

## A Novel Macrodilide Synthesis Using the Mn(III)-Based Radical Cyclization of Terminal Alkadienes and Oligomethylene Di(3-oxobutanoate)s

Tomomi Yoshinaga,<sup>a</sup> Hiroshi Nishino,<sup>\*\*</sup> and Kazu Kurosawa<sup>b</sup>

<sup>a</sup>Department of Chemistry, Faculty of Science, Kumamoto University, Kurokami, Kumamoto 860-8555, Japan

<sup>b</sup>Department of Environmental Science, Faculty of Science, Kumamoto University, Kurokami, Kumamoto 860-8555, Japan

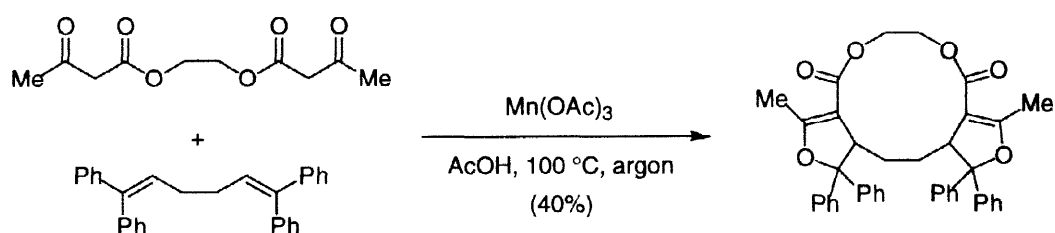
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**Abstract:**  $\alpha,\alpha,\omega,\omega$ -Tetraphenyl- $\alpha,\omega$ -alkadienes reacted with oligomethylene di(3-oxobutanoate)s in the presence of manganese(III) acetate at 100 °C under an argon atmosphere to give new 12 to 22-membered macrocyclic compounds which were two fused dihydrofuran rings in a one-step procedure.

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**Keywords:** Macrodilides; Radical cyclization; Manganese(III) acetate; Oxidation

Many naturally occurring macrocyclic compounds, which were isolated from actinomyce soil bacteria,<sup>1</sup> marine sponges,<sup>2</sup> sea hares,<sup>3</sup> senecio plants,<sup>4</sup> pathogenic fungi,<sup>5</sup> lichens,<sup>6</sup> etc., are known and some have significant biological activities. On the other hand, some macrocyclic compounds reveal supramolecular behavior such as molecular recognition, metal ion transport, enzymatic catalysis, chemical switching, and so on.<sup>7</sup> Therefore, many chemists have been attracted by the total synthesis and physicochemical properties of these macrolides for over three decades.<sup>8</sup> We were interested in the synthesis of macrodilides in the course of our manganese(III)-based radical cyclization of  $\alpha,\omega$ -alkadienes. Although a double ionic lactonization strategy was employed to synthesize most of the macrodilides,<sup>4b-d,5c,9</sup> we developed oxidative radical macrocyclization promoted by manganese(III)-enolate system.<sup>10</sup> A mixture of 1,1,6,6-tetraphenyl-1,5-hexadiene and ethylene di(3-oxobutanoate) was oxidized with manganese(III) acetate in acetic acid at 100 °C under an argon atmosphere to give a new 12-membered macrodilide which was two fused dihydrofuran rings in 40% yield.<sup>10</sup> The reaction



could be explained as the oxidative radical cyclization involving the manganese(III)-enolate complex.<sup>11</sup> Construction of rings larger than six members by radical cyclization was rarely reported except for the macrocyclization using tributyltin hydride.<sup>12</sup> In order to accomplish the manganese(III)-based radical cyclization as a practical synthetic method of macrodilides, we scrutinized the reaction and developed new 12-22-membered macrodilides in high yields according to a precise reaction control. Here we report the results of our experiments.

\*Corresponding author. Hiroshi Nishino, Fax: +81(96)342-3320; E-mail: nishino@aster.sci.kumamoto-u.ac.jp

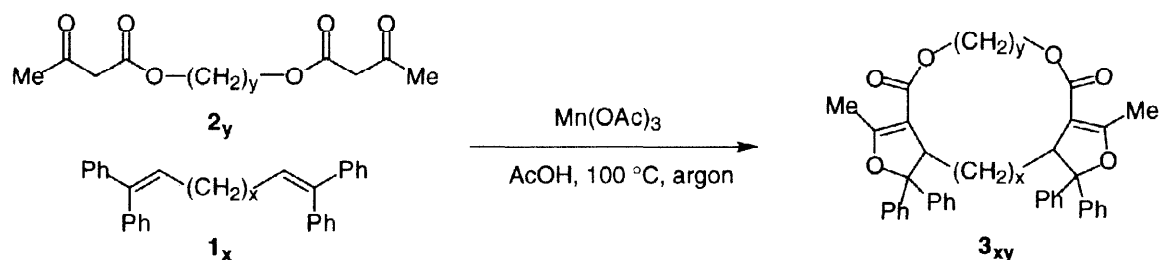


Table 1. Reaction of  $\alpha, \alpha, \omega, \omega$ -Tetraphenyl- $\alpha, \omega$ -alkadienes  $1_x$  with Oligomethylene Di(3-oxobutanoate)s  $2_y$  in the Presence of Manganese(III) Acetate<sup>a</sup>

