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Lactone Radical Cyclizations and Cyclization Cascades Mediated by SmI_2–H_2O

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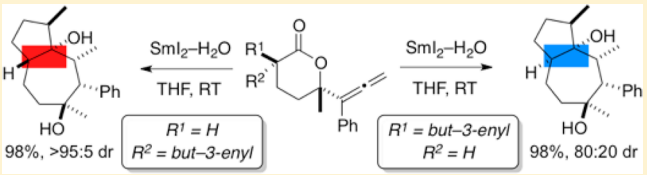
Supporting Information

ABSTRACT: Unsaturated lactones undergo reductive radical cyclizations upon treatment with SmI_2–H_2O 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 transfer[2] 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 allenyllactones **1a**,**b** using SmI_2–H_2O (Scheme 1).[6] In particular, we disclose for the first time that the cyclization of allenyllactones **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 SmI_2–H_2O 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 allenyllactones **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 alkynyllactones **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 DISCUSSSION

We began by studying the behavior of readily prepared[8] alkenyllactones **3a**−**e** with SmI_2–H_2O. 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 diastereoisomeric 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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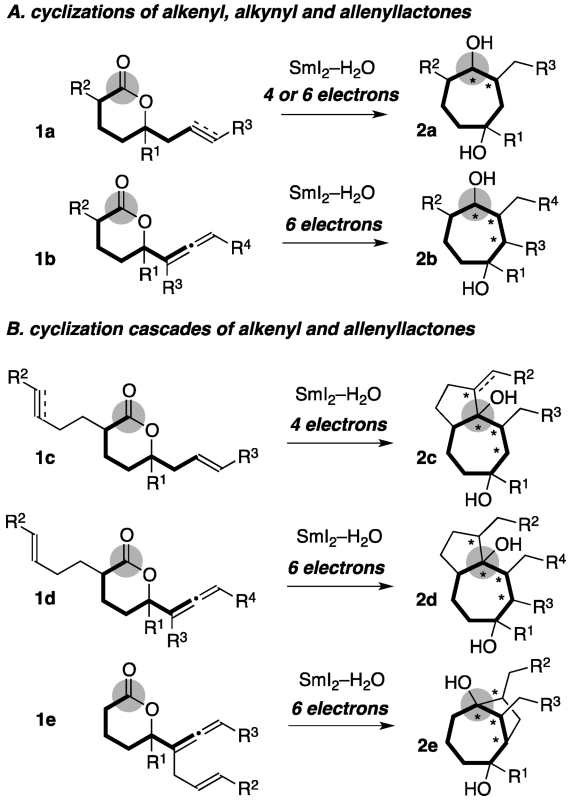
Scheme 1. Decorated Cycloheptane Scaffolds from the Reductive Cyclizations of Unsaturated Lactones with SmI_2–H_2O



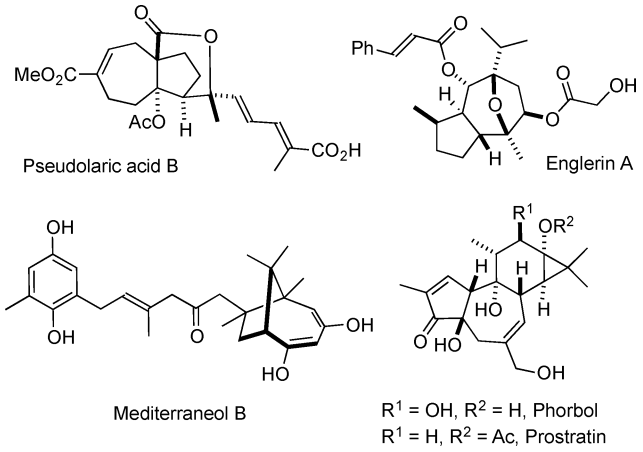
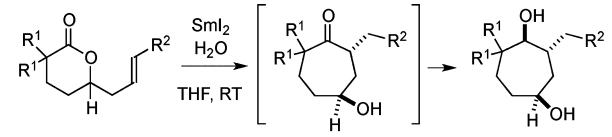


Figure 1. Selected natural products possessing [5.3.0] or [4.2.1] bicyclic ring systems.

