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Radical–Radical Cyclization Cascades of Barbiturates Triggered by Electron-Transfer Reduction of Amide-Type Carbonyls

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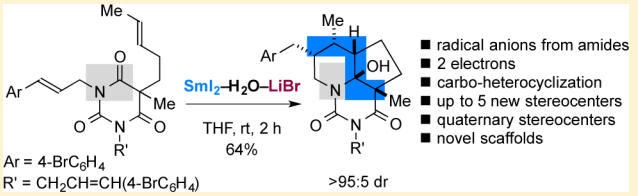
Supporting Information

ABSTRACT: Radical–radical cyclization cascades, triggered by single-electron transfer to amide-type carbonyls by SmI_2–H_2O, convert simple achiral barbiturates in one step to hemiaminal- or enamine-containing tricyclic scaffolds containing up to five contiguous stereocenters (including quaternary stereocenters). Furthermore, we describe the surprising beneficial effect of LiBr on the most challenging of the radical–radical cyclization cascades. An alternative fragmentation–radical cyclization sequence of related substrates allows access to bicyclic uracil derivatives. The radical–radical cyclization process constitutes the first example of a radical cascade involving ET reduction of the amide carbonyl. Products of the cascade can be readily manipulated to give highly unusual and medicinally relevant bi- and tricyclic barbiturates.



INTRODUCTION

Cascade cyclizations have the ability to convert simple starting materials to complex polycyclic molecular architectures in a single synthetic operation.[1] Such processes are particularly powerful when they operate on medicinally relevant feedstocks, use commercially available reagents, and efficiently deliver unprecedented scaffolds. We have recently developed cascade cyclizations, triggered by SmI_2-mediated[2] electron transfer (ET) to the carbonyl groups of ester derivatives,[3] that deliver complex structures through the formation of two carbocyclic rings (Scheme 1A).[4] While such cascades convert esters to complex carbobicyclic products, they are ET intensive, in that they feature four ET events and deliver products at the alcohol oxidation level that are not amenable to further manipulation.[4] Here we describe SmI_2-mediated radical–radical cyclization cascades of amide-type groups[5] in medicinally important barbiturates[6] that construct both a heterocyclic and a carbocyclic ring, generate up to five contiguous stereocenters including quaternary stereocenters, involve only two ET events, and deliver readily manipulated polycyclic hemiaminals or enamines similar in structure to motifs found in important targets[7] (Scheme 1B,C). Furthermore, we describe the surprising beneficial effect of LiBr on the most challenging of the radical–radical cyclization cascades, an alternative fragmentation radical-cyclization pathway that delivers important bicyclic uracil derivatives, and the synthesis of several unprecedented barbiturate scaffolds. The ubiquity and importance of amide groups, their resistance to ET reduction, and the limited precedent for radical C–C bond formation using the resultant radical anions[5] highlights the significance of the findings. The radical–radical cyclization cascade process constitutes the first example of a radical cascade involving ET reduction of the amide carbonyl.

RESULTS AND DISCUSSION

Optimization of the First Radical Cascade Cyclizations Involving ET Reduction of the Amide Carbonyl. We began by optimizing the cascade cyclization of readily accessible barbituric acid derivative **1a**, synthesized in 3 steps from diethyl-2-methymalonate (Table 1). H_2O facilitates the reduction of carboxylic acid derivatives using SmI_2 in THF,[2c,3] and the use of H_2O as a cosolvent was essential for the reduction of **1a** (entry 1). Upon treatment of **1a** with SmI_2–H_2O in THF, hemiaminal and enamine cascade products, **2a** and **3a**, respectively, were obtained in good yield (entry 2) accompanied by heminal byproduct **4a**.[5a] Reducing the amount of H_2O cosolvent improved conversion; however, **4a** was still formed in significant amounts (entry 3). The use of LiBr as an additive with SmI_2–H_2O (*vide infra*) gave similar results (entry 4).[8] The use of an alternative proton donor, ethylene glycol,[9] resulted in no conversion (entry 5). Pleasingly, when SmI_2 was added over 1 h, **2a**/**3a** were obtained in 85% NMR yield with little formation of **4a** (entry 6). From this experiment, hemiaminal **2a** could be isolated as the major product in 60% yield and 95:5 dr. Finally, quenching of the reaction with HCl triggered dehydration of hemiaminal **2a**, and enamine **3a** was obtained in 88% isolated yield and 75:25 dr (entry 7). (In some cases, the minor diastereoisomers from the cascade cyclization undergo more facile dehydration to the corresponding enamines; thus, diastereoisomeric ratios for hemiaminals **2** can be higher than for enamines **3**).

