

Published in final edited form as:

Org Lett. 2009 June 4; 11(11): 2285–2288. doi:10.1021/ol900590t.

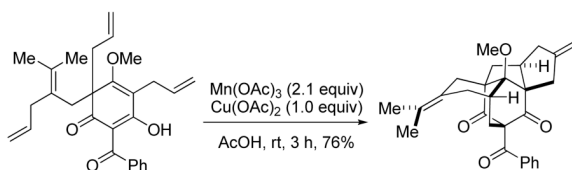
Manganese(III)-Mediated Transformations of Phloroglucinols: A Formal Oxidative [4+2] Cycloaddition Leading to Bicyclo[2.2.2]octadiones

Branko Mitasev and John A. Porco Jr

Department of Chemistry and Center for Chemical Methodology and Library Development (CMLD-BU), Boston University, Boston, Massachusetts 02215

Branko Mitasev ; John A. Porco: porco@bu.edu

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 -acetoxylation³ 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 bioactive natural products. For example, we have developed synthetic approaches to polyprenylated acylphloroglucinol natural products⁹ *via* alkylative dearomatization/annulation of phloroglucinol (1,3,5-trihydroxybenzene) derivatives. Along these lines, we have reported the synthesis of (\pm)-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 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), 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

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.^{17,1e} 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+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. 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 one equivalent 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), thus 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 coworkers.^{1e} A limited number of other metal oxidants were also tested. Use of Ce(NH₄)₂(NO₃)₆ in CH₃CN 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 cycloaddition 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 non-allylic derivatives (**22–24**, Table 2).¹³

As expected, precursor **20** reacted much slower at rt (~20% yield of **25** after 16h 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

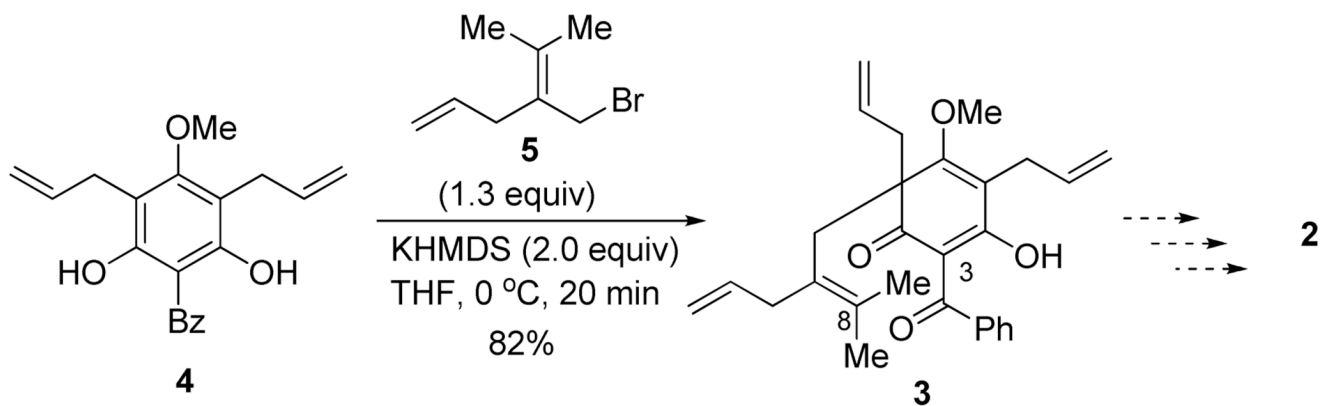
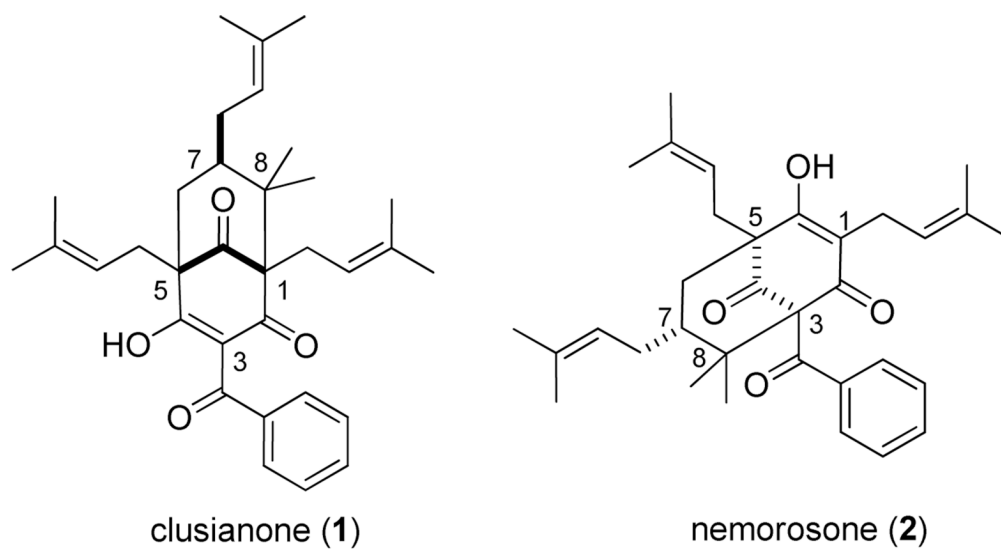
Acknowledgment