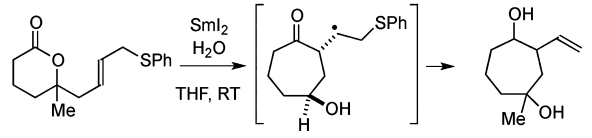
Scheme 4 for representative substrate **3m**. Activation of the lactone by coordination to Sm(II) and electron transfer generates an anomerically stabilized axial radical anion **6**.[10] Cyclization then takes place with the major product appearing to arise from a transition state in which the alkene assumes an *endo*-orientation relative to the heterocyclic ring. The ring-open form **7** of the resultant hemiketal intermediate is then reduced further by Sm(II) to give a second ketyl radical anion and a final electron transfer from Sm(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]



3a R^1 = H, R^2 = Ph
3b R^1 = Me, R^2 = Ph
3c R^1 = Me, R^2 = 2–ClC_6H_4
3d R^1 = Me, R^2 = 3–MeC_6H_4
3e R^1 = Me, R^2 = 4–BrC_6H_4

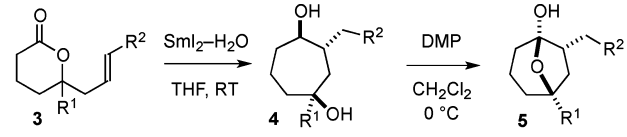
4a 55%, 82:18 dr[b]
4b 83%, 77:23 dr[b]
4c 82%, 63:37 dr[b]
4d 69%, 57:43 dr[b]
4e 78%, 61:39 dr[b]



3f **4f** 70%[c]

[a]Conditions: SmI_2 (8 equiv), THF, H_2O (100 equiv with respect to SmI_2), RT, 5–20 h. [b]The dr values give the ratio of the major diastereoisomer to the sum of the other diastereoisomers. [c]Mixture of 4 diastereoisomers.

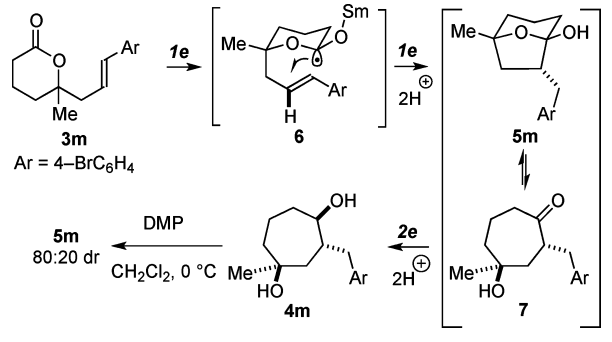
Scheme 3. Lactone Radical Cyclizations To Form Cycloheptan-1,4-diols and Oxidation to the Corresponding Hemiketals[a]



lactone **6**	product **5** (% yield[b], dr[c])
3g R^1 = Me **3h** R^1 = allyl	**5g** 75%, 50:50 dr **5h** 93%, 50:50 dr
3i R^2 = Ph **3j** R^2 = 3–MeC_6H_4 **3k** R^2 = 2,5–$Me_2C_6H_3$ **3l** R^2 = 4–$MeOC_6H_4$ **3m** R^2 = 4–BrC_6H_4 **3n** R^2 = 2–ClC_6H_4	**5i** 91%, 80:20 dr **5j** 72%, 80:20 dr **5k** 67%, 75:25 dr ***X–ray*** **5l** 89%, 80:20 dr **5m** 82%, 80:20 dr ***X–ray*** **5n** 75%, 86:14 dr

[a]Conditions: SmI_2 (8 equiv), THF, H_2O (100 equiv with respect to SmI_2), RT, 5–20 h. [b]Yields for two steps. [c]Ratio of two diastereoisomers.

Scheme 4. Proposed Mechanism for the Reductive Cyclizations of Alkenyllactones



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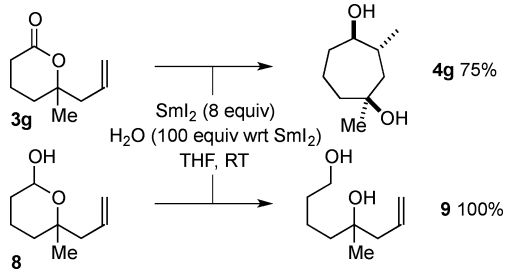
2-fold excess of reagent is used to ensure reactions are complete.

