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Novel synthesis of dihydropyrans and 2,8-dioxabicylo[3.3.0]-oct-3-enes using Mn(III)-based oxidative cyclization ☆

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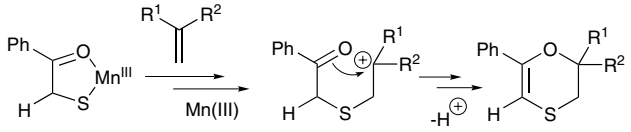
Abstract—The Mn(III)-based reaction of 1,1-disubstituted alkenes with 2-(2-oxoethyl)malonates and 3-acetylpentane-1,4-diones gave novel substituted dihydropyrans and 2,8-dioxabicyclo[3.3.0]oct-3-enes in good yields, respectively. These routes rely on the nucleophilic character of the carbonyl-oxygen atoms of the malonates and pentanediones used to obtain the products by a cycloaddition reaction or cycloaddition–tandem cyclization reactions.

The 2,8-dioxabicyclo[3.3.0]oct-3-ene moiety is an important building block found in a variety of biologically active compounds, particularly in some insect antifeeding compounds such as clerodine.[1] Recently, there has been considerable interest in the development of new methods for the synthesis of this skeleton, either by ionic reactions[2] or radical reactions.[3] In general, the Mn(III)-induced radical reaction requires two moieties to make a carbon–carbon bond.[4] One moiety, usually a carbonyl partner having an α-hydrogen, is used to produce the corresponding Mn(III)–enolate complex (acceptor).[4f,5] The other, usually an election-rich carbon–carbon double bond partner (donor), is used to oxidatively transfer one electron to the enolate complex.[6] We previously reported the Mn(III)-based cycloaddition of alkenes with 2-oxothiols that produced 2,3-dihydro-1,4-oxathiins; the key step in the reaction being the cyclization of the carbocation intermediate formed during the reaction (Scheme 1).[7] We believed that by selecting carbonyl compounds having two or more carbonyl groups at suitable positions we would be able to obtain a range of interesting heterocyclic compounds from the rather simple dihydropyrans to the more complicated heterocycles such as the 2,8-dioxabicyclo[3.3.0]oct-3-enes. In this study, we describe a brief account of the synthesis of dihydropyrans **3** and dioxabicyclo[3.3.0]-octenes **6** by the Mn(III)-based cycloaddition and tandem cyclization of alkenes **1** with 2-(2-oxoethyl)malonates **2** and 3-acetylpentane-1,4-diones **5**, respectively (Scheme 2).



Scheme 1.

Initially, we selected dimethyl 2-(2-oxo-2-phenylethyl)malonate (**2**: $R^3 = Me$, $Ar = Ph$) to explore the Mn(III)-based cycloaddition with 1,1-disubstituted ethenes. Although the preparation of **2** has been reported,[8] we easily obtained **2** in 60% yield from the reaction of dimethyl malonate with phenacyl bromide in EtONa/EtOH medium. A mixture of **1** ($R^1 = R^2 = Ph$, 1 mmol) and **2** (2 mmol) was heated in glacial acetic acid (15 mL) using an oil bath, and then manganese(III) acetate dihydrate (3 mmol) was added to the mixture just before refluxing in order to avoid the direct oxidation of **1**.[9] The reaction mixture was stirred under reflux until the dark-brown color of the Mn(III) disappeared (15 min). After work-up,[10] the reaction mixture was separated by thin-layer chromatography using chloroform as the developing solvent to give the desired dihydropyran **3** ($R^1 = R^2 = Ar = Ph$, $R^3 = Me$) in 79% yield together with a small amount of expected γ-lactone **4**

Keywords: Manganese(III) acetate; Oxidative cycloaddition; Tandem cyclization; Dihydropyrans; 2,8-Dioxabicyclo[3.3.0]oct-3-enes.
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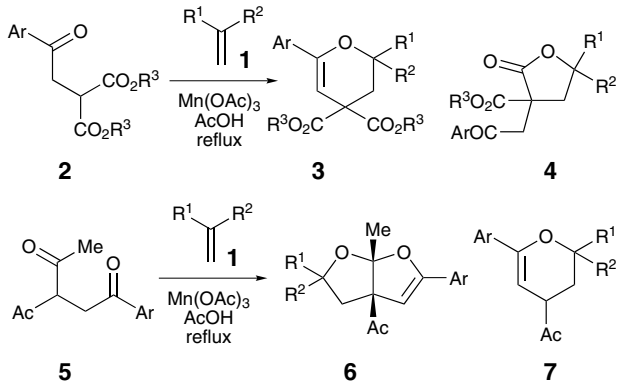


Scheme 2.

