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Manganese(III)-Mediated Transformations of Phloroglucinols: A Formal Oxidative [4 + 2] Cycloaddition Leading to Bicyclo[2.2.2]octadiones

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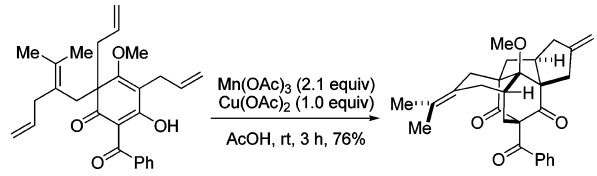
ABSTRACT



Manganese(III)-mediated oxidative transformations of dearomatized phloroglucinol (1,3,5-trihydroxybenzene) derivatives are reported. A number of cyclization modes have been observed, including polycyclization to afford bicyclo[2.2.2]octadiones via a formal oxidative radical [4 + 2] cycloaddition.

Oxidative transformations involving an enolized carbonyl moiety have significantly attracted the attention of synthetic chemists. Metal ions such as Mn(III), Cu(II), Fe(III), and Ce(IV) are well-known for their potential to extract electrons from electron-rich enols and enolates generally resulting in the formation of an electrophilic α-carbonyl radical. This general reactivity has found numerous synthetic applications. Examples include Mn(III)-mediated oxidative free radical cyclizations,[1] Mn(III)-mediated cycloadditions,[2] α-acetoxylation[3] and arylation,[1b,4] and Fe(III)- or Cu(II)-mediated enolate hetero-[5] and homocoupling.[6] Some of these methods have found use in the synthesis of complex natural product targets and medicinal agents.[7] Mn(III)-based oxidative radical cyclizations of carbonyl compounds onto unactivated olefins, extensively studied by Snider and others,[1,8] are particularly attractive for their potential to rapidly generate molecular complexity.

Our laboratory has a continuing interest in dearomatization of electron-rich aromatic compounds in the synthesis of

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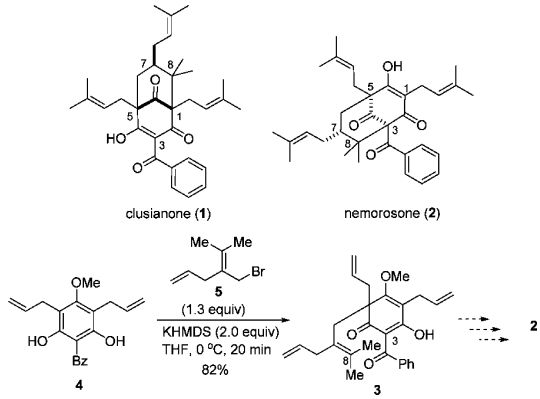
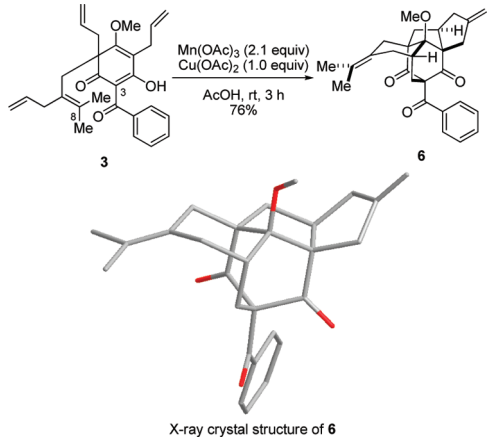
bioactive natural products. For example, we have developed synthetic approaches to polyprenylated acylphloroglucinol natural products[9] via alkylative dearomatization/annulation of phloroglucinol (1,3,5-trihydroxybenzene) derivatives. Along these lines, we have reported the synthesis of (±)-clusianone (**1**)[10] employing a Michael addition/elimination/Michael addition cascade for rapid assembly of the bicyclo[3.3.1]nonane core.[11] In studies aimed at developing a related approach to the regioisomeric natural product nemorosone (**2**),[12] tetraene precursor **3** was prepared via alkylative dearomatization of **4** with allylic bromide **5** (Scheme 1).[13] With the aim of effecting the desired C3−C8

