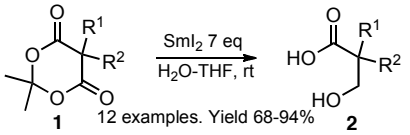
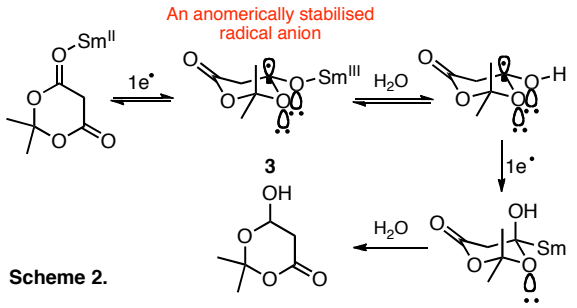
Research Summary

Selective reductive cyclisations of cyclic 1,3-diesters using SmI_2 and H_2O

Until recently, it was believed that simple aliphatic ester derivatives lay beyond the reducing range of SmI_2. We have now established that with the addition of water as a co-solvent this is not the case, and have recently reported the highly selective mono-reduction of cyclic 1,3-diesters **1** to 3-hydroxyacids **2** using SmI_2 and H_2O (scheme 1).[1]



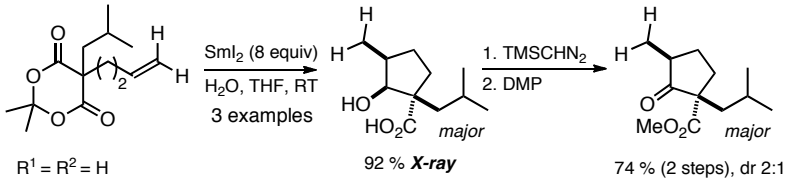
Scheme 1.



Scheme 2.

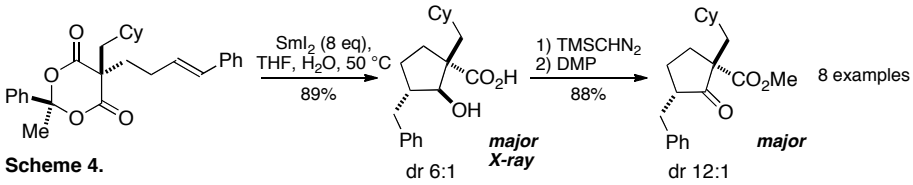
No over-reduction to the corresponding diol is observed, even in the presence of excess reagent, and the reaction is completely selective for cyclic 1,3-diesters over acyclic 1,3-diesters and esters. We suggest that the observed selectivity has its origin in the rate of the initial electron transfer to the carbonyl of cyclic 1,3-diesters, and that anomeric stabilisation of the radical anion intermediate **3** is crucial for promoting the initial reduction (scheme 2). Acyclic diesters and esters are unable to form such stable radical anions and hence are not reduced. Theoretical calculations support this hypothesis.[1]

Initially we exploited the ketyl radical intermediates formed *via* single electron reduction of diesters in intramolecular additions to alkene acceptors (scheme 3). Esterification and oxidation allowed the diastereomeric ratios achieved in the cyclisations to be determined.



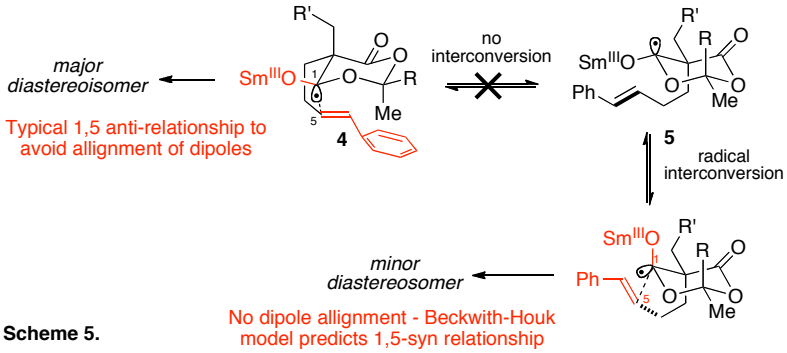
Scheme 3.

Investigating the effect of the ketal unit of the cyclic diester and of the reaction temperature on cyclisation, gave our optimised conditions. We found that a larger ketal unit increased the diastereoselectivity of cyclisation, and interestingly, that these radical cyclisations display highly atypical behaviour with improved diastereoselectivity observed with an increase in reaction temperature. The exploitation of these unusual ketyl radical intermediates is efficient, and cyclisations proceed in excellent yield (72-90%) and with moderate to excellent (3:1-33:1) diastereoselectivity (scheme 4).[2]

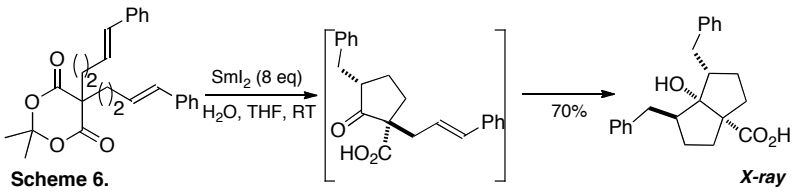


Scheme 4.

We propose that the observed increase in diastereoselectivity with an increase in the size of the ketal unit is due to the viability of two cyclisation pathways involving pseudoaxial radical anions **4** and **5**. We suggest that for the dimethyl ketal (R = Me) both axial radicals are similar in energy and therefore readily accessible. In contrast, the acetophenone ketal (R = Ph) may exert greater control over the conformation of the radical anion, favouring **4,** thus accounting for the improvement in diastereoselectivity (scheme 5). It is not yet clear why diastereoselectivity increases with temperature.



Scheme 5.



Scheme 6.

We have subsequently demonstrated the viability of extended reaction cascades, synthesising bicyclic systems in a single synthetic operation with complete diastereocontrol (scheme 6).

In summary, we have successfully demonstrated the first mono-reductions of cyclic 1,3-diesters. We have also shown that the SmI_2-H_2O reducing agent system is selective for cyclic 1,3-diesters, and will not reduce acyclic diesters or simple esters. Furthermore, unusual radical intermediates formed by one-electron reduction of the ester carbonyl have been exploited in unprecedented ketyl radical-olefin cyclisations. This methodology has since been optimised, and the viability of reaction cascades confirmed.

[1]Guazzelli, G.; Grazia, S. D.; Collins, K. D.; Matsubara, H.; Spain, M.; Procter, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 4214. [2]Collins, K. D.; Oiveria, J. M.; Guazzelli, G.; Sautier, B.; Grazia, S. D.; Matsubara, H.; Helliwell, H.; Procter, D. J. *Chem. Eur. J.* **2010**, *16*, 10240. [3]Hutton, T. K.; Muir, K. W.; Procter, D. J. *Org. Lett.* **2003**, *5*, 4811. [4]Harb Hassan Y. H.; Collins, K. D.; Garcia, J. V. A.; Bowker, S.; Campbell, L.; Procter, D. J. *Org. Lett.* **2010**, *12,* 5446.