Pergamon

Tetrahedron Letters 43 (2002) 9031–9034

TETRAHEDRON LETTERS

Manganese(III)-based intramolecular macrocyclization of 3,3-diphenyl-2-propenyloxyoligomethylene 3-oxobutanoates

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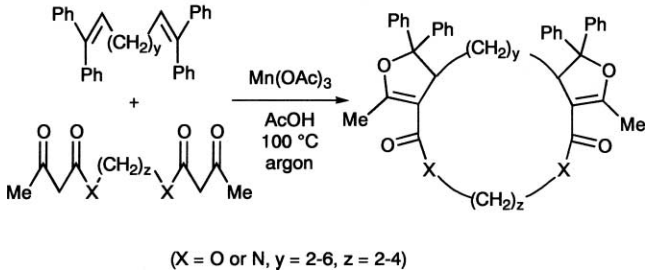
Received 21 September 2002; revised 11 October 2002; accepted 15 October 2002

Abstract—The reaction of 3,3-diphenyl-2-propenyloxytetramethylene 3-oxobutanoate ($\mathbf{1_4}$) with manganese(III) acetate dihydrate in boiling acetic acid caused the oxidative intramolecular radical cyclization to produce 13-methyl-11,11-diphenyl-3,8,12-trioxabicyclo[8.3.0]tridec-13-en-2-one ($\mathbf{2_4}$) in 94% yield. A similar oxidation of the 3,3-diphenyl-2-propenyloxyoligomethylene 3-oxobutanoates ($\mathbf{1_n}$: $n=2$, 3, 6, 8) gave the corresponding macrolides $\mathbf{2_n}$ ($n=2$, 3, 6, 8) in moderate to good yields. A 17-membered crown ether-type macrolide $\mathbf{2_{11}}$ was also obtained in 80% yield by the intramolacular radical cyclization of the oxaethylene-tethered 3-oxobutanoate ($\mathbf{1_{11}}$). The structure of the macrolides $\mathbf{2_n}$ ($n=2$, 3, 4, 6, 11) has been corroborated by an X-ray crystal structure analysis.

Recently, we reported the straightforward access to functionalized large ring compounds which were obtained by the oxidation of oligomethylene di(3-oxobutanoate)s or *N*,*N*′-oligomethylenebis(acetoacetamide)s with manganese(III) acetate in the presence of terminal alkadienes.[1,2] In the method, we obtained from 11- to 22-membered macrodiolides or macrodiamides, each possessing two fused dihydrofuran rings, in good yields. It was postulated that the macrocyclization took place by the intermolecular mono-cyclization of the terminal alkadiene with the manganese(III)–enolate complex of 1,3-dicarbonyl moiety, followed by the intramolecular dihydrofuranation according to electron donor–acceptor like complex formation of a carbon–carbon double bond (donor) with the manganese(III)–enolate complex (acceptor) (Scheme 1).[3]



Scheme 1.

Although many ionic macrocyclizations promoted by metal cations are known,[4] the oxidative radical macrocyclization was apparently characteristic of manganese(III)-based oxidation chemistry. In connection with the inter- and intramolecular large ring formations, we were interested in the ability of the manganese(III)-based intramolecular macrocyclization since five-, six-, and seven-membered cyclic compounds could be formed by the manganese(III)-[5] or other transition metal-based intramolecular cyclization.[6] In order to explore the intramolecular macrocyclization, 3,3-diphenyl-2-propenyloxytetramethylene 3-oxobutanoate ($\mathbf{1_4}$) was prepared and allowed to react with manganese(III) acetate. Surprisingly, the reaction afforded the corresponding 10-membered cyclic compound which would be difficult to form by the oxidative radical cyclization. This fact prompted us to scrutinize the manganese(III)-based macrocyclization.

3-Oxobutanoate ($\mathbf{1_4}$, 0.5 mmol) prepared in four steps from benzophenone was oxidized with a stoichiometric amount of manganese(III) acetate (1.0 mmol) in acetic acid (250 mL) at 100°C under an argon atmosphere to give the desired bicyclic compound $\mathbf{2_4}$ in 35% yield along with a small amount of unchanged $\mathbf{1_4}$ (15%) (Scheme 2 and Table 1, entry 1). Although the stoichiometry of the intramolecular macrocyclization was $\mathbf{1_4}$:$Mn(OAc)_3=1:2$, the oxidative macrocyclization at 100°C was not efficient because of the competitive electron-transfer oxidation of the carbon–carbon double bond of $\mathbf{1_4}$ and the oxidation of the solvent (entry

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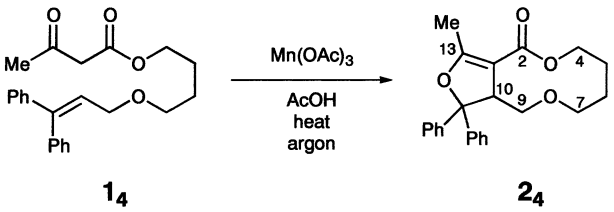
PII: S0040-4039(02)02282-7



$\mathbf{1_4}$ $\mathbf{2_4}$

Scheme 2.