Scheme 1

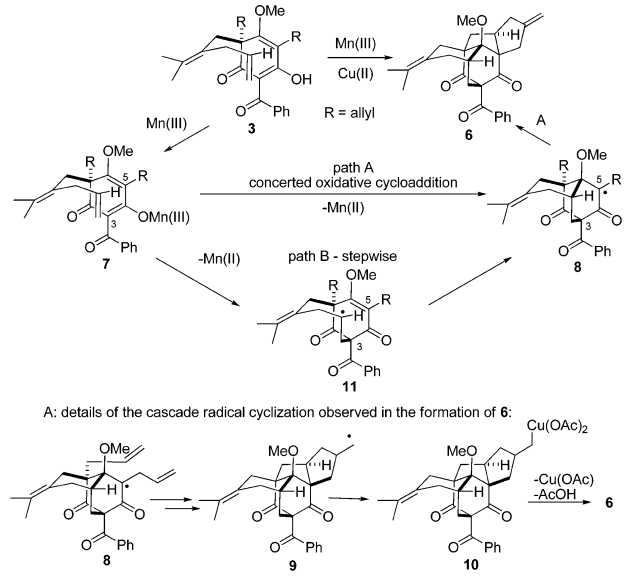


bond formation (nemorosone numbering) via an oxidative generation of a radical at C3 and subsequent cyclization onto the tetrasubstituted olefin,[14] we examined the reactivity of **3** in the presence of metal oxidants. It was serendipitously found that treatment of **3** with $Mn(OAc)_3$ (2.1 equiv) and $Cu(OAc)_2$ (1.0 equiv) in AcOH at rt led to formation of the bridged pentacyclic compound **6** in 76% yield as a single isolable product (Scheme 2). The structure of **6** was unambiguously confirmed by X-ray crystallography.[13]

Scheme 2



Scheme 3



A proposed mechanism rationalizing the formation of **6** is outlined in Scheme 3. Formation of Mn(III) enolate **7** is likely a facile and reversible process as **3** already exists in the enol form.[15] Next, an overall [4 + 2] cycloaddition may occur leading to bicyclo[2.2.2]octadione **8** and a radical at C5. A cascade of two 5-*exo* radical cyclizations of intermediate **8** via the sequence outlined in Scheme 3 then results in cyclopentanemethyl radical **9** which reacts with Cu(II) to give a Cu(III) intermediate **10**.[16] Finally, loss of AcOH and Cu(OAc) affords polycycle **6**. The most intriguing aspect of this cascade cyclization is the initial [4 + 2]-cycloaddition event which may be envisioned to occur in a concerted manner (path A) or a stepwise cascade radical cyclization (path B). The latter would proceed via an 8-*endo* cyclization to intermediate **11**. Early studies by Snider have shown a similar preference for 8-*endo* cyclization in acyclic acetoacetate systems.[1e,17] While oxidative conditions have been used to promote formal [4 + 2] cycloadditions,[18] to our knowledge this is the first example of a Mn(III)/Cu(II)-mediated [4 +

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(13) See the Supporting Information for complete experimental details.
(14) For previous use of Mn(III)-based oxidative cyclization toward phloroglucinol natural products, see: Kraus, G. A.; Dneprovskaia, E.; Nguyen, T. H.; Jeon, I. *Tetrahedron* **2003**, *59*, 8975.
(15) In the ^{1}H NMR spectra of dearomatized benzoylphloroglucinol derivatives such as **3**, the enolic hydrogen appears in the far downfield region (16−18 ppm) suggesting complete enolization. The compound exists as a mixture of two enol tautomers. See ref 1a,d for a discussion on the mechanistic details of Mn(III)-based oxidations of 1,3-dicarbonyl compounds.
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(17) Snider, B. B.; Merrit, J. E. *Tetrahedron* **1991**, *47*, 8663.
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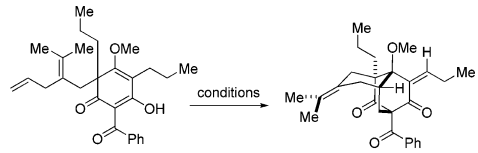
2] cycloaddition process. Moreover, the central bicyclo[2.2.2]-octanone core is present in numerous bioactive natural products.[19] These considerations prompted further studies on this transformation.

