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Mn(OAc)₃ catalyzed intermolecular oxidative peroxycyclization of naphthoquinone†

 Alex Meye Biyogo,^a Christophe Curti,^a Hussein El-Kashef,^b Omar Khoumeri,^a Thierry Terme^a and Patrice Vanelle^{*a}

Manganese(III) acetate-mediated peroxycyclization between 2-hydroxy-3-methylnaphthoquinone and various alkenes was performed to obtain dihydronaphtho[2,3-c][1,2]dioxine-5,10(3H,10aH)-diones. The reactivity of symmetrical or unsymmetrical 1,1-disubstituted alkenes and monosubstituted alkenes allowed the synthesis of more than 50 original molecules. Focusing on the excellent reactivity of 2-hydroxy-3-methylnaphthoquinone, we describe the first example of Mn(OAc)₃ reactivity with nitro-substituted alkenes. The scope, limitations and stereochemistry of the products synthesized are discussed. Starting from monosubstituted alkenes, the instability of a pair of diastereoisomers was observed, leading to ring opening.

Introduction

Manganese(III) acetate is a useful tool in organic chemistry, but remains underestimated in medicinal chemistry. Over the past four decades, the literature has contained accounts of its applications in C–C bond-forming reactions starting from various substrates.^{1–3} Among these substrates, the reactivity of quinones was studied under anaerobic conditions with stoichiometric quantities of Mn(OAc)₃.⁴

Mn(OAc)₃ under aerobic conditions was also described as an efficient catalytic system, leading to C–C bond formation and oxygen insertion *via* a radical pathway, yielding 1,2-dioxane derivatives.^{5–7}

Other synthetic pathways to heterocyclic peroxides were described in a recent review.⁸ They are based on three key reagents: oxygen, ozone and hydrogen peroxide. In particular, synthesis of 1,2-dioxanes can be realized with oxygen. Such reactions were described with singlet oxygen,⁹ with thiols by oxidation of 1,5-dienes^{10,11} or by the Isayama–Mukaiyama method.¹² Ozonolysis of double bonds also afforded hydroperoxides, which can be then cyclized.¹³ The Kobayashi method involving an urea–hydrogen peroxide complex allowed the peroxidation of carbonyl group of unsaturated ketones followed by a cyclization.^{14,15}

^aAix-Marseille Université, CNRS, Institut de Chimie Radicalaire ICR, UMR 7273, Laboratoire de Pharmaco-Chimie Radicalaire, Faculté de Pharmacie, 27 boulevard Jean Moulin CS 30064, Marseille Cedex 05, 13385, France. E-mail: patrice.vanelle@univ-amu.fr

^bChemistry Department, Faculty of Science, Assiut University, Egypt

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Saturated heterocyclic endoperoxides, such as 1,2-dioxane, were described as powerful antiinfectious compounds, with applications against trypanosomiasis,^{16,17} leishmaniasis,¹⁶ helminthiasis,¹⁸ and trichomoniasis.¹⁹ Despite these applications, heterocyclic endoperoxides are mainly known for being potent antimalarial compounds. In addition to the well-known commercial drug artemisinin,²⁰ trioxolanes arterolane and artefenomel,²¹ a wide variety of 1,2-dioxanes showed potential antimalarial activity.^{22–26} Quinone derivatives have important biological applications, mainly as anticancer²⁷ and antiparasitic²⁸ compounds. The 2-hydroxy-3-alkylnaphthoquinone lapachol derivatives antimalarial activity²⁹ encouraged us to seek an easily reproducible procedure to obtain chimeric 2-hydroxy-3-alkylnaphthoquinone/endoperoxide molecules.

Expanding on our previous work on the synthesis of anti-parasitic compound^{30–33} and Mn(OAc)₃ reactivity,^{34–37} we present herein the first example of this original reactivity on 2-hydroxy-3-methylnaphthoquinone with various alkenes, under Mn(OAc)₃ catalytic conditions.

