International Journal of Academic Research
ISSN: 2348-7666; Vol.8, Issue-10, October, 2021
Impact Factor: 6.023; Email: drtvramana@yahoo.co.in

Updates on Synthetic Approaches of Ring Expanded Hexoses: Septanosides

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Abstract : *The current paper dwells on the synthetic methods of monosaccharide-based carbohydrates incorporating a seven-membered ring system, often termed septanosides. Septanoside-based oxepanes synthesis has generated significant interest because of its structural peculiarity and because of the possible biological role as carbohydrate analog. These analogues of seven sugars offer valuable scaffolds in drugs design and offer valuable frameworks to study structure-activity relationships in glycobiology. The main goal of this review is to outline effective synthetic methodologies of carbohydrate-derived oxepanes, which are important in ring-expansion of hexoses and the production of new glycomimetics. Extra attention is paid to the procedures used, difficulties faced, and innovations made during the synthesis of septanosides. Moreover, the review summarizes the known synthetic approaches to the most common synthetic routes, thus providing a clear insight into the evolution of septanosides as useful molecular scaffolds in carbohydrate chemistry and medicine*

Key Words: *Septanosides, Ring Expanded Hexoses, Oxepanes, Synthetic strategies and Glycomimetics*

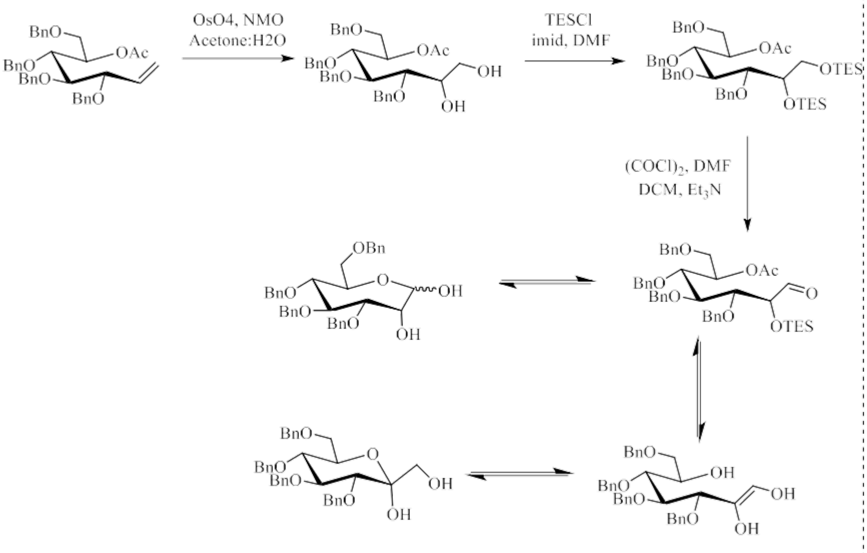
1. INTRODUCTION

An expanded monomer approach of hexoses applied to carbohydrates, which leads to cyclic seven membered sugars called as septanoides. They have a great attention to synthetic targets in a variety of natural products and pharmaceutical applications. Larger ring size also gives more flexibility leading to various conformations of similar energy with minimal barrier.1 Several methodologies were developed to synthesise the septanosides including expansion of smaller rings and the formation of new C-C and C-O bonds by cyclisation of open chain precursors as key steps2 were discussed, for example acetal formation from a linear precursor containing aldehyde and an appropriately positioned hydroxyl group,3 knoevenagel condensation of sugar aldehydes with active methylene compounds,4 ring closing metathesis reactions of appropriately installed diene derivatives,5 ring expansion of 1,2 – cyclopropanated sugars,6 Bayer Villiger oxidation of inositol derivatives7 electrophile induced cyclisation,8 ring opening of cyclopropyl moiety with a nucleophile and oxidation reduction reactions. Moreover in recent years Hoberg,9 Nagarajan,10 Ramusridhar,11 Peczuh and coworkers.12 reported the synthesis of septanosides including the ring expansion strategies. These synthetic approaches are exclusively based on the development of glycosidase inhibitors and their therapeutic potential13,14 and they may be able to adopt distorted conformations in glyco- enzyme binding sites,15 as well as ring expanded nucleosides which are closely related to the natural nucleosides, hence their synthesis gained an increased attention.16 Septanoses are also used as analogs of natural pyranose sugars to investigate protein- carbohydrate interactions.17-19

Further, Kuszmann etal., revealed that the sepatanose mimics of thiopyranose which exhibits a 10 fold increase in activity with reference to the basiparcil, an oral anti thrombotic drug.20 Similarly, methyl β-septanoside mimic of α-mannopyranoside was found to be a competitive ligand for concanavalin A, a natural lectin for α-mannosides.21 Glycosylation involving septanoses have donor strategies from pyranose to ring expansion as well as the functionalization sequences. J.Saha and M.W.Peczuh has developed a transient 1,2-anhydroseptanose in presence of acceptor and in appropriate conditions to convert septanose containing glycoconjugates.

