Chiral Cyclobutanols and Cyclopentane Dimers via Samarium(II) Iodide Induced Keto-Olefin Cyclisations of Carbohydrate-Derived Unsaturated Ketones

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Abstract: Some pentose and hexose sugars were converted into unsaturated ketone derivatives, which themselves served as substrates for 4-exo-trig radical cyclisation reactions mediated by SmI₂. Depending on the order of addition of reagents, the keto-olefins could also be made to undergo a surprising tandem 5-endo-trig cyclisation/dimerisation reaction to a cyclopentane dimer or a cyclobutane monomer.

Key words: carbocycles, carbohydrates, radical reactions, samarium, ring closure

Carbohydrates are ubiquitous in nature and chemists have recognised the potential of these flexible starting materials, applying them to their use as starting materials in the synthesis of chiral products.¹ The use of carbohydrates as precursors for the synthesis of cyclopentane derivatives was recognised some time ago.² Since then, significant attention has been paid to this strategy, resulting in many new syntheses of substituted stereodefined cyclopentanes.¹ In addition to the SmI₂-mediated synthesis of cyclopentanes in our group,³ we have also recently reported on the synthesis of cyclobutanes, using that reagent.⁴ A number of routes toward the synthesis of compounds 1–3 (Figure 1), which contain thymine or guanine moieties and which are bioactive (antiviral agents), have been devised.⁵ It is the synthesis of analogues of the guanine-containing cyclobutane derivative 3 that our strategy attempts to address. Therefore, we decided to utilise the methodology developed in our laboratories,⁶ revolving around SmI₂, a selective single-electron reductant, towards the synthesis of functionalised cyclobutanes from carbohydrate precursors in 4-exo-trig ‘keto-olefin’ cyclisation reactions of some carbohydrate derivatives.

Our previous work has shown that a conformationally restricted system is required before cyclisations to small rings will take place.⁵ With this in mind, 2,3,5,6-di-O-isopropylidene-D-mannofuranose (4) was subjected to a Wittig reaction⁴ and in situ (to prevent unwanted Michael addition reactions⁸) Dess–Martin oxidation⁹ to provide keto-olefins 5a (63%) and 5b (5%) (Scheme 1).

Reaction of 5a with SmI₂ by slow dropwise addition of the sugar substrate to the SmI₂/HMPA–THF mixture at −78 °C gave the desired chiral cyclobutane products 6a (50%) and 6b (33%), arising from a favoured 4-exo-trig cyclisation according to Baldwin’s rules,¹⁰ in good yields (Figure 2). Reversal of the mode of addition, that is, addition of the SmI₂ solution to the keto-olefin substrate, again afforded products 6a and 6b, but also allowed the isolation of a third isomer 7c in trace amounts. The keto-olefin coupling reaction¹¹ has been used in many guises, to effect, for example, 3-exo-trig,¹² 4-exo-trig,¹³ and 5-exo-trig¹⁴ cyclisation reactions. For unactivated alkene systems and for most α,β-unsaturated ester substrates, the mechanism is generally held to proceed via the ketyl radical anion¹⁴,¹¹–¹³ cyclising onto the alkene, although there is some evidence that the process may proceed via initial re-
duction of the enoate system followed by cyclisation onto the keto moiety in certain instances.\textsuperscript{12}

The diastereoselectivity observed presumably relates to the steric bulk of the two acetonide protecting groups preferring a\textit{trans} set-up in the transition state, which would select 6\textit{a} as the major product with 6\textit{b} as the minor. In the event, the 4-\textit{exo-trig} cyclisation reactions typically proceed such that the hydroxyl group and the ester function maintain a\textit{trans} relative stereochemistry in the product.\textsuperscript{4c,d,11c}

We have previously observed analogous cyclisations based on ribose-derived materials.\textsuperscript{4} Here, identical reactions could be carried out to prepare cyclobutane derivatives of opposite stereochemistry, when making use of D-lyxose (7) as starting material. Synthesis of the lyxose derivative 10 for treatment with SmI\textsubscript{2} was carried out with ease, using known chemistry (Scheme 2) (53\% total yield over three steps, \textit{cis}/\textit{trans} = 2:7).\textsuperscript{4}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Scheme_2.png}
\caption{Cyclobutane derivatives 6\textit{a}–\textit{c} prepared from keto-enoate 5\textit{a}}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Scheme_3.png}
\caption{Cyclobutane derivatives 11\textit{a}–\textit{d} prepared from enoate 10}
\end{figure}

A remarkable change in the selectivity of the reaction occurred, for some substrates, when the order of the addition of reagents was reversed. As already stated, keto-olefin 5\textit{b} provided essentially identical product distributions, irrespective of whether the substrate was added to the SmI\textsubscript{2} solution or the SmI\textsubscript{2} solution was added to the substrate. However, when the SmI\textsubscript{2} solution was added to either the ribose-derived substrate 13\textsuperscript{4a} or the lyxose-derived analogue 10, we unexpectedly isolated dimeric materials 14 (Scheme 4).