To examine the unique cycloaddition event without interference from subsequent tandem radical cyclization, we prepared precursor **12** bearing *n*-propyl groups on the phloroglucinol core (Table 1). Treatment of **12** under identical reaction conditions ($Mn(OAc)_3$ (2.1 equiv), $Cu(OAc)_2$ (1 equiv), AcOH, rt) led to formation of the bridged tricyclic enone **13** in 66% yield as a 5:1 mixture of *Z* and *E* isomers (Table 1, entry 1). Employment of 1 equiv

Table 1. Conditions for Oxidative Cycloaddition of **12**



12 **13**

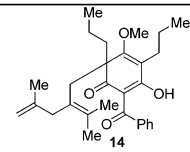
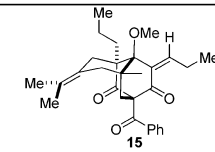
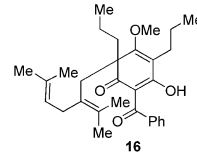
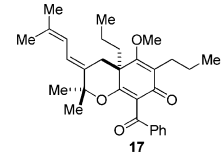
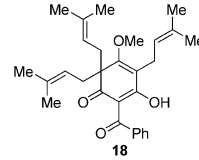
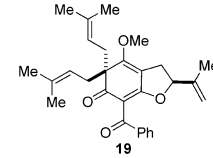
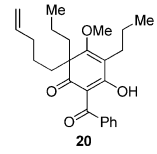
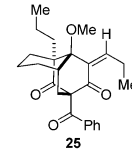
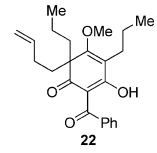
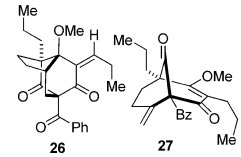
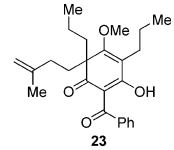
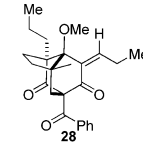
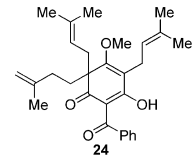
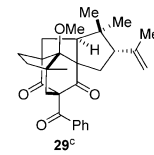
entry	oxidant (equiv)[a]	solvent	time (h)	% yield
	$Mn(OAc)_3$ (2.1)	AcOH	4	66[b]
1	$Cu(OAc)_2$ (1.0)			
	$Mn(OAc)_3$ (1.0)	AcOH	6	31[d]
2	$Cu(OAc)_2$ (1.0)			
3	$Mn(OAc)_3$ (2.1)	AcOH	16	trace[c]
4	$Cu(OAc)_2$ (1.0)	AcOH	16	*d*
5	$Mn(OAc)_3$ (0.1)	AcOH	16	trace[d]
	$Mn(OAc)_3$ (2.1)	THF	16	*c*
6	$Cu(OAc)_2$ (1.0)			
	$Mn(OAc)_3$ (2.1)	MeCN	16	*c*
7	$Cu(OAc)_2$ (1.0)			
8	$Ce(NH_4)_2(NO_3)_6$ (2.0)	MeCN	3	*e*
9	$PhI(OAc)_2$ (1.2)	MeCN	16	NR[d]

[a] All reactions were carried out at ambient temperature except where noted; $Mn(OAc)_3 \cdot 2H_2O$ and $Cu(OAc)_2 \cdot H_2O$ were used. [b] Isolated as a 5:1 mixture of olefin isomers (^1H NMR). [c] Slow decomposition of the starting material occurred. [d] Starting material was recovered unreacted. [e] Reaction performed at −20 °C and resulted in a complex mixture of products.

of $Mn(OAc)_3$ led to incomplete reaction (entry 2). Omission of $Cu(OAc)_2$ led to slow decomposition of the starting material (entry 3), suggesting that Cu(II) may be required in the terminating oxidative elimination step. It was found that Cu(II) alone does not promote the cycloaddition (entry 4). Attempts to use a catalytic amount of $Mn(OAc)_3$ in the absence of Cu(II) provided only trace amounts of product **13** (entry 5). It was also found that the reaction was not compatible with nonprotic solvents (THF, MeCN) in accordance with previous observations made by Snider and co-workers.[1e] A limited number of other metal oxidants were also tested. Use of $Ce(NH_4)_2(NO_3)_6$ in CH_3CN resulted in a complex mixture of products,[20] whereas $PhI(OAc)_2$ as an oxidant resulted in no reaction (entries 8 and 9).