Table 1. The reaction of alkenes **1** with (2-aryl-2-oxoethyl)malonates **2** in the presence of manganese(III) acetate[a]

Entry	1		2		Reaction time (min)	Product (yield %)[b]	
	R^1	R^2	R^3	Ar		**3**	**4**
1	Ph	Ph	Me	Ph	15	79	10
2	4-MeC_6H_4	4-MeC_6H_4	Me	Ph	11	64	9
3	4-ClC_6H_4	4-ClC_6H_4	Me	Ph	14	73	15
4	4-FC_6H_4	4-FC_6H_4	Me	Ph	14	74	—
5	Ph	Me	Me	Ph	11	37	—
6	Ph	Ph	Me	4-MeC_6H_4	7	74	13
7	Ph	Ph	Me	4-ClC_6H_4	8	71	—
8	Ph	Me	Me	2-Naph	5	51	9
9	Ph	Ph	Et	Ph	6	61	—

[a] The reaction was carried out at the molar ratio **1**:**2**:$Mn(OAc)_3 \cdot 2H_2O = 1:2:3$ in boiling glacial acetic acid (15 mL) except for entry 8, which used acetic acid (12 mL).
[b] Isolated yield based on the amount of **1** used.

($R^1 = R^2 = Ar = Ph$, $R^3 = Me$) (Table 1, entry 1). The structures of **3** and **4** were confirmed by spectroscopic methods and elemental analyses.[11,12] Next, we explored the use of a variety of alkenes **1** and malonates **2**, and obtained the desired dihydropyrans **3** in almost comparable yields (Table 1, entries 2–9). Surprisingly, the introduction of an electron-releasing group to the phenyl ring of **1** lowered the yield of **3** (Table 1, entry 2), while the presence of an electron-withdrawing group led to a similar yield of **3** (Table 1, entries 3 and 4).

From the reaction using 2-(2-oxoethyl)malonates **2** to mainly produce dihydropyrans **3**, it is worth noting that a 6-*endo-trig* cyclization involving a ketone carbonyl preferentially occurred even though the malonates **2** had two other ester carbonyls. This means that the use of 2,4-pentanedione substituted an oxoethyl group at the C-3 position may lead to a tandem cyclization product in a similar reaction. Thus, we selected 3-acetyl-1-phenylpentane-1,4-dione (**5**: Ar = Ph) to examine the reaction. The triketone **5** has been used to synthesize pyrrols and related compounds.[13] The reaction of **1** ($R^1 = R^2 = Ph$) with **5** was performed in a similar manner as described above, and we obtained the desired 2,8-dioxabicyclo[3.3.0]oct-3-ene **6** ($R^1 = R^2 = Ar = Ph$) in 67% yield along with the monocyclic dihydropyran **7** ($R^1 = R^2 = Ar = Ph$) (Table 2, entry 1). The ^{13}C NMR spectrum of **6** showed no signal between 190 and

Table 2. The reaction of alkenes **1** with 3-acetylpentane-1,4-diones **5** in the presence of manganese(III) acetate[a]

Entry	1		5	Product (yield %)[b]	
	R^1	R^2	Ar	**6**	**7**
1	Ph	Ph	Ph	67	22
2	4-MeC_6H_4	4-MeC_6H_4	Ph	76	—
3	4-$MeOC_6H_4$	4-$MeOC_6H_4$	Ph	78	—
4	4-ClC_6H_4	4-ClC_6H_4	Ph	66	13
5	Ph	Me	Ph	53	11
6	Ph	Ph	4-MeC_6H_4	61	24
7	Ph	Ph	4-ClC_6H_4	66	19
8	Ph	Ph	4-FC_6H_4	61	14
9	Ph	Ph	2-Naph	54	18

[a] The reaction was carried out at the molar ratio of **1**:**5**:$Mn(OAc)_3 \cdot 2H_2O = 1:2:3$ in boiling glacial acetic acid (15 mL) until the dark-brown color of the Mn(III) disappeared (within 1 min).
[b] Isolated yield based on the amount of alkene **1** used.