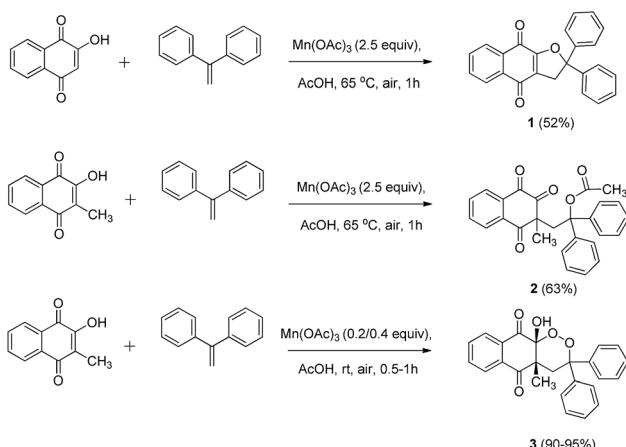
Results and discussion

First, best reaction conditions were studied with 1,1-diphenylethylene (Scheme 1). According to previous Mn(OAc)₃ reactivity studies, good yields can be obtained with this alkene, as the intermediate benzylic tertiary radical is highly stabilized.^{38,39}

2-Hydroxynaphthoquinones were chosen both without and with a methyl in position 3. Results are summarized in Table 1.

Starting from 2-hydroxynaphthoquinone in the presence of Mn(OAc)₃ at 65 °C, dihydrofuranaphthoquinone 1 was obtained in moderate yields (entry 1) according to a previously reported mechanism.⁴ We obtained lower yields (52%) than those reported with similar 1,1-diaromatic alkenes, perhaps due to the





Scheme 1 $\text{Mn}(\text{OAc})_3$ mediated cyclization of 2-hydroxynaphthoquinones with 1,1-diphenylethylene under aerobic conditions.

Table 1 $\text{Mn}(\text{OAc})_3$ mediated cyclization of 2-hydroxynaphthoquinones and 1,1-diphenylethylene under aerobic conditions

Entry ^a	R	$\text{Mn}(\text{OAc})_3$ (equiv.)	Temperature (time)	Product (yield)
1	-H	2.5	65 °C (1 h)	1 (52%) ^b
2	-H	2.5	RT (3 h)	—
3	-H	0.4	RT (24 h)	—
4	-H	0.4	65 °C (1 h)	1 (30%) ^b
5	-CH ₃	2.5	65 °C	2 (63%) ^b
6	-CH ₃	0.2	RT (1 h)	3 (95%) ^b
7	-CH ₃	0.4	RT (0.5 h)	3 (90%) ^b
8 ^c	-CH ₃	0.2	RT (1 h)	3 (90%) ^d
9 ^e	-CH ₃	0.2	RT (1 h)	3 (82%) ^b

^a Reaction conditions: 2-hydroxynaphthoquinone (1 equiv.), 1,1-diphenylethylene (0.5 equiv.). ^b Isolated yields based on number of alkenes equiv. ^c Reaction conditions: 2-hydroxynaphthoquinone (1 equiv.), 1,1-diphenylethylene (1.1 equiv.). ^d Isolated yields based on number of naphthoquinone equiv. ^e Reaction under an oxygen atmosphere.

presence of oxygen under our conditions. Catalytic quantities of $\text{Mn}(\text{OAc})_3$ only decreased yields without any oxygen insertion (entry 4), and lower temperature (RT) left the unchanged starting material (entries 2 and 3).

