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# Synthesis of Macrocyclic Ketoesters by an n + 1 Strategy Based on Free-Radical Carbonylation

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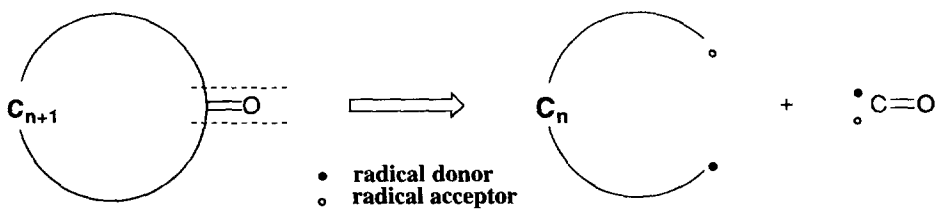
***Abstract:*** The synthesis of 10-17 membered 4-oxolactones **2** from alkyl iodides **1** having an acryloxy moiety at the termini, carbon monoxide, and TTMSS (or tin hydride) was achieved under free radical reaction conditions. The allyltin mediated reaction of **1** also proceeded successfully to furnish 2-allyl-substituted 4-oxolactones **3** in moderate to good yields. In this n + 1 type macrocyclization, high dilution conditions ([**1**] = 0.005-0.01 M) are beneficial for both the intermolecular trapping of CO and the intramolecular acyl radical addition to the C-C double bond. © 1997 Elsevier Science Ltd.

Radical carbonylations have become promising tools for the introduction of carbon monoxide into organic molecules.[1] The methodology is especially advantageous for aliphatic carbonylation, for which transition metal catalyzed carbonylations have not been extensively applied because of undesirable β-hydride elimination. Radical carbonylation-cyclization sequences provide a powerful tool for the construction of cyclopentanones and cyclohexanones[2] and recent advances in this area include double carbonylation reactions[2c, 2d] as well as carbonylative cyclization onto C-N double bond.[2e] In view of the fact that numerous antibacterial agents contain macrolide skeletons, a wide range of synthetic methods for macrocyclizations have been developed thus far.[3, 4] To the best of our knowledge, however, a transformation that utilizes CO as the C1 unit for macrocyclic ring construction has not been well established in conjunction with transition metal catalyzed or mediated carbonylations.[5, 6] In this article we describe a synthetic method for the preparation of macrocyclic 4-oxolactones via n + 1 type free-radical annulation using carbon monoxide as the C1 unit.[7, 8] Scheme 1 illustrates a typical strategy, for which radical retrosynthesis notation is used.[9] It should be noted that the pioneering studies of Porter and coworkers have established the steric and electronic requirements for successful alkyl radical macrocyclization reactions.[10, 11] Although it does not contain a

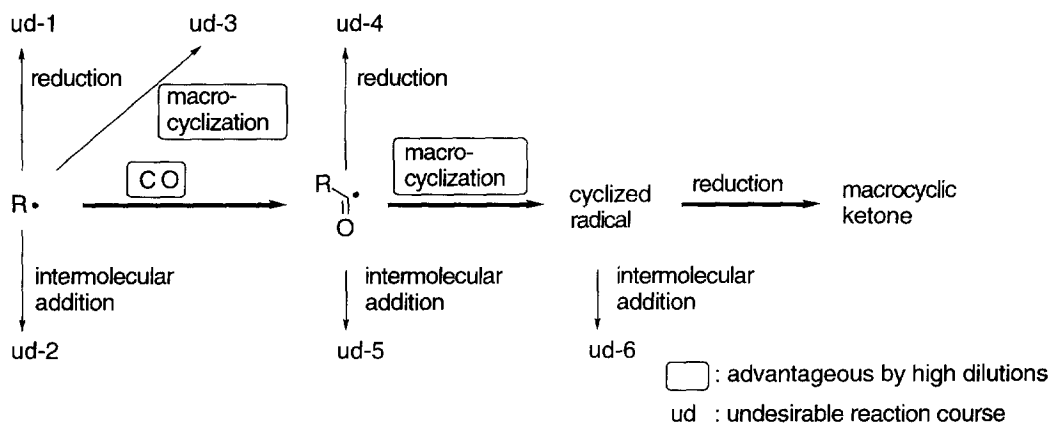



**Scheme 1**

carbonylation step, the related macrocyclization of acyl radicals, having electron deficient olefins at thetermini, have been reported.[12, 13]

## RESULTS AND DISCUSSION

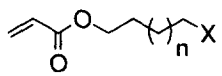
It is generally thought that high dilution conditions are favorable for macrocyclizations in terms of competing intermolecular reactions. Such conditions, however, also have merit for the present n + 1 strategy using carbon monoxide as the C1 unit as well. While high dilution does not affect the concentration of carbon monoxide, it can suppress premature quenching of key radicals by decreasing the concentration of radical mediators. Scheme 2 summarizes possible reaction courses associated with the present macrolide synthesis, in which reactions which benefit from high dilutions are enclosed in a box. Thus, the desired reaction must compete with six undesirable reaction pathways (ud-1 – ud-6). Undesirable reactions involve premature quenching of alkyl and acyl radicals to give an alkane and an aldehyde, respectively (ud-1 and ud-4). In this study, tin hydride was replaced with tris(trimethylsilyl)silane (TTMSS) as a mediator to suppress the simple reduction course, since TTMSS is a slow hydrogen donor relative to $Bu_3SnH$.[14, 15] We also examined an allyltin mediated carbonylative annulation system to furnish 2-allylated macrocyclic oxolactones, which also proved to be successful.



