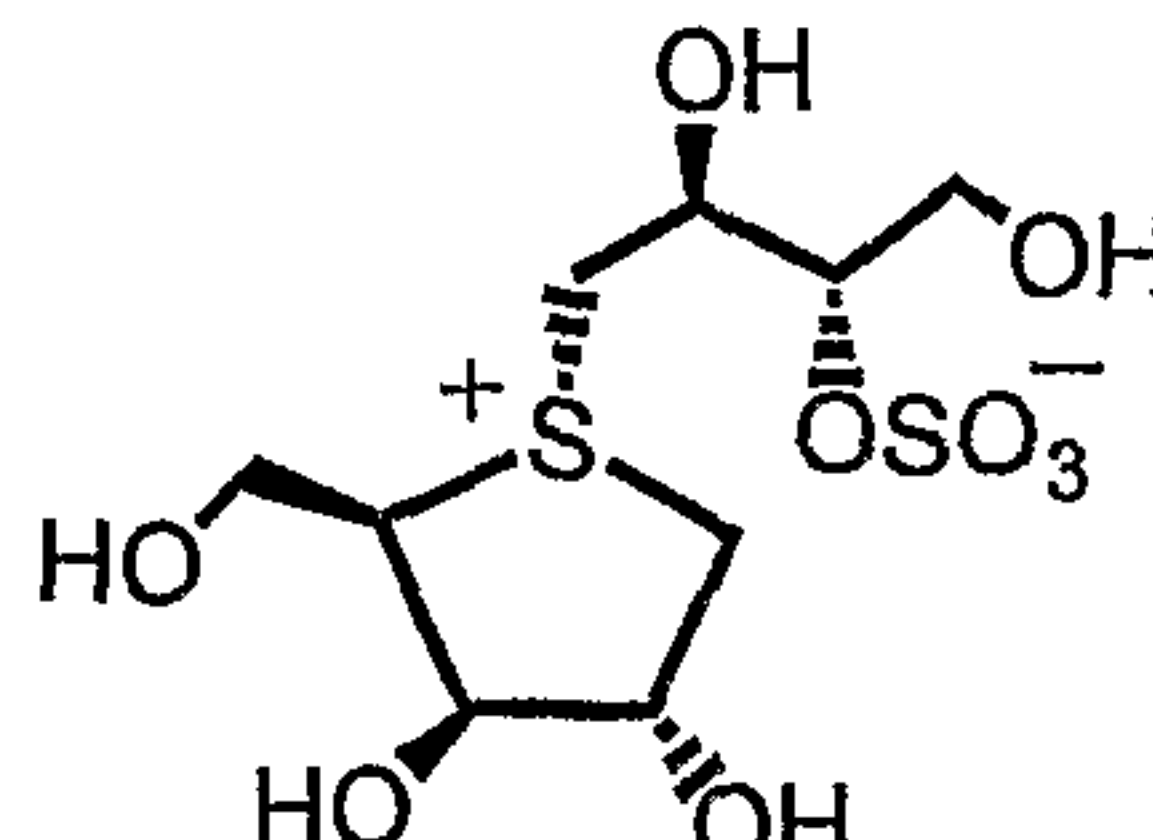
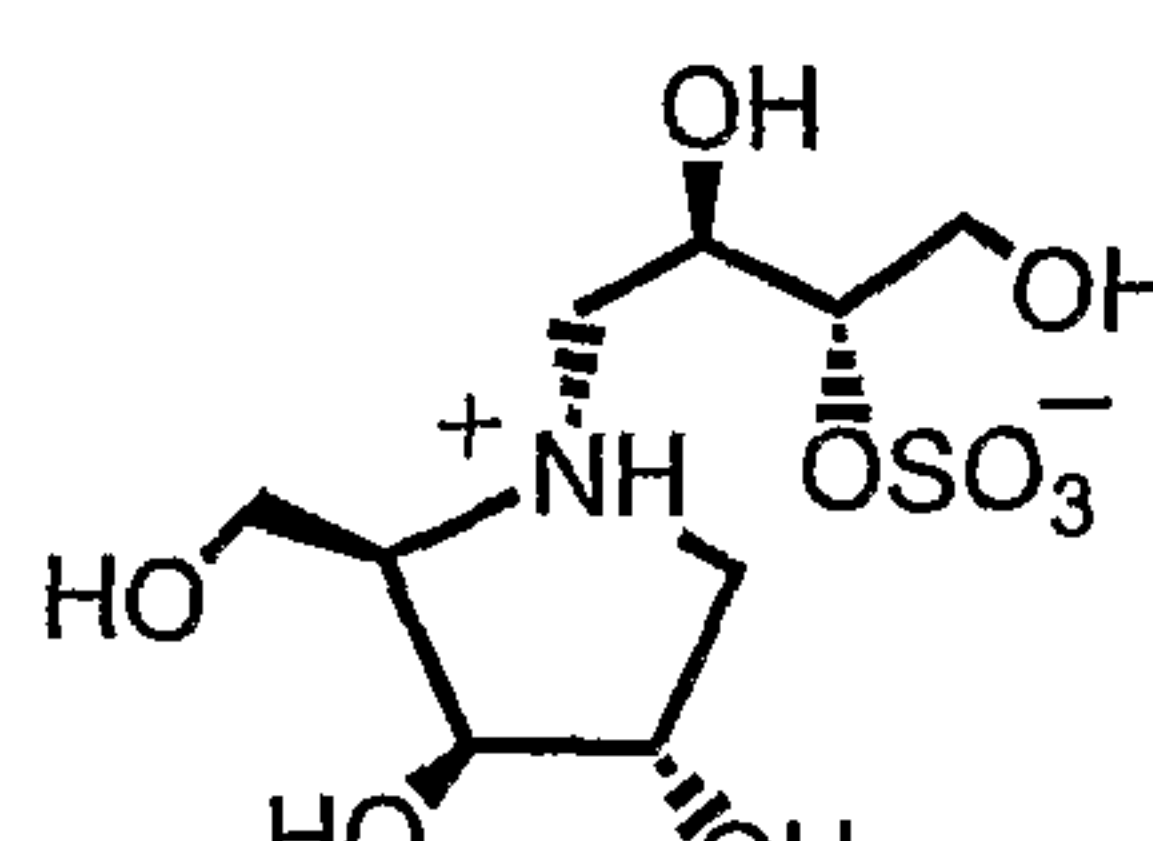
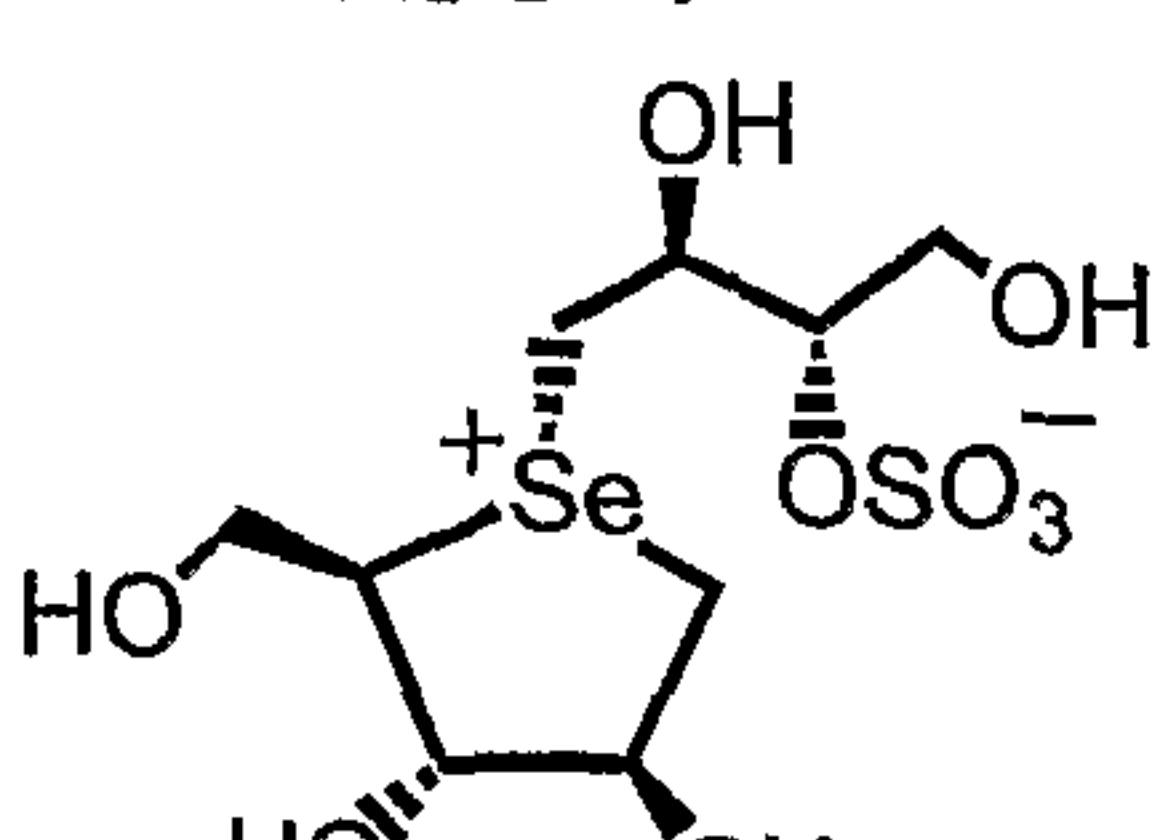
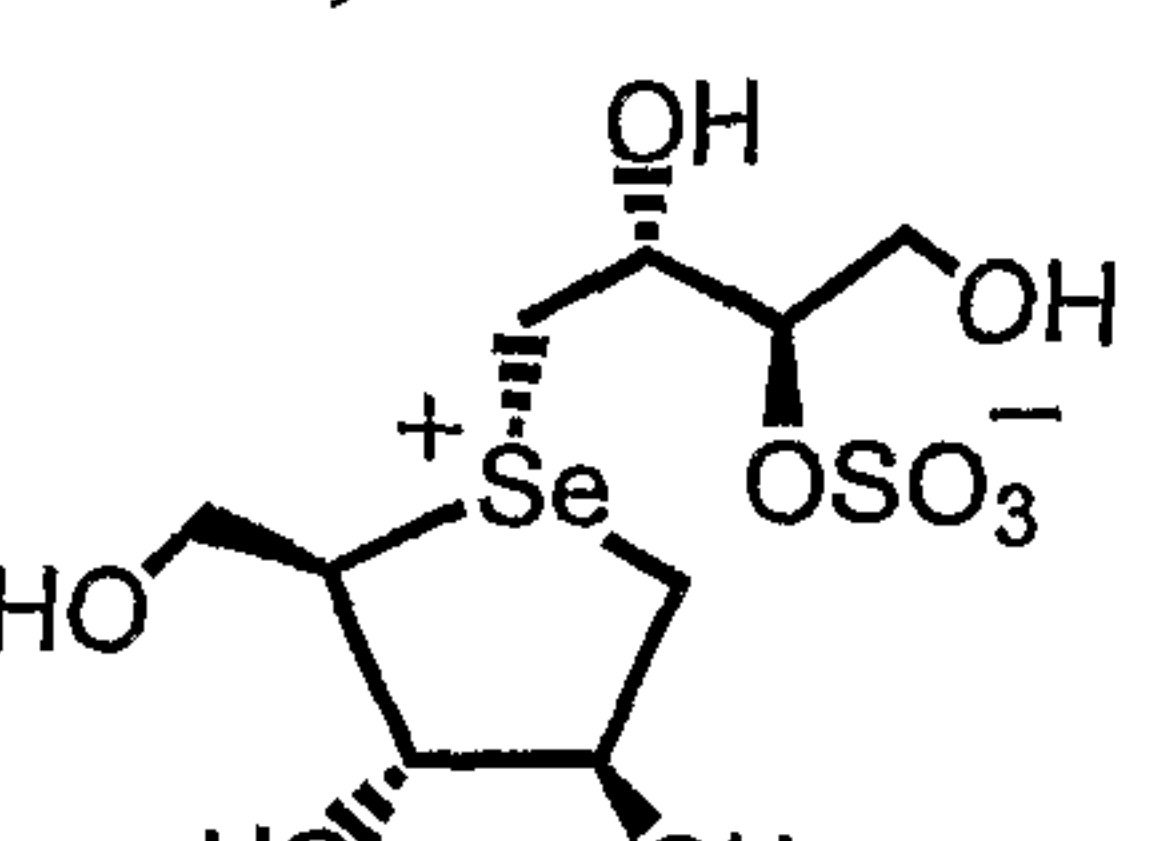
Compound	K _i (mM)				
	AMY1 ^a	PPA ^b	HPA ^c	GA ^d	MGA ^e
 AG-5	>5	>5	0.4	>8	n.a.
 AG-6	0.109	0.052	—	>5	—
 AG-7	>5	>5	—	>30	—
 BJ-24-77-3, BJ-24-78-1, BJ-24-79-1	>5	>5	>5	0.72	nM
 BJ-24-92-1	>5	>5	n.a.	>9	n.a.

Table 11 Continued

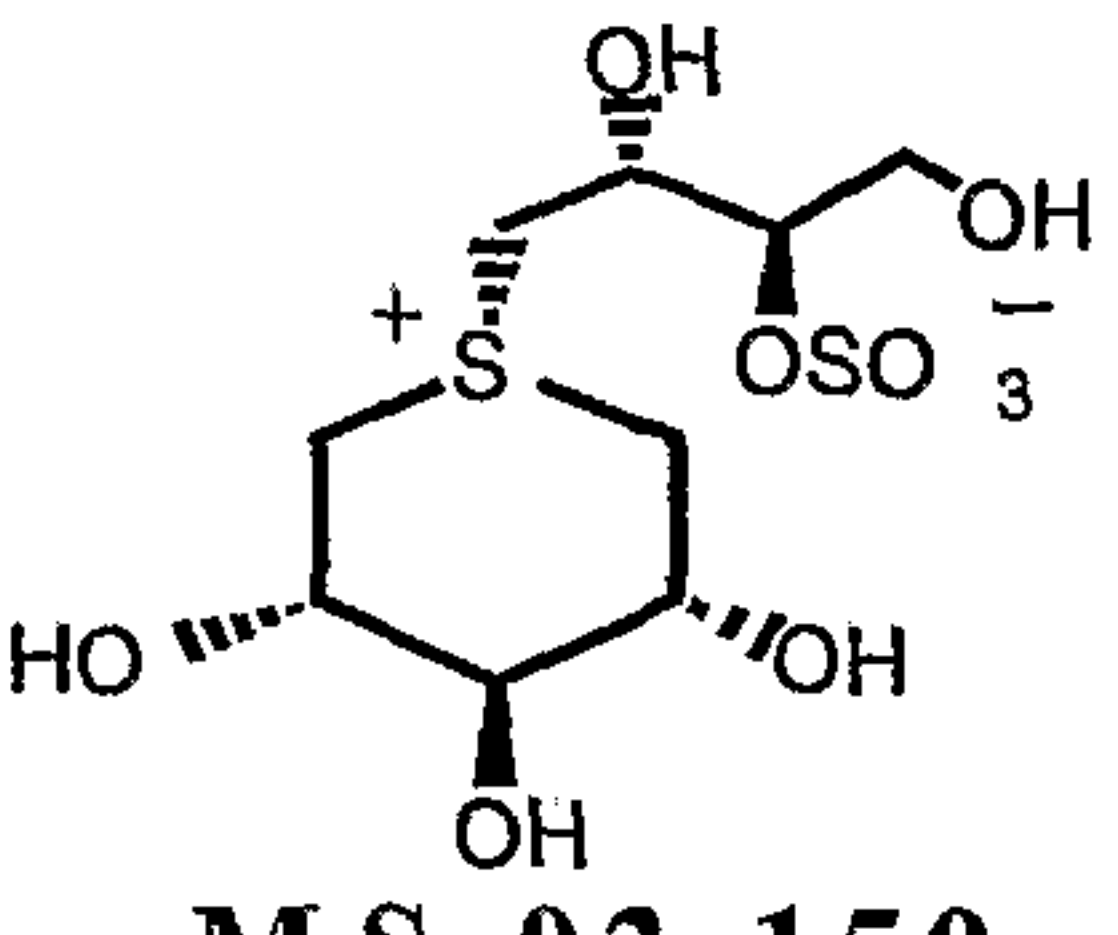
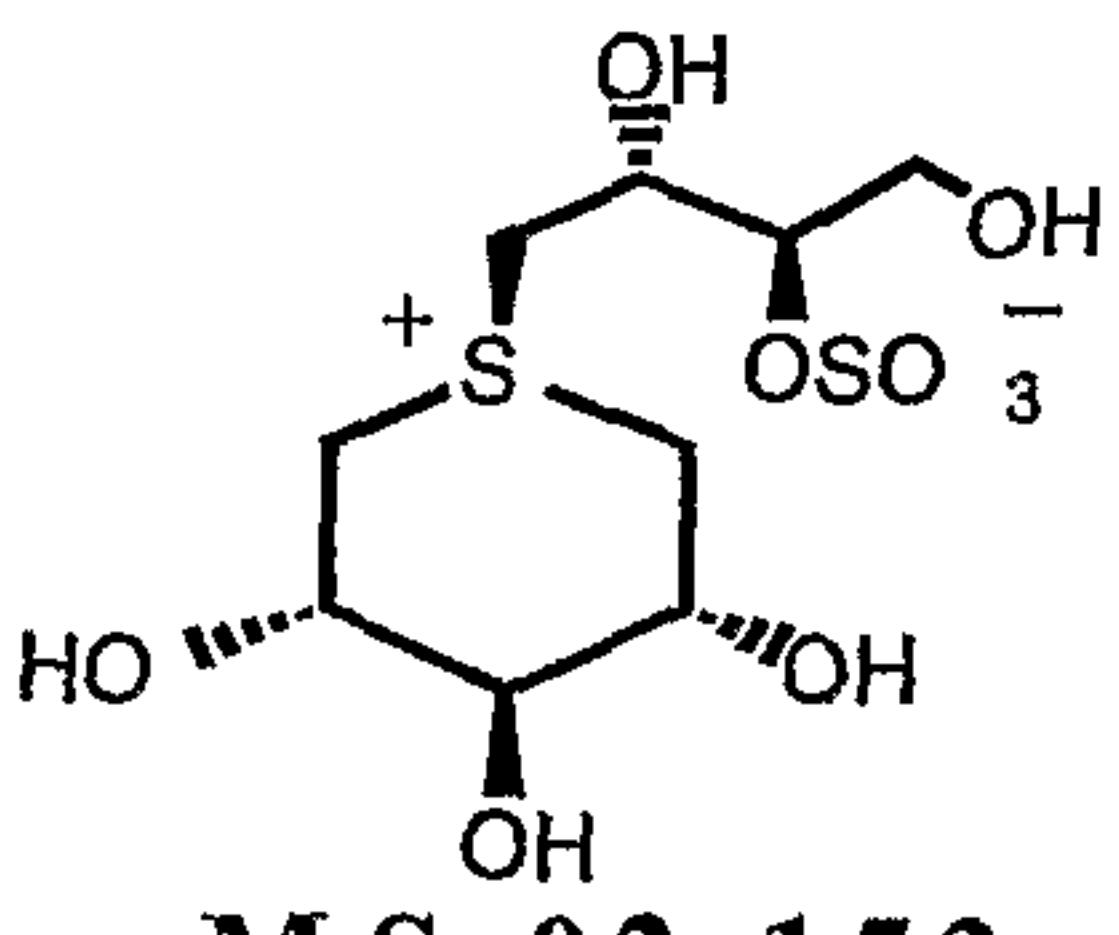
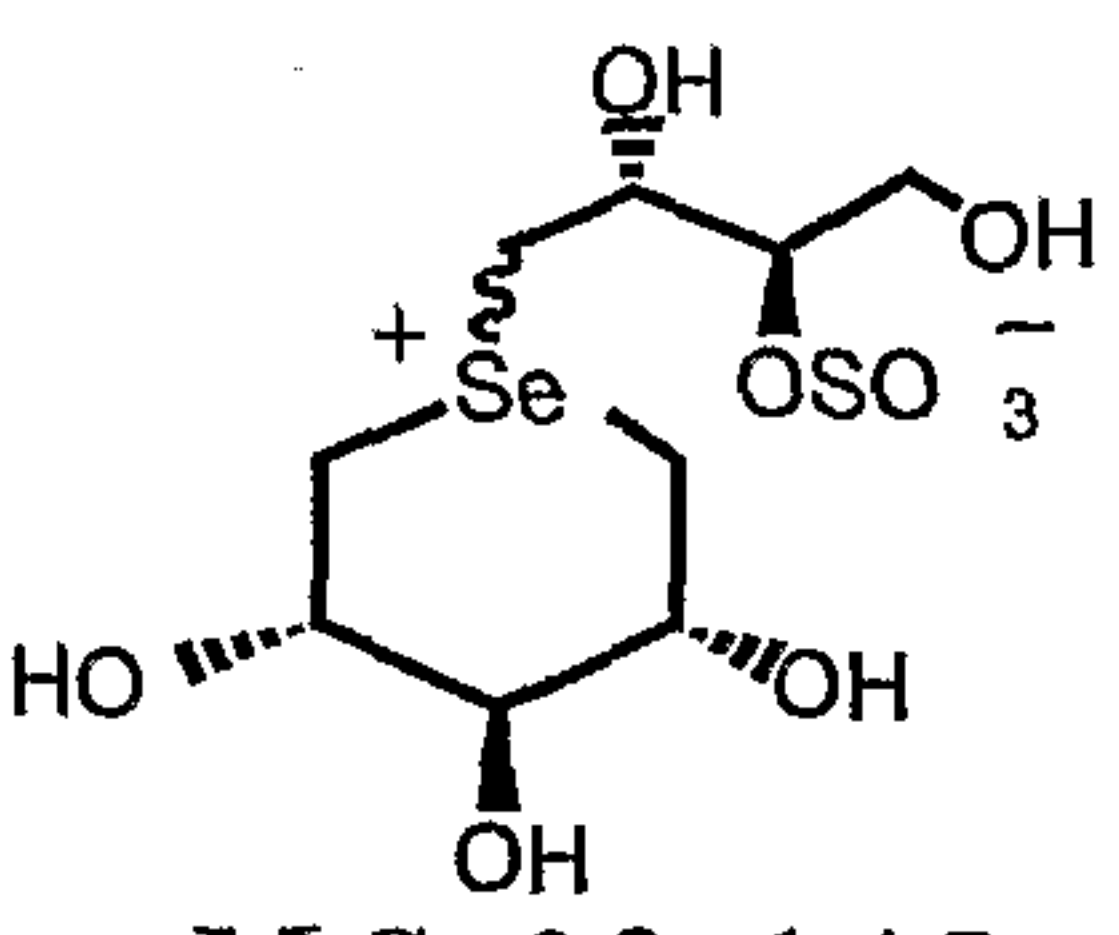
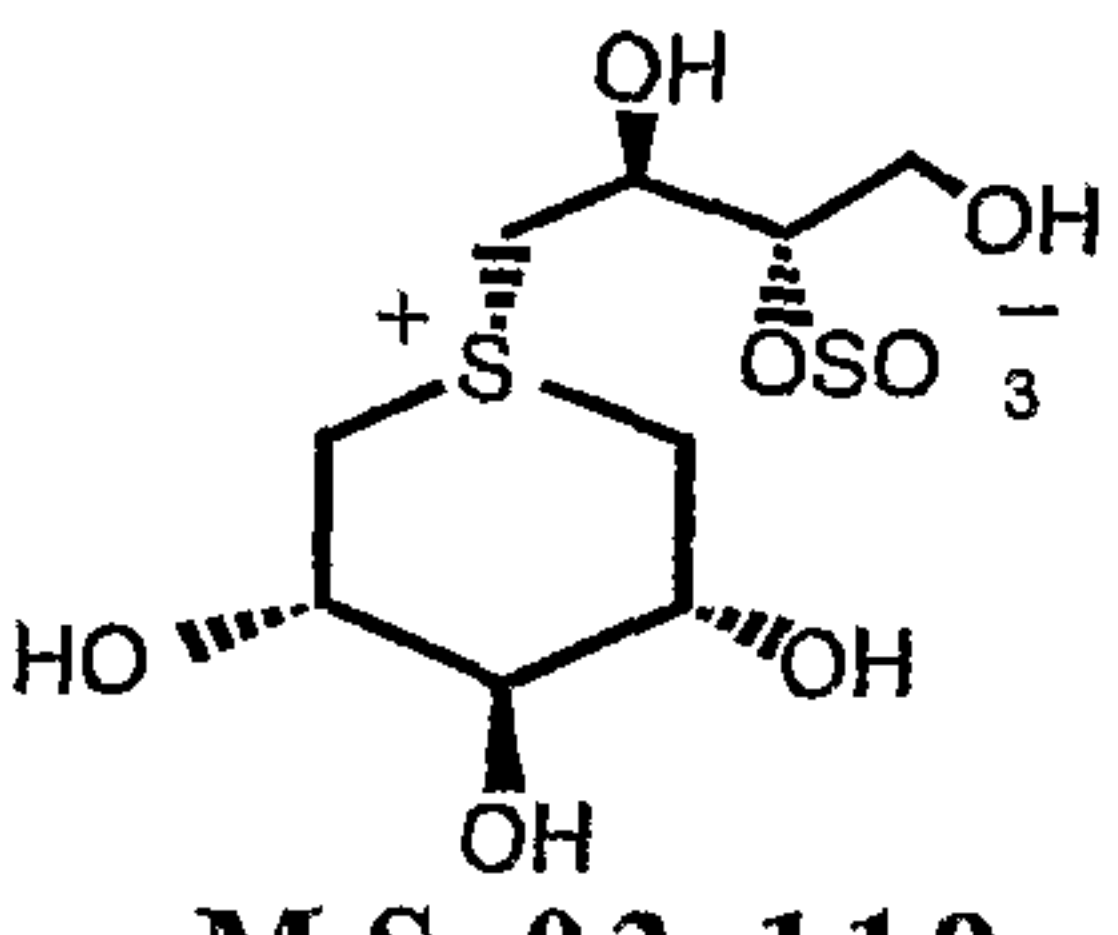
Compound	K _i (mM)				
	AMY1 ^a	PPA ^b	HPA ^c	GA ^d	MGA ^e
 MS-02-159	—	—	>5	—	n.a.
 MS-02-153	—	—	>5	—	mM
 MS-02-145	—	—	>5	—	n.a.
 MS-03-119	—	—	—	—	n.a.

