Samarium(II) Iodide Promoted Ring Contraction of Carbohydrate Derivatives: an Expeditious Synthesis of Functionalised Cyclopentanes

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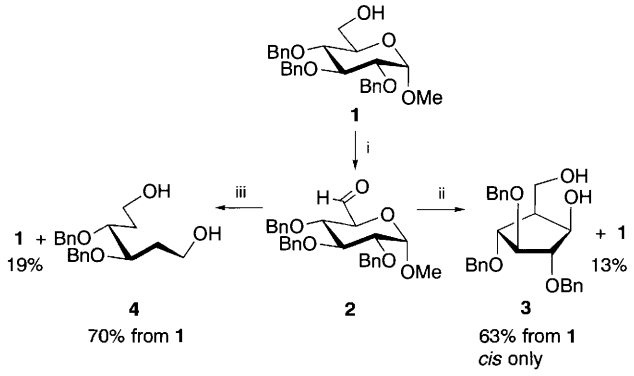
Aldehydo methyl pyranosides undergo ring contraction induced by treatment with samarium(ii) iodide, in the presence of HMPA and *tert*-butyl alcohol, to give highly functionalised cyclopentanes.

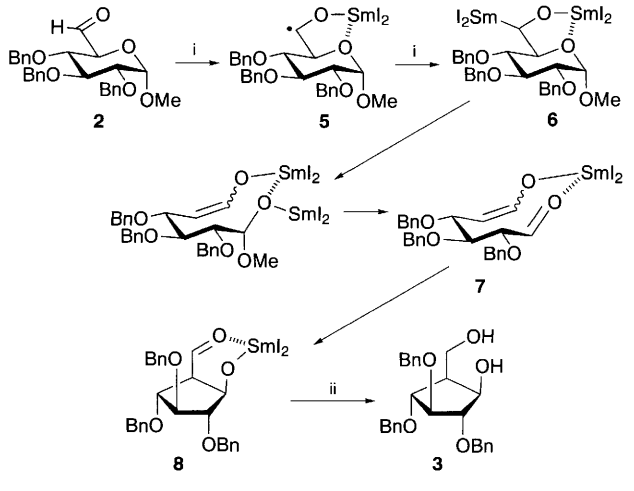
The conversion of carbohydrate derivatives into functionalised and enantiomerically pure cyclopentanes is well documented[1] and is most often the result of multistep reaction sequences. We report herein an efficient samarium(II) iodide mediated stereoselective ring contraction[2] of aldehydo pyranoside derivatives, which leads, in a single synthetic step, to highly functionalised cyclopentanes.

Compound **1**[3] was transformed into aldehydo sugar **2**[4] (modified Swern oxidation[5]) which was then treated† at room temp. with a solution of SmI_2 in THF (5 equiv.) in the presence of HMPA and *tert*-butyl alcohol (2 equiv.), as shown in Scheme 1. The crystalline cyclopentane **3**‡ was obtained as a single isomer§ (63% yield from **1**), which was easily separated from **1** (13% yield). This yield was substantially lowered when either HMPA (46%) or both HMPA and *tert*-butyl alcohol (30%) were omitted. It is interesting to note that when *tert*-butyl alcohol was replaced by ethylene glycol[6] as the proton source, in the absence of HMPA, little or no cyclopentane was detected and the diol **4**‡ was isolated in 70% yield.

A possible mechanistic rationale which accounts for this remarkable one-step transformation is depicted in Scheme 2.