Scope of the Radical–Radical Cyclization Cascade of Amides. The scope of the radical–radical, heterocyclization–carbocyclization cascade of amides **1** was assessed. In general,

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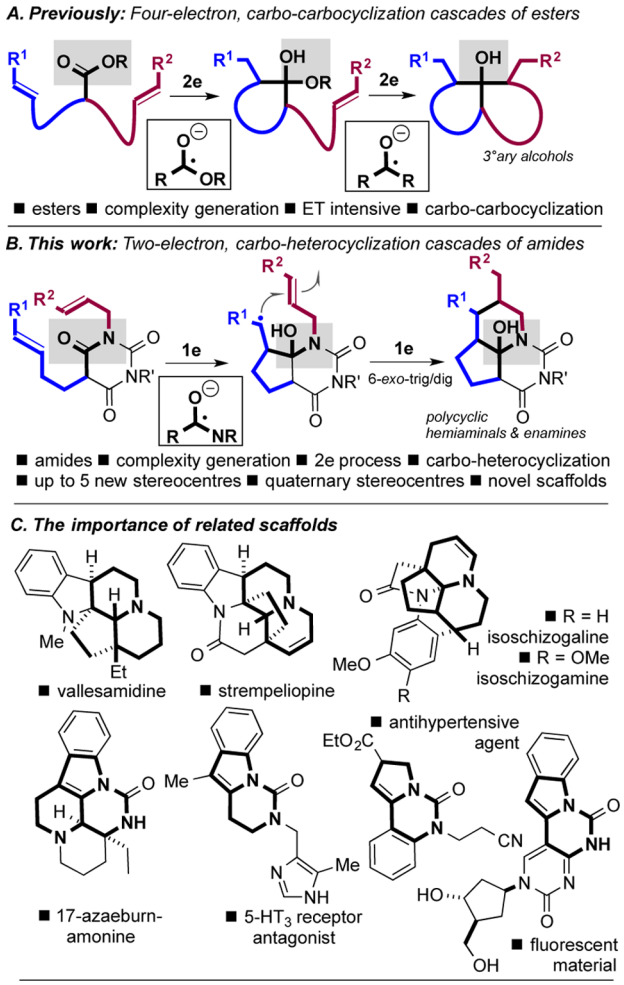
Scheme 1. Cascade Cyclizations of Esters, Radical−Radical Cascade Cyclizations of Amides, and Importance of Related Scaffolds[a]

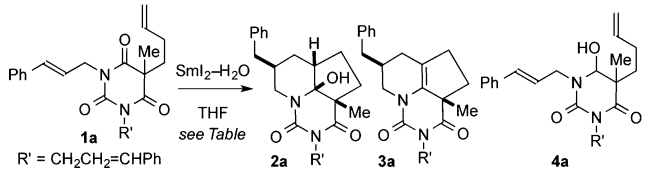


[a](A) Cascade cyclizations of esters forming tertiary alcohols and two new carbocyclic rings. (B) Radical−radical cascade cyclizations of amides that form hemiaminals/enamines possessing a new heterocyclic ring and a new carbocyclic ring. (C) Importance of related scaffolds.

