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European Journal of Organic Chemistry

EurJOC
European Journal of Organic Chemistry

Chemistry Europe
European Chemical Societies Publishing

RESEARCH ARTICLE OPEN ACCESS

A Practical and Flexible *De Novo* Synthesis of Deoxygenated Carbasugars and Their Cyclitol Epoxides

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Received: 1 December 2025 | **Revised:** 24 February 2026 | **Accepted:** 26 February 2026

Keywords: carbasugars | *de novo* synthesis | enantioselective synthesis | glycomimetics | pseudosugars

ABSTRACT

Literature on carbasugar and cyclitol epoxide glycomimetics is largely biased towards fully hydroxylated cyclitol structures. Partially deoxygenated sugars of varying configuration are widespread in nature and merit translation into the corresponding carbasugars and cyclitol epoxides as well. For this purpose, we developed a *de novo* synthesis route comprising enantioselective Brown crotylation and ring-closing metathesis as the key steps and enabling the synthesis of α- and β-carba-paratose, α- and β-carba-colitose as well as four configurational deoxycyclophellitol isosteres in a strategy that allows the synthesis of other configurational isomers.

1 | Introduction

Carbasugars, also termed pseudosugars, comprise carbohydrate analogues in which the ring oxygen is substituted for carbon. This single substitution, exemplified by carba-glucopyranose **1** (Figure 1), renders carbasugars stable towards acid-catalysed hydrolysis, a virtue based on which a wide array of configurational carbasugars has been employed in the search for competitive glycosidase inhibitors [1–3]. Endowing a carbasugar with an epoxide bridging the two carbons, emulating the ring oxygen and the anomeric carbon of the parent sugar, yields cyclitol epoxides, or cyclophellitols, a distinct carbasugar family with the glucopyranose-mimetic natural product, cyclophellitol **2** as the founding member [4, 5]. These have been widely used as mechanism-based retaining glycosidase inactivators and activity-based probes [6].

Carbasugars are widely spread in nature, and a multitude of synthesis strategies have appeared in the last decade, through which a broad array of configurational and functional carbasugars have become available [1–5]. By and large, however, these natural and synthetic carbasugars comprise structural analogues of fully functionalised monosaccharides such as α-glucose, β-galactose and β-N-acetylglucosamine. In other words, glycomimetic structures of essential mammalian carbohydrates targeting mammalian glycoprocessing enzymes. This, while the structural and functional diversity of monosaccharides (and from there oligo/polysaccharides and glycoconjugates), is much larger. The microbial world produces hundreds of structurally and functionally diverse monosaccharides, amongst which an array of partially deoxygenated structures [7–10]. Monosaccharides were deemed worthy of translating into their corresponding carbasugars, and we reasoned that *de novo* synthesis methods would be most suited for the creation of structurally and configurationally diverse compound libraries.

Our work around carbasugars has focussed predominantly on the synthesis of configurational and functional cyclophellitol isosteres and their use in activity-based protein profiling of retaining glycosidases [6]. We accessed and assessed an array of fully hydroxylated cyclophellitols and their glycosylated derivatives as activity-based probes to visualise and identify retaining exo- and endoglycosidases. By and large, these compounds, emulating the configuration and substitution pattern of aldohexoses, are considerably to fully selective for the corresponding retaining glycosidases: cyclophellitol targets retaining β-glucosidases mostly [11, 12], while α-galactopyranose configured cyclophellitol is selective for a-galactosidases [13] and α-mannose-configured

cyclophellitol for a-mannosidases [14]. With the aim of creating broad-spectrum retaining glycosidase probes, we also reported on the synthesis of several 3- and 3,6-dideoxycyclophellitols [15, 16]. We found that, while inhibitory potency towards specific retaining glycosidases drops, some of these compounds indeed target members of multiple glycosidase families at once: retaining glucosidases, galactosidases and mannosidases. These compounds were synthesised by site-selective deoxygenation of the fully substituted cyclophellitols in multi-step synthesis routes. Here, we report the *de novo* synthesis of the pseudosugar counterparts of α- and β-D-paratose and α- and β-L-colitose, as well as β-paratose and abequose cyclophellitols. Our route of synthesis builds on the enantioselective Brown crotylation [17–19] of substituted pentenals, which were obtained through an aldol condensation of *tert*-butyl acrylate and acrolein, followed by enzymatic kinetic resolution. The so-obtained dienes were subjected to ring-closing metathesis to furnish the decorated cyclohexene scaffolds that could be further modified to the target compounds. This route is short and flexible, such that configurational analogues of both carbasugars and cyclophellitols are within reach.