Table 1. Manganese(III)-based oxidation of 3,3-diphenyl-2-propenyloxytetramethylene 3-oxobutanoate ($\mathbf{1_4}$)[a]

Entry	Molar ratio[b]	Temperature (°C)	Time (min)	Yield of $\mathbf{2_4}$ (%)[c]
1	1:2	100	120	35
2	1:4	100	120	47
3	1:10	100	60	75
4	1:4	120	15	69
5	1:5	120	15	94

[a] The reaction of $\mathbf{1_4}$ (0.5 mmol) with manganese(III) acetate dihydrate was carried out in acetic acid (250 mL) under an argon atmosphere.
[b] $\mathbf{1_4}$: manganese(III) acetate.
[c] Isolated yield based on the amount of $\mathbf{1_4}$ used.

1).[7] The use of an excess amount of manganese(III) acetate at 100°C led to increase the yield of $\mathbf{2_4}$, however, the concomitant oxidation of the solvent and the competitive electron-transfer oxidation of $\mathbf{1_4}$ still occurred (entries 2 and 3). In general, to avoid the electron-transfer oxidation of carbon–carbon double bond during the manganese(III) oxidation, it is known that the reaction is carried out at the reflux temperature.[8] In addition, the oxidation of the solvent is also controlled since the reaction time shortens at the reflux temperature. Therefore, we adopted the reaction conditions and the best yield of $\mathbf{2_4}$ (94% yield) was achieved (entry 5). The peaks in the ^{1}H NMR spectrum of $\mathbf{2_4}$ were well split[9] and the correlation of the HC COSY spectrum showed a good agreement. That is, the peak at δ 4.34 showed a ddq splitting pattern assigned to the H-10 proton coupled with the H-9 methylene protons ($J=11.71$ and 4.96 Hz) and methyl protons ($J=0.80$ Hz). A triplet at δ 3.12 (1H, $J=11.71$ Hz) and double doublets at δ 2.90 (1H, $J=11.71$ and 4.96 Hz) were due to the H-9 methylene protons. A peak deshielded by the carbonyl group appeared at δ 4.83 (1H, ddd, $J=10.91$, 5.28, and 2.94 Hz) and assigned to one of the methylene protons of H-4. The double triplets at δ 3.79 (1H, $J=10.91$ and 1.70 Hz) were due to the other methylene proton of H-4. The H-7 methylene proton peaks also turned up at δ 3.88 (1H, ddd, $J=11.75$, 8.38, and 2.94 Hz) and δ 3.40 (1H, ddd, $J=8.38$, 4.72, and 2.40 Hz), along with the four methylene protons of H-5 and H-6 as four multiplets at δ 2.02, 1.78, 1.60, and 1.50. The ^{13}C NMR spectrum showed a lactone carbonyl carbon and the characteristic sp^2 carbons of dihydrofuran.

Although the result of the FAB mass spectrum and elemental analysis of $\mathbf{2_4}$ was also supported the structure shown in Scheme 2, in order to corroborate the exact structure, a single crystal of $\mathbf{2_4}$ was successfully grown from hexane and measured by X-rays. As a result, the structure of $\mathbf{2_4}$ was finally characterized as 13-methyl-11,11-diphenyl-3,8,12-trioxabicyclo[8.3.0]tridec-13-en-2-one (Fig. 1).[10]

The manganese(III)-based oxidative intramolecular radical cyclization deserves attention since it is known that the cyclodecane ring system is kinetically and thermodynamically the most difficult to prepare by intramolecular cyclization.[11] We next investigated a similar reaction of other 3,3-diphenyl-2-propenyloxy-oligomethylene 3-oxobutanoates ($\mathbf{1_n}$: $n=2$, 3, 6, 8) and obtained the corresponding macrocyclic compounds $\mathbf{2_n}$ ($n=2$, 3, 6, 8) in moderate to good yields (Scheme 3, Table 2). In addition, 15,15-diphenyl-3,6,9,12-tetraoxa-14-pentadecenyl 3-oxobutanoate ($\mathbf{1_{11}}$) was also prepared and oxidized under similar reaction conditions to give the 17-membered crown ether-type macrolide $\mathbf{2_{11}}$ in 80% yield.

