Progress in Kdo-glycoside chemistry

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Abstract

Glycosylation chemistry of 3-deoxy-D-*manno*-oct-2-ulosonic acid units has been considerably developed within the last decade. This review covers major achievements with respect to improved yields and anomeric selectivity as well as suppression of the elimination side reaction via selection of dedicated protecting groups and appropriate activation of the anomeric center.

Keywords

Kdo; Oligosaccharide; Synthesis; Glycal; Glycosyl donor

Introduction

3-Deoxy-D-*manno*-oct-2-ulosonic acid (Kdo) is a non-mammalian higher-carbon saccharide which occurs in the cell wall glycans of Gram-negative bacteria, but has also been found in plants and algae.[1–3] Kdo residues are of particular biomedical importance as constituents of bacterial lipopolysaccharides (LPS) as well as capsular polysaccharides.[4] Due to their non-mammalian origin, Kdo units are recognized by components of the native and adaptive immune system as demonstrated by binding studies and crystal structures of liganded Kdo units in the binding sites of germ-line encoded antibodies and in complex with Toll-like receptor 4/MD-2.[5] In LPS, Kdo is part of the structurally conserved inner core region, which interlinks the lipid A region to the outer core sugars and the O-antigenic polysaccharide. Figure 1 illustrates the most relevant Kdo-structures in the inner core of Gram-negative bacterial LPS.[4] The synthesis of these oligosaccharide ligands and neoglycoconjugates derived therefrom is thus regarded as a highly relevant task for development of glycoarrays, immunoreagents and vaccines.

The synthesis of glycosides of Kdo shares several features with the structurally related 5-*N*-acetyl neuraminic acid (Neu5Ac), albeit with the difference that Kdo glycosides have been found in both anomeric configurations. Most of the synthetic work on Kdo chemistry in the past had been directed to the preparation of α-glycosides. Glycosylation reactions of Kdo donors are impaired by facile formation of a 2,3-dehydro product (glycal ester), the strong deactivation of the anomeric position by the adjacent carboxylic group and the absence of a stereodirecting group next to the anomeric center which limits stereochemical control of

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product formation. In addition, the increased steric load being present across a ketosidic linkage and the instability of the ketoside under acidic conditions has to be considered (Fig 2). Glycosylation reactions of Kdo monosaccharide derivatives with primary alcohols and reactive glycosyl acceptors, however, are usually doable in good yields and anomeric selectivities.

The unfavorable properties, however, are much more demanding in the assembly of Kdo oligomers such as those depicted in Figure 1, resulting in many cases in poor to modest yields only and requiring substantial efforts in product purification. A number of reviews covering the synthesis of Kdo and important Kdo-containing bacterial oligosaccharides have been published previously and the reader should consult these for further information.[6] The present review summarizes and highlights recent accomplishments, which have been reported in the past decade in the field of Kdo-oligosaccharide synthesis with a focus on α-ketosides, but will also cover selected examples for β-Kdo glycosides. The synthesis of the Kdo monosaccharide is beyond the scope of this review, but the reader is referred to a past review and two reports for multigram-preparation of Kdo.[7–9]

Kdo halide donors

Kdo bromide donors have mostly been used in the 1980ies and 1990ies under Koenigs-Knorr and Helferich conditions with varying success in the synthesis of Kdo oligosaccharides. The donors are easily available by reaction of the anomeric acetate in HBr/AcOH or $TiBr_4$ in CH_2Cl_2 and are fairly stable when stored at low temperature. The use of toxic heavy-metal based promoters, the modest stereoselectivities and facile elimination side reaction leading to glycal ester byproducts, however, limits the use of Kdo bromide donors, in particular for preparation of oligosaccharides in a larger scale.

Kdo fluoride donors are accessible from the respective hemiketal precursors such as **1** and **3** by reaction with DAST, which leads to preferential formation of the α-anomeric fluorides, while reaction of **3** with *N,N*-diethyl-α,α-difluoro-(*m*-methylbenzyl)amine (DFMBA) mainly gives the β-anomeric product **4**.[10] Both reactions proceed with concomitant formation of glycal ester byproducts **5** and **6**. Another option is the conversion of the anomeric acetate **7** with HF in pyridine to yield the α-fluoride **8** (Scheme 1).[11]

The groups of Kusumoto and Fukase have to be credited for developing these Kdo fluoride donors into a methodology, which is suitable for efficient coupling to protected lipid A derivatives. As a highlight, the total synthesis of R*e*-LPS from *Escherichia coli* is to be mentioned, wherein the Kdo fluorides served for constructing the α-(2→6)-linkage to the glucosamine disaccharide backbone as well as introduction of the lateral Kdo unit in an α-(2→4)-linkage.[12] The introduction of bulky silyl substituents, or alternatively, the locking of the pyranose ring in a skew/boat conformation by an isopropylidene group at O-4 and O-5, allowed for significant improvement of the α-selectivity in the glycosylation reaction, presumably by sterically shielding the β-face.[13] In general, however, an excess of donor and promoter has to be employed and significant amounts of glycal ester byproducts **5** and **6** were formed. A useful feature of the fluoride donors is the option of a glycodesilylation

approach induced by liberation of HF from the $BF_3 \cdot Et_2O$ promoter. Two recent examples are illustrated in schemes 2 and 3.

In 2007, Fukase *et al* succeeded in synthesizing an LPS fragment from *Helicobacter pylori*. 10 Coupling of the 6-*O*-triethylsilyl protected disaccharide acceptor **9** was performed using 10 equivalents of promoter and 2.6 equivalents of fluoride donor **4** to give a high yield of the α-(2→6)-linked trisaccharide **10**. Molecular sieves 5Å had been added to scavenge HF, which was formed in the reaction (Scheme 2). In 2008, the group of Boons synthesized a trisaccharide corresponding to a Kdo-lipid A fragment of *Neisseria meningitidis* LPS along similar lines (Scheme 3).14

Coupling of donor **2** to 3'-*O*-acylated disaccharide acceptor **11** was achieved with only a slight excess of promoter (relative to **11**) and produced a 9:1 α/β mixture of trisaccharide **12**. Separation of the anomeric mixture was achieved after 4'-*O*-phosphotriester formation with Watanabe reagent, which gave **13** in 88% yield.

The reactivity of these Kdo donors, however, also depends on their protecting group patterns. "Disarming" substituents introduced at the side chain lead to decreased yields in glycosylation reactions. In 2011, Ichiyanagi *et al* employed the 7,8-di-*O*-benzoyl protected donor **14** for coupling reactions to 4-OH and 8-OH Kdo acceptors (Scheme 4).15 Again, a large excess of promoter was employed and triethylamine was added to capture released HF and to increase the product yield. While coupling to the 4-OH group of diol acceptor **15** produced a good yield of the disaccharide **16** and in fair anomeric selectivity, the α-(2→8)-linked disaccharide **18** was obtained in a rather poor yield only. The authors did not disclose the amount of elimination product **19** formed.

3-Iodo-Kdo fluoride donors

In order to work around the lack of stereochemical control, auxiliary stereodirecting groups at C-3 such as 3-iodo, 3-phenylselenyl and 3-thio groups had previously been used for Kdo-glycoside formation, but also in the field of neuraminic acid chemistry.17,18 Recently the favorable stereodirecting effect of a 3-iodo substituent has been combined with a fluoride leaving group. In contrast to fluoride donors **2**, **4** and **14**, 3-iodo-Kdo donors do not require bulky or acetal type protecting groups at O-4 and O-5, which tend to increase the formation of the elimination products. Furthermore, these donors are easily accessible in good overall yields from Kdo glycal esters via an acetoxyiodination reaction to give mainly the 2,3-*trans*-diaxial products followed by treatment with HF-pyridine (Scheme 5).19,20 This way, fluoride **22** was obtained as single anomer and was bench-stable at room temperature for several weeks.

The favorable glycosylation properties were demonstrated then in the assembly of the α-(2→4)- and α-(2→8)-linked Kdo disaccharides **26** and **29**, respectively.21 Reaction of an equimolar amount of fluoride **22** with diol **23** afforded **24** as single anomer with only minor formation of glycal ester byproduct (4%). The glycodesilylation approach was equally effective using the 8-*O*-TES derivative **27** to yield **28** in 62% yield. Both 3-iodo disaccharides were reduced in excellent yields to the corresponding Kdo-derivatives **26** and

29, respectively, using atom transfer hydrogenation with lauroyl peroxide in refluxing cyclohexane, thereby avoiding the use of toxic tin reagents.22

Eventually donor **22** was applied to prepare the *Chlamydia* and *Chlamydophila* specific Kdo trisaccharides (Scheme 6). Indeed, glycosylation of the tetraol **30** could be directed in a regioselective fashion to provide the 4,8-branched trisaccharide. The use of 2.4 equivalents of donor **22** was sufficient to give trisaccharide **31** in 58% yield accompanied by isolation of the α-(2→7)-linked regioisomeric trisaccharide (7%) and elimination product **20** (11%). Subsequent *O*-acetylation and deiodination was straightforward to give the branched *Chl. psittaci* trisaccharide **31** in high yield and in a minimum number of steps. The strategy was then further elaborated to include a disaccharide fluoride donor derived from the respective disaccharide glycal and again capitalizing on a glycodesilylation approach (Scheme 7). Reaction of the 8-*O*-TES glycal ester **34** with donor **22** afforded disaccharide glycal ester intermediate, which was directly subjected to acetoxyiodination giving **35** in 57% yield. Conversion into fluoride **36** followed by TMSOTf-promoted coupling to diol **23** proceeded smoothly (→ **37**) as well as the subsequent steps (→ **38**, **39**).

While the electron-deficient double bond in glycal ester **34** was fully compatible with the glycosylation conditions, electron rich alkenes compete via an iodonium ion transfer reaction which leads to significant consumption of donor due to formation of the elimination product **20**. This feature excludes allyl protecting groups on 3-iodo-Kdo glycosyl donors and glycosyl acceptors.23

As seen from the previous examples, glycosylation of Kdo 4,5-diol acceptors never gave any (2→5)-linked products, due to the steric crowding at the acceptor site as well as expected for a ketosidic linkage being close to an ester group at the anomeric center of the donor. In fact, donor **22** also failed in forming a 5-*O*-substituted product when subjecting the "armed" 4,7,8-tri-*O*-benzyl Kdo acceptor **40** to the aforementioned glycosylation conditions. Hence, the "armed" glycosyl donor **42** was elaborated, and under careful temperature control the first successful 5-*O*-glycosylation with a Kdo donor derivative to produce **43** was accomplished in 71% yield, again with no β-product detected and only very minor formation of glycal ester **41**.24 The ensuing sequence of hydrogenation/reacetylation and global deprotection gave the α-(2→5)-linked Kdo disaccharide **44** (Scheme 8). This approach opens future perspectives for the assembly of larger fragments of the *Acinetobacter baumannii* LPS core region.

Kdo glycal donors

Kdo glycal ester derivatives can also directly serve as glycosylating agents of reactive glycosyl acceptor derivatives upon suitable activation, mostly using triflic acid as promoter. The merit of this approach is seen in a straightforward introduction of spacer groups on Kdo monosaccharide units allowing for subsequent application in neoglycoconjugate synthesis and generation of ligands for glycoarray preparation. As examples, following the first reports by Achiwa *et al*,25 reaction of glycal ester **20** with primary alcohols **45** and **47**, respectively, promoted with AgOTf/TMSOTf and exploiting the stereochemical control of a

temporary phenylselenyl auxiliary group were high-yielding and α-selective and furnished the protected spacer glycosides **46** and **48**.26,27

In 2006, the group of Takahashi developed a high-yielding and α-selective methodology on the basis of the electron-rich glycal ester **49**, which -in the presence of triflic acid as promoter- could directly be activated leading to 3-iodo-Kdo glycosides when reacted with "armed" glycosyl acceptors (Scheme 10).28 This way, the 3-iodo-Kdo-(2→6)-, (2→3)- and (2→8)-linked *gluco*-, *galacto*- and Kdo-disaccharides **50-52** were isolated in very good yields and α-selectivities.

A similar α-glycoside formation of 3-iodo-Kdo had previously been observed by Oscarson in a TfOH-promoted reaction of glycal ester **20** with a spacer alcohol nucleophile.26

An iterative sequence was then elaborated starting from 2,3-di-*O*-benzyl-4,5-*O*-benzylidene mannitol **53**, which was converted into the open-chain Kdo precursor **54**. NIS/TfOH promoted coupling with the perbenzyl Kdo donor **49** gave an excellent yield of the α-(2→8)-pseudodisaccharide **55** followed by ring-closure and elimination of the thio-appendix to regenerate the glycal ester moiety (**56**). Repetition of the sequence and coupling of trisaccharide glycal **57** to glucoside acceptor **58** was carried out with reduced yield and anomeric selectivity to give tetrasaccharide **59**. Removal of the iodo and benzyl substituents and ester hydrolysis afforded **60**. It might be noted that α-(2→8)-Kdo trimers have not yet been found in nature.