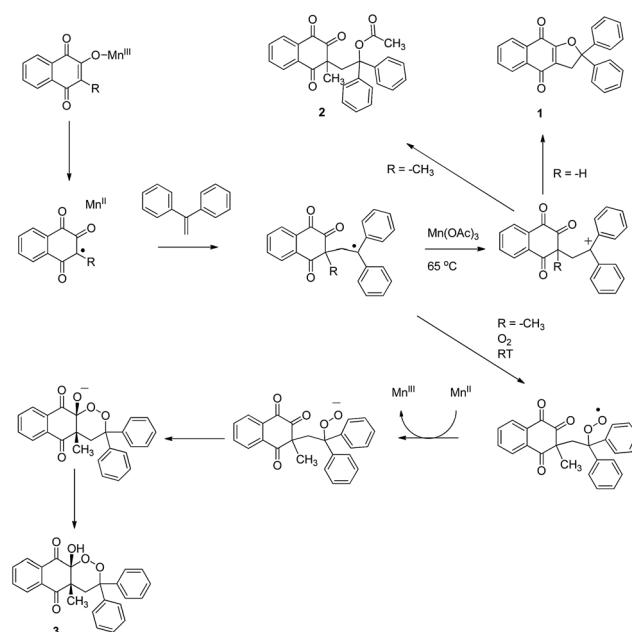
With 2-hydroxy-3-methylnaphthoquinone in the presence of 2.5 equiv. of $\text{Mn}(\text{OAc})_3$ at 65 °C, product **2** was formed, without traces of 1,2-dioxane ring formation (entry 5). This structure was obtained *via* the same mechanism observed for product **1**, but the presence of a methyl group in position 3 did not allow cyclization. Instead, acetate reacted with the intermediate carbocation to form product **2**. Reactivity allowing the purification of product **3** in very good yields was finally observed with catalytic quantities of $\text{Mn}(\text{OAc})_3$ at room temperature in only 1 h (entry 6). When $\text{Mn}(\text{OAc})_3$ quantities were doubled to 0.4 equiv., time reaction was decreased to 30 min with a moderate yield decrease (entry 7). When alkene quantities were increased to 1.1 equiv., yields were also slightly decreased (entry 8). Moreover, lower yields were observed when reaction was launched under an oxygen atmosphere (entry 9), as previously reported in similar $\text{Mn}(\text{OAc})_3$ catalyzed reactivity.^{40,41}

Temperature was previously reported to influence the $\text{Mn}(\text{OAc})_3$ reactivity.^{5,38,39} At high temperature, under anaerobic conditions, a dihydrofuran ring is obtained, and at room temperature under aerobic conditions, oxygen trapping led to a 1,2-dioxane ring. Catalytic quantities of $\text{Mn}(\text{OAc})_3$ are sufficient for this mechanism, summarized in Scheme 2.

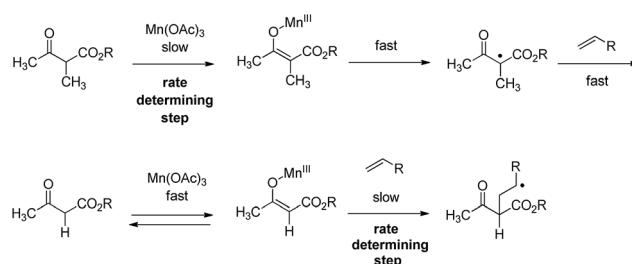
Methyl group substitution in position 3 of naphthoquinone highly influenced $\text{Mn}(\text{OAc})_3$ reactivity, appearing to be an important parameter leading to the formation of the 1,2-dioxane ring of product **3**. The influence of the alkyl groups on $\text{Mn}(\text{OAc})_3$ reactivity was previously studied, for example with α -alkyl- β -keto esters *versus* α -unsubstituted- β -ketoesters as summarized in Scheme 3.⁴²

2-Hydroxynaphthoquinones are already enolized and the Mn(III) enolate should form readily. Moreover, a methyl group in position 3 should facilitate oxidation, forming a stabilized radical. Without this methyl group, 2-hydroxynaphthoquinone reactivity would probably not be sufficient to initiate the mechanism with catalytic quantities of $\text{Mn}(\text{OAc})_3$ and/or room temperature.

The structure of product **3** was confirmed by X-ray crystallography and an ORTEP view is reported to Fig. 1. This



Scheme 2 Naphthoquinone/ $\text{Mn}(\text{OAc})_3$ proposed reactivity mechanism.



Scheme 3 $\text{Mn}(\text{OAc})_3$ reactivity with β -ketoesters.⁴²



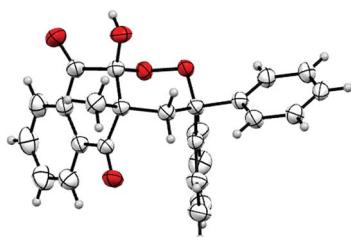


Fig. 1 ORTEP view of product 3.

crystallographic analysis confirmed that oxidative cyclization, theoretically possible on carbon 2 or on carbon 4 of naphthoquinones, only took place on carbon 2, probably because of its greater electrophilic nature.