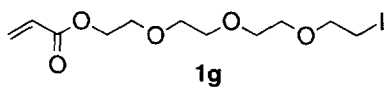

**Scheme 2**

Control experiments were carried out for the reaction of 6-iodohexyl acrylate (**1b**) with carbon monoxide in the presence of tris(trimethylsilyl)silane (TTMSS) and AIBN (catalytic) in benzene (Table 1). As anticipated, when a reaction involving a low concentration of **1b** (0.005-0.01 M) with TTMSS (1.5-2.0 equiv) was carried out under 30 atm of CO pressure at 80 °C for 5 h, the desired 11 membered 4-oxolactone **2b** was formed in reasonable to good yields (entries 3-6). In principle, in this system, the acyl radical cyclization step competes with the intermolecular reaction with TTMSS to give an aldehyde and the intermolecular alkene addition to give a dimer and/or oligomers (ud-4 and ud-5 in Scheme 2). However, $^1$H-NMR analysis of the crude reaction mixtures showed that aldehyde was formed in trace amounts, but the intermolecular addition reaction competed to some extent. On the other hand, no apparent effect was

observed for dilutions of less than 0.005 M (entries 7 and 8). In accord with our previous results,[15] the TTMSS mediated system permits a relatively low pressure carbonylation system to be used. While 10 atm of CO gave satisfactory results, the yield of **2b** decreased to 28% under 2 atm of CO (entries 9 and 10).

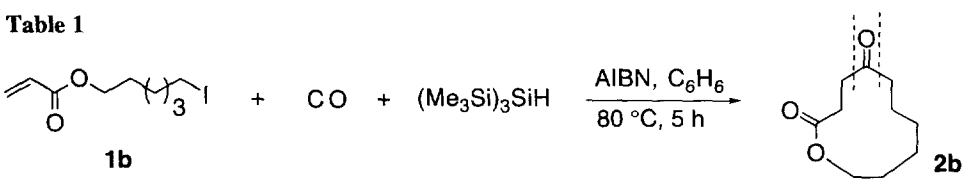


**1a**: n = 2, X = I
**1b**: n = 3, X = I
**1c**: n = 5, X = I
**1d**: n = 7, X = I
**1e**: n = 8, X = I
**1e'**: n = 8, X = SePh
**1f**: n = 9, X = I



**1g**

**Table 1**



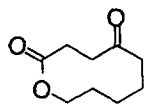
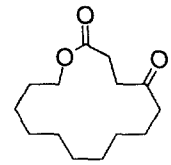
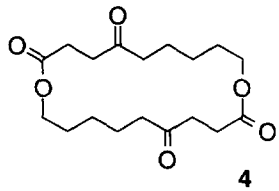
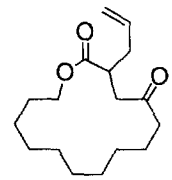
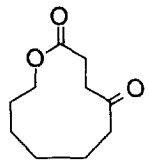
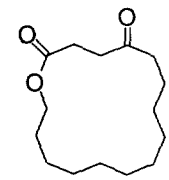
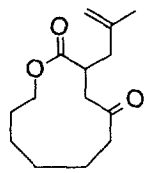
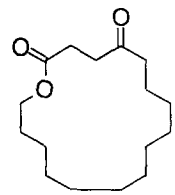
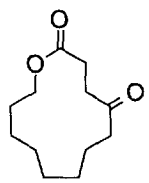
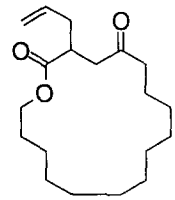
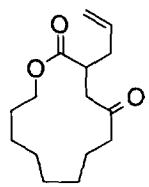
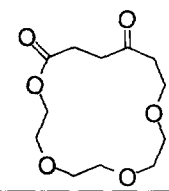
**1b** + CO + $(Me_3Si)_3SiH$ → AIBN, $C_6H_6$, 80 °C, 5 h → **2b**

| entry | [**1b**] (M) | CO (atm) | $(Me_3Si)_3SiH$ (equiv) | AIBN (equiv) | GC yield (%) |
|---|---|---|---|---|---|
| 1 | 0.100 | 30 | 1.5 | 0.2 | 5 |
| 2 | 0.050 | 30 | 1.5 | 0.2 | 20 |
| 3 | 0.010 | 30 | 1.5 | 0.2 | 54 |
| 4 | 0.005 | 30 | 1.5 | 0.2 | 57 |
| 5 | 0.005 | 30 | 2.0 | 0.2 | 68[a] |
| 6 | 0.005 | 30 | 4.0 | 0.5 | 65 |
| 7 | 0.002 | 30 | 1.5 | 0.3 | 59 |
| 8 | 0.002 | 30 | 4.0 | 0.3 | 59 |
| 9 | 0.005 | 10 | 1.5 | 0.2 | 59 |
| 10 | 0.005 | 2 | 1.5 | 0.2 | 28 |

[a] Isolated yield by flash chromatography on silica gel.

The synthesis of 13, 15, 16, and 17 membered ring oxolactones **2c-2f** from **1c-1f** and CO was performed by similar high dilution procedures (0.005-0.01 M, TTMSS 1.5-2 equiv, CO 30 atm, $C_6H_6$, AIBN, 80 °C, 5 h) (Table 2) in a straightforward manner. In general, Porter type macrocyclic lactones[10b] (direct cyclization products) were formed in less than a 1/10 ratio to macrocyclic oxolactones under the conditions specified, as evidenced by $^1$H-NMR spectra of crude products (ud-3 in Scheme 2). Although formed in the low yield, 10 membered oxolactone **2a** was formed from **1a** and CO (entry 1). In addition, dimeric compound **4** which had incorpotated two molecules of CO, was also isolated in 10% yield as a byproduct. In this case, intermolecular addition to give oligomers was the major competing reaction. On the other hand, carbonylation of 4-iodobutyl acrylate did not provide the 9 membered ring product, 4-oxo-8-octanolide, at all, presumably because of steric effects in the cyclization step. Tributyltin hydride was also examined for the conversion of **1b** to **2b**, and the yield was somewhat lower compared to TTMSS (entry 3). The reaction of the