Financial support from the NIH (GM073855), Eisai, Merck, and Wyeth is gratefully acknowledged. We thank Prof. Barry Snider (Brandeis University), Ji Qi, and Qiang Zhang (Boston University) for helpful discussions and Dr. Emil Lobkovsky (Cornell University) for x-ray crystallographic analysis.

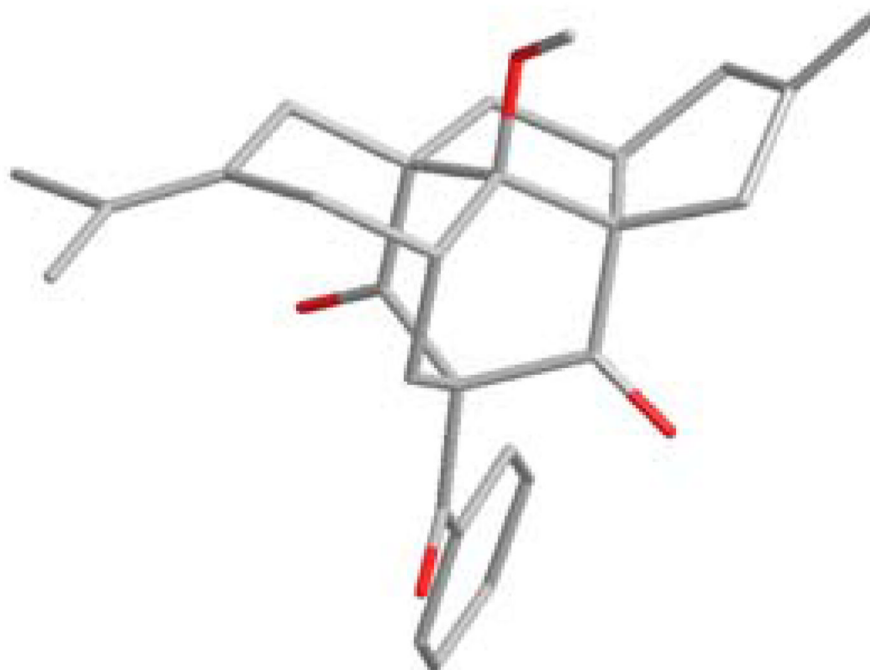
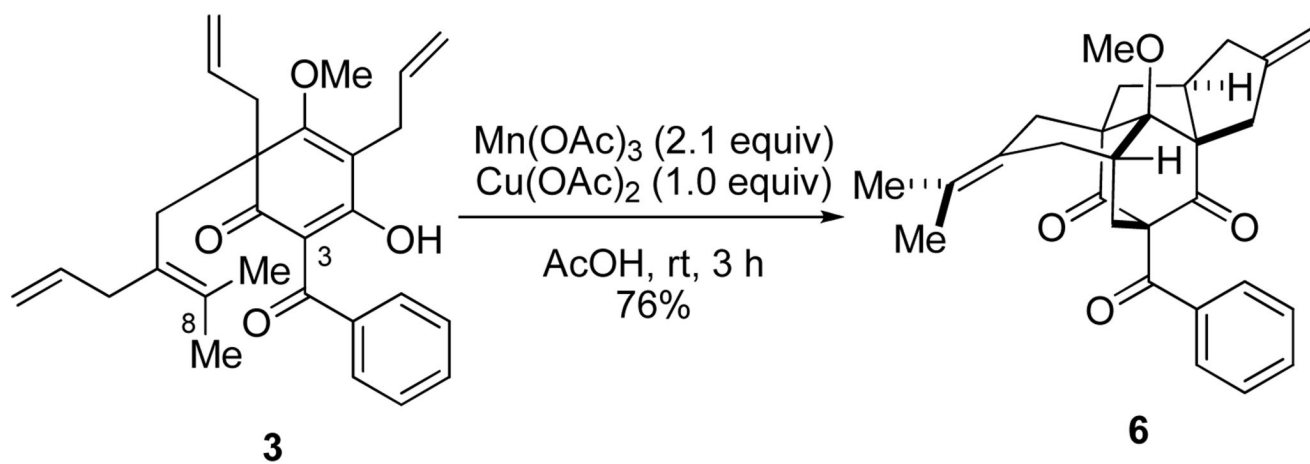
References