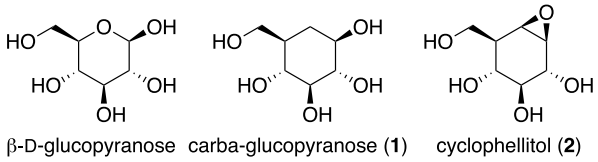
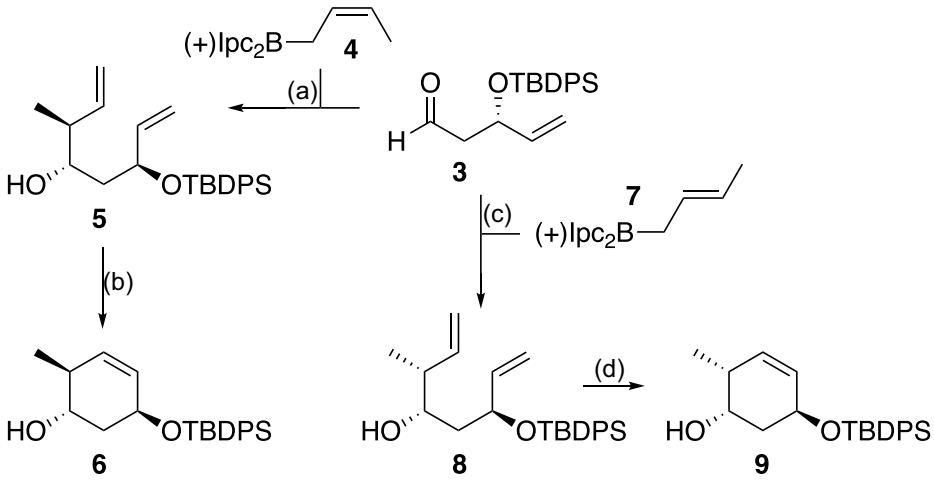
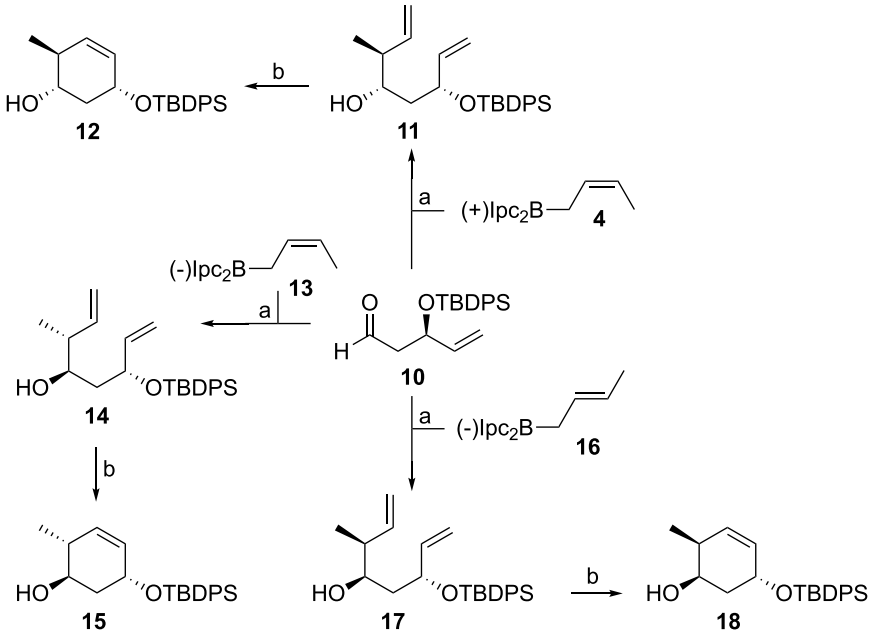


FIGURE 1 | Structure of the glucopyranose-mimetic carbasugars, pseudoglucose (**1**) and cyclophellitol (**2**).



SCHEME 1 | Reagents and conditions: (a) NaOH, H_2O_2; (b) Grubbs 2 catalyst, CH_2Cl_2, reflux (43%, two steps); (c) NaOH, H_2O_2; (d) Grubbs 2 catalyst, CH_2Cl_2, reflux (43% **6**, 48%, **9**, two steps).



