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# Radical Cyclization Cascades of Unsaturated Meldrum's Acid Derivatives

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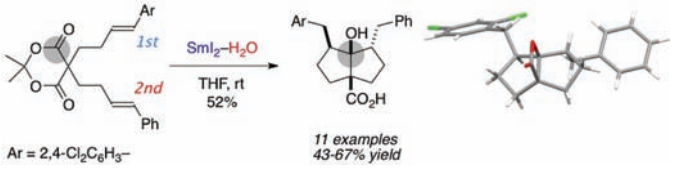
## ABSTRACT




**Unsaturated, differentially substituted Meldrum's acid derivatives undergo cascade cyclizations upon ester reduction with $SmI_2$–$H_2O$. The cascade cyclizations proceed in good yield and with high diastereocontrol and convert simple, achiral starting materials to complex molecular architectures, bearing up to four stereocenters, in a single operation. The cascades are triggered by the generation and trapping of unusual radical-anions formed by electron transfer to the ester carbonyl.**

Electron-transfer to the carbonyl groups of unactivated esters forms the basis of classical organic transformations such as the acyloin condensation[1] and the Bouveault–Blanc reduction.[2] Prior to our recent studies,[3] the possibility of exploiting the radical-anions formed by electron transfer to the ester carbonyl group in additions to alkenes had received little attention.[4] Here we report radical cascade reactions of unsaturated Meldrum's acid derivatives that allow complex carbocyclic motifs to be assembled in a single operation. The cyclization cascade is triggered by the generation and trapping of unusual radical anions formed from the ester carbonyl by electron transfer from $SmI_2$–$H_2O$.[5]

We recently reported the first reductions of lactones and Meldrum's acid derivatives by $SmI_2$ using $H_2O$ as an activating cosolvent[6] (e.g., Scheme 1, eq 1).[3a–c] We have since shown that unactivated acyclic aliphatic esters can be reduced using $SmI_2$–$H_2O$–$NEt_3$.[7] Furthermore, we have shown 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 (e.g., Scheme 1, eq 2).[3b–e]

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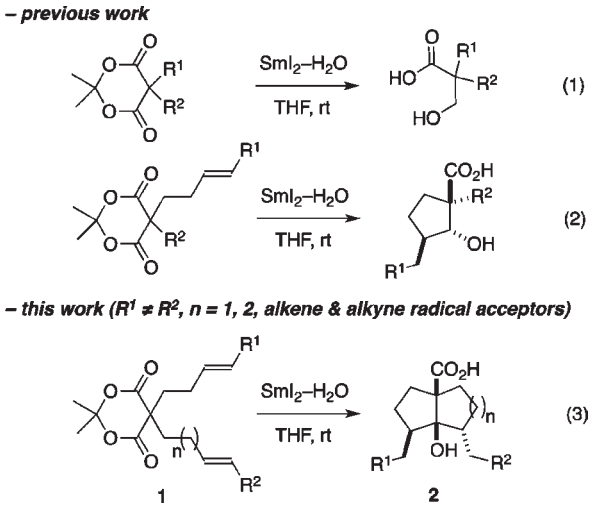
**Scheme 1.** Cyclization Cascades of Meldrum's Acid Derivatives

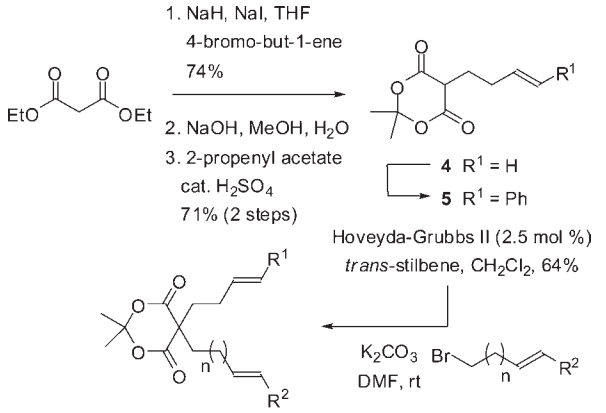



In preliminary studies we have shown that two readily accessible, symmetrical substrates **1** ($R^1 = R^2 = Ph$, $n = 1$ and $R^1 = R^2 = 4\text{-}C_6H_4Br$, $n = 1$) underwent cascade cyclization to give bicyclic tertiary alcohols **2**.[3d] The cyclization cascade involves the generation and trapping of two radical-anion intermediates formed during ester carbonyl reduction (Scheme 1, eq 3).

