HETEROCYCLES, Vol. 60, No. 4, 2003, pp. 899 - 908

Received, 10th February, 2003, Accepted, 19th February, 2003, Published online, 3rd March, 2003

A NEW METHOD FOR SYNTHESIS OF CROWN ETHER TYPE PYRIDINOPHANES

Masayuki Sato,* Tsunehisa Oda, Ken-ichi Iwamoto, and Satoshi Fujii

School of Pharmaceutical Sciences, University of Shizuoka,
52-1 Yada, Shizuoka 422-8526, Japan

Abstract-Bis(acylketene) (**3)** thermally generated from Meldrum's acid derivative (**2)** underwent intramolecular [4+2] cycloaddition to produce bridged dehydroacetic acid derivative (**4)**. Heating **4** with methylamine and ammonia afforded crown ether type pyridinophanes (**5)** and (**6)** (12-crown-4), respectively. Reaction of the ketene (**3)** with (ethylene glycol)s afforded macrolactones (**11**~**13)** in satisfactory yields. Molecular structures of **4** and **6** are discussed based on X-Ray crystallographic analysis.

INYTRODUCTION

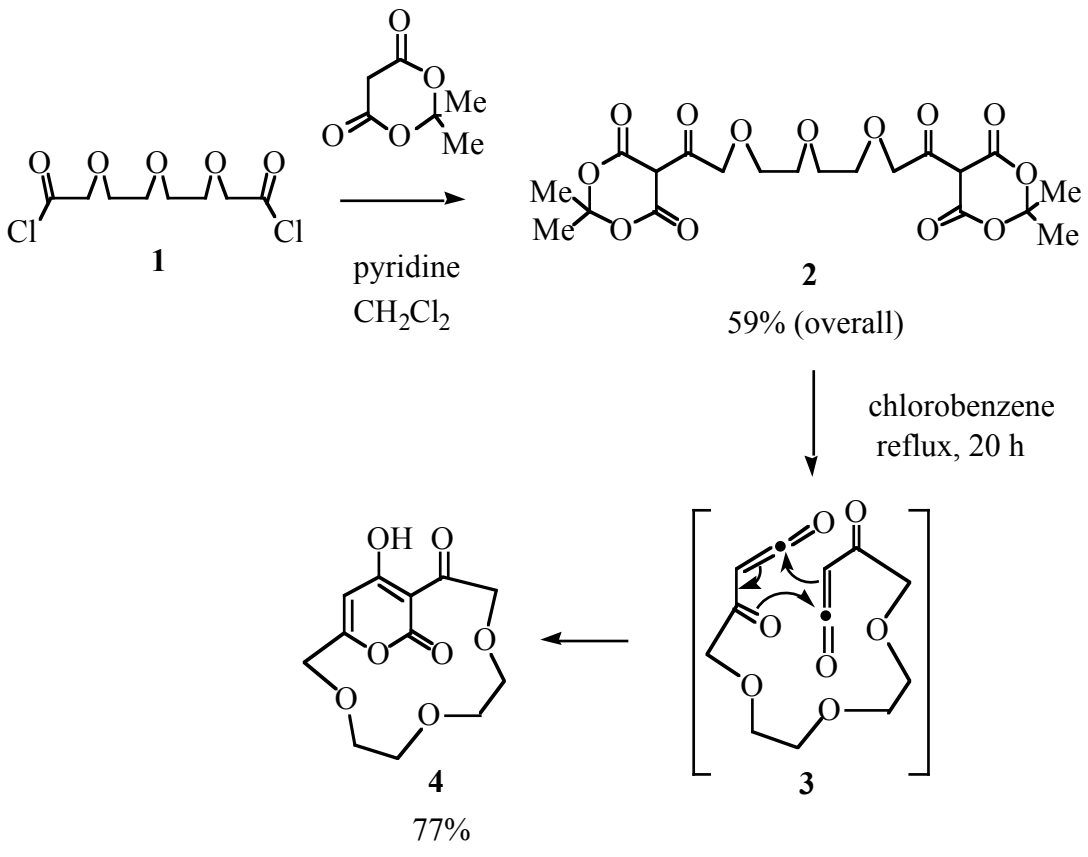
It is well documented that crown ether type compounds having heterocyclic subunit such as pyridine, furan, and thiophene are useful as host molecules which show selectivity towards guest molecules and ions.[1] Among a variety of methods for constructing this type of crown ethers, two-component coupling method is the most frequently employed. However, this method is not always efficient because of the considerable formation of oligomeric byproducts.[2] Recently, ring-closing metathesis has emerged as a powerful method for constructing diverse ring systems including macrocycles.[3] However, this method is not applicable to synthesis of crown ether type pyridinophanes.