tricyclic hemiaminals **2** were the major products, whereas tricyclic enamines **3** could be isolated if a HCl quench was employed. Good diastereocontrol was observed in both cases. A range of alkyl substituents on the barbituric acid substrates (R = Me, *i*Bu, *i*Pr, and allyl) was tolerated in the cascade (e.g., formation of **3a**, **3b**, **3h**, and **3i**). Furthermore, bromo (**2c**, **3c**, and **3j**), fluoro (**2e** and **3e**), trifluoromethyl (**2d** and **3d**), methoxy (**3n**, **3o**, and **3p**), acetal (**3m**), and thienyl (**2f** and **3f**) groups were compatible with the reaction conditions. Finally, employing an alkyne as the second radical trap in the cascade delivered alkene products **2g** and **3g** (Scheme 2). The cyclization of an alkyne substrate to give **2g** essentially as a single diastereoisomer (2.3:1 mixture of alkene isomers) confirms that hemiaminals **2** are diastereoisomeric mixtures at the homobenzylic stereocenter generated in the last step of the cascade. The relative stereochemistry of the major products was confirmed by X-ray crystallographic analysis of **2c** and **3a**.[10]

Beneficial Effect of LiBr on the Radical−Radical Cyclization Cascades of Amides. Barbituric acid derived substrates **1q−t** possessing additional substituents on the second alkene radical trap were used to further explore the scope of the

Table 1. Optimization of the Radical−Radical Cyclization Cascade of Amide 1a[a]



			yield (%)[b]			
entry	SmI_2 (equiv)	H_2O (equiv)	**1a**	**2a**	**3a**	**4a**
1	3		100	0	0	0
2	3	200	10	40	20	22
3	3	100		40	20	40
4[c]	3	100		51	15	10
5	3	*d*	100			
6[e]	3	100		65[g]	20	5
7[e,f]	3	100			92[h]	

[a]Reaction conditions: To **1a** (0.1 mmol, in THF) under N_2 was added H_2O, followed by SmI_2, and the reaction was quenched after for 1 h. [b]Yield was determined by ^1H NMR spectroscopy using 2,3,5,6-tetrachloronitrobenzene as internal standard. [c]LiBr (20 equiv wrt SmI_2) was used. [d]Ethylene glycol (36 or 100 equiv) was used in place of H_2O. [e]SmI_2 (3 equiv, 0.1 M, 3 mL) was added by syringe pump over 1 h, and the reaction was quenched after 1 h. [f]After 1 h, HCl (1 M, 2 mL) was added and stirred for 2 h. [g]60% isolated yield; >95:5 dr. [h]88% isolated yield; 75:25 dr.

reaction and the feasibility of generating quaternary stereocenters in the cascade process. Treatment of **1q** with SmI_2−H_2O gave hemiaminal **2q** and/or enamine **3q** bearing a new quaternary stereocenter in low yield (40%), the major product being that of monocyclization (30%) (i.e., reduction and protonation of radical intermediate analogous to **14** in Scheme 8). Interestingly, the addition of LiBr to the SmI_2−H_2O reagent system resulted in more efficient cascade cyclization and improved isolated yields of **2q** (57%) and **3q** (76%), depending on the conditions employed (Scheme 3).[11] Additional substrates **1r−t** with various alkyl substitution on the barbituric acid ring and on the alkene radical acceptor underwent cascade reactions to give hemiaminals **2r−t** or enamines **3r−t** in good isolated yield. Notably, the use of larger alkyl substituents on the barbituric acid ring resulted in the formation of cascade products with higher diastereoselectivity (e.g., compare the formation of **2q** and the formation of **2r**).

We next turned to the cascade cyclization of substrate **1u** bearing an additional substituent at the terminus of the first alkene radical acceptor. Pleasingly, exposure of **1u** to SmI_2−H_2O and LiBr gave **2u** containing five new contiguous stereocenters in good yield and essentially as a single diastereoisomer: The secondary alkyl radical undergoes more selective 6-*exo*-cyclization than the corresponding primary radicals (cf. **14** in Scheme 8), possibly through boat transition structure **5** in which substituents adopt pseudoequatorial orientations and transannular interactions are minimized (Scheme 4).

Flowers has proposed that the combination of SmI_2 and LiBr generates $SmBr_2$ *in situ*.[8] Thus, the addition of LiBr may generate $SmBr_2$−H_2O.[12] Although $SmBr_2$ (approximately −1.55 V vs SCE) has a higher reduction potential than SmI_2 (−0.9 V vs SCE),[8,12] the radical intermediate in the cascade appears less susceptible to reduction to the anion under the SmI_2−H_2O/LiBr conditions, and radical cyclization is more efficient. A hindered approach of $SmBr_2$−H_2O to the radical may lie behind the slower outer-sphere process.