1. (a) Snider BB, Patricia JJ, Kates SA. *J. Org. Chem* 1988;53:2137. (b) Kates SA, Dombroski MA, Snider BB. *J. Org. Chem* 1990;55:2425. (c) Snider BB, McCarthy BA. *J. Org. Chem* 1993;58:6217. (d) Snider BB. *Chem. Rev* 1996;96:339. [PubMed: 11848756] (e) Cole BM, Han L, Snider BB. *J. Org. Chem* 1996;61:7832. [PubMed: 11667741]
2. (a) Melikyan GG. *Synthesis* 1993:833. (b) Mellor JM, Mohammed S. *Tetrahedron* 1993;49:7557. (c) Snider BB, Han L, Xie C. *J. Org. Chem* 1997;62:6978. (d) Chowdhury FA, Nishino H, Kurosawa K. *Tetrahedron Lett* 1998;39:7931. (e) Tsai A-I, Lin C-H, Chuang C-P. *Heterocycles* 2005;65:2381.
3. (a) Williams GJ, Hunter NR. *Can. J. Chem* 1976;54:3830. (b) Dunlap NK, Sabol MR, Watt DS. *Tetrahedron Lett* 1984;25:5839. (c) Gross RS, Kawada K, Kim M, Watt DS. *Synth. Commun* 1989;19:1127. (d) Tanyeli C, Sezen B, Iyigun C, Elmali O. *Tetrahedron Lett* 2001;42:6397.
4. Bhowmik DR, Venkateswaran RV. *Tetrahedron Lett* 1999;40:7439.
5. (a) Baran PS, DeMartino MP. *Angew. Chem. Int. Ed* 2006;45:7083. (b) DeMartino MP, Chen K, Baran PS. *J. Am. Chem. Soc* 2008;130:11546. [PubMed: 18680297]
6. (a) Rathke MW, Lindert A. *J. Am. Chem. Soc* 1971;93:4605. (b) Ito Y, Konoike T, Saegusa T. *J. Am. Chem. Soc* 1975;97:2912. (c) Frazier RH Jr, Harlow RL. *J. Org. Chem* 1980;45:5408–5411.
7. (a) Pettus TRR, Inoue M, Chen XT, Danishefsky SJ. *J. Am. Chem. Soc* 2000;122:6160. (b) Snider BB, Mohan R, Kates SA. *J. Org. Chem* 1985;50:3659. (c) Paquette LA, Schaefer AG, Springer JP. *Tetrahedron* 1987;43:5567. (d) Nicolaou KC, Gray DLF. *J. Am. Chem. Soc* 2004;126:607. [PubMed: 14719960] (e) Baran PS, Richter JM, Lin DW. *Angew. Chem., Int. Ed* 2005;44:609.
8. (a) Corey EJ, Kang MC. *J. Am. Chem. Soc* 1984;106:5384. (b) Ernst AB, Fristad WE. *Tetrahedron Lett* 1985;26:3761. (c) Yang D, Ye X-Y, Gu S, Xu M. *J. Am. Chem. Soc* 1999;121:5579.
9. Ciochina R, Grossman RB. *Chem. Rev* 2006;106:3963. [PubMed: 16967926]
10. Mccandlish LE, Hanson JC, Stout GH. *Acta Cryst* 1976;B32:1793.
11. Qi J, Porco JA Jr. *J. Am. Chem. Soc* 2007;129:12682. [PubMed: 17902679]

