

Lactone Radical Cyclizations and Cyclization Cascades Mediated by $\text{SmI}_2\text{-H}_2\text{O}$

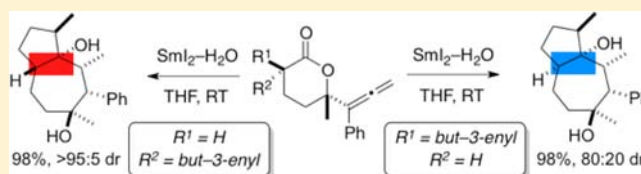
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S Supporting Information

ABSTRACT: Unsaturated lactones undergo reductive radical cyclizations upon treatment with $\text{SmI}_2\text{-H}_2\text{O}$ to give decorated cycloheptanes in a single highly selective operation during which up to three contiguous stereocenters are generated. Furthermore, cascade processes involving lactones bearing two alkenes, an alkene and an alkyne, or an allene and an alkene allow “one-pot” access to biologically significant molecular scaffolds with the construction of up to four contiguous stereocenters. The cyclizations proceed by the trapping of radical anions formed by electron transfer reduction of the lactone carbonyl.



1. INTRODUCTION

Carbonyl reduction is a fundamental transformation that underpins synthetic chemistry.¹ The rerouting of carbonyl reduction through less-conventional intermediates allows new selectivity and reactivity to be exploited. For example, our recent work on metal-mediated electron transfer² has resulted in unprecedented selectivity in the reduction of lactones,^{3a-c} cyclic 1,3-diesters,^{3d-g} and acyclic esters and acids.^{3h,i} Furthermore, we have shown for the first time that the radical anions formed by electron transfer to the ester carbonyl group can be exploited in additions to alkenes.^{3b,d-f} The lanthanide reductant samarium diiodide (SmI_2),⁴ activated by H_2O ,⁵ was used to achieve electron transfer in these studies. The use of H_2O is crucial because it coordinates to samarium(II), increasing the reduction potential of the metal and providing a proximal proton source for the quenching of intermediates.⁵

Here we report in full our studies on the formation of oxygenated cycloheptanes **2a,b** by reductive cyclization of alkenyl, alkynyl, and allenyl lactones **1a,b** using $\text{SmI}_2\text{-H}_2\text{O}$ (Scheme 1).⁶ In particular, we disclose for the first time that the cyclization of allenyl lactones **1b** delivers highly decorated cycloheptanes **2b** in a single, often highly selective operation during which three stereocenters are generated. Furthermore, treatment of lactones bearing two alkenes, an alkene and an alkyne, or an allene and an alkene, **1c-e**, with $\text{SmI}_2\text{-H}_2\text{O}$ results in cascade cyclizations involving four or six electron transfer steps that generate two rings and up to four stereocenters and deliver complex molecular architectures **2c-e** in a single step. The cyclizations are triggered by the generation and trapping of radical anions formed from the ester carbonyl by electron transfer. In the case of allenyl lactones **1b**, stereochemistry is constructed, post-cyclization, by a relay from center to center around the ring, with a high level of diastereocontrol that is not possible in analogous cyclizations of alkenyl or alkynyl lactones **1a**.⁶ Furthermore, the use of allene

radical acceptors allows an additional stereocenter bearing an additional substituent to be constructed.⁶ The bicyclic motifs **2c-e** form the centerpiece of a number of biologically important natural products including pseudolaric acid **B**,^{7a,b} englerin **A**,^{7c-j} phorbol, prostratin, 12-deoxyphorbol-13-phenylacetate (**DPP**),^{7k-n} and mediterraneol **B**^{7o} (Figure 1).

2. RESULTS AND DISCUSSION

We began by studying the behavior of readily prepared⁸ alkenyllactones **3a-e** with $\text{SmI}_2\text{-H}_2\text{O}$. Pleasingly, cycloheptan-1,4-diols **4a-e** were obtained in moderate to good yield as a mixture of diastereoisomers (Scheme 2). In addition, the cyclization of **3f** gave **4f** as a mixture of four diastereoisomers after elimination of a thiyl radical.