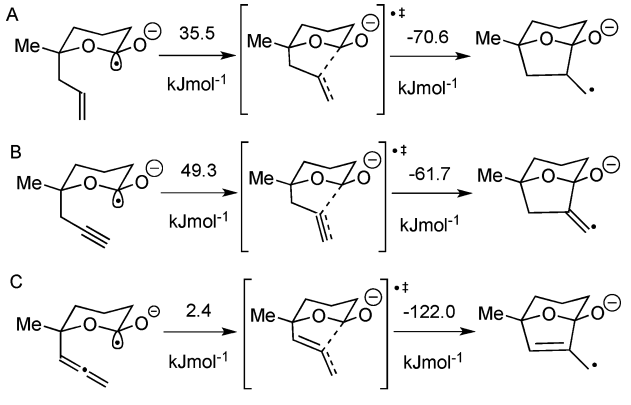
Attempts to isolate the hemiketal (or cycloheptanone) intermediates by the use of fewer equivalents of SmI_2 were unsuccessful: a mixture of starting material and cycloheptan-1,4-diols were obtained in low yield. To unequivocally determine whether the cyclization proceeded through an ester-derived radical 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 enolates[11] post-cyclization, rather than during seven-membered ring formation (*vide infra*). Computational studies[12] 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 compared with the analogous cyclization of an alkenyllactone (Scheme 6A).

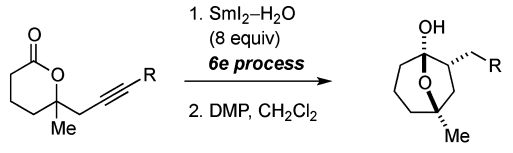
Scheme 6. Computational Studies on the Cyclization of Alkenyl, Alkynyl, and Allenyllactones



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

Therefore, in our search for more stereoselective routes to decorated cycloheptanes, we prepared alkynyllactones **10a**,**b**. Upon treatment with SmI_2–H_2O 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 Alkynyllactones Followed by Oxidation To Give Hemiketals[a]



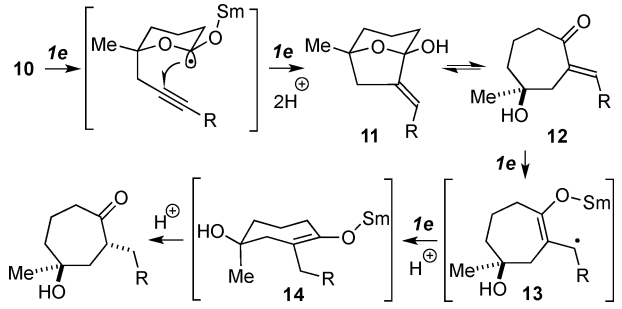
10a R = H
10b R = $SiMe_3$

5g 68%[b], 75:25 dr[c]
5o 93%[b], 86:14 dr[c]

[a]Conditions: SmI_2 (8 equiv), THF, H_2O (100 equiv with respect to SmI_2), RT, 20 h. [b]Yields for two steps. [c]Ratio of two diastereoisomers.

The cyclization of alkynyllactones proceeds via hemiketals **11** and enones **12** that are reduced[13] further to radical anions **13**. Further reduction and protonation then generates samarium enolates[11] **14** (alternatively, protonation of **13** on oxygen, electron transfer and proton transfer may lead to **14**).[S1] 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 Alkynyllactones



We proposed that seven-membered ring products would be delivered with a further improvement in diastereoselectivity by the analogous cyclizations of allenyllactones. With allene[14] 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 alkenyl and alkynyllactones. 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 SmI_2–H_2O 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

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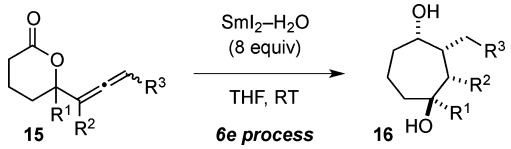
diastereocontrol was observed in the construction of three stereocenters (Table 1). Variation of substituents on the