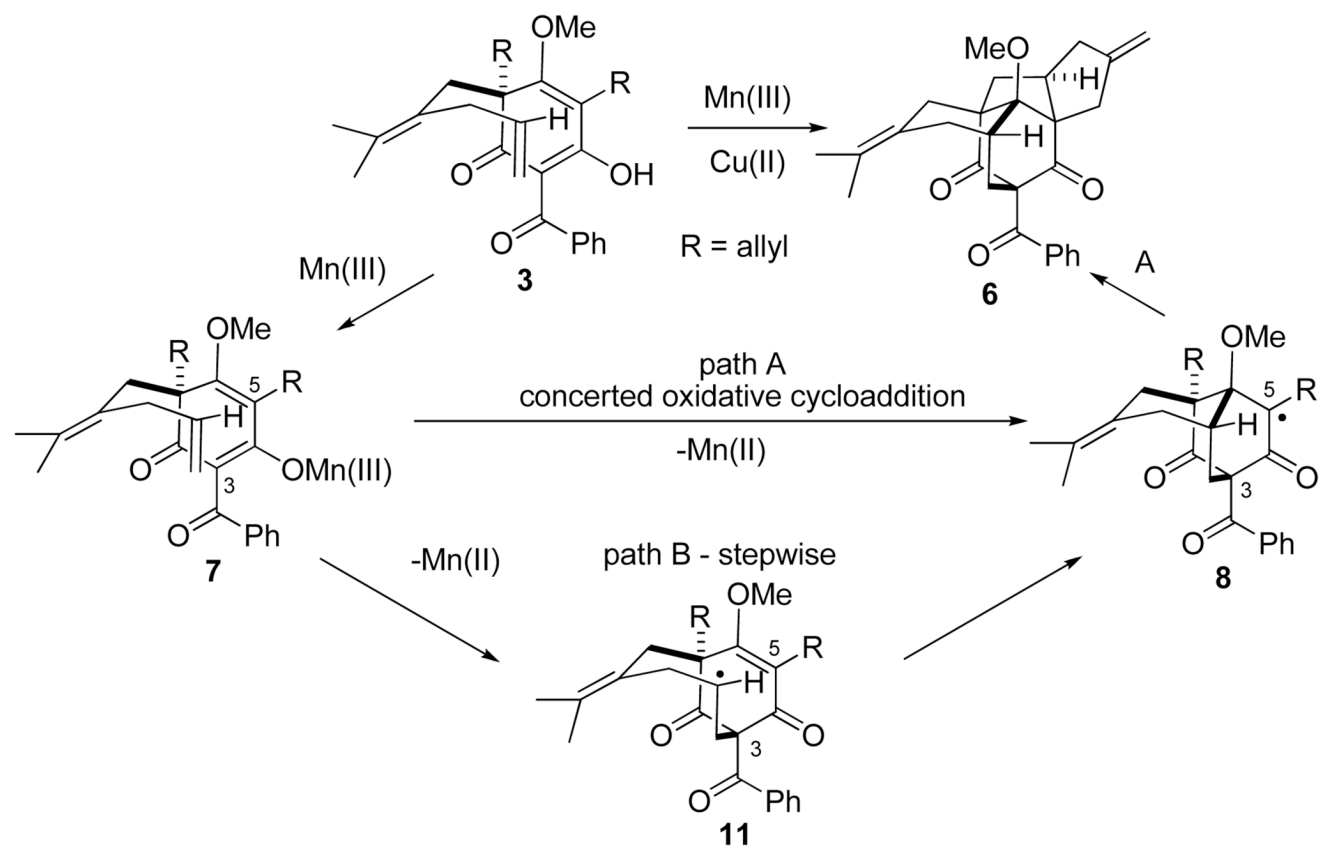
12. Cuesta-Rubio O, Velez-Castro H, Frontana-Uribe BA, Cardenas J. *Phytochemistry* 2001;57:279. [PubMed: 11382245]
13. See Supporting Information for complete experimental details.
14. For previous use of Mn(III)-based oxidative cyclization towards phloroglucinol natural products, see: Kraus GA, Dneprovskaja E, Nguyen TH, Jeon I. *Tetrahedron* 2003;59:8975. [PubMed: 16971963]
15. In the ^1H 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 references 1a and 1d for a discussion on the mechanistic details of Mn(III)-based oxidations of 1,3-dicarbonyl compounds.
16. Kochi, JK. *Free Radicals*. Kochi, JK., editor. Vol. 1. New York: Wiley; 1973. (b) Kochi JK. *Acc. Chem. Res* 1974;7:351.
17. Snider BB, Merrit JE. *Tetrahedron* 1991;47:8663.
18. (a) Yueh W, Bauld NLJ. *Phys. Org. Chem* 1996;9:529. (b) Gao D, Bauld NL. *J. Org. Chem* 2000;65:6276. [PubMed: 10987978] (c) Zhou Y, Jia X, Li R, Liu Z, Liu Z, Wu L. *Tetrahedron Lett* 2005;45:8937.
19. (a) Carman RM, Lambert LK, Robinson WT, Van Dongen JMAM. *Aust. J. Chem* 1986;39:1843. (b) Bringmann G, Lang G, Gulder TAM, Tsuruta H, Mühlbacher J, Maksimenka K, Steffens S, Schaumann K, Stöhr R, Wiese J, Imhoff JF, Perović-Ottstadt S, Boreiko O, Müller WEG. *Tetrahedron* 2005;61:7252. (c) Chien S-C, Chang J-Y, Kuo C-C, Hsieh C-C, Yang N-S, Kuo Y-H. *Tetrahedron Lett* 2007;48:1567.
20. These products appear to result from multiple cyclization modes onto the tetrasubstituted olefin (O vs C, 6-endo vs 5-exo).
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 CG, Vetelino MG, Wirtz MC, Brooks PR, Frost HN, McDermott RE, Whritenour DC, Ragan JA, Rutherford JL, Makowski TW, Brenek SJ, Coe JW. *Org. Lett* 2006;8:5947. [PubMed: 17165901]
22. Enones **25**, **26**, and **28** were isolated as a single (*Z*) isomer (^1H NMR).
23. Winkelmann K, Heilmann J, Zerbe O, Rali T, Sticher O. *J. Nat. Prod* 2000;63:104. [PubMed: 10650088]



