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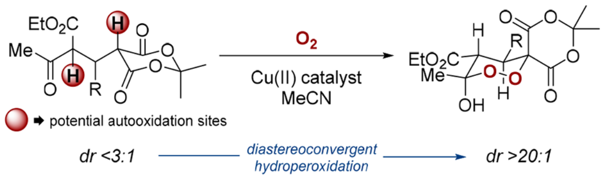
Chemoselective and Diastereoconvergent Cu(II)-Catalyzed Aerobic Endoperoxidation of Polycarbonyls

James Giarrusso, Dung T. Do, and Jeffrey S. Johnson*

Department of Chemistry, The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599, United States

Ⓢ *Supporting Information*

ABSTRACT: The diastereoconvergent synthesis of spirocyclic endoperoxides using a Meldrum's acid scaffold has been accomplished by employing readily available feedstock chemicals. Site selective C−H oxidation of the bis(β-dicarbonyl) substrates was performed using elemental oxygen as the stoichiometric oxidant and a commercial Cu(II) catalyst. Sequential hydrogenolysis and ionic reduction of these endoperoxides provided fully substituted tetrahydrofurans in high yields and diastereoselectivity.

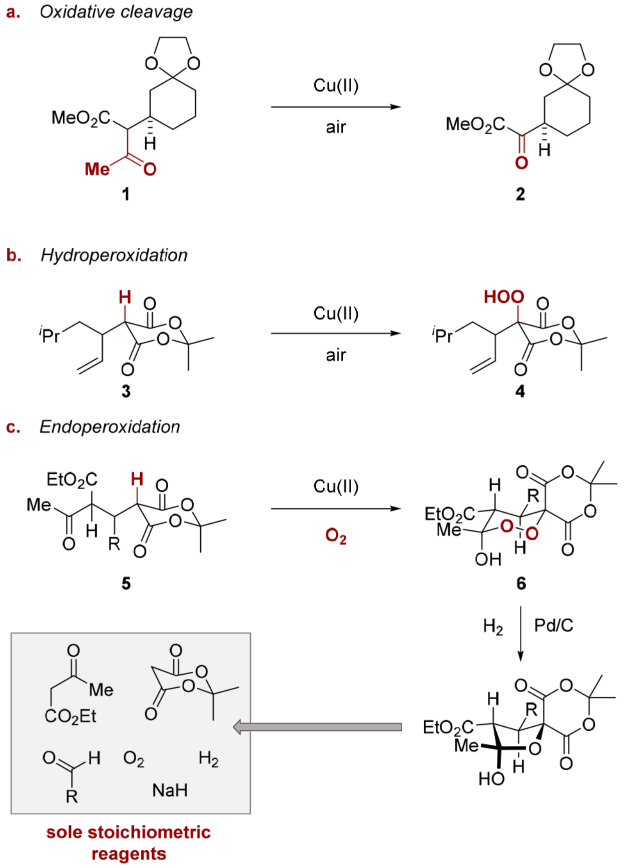


Cyclic peroxides exhibit a variety of therapeutic properties.[1] Perhaps the most well-known naturally occurring endoperoxide is the antimalarial artemisinin isolated from the leaves of *Artemisia annua*.[2−5] The endoperoxide motif is located in numerous other natural products and exhibits a wide variety of bioactivities including anticancer, antitumor, and antiviral properties.[6] The formation of endoperoxides is commonly accomplished by oxidations employing molecular oxygen.[7,8] Oxidations of β-dicarbonyls to generate peroxides[9] and endoperoxides[10−16] are also precedented, typically via oxidation of an enolate. Previous work involving enolate oxidations showed that subjecting α-substituted β-dicarbonyls **1** to catalytic Cu(II) under aerobic conditions resulted in α-keto ester **2** via oxidative deacylation (Scheme 1a).[17−20] Attempts to extend this oxidative cleavage to substituted Meldrum's acids **3** yielded the corresponding hydroperoxide **4** instead of the expected α-keto acid (Scheme 1b).[21] An important feature of that work was the compatibility of the reaction conditions with oxidation-sensitive functionality such as alkenes and alkynes. This finding enabled downstream transformations that utilized the elevated oxidation state of the enolate functionalization.

We were interested in testing the notion that other transformations could be developed under this general paradigm whereby molecular complexity is generated via straightforward carbon skeleton constructions followed by redox reactions that create the functional and stereochemical features.[22] In the ideal scenario, the oxidation and reduction operations would be mediated by green oxidants like O_2[23] and H_2.[24] A polyfunctional substrate such as keto triester **5** would permit us to test the relative rates of the previously validated deacylation and hydroperoxidation pathways. This letter provides details of a straightforward sequence for the *de novo* creation of highly substituted tetrahydrofurans that relies on an enabling chemoselective Cu(II)-catalyzed aerobic oxidation and sequential reductions of the resultant endoperoxides (Scheme 1c).

