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Triisobutylaluminium mediated carbocyclisation of sugar derived spiroketals and ketosides

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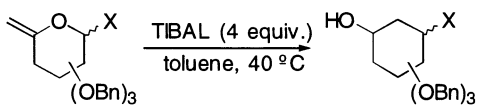
Abstract—The carbocyclisation of sugar derived spiroketals and ketosides under the agency of triisobutylaluminium is presented. In addition, the synthetic usefulness of cyclooctenic product **21**, derived from the corresponding *exo*-glycal **20**, was shown by its transformation into conformationally locked L-idose analogues **22** and **23**. © 2001 Elsevier Science Ltd. All rights reserved.

In 1997, Sinaÿ et al.[1] reported for the first time that fully benzylated α- or β-methyl 5-hexeno-D-pyranosides **1a** (*gluco*, *galacto* and *manno*) undergo a triisobutylaluminium (TIBAL) promoted rearrangement (see Scheme 1) to give cyclohexane derivatives **2a** with retention of configuration at the anomeric centre. Later on, it was shown[2] that the same rearrangement also occurred in the case of *exo*-glycals bearing other anomeric electron donating groups. Thus, rearrangement of the *exo*-glycals having 1-thio(seleno)phenyl (i.e. compounds **1b**) or *C*-aryl/furanyl groups (i.e. compounds **1c**) resulted in the corresponding carbocycles **2b–c**.[2]

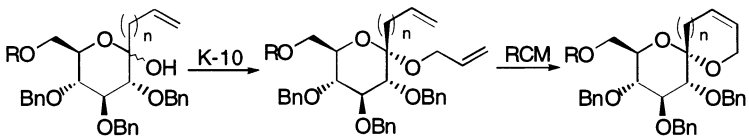


1 a-c **2 a-c**

Scheme 1. a: X = OMe; **b**: X = S(Se)phenyl; **c**: X = *C*-aryl/furanyl.

Two years ago, we revealed[3] that perbenzylated ketosides **4a** (see Scheme 2), accessible by K-10 clay[4] mediated stereoselective glycosidation of ketoses **3a** with allyl alcohol, were easily converted into the corresponding spiroketals **5a** by ring-closing metathesis[5] (RCM). It was also established[6] that the use of the mono-silylated ketoses **3b–c** led to the ketosides **4b–c** and spiroketals **5b–c**. The ease of transforming the latter orthogonally protected derivatives into the corresponding *exo*-glycals urged us to explore whether these compounds were amenable to TIBAL-mediated carbocyclisation.[7]

In order to substantiate this assumption, we initially explored (see Scheme 3) the carbocyclisation of the requisite dioxaspiro[4.5]decene **7**, the synthesis of which can be readily accomplished by the following three-step sequence. Thus, desilylation of **5b**, followed by iodination[8] gave iodide **6**.[9] Hydrogen iodide elimination of **6** proved to be most effective using sodium hydride



3 a-c **4 a-c** **5 a-c**

Scheme 2. a: R = Bn, *n* = 0, 1; **b**: R = TBDMS, *n* = 0; **c**: R = TBDMS, *n* = 1.