200 ppm due to an aryl-conjugated carbonyl carbon, but one signal at 117.8 ppm was assigned to an acetal carbon along with an acetyl carbonyl carbon signal at 207.4 ppm.[14] This clearly proves that the tandem cyclization occurred both at the acetyl oxygen and the benzoyl oxygen. Although the bicyclic ring of **6** was thought to be fused in a *cis* manner,[1] the exact stereochemistry of the bicyclooctene **6** ($R^1 = R^2 = 4\text{-}ClC_6H_4$, Ar = Ph) was finally confirmed by X-ray crystallography (Fig. 1).[15] The reaction of other alkenes **1** with 3-acetylpentane-1,4-diones **5** also gave the expected bicyclooctenes **6** in comparable yields (Table 2, entries 2–9). As expected in view of the formation process of bicyclooctene **6** involving the carbon radical **A** and the carbocation intermediates **B** (Scheme 3), the yield of **6** was improved using the alkenes **1** substituted by electron-releasing aromatic groups (Table 2, entries 2 and 3). From these reactions, it has been possible to isolate a small amount of dihydropyrans **7** in some cases (Table 2, entries 1,4–9).[16] Since it is known that the formation of a five-membered ring such as **C** (path a) is much faster than that of six-membered ring affording **D** (path b),[17] these results convinced us of the triketone system. However, it seemed that the *6-endo-trig* cyclization was favored in the reaction with oxoethylmalonates **2** depending on the nucleophilicity of the carbonyl oxygen, which produce dihydropyrans **3**.[18]

In order to explore the reactivity of a tricarbonyl compound including a carboxamide carbonyl group, a barbituric acid **8** was prepared bearing a benzoylmethyl group, and the reaction was conducted under similar oxidation conditions. Since the nucleophilicity of the carboxamide oxygen would be weaker than that of the benzoyl oxygen, it was expected that the cyclization might occur at the ketone carbonyl to afford a spirobarbituric acid derivative such as **9**. However, all attempts were unsuccessful and substitution products **10** and **11** were obtained together with a dimeric compound **12** (Scheme 4).

In summary, we have presented a novel Mn(III)-based procedure for the synthesis of dihydropyrans **3** and 2,8-dioxabicyclo[3.3.0]oct-3-enes **6** using the reaction of alkenes **1** with 2-(2-oxoethyl)malonates **2** and 3-acetyl-1,4-pentanediones **5**, respectively. To the best of our

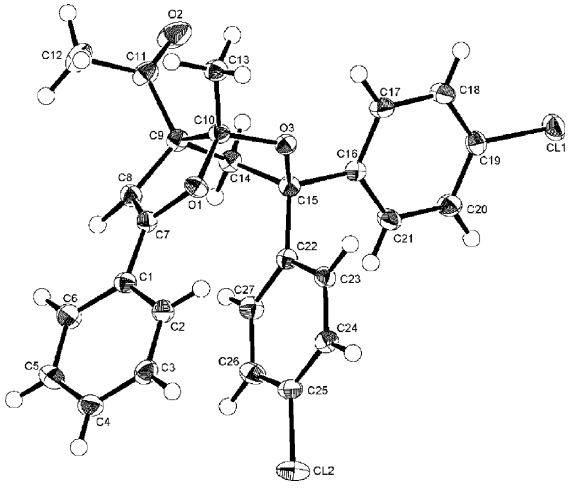
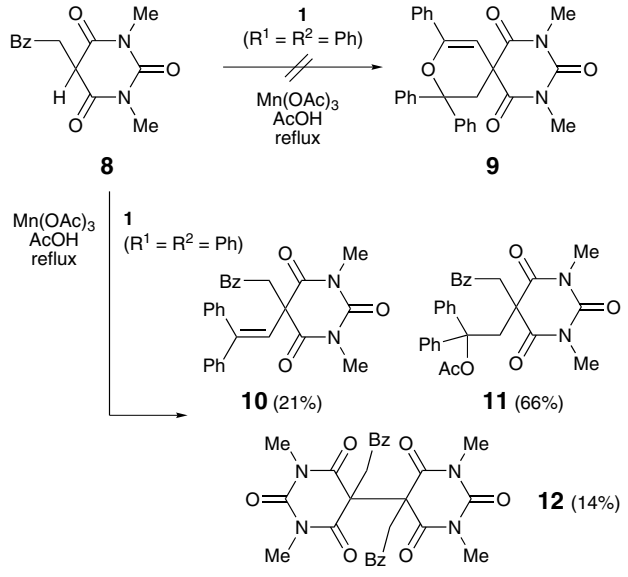
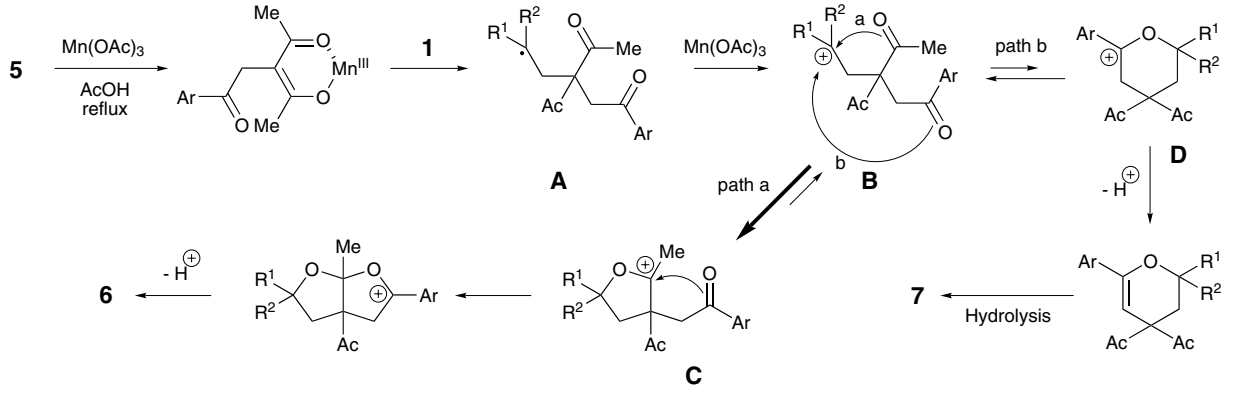