The structure of the macrolides $\mathbf{2_n}$ was determined by spectroscopic analysis and X-ray crystallography except for $\mathbf{2_8}$. The crystal structure of the 17-membered macrolide $\mathbf{2_{11}}$ deserves comment. The maximum cavity size observed was 7.319 Å (between C2 and C10 in Fig. 2) in the solid state and a water molecule has been trapped in the cavity by the hydrogen-bonding between the ether oxygens (O4 and O6 in Fig. 2).[12,13] This reminds us of the inclusion ability of a crown ether.

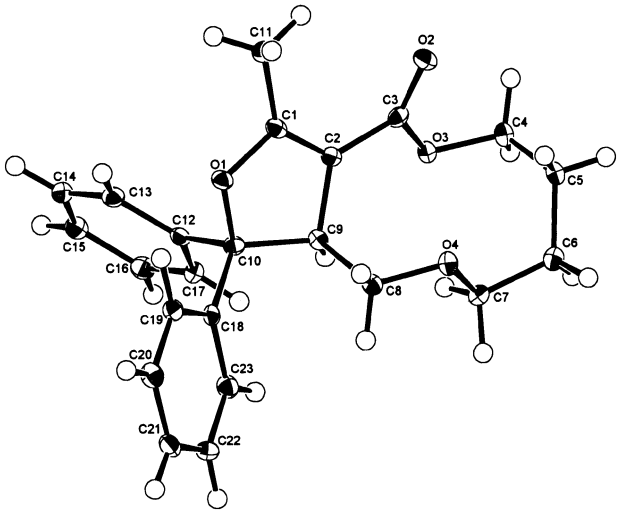
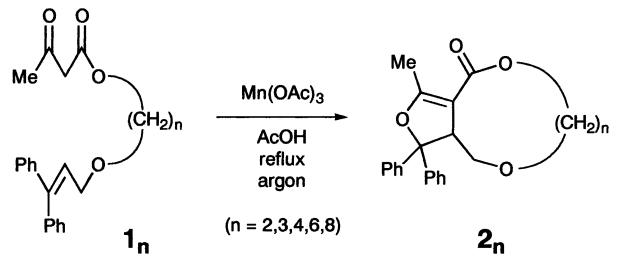


Figure 1. ORTEP drawing of $\mathbf{2_4}$.



$\mathbf{1_n}$ $\mathbf{2_n}$

Scheme 3.

Table 2. Manganese(III)-based oxidation of 3,3-diphenyl-2-propenyloxyoligomethylene 3-oxobutanoate $\mathbf{1}_n$[a]

Entry	Substrate $\mathbf{1}_n$	Time (min)	Yield of $\mathbf{2}_n$ (%)[b]	Ring size[c]
1	$\mathbf{1}_2$	15	$\mathbf{2}_2$ (55)	8
2	$\mathbf{1}_3$	10	$\mathbf{2}_3$ (82)	9
3	$\mathbf{1}_4$	15	$\mathbf{2}_4$ (94)	10
4	$\mathbf{1}_6$	15	$\mathbf{2}_6$ (51)	12
5	$\mathbf{1}_8$	15	$\mathbf{2}_8$ (51)	14
6	$\mathbf{1}_{11}$[d]	15	$\mathbf{2}_{11}$ (80)	17

[a] The reaction of $\mathbf{1}_n$ (0.5 mmol) with manganese(III) acetate dihydrate was carried out in boiling acetic acid (250 mL) under an argon atmosphere at the molar ratio of $\mathbf{1}_n$:manganese(III) acetate = 1:5.
[b] Isolated yield based on the amount of $\mathbf{1}_n$ used.
[c] The ring size revealed the biggest ring in the bicyclic system.
[d] 15,15-Diphenyl-3,6,9,12-tetraoxa-14-pentadecenyl 3-oxo-butanoate.

