

# Synthesis of Macrocyclic Compounds Using Oxidative Radical Cyclization

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**Abstract**—Manganese(III)-based oxidative free-radical macrocyclization was examined.  $\alpha,\alpha,\omega,\omega$ -Tetraaryl- $\alpha,\omega$ -alkadienes **1<sub>x</sub>** ( $x = 6, 8, 12, 16, 18, 28$ ) and oligomethylene bis(3-oxobutanoate)s **2<sub>y</sub>** ( $y = 6, 10, 12, 16, 20, 26$ ) were allowed to react with manganese(III) acetate in acetic acid at 100 °C under an argon atmosphere to give the 20- to 62-membered huge macrocyclic compounds **3<sub>xy</sub>** in good to moderate yields. A similar reaction of alkadienes **4<sub>5</sub>**, **7<sub>2</sub>** with bis(3-oxobutanoate)s **5<sub>7</sub>**, **8<sub>1</sub>**, **8<sub>2</sub>** containing *p*-phenylene in the alkyl chain also afforded the cyclophane-type macrocyclic compounds **6**, **9<sub>1</sub>**, **9<sub>2</sub>**, **10<sub>1</sub>**, **10<sub>2</sub>** in acceptable yields. The mechanism for the formation of the macrodiolides was explained by the production of intramolecular electron donor-acceptor-type complex **E** between the donor terminal olefin part and the acceptor manganese(III)-enolate moiety.

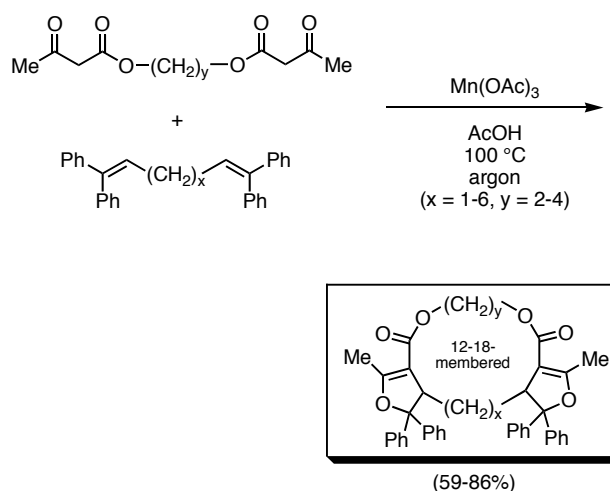
## 1. Introduction

Many naturally occurring macrocyclic compounds 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> and etc., are known, and some have significant biological activities. Some other 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 four decades.<sup>8</sup>

Recently, the radical cyclization using transition metal complexes has been extensively investigating.<sup>9</sup> We have investigated the oxidative radical reaction using manganese(III) complexes as a carbon radical promoter, and reported many novel reactions and new interesting compounds.<sup>10</sup> The reaction of alkenes with 1,3-dicarbonyl compounds in the presence of manganese(III) acetate gave the corresponding 4,5-dihydrofurans<sup>11</sup> and 1,2-dioxan-3-ols<sup>10b,12</sup> in good yields. Yoshida et al. reported that a similar reaction of  $\alpha,\alpha,\omega,\omega$ -tetraaryl- $\alpha,\omega$ -alkadienes with  $\beta$ -ketoesters gave bis(dihydrofuran)s.<sup>13</sup> Ouyang et al. also reported that the reaction of 1,1-diarylethenes with oligomethylene di(3-oxobutanoate)s afforded oligomethylene bis(dihydrofuran-carboxylate)s in good yields.<sup>14</sup> In addition, a similar reaction of 1,1,6,6-tetraphenyl-1,5-hexadiene with ethylene bis(3-oxobutanoate) gave a new 12-membered macrocyclic diester annulated two sets of dihydrofuran in a 40% yield. Yoshinaga et al. have achieved the facile macrocyclization of  $\alpha,\alpha,\omega,\omega$ -tetraaryl- $\alpha,\omega$ -alkadienes with oligomethylene bis(3-oxobutanoate)s in the presence of manganese(III) acetate (Scheme 1).<sup>15</sup> Kawanabe, Tomiyasu, Uemura, and Ushimizu also have accomplished the synthesis of cyclophane-type macrodiolides using a similar macrocyclization of  $\alpha,\alpha,\omega,\omega$ -tetraaryl- $\alpha,\omega$ -alkadienes with phenylene bis(3-oxobutanoate)s in the presence of manganese(III)

