A general norbornyl based synthetic approach to carbasugars and 'confused' carbasugars

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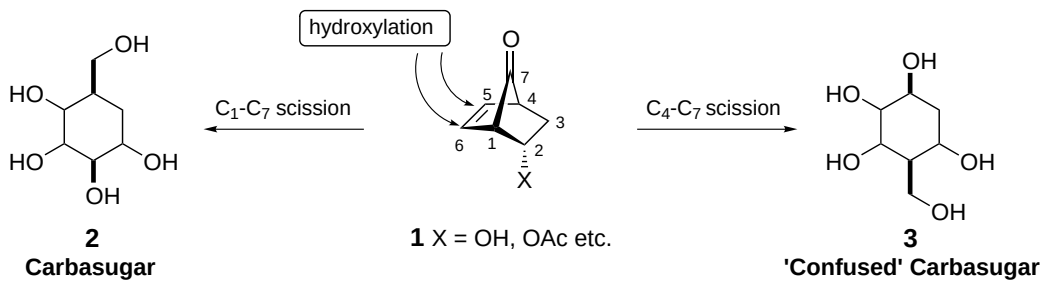
Abstract—The norbornyl system has been recognized simply as a 'locked' carbasugar and a short, general approach to carbasugars and their new siblings, 'confused' carbasugars, from readily available 7-ketonorbornanes is reported.

In the pursuit of scientific research, sometimes the most obvious is either taken for granted or escapes attention. The bicyclo[2.2.1]heptane (norbornyl) system has been explored by generations of organic chemists in a myriad ways ranging from mechanistic and stereochemical probes to starting point for diverse syntheses.[1] However, the C_7-framework of the norbornyl system has not been recognized as a simple 'locked' carbasugar from which the six-membered C_7-carbasugar skeleton can be easily retrieved through 'unlocking' involving C1–C7 or C4–C7 bond scission. Considering the current widespread interest in the synthesis of carbasugars,[2] we regard our norbornyl approach as short, simple and conceptually different. We demonstrate here that indeed, a simple 7-norbornenone derivative like **1** can be readily elaborated to a variety of carbasugars **2** and to related new entities that we name 'confused' carbasugars **3**. The 'confused' carbasugars **3** have the same level of oxygenation on the cyclohexanoid framework as the carbasugars, but the hydroxymethyl and the '*para*' hydroxy groups are interchanged (see bold portions in **2** and **3**). In view of the well-established importance of carbasugars **2** and its congeners in glycomimicry, the first time access to their new siblings, the 'confused' carbasugars **3**, should stimulate interest in the evaluation of their biological activity profile.

endo-2-Acetoxy-7-norbornenone **5** and its precursor ketal **4**, readily available through Diels–Alder reaction between 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene and vinyl acetate, followed by reductive dehalogenation,[2b,3] were chosen as the starting points of our projected syntheses.[4] We recognized that dihydroxylation of the norbornene double bond and cleavage of the C1–C7 bond with amplification of functionality would provide direct access to carbasugars. Consequently, **4** was subjected to OsO_4-mediated dihydroxylation exclusively from the *exo*-face to furnish **6**. A one-pot *cis*-diol protection and acetal deprotection in **6** delivered the keto-acetonide **7** (Scheme 1). Baeyer–Villiger oxidation of **7** led to a regioisomeric mixture of lactones **8** and **9** (13:87). $LiAlH_4$ reduction of **8** and **9** yielded triols **10** and **11**, respectively. Acetonide deprotection in **10** led to the pseudo-α-DL-talopyranose carbasugar **12a** (characterized as the pentaacetate **12b**[4a,5]). The same deprotection in **11** delivered the 'confused' carbasugar **13a** (characterized as the pentaacetate **13b**[6]) quite easily (Scheme 1).