Herein, we describe a highly efficient method for synthesis of crown ethers having 4-pyridone or 4-hydroxypyridine as subunit by ring transformation of a dehydroacetic acid derivative.

RESULTS AND DISCUSSION

Previously, we reported a convenient synthesis of dehydroacetic acid derivatives bridged by

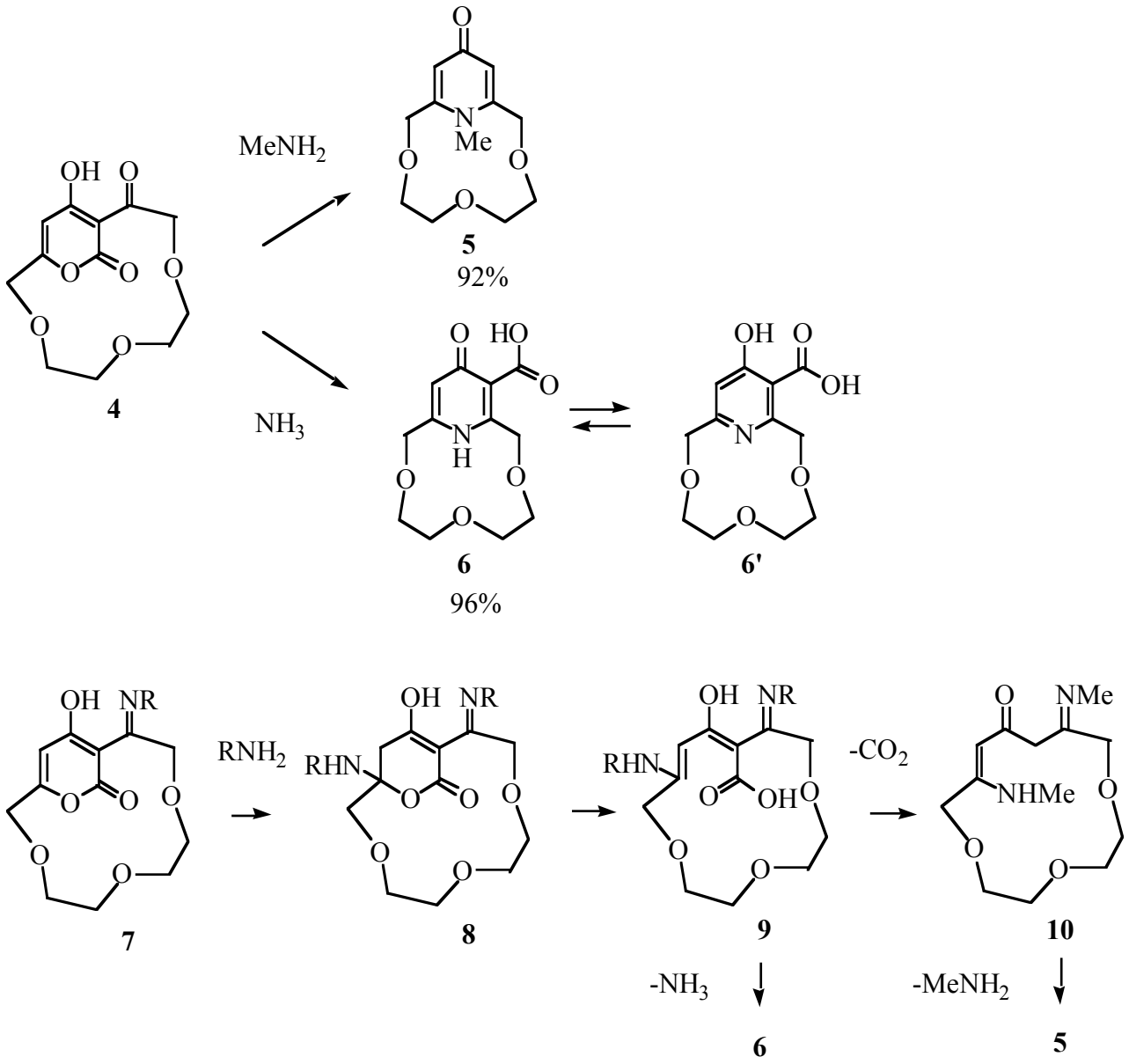
polymethylene chain at the acetyl methyl and 6-methyl groups by intramolecular [4+2] cycloaddition of bis(acylketene).[4,5] We applied the cycloaddition methodology to synthesis of pyridines bridged by di(ethylene glycol) unit at the 2- and 6-positions (12-crown-5). The ketene precursor (**2)** was readily synthesized by condensation of 3,6,9-trioxaundecanedioyl dichloride (**1)**[6] with Meldrum's acid in the presence of pyridine in 59% yield. When a solution of **2** was added to refluxing chlorobenezene over 20 h, bridged dehydroacetic acid (**4)** was obtained in 77% yield. Compound (**4)** has a considerable ring strain due to the short bridge (*vide infra*). The efficient formation of such strained molecule indicates an extremely high reactivity of intermediate bis(ketene) (**3)**.[7]