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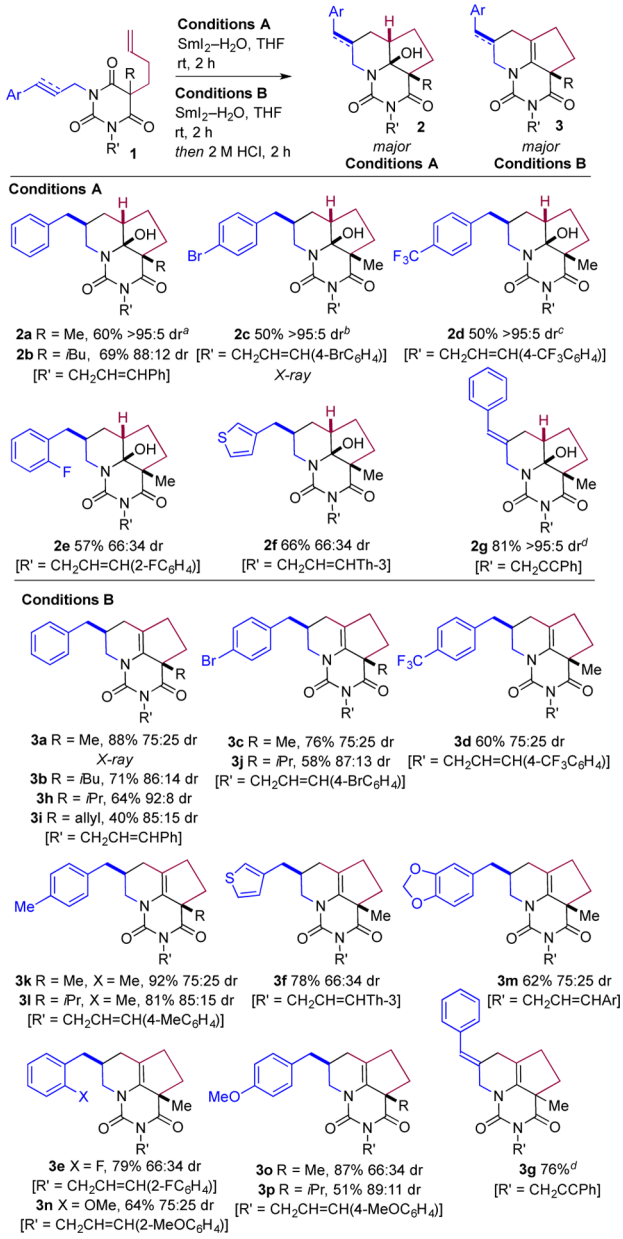
Scheme 2. Scope of the Radical–Radical Cyclization Cascade of Amides 1

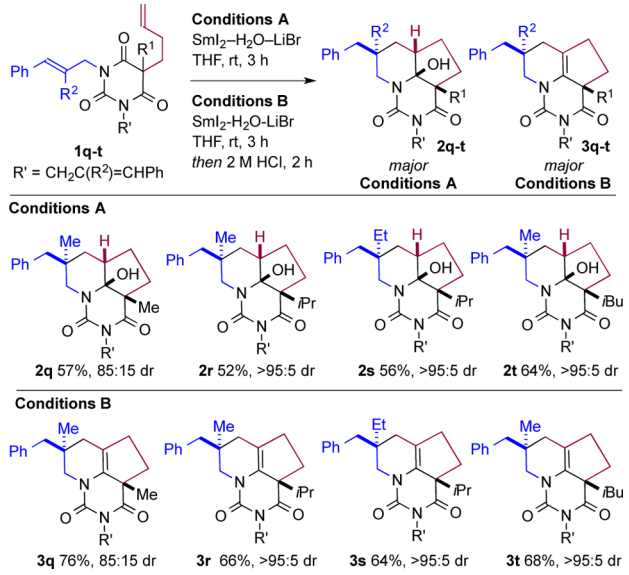


[a]17% enamine **3a** was also isolated (dr 25:75). [b]14% enamine **3c** was also isolated (dr 25:75). [c]10% enamine **3d** was also isolated (dr 25:75). [d]*E*/*Z* ratio of alkene isomers ≈ 2.3:1 . Diastereoisomeric ratios determined by ^{1}H NMR of crude mixtures.