In this paper, we describe cyclization cascades involving substrates **1** in which $R^1$, $R^2$ were different, the tether length $n$ was varied, and alkenes and alkynes were employed as radical acceptors (Scheme 1, eq 3). Provided the two unsaturated units had differing reactivity, courtesy of the substituent on the multiple bond or tether length, we speculated that the cascades should proceed with high sequence integrity and high diastereoselectivity. Thus, the cyclization cascades would convert simple, achiral substrates to complex products bearing multiple stereocenters in a single operation.

Difficulties in monoalkylating Meldrum's acid[8] necessitated that routes to cascade substrates bearing different tethered alkenes/alkynes began from diethylmalonate (Scheme 2). Monoalkylation of diethyl malonate with 4-bromobut-1-ene, hydrolysis, and cyclic ketal formation gave Meldrum's acid **4**. This procedure was unfortunately incompatible with styrene-like olefins.[9] When necessary,

**Scheme 2.** Preparation of Alkenyl/Alkenyl Cascade Substrates

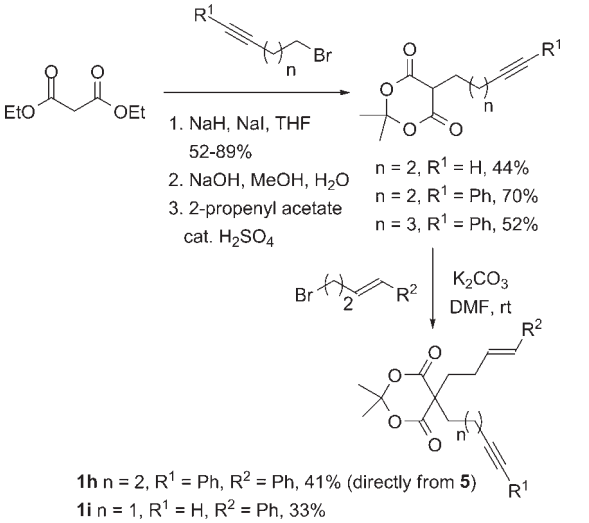



**1a** $R^1 = H$, $R^2 = Ph$, n = 1, 66%
**1b** $R^1 = H$, $R^2 = 4\text{-}C_6H_4Br$, n = 1, 32%
**1c** $R^1 = H$, $R^2 = 2,4\text{-}C_6H_3Cl_2$, n = 1, 62%
**1d** $R^1 = H$, $R^2 = 2\text{-Naphthyl}$, n = 1, 51%
**1e** $R^1 = Ph$, $R^2 = 2,4\text{-}C_6H_3Cl_2$, n = 1, 37%
**1f** $R^1 = Ph$, $R^2 = 4\text{-}C_6H_4Br$, n = 1, 33%
**1g** $R^1 = Ph$, $R^2 = Ph$, n = 2, 48%

functionalization of the olefin was achieved by cross-metathesis using the Hoveyda–Grubbs II catalyst[10] and *trans*-stilbene to give **5**. Finally, alkylation of **4** and **5** with a range of homoallyl bromides, gave substrates **1a**–**f** in moderate to good yield (Scheme 2). Alternatively, alkylation with *E*-1-bromo-5-phenylpent-4-ene gave substrate **1g** that would allow the feasibility of forming six membered rings in the second stage of the cascade to be explored.

Alkynyl-substituted substrates were prepared by alkylation of **5** with an alkynyl bromide (to give **1h**) *or* alkylation of diethylmalonate with an alkynyl bromide, cyclic

**Scheme 3.** Preparation of Alkenyl/Alkynyl Cascade Substrates




**1h** n = 2, $R^1 = Ph$, $R^2 = Ph$, 41% (directly from **5**)
**1i** n = 1, $R^1 = H$, $R^2 = Ph$, 33%
**1j** n = 1, $R^1 = Ph$, $R^2 = Ph$, 30%
**1k** n = 2, $R^1 = Ph$, $R^2 = 2,4\text{-}C_6H_3Cl_2$, 43%

(6) For selected studies on the role of alcohols and water in $SmI_2$-mediated reactions, see: (a) Hutton, T. K.; Muir, K. W.; Procter, D. J. *Org. Lett.* **2003**, *5*, 4811. (b) Chopade, P. R.; Prasad, E.; Flowers, R. A., II. *J. Am. Chem. Soc.* **2004**, *126*, 44. (c) Prasad, E.; Flowers, R. A., II. *J. Am. Chem. Soc.* **2005**, *127*, 18093. (d) Sadasivam, D. V.; Teprovich, J. A., Jr.; Procter, D. J.; Flowers, R. A., II. *Org. Lett.* **2010**, *12*, 4140. (e) Yacovan, A.; Hoz, S.; Bilkis, I. *J. Am. Chem. Soc.* **1996**, *118*, 261. (f) Tarnopolsky, A.; Hoz, S. *Org. Biomol. Chem.* **2007**, *5*, 3801. (g) Tarnopolsky, A.; Hoz, S. *J. Am. Chem. Soc.* **2007**, *129*, 3402. (h) Amiel-Levy, M.; Hoz, S. *J. Am. Chem. Soc.* **2009**, *131*, 8280. (i) Upadhyay, S. K.; Hoz, S. *J. Org. Chem.* **2011**, *76*, 1355.