**Table 2.** TTMSS and Allyltin Mediated Free-Radical Macrocyclization by an n + 1 Strategy

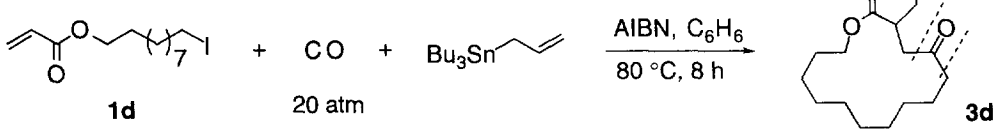
| entry | substrate, conditions[a] | product | isolated yield | entry | substrate, conditions[a] | product | isolated yield |
|---|---|---|---|---|---|---|---|
| 1 | **1a** A |  | **2a** 28% | 7 | **1d** D |  | **2d** 61% |
| | |  | **4** 10% | 8 | **1d** F |  | **3d** 61% |
| 2 | **1b** A |  | **2b** 68% | 9 | **1e** D |  | **2e** 50% |
| 3 | **1b** B | | 57%[b] | 10 | **1e'** B | | 32%[c] |
| 4 | **1b** C |  | **3b** 47% | 11 | **1f** A |  | **2f** 78% |
| 5 | **1c** D |  | **2c** 70% | 12 | **1f** E |  | **3f** 70% |
| 6 | **1c** E |  | **3c** 56% | 13 | **1g** G |  | **2g** 36% |

[a]Conditions: A, [**1**] = 0.005 M, CO 30 atm, AIBN (0.2 equiv), TTMSS (2 equiv), 80 °C, 5 h; B, [**1**] = 0.005 M, CO 30 atm, AIBN (0.2 equiv), $Bu_3SnH$ (1.5 equiv), 80 °C, 5 h; C, [**1b**] = 0.005 M, CO 20 atm, AIBN (0.6 equiv), methallyltin (5 equiv), 80 °C, 8 h; D, [**1**] = 0.01 M, CO 30 atm, AIBN (0.2 equiv), TTMSS (1.5 equiv), 80 °C, 5 h; E, [**1**] = 0.005 M, CO 20 atm, AIBN (0.6 equiv), allyltin (6 equiv), 80 °C, 8 h; F, [**1d**] = 0.005 M, CO 20 atm, AIBN (0.6 equiv), allyltin (10 equiv), 80 °C, 8 h; G, [**1g**] = 0.01 M, CO 80 atm, AIBN (0.2 equiv), $Bu_3SnH$ (1.5 equiv), 80 °C, 5 h. [b]GC yield. [c]Recovery of **1e'** (15%).

tetraethyleneglycol derivative **1g** gave the desired product **2g** (80 atm), while the yield was rather modest due to the formation of the direct intramolecular addition product as a major byproduct in spite of the fact that the reaction was conducted at high CO pressure (entry 13).

We also tested the allyltributyltin mediated systems.[16] Table 3 summarizes the control experiments using **1d** and allyltributyltin. The higher dilution conditions are effective for carbonylation and macrocyclization in the TTMSS mediated system as well, but for chain-propagation, dilution is disadvantageous owing to the slow addition rate of the cyclized radical to allyltin (entry 3).[17] We solved this problem by increasing the amount of allyltin. Indeed, the use of 6-10 equiv of allyltin gave good yields of **3d** (entries 4 and 5). As also summarized in Table 2, the reaction of ω-iodoalkyl acrylates **1b-1d**, **1f** and CO in the presence of allyltin gave allylated macrocyclic products **3b-3d**, **3f** in moderate to good yields (0.005 M, allyltin 5-10 equiv, CO 20 atm, $C_6H_6$, AIBN, 80 °C, 8 h).

**Table 3**



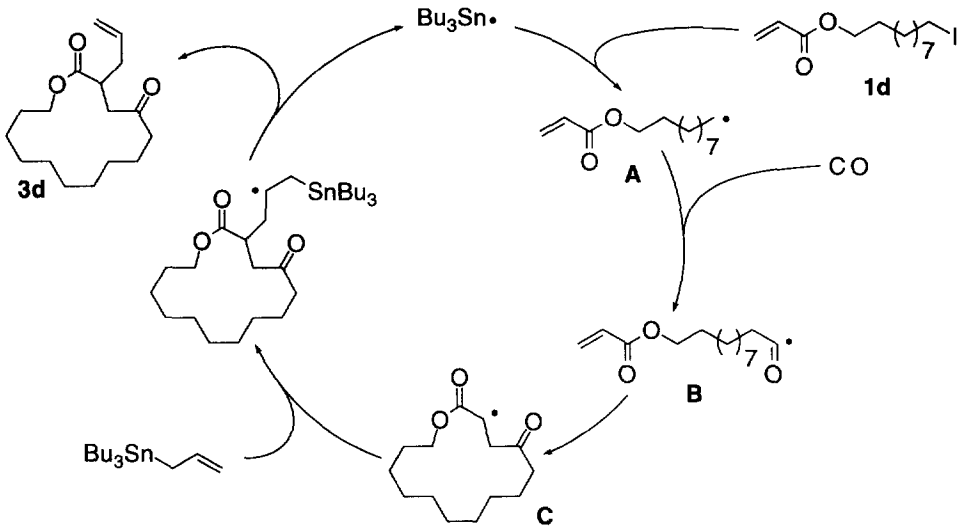

**1d** 20 atm **3d**

| entry | [**1d**] (M) | CO (atm) | allyltin (equiv) | AIBN (equiv) | GC yield (%) |
|---|---|---|---|---|---|
| 1 | 0.100 | 20 | 2 | 0.3 | 12 |
| 2 | 0.025 | 20 | 2 | 0.3 | 29 (23[a]) |
| 3 | 0.010 | 20 | 3 | 0.4 | 46 |
| 4 | 0.005 | 20 | 6 | 0.6 | 64 |
| 5 | 0.005 | 20 | 10 | 0.6 | 72 (61[a]) |

[a] Isolated yields.

A radical chain mechanism is illustrated for the allyltin mediated system (Scheme 3). Radical **A** adds to CO, and the subsequent intramolecular cyclization of the resulting acyl radical **B** to the alkene terminus leads to the cyclized radical **C**. $S_H2'$ type reaction of **C** with allyltin provides 2-allylated 4-oxomacrolide and tin radical. The tin radical propagates the chain by abstraction of the iodine atom from the substrate.