Crystallographic analysis also showed that 10-hydroxyl and 4-methyl groups of product 3 were *cis*-substituted. A hydroxyl group occupies the axial position, due to the anomeric effect.^{43,44} During the intramolecular cyclization (Scheme 2), nucleophilic addition on carbonyl only occurs on the opposite side of the methyl group, yielding to a mixture of two *cis*-enantiomers.

The reaction was extended to various substrates, starting from symmetrical alkenes (Scheme 4). Results are summarized in Table 2.

cis-Substitution was observed for every product obtained from aromatic and aliphatic symmetrical alkenes. Yields obtained ranged from excellent with aromatic alkenes (entries 1–3), even when they carried electron-withdrawing substituents such as –Cl or –F, to moderate (entries 4 and 5) with aliphatic alkenes. This can be explained by the stability of intermediate radical formed during the reaction just after the C–C bond formation. For each type of alkene, a tertiary radical was formed, sufficiently stabilized to react with oxygen, but for

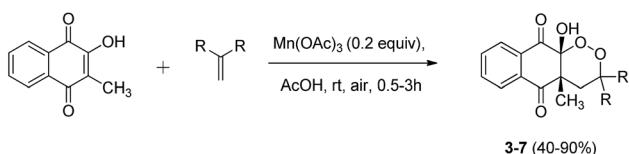
Scheme 4 $\text{Mn}(\text{OAc})_3$ catalyzed cyclization of 2-hydroxy-3-methylnaphthoquinone and symmetrical alkenes under aerobic conditions.

Table 2 Symmetrical alkenes reactivity

Entry	R	Product (yield) ^a
1 ^b	–Ph	3 (90%)
2 ^b	–4-Cl-Ph	4 (86%)
3 ^b	–4-F-Ph	5 (79%)
4 ^c	–CH ₂ –CH ₃	6 (54%)
5 ^c	–(CH ₂) ₅ –	7 (40%)

^a Isolated yields based on number of alkenes equiv. ^b Reaction conditions: 2-hydroxy-3-methylnaphthoquinone (1 equiv.), alkene (0.5 equiv.). ^c Reaction conditions: 2-hydroxy-3-methylnaphthoquinone (1 equiv.), alkene (1 equiv.).

aromatic alkenes the stability of this tertiary benzylic radical was increased by resonance.

From these promising results, we extended this reactivity to 1,1-disubstituted unsymmetrical alkenes, in order to generate a new asymmetric center (Scheme 5). Results are summarized in Table 3.

As expected, the reactivity of 2-hydroxy-3-methylnaphthoquinone and unsymmetrical alkenes led to a mixture of diastereoisomers. Two fractions were easily separable by column chromatography. The first fraction corresponded to products with the R₂ and 4-methyl group *cis*-substituted (8–16), and the second fraction to products with the R₂ and 4-methyl group *trans*-substituted (8'–16').

These results are evidence of the excellent reactivity of 2-hydroxy-3-methylnaphthoquinone for $\text{Mn}(\text{OAc})_3$ C–C bond forming reactions, even with deactivated alkenes such as nitrile- (entry 7) or nitro- (entries 1, 8 and 9) substituted alkenes. $\text{Mn}(\text{OAc})_3$ reactivity of the double bond decreases with aromatic substitution of electron-withdrawing substituents. To our knowledge, this is the first example of a C–C bond forming reaction mediated with $\text{Mn}(\text{OAc})_3$ and nitro-substituted alkenes. We did not observe reactivity for 1-nitro-2-(prop-1-en-2-yl)benzene (entry 10), probably because of steric hindrance due to the proximity of nitro and methyl groups with a double bond. Methoxy-substituted alkenes allowed the synthesis of products 12/12' (entry 4) in lower yields than other alkenes. This