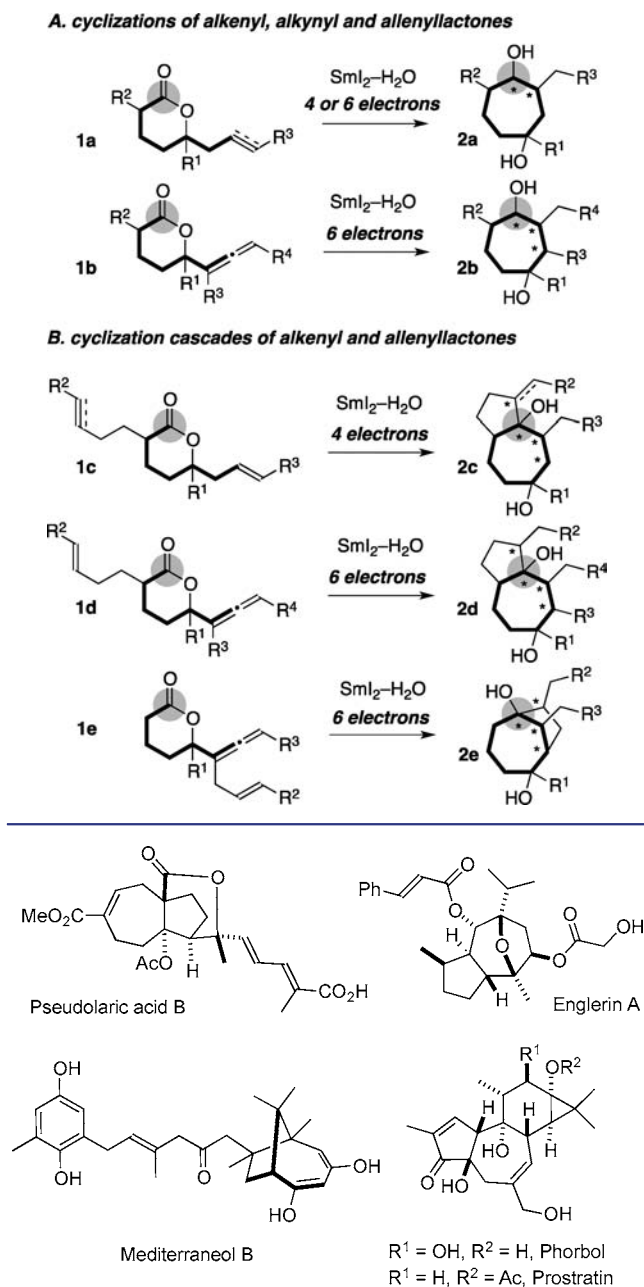
Efficient cyclization was also observed in the case of alkenyllactones **3g-n** bearing 5-alkyl substituents. In this case, crude cycloheptan-1,4-diol products were oxidized to the corresponding hemiketals **5g-n** so that diastereomeric ratios resulting from the carbon-carbon bond-forming step could be easily determined (Scheme 3). Moderate diastereocontrol (75:25 to 86:14 dr) was observed in the cyclizations of substrates bearing aryl-substituted alkenes. The relative configuration of the major diastereoisomers was assigned on the basis of X-ray crystallographic analyses of **5k** and **5m** (Scheme 3).⁹

As in our previous studies, the addition of H_2O to SmI_2 was crucial to the success of the reaction.^{3,5} For example, treatment of lactone **3g** with SmI_2 in the absence of H_2O led to the recovery of starting material. As little as 10 equiv of H_2O (with respect to SmI_2) led to significant reductive cyclization, although the use of 100 equiv gave the best yield of **4g**. The mechanism of the cyclization of alkenyllactones is shown in

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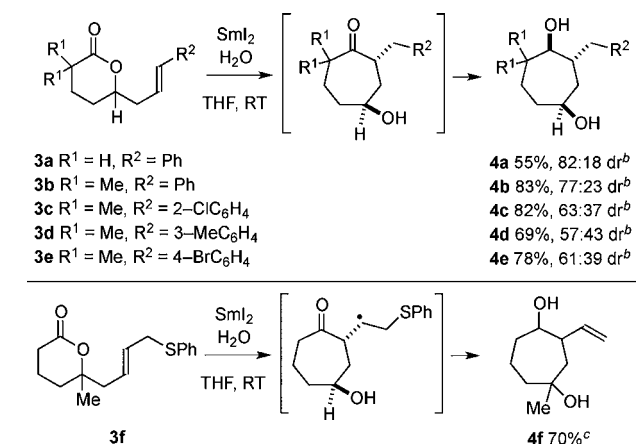
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Scheme 1. Decorated Cycloheptane Scaffolds from the Reductive Cyclizations of Unsaturated Lactones with $\text{SmI}_2\text{-H}_2\text{O}$