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_6H_5	H	**16a**	68	>95:5
2	Me	4-$OMeC_6H_4$	H	**16b**	99	>95:5
3	Me	2-BrC_6H_4	H	**16c**	63	>95:5
4	Me	3-MeC_6H_4	H	**16d**	97	93:7
5	Me	3-ClC_6H_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_6H_4	H	**16h**	78	80:20
9	Cy	4-$OMeC_6H_4$	H	**16i**	62	>95:5
10	Me	C_6H_5	Me	**16j**	66[d]	86:14

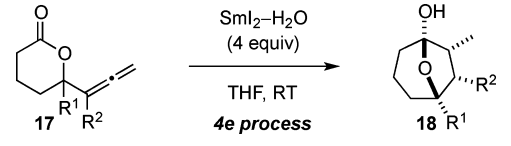
[a]Conditions: SmI_2 (8 equiv), THF, H_2O (500 equiv with respect to SmI_2), RT. [b]Isolated yield. [c]Determined by ^1H NMR. [d]Reaction was carried out on a 2:1 diastereoisomeric mixture of **15j**.

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 SmI_2-H_2O 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 SmI_2-H_2O generates axial radical anion **19**,[3b,d–f,10] which undergoes cyclization. Further reduction and protonation steps, then give enone **21**, via opening of

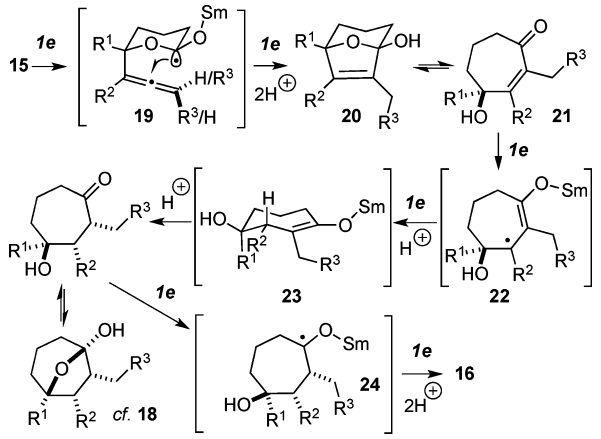
Table 2. Cyclopheptanone Hemiketals from the Reductive Cyclizations of Allenyllactones[a]



entry	R^1	R^2	product	yield (%)[b]	dr[c]
1	Me	C_6H_5	**18a**	27[d]	>95:5
2	Me	$SiMe_3$	**18b**	64[e]	>95:5
3	Me	$SiMe_2Ph$	**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

[a]Conditions: SmI_2 (4 equiv), THF, H_2O (500 equiv with respect to SmI_2), RT. [b]Isolated yield. [c]Determined by ^1H NMR. [d]X-ray crystal structure on the keto form (see Supporting Information). Major product was diol **16a**. [e]X-ray crystal structure (see Supporting Information). [f]Characterized as a mixture of keto and hemiketal forms.

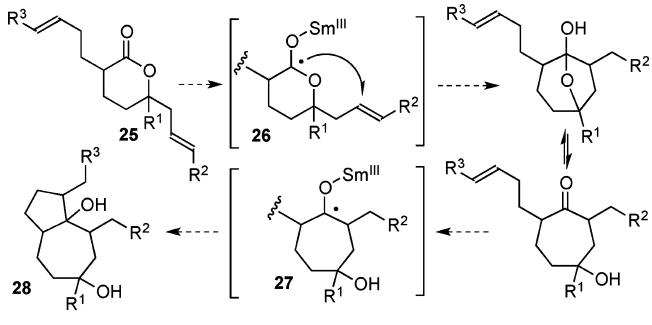
Scheme 9. Proposed Mechanism for the Reductive Cyclizations of Allenyllactones



hemiketal **20**. Reduction of the enone moiety[13] generates a second radical anion **22** that undergoes diastereoselective protonation at the β-position. A further reduction then gives samarium(III) enolate[11] **23** that undergoes diastereoselective protonation at the α-position. (Alternatively, protonation of **22** on oxygen, electron transfer, and proton transfer may lead to **23**).[5l] 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)–H_2O 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 SmI_2-H_2O