At the core of our reaction design was an interest in straightforward carbon skeleton buildup. The required Michael adducts **5** were obtained by treating Meldrum's acid alkylidene **7**

Scheme 1. Divergent Modes of Cu(II)-Catalyzed Aerobic Oxidations of β-Dicarbonyl Compounds



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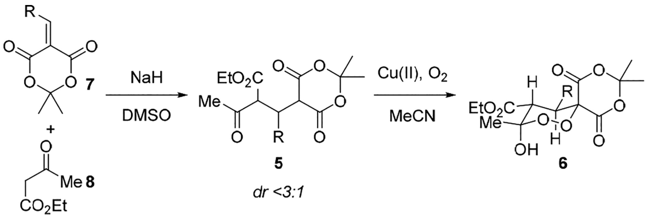
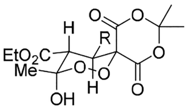
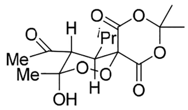
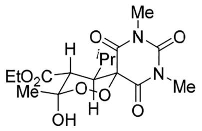
with the sodium enolate of ethyl acetoacetate (**8**).[25] Michael adducts **5** were chromatographically unstable, owing to a facile retro-Michael fragmentation on silica. To circumvent this instability, the unpurified adducts were used directly in the catalyzed oxidation step. Prior work validated that oxidation at either the Meldrum's acid C–H methine[21] or *β*-keto ester C–H methine[17] is possible; therefore, an open question was the possibility and degree of site selectivity. In the event, under aerobic copper catalysis, we observed complete site selectivity for Meldrum's acid oxidation over the acetoacetate moiety. The resultant hydroperoxide was readily trapped by the pendant ketone electrophile, furnishing endoperoxides **6** in moderate yields (Table 1). The process was amenable to both alkyl- and aryl-substituted Meldrum's acid derivatives (**6a**–**6e**), tolerating *ortho*-substituted aryl groups **6f**, albeit with diminished yields. Modest diastereoselectivity was observed in the local desymmetrization product **9** of 2,4-pentanedione-substituted Michael adduct. *N*-Methylated barbituric acid could be substituted for the Meldrum's acid, with no loss in efficiency of the oxidation.

Table 1. Michael Addition and Endoperoxidation of Meldrum's Acid Derivatives: Substrate Scope[a]

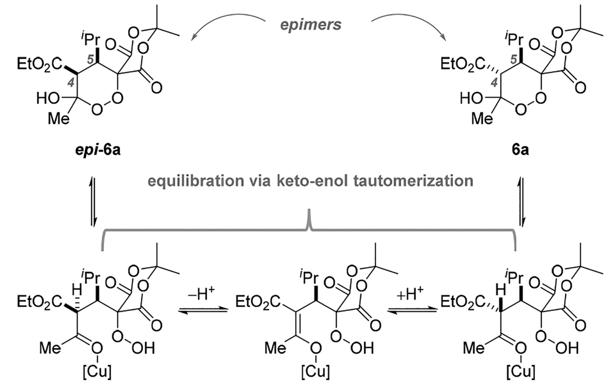


product			yield (%)[b]	dr[c]
	R = ^{i}Pr	**6a**	56	>20:1
	^{c}Pr	**6b**	70	>20:1
	^{c}Hex	**6c**	51	>20:1
	4-OMe-C$_6$H$_4$	**6d**	35	>20:1
	Ph	**6e**	42	>20:1
	2-Me-C$_6$H$_4$	**6f**	31	>20:1
	4-MeO$_2$C-C$_6$H$_4$	**6g**	56	>20:1
		**9**[d]	51	2.1:1
		**10**[e]	70	7.9:1

[a] 1.15 equiv of NaH, 1.2 equiv of dicarbonyl, [**7**]$_0$ = 0.35 M. Cu(NO$_3$)$_2$·3H$_2$O (20 mol %), 1 atm O$_2$, [**5**]$_0$ = 0.1 M, 0 °C to rt. [b] Isolated yields over two steps. [c] Diastereomeric ratio (dr) reported after silica gel chromatography. [d] 2,4-pentanedione used in place of **8**. [e] *N*,*N*-dimethylbarbituric acid alkylidene used in place of **7**.

Michael adducts **5** are formed with negligible diastereocontrol, while the derived endoperoxides **6** are isolated with high diastereomeric purity as a result of apparent stereochemical convergence. Scheme 2 depicts a proposal for this stereochemical correction. Hemiketalization is presumed to be reversible and in the open chain form the *β*-keto ester engenders considerable acidity to the methine C–H bond. Enolization would facilitate interconversion of the diastereomeric open chain forms. An ultimate thermodynamic preference for the bis(equatorial) disposition of the C4 and C5 substituents in the hemiketal would drive the final observed preference.

