Pergamon

Tetrahedron Letters 41 (2000) 3505–3508

TETRAHEDRON LETTERS

A norbornyl route to cyclohexitols: structural diversity in fragmentation through functional group switching. Synthesis of α- and β-galactose, α-talose and α-fucopyranose carbasugars

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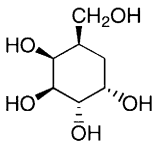
Received 14 February 2000; accepted 7 March 2000

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-α-galactose **1**, condutriols, e.g. condutriol-A **2**, inositols, e.g. *myo*-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 *cis*-cyclohexadiene diols[2b,4a] or 1,4-cyclohexadienylsilanes;[4b] (iii) [4+2]-cycloaddition chemistry based on α-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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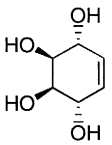

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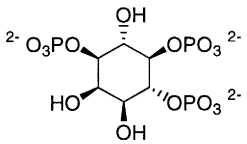

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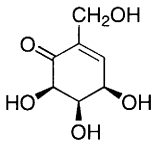

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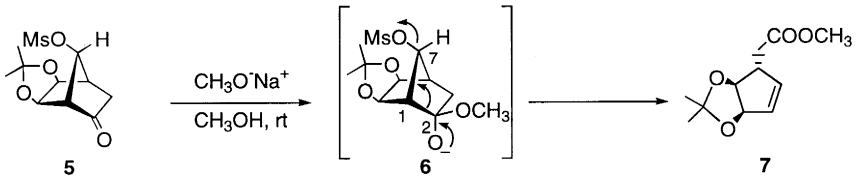
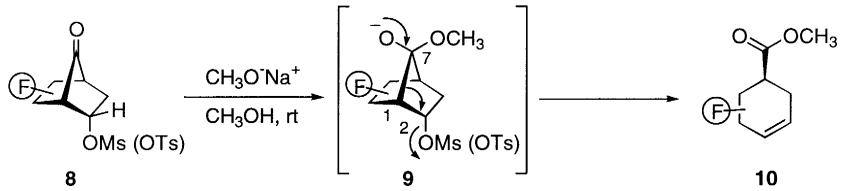
0040-4039/00/$ - see front matter
PII: S0040-4039(00)00408-1

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.[8] 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 C_1–C_2 bond **6**, and extraction of the five-membered ring **7** from the bridged bicyclic frame with full functionalization, Scheme 1.



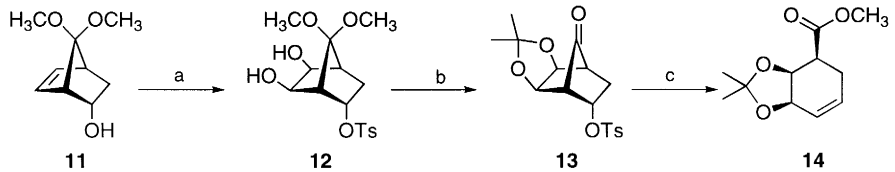
Scheme 1.

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 C_7–C_1 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.