Recently, the group of Mong developed a strategy towards β-Kdo glycosides exploiting similar reactions of the bis-isopropylidene protected Kdo glycal ester **61**.29 Reactions of **61** with various glycosyl aceptors was promoted by NIS/TMSOTf and led to preferential formation of β-glycosides **62a-e**, due to the stereodirecting effect of the equatorial 3-iodo-group (Scheme 12). The predominant formation of the D-*glycero*-D-*galacto* configuration at C-3 can be rationalized on the basis of a steric collision of the incoming nucleophile with one of the methyl groups of the 4,5-*O*-isopropylidene group, which effectively shields the top position. The ratio of epimeric iodo products was also influenced by the choice of solvent and amount of NIS in the reaction. The presence of 2 equivalents of NIS and a MeCN-CH_2Cl_2 solvent mixture led to improved β-selectivity. Dehalogenation of **63a-e** under radical conditions generated the corresponding Kdo-glycosides **64a-e**.

The methodology was further expanded to include β-(2→7)-linked Kdo di- and trimers, which correspond to fragments of capsular polysaccharides from *E. coli*, *N. meningitidis* and *Sinorhizobium meliloti* strains (Scheme 13).30,31 First, the glycal glycosyl acceptor **65** was derived from **61** via selective cleavage of the side-chain acetonide with aqueous Zn-nitrate followed by regioselective 8-*O*-benzylation and conversion into the methyl β-ketoside **66** in a 6:1 diastereomeric ratio. Reaction of **66** with glycal ester **61** afforded disaccharide **67** in 60% yield. The sequence of protecting group manipulation was repeated (→**68**) followed by a third glycosylation step and eventually provided the trimer **69**. Simultaneous removal of three iodo-substituents under radical conditions gave trisaccharide **70**, which, however, was not deprotected.

Kdo thioglycoside donors

Kdo thioglycoside donors allow for various activation protocols using thiophilic promoters, but are susceptible to pronounced elimination reactions with less reactive glycosyl acceptors. These donors have mainly been applied for the preparation of spacer glycosides, in particular of those with a β-anomeric configuration.32,33 In 2007, Oscarson *et al* published a detailed and systematic model study with several Kdo thioglycoside donors equipped with acetyl, benzoyl and isopropylidene protecting groups in different solvents and with variations of reaction temperature and activating agents such as dimethyl(methylthio)sulfonium trifalte (DMTST), NIS/AgOTf, NIS and IBr.34 In short, this investigation showed preferential formation of β-ketosides at low temperatures, a shift towards higher α/β ratios in ether solvents (at the expense of reduced yields). Preferred formation of α-glycosides was again seen when using 4,5-*O*-isopropylidene protected donors. The moderate anomeric selectivities with thioglycoside donors are also evident in a pentasaccharide synthesis by Baasov, wherein the Kdo fluoride **8** was coupled to acceptor **71** to give the α-(2→8)-linked Kdo disaccharide thioglycoside **72** in 65% yield, but subsequent coupling to a triglucosamine acceptor **73** resulted in a 1:1 mixture of anomeric pentasaccharide **74** in moderate yield only (Scheme 14).35

In 2015, however, a new type of conformational locking of Kdo was introduced by the Yang group, who elaborated a multistep synthesis of 5,7-*O*-tethered thioglycosyl donors.36 These donors exert excellent α-selectivity but also suffer from significant elimination, which require 2-4 equivalents of donor in order to achieve high yields. This was even the case with reactive glycosyl acceptors and primary alcohols and since the preparation of the donor is lengthy (Scheme 15), precious donor material is wasted. Nevertheless, this strategy is of significant value, as demonstrated in successful coupling of these donors to all acceptor positions of Kdo, including the unreactive 5-OH group.

Donor synthesis started from selective protection of position 8 of the ethyl 2-β-thio ketoside **75** by dimethoxytrityl (→**76**) and TBS (→**77**) groups, respectively, followed by introduction of a 5,7-*O*-DTBS or benzylidene tether to give the ethyl β-thioglycosides **78**, **82** and **84** in high to modest yields. 4-*O*-Benzoylation gave **79**, **83** and **85**, respectively, and allowed for subsequent preparation of the 8-OH glycosyl acceptors via selective cleavage of the respective 8-*O*-protecting group (→**80**). Reprotection of **80** by a 2-naphthylmethyl group was followed by cleavage of the 4-*O*-benzoyl group to give the 4-OH acceptor **82**. The allyl glycosides **86-88** were then prepared from donors **81**, **83** and **85**, respectively, using tris(4-bromophenyl)ammoniumyl hexachloroantimonate (TBPA) as promoter in MeCN. Notably, the 5,7-*O*-benzylidene protected donor **85** led to a poor anomeric ratio of the allyl glycoside **88**, whereas the DTBS donors **81** and **83** afored only the α-products **86**and **87**.

The Chlamydia-specific Kdo trisaccharide, disaccharide fragments derived therefrom, and the α-(2→5)-linked Kdo disaccharide were then prepared in a protected form (Scheme 16). Acceptor **89** was derived from allyl glycoside **87** by Zemplén transesterification and coupled with 2 equivalents of donor **81** in the presence of TBPA to give the α-(2→4)-linked disaccharide **90** in 72% yield (based on acceptor **89**). DDQ-oxidation then afforded the alcohol **91**, which was reacted with **81** under NIS/TfOH promotion to yield trisaccharide **93**

in a respectable yield. The glycosylation of the β-allyl acceptor **94** was explored using both promoter systems. Again, the TBPA activation was superior in the glycosylation of the "armed" but still unreactive acceptor **94**, as seen in the lower product yield of the NIS/TfOH promoted reaction and conversely, the higher amount of isolated elimination product **92**. In view of the difficult and challenging formation of the α-(2→5)-linkage, this is an excellent result.

Eventually the authors also applied these new donors for the preparation of a protected trisaccharide corresponding to the inner core of *Burkholderia* and *Proteus* LPS (Scheme 17).

The primary alcohol **96** generated from **86** upon DDQ-oxidation was coupled with 4-amino-4-deoxy-L-arabinosyl donor **97** in very high yield but poor anomeric selectivity to give disaccharide **97**.37,38 Subsequent removal of the 4-*O*-benzoyl group was followed by coupling of **98** with donor **81** in the presence of TBPA to give a good yield of the branched trisaccharide **99**.

A similar trisaccharide had previously been obtained with minimized protecting group manipulation via coupling of alcohol **100** with **97** to give an anomeric mixture of **101** and eventually an isolated overall yield of 36% for the 4,5,7-triol **102**.38 Regioselective glycosylation of **102** was then achieved with 1 equivalent of the Kdo bromide donor **103** to give trisaccharide **104** in low yield.

Kdo trifluoroacetimidate donors

A few reports have been published describing the use of *N*-phenyltrifluoroacetimidate (NPTFA) donors of Kdo, which can be activated with TfOH or TBSOTf and TMSOTf as promoters. Fukase *et al* investigated the glycosylating properties of Kdo imidates **105** and **106**, equipped with protecting groups identical to the previously used Kdo fluorides **2** and **4**.39 Coupling of these donors to position 6 of mono- and disaccharide glucosamine acceptors **107** and **110** gave a fair anomeric selectivity but needed considerable excess of donor to achieve high yields of disaccharides **108**, **109** and trisaccharide **111**. Cyclopentyl methylether as well as acetonitrile as solvents led to an improved α-selectivity, and the use of microfluidic conditions reduced formation of the undesirable elimination product (Scheme 18). Trisaccharide **111** was then further transformed into a *Helicobacter pylori* LPS fragment.40

In addition, coupling of donor **105** to Kdo allyl glycoside **112** was performed under similar conditions to give Kdo disaccharide **113** in fair anomeric selectivity (Scheme 19).

A similar anomeric ratio was also observed by Ichiyanagi using the 7,8-di-*O*-benzoyl protected imidate **114** to give disaccharide **16**.41 The authors also employed a related Kdo-phosphite donor, which, however, exhibited poor glycosylating properties.

Kdo 1-*C*-Arylglycal donors

Recently, an indirect method toward β-linked Kdo glycosides was developed via formation of a glycal containing an anomeric carbon-linkage to an electron-rich aromatic group via

ring-closure of olefin **115**.[42] Thus, NIS-treatment of **115** afforded an epimeric mixture of 2-iodo-2-deoxy-*C*-glycosides **116**, which were converted into the corresponding *p*-methoxyphenyl glycal **117** under basic conditions (Scheme 20). Subsequent reaction with a series of alcohols in the presence of NIS proceeded via preferred formation of 2-iodo β-glycosides **118**. The selective formation of the β-glycosides was rationalized on stereoelectronic grounds and on the skewed conformation enforced by the 4,5-*O*-isopropylidene group, thereby preventing the NIS attack from the top face and eventually leading to a pseudo *trans*-diaxial arrangement of the iodo-group and the anomeric OR group (see also Scheme 13). Radical deiodination of the methyl glycoside gave **119** and was followed by oxidative removal of the aromatic appendix to generate the carboxylic function leading to **120**.

Conclusions and Outlook

As illustrated in this review, remarkable progress has been achieved in the past in the synthesis of α-glycosides of Kdo. In particular, locking of the pyranose ring conformation by 4,5-*O*-isopropylidene or 5,7-*O*-TDBS groups provides mainly the α-ketosides, albeit at the cost of a more pronounced elimination side reaction. The 3-iodo-Kdo fluoride donors have been proven to be versatile donors in α-Kdo oligomer assembly with options for block and regioselective synthesis, but have some limitations in selection of protecting groups. As a main very recent accomplishment the first syntheses of α-(2→5)-linked Kdo disaccharides should be mentioned. The stereodirecting temporary 3-iodo-group has also been of value in the construction of β-anomeric Kdo glycosides. Still, the chemistry of β-Kdo units needs to be further developed in the future and presently lags behind its α-anomeric counterparts.

