Current Synthetic Approaches to the Synthesis of Carbasugars from Non-Carbohydrate Sources

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Abstract

Carbasugars are a group of carbohydrate derivatives in which the ring oxygen is replaced by a methylene group, producing a molecule with a nearly identical structure but highly different behavior. Over time, this definition has been extended to include other unsaturated cyclohexenols and carba-, di-, and polysaccharides. Such molecules can be found in bacterial strains and the human body, acting as neurotransmitters (e.g., inositol trisphosphate). In science, there are a wide range of research areas that are affected by, and involve, carbasugars, such as studies on enzyme inhibition, lectin-binding, and even HIV and cancer treatment. In this review article, different methods for synthesizing carbasugars, their derivatives, and similar cyclohexanes presenting comparable characteristics are summarized and evaluated, utilizing diverse starting materials and synthetic procedures.

Keywords Carbasugars · Carbohydrate chemistry · Synthesis · Pseudosugars

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1 Introduction

Carbohydrate chemistry is associated with a wide range of fields, such as organic chemistry, pharmaceuticals, medicine, and electrochemistry [1–3]. The broad range of functions of carbohydrate biomolecules, for example, the storage of energy, is made possible by the fact that carbohydrates are components of glycoproteins and glycolipids [4, 5]. As components in these types of compounds, carbohydrates are involved in an extensive range of processes, such as signalling, cell–cell communication, and molecular and cellular targeting [6]. Further biological processes, such as blood clotting and fertilization, require carbohydrates, and the biological implications of these compounds are strongly related to diseases such as cancer, diabetes, and inflammatory processes [7].

Based on these factors, the search for new derivatives with analogous or even improved biological properties compared with those of the natural parent structures represent a logical focus of research. The term “carbohydrate mimetic” is used frequently to refer to any carbohydrate derivative or other compound that has multiple hydroxy groups and thereby resembles a saccharide. Between 1966 and 1968, the research group of McCasland developed a series of derivatives in which the ring oxygen of a monosaccharide was replaced by a methylene group; these authors neologized the term “pseudo sugars” for this family of compounds, though such compounds are currently called “carbasugars” (Scheme 1) [8, 9]. The researchers hypothesized that the structural resemblance of carbasugars to the original sugars would enable their identification by enzymes or other biological systems in place of the related true sugars. Importantly, while guaranteeing a high similarity with true natural sugars, the slight change affords compounds with greater stability toward endogenous degradative enzymes.

McCasland et al. synthesized 5a-carba-R-DL-talopyranose (the first reported carbasugar) [8], 5a-carba-R-DL-galactopyranose [10], and 5a-carba-α-DL-glucopyranose. Notably, 7 years later, 5a-carba-R-D-galactopyranose was isolated as a truly natural product from a fermentation broth of Streptomyces sp. [11]. In the following four decades, the chemical, biological, and conformational aspects of carbasugars were extensively studied [12, 13], resulting in studies on enzyme inhibition, lectin-binding, and even HIV and cancer treatment [14–16].
Various strategies have been employed for the synthesis and isolation of carbasugars, mostly starting from simple monosaccharides such as glucosamine and resulting in the corresponding carbasugars [17–19]. Other approaches work from simple hexopyranoses to more complex carbafruranoses such as carbaarabinofuranosides [20, 21] or even more complex carbasugar derivatives such as fluorinated carbasugars [22]. All these methods start from simple monosaccharidic compounds and require numerous synthetic steps to produce the final product [23–29]. In past years, scientists have developed and investigated possibilities for easily accessible alternative approaches. Starting with more basic chemical structures, a wide range of different strategies have been employed to achieve the goal of synthesizing carbasugars from non-carbohydrate sources.

Natural products containing carbasugar subunits fall beyond the scope of this review and will not be dealt with here, though their application in medicinal chemistry is of course important [11]. The chemical synthesis of carbasugars and their derivatives comprises the topic of this review. There are different approaches to these compounds, which are classified broadly into two groups: synthetic methods that use non-carbohydrates as starting materials, and procedures that make use of carbohydrates as precursors [12]. In pharmaceutical production, carbasugar synthesis is not being used, as it is based most dominantly on carbohydrate sources. Due to the complexity and inefficiency of the synthesis pathways, mass production of carbasugar-based pharmaceuticals is not feasible. Thus, a new type of carbomimetic synthesis is desired in order to ensure an efficient access to carbasugar production. Therefore, in this review, we concentrate on strategies that start from non-carbohydrate sources.

2 Synthesis Methods

The following sections will review six methods for synthesizing carbasugars from non-carbohydrate sources. The methods discussed are based on cyclohexadien-diol, Norbornene, the Diels–Alder reaction, iodobenzene, methyl benzoate, or benzoquinone.

2.1 Synthesis Based on Cyclohexadien-diol

In this section, we analyze the synthesis of pseudosugars based on cyclohexadien-diol. The pericosines A (1), B (3), and C (4), shown in Scheme 2, occur naturally and were isolated originally from the fungus Periconia byssoides. This fungus can be found in the gastrointestinal tract of the sea hare Aplysia kurodai [30, 31]. The initial synthesis of pericosine was accomplished by Donohoe in 1998 [32]. Since then, interest in synthesizing pericosines has increased steadily.

Periscosines are known for their cytotoxicity against P388 lymphocytic leukaemia cells, antitumor activity against murine P388 cells, and selective growth inhibition against human cancer cell lines HBC-5 and SNB-75 [33]. By fulfilling these functions, pericosines may be important in treating cancer. In addition, the structural
similarities between pericosines (polyhydroxylated cyclohexenes) and pseudosugars (polyhydroxylated cyclohexanes) suggest that both could be classified as carbasugars [34].

Based on the reactions shown in Scheme 3, the dihydroxylation of cis-dihydrodiol 5, using the Donohoe procedure [35], gave a 4:1 mixture of two cis,cis-tetraol diastereoisomers. These diastereoisomers sequentially resulted from an oxidative attack on the same face at the 5,6 and 3,4 double bonds. Following the reaction in Scheme 3, the authors were able to isolate, after chromatography, regioisomer 6 with a 70% yield [34].