Table 11 Continued

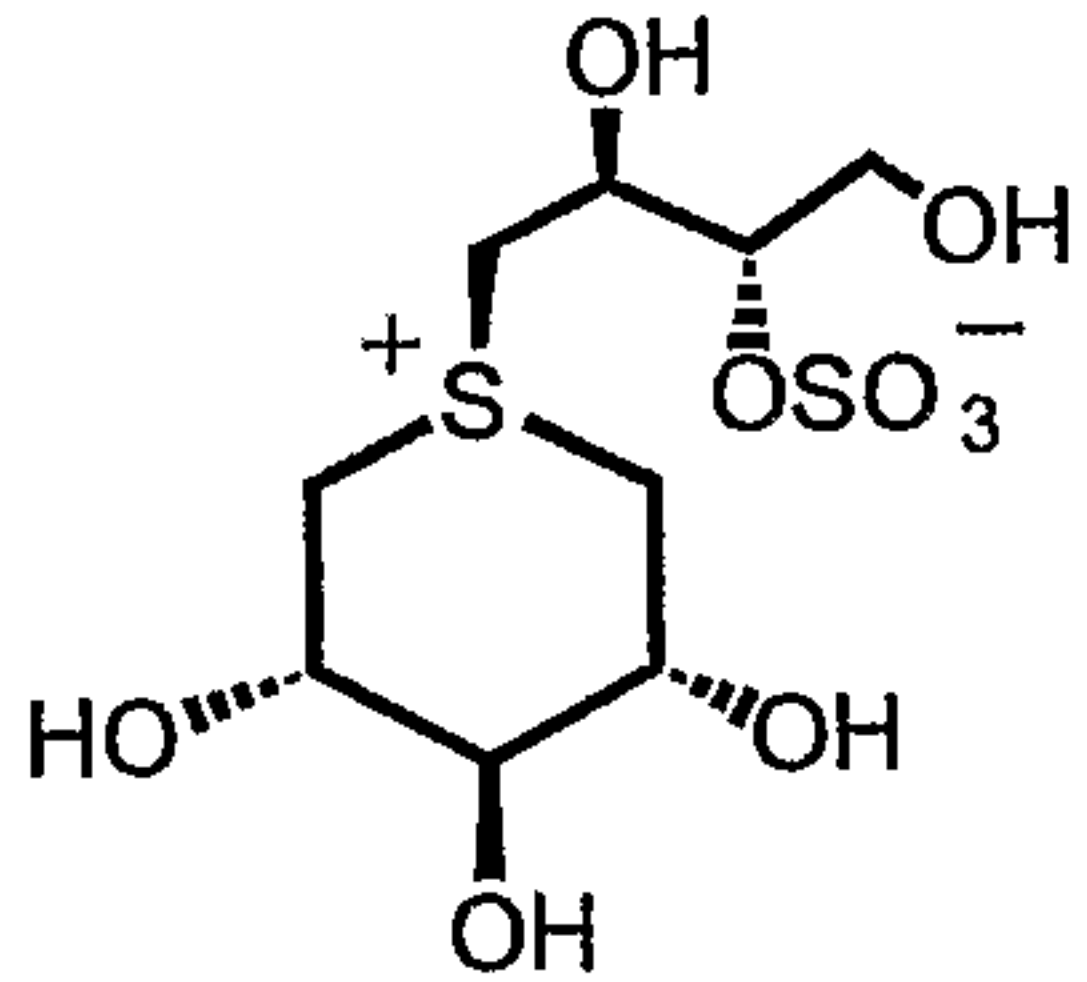
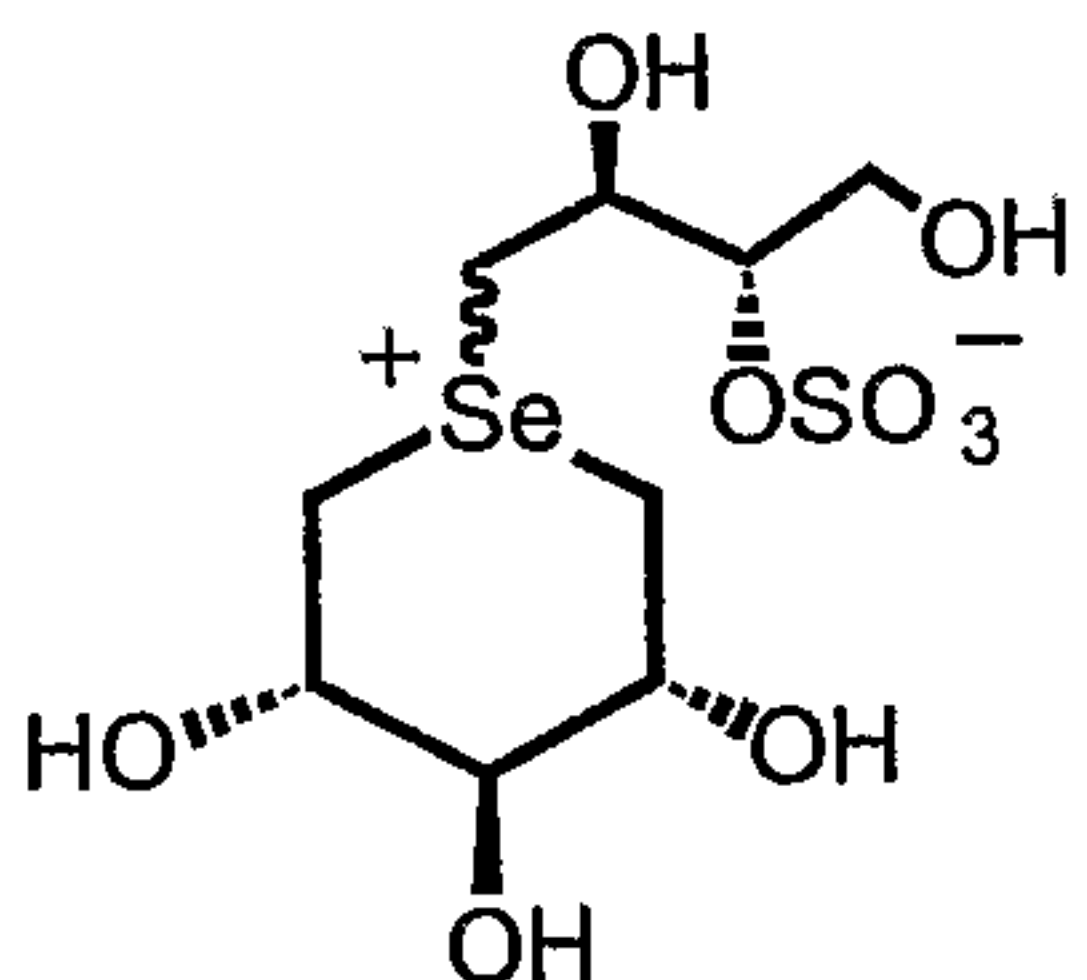
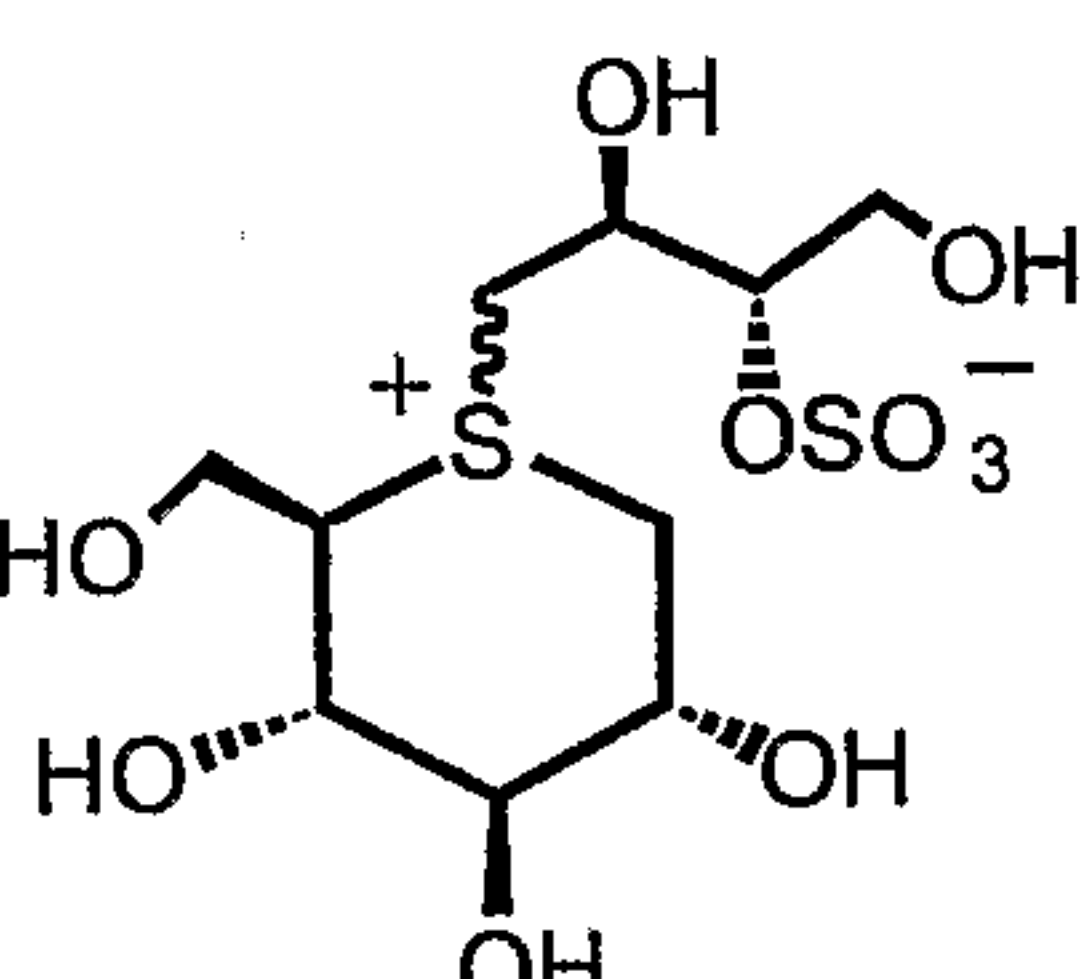
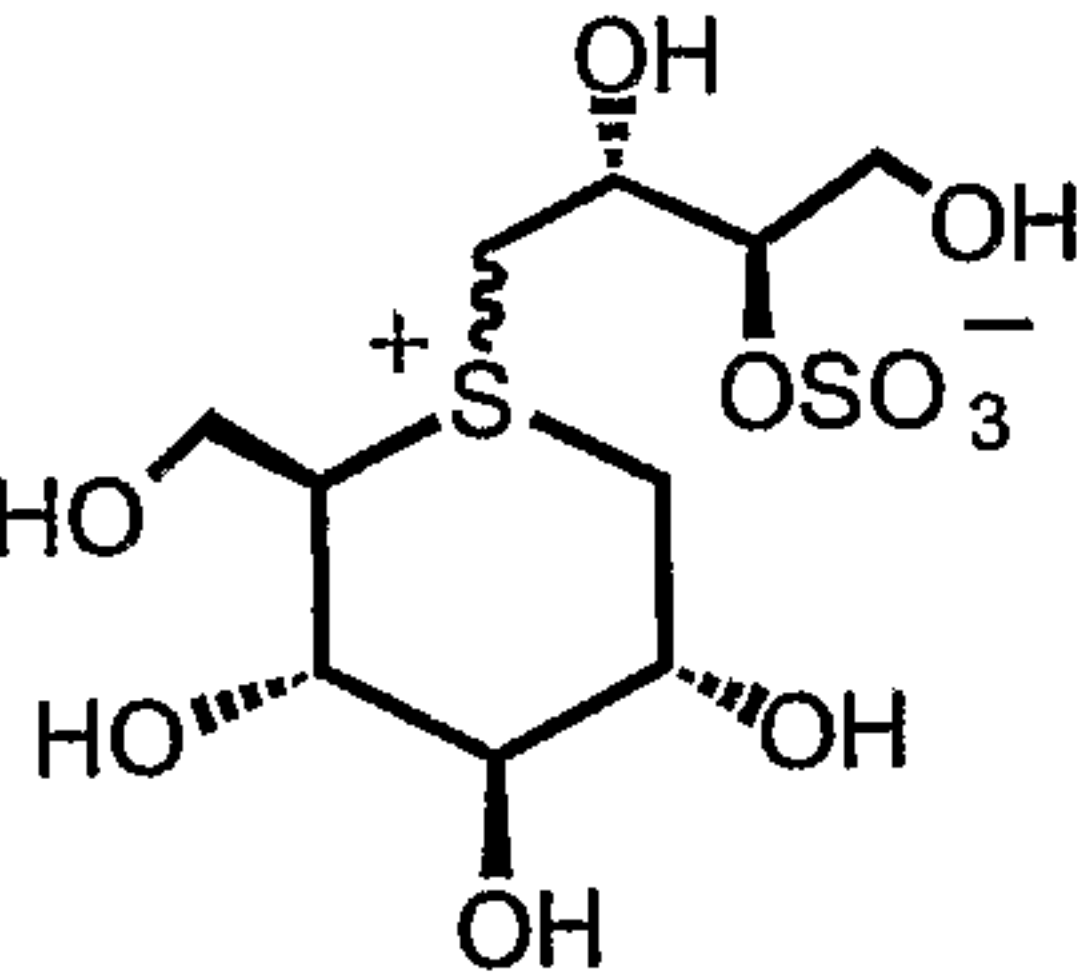
Compound	<i>K_i</i> (mM)				
	AMY1 ^a	PPA ^b	HPA ^c	GA ^d	MGA ^e
 MS-03-125	—	—	—	—	n.a.
 MS-03-163B	—	—	—	—	n.a.
 MS-03-175	—	—	—	—	n.a.
 MS-03-171	—	—	—	—	n.a.

Table 11 Continued

5.3.3 In Vivo Inhibition Studies of Blintol and Salacinol

In this Example the efficacy of Blintol in inhibiting glucose absorption and lowering post-prandial glucose levels *in vivo* was compared to Salacinol and Acarbose.

5 Five week old Sprague-Dawley rats were housed singly under a 12:12-h light-dark photoperiod and given free access to water and rat chow (Purina rodent chow). After one week of acclimation, chronic indwelling catheters were implanted. Animals were anesthetized with a combination of Ketamine-Xylazine-Butorphanol (0.1 ml/100g im). Analgesic (Butorphenol, 1mg/kg sc) was administered following
10 recovery from anesthesia and the following morning. Antibiotic was administered by one dose sc and in the drinking water for 4 days post-operative (Baytril, 5 mg/kg sc, Bayer, Toronto, Canada; Baytril, 50 mg/ml: 0.36 ml solution in 250 ml drinking water). A sterile catheter (Intramedic PE-50 with ~3 cm beveled Silastic tip) was placed in the left carotid artery and the distal end of the catheter was tunneled
15 subcutaneously, exteriorized, and anchored at the nape of the neck. The catheters were protected from chewing by a stainless steel tether connected to a swivel system which allowed free movement of the animal and easy access to the catheter by the investigator.

The animals were allowed to recover for 1 week. Experiments were
20 performed on conscious, unrestrained animals that had been fasted overnight by removal of chow from the cage hoppers at 2100. At 0800 the following morning animals were weighed and Atropine (0.05mg/kg sc) was administered as a muscle relaxant. At baseline, animals were administered a bolus of maltose by oral gavage (1000 mg/kg body weight) with or without drug (25 mg/kg body weight for all
25 agents). Blood samples (0.1mL) were taken via the implanted carotid line at -15 and -5 min for the baseline and at 7, 15, 30, 60, 90, 120, 210, 300 min.

Blood samples were kept on ice in microcentrifuge tubes and then were centrifuged. The plasma was stored at -20°C until it was assayed. Plasma volume was triple replaced with heparinized saline (10u/mL), but red blood cells were not
30 reinfused. Plasma glucose was assayed with the glucose oxidase method (Trinder RAICHEM Division of Hemagen Diagnostics, Inc. San Diego, CA). Plasma insulin

concentrations were measured by rat insulin ELISA (Crystal Chem INC, Downers Grove, IL). Six experiments were performed for each treatment (control, Blintol, Acarbose, Salacinol).

5 The AUC (Area Under the Curve) was calculated for glucose, glucose absorption, and insulin by applying the trapezoidal method over the 0 to 90 minute time points. For glucose the AUC was calculated for the excursion from each sample above the basal value (average of the -5 and -15 minute samples), and for insulin and glucose absorption for the excursion above 0.

10 All data are presented as means $\pm$ SE. The significance of changes in plasma glucose and insulin were tested by two-way repeated-measures analysis of variance and were performed with the Statistical Analysis System for Windows (version 6.3, SAS Institute, Cary, NC). AUCs were compared using unpaired *t*-tests.

5.3.3.1 Plasma glucose concentrations

15 The plasma glucose profiles for all treatments were significantly lower than Control ($P < 0.0001$; all treatments versus Control), and the Blintol group had a lower profile than Acarbose ($P < 0.01$) but there was no difference between other treatments (see Fig. 3). Plasma glucose concentrations for all groups increased immediately following gavage ($P < 0.01$), reaching a peak at 15 minutes. For the Control group, the 15 minute glucose excursion from basal was 98.0 ± 12.4 mg/dL
20 and this excursion was decreased with all treatments (Blintol: 29.3 ± 6.5 , Acarbose: 34.2 ± 3.5 , Salacinol: 26.0 ± 5.1 ; $P < 0.005$). All groups exhibited an exponential glucose decay following the 15 minute peak. For the control group glucose values did not return to basal values until 210 minutes ($P = 0.46$). Blintol ($P = 0.40$) and Salacinol ($P = 0.43$) groups returned to basal at 60 minutes, and Acarbose at 90 minutes
25 ($P = 0.19$).

The Area Under the Curve was significantly decreased with all treatments. Blintol and Salacinol yielded slightly lower 90 minute AUC's than Acarbose, though the difference was not significant (Blintol: $P = 0.16$, Salacinol: $P = 0.6$; versus Acarbose).

5.3.3.2 Plasma insulin concentrations

Plasma insulin profiles were decreased with all treatments versus Control ($P < 0.0001$) (Fig. 4). Consistent with the peak glucose at 15 minutes, the insulin for all groups was also peaked between 7 and 15 minutes; however the insulin profile was more rounded and did not show an exponential decay for any group. While the Control and Acarbose insulin values were different from basal for the 15 to 90 minute range, the Blintol and Salacinol insulin values were only different from basal at 15 minutes ($P < 0.05$). The 90 minute insulin AUC was decreased with Blintol, Acarbose, and Salacinol treatments by 53%, 49%, and 65% respectively. There was no statistical difference between treatment groups.

The results of this experiment show that Blintol, Acarbose, and Salacinol, at a 25mg/kg body weight dosage significantly lower post-prandial plasma glucose and insulin concentrations in normal, catheterized rats. Importantly, at this dosage, Blintol had a decreased glucose profile compared to Acarbose. The improvement in the glucose profile with all treatments seems to be directly attributable to an inhibited glucose absorption, consistent with the agents' expected mechanisms of action.

The inhibition of the post-prandial glucose peak observed with all treatments may contribute to a reduction in diabetic complications when these agents are used chronically. The reduced glucose levels decreased the demand on the insulin secreting β -cells and chronically may contribute to a preservation of β -cell mass and function. Moreover, the better controlled glucose levels may decrease a glucose-toxic effect which can kill or impair the function of the insulin-secreting β -cells. Chronic administration of drug studies will help elucidate if these factors are able to slow or prevent the onset of diabetes in a diabetes-prone animal model.

As will be apparent to those skilled in the art in the light of the foregoing disclosure, many alterations and modifications are possible in the practice of this invention without departing from the spirit or scope thereof.

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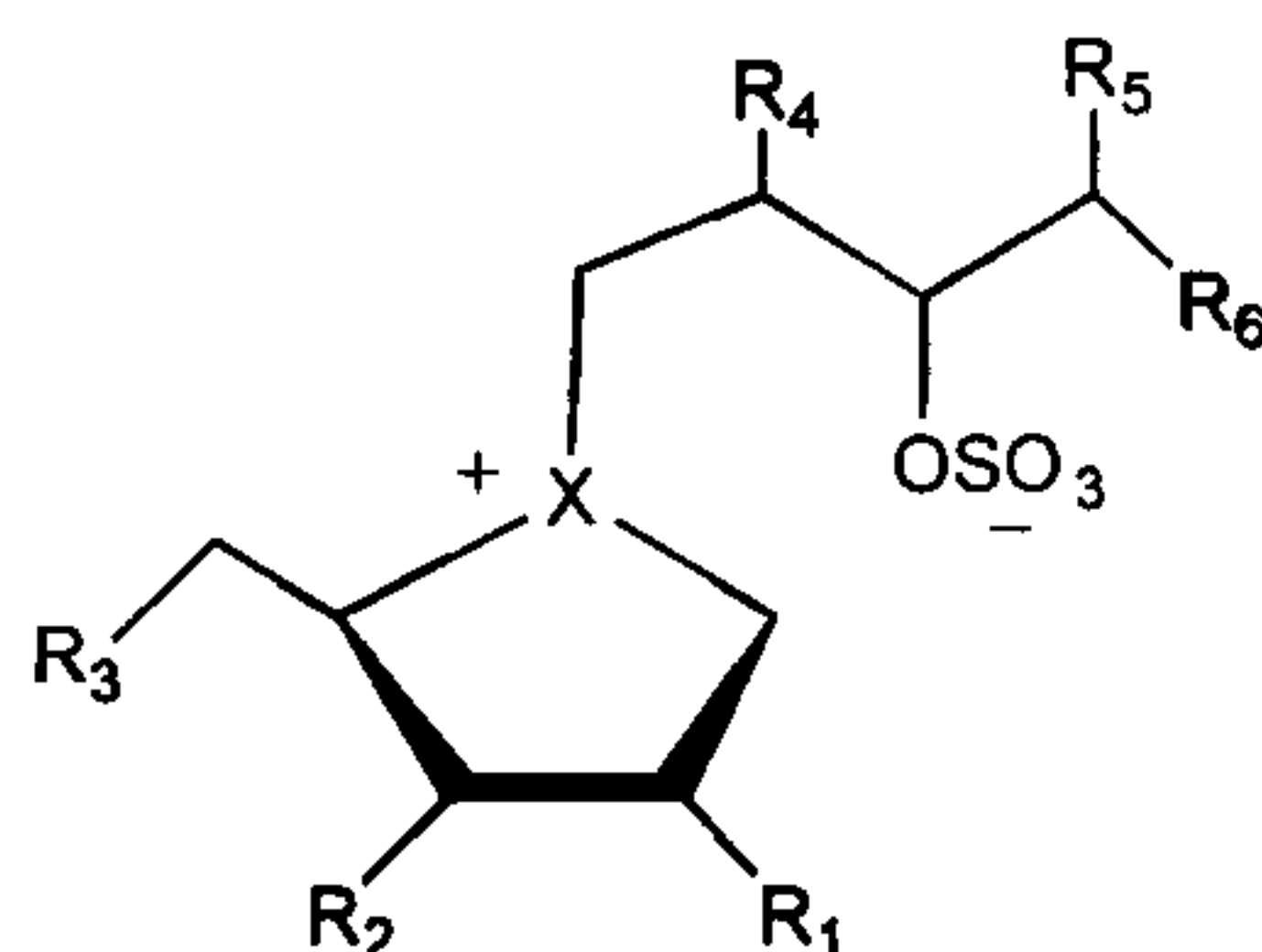
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WHAT IS CLAIMED IS:

1. A non-naturally occurring compound selected from the group consisting of compounds represented by the general formula (I) and stereoisomers and pharmaceutically acceptable salts thereof:



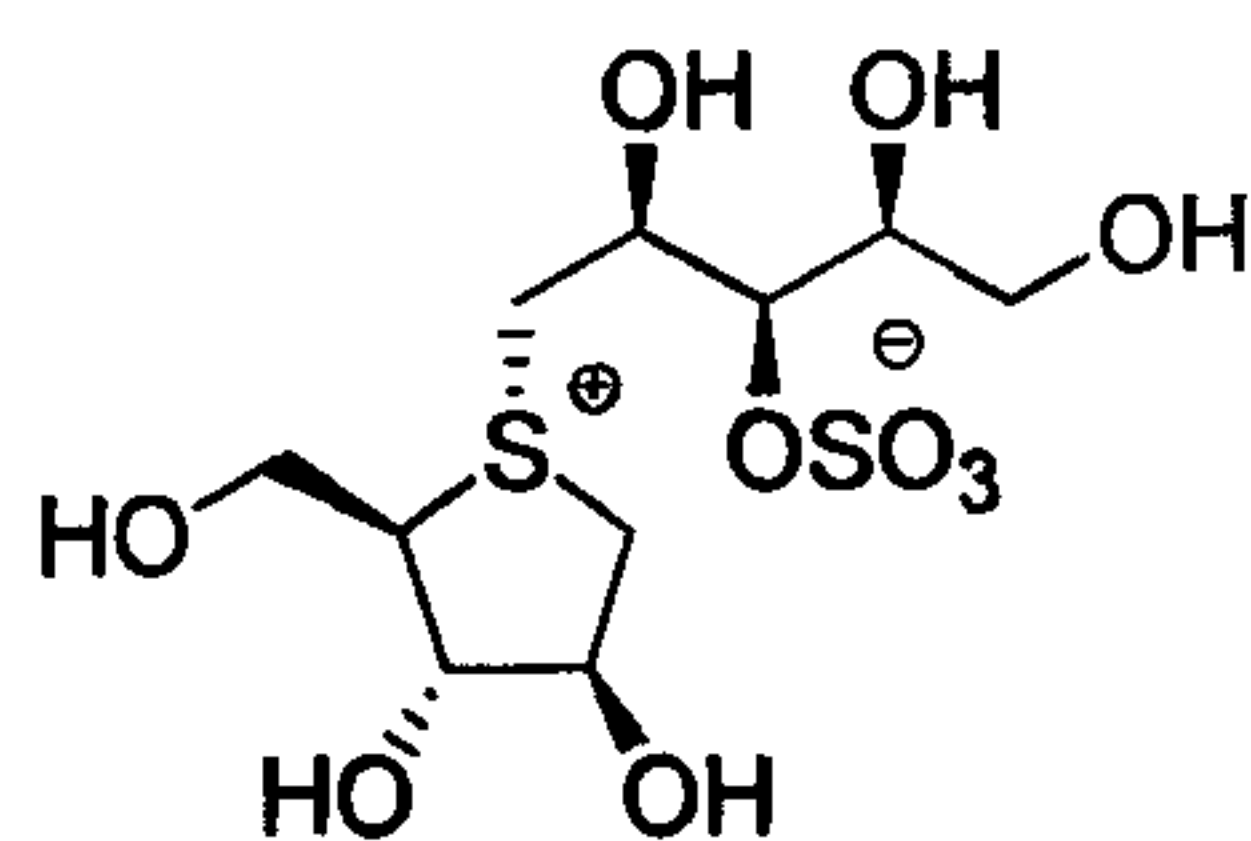
(I)

- 10 where X is selected from the group consisting of S, Se and NH; R₁, R₂, R₃, R₄ and R₅ are the same or different and are selected from the group consisting of H, OH, SH, NH₂ and halogens; and R₆ is selected from the group consisting of H, OH and optionally substituted straight chain, branched, or cyclic, saturated or unsaturated hydrocarbon radicals, wherein the carbon side chain connected to the X heteroatom of
- 15 formula (I) comprises between 4-10 carbon atoms.
2. The compound as defined in claim 1, wherein R₆ is an alditol chain.
3. The compound as defined in claim 1, wherein R₆ comprises between 1
- 20 and 3 carbons.
4. The compound as defined in claim 1, wherein said side chain is a polyhydroxylated acyclic side chain comprising 5 or 6 carbons.
- 25 5. The compound as defined in any one of claims 1-4, wherein X=S and wherein said compound is a chain-extended homologue of Salacinol.
6. The compound as defined in claim 3, wherein R₁, R₂, R₃, R₄ and R₅ are OH.

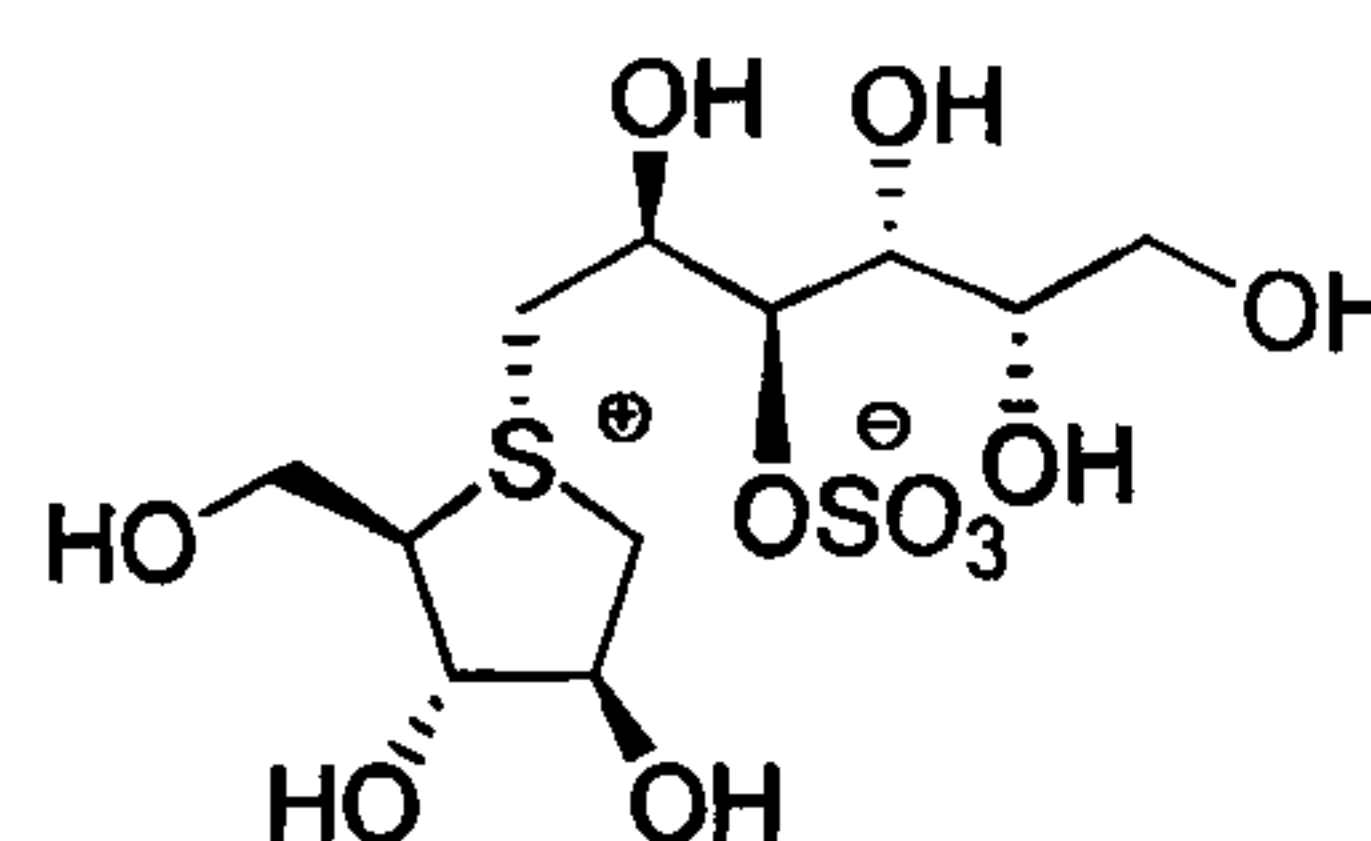
7. The compound as defined in claim 3, wherein said compound is 1,4-Dideoxy-1,4-[[2*R*,3*R*,4*R*,5*S*-2,4,5,6-tetrahydroxy-3-(sulfooxy)hexyl]episulfonium-ylidene]-D-arabinitol.

5

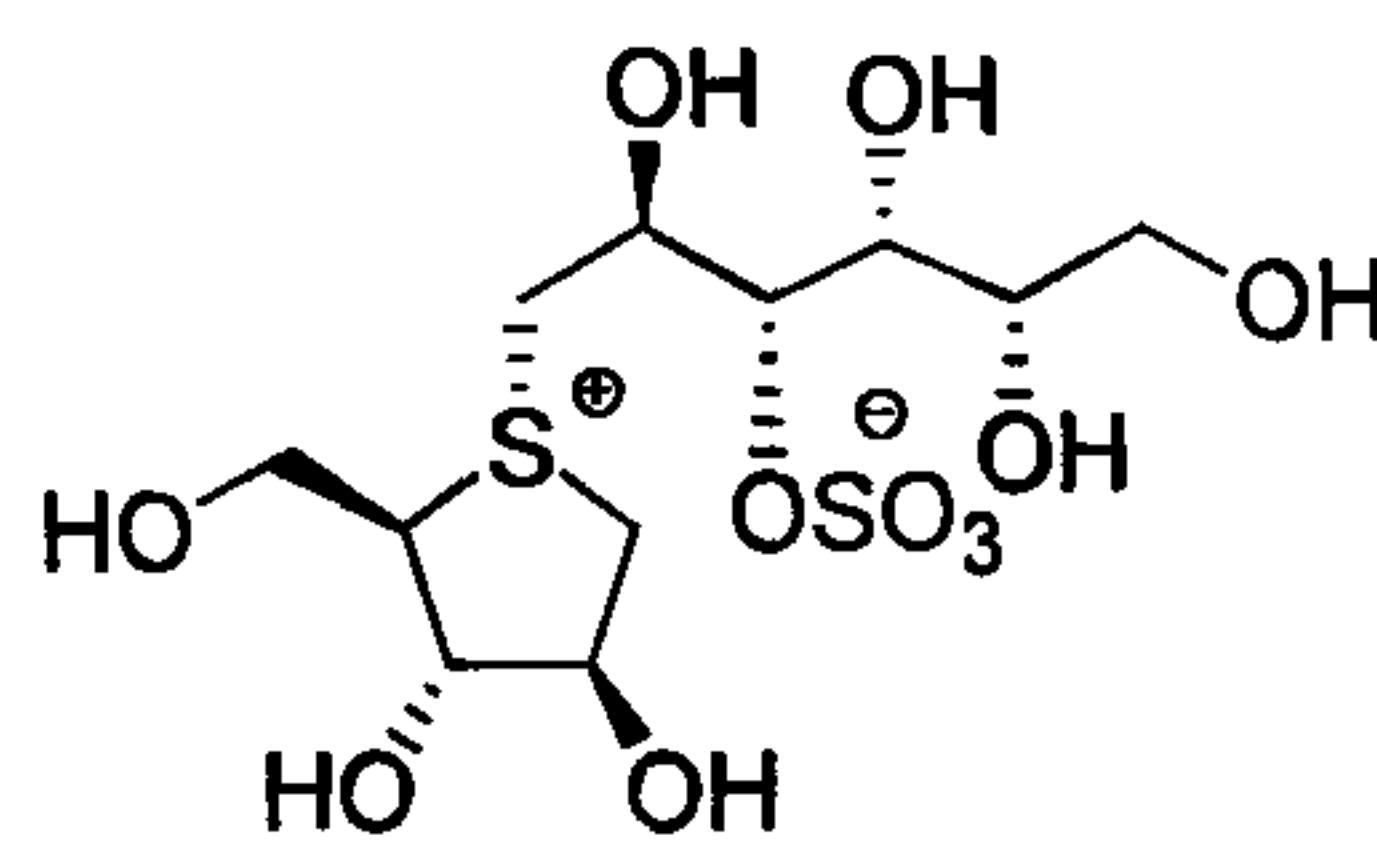
8. A compound as defined in claim 1, selected from the group consisting of compounds 94, 95, 96 and 97 set forth below



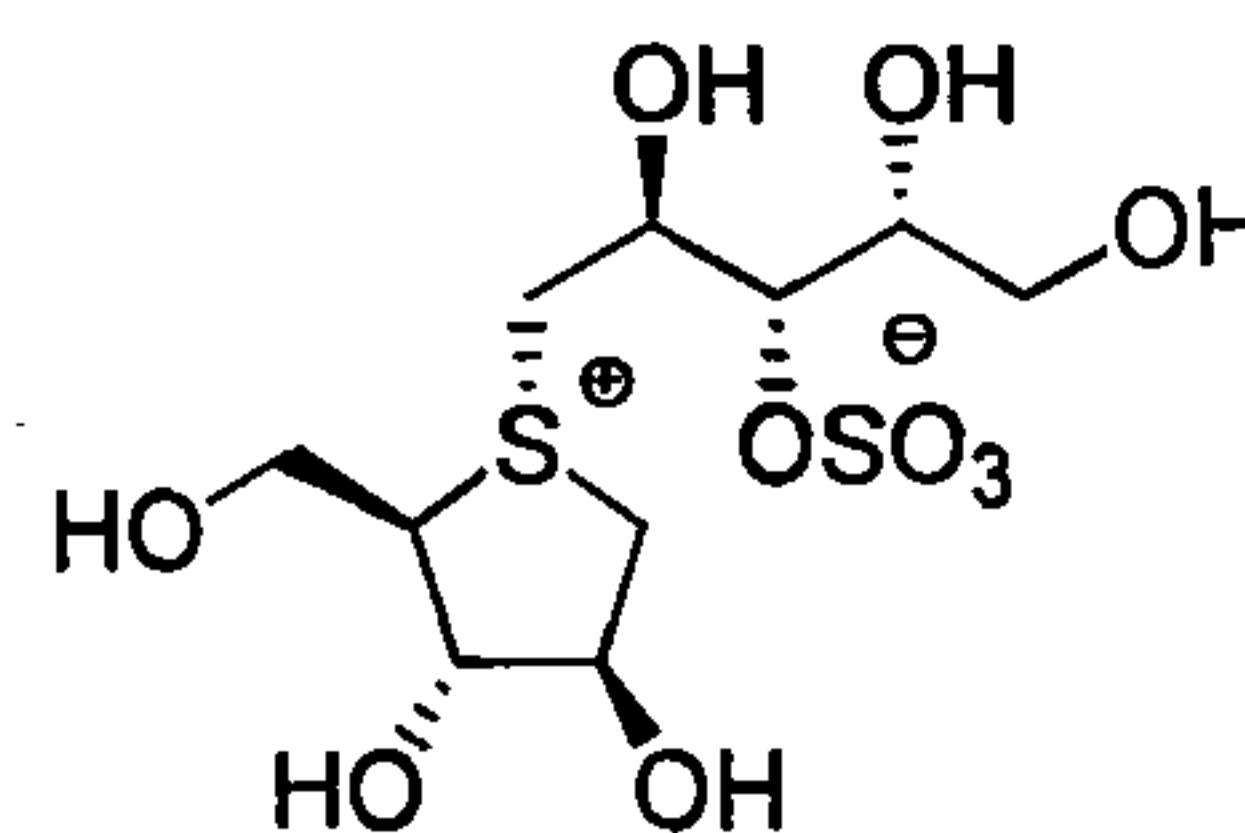
94



95



96



97

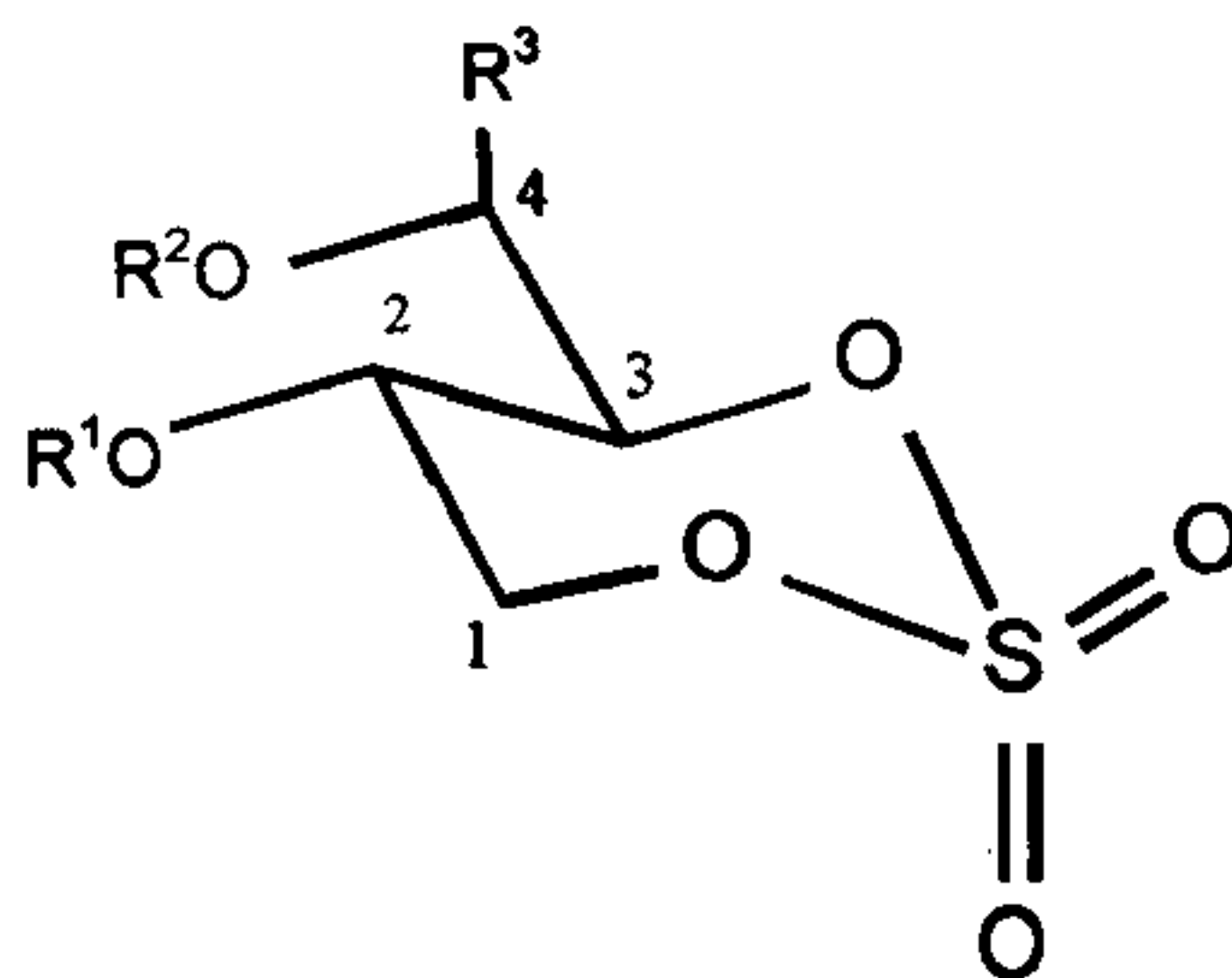
9. A compound as defined in claim 5, wherein said homologue comprises a 1,4-anhydro-1,4-thio-D-arabinitol core moiety and a polyhydroxylated acyclic moiety constituting said side chain, and wherein said homologue is at least as bioactive as a glycosidase inhibitor as Salacinol.

10. A process for synthesis of the compound (I) of claim 1 comprising:

15

- (a) providing a cyclic sulfate having the general formula (III)

(b)



5

(III)

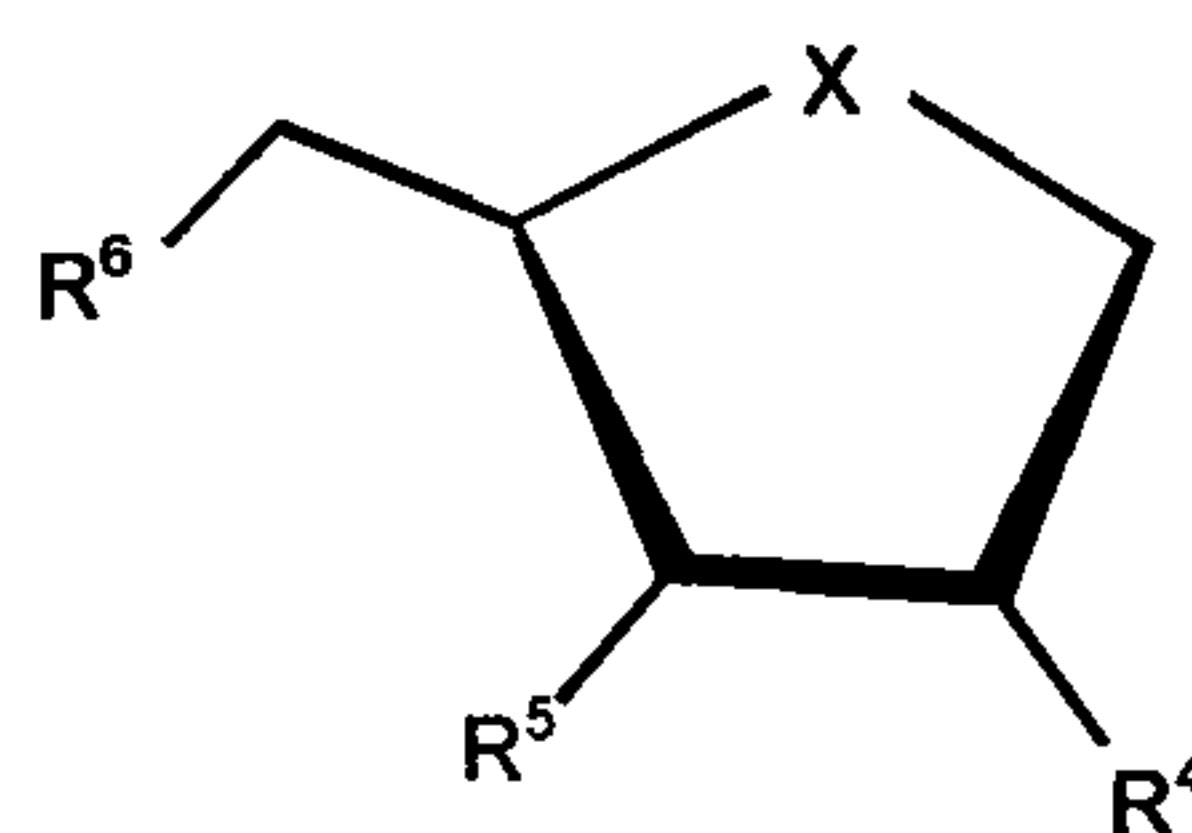
10

wherein R^1 and R^2 are H or comprise a protecting group and R^3 is selected from the group consisting of H and optionally substituted straight chain, branched, or cyclic, saturated or unsaturated hydrocarbon radicals and their protected derivatives;

(b)

15

providing a 5-membered heterocycle ring compound of the general formula (IV),



20

(IV)

25

wherein X is selected from the group consisting of S, Se, and NH and R^4 , R^5 and R^6 are selected from the group consisting of OH and a protected hydroxyl group;

(c)