Next, we examined the scope of the oxidative [4 + 2] cycloaddition on a series of phloroglucinol substrates (Table 2). Oxidation of 2,2-disubstituted alkene substrate **14** (entry 1) resulted in clean conversion to cycloadduct **15** in 82% yield (>10: 1 mixture of *Z*/*E* isomers). When a terminally disubstituted olefin **16** was employed (entry 2), the cycload-

Table 2. Scope of the Mn(III)-Mediated Cycloaddition[a]

entry	substrate	Products	% yield
1	 **14**	 **15**	82 *Z*/*E* > 10:1
2	 **16**	 **17**	70
3[a]	 **18**	 **19**	76
4[b]	 **20**	 **25**	72
5	 **22**	 **26** **27**	**26** (23) **27** (60)
6	 **23**	 **28**	69
7	 **24**	 **29**[c]	74

[a] Reaction conditions: $Mn(OAc)_3 \cdot 2H_2O$ (2.1 equiv), $Cu(OAc)_2 \cdot H_2O$ (1.0 equiv), AcOH, rt, 4 h. (a) Reaction performed at 65 °C for 15 min. (b) Reaction performed at 35 °C for 4 h. (c) dr = 4:1 (major diastereomer shown).

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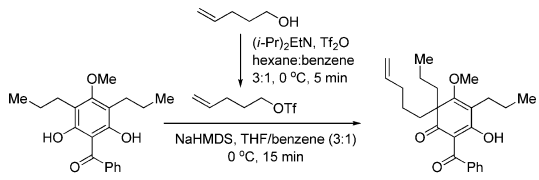
(20) These products appear to result from multiple cyclization modes onto the tetrasubstituted olefin (O vs C, *6-endo* vs *5-exo*).

dition pathway was replaced by *O*-cyclization onto the proximal tetrasubstituted olefin resulting in diene **17**. A related 5-*exo* *O*-cyclization was observed with the triprenylated phloroglucinol derivative **18** affording dihydrofuran **19** in 76% yield (entry 3). It was reasoned that the unique cycloaddition reactivity observed in substrates **3**, **12**, and **14** may be facilitated by conformational constraints imposed by the tetrasubstituted olefin in the tether placing the terminal alkene close to the reactive enol. To access substrate **20** that does not contain a constraining element, a protocol for alkylative dearomatization of phloroglucinol derivative **21** with the freshly prepared triflate of 4-penten-1-ol was developed (Scheme 4).[21] This procedure was used to prepare three additional nonallylic derivatives (**22**−**24**, Table 2).[13]

Scheme 4



As expected, precursor **20** reacted much slower at rt (~20% yield of **25** after 16 h at rt); however, only mild heating at 35 °C led to the production of cycloadduct **25** in 72% yield (Table 2, entry 4).[22] Reducing the tether length by one carbon as in **22** resulted in only 23% isolated yield of cycloaddition product **26**. The major product of this reaction was bicyclo[3.3.1]nonane **27** (60%) resulting from a *6-exo* cyclization onto the olefin (entry 5).[14] However, by using a 2,2-disubstituted olefin, the cycloaddition mode of reactivity was fully restored as substrate **23** afforded bicyclo[2.2.2]octadione **28** as a single product in 69% yield (entry 6). Similar reactivity was observed using diprenylated substrate **24** leading to a cascade reaction to afford pentacycle **29** in 74% yield as a 3: 1 mixture of epimers (entry 7).[13] The bicyclo[3.3.0]octane portion of **29** resembles the acylphloroglucinol natural products ialibinones A-D.[23]

In conclusion, we have examined the reactivity of a number of dearomatized acylphloroglucinol derivatives under Mn(III)/Cu(II)-mediated oxidative radical conditions. It is evident that a number of modes of cyclization are possible (cycloaddition, O-cyclization, C-cyclization) and that the reaction outcome is strongly influenced by the substitution pattern of the olefin and the tether. A novel mode of oxidative [4 + 2] cycloaddition was observed leading to a rapid increase of molecular complexity via cascade radical cyclizations. Further studies aimed at extending the scope and utility of this transformation are ongoing and will be reported in future publications.

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Supporting Information Available: Detailed experimental procedures and spectral data for all compounds. X-ray crystal structure coordinates and files in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) Attempts to use non-allylic bromides led to low reactivity mainly resulting in alkylation of the phenolic oxygens. The alkyl triflate was prepared using a modified literature procedure: Bashore, C. G.; Vetelino, M. G.; Wirtz, M. C.; Brooks, P. R.; Frost, H. N.; McDermott, R. E.; Whritenour, D. C.; Ragan, J. A.; Rutherford, J. L.; Makowski, T. W.; Brenek, S. J.; Coe, J. W. *Org. Lett.* **2006**, *8*, 5947.

(22) Enones **25**, **26**, and **28** were isolated as a single (*Z*) isomer (^{1}H NMR).

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