Scheme 1

Next, we studied ring transformations of **4** into pyridinophanes.[8] A solution of **4** and methylamine in ethanol was heated at 130 °C for 2 days in a stainless steel cylinder to produce 2,6-bridged *N*-methyl-4-pyridone (**5)** in 92% yield. When compound (**4**) was heated with ammonia in ethanol, pyridonecarboxylic

acid (**6)** was obtained in 96% yield. To our knowledge, compound (**6)** is the first example of 12-crown-4 having pyridine ring as subunit (Scheme 2).



Scheme 2

The most plausible mechanism for the ring transformation is shown in Scheme 2. It is well known that ammonia or primary amines readily condenses with dehydroacetic acid at the acetyl carbonyl group to produce imines.[5,8,9] The imine (**7)** thus formed from **4** reacts with another molecule of methylamine or ammonia to give carboxylic acid (**9)**. Decarboxylation of **9** (R = Me) followed by intramolecular cyclization by elimination of methylamine affords **5**. The carboxylic acid (**9)** derived from ammonia

cyclizes to **6** in preference to decarboxylation, because **9** (R = H) has less steric interaction for the cyclization compared to the *N*-methyl analogue (**9**: R = Me).

It is of much interest to study the molecular structure of **4**, because this compound bridged by 10 atoms at the 3- and 6-positions of 2-pyrone seems to have a considerable ring strain. The molecular structure obtained by X-Ray crystallographic analysis is shown in Figure 1. The heterocycle plane is bent to the direction of the bridge, and 4-hydroxy group forms hydrogen bond to the ketone carbonyl group. The bending of heterocycle is attributed to the short bridge. The hydrogen bond restricts the rotation of ketone carbonyl plane resulting in further stain in the molecule.