Even more surprising was the fact that these products were not dimeric cyclobutanes (i.e., simple dimers of, for example, 11\textit{b}), but were dimeric cyclopentanes, the products of a tandem cyclisation/dimerisation reaction. This was unexpected in the face of Baldwin’s rules\textsuperscript{10} of cyclisation, under which it is anticipated that a 4-\textit{exo-trig} cyclisation dominates over a 5-\textit{endo-trig} competing possibility. The structure of one of the ribose-derived dimeric products 14\textit{a} was confirmed by X-ray crystallography.\textsuperscript{16}

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Carrying out the SmI\textsubscript{2}-mediated ring-closing reaction by adding the\textit{trans} substrate to the SmI\textsubscript{2}/HMPA–THF mixture gave four monomers 11\textit{a}–\textit{d} in a total yield of 65\% (5\%:30\%:13\%:17\%) (Figure 3), the major products having the alcohol and ester groups \textit{cis} with respect to each other, as anticipated from our previous work.\textsuperscript{3a} The change in the selectivity from \textit{trans} to \textit{cis} in the present instance presumably relates to the large size of the TBDMS group dominating steric interactions in the cyclisation transition state.

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\end{figure}

In all of the cases shown above, the stereochemistry of the isomers obtained was deduced and assigned on the basis of extensive NOE NMR experiments. A single crystal X-ray structure determination\textsuperscript{14} of the fully deprotected lactone 12 (Scheme 3), derived from 11\textit{c} by acid-catalysed hydrolysis, offered conclusive evidence of the stereochemistry of this product. Indeed, triol 12\textsuperscript{14} (and its ribose-derived analogue\textsuperscript{15}) is now perfectly set up for further manipulation towards a nucleoside, which is part of our ongoing studies in this area.

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Interestingly, the ribose-derived trityl-protected keto-olefin $15^a$ failed to afford the dimeric product (Scheme 5), instead producing only the monomeric cyclobutane products already described elsewhere,$^4a$ regardless of the order of addition. This was also the case for the mannose derivative $5$, as described above.

Scheme 5

From these data, it appears as if the outcome of the reaction is dependent on two factors. Firstly, the reaction is sensitive to the order of addition of substrate and reagent: addition of the keto-olefin substrates to SmI$_2$ facilitates monomer formation only, in all cases, while the reverse addition allows the possibility of generating dimers. Secondly, in instances in which dimerisation is at all a possibility, namely when the SmI$_2$ is slowly added to the keto-olefin substrate, steric factors may inhibit the dimerisation reaction altogether, as was found to be the case with the sterically demanding enoate substrates $5$ and $15$. The reason why dimer formation occurs probably lies in a change in the mechanism of the reaction. Literature reports have indicated that the cyclisation of keto-enoate substrates may also be initiated at the enoate group.$^{12,13}$ Since the reduction of the ketone to the ketyl radical is reversible,$^{17}$ and the fact that 4-exo-trig reactions are held to be relatively slow,$^{19}$ the reaction may well favour reaction at the enoate under the particular reaction conditions cited here. Such cyclisations to monomeric systems have previously been observed when the reactions are performed in the presence of a proton source.$^{19}$ (Proton sources have been shown to dramatically effect SmI$_2$-mediated reactions, also permitting stereoselective reactions to be secured from chiral alcohols.$^{20}$) Furthermore, such reactions at the enoate are also known to lead to dimerisation products in some instances.$^{21}$ Here, the process is generally believed to proceed via radical addition, but one different mechanism has also been proposed.$^{21c}$ In any case, a recent detailed study by Flowers$^{22}$ indicates that the keto-olefin reaction, particularly the role of HMPA therein, is difficult to predict. In the present case, it is quite possible that the mechanism switches from the usual ketyl radical cyclisation to an anion cyclisation/radical dimerisation or similar mechanism of the enoate moieties to produce $16$ and $17$ and so generate the five-membered rings (Scheme 6). In this way, the preferred 5-exo-trig cyclisation is followed.