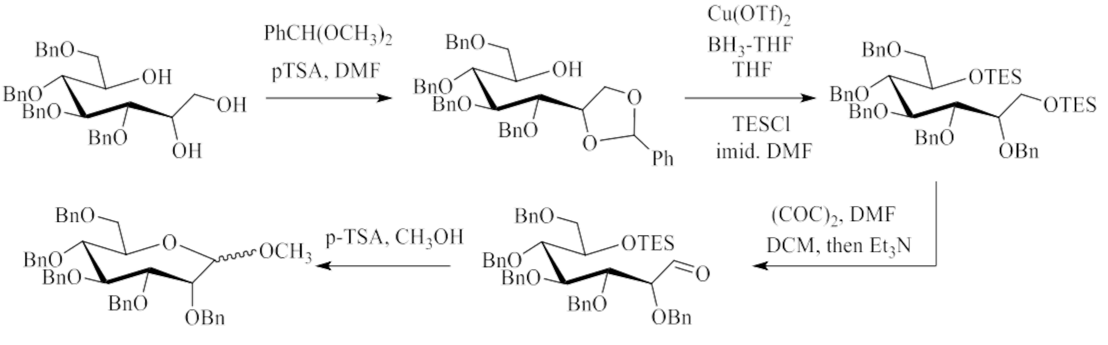
2. Synthetic Approaches of Septanosides

A new approach was developed by Peczuh to prepare septanoside from heptenitol which was derived by the known Wittig methylenation of D-Glucose22, 23 dihydroxylation of heptenitol followed by TES protection, under Swern oxidation conditions TES group on the primary alcohol was selectively to give a carbonyl compound followed by glycosylation between aldehyde and diol. (scheme 1).



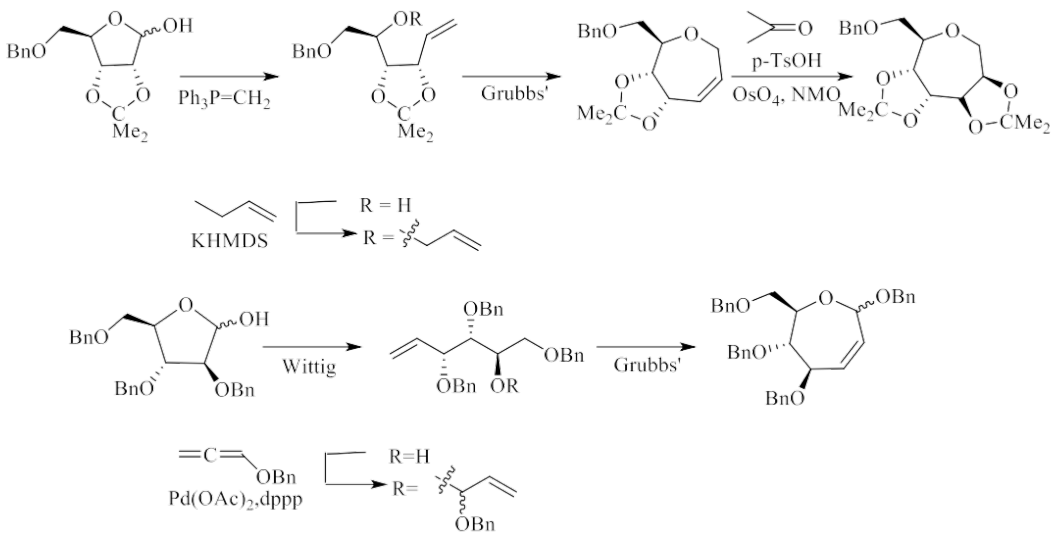
Scheme 1: Synthesis of septanoside from heptenitol followed by aldehyde alcohol equilibration

Peczuh has reported that the methyl D-glycero-D-gulo septanoside and allyl D-glycero –D-gulo septanoside was synthesised from heptenitol. Heptenitol was derived by the known wittig methylenation of D-glucose, this undergoes dehydroxylation to lead 1,2-diol was selectively converted to the corresponding benzylidene, the benzyl ether at C-2 are stable to the acidic conditions. Exposure of aldehyde to acidic methanol or acidic allylic solutions leads to corresponding methyl or allylic septanosides. Silyl ether deprotection at C-6, followed by tandem cyclisation and acetalization /glycosylation leads to D-glycero D-gulo-septanoside (scheme 2).