acetate.<sup>16</sup> In general, it was difficult to synthesize larger macrocyclic compounds than six-membered cyclic compounds using radical cyclization instead of ionic strategy. We applied the macrocyclization to much longer methylene-tethered terminal dienes with oligomethylene bis(3-oxobutanoate)s, in order to synthesize huge macrocyclic compounds larger than 18-membered macrodiolide and examine the limitation of the macrocyclization.<sup>17</sup> We also attempted to prepare  $\alpha,\alpha,\omega,\omega$ -tetraaryl- $\alpha,\omega$ -alkadienes containing benzene ring and synthesize cyclophane-type macrodiolides including two benzene rings.<sup>18</sup>

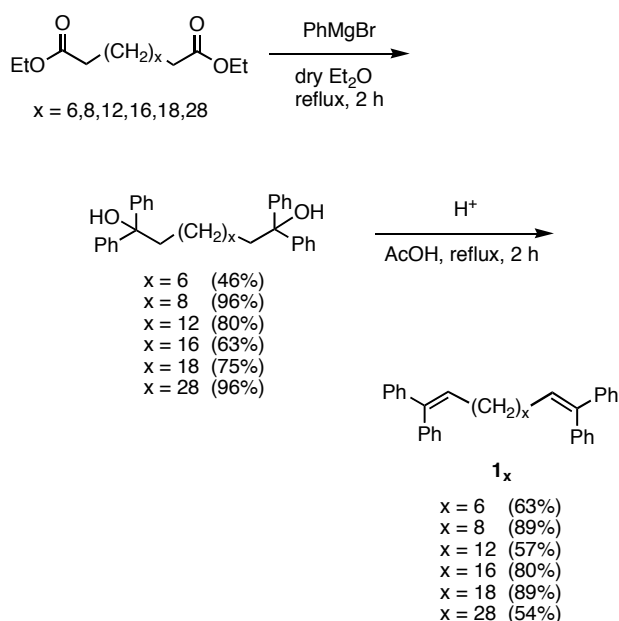
## 2. Results and Discussion



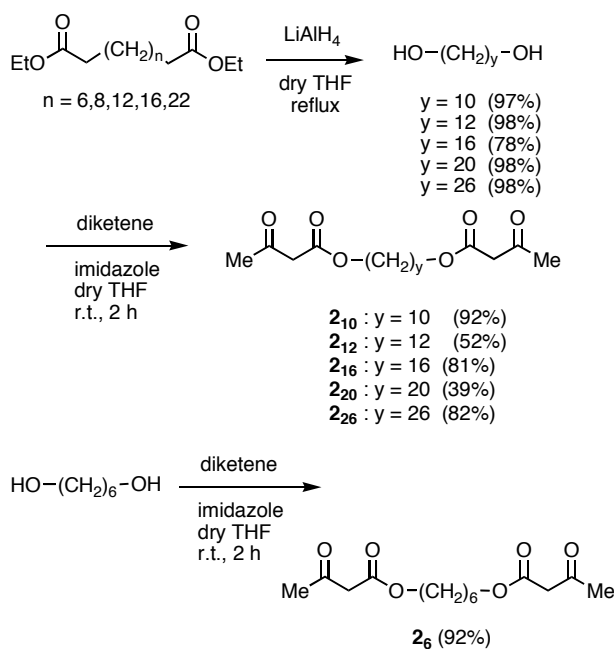
Scheme 1.

Methylene-tethered diethyl esters were prepared according to the literature.  $\alpha,\alpha,\omega,\omega$ -Tetraaryl- $\alpha,\omega$ -alkadienes **1** were synthesized by dehydration of the corresponding diols which were prepared by the reaction of the diethyl esters with phenylmagnesium bromide (Scheme 2).