X-Ray crystallographic analysis of **6** (Figure 2) revealed that this compound exists as 4-pyridone form (**6)** but not as 4-hydroxypyridine form (**6')** in crystal (Scheme 2). The preference of 4-pyridone form to 4-hydroxypyridine form in crystals and in solutions is well known.[10]

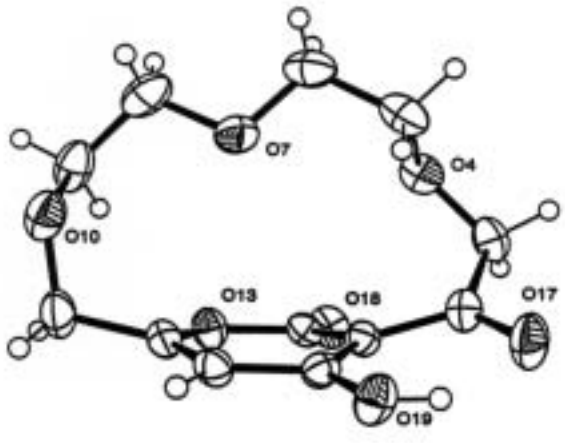


Figure 1 Molecular structure of **4**

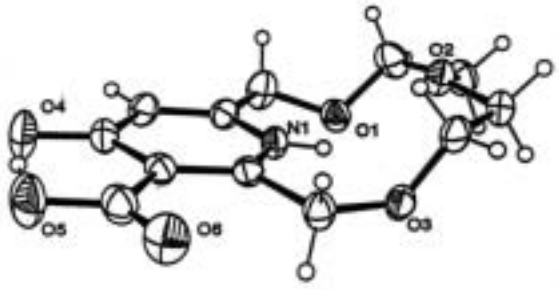
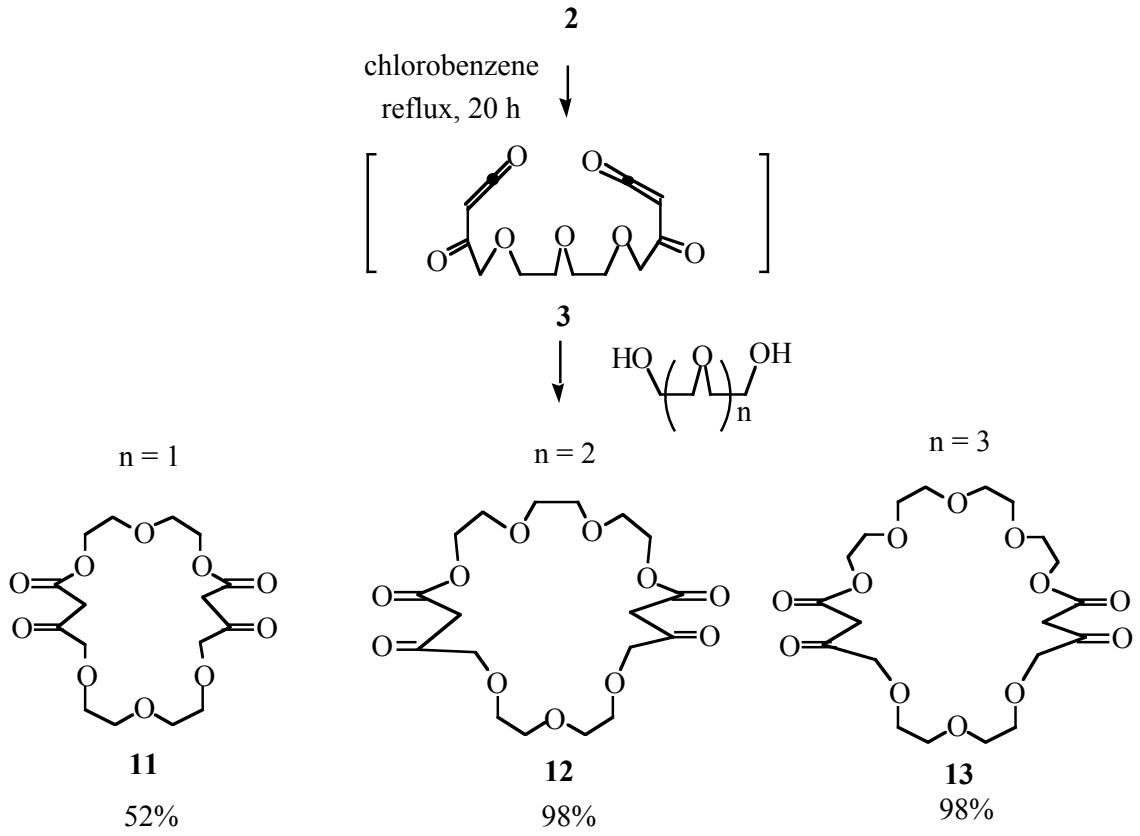