Acknowledgments

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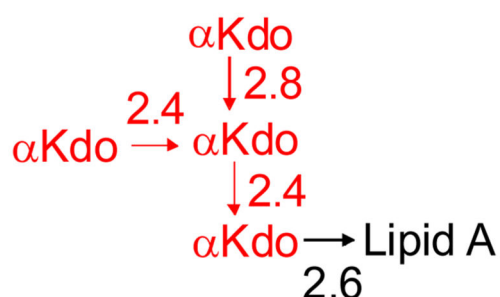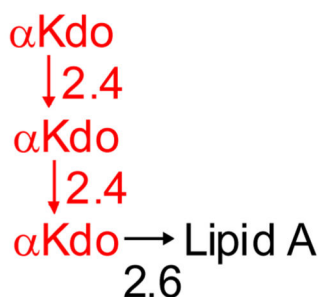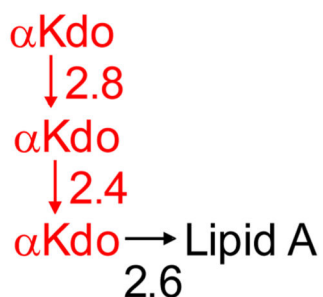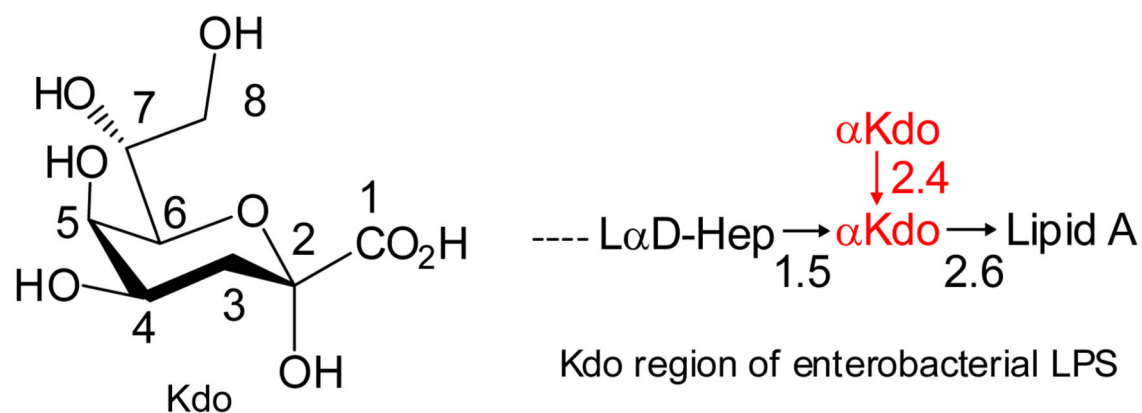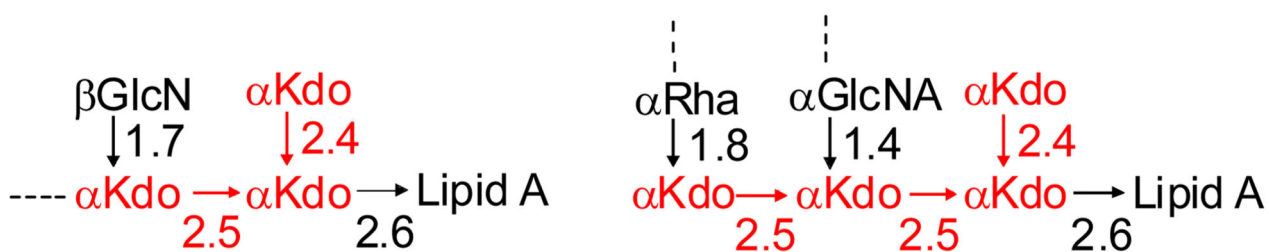
Figure 1.
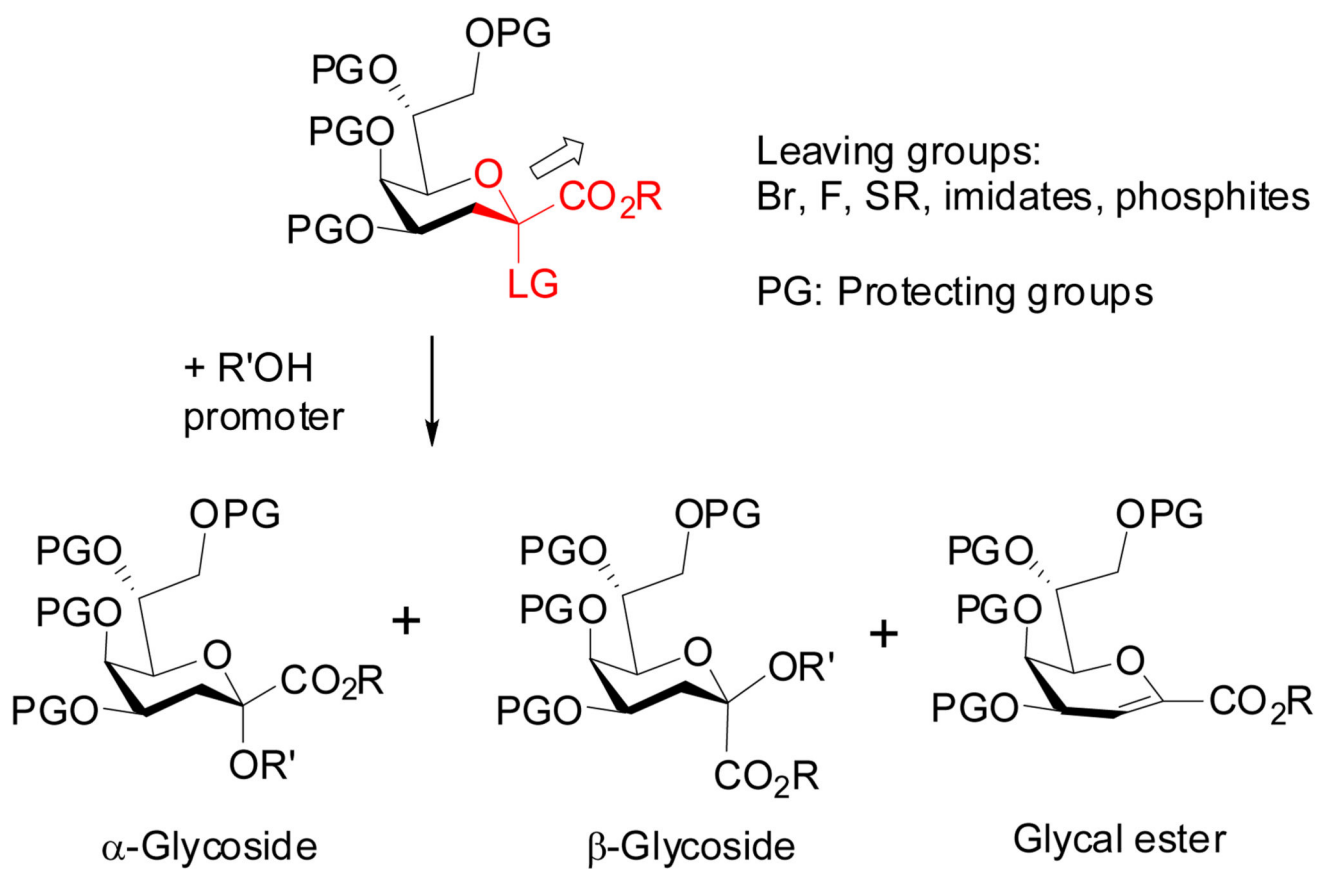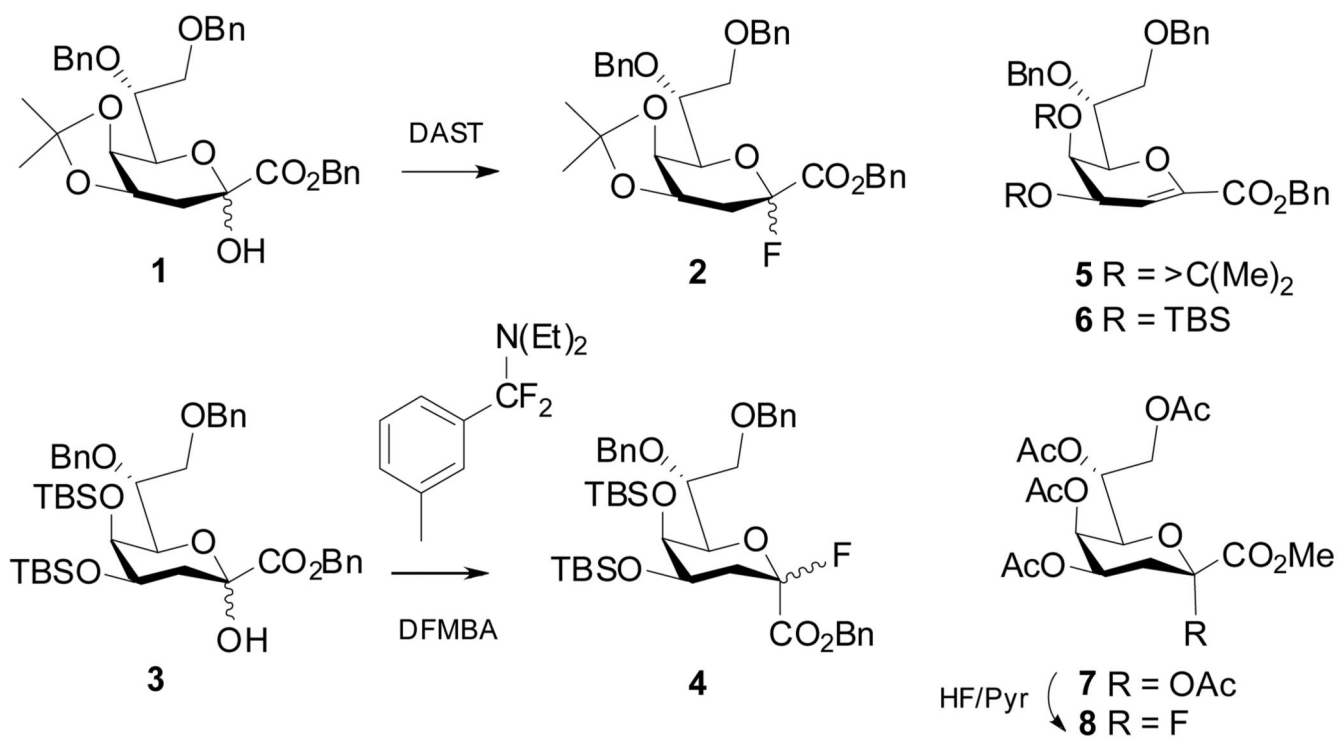Numbering scheme for Kdo and structures of selected Kdo oligosaccharides from pathogenic bacteria.

