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Reductive Cyclization Cascades of Lactones Using SmI_2-H_2O

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Supporting Information

ABSTRACT: Lactones bearing two alkenes or an alkene and an alkyne undergo reductive cyclization cascades upon treatment with SmI_2-H_2O, giving decorated azulene motifs in excellent yields with good diastereocontrol.

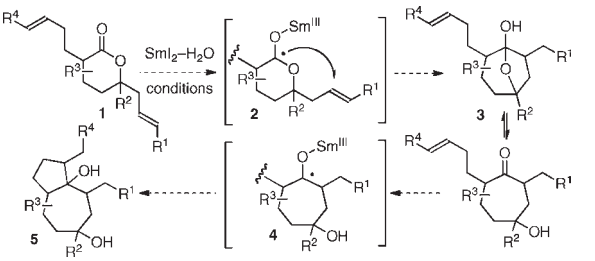
If fundamental synthetic transformations can be rerouted through less-conventional intermediates, new selectivity and reactivity may be found in the resultant reaction space. For example, our recent studies on the use of SmI_2[1] as a reductant for the ester carbonyl group led us to identify SmI_2-H_2O as a reagent system that exhibits unprecedented selectivity in the reduction of lactones and cyclic 1,3-diesters to alcohols.[2] Here we report that the reduction of unsaturated lactones under the above conditions results in radical cascade reactions that allow complex azulene motifs to be constructed in a single step. The cyclization cascade is triggered by the generation and trapping of unusual radical anions formed from the ester carbonyl by electron transfer.

We recently reported the first reductions of unactivated, cyclic, aliphatic esters by SmI_2[1] using H_2O[3] as an activating cosolvent. Furthermore, we showed for the first time that the unusual radical anions formed by electron transfer to the ester carbonyl group can be exploited in additions to alkenes.[2b−2d,4] We speculated that locating a tethered alkene at the 5-position of the lactone scaffold in **1** would allow access to seven-membered carbocycles **3** by cyclization of radical anions **2**. Furthermore, the presence of a second alkene located at the 2-position of the scaffold would allow the second radical anion intermediates **4** to be trapped, resulting in the formation of bicyclic tertiary alcohols **5** (Scheme 1).

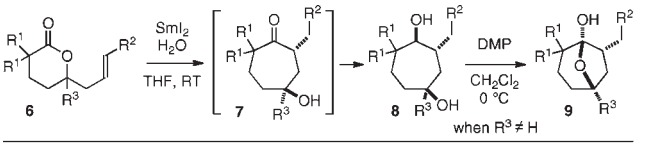
The azulene ring system present in **5** forms the centerpiece of a number of biologically active natural products[5] and is therefore an important target structure for new synthetic methods. For example, the tigliane family of natural products boasts phorbol, prostratin, and 12-deoxyphorbol-13-phenylacetate (DPP) among its members.[5a−5c] In addition, the anticancer compounds pseudolaric acid B[5d] and englerin A[5e−5g] have attracted significant attention from synthetic groups in recent years.

To investigate the first stage of the proposed cascade, we studied the behavior of readily prepared[6] lactones **6** with SmI_2-H_2O. Pleasingly, cycloheptane-1,4-diols **8** were obtained in moderate to good yields as mixtures of diastereoisomers (Scheme 2). Efficient cyclization was also observed in the case of lactones bearing 5-alkyl substituents. In this case, the crude cycloheptane-1,4-diol products were oxidized to the corresponding hemiketals **9** to allow the diastereoisomeric ratios resulting from the carbon−carbon bond-forming step to be determined easily.

Scheme 1. Proposed Lactone Radical Cyclization Cascades Using SmI_2-H_2O



Scheme 2. Lactone Radical Cyclizations To Form Cycloheptanediols[a]



lactone **6**	product **8** *or* **9** (% yield, dr)
6a R^1 = H, R^2 = Ph **6b** R^1 = Me, R^2 = Ph **6c** R^1 = Me, R^2 = 2–ClC_6H_4 **6d** R^1 = Me, R^2 = 3–MeC_6H_4 **6e** R^1 = Me, R^2 = 4–BrC_6H_4	**8a** 55%, 9:2 dr[b] **8b** 83%, 10:3 dr[b] **8c** 82%, 5:3 dr[b] **8d** 69%, 4:3 dr[b] **8e** 78%, 11:7 dr[b]
6f R^3 = Me **6g** R^3 = allyl	**9f** 75%[c], 1:1 dr[d] **9g** 93%[c], 1:1 dr[d]
6h R^2 = Ph **6i** R^2 = 3–MeC_6H_4 **6j** R^2 = 2,5–$Me_2C_6H_3$ **6k** R^2 = 4–$MeOC_6H_4$ **6l** R^2 = 4–BrC_6H_4 **6m** R^2 = 2–ClC_6H_4	**9h** 91%[c], 4:1 dr[d] **9i** 72%[c], 4:1 dr[d] **9j** 67%[c], 3:1 dr[d] ***X-ray*** **9k** 89%[c], 4:1 dr[d] **9l** 82%[c], 4:1 dr[d] ***X-ray*** **9m** 75%[c], 6:1 dr[d]
6n	**8n** 70%[e]

[a] Conditions: SmI_2 (8 equiv), THF, H_2O (100 equiv), room temperature, 5−20 h. [b] Ratio of the major diastereoisomer to the sum of the other diastereoisomers. [c] Yields for two steps. [d] Ratio of the two diastereoisomers. [e] Mixture of four diastereoisomers.

