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Synthesis of the β-Rhamnopyranosides and the 6-Deoxy-β-mannoheptopyranosides

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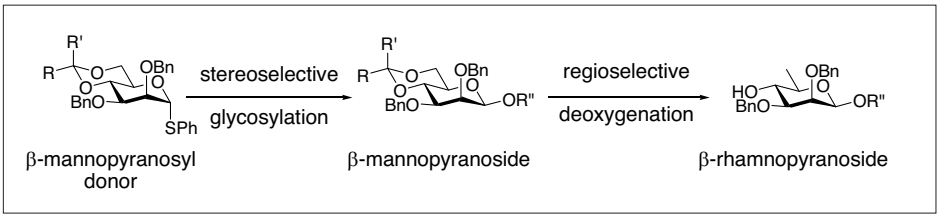
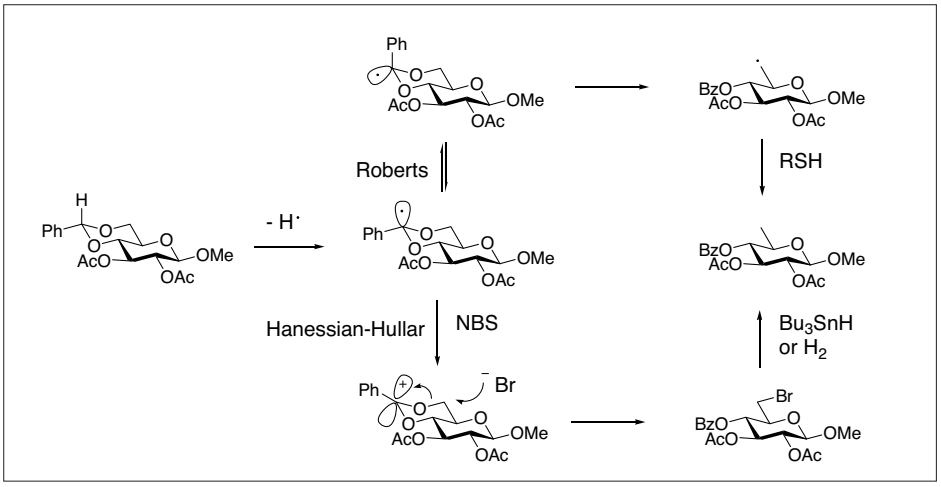
Abstract: A review is presented of the development of methods for the synthesis of β-rhamnopyranosides and the related 6-deoxy-β-mannoheptopyranosides based on the 4,6-*O*-alkylidene directed synthesis of mannopyranosides and their 6-thia derivatives followed by selective reduction at the 6-position. Applications to total synthesis of complex bacterial oligosaccharides containing the title moieties are presented.

Keywords: Desulfurization · Glycosylation · Oligosaccharide synthesis · Radical reaction · Stereoselectivity

The stereochemical problem posed by the synthesis of the β-rhamnopyranosides is closely related to that of the β-mannopyranosides in so far as the two classes differ only by single C–O bond. Indeed, many of the same methods developed for the synthesis of the mannopyranosides have been applied to the rhamnopyranosides with the same attendant problems of inadequate stereocontrol, irreproducibility, and indirectness.[1–7] The discovery that the presence of a 4,6-*O*-benzylidene or related acetal unit enables the direct synthesis of many β-mannopyranosides with high levels of stereocontrol[8–12] opened up a potential new avenue to the β-rhamnopyranosides provided that removal of the extra oxygen atom could be achieved efficiently post-glycosylation (Scheme 1).



Scheme 1. The concept.



Scheme 2. Key mechanistic differences between the Hanessein-Hullar and Roberts fragmentations.

The well-known Hanessian-Hullar reaction involving the oxidative fragmentation of a 4,6-*O*-benzylidene acetal with *N*-bromosuccinimide to give a 4-*O*-benzoyl-6-bromo-6-deoxy sugar,[13–19] with its many applications in carbohydrate chemistry, would be well-suited for this task were it not for its incompatibility with benzyl ethers.[20] We note in passing that this restriction is lifted for the fragmentation of five-membered cyclic benzylidene acetals,[21] owing to the documented more rapid abstraction of hydrogen from 1,3-dioxolanes than from 1,3-dioxanes.[22] Robert's variant on the Hanessian-Hullar reaction,[23,24] in which a catalytic thiol and a radical initiator convert a 4,6-*O*-benzylidene acetal directly into a 4-*O*-benzoyl-6-deoxy sugar, suffers from the same problem but teaches the essential lesson that the intermediate dioxanyl radical fragments with high contrathermodynamic selectivity to give the required primary radical at the 6-position, to which we will return later (Scheme 2). The Hanessian-Hullar reaction is more readily understood and achieves its regioselectivity through an ionic process invoking nucleophilic attack by bromide anion at the least substituted position of a 2-phenyl-1,3-dioxanyl cation (Scheme 2).[25,26]

