Synthesis of Macrocyclic Amides Using Manganese(III)-Based Intramolecular Cyclization of *N*-(ω-Alkenyl)-3-oxobutanamides

Yosuke Ito and Hiroshi Nishino[1]

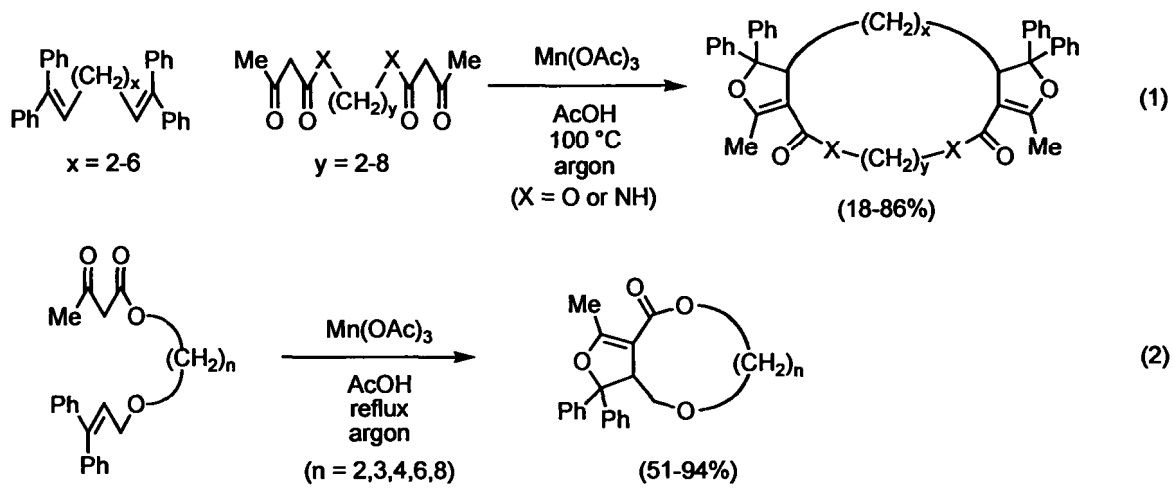
Department of Chemistry, Graduate School of Science and Technology, Kumamoto University, Kurokami 2-39-1, Kumamoto 860-8555, Japan

ABSTRACT:

The reaction of *N*-(ω-alkenyl)-3-oxobutanamides with manganese(III) acetate in glacial acetic acid at reflux temperature under an argon atmosphere resulted in the oxidative intramolecular radical cyclization that produced bicyclomacrocyclic amides in moderate to good yields.

Key Words: Macrocyclization, oxidation, macrocyclic amides, intramolecular cyclization, manganese(III) acetate.

We previously developed the manganese(III)-based macrocyclization using terminal dienes and oligomethylene-tethered bis(3-oxobutanoate)s[1] and bis(3-oxobutanamide)s,[2] and the macrocyclic compounds from eleven to twenty-two members having two fused dihydrofurans were synthesized (Scheme 1, eq. 1). The reaction is not necessarily run under dilute conditions and proceeds during the intermolecular followed by intramolecular cyclization. On the other hand, we found that the 2-propenoxyoligomethylene 3-oxobutanoates underwent the oxidative intramolecular cyclization to



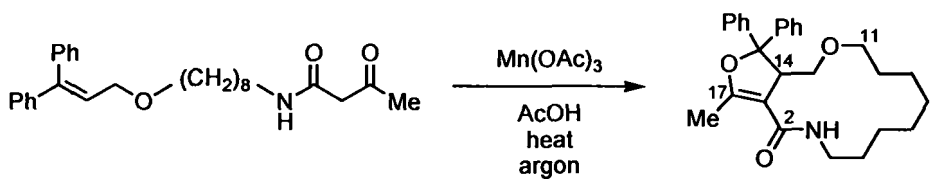
Scheme 1

[1] Corresponding author. E-mail: *nishino@sci.kumamoto-u.ac.jp*

produce the macrolides (Scheme 1, eq. 2).[3] These reactions prompted us to undertake an investigation of the oxidative intramolecular cyclization of *N*-(ω-alkenyl)-3-oxobutanamides since many biologically active macrocyclic lactams from fourteen to twenty members were isolated from natural sources,[4] e.g., the anticancer antibiotic vicenistatin[5] and hitachimycin,[6] the endothelial adhesion inhibitor cyclamenol,[7] and influenza A virus inhibitor fluvirucinine A_1.[8]

