A norbornyl route to cyclohexitols: structural diversity in fragmentation through functional group switching. Synthesis of \(\alpha\)- and \(\beta\)-galactose, \(\alpha\)-talose and \(\alpha\)-fucopyranose carbasugars

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Abstract

A novel fragmentation sequence has been executed within the norbornane system, involving C\(_1\)–C\(_7\) bond scission, to extract a versatile, highly functionalized cyclohexanoid moiety. Its further evolution towards a range of carbasugars is described.

Keywords: fragmentation reactions; carbasugars; hydroxylation.

There is a great deal of current interest in cyclitols, the polyhydroxylated cyclohexanoids, as these structural entities not only constitute important segments of a diverse range of natural products, e.g. antibiotics, but also exhibit promising biological activity profiles ranging from glycosidase inhibitors to antidiabetes and anticancer agents.\(^1\) Some of the better known examples of cyclohexitols of natural occurrence are the carbasugars, e.g. pseudo-\(\alpha\)-galactose 1, condutriols, e.g. condutriol-A 2, inositols, e.g. \(\text{myo-}\text{inositol}\) 1,4,5-triphosphate 3 and gabosines, e.g. gabosine-C 4, displaying dense and stereochemically varied oxygenation patterns on the six-membered ring. Not surprisingly, the cyclohexitols have attracted the widespread attention of synthetic chemists.\(^2\) Among the main synthetic strategies that have been explored in this context are: (i) restructuring of carbohydrates to carbocycles;\(^3\) (ii) aromatics to carbasugars via either the microbially produced \textit{cis}-cyclohexadiene diols\(^2b,4a\) or 1,4-cyclohexadienylsilanes;\(^4b\) (iii) \[4+2\]-cycloaddition chemistry based on \(\alpha\)-pyrone and 1,3-butadiene derivatives;\(^5\) (iv) 7-oxabicyclo[2.2.1]heptanes as ‘naked sugars’;\(^6\) and (v) 7-keto-norbornyl systems as cyclohexanoid equivalents.\(^7\)

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Recently, we have delineated a new and fairly general approach to cyclopentitols, based on the bicyclo[2.2.1]heptane (norbornane) framework, in which the inherent stereo- and regioselective preferences of the norbornyl system are fully exploited. The main feature of this approach was the setting up of a Grob-like ‘bottom-to-top’ fragmentation process in a suitably crafted 2,7-disubstituted norbornane derivative 5 to cleave the C1–C2 bond 6, and extraction of the five-membered ring 7 from the bridged bicyclic frame with full functionalization, Scheme 1.

![Scheme 1](image)

We have now envisioned a new fragmentation process in the norbornyl system by switching functionalities in 5 to 8, to orchestrate a ‘top-to-bottom’ sequence through C7–C1 bond cleavage (see 9) to deliver a functionally embellished cyclohexanoid 10 in a regio- and stereoselective manner, Scheme 2. Implementation of this theme, leading to the stereoselective syntheses of diverse cyclohexitols, particularly several carbasugars is reported here.

![Scheme 2](image)

In order to execute Scheme 2, easy access to a precursor corresponding to 8 was required and this was accomplished as shown in Scheme 3. Bicyclic alcohol 11 readily available from 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene and vinyl acetate, was tosylated and subjected to OsO4-mediated catalytic dihydroxylation to furnish exo,exo-diol 12. It is interesting to note that despite considerable steric hindrance on the exo- as well as the endo-face, the norbornene double bond in 11 is smoothly and stereoselectively dihydroxylated in keeping with our earlier observations on this system. Amberlyst mediated single-pot protection–deprotection in 12 led to the desired 7-norbornanone derivative 13. Exposure of 13 to NaOMe resulted in a smooth ‘top-to-bottom’ fragmentation (see, Scheme 2) to furnish the cyclohexene methyl ester 14 as a single product. In the cyclohexenoid 14 of secured stereochemistry, five ring carbons had substitution pattern well poised for further elaboration to carbasugars.

![Scheme 3](image)

Osmylation of cyclohexenoid ester 14 proceeded in a stereoselective manner from the face opposite to the acetonide and ester moieties to furnish cis-diol 15 in excellent yield, Scheme 4. LAH reduction of the ester group and acetonide deprotection furnished the naturally occurring carbasugar pseudo-α-galactose 1, which is conveniently characterised as its penta-acetate 16. Alternately, the ester group
in 14 was reduced with LAH and acetylated to give 17. Epoxidation of 17 proceeded stereoselectively from the less hindered α-face to deliver 18. Acid catalysed epoxide ring opening and concomitant acetone deprotection furnished a (5:2:3) mixture of pseudo-β-galactose 19a, pseudo-α-talose 20a and the bicyclic ether 21a, which were best separated and characterised as the corresponding acetates 19b, 20b and 21b, respectively, Scheme 4.

### Scheme 4

Reagents and conditions: (a) OsO₄, NMMO, 30 h, 95%; (b) i. LAH, THF, rt, 88%; ii. Amberlyst-15, aq. MeOH, 3 h; iii. Ac₂O, Py, 20 h, 74% (two steps); (c) i. LAH, THF, 0–5°C, 1 h, 90%; ii. Ac₂O, DMAP, DCM, 95%; (d) MCPBA, Na₂CO₃, DCM, 6 h, 65%; (e) i. cat. HClO₄ (70%), H₂O, 30 h; ii. Ac₂O, Py, 67% (two steps)

Lastly, ester 14 was elaborated into pseudo-α-fucopyranose 22, a carbasugar that has evoked much attention due to its possible application as an inhibitor of fucosyltransferases. Four syntheses of 22 have been reported in literature in recent years but our synthetic approach is notable for its brevity and stereoselectivity. The diol ester 15 obtained from 14 was transformed into the bis-acetonide and subjected to LAH reduction to give 23. Tosylation of 23 followed by reductive detosylation employing sodium borohydride in DMSO led to the installation of the β-methyl group and bis-acetonide 24 was realised quite conveniently, Scheme 5. Deprotection in 24 delivered pseudo-α-fucopyranose 22, whose spectroscopic characteristics were identical to those reported in the literature.

### Scheme 5

Reagents and conditions: (a) i. Me₂CO, Amberlyst-15, mol. sieves 4 Å, rt, 1 h, 85%; ii. LAH, THF, 0°C, 2 h, 82%; (b) i. TsCl, Py, DCM, rt, 94%; ii. NaBH₄, DMSO, 70°C, 6 h, 72%; (c) Amberlyst-15, aq. MeOH, rt, 10 h, 75%

In short, we have disclosed here a new and versatile approach towards carbasugars from a readily accessible 2,7-disubstituted norbornane precursor, involving a novel ‘top-to-bottom’ Grob-like fragmentation as the pivotal step. In the accompanying letter, we demonstrate the general utility of the polyhydroxylated cyclohexenoid synthesis developed here. An interesting aspect of our effort is that both 5 and 13, precursors of cyclopentitols and cyclohexitols, respectively, are obtained from the same starting material 11. Thus, by simply interchanging functional groups (see 5 and 13), it is possible to extract either five- or six-membered ring from the norbornyl system.
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References


9. All new compounds reported here were racemic and characterized on the basis of spectroscopic data and elemental analyses. Selected spectroscopic data (in Hz).
