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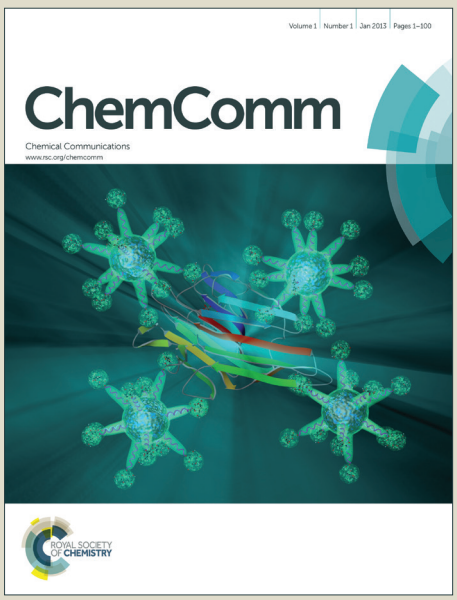

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SmI_2–H_2O-Mediated 5-*exo*/6-*exo* Lactone Radical Cyclisation Cascades

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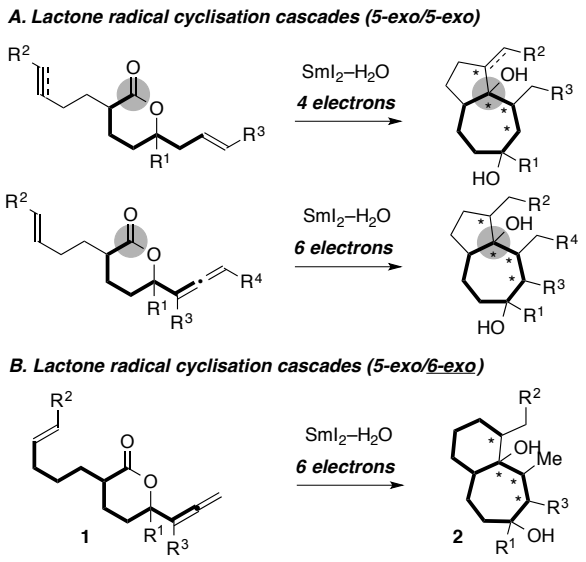
The SmI_2–H_2O reagent system mediates challenging 5-*exo*/6-*exo* lactone radical cascade cyclisations that deliver carbo[5.4.0]bicyclic motifs in a diastereoselective, one-pot process that establishes two new carbocyclic rings and four stereocentres.

Cascade processes have the potential to assemble complex molecular architectures in a single synthetic operation.[1] If such processes can be mediated by simple, commercial reagents and can be harnessed to deliver structures possessing important biological or physical properties they become even more desirable. We have recently exploited carbonyl reduction by the well-known electron-transfer reductant SmI_2[2-4] to trigger cascade processes that deliver natural and unnatural product structural motifs.[5] For example, we have used a dialdehyde cyclisation cascade to deliver the tricyclic skeleton of the antibactieral natural product pleuromutilin,[5d,e] and have prepared novel organic materials and bioactive targets using cascades involved phase-tag removal and cyclisation.[5f-h] Of most relevance to the current study, we have used SmI_2–H_2O[6,7] to trigger cyclisation cascades of alkenyl- and allenyllactone substrates that allow one-pot access to [5.3.0] and [4.2.1]bicyclic motifs found in biologically important natural products (Scheme 1A).[5a,b] The lactone radical cyclisation cascades explored to date have in common a final radical 5-*exo*-cyclisation event.[5a,b] In this study we report the evaluation of lactone radical cyclisation cascades terminated by far less usual and more challenging 6-*exo*-cyclisations[8] (Scheme 1B). The new cascades allow one-pot access to carbo[5.4.0]bicyclic motifs found in important natural product targets such as phorbol and prostratin.[9]