We first undertook the preparation of the *N*-(9-oxa-12,12-dipehnyl-11-dodecenyl)-3-oxobutanamide ($\mathbf{1_8}$). The Williamson ether synthesis of 1,8-octanediol with 3-bromo-1,1-diphenyl-1-propene in the presence of sodium hydride gave 8-(3,3-diphenyl-2-propenoxy)octan-1-ol (60%), which was converted under Mitsunobu conditions[9] into the corresponding phthalimide (93%) followed by hydrolysis using ethylenediamine according to the Gabriel amine synthesis. The obtained amine was then condensed using diketene to finally produce $\mathbf{1_8}$ (73%).

With the oxobutanamide $\mathbf{1_8}$ in hand, we initially examined the oxidation of $\mathbf{1_8}$ (0.2 mmol) with manganese(III) acetate (1.0 mmol) in acetic acid (100 mL) at 100 °C for 60 min under an argon atmosphere (Scheme 2 and Table 1). Fortunately, the expected intramolecular cyclization proceeded and the desired macrocyclic compound $\mathbf{2_8}$ was obtained in 32 % yield together with an intractable mixture (Entry 5). In order to improve the yield of $\mathbf{2_8}$, the reaction conditions were further examined. As a result, the yield of $\mathbf{2_8}$ increased to 47% when the reaction was carried out at reflux temperature using four equivalents of manganese(III) acetate (Entry 3).[10]



$\mathbf{1_8}$ $\mathbf{2_8}$

Scheme 2

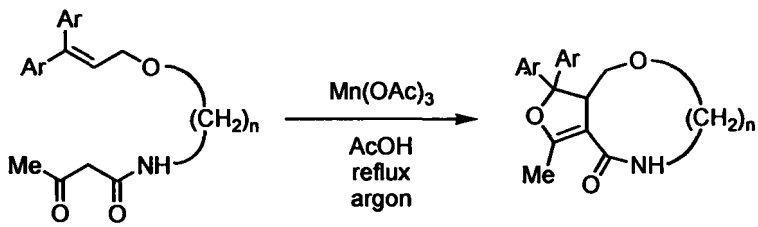
Table 1. Oxidation of *N*-(9-Oxa-11-dodecenyl)-3-oxobutanamide $\mathbf{1_8}$ with Manganese(III) Acetate[a]

Entry	$\mathbf{1_8}$:Mn(III)[b]	Temp/°C	Time/min	$\mathbf{2_8}$/%[c]	Recovery/%[c]
1	1:2	reflux	2	35	29
2	1:3	reflux	5	39	15
3	1:4	reflux	10	47	-
4	1:5	reflux	10	36	-
5	1:5	100	60	32	-
6	1:6	reflux	50	33	-

[a] The reaction of $\mathbf{1_8}$ (0.2 mmol) was carried out in glacial acetic acid (100 mL) under an argon atmosphere. Before the reaction, the mixture was degassed under reduced pressure for 30 min using an ultrasonicator followed by the displacement with argon. [b] Molar ratio. [c] Isolated yield based on $\mathbf{1_8}$.