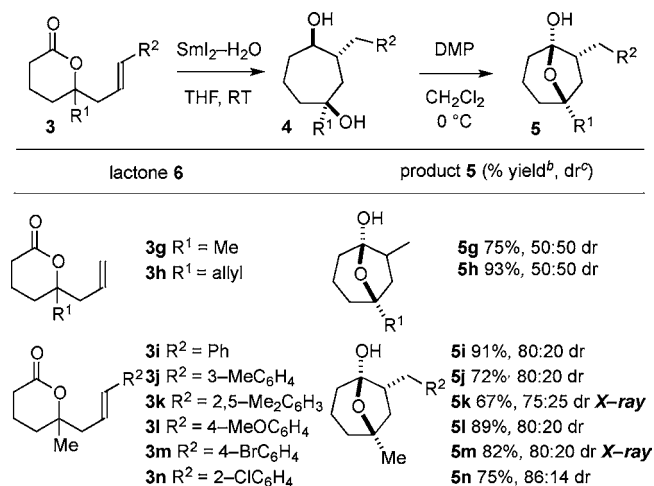
Scheme 4 for representative substrate **3m**. Activation of the lactone by coordination to $\text{Sm}(\text{II})$ and electron transfer generates an anomerically stabilized axial radical anion **6**.¹⁰ Cyclization then takes place with the major product appearing to arise from a transition state in which the alkene assumes an *endo*-orientation relative to the heterocyclic ring. The ring-open form **7** of the resultant hemiketal intermediate is then reduced further by $\text{Sm}(\text{II})$ to give a second ketyl radical anion and a final electron transfer from $\text{Sm}(\text{II})$ gives an organosamarium that is protonated by H_2O . The amount of SmI_2 (approximately 8 equiv) used is consistent with the four-electron mechanism; a

Scheme 2. Lactone Radical Cyclizations To Form Cycloheptan-1,4-diols^a



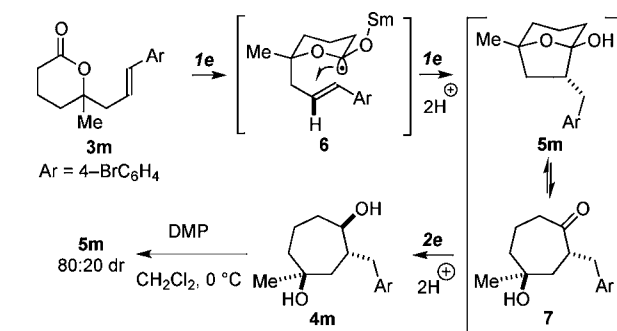
^aConditions: SmI_2 (8 equiv), THF, H_2O (100 equiv with respect to SmI_2), RT, 5–20 h. ^bThe dr values give the ratio of the major diastereoisomer to the sum of the other diastereoisomers. ^cMixture of 4 diastereoisomers.

Scheme 3. Lactone Radical Cyclizations To Form Cycloheptan-1,4-diols and Oxidation to the Corresponding Hemiketals^a



^aConditions: SmI_2 (8 equiv), THF, H_2O (100 equiv with respect to SmI_2), RT, 5–20 h. ^bYields for two steps. ^cRatio of two diastereoisomers.

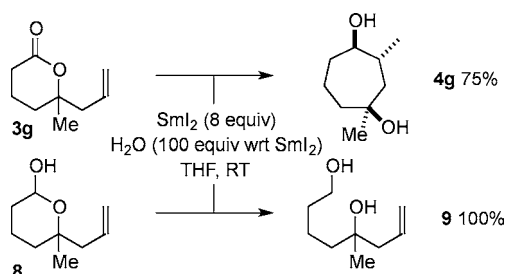
Scheme 4. Proposed Mechanism for the Reductive Cyclizations of Alkenyllactones



2-fold excess of reagent is used to ensure reactions are complete.

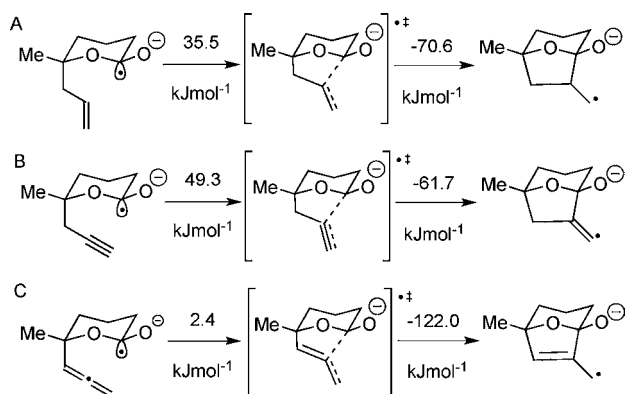
Attempts to isolate the hemiketal (or cycloheptanone) intermediates by the use of fewer equivalents of SmI_2 were unsuccessful: a mixture of starting material and cycloheptan-1,4-diols were obtained in low yield. To unequivocally determine whether the cyclization proceeded through an ester-derived radical anion such as **6**, lactone **3g** and lactol **8** were exposed to the conditions for cyclization. While lactone **3g** underwent smooth cyclization and reduction to yield diol **4g**, lactol **8** underwent reduction to acyclic diol **9** with no trace of cyclization observed (Scheme 5). Thus, it is clear that cyclization involves an ester-derived ketyl radical anion (cf. **6**) rather than a more conventional, aldehyde-derived ketyl radical anion.