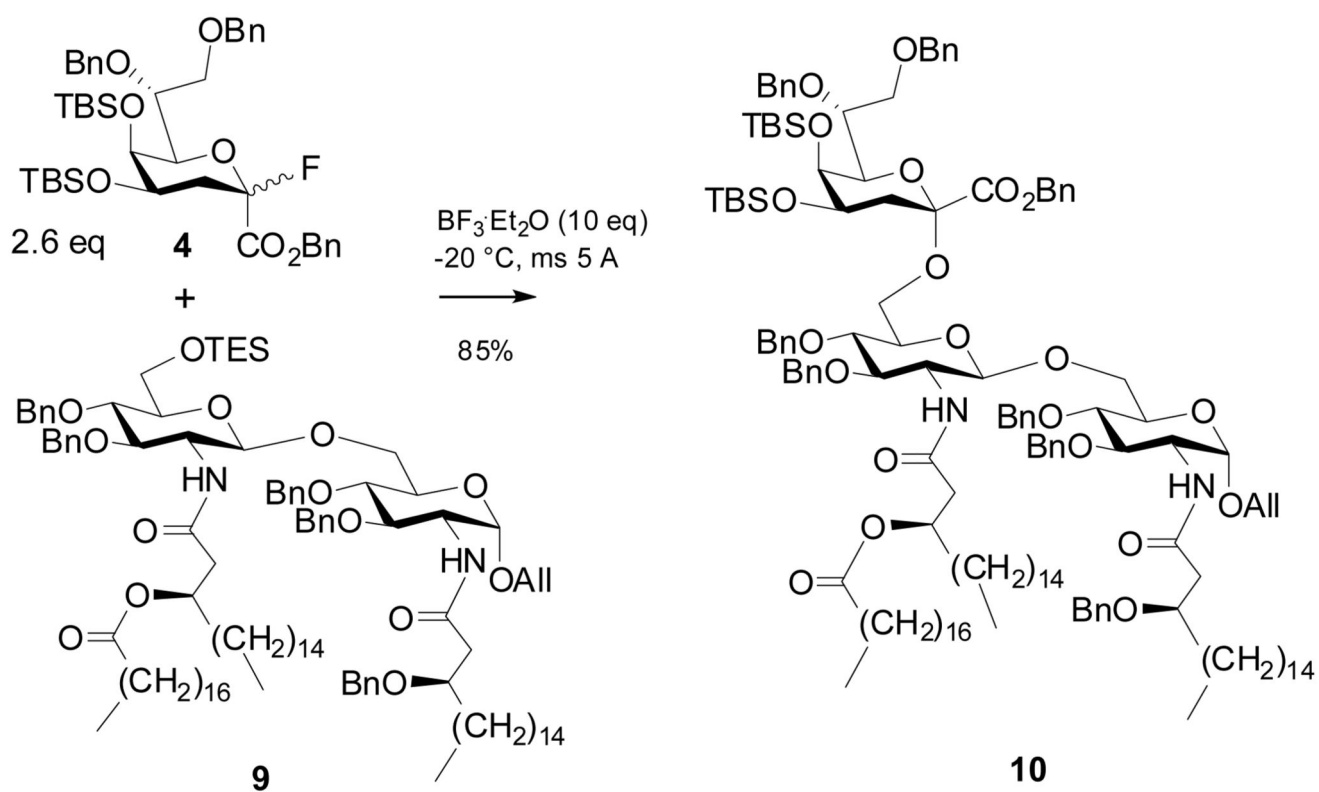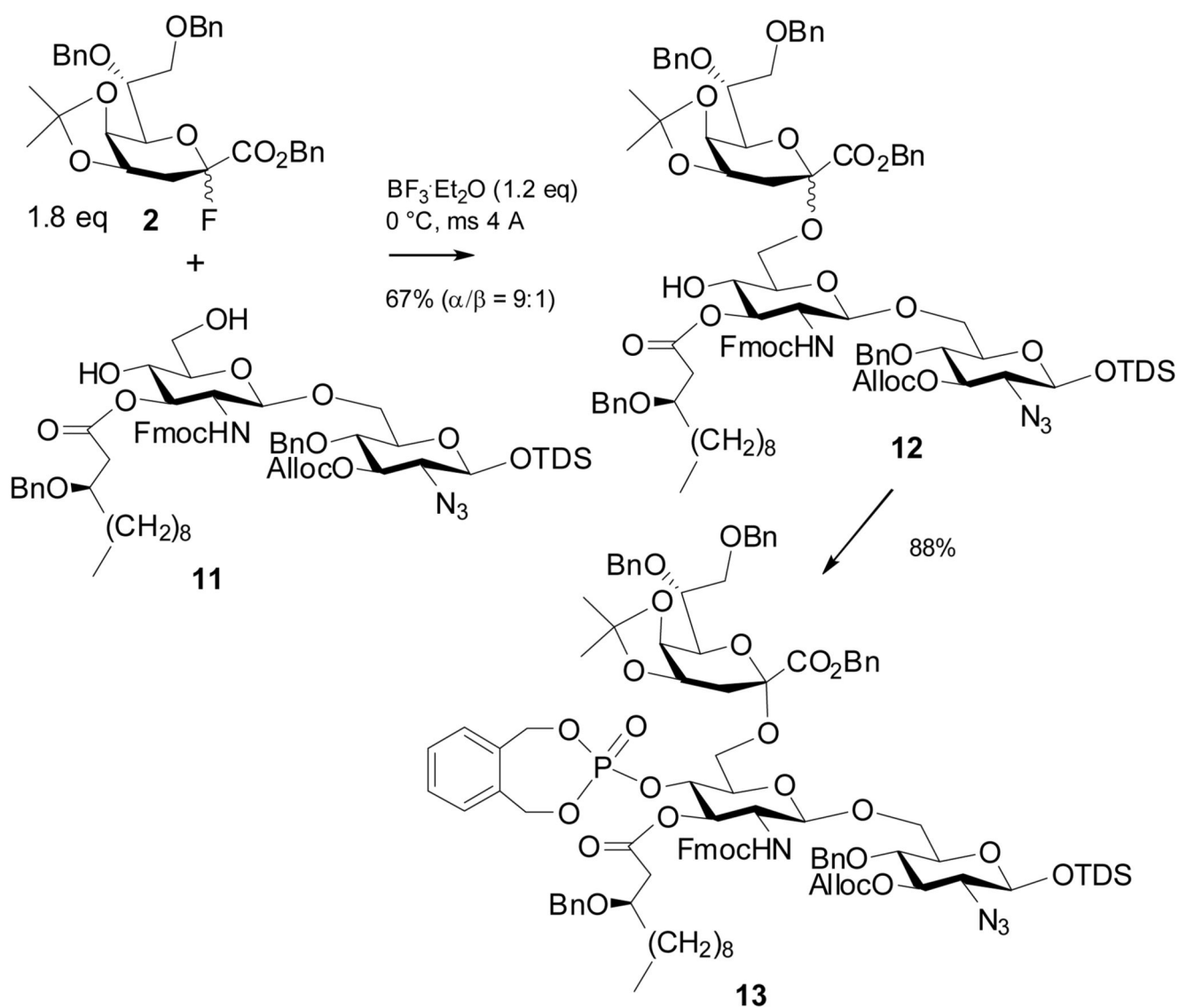**Figure 2.**
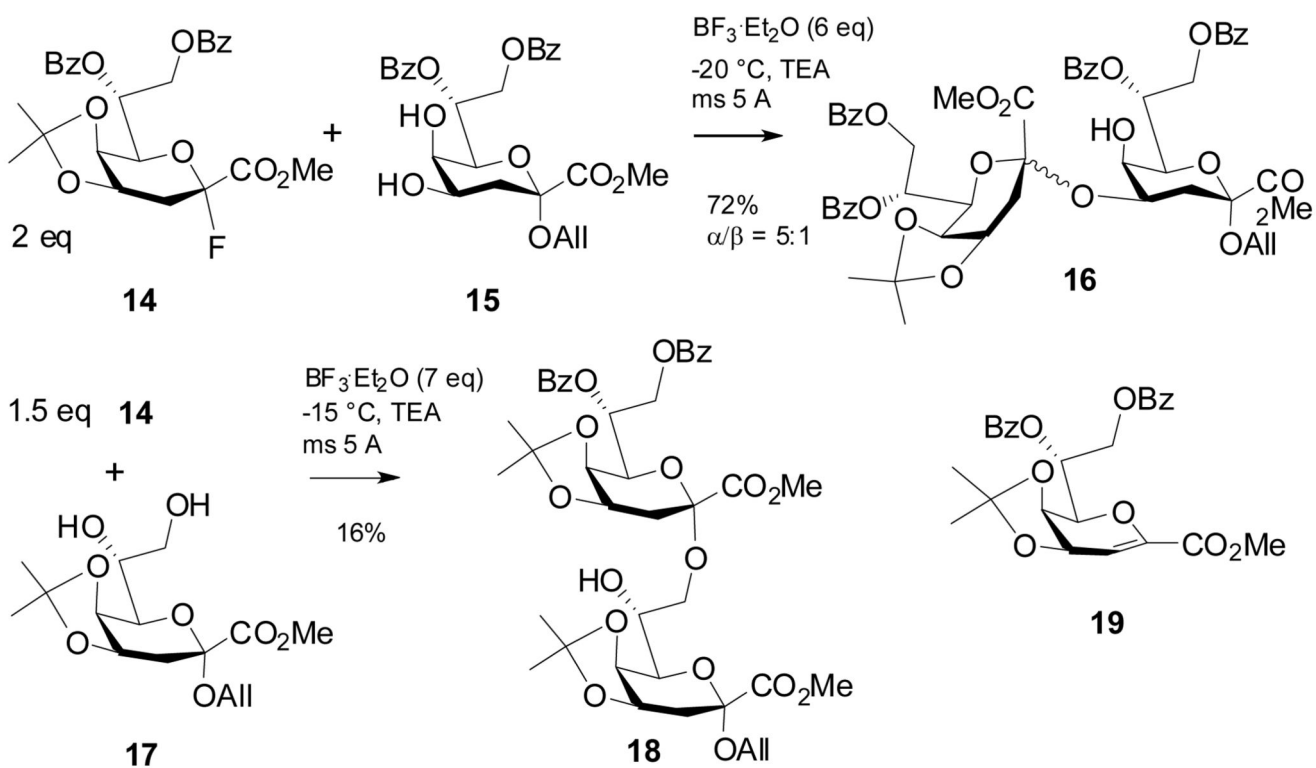Glycosylation products of Kdo donors.

Scheme 1.
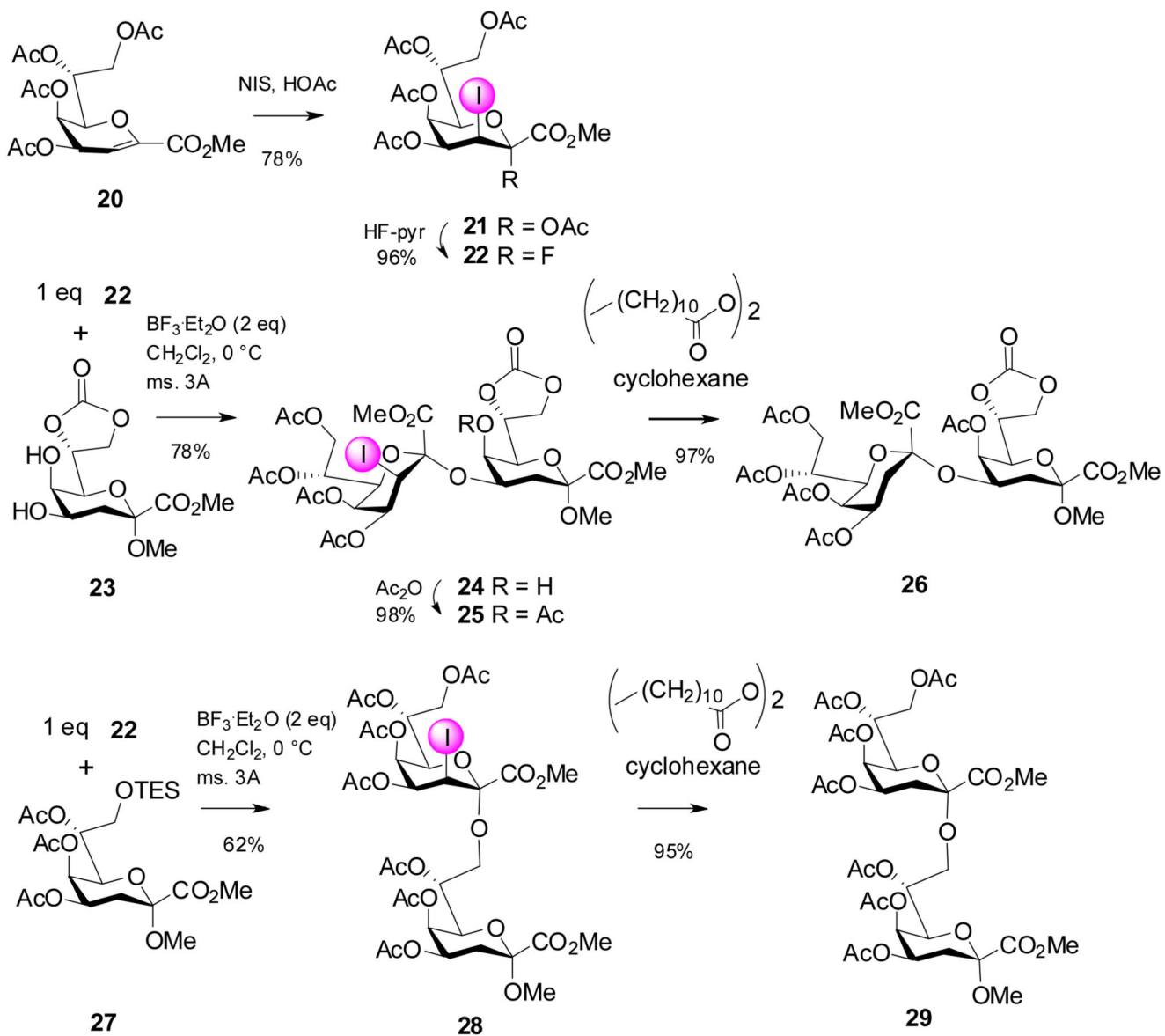Synthesis of Kdo fluoride donors.

Scheme 2.
Glycosylation of a 6-*O*-TES-protected diglucosamine acceptor.

Scheme 3.
Glycosylation of a diglucosamine acceptor *en route* to Kdo-lipid A of *Neisseria meningitidis.*
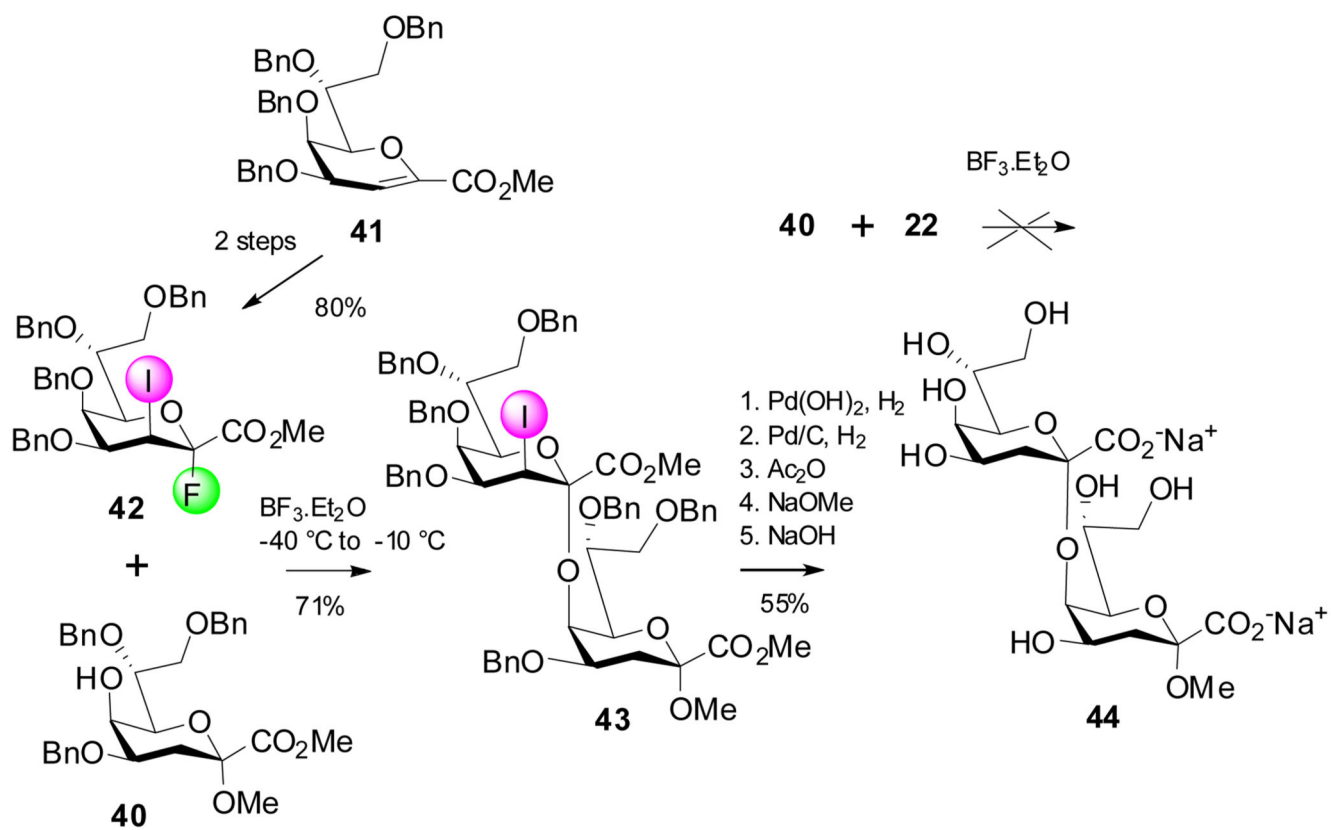
Scheme 4.
Glycosylation of **17** with a peracetylated Kdo bromide donor was also low-yielding according to a previous report.16

Scheme 5.
Synthesis of Kdo disaccharides.