Following on from Roberts, logically, if the crucial intermediate 4,6-*O*-benzylidene radical can be generated by means other than intermolecular hydrogen atom

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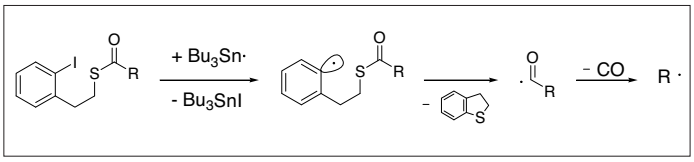
abstraction, then the path should be clear for the development of a method for the synthesis of β-rhamnopyranosides involving 4,6-*O*-benzylidene directed β-mannosylation followed by reductive radical fragmentation of the acetal. Initial attempts centered on the intramolecular 1,5- abstraction of the acetal hydrogen atom with the help of a suitably placed aryl radical (generated from a 3-(2-iodophenyl)propanylidene acetal) failed,[27] and we turned to fragmentation approaches to generate the key radical. Our earlier work on the use of *S*-2-(2-iodophenyl)ethyl thioesters as a means of entry, *via* radical homolytic substitution at sulfur and decarbonylation (Scheme 3),[28,29] to nucleotide C(4') radicals[30] prompted our application of this type of radical trigger.

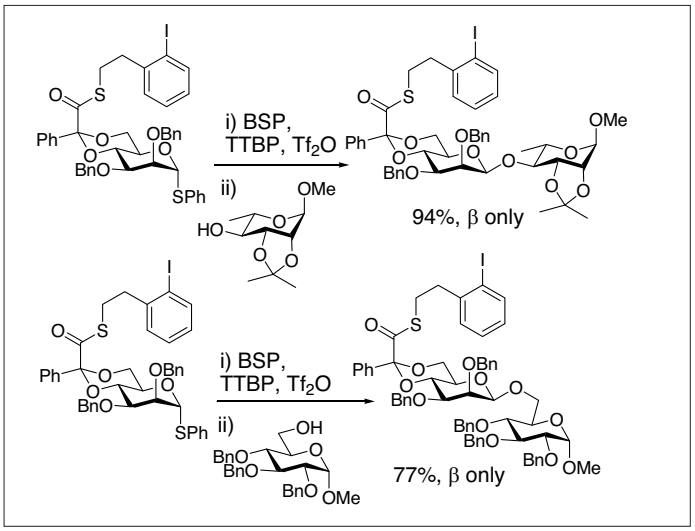
The requisite functionality could be introduced into the carbohydrate framework by a standard transacetalization with methyl 2,2-dimethoxyphenylacetate followed by aluminum-mediated transesterification with the appropriate thiol.[27,31] A mixture of stereoisomers was formed in this process, and although these were typically separated and used as single isomers, it was readily shown that this was of no consequence with both isomers performing more or less identically in all subsequent chemistry.[27] Turning to the glycosylation reaction the new acetal performed very similarly to the standard 4,6-*O*-benzylidene system and provided excellent β-selectivity with a number of model alcohols. Importantly, although not unexpectedly, the thioester function was stable to the conditions for the activation of the thioglycoside with typical thiophilic combinations selected so as to provide an intermediate glycosyl triflate.[27,31] Indeed, the presence of the electron-withdrawing thioester group enhanced the disarming nature of the acetal function forcing us to employ the more potent activating system of diphenyl sulfoxide and triflic anhydride[32] in some cases rather than our in house combination of 1-benzenesulfinyl piperidine (BSP) and triflic anhydride (Tf_2O)[10] (Scheme 4).