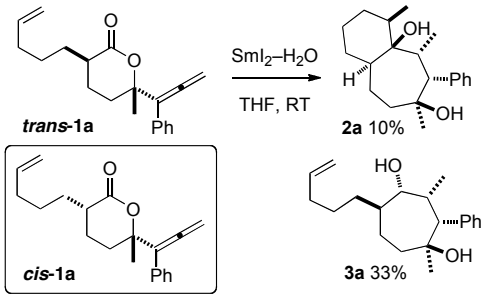
We chose to study the feasibility of 5-*exo*/6-*exo* lactone radical cyclisation cascades of allenyllactone substrates **1**. In the case of allenyllactones, stereochemistry is constructed, post–cyclisation, by a relay from centre to centre around the ring, with a high level of diastereocontrol that is not possible in analogous cyclisations of alkenyl or alkynyllactones.[5b] Furthermore, the use of allene radical acceptors allows an additional stereocenter bearing an additional substituent to be introduced to the complex products **2**.[5b]



Scheme 1 (A) Lactone radical cyclisation cascades terminated by 5-*exo*-cyclisations; (B) This work: Lactone radical cyclisation cascades terminated by challenging 6-*exo*-cyclisations.

Our investigations began with diastereoisomeric lactones **1a**, prepared by adapting our previously reported route.[5a,b] Pleasingly, treatment of *trans*-allenyllactone ***trans*-1a** bearing an

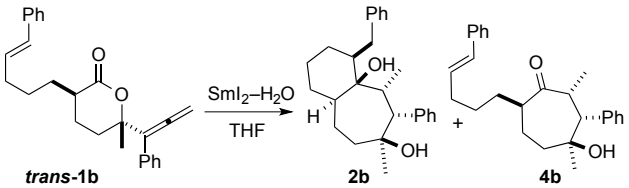
unactivated terminal alkene with SmI_2–H_2O gave cascade product **2a** as a single diastereoisomer in 10% yield with monocyclisation product **3a** obtained as the major product in 37% yield. Monocyclisation product **3a** arises from competing reduction of the radical-anion intermediate required for 6-*exo*-cyclisation (*cf.* **8** in Figure 3). In line with our previous observations,[5a,b] *cis*-allenyllactone ***cis*-1a** yielded a complex mixture of products (Scheme 2).[†]



Scheme 2

Given the relative scarcity of literature precedent for 6-*exo*-trig ketyl-olefin cyclisations mediated by SmI_2 involving simple alkenes,[8] the isolation of **2a**, albeit in low yield, was surprising and we attempted to increase the efficiency of the cascade by the installation of a radical stabilizing aryl group on the tethered alkene. Allenyllactone ***trans*-1b** was therefore prepared and its behaviour upon exposure to SmI_2–H_2O was studied (Table 1).

Table 1



Entry	SmI_2 (eq)	H_2O (eq)	time (h)	conv. (%)[a]	**2b** (%)[a]	**4b** (%)[a]
1[b]	8	4000	17	86	19	4
2[b]	8	800	17	96	11	13
3[b]	8	8000	17	64	16	9
4[b]	16	4000	17	100	36	8
5[c]	8	4000	17	96	24	9
6[b]	8	4000	0.5	31	0	8
7[b]	8	4000	6	93	15	14
8[b]	8	4000	17	95	22	7

[a] NMR yields from crude spectra using 2,3,5,6-tetrachloronitrobenzene as a standard. [b] 30 min addition of SmI_2 to H_2O and substrate at rt. [c] *Inverse addition:* 30 min addition of substrate to SmI_2–H_2O at rt.