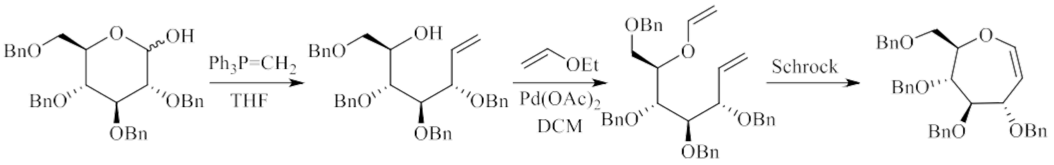
Scheme 2 : Synthesis of D-glycero-D-gulo-septanoside via cyclisation

Here are some reports that presented oxepines can be afforded by ring closing metathesis and cyclomerisation of terminal alkynes. Sturino and co-workers prepared polyoxegenated oxepanes, which are 1,6-anhydroaldoses but they were considered as1-deoxyseptanoses by RCM. For example wittig methylenation of 6-O-benzyl 2,3-O-isopropylidene-D-ribose gave alcohol alkylation of exposed alcohol group gave alkenyl compound which was undergoing ring closing metathesis by using Grubbs' first generation ruthenium catalyst to provide oxepine. Earlier van Boom et al.24 utilised essentially the same RCM-based approach for the synthesis of oxepines. 2,3,5-tri-O-acetyl-D-arabinofuranose was converted into the alkene, which on treatment with benzyloxy -1,2-propadiene in the presence of catalytic palladium yielded the allylic acetal as a mixture of diastereomers, which on ring closing metathesis can form oxepine (Scheme3).



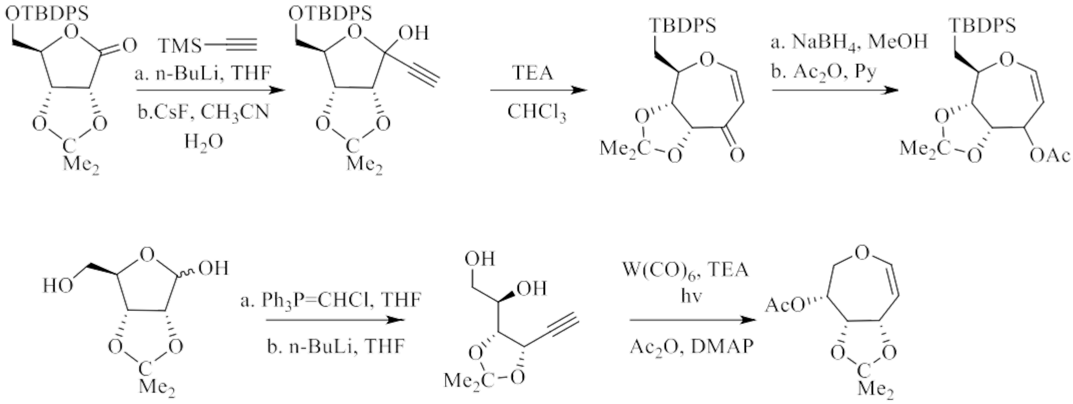
Scheme 3: Synthesis of polyoxygenated oxepines, oxepines by RCM

Wittig methylenation of 2,3,4,5-tetra-O-benzyl-D-glucose gave alkene, then vinylether was formed at alcohol generates diene ring closing metathesis of diene by Schrock method to provide septanose in good yield (Scheme 4).



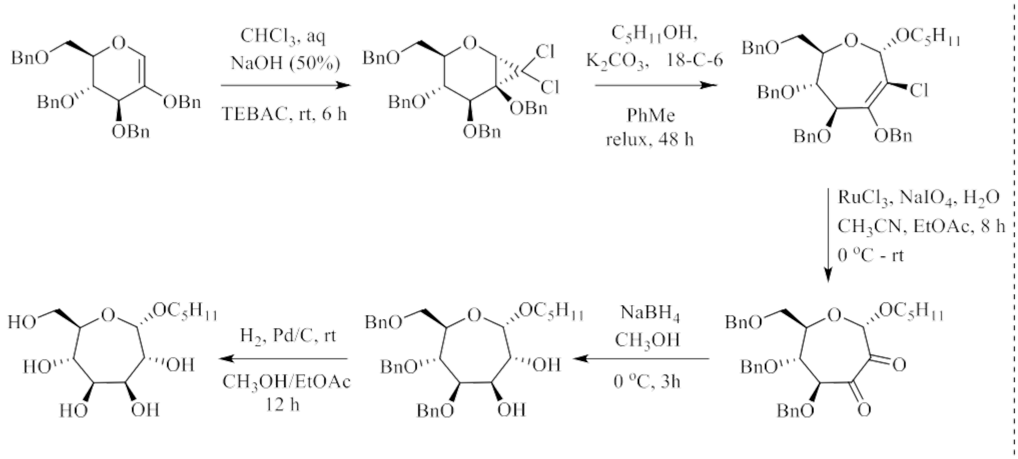
Scheme 4: Synthesis of septanoside/oxepine from ring closing metathesis