Radical fragmentation of the so-formed β-mannosides, conducted with tributyltin hydride and AIBN in hot toluene or xylene, proceeded with exquisite regioselectivity to provide the corresponding β-rhamnosides in good yield (Scheme 5).[27,31]

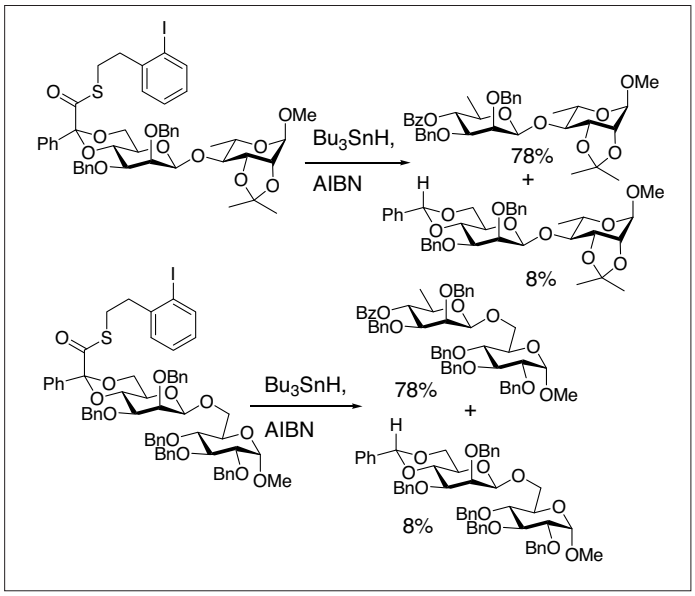
In parallel with the observations of Roberts and coworkers using their catalytic system,[23] when the radical fragmentation is applied in the galactopyranose system, with its *cis*-fused ring junction and axial C(4)–O bond, regioisomeric mixtures of 4- and 6-deoxy sugars were obtained.[33] The regioselectivity of the radical fragmentation reaction is explained, as discussed by Roberts[23] in Scheme 6.



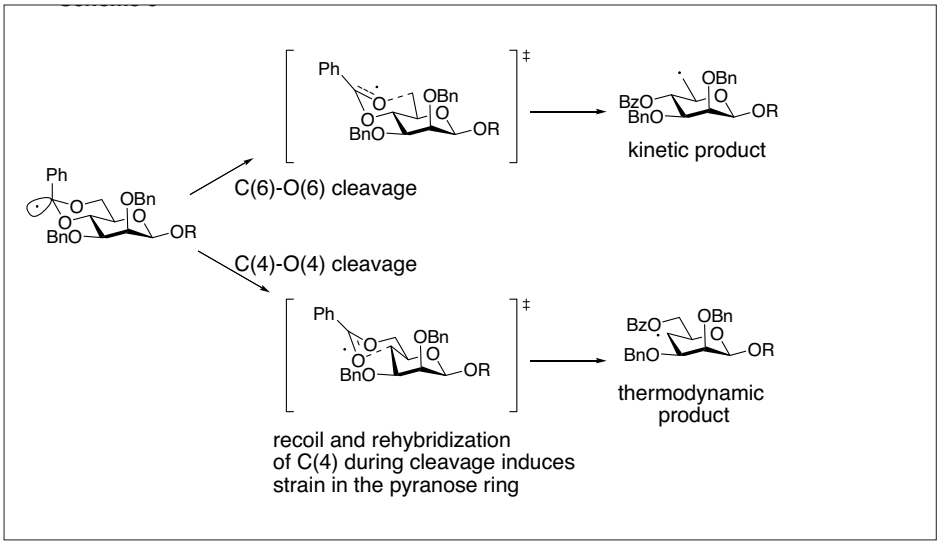
Scheme 3. Key steps in the generation of alkyl radicals from *S*-2-(2-iodophenyl)ethyl thioesters.



Scheme 4. Examples of glycosylation reactions with the thioester system (BSP = 1-benzenesulfinyl piperidine; TTBP = 2,4,6-tri-*tert*-butylpyrimidine).



Scheme 5. Examples of the mannoside to rhamnoside thioester fragmentation. (AIBN = $N{\equiv}C\text{-}C(Me)_2\text{-}N{=}N\text{-}C(Me)_2\text{-}CN$).



Scheme 6. Transition states for radical fragmentation of D-mannose derivatives.