Scheme 6.
Synthesis of a 4,8-dibranched Kdo trisaccharide.
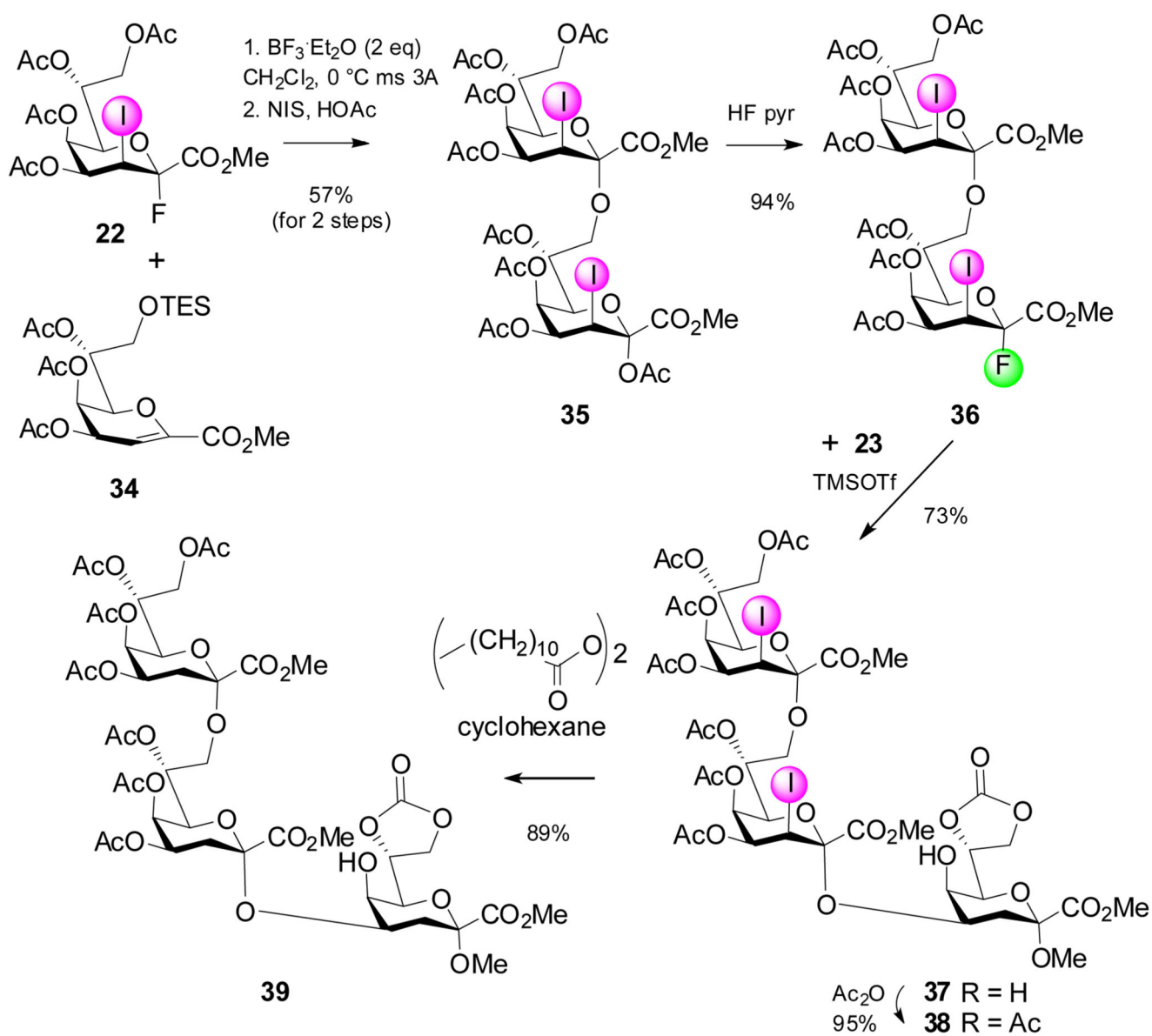
Scheme 7.
Synthesis of the linear Chlamydia-specific Kdo trisaccharide **39**.