Furthermore, the authors theorized that the hydroxyl group at the C6 position of compound 6 would be less reactive in the subsequent acetal reaction because the C6 hydroxyl was hydrogen-bonded to the adjacent carbomethoxy group. Following

\[ \text{Scheme 2} \quad \text{The conversion of cis-dihydrocatechols into pericosines A, B, and C} \]

\[ \text{Scheme 3} \quad \text{Synthesis of pericosine A. Reagents and conditions: a OsO}_4, \text{Me}_3\text{NO, CH}_2\text{Cl}_2, \text{rt, 12 h (70%)}; b \text{Me}_2\text{CO, PTSA, rt, 12 h (74%)}; c \text{MeCN, 0 °C, 15 min, rt, 1 h (94%)}; d \text{MeOH, cat. MeCOCl, rt, 12 h (84%)}. \]
the reaction, tetraol 6 was treated at room temperature with acetone under acidic conditions, which resulted in a 7:4:9-mixture of acetonides 7, 8, and 9. There was no acetal formation between the hydroxyl groups at C4 and C5. Acetonide 7 (74% overall yield) was produced by separating the mono- and bis-acetonides, repeatedly recycling the unwanted acetals 8 and 9 via hydrolysis, and reacetalizing the recovered tetraol 6 [34].

The authors also achieved synthesis of (+)-pericosine B (3) after hypothesizing that this form could be synthesized from tetraol 6. Synthesis was achieved after selective protection of the three hydroxyl groups on carbons C3, C4, and C5. To achieve the stated protection, the authors used the bulky TBS protecting group. However, the remaining hydroxyl group at C6 proved resistant to methylation under a broad range of conditions. Another way to accomplish this synthesis was to employ (1S,2R)-3-cyanocyclohex-3-ene-1,2-diol 11 bearing a CN group that was less bulky than a CO2Me group (Scheme 4). By following the same steps used for the reaction of cis-dihydrodiols 5 and 19, the authors produced a 4:1 mixture of cis,cis- and cis,trans-tetraols in the dihydroxylation of diol 11. From this, the authors isolated the major cis,cis isomer 12 with a 54% yield based on

Scheme 4  Synthesis of pericosine B. Reagents and conditions: a OsO4, Me3NO, CH2Cl2, rt, 48 h (55%), b TBSOTf, 2,6-lutidine, DMF, rt, 3 h (85%), c NaH, Mel, THF, rt, 40 h (62%), d DIBAL-H, Et2O, 0 °C→rt, 3 h (55%), e NaClO2, t-BuOH, NaH2PO4, rt, 24 h (93%), f CH3N2, Et2O, 30 min, 0 °C→rt (57%), g Mel, K3CO3, Me2CO, 35 °C, 25 min (91%), h TFA/H2O, CH2Cl2, rt, 24 h (90%)
The reaction of tetraol 12 with tert-butyldimethylsilyl triflate produced the tri-TBS derivative 13 as the major product with 85% overall yield, together with small amounts of other unidentified inseparable isomers. The free C6 hydroxyl group of the coarse sample of silyl derivative 13 was then methylated, under mild conditions, and a purified sample of methyl ether 14 was isolated easily from the product mixture. The nitrile group in compound 14 was partially reduced to the aldehyde 15, followed by oxidation with sodium chlorite, resulting in 16. The authors then attempted to form the methyl ester 18 by reaction of carboxylic acid 16 with excess diazomethane. Instead of achieving the desired compound 18, the crystalline pyrazoline cycloadduct 17 resulted from this reaction. Thus, synthesis of compound 18 is achieved by base-mediated methylation of carboxylic acid 16, followed by acid-catalyzed removal of the TBS protecting groups, which produced (+)-pericosine B (3) through seven steps, with an overall yield of 12% [34].

To synthesize (+)-pericosine C (4), as shown in Scheme 5, the authors used (1S,2S)-3-iodocyclohexa-3,5-diene-1,2-ol 19 as the starting material for the reaction. Under this alternative approach, cis-dihydrodiol 19 was dihydroxylated using the procedure in the literature (OsO4, TMNO, DCM) [34], thereby giving

\[ \text{Scheme 5 Synthesis of pericosine C. Reagents and conditions: a OsO}_4 \cdot \text{Me}_3\text{NO}, \text{CH}_2\text{Cl}_2, \text{rt, 3 d (71%)}, \]  
\[ \text{b PTSA, Me}_2\text{CO, rt, 24 h (70%)}, \text{c MeCN, 0 °C, 15 min, rt, 1 h (95%)}, \text{d NaOMe, Et}_2\text{O, 0 °C, 15 min, rt, 1 h (95%)}, \text{e NaOMe, MeOH, rt, 12 h (68%)}, \text{f NaOAc, MeOH, CO, Pd(OAc)}_2, \text{rt, 12 h (89%)}, \text{g MeOH, cat. MeCOCl, rt, 12 h (80%)}. \]
a 10:1 mixture of cis,cis- and cis,trans-tetraol diastereoisomers from which the required major cis,cis isomer 20 could be isolated with a 71% yield according to column chromatography. Through selective acetalization accomplished under kinetic control, along with repeated recycling of the unwanted acetals 22 and 23, the required acetal 21 was obtained with a 70% yield. The monoacetinide 22 formed upon partial hydrolysis of bis-acetonide 23, thereby giving access to both mono-protected forms of the tetraol (21 and 22). The reaction of diol 21 with 1-chlorocarbonyl-1-methylethyl acetate resulted in chloroacetate 24. Exposing 24 to sodium methoxide and diethyl ether, provided the desired epoxide 25. Further treatment of 25 with sodium methoxide in a methanol solution resulted in a regioselective ring opening thereby producing the methyl ether 26. Furthermore, room temperature palladium was used to catalyze carbomethoxylation of the vinyl iodide 26 with carbon monoxide in the methanol solution, which resulted in the methyl ester 27. Finally, the authors removed the acetonide group from ester 27 under acidic conditions in methanol, which produced (+)-pericosine C (4). In the authors’ opinion, this method of synthesizing (+)-pericosine C (4) is the most straightforward option to date, requiring only six steps from (1S,2S)-3-iodocyclohexa-3,5-diene-1,2-ol 19, with an overall yield of 17% [34].