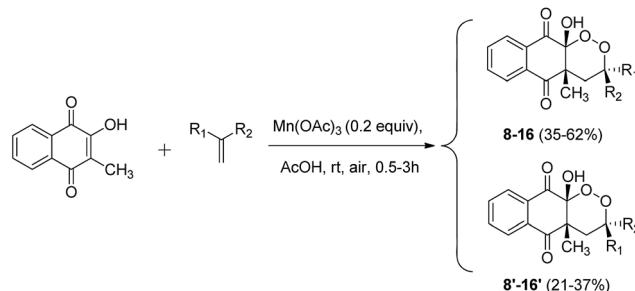
Scheme 5 $\text{Mn}(\text{OAc})_3$ catalyzed cyclization of 2-hydroxy-3-methylnaphthoquinone and unsymmetrical alkenes under aerobic conditions.

Table 3 Unsymmetrical 1,1-disubstituted alkenes reactivity

Entry ^a	R ₁	R ₂	Products (yields; diastereoisomeric ratio) ^b
1	–Ph	–4-NO ₂ -Ph	8/8' (83%; 75/25)
2	–CH ₃	–Ph	9/9' (83%; 55/45)
3	–CH ₃	–4-CH ₃ -Ph	10/10' (82%; 60/40)
4	–CH ₃	–3-OCH ₃ -Ph	11/11' (59%; 60/40)
5	–CH ₃	–4-Cl-Ph	12/12' (80%; 60/40)
6	–CH ₃	–2,5-diCl-Ph	13/13' (63%; 60/40)
7	–CH ₃	–4-CN-Ph	14/14' (70%; 60/40)
8	–CH ₃	–4-NO ₂ -Ph	15/15' (75%; 60/40)
9	–CH ₃	–3-NO ₂ -Ph	16/16' (58%; 60/40)
10	–CH ₃	–2-NO ₂ -Ph	—

^a Reaction conditions: 2-hydroxy-3-methylnaphthoquinone (1 equiv.), alkene (0.5 equiv.). ^b Isolated yields based on number of alkenes equiv.



phenomenon was already observed with methoxy-substituted alkenes, and an interaction between oxygen and $\text{Mn}(\text{OAc})_3$ was hypothesized.³⁷ Under conditions involving stoichiometric quantities of manganese, this limitation dealt by increasing manganese equivalents, but it remains problematic with catalytic quantities.

The structure of products **15/15'** was confirmed by X-ray crystallography and an ORTEP view is reported in Fig. 2.

As previously described for 1,1-disubstituted symmetrical alkenes, 10-hydroxyl and 4-methyl groups were *cis*-substituted. Moreover, for product **15**, the R_2 substituent and 4-methyl group were also *cis*-substituted, while they were *trans*-substituted for product **15'**. We noticed a slight stereoselectivity, with a diastereoisomeric excess for products *cis*-substituted with 10-hydroxyl and R_2 substituents. Similar selectivity was previously described and discussed for radical induced peroxycyclization.^{45,46}

Next, given the excellent reactivity of 2-hydroxy-3-methylnaphthoquinone, we extended reactivity to mono-substituted terminal alkenes (Scheme 6). Several vinyl derivatives reacted with naphthoquinone in moderate to excellent yields. Results are summarized in Table 4.

Starting from styrene or monosubstituted alkenes bearing electron-donating substituents, diastereoisomer products were