Figure 2 Molecular structure of **6**

Finally, we studied synthesis of macrolactones using bis(ketene) (**3)**. Heating a solution of **2** and di, tri- and tetra(ethylene glycol)s in boiling chlorobebzene afforded the corresponding macrolactones (**11**~**13)** in satisfactory yields. From this reaction, none of **4** or oligomeric products from **3** and glycols was obtained. The result indicates the extremely high reactivity of intermediate bis(ketene) (**3)** toward nucleophiles;

rapid intermolecular 1:1 addition of **3** to the glycol prevents the formation of **4** as well as formation of intermolecular oligomers. These macrolactones have ethylene glycol unit and β-keto ester unit, both of which can coordinate to metal ions. Complex formation of these hybrid molecules with metal ions is of interest from the viewpoint of coordination chemistry.



Scheme 3

In conclusion, bis(acylketene) (**3**) underwent intramolecular [4+2] cycoaddition to produce bridged dehydroacetic acid (**4**). Crown ether type pyridinophanes (**5**) and (**6**) were efficiently synthesized by ring transformation of **4**. X-Ray crystallographic analysis of **4** revealed much strain in this molecule indicating high reactivity of bis(ketene) intermediate (**3**). Using powerful **3** as acylation reagent, unique macrolactones (**11**~**13**) were also synthesized efficiently. Studies on selectivity of **6** towards lithium ion and complex formation of the lactones **11**~**13** with metal ions will be reported elsewhere.

EXPERIMENTAL

General Methods.

Melting points were determined with a Yazawa micro melting point apparatus without correction. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a JEOL JNM-GSX 270 or JNM-GSX 500 spectrometers with tetramethylsilane as an internal standard. IR spectra were determined on a JASCO FT/IR-8000 spectrophotometer. HRMS spectra were recorded on a JEOL JMS-700 MStation spectrometer by using *m*-nitrobenzyl alcohol or poly(ethylene glycol) matrix. Column chromatography was done with Silica Gel 60 N (Kanto Chemical Co., Inc.). The ratios of solvent mixtures for chromatography are shown as volume/volume. 3,6,9-Trioxaundecanedioic acid was purchased from Fluka.

1,11-Bis(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-3,6,9-trioxaundecane-1,11-dione (2)

A solution of 3,6,9,-trioxaundecanedioic acid (8.6 g, 38 mmol), a drop of pyridine and oxalyl chloride (14.4 g, 114 mmol) in anhydrous benzene (45 mL) was stirred at rt for 20 h and then evaporated *in vacuo* to give compound (**1**).[6] A solution of **1** in dichloromethane (38 mL) was added dropwise to a stirred solution of Meldrum's acid (10.94 g, 76 mmol) and pyridine (15.0 g, 190 mmol) in dichloromethane (150 mL) under ice-cooling over 15 min. The mixture was stirred for 30 min under ice-cooling and then for 2 h at rt. The reaction mixture was made acidic by addition of 10% hydrochloric acid. The mixture was extracted with dichloromethane and organic layer was washed with brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent *in vacuo* gave crystalline residue. Recrystallization from mixture of acetone and ether in a freezer gave **2** as colorless powder. Yield 10.7 g (59%), mp 48-54 ℃. ^{1}H-NMR (270 MHz, $CDCl_3$) δ :1.75 (12H, s), 3.76-3.78 (8H, m), 4.98 (4H, s). ^{13}C-NMR (68 MHz, $CDCl_3$) δ : 29.9, 70.7, 71.1, 71.5, 90.0, 105.8, 126.4, 132.5, 194.4. IR (KBr): 1729, 1653, 1572 cm^{-1}. MS (FAB) *m*/*z*: 475 $[M+H]^+$. HRMS (FAB) Calcd for $C_{20}H_{27}O_{13}$ $[M+H]^+$: 475.1452. Found: 475.1430.