In conclusion, it was demonstrated that cis-dihydrodiols derived from methyl benzoate, iodobenzene, and cyanobenzene are versatile complementary intermediates for the rapid synthesis of pericosines A, C, and B, respectively.

Additionally, the laboratories used mutant strains (e.g., UV4, 39D) of the soil bacterium *Pseudomonas putida* and *Escherichia coli*, each containing toluene dioxygenase. This factor provided access to a vast range of over 400 metabolites [34].

The strategic approach for strains to produce 2,3-trans-CHD 28 can be compared to the work performed using *Klebsiella pneumoniae* strains. Non-pathogenic *E. coli* strains are common hosts for genetic modification because of the availability of potent *E. coli* mutants and their well-established fermentation conditions. In this way, previous studies acknowledged another host for synthesizing carbasugars [34, 36].

### 2.2 Synthesis Based on Norbornene

In this section, we analyze carbasugar synthesis based on norbornene, hereby covering only one paper reporting this approach. The structural entities of cyclitols and the polyhydroxylated cyclohexanoids compose important segments of a wide
range of natural products, like antibiotics, and they exhibit biological activity profiles extending from glycosidase inhibitors to antidiabetes and anticancer agents. Better known examples for the mentioned cyclohexitols are the carbasugars. Examples would include pseudo-alpha-galactose (29), conduritol-A (30), myo-inositol 1,4,5-triphosphate (31), and gabosine-C (32) (Scheme 6).

To achieve the synthesis pathway for the carbasugars, the authors first used a ‘bottom-to-top’ Grob-like fragmentation process in an easily accessible 2,7-disubstituted norbornane derivative 33 to cleave the C1–C2 bond 34. Furthermore, the process included extraction of the five-membered ring 35 from the bridged bicyclic frame while retaining full functionalization (see Scheme 7). Taking the paper under consideration, the authors developed a beneficial method for polyhydroxylated cyclohexenoid synthesis. In the following, polyhydroxylated cyclohexenoids are obtained from the same starting materials and subsequently interchanged with functional groups, thereby showing the possibility of extracting either five- or six-membered rings from the norbornyl system [37].

In the cited paper, the authors tested a new approach that involved switching the functionalities in 33 to those in 36. By doing so, the authors arranged a “top-to-bottom” sequence involving C7–C1 bond cleavage (see 37, Scheme 8) to deliver a functionally adorned cyclohexanoid 38 in a regio- and stereoselective manner [37].

To execute the approach shown in Scheme 8, clear access to 36 is needed. To ensure passage, the process in Scheme 9 was followed. Bicyclic alcohol 39, available from 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene and vinyl acetate, was tosylated and exposed to OsO₄-mediated catalytic dihydroxylation to yield exo-exodiol 40. By designing an amberlyst mediated single-pot protection–deprotection in 40, the authors achieved the 7-norbornanone derivative 41. By exposing 41 to

Scheme 6  Four polyhydroxylated cyclohexenoids: pseudo-α-galactose (29), conduritol-A (30), myo-inositol 1,4,5-triphosphate (31) and gabosine-C (32)
NaOMe, the authors achieved smooth top-to-bottom fragmentation, yielding the cyclohexene methyl ester as a single product. The secured stereochemistry of the six ring carbons in cyclohexenoid \( \text{42} \) can be further elaborated to carbasugars [37].

Dihydroxylation across the C5–C6 double bond in cyclohexenoid ester \( \text{42} \) occurred through addition of osmium tetroxide, producing a large yield of cis-diol \( \text{43} \) in a stereoselective manner (Scheme 10). Lithium aluminium hydride (LAH) reduction of the ester group of \( \text{43} \), followed by acetonide deprotection provided the
naturally occurring carbasugar pseudo-α-galactose (29). This carbasugar was characterized as penta-acetate 44. Another method would involve the reduction of the ester group in 42 with LAH and acetylation, resulting in 45 (Scheme 10). To create 46, the carbon–carbon double bond of 45 must be converted to an oxirane (Scheme 10). In the study, acid-catalyzed epoxide ring-opening and naturally accompanying acetonide deprotection provided a 5:2:3 mixture of pseudo-β-galactose 47a, pseudo-α-talose 48a, and bicyclic ether 49a, respectively. Those components of the mixture were well separated and characterized as the corresponding acetates, 47b, 48b, and 49b.

Finally, pseudo-α-fucopyranose (50), which was synthesized from ester 42, showed a possible use as an inhibitor of fucosyltransferases. Due to this potential, the authors found another method for synthesizing 50. Instead of using 39 as a starting point, the authors used the diol ester 43 obtained from 42. This structure was converted into bis-acetonide and subjected to LAH reduction, yielding 51. Next, 51 was tosylated, and reductive detosylation using sodium borohydride was carried out in DMSO. This led to installation of the β-methyl group and bis-acetonide 52. Deprotection of 52 provided pseudo-α-fucopyranose (50), which presented spectroscopic characteristics identical to those noted in previous research [37] (Scheme 11).

### 2.3 Synthesis Based on Diels–Alder Reaction

This reaction, named after its discoverers Diels and Alder from Kiel [38], involves the formation of a ring of six carbon atoms, wherein a conjugated diene and dienophile are linked. The importance of the Diels–Alder reaction is that C–C bonds can be created with high stereoselectivity. Diels–Alder reactions play an important role in the synthesis of natural substances, such as the production of steroids (e.g., the female sex hormone estradiol). In this instance, the racemic cyclohexadiene derivative 53 reacted selectively in a catalytic enantioselective Nitroso–Diels–Alder reaction to give the two main products ent-anti-54 and anti-55, thereby showing the selective formation of two products from eight possible isomers (Scheme 12) [39].