30

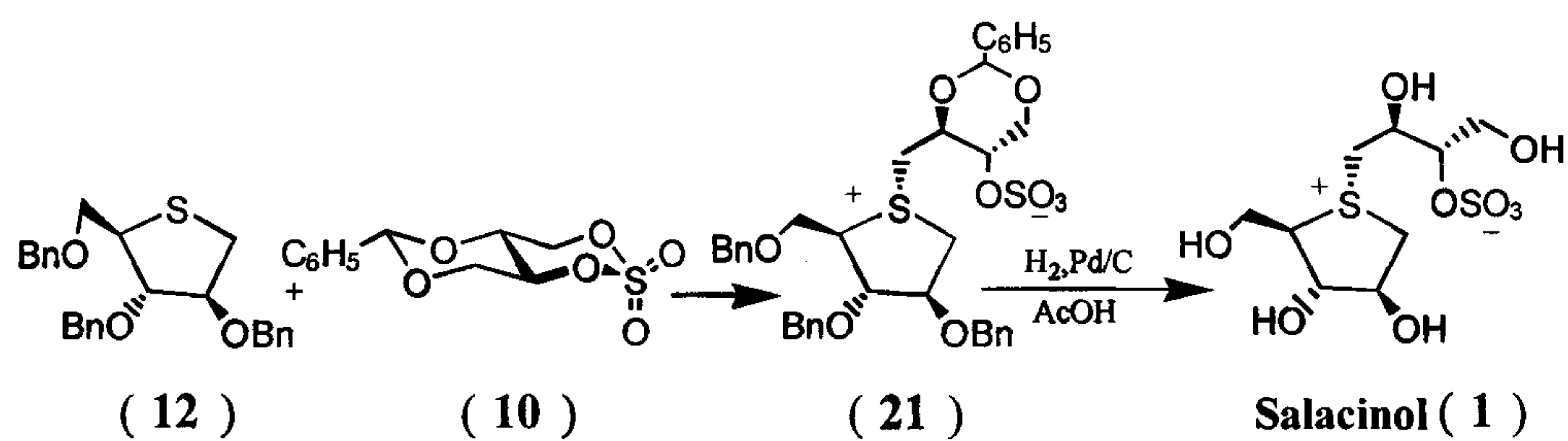
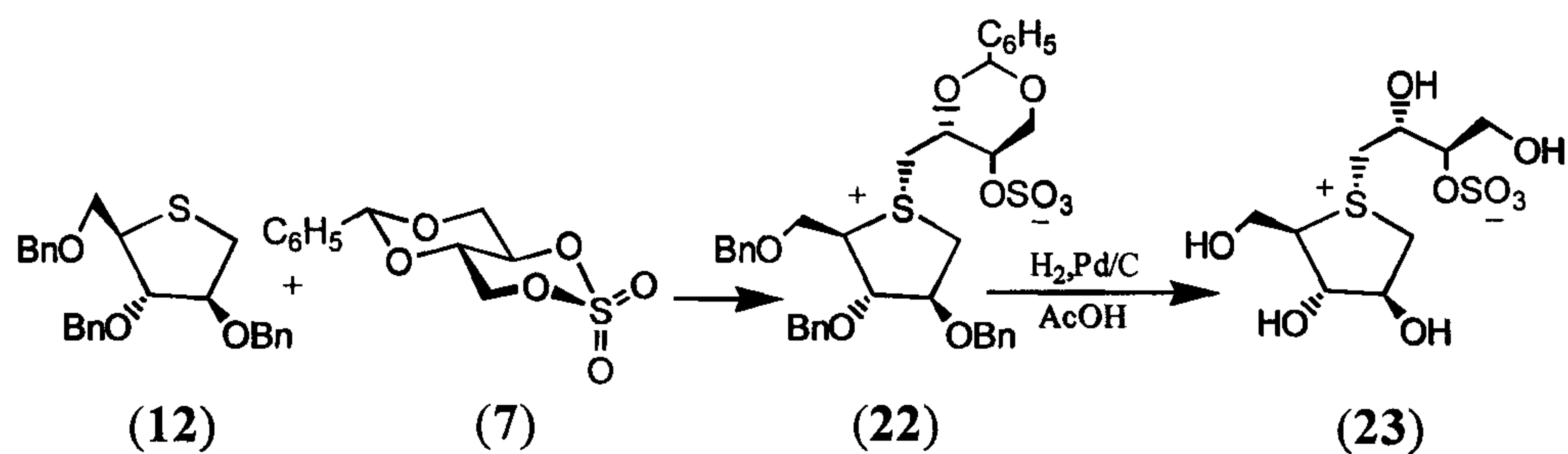
reacting the cyclic sulfate with the 5-membered heterocycle ring compound to produce an intermediate compound having an internal salt structure comprising a positively charged heteroatom X and a negatively charged sulfate counterion; and

(d)

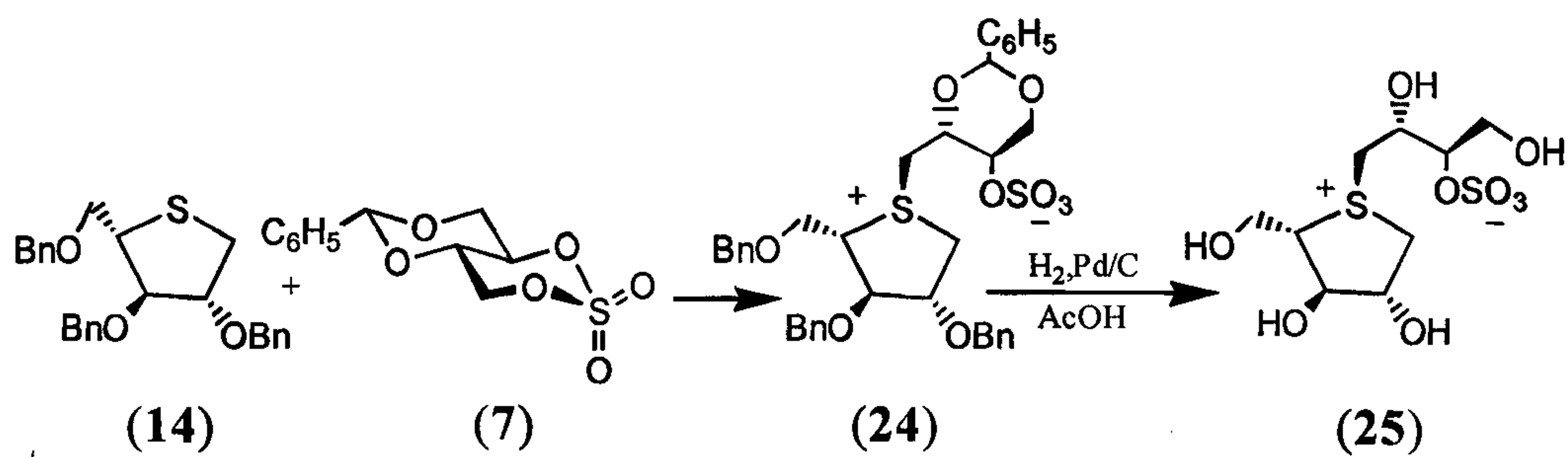
removing any protecting groups from said intermediate compound.

11. The process as defined in claim 10, wherein said reacting of said cyclic sulfate and said heterocycle ring compound is performed in a polar solvent.
12. The process as defined in claim 11, wherein said polar solvent
5 comprises hexafluoroisopropanol.
13. The process as defined in claim 10, wherein said cyclic sulfate is derived from D-glucose.
- 10 14. The process as defined in claim 10, wherein said cyclic sulfate is a benzylidene-protected cyclic sulfate.
- 15 15. The process as defined in claim 14, wherein one or more benzylidene protecting groups are installed on said benzylidene-protected cyclic sulfate in the presence of the catalyst pyridinium – p-toluenesulfonate (PPTS).
16. The process as defined in claim 10, wherein said protected hydroxyl group of said heterocycle ring compound is p-methoxybenzyl.
- 20 17. The process as defined in claim 10, wherein said heterocycle ring compound is p-methoxybenzyl-protected 1, 4-anhydro-4-seleno-D-arabinitol.
18. The process as defined in claim 10, wherein the removal of the protecting groups is performed by hydrogenolysis of said intermediate compound.
25
19. The process as defined in claim 10, wherein the removal of the protecting groups is performed by acid hydrolysis.
20. The process as defined in claim 19, wherein said acid hydrolysis is
30 performed with trifluoroacetic acid.
21. The process as defined in claim 10, wherein said heterocycle ring compound is derived from L-xylose.

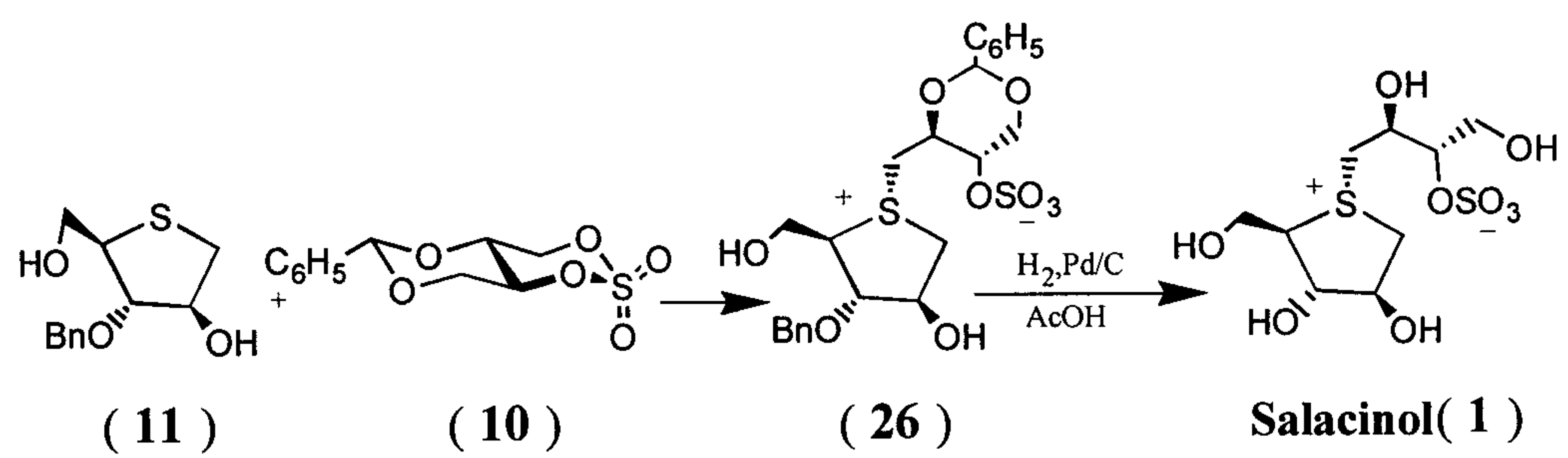
22. The process as defined in claim 10, wherein said intermediate compound comprises a sulfonium-sulfate disaccharide analogue.
- 5 23. The process as defined in claim 10, wherein said intermediate compound is a sulphonium sulfate derivative of a monosaccharide selected from the group consisting of glucose, galactose, arabinose and xylose.
24. The process as defined in claim 10, further comprising reducing said
10 intermediate compound with sodium borohydride to yield the target compound (I).
25. The use of the compound (I) of claim 1 for inhibiting the activity of a glucosidase enzyme.
- 15 26. The use as defined in claim 25, wherein said glycosidase enzyme is selected from the group consisting of intestinal maltase-glucoamylase and pancreatic alpha amylase.
27. The use of Blintol for inhibiting the activity of intestinal maltase-
20 glucoamylase.
28. A pharmaceutical composition comprising an effective amount of a compound according to claim 1 together with a pharmaceutically acceptable carrier.
- 25 29. The use of a compound according to claim 1 for treating a carbohydrate metabolic disorder in an affected patient.
30. The use as defined in claim 29, wherein said carbohydrate metabolic disorder is non-insulin dependent diabetes.
- 30 31. Salacinol or an isomer thereof produced or partially produced by a synthetic process defined in any one or more of schemes 7, 8, 9, 10, 10a, 10b and 10c

5 **Scheme 7. Synthesis of Salacinol (1)****Scheme 8. Synthesis of compound (23)**

10

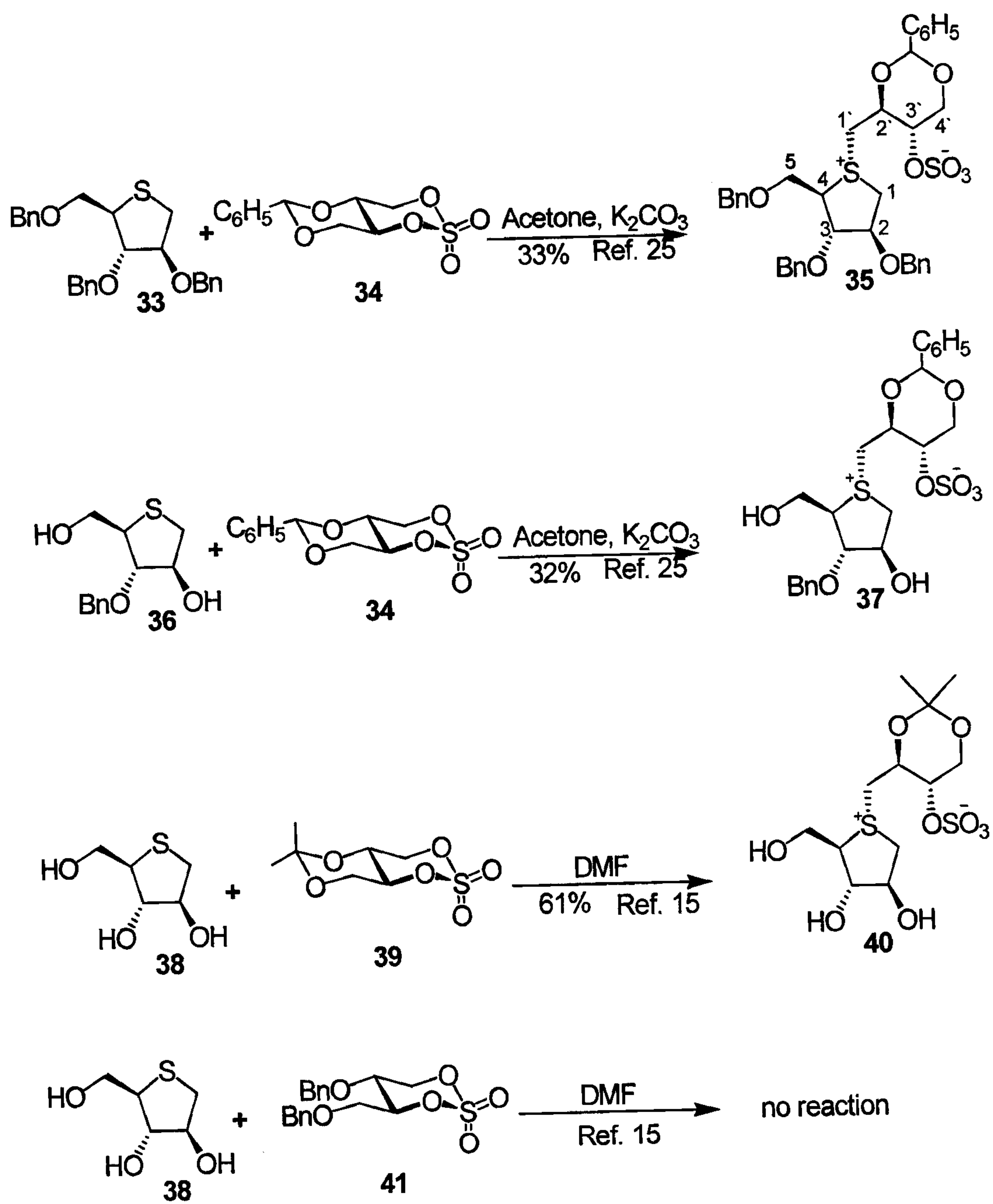
**Scheme 9. Synthesis of compound (25)**

15

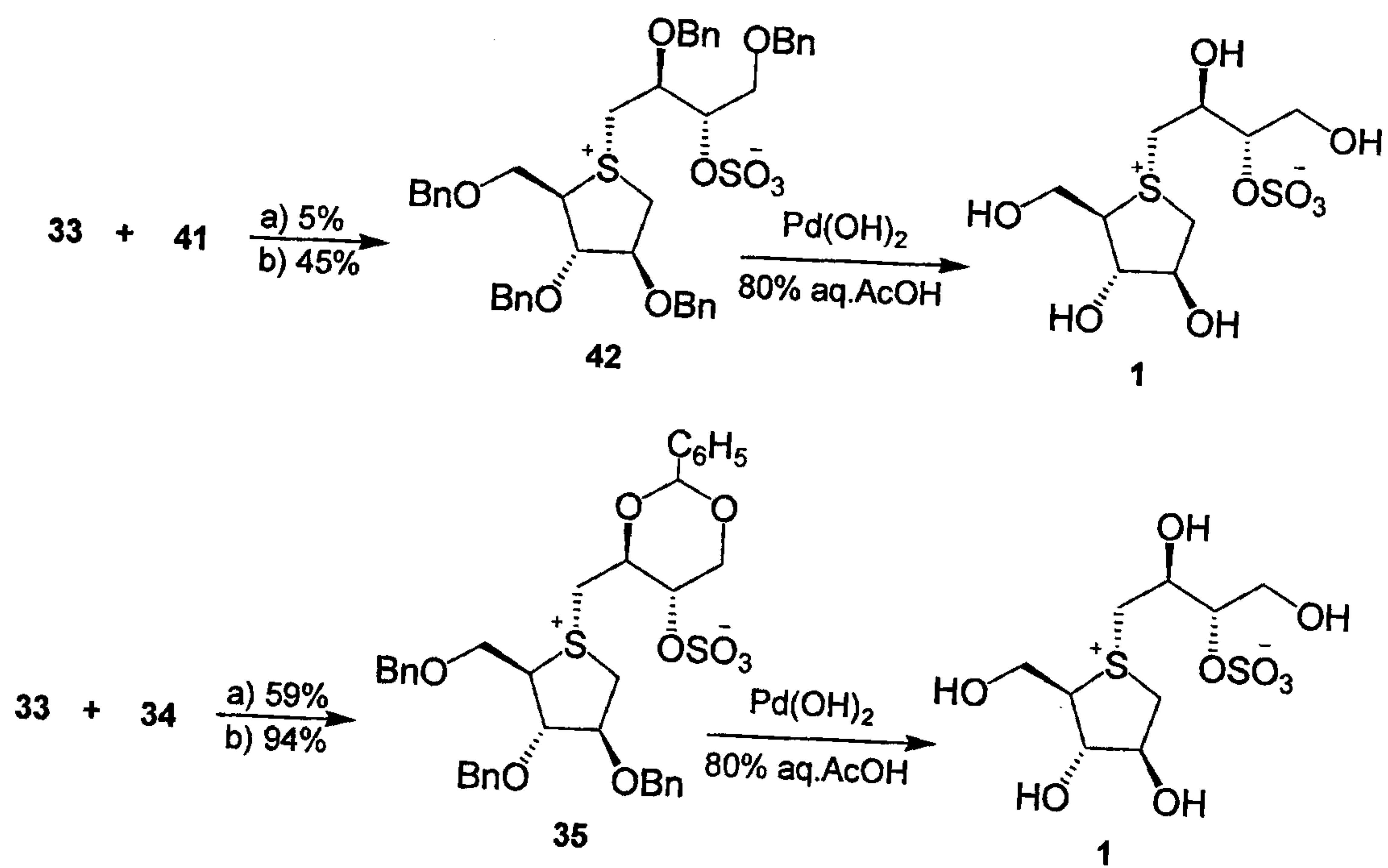


Scheme 10. Synthesis of Salacinol

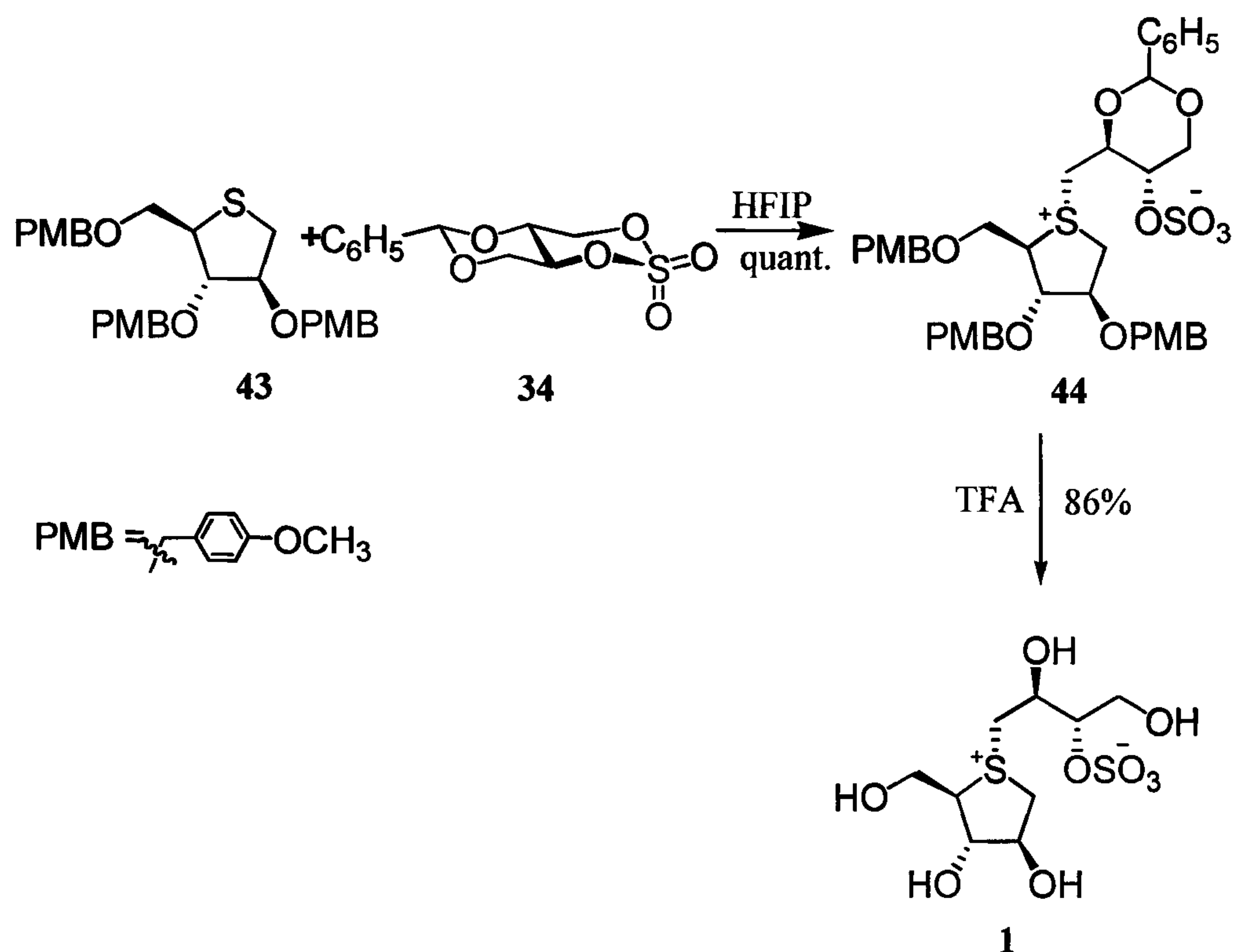
(1)



Scheme 10a



Scheme 10b

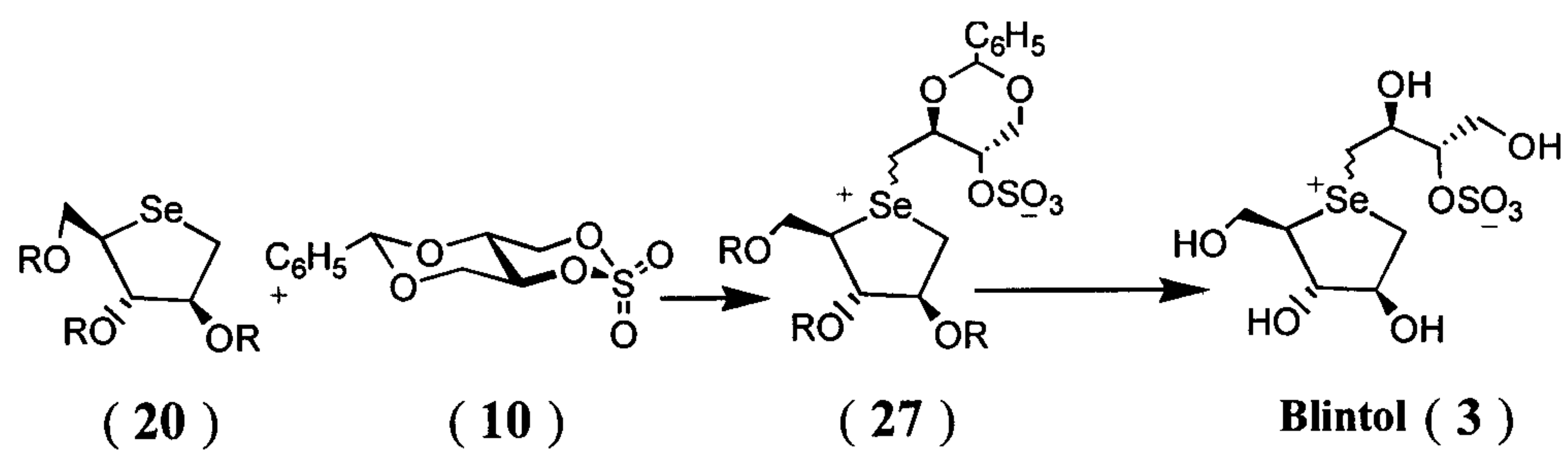


Scheme 10c

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32. Blintol or an isomer thereof produced or partially produced by a synthetic process defined in any one or more of schemes 11, 12, 12a, 12b, 12c, 12d, 12e, and 12f