15-Hydroxy-13-oxabicyclo[10.2.2]-4,7,10-trioxahexadecane-1(15),12(16)-diene-2,14-dione (4)

Chlorobenzene (1 L) was boiled on an oil bath until about 50 mL of chlorobenzene was distilled off. A

solution of **2** in chlorobenzene (50 mL) was added dropwise to the refluxing chlorobenzene over 20 h by a syringe pump. The solution was heated under reflux for an additional 30 min, and then evaporated *in vacuo*. Purification of the residue by silica gel column chromatography using chloroform as an eluent furnished **4** as crystals. Yield 1.31 g (77%), colorless prisms, mp 117-119 ℃ (hexane-acetone). ^{1}H-NMR (270 MHz, $CDCl_3$) δ : 3.01 (1H, m), 3.22-3.36 (2H, m), 3.49-3.67 (4H, m), 3.77 (1H, d, *J* = 14.7 Hz), 4.02 (1H, m), 4.05 (1H, d, *J* = 13.1 Hz), 4.40 (1H, d, *J* = 13.1 Hz), 5.02 (1H, d, *J* = 14.7 Hz), 6.11 (1H, s), 12.70 (1H, br). ^{13}C-NMR (68 MHz, $CDCl_3$) δ : 70.1, 70.2, 70.3, 70.6, 72.0, 74.5, 102.1, 160.8, 166.5, 175.0, 205.7. IR (KBr): 1729, 1651, 1566 cm^{-1}. MS (FAB) *m*/*z*: 271 $[M+H]^+$. *Anal*. Calcd for $C_{12}H_{14}O_7$: C, 53.33; H, 5.22. Found: C, 53.14; H, 5.06.

15-Methyl-15-azabicyclo[9.3.1]-3,6,9-trioxapentadecane-1(14),11-dien-13-one (5)

A solution of **4** (270 mg, 1.0 mmol) and 40% methylamine solution (3 mL) in ethanol (20 mL) was heated in a stainless steel cylinder (100 mL) at 130℃ for 2 days. The reaction mixture was evaporated *in vacuo* and the residue was purified by silica gel column chromatography using chloroform as an eluent to give **5**. Yield 219 mg (92%), colorless needles, mp 246-249 ℃ (hexane-acetone). ^{1}H-NMR (270 MHz, $CDCl_3$) δ : 3.24-3.48 (6H, m), 3.72 (3H, s), 3.81 (2H, m), 4.12 (2H, d, *J* = 14.5 Hz), 4.94 (2H, d, *J* = 14.5 Hz), 6.32 (2H, s). ^{13}C-NMR (68 MHz, $CDCl_3$) δ : 36.4, 67.6, 70.6, 71.6, 120.6, 149.2, 179.0. IR (KBr): 1625, 1539 cm^{-1}. MS (FAB) *m*/*z*: 240 $[M+H]^+$. HRMS (FAB) Calcd for $C_{12}H_{18}NO_4$ $[M+H]^+$: 240.1236. Found: 240.1235.