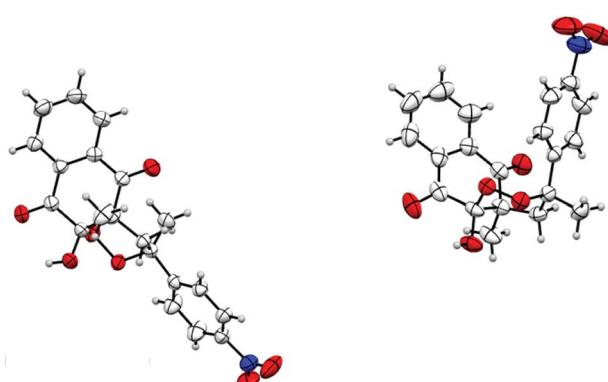
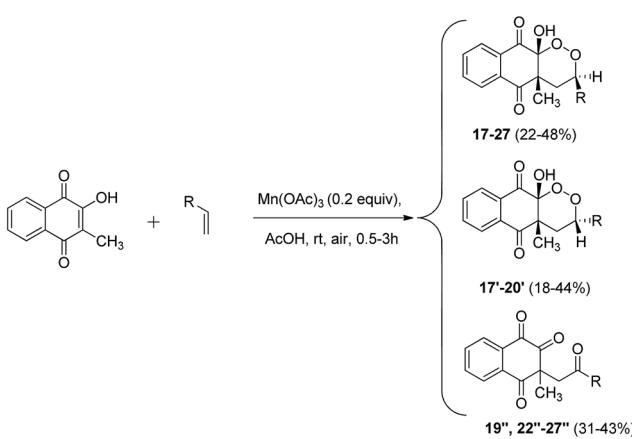


Fig. 2 ORTEP view of products **15/15'**.



Scheme 6 $\text{Mn}(\text{OAc})_3$ catalyzed cyclization of 2-hydroxy-3-methyl naphthoquinone and monosubstituted alkenes under aerobic conditions.

Table 4 Monosubstituted alkenes reactivity

Entry ^a	R	Diastereoisomer products (yield; diastereoisomeric ratio) ^b	Ring opening products (yield) ^b
1	-Ph	17/17' (88%; 50/50)	
2	-4-CH ₃ -Ph	18/18' (80%; 60/40)	
3	-3-CH ₃ -Ph	19/19' (58%; 60/40)	
4 ^c	-3-CH ₃ -Ph	19 (23%)	19'' (31%)
5	-2-CH ₃ -Ph	20/20' (52%; 65/35)	
6	-4-Cl-Ph	21 (28%)	21'' (40%)
7	-4-F-Ph	22 (23%)	22'' (34%)
8	-4-CN-Ph	23 (22%)	23'' (33%)
9	-3-Br-Ph	24 (25%)	24'' (37%)
10	-4-NO ₂ -Ph	25 (29%)	25'' (43%)
11	-3-NO ₂ -Ph	26 (24%)	26'' (35%)
12	-2-NO ₂ -Ph	27 (22%)	27'' (32%)

^a Reaction conditions: 2-hydroxy-3-methylnaphthoquinone (1 equiv.), alkene (0.5 equiv.). ^b Isolated yields based on number of alkenes equiv. ^c Reaction was left under stirring for 2 hours after starting material consumption.

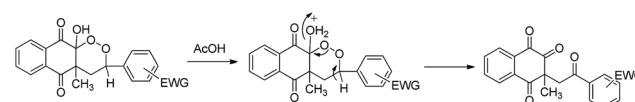
synthesized in good yields in a similar way to that described previously. Surprisingly, stereoselectivity was not observed for styrene (entry 1). *para*-Substitution for alkenes led to better yields than *meta*- or *ortho*-substitution (entries 2, 3 and 5). When alkenes bearing electron-withdrawing substituents were used as starting material, only one diastereoisomeric product was purified and a major product identified as a ring opening structure (entries 6–12). To confirm whether this new product came from a secondary reaction or from the degradation of peroxycyclized products, a reaction that only yielded to diastereoisomeric products was left under stirring for 3 hours (entry 4). Similar formation of ring opening product **19''** was observed, clearly indicating that diastereoisomer **19'** was totally cleaved.

Decomposition of a 1,2-dioxane ring to afford γ -diketones was previously described.^{47,48} Thus, the formation of the ring opening structure could be explained by the acid-catalyzed rearrangement of the less stable diastereoisomer (Scheme 7).

Electron-withdrawing substituents on the benzene ring decrease the stability of the 1,2-dioxane ring by their influence on O–O bond stability and on benzylic hydrogen acidity. Therefore, spontaneous decomposition of peroxycyclized products could occur.

The structure of products **27/27''** was confirmed by X-ray crystallography and an ORTEP view is shown in Fig. 3.