In this study we demonstrated that a free radical mediated n + 1 strategy is useful for the synthesis of macrocyclic 4-oxolactones. High dilution conditions are beneficial for both the intermolecular CO trapping and the intramolecular acyl radical cyclization over other side reactions. TTMSS, a slow radical mediator, contributes to the selectivity of the desired reaction and the creation of a low pressure carbonylation system. In an allyltin mediated three-component coupling system, a large excess of allyltin is effective, in order to ensure satisfactory chain-propagation under high dilution conditions. In general, the yields of macrolides increase with increasing ring size. The n + 1 type macrocyclization is possible for 10 membered rings, but can be most effectively applied to systems, which contain 11 atoms or more.




**Scheme 3**

## EXPERIMENTAL

**General:** $^1$H-NMR spectra were recorded with a JEOL JNM-GX67S (270 MHz) spectrometer, a JEOL JNM-Alice 400 (400 MHz) spectrometer, and a Bruker AM600 (600 MHz) spectrometer. Chemical shifts are reported in parts per million (δ) downfield from internal TMS. $^{13}$C-NMR spectra were recorded with a JEOL JNM-GX67S (68MHz) spectrometer and a JEOL JNM-Alice 400 (100 MHz) spectrometer. Infrared spectra were recorded with a Perkin-Elmer FT-IR (Model 1600). Both conventional and high resolution mass spectra were recorded with a JEOL JMS-DX303HF spectrometer. Elemental analyses were performed on a Perkin Elmer 240C apparatus. GC yields were assayed with a Shimadzu GC-14A gas chromatograph equipped with a Shimadzu capillary Column CBP1-M25-025. The products were purified by flash chromatography on silica gel (Fuji Silysia BW-820MH, 70-200 mesh). $Bu_3SnH$, tris(trimethylsilyl)silane, and allyltributyltin were purchased from Aldrich Chemical Company, Inc. and AIBN was purchased from Wako Pure Chemical Industries, Ltd. Benzene was distilled from $CaH_2$. 2-Methylprop-2-enyltributyltin was synthesized from 1-chloro-2-methylprop-2-ene and tributyltin chloride by a Grignard reaction.

**Spectral data for 1a, 1b, 1d, 1e', and 1g:** ω-Iodoalkyl acrylates **1a-1g** were synthesized from the reaction of ω-haloalcohols that were provided by monohalogenation of diols and acryloyl chloride in the presence of $Et_3N$.[10b] *Se*-Phenyl 11-selenoundecyl acrylate (**1e'**) was obtained from *Se*-Phenyl 11-selenoundecanol and acryloyl chloride by a similar method. *Se*-Phenyl 11-selenoundecanol was obtained from 11-bromoundecanol and diphenyl diselenide.[11b] **1c**, **1e**, and **1f** are known compounds and the properties of these compounds ($^1$H-NMR and $^{13}$C-NMR) were consistent with those previously reported in reference 10b.

**5-Iodopentyl acrylate (1a):** oil; $^1$H-NMR ($CDCl_3$, 270 MHz) δ 1.45-1.56 (m, 2 H), 1.66-1.76 (m, 2

H), 1.82-1.92 (m, 2 H), 3.20 (t, 2 H, $J$ = 7.0 Hz), 4.17 (t, 2 H, $J$ = 6.5 Hz), 5.83 (dd, 1 H, $J$ = 10.5, 1.7 Hz), 6.12 (dd, 1 H, $J$ = 17.3, 10.5 Hz), 6.41 (dd, 1 H, $J$ = 17.3, 1.7 Hz); $^{13}$C-NMR ($CDCl_3$, 68 MHz) δ 6.5, 26.9, 27.6, 33.0, 64.2, 128.5, 130.7, 166.2; IR (neat) 2939, 2862, 1724, 1636, 1619, 1408, 1296, 1272, 1193, 1060, 985, 810 cm$^{-1}$; EIMS (relative intensity) m/z 269 ($M^+$+1, 2), 197 (13), 155 (9), 141 (36), 128 (3), 85 (3), 73 (17), 69 (100), 55 (79), 41 (30); HRMS (EI) calcd for $C_8H_{13}IO_2$: m/z 267.9960, found: 267.9974.

**6-Iodohexyl acrylate (1b):** oil; $^1$H-NMR ($CDCl_3$, 270 MHz) δ 1.34-1.53 (m, 12 H), 1.60-1.76 (m, 2 H), 1.78-1.85 (m, 2 H), 3.19 (t, 2 H, $J$ = 7.0 Hz), 4.15 (t, 2 H, $J$ = 6.9 Hz), 5.82 (dd, 1 H, $J$ = 10.5, 1.7 Hz), 6.12 (dd, 1 H, $J$ = 17.3, 10.5 Hz), 6.40 (dd, 1 H, $J$ = 17.3, 1.7 Hz); $^{13}$C-NMR ($CDCl_3$, 68 MHz) δ 6.8, 24.9, 28.4, 30.0, 33.2, 64.3, 128.5, 130.5, 166.2; IR (neat) 2934, 2857, 1720, 1636, 1619, 1407, 1296, 1273, 1191, 1060, 985, 811 cm$^{-1}$; EIMS (relative intensity) m/z 283 ($M^+$+1, 2), 210 (7), 155 (29), 128 (2), 83 (78), 73 (20), 67 (3), 55 (100), 41 (17); HRMS (EI) calcd for $C_9H_{15}IO_2$: m/z 282.0116, found: 282.0096.

**10-Iododecyl acrylate (1d):** oil; $^1$H-NMR ($CDCl_3$, 270 MHz) δ 1.23-1.50 (br.s, 4 H), 1.69 (quint, 2 H, $J$ = 7.1 Hz), 1.84 (quint, 2 H, $J$ = 7.1 Hz), 3.19 (t, 2 H, $J$ = 7.1 Hz), 4.16 (t, 2 H, $J$ = 6.6 Hz), 5.81 (dd, 1 H, $J$ = 10.5, 1.7 Hz), 6.12 (dd, 1 H, $J$ = 17.3, 10.5 Hz), 6.40 (dd, 1 H, $J$ = 17.3, 1.7 Hz); $^{13}$C-NMR ($CDCl_3$, 68 MHz) δ 7.2, 25.8, 28.4, 28.5, 29.1, 29.25, 29.33, 30.4, 33.5, 64.6, 128.6, 130.4, 166.3; IR (neat) 2927, 2854, 1724, 1636, 1619, 1407, 1295, 1273, 1192, 1060, 984, 810 cm$^{-1}$; EIMS (relative intensity) m/z 339 ($M^+$+1, 3), 266 (3), 224 (3), 211 (24), 155 (7), 139 (23), 128 (2), 111 (2), 97 (49), 83 (100), 73 (17), 69 (55), 55 (95), 41 (21); HRMS (EI) calcd for $C_{10}H_{23}IO_2$: m/z 338.0743, found: 338.0754.