The dienes used for cycloaddition were noted by the authors to be easily accessible, and the products were highlighted as valuable starting materials for the synthesis of carbasugars, such as peracetylated 2-epi-validamine (58, Scheme 15) [40]. It was hypothesized that divergent reactions from racemates are also possible in other Diels–Alder reactions of unsymmetrical dienophiles with racemic
cyclic dienes. This approach could lead to a new concept in the field of stereoselective cycloadditions [39].

A Nitroso–Diels–Alder reaction with the highly enantiomerically enriched diene 53a \((R = (S)-CHPhOTBDPS, 98\% \text{ ee})\) was then examined. The authors found that 53a could be produced easily by desymmetrizing 1,4-cyclohexadiene. At the same time, the ent-compounds in Scheme 12 were not considered. The formation of adducts 54a and 55a occurred in CH2Cl2 in the presence of \([\text{Cu(MeCN)}_4]\)PF6 (10 mol%), a chiral diphosphine (10 mol%), and 2-nitrosopyridine (6 h at −78 °C and then 12 h at −20 °C). The resulting two products, ent-anti-54a and ent-anti-55a, were produced in excellent yields (column chromatography, SiO2) and isolated with high enantiomeric excesses (see Scheme 13) [39].

![Scheme 12](image)

Scheme 12 Possible isomers that can be formed through the reaction of racemic diene 53 with an aryl nitroso compound. \(R^1 = \text{phenyl, alkyl; } R^2 = \text{2-pyridyl}\)

![Scheme 13](image)

Scheme 13 Nitroso–Diels–Alder reaction on the racemic diene 53a. Reagents and conditions: a \([\text{Cu(MeCN)}_4]\)PF6/disphosphine (10 Mol-%), CH2Cl2, −78 °C → −20 °C
Next, a Nitroso–Diels–Alder reaction was carried out with the racemic dienes 53b–f (Scheme 14). The implementation of 53b was successful and presented excellent anti/syn-selectivity. The adducts ent-anti-54b and anti-55b were developed with high enantioselectivities. The diene 53c showed poorer diastereoselectivity (anti/syn = 7:1) since the less sterically demanding CH2OTBDPS group represents a less efficient shield for the syn-side than the alpha-branched substituents. Similar results were observed for the benzyl-substituted diene 53d and the diene 53e, which carries an acetoxymethyl group. The best result was shown for the Ph-substituted diene 53f (see Scheme 14) [39].

Finally, the method presented above was used for the synthesis of peracetylated 2-epi-validamine (58). Reductive N–O-bond cleavage at ent-anti-55c (89% ee), which was synthesized easily from rac-53c using an enantiomer of the Walphos ligand, with [Mo(CO)6] and NaBH4, was followed by desilylation (TBAF) and subsequent acetylation, thereby producing the cyclohexadiene 56 (Scheme 15). Diastereoselective OsO4-catalyzed dihydroxylation and subsequent acetylation led to the pentaacetylated carbo-sugar 57. The N-2-pyridyl group was then cleaved using H2 and Rh/C, thus forming 58 [39].

Another approach for the synthesis of a racemate corresponding to validamine 65 was developed by Suami et al. [41, 42], whose approach was based on the Diels–Alder addition of furan to acrylic acid, resulting in oxanorbornene 59 (Scheme 16). Through hydrogenation in ethyl acetate and oxidation utilizing H2O2, an intermediate compound was achieved in 76% yield. Reduction and acetylation gave 69% of oxanorbornane 60, followed by acetylosis with AcOH and H2SO4, giving protected 5a-carba-β-DL-glucopyranose 61 (20% yield). Deprotection of 61 resulted in 5a-carba-β-DL-glucopyranose (62). Reaction of compound 62 with DMP in dimethylformamide (DMF) in the presence of p-TSA and subsequent crystallization resulted in an inseparable 2:3 crystalline sulfonate mixture of compound 63 and 3-p-toluenesulfonate. Sodium azide in DMF caused creation of a new hexane compound from 63, while preserving the 3-p-toluenesulfonate (11%). Evaporation gave 67% of the new azide compound 64. Reduction with H2 in the presence of Raney nickel in ethanol, followed by acid hydrolysis of the protective groups resulted in the racemate corresponding to validamine 65. The racemate was isolated as penta-N,O-acetyl-DL-validamine (28%, Scheme 16) [41, 42].
2.4 Synthesis Based on Iodobenzene

The next major sources of non-carbohydrate sources for carbasugar synthesis are monosubstituted benzenes. These include regular benzene, methyl benzoate, toluene, and other derivatives of the benzene molecule [43–45]. Here, we outline the various synthetic pathways based on iodobenzene, while reactions based on methyl benzoate are described in the next section.

The research of Boyd et al. [43] precisely describes the synthesis of four 5-(hydroxymethyl)cyclohexane-1,2,3,4-tetraol stereoisomers and their penta-acetylated analogues based on iodobenzene (1S,2S)-cis-dihydrodiol 67. By using the (1R,2R)-cis-dihydrodiol metabolite of iodobenzene, the same reaction processes yielded four additional stereoisomeric forms [43]. In the following section, we explain the different reactions used to obtain the four carbasugars presented in Scheme 17, carba-β-D-altropyranose (68), carba-α-L-galactopyranose (69), carba-β-D-idopyranose (70), and carba-β-L-glucopyranose (71), including their penta-acetate derivatives (not shown) [43].