13-Oxo-3,6,9-trioxa-15-azabicyclo[9.3.1]pentadeca-1(14),11-diene-12-carboxylic Acid (6)

A solution of **4** (270 mg, 1.0 mmol) in ethanol (10 mL) was cooled in an ice-bath and then saturated with NH_3. The solution was heated in a stainless steel cylinder (100 mL) at 130℃ for 2 days. The reaction mixture was evaporated *in vacuo* and the residue was purified by silica gel column chromatography using chloroform as an eluent to give **6**. Yield 258 mg (96%), colorless prisms of mp 213-215 ℃ (methanol). ^{1}H-NMR (500 MHz, DMSO) δ : 3.62 (4H, m), 3.85 (4H, m), 4.81 (2H, s), 5.17 (2H, s), 6.64 (1H, s), 12.0

(1H, s). ^{13}C-NMR (125 MHz, DMSO-d_6) δ : 68.6, 68.7, 69.1, 69.2, 71.9, 72.2, 110.5, 112.4, 150.6, 156.9, 166.4, 179.1. IR ($CHCl_3$): 1696, 1631, 1584 cm^{-1}. MS (FAB) *m*/*z*: 270 $[M+H]^+$. *Anal*. Calcd for $C_{12}H_{15}NO_6$: C, 53.53; H, 5.62; N, 5.20. Found: C, 53.42; H, 5.52; N, 5.34.

1,4,7,12,15,18-Hexaoxacyclodocosane-8,10,20,22-tetraone (11)

General procedure for preparation of **11**~**13**: Chlorobenzene (1 L) was boiled on an oil bath until about 50 mL of chlorobenzene was distilled off. Then, a solution of **2** (948 mg, 2.0 mmol) and di(ethylene glycol) (212 mg, 2.0 mmol) in chlorobenzene (50 mL) was added dropwise to the refluxing chlorobenzene over 20 h by a syringe pump. The solution was heated under reflux for an additional 30 min, and then the solvent was evaporated *in vacuo*. Purification of the residue by silica gel column chromatography using chloroform as an eluent gave **11**. Yield 391 mg (52%), yellowish oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ : 3.63 (4H, s), 3.67 (4H, m), 3.70 (8H, m), 4.22 (4H, s), 4.31 (4H, m). ^{13}C-NMR (125 MHz, $CDCl_3$) δ : 45.9, 64.2, 68.7, 70.9, 71.1, 76.2, 167.1, 202.3. IR ($CHCl_3$): 1728 cm^{-1}. MS (FAB) *m*/*z*: 377 $[M+H]^+$. HRMS (FAB) Calcd for $C_{16}H_{25}O_{10}$ $[M+H]^+$: 377.1448. Found: 377.1429.

1,4,7,10,15,18,21-Heptaoxacyclopentacosane-11,13,23,25-tetraone (12)

Yield 823 mg (98%), yellowish oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ : 3.60-3.72 (20H, m), 4.22 (4H, s), 4.31 (4H, m). ^{13}C-NMR (125 MHz, $CDCl_3$) δ :46.0, 64.5, 68.9, 70.7, 70.8, 71.2, 76.2, 167.1, 202.2. IR ($CHCl_3$): 1730 cm^{-1}. MS (FAB) *m*/*z*: 421 $[M+H]^+$. HRMS (FAB) Calcd for $C_{18}H_{29}O_{11}$ $[M+H]^+$: 421.1710. Found: 421.1700.

1,4,7,10,13,18,21,24-Octaoxacyclooctacosane-14,16,26,28-tetraone (13)

Yield 911 mg (98%), yellowish oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ : 3.60 (6H, s), 3.65-3.73 (18H, m), 4.22 (4H, s), 4.31 (4H, m). ^{13}C-NMR (125 MHz, $CDCl_3$) δ :45.9, 64.5, 68.9, 70.6, 70.7, 70.7, 71.2, 76.2, 167.1, 202.2. IR ($CHCl_3$): 1726 cm^{-1}. MS (FAB) *m*/*z*: 465 $[M+H]^+$. HRMS (FAB) Calcd for $C_{20}H_{33}O_{12}$ $[M+H]^+$: 465.1972. Found: 465.1960.

X-Ray crystallographic analysis

X-Ray structures were determined on a Rigaku AFC7R diffractometer, using Cu Kα radiation (graphite crystal monochromator, λ = 1.5418 Å).