Scheme 5. Exploring the Nature of the Radical Anion Involved in Cyclization



Although the reductive cyclization of alkenyllactones was found to proceed efficiently, the diastereoselectivity of the process was modest. We proposed that analogous cyclizations of alkynyl- and allenyllactones might deliver cyclic products with improved levels of stereocontrol because stereochemistry in such processes would be generated by protonation of samarium enolates¹¹ post-cyclization, rather than during seven-membered ring formation (*vide infra*). Computational studies¹² were carried out to compare cyclizations involving alkynes and allenes with those of alkenyllactones (Scheme 6). Pleasingly, calculations suggested that the cyclizations of axial radical anions^{3b,d-f,10} derived from model alkynyl and allenyllactones by electron transfer would be possible (Scheme 6B,C). The cyclization of allenyllactones appeared to be particularly facile

Scheme 6. Computational Studies on the Cyclization of Alkenyl, Alkynyl, and Allenyllactones

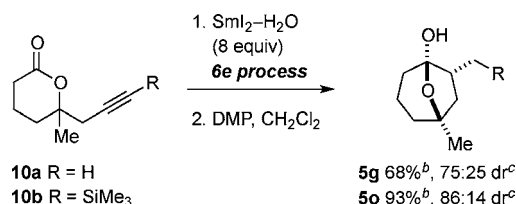


MP2/aug-cc-pVDZ//MP2/cc-pVDZ with solvation in THF.

compared with the analogous cyclization of an alkenyllactone (Scheme 6A).

Therefore, in our search for more stereoselective routes to decorated cycloheptanes, we prepared alkenyllactones **10a,b**. Upon treatment with $\text{SmI}_2\text{-H}_2\text{O}$ in THF, **10a,b** underwent efficient reductive cyclization. Subsequent oxidation of the crude cycloheptan-1,4-diols then gave hemiketals **5g** and **5o** in good overall yield and with improved diastereoselectivity (Scheme 7; see also Scheme 3).

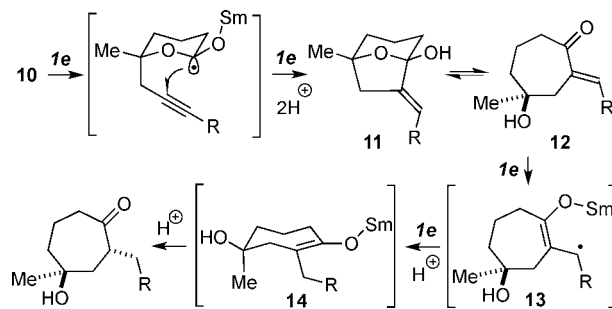
Scheme 7. Radical Cyclizations of Alkenyllactones Followed by Oxidation To Give Hemiketals^a



^aConditions: SmI_2 (8 equiv), THF, H_2O (100 equiv with respect to SmI_2), RT, 20 h. ^bYields for two steps. ^cRatio of two diastereoisomers.

The cyclization of alkenyllactones proceeds via hemiketals **11** and enones **12** that are reduced¹³ further to radical anions **13**. Further reduction and protonation then generates samarium enolates¹¹ **14** (alternatively, protonation of **13** on oxygen, electron transfer and proton transfer may lead to **14**).⁵¹ Protonation of the enolate then determines the stereoselectivity of the process. Cycloheptanone intermediates are then reduced further to give cycloheptan-1,4-diols **4** (Scheme 8).

Scheme 8. Proposed Mechanism for the Reductive Cyclizations of Alkenyllactones

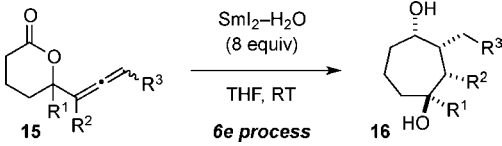


We proposed that seven-membered ring products would be delivered with a further improvement in diastereoselectivity by the analogous cyclizations of allenyllactones. With allene¹⁴ radical acceptors,¹⁵ we proposed that stereochemistry would be constructed in an efficient relay around the ring (*vide infra*) and deliver high diastereoselectivities not possible using analogous alkynyl and alkenyllactones. Furthermore, the use of allene radical acceptors would allow an additional stereocenter bearing an additional substituent to be constructed during the cyclizations.