Scheme 8.
Synthesis of the α-(2→5)-linked Kdo disaccharide **44**.
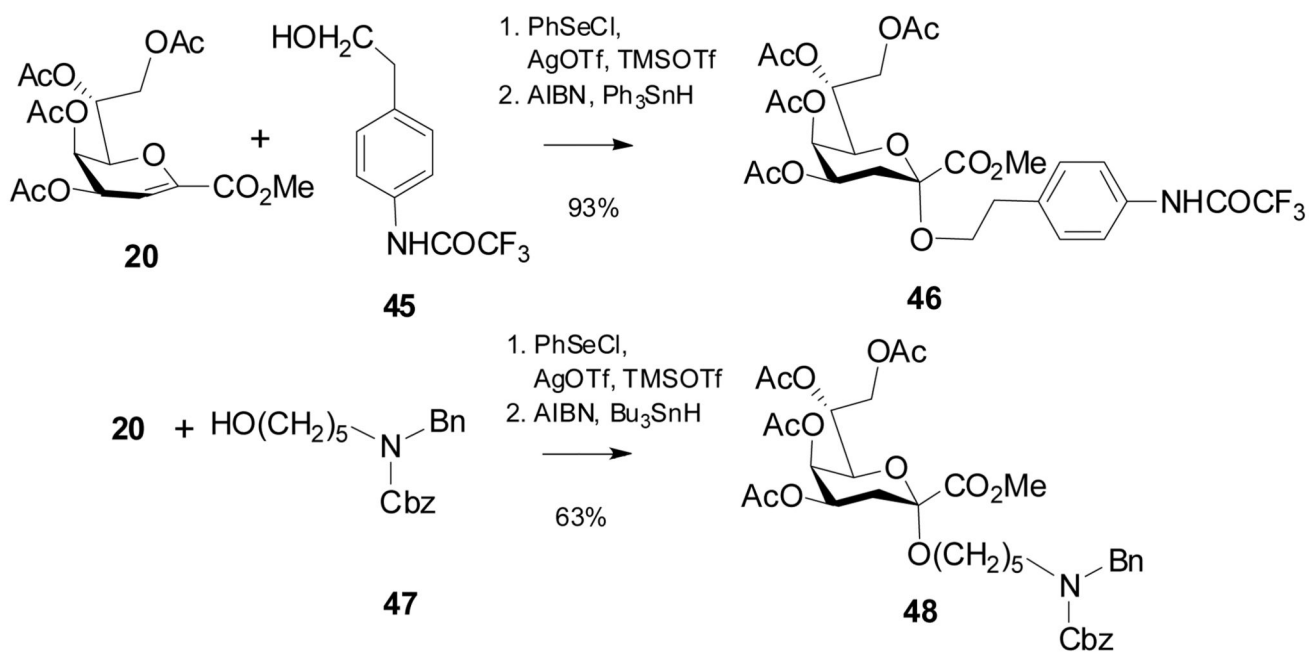
Scheme 9.
Synthesis of spacer α-glycosides from glycal ester **20**.
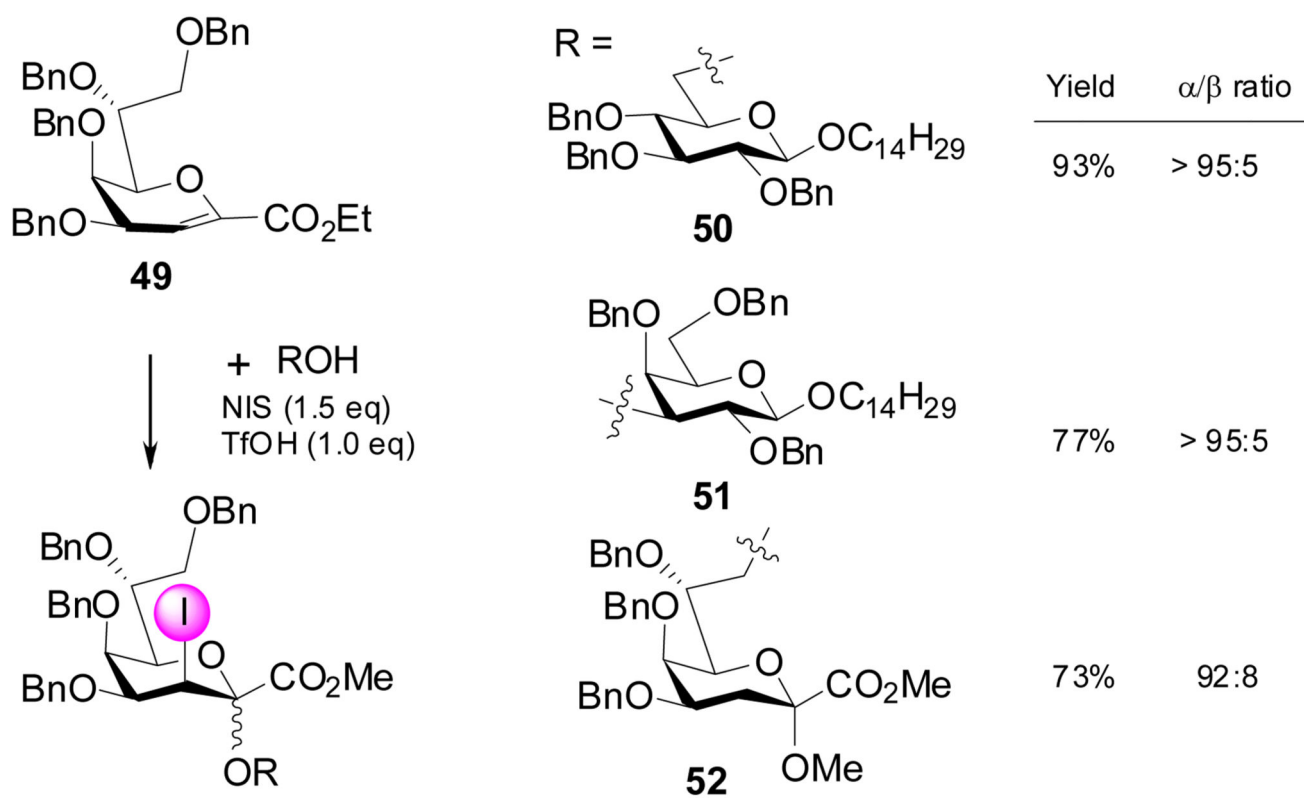
Scheme 10.
Activation of benzyl glycal ester with NIS/TfOH.
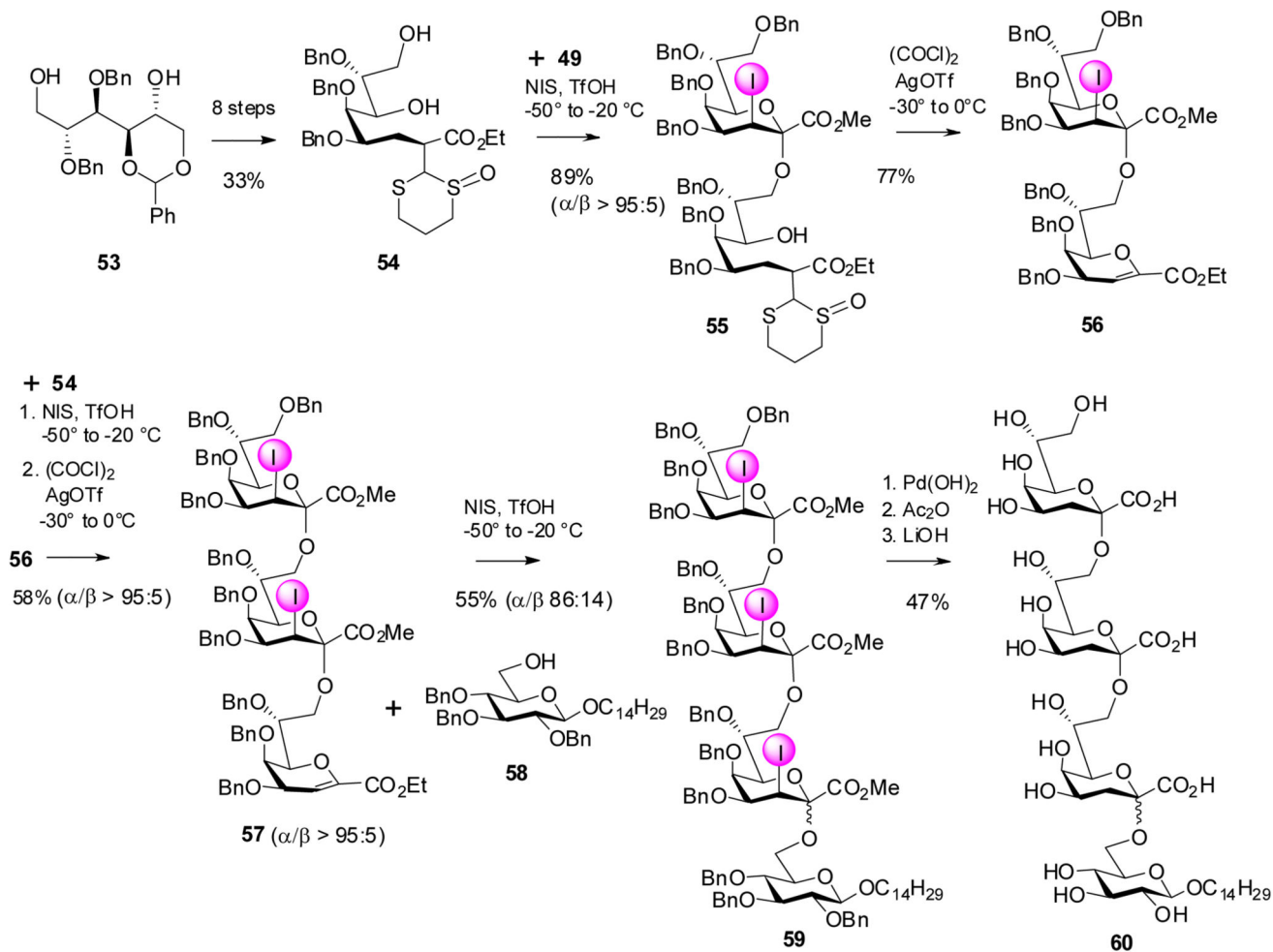
Scheme 11.
Synthesis of α-(2→8)-Kdo trimers.
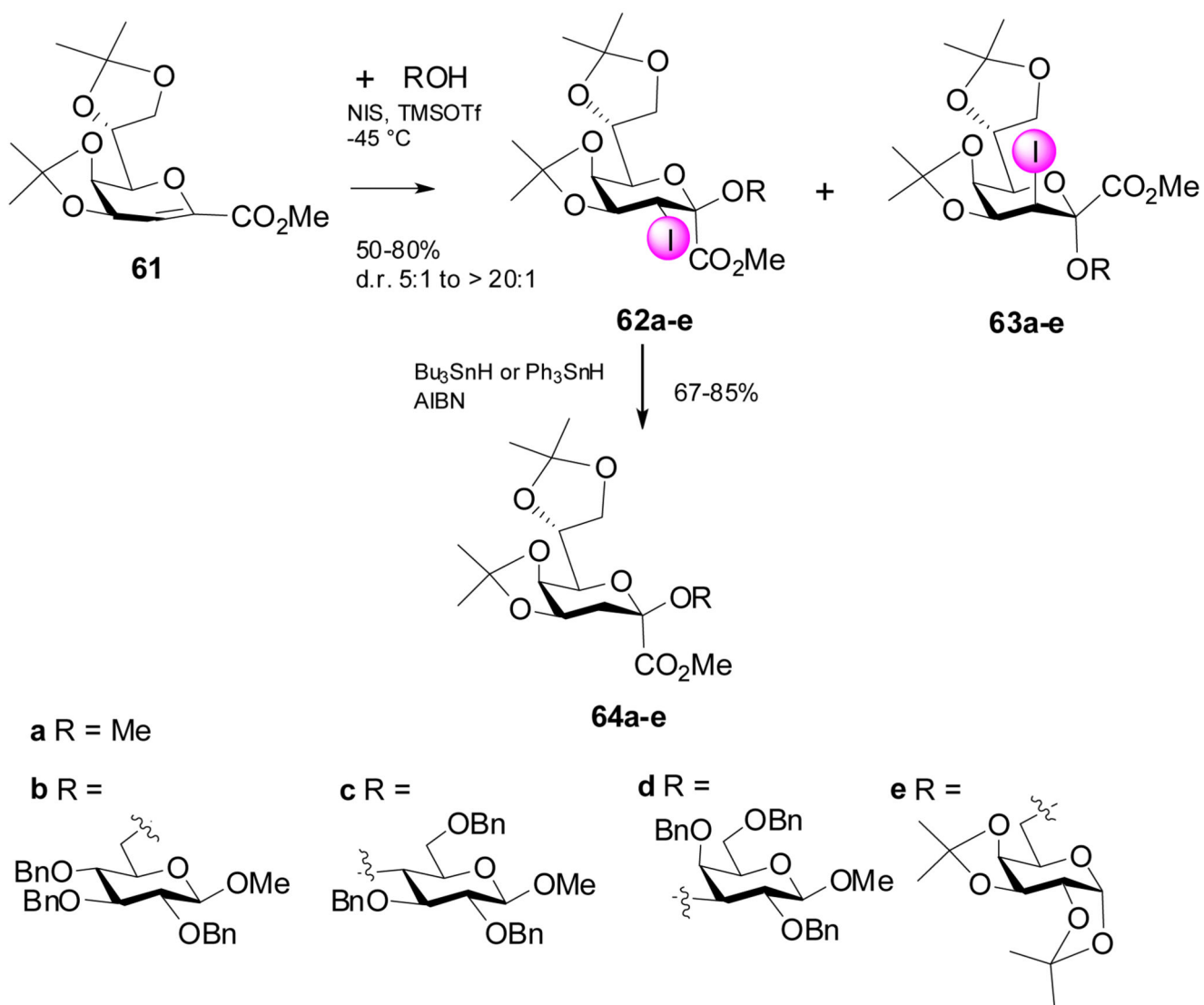
Scheme 12.
Synthesis of β-Kdo derivatives.
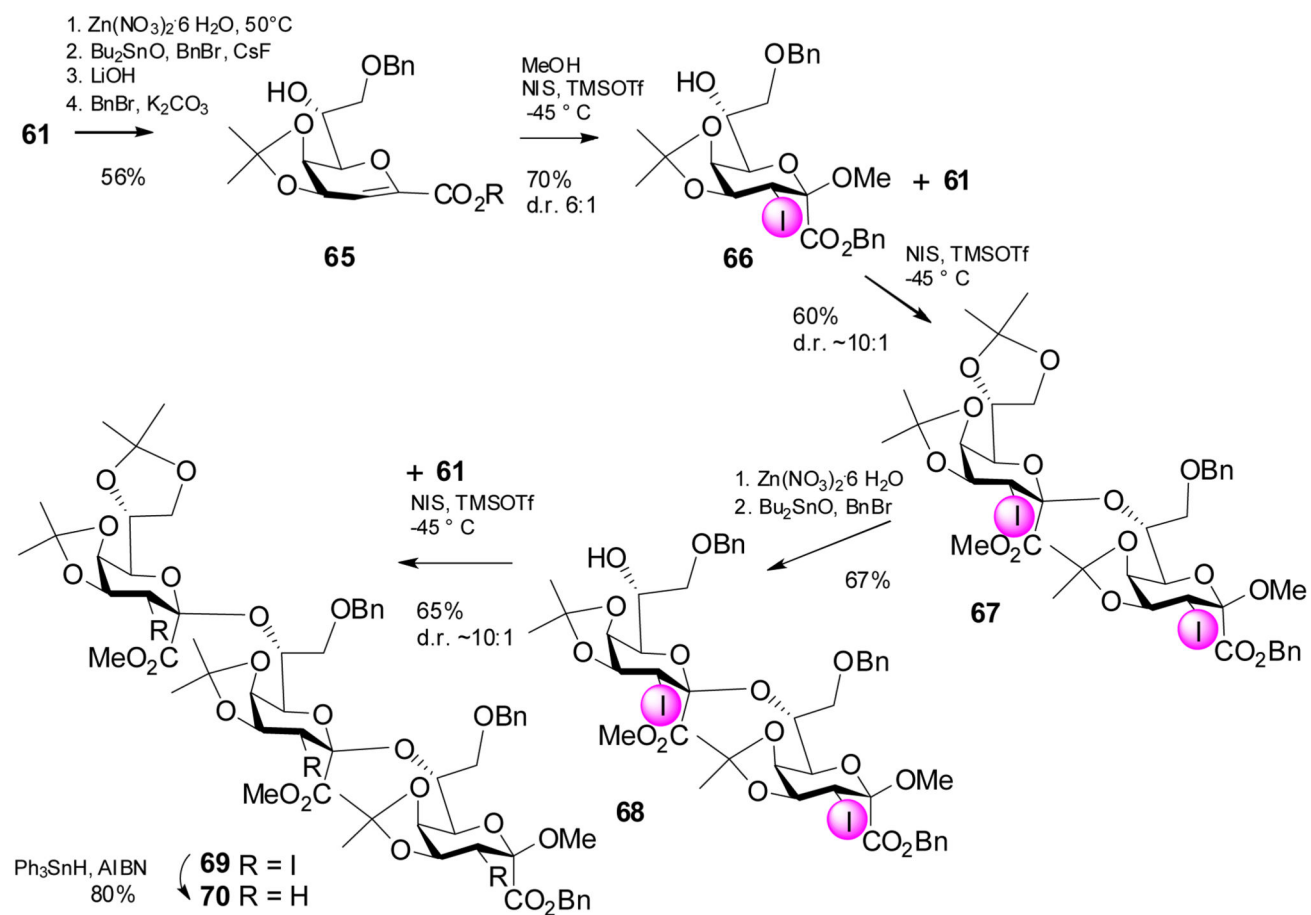
Scheme 13.
Synthesis of a β-(2→7)-linked Kdo trimer.