***Se*-Phenyl 11-selenoundecyl acrylate (1e'):** oil; $^1$H-NMR ($CDCl_3$, 270 MHz) δ 1.21-1.47 (m, 14 H), 1.60-1.77 (m, 4 H), 2.90 (t, 2 H, $J$ = 7.5 Hz), 4.14 (t, 2 H, $J$ = 6.7 Hz), 5.80 (dd, 1 H, $J$ = 10.5, 1.7 Hz), 6.11 (dd, 1 H, $J$ = 17.3, 10.5 Hz), 6.39 (dd, 1 H, $J$ = 17.3, 1.7 Hz), 7.20-7.28 (m, 3 H), 7.46-7.49 (m, 2 H); $^{13}$C-NMR ($CDCl_3$, 68 MHz) δ 25.9, 27.9, 28.6, 29.0, 29.2, 29.4 (strong peak), 29.7, 30.1, 64.6, 126.5, 128.6, 128.9, 130.3, 130.7, 132.3, 166.2; IR (neat) 2926, 2853, 1725, 1636, 1619, 1579, 1477, 1407, 1295, 1272, 1193, 1063, 1023, 984, 810, 735, 691 cm$^{-1}$; EIMS (relative intensity) m/z 382 ($M^+$, 100), 310 (6), 158 (25), 111 (7), 97 (26), 91 (4), 83 (25), 69 (26), 55 (45), 41 (10); HRMS (EI) calcd for $C_{20}H_{30}O_2Se$: m/z 382.1411, found: 382.1402.

**11-Iodo-3,6,9-trioxaundecyl acrylate (1g):** oil; $^1$H-NMR ($CDCl_3$, 270 MHz) δ 3.26 (t, 2 H, $J$ = 7.0 Hz), 3.67 (s, 4 H), 3.68 (s, 4 H), 3.71-4.00 (m, 4 H), 4.32 (t, 2 H, $J$ = 4.9 Hz), 5.84 (dd, 1 H, $J$ = 10.5, 1.7 Hz), 6.16 (dd, 1 H, $J$ = 17.3, 10.5 Hz), 6.43 (dd, 1 H, $J$ = 17.3, 1.7 Hz); $^{13}$C-NMR ($CDCl_3$, 68 MHz) δ 2.9, 63.7, 69.1, 70.2, 70.61 (strong peak), 70.64, 71.9, 128.3, 131.0, 166.1; IR (neat) 2871, 1724, 1636, 1619, 1408, 1351, 1296, 1271, 1195, 1110, 1068, 985, 810 cm$^{-1}$; EIMS (relative intensity) m/z 359 ($M^+$+1, 1), 273 (1), 242 (3), 231 (3), 198 (12), 187 (3), 155 (65), 143 (4), 99 (100), 87 (8), 73 (8), 55 (31), 45 (6); HRMS (EI) calcd for $C_{11}H_{19}IO_5$: m/z 358.0277, found: 358.0258.

**Control experiments for macrocyclization of 1 (general procedures).**

**(i) Tris(trimethylsilyl)silane (TTMSS) mediated process (reaction of 1b):** Benzene (50 mL), 6-iodohexyl acrylate (**1b**; 72 mg, 0.26 mmol, 0.005 M), tris(trimethylsilyl)silane (95 mg, 0.38 mmol), tetradecane

(internal standard, 24 mg), and AIBN (9 mg, 0.05 mmol) were placed in a 100-mL stainless steel autoclave lined with a round bottomed glass tube. The autoclave was closed, purged twice with carbon monoxide, and then pressurized with 30 atm of CO and then heated with stirring at 80 °C for 5 h. After excess CO was discharged at room temperature, the ratio of the product to internal standard was determined by GC.

**(ii) Allyltin mediated process (reaction of 1d):** Benzene (50 mL), 10-iodohexyl acrylate (**1d**; 84 mg, 0.25 mmol, 0.005 M), allyltributyltin (826 mg, 2.49 mmol), tetradecane (internal Standard, 15 mg), and AIBN (25 mg, 0.15 mmol) were placed in a 100-mL stainless steel autoclave lined with a round bottomed glass tube. The autoclave was closed, purged twice with carbon monoxide, and then pressurized with 20 atm of CO and then heated with stirring at 80 °C for 8 h. After excess CO was discharged at room temperature, the ratio of the product to internal standard was determined by GC.

**General procedures for macrocyclization of 1a-1g, 1e'.**

**(i) Tris(trimethylsilyl)silane (TTMSS) mediated process:** Benzene (50 mL), 8-iodooctyl acrylate (**1c**; 157 mg, 0.51 mmol, 0.01 M), tris(trimethylsilyl)silane (187 mg, 0.75 mmol), and AIBN (16 mg, 0.1 mmol) were placed in a 100-mL stainless steel autoclave lined with a round bottomed glass tube. The autoclave was closed, purged twice with carbon monoxide, and then pressurized with 30 atm of CO and then heated with stirring at 80 °C for 5 h. After excess CO was discharged at room temperature, the benzene was evaporated, and the residue was dissolved in 40 mL of $CH_3CN$ and washed with pentane (3 x 15 mL).[18] The $CH_3CN$ layer was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (hexane, 10% $Et_2O$-hexane). The major fraction (10% $Et_2O$-hexane eluent) which eluted from the column contained 75 mg (70%) of 4-oxo-12-dodecanolide (**2c**). In some cases, aqueous KF workup was carried out instead of pentane/MeCN extraction (entries 7, 9, and 11 in Table 2). $Bu_3SnH$ was used instead of TTMSS in a similar method and the product was purified by flash chromatography without pentane/MeCN extraction (entry 10 in Table 2).