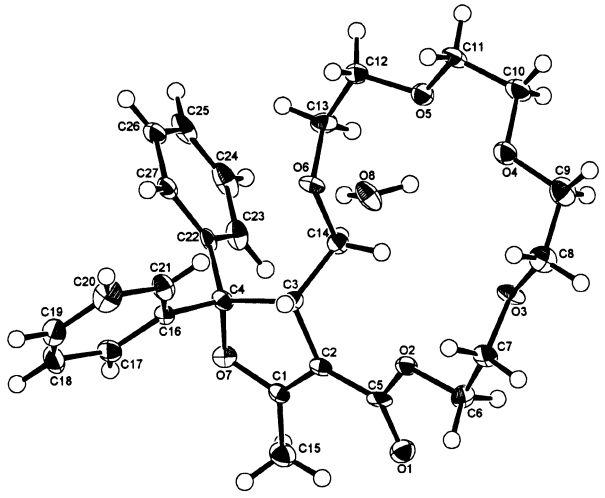
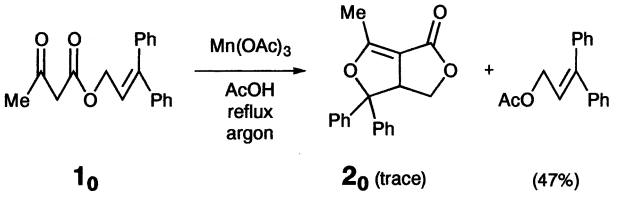


Figure 2. ORTEP drawing of $\mathbf{2}_{11}\cdot H_2O$.

Actually, we examined the extraction ability of $\mathbf{2}_{11}$ using alkaline picrates in two-phase system of deuteriochloroform and water at room temperature. As a result, sodium picrate in water was extracted into the organic layer containing $\mathbf{2}_{11}$.[4a]

In order to synthesize the dioxabicyclo[3.3.0]octenone as the smallest ring size in the reaction, 3,3-diphenyl-2-propenyl 3-oxobutanoate ($\mathbf{1}_0$) was prepared in three steps from 3-chloro-1,1-diphenyl-1-propene and allowed to react with manganese(III) acetate (Scheme 4). It was strange, but only a trace amount of the corresponding bicyclic compound $\mathbf{2}_0$ was formed together with 3,3-diphenyl-2-propenyl acetate in 47% yield, nevertheless, the 5-*exo*-trig cyclization was favored in the radical cyclization.[11b,14] Probably, the electron-transfer oxidation of the carbon–carbon double bond of $\mathbf{1}_0$ might be favored because of the electronic reason of the allyl substituent.[15]



Scheme 4.

In conclusion, we have demonstrated the unique manganese(III)-based oxidative radical macrocyclization of 3,3-diphenyl-2-propenyloxyolygomethylene 3-oxobutanoates and their derivatives. Efforts are currently underway in our laboratories to investigate the limitation of the manganese(III)-based radical large ring formation.

Acknowledgements

We thank Professor Emeritus Kazu Kurosawa, Kumamoto University, Japan, for his helpful discussions and suggestions. This research was supported by Grant-in-Aid for Scientific Research on Priority Areas (A) 'Exploitation of Multi-Element Cyclic Molecules' No. 13029088 and No. 14044078, from the Ministry of Education, Culture, Sports, Science and Technology, Japan, and also by a Grant-in-Aid for Scientific Research, No. 13640539, from the Japan Society for the Promotion of Science.