Figure 1. ORTEP drawing of 2,8-dioxabicyclo[3.3.0]oct-3-ene **6** ($R^1 = R^2 = 4\text{-}ClC_6H_4$, Ar = Ph).



Scheme 4.



Scheme 3.

knowledge, this is the first example using the tricarbonyl system for the Mn(III)-based oxidative cyclization.[4d] Although only a limited number of examples are provided here, we believe that the ease of operation and the high yields would be useful as a synthetic method in organic synthesis. We are currently investigating further applications of this and the related addition–tandem cyclizations and will report our findings in due course.

Supplementary material

The X-ray structural information of **6** ($R^1 = R^2 = 4\text{-}ClC_6H_4$, Ar = Ph) is collected in Table 3. Copies of ^1H NMR, ^{13}C NMR, DEPT, IR, and MS spectra of dihydropyran **3** ($R^1 = R^2 = Ar = Ph$, $R^3 = Me$, γ-lactone) **4** ($R^1 = R^2 = Ar = Ph$, $R^3 = Me$), 2,8-dioxabicyclo[3.3.0]oct-3-ene **6** ($R^1 = R^2 = Ar = Ph$), and dihydropyran **7** ($R^1 = R^2 = Ar = Ph$).

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10. After the Mn(III) oxidation was completed, the acetic acid solvent was removed under reduced pressure. The resulting residue was treated with water (12 mL) followed by extraction with chloroform.
11. Dimethyl 2,2,6-triphenyl-2,3-dihydropyran-4,4-dicarboxylate (**3**: $R^1 = R^2 = Ar = Ph$, $R^3 = Me$): colorless needles (from $CHCl_3$–hexane); mp 178–179 °C; IR ($CHCl_3$) *ν* 1736 (COO); ^1H NMR ($CDCl_3$) *δ* 7.84–7.20 (15H, m, arom H), 5.63 (1H, s, =CH), 3.49 (6H, s, Me × 2), 3.44 (2H, s, CH_2); ^{13}C NMR ($CDCl_3$) *δ* 170.6 (COO), 151.2 (C-6), 143.1, 134.5 (arom C), 129.0, 128.4, 128.2, 127.4, 126.0, 125.1 (arom CH), 94.9 (C-5), 81.2 (C-2), 53.0 (Me), 52.4 (C-4), 36.9 (C-3). Anal. Calcd for $C_{27}H_{24}O_5$: C, 75.68; H, 5.65. Found: C, 75.42; H, 5.58.
12. Methyl 3-(2-oxo-2-phenylethyl)-5,5-diphenyltetrahydro-2-furanone-3-carboxylate (**4**: $R^1 = R^2 = Ar = Ph$, $R^3 = Me$): colorless liquid; IR ($CHCl_3$) *ν* 1778, 1738 (COO), 1688 (CO); ^1H NMR ($CDCl_3$) *δ* 7.81–7.23 (15H, m, arom H), 3.87 (1H, d, $J_{ab} = 18.2$, CH_2–H_a), 3.84 (1H, d, $J_{cd} = 13.8$, CH_2–H_c), 3.45 (3H, s, OMe), 3.30 (1H, d, $J_{cd} = 13.8$, CH_2–H_d), 3.25 (1H, d, $J_{ab} = 18.2$, CH_2–H_b); ^{13}C NMR ($CDCl_3$) *δ* 195.6 (C=O), 173.4, 169.6, (COO), 143.9, 142.9, 135.9 (arom C), 133.7 (arom CH), 128.7 (2C), 128.7 (2C), 128.4 (2C), 128.0, 127.8 (3C), 125.6 (2C), 125.3 (2C), 88.2 (C-5), 53.7 (C-3), 44.2, 42.3 (Ph *C*H_2 and C-4), 53.1 (Me); FAB HRMS found *m*/*z* 415.1575, calcd for $C_{26}H_{23}O_5$ M^{+1}, 415.1545.