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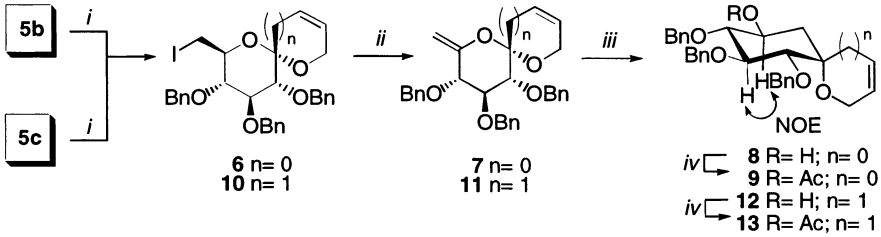
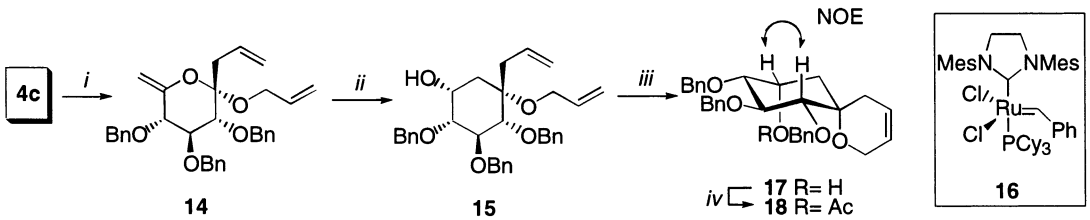
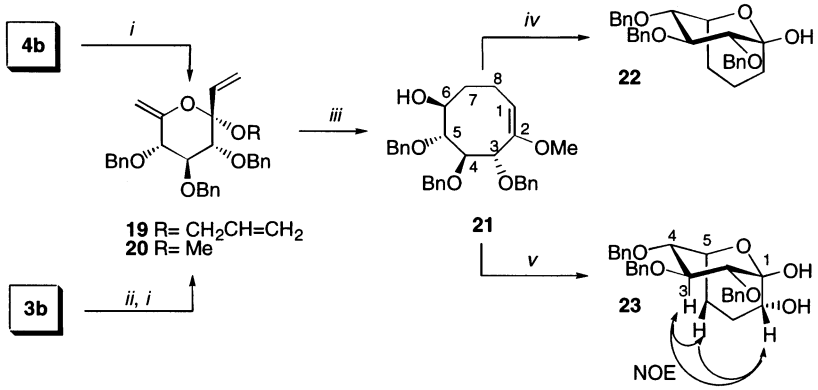


Scheme 3. *Reagents and conditions*: (*i*) (a) TBAF, THF, (b) I_2, imidazole, PPh_3, toluene, Δ (**6**, **10**: 86%); (*ii*) NaH (60% disp.), DMF, 20°C; (*iii*) TIBAL (4 equiv.), toluene, 20°C (**8**: 76% based on **6**; **12**: 81% based on **10**); (*iv*) Ac_2O, pyridine (**9**, **13**: 99%).



Scheme 4. *Reagents and conditions:* (*i*) (a) TBAF, THF, (b) I_2, imidazole, PPh_3, toluene, Δ, (c) NaH (60% disp.), DMF, 20°C; (*ii*) TIBAL (4 equiv.), toluene, 20°C (38% based on **4c**); (*iii*) **16** (0.002 equiv.), CH_2Cl_2, Δ (92%); (*iv*) Ac_2O, pyridine, 20°C (84%).



Scheme 5. *Reagents and conditions:* (*i*) (a) TBAF, THF, (b) I_2, imidazole, PPh_3, toluene, Δ, (c) NaH (60% disp.), DMF, 20°C (**19**: 82%; **20**: 99%); (*ii*) MeOH (6 equiv.), K-10 clay (200 mass%), 3 Å sieves, CH_2Cl_2, 20°C (74%); (*iii*) TIBAL (4 equiv.), toluene, 20°C (83%); (*iv*) *p*-TsOH, aq. THF, 20°C (86%); (*v*) *m*-CPBA, CH_2Cl_2, 20°C (51%).

resulting in the isolation of the spiroketal **7**. Ensuing rearrangement of crude **7** under the agency of excess TIBAL proceeded smoothly to afford the 1-oxaspiro[4.5]decene **8** in 65% overall yield as one diastereoisomer, the identity of which was firmly established by NOE experiments for the mono-acetylated spirocycle **9**.[9]

Similarly, TIBAL-mediated rearrangement of dioxaspiro[5.5]undecene **11**, prepared by subjecting **5c** to the same sequence of reactions as mentioned for the conversion of **5b** into **7**, resulted in the isolation of the 1-oxaspiro[5.5]undecene **12** in a 67% overall yield. The assignment of the (*S*)-configuration to C-8 in **12** was also in this case based on NOE measurements for the mono-acetylated spirocycle **13**.[9] The observed stereochemical outcome of both carbocyclisation reactions is in sharp contrast with the previously reported[1,2] TIBAL-mediated rearrangement of the 5-hexeno-D-glucopyranosides **1a**–**c**, all of which proceeded with a high preference for hydrogen delivery from the β-face of the newly formed cyclohexane ring to give an axial orientated hydroxyl function (i.e. (*R*)-configuration).