**(ii) Allyltin mediated process:** Benzene (50 mL), 12-iododododecyl acrylate (**1f**; 92 mg, 0.25 mmol, 0.005 M), allyltributyltin (493 mg, 1.49 mmol), and AIBN (24 mg, 0.15 mmol) were placed in a 100-mL stainless steel autoclave lined with a round bottomed glass tube. The autoclave was closed, purged twice with carbon monoxide, and then pressurized with 20 atm of CO and then heated with stirring at 80 °C for 8 h. After excess CO was discharged at room temperature, the benzene was evaporated, and the residue was purified by flash chromatography on silica gel (hexane, 8% $Et_2O$-hexane). The major fraction (8% $Et_2O$-hexane eluent) which eluted from the column contained 54 mg (70%) of 2-(prop-2-enyl)-4-oxo-16-hexadecanolide (**3f**). 2-Methylprop-2-enyltributyltin was used instead of allyltributyltin in a similar method (entry 4 in Table 2).

**Spectral and analytical data for 4-oxolactones 2a-2g, 3b-3d, 3f, and 4.**

**4-Oxo-9-nonanolide (2a):** colorless oil; $^1$H-NMR ($CDCl_3$, 270 MHz) δ 1.49-1.58 (m, 2 H), 1.62-1.71 (m, 2 H), 1.80-1.86 (m, 2 H), 2.51-2.61 (m, 4 H), 2.76 (t, 2 H, $J$ = 6.5 Hz), 4.08 (t, 2 H, $J$ = 5.5 Hz); $^{13}$C-NMR ($CDCl_3$, 68 MHz) δ 24.0, 24.3, 26.0, 31.9, 36.2, 42.8, 65.7, 170.9, 212.0; IR (neat) 2935, 1740, 1707, 1448, 1261, 1212, 1151, 1049, 1009 cm$^{-1}$; EIMS (relative intensity) m/z 170 ($M^+$, 37), 152 (2),

142 (19), 125 (2), 115 (100), 111 (31), 101 (96), 97 (61), 83 (5), 73 (21), 69 (50), 55 (67), 42 (42), 28 (27); HRMS (EI) calcd for $C_9H_{14}O_3$: m/z 170.0943, found: 170.0950.

**1,11-Dioxa-2,5,12,15-tetraoxocycloeicosane (4):** This compound was isolated from the reaction of **1a** with TTMSS in the presense of carbon monoxide to give **2a** as a byproduct. The crude mixture was subject to flash chromatography on silica gel to afford, in order of elution, first the 10 membered oxolactone **2a** (8% $Et_2O$-hexane eluent), then the dimeric compound **4** (25% $Et_2O$-hexane eluent). White solid, mp 130.0-131.0 °C; $^1$H-NMR ($CDCl_3$, 400 MHz) δ 1.35-1.43 (m, 4 H), 1.58-1.64 (m, 8 H), 2.48 (t, 4 H, *J* = 7.0 Hz), 2.58 (t, 4 H, *J* = 6.4 Hz), 2.74 (t, 4 H, *J* = 6.4 Hz), 4.12 (t, 4 H, *J* = 5.6 Hz); $^{13}$C-NMR ($CDCl_3$, 100 MHz) δ 23.25, 25.71, 28.37, 28.77, 37.49, 42.37, 64.09, 172.12, 208.42; IR (neat) 2934, 2874, 2853, 1731, 1718, 1709, 1460, 1404, 1380, 1258, 1193, 1121, 1088, 1076, 1033, 998, 975 cm$^{-1}$; EIMS (relative intensity) m/z 340 ($M^+$, 3), 322 (52), 269 (7), 240 (4), 225 (24), 171 (63), 152 (100), 135 (12), 125 (72), 111 (71), 99 (64), 83 (10), 69 (25), 55 (68), 41 (28), 28 (11); HRMS (EI) calcd for $C_{18}H_{28}O_6$: m/z 340.1886, found: 340.1891.

**4-Oxo-10-decanolide (2b):** white solid, mp 59.0-60.0 °C; $^1$H-NMR ($CDCl_3$, 270 MHz) δ 1.26-1.41 (m, 2 H), 1.50 (quint-like, 2 H, *J* = 6.1 Hz), 1.71-1.83 (m, 4 H), 2.42 (t, 2 H, *J* = 6.2 Hz), 2.61-2.63 (m, 2 H), 2.68-2.72 (m, 2 H), 4.03 (t, 2 H, *J* = 4.9 Hz); $^{13}$C-NMR ($CDCl_3$, 68 MHz) δ 21.3, 24.0, 24.6, 25.6, 29.8, 34.8, 44.1, 65.5, 170.8, 210.9; IR (KBr) 2981, 2956, 2923, 2907, 2872, 2852, 1728, 1702, 1458, 1446, 1411, 1263, 1161, 1038, 1020, 995 cm$^{-1}$; EIMS (relative intensity) m/z 184 ($M^+$, 12), 156 (23), 111 (63), 101 (100), 98 (96), 83 (32), 68 (40), 55 (84), 41 (45), 28 (22); HRMS (EI) calcd for $C_{10}H_{16}O_3$: m/z 184.1100, found: 184.1109.