To introduce stereochemical diversity in our synthetic approach and to fine-tune the relative ratios of the carba- and 'confused' carbasugar formation, an alternate strategy was executed. Chemoselective Baeyer–Vil-



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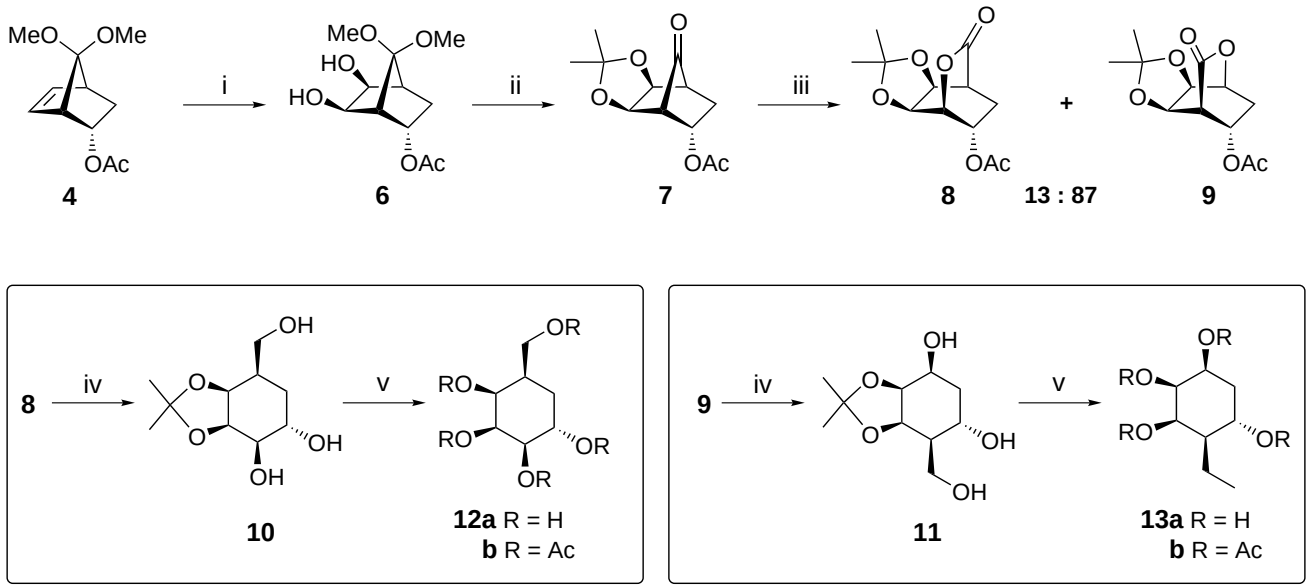
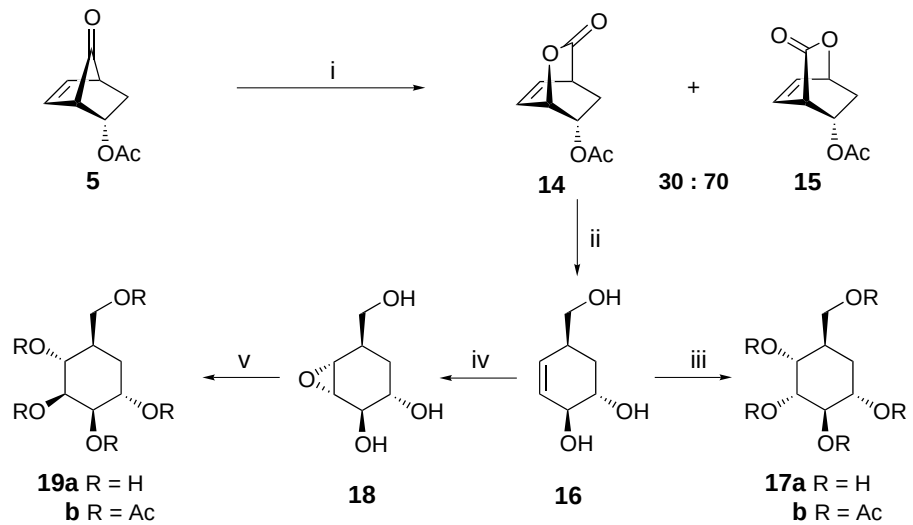
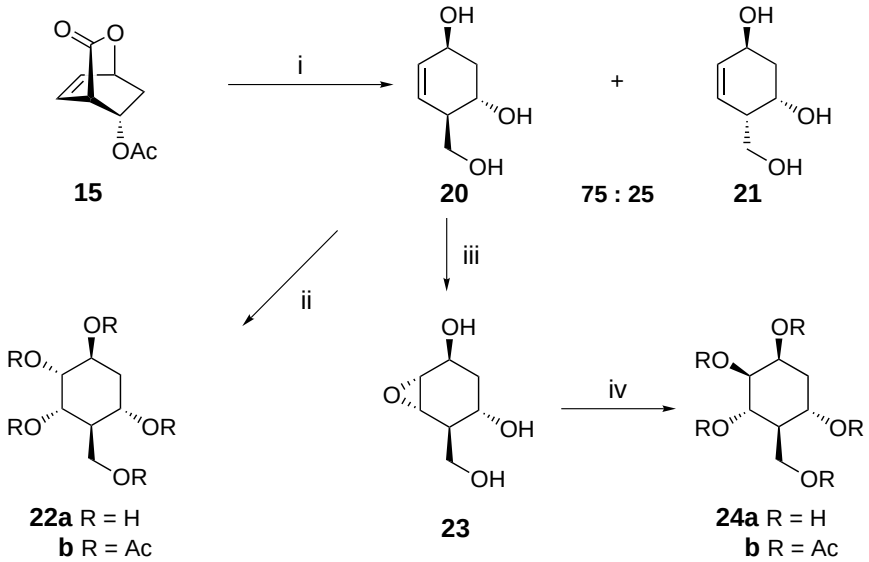