Compound (4) Crystal data: $C_{12}H_{14}O_7$; M = 270.07; monoclinic; space group $P2_1/c$; a = 8.458(9), b = 20.11(1), c = 7.54(1) Å; α = 90°, β = 70.200(8)°, γ= 90°; V = 1207.4(2) Å^3, Z = 4; D = 1.115 mg/m^3; No. of reflections collected: 2497, No. of observed reflections: 2240; R = 0.039, R_w = 0.061.[11]

Compound (6) Crystal data: $C_{12}H_{15}NO_6$; M = 269.09; monoclinic; space group $C2/c$; a = 20.099 (3), b = 8.428(1), c = 18.089(3) Å; α = 90°, β = 127.80(1)°, γ= 90°; V = 2420.9(6) Å^3, Z = 8; D = 1.472 mg/m^3; No. of reflections collected: 2796, No. of observed reflections: 1811; R = 0.047, R_w = 0.071.[11]

ACKNOWLEDGEMENTS

The authors thank Dr. M. Uchida of the School of Pharmaceutical Sciences, University of Shizuoka for the MS spectra measurements. This work was supported in part by Grant-in-Aid for Scientific Research No. 12470484 from the Ministry of Education, Science, Sports, Culture and Technology, Japan.

REFERENCES AND NOTES

1. For reviews: G. R. Newkome, J. D. Sauar, J. M. Roper, and D. C. Hader, *Chem. Rev.*, 1977, **77**, 513. R. M. Izatt, K. Pawlak, and J. S. Bradshaw, *Chem. Rev.*, 1995, **95**, 2529. X. X. Zhang, J. S. Bradshaw and R. M. Izatt, *Chem. Rev.*, 1997, **97**, 3313.
2. E.g.: M. Newcomb, G. W. Gokel, and D. J. Cram, *J. Am. Chem. Soc*., 1974, **96***,* 6811. J. S. Bradshaw, Y. Nakatsuji, P. Huszthy, B. E. Wilson, N. K. Dalley, and R. M. Izatt, *J. Heterocycl. Chem*., 1986, **23**, 353. A. Tahri, E. Cielen, K. J. Van Aken, G. J. Hoornaert, F. C. De Schryver, and N. Boens, *J. Chem. Soc., Perkin Trans. 2,* 1999, 1739.
3. R. H. Grubbs and S. Chang, *Tetrahedron*, 1998, **54**, 4413. R. H. Grubbs, S. J. Miller, and G. C. Fu, *Acc. Chem. Res*., 1995, **28**, 446. A. Fürstner, *Angew. Chem., Int. Ed.*, 2000, **39***,* 3013.
4. For review of acylketene: C. Kaneko, M. Sato, J. Sakaki, and Y. Abe, *J. Heterocycl. Chem*., 1990, **27**, 25. C. Wentrup, W. Heilmayer, and G. Kollenz, *Synthesis*, 1994, 1219. M. Sato and K. Iwamoto, *J.*

Synth. Org. Chem. Jpn., 1999, **57**, 76.

5. M. Sato, F. Uehara, K. Sato, M. Yamaguchi, and C. Kabuto, *J. Am. Chem. Soc*., 1999, **121**, 8270.
6. B. Dietlich, J. M. Lehn, J. P. Sauvage, and J. Blanzat, *Tetrahedron*, 1973, **29**, 1629.
7. For mechanistic studies on intermolecular dimerization of acylketene in [4+2] manner, see: W. W. Shumway, N. Dalley, and D. M. Birney, *J. Org. Chem.*, 2001, **66**, 5832 and references cited therein.
8. S. Iguchi, A. Inoue, and C. Kurahashi, *Chem. Pharm. Bull*., 1962, **11**, 38. S. Iguchi and A. Inoue, *Chem. Pharm. Bull*., 1962, **11**, 390.
9. J. F. Stephen and E. Marcus, *J. Org. Chem*., 1969, **34**, 2537.
10. A. R. Katritzky and J. M. Lagowski, *"Advances in Heterocyclic Chemistry"*, Vol. 1, p. 341, Academic Press, New York, 1963.
11. The authors have deposited the atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.