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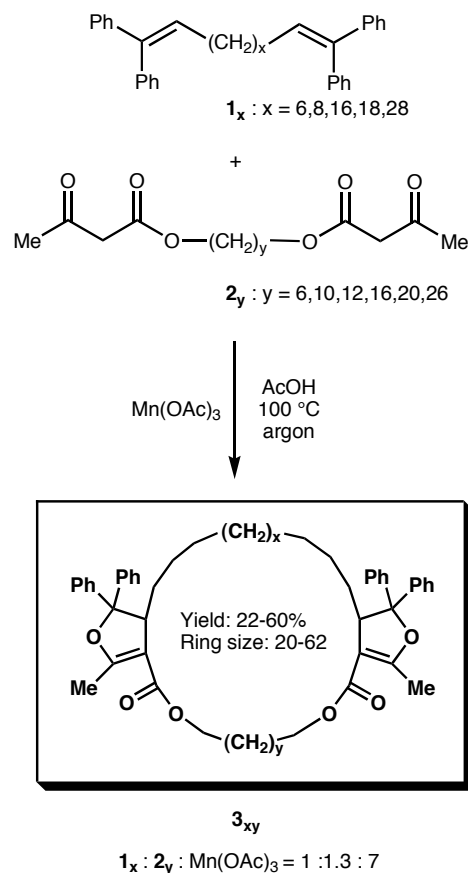
Scheme 2.



Scheme 3.

Oligomethylene bis(3-oxobutanoate)s **2** were synthesized by the reaction of diketene with the corresponding diols prepared by the reduction of the diethyl esters with lithium aluminum hydride (Scheme 3). A mixture of terminal dienes **1** and oligomethylene bis(3-oxobutanoate)s **2** was allowed to react with manganese(III) acetate in acetic acid at 100 °C under an argon atmosphere, giving new from the 20- to 62-membered macrodiolides **3** in 22-60% yields (Scheme 4). Since the methylene-tethered terminal dienes **1** and

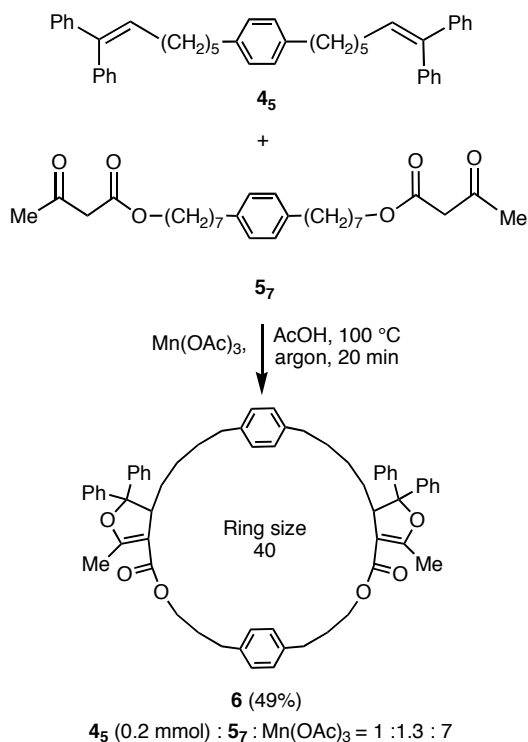
oligomethylene bis(3-oxobutanoate)s **2** must be more flexible than those synthesized by Yoshinaga et al., it was predicted that the macrocyclization should be effective. However, the yield of the obtained macrodiolides **3** was not excellent but moderate.



Scheme 4.

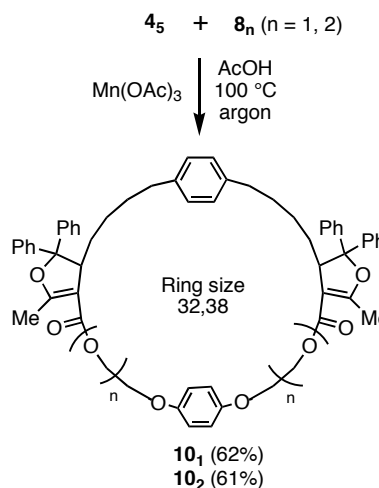
A similar reaction of *p*-phenylenebis(7,7-diphenyl-6-heptene) **4**<sub>5</sub> with *p*-phenylenebis(heptamethylene) bis(3-oxobutanoate) **5**<sub>7</sub> was carried out in acetic acid at 100 °C under an argon atmosphere, and new 40-membered cyclophane-type macrodiolide **6** was obtained in a 49% yield (Scheme 5).