Scheme 1. *Reagents and conditions*: (i) OsO_4, NMMO (50% aq. solution, 4 equiv.), Me_2CO–H_2O (4:1), rt, 30 h, 80%; (ii) Amberlyst-15, Me_2CO, rt, overnight, 70%; (iii) MCPBA, $NaHCO_3$, DCM, 0–5°C, 3–4 h, quant.; (iv) LAH, THF, 0–5°C, 2–3 h, 70%; (v) (a) Amberlyst-15, aq. MeOH, rt, overnight, (b) Ac_2O, Py, rt, overnight, 72% (two steps).

liger oxidation of norbornenone **5** furnished the lactones **14** and **15** (30:70) (Scheme 2). The minor lactone **14** was first subjected to $LiAlH_4$ reduction to furnish cyclohexene triol **16**. OsO_4-mediated dihydroxylation on **16** was stereospecific from the face opposite to the allylic hydroxyl group and furnished pseudo-α-DL-altropyranose carbasugar **17a** and was fully characterized as its pentaacetate **17b**.[7] In an alternate sequence, **16** was subjected to epoxidation with *m*-chloroperbenzoic acid in aqueous medium to furnish *trans*-epoxide **18** in a stereoselective manner. Interestingly, the epoxidation of **16** was dictated by steric considerations rather than by the usually encountered directing influence of the allylic hydroxyl group.[8,9] Acid-catalyzed opening of the epoxide ring in **18** was regioselective and pseudo-α-DL-mannopyranose **19a** (characterized as the pentaacetate **19b**[5,10]) was the main product formed with only traces of the regioisomeric pseudo-α-DL-idopyranose.[11] In an analogous manner, the major lactone **15** from **5** was reduced with $LiAlH_4$ to furnish two cyclohexene triols **20** and **21** (75:25) (Scheme 3). Quite unexpectedly, epimerization had occurred during the hydride reduction of **15**, possibly at the intermediate aldehyde stage and the hydroxymethyl group in **21** was *cis* to the neighbouring hydroxyl group. Dihydroxylation of **20** with OsO_4 proceeded stereoselectively to furnish the 'confused' carbasugar **22a** (characterized as pentaacetate **22b**[6]). Epoxidation of **20** took a course analogous to **16** and furnished the *trans*-epoxide **23**.[8,9] Acid-catalyzed opening in **23** led to a new 'confused' carbasugar



Scheme 2. *Reagents and conditions*: (i) MCPBA, Na_2CO_3, DCM, 0°C–rt, 4–5 h, 94%; (ii) LAH, THF, −15°C, 2 h, 70%; (iii) (a) OsO_4, NMMO (50% aq. solution, 4 equiv.), Me_2CO–H_2O (4:1), rt, overnight, (b) Ac_2O, Py, rt, 36 h, 78% (two steps); (iv) MCPBA, H_2O, rt, 2 days, 75%; (v) (a) cat. $HClO_4$ (70%), H_2O, rt, 24 h, (b) Ac_2O, Py, rt, 35 h, 73% (two steps).



Scheme 3. *Reagents and conditions*: (i). LAH, THF, −15°C, 2 h, 70%; (ii) (a) OsO_4, NMMO (50% aq. solution, 4 equiv.), Me_2CO–H_2O (4:1), rt, overnight, (b) Ac_2O, Py, rt, 36 h, 76% (two steps); (iii) MCPBA, H_2O, rt, 2 days, 77%; (iv) (a) cat. $HClO_4$ (70%), H_2O, rt, 24 h, (b) Ac_2O, Py, rt, 40 h, 72% (two steps).