To probe the applicability of the thioester fragmentation chemistry we targeted the tetrasaccharide repeating unit of the antigenic lipopolysaccharide from *Escherichia hermannii* ATCC 33650 and 33652 that contains an unusual concatenation of a β-D-rhamnopyranoside and an α-D-rhamnopyranoside. The highlights of this synthesis were the fully stereocontrolled formation of the β- and α-mannopyranosidic bonds in the presence of the modified acetal unit, with the stereochemical outcome of these reactions depending on the protecting group (ether or ester, respectively), on O(3) of the donor, and the one-pot double radical fragmentation sequence in the presence of seven benzyl ethers for the formation of the two rhamnopyranosides (Scheme 7).[27]

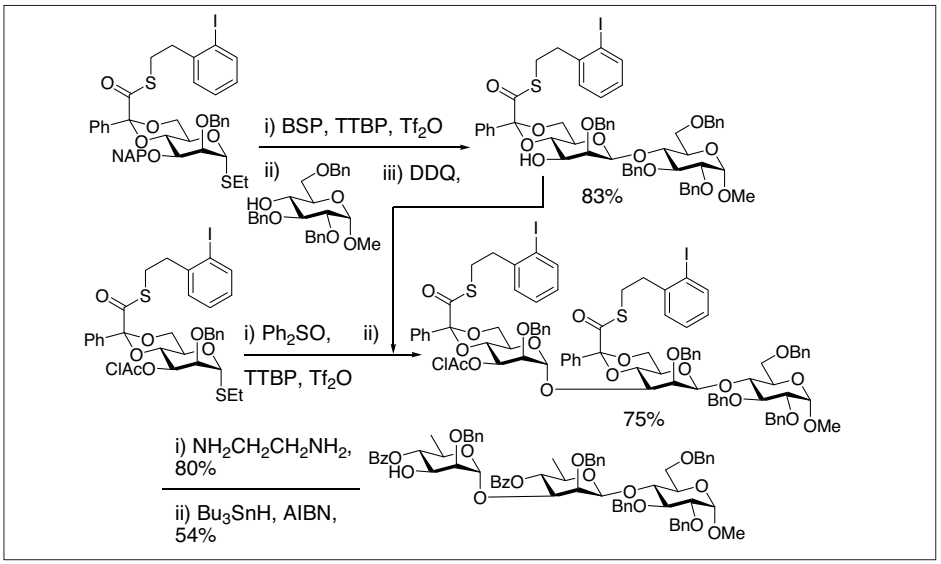
To circumvent the limitations arising from the thioester moiety we turned to intramolecular radical transfer[33] of a nitrile group as introduced by Beckwith and coworkers[34] and subsequently exploited in synthesis by the Rychnovsky group[35] (Scheme 8).

In practice the requisite cyanoacetal group was installed by *trans*-orthoesterification of a 4,6-diol with triethyl (2-iodophenyl)orthoacetate resulting in an isolable stereoisomeric mixture of cyclic orthoesters, which was nevertheless typically converted into the desired cyanoacetal by reaction with trimethylsilyl cyanide (TMSCN) and Lewis acid (Scheme 9).[33] These substances were formed and isolated as single stereoisomers, with the nitrile group in the axial site as determined crystallographically.

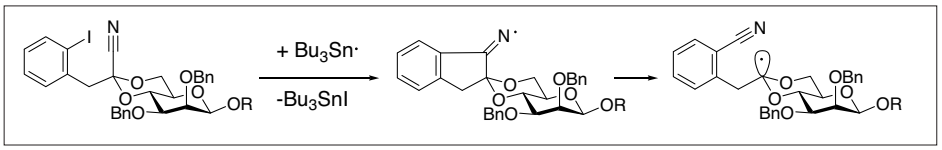
As anticipated the so-formed cyanoacetals proved to be somewhat more robust than the thioesters used in the first generation approach and also to be significantly electron-withdrawing requiring the use of the potent diphenyl sulfoxide/trifluoromethane sulfonic anhydride system[32] to bring about the activation of the thioglycoside. In accordance with the powerful disarming effect of the cyanoacetal and our general mechanistic hypothesis for glycosylation, model coupling reactions conducted in this manner were highly β-selective (Scheme 10).[33]

The subsequent radical fragmentation reactions also took place in high yield and with the anticipated exquisite selectivity for the fragmentation of the primary bond to give the 6-deoxy system (Scheme 11).[33]