An interesting synthesis of Oxepanes by cyclomerisation of terminal alkynes, alkyne hemiacetal compound was prepared by the addition of ethynyltrimethyl silane to 5-O-tertiary butyl diphenyl silyl – 2,3-O-isopropylideneD-ribonolactone followed by desilylation in two steps. Triethylamine mediated cyclomerisation provided an oxepinone in 41% yield. 1,2-addition of enone followed by acetylation under standard conditions provide oxepane. In a similar way alkynyl diol was prepared from 2,3-O-isopropylidene-D-ribose by wittig chloromethylation followed by dehalogenation. Photoinitiated dissociation of one of the CO ligands from $(WCO)_6$ catalyst in the presence of triethylamine formed the tungsten complex $Et_3NW(CO)_5$, which is the active catalyst for cycloisomerisation (Scheme 5).



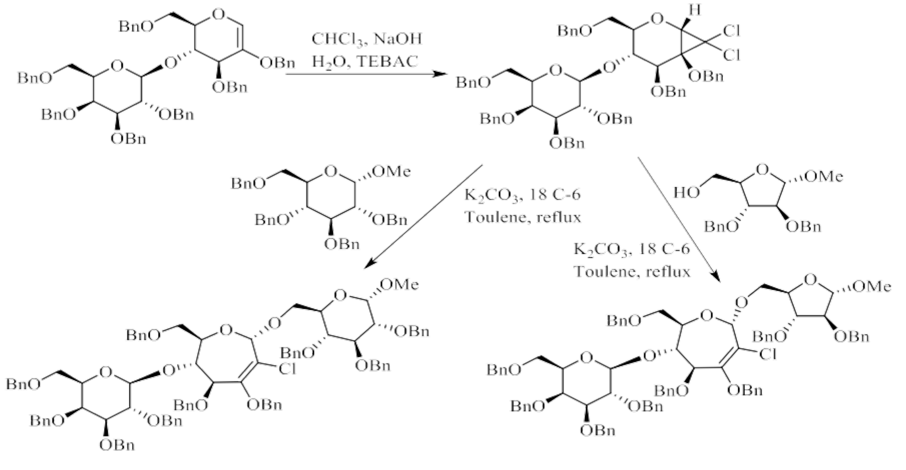
Scheme 5: endo selective cycloisomerisation of alkynyl alcohols in presence of tungsten catalyst

Jayaraman's group was developed a methodology to prepare septanosides from an oxyglycal shown in the oxygen atom at C-2 position was retained till the septanoside. Vinylhalides and diketones are intermediates which could provide to expand the sequence of the reaction. Synthesis of n-pentyl septanoside was prepared by oxyglycal which could generate dichlorocarbene, the reaction of n-pentanol with dichlorcarbene by using K_2CO_3 and 18-crown ether in toluene provided chlorooxepine, further reaction sequence was continued (Scheme 6).



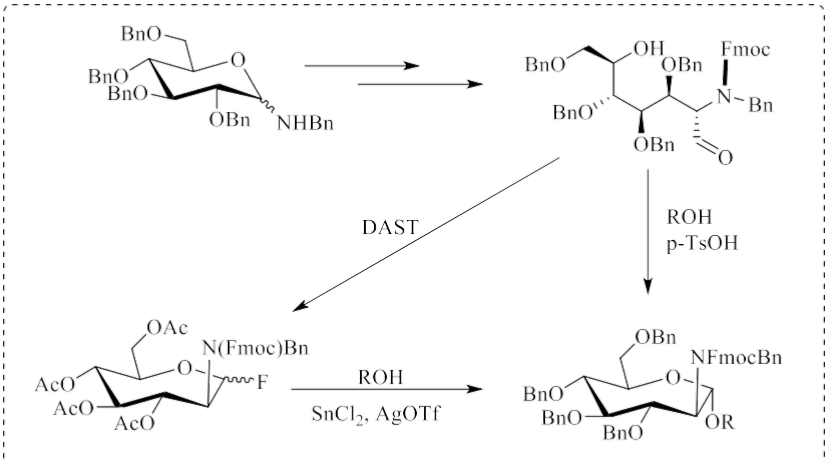
Scheme 6: Synthesis of n-pentyl D-glycero-D-galacto- septanoside

They recently developed lactose derived septanoside from 2-oxy-glucal disaccharide reacted with chloroform under Makosza conditions to afforded gemdichloro cyclopropane, base hydroxyl promoted ring expansion in presence of 5-hydroxy pentofuranoside generate the trisacharide, in the same way 6-hydroxy hexopyranoside provide the trisacharide therefore they reported that the 2-oxyglycal derived cyclopropanes undergo ring expansion even under the basic conditions to form 2-C-branched products in glycal series (Scheme 7).



