

Radical Addition of 2-Iodoalkanamide or 2-Iodoalkanoic Acid to Alkenes with a Water-Soluble Radical Initiator in Aqueous Media: Facile Synthesis of γ-Lactones

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(Received May 1, 2001)

Radical reactions in water or aqueous ethanol using a water-soluble radical initiator are described. Heating a mixture of 2-iodoacetamide and 5-hexen-1-ol in water at 75 °C in the presence of a water-soluble radical initiator, 4,4′-azobis(4-cyanopentanoic acid), afforded 5-(4-hydroxybutyl)dihydrofuran-2(3*H*)-one in 95% yield. The use of 2-iodoacetic acid in place of 2-iodoacetamide also gave the same γ-lactone in 93% yield. The reaction of 2-iodoacetamide with 1-octene in aqueous ethanol was initiated by 2,2′-azobis(2-methylpropanamidine) dihydrochloride to provide γ-decanolactone. Employing water as a solvent is crucial to obtain lactone in satisfactory yield.

Recently, processes using a less toxic solvent or no solvent have been required in the design of new synthetic methods from the ecological point of view. Water might be the best among many kinds of solvents. In the last decade, there has been increasing recognition that organic reactions carried out in aqueous media may offer advantages over those occurring in organic solvents.[1] For example, pericyclic reactions, such as the Diels–Alder reaction,[2] were carried out in water, and rate enhancement was observed. Indium-mediated allylation of aldehyde is also a well-known reaction in water.[3] However, methods for carbon–carbon bond formation based on a radical process in aqueous media have been limited.[4] We have studied radical reactions in aqueous media,[5] and more recently have focused on the reaction with water-soluble radical initiators. Here we chose the following two commercially available initiators (Fig. 1),[6] 4,4′-azobis(4-cyanopentanoic acid) (**1a**, $t_{1/2}$ = 10 h, 69 °C in H_2O) and 2,2′-azobis(2-methylpropanamidine) dihydrochloride (**1b**, $t_{1/2}$ = 10 h, 56 °C in H_2O). We describe in this paper[7] that (1) the addition of PhSH to alkene or alkyne proceeds smoothly to give the corresponding adducts, (2) atom transfer cyclization of *N*,*N*-diallyl-2-iodoacetamide affords γ-lactams in excellent yields, and (3) the addition of 2-iodoacetamide to alkene followed by ionic cyclization gives γ-lactone in good yield. Particularly, (3) provides a much less toxic and safer synthesis of γ-lactone. Kharasch's addition of α-bromoacetate to alkene employed highly explosive peracetic acid.[8] Radical addition of tributylstannyl iodoacetate to alkene also provided γ-lactone.[9,10] In this case, the stannyl ester should be prepared in advance, and the toxic residual tin compounds might be troublesome to handle.

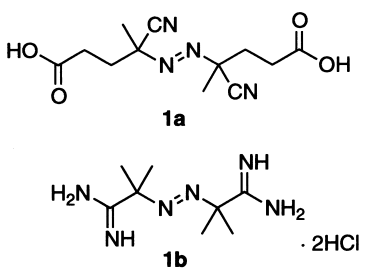
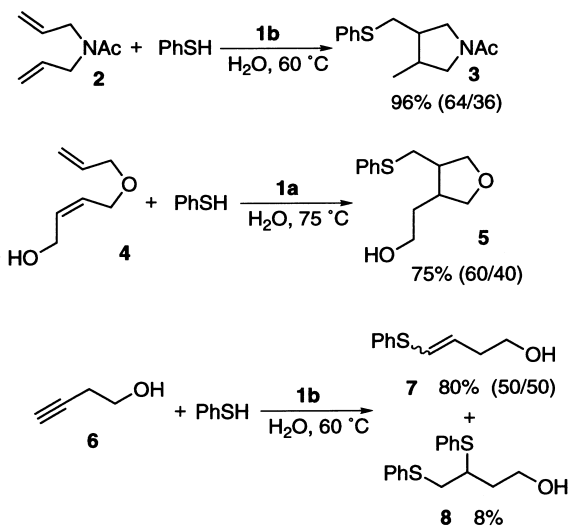


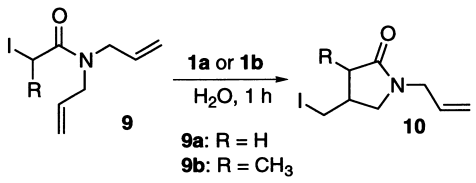
Fig. 1. Water-soluble radical initiators.