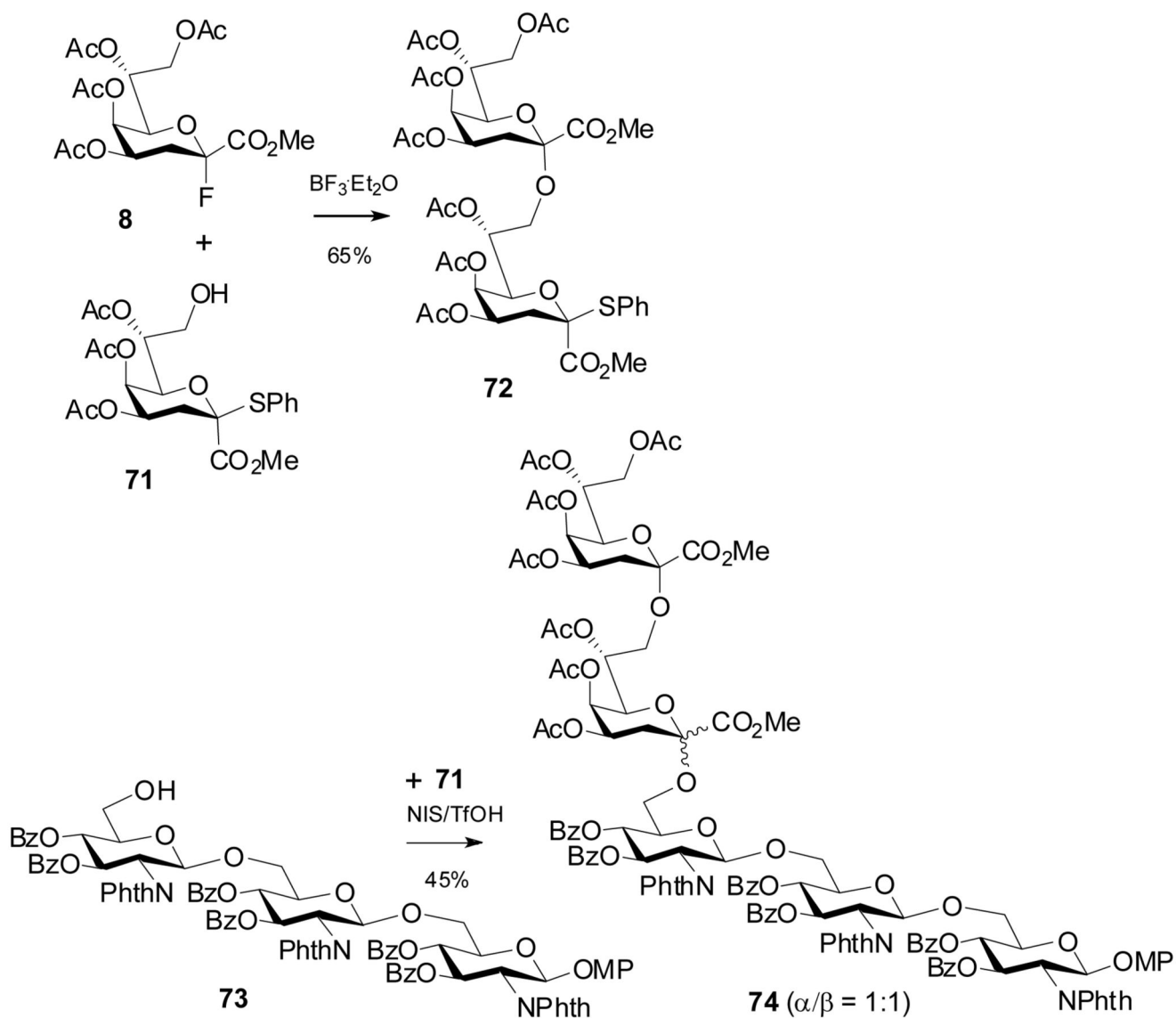
Scheme 14.
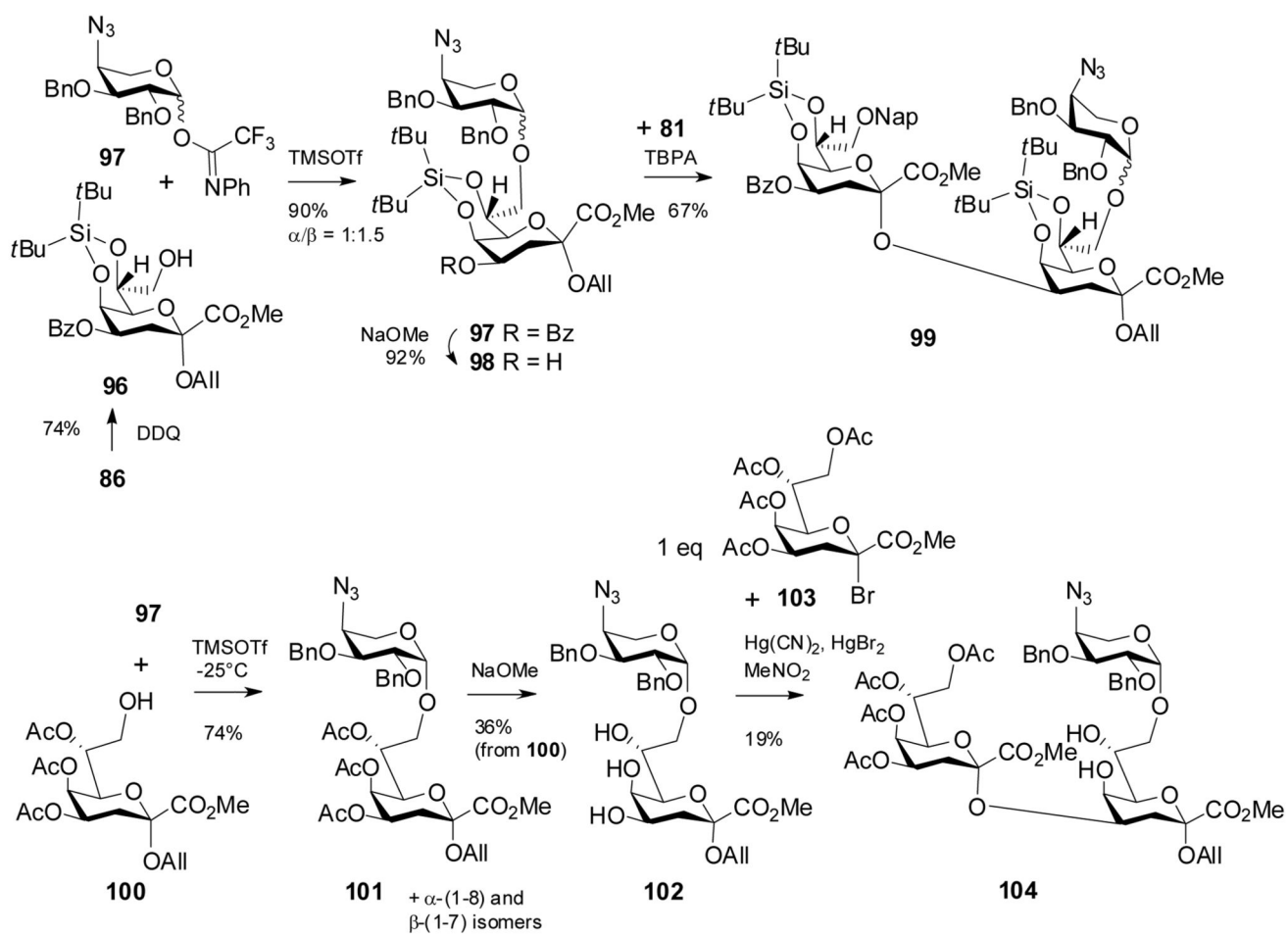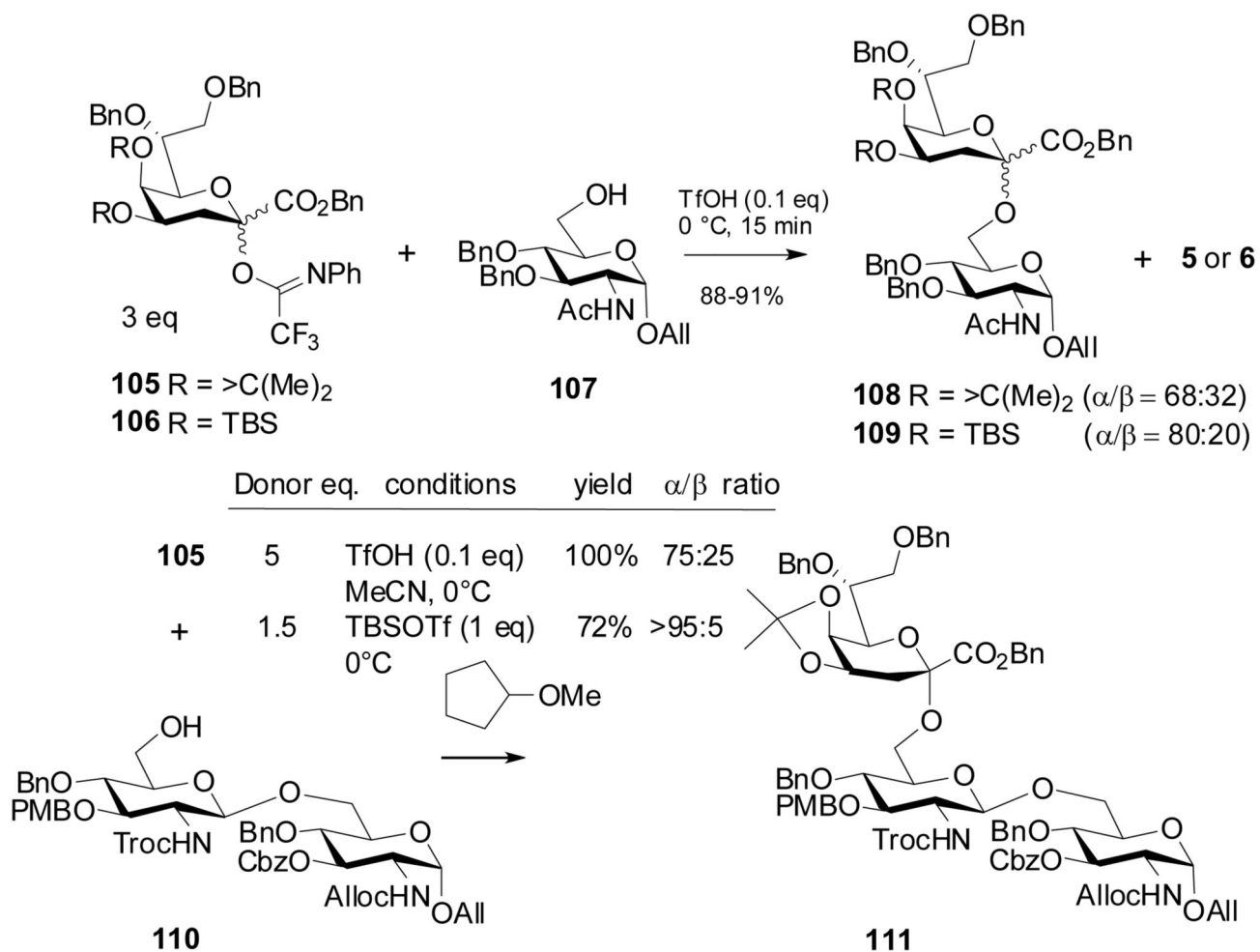Synthesis and glycosidation of a Kdo disaccharide donor
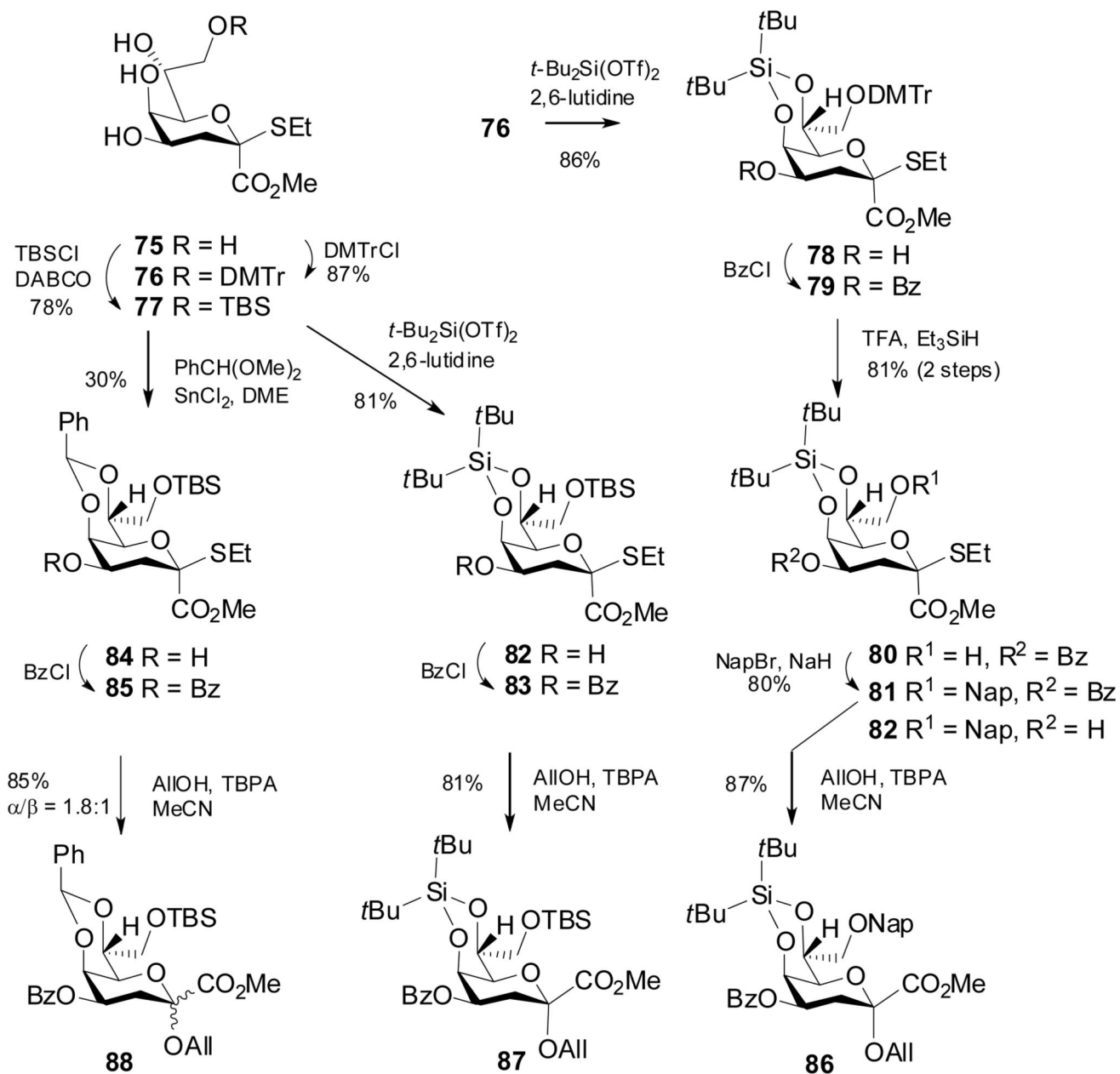
Scheme 15.
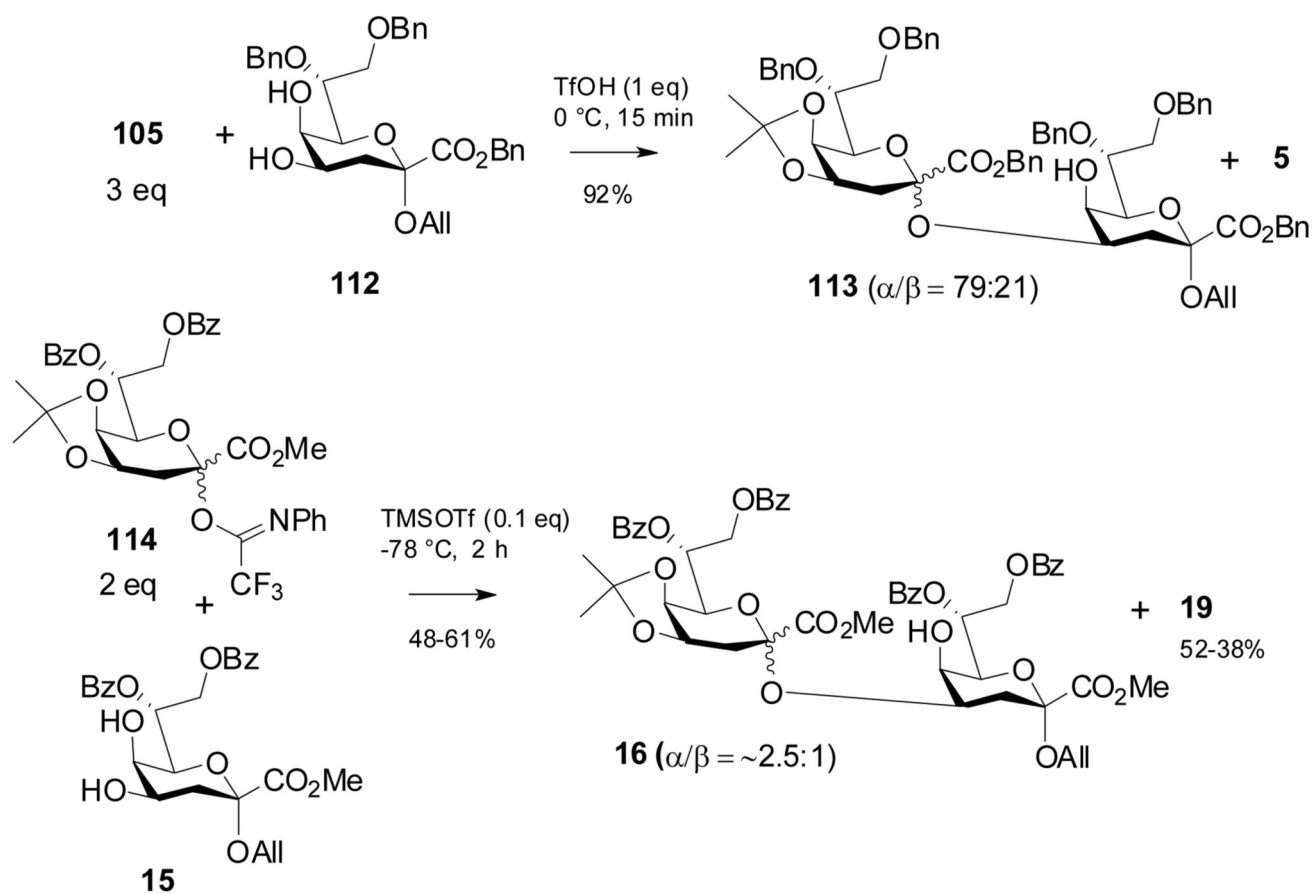Synthesis of 5,7-*O*-locked Kdo thioglycoside donor and acceptor derivatives.
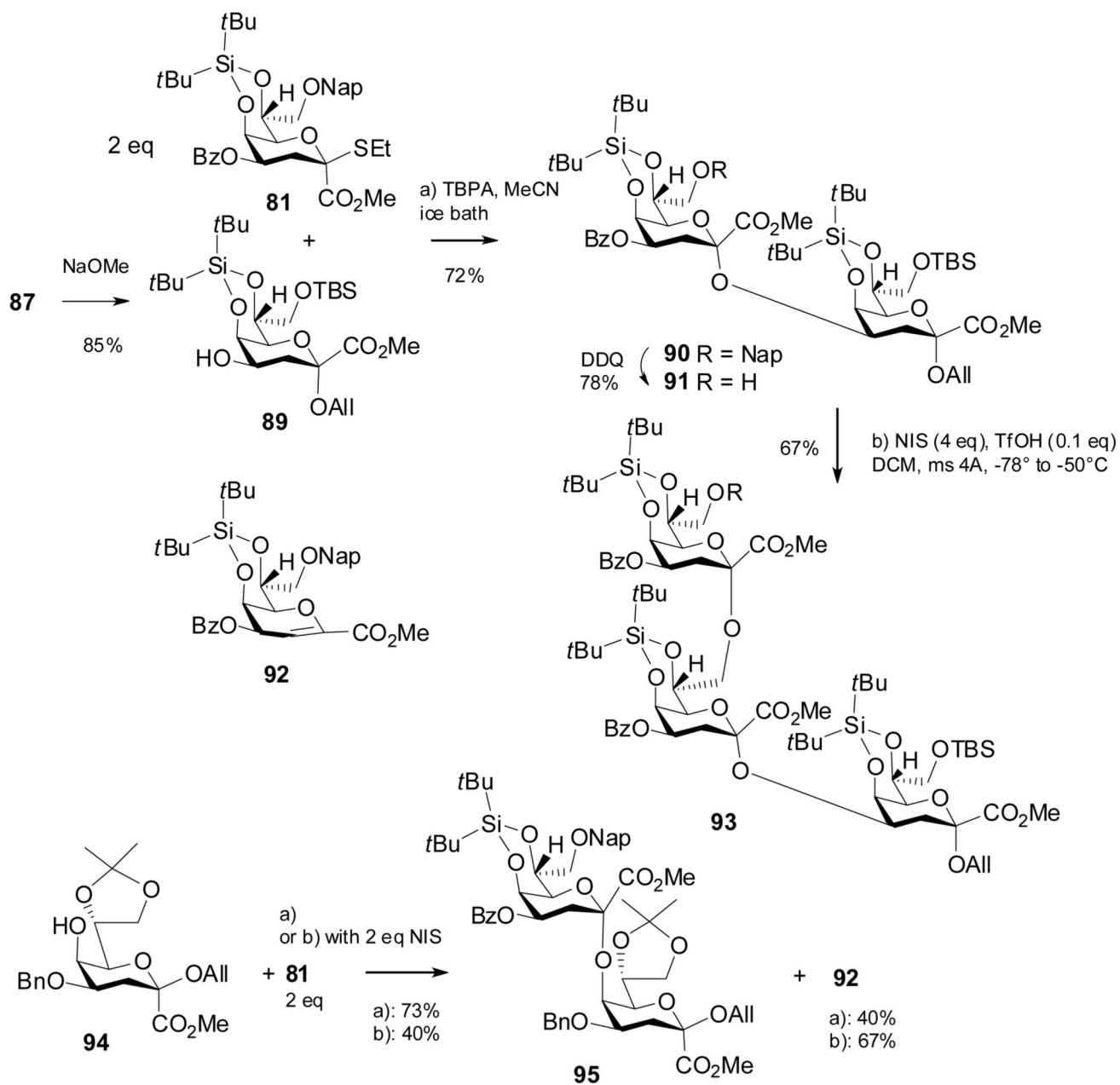
Scheme 16.
Synthesis of the Chlamydia-related Kdo trisaccharide and the α-(2→5)-linked Kdo disaccharide.