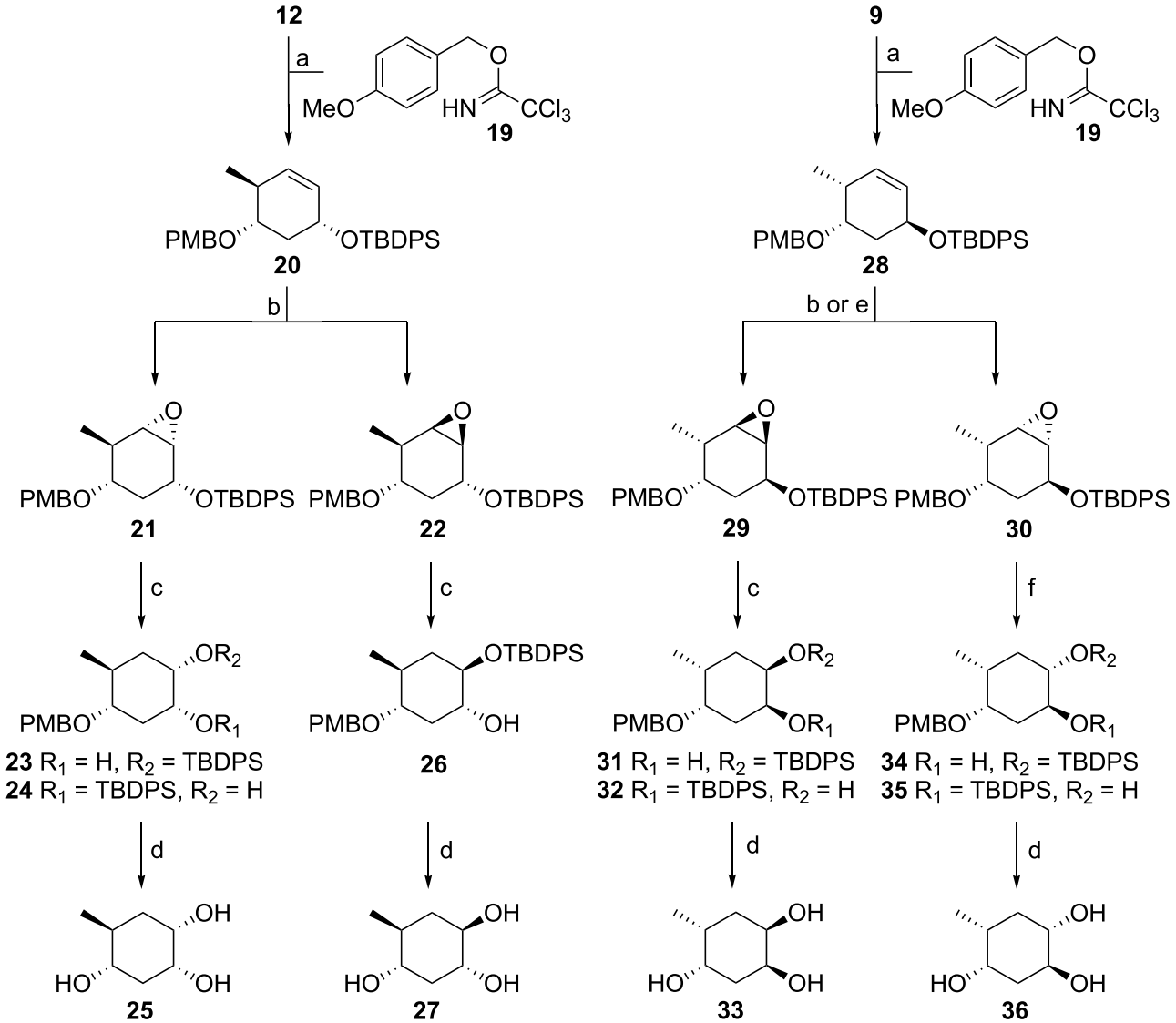
SCHEME 2 | Reagents and conditions: (a) NaOH, H_2O_2; (b) Grubbs 2 catalyst, CH_2Cl_2, reflux (76% **12**, 49% **15**, 61% **18**, two steps).

2 | Results and Discussion

The synthesis towards the target deoxygenated pseudosugars and cyclophellitols commenced with the enantiomeric pair of (*S*)-3-*O*-TBDPS-4-pentenal (**3**, Scheme 1) and (*R*)-3-*O*-TBDPS-4-pentenal (**10**, Scheme 2), which we prepared by adapting the literature procedure (see Supporting Information) [20, 21].