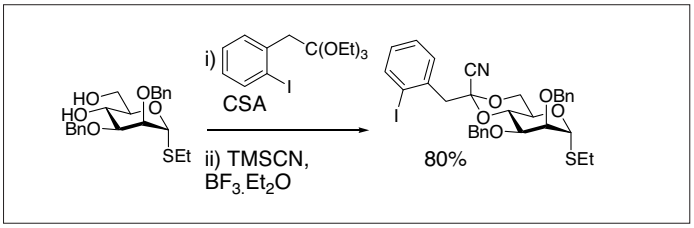
To prove this system in synthesis we selected the tetrasaccharide repeating unit from of the lipopolysaccharide from *Plesimonas shigelloides* with its most unusual 6-deoxy-β-D-mannoheptoside unit coupled to another β-D-mannoheptoside unit, this time retaining the 6-OH bond.[36] A suitable glycosyl donor in the form of a 4,6-diol was synthesized in several steps



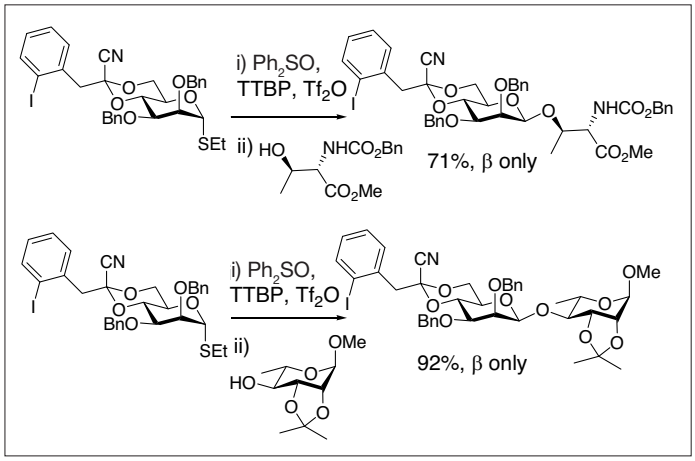
Scheme 7. Double radical fragmentation to access a β- and α-rhamnopyranoside-containing moiety (DDQ = 2,3-dichloro-5,6-dicyanobenzoquinone).



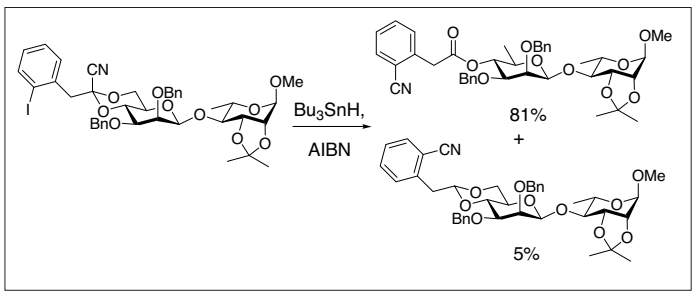
Scheme 8. The nitrile transfer route to alkylidene radicals.



Scheme 9. Installation of the cyanoacetal (CSA = camphorsulfonic acid).



Scheme 10. Model coupling reactions directed by the cyanoacetal group.



Scheme 11. Radical fragmentation of the cyanoacetal group.

from D-mannose, with subsequent improvements in the synthesis trimming several steps.[36,37] Two glycosyl donors were obtained from this diol, differing only in the nature of the 4,6-*O*-acetal protecting group, and were used in the construction of the tetrasaccharide (Scheme 12). The radical fragmentation reaction was carried out after the first glycosidic bond forming event and took place with exclusive cleavage of the C(6)–O(6) bond consistent with the earlier work.[36]