Moderate to good diasterocontrol (3:1 to 6:1 dr) was observed in the cyclizations of substrates bearing aryl-substituted

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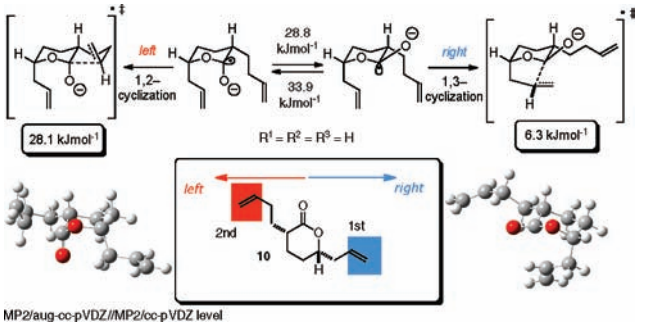
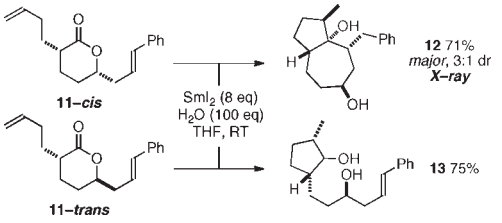


Figure 1. Calculations to assess the cyclization cascades.

Scheme 3. Effect of Lactone Relative Configuration on Sequence Integrity



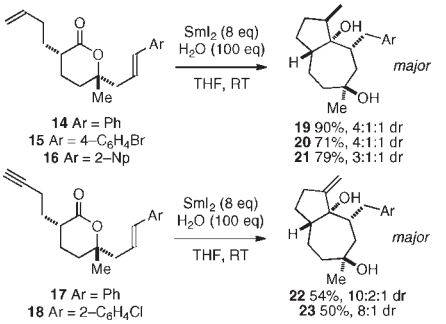
alkenes. The relative configuration of the major diastereoisomers was assigned on the basis of X-ray crystallographic analyses of **9j** and **9l** (Scheme 2).[6] The cyclization of **6n** gave **8n** after elimination of a thiyl radical.

The cyclization proceeds by activation of the lactone by coordination to Sm(II) followed by electron transfer to generate an anomerically stabilized axial radical anion[7] that undergoes diastereoselective cyclization. The hemiketal intermediate is then reduced further by Sm(II) to give a second ketyl radical anion. A final electron transfer from Sm(II) gives an organosamarium that is protonated by H_2O. The amount of SmI_2 used (~8 equiv) is consistent with the proposed four-electron mechanism: a 2-fold excess of reagent was used to ensure that the reactions were complete. As in our previous studies, H_2O was crucial for successful reaction:[2] treatment of lactone **6f** with SmI_2 in the absence of H_2O led to the recovery of starting material, while as little as 10 equiv of H_2O led to significant reductive cyclization, although the use of 100 equiv gave the best yield of **8f**.

Calculations[8] suggested that selective reductive cyclization cascades of lactones **1** possessing cis relative configurations should be possible (Figure 1). For example, considering theoretical substrate **10**, the activation energy for 5-exo-trig cyclization of the lactone-derived radical anions involving alkenes attached to the 5-position of the lactone ring was calculated to be ~6 kJ mol^{-1}, whereas 5-exo-trig cyclization of the lactone-derived radical anions (after radical inversion) involving alkenes attached to the 2-position of the ring were calculated to have much higher activation energies (~28 kJ mol^{-1}).[8] Thus, generic substrates **1** should selectively undergo "right then left" cyclization cascades to give bicyclic products, as outlined in Scheme 1.

To explore the predicted impact of the relative configuration in the lactone substrate on the sequence integrity of the cyclization cascade, **11-*cis*** and **11-*trans*** were treated with SmI_2–H_2O. As predicted, **11-*cis*** underwent efficient cascade cyclization to give **12** in 71% yield as a separable 3:1 mixture of two

Scheme 4. Cyclization Cascades of Lactones Using SmI_2–H_2O



diastereoisomers, while the attempted cascade reaction of **11-*trans*** misfired, affording cyclopentanol **13** as a mixture of diastereoisomers (Scheme 3). The relative configuration of **12** was determined by X-ray crystallographic analysis.[6]

Lactone substrates **14**–**18** bearing cis-oriented alkene/alkyne chains were prepared[6] and exposed to SmI_2–H_2O. In all cases, efficient cascade cyclization resulting in a rapid increase in molecular complexity was observed. The lactone cyclization cascades gave bicyclic products **19**–**23** with good diastereocontrol, and the diastereoisomeric products were readily separable (Scheme 4).

In summary, the cyclization of unsaturated lactones using SmI_2–H_2O proceeds through unusual radical anion intermediates and provides cycloheptane-1,4-diols with moderate diastereocontrol. When two alkenes or an alkene and an alkyne are appropriately positioned in the substrate, radical cascade cyclizations utilizing two radical anion intermediates are possible. The cyclization cascades provide access to complex bicyclic scaffolds in a single reaction using a simple, readily-available reagent.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, characterization data, ^1H and ^{13}C spectra, X-ray crystallographic data, and additional calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) The calculations did not take into account the presence of Sm(III). "Left" cyclizations of axial radicals are disfavored because of the development of 1,3-diaxial interactions in the transition states. Cyclizations of an axial radical in which alkenes at the 5-position and 2-position are equatorial and axial, respectively, are impossible because the alkenes lie out of reach. See the Supporting Information for further details.