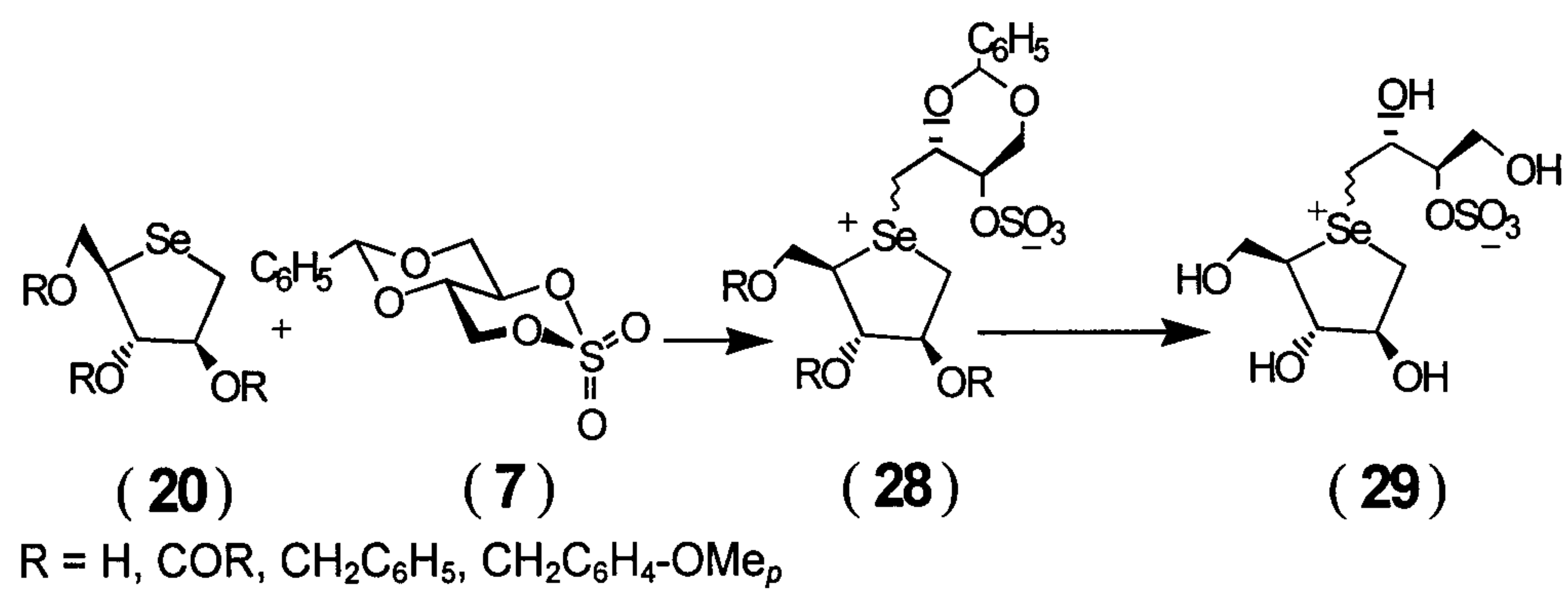
10



R = H, COR, CH₂C₆H₅, CH₂C₆H₄-OMe_p

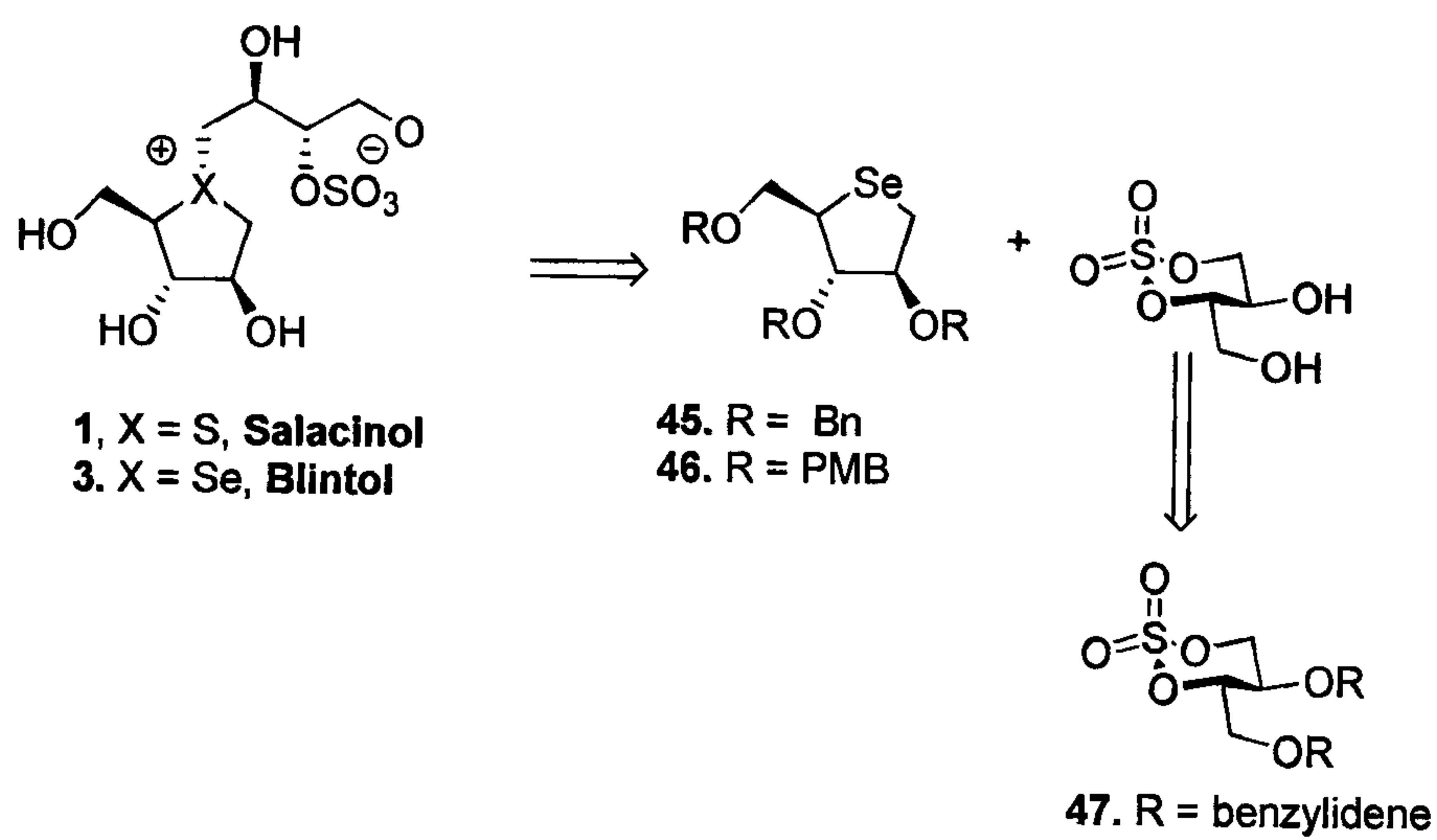
Scheme 11. Synthesis of Blintol (3)

5



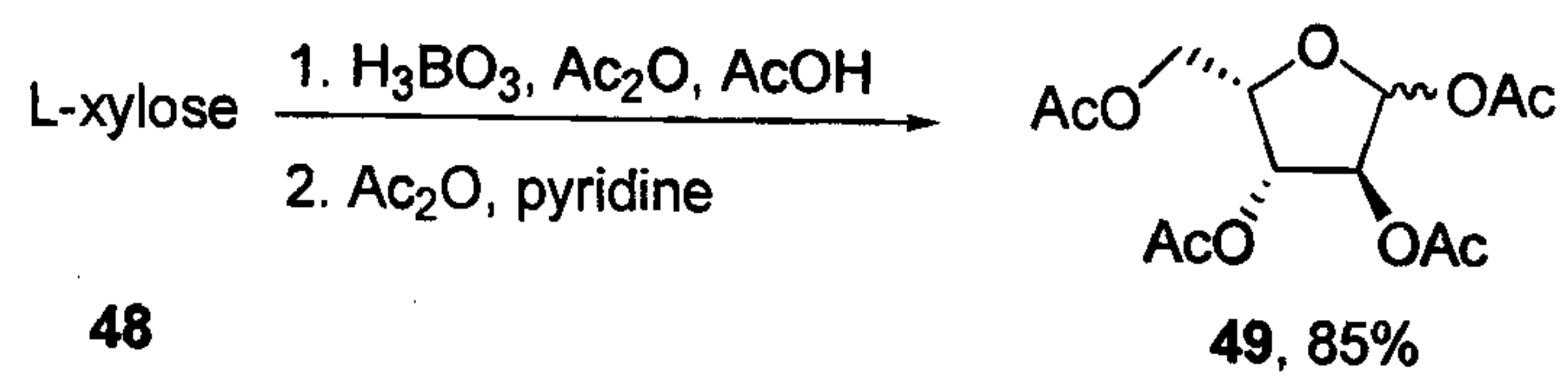
Scheme 12. Synthesis of compound (29)

10

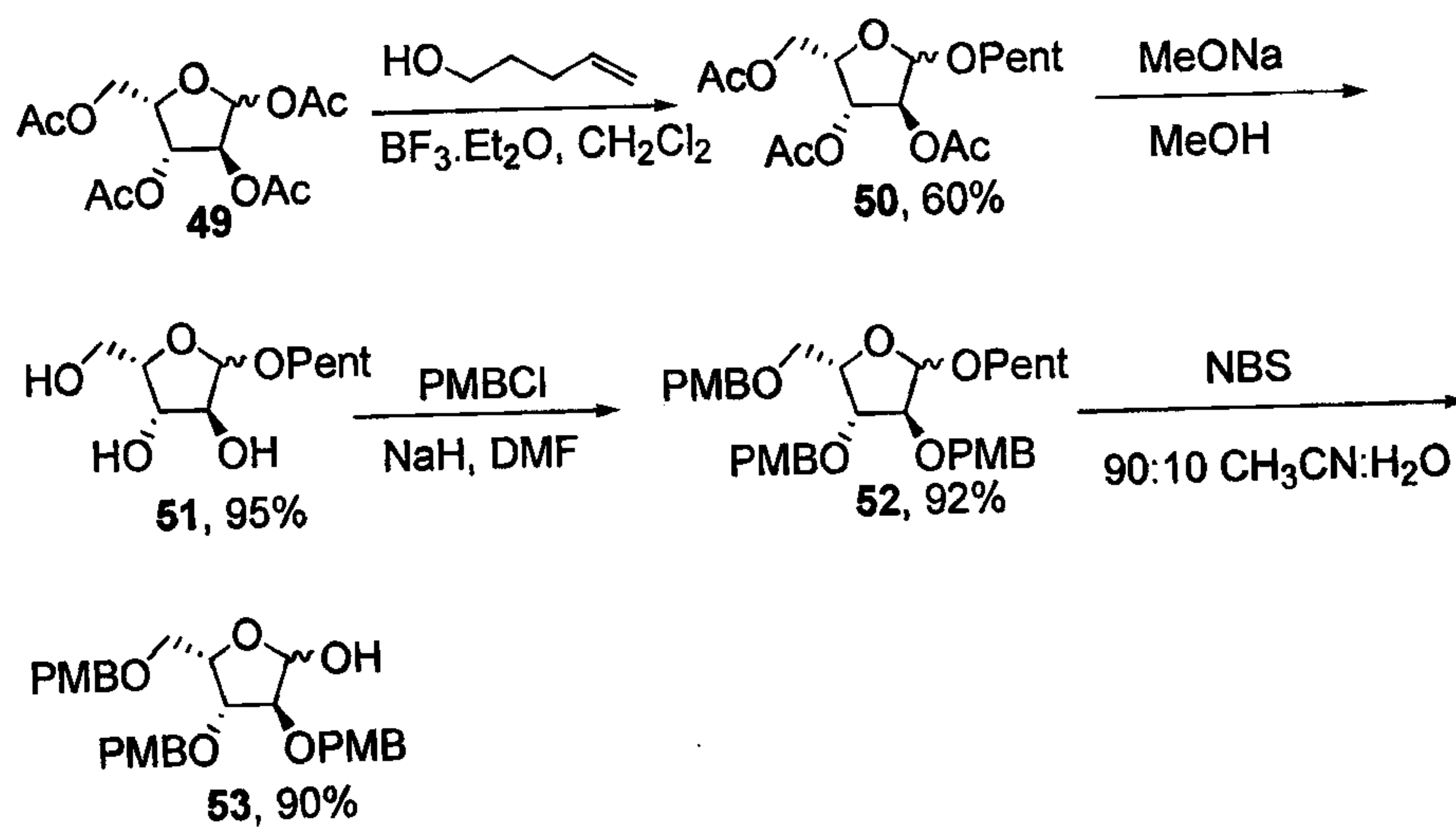


Scheme 12a

5

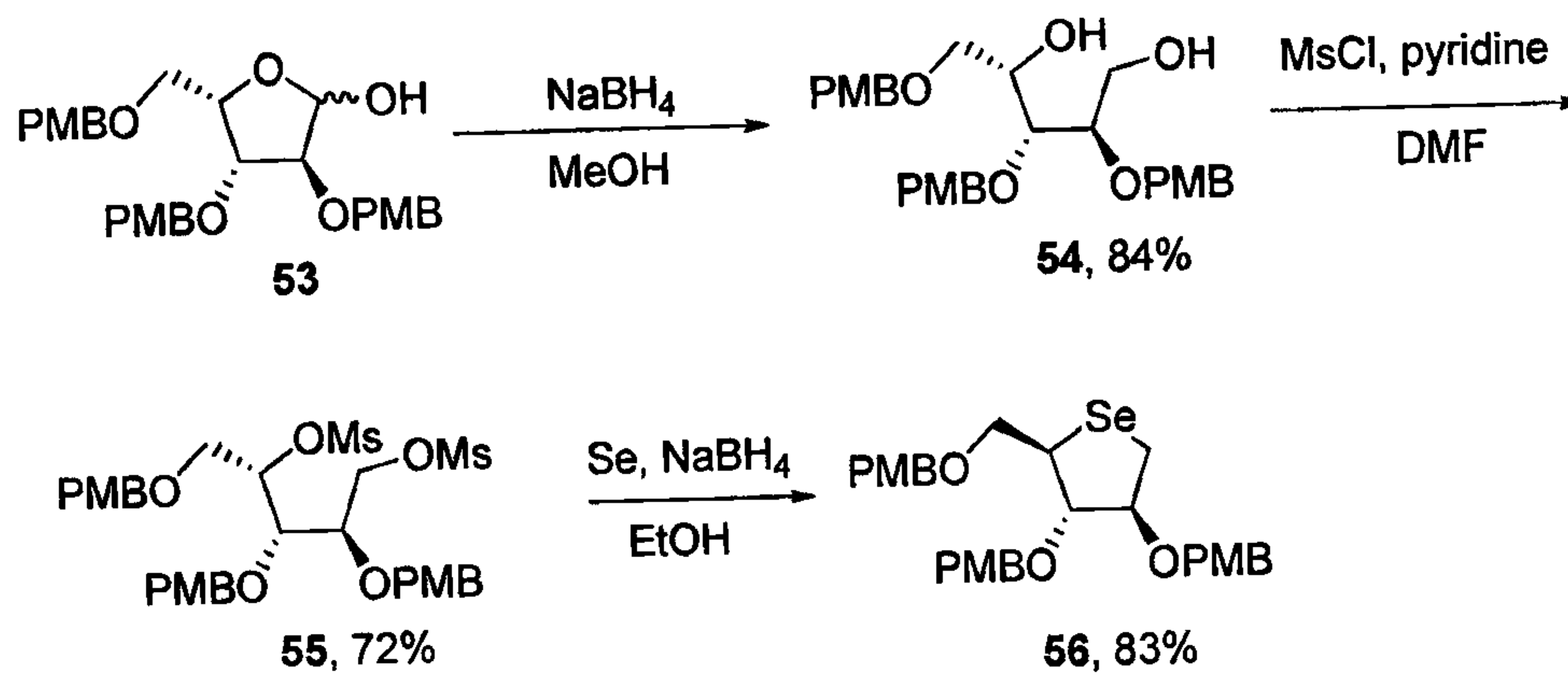


Scheme 12b



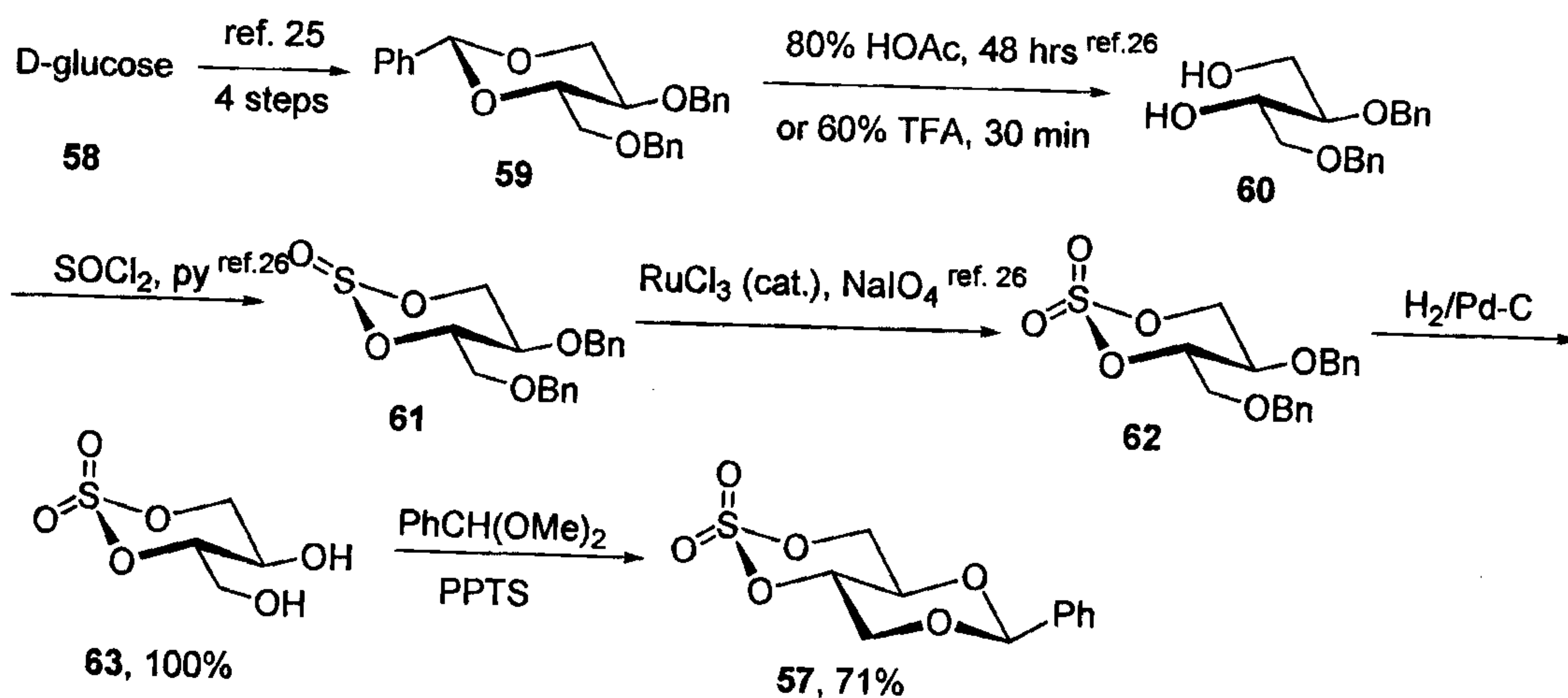
Scheme 12c

5



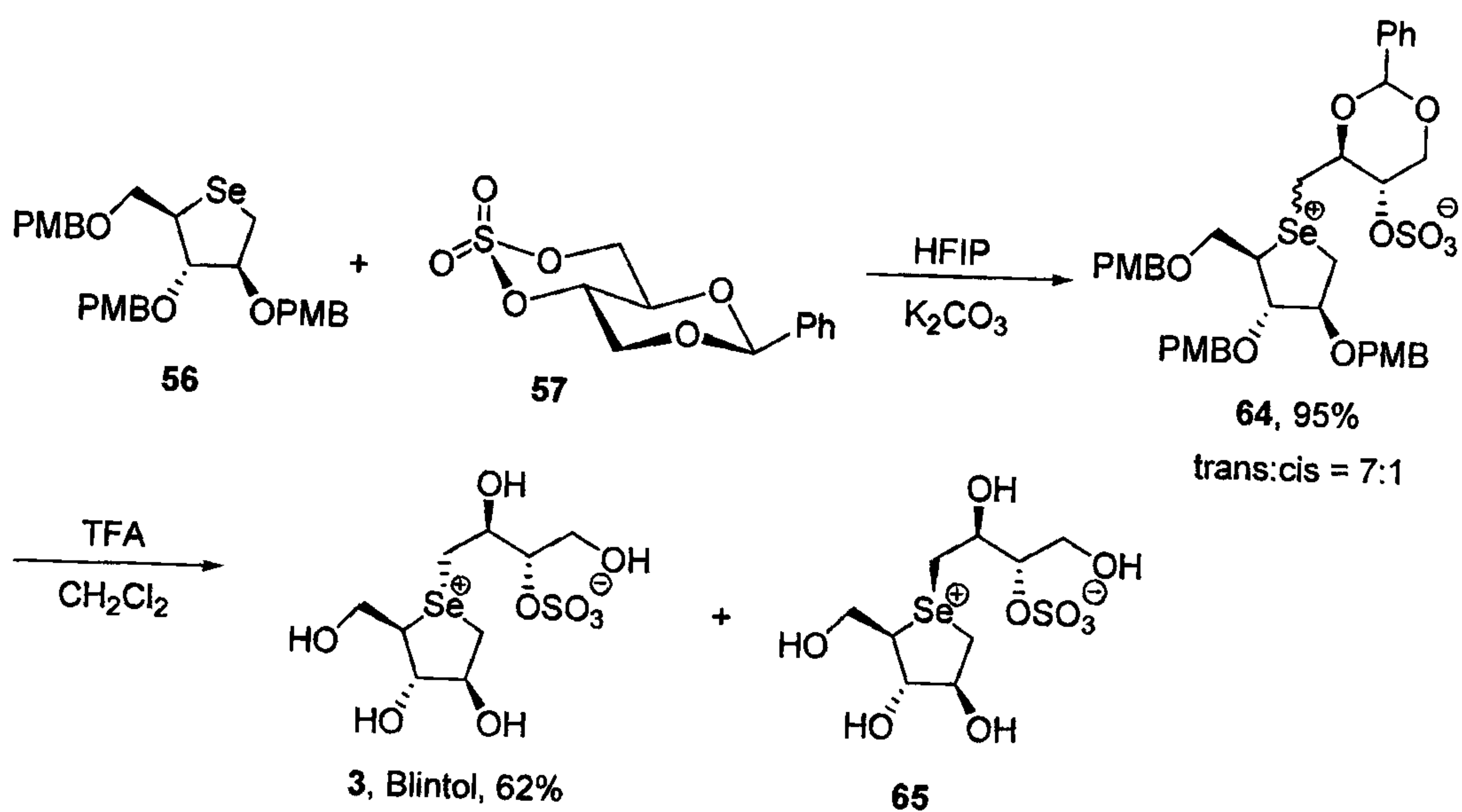
Scheme 12d

10



Scheme 12e

5

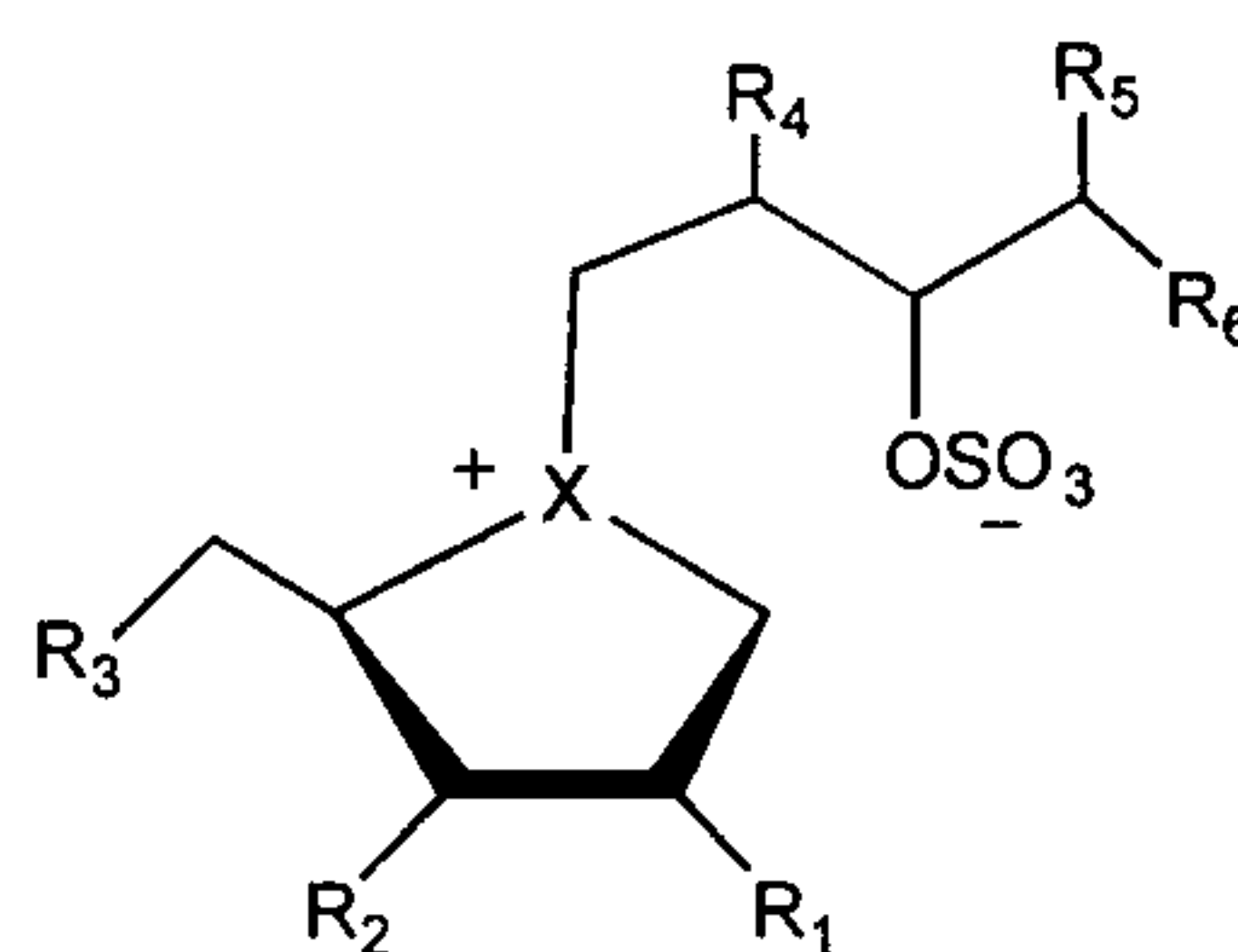


Scheme 12f

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33. A pharmaceutical comprising an effective amount of Salacinol and Blintol for treatment of a carbohydrate metabolic disorder together with a pharmaceutically acceptable carrier.