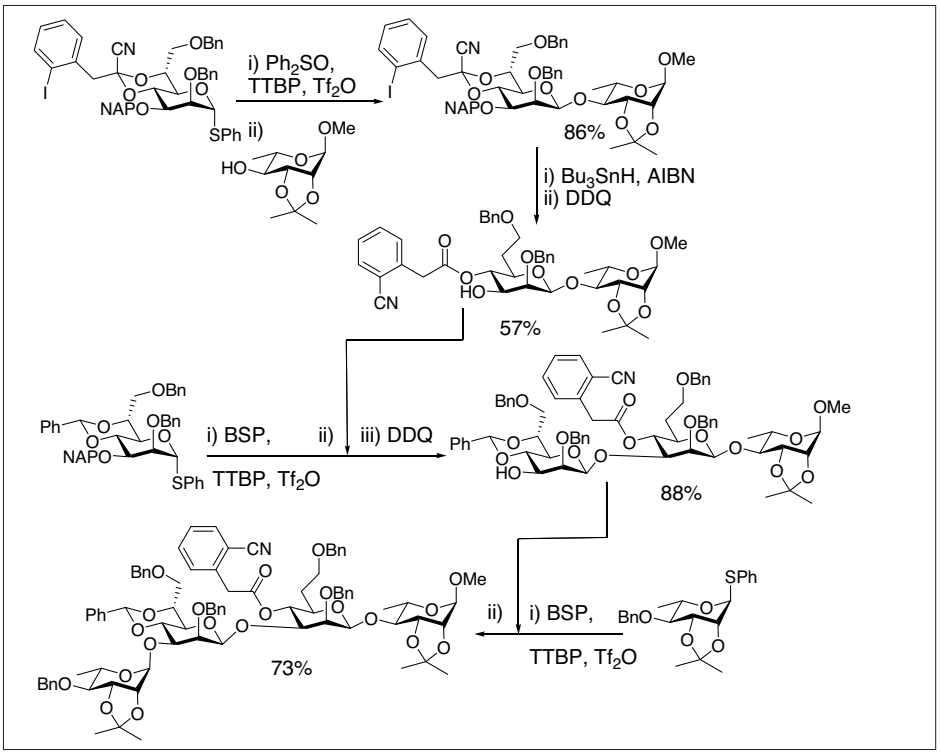
The cyanoacetal system was further tested by application to a β-D-rhamnotetroside, as a representative portion of the β-(1→3)-D-rhamnan from *Escherichia hermanii* ATCC 33651. The radical precursor was assembled in a two-step iterative fashion, with excellent β-selectivity from a standard donor, and the four radical fragmentations conducted in a single step. After saponification of the esters formed in the fragmentation step, the rhamnan was obtained in 22% yield indicating an average yield of over 68% for each of the four parallel sequences (Scheme 13).[38]

Searching for an alternative and more practical method we turned to the desulfurization of cyclic thiocetals derived from 6-deoxy-6-thia sugars. In view of the accepted basis for the influence of the 4,6-*O*-acetals on the β-mannopyranosylation,[11] namely a combination of torsional effects[39,40] and the maximization of the electron-withdrawing effect of the C(6)–O(6) bond by the locking of the C(5)–C(6) bond in the *tg* conformation,[41,42] it was by no means clear that the thioacetal, with the longer C–S bonds and the less electronegative sulfur atom, would have the desired effect. Added to this fundamental question was the more mundane one of chemoselectivity concerning the ability of the thioacetal to survive the conditions required for activation of the thioglycoside function in the course of the glycosylation reaction. Indeed, exploratory reactions with a simple 4-*O*,6-*S*-benzylidene monothioacetal were less than promising. Taking into account the powerful disarming nature of the cyanoacetal group employed in the second generation radical fragmentation approach we installed, therefore, a cyanothioacetal by the same two-step *trans*-orthoesterification, cyanation approach developed previously (Scheme 14).[43]

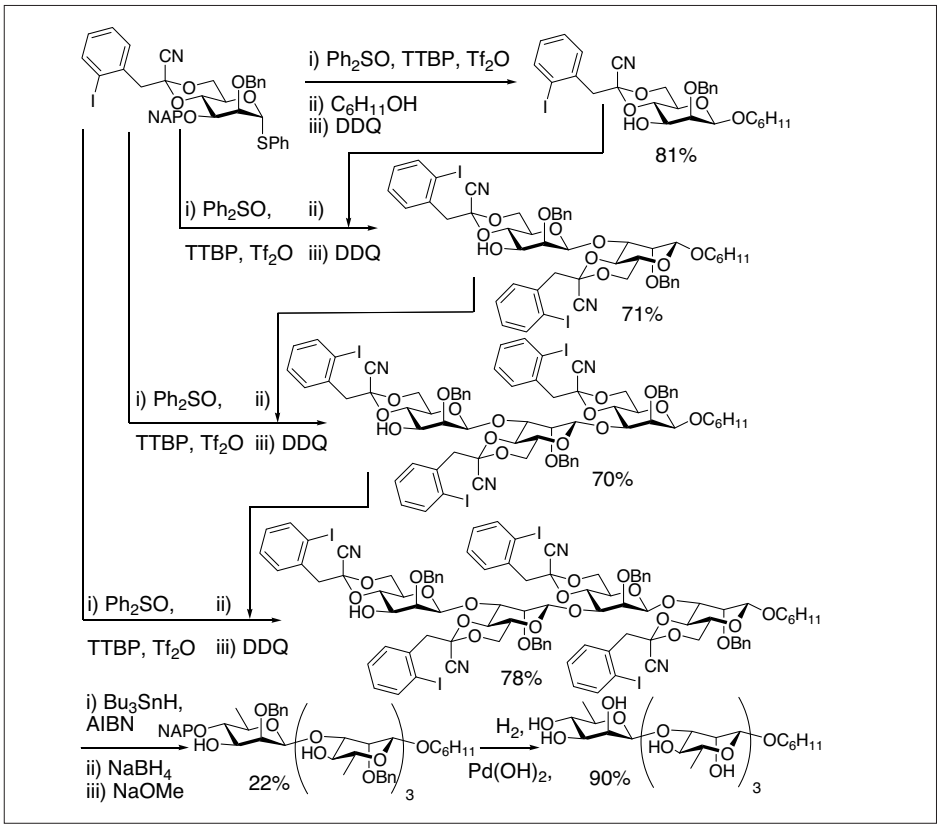
This D-mannopyranosyl donor was then coupled to several acceptor alcohols with generally good yield and selectivity as set out in Scheme 15.[43]