**4-Oxo-12-dodecanolide (2c):** white solid, mp 45.0-46.0 °C; $^1$H-NMR ($CDCl_3$, 600 MHz) δ 1.28-1.33 (m, 4 H), 1.32-1.38 (m, 2 H), 1.42 (quint-like, 2 H, *J* = 6.8 Hz), 1.59-1.63 (m, 2 H), 1.67-1.71 (m, 2 H), 2.46 (t-like, 2 H, *J* = 6.1 Hz), 2.65 (t-like, 2 H, *J* = 6.2 Hz), 2.75 (t-like, 2 H, *J* = 5.2 Hz), 4.08 (t, 2 H, *J* = 5.2 Hz); $^{13}$C-NMR ($CDCl_3$, 68 MHz) δ 22.3, 24.2, 25.0, 25.8, 25.9, 26.0, 28.9, 37.8, 41.4, 65.4, 171.9, 209.5; IR (KBr) 2938, 2858, 1728, 1707, 1459, 1420, 1394, 1372, 1258, 1169, 1143, 1076, 1017, 998 cm$^{-1}$; EIMS (relative intensity) m/z 212 ($M^+$, 24), 194 (7), 184 (3), 165 (7), 152 (5), 139 (9), 129 (7), 116 (13), 111 (42), 101 (61), 98 (100), 83 (19), 69 (35), 55 (65), 41 (26), 29 (8); HRMS (EI) calcd for $C_{12}H_{20}O_3$ m/z 212.1412, found, 212.1393. Anal. calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.64; H, 9.52.

**4-Oxo-14-tetradecanolide (2d):** white solid, mp 42.5-43.5 °C; $^1$H-NMR ($CDCl_3$, 270 MHz) δ 1.16-1.41 (m, 12 H), 1.56-1.74 (m, 4 H), 2.47 (t, 2 H, *J* = 6.6 Hz), 2.60-2.65 (m, 2 H), 2.69-2.73 (m, 2 H), 4.13 (t-like, 2 H, *J* = 5.4 Hz); $^{13}$C-NMR ($CDCl_3$, 68 MHz) δ 20.9, 24.5, 24.9, 25.5, 26.0, 26.7, 27.2, 28.4, 28.9, 37.2, 41.1, 64.2, 172.2, 209.1; IR (KBr) 2947, 2926, 2849, 1733, 1718, 1710, 1459, 1408, 1382, 1291, 1252, 1194, 1144, 1082, 1051, 1026, 990, 976 cm$^{-1}$; EIMS (relative intensity) m/z 240 ($M^+$, 28), 222 (9), 194 (3), 179 (3), 165 (9), 149 (6), 140 (11), 124 (23), 117 (19), 111 (45), 98 (100), 83 (35), 69 (38), 55 (65), 41 (31), 29 (10); HRMS (EI) calcd for $C_{14}H_{24}O_3$ m/z 240.1725, found, 240.1728. Anal. calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07. Found: C, 69.77; H, 10.19.

**4-Oxo-15-pentadecanolide (2e):** colorless oil; $^1$H-NMR ($CDCl_3$, 270 MHz) δ 1.22-1.42 (br. s, 14

H), 1.55-1.66 (m, 4 H), 2.45 (t, 2 H, $J$ = 6.4 Hz), 2.55-2.59 (m, 2 H), 2.74-2.78 (m, 2 H), 4.14 (t, 2 H, $J$ = 5.7 Hz); $^{13}$C-NMR ($CDCl_3$, 68 MHz) δ 22.3, 24.6, 25.6, 26.2, 26.4, 26.6, 26.7, 27.1, 28.4, 28.7, 37.6, 41.7, 64.4, 172.6, 209.2; IR (neat) 2928, 2857, 1732, 1716, 1461, 1410, 1355, 1257, 1190, 1167 $cm^{-1}$; EIMS (relative intensity) m/z 254 ($M^+$, 43), 236 (13), 226 (1), 208 (4), 193 (3), 179 (4), 165 (9), 151 (8), 138 (30), 124 (7), 117 (31), 111 (41), 98 (100), 83 (31), 69 (31), 55 (63), 41 (28), 29 (8); HRMS (EI) calcd for $C_{15}H_{26}O_3$ m/z 254.1882, found, 254.1905. This is a known compound and the properties of this compound ($^1$H-NMR, IR, MS and HRMS) were consistent with those previously reported in reference 12.

**4-Oxo-16-hexadecanolide (2f):** colorless oil; $^1$H-NMR ($CDCl_3$, 270 MHz) δ 1.16-1.25 (m, 16 H), 1.42-1.58 (m, 4 H), 2.33 (t-like, 2 H, $J$ = 6.4 Hz), 2.43-2.52 (m, 2 H), 2.54-2.68 (m, 2 H), 4.01 (t-like, 2 H, $J$ = 5.9 Hz); $^{13}$C-NMR ($CDCl_3$, 68 MHz) δ 22.8, 24.9, 26.7, 26.8 (strong peak), 26.9, 27.3, 27.4, 27.7, 28.6, 28.7, 37.4, 41.9, 64.3, 172.5, 209.1; IR (neat) 2929, 2857, 1738, 1732, 1716, 1462, 1410, 1246, 1185 $cm^{-1}$; EIMS (relative intensity) m/z 268 ($M^+$, 25), 250 (8), 222 (2), 208 (2), 193 (2), 179 (2), 165 (4), 152 (16), 140 (5), 124 (6), 117 (24), 111 (31), 99 (100), 83 (22), 69 (29), 55 (45), 41 (21); HRMS (EI) calcd for $C_{16}H_{28}O_3$ m/z 268.2038, found, 268.2054. Anal. calcd for $C_{16}H_{28}O_3$: C, 71.60; H, 10.52. Found: C, 71.77; H, 10.86.

**7,10,13-Trioxa-4-oxo-15-pentadecanolide (2g):** colorless oil; $^1$H-NMR ($CDCl_3$, 400 MHz) δ 2.60 (t, 2 H, $J$ = 7.0 Hz), 2.65 (t, 2 H, $J$ = 5.7 Hz), 2.95 (t, 2 H, $J$ = 7.0 Hz), 3.63 (br. s, 8 H), 3.66-3.68 (m, 2 H), 3.76 (t, 2 H, $J$ = 5.7 Hz),4.25 (t, 2 H, $J$ = 4.5 Hz); $^{13}$C-NMR ($CDCl_3$, 100 MHz) δ 29.06, 38.55, 43.20, 63.40, 66.64, 68.75, 70.35, 70.38 (strong peak), 70.65, 172.08, 207.69; IR (neat) 2870, 1736, 1716, 1453, 1350, 1261, 1130 $cm^{-1}$; EIMS (relative intensity) m/z 260 ($M^+$, 2), 242 (1), 217 (9), 189 (6), 173 (48), 155 (31), 142 (10), 129 (40), 111 (69), 99 (100), 89 (27), 73 (32), 55 (50), 45 (68), 28 (32); HRMS (EI) calcd for $C_{12}H_{20}O_6$ m/z 260.1260, found, 260.1240.