The structure of $\mathbf{2_8}$ was characterized by a spectroscopic method. The carbonyl absorption at 1712 cm^{-1} in the IR, the peak at δ204.9 ppm assigned to a keto-carbonyl carbon in the ^{13}C NMR, an olefinic proton at δ6.22 ppm (1H, t, J = 6.6 Hz) and methylene protons of the β-ketoamido group at δ3.39 ppm (2H, s) in the ^1H NMR spectrum of the starting material $\mathbf{1_8}$ disappeared from those of the product $\mathbf{2_8}$, while a methine proton at δ3.82 (1H, dd, J = 9.2 and 3.7 Hz), the carbon at δ 50.0 ppm, and three quaternary carbons at δ 164.7, 110.0 and 93.3 ppm newly appeared in those of the

product 2_8. These results indicated that the intramolecular cyclization occurred and the fused dihydrofuran ring must have been formed. In addition, the positive FAB HRMS of 2_8 showed the molecular ion peak at *m/z* 420.2534 (M+H) which agreed with the exact molecular formula of $C_{27}H_{34}NO_3$. Therefore, the structure was determined to be 3-aza-17-methyl-12,16-dioxa-15,15-diphenylbicyclo[12,3,0]heptadec-17-en-2-one (2_8).[11]



1_n 2_n

Scheme 3

Table 2. Oxidation of *N*-(*ω*-Alkenyl)-3-oxobutanamides 1_n with Manganese(III) Acetate[a]

Entry	1_n		1_n:Mn(III)[b]
	Ar	n	
1	Ph	2	1:4
2	Ph	3	1:5
3	Ph	4	1:4
4	Ph	5	1:4
5	Ph	6	1:4
6	Ph	8	1:4
7	4-ClC_6H_4	8	1:4
8	4-MeC_6H_4	8	1:4
9	Ph	10	1:5
10	Ph	20	1:6

[a] The reaction of 1_n (0.2 mmol) was carried out in glacial acetic acid (100 mL) under an argon atmosphere. Before the reaction, the mixture was degassed under reduced pressure for 30 min using an ultrasonicator followed by the displacement with argon. [b] Molar ratio. [c] Isolated yield based on 1_n.

In order to scrutinize the intramolecular cyclization, other *N*-(*ω*-alkenyl)-3-oxobutanamides (Ar = Ph, 4-ClC_6H_4, 4-MeC_6H_4; n = 2-6,8,10,20) were synthesized according to the above Williamson reaction followed by the Gabriel method, and subjected to the reaction under similar conditions (Scheme 3). As a result, the desired macrocyclic amides from eight to twenty-six members having a dihydrofuran ring were isolated in good to moderate yields (Table 2). The best yield of the macrocyclic amide 2_3 (67%) was achieved by the reaction using *N*-(4-oxa-7,7-dipehnyl-6-heptenyl)-3-oxobutanamide (1_3: Ar = Ph, n = 3) (Entry 2).

Fortunately, a single crystal of 2_5 (Ar = Ph, n = 5) was successfully grown from chloroform-hexane in the monoclinic space group $P2_1/a$ with the cell constants a = 19.394(7), b = 9.160(2), c = 11.266(5) Å, α = 90.00, β = 95.51(3), and γ = 90.00°. The crystal structure was solved by direct methods, and confirmed that the macrocyclic amide

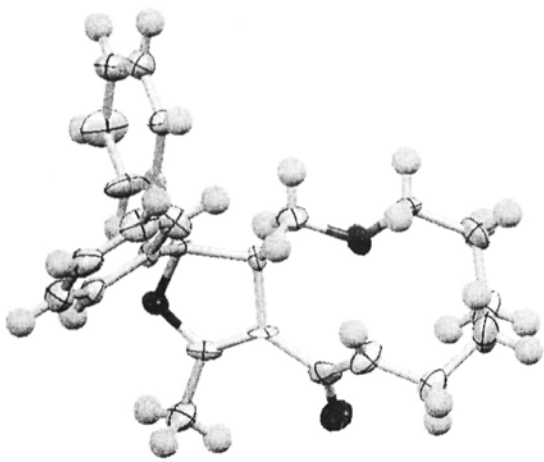
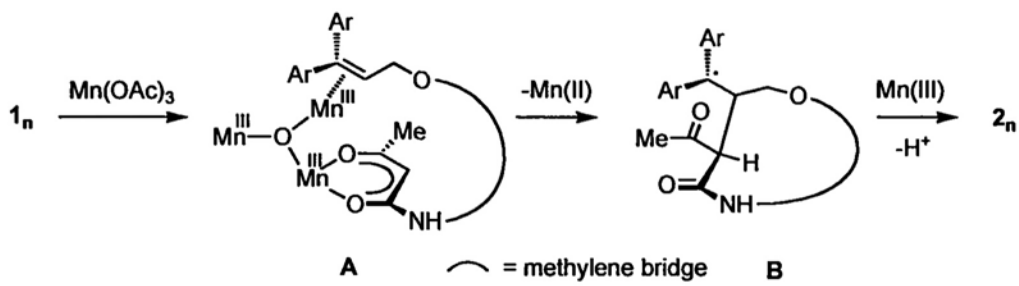