2.4.1 Synthesis of Carba-β-D-Altropyranose and Carba-α-L-Galactopyranose

The reaction processes for all four carbasugars are based on iodobenzene cis-dihydrodiol 67 (Scheme 18). The synthesis of iodobenzene cis-dihydrodiol from iodobenzene through the use of Pseudomonas putida was clearly reported by Derek et al. [46] and will not be elaborated. The first reaction step involved the
addition of a protecting group at the two hydroxyl substituents. This was performed via the addition of 2,2-dimethoxypropane, thereby forming an acetonide protecting group and resulting in a 98% yield of the (3a\text{S},7a\text{S})-acetonide derivative 72 (Scheme 18). This step was followed by dihydroxylation through the use of catalytic amounts of osmium tetroxide in acetone and water in the presence of \(\text{N}-\text{methylmorpholine N-oxide}\). This process resulted in the (3a\text{S},4\text{R},5\text{R},7a\text{S})-dial acetonide isomer 73 with a yield of 87%. Under a carbon monoxide atmosphere

\[ \begin{align*}
\text{Scheme 16} & \quad \text{Synthesis of the racemate corresponding to validamine 65. Reagents and conditions: a hydroquinone, \text{N}_2, 105 \text{ d}; b \text{i) ethyl acetate, palladium black, H}_2, 30 \text{ min; ii) formic acid (95%), H}_2\text{O}_2 (30%), 45 \text{ °C, 5 min; e i) LiAlH}_4, \text{THF, H}_2\text{O, 5 °C, 15 min; ii) CH}_3\text{CO}_2\text{H, H}_2\text{SO}_4, 22 \text{ h, C}_2\text{H}_5\text{N; e i) 2,2-DMP, DMF, p-TSA, 60 °C, 3 h; ii) MeONa, 70 °C, 1 h, Amberlite IR-120(H\text{\textsuperscript{+}}); f i) NaN}_3, \text{DMF, 2 h; g EtOH, Raney Ni, H}_2, 18 \text{ h; h i) HCl, 80 °C, 1 h, IRA-400(OH\text{\textsuperscript{−}}); j Ac}_2\text{O, C}_2\text{H}_5\text{N, 2 d}}
\end{align*} \]

\[ \begin{align*}
\text{Scheme 17} & \quad \text{Four carbasugar isomers}
\end{align*} \]
with sodium acetate and methanol, the (3aR,6R,7R,7aS)-α,β-unsaturated ester 74 was created with a yield of 81% after being catalyzed through palladium(II) acetate [43].

Under a pressure of 55 psi, catalytic hydrogenation occurred, resulting in an inseparable mixture consisting of the two epimers (3aR,4S,6R,7R,7aS) 76 and (3aR,4R,6R,7R,7aS) 80 (Scheme 19), with yields of 35% and 65%, respectively. The next step involved converting both isomers into their dibenzoate derivatives to enable chromatographic separation by preparative thin layer chromatography (PTLC), yielding about 80% and 86%, respectively (or 28% and 56% relative to the catalytic hydrogenation step). After separation of the mixture, the three ester groups of the (3aR,4S,6R,7S,7aR)-dibenzoate compound 77 were reduced using LAH, yielding (3aS,4R,5R,7R,7aR)-acetonide triol 78 (74%). Using acid-catalyzed deprotection with trifluoroacetic acid, the reactions yielded the desired carba-β-d-altropyranose (68, 90%), which was then purified via charcoal/celite chromatography. The carbasugar was further transformed into its penta-acetate derivative 79 through the use of acetic anhydride and pyridine. The reaction process for carba-α-l-galactopyranose (69) occurred under the same conditions.

After separation through PTLC, the other compound (3aR,4R,6R,7S,7aR)-dibenzoate 81 was treated with LAH, forming (3aS,4R,5R,7S,7aR)-acetonide triol 82 in 76% yield (Scheme 19). Removal of the protecting group, purification, and conversion to the penta-acetate followed the same reaction pathway as that for carba-β-d-altropyranose, yielding 81% of carba-β-l-galactopyranose (69) and 84% of its penta-acetate derivative 83 [43].
2.4.2 Synthesis of Carba-β-d-Idopyranose

The synthesis of carba-β-d-idopyranose (70) was more challenging. With the synthesis of carba-β-d-altropyranose (68) and carba-α-l-galactopyranose (69), the relative configuration of C2 and C3 was identical to those at the iodobenzene dihydrodiol 67. However, with carba-β-d-idopyranose 70, the relative configuration at C2 and C3 was trans, thus requiring inversion at C2. The reaction began by treating the previously synthesized (3aS,4R,5R,7aS)-diol acetonide isomer 73 with benzoyl chloride and pyridine, giving a 95% yield of (3aR,4S,5R,7aR)-dibenzoate 75 (Scheme 20).

This compound was deprotected by hydrochloric acid in methanol, resulting in a 90% yield of dibenzoate 84. Using triphenylphosphine, diethyl azodicarboxylate (DEAD), and 4-nitrobenzoic acid, with Mitsunobu inversion occurring at the targeted allylic position, the dibenzoate resulted in (1R,4R,5S,6S)-p-nitrobenzoate 85 (70% yield). By utilization of sodium hydride in methanol, esters R and R' (see Scheme 20) were hydrolyzed, resulting in (1R,2R,3S,4R)-tetraol 86 with a yield of 87%. Subsequently, a protective acetonide group was added through the addition of 2,2-DMP and p-toluenesulfonic acid (p-TSA), yielding 89% of (3aS,4R,5R,7aR)-acetonide 87, which was then diacetylated at the two trans hydroxyl groups, forming (3aR,4S,5R,7aR)-diacetate 88 (95% yield) with Ac₂O and pyridine. Carbonylation with CO, catalyzed by palladium(II) acetate and sodium acetate in methanol, was used to replace the iodine with a carbomethoxy group, thereby forming the (3aR,6S,7S,7aR)-triester 89. Removing the alkene while also ensuring the desired
relative configuration via catalytic hydrogenation (similar to Scheme 19) through Rh/Al₂O₃ and H₂ in ethanol yielded 40% of (3aR,5S,6S,7aR)-triester 90. However, due to the competing hydrogenolysis, there was also a 60% yield of an undesired (3aR,5S,7aR)-diester 91 (Scheme 20), which was separated easily by chromatography. The reaction continued with triester 90, which was deprotected via the removal of the three ester groups produced by LAH and tetrahydrofuran (THF), giving (3aR,4S,5R,6S)-trimethylethyl acetonide (81% yield), followed by the removal of the acetoxy group through HCl in methanol, yielding 79% of carba-β-d-idopyranose (70).