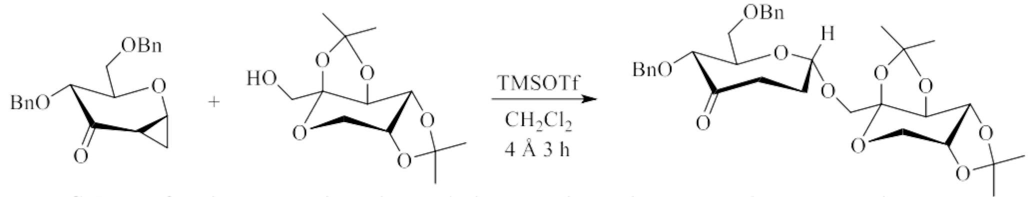
Scheme 7: Ring expansion of 2-oxyglycal-derived gem dihalocyclopropanes to afford trisacharide

Moreover heptanose glycoconjugates was prepared by glycosylation of 1,2:3,4-di-O-isopropylidene-D-galactose under lewis acidic conditions with the 1,2-anhydro sugars. Further Peczuh group has recently reported the preparation of 2-amino septanosides that utilised septanosyl flourides as donors. Septanosyl fluoride in turn could be synthesised from hydroxyl aldehyde using DAST as the fluoride source. Hydroxyl aldehyde itself prepared from glucosyl amine (Scheme 8).



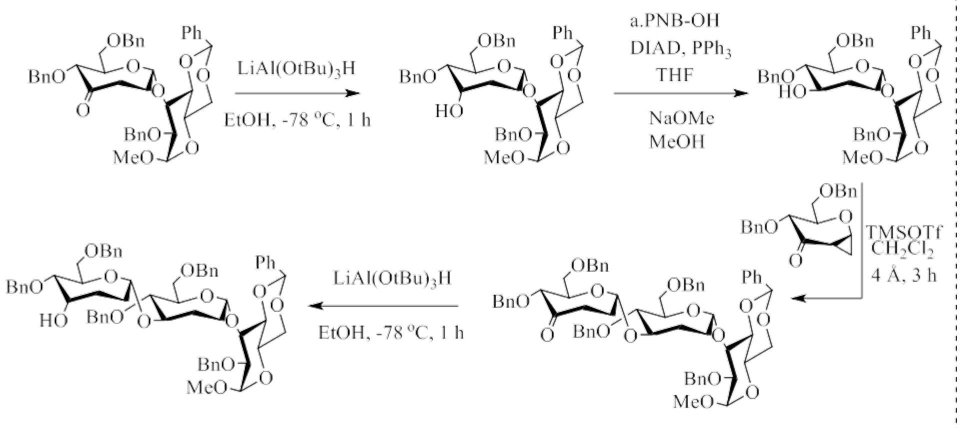
Scheme 8: Synthesis and glycosylation of 2-amino septanosyl fluorides

Another interesting synthesis of carbohydrate based oxepanes by using cyclopropanated sugars has also been reported. C-3 position of 1,2-cyclopropanated sugar derivatives undergo regioselective electrophilic ring opening reaction by an assistance of endocyclic oxygen to provide oxepine derivative. 1,2-cyclopropa-3-pyranone was glycosylated with 2,3,4,5-di-O-isopropylidene-α-D-fructopyranose as an acceptor in DCM at -78 °C using $BF_3.Et_2O$ as Lewis acid, the glycosylation reaction proceeded smoothly and provided the septanohexose disaccharide in 65% yeild. A slight improvement was favoured the α-glycoside formation by using $(CF_3SO_2)_2O$ or $InCl_3$ as under similar reaction conditions. When TMSOTf was used as a catalyst the ring expansion glycosylation proceeded successfully with an excellent α-selectivity. (Scheme 9)



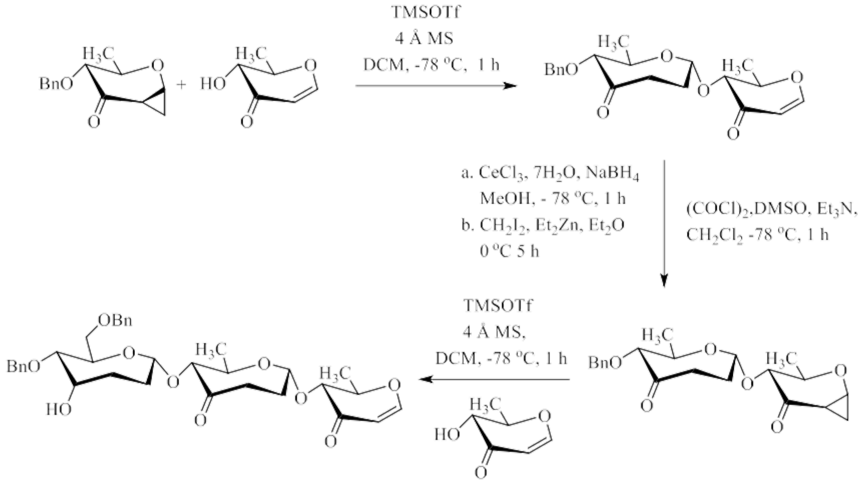
Scheme 9: Ring expansion glycosylation reaction using 1,2-cyclopropanated sugar