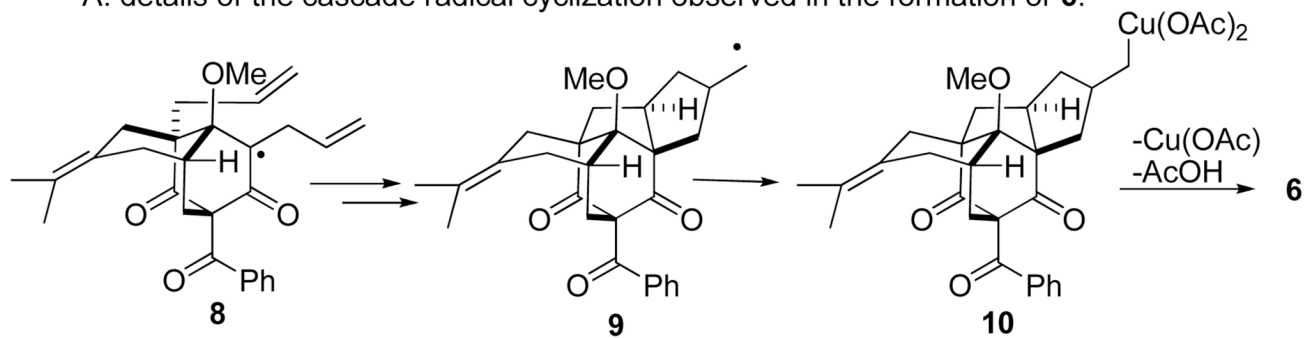
Scheme 1.

X-ray crystal structure of **6**

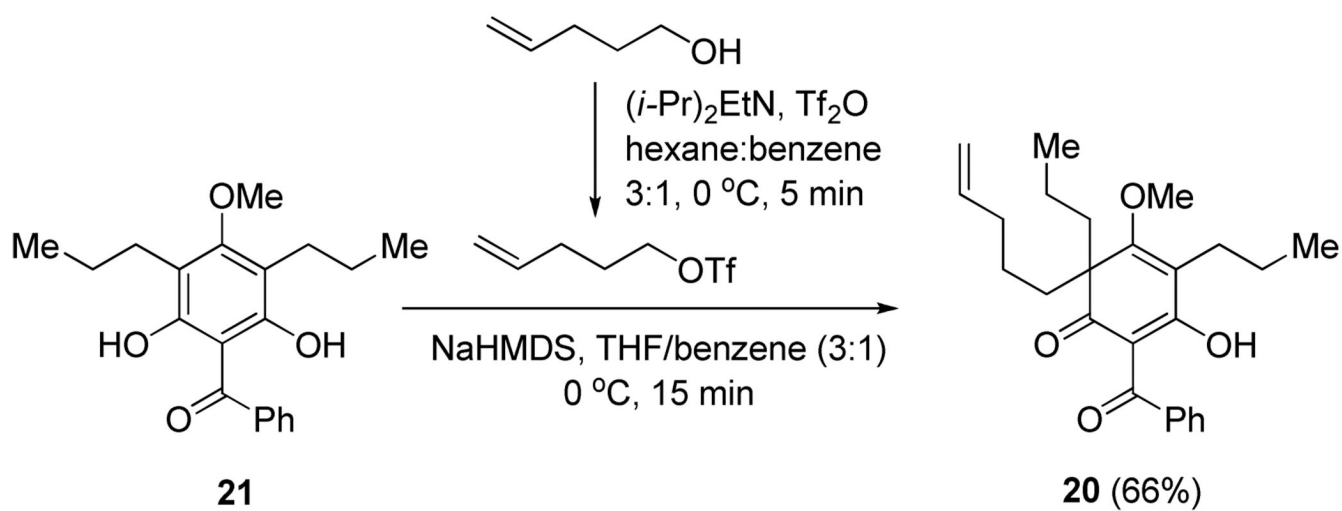
Scheme 2.



A: details of the cascade radical cyclization observed in the formation of **6**:

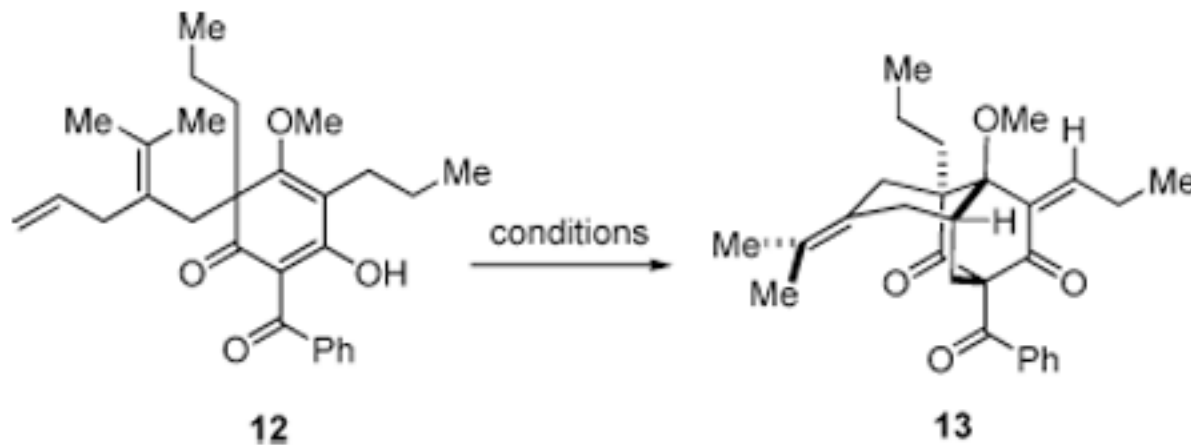


Scheme 3.



Scheme 4.

Table 1

Conditions for oxidative cycloaddition of **12**.

entry	oxidant (equiv) ^a	solvent	time (h)	% yield
1	Mn(OAc) ₃ (2.1) Cu(OAc) ₂ (1.0)	AcOH	4	66 ^b
2	Mn(OAc) ₃ (1.0) Cu(OAc) ₂ (1.0)	AcOH	6	31 ^d
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
6	Mn(OAc) ₃ (2.1) Cu(OAc) ₂ (1.0)	THF	16	-- ^c
7	Mn(OAc) ₃ (2.1) Cu(OAc) ₂ (1.0)	MeCN	16	-- ^c
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 when noted; Mn(OAc)₃·2H₂O, and Cu(OAc)₂·H₂O were used;

^b Isolated as a 5:1 mixture of olefin isomers (¹H NMR);

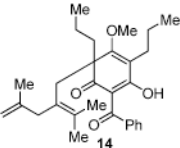
^c Slow decomposition of the starting material occurred.

^d Starting material was recovered unreacted.

^e Reaction performed at -20 °C and resulted in a complex mixture of products.

Table 2

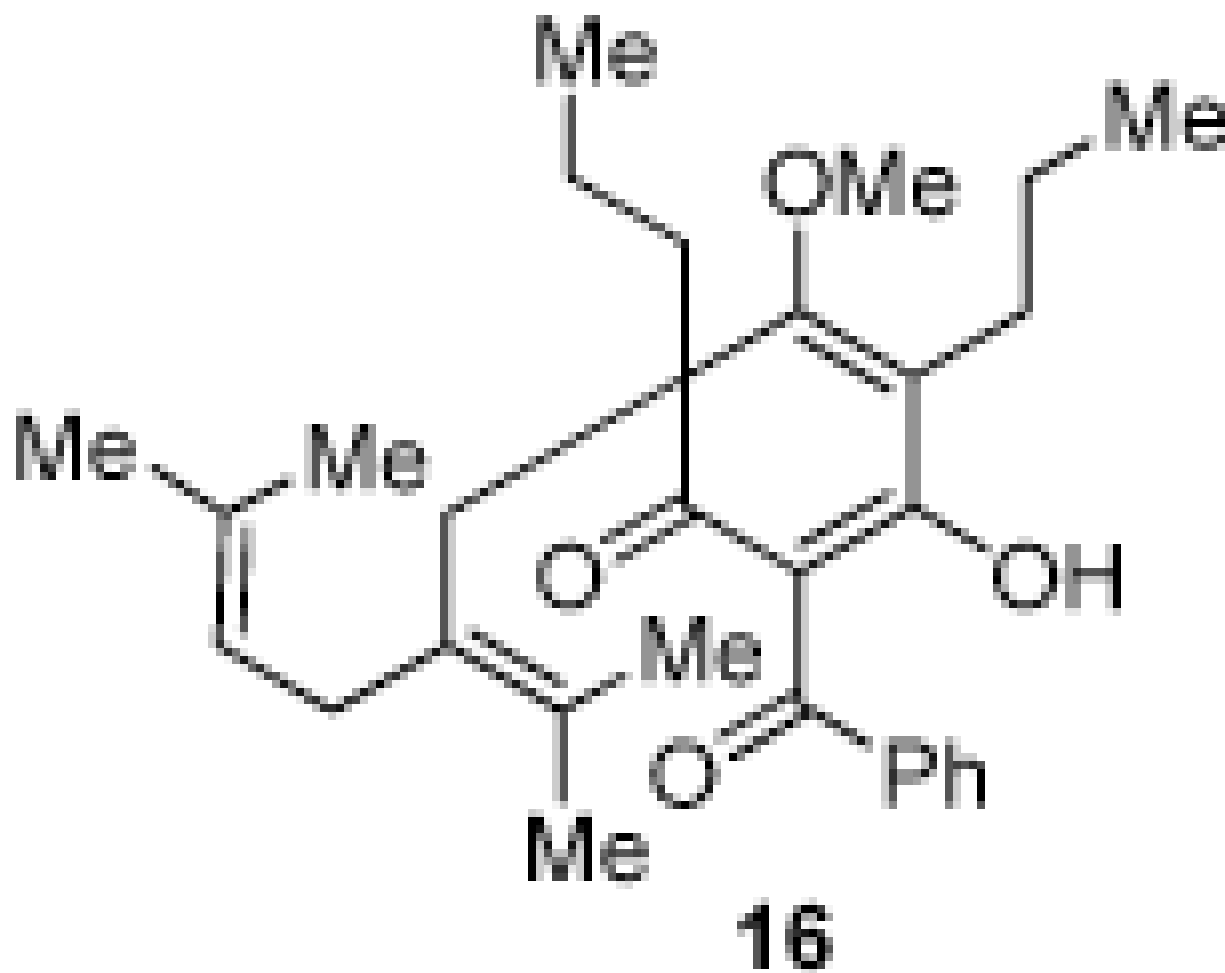
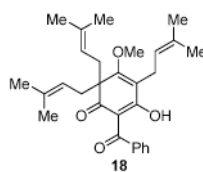
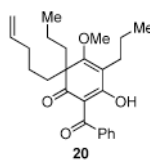
Scope of the Mn(III)-mediated cycloaddition