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14. 5-Acetyl-1-methyl-3,7,7-triphenyl-2,8-dioxabicyclo[3.3.0]-oct-3-ene (**6**: $R^1 = R^2 = Ar = Ph$): colorless cubics (from $CHCl_3$–hexane); mp 154–155 °C; IR ($CHCl_3$) *ν* 1706.9 (Ac); ^1H NMR ($CDCl_3$) *δ* 7.44–6.83 (15H, m, arom H), 4.87 (1H, s, =CH), 3.38 (1H, d, $J = 13.1$, CH_2–H^b), 3.00 (1H, d, $J = 13.1$, CH_2–H^a), 2.23 (3H, s, Ac), 1.71 (3H, s, Me); ^{13}C NMR ($CDCl_3$) *δ* 207.4 (C=O), 157.5 (C-3), 146.8, 144.8, 129.6 (arom C), 128.9, 128.1, 127.8, 127.6, 126.8, 126.1, 125.4, 125.3 (arom CH), 117.8 (C-1), 99.1 (C-4), 89.1 (C-7), 72.3 (C-5), 45.1 (C-6), 28.9 (Ac), 22.8 (Me). Anal. Calcd for $C_{27}H_{24}O_3$: C, 81.79; H, 6.10. Found: C, 81.66; H, 6.01.
15. X-ray crystallographic data of **6** ($R^1 = R^2 = 4\text{-}ClC_6H_4$, Ar = Ph): empirical formula $C_{27}H_{22}Cl_2O_3$; formula weight 465.38; colorless chunk; crystal dimensions 0.97 × 0.30 × 0.27 mm; monoclinic; promitive, space group $P2_1/n$ (# 14); $a = 14.2629(4)$, $b = 10.3721(3)$, $c = 15.9359(4)$ Å, $\beta = 107.6504(4)°$, $V = 2246.53(10)$ Å^3, $Z = 4$; $D_{calcd} = 1.376$ g/cm^3; $F_{000} = 968.00$; μ (MoKα) = 3.16 cm^{-1}; $2\theta_{max} = 55.0°$; number of reflections measured total: 20719, unique: 5160 ($R_{int} = 0.051$); number of reflections (all, $2\sigma < 54.96°$) 5160; number of variables 289; reflection/parameter ratio 17.85; $R = 0.062$; $R_w = 0.111$. The X-ray crystallographic data have been deposited as supplementary publication number CCDC 230145. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk.

16. For example, the spectroscopic data of a mixture of (*R*)- and (*S*)-isomers of 4-acetyl-2,2,6-triphenyl-2,3-dihydropyran (**7**: $R^1 = R^2 = Ar = Ph$) were shown as follows: colorless liquid; IR ($CHCl_3$) v 1709; ^1H NMR ($CDCl_3$) δ 7.81–7.24 (15H, m, arom H), 5.47 (1H, d, $J = 1.4$ Hz, =CH), 3.13 (1H, dd, $J = 11.1$, 5.88 Hz, CH_2–H_a), 3.01 (1H, ddd, $J = 13.6$, 5.9, 1.4 Hz, H-4), 2.50 (1H, dd, $J = 13.6$, 11.1, CH_2–H_b), 2.19 (3H, s, Ac); ^{13}C NMR ($CDCl_3$) δ 208.4 (C=O), 151.1 (C-6), 145.2, 143.0, 135.1, (arom C), 128.64 (2C), 128.58, 128.4 (2C), 128.3 (2C), 127.5 (2C), 125.8 (2C), 125.6 (2C), 124.7 (2C) (arom CH), 94.7 (C-5), 82.0 (C-2), 45.4 (C-4), 34.1 (C-3), 27.7 (Me); FAB HRMS found m/z 355.1678, calcd for $C_{25}H_{23}O_2$ M^{+1}, 355.1698.
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