After synthesising the septanohexose disaccharide derivatives, further focussed on the synthesis of diseptanohexose trisacharides. Hence the stereoselective reduction of disaccharide with lithium tri tertiary butoxy aluminium hydride in ethanol at -78 °C provided an acceptor, glycosydation of 3-oxo-1,2-cyclopropanated sugar with a disaccharide did not proceed under optimized conditions. Under Mitsunobu conditions provided an acceptor which on glycosylation was provided a trischaride. (Scheme 10)



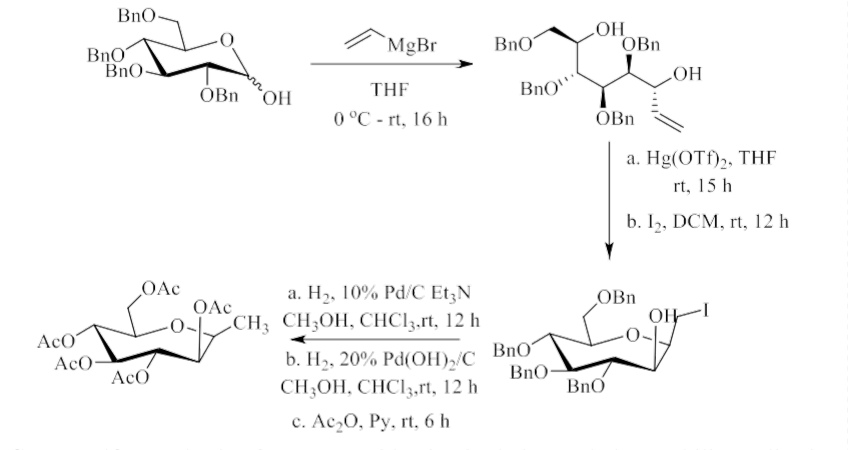
Scheme 10: Synthesis of diseptanohexose trisacharide

Based on this protocol reports the stereoselective ring opening of 3-oxo-1,2-cyclopropanated sugar derivatives with carbohydrate nucleophilic acceptors in the synthesis of oligosaccharides, and further glycosylation technology has been developed and synthesised diseptanohexose oligosaccharide. (Scheme 11)



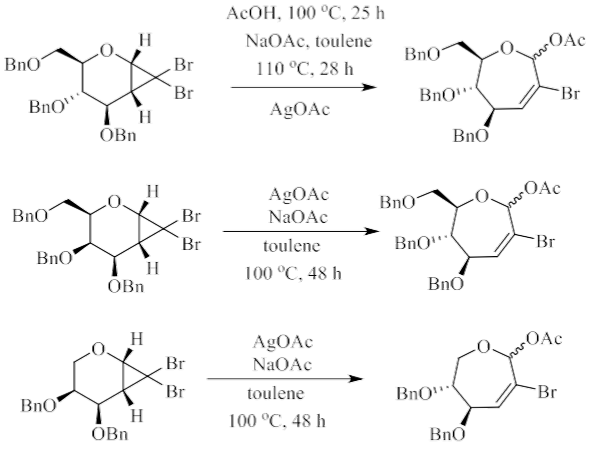
Scheme 11: Synthesis of septanooligosacharide

M.W.Peczuh et al25., reported as C-septanosides, which could be prepared via electrophilic cyclisation of the appropriate enitols. The generation of enitol by wittig olefination of a pyranose or vinyl addition to a pentose followed by Hg2+ cyclisation.26-27 The cyclisation of enitol to form a seven membered ring was more favourable than the other reactions such as intermolecular etherification, intramolecular attack of benzylether etc (Scheme 12).