Similar to both preceding reactions, the carbasugar was transformed into its pentaacetate derivative 93, again through the use of Ac₂O and pyridine, with a yield of 97% [43].

### 2.4.3 Synthesis of Carba-α-L-Glucopyranose

The reaction pathway for the final carbasugar carba-α-L-glucopyranose (71) started with (3aS,4R,5R,7aS)-diol acetonide isomer 73, synthesized under the carba-b-d-altropyranose pathway (Scheme 18). Again, the trans-configuration at C2 and C3 differed from that of iodobenzene cis-dihydrodiol 67, as well as that at C4 and C5, requiring inversion at C2 and C5. The reaction started by deprotecting compound 73 using HCl in methanol (Scheme 21), yielding 85% of (1R,2R,3S,4S)-anti-tetraol 94, followed by treatment with 1-bromocarbonyl-1-methylethyl acetate, which produced

![Scheme 20](image-url)
the desired inversion at C2 and C5 and yielded 87% of (1S,2R,5S,6S)-dibromo diacetoxy derivative 95. Utilizing Woodward–Winstein conditions [47], silver acetate, acetic acid, and Ac₂O yielded 77% (1R,2S,5R,6S)-tetra-acetate 96, preserving all four desired chiral configurations. The addition of palladium(II) acetate, NaOAc, THF, and water under a carbon monoxide atmosphere was performed to replace the iodine with a carbomethoxy group, yielding 73% of unsaturated (3S,4R,5R,6S)-tetra-acetate 97, followed by catalytic hydrogenation, which resulted in saturated (1R,2S,3R,4R,5S)-tetra-acetate 98 with a yield of 80% under similar conditions to those employed in earlier synthesis pathways, using Rh/Al₂O₃ and H₂. Reducing the tetra-acetate with LAH yielded 12% of carba-α-carboxylic acid 71. Due to this surprisingly low yield, another synthesis pathway using a higher step count was developed. Similar to all three other carbasugars, (1S,2S,3R,4R,5S)-penta-acetate 99 was formed under the same conditions, yielding 95% (Scheme 21) [43].

2.4.4 Alternate Synthesis of Carba-β-L-Glucopyranose

As noted earlier, the previously presented synthesis pathway for carba-β-L-glucopyranose did not yield a suitable amount of the desired carbasugar. Thus, a longer yet more efficient synthesis pathway was developed.

The reaction started with the same reactant used in 2.4.3: (3aS,4R,5R,7aS)-cis-diol acetonide 73. Utilizing Mitsunobu inversion conditions similar to those presented in Scheme 20, inversion occurred at C5, yielding 80% (3aS,4S,5S,7aS) 4-nitrobenzoate 100 (Scheme 22). Through the use of potassium carbonate in methanol, the nitrobenzoate compound 100 was transformed into (3aS,4R,5S,7aS)-trans-diol acetonide 101 (82% yield), in which the two trans hydroxyl groups were protected by the benzoyl groups, yielding 93% (3aS,4S,5R,7aS)-trans-dibenzoate acetonide 102. An acid-catalyzed reaction led to removal of the acetonide group from compound 102, forming (1S,4S,5R,6S)-cis-diol dibenzoate 103 with a yield of 86%. A second Mitsunobu reaction was then required to achieve the final relative configuration of all five carbon atoms. This occurred under the same conditions reported previously, resulting in
inversion at C2 and yielding 80% of the (1R,4S,5S,6S)-triester compound 104. The hydroxyl group at C3 was protected by the addition of trifluoromethanesulfonic acid tert-butyldimethylsilyl ester (TBDMSOTf), giving a 93% yield of (1R,4S,5R,6S)-TBDMS ether 105, followed by deprotection of the three remaining hydroxyl groups using NaOH in methanol, thereby yielding 86% of (1S,2R,3S,4R)-triol 106 (Scheme 22). The next step involved substitution of the iodine with a carbomethoxy group using similar conditions to those employed in previous schemes, thus forming an unsaturated (3S,4R,5R,6S)-ester 107 with a yield of 69%. This ester compound was hydrogenated into the saturated (1R,2S,3R,4R,5S)-ester 108 with a yield of 80% and trans configuration between the carbomethoxy and adjacent hydroxyl group. Through the addition of TBDMSOTf, (1S,2S,3R,4R,5S)-tri-TBDMS ester 109 was achieved. Similar to previously described schemes, the addition of LAH resulted in reduction of the carbomethoxy group to a hydroxyl methyl group, yielding compound (1S,2R,3R,4S,5S)-tri-TBDMS ether 110.

Deprotection in HCl and methanol using tetra-n-butylammonium fluoride (TBAF) and THF resulted in a 78% yield of the desired carba-β-l-gluco.pyranose (71). As with all previous reactions, the carbasugar was purified using charcoal/Celite and further characterized as its penta-acetate derivative 99 (Scheme 22) [43].

**Scheme 22** Alternate synthesis of carba-β-l-gluco.pyranose. Reagents and conditions: a PPh₃, DEAD, 4-NO₂C₆H₄CO₂H, 80% yield, b K₂CO₃, MeOH, 82% yield, c BzCl, C₅H₅N, 93% yield, d HCl, MeOH, 86% yield, e PPh₃, DEAD, 4-NO₂C₆H₄CO₂H, 80% yield, f TBDMSOTf, 93% yield, g NaOH, MeOH, 82% yield, h CO, Pd(OAc)₂, NaOAc, THF, H₂O, 69% yield, i Rh/Al₂O₃, H₂, 80% yield, j TBDMSOTf, 95% yield, k LiAlH₄, 82% yield, l TBAF, THF, 78% yield, m Ac₂O, C₅H₅N, 97% yield.
2.4.5 Synthesis of (−)-Gabosine A

Based on iodobenzene (1S,2S)-cis-dihydrodiol 67, Banwell et al. [48] presented a pathway that provides (−)-gabosine A (116) over six steps (Scheme 23). The reaction started by protecting compound 67 at the less sterically hindered hydroxyl group at C1 under a nitrogen atmosphere, thus forming TBDPS-ether 111. Utilizing UpJohn dihydroxylation conditions [49], two hydroxyl groups were formed at the non-halogenated carbon–carbon double bond, yielding triol 112. The addition of an acetonide occurred under known conditions in the presence of triethylamine, thereby forming acetonide compound 113. This compound was oxidized under Swern conditions, yielding the ketone 114, followed by replacement of the iodine with a methyl group, utilizing iron-catalyzed reactions developed by Cahiez and Avedissian [50]. Deprotection under acidic conditions and THF gave a 1:2 mixture of (−)-gabosine A (116) and its 6-TBDPS ether derivative, which was then treated with THF and tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF), to remove the silyl ether group and form the desired (−)-gabosine A (116, Scheme 23) [48].