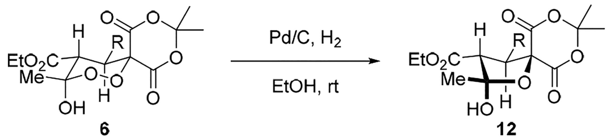
Scheme 2. Proposed Rationale for Diastereoselectivity

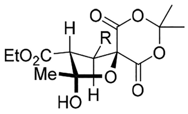
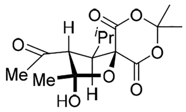
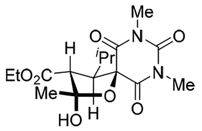


Due to their reactive nature, organic peroxides often require special consideration when handling.[26] Meldrum's acid hydroperoxides (e.g., **4**) decompose rapidly at a low onset temperature upon subjection to thermogravimetric analysis;[21] however, this phenomenon was not seen with the related endoperoxides **6**, **9**, and **10**. These compounds are bench-stable and exhibit significant thermal stability (see the Supporting Information (SI)).

Endoperoxides **6** undergo catalyzed hydrogenolysis[27] yielding spirocyclic hemiketals **12** in good yields (Table 2). Both alkyl and aryl substrates tolerated these conditions, albeit with some variability in diastereomer ratio at the anomeric center. An endoperoxide with an electron deficient arene (**6g**) was not tolerated in the hydrogenolysis; those trials resulted in substrate decomposition. The hydrogenolysis was also amenable to the acyl and barbituric acid substrates **9** and **10**, providing the respective lactol products **13** and **14** in high yields.

Table 2. Hydrogenolysis of Endoperoxides: Substrate Scope[a]

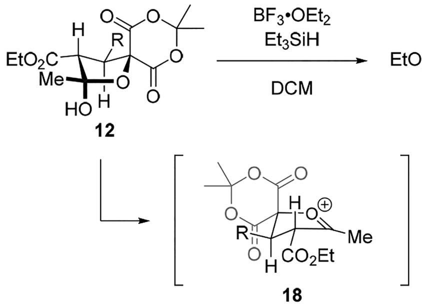


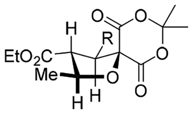
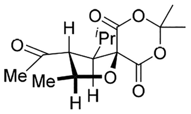
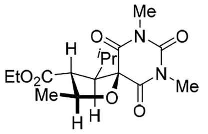
product			yield (%)[b]	dr[c]
	R = ^{i}Pr	**12a**	55	5.0:1
	^{c}Pr	**12b**	79	5.6:1
	^{c}Hex	**12c**	70	10:1
	4-OMe-C$_6$H$_4$	**12d**	62	>20:1
	Ph	**12e**	51	4.2:1
		**13**	88	2.9:1
		**14**	91	9.4:1

[a] 100 mg Pd/C per mmol **6**, 1 atm H$_2$, [**6**]$_0$ = 0.1 M. [b] Isolated yield. [c] Diastereomer ratio at the acetal center.

Subsequent Lewis acid mediated ionic reduction[28,29] of hemiketals **12** furnished spirocyclic tetrahydrofurans **15** in high diastereoselectivity in most cases (Table 3). The presumed intervention of a C2 oxocarbenium ion meant that the anomer ratio of the starting material input was irrelevant for the observed product diastereomer ratio; diastereoconvergence was again observed. The relative stereochemistry was confirmed by obtaining crystal structures of compounds **15a**, **15c**, and **16** (see SI), and the remainder were assigned by analogy.[30] The stereochemistry of these compounds conform to the model of nucleophilic attack "inside" the envelope of oxocarbenium ion **18**, generating the staggered product as proposed by Woerpel.[31]

Table 3. Ionic Reduction of Hemiketals: Substrate Scope[a]



product			yield (%)[b]	dr
	R = ^{i}Pr	**15a**	85	>20:1
	^{c}Pr	**15b**	44	>20:1
	^{c}Hex	**15c**	74	>20:1
	4-OMe-C_6H_4	**15d**	25	5.1:1
	Ph	**15e**	55	>20:1
		**16**	85	>20:1
		**17**	91	>20:1

[a] $BF_3 \cdot OEt_2$ (5.34 equiv), Et_3SiH (10 equiv), $[\mathbf{12}]_0 = 0.1$ M, 0 °C, 30 min. [b] Isolated yield.

In summary, a simple protocol for the preparation of spirocyclic endoperoxides has been established through the aerobic oxidation of substituted Meldrum's acid derivatives. The strategy utilizes nearly every atom of the stoichiometric inputs, all of which are cheap, readily available feedstock materials. Two subsequent reductions provided highly substituted tetrahydrofurans in diastereomerically pure form. The productive merger of straightforward carbon skeletal assembly with downstream complexity-building redox editing represents an attractive tactic for the generation of polyfunctional structures.[32]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01225.

X-ray data of **15a** (CIF), **15c** (CIF), and **16** (CIF)

Experimental procedures and spectroscopic data for all new compounds; general experimental procedures; 1D NMR data; HR ESI-MS and IR data of new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jsj@unc.edu

ORCID

Jeffrey S. Johnson: 0000-0001-8882-9881

Notes

The authors declare no competing financial interest.

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