Moreover, *p*-phenylenebis(1,4,7-trioxa-10,10-diphenyl-9-decene) **7**<sub>2</sub> was synthesized by the reaction of the corresponding alcohol with 3-bromo-1,1-diphenylpropene. Bis(3-oxobutanoate)s **8**<sub>n</sub> ( $n = 1, 2$ ) were synthesized by the esterification of the corresponding alcohols with diketene. The reaction of *p*-phenylenebis(1,4,7-trioxa-10,10-diphenyl-9-decene) **7**<sub>2</sub> with bis(3-oxobutanoate)s **8**<sub>n</sub> was conducted in the presence of manganese(III) acetate in acetic acid at 100 °C under an argon atmosphere, giving new 38- and

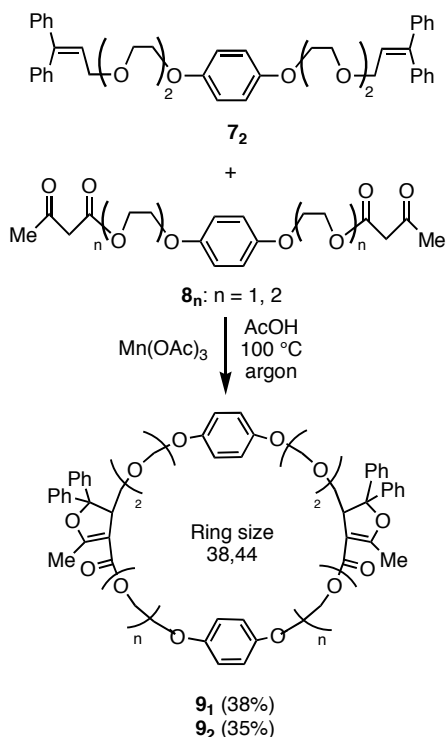


Scheme 5.

allowed to react with manganese(III) acetate in acetic acid at 100 °C under an argon atmosphere and new 32- and 38-membered cyclophane-type macrodiolides **10<sub>1</sub>** and **10<sub>2</sub>** were produced in 62 and 61% yields, respectively (Scheme 7). Since the yields of the cyclophane-type macrodiolides were not reproducible, it seemed that the  $\pi$ - $\pi$  interaction between the benzene ring of **4** and **8** did not work during



Scheme 7.



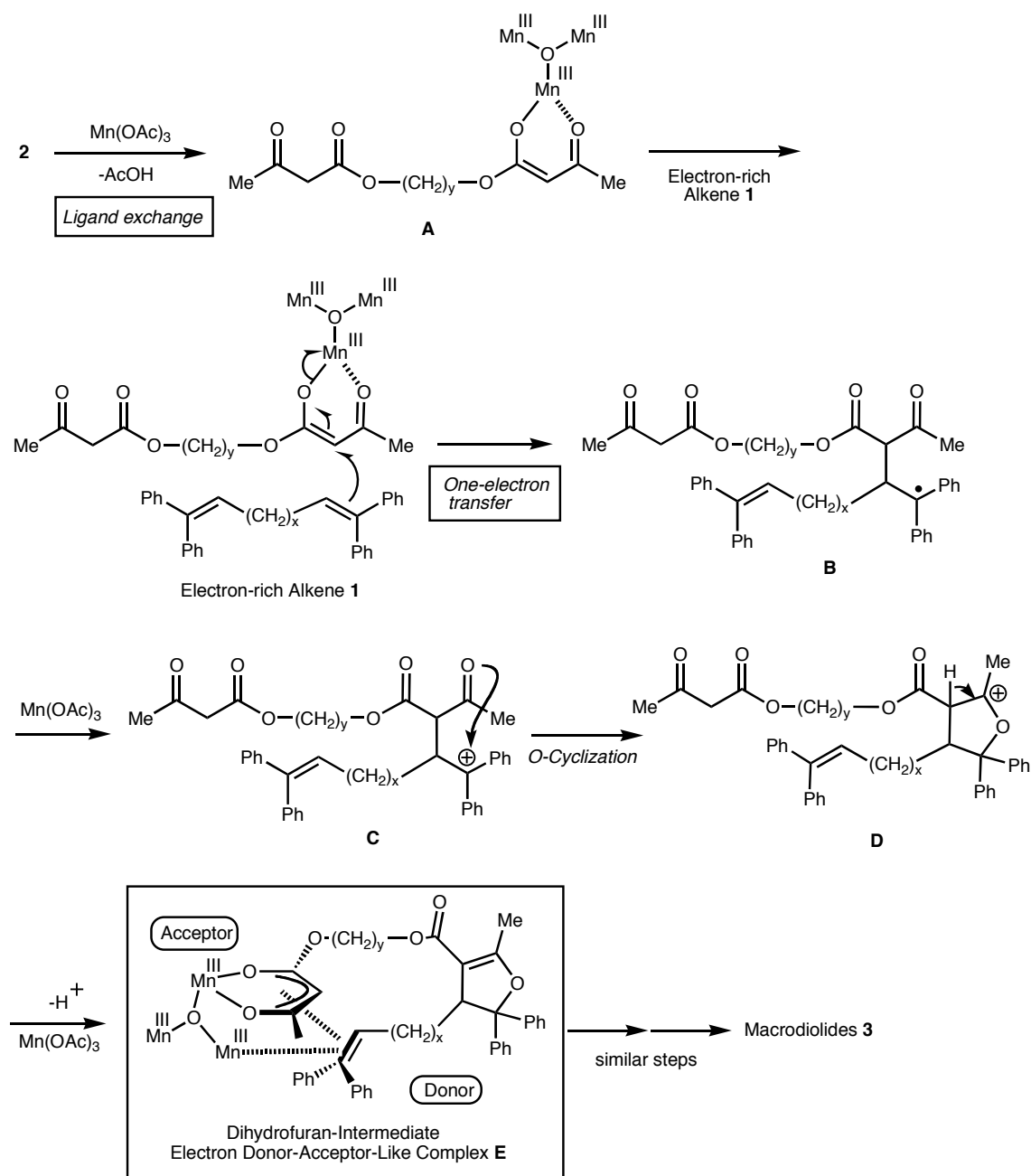
Scheme 6.