5 34. A non-naturally occurring compound selected from the group consisting of compounds represented by the general formula (I) and stereoisomers and pharmaceutically acceptable salts thereof:



10

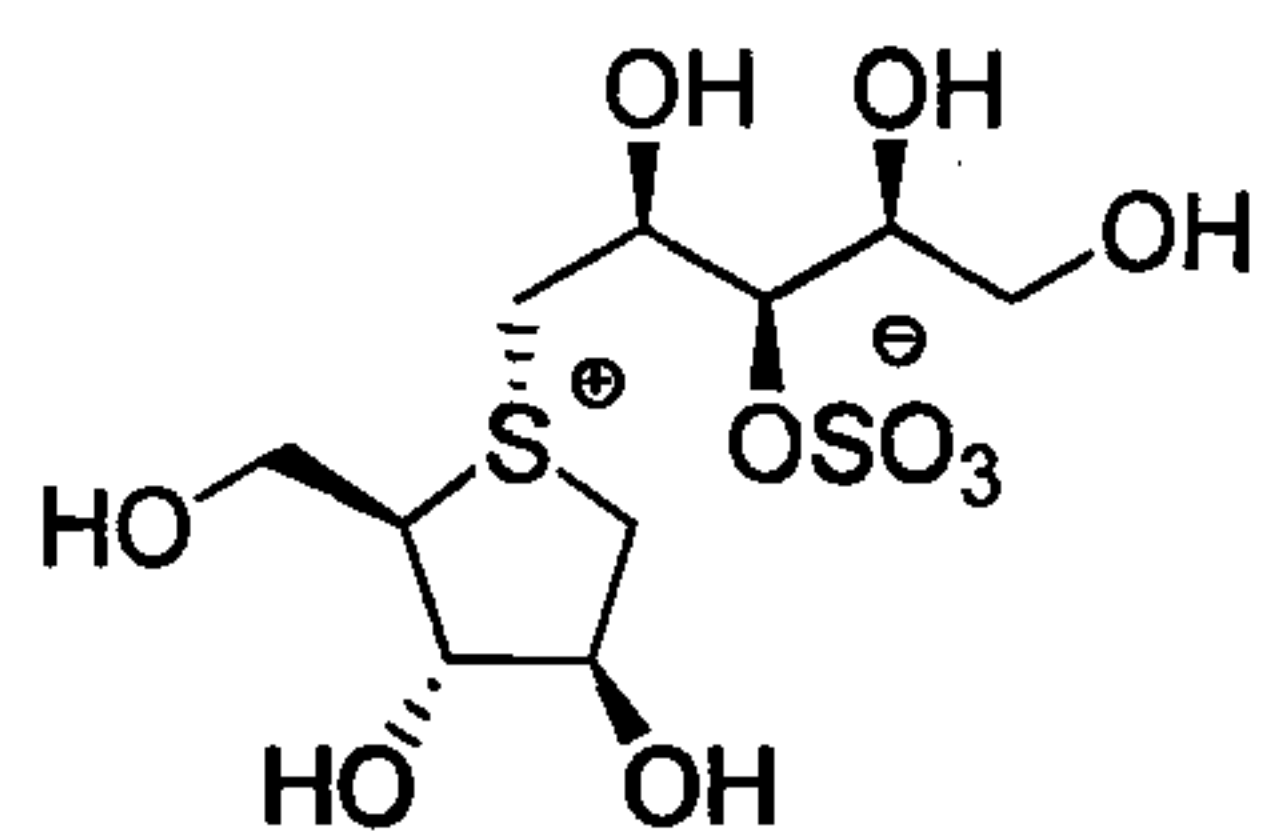
(I)

where X=S; R₁, R₂, R₃, R₄ and R₅ are OH; and wherein R₆ is a hydroxylated chain comprising 1 or 2 carbons; and wherein said compound is a chain-extended homologue of Salacinol.

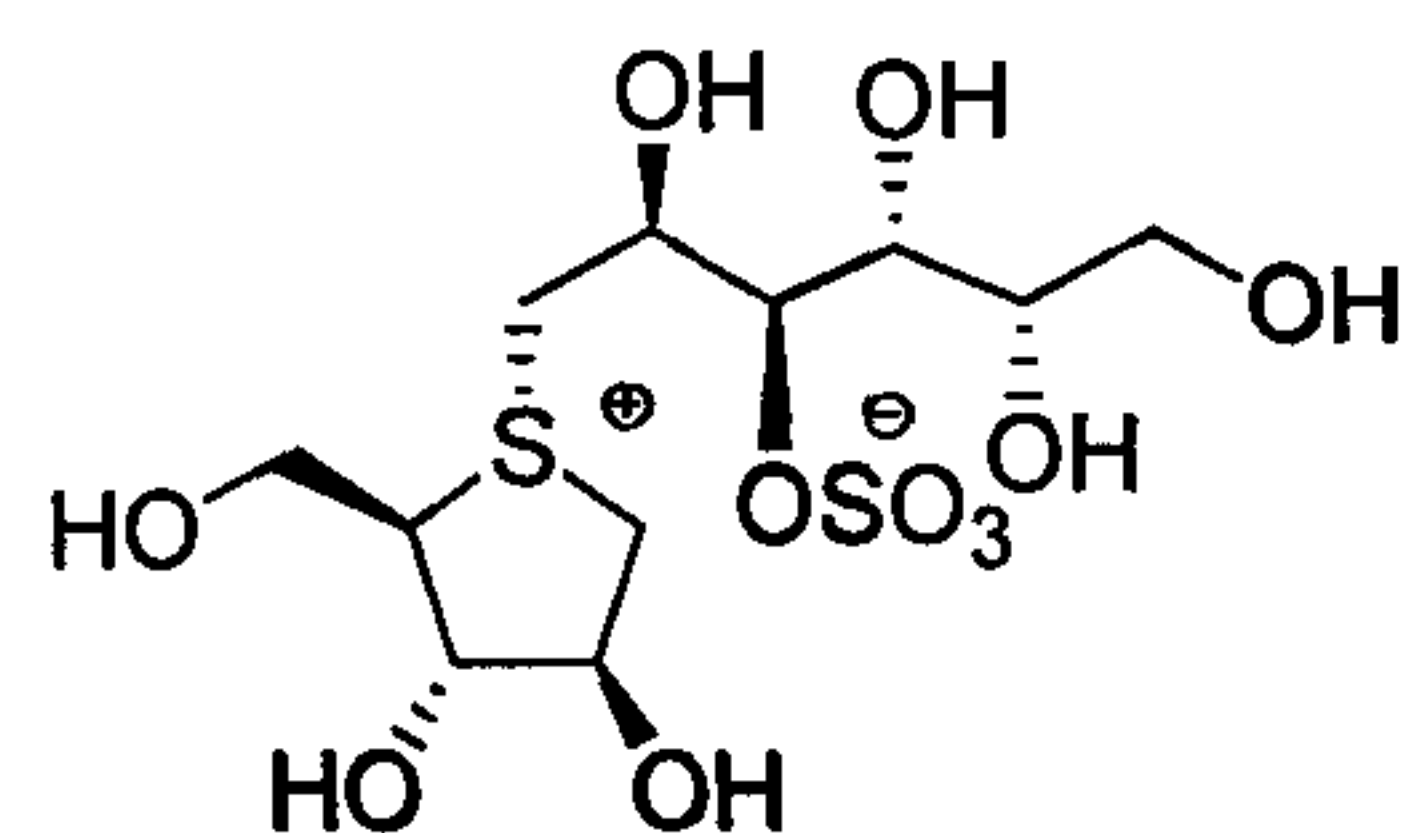
15

35. The compound as defined in claim 34, wherein said compound is 1,4-Dideoxy-1,4-[[2*R*,3*R*,4*R*,5*S*-2,4,5,6-tetrahydroxy-3-(sulfooxy)hexyl]episulfonium-ylidene]-D-arabinitol.

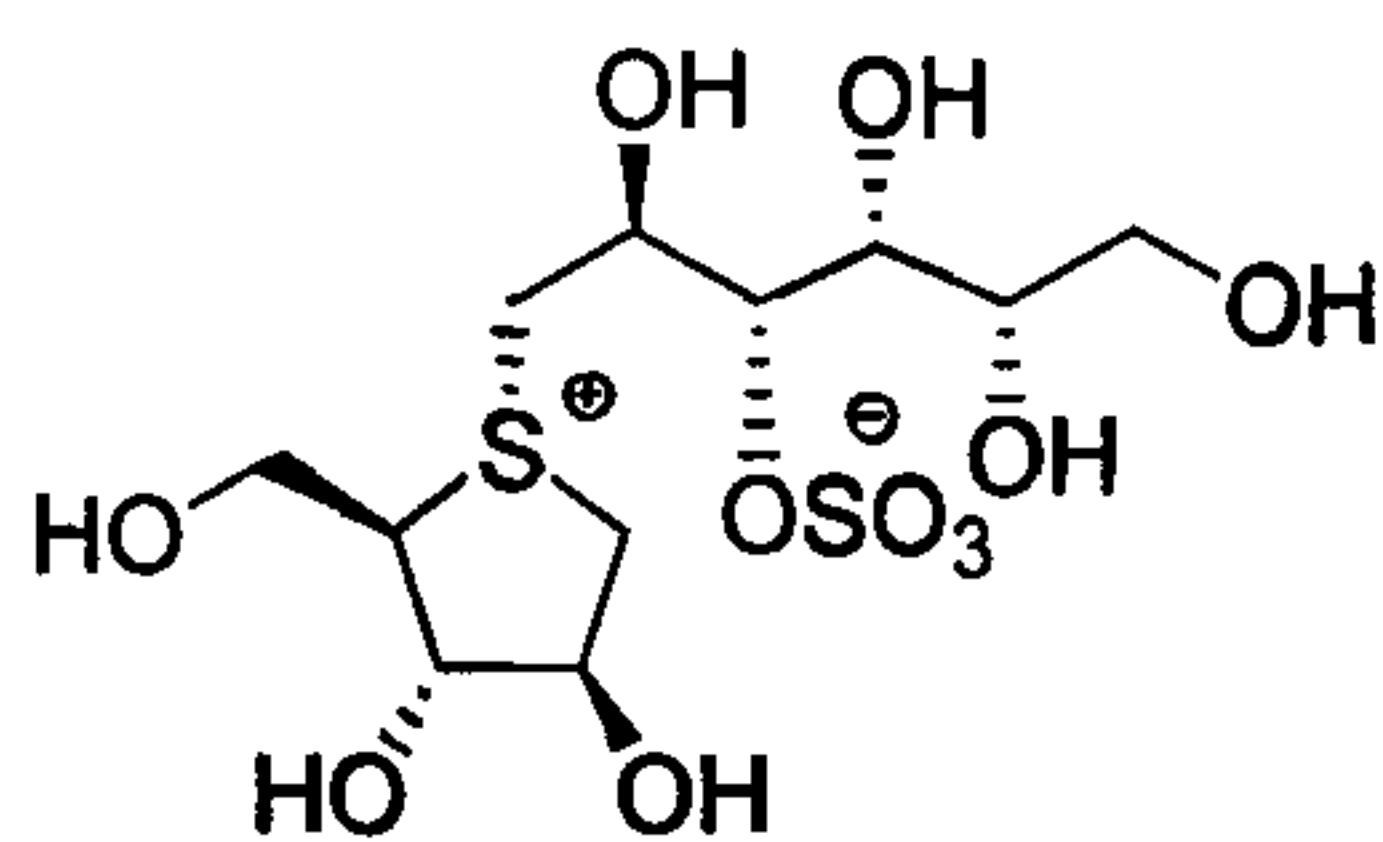
20 36. A compound as defined in claim 34, selected from the group consisting of compounds 94, 95, 96 and 97 set forth below



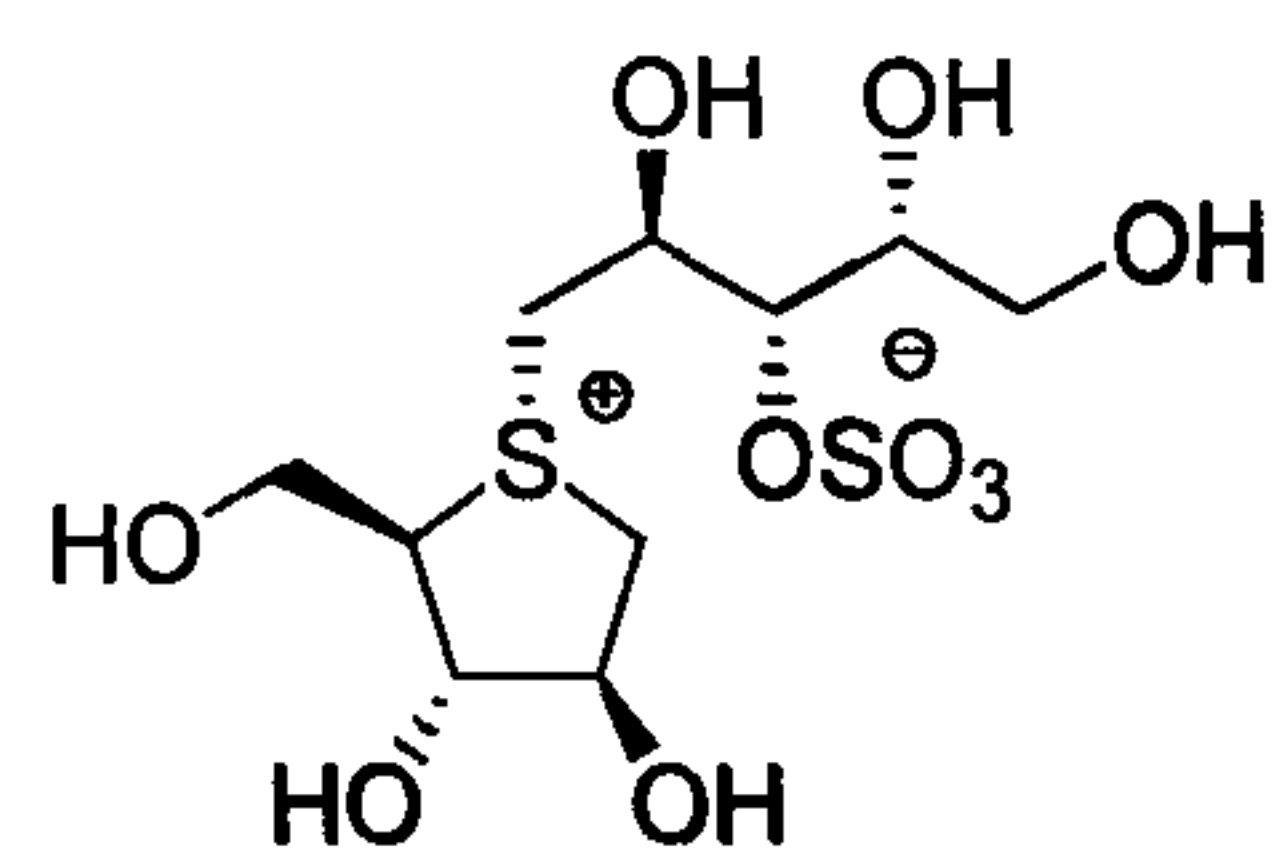
94



95



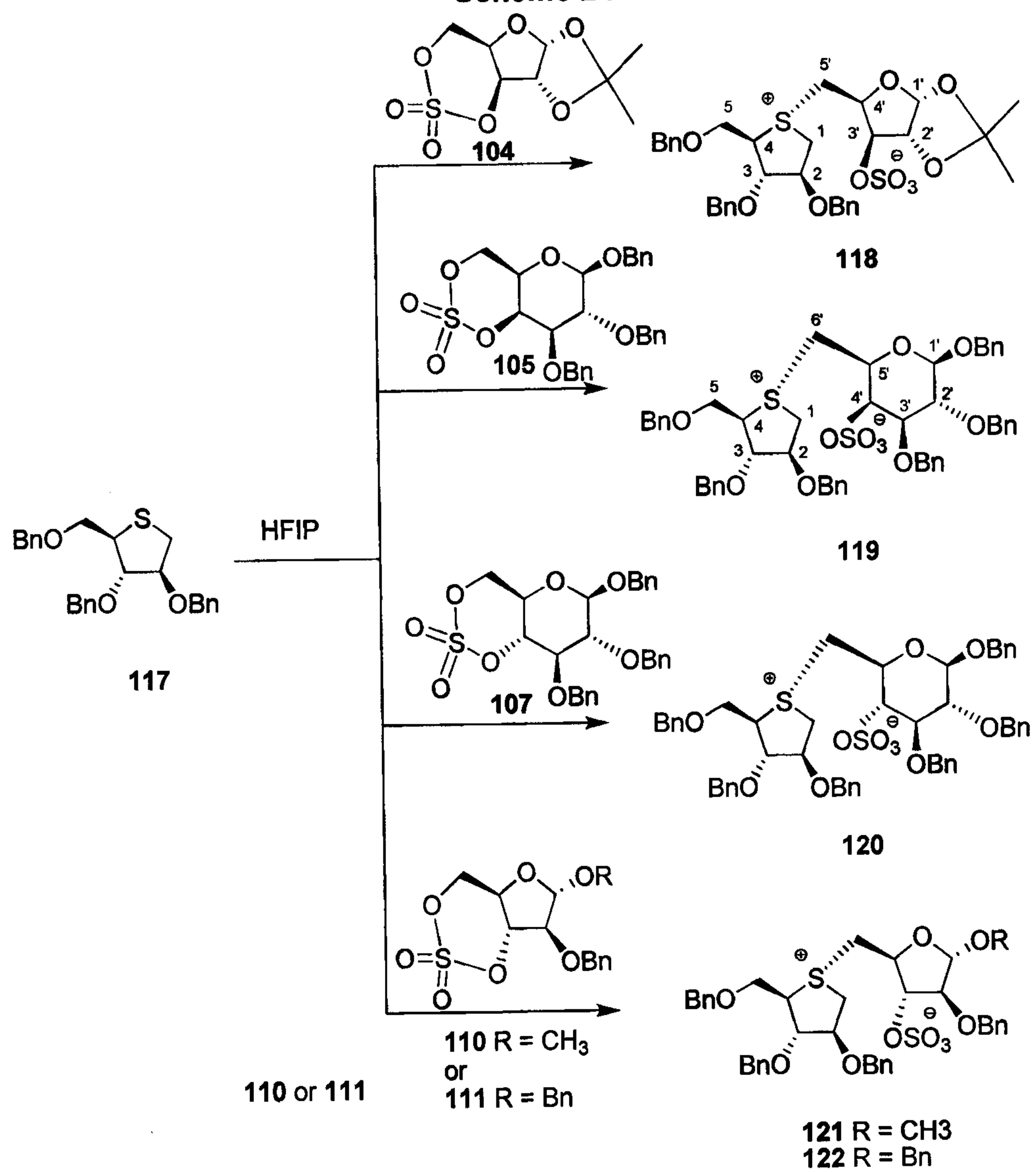
96



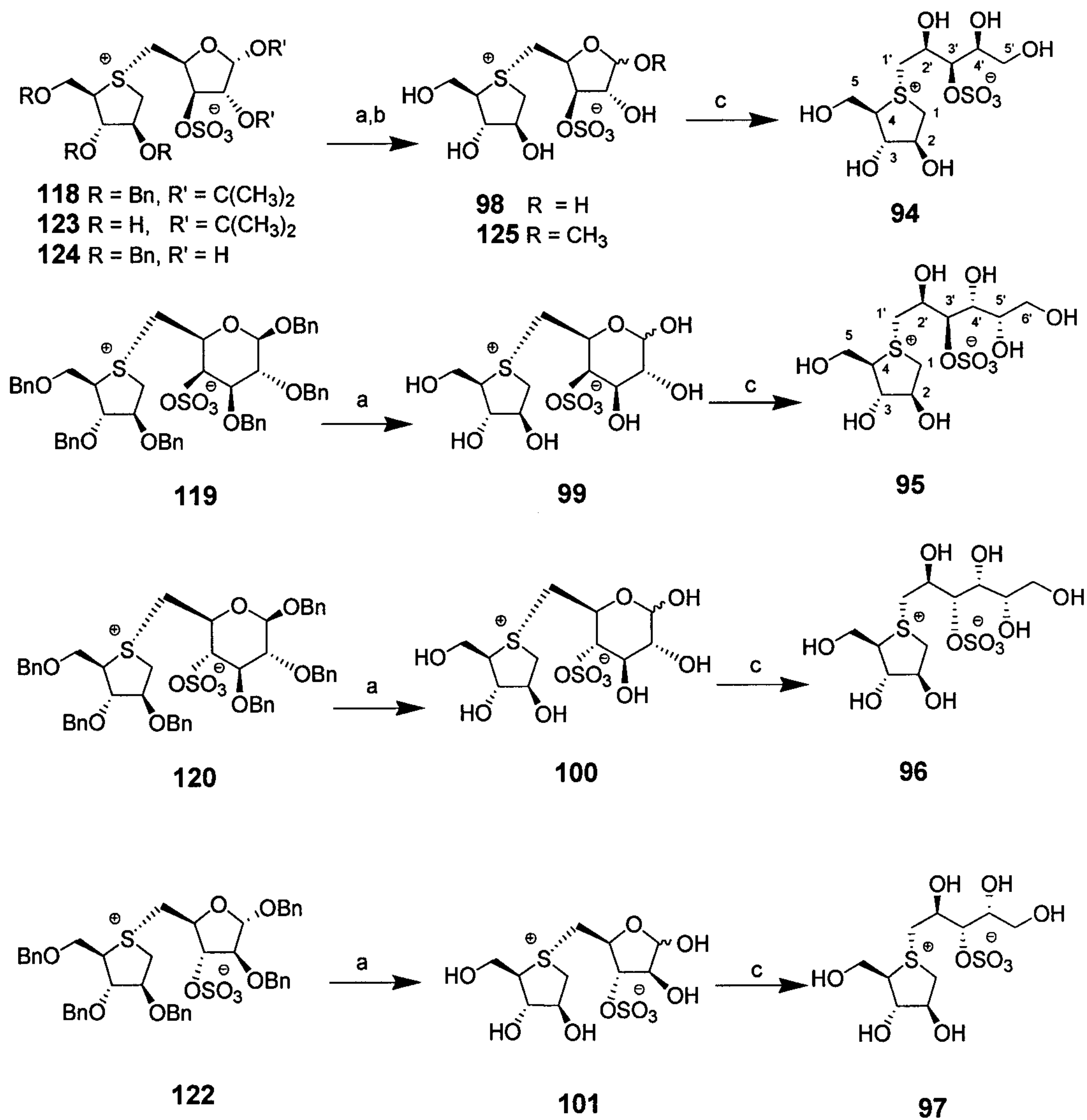
97

37. A method of synthesizing a compound as defined in claim 36 comprising synthetic steps as defined in Schemes 24 and 25.