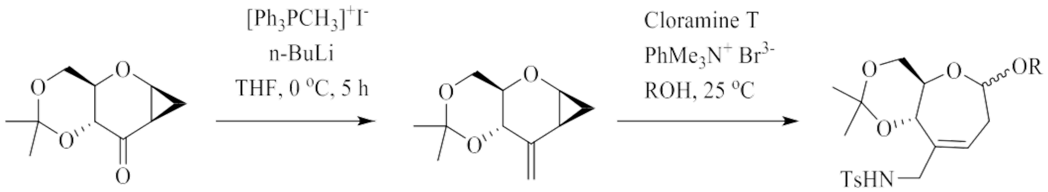
Scheme 12: Synthesis of C-septanoside via vinylation and electrophilic cyclisation

J.E.Harvey and co-workers reported silver promoted ring expansion of glycal derived gem di halo cyclopropanes with acetates afforded septanosides. Where as in the galactal system the top face is more crowded than the bottom face and exclusively α-anomer was observed. D-glucal and D-xylal would affect with thesteric crowding on both faces of the sugar ring hence mixture of isomers were obtained (Scheme 13)



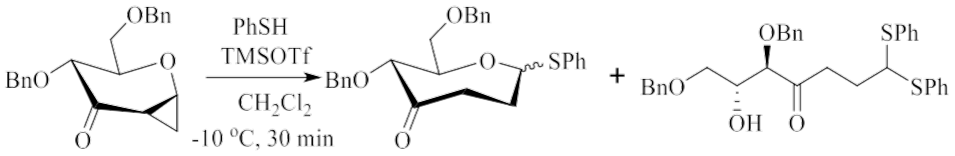
Scheme 13: Silver promoted ring expansion of glycal derived gem dihalocyclopropane with acetate

Further cyclopropyl lactone28 was converted into vinyl cyclopropane by using a wittig reaction. Solvolytic ring opening cyclopropane mediated by chloramine -T and catalytic amount of PTAB in presence of alcohol provided the corresponding oxepane derivative (Scheme 14).



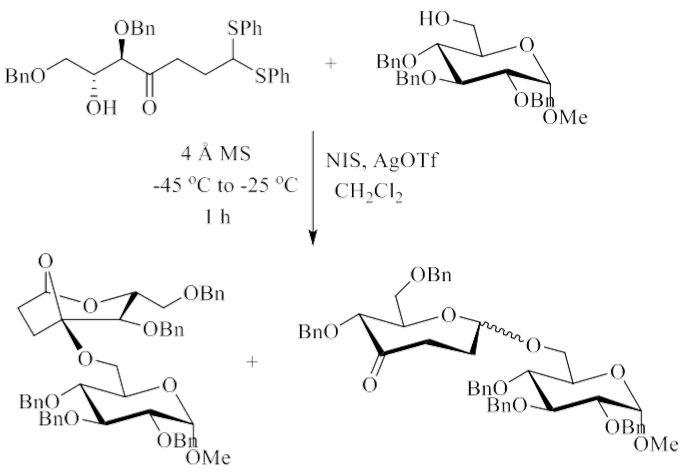
Scheme 14: Ring expansion from Sugar derived VCP

The recent reports of septanoside derived thioglycoside donors from 3-oxo cyclopropanated sugars. Initially dithioacetal derivative of glucose has been converted to D-glucoseptanose in very less yield.



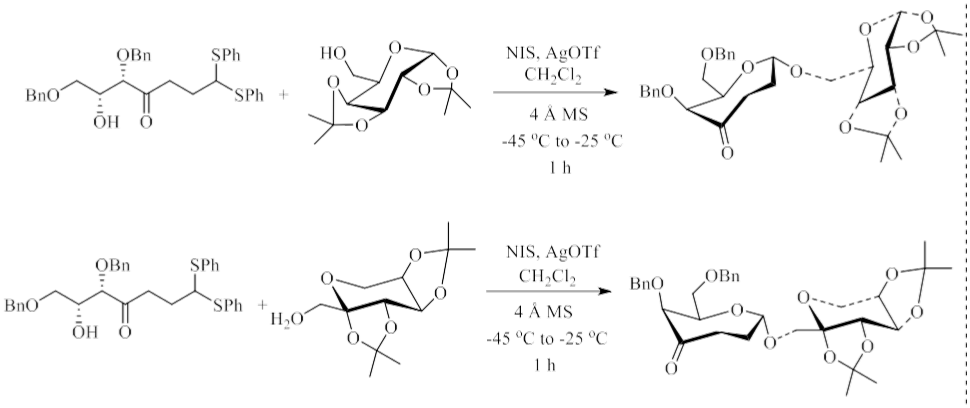
Scheme15: Reaction of 1,2-cyclopropapyranose with thiolphenol

The dithioacetals obtained from cyclopropanated sugar reacted with thiophenol (1.2equiv) in presence of TMSOTf (0.2equiv) the expected product is 3-oxo-septanose donor but dithioacetals is also obtained, (Scheme 15) this was treated with N-Iodosuccinimide (NIS) and catalytic AgOTf in CH_2Cl_2 in presence of 4 Å molecular seives at -10 ^{o}C. However the reaction was performed in presence of a glycosyl acceptor which produced the disaccharides along with the bridged bicyclic glycoside in 2:3 ratios (Scheme 16)29 the product was formed due to intramolecular septanoside formation followed by the glycosylation reaction.