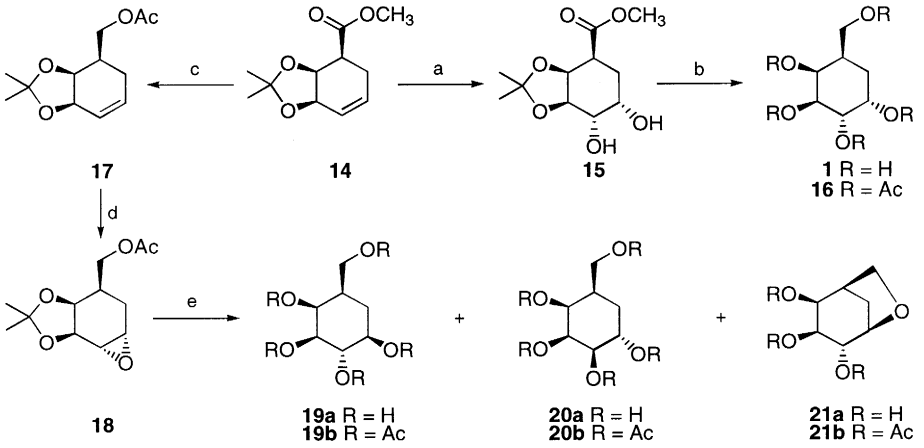
In order to execute Scheme 2, easy access to a precursor corresponding to **8** was required and this was accomplished as shown in Scheme 3. Bicyclic alcohol **11**,[7,8] readily available from 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene and vinyl acetate, was tosylated and subjected to OsO_4-mediated catalytic dihydroxylation to furnish *exo,exo*-diol **12**.[9] 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.[7,8] Amberlyst mediated single-pot protection–deprotection in **12** led to the desired 7-norbornanone derivative **13**.[9] Exposure of **13** to NaOMe resulted in a smooth 'top-to-bottom' fragmentation (see, Scheme 2) to furnish the cyclohexene methyl ester **14**[9] 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. Reagents and conditions: (a) i. TsCl, Py, DMAP, DCM, rt, 90%; ii. OsO_4, NMMO, Me_2CO:H_2O (4:1), rt, 2 days, 84%; (b) Amberlyst-15, aq. Me_2CO, rt, 90%; (c) NaOMe, MeOH, rt, 3 h, 70%

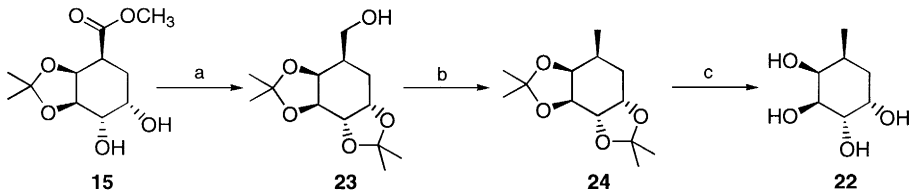
Osmylation of cyclohexenoid ester **14** proceeded in a stereoselective manner from the face opposite to the acetonide and ester moieties to furnish *cis*-diol **15**[9] in excellent yield, Scheme 4. LAH reduction of the ester group and acetonide deprotection furnished the naturally occurring carbasugar pseudo-α-galactose **1**,[10] which is conveniently characterised as its penta-acetate **16**.[9] Alternately, the ester group

in **14** was reduced with LAH and acetylated to give **17**.[9] Epoxidation of **17** proceeded stereoselectively from the less hindered α-face to deliver **18**.[9] Acid catalysed epoxide ring opening and concomitant acetonide 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**,[9] **20b**[9] and **21b**,[9] respectively, Scheme 4.



Scheme 4. Reagents and conditions: (a) OsO_4, NMMO, 30 h, 95%; (b) i. LAH, THF, rt, 88%; ii. Amberlyst-15, aq. MeOH, 3 h; iii. Ac_2O, Py, 20 h, 74% (two steps); (c) i. LAH, THF, 0–5°C, 1 h, 90%; ii. Ac_2O, DMAP, DCM, 95%; (d) MCPBA, Na_2CO_3, DCM, 6 h, 65%; (e) i. cat. $HClO_4$(70%), H_2O, 30 h; ii. Ac_2O, 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[11] 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**.[9] 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**[9] 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.[9,11]



Scheme 5. Reagents and conditions: (a) i. Me_2CO, 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. $NaBH_4$, 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.

Acknowledgements

N.M. and S.L. thank CSIR for the award of Research Fellowships. Part of this work was carried out at the University of Hyderabad.