(7) Szostak, M.; Spain, M.; Procter, D. J. *Chem. Commun.* **2011**, *47*, 10254.

(8) For a review of the chemistry of Meldrum's acid, see: McNab, H. *Chem. Soc. Rev.* **1978**, *7*, 345.

(9) Styrene-like double bonds were incompatible with the acidic conditions used during ketalization.

1,3-diester formation, and alkylation with an alkenyl bromide. The resultant substrates **1h**–**k** allowed us to probe the feasibility of incorporating 5-*exo-dig* and 6-*exo-dig* cyclizations in the cascade reactions (Scheme 3).

Pleasingly, slow addition of $SmI_2$ to Meldrum's acids **1a**–**f** in THF and $H_2O$ at room temperature resulted in cascade cyclization to give bicyclic products **2a**–**f** in 43–63% yield and with good diastereocontrol (Figure 1).[11] It is important to note that overall yields in this range arise from impressive yields in each cyclization event in the cascade. The feasibility of forming other ring sizes in the reaction cascades was confirmed by isolation of **2g** from the cyclization of **1g**. Bicyclic adduct **2g** was obtained as a 1.3:1 mixture of diastereoisomers presumably as a result of an unselective second cyclization (Figure 1).

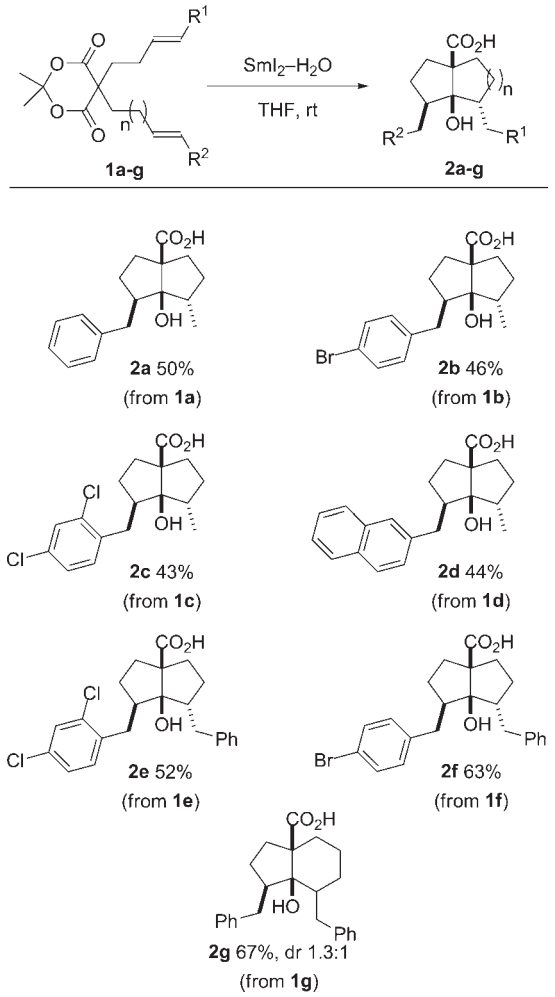



**Figure 1.** Products of *exo-trig*/*exo-trig* cyclization cascades.

(10) (a) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168. For recent reviews on olefin metathesis, see: (b) Samojłowicz, C.; Bieniek, M.; Grela, K. *Chem. Rev.* **2009**, *109*, 3708. (c) Vougioukalakis, G. C.; Grubbs, R. H. *Chem. Rev.* **2010**, *110*, 1746.

(11) Only one diastereoisomer of the products could be isolated from these reactions. From the crude $^1H$ NMR spectra we believe the dr to be ~ 90:10, major diastereoisomer to an unknown minor diastereoisomer.