To explore the first ester–allene radical cyclizations, a range of allenyllactones was prepared by allenylmetal addition to δ -ketoesters followed by lactonization.¹⁶ Upon treatment with $\text{SmI}_2\text{-H}_2\text{O}$ in THF at room temperature, allenyllactones **15** underwent cyclization to give cycloheptan-1,4-diols **16** in high yield and with high diastereoselectivity. In the cyclization of substrates bearing aryl substituents, essentially complete

diastereocontrol was observed in the construction of three stereocenters (Table 1). Variation of substituents on the

Table 1. Cycloheptan-1,4-diols from the Reductive Cyclizations of Allenyllactones^a



entry	R ¹	R ²	R ³	product	yield (%) ^b	dr ^c
1	Me	C ₆ H ₅	H	16a	68	>95:5
2	Me	4-OMeC ₆ H ₄	H	16b	99	>95:5
3	Me	2-BrC ₆ H ₄	H	16c	63	>95:5
4	Me	3-MeC ₆ H ₄	H	16d	97	93:7
5	Me	3-ClC ₆ H ₄	H	16e	67	>95:5
6	Me	Me	H	16f	98	86:14
7	Me	Et	H	16g	86	66:34
8	Me	4-MeC ₆ H ₄	H	16h	78	80:20
9	Cy	4-OMeC ₆ H ₄	H	16i	62	>95:5
10	Me	C ₆ H ₅	Me	16j	66 ^d	86:14

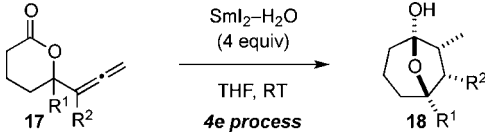
^aConditions: SmI₂ (8 equiv), THF, H₂O (500 equiv with respect to SmI₂), RT. ^bIsolated yield. ^cDetermined by ¹H NMR. ^dReaction was carried out on a 2:1 diastereoisomeric mixture of 15j.

lactone and at the internal and terminal positions of the allene was tolerated. For 15j, diastereoisomers at the allene chiral axis showed similar reactivity to give 16j. The relative configuration of the products was determined by ¹H NMR and by X-ray crystallographic analysis of related products (*vide infra*).

In contrast to our studies on alkenyllactones, in allenyllactone substrates 17 bearing bulky substituents on the internal double bond of the allene or at the δ -position of the lactone, the use of less SmI₂-H₂O allowed the hemiketal products 18 of a four-electron process to be isolated in moderate to good yield and in high diastereoisomeric excess (Table 2).

The cyclizations of allenyllactones proceed according to the mechanism outlined in Scheme 9. Electron transfer to the ester carbonyl from SmI₂-H₂O generates axial radical anion 19,^{3b,d-f,10} which undergoes cyclization. Further reduction and protonation steps, then give enone 21, via opening of

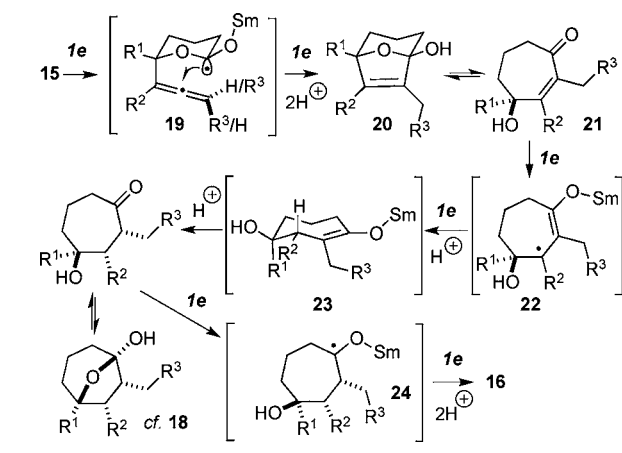
Table 2. Cycloheptanone Hemiketals from the Reductive Cyclizations of Allenyllactones^a



entry	R ¹	R ²	product	yield (%) ^b	dr ^c
1	Me	C ₆ H ₅	18a	27 ^d	>95:5
2	Me	SiMe ₃	18b	64 ^e	>95:5
3	Me	SiMe ₂ Ph	18c	78	>95:5
4	Me	SiMe ₂ vinyl	18d	87 ^e	93:7
5	Ph	Me	18e	90 ^f	75:25
6	Ph	Et	18f	77 ^f	83:17

^aConditions: SmI₂ (4 equiv), THF, H₂O (500 equiv with respect to SmI₂), RT. ^bIsolated yield. ^cDetermined by ¹H NMR. ^dX-ray crystal structure on the keto form (see Supporting Information). Major product was diol 16a. ^eX-ray crystal structure (see Supporting Information). ^fCharacterized as a mixture of keto and hemiketal forms.