Scheme 24



Scheme 25

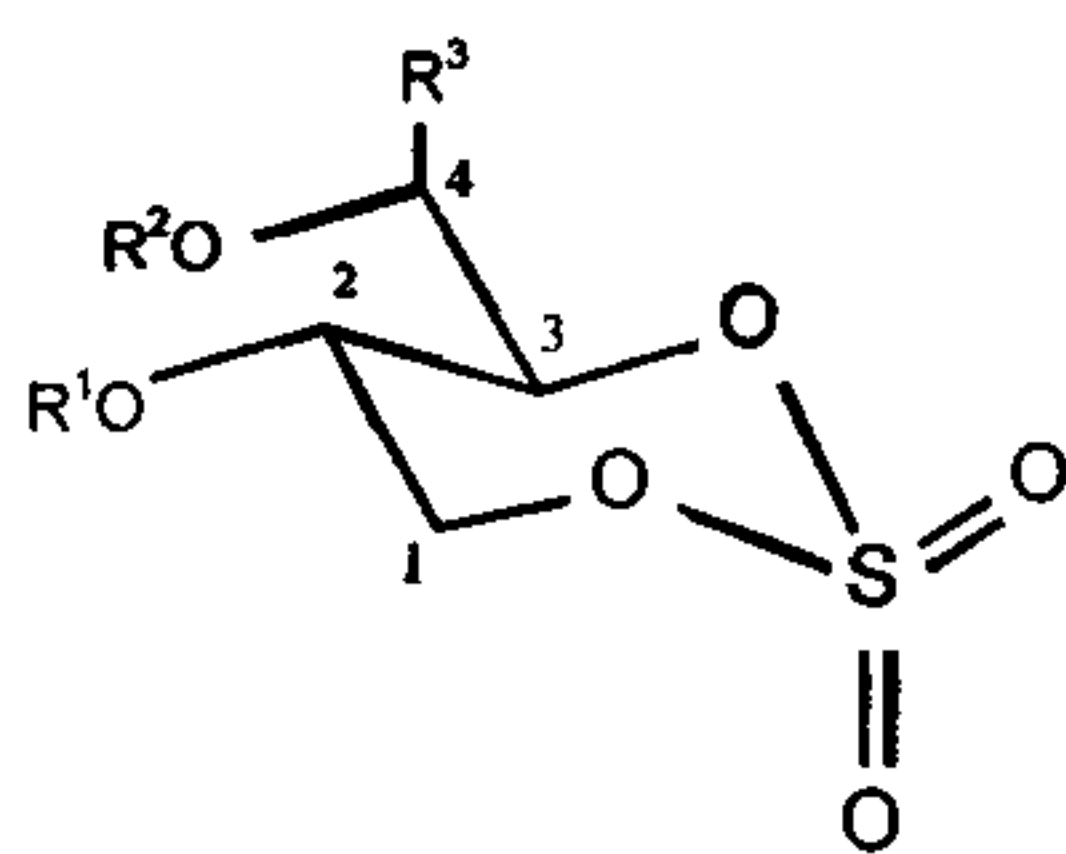


a H₂, Pd(C), b TFA/H₂O, c NaBH₄/H₂O

38. A process for synthesis of the compound (I) of claim 34 comprising:

5

(c) providing a cyclic sulfate having the general formula (III)



5

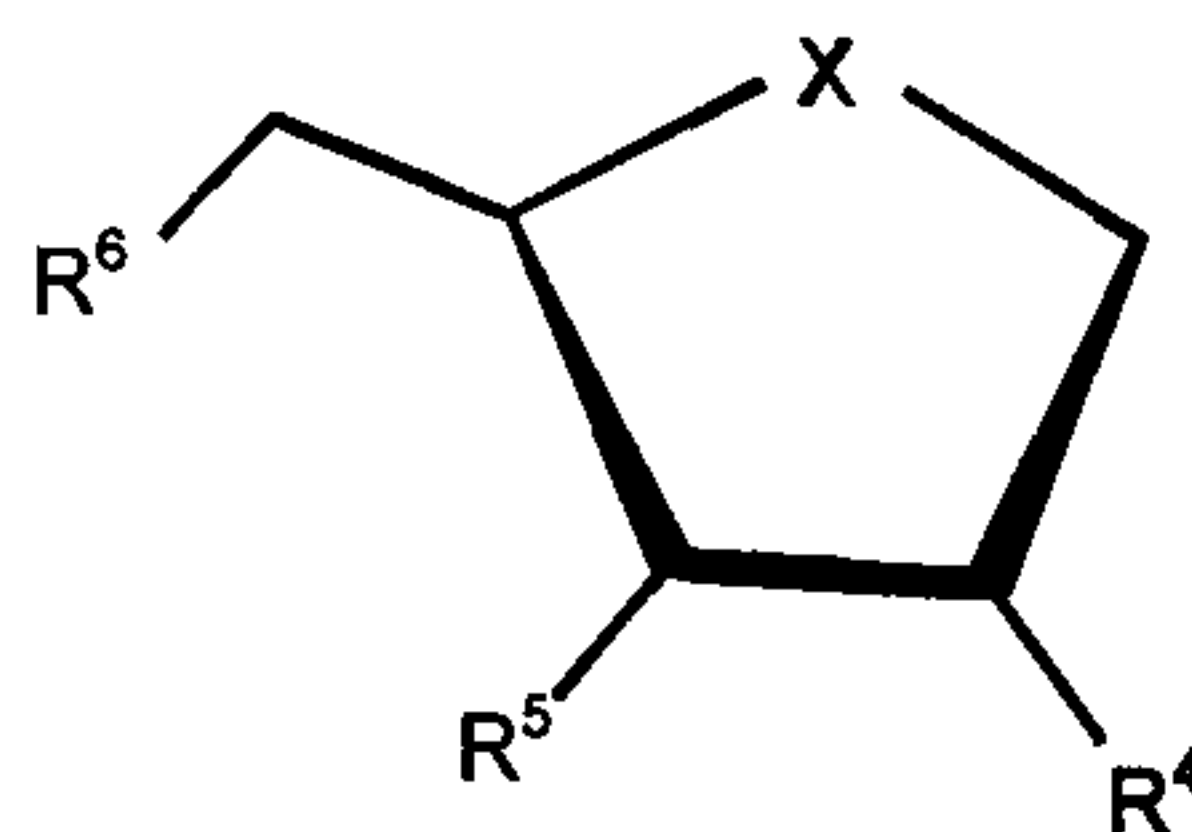
(III)

wherein R^1 and R^2 are H or comprise a protecting group and R^3 is selected from the group consisting of H and optionally substituted straight chain, branched, or cyclic, saturated or unsaturated hydrocarbon radicals and their protected derivatives;

10

- (b) providing a 5-membered heterocycle ring compound of the general formula (IV),

15



20

(IV)

wherein $X = S$ and R^4 , R^5 and R^6 are selected from the group consisting of OH and a protected hydroxyl group;

25

- (d) reacting the cyclic sulfate with the 5-membered heterocycle ring compound to produce an intermediate compound having an internal salt structure comprising a positively charged heteroatom X and a negatively charged sulfate counterion; and

30

- (d) removing any protecting groups from said intermediate compound.

39. The process as defined in claim 38, wherein said reacting of said cyclic sulfate and said heterocycle ring compound is performed in a polar solvent.

40. The process as defined in claim 39, wherein said polar solvent
5 comprises hexafluoroisopropanol.

41. The process as defined in claim 38, wherein said cyclic sulfate is derived from D-glucose.

10 42. The non-therapeutical use of the compound (I) of claim 34 for inhibiting the activity of a glucosidase enzyme.

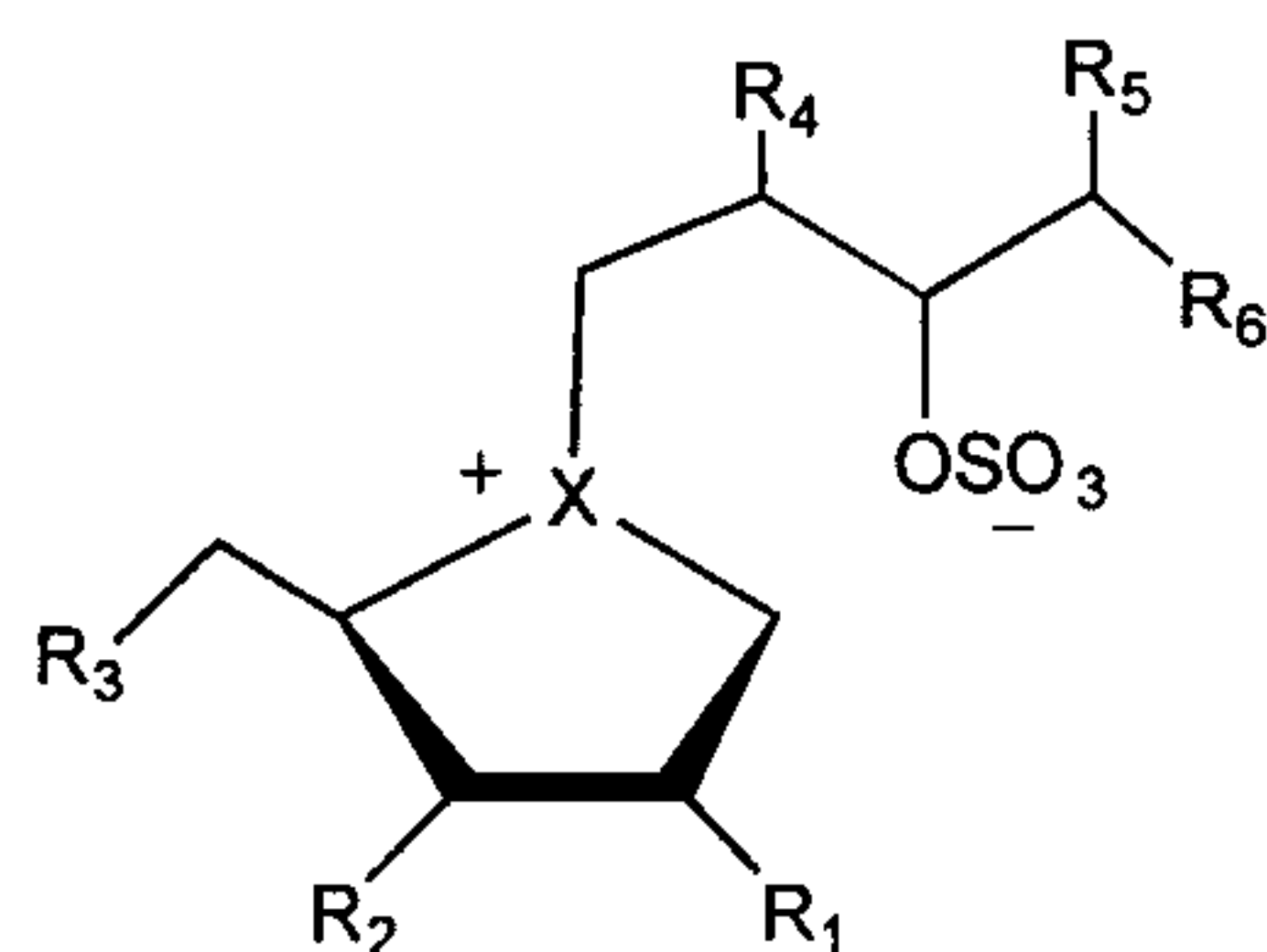
43. The use as defined in claim 42, wherein said glycosidase enzyme is selected from the group consisting of intestinal maltase-glucoamylase and pancreatic
15 alpha amylase.

44. A pharmaceutical composition comprising an effective amount of a compound according to claim 34 together with a pharmaceutically acceptable carrier.

20 45. The use of a therapeutically effective amount of a compound according to any one of claims 34-36 in the manufacture of a medicament for treating a carbohydrate metabolic disorder.

46. The use of claim 12, wherein said carbohydrate metabolic disorder is
25 non-insulin dependent diabetes.

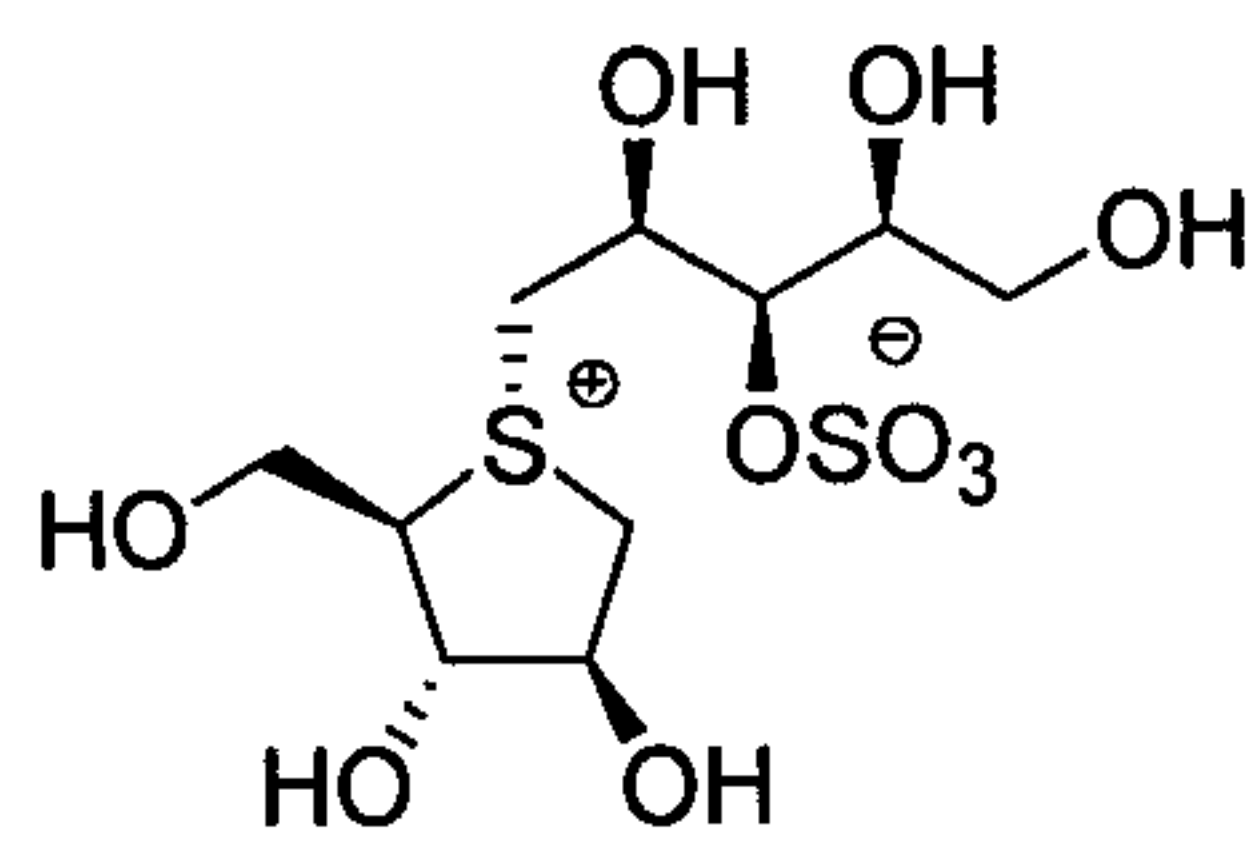
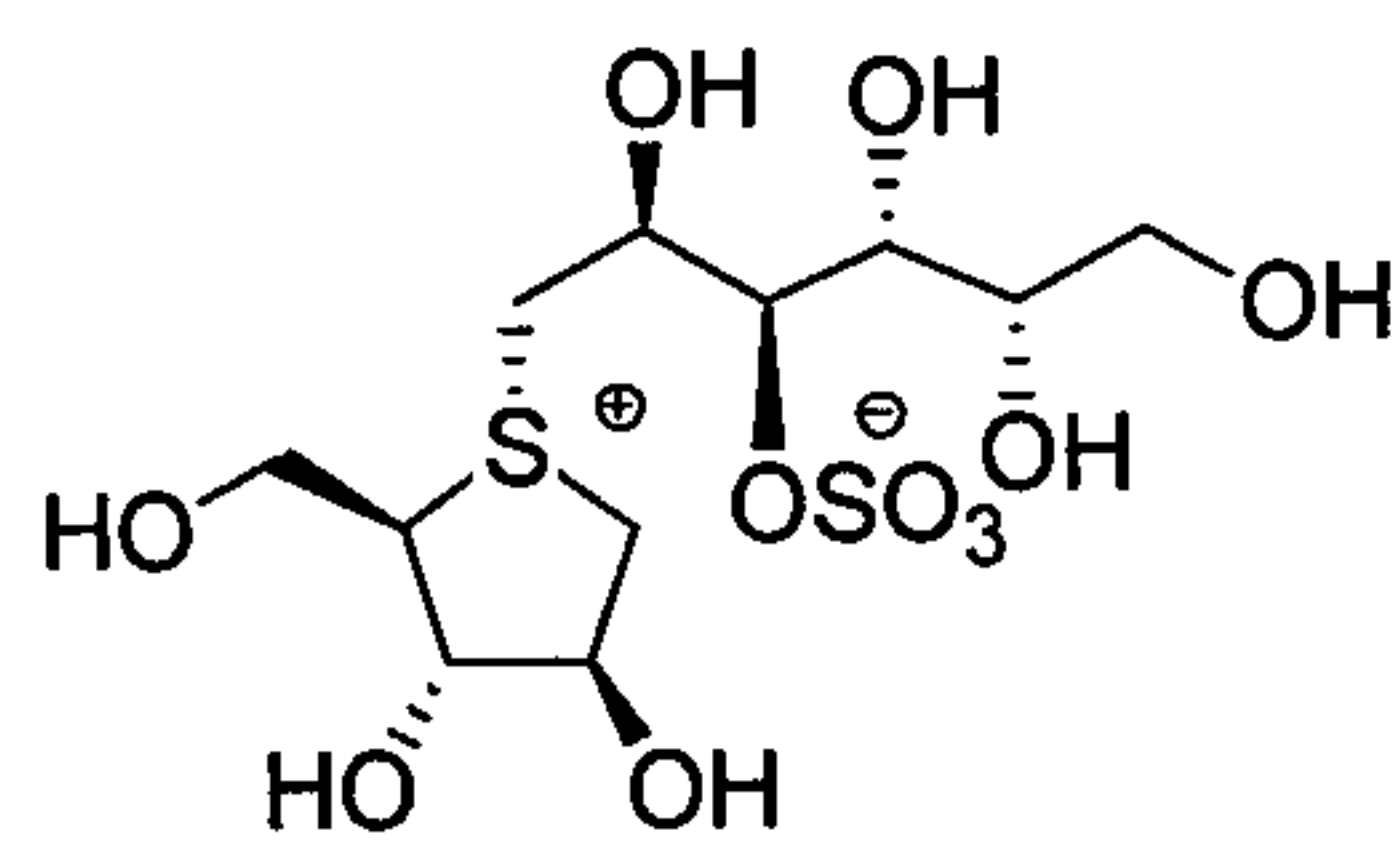
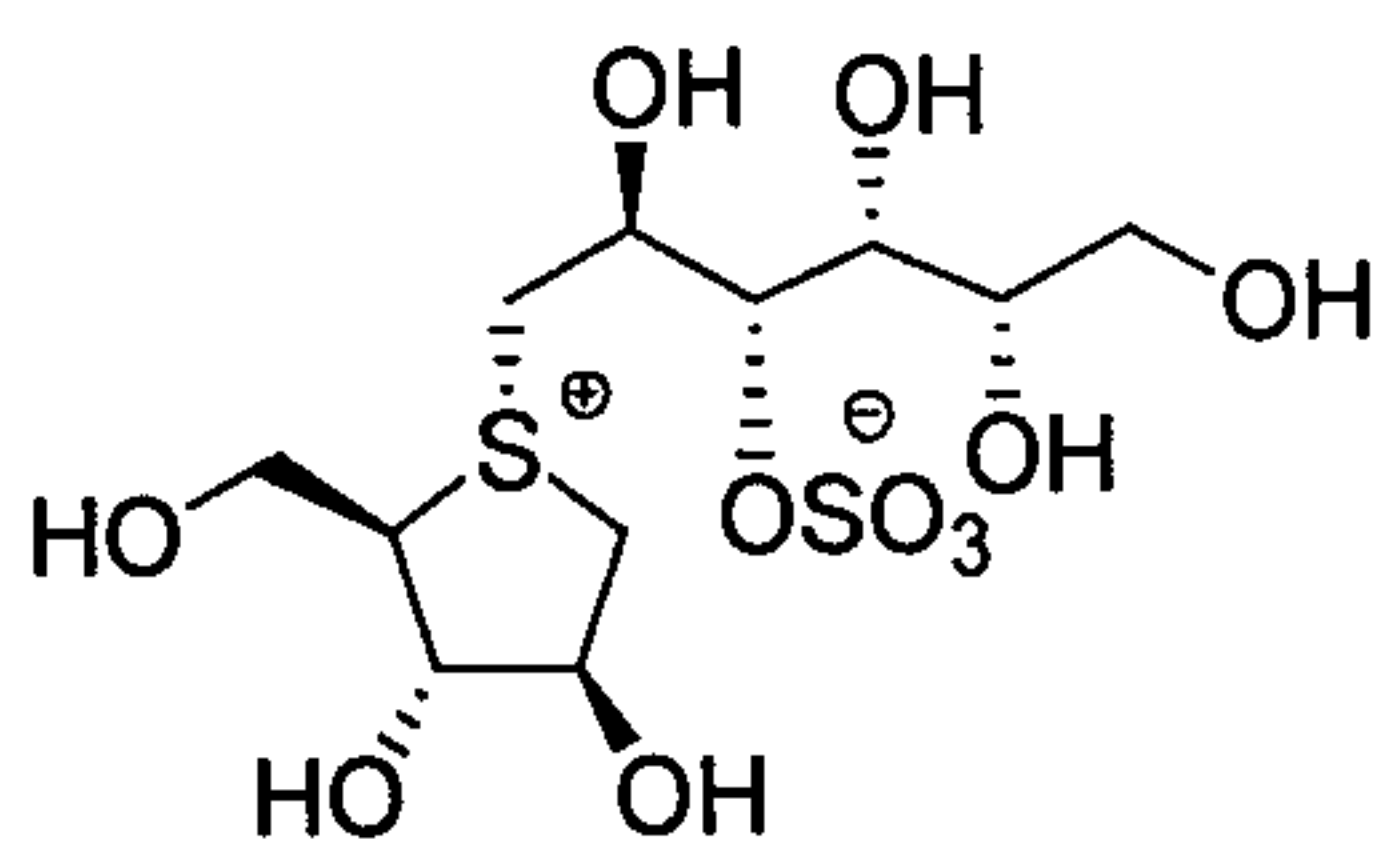
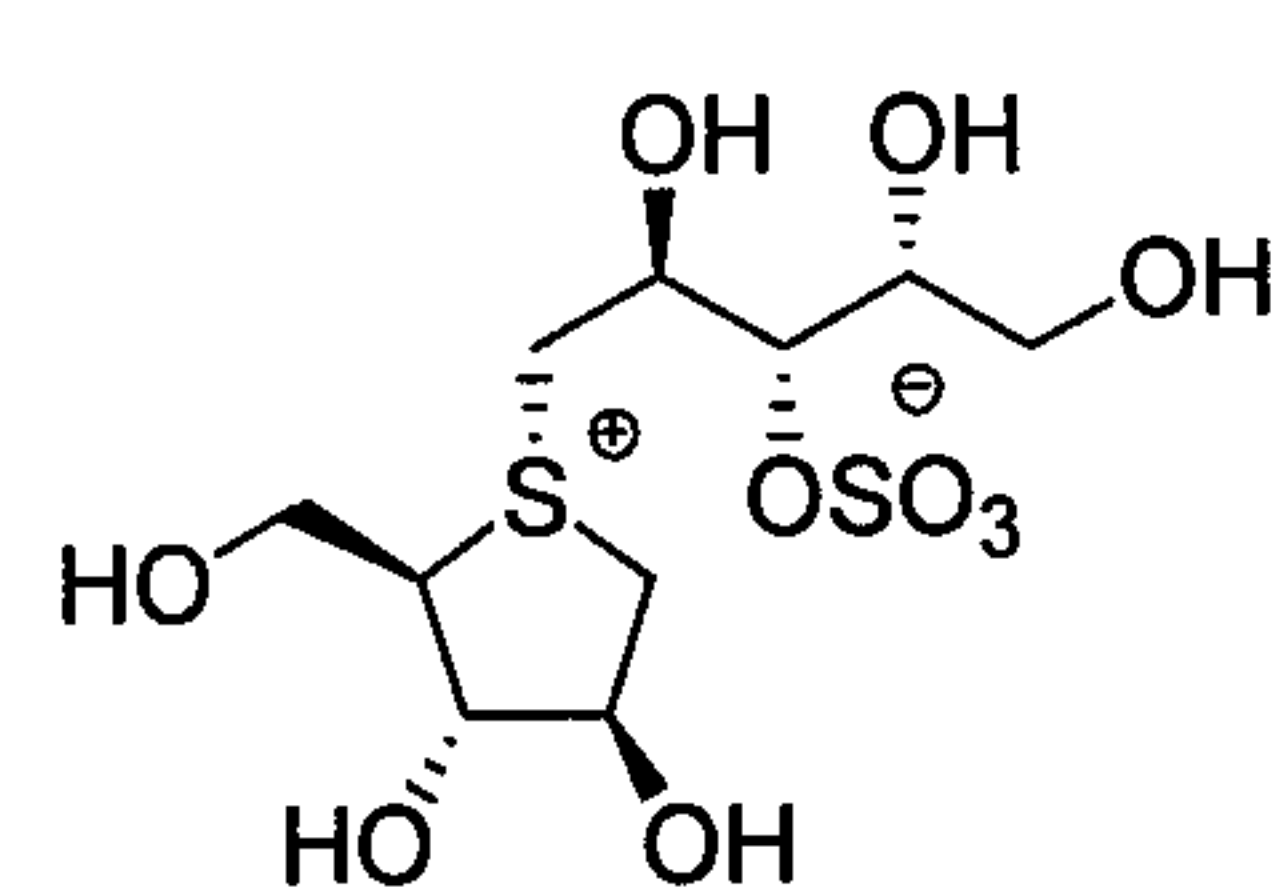
47. A non-naturally occurring compound selected from the group consisting of compounds represented by the general formula (I) and stereoisomers and pharmaceutically acceptable salts thereof:
30



(I)

where X is selected from the group consisting of S, Se and NH; R₁, R₂, R₃, R₄ and R₅ are the same or different and are selected from the group consisting of H, OH, SH, NH₂ and halogens; and R₆ is selected from the group consisting of H, OH and alkyl, alkenyl, alkynyl, aryl and alkoxy substituents, wherein the carbon side chain connected to the X heteroatom of formula (I) comprises between 4-10 carbon atoms.