Scalability of the Radical–Radical Cyclization Cascade and the Synthetic Utility of the Unusual Tricyclic Products. The scalability of the radical–radical cyclization cascade has been assessed: Conversion of **1g** to tricyclic hemiaminal **2g** was conveniently carried out on a gram scale and gave **2g** in 80% isolated yield after 2 h (Scheme 5).

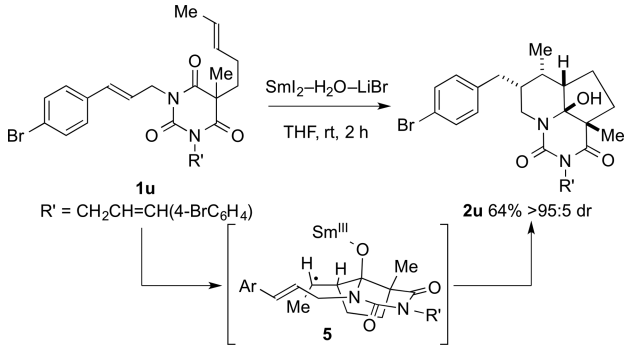
The synthetic potential of the products arising from the amide radical–radical cyclization cascade has been assessed (Scheme 6). The *N*-alkyl substituent in cascade products can be removed. For example, Wacker oxidation[13] of **3a** and eliminative cleavage of the intermediate aryl ketone gave N–H product **6**. Preliminary studies have also shown that the unusual tricyclic cascade products can be manipulated to give additional intriguing architectures. Treatment of **3a** with *m*CPBA gave the unprecedented 9-membered heterocyclic system present in **7**

Scheme 3. Amide Radical–Radical Cyclization Cascades Forming Quaternary Stereocenters[a]



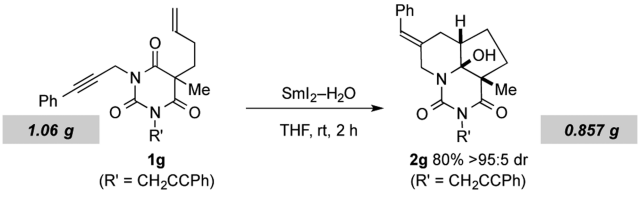
[a]Reaction conditions A: To the substrate (0.1 mmol, in THF) under N_2 was added H_2O (100 equiv), followed by slow addition of a premixed solution of SmI_2 in THF (3 equiv) and LiBr (20 equiv wrt SmI_2) over 1 h, and the reaction was quenched after a further 2 h. Reaction conditions B: To the substrate (0.1 mmol, in THF) under N_2 was added H_2O (100 equiv), followed by slow addition of a premixed solution of SmI_2 in THF (3 equiv) and LiBr (20 equiv wrt SmI_2) over 1 h. After a further 2 h, HCl (2 M in Et_2O) was added, and the reaction was stirred for a further 2 h.

Scheme 4. Amide Radical–Radical Cyclization Cascade Forming Five Contiguous Stereocenters[a]



[a]Reaction conditions: To the substrate (0.1 mmol, in THF) under N_2 was added H_2O (100 equiv), followed by slow addition of a premixed solution of SmI_2 in THF (5 equiv) and LiBr (12 equiv wrt SmI_2) over 1 h, and the reaction was quenched after a further 1 h.