Desulfurization of these compounds was then achieved with Raney-Ni (H_2, MeOH), conditions which also cleaved the benzyl ether protecting groups (Scheme 16).[43]

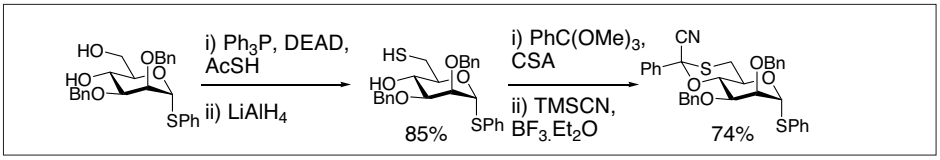
Finally, with a practical method established for the increasingly common β-D-rhamnopyranosides from the readily



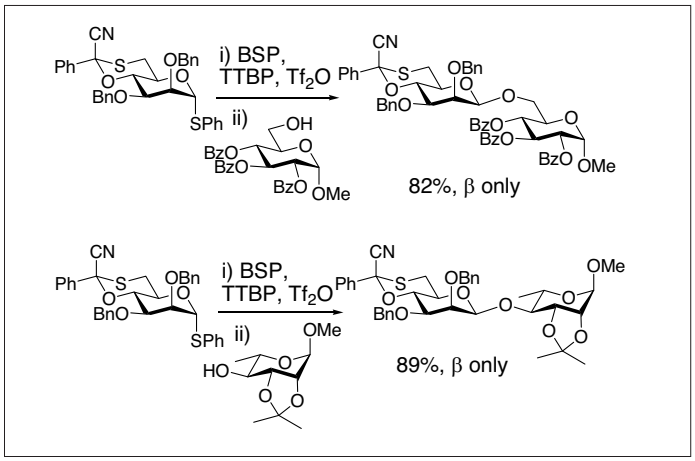
Scheme 12. Key steps in the construction of the tetrasaccharide repeating unit of the *Plesimonas shigelloides* lipopolysaccharide.



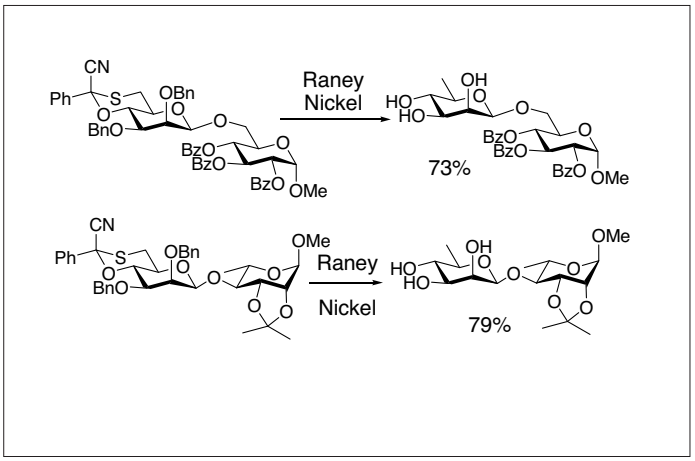
Scheme 13. Synthesis of a β-D-rhamnan.



Scheme 14. Synthesis of a 6-mercapto sugar and installation of the cyanothioacetal.