On the basis of the above results it was of interest to establish whether the stereochemical outcome of the TIBAL-mediated rearrangement of allylketoside **14** would afford a cyclohexane derivative with the same stereochemistry at C-8. However, carbocyclisation of substrate **14** (see Scheme 4), easily prepared from **4c** by the earlier mentioned three-step sequence, led to the exclusive isolation of product **15** having an axial hydroxyl at C-8, as gauged by NMR spectroscopy. The assignment of (*R*)-configuration of the latter stereogenic centre was also fully ascertained by comparison of the NMR data of the mono-acetylated spiroketal **13** with those of its epimer **18**,[9] resulting from a high yielding RCM of **15** using 0.2 mol% of the new Grubbs' pre-catalyst **16**,[10] and subsequent acetylation.

At this stage, the carbocyclisation of the vinylketoside **19** was undertaken (see Scheme 5). Unfortunately, reaction of compound **19**, prepared in the usual way starting from **4b**, with TIBAL led to a complex mixture of products instead of the expected [3,3]-sigmatropic rearrangement.[2a] On the other hand, subjection of the methyl vinylketoside **20**, constructed by K-10 mediated condensation of **3b** with excess methanol and further processing as mentioned before, gave the cyclooctenic carbocycle **21**,[9] the identity of which was firmly established by NMR spectroscopy.

The synthetic usefulness of this functionalised Claisen rearrangement product[11] was demonstrated by its conversion into the conformationally restricted L-idose derivative **22**. Thus, acid catalysed ring-closure of compound **21** led to the exclusive formation of L-idose analogue **22**.[9] ^{1}H NMR spectroscopy of **22** clearly indicated that the pyranose ring adopts a $^4C_1$-conformation, based on the *trans* configuration of H-2, 3 and 4. Moreover, treatment of **21** with *m*-CPBA led to the isolation of the L-idose analogue **23** containing an additional equatorial hydroxyl group, as gauged by NMR spectroscopy. The stereochemical outcome of the latter reaction results from a stereoselective epoxidation followed by acid catalysed intramolecular ring-closure.

In conclusion, the results presented in this paper clearly show that the TIBAL-mediated rearrangement of *exo*-glycal derivatives **1a**–**c** can be extended to sugar derived spiroketals as well as ketosides to give the corresponding carbacyclic derivatives in a highly diastereoselective fashion. The synthetic usefulness of cyclooctenic derivative **21**, obtained by a TIBAL-catalysed Claisen rearrangement of methyl vinylketoside **20**, was illustrated by its conversion into conformationally restricted analogues of L-idose. Further exploitation of **21** is currently under investigation and will be reported in due course.