**2-(2-Methylprop-2-enyl)-4-oxo-10-decanolide (3b):** colorless oil; $^1$H-NMR ($CDCl_3$, 600 MHz) δ 1.30-1.90 (m, 8 H), 1.73 (s, 3 H), 2.13-2.23 (m, 3 H), 2.54 (br. dd, 1 H, $J$ = 14.0, 5.0 Hz), 2.64 (ddd, 1 H, $J$ = 12.1, 7.0, 2.8 Hz), 2.92 (dd, 1 H, $J$ = 16.0, 11.4 Hz), 3.15-3.26 (m, 1 H), 3.89-3.99 (m, 1 H), 4.19-4.28 (m, 1 H), 4.73 (s, 1 H), 4.82 (s, 1 H); $^{13}$C-NMR ($CDCl_3$, 68 MHz) δ 21.4, 21.7, 24.3, 24.7, 25.6, 39.5, 39.9, 41.0, 44.1, 65.6, 113.2, 142.4, 173.7, 211.1; IR (neat) 2955, 2872, 2856, 1738, 1732, 1712, 1649, 1642, 1415, 1364, 1259, 1203, 1160, 1043, 987, 894 $cm^{-1}$; EIMS (relative intensity) m/z 238 ($M^+$, 100), 150 (23), 137 (22), 126 (23), 111 (28), 109 (66), 95 (100), 83 (31), 81 (27), 69 (33), 68 (38), 55 (77), 41 (33); HRMS (EI) calcd for $C_{14}H_{22}O_3$ m/z 238.1569, found, 238.1571.

**2-(Prop-2-enyl)-4-oxo-12-dodecanolide (3c):** colorless oil; $^1$H-NMR ($CDCl_3$, 270 MHz) δ 1.30-1.89 (br. m, 12 H), 2.23-2.39 (m, 2 H), 2.42-2.61 (m, 3 H), 2.89-3.06 (m, 2 H), 4.01-4.18 (m, 2 H), 5.07 (d, 1 H, $J$ = 10.7 Hz), 5.08 (d, 1 H, $J$ = 16.1 Hz), 5.63-5.80 (m, 1 H); $^{13}$C-NMR ($CDCl_3$, 68 MHz) δ 22.0, 24.0, 25.0, 25.6, 25.8, 26.2, 36.3, 40.1, 41.4, 43.9, 65.1, 117.5, 135.0, 174.2, 209.5; IR (neat) 2933, 2862, 1732, 1716, 1641, 1443, 1370, 1259, 1222, 1179, 917 $cm^{-1}$; EIMS (relative intensity) m/z 252 ($M^+$, 41), 157 (25), 139 (51), 123 (64), 111 (58), 97 (86), 96 (41), 95 (42), 81 (48), 69 (56), 55 (100), 41 (46); HRMS (EI) calcd for $C_{15}H_{24}O_3$ m/z 252.1725, found, 252.1696.

**2-(Prop-2-enyl)-4-oxo-14-tetradecanolide (3d):** colorless oil; $^1$H-NMR ($CDCl_3$, 270 MHz) δ 1.12-1.50 (br. m, 12 H), 1.50-1.90 (m, 4 H), 2.18-2.33 (m, 1 H), 2.34-2.57 (m, 4 H), 2.82-3.01 (m, 2 H), 3.94-4.05 (m, 1 H), 4.22-4.31 (m, 1 H), 5.06 (d, 1 H, *J* = 11.2 Hz), 5.07 (d, 1 H, *J* = 15.9 Hz), 5.64-5.81 (m, 1 H); $^{13}$C-NMR ($CDCl_3$, 68 MHz) δ 20.8, 24.5, 25.0, 25.5, 25.9, 26.8, 27.2, 28.4, 36.2, 40.2, 41.3, 43.4, 64.1, 117.4, 134.9, 174.4, 208.9; IR (neat) 2928, 2857, 1736, 1732, 1717, 1641, 1460, 1372, 1258, 1182, 917 $cm^{-1}$; EIMS (relative intensity) m/z 280 ($M^+$, 44), 239 (44), 123 (53), 111 (54), 95 (44), 83 (68), 81 (51), 69 (73), 55 (100), 41 (55); HRMS (EI) calcd for $C_{17}H_{28}O_3$ m/z 280.2038, found, 280.2015.

**2-(Prop-2-enyl)-4-oxo-16-hexadecanolide (3f):** colorless oil; $^1$H-NMR ($CDCl_3$, 270 MHz) δ 1.20-1.46 (br. s, 16 H), 1.47-1.81 (m, 4 H), 2.18-2.31 (m, 1 H), 2.37-2.54 (m, 4 H), 2.84 (dd, 1 H, *J* = 17.0, 9.4 Hz), 2.90-3.02 (m, 1 H), 3.95-4.00 (m, 1 H), 4.24-4.33 (m, 1 H), 5.05 (d, 1 H, *J* = 10.5 Hz), 5.06 (d, 1 H, *J* = 17.1 Hz), 5.64-5.80 (m, 1 H); $^{13}$C-NMR ($CDCl_3$, 68 MHz) δ 22.6, 24.9, 26.5, 26.6, 26.7, 26.8, 27.30, 27.34, 27.5, 28.6, 36.0, 40.0, 42.1, 43.6, 64.3, 117.4, 135.0, 174.6, 208.8; IR (neat) 2929, 2857, 1732, 1716, 1642, 1460, 1369, 1237, 1183, 916 $cm^{-1}$; EIMS (relative intensity) m/z 308 ($M^+$, 66), 267 (76), 195 (32), 139 (66), 123 (49), 111 (77), 97 (71), 95 (52), 83 (68), 82 (36), 81 (52), 71 (36), 69 (59), 55 (100), 43 (39), 41 (50); HRMS (EI) calcd for $C_{19}H_{32}O_3$ m/z 308.2352, found, 308.2378.

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