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9. All new compounds reported here were racemic and characterized on the basis of spectroscopic data and elemental analyses. Selected spectroscopic data (*J* in Hz). **14**: δ_H (200 MHz, $CDCl_3$): 5.83 (1H, ddd, *J* 10, 6, 2), 5.66–5.58 (1H, m), 4.72–4.69 (1H, m), 4.62–4.59 (1H, m), 3.75 (3H, s), 2.75 (1H, ddd, *J* 11.5, 5.5, 2), 2.6–2.41 (1H, m), 2.29–2.14 (1H, m), 1.37 (6H, s); δ_C (50 MHz, $CDCl_3$): 172.52, 127.85, 126.53, 109.45, 73.01 (2C), 52.01, 42.04, 27.64, 26.85, 21.22. **16**: δ_H (300 MHz, $CDCl_3$): 5.57 (1H, dd as t, *J* 2.5), 5.50 (1H, dd as q, *J* 3), 5.20 (2H, dABq, *J* 11, 3), 4.01–3.85 (2H, m), 2.5–2.45 (1H, m), 2.11 (6H, s), 2.03 (3H, s), 2.0 (3H, s), 1.99 (3H, s), 1.79–1.75 (2H, m); δ_C (50 MHz, $CDCl_3$): 170.51, 170.03 (2C), 169.83 (2C), 69.65, 69.38, 68.35 (2C), 62.93, 33.31, 26.71, 20.84, 20.56 (4C). **19b**: δ_H (300 MHz, $CDCl_3$): 5.49 (1H, br s), 5.39 (1H, dd as t, *J* 10), 4.97–4.89 (1H, m), 4.89 (1H, dd, *J* 10.5, 3), 4.0 (1H, dd, *J* 11, 9), 3.87 (1H, dd, *J* 11, 6), 2.25–2.13 (1H, m), 2.13 (3H, s), 2.04 (6H, s), 2.03 (3H, s), 2.03–1.95 (1H, m), 1.98 (3H, s), 1.70–1.58 (1H, m); δ_C (75 MHz, $CDCl_3$): 170.66, 170.10, 170.02 (2C), 169.9, 72.0, 71.29, 70.77, 67.53, 62.72, 34.71, 27.09, 20.85, 20.68 (3C), 20.55. **20b**: δ_H (300 MHz, $CDCl_3$): 5.40 (1H, dd as t, *J* 3), 5.21 (1H, dd as t, *J* 3.5), 5.18–5.11 (2H, m), 4.10 (1H, dd, *J* 11, 8), 3.97 (1H, dd, *J* 11, 6.5), 2.44–2.41 (1H, m), 2.10 (3H, s), 2.09 (6H, s), 2.05 (3H, s), 2.02 (3H, s), 2.01–1.92 (1H, m), 1.71–1.65 (1H, m); δ_C (75 MHz, $CDCl_3$): 170.80, 169.91, 169.79, 169.45, 169.36, 68.55 (2C), 68.38, 67.34, 62.97, 33.71, 24.00, 21.01, 20.70 (4C). **21b**: δ_H (200 MHz, $CDCl_3$): 5.19 (1H, d, *J* 6), 5.12 (1H, dd, *J* 6, 3), 4.89 (1H, br d, *J* 4), 4.32 (1H, d, *J* 9.5), 4.30 (1H, d, *J* 8.5), 3.73 (1H, dd, *J* 8.5, 4), 2.51 (1H, m), 2.13 (3H, s), 2.08 (3H, s), 2.01 (3H, s), 1.98–1.91 (2H, m); δ_C (50 MHz, $CDCl_3$): 169.67, 169.53, 168.81, 73.51, 72.58, 69.16 (2C), 67.93, 38.77, 31.16, 20.77, 20.67 (2C). **22**: δ_H (200 MHz, CD_3OD): 3.93 (1H, dd, *J* 6, 3), 3.73 (1H, br s), 3.7–3.55 (2H, m), 2.09–1.93 (1H, m), 1.62–1.45 (2H, m), 0.97 (3H, d, *J* 7); δ_C (50 MHz, CD_3OD): 75.48, 73.45, 72.71, 70.93, 34.30, 30.35, 17.68.
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