Radical Addition of Benzenethiol to Carbon–Carbon Multiple Bonds and Radical Cyclization of *N*-Allyl-2-iodoalkanamide in Water

We first examined radical addition of benzenethiol to alkenes or alkynes (Scheme 1).[11] Heating a mixture of *N*,*N*-dial-



Scheme 1.



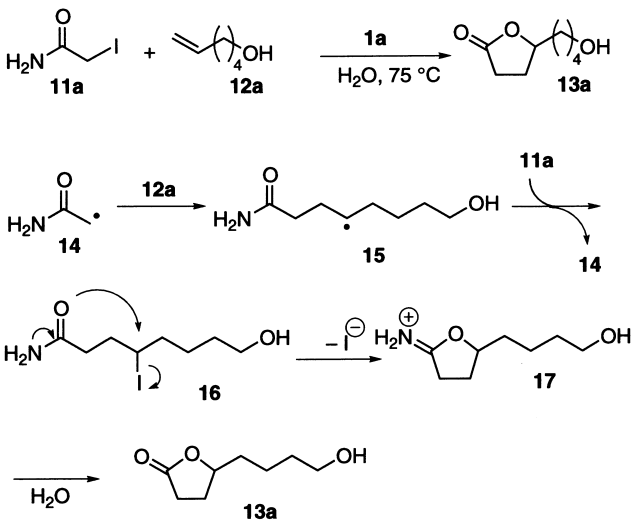
Scheme 2.

lylacetamide (**2**, 1.0 mmol), benzenethiol (1.5 mmol), and **1b** (0.30 mmol) in water (10 mL) at 60 °C for 2 h provided *N*-acetylpyrrolidine derivative **3** in 96% yield. In similar fashion, treatment of diallylic ether **4** with benzenethiol in the presence of **1a** at 75 °C gave tetrahydrofuran derivative **5** in 75% yield. The reaction of 3-butyn-1-ol (**6**) with PhSH at 60 °C in the presence of **1b** afforded 4-(phenylthio)-3-buten-1-ol (**7**) in 80% yield, in addition to 3,4-bis(phenylthio)-1-butanol (**8**, 8%).

These radical initiators were highly effective for the atom transfer radical cyclization of 2-iodo amide **9** in water (Scheme 2).[12] Stirring a mixture of *N*,*N*-diallyl-2-iodoacetamide **9a** (1.0 mmol) and **1a** or **1b** (0.30 mmol) at 75 °C or 60 °C in water (30 mL) for 1 h provided γ-lactam **10a** in 80% or 99% yield, respectively. 2-Iodopropanamide **9b** also underwent cyclization in the presence of **1a** or **1b** to afford the corresponding lactam **10b** in 95% or 85% yield, respectively.[13] The effectiveness of **1a** and **1b** as an initiator in water was confirmed by these experiments.