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9. All new compounds were fully characterised by ^{1}H (200 or 300 MHz) and ^{13}C (50 or 75 MHz) NMR spectroscopy as well as mass spectrometry. Relevant spectroscopic data of the selected compounds **9**, **13**, **18**, **21** and **22** are as follows. **9**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.99 (d, 1H, *J* 6.1 Hz, H-3), 5.49 (m, 1H, H-4), 5.18–5.27 (m, 1H, H-7), 4.67–4.89 (m, 5H, H-2a,2b and CH_2 Bn), 4.58 (d, 1H, *J* 10.9 Hz, CH_2 Bn), 3.96 (t, 1H, *J* 9.5 Hz, H-9), 3.53 (t, 1H, *J* 9.5 Hz, H-8), 3.40 (d, 1H, *J* 9.5 Hz, H-10), 2.03 (dd, 1H, *J* 5.1 and 13.1 Hz, H-6a), 1.93 (s, 3H, CH_3 Ac), 1.51 (t, 1H, *J* 12.9 Hz, H-6b); ^{13}C NMR (75 MHz, $CDCl_3$): δ 105.4 (C-5), 91.0 (C-2), 72.5, 83.9, 84.6 and 84.8 (C-6,7,8,9), 76.0, 76.2 and 76.9 (CH_2 Bn), 38.4 (C-10), 22.0 (CH_3 Ac); MS (ESI): calcd for $C_{32}H_{34}O_6$ 514.2, found *m*/*z* 537.2 [M+Na]$^+$. **13**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.66 (m, 2H, H-3,4), 4.94–5.08 (m, 1H, H-8), 4.65, 4.76, 4.87 and 4.98 (4d, each 1H, *J* 11.3 Hz, CH_2 Bn), 4.90 (s, 2H, CH_2 Bn) 4.14–4.38 (m, 2H, H-2a,2b), 4.16 (t, 1H, *J* 9.3 Hz, H-10), 3.61 (t, 1H, *J* 9.4 Hz, H-9), 3.28 (d, 1H, *J* 9.6 Hz, H-11), 2.59–2.65 (m, 1H, H-5a), 2.58 (dd, 1H, *J* 4.5 and 13.9 Hz, H-7a), 1.95 (s, 3H, CH_3 Ac), 1.30 (m, 1H, H-5b), 1.03 (dd, 1H, *J* 12.1 and 13.9 Hz, H-7b); MS (ESI): calcd for $C_{33}H_{36}O_6$ 528.3, found *m*/*z* 551.5 [M+Na]$^+$. **18**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.67–5.80 (m, 2H, H-3,4), 5.57 (d, 1H, *J* 3.3 Hz, H-8), 4.66, 4.73, 4.83, 4.93, 5.04 and 5.12 (6d, each 1H, *J* 11.4, 11.3 and 10.7 Hz, CH_2 Bn), 4.41 (t, 1H, *J* 9.6 Hz, H-10), 4.34 (m, 1H, H-2a), 4.09 (bd, 1H, *J* 17.7 Hz, H-2b), 3.60 (dd, 1H, *J* 3.7 and 9.7 Hz, H-9), 3.28 (d, 1H, *J* 9.6 Hz, H-11), 2.75 (bd, 1H, *J* 17 Hz, H-5a), 2.62 (dd, 1H, *J* 3.0 and 16.2 Hz, H-7a), 2.19 (s, 3H, CH_3 Ac), 1.33–1.42 (m, 1H, H-5b), 1.19 (dd, 1H, *J* 3.0 and 16.2 Hz, H-7b); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6 (C=O), 122.1 and 124.6 (C-3,4), 66.8, 79.6, 81.0 and 83.8 (C-7,8,9,10), 72.1, 73.4, 75.6 and 76.0 (C-6 and CH_2 Bn), 60.9 (C-2), 30.1 and 30.6 (C-5,7), 22.4 (CH_3 Ac); MS (ESI): calcd for $C_{33}H_{36}O_6$ 528.3, found *m*/*z* 551.4 [M+Na]$^+$. **21**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.80 (t, 1H, *J* 6.6 Hz, H-1), 4.78 (d, 1H, *J* 8.8 Hz, H-3), 4.28, 4.43, 4.55, 4.63, 4.66 and 4.90 (6d, each 1H, *J* 11.0 and 11.7 Hz, CH_2 Bn), 4.19 (m, 1H, H-6), 4.03 (dd, 1H, *J* 4.4 and 8.8 Hz, H-4), 3.73 (dd, 1H, *J* 4.4 and 8.0 Hz, H-5), 3.44 (s, 3H, CH_3), 3.35 (s, 1H, OH), 2.34–2.41 (m, 1H, H-7a), 1.76–2.02 (m, 3H, H-7b,8a,8b); ^{13}C NMR (50 MHz, $CDCl_3$): δ 151.8 (C-2), 101.0 (C-1), 83.0 (C-4), 79.6 (C-5), 77.8 (C-3), 70.9, 72.8 and 74.7 (CH_2 Bn), 71.2 (C-6), 54.3 (CH_3), 33.8 (C-7), 18.7 (C-8); MS (ESI): calcd for $C_{30}H_{34}O_5$ 474.2, found *m*/*z* 497.5 [M+Na]$^+$. **22**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.58, 4.66, 4.73 and 4.93 (4d, each 1H, *J* 11.7 Hz, CH_2 Bn), 4.85 (s, 2H, CH_2 Bn), 4.21 (m, 1H, H-5), 4.04 (t, 1H, *J* 8.8 Hz, H-3), 3.78 (dd, 1H, *J* 6.6 and 8.8 Hz, H-4), 3.50 (d, 1H, *J* 8.8 Hz, H-2), 2.70 (s, 1H, OH), 2.36 (bd, 1H, *J* 13.2 Hz, H-7a), 1.91 (bd, 1H, *J* 11.0 Hz, H-6a), 1.60–1.80 (m, 3H, H-6b,7b,8a), 1.43 (m, 1H H-8b); ^{13}C NMR (50

MHz, $CDCl_3$): δ 97.4 (C-1), 81.2, 83.4 and 86.3 (C-2,3,4), 72.8, 74.7 and 75.2 (CH_2 Bn), 71.4 (C-5), 30.7 (C-6), 21.5 (C-8), 18.9 (C-7); MS (ESI): calcd for $C_{29}H_{32}O_5$ 460.2, found m/z 483.3 $[M+Na]^+$.

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