Scheme 6

In summary, chiral cyclobutane derivatives can be readily prepared from chiral carbohydrate precursors of varying carbon number and chirality using a reductive cyclisation protocol. Furthermore, depending on the steric bulk around the ketone functionality and the order of addition of reagents, cyclopentane dimers may also be prepared from common intermediates. Excessive steric bulk prevents the formation of such dimers, regardless of the order of addition of the reagents, producing cyclobutane derivatives in all instances. We are currently in the process of preparing analogues of $3$, from products of this study, with the view to their biological evaluation, the results of which will be disclosed in due course.

TLC was conducted quantitatively on Merck GF254 precoated silica gel glass plates (0.25 mm layer). Various solvent mixtures were used to elute the chromatograms with the mixture of hexanes and EtOAc usually being the eluent of choice. Aromatic derivatives were visualised by their fluorescence under UV light (254 nm).
while carbohydrate substrates were detected after spraying the TLC plate with a chromic acid solution and then heating it over an open flame. Flash column chromatography refers to column chromatography under N₂ pressure (ca. 50 kPa). The columns were loaded with Merck Kieselgel 60 (230–400 mesh) and eluted with appropriate solvent mixtures in a volume per volume ratio. THF was pre-dried over freshly ground KOH. The KOH was then filtered off and the solvent distilled from sodium-benzophenone under N₂ immediately prior to use, and once a sustained blue colour was present. HMPA was heated over CaH₂ under argon for one week prior to its use. The solvent was only used if freshly distilled. NMR-spectra were recorded using a Varian Gemini 2000, 300 MHz spectrometer. The samples were usually made up in CDCl₃ and for more polar samples D₂O was used. The 1H NMR data are listed in order: Chemical shift (δ, reported in ppm and referenced to the residual solvent peak of CDCl₃ [δ = 7.24]), the multiplicity, the coupling constant J expressed in Hz, the proton integration, and finally the specific hydrogen allocation. Spin-decoupling experiments aided in the determination of the coupling constants and hydrogen allocation. The relative stereocchemistry was determined after studying nuclear Overhauser effect spectra (1D NOE difference). 13C NMR data are listed in the order: chemical shift (δ, reported in ppm referenced to the solvent peak of CDCl₃ [δ = 77.0]) and the specific carbon atom allocation. DEPT and HETCOR spectroscopy were used to assist in the allocation of difficult spectra where necessary. Mass spectra were recorded on a Finnigan Matt 8200 spectrometer at an electron impact of 70 eV, while FAB-HRMS spectra were recorded on a Finnigan Matt 8200 spectrometer. A Jasco model DIP-730 spectropolarimeter having a cell with a 10 mm path length was used to determine optical rotations. The concentration (c) indicates the concentration of the sample in grams per 100 mL of solution. All re-actions were performed in flame out glass apparatus using anhyd solvents unless otherwise stated. All SmI₂ reactions were carried out under argon using degassed solvents while standard chemistry actions were performed in flamed out glass apparatus using anhyd solvents. Reversed addition allowed to be isolated in a separate reaction as a colourless oil.

**Cyclobutane 6a**

Yield: 35 mg (50%); Rₚ = 0.47 (2:1 hexanes–EtOAc); [α]D = +611.1 (c 1.0, CHCl₃).

**Cyclobutane 6b**

IR (CHCl₃): 3568, 2949, 1733, 1730, 1066 cm⁻¹.

**Cyclobutane 6c**

IR (CHCl₃): 3429, 3033, 2935, 1735, 1222 cm⁻¹.

**Cyclobutane 6c**

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**Keto-Enoate 5a**

To a solution of 2,3,5,6-di-O-isopropylidene-t-mannofuranose (4; 100 mg, 0.37 mmol) in anhyd CH₄Cl₂ (1.5 mL) was added ethyl(triphenylphosphoranylidene)acetate (157 mg, 0.45 mmol) and the reaction mixture stirred at r.t. Upon completion of the reaction, cyclobutane 6 was obtained as oils (total yield: 83%).

**Mannofuranose Monomers 6a-c**

Keto-enoate 5a (69 mg, 0.21 mmol) was dissolved in degassed THF (5 mL) and the solvent removed by vacuum distillation to ensure an oxygen-free system. The residue was then dissolved in THF (20 mL) and added dropwise over 20 min with stirring to a freshly prepared solution of SmI₂ in THF (8.8 mL of a 0.1 M solution, 0.88 mmol, 4.2 equiv) and HMPA (0.21 mL, 1.43 mmol, 6.8 equiv) at −78 °C. The mixture was stirred at −78 °C for 2 h, after which it was diluted with EtOAc (20 mL) and filtered through a thin pad of silica gel. The solvent was removed in vacuo and the residue was purified by flash column chromatography (3:1 hexanes–EtOAc). Two isomeric monomers 6a and 6b were obtained as oils (total yield: 83%).