Calculations[12] 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

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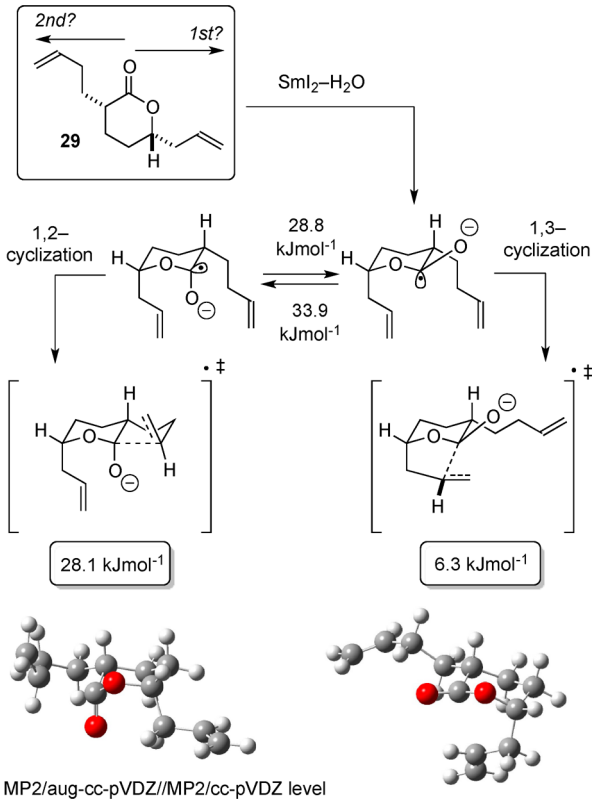


Figure 2. Calculations To Assess the Feasibility of Cyclization Cascades.

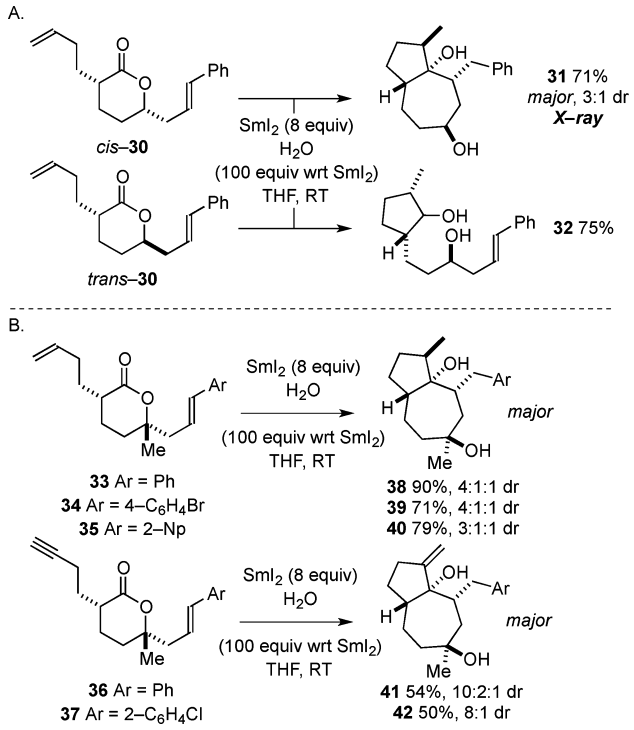
cyclization of the lactone-derived radical anion (after radical inversion) involving the alkene attached to the 2-position of the ring was calculated to have a much higher relative activation energy (~28 kJ mol^{-1}).[12] Thus, generic substrate *cis*-**29** should selectively undergo a "right then left" 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 SmI_2–H_2O. 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 prepared[8] 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 **38**–**42** with good diastereocontrol and diastereoisomeric products were readily separable (Scheme 11B).

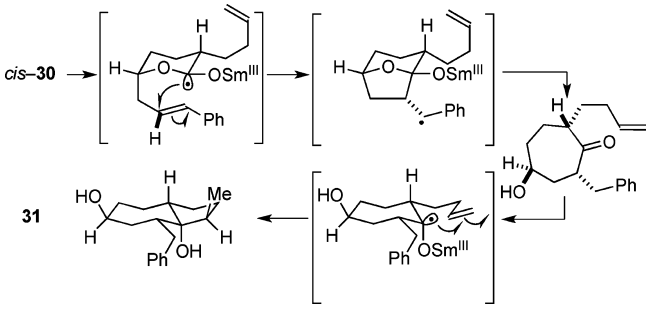
The mechanism and stereochemical course of the cascade cyclization for lactone *cis*-**30** is shown in Scheme 12.