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9. 13 - Methyl - 11,11 - diphenyl - 3,8,12 - trioxabicyclo[8.3.0]-tridec-13-en-2-one (**2$_4$**): R_f = 0.11 (chloroform); mp 154.5–155.0°C (from hexane); IR (KBr) ν 1697 (C=O), 1654 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52–7.49 (2H, m, arom H), 7.33–7.24 (8H, m, arom H), 4.83 (1H, ddd, J = 10.91, 5.28, 2.94 Hz, H-4a), 4.34 (1H, ddq, J = 11.71, 4.96, 0.80 Hz, H-10), 3.88 (1H, ddd, J = 11.75, 8.38, 2.94 Hz, H-7a), 3.79 (1H, dt, J = 10.91, 1.70 Hz, H-4b), 3.40 (1H, ddd, J = 8.38, 4.72, 2.40 Hz, H-7b), 3.12 (1H, t, J = 11.71 Hz, H-9a), 2.90 (1H, dd, J = 11.71, 4.96 Hz, H-9b), 2.28 (3H, d, J = 0.80 Hz, CH_3), 2.02 (1H, m, H-5a), 1.78 (1H, m, H-6a), 1.60 (1H, m, H-6b), 1.50 (1H, m, H-5b); ^{13}C NMR (300 MHz, $CDCl_3$) δ 166.25 (C=O), 165.98 (C-13), 144.34, 139.72 (arom C), 128.18 (2C), 127.99 (2C), 127.94, 127.22, 126.20 (2C), 126.15 (2C) (arom CH), 108.01 (C-1), 92.99 (C-11), 71.78 (C-9), 67.28 (C-7), 65.01 (C-4), 44.36 (C-10), 27.95 (C-6), 24.31 (C-5), 13.96 (CH_3); FAB HR MS found m/z 365.1753, calcd for $C_{23}H_{25}O_4$ M+1, 365.1753. Anal. calcd for $C_{23}H_{24}O_4$: C, 75.80; H, 6.64. Found: C, 75.60; H, 6.80%.
10. X-Ray crystallographic data of **2$_4$**: empirical formula $C_{23}H_{24}O_4$; formula weight 364.44; colorless prisms; crystal dimensions 0.20×0.30×0.50 mm; monoclinic; space group $P2_1/c$ (#14); a = 12.4571(4), b = 11.1574(4), c = 13.9385(4) Å, β = 107.8410(7)°, V = 1844.13(10) Å^3, Z = 4; D_{calcd} = 1.313 g/cm^3; $F(000)$ = 776.00; μ(MoKα) = 0.89 cm^{-1}; $2\theta_{max}$ = 55.0°; No. of reflections measured 17268; no. of observations (I>3.00$\sigma(I)$) 2383; no. of variables 341; reflection/parameter ratio was 6.99; R = 0.030; R_w = 0.028; GOF = 1.07.
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12. 20-Methyl-18,18-diphenyl-3,6,9,12,15,19-hexaoxabicyclo-[15.3.0]icos-20-en-2-one (**2$_{11}$**): R_f = 0.19 (chloroform); mp 113.6–114.0°C (from ethanol); IR (KBr) ν 1694 (C=O), 1645 (-O-C=); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64–7.59 (2H, m, arom H), 7.36–7.15 (8H, m, arom H), 4.39 (1H, dt, J = 12.19, 4.42 Hz, -H$_b$C$\underline{H}_a$-), 4.13 (1H, dt, J = 12.19, 4.42 Hz, -H$_a$C$\underline{H}_b$-), 4.08 (1H, dq, J = 8.51, 1.30 Hz, H-17), 3.73–3.56 (11H, m, -O-C$\underline{H}_2$-O-), 3.38 (2H, t, J = 4.38 Hz, C$\underline{H}_2$), 3.09 (1H, dd, J = 9.49, 8.51 Hz, H-16), 2.82 (1H, dt, J = 11.81, 4.38 Hz, -H$_d$C$\underline{H}_c$-), 2.65 (1H, dt, J = 11.81, 4.38 Hz, -H$_c$C$\underline{H}_d$-), 2.34 (3H, d, J = 1.30 Hz, CH_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ 168.36 (C=O), 165.42 (C-20), 144.90, 140.50 (arom C), 127.97 (2C), 127.61 (2C), 127.17, 127.04, 126.88 (2C), 126.42 (2C) (arom CH), 102.96 (C-1), 94.72 (C-18), 70.58 (2C), 70.51, 70.49, 70.14, 69.88, 69.39, 69.23 (-O-CH$_2$-O-), 62.65 (-O-CH$_2$-O-), 51.35 (C-17), 14.39 (-CH$_3$); FAB HR MS found m/z 469.2252, calcd for $C_{27}H_{33}O_7$ M+1, 469.2226. Anal. calcd for $C_{27}H_{32}O_7 \cdot 1/4H_2O$: C, 68.56; H, 6.92%. Found: C, 68.71; H, 6.87%.
13. X-Ray crystallographic data of **2$_{11}$**: empirical formula $C_{27}H_{32}O_7$; formula weight 468.21; colorless prisms; crystal dimensions 0.30×0.40×0.30 mm; triclinic; space group $P\bar{1}$ (#2); a = 12.489(2), b = 13.727(1), c = 10.205(1) Å, α = 105.763(4), β = 109.474(3), γ = 66.135(3)°, V = 1489.2(3) Å^3, Z = 2; D_{calcd} = 1.344 g/cm^3; $F(000)$ = 630.00; μ(MoKα) = 31.83 cm^{-1}; $2\theta_{max}$ = 100.9°; no. of reflections measured 10729; no. of observations (I>3.00$\sigma(I)$, 2θ< 100.87°) 2542; no. of variables 352; reflection/parameter ratio was 7.22; R = 0.052; R_w = 0.076; GOF = 1.91.
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