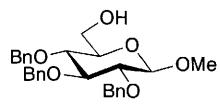
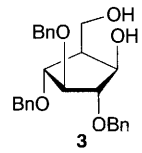
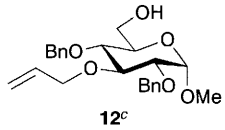
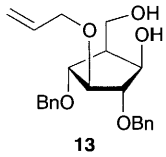
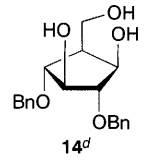
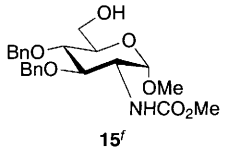
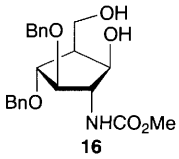
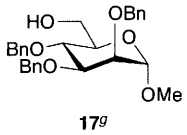
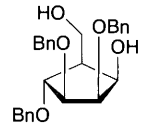
Scheme 1 *Reagents and conditions*: i, Swern oxidation; ii, SmI_2–THF, HMPA, Bu^tOH (2 equiv.); iii, SmI_2–THF, ethylene glycol (27 equiv.)



Scheme 2 *Reagents*: i, SmI_2; ii, $2SmI_2$, ROH

We envisage that the first equivalent of SmI_2 reduces the aldehyde **2** to the samarium ketyl **5**.[7] A second equivalent of samarium reduces **5** to the disamarium species **6**, which then undergoes ring opening[8] followed by methoxide elimination to give the key intermediate **7**. The beauty of this reaction is that it uniquely generates a system which is ideally suited for a subsequent aldol cyclisation reaction involving intramolecular nucleophilic attack of the samarium enolate onto the aldehyde through a 5-enol *exo-exo-trig* process.[9] It is conceptually interesting to compare this contraction with the well established Ferrier reaction[10] similarly involving *in situ* generation from a

Table 1 SmI_2-mediated ring contraction reaction

Entry	Substrate	Product	Yield (%)[a]
1	 **11**[b]	 **3**	55 (66)
2	 **12**[c]	 **13**  **14**[d]	59 (72)[e] **13**:**14** = 26:33
3	 **15**[f]	 **16**	55 (61)
4	 **17**[g]	 **18**[h] Major isomer	39 (47)[i]

[a] Numbers in parentheses are corrected yields calculated on the basis of recovered starting alcohols. [b] See ref. 13. [c] See ref. 14. [d] Formation of this compound probably occurs *via* transannular abstraction of one of the two allylic hydrogen atoms by the samarium ketyl radical formed during reduction of the cyclopentane aldehyde (allylic analogue of **8**, Scheme 2). Reduction of the allylic radical which is accompanied by isomerisation leads to the formation of an enol ether which is hydrolysed during the acidic work-up and produces an overall net deallylation. [e] Combined yield of **13** and **14**. [f] Prepared in three steps from the known methyl 2-deoxy-2-methoxycarbonylamino-α-D-glucopyranoside. See ref. 18. [g] See ref 15. [h] The stereochemistry of the minor isomer was not determined. Ratio of the isomers = 8.3. [i] Combined yield of the two isomers.

sugar of a 'mercury enolate' and an aldehyde, followed by an aldol-like intramolecular cyclisation to give a cyclohexanone. The stereoselectivity of this cyclisation was expected to ensue from a samarium-linked medium-sized chelate, from which the carbon–carbon bond formation would take place like a ring contraction.[11] Final reduction of **8** affords the observed product **3**.¶ This reaction has been extended to other substrates as shown in Table 1.

In conclusion, we have discovered a novel carbohydrate ring contraction which provides an efficient entry to fully functionalised cyclopentanes. It complements the remarkable zirconium mediated ring contraction developed by T. Taguchi *et al.*,[12] and illustrates the potential offered by the use of SmI_2 in organic chemistry.

We would like to thank Professor T. Taguchi for the communication of unpublished ^1H and ^{13}C NMR spectra of compound **3**.