Scheme 5. Gram-Scale Amide Radical–Radical Cyclization Cascade



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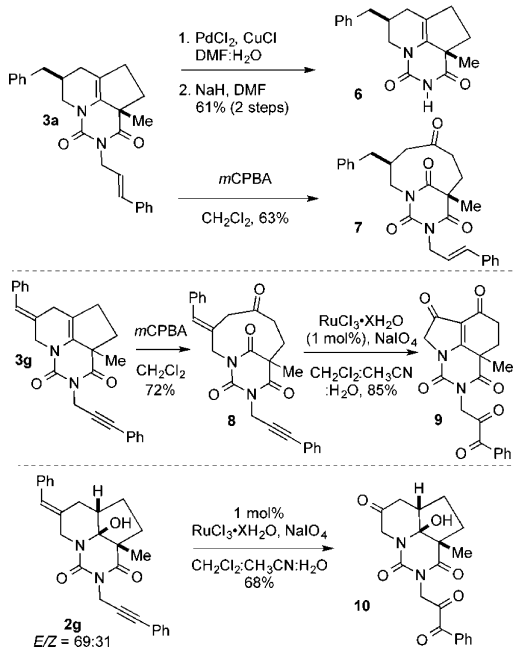
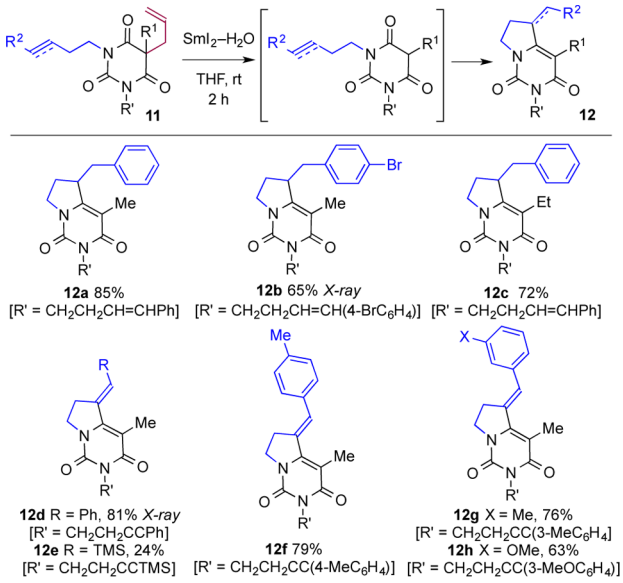
Scheme 6. Manipulating the Novel Tricyclic Products of the Amide Radical–Radical Cyclization Cascade



Scheme 7. Sequential Fragmentation–Radical Heterocyclization of Amides 11[a]



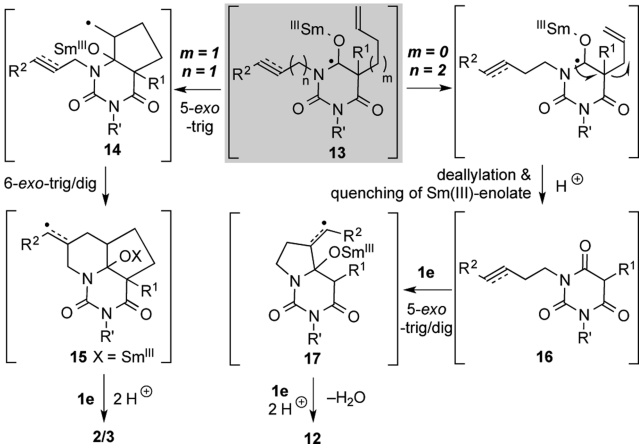
[a]Reaction conditions: To **11** (0.1 mmol, in THF) under N_2 was added H_2O (100 equiv), followed by slow addition of SmI_2 (4.5 equiv) over 1 h, and the reaction was quenched after a further 1 h.

by oxidative cleavage.[14] Analogous ring-opening of **3g** gave **8**, which upon Ru-catalyzed oxidation[15] resulted in diketone formation, alkyne oxidation, and cyclization to give reconfigured tricyclic barbiturate **9**. Finally, catalytic oxidation of tricyclic hemiaminal **2g** resulted in formation of cyclic ketone **10**. Attractively, in the formation of **9** and **10**, catalytic oxidative alkene cleavage was accompanied by conversion of the *N*-alkyl substituent to a removable[16] or functionalizable group.