48. The compound as defined in claim 47, wherein R₆ is an alditol chain.
49. The compound as defined in claim 47, wherein R₆ comprises between 1 and 3 carbons.
50. The compound as defined in claim 47, wherein said side chain is a polyhydroxylated acyclic side chain comprising 5 or 6 carbons.
51. A compound as defined in claim 47, selected from the group consisting of compounds 94, 95, 96 and 97 set forth below

**94****95****96****97**

5

10

Sheet 1/4

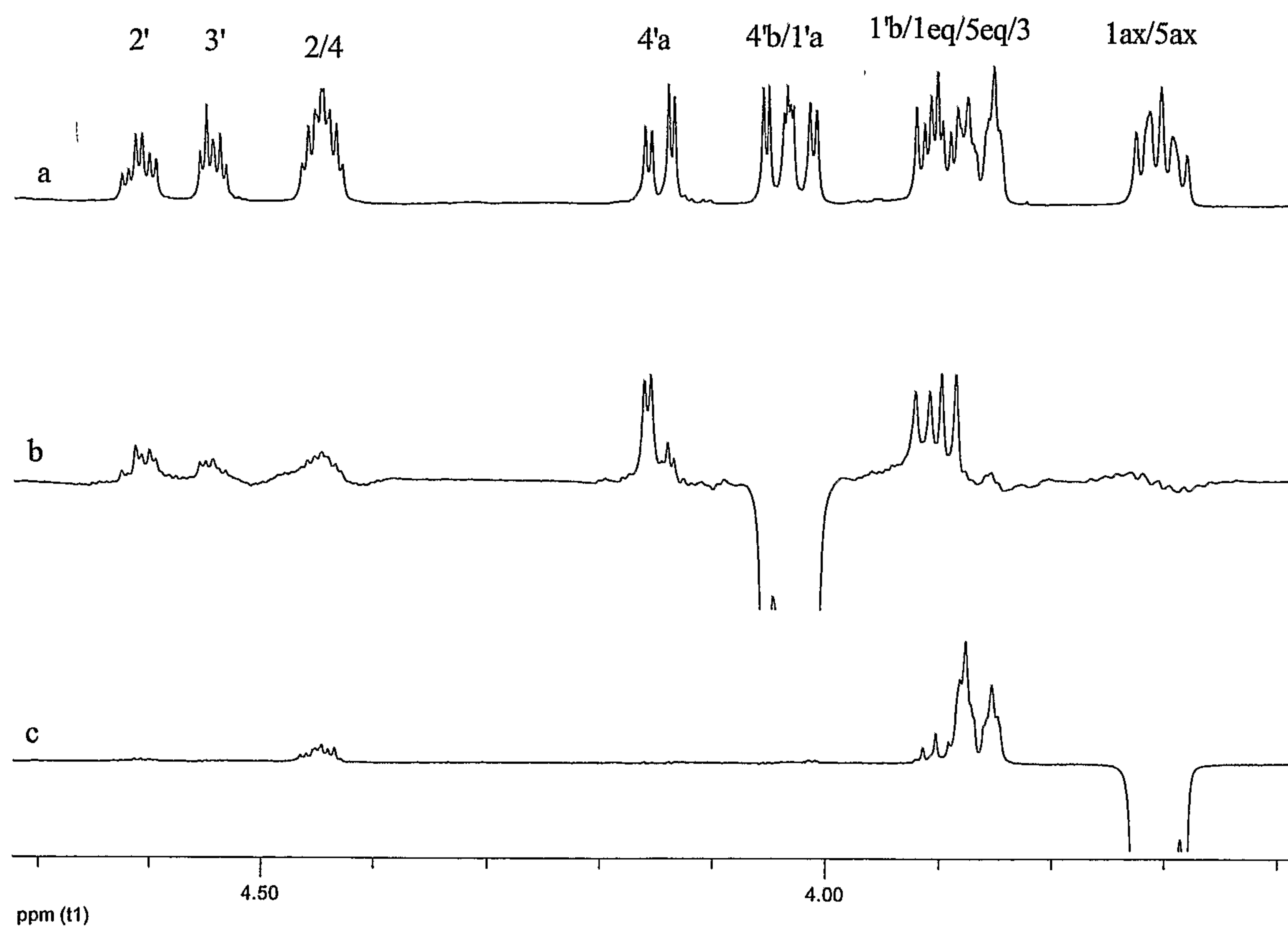


Fig. 1

Sheet 2/4

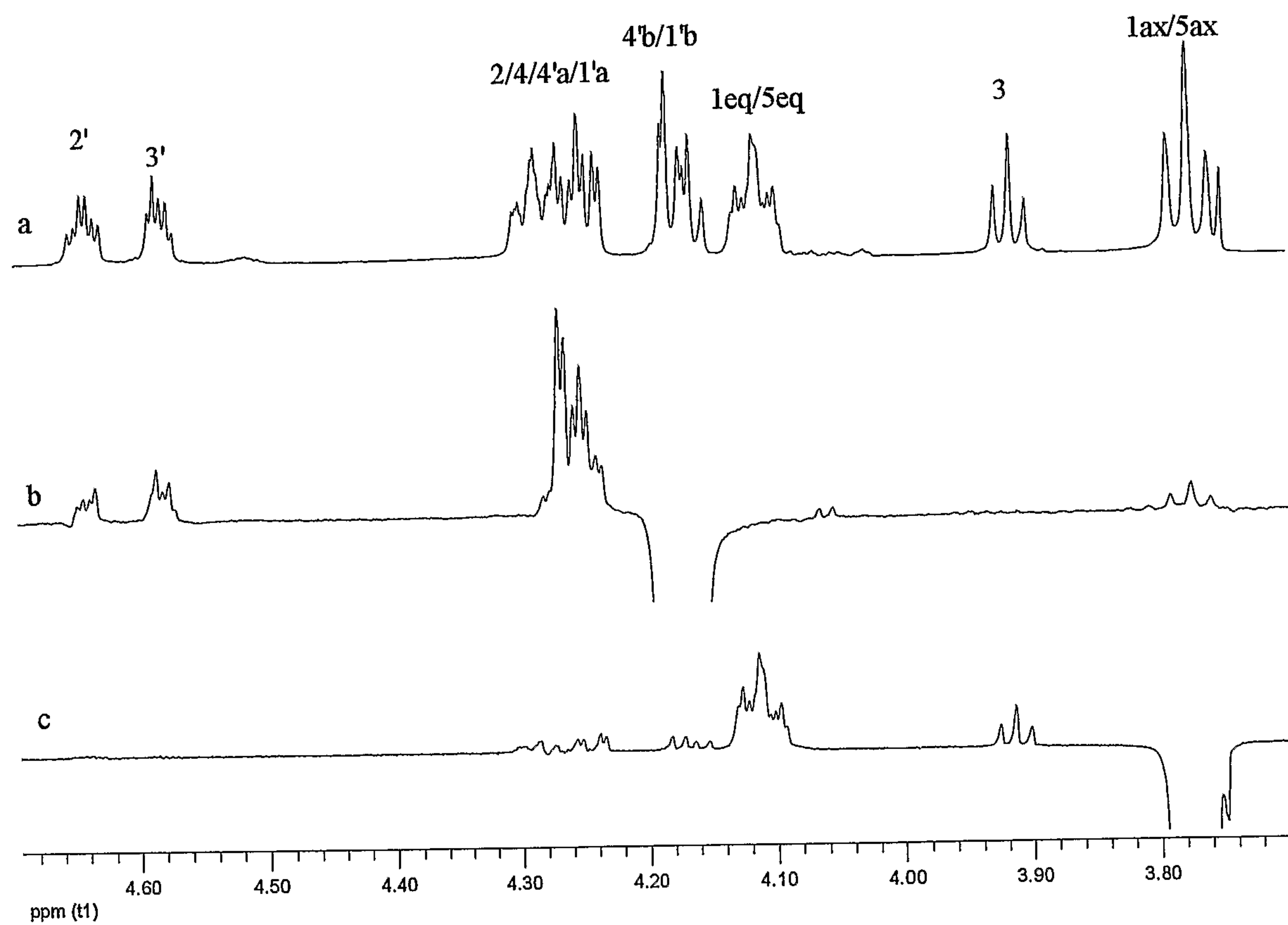


Fig. 2

Sheet 3/4

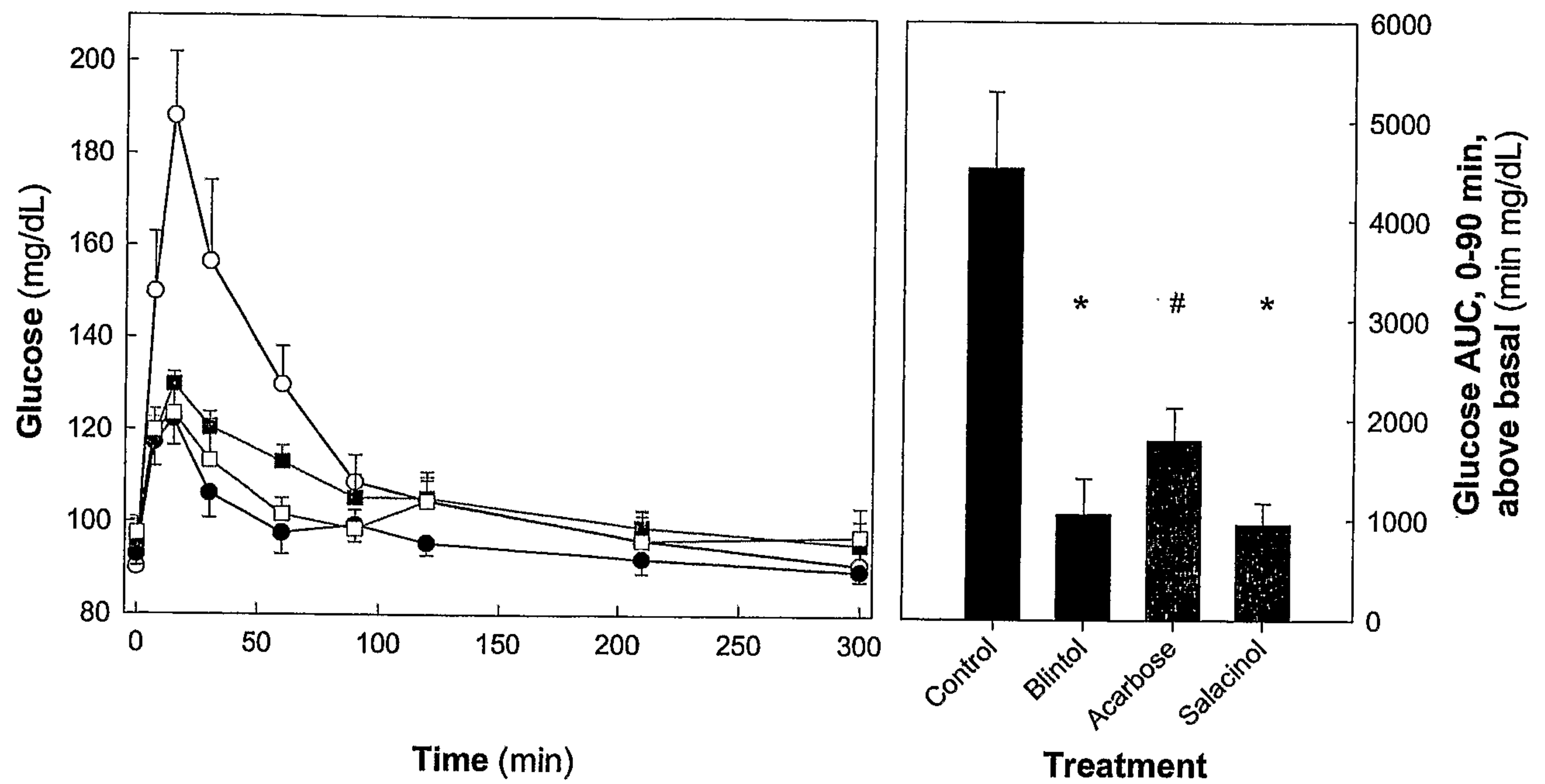


Fig. 3

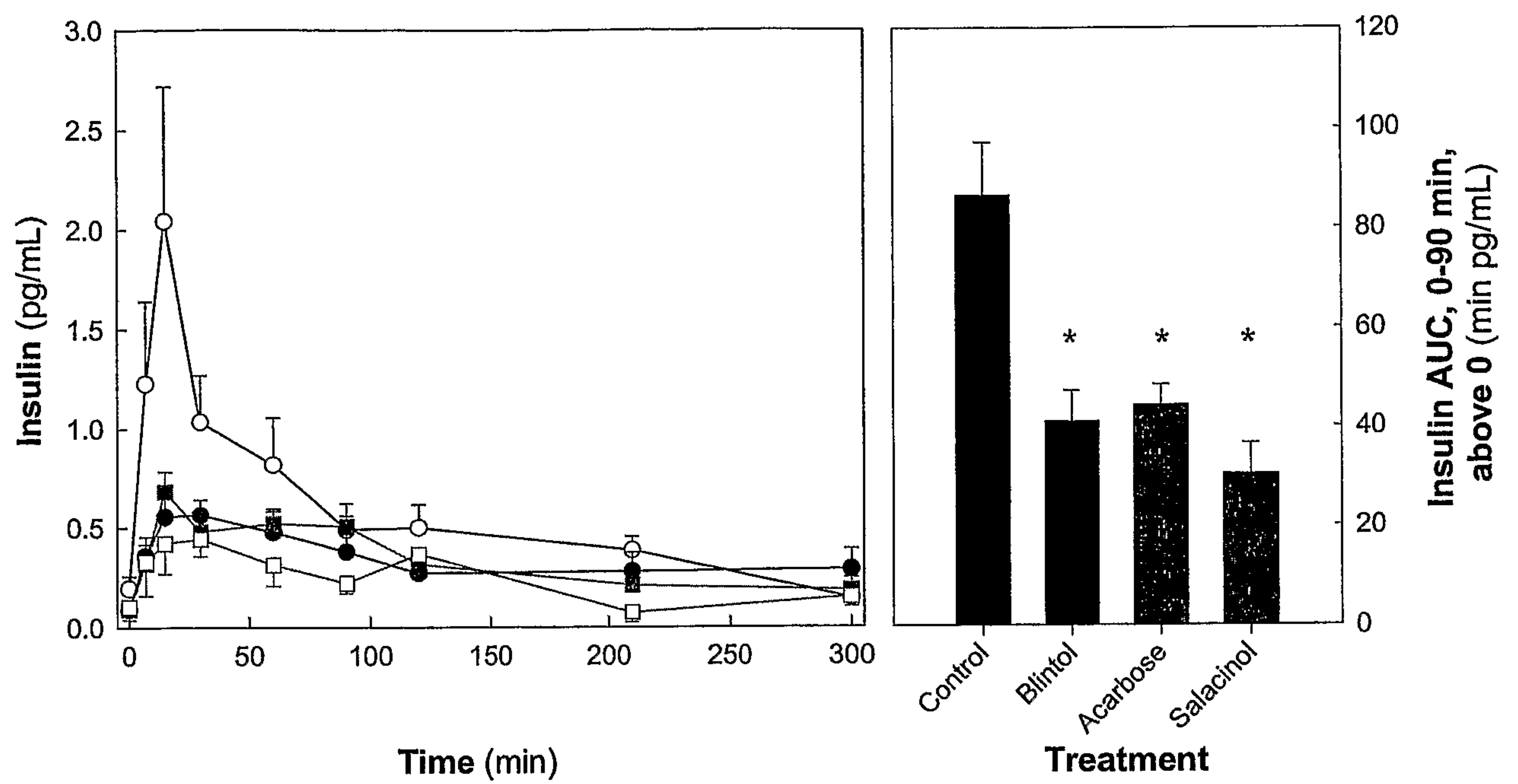
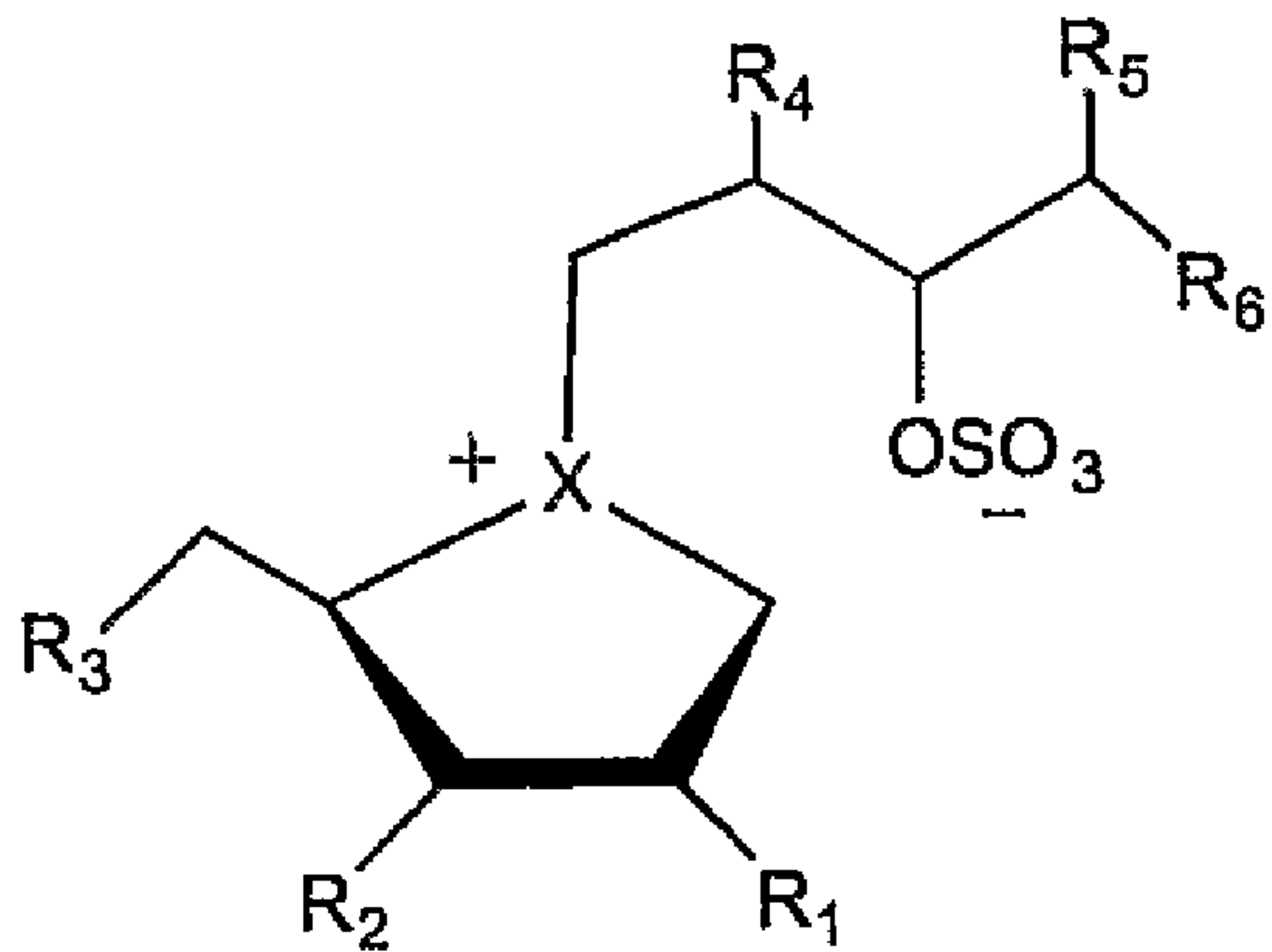
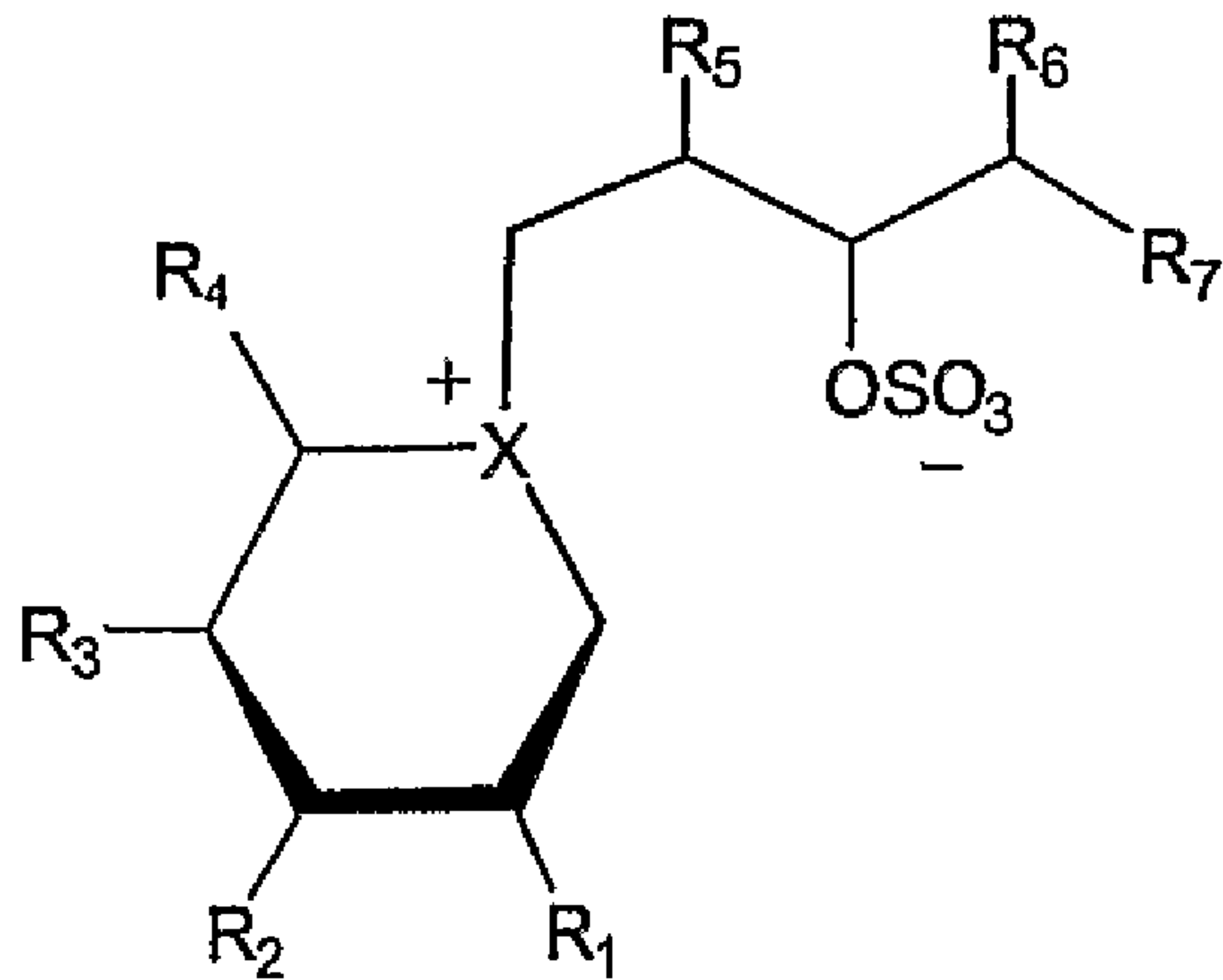


Fig. 4



(I)



(II)