entry	substrate
1	 <p>The chemical structure of substrate 14 is a complex polycyclic molecule. It features a central ring system with several substituents: a methyl group (Me) at the top, a methoxy group (OMe) and another methyl group (Me) on the right side, a hydroxyl group (OH) below the OMe group, a phenyl group (Ph) at the bottom right, and a methyl group (Me) at the bottom. A side chain on the left consists of a methyl group (Me) attached to a carbon that is also bonded to a double bond and a ring oxygen atom. The number 14 is printed below the structure.</p>

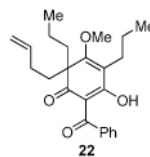
entry

substrate

2

3^a4^b

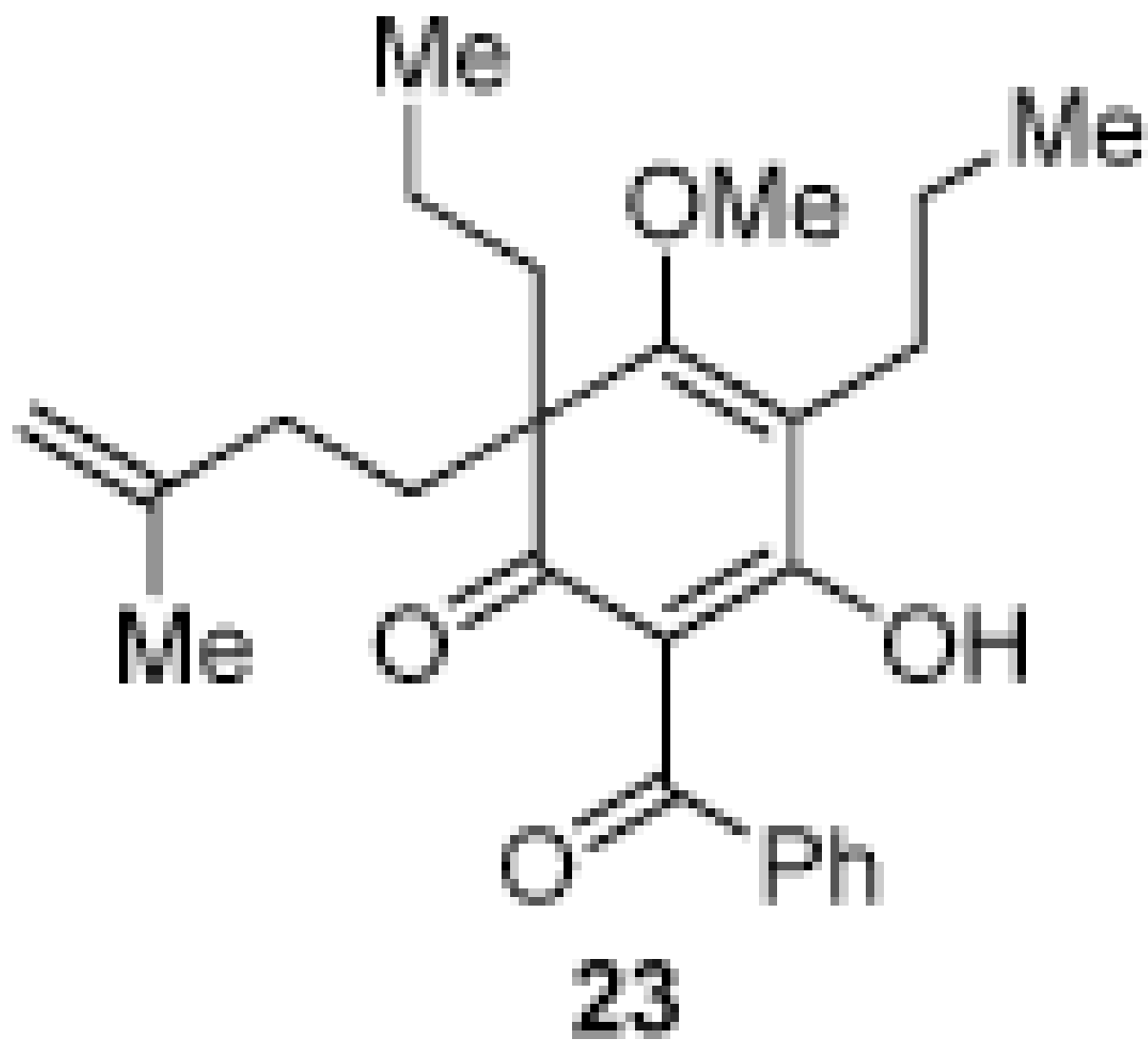
5



entry

substrate

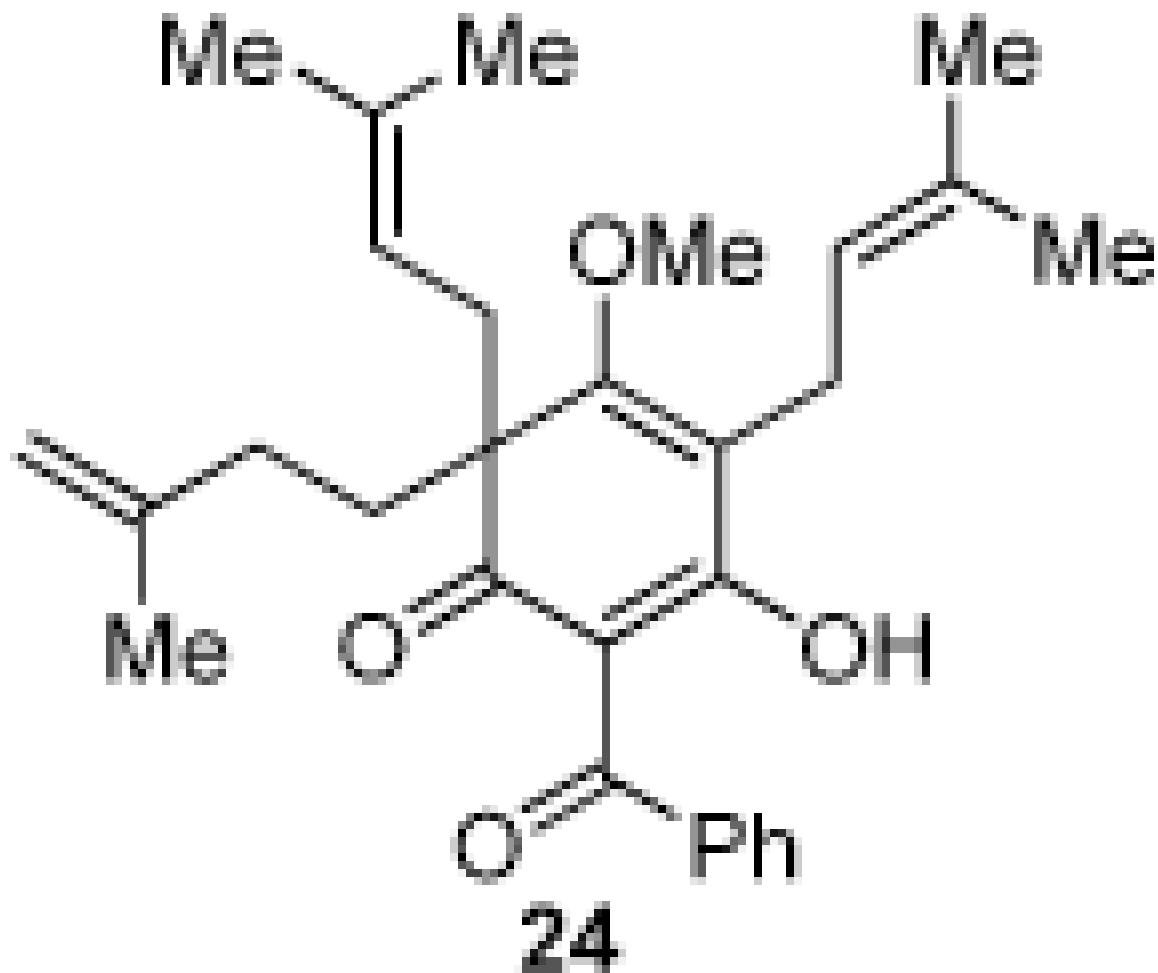
6



entry

substrate

7



Reaction conditions: $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ (2.1 equiv), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (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).