Scheme 17.
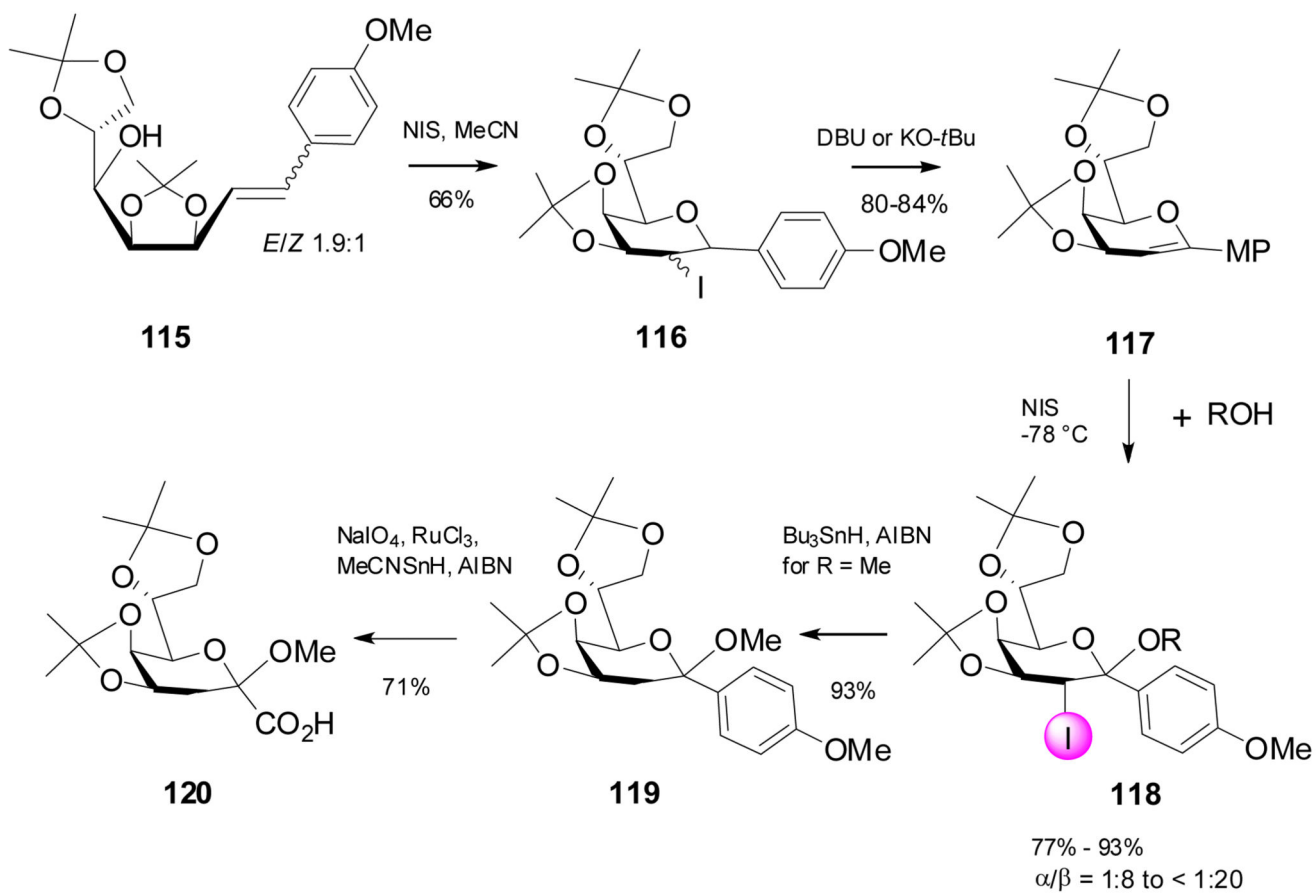Synthesis of *Burkholderia* and *Proteus*-related LPS core structures.

Scheme 18.
Glycosylation reactions with Kdo *N*-phenyl trifluoroacetimidates.

Scheme 19.
Kdo disaccharide synthesis with Kdo *N*-phenyl trifluoroacetimidates.

Scheme 20.
β-Kdo synthesis from 1-*C*-aryl glycal.