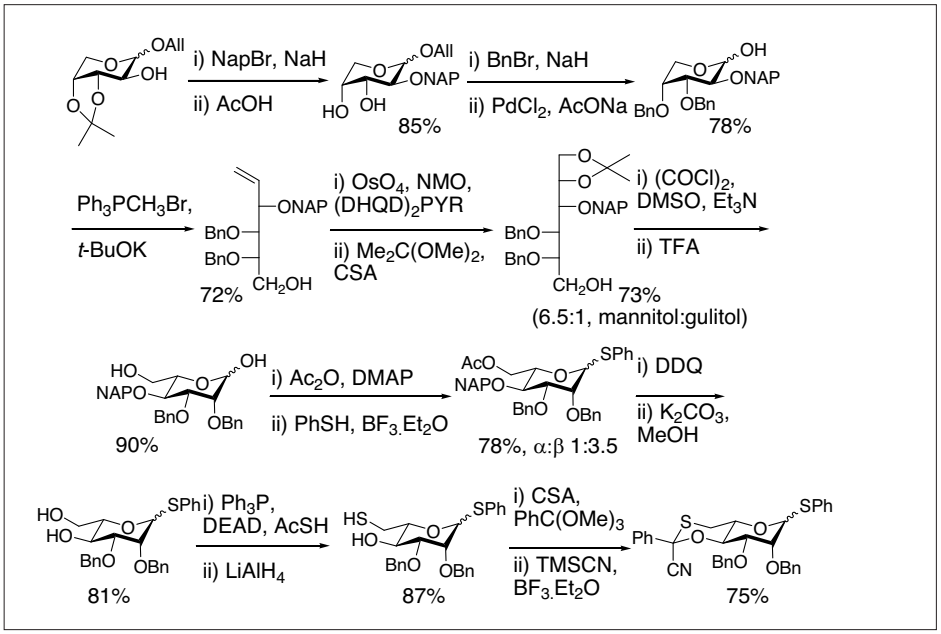
Scheme 15. Glycosylations in the D-series with the 6-mercapto mannopyranoside donor.



Scheme 16. Desulfurization in the D-series.

available D-mannose, we focused on the more abundant L-series. L-Mannose being a rare sugar we addressed this problem by the synthesis of the L-enantiomer from L-arabinose as shown in Scheme 17.[43]

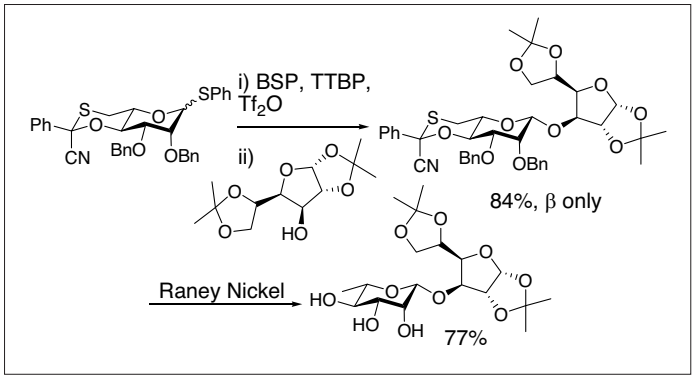
Not surprisingly, this L-mannosyl donor functioned just as its enantiomer and enabled the synthesis of a series of β-L-rhamnopyranosides by the two-step sequence of glycosylation followed by desulfurization (Scheme 18).[43] Of some interest was the differing β-selectivity between the two enantiomeric donors for some acceptors, indicating a measure of double diastereoselection[44,45] in some cases, while other acceptors gave essentially perfect selectivity with both enantiomorphic modifications of the donor.



Scheme 17. Synthesis of the L-donor.

Conclusions

A 4,6-*O*-alkylidene group is an extremely useful device for the control of stereochemistry in the direct formation of β-mannopyranosides. When suitably substituted the acetal can be caused to undergo highly regioselective reductive free radical cleavage of the primary C(6)–O(6) bond to give the corresponding β-rhamnopyranosides. An alternative sequence employing a 4-*O*,6-*S*-monothioacetal of a 6-thiamannopyranosyl donor enables equally selective β-mannopyranoside formation with subsequent reduction to the β-rhamnopyranosides by means of Raney nickel. The viability of the methods is established by their application to the synthesis of complex bacterial oligosaccharides.



Scheme 18. Glycosylations in the L-series.

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