Thus, Brown crotylborylation of **3** with Z-$H_3CCH{=}CHCH_2B((+)\text{-ipc})_2$ (**4**), generated by treatment of (+)-*B*-methoxydiisopinocam pheylborane with Z-but-2-enylpotassium (prepared in situ by treatment of Z-2-butene with a mixture of *n*-butyllithium and potassium *tert*-butoxide) and then treatment with BF_3 etherate, yielded 1,7-diene **5** as the major product, which was separated by silica gel chromatography from small amounts of the diastereomeric alcohol also formed. The choice of Brown's reagent provides control over the stereochemistry at the C5 and C6 atoms, by leveraging the steric hindrance arising in the possible six-membered transition states. Ring-closing metathesis of **5** using Grubbs second generation catalyst yielded cyclohexene **6** in 43% yield over the two steps starting from **3**. Cyclohexene **9** was prepared in similar efficiency, now reacting aldehyde **3** with Brown's E-crotylboron reagent **7**. In a similar vein, enantiomeric (with respect to **3**) aldehyde **10** was transformed into cyclohexenes **12**, **15** and **18** in a two-step sequence now featuring Brown's reagents **4**, **13** and **16**, respectively, followed by ring-closing metathesis of the respective diastereomeric 1,7-dienes **11**, **14** and **17**.

The versatility of the obtained cyclohexenes as starting material for the preparation of pseudosugars is demonstrated with the synthesis of D-carbaparatoses **25** and **27** and L-carbacolitoses **33** and **36**, in both pseudo-anomeric forms, from cyclohexenes **9** and **12** (Scheme 3). Thus, protection of the secondary alcohol in **12** as the *para*-methoxybenzyl ether using para-methodybenzyl (PMB)-imidate **19** and camphor sulphonic acid yielded orthogonally protected cyclohexene **20**. Treatment of **20** with in situ-generated methyl(trifluoromethyl)dioxirane provided diastereomeric epoxides **21** and **22** in 28% and 47% yield, respectively, following separation by silica gel column chromatography. We found that the



SCHEME 3 | Reagents and conditions: (a) Campher sulfonic acid (CSA), CH_2Cl_2 (60% **20**, 64% **28**); (b) Oxone, $AcCF_3$ (12% **21**, 45% **22**, **49**% **29**, 29% **30**); (c) $LiEt_3H$, tetrahydrofuran (THF) (40% **23**, 58% **24**, 53% **26**, 14% **31**, 33% **32**); (d) i) TBAF, THF, ii) TFA, CH_2Cl_2 (92% **25**, 94% **27**, 82% **33**, 90% **36**); (e) mCPBA, CH_2Cl_2 (28% **29**, 47% **30**) and (f) L-Selectride, THF, 65°C (26% **34**, 52% **35**).

regioselectivity of the reductive opening of the epoxide could be controlled by the nature of the nucleophile and the reaction temperature. The use of lithium triethylborohydride at ambient temperature led to opening of the α-configured epoxide **21**, following a Fürst–Plattner trajectory (Figure 2) [22–24] on the ground state $^4H_3$ conformer in a regioselective manner to provide the C1-alcohol (parent carbohydrate numbering; regioselectivity as established by proton and carbon NMR).

This reductive opening proceeded almost quantitatively to provide partially protected α-D-carbaparatoses **23** and **24** as a mixture because of partial silyl ether migration to the emerging alcoholate (silyl migrations have been observed previously to occur under basic conditions on carbohydrate-(like) diols [25]). Consecutive treatment of this mixture with tetrabutylammonium fluoride (to remove the silyl protective group) and trifluoroacetic acid (to remove the PMB protective group) provided α-D-carbaparatose **25** in good yield as the single stereoisomer.

In a similar fashion and with equal efficiency, β-L-carbaparatose **27** was prepared from epoxide **22**. Regioselective reductive opening of this epoxide could be achieved using a bulkier reducing agent (L-selectride) at elevated temperature to deliver **26**, which was formed upon complete silyl migration. Likewise, and now starting from cyclohexene **9**, α-L-carbacolitose **33** and β-L-carbacolitose **36** were prepared. Thus, after protection and epoxidation using either in situ-generated methyl (trifluoromethyl) epoxirane or mCPBA, α-epoxide **29** and β-epoxide **30** were obtained. Regioselective opening of the α-epoxide **29** could again be achieved using lithium triethylborohydride, while the β-epoxide **30** required the use of L-selectride. Also in these reactions, partial silyl migration was observed. Tetrabutylammonium fluoride-mediated desilylation and PMB deprotection delivered the target carba α-L-carbacolitose **33** and β-L-carbacolitose **36**. Of note, during these studies, we found that PMB protection (as in **12** to **20** and **9** to **28**) helped to prevent silyl migration, which otherwise would lead to more complex reaction mixtures.