2.5 Synthesis Based on Methyl Benzoate

As stated in the previous section, various different types of benzene derivatives are used for carbasugar synthesis. This section explores methyl benzoate as a reactant. Similarly, methyl benzoate was converted into its cis-dihydrodiol metabolite, thereby ensuring the same skeletal structure as mono carbasugars along with the desired relative configuration at C2 and C3 to synthesize more three sugar analogues.

The work of Boyd et al. explored the synthesis of three more carbasugars, carba-β-L-galactopyranose (117), carba-β-L-talopyranose (118), and carba-α-L-talopyranose

Scheme 23 Synthesis of (−)-gabosine A (116). Reagents and conditions: a TBDPSCI, imidazole, CH2Cl2, b OsO4, NMO, acetone-H2O, c 2,2-DMP, p-TSA, Et3N, d COCl2, DMSO, Et3N, e MeMgCl, FeCl3, NMP, THF, f HCl, MeOH, (Me2N)3S+F2SiMe3, THF
(119, Scheme 24), based on the same starting material presented in the previous paragraph, iodobenzene cis-dihydrodiol 67, which was carbonylated using palladium(II) acetate and NaOAc·3H2O in methanol under a carbon monoxide atmosphere to yield the (1S,2R)-cis-dihydrodiol derivative 120 of methyl benzoate [51]. This cis-dihydrodiol was the starting point for all three synthesis pathways.

### 2.5.1 Synthesis of Carba-β-L-Galactopyranose

The synthesis started by protecting the previously created cis-dihydrodiol derivative 120 with DMP and p-TSA, yielding 93% of the acetonide compound 121 (see Scheme 25). Epoxidation occurred at C5 and C6 via epoxidation using meta-chloroperoxybenzoic acid (MCPBA) in dichloromethane to yield epoxide 122 (77% yield). Using tert-butanol in water with a pH 8 buffer led to ring opening at the epoxide, yielding 70% of trans-dihydrodiol 123. This compound was protected by tert-butyldimethylsilyl trifluoromethanesulfonate (TBDMsOTf) at C4 and C5 to give the di-TBDMs derivative 124 and hydrogenation similar to the previous reactions.
catalyzed by Rh/Al₂O₃ yielded 82% of the saturated compound 125. This was followed by treatment with LAH in Et₂O, resulting in 84% of the protected carba-β-l-galactopyranose 126. The compound was deprotected under acidic conditions, yielding 84% of carba-β-l-galactopyranose (117) [51].

2.5.2 Synthesis of Carba-β-L-Talopyranose

The next reactions started with the previously synthesized cis-dihydrodiol methyl benzoate derivative 120 (Scheme 26). The addition of osmium tetroxide with tri-methylamine-N-oxide in a dichloromethane solution resulted in a 70% yield of the tetraol compound 127. Catalytic hydrogenation resulted primarily in the saturated tetraol compound 128, while also yielding 30% of the achiral meso-triol 129. This mixture was inseparable under charcoal/Celite chromatography and was treated with 2,2-DMP and p-TSA, resulting in a mono acetonide 131/bis-acetonide 130 mixture, which was then separated using flash-column chromatography to yield 59% of the bis-acetonide compound 130.

An alternative synthesis route was also explored. This route began with compound 127 and results in the same saturated bis-acetonide compound 130. This synthesis was achieved by changing the order of the two reactions (hydrogenation and protecting). This process started by protecting all four hydroxyl groups with an acetone using 2,2-DMP and p-TSA to yield 80% of another bis-acetonide compound.
and was followed by catalytic hydrogenation utilizing the previously presented conditions. This process afforded 91% of the desired saturated bis-acetonide while completely suppressing the competing hydrogenation reaction (i.e., $\text{127} \rightarrow \text{128/129}$). Both remaining steps were similar to all previous reactions, starting with reduction of the carbomethoxy group function to a hydroxymethyl group (Scheme 26) using LAH in Et$_2$O to give alcohol compound $\text{132}$ (76% yield) and deprotection using TFA in aqueous THF to yield 86% of carba-β-talopyranose ($\text{118}$). The carbasugar was then converted to its penta-acetate derivative $\text{133}$ using Ac$_2$O and pyridine (85% yield) for characterization [51].

### 2.5.3 Synthesis of Carba-α-t-Talopyranose

Finally, carba-α-t-talopyranose ($\text{119}$) was synthesized in seven steps (Scheme 27). The reaction started with the installation of an epoxide group at C4 and C5 of the cis-dihydrodiol derivative of methyl benzoate $\text{120}$. This was achieved via the addition of MCPBA in dichloromethane to give 82% cis-diol epoxide $\text{135}$. Compound $\text{135}$ was protected by an acetonide (98% yield), followed by opening the epoxide ring using tert-butanol in water (pH 8 buffer) to produce 68% of cyclohexene trans-diol $\text{137}$. The two hydroxyl groups were then protected by acetylation, yielding 98% triester $\text{138}$. Through catalytic hydrogenation similar to previous reactions, compound $\text{138}$ was transformed into the saturated ester $\text{139}$ (83% yield). LAH was added to a Et$_2$O solution to afford the trihydroxy acetonide-protected carba-α-t-talopyranose ($\text{140}$, 71% yield). The compound was deprotected using TFA and THF in water, yielding 88% of the desired carbasugar $\text{119}$. Furthermore, the compound...
was transformed into its penta-acetate derivative under the same conditions, with a yield of 82% (141) [51].