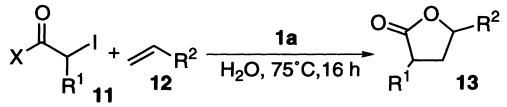
Radical Addition of 2-Iodoalkanamide or 2-Iodoalkanoic Acid to Alkenes in Aqueous Media to Yield γ-Lactones

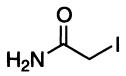
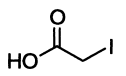
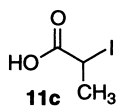
The success of intramolecular radical cyclization of 2-iodoalkanamide encouraged us to investigate an intermolecular radical addition reaction. Thus, we turned our attention to the reaction of 2-iodoacetamide with alkenol. The addition of 2-iodoacetamide to alkenol in water afforded γ-substituted γ-lactone in high yields. For instance, the reaction of 2-iodoacetamide (**11a**) with 5-hexen-1-ol (**12a**) in the presence of **1a** at 75 °C for 16 h provided 5-(4-hydroxybutyl)dihydrofuran-2(3*H*)-one (**13a**) in an isolated yield of 95% (Scheme 3). The reaction would proceed as follows: Radical **14** derived from **11a** adds readily to the alkenyl terminal carbon of alkenol **12a** to provide **15**. The iodine atom transfer reaction between the radical **15** and **11a** affords 8-hydroxy-4-iodooctanamide (**16**) and regenerates **14**. The compound **16** cyclizes to γ-lactone **13a** via **17** under the reaction conditions[14] due to the well-known ionic lactonization[15,16] of 4-iodoalkanamide. Typical examples are shown in Table 1.[17,18] Alcohol, having a terminal alkene moiety, as well as 4-pentenoic acid (**12f**) was converted into the corresponding lactone in excellent yield. However, the addition to alkenol containing an internal double bond such as 2-buten-1-ol did not take place. 1-Octene did not give lactone under the same reaction conditions because of the insolubility of 1-octene in water, whereas hydrophilic allyl ether **12e** gave **13e**.



Scheme 3.

Table 1. γ-Lactone Synthesis by Tandem Radical-Ionic Reaction between 2-Iodoacetamide or 2-Iodoacetic Acid and Alkenol[a)]

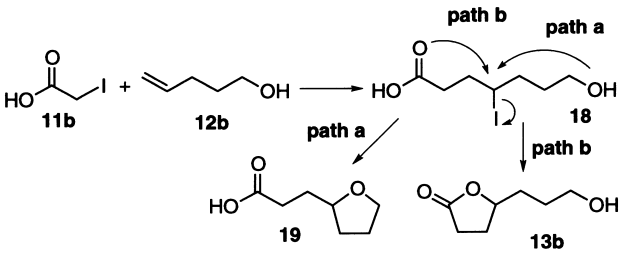


2-Iodocarbonyl Compound	R^2 in alkenol	Product/%
 **11a**	**12a**: $(CH_2)_4OH$	**13a**: 95
	12b: $(CH_2)_3OH$	**13b**: 85
	12c: $(CH_2)_2OH$	**13c**: 91[b)]
	12d: CH_2OH	**13d**: 88[b)]
	12e: $CH_2O(CH_2)_2O$*i*-Pr	**13e**: 84
	12f: $(CH_2)_2COOH$	**13f**: 94[c)]
	12g: $CH(CH_3)OH$	**13g**: 84 (54/46)
 **11b**	**12a**: $(CH_2)_4OH$	**13a**: 93
	12c: $(CH_2)_2OH$	**13c**: 95
	12d: CH_2OH	**13d**: 76
	12f: $(CH_2)_2COOH$	**13f**: 100[c)]
 **11c**	**12a**: $(CH_2)_4OH$	**13h**: 86 (55/45)

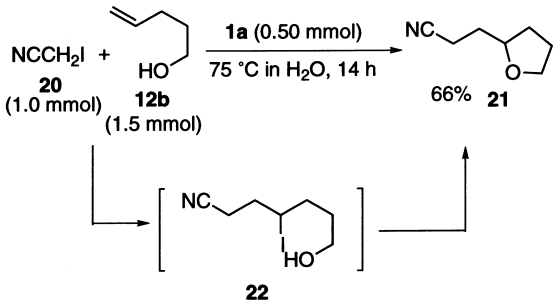
a) 2-Iodoacetamide or 2-iodoacetic acid (1.0 mmol), alkenol (1.5 mmol), and **1a** (0.50 mmol) were employed unless otherwise noted. b) Three molar amounts of alkenol were employed. c) The product was isolated as allyl ester after treatment with allyl bromide in the presence of K_2CO_3 in acetone.