Pleasingly, cascade product **2b** was obtained as a single diastereosiomer in almost all cases. As expected the amount of water additive used had an effect on the transformation (entries 1-3): at lower concentrations of H_2O, intermediate ketone **4b** was obtained as the major product, while at higher concentrations of water, lower conversion was observed. The latter observation can be explained by considering the saturation of the Sm(II) centre at high concentrations of water thus preventing coordination to the substrate and inner sphere electron transfer.[11] The highest reaction conversion and yield of **2b** was obtained using an excess of SmI_2 (36% of **2b** – *corresponding to an average of 84% for the six bond forming events*) (entry 4). Somewhat surprisingly, the order of addition had little impact on the process: addition of substrate to SmI_2–H_2O proved as effective as the addition of SmI_2 to the substrate and H_2O (*cf.* entry 1 and 5). Finally, quenching the reaction after 0.5, 6 and 17 h (entries 6-8) led to the formation of increasing amounts of cascade product **2b** at the expense of monocyclisation product **4b** showing that, as expected, the 6-*exo*-cyclisation is the slow component in the cascade.[¥] The relative stereochemistry of **2b** was confirmed by X-ray crystallographic analysis (Figure 1).[10]

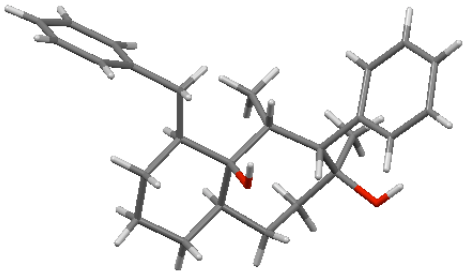
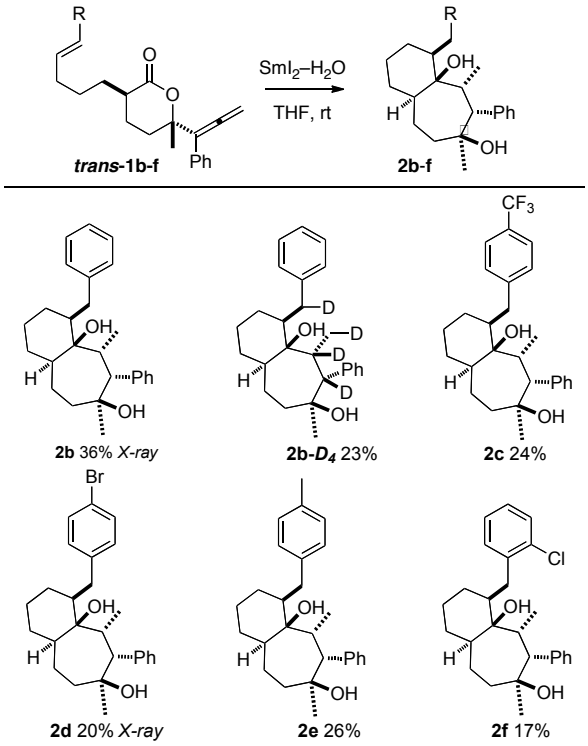


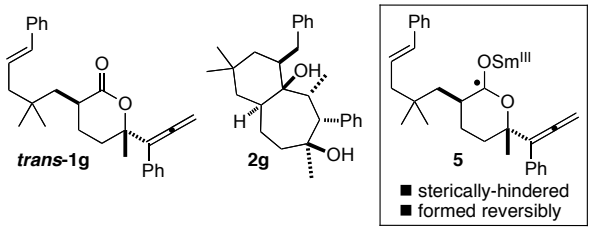
Figure 1 X-ray crystal structure of **2b**

We next studied the cascade cyclisation of a series of *trans*-allenyllactone substrates ***trans*-1b-f** with different substituents on the alkene moiety (Scheme 3). Bicyclic cascade products **2b-f** were obtained as single diastereosiomers in moderate overall isolated yield for the 6-electron-process. Treatment of ***trans*-1b** with SmI_2–D_2O gave **2b-*D*₄** illustrating that anions are generated and protonated during the six-electron cascade process. Interestingly, deuteration at the benzylic position occurs to give a single diastereoisomer suggesting that a configurationally stable benzylic organosamarium is formed and quenched during the cascade.[7b] Reduceable substituents such as trifluoromethyl (**2c**), bromo (**2d**) and chloro (**2f**) were tolerated and no over-reduction products were observed in these cases (Scheme 3).