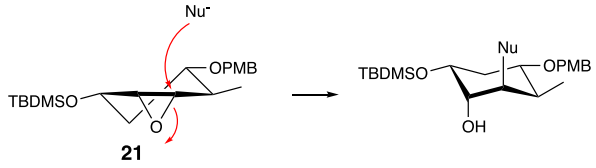
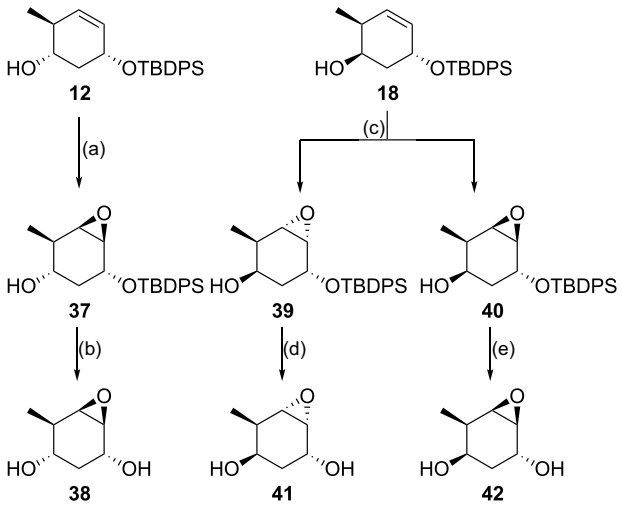


FIGURE 2 | Reductive opening of epoxide **21** following a Fürst–Plattner trajectory, revealing the regioselective outcome.



SCHEME 4 | Reagents and conditions: (a) mCPBA, CH_2Cl_2 (63%); (b) $Et_3N.3HF$, THF (88%); (c) mCPBA, CH_2Cl_2 (12% **39**, 46% **40**); (e) $Et_3N.3HF$, THF (84%) and (d) $Et_3N.3HF$, THF (97%).

Foregoing the reductive epoxide opening step provides a straightforward entry to cyclitol epoxides, which are of interest as potential retaining glycosidase inhibitors. Removal of the protective groups in **21**, **22**, **29** and **30** in this vein would provide the corresponding paratose and colitose cyclophellitols. Since the silyl migration observed during the reductive epoxide openings would not be an issue, a more straightforward strategy comprises direct epoxidation of the ring-closing metathesis products (Schemes 1 and 2), followed by desilylation. This strategy is highlighted in Scheme 4 for the synthesis of three configurational cyclophellitol isosteres starting from partially protected cyclohexenes **12** and **18**. Treatment of **12** with mCPBA yielded epoxide **37** in 63% yield, along with about 20% of the epimeric epoxide. HF-triethylamine treatment then readily afforded β-D-paratose-configured cyclophellitol **38**. Executing the same sequence of events on cyclohexene **18** yielded α- and β-D-abequose-configured cyclophellitols **41** and **42**.

3 | Conclusion

In summary, this work comprises a straightforward entry into 3,6-deoxygenated pseudosugars and cyclophellitols as two major classes of glycomimetics acting as potential competitive inhibitors and mechanism-based inhibitors, respectively. The key steps in our strategy comprise enantioselective Brown crotylboronation of protected, chiral 3-hydroxy-1-pentanal, itself prepared following adaptation of the literature kinetic resolution strategy, followed by ring-closing metathesis of the resulting trisubstituted 1,7-dienes. Epoxidation of the resulting cyclohexenes provided cyclophellitols, while regioselective epoxide reduction gave the corresponding carbasugars. We prepared a range of each and present the synthesis strategy as an easy entry into configurational isosteres of the compounds presented here by further variation of the stereochemistry of the Brown boron reagent and/or that of the aldehyde. Structural isomers may further become available through variation of the substitution pattern of the aldehyde and Brown's reagent used, while substitution of the epoxide in the cyclophellitols for aziridine would provide access to new activity-based retaining glycosidase probes. In all, our work, therefore, adds to the growing body of glycomimetics and gives an entry into deoxygenated ones, which are perhaps easier obtained through *de novo* synthesis routes as presented here, contrasting that of fully substituted glycomimetics, which are most often prepared from chiral pool materials, including sugars.

Funding

This work was supported by the European Research Council (Grant ERC- 2020-SyG-951231 "CARBOCENTRE" to H.S.O.) and the Netherlands Organization for Scientific Research (Grant 2018−714.018.002 "ENDOGLYCOPROBE" to H.S.O.).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.