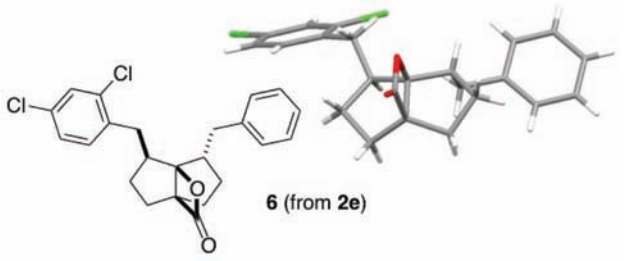
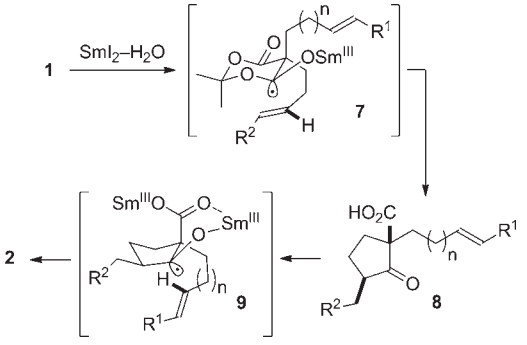



**Figure 2.** X-ray crystallographic analysis of $\beta$-lactone **6**.

The stereochemistry of the products was confirmed by NOE studies on the methyl ester derived from **2f** and X-ray crystallographic analysis of **6**,[12] obtained from **2e** by $\beta$-lactone formation (benzoyl chloride, $Et_3N$, DMAP, THF, 86%) (Figure 2).

As proposed, differential activation of the two radical acceptors is crucial if high sequence integrity and diastereoselectivity are to be observed.[13] Selection of the most favored cyclization by the first radical-anion **7** leads to ketone intermediate **8** with high diastereoselectivity through an *anti*-transition state.[5c] Further reduction by $SmI_2$–$H_2O$ forms a second radical-anion **9** which reacts with the remaining acceptor with high diastereoselectivity, again through a favored *anti*-transition state,[5c] to give the cascade products (Scheme 4).

**Scheme 4.** Rationalizing the Stereochemical Outcome of the Cascades




The possibility of exploiting 5-*exo-dig* and 6-*exo-dig* cyclizations as part of the cascades was also confirmed: **1h**–**k** underwent cascade cyclization to give **2h**–**k** with good selectivity and in 52–64% yield (Figure 3).[14,15] The double bond stereochemistry in the products was confirmed by X-ray crystallographic analysis of **2k**.[12]

(12) See the Supporting Information for CCDC numbers.

(13) When a substrate containing similarly activated alkenes bearing different substituents was used in the cascade cyclization, a mixture of isomeric products was obtained. For an example of the outcome of the cyclization of such a substrate, see the Supporting Information.

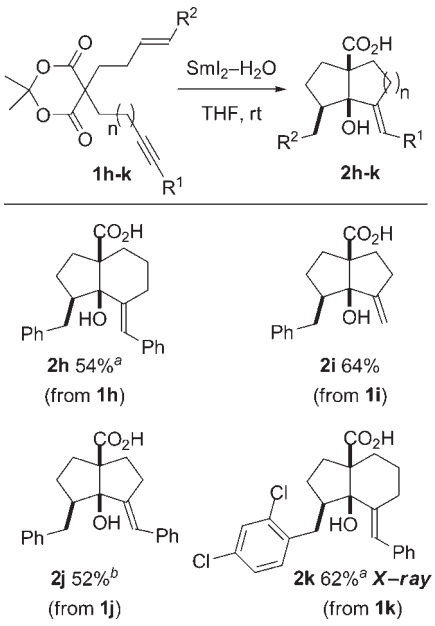



**Figure 3.** Cyclization Cascades Exploiting Alkene and Alkyne Radical Acceptors.

In summary, unsaturated, differentially substituted Meldrum's acid derivatives undergo cascade cyclizations upon ester reduction with $SmI_2-H_2O$. The cascade cyclizations proceed in good yield and with high diastereocontrol and convert simple, achiral starting materials to complex molecular architectures, bearing up to four stereocenters, in a single operation.

**Acknowledgment.** We thank the EPSRC (Project Studentship to B.S. and Organic Synthesis Studentship to S.E.L.), GlaxoSmithKline (CASE Award to S.E.L.) and the University of Manchester.

**Supporting Information Available.** Additional experiments, full experimental details, characterization data, $^1H$ and $^{13}C$ NMR spectra for all new compounds, X-ray crystal structure for **6** and **2k**, and CCDC numbers. This material is available free of charge via the Internet at http://pubs.acs.org.

(14) The cascade cyclization of **1j** using $SmI_2-D_2O$ gave **2j** with deuterium incorporation at the benzylic and vinylic positions suggesting that each cyclization is terminated by protonation of an organosamarium intermediate. See the Supporting Information.

(15) The *E*-alkene stereochemistry in the major products of **2h**, **2j**, and **2k** appears to arise from the formation of the most stable vinyl radical/vinyl samarium species. Selectivity for the *E*-alkene is higher in the 6-membered ring systems due to greater steric clashes in the *Z*-alkene. These steric clashes arise between the phenyl substituent and the bridgehead hydroxyl and are exacerbated by the chair conformation of the 6-membered ring. See the X-ray crystal structure of **2k** in the Supporting Information.