Scheme 3

In an attempt to facilitate the challenging 6-*exo*-trig-ketyl-olefin cyclisation we prepared allenyllactone ***trans*-1g** bearing a *gem*-dimethyl group. Surprisingly, treatment of ***trans*-1g** with SmI_2–H_2O returned starting material with no trace of **2g**. This is consistent with the reversible formation of sterically-hindered ketyl-radical anion **5** (Scheme 4).[11]



Scheme 4

Attempted cascade cyclisation of allenyllactone ***trans*-1h**, bearing a tethered alkyne, and alkenyllactone ***trans*-1i** gave products of monocyclisation (Figure 2). These observations again show the challenge presented by these cascades: 6-*exo*-dig cyclisations (***trans*-1h**) and 6-*exo*-trig cyclisations of ketones derived from alkenyllactone cyclisations (***trans*-1i**) are inefficient.[5a,b]

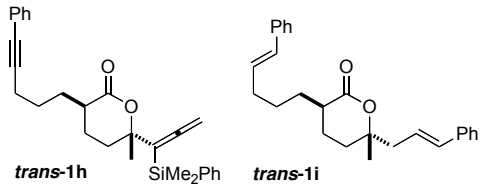


Figure 2

Figure 3 sets out a proposed mechanism and the stereochemical course for the successful 5-*exo*/6-*exo* cascade cyclisations of allenyllactones ***trans*-1b-f**. For example, reduction of ***trans*-1b** with SmI_2–H_2O gives axial radical anion **6** that undergoes 5-*exo*-cyclisation on to the allene to give unsaturated ketal **7** after a further reduction and a protonation. Selective conjugate reduction of the enone, in equilibrium with **7**, then gives ketone **4b** as a single diastereoisomer. Finally, reduction of **4b** gives radical anion **8** that undergoes selective 6-*exo*-trig cyclisation on to the alkene to give **2b** as a single diastereoisomer after a further reduction and a protonation (Figure 3).[5a,b]

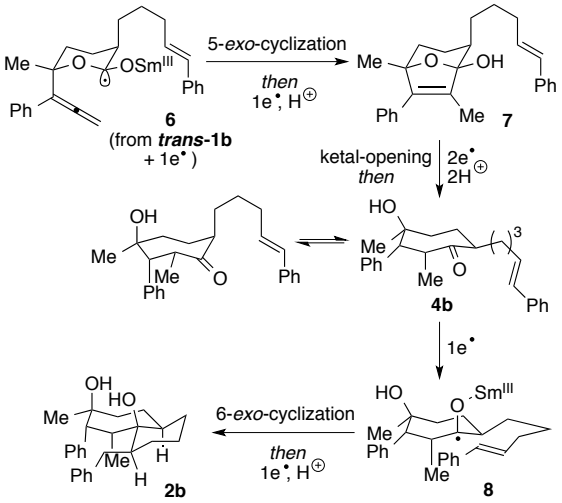


Figure 3

In summary, allenyllactones bearing a tethered alkene undergo 5-*exo*/6-*exo* radical cyclisation cascades that deliver carbo[5.4.0]bicyclic motifs in a diastereoselective, one-pot process using the commercially-available reagent SmI_2 in the presence of H_2O. The cascades establish two new carbocyclic rings and four stereocentres in moderate overall yield for the 6-electron-process. Further studies on these and other complexity-generating cascade processes are underway in our laboratories.

Notes and references

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[b] Medicines Research Centre, GlaxoSmithKline, Gunnels Wood Road, Stevenage, Herts, SG1 2NY, U.K.

† Treatment of ***cis*-1b** with SmI_2–H_2O gave a complex mixture of products from which a cascade product could be isolated as a single unknown diastereoisomer in 10% yield.

¥ The low mass balance reported is due to difficulties isolating the cascade products from monocyclisation by-products (*e.g.* ketones, hemi-ketals and alcohols [diastereoisomeric at the new hydroxyl bearing centre]).

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

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