Peroxycyclized products *trans*-substituted with 10-hydroxyl and R substituent appeared to be less stable than *cis*-substituted ones. This difference in stability may also explain the stereoselectivity observed during cyclization. Moreover, starting from monosubstituted alkenes, when R bears an electron-



Scheme 7 Acid-catalyzed decomposition of peroxycyclized diastereoisomer.



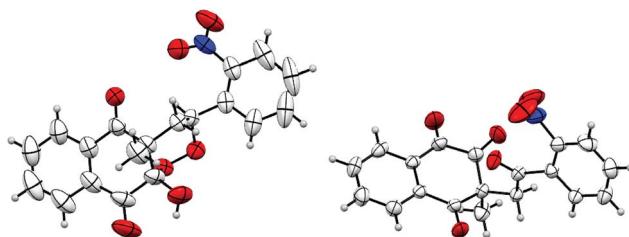


Fig. 3 ORTEP view of products 27/27''.

withdrawing substituent, *trans*-substituted diastereoisomers were probably spontaneously cleaved very close to their formation. On the other hand, if R is substituted by an electron-donating group, the increased reaction time could lead to the same decomposition on *trans*-substituted diastereoisomers.

Conclusions

A new protocol of manganese(III) acetate catalyzed peroxycyclization of 2-hydroxy-3-methylnaphthoquinone was established and extended to a wide variety of alkenes. The high reactivity of quinones allowed deactivated alkenes to react with good yields. Thus, we report herein the first example of nitro-substituted alkene Mn(OAc)₃ radical reactivity. Symmetrical or unsymmetrical 1,1-disubstituted alkenes and monosubstituted alkenes allowed the synthesis of 26 original molecules as a mixture of diastereoisomers or enantiomers. Differences in stability between diastereoisomers could explain stereoselectivity. Moreover, reactivity of monosubstituted alkenes bearing an electron-withdrawing group led to ring opening of the less stable diastereoisomers.

Experimental section

Typical procedure for the synthesis of 3

A solution of 2-hydroxy-3-methyl-1,4-naphthoquinone (1.06 mmol, 200 mg, 1 equiv.) in 25 mL of glacial acetic acid was stirred at room temperature in an open vessel. 1,1-Diphenylethylene (0.53 mmol, 96 mg, 0.5 equiv.) and manganese(III) acetate dihydrate (0.21 mmol, 57 mg, 0.2 equiv.) were added and the reaction was controlled by TLC until consumption of alkene. After 1 h, the reaction mixture was poured into 60 mL of cold water and extracted with dichloromethane (3 × 20 mL). The organic extracts were collected and dried (Na₂SO₄). Solvent was evaporated under reduced pressure and crude product was purified by column chromatography (CH₂Cl₂/petroleum ether, 70/30), and the product obtained was recrystallized to afford product 3 (202 mg, 95%) as a white solid, mp = 167–168 °C (petroleum ether/CH₂Cl₂, 9/1). ¹H NMR (250 MHz, CDCl₃): δ = 7.96–7.99 (m, 1H, Ar-H), 7.53–7.77 (m, 3H, Ar-H), 7.23–7.40 (m, 7H, Ar-H), 7.11–7.14 (m, 3H, Ar-H), 5.04 (s, 1H, OH), 3.68 (d, *J* = 13.6 Hz, 1H, CH), 2.88 (d, *J* = 13.6 Hz, 1H, CH), 1.25 (s, 3H, CH₃). ¹³C NMR (62.5 MHz, CDCl₃): δ = 195.5 (C), 190.5 (C), 142.8 (C), 140.4 (C), 135.6 (CH), 134.0 (CH), 133.9 (C), 131.1 (C), 128.4 (2CH), 128.3 (CH), 127.7 (2CH), 127.5 (2CH), 127.4 (CH), 126.8 (CH), 126.7 (CH), 126.4

(2CH), 98.8 (C), 86.2 (C), 49.0 (C), 37.7 (CH₂), 23.8 (CH₃). HRMS (ESI): *m/z* [M + Na]⁺ calcd for C₂₅H₂₀O₅: 423.1203; found: 423.1204.

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