We have also investigated cyclization cascades of allenyllactones. Pleasingly, treatment of substrates **43** with SmI_2–H_2O 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 programing 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 Alkenyllactones Using SmI_2–H_2O



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.

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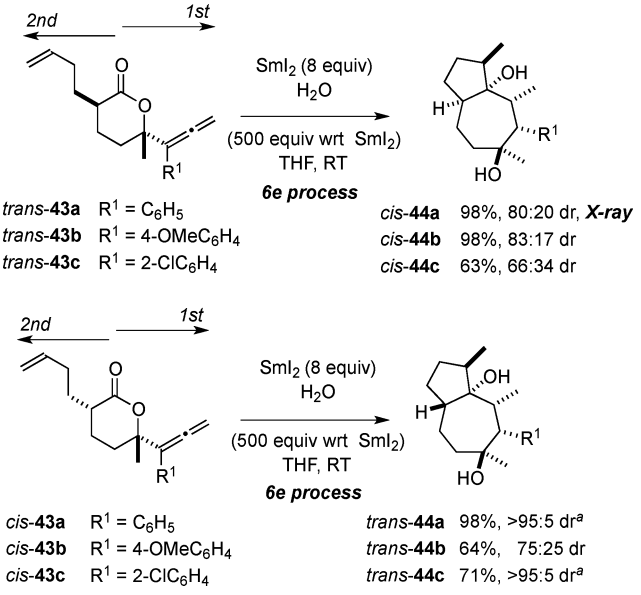
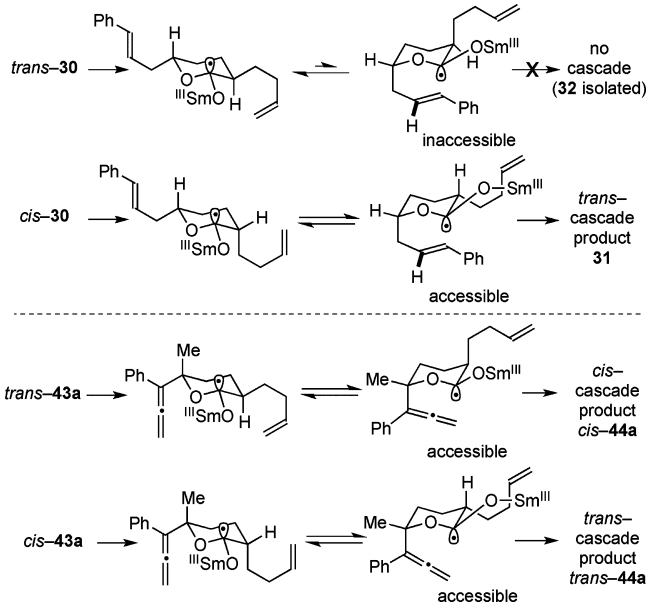
Scheme 13. Reductive Cyclization Cascades of *cis*- or *trans*-Allenyllactones to give [5.3.0] Bicyclic Ring Systems



[a]Yield 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 SmI_2–H_2O.

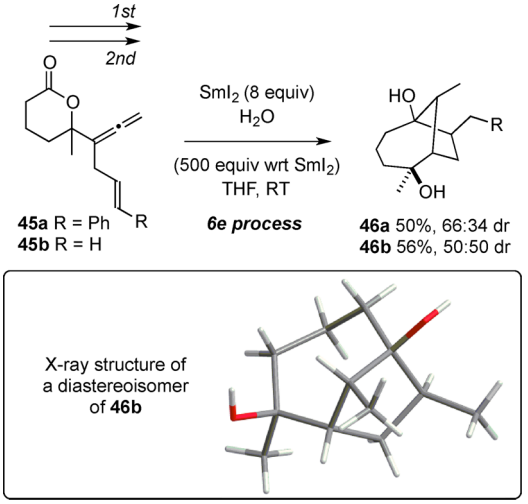
Scheme 14. The Impact of Lactone Conformation on the Feasibility of Cyclization Cascades



Finally, we have also investigated the feasibility of cyclization cascades of allenyllactones **45**. Pleasingly, treatment of substrates **45a,b** with SmI_2–H_2O 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 SmI_2–H_2O 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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