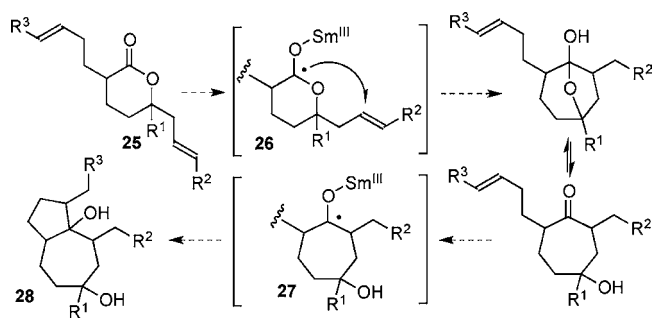
Scheme 9. Proposed Mechanism for the Reductive Cyclizations of Allenyllactones



hemiketal 20. Reduction of the enone moiety¹³ generates a second radical anion 22 that undergoes diastereoselective protonation at the β -position. A further reduction then gives samarium(III) enolate¹¹ 23 that undergoes diastereoselective protonation at the α -position. (Alternatively, protonation of 22 on oxygen, electron transfer, and proton transfer may lead to 23).⁵¹ Finally, the cycloheptanone intermediate (in equilibrium with the corresponding hemiketal) is reduced to give 16, with high diastereocontrol, via a third radical anion 24 (Scheme 9). Thus, reduction of the intermediate enone allows stereochemical information to be passed from carbon to carbon, post-cyclization, in the newly formed cycloheptane ring. The high diastereoselectivity observed in the protonation steps may arise from the bulky nature of the Sm(II)-H₂O complex^{5,5k,m} or its coordination to the hydroxyl group on the cycloheptane ring in 22 and 23.

Having studied the cyclizations of alkenyl, alkynyl, and allenyllactones, we speculated that the location of unsaturated groups at both the 5- and 2-positions of the lactone scaffold in generic substrates such as 25 should allow both radical anion intermediates 26 and 27 to be trapped resulting in the formation of bicyclic tertiary alcohols 28 (Scheme 10).

Scheme 10. Proposed Lactone Radical Cyclization Cascades Using SmI₂-H₂O



Calculations¹² suggested that selective reductive cyclization cascades of lactones 25 possessing *cis* relative configurations should be possible (Figure 2). For example, considering theoretical substrate 29, the relative activation energy for 5-*exo*-trig cyclization of the lactone-derived radical anion involving the alkene attached to the 5-position of the lactone ring was calculated to be ~ 6 kJ mol⁻¹, whereas 5-*exo*-trig

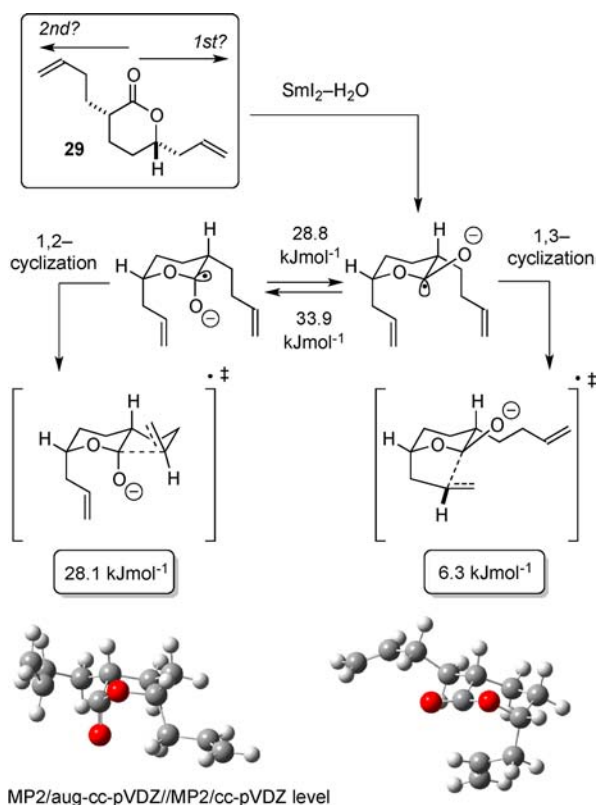


Figure 2. Calculations To Assess the Feasibility of Cyclization Cascades.

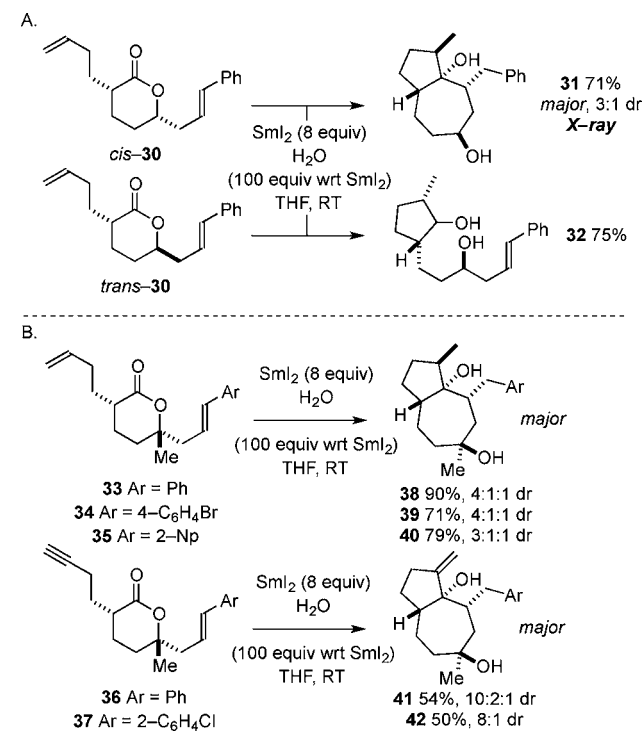
cyclization of the lactone-derived radical anion (after radical inversion) involving the alkene attached to the 2-position of the ring was calculated to have a much higher relative activation energy (~ 28 kJ mol $^{-1}$).¹² Thus, generic substrate *cis*-**29** should selectively undergo a “right then left” cyclization cascade to give a bicyclic product as outlined in Scheme 10.