44-membered cyclophane-type macrodiolides **9<sub>1</sub>** and **9<sub>2</sub>** in 38% and 35% yields, respectively (Scheme 6).

Finally, a combination of *p*-phenylenebis(7,7-diphenyl-6-heptene) **4<sub>5</sub>** and bis(3-oxobutanoate)s **8<sub>n</sub>** ( $n = 1, 2$ ) was

the macrocyclization.

The proposed mechanism for the formation of the macrodiolides **3** is outlined in Scheme 8. The manganese(III)-based oxidative macrocyclization could be explained by a similar mechanism for the reaction using the 2-(2-oxoethyl)malonates.<sup>11,16</sup> The enolate complex **A** would be formed by the reaction of the bis(3-oxobutanoate) **2** with manganese(III) acetate during the first stage. It is known that the manganese(III)-enolate complex formation is the rate-determining step.<sup>8a,9c</sup> The enolate complex **A** easily oxidized the electron-rich alkadiene **1** via a weak interaction between the complex **A** and the alkene **1** such as an electron donor-acceptor-like complex,<sup>9c</sup> giving the corresponding tertiary carbon radicals **B**, which were rapidly oxidized by sufficient amounts of manganese(III) acetate under the present conditions. As a result, the carbocations **C** would be formed and then cyclized at the keto carbonyl oxygen of the oxobutanoate to produce the monodihydrofuran intermediate *via* the deprotonation of the thermodynamically more stable carbocations **D**. A similar enolate formation of the dihydrofuran intermediate with manganese(III) acetate would again occur and the intramolecular electron donor-acceptor-type complex **E** between the donor terminal olefin part and the acceptor manganese(III)-enolate moiety should be produced. Accordingly, the intramolecular oxidative cyclization would be favored and the desired macrodiolides **3** would be finally obtained. The formation of the cyclophane-type macrodiolides **6**, **9**, and **10** would be also explained by a similar mechanism described above.



Scheme 8.

### 3. Conclusion

The synthesis from the 20- to 62-membered macrodiolides and cyclophane-type macrodiolides were accomplished by the oxidative radical cyclization using manganese(III) acetate. It was found that the product yields depended on the ring size regardless of the flexibility and length of the spacer. It was also found that the  $\pi$ - $\pi$  interaction of the benzene rings did not work during the reaction between alkydienes and bis(3-oxobutanoate)s.

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