### 2.6 Based on Benzoquinone

The final section covers the synthetic pathways for various unsaturated carbasugars, including streptol and gabosine, resulting from masked p-benzoquinone. Leermann et al. [16] explored the synthesis of several unsaturated carbasugars used in lectin-binding studies to determine the influence of sugar derivatives on enzyme inhibition and cancer therapy.

#### 2.6.1 Synthesis of Dibromo Acetate Intermediates

The starting materials for all pathways in this section were the two intermediates 145 and 149 formed from 2-acetoxyethyl benzoquinone (142) and 2-methyl benzoquinone (146), respectively (Schemes 28, 29). 2-Acetoxyethyl benzoquinone (142) was dibrominated regioselectively at the unsubstituted double bond, yielding 98% of dibromo acetate 143. This compound was further reduced using sodium borohydride in diethyl ether and water (82% yield) and acetylated under the conditions described in previous sections to form the racemic dibromo acetoxymethyl diacetate intermediate 145 [16].

Under equal reaction conditions, 2-methyl benzoquinone (146) was transformed into the dibromo compound 147 (96% yield) and reduced to generate 91% of compound 148. This compound was acetylated to form the dibromo methyl diacetate intermediate 149 with a 60% yield (Scheme 29) [16].
2.6.2 Synthesis of Unsaturated Penta- and Tetraols

By utilizing Prévost conditions [52], silver acetate, acetic acid, and acetic anhydride, the dibromo acetoxyethyl diacetate intermediate 145 was transformed into penta-acetate 150 in 71% yield (Scheme 30). The entire yield of compound 150 was deacetylated via sodium methoxide in methanol, forming pentaol 152. Similarly, the intermediate compound 149 was acetylated to give the tetra acetate 151 (67% yield) and deprotected to afford unsaturated rac-tetraol 153 (88% yield, Scheme 31) [16].

The penta-acetate 154 and tetra acetate 155 were obtained from intermediates 145 and 149, respectively, through the use of Woodward conditions [50] (silver...
acetate in 90% aqueous acetic acid) alongside acetylation with acetic anhydride and pyridine, yielding 35% and 32% of compounds 154 and 155 (Schemes 30, 31), respectively. These two compounds were then converted into their corresponding alcohol compounds, rac-MK7607 (156, 82% yield) and 157 (88% yield) [16].

2.6.3 Synthesis of Streptol

Streptol (164) can be obtained from intermediate compound 145 in four steps, starting with the formation of an epoxide from the trans bromide and acetoxy group via addition of lithium hydroxide in Et₂O and methanol, preserving relative configuration at C4 and C5 and yielding epoxide 158 (83% yield). Nucleophilic ring opening in water, followed by acetylation, yielded 51% of bromide diacetate 160. Inversion and acetylation of the bromide group resulted in penta-acetate 162. Deacetylation of 162 with methanolic sodium provided the desired rac-streptol (164) with an 81% yield (Scheme 32) [16].

2.6.4 Synthesis of Unsaturated Pentaol 165

Similar to Scheme 32, the synthesis from compound 149 began with epoxidation to 159 (Scheme 33). Ring opening occurred through the addition of carbon tetrabromide in water, followed by acetylation, yielding 37% of the bromide triacetate compound 161. Through bromide displacement by acetate, the authors obtained the methyl tetraol 165 (Scheme 33) with the same relative configuration as streptol (164) [16].
2.6.5 Synthesis of Unsaturated Pentaol 171

The last pentaol compound was obtained in six steps (Scheme 34). Initially, intermediate 145 was deacetylated using potassium carbonate in methanol, resulting in dibromide diol 166, whose vicinal hydroxyl groups were protected using 2,2-DMP and p-TSA in acetone, ultimately yielding 100% acetonide 167. Epoxidation occurred via the addition of sodium hydroxide in Et$_2$O and water with a 52% yield of epoxide 168, followed by deprotection and acetylation comparable to those described in earlier pathways, yielding 52% of bromide tetra acetate 169. The Woodward reaction conditions [47] ensured inversion and acetylation

![Scheme 33](image-url)  
**Scheme 33** Synthesis of racemic tetraol 165. Reagents and conditions: a LiOH, Et$_2$O/MeOH, 72% yield, b CBr$_4$, H$_2$O, Ac$_2$O, C$_3$H$_7$N, 37% yield, c AgOAc, AcOH, Ac$_2$O, C$_3$H$_7$N, 38% yield, d NaOMe, MeOH, 88% yield

![Scheme 34](image-url)  
**Scheme 34** Synthesis of racemic pentaol 171. Reagents and conditions: a K$_2$CO$_3$, MeOH, 100% yield, b 2,2-DMP, p-TSA, acetone, 100% yield, c NaOH, Et$_2$O/H$_2$O, 52% yield, d AcOH, H$_2$O, Ac$_2$O, C$_3$H$_7$N, 52% yield, e AgOAc, AcOH, Ac$_2$O, C$_3$H$_7$N, 54% yield, f NaOMe, MeOH, 79% yield
producing penta-acetate $\textbf{170}$ in 54% yield. Finally, the deprotection of compound $\textbf{170}$ yielded 79% of the desired unsaturated pentaol $\textbf{171}$ [16].

3 Summary

The present review highlights the success of carbasugar synthesis from non-sugar compounds. Due to their structural and configuration similarities with the desired products, the reactants used were able to deliver the products in few synthetic steps with comparatively high efficiency. These results suggest that future experiments may permit generation of the same products even faster and with higher yields. Due to the great diversity in the structures already known, the road is now paved for successful research in chemical and clinical medicine, including HIV and tumor treatment [14, 53, 54]. Due to the growing population and prevalence of common diseases, the importance of pseudo-sugar synthesis is greater than ever before. Ultimately, the synthetic routes described in this review offer information on already successful research and provide an impetus for the development of new discoveries in the field of carbasugars.

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Declarations

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