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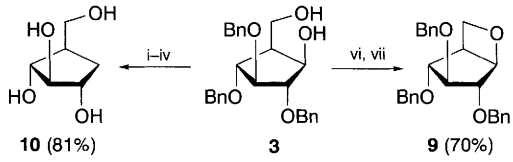
Footnotes

† *Typical experimental procedure*: Dimethyl sulfoxide (49 μl, 1.5 equiv.) was added to a stirred solution of oxalyl chloride (43 μl, 1.3 equiv.) in CH_2Cl_2 (2 ml) at −40 °C under argon. After 10 min a solution of the alcohol **1** (174 mg, 377 μmol) in CH_2Cl_2 (0.7 ml) was added and the resulting mixture stirred at −40 °C for 1 h. Triethylamine (157 μl, 3 equiv.) was then added and the reaction temperature allowed to warm to room temp. over a period of 30 min. The resulting solution was then washed with saturated aqueous $NaHCO_3$ (2 × 5 ml), and water (5 ml portions until neutral pH). The organic phase was then dried ($MgSO_4$), filtered, the solvent removed and the residue dried *in vacuo* for 48 h in a dessicator. A solution of this crude product in THF (2 ml) was then added to a stirred solution of SmI_2 in THF (0.1 mol dm^{-3}, 18.5 ml, 4.9 equiv.), *tert*-butyl alcohol (71 μl, 2 equiv.) and HMPA (0.94 ml, 5% *v/v*) at room temp. under argon over 15 min. After 1 h, a solution of HCl (1 mol dm^{-3}, 2 ml) was added, the reaction mixture diluted with diethyl ether (20 ml) and washed with a 5% solution of $Na_2S_2O_5$ (20 ml). The aqueous phase was then washed with diethyl ether (5 × 20 ml), the organic extracts combined, washed with brine, dried ($MgSO_4$), filtered, the solvent removed and the residue purified by flash chromatography (cyclohexane–ethyl acetate, 2:1, increasing polarity to 1:1), to yield starting alcohol **1** (23 mg, 13%) and the cyclopentane **3** (103 mg, 63%).

‡ All new products possess ^1H and ^{13}C NMR data in agreement with the proposed structures. Correct microanalyses were obtained for compounds **3**, **4**, **9**, **13** and **14**. *Selected data* for **3**: mp 95 °C (ethyl acetate–cyclohexane), $[\alpha]_D^{20}$ + 26 (*c* 1.1, $CHCl_3$); **4**: $[\alpha]_D^{20}$ + 47 (*c* 1.1, $CHCl_3$); **9**: $[\alpha]_D^{20}$ + 22 (*c* 1.0, $CHCl_3$); **13**: $[\alpha]_D^{20}$ + 31 (*c* 1.5, $CHCl_3$); **14**: $[\alpha]_D^{20}$ +33 (*c* 1.2, $CHCl_3$); **15**: mp 107–108 °C (ethyl acetate–hexane), $[\alpha]_D^{20}$ + 56 (*c* 0.8, $CHCl_3$); **16**: mp 129 °C (ethyl acetate–hexane), $[\alpha]_D^{20}$ + 36 (*c* 1.0, $CHCl_3$); **18**: $[\alpha]_D^{20}$ + 15 (*c* 1.0, $CHCl_3$).

§ The *cis*-stereochemistry of **3** was confirmed by the transformation into the oxetane **9**. Furthermore, **3** was easily converted (81% overall yield) into known pseudo-α-D-arabinofuranose[16] (Scheme 3). Also, the ^1H and ^{13}C NMR spectra of **3** were identical with those kindly provided by Professor Taguchi.

¶ Although the precise contribution of the proton source alcohol to the reaction mechanism is not clear, it has often been used in α-keto deoxygenations.[6,17] In the presence of ethylene glycol, the samarium enolate is probably protonated, so that the aldol rection does not occur and is replaced by the observed acyclic α-keto deoxygenation followed by reduction to the diol **4**.



10 (81%) **3** **9** (70%)

Scheme 3 *Reagents*: i, TrCl, pyridine; ii, NaH, CS_2, MeI; iii, Bu_3SnH, AIBN; iv, AcOH, H_2O, AcOEt; v, H_2, Pd; vi, TsCl, pyridine; vii, NaH, DMF

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