Entry	$1_x$ x	$2_y$ y	Molar ratio <sup>b</sup>	Reaction time min	Product $3_{xy}$ Yield/% <sup>c</sup>	Ring size
1	1	2	1:1.5:7	60	0	11
2	2	2	1:1.5:7	30	71	12
3	2	3	1:1.5:7	60	64	13
4	2	4	1:1.5:7	60	66	14
5	3	2	1:1.5:7	50	64	13
6	4	2	1:1.5:7	50	76	14
7	4	3	1:1.5:7	60	75	15
8	4	4	1:1.5:7	60	74	16
9	5	4	1:1.5:7	60	86	17
10	6	4	1:1.3:6.5	45	49	18

<sup>a</sup> The reactions were carried out in acetic acid (250 mL) at 100 °C under an argon atmosphere except for entry 2 which was conducted under similar conditions in acetic acid (500 mL).

<sup>b</sup> The molar ratio was determined to be  $1_x$  (0.5 mmol): $2_y$ :manganese(III) acetate.

<sup>c</sup> Isolated yield based on the amount of the alkadiene  $1_x$  used.

1,1,6,6-Tetraphenyl-1,5-hexadiene ( $1_2$ ) (0.5 mmol), ethylene di(3-oxobutanoate) ( $2_2$ ) (0.75 mmol), and manganese(III) acetate (3.5 mmol) were added to acetic acid (250 mL), and the mixture was sufficiently degassed under reduced pressure using an ultrasonicator for exchange with an argon atmosphere. The mixture was then heated at 100 °C until the brown color of Mn(III) disappeared (usually for 30 min). After removal of the solvent, followed by addition of water, the almost purely crystalline 12-membered macrodiolide  $3_{22}$  was formed and filtered off (60% yield). The filtrate was extracted with chloroform, followed by TLC separation with diethyl ether/hexane (7:3 v/v), giving additional  $3_{22}$  (11% yield) (Table 1, Entry 2). The IR, NMR, FAB MS spectral data and mp of  $3_{22}$  were identical with that already reported.<sup>10</sup> The most important technique to improve the yield was the dilution method and degassing procedure. A similar reaction with  $2_2$  was applied to 1,1,5,5-tetraphenyl-1,4-pentadiene ( $1_1$ ), 1,1,7,7-tetraphenyl-1,6-heptadiene ( $1_3$ ), and 1,1,8,8-tetraphenyl-1,7-octadiene ( $1_4$ ). The reaction of  $1_3$  and  $1_4$  gave the corresponding macrodiolides  $3_{32}$  and  $3_{42}$  (Entries 5 and 6), however,  $1_1$  did not afford any macrodiolides (Entry 1), probably due to steric hindrance of the four phenyl groups. A similar treatment of  $1_{2,4}$  with trimethylene and tetramethylene di(3-oxobutanoate)s  $2_3$  and  $2_4$  gave the desired novel 13-18-membered macrodiolides in good yields (Entries 3, 4, 7-10).

In order to synthesize larger macrodiolides, oxadiethylene di(3-oxobutanoate) ( $4_2$ ) and dioxatriethylene di(3-oxobutanoate) ( $4_3$ ) were prepared by substitution of the diketene with di(ethylene glycol) or tri(ethylene glycol) and reacted with  $\alpha, \alpha, \omega, \omega$ -tetraphenyl- $\alpha, \omega$ -alkadienes  $1_x$  ( $x = 1-6$ ) under similar conditions. The reaction gave the corresponding new 14-22-membered macrodiolides  $5_{xz}$  ( $x = 1-6$ ,  $z = 2,3$ ) in moderate to high

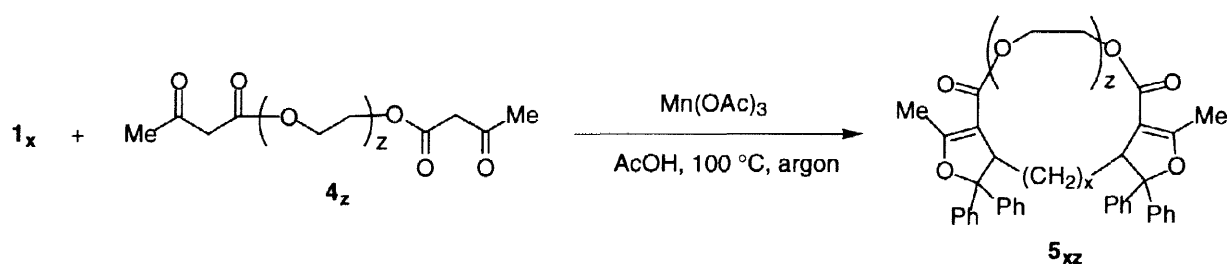


Table 2. Reaction of  $\alpha, \alpha, \omega, \omega$ -Tetraphenyl- $\alpha, \omega$ -alkadienes  $1_x$  with Oxaethylene Di(3-oxobutanoate)s  $4_z$  in the Presence of Manganese(III) Acetate<sup>a</sup>