Figure 1

2_5 consisted of a dihydrofuran-fused eleven-membered ring (Figure 1).[12,13]

Although the mechansm of the manganese(III)-based oxidative intramolecular cyclization was well-documented by us[14] and other groups,[15] it was postulated that the formation of an electron-donor-acceptor-like complex (EDA complex) **A** during the first stage of the reaction of the butanamides $\mathbf{1}_n$ with manganese(III) acetate must play an important role in the head-to-tail intramolecular cyclization reaction and, subsequently, a one electron-transfer should occur to give the cyclic radical **B**, which would be further oxidized to finally produce the macrocyclic amides $\mathbf{2}_n$ (Scheme 4).

In summary, we have accomplished the unique synthesis of several macrocyclic amides $\mathbf{2}_n$ (n = 2-6,8,10.20) from eight to twenty-six members using the manganese(III)-based intramolecular cyclization of the *N*-(*ω*-alkenyl)-3-oxobutanamides $\mathbf{1}_n$. A further study of the macrocyclization and biological screening of the macrocyclic amides are currently in progress.



Scheme 4

ACKNOWLEDGMENTS

This research was supported by Grans-in-Aid for Scienetific Research (C), No. 15550039 and No. 19550046, from the Japan Society for the Promotion of Science.

REFERENCES

1. (a) Ouyang, J.; Nishino, H.; Kurosawa, K. *J. Heterocycl. Chem.* **1995**, *32*, 1783-1791. (b) Yoshinaga, T.; Nishino, H.; Kurosawa, K. *Tetrahedron Lett.* **1998**, *39*, 9197-9200.
2. Chowdhury, F. A.; Nishino, H.; Kurosawa, K. *Heterocycl. Commun.* **1999**, *5*, 111-112.
3. Jogo, S.; Nishino, H.; Yasutake, M.; Shinmyozu, T. *Tetrahedron Lett.* **2002**, *43*, 9031-9034.
4. (a) Smith, III, A. B.; Wood, J. L.; Wong, W.; Gould, A. E.; Rizzo, C. J.; Barbosa, J.; Komiyama, K.; Omura, S. *J. Am. Chem. Soc.* **1996**, *118*, 8308-8315. (b) Xu, Z.; Johannes, C. W.; Houri, A. F.; La, D. S.; Cogan, D. A.; Hofilena, G. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 10302-10316. (c) Creighton, C. J.; Reitz, A. B. *Org Lett.* **2001**, *3*, 893-895. (d) Chow, C. P.; Shea, K. J.; Sparks, S. M. *Org Lett.* **2002**, *4*, 2637-2640. (e) Liu, L.; Chen, Q.; Wu, Y.-D.; Li, C. *J. Org. Chem.* **2005**, *70*, 1539-1544. (f) Llàcer, E.; Urpí, F.; Vilarrasa, J. *Org Lett.* **2009**, *11*, 3198-3201.
5. (a) Mitchell, S. S.; Nicholson, B.; Teisan, S.; Lam, K. S.; Potts, B. C. M. *J. Nat. Prod.* **2004**, *67*, 1400-1402. (b) Araki, H.; Matsushima, Y.; Eguchi, T.; Shindo, K.; Kakinuma, K. *Tetrahedron Lett.* **1998**, *39*, 3181-3184. (c)

Otsuka, M.; Eguchi, T.; Shindo, K.; Kakinuma, K. *Tetrahedron Lett.* **1998**, *39*, 3185-3188. (d) Kudo, F.; Kakinuma, K.; Eguchi, T. *Tetrahedron Lett.* **2006**, *47*, 1529-1532. (e) Bode, H. B.; Müller, R. *Angew. Chem. Int. Ed.* **2007**, *46*, 2147-2150.