To explore the predicted impact of relative configuration in the lactone substrate on the sequence integrity of the cyclization cascade, *cis*-**30** and *trans*-**30** were treated with $\text{SmI}_2\text{-H}_2\text{O}$. As predicted, *cis*-**30** underwent efficient cascade cyclization to give **31** in 71% yield as a separable 3:1 mixture of two diastereoisomers, while the attempted cascade reaction of *trans*-**30** misfired, and cyclopentanol **32** was obtained as a mixture of diastereoisomers (Scheme 11A). The relative configuration of **31** was determined by X-ray crystallographic analysis.⁹ Lactone substrates **33**–**37** bearing *cis*-orientated alkene/alkyne chains were prepared⁸ and exposed to $\text{SmI}_2\text{-H}_2\text{O}$. In all cases, efficient cascade cyclization resulting in a rapid increase in molecular complexity was observed. The lactone cyclization cascades gave bicyclic products **38**–**42** with good diastereocontrol and diastereoisomeric products were readily separable (Scheme 11B).

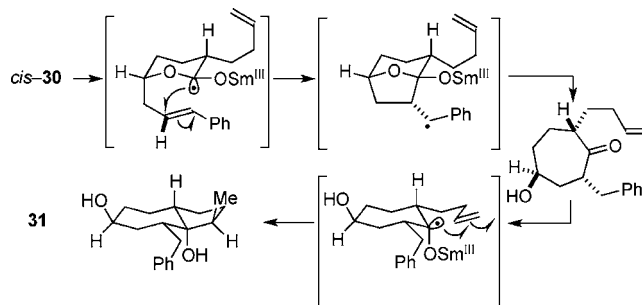
The mechanism and stereochemical course of the cascade cyclization for lactone *cis*-**30** is shown in Scheme 12.

We have also investigated cyclization cascades of allenyllactones. Pleasingly, treatment of substrates **43** with $\text{SmI}_2\text{-H}_2\text{O}$ gave highly decorated bicyclic products **44** bearing four new stereocenters in high yield and with high diastereoselectivity (Scheme 13). Importantly, in contrast to observations made during studies involving lactone **30**, both *cis* and *trans*-fused bicyclic products **44** could be obtained by programming the correct relative configuration into the starting allenyllactone **43**.

Scheme 11. (A) The Effect of Relative Configuration in Lactone **30** on the Sequence Integrity of a Cyclization Cascade and (B) Cyclization Cascades of Allenyllactones Using $\text{SmI}_2\text{-H}_2\text{O}$

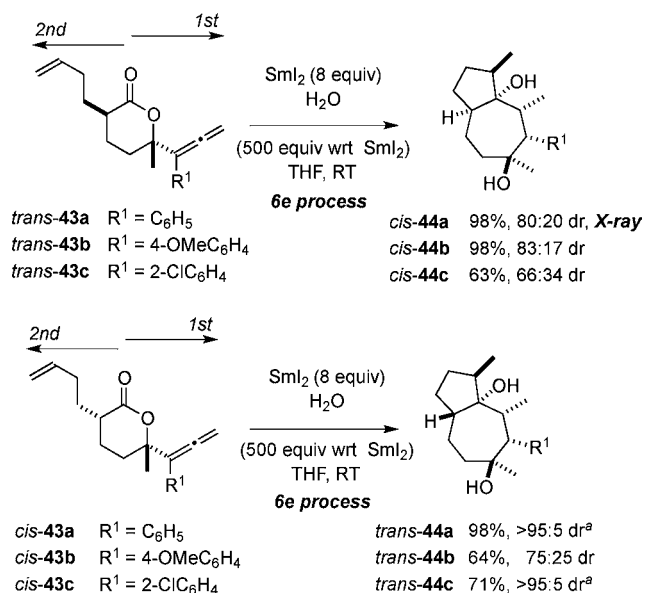


Scheme 12. Mechanism and Stereochemical Course of the Cascade Cyclization of Lactone *cis*-**30**