**Keto-Enoate 10**

The general procedure to perform a Wittig reaction with ethyl(triphenylphosphoranylidene)acetate in CH₄Cl₂ was carried out on protected lyxose derivative 8 (1.050 mg, 3.44 mmol) followed by in

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**Lysyxe Monomers IIA–d**

The general procedure to form monomers with SmI₂ in THF in the presence of HMPA via normal addition was used to form monomers from enolate 10 (78 mg, 0.21 mmol). The residue was purified by flash column chromatography (3:1 hexanes–EtOAc). Four monomer isomers were obtained as oils; total yield: 55%.

**Cyclobutane 11a**

Yield: 4 mg (5%); [α]D = -28.2 (c 2.0, CHCl₃); Rf = 0.56 (5:1 hexanes–EtOAc).

**IR (CHCl₃):** 1723, 1579, 1313, 1267, 1191, 1111, 1080, 1034, 982, 847 cm⁻¹.

**HRMS-FAB:** m/z calc for C₁₈H₃₃SiO₆: 373.2046 ([M + 1]+); found: 373.2037.

**Cyclobutane 11b**

Yield: 27 mg (30%); [α]D = -138.9 (c 16.0, CHCl₃); Rf = 0.46 (5:1 hexanes–EtOAc).

**IR (CHCl₃):** 3040, 2960, 2880, 1790, 1740, 1650, 1540, 1390, 1270 cm⁻¹.

**HRMS-FAB:** m/z calc for C₁₈H₃₃SiO₆: 373.2046 ([M + 1]+); found: 373.2202.

**Cyclobutane 11c**

Yield: 15 mg (13%); [α]D = +57.7 (c 2.0, CHCl₃); Rf = 0.31 (5:1 hexanes–EtOAc).

**HRMS-FAB:** m/z calc for C₁₈H₃₃SiO₆: 373.2203 ([M + 1]+); found: 375.2203.

**Cyclobutane 11d**

Yield: 12 mg (17%); [α]D = +61.7 (c 5.0, CHCl₃); Rf = 0.27 (4:1 hexanes–EtOAc).

**IR (CHCl₃):** 3040, 2960, 2880, 1790, 1740, 1650, 1540, 1390, 1270, 1220 cm⁻¹.

**HRMS-FAB:** m/z calc for C₁₈H₃₃SiO₆: 373.2046 ([M + 1]+); found: 373.2202.

**Dimers 14a–d; General Procedure**

The keto ester 10 or 13 (0.21 mmol) was dissolved in degassed THF (5 mL) and the solvent removed by vacuum distillation to ensure an oxygen-free system. The residue was then dissolved in THF (20 mL) and HMPA (0.21 mL, 1.43 mmol, 6.8 equiv) and subsequently cooled to −78 °C. A freshly prepared solution of SmI₂ in THF (6.3 mL of a 0.1 M solution, 0.63 mmol, 5.0 equiv) was then added dropwise over 20 min with stirring. The stirring was continued at −78 °C for 2 h, after which it was diluted with EtOAc (20 mL) and filtered through a thin pad of silica gel. The solvent was removed in vacuo and the residue purified by flash column chromatography.

**Ribose-Derived Pivaloyl Dimer 14a**

Yield: 24 mg (0.035 mmol, 33%); colourless oil; Rf = 0.37 (2:1 hexanes–EtOAc).

**IR (CHCl₃):** 3520, 3040, 2960, 2870, 1740, 1715, 1570, 1220, 1170 cm⁻¹.

**HRMS-FAB:** m/z calc for C₃₄H₅₆O₁₄: 688.3670 ([M + 2]+); found: 688.3672.

**Ribose-Derived Pivaloyl Dimer 14b**

Yield: 20 mg (0.030 mmol, 28%); white needle-like, gummy crystals; Rf = 0.25 (2:1 hexanes–EtOAc).

**IR (CHCl₃):** 3600, 3040, 2960, 1740, 1715, 1390, 1220, 1170 cm⁻¹.

**HRMS-FAB:** m/z calc for C₃₄H₅₆O₁₄: 688.3670 ([M + 2]+); found: 688.3672.

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$\text{IR (CHCl}_3\text{): 3040, 2960, 1740, 1715, 1660, 1570, 1220, 1100 cm}^{-1}$.

HRMS-FAB: $m/z$ calcd for C$_{34}$H$_{55}$O$_{14}$: 687.3588; found: 687.3592.

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References

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