6. (a) Umezawa, I.; Takeshima, H.; Komiyama, K.; Koh, Y.; Yamamoto, H.; Kawaguchi, M. *J. Antibiot.* **1981**, *34*, 256-265. (b) Smith, III, A. B.; Rano, T. A.; Chida, N.; Sulikowski, G. A. *J. Org. Chem.* **1990**, *55*, 1136-1138. (c) Smith, III, A. B.; Rano, T. A.; Chida, N.; Sulikowski, G. A.; Wood, J. A. *J. Am. Chem. Soc.* **1992**, *114*, 8008-8022. (d) Touré, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439-4486.
7. (a) Nazaré, M.; Waldmann, H. *Angew. Chem. Int. Ed.* **2000**, *39*, 1125-1128. (b) Nazaré, M.; Waldmann, H. *Chem. Eur. J.* **2001**, *7*, 3363-3376.
8. (a) Suh, Y.-G.; Kim, S.-A.; Jung, J.-K.; Shin, D.-Y.; Min, K.-H.; Koo, B.-A.; Kim, H.-S. *Angew. Chem. Int. Ed.* **1999**, *38*, 3545-3547. (b) Liang, B.; Negishi, E. *Org Lett.* **2008**, *10*, 193-195.
9. Clive, D. L. J.; Huang, X. *Chem. Commun.* **2003**, 2062-2063.
10. A typical procedure is as follows. To a solution of the *N*-(*ω*-alkenyl)-3-oxobutanamides $\mathbf{1_n}$ (0.2 mmol) in glacial acetic acid (100 mL), manganese(III) acetate dehydrate (0.8 mmol) was added and the mixture was sufficiently degassed under reduced pressure for 30 min using an ultrasonicator for exchange with an argon atmosphere. The mixture was then heated at 100 °C under an argon atmosphere for the period mentioned in the tables until the brown color of manganese(III) disappeared. The color typically turned a transparent yellow. The solvent was removed *in vacuo*, and the residue was triturated with water (20 mL), and then extracted with $CHCl_3$ (20 mL x 3). The combined extracts were washed with a saturated aqueous solution of $NaHCO_3$ (30 mL) and water, and then concentrated to dryness. The crude products $\mathbf{2_n}$ were separated by silica gel TLC (Wako B-10 or Whatman K6F 60A) while eluting with $CHCl_3$, $CHCl_3$/MeOH, or Et_2O/hexane. The analytical samples were further purified by recrystallization from the appropriate solvent.
11. **3-Aza-17-methyl-15,15-diphenyl-12,16-dioxabicyclo[12.3.0]heptadec-17-en-2-one ($\mathbf{2_8}$)**: colorless microcrystals; mp 208-209 °C; R_f = 0.39 ($CHCl_3$); IR (KBr) ν 3500 (NH), 1663, (C=O), 1626 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52-7.22 (10H, m, arom. H), 6.89 (1H, br. s, -CONH-), 3.81 (1H, dd, J = 9.0 and 3.6 Hz, >CH-), 3.50-3.40 (1H, m, -NHCH_2-), 3.32-3.24 (2H, m, >CH-CH_2OCH_2- and -CONHCH_2-), 3.22-3.16 (1H, m, >CHCH_2OCH_2-), 3.18 (1H, t, J = 9.0 Hz, >CHCH_2OCH_2-), 2.95 (1H, dd, J = 9.0 and 3.6 Hz, >CHCH_2OCH_2-), 2.34 (3H, s, -CH_3), 1.69-1.38 (12H, m, -CH_2-); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4 (1C, -CONH-), 164.7 (1C, -C(-CH_3)=C-), 144.6, 140.6 (2C, arom. C), 128.2, 127.9, 127.8, 127.4, 126.5, 126.0 (10C, arom. CH), 110.0 (1C, -C(CH_3)=C<), 93.3 (1C, Ph_2>C), 74.2, 71.1 (2C, -CH_2OCH_2-), 50.0 (1C, >CH-), 36.9 (1C, -CONHCH_2-), 26.9, 26.3, 24.6, 23.2, 22.0, 21.7 (6C, -CH_2-), 12.7 (1C, -CH_3); FAB HRMS (acetone/NBA) calcd for $C_{27}H_{34}O_3N$ 420.2539 (M+H). Found 420.2534.
12. **3-Aza-14-methyl-12,12-diphenyl-9,13-dioxabicyclo[9.3.0]tetradec-14-en-2-one ($\mathbf{2_5}$)**: colorless microcrystals; mp 188-189 °C; R_f = 0.13 ($CHCl_3$); IR ($CHCl_3$) ν 3310 (CONH), 1666, (C=O), 1620 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (1H, m, -CONH-) 7.54-7.17 (10H, m, arom. H), 3.97 (1H, d, J = 10.2 Hz, >CH-), 3.91-3.84 (1H, m, -NHCH_2-), 3.54-3.48 (2H, m, >CHCH_2- and >CHCH_2OCH_2-), 3.34 (1H, t, J = 10.5 Hz, >CHCH_2OCH_2-), 2.89 (1H, t, J = 10.2 Hz, >CHCH_2-), 2.79 (1H, t, J = 11.6 Hz, -NHCH_2-), 2.42 (3H, s, -CH_3), 1.73-1.67, 1.53-1.43 (6H, m, -CH_2-); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9 (1C, -CONH-), 164.6 (1C, -C(-CH_3)=C-), 144.4, 140.7 (2C, arom. C), 128.3, 128.02, 127.96, 127.7, 126.5, 126.1 (10C, arom. CH), 109.4 (1C, -C(CH_3)=C<), 92.3 (1C, Ph_2>C), 75.0, 69.8 (2C, -CH_2-O-CH_2-), 51.0 (1C, >CH-), 39.7 (1C, -CONHCH_2-), 28.9, 25.5, 22.2 (3C, -CH_2-), 14.3 (1C, -CH_3); FAB HRMS (acetone-NBA) calcd for $C_{24}H_{28}O_3N$ 378.2069 (M+H). Found 378.2064.
13. X-ray crystallographic data of $\mathbf{2_5}$: empirical formula $C_{24}H_{27}O_3N$; formula weight 377.48; colorless prisms; crystal dimensions 0.20 x 0.20 x 0.20 mm; monoclinic; space group $P2_1/a$ (#14); a = 19.394(7), b = 9.160(2), c = 11.266(5) Å, α = 90.00, β = 95.51(3), and γ = 90.00°, V = 1992.1(12) Å^3, Z = 4; D_{calcd} = 1.259 g/cm^3; F(000) = 808.00; μ(MoKα) = 0.822 cm^{-1}; $2\theta_{max}$ = 55.0°; No. of reflections measured 5437; No. of observations ($I > 4.00\sigma(I)$) 595; No. of variables 283; Reflection/parameter ratio was 2.10; R = 0.0413; R_w = 0.0497; GOF = 1.448.
14. (a) Tsubusaki, T.; Nishino, H. *Heterocycl. Commun.* **2009**, *1*, 79-83. (b) Tsubusaki, T.; Nishino, H. *Tetrahedron* **2009**, *65*, 9448-9459. (c) Asahi, K.; Nishino, H. *Synthesis* **2009**, 409-423. (d) Cong, Z-Q.; Nishino, H. *Synthesis* **2008**, 2686-2694. (e) Asahi, K.; Nishino, H. *Heterocycl. Commun.* **2008**, *14*, 21-26. (f) Asahi, K.; Nishino, H. *Tetrahedron* **2008**, *64*, 1620-1634.
15. (a) Snider, B. B. *Tetrahedron* **2009**, *65*, 10738-10744. (b) Demir, A. S.; Emrullahoglu, M. *Cur. Org. Synth.* **2007**, *4*, 321-351.

Received on December 28, 2009.