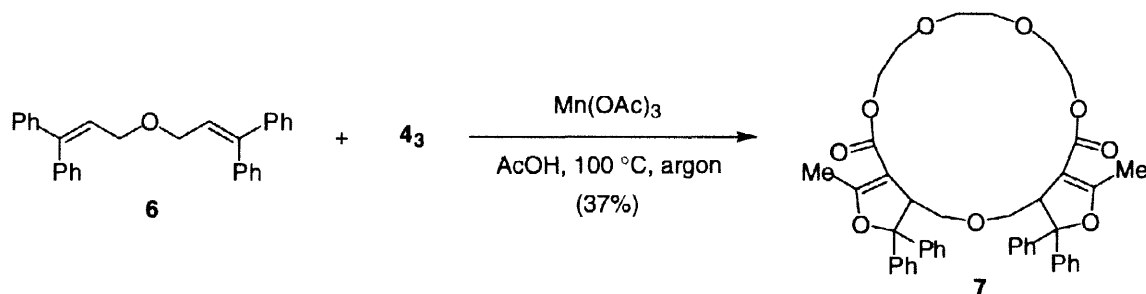
Entry	$1_x$ x	$4_z$ z	Molar ratio <sup>b</sup>	Reaction time min	Product $5_{xz}$ Yield/% <sup>c</sup>	Ring size
11	1	2	1:1.5:7	80	27	14
12	2	2	1:1.3:7	50	71	15
13	3	2	1:1.3:7	50	77	16
14	4	2	1:1.3:7	30	86	17
15	1	3	1:1.3:7	60	0	17
16	2	3	1:1.3:7	80	45	18
17	3	3	1:1.3:7	60	56	19
18	4	3	1:1.3:7	70	68	20
19	5	3	1:1.3:7	80	55	21
20	6	3	1:1.3:7	60	56	22

<sup>a</sup> The reaction was carried out in acetic acid (250 mL) at 100 °C under an argon atmosphere except for entries 12, 13, and 14 which were conducted under similar conditions in acetic acid (100, 200, and 150 mL, respectively).

<sup>b</sup> The molar ratio was determined to be  $1_x$  (0.5 mmol): $4_z$ :manganese(III) acetate.

<sup>c</sup> Isolated yield based on the amount of the alkadiene  $1_x$  used.

yields (Table 2).<sup>13</sup> Although pentadiene  $1_1$  reacted with  $4_2$  to afford the 14-membered macrodiolide  $5_{12}$  (Entry 11), the yield was quite low (27%) as expected together with 2-methyl-3-(2,5,8-trioxo-1,9,11-trioxododecyl)-4-(3,3-diphenyl-2-propenyl)-5,5-diphenyl-4,5-dihydrofuran in 11% yield. The best yield of the macrocyclization was achieved when the combination of  $1_5$  and  $2_4$  or  $1_4$  and  $4_2$  was used, and the corresponding 17-membered macrodiolide  $3_{54}$  or  $5_{42}$  was obtained in 86% yield (Entries 9 and 14). The novel pseudo-crown type 19-membered macrodiolide (**7**) was also synthesized by the reaction of bis(3,3-diphenyl-2-propenyl) ether (**6**) with  $4_3$  under similar conditions.



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  13. For example, **5**<sub>32</sub>: Colorless crystals (from CH<sub>2</sub>Cl<sub>2</sub>/hexane), mp 258-260 °C; IR (CHCl<sub>3</sub>)  $\nu$  1690, 1644; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.34-7.01 (20H, m), 4.37-4.34 (2H, m), 4.01-3.91 (2H, m), 3.64-3.53 (6H, m), 2.19 (3H, s), 2.17 (3H, s), 1.20-0.67 (6H, m); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  166.02, 165.96, 164.78, 164.68, 144.40, 144.33, 139.90, 139.81, 127.01, 126.70, 126.57, 125.93, 125.88, 125.57, 125.49, 125.15, 125.07, 107.08, 106.64, 94.33, 94.18, 68.29, 68.18, 61.59, 61.45, 48.54, 48.08, 31.09, 30.76, 23.08, 22.28, 13.42, 13.26; FAB MS *m/z* 671 (M+1). Anal. Calcd for C<sub>43</sub>H<sub>42</sub>O<sub>7</sub>: C, 76.99; H, 6.31. Found: C, 76.69; H, 6.31.