Scheme 16: One pot septanoside formation and glycosylatipon reaction of sugar derived acyclic dithio acetal donor.

Other Septanoside derivatives from glycosylation and dithio acetals is shown in scheme 17

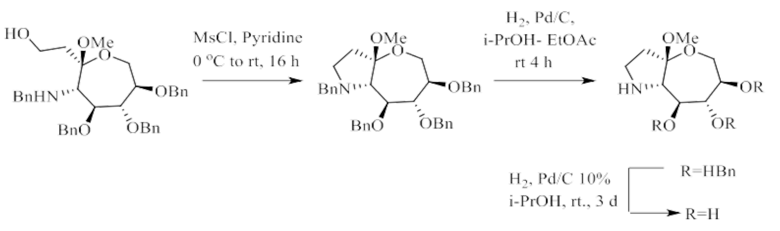


Scheme 17: Synthesis of septano hexoses from sugar derived acyclic dithio acetal donors

3. MISCELLANEOUS SEPTANOSIDE SYNTHESIS:

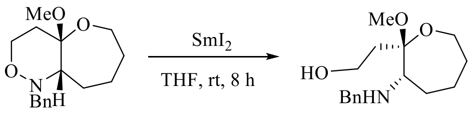
In addition to the well-established synthetic strategies for septanosides, several miscellaneous approaches have also been reported which highlight the structural diversity and synthetic flexibility of carbohydrate-derived oxepane systems. These methods often involve novel reagents or specific reaction conditions that allow ring expansion, rearrangements, or selective functional group modifications.

Scheme 18 demonstrates the synthesis of a D-Xylose-derived oxepanopyranoside derivative. The route proceeds through mesylation of the precursor in the presence of MsCl and pyridine (0 °C to room temperature, 16 h), followed by hydrogenolysis (H_2, Pd-C) and subsequent treatment with i-PrOH–BnBr, affording the desired oxepane derivative in good yield. The synthetic transformation is particularly noteworthy since it achieves selective ring expansion of the hexose framework, giving rise to a stable septanoside system that retains the stereochemical integrity of the carbohydrate precursor. Such synthetic methods provide an efficient entry point into biologically relevant oxepane scaffolds.



Scheme 18: Synthesis of D-Xylose-derived oxepanopyrrolidine derivative

Scheme 19 presents an alternative method wherein Samarium(II) iodide (SmI_2) plays a crucial role in promoting the ring-opening transformation. Treatment of the bicyclic precursor with SmI_2 in THF at room temperature for 8 hours affords the oxepane derivative in high stereoselectivity. This reductive methodology exemplifies how single-electron transfer reagents can be harnessed to generate septanosides under mild reaction conditions. The advantage of this route lies in its operational simplicity and the ability to functionalize sensitive carbohydrate derivatives without extensive protecting group manipulations.



Scheme 19: Samarium (II) iodide mediated ring opening leads to oxepane derivative

Together, these approaches underline the versatility of septanoside synthesis. While traditional strategies often rely on ring-expansion of hexoses, the miscellaneous pathways highlight how tailored reaction conditions and specific reagents—such as MsCl or SmI_2—can open up new possibilities for accessing structurally diverse oxepane-based carbohydrates. These methodologies not only expand the synthetic toolbox but also pave the way for designing analogues with potential biological applications in medicinal chemistry and glycoscience.

4. Conclusion

The synthesis of septanoside-based oxepanes represents an emerging and important area in carbohydrate chemistry, primarily because of their structural novelty and potential biological applications. Septanosides, as seven-membered carbohydrate ring systems, provide valuable mimics of naturally occurring monosaccharides and offer new opportunities for the design of biologically active glycomimetics. In this article, an overview of the synthetic strategies employed for the ring expansion of pyranosides into septanosides has been presented. Key transformations such as Wittig methylenation of D-glucose, cyclopropanation, cyclomerisation of terminal alkynes, ring opening reactions, electrophilic cyclisation, oxidation, and reduction have been highlighted as efficient methodologies in accessing oxepane derivatives. These diverse approaches demonstrate the flexibility and creativity of modern synthetic chemistry in constructing complex carbohydrate frameworks. Overall, the systematic exploration of these synthetic routes not only enriches the field of carbohydrate chemistry but also paves the way for potential applications of septanosides in drug discovery, biomolecular recognition, and material science. Further research in this area is expected to yield novel analogues with enhanced stability, selectivity, and therapeutic relevance.

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