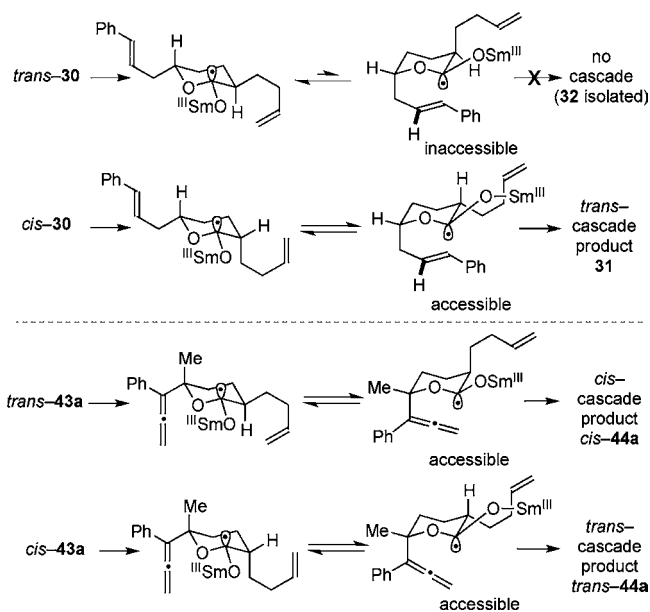
The ability of both *cis* and *trans* isomers of allenyllactones **43** to undergo efficient cyclization cascades, compared with the requirement for the *cis*-relative configuration in lactone **30**, can be rationalized by considering the conformation of lactones **43a**, for example, and **30**. Assuming cyclizations involve radical anions in chair conformations with the radical acceptor at the 5-position of the lactone ring assuming a pseudo-axial orientation, cyclization of *trans*-**30** requires the adoption of an inaccessible, high-energy conformation with both substituents pseudo-axial. In contrast, *cis*-**30** undergoes cyclization through an accessible conformation in which the 2-substituent adopts a pseudo-equatorial orientation (Scheme 14).

In allenyllactones **43a**, the presence of a methyl substituent at the 5-position of the lactone ring renders accessible reactive conformations in which the 5-allenyl substituent adopts a pseudoaxial orientation for both *cis* and *trans* isomers and thus both isomers undergo efficient cascade processes.

Scheme 13. Reductive Cyclization Cascades of *cis*- or *trans*-Allenyllactones to give [5.3.0] Bicyclic Ring Systems

^aYield based on recovered hemiketal. In some cases, hemiketal products of a stalled process were isolated as byproducts. These intermediates resulting from the first cyclization stage could be isolated and converted to the cascade products by treatment with SmI₂-H₂O.

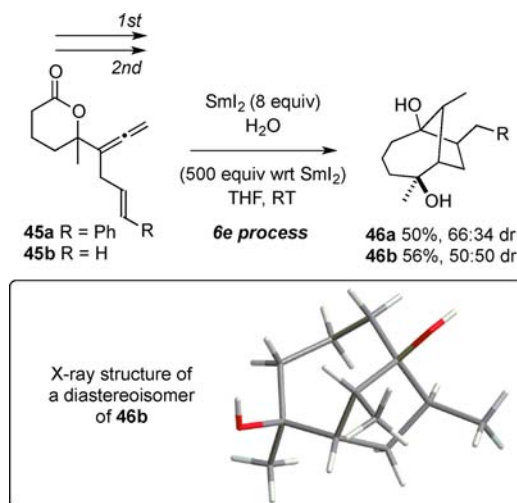
Scheme 14. The Impact of Lactone Conformation on the Feasibility of Cyclization Cascades



Finally, we have also investigated the feasibility of cyclization cascades of allenyllactones **45**. Pleasingly, treatment of substrates **45a,b** with SmI₂-H₂O gave bicyclo[4.2.1]nonanes **46a,b** in moderate yield (Scheme 15).

The high sequence integrity observed in all lactone cyclization cascades is a result of the high rate of cyclization of the ester-derived ketyl radical anion and the radical acceptor at the 5-position of the lactone ring.

Scheme 15. Reductive Cyclization Cascades of Allenyllactones to give [4.2.1] Bicyclic Ring Systems



3. CONCLUSIONS

In summary, electron transfer from SmI₂-H₂O to the carbonyl group of alkenyl and alkynyllactones triggers cyclization to give cycloheptan-1,4-diols with moderate diastereocontrol. In contrast, cyclizations involving allenyllactones allow decorated cycloheptanes to be constructed in a single, highly diastereoselective operation during which three stereocenters are generated. The generation of stereochemistry, post-cyclization, in a relay around the ring is key to the high diastereoselectivities that are observed. When two alkenes, an alkene and an alkyne, or an allene and an alkene are appropriately positioned in the substrate, radical cascade cyclizations, utilizing two radical anion intermediates, are possible. The cyclization cascades allow access to complex molecular architectures in a single reaction using a simple, readily-available reagent.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, compound characterization data, details of calculations, and X-ray crystal structures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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