24a (characterized as pentaacetate **24b**[6]) in a regioselective manner (Scheme 3). Similar transformations, dihydroxylation and epoxidation ring opening could also be executed on **21**, thus providing additional diversity among the 'confused' carbasugar family. We have carried out preliminary studies of the glycosidase inhibition ability of 'confused' carbasugars **13a**, **22a** and **24a** towards a panel of six glycosidases. However, no significant inhibition has been observed.

In summary, we have delineated a new and exceptionally simple approach to carbasugars and their siblings the 'confused' carbasugars, which has built-in flexibility to create stereochemical diversity. The 'confused' carbasugars being new entities, deserved to be evaluated further and elaborated to their amino derivatives as well as to oligomers. Efforts along these lines are in progress.

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6. All compounds reported here were fully characterized on the basis of their spectral (IR, ^1H, ^{13}C NMR, MS) and analytical data. Selected spectral data. **13b**: Mp = 116–117°C; IR (neat) ν_{max} 1746 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$) δ 5.42–5.41 (m, 1H), 5.28–5.13 (m, 3H), 4.26 (dd, 1H, J = 11.5, 6.0 Hz), 4.15 (dd, 1H, J = 11.5, 8.1 Hz), 2.42–2.34 (m, 1H), 2.30–2.15 (m, 1H), 2.08 (s, 9H), 2.06 (s, 3H), 2.05 (s, 3H), 1.86–1.81 (m, 1H); ^{13}C NMR (50 MHz; $CDCl_3$) δ 170.93, 170.00, 169.90, 169.85, 169.70, 69.57, 67.49, 67.28, 67.12, 60.79, 41.82, 29.43, 21.15, 20.92, 20.86, 20.82, 20.75; MS (EI, 70 eV) m/z 388 (M^+, <1%), 328 (5), 166 (90), 124 (70), 83 (74), 43 (100); anal. found: C, 52.49; H, 6.26. $C_{17}H_{24}O_{10}$ requires C, 52.57; H, 6.23. **22b**: Mp = 102–103°C; IR (thin film) ν_{max} 1744 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$) δ 5.31–5.27 (m, 1H), 5.17 (dd, 1H, J = 11.3, 2.7 Hz), 5.13–5.03 (m, 2H), 4.19 (dd, 1H, J = 11.7, 2.1 Hz), 4.12 (dd, 1H, J = 11.7, 2.7 Hz), 2.36–2.17 (m, 1H), 2.23 (m, 1H), 2.15 (s, 3H), 2.13 (s, 3H), 2.10 (s, 3H), 2.06 (s, 3H), 2.02 (s, 3H), 1.89–1.80 (m, 1H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 170.91, 169.91, 169.79, 169.39, 169.27, 68.10, 67.40, 67.09, 66.29, 58.18, 40.34, 30.67, 21.04, 20.99, 20.83, 20.77, 20.69; MS (EI, 70 eV) m/z 388 (M^+, <1%), 328 (20), 166 (44), 124 (66), 43

(100); anal. found: C, 52.61; H, 6.25. $C_{17}H_{24}O_{10}$ requires C, 52.57; H, 6.23. **24b**: Mp = 108–110°C; ν_{max} (thin film) 1745 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$) δ 5.48–5.38 (m, 2H), 5.14 (dt, 1H, J = 11.4, 4.5 Hz), 4.93 (dd, 1H, J = 9.9, 3.3 Hz), 4.09 (d, 2H, J = 3.0 Hz), 2.34 (td, 1H, J = 13.8, 4.5 Hz), 2.16 (s, 3H), 2.08 (s, 3H), 2.07 (s, 3H), 2.07–2.05 (m, 1H), 2.05 (s, 3H), 1.99 (s, 3H), 1.73–1.63 (m, 1H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 170.82, 170.20, 169.99, 169.87, 169.62, 73.09, 67.28, 67.05, 65.97, 58.25, 44.95, 33.21, 20.99, 20.92, 20.69, 20.61 (2C); MS (EI, 70 eV) m/z 388 (M^+), 328, 166, 124, 95, 43; anal. found: C, 52.74; H, 6.26. $C_{17}H_{24}O_{10}$ requires C, 52.57; H, 6.23.

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