Related Fragmentation–Radical Cyclization Sequence. The choice of tether lengths anchoring the radical acceptors to the barbituric acid core is key to the sequence integrity of the radical–radical cascade cyclizations of **1**; 5-*exo*-trig carbocyclization precedes heterocyclization. Adjusting the lengths of the tethers gave related substrates **11**. Interestingly, upon treatment with SmI_2–H_2O, barbiturates **11** underwent a fragmentation-radical heterocyclization sequence to give bicyclic uracil derivatives **12** in good isolated yield (Scheme 7). Variation of the alkyl substituents on the barbituric acid ring (R^1 = Me and Et) and functionality [bromo (**12b**), TMS (**12e**), and methoxy (**12h**)] proved compatible with the process. The structure of **12b** was confirmed by X-ray crystallographic analysis. The use of alkyne radical acceptors selectively delivered dienyl uracil derivatives **12d–h** containing exocyclic *E*-alkenes as confirmed by X-ray crystallographic analysis of **12d**.[10] Importantly, expulsion of the allyl unit allows the final dehydration to occur into conjugation with the amide carbonyl, thus delivering important 5-alkyl uracil derivatives.[17] Notably, these products cannot readily be prepared from the corresponding monoalkylated barbituric acid derivatives because of the synthetic inaccessibility of such substrates (*vide infra*).

Proposed Mechanisms for the Radical–Radical Cyclization Cascade and the Fragmentation–Radical Heterocyclization Sequence. Both the radical–radical cyclization cascade (substrates **1**) and the fragmentation–radical heterocyclization sequence (substrates **11**) are triggered by ET to the amide-type carbonyl group to give radical anions **13**.[3] For substrates **1** (m = 1, n = 1; left-hand pathway), 5-*exo*-trig radical cyclization gives radical intermediate **14** that then undergoes 6-*exo*-trig/dig cyclization to give **15**. Further reduction and protonation gives tricyclic hemiaminals **2** or the corresponding enamines **3** after dehydration (Scheme 8). For substrates **11**

Scheme 8. Proposed Mechanism for the Formation of 2/3 and 12



(m = 0, n = 2; right-hand pathway), radical anion **13** undergoes fragmentation[18] to give a Sm(III)-enolate[19] that is protonated to give **16**. Further reduction and 5-*exo*-trig/dig cyclization gives radical **17** that undergoes further reduction and protonation to give bicyclic uracil derivatives **12** after dehydration. Notably, monoalkyl barbituric acids **16** are hard to prepare because of their acidity, and their *in situ* formation by fragmentation of **11** is an attractive synthetic solution.

In support of the proposed fragmentation–radical cyclization mechanism, we investigated the use of established radical leaving groups in the sequence. Pleasingly, barbituric acid derivatives **11i** and **11j**, bearing strained rings alpha to the amide

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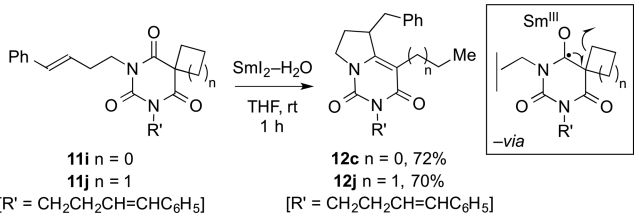
carbonyl,[20] undergo efficient fragmentation followed by cyclization to give bicyclic uracils **12c** and **12j**, respectively (Scheme 9). The radical fragmentation of carbonyl compounds bearing cyclopropyl rings in the α-position is well-known.[20]

Scheme 9. Alternative Fragmentation−Radical Cyclization Sequences



CONCLUSIONS

Single-electron transfer to the amide-type carbonyl of simple achiral barbiturates using SmI_2−H_2O triggers a two electron, radical−radical cyclization cascade that allows the formation of quaternary stereocenters and provides direct access to structurally complex and synthetically versatile hemiaminal- or enamine-containing tricyclic scaffolds containing up to five contiguous stereocenters. In addition, related substrates undergo alternative fragmentation−radical cyclization cascades to give bicyclic uracil derivatives. The addition of LiBr was found to have a surprising beneficial effect on the most challenging of the radical−radical cyclization cascades. The process constitutes the first example of a radical cyclization cascade involving ET reduction of the amide carbonyl.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b04086.

Experimental details, characterization data and spectra, X-ray structures, NOE studies (PDF)

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Notes

The authors declare no competing financial interest.

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