Not only 2-iodoacetamide but 2-iodoacetic acid (**11b**) provided γ-lactones in the reaction with alkenol in water at 75 °C in the presence of **1a**. Some representative results are also summarized in Table 1. Interestingly, **11b** was added to 4-penten-1-ol (**12b**) to give tetrahydrofuran derivative **19** in 40% yield in addition to the expected γ-lactone **13b** (54%) (Scheme 4). The former compound **19** was obtained by an intramolecular etherification of the iodine transfer product **18**.

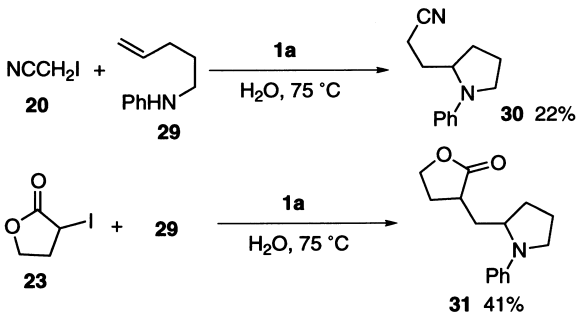
The formation of **19** prompted us to examine the reaction of



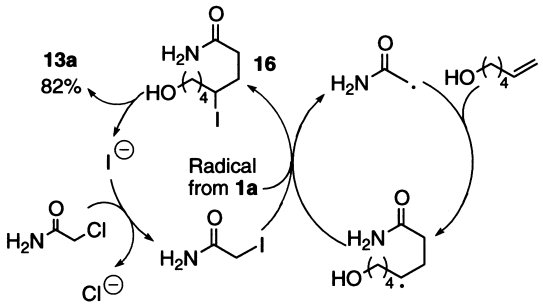
Scheme 4.



Scheme 5.

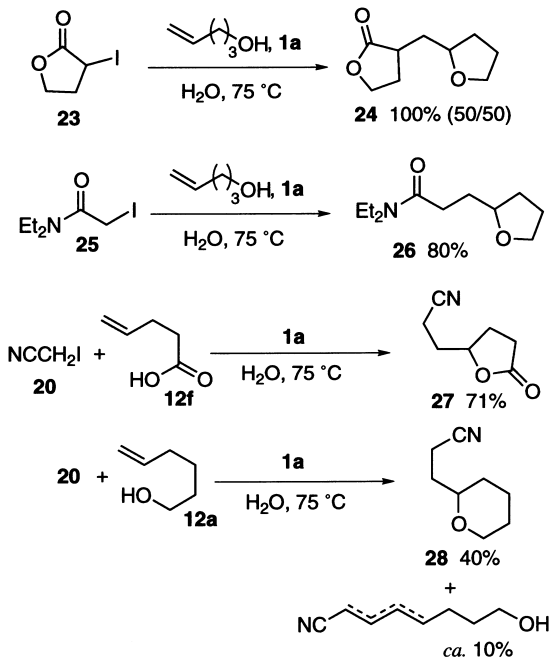


Scheme 7.



Scheme 8.

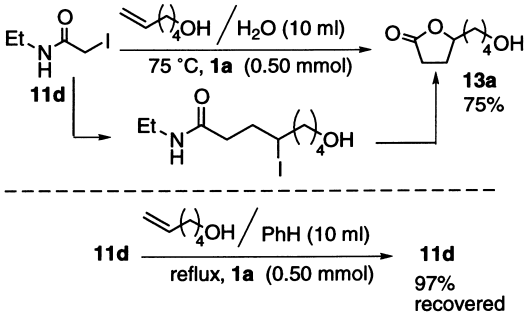
iodoacetonitrile (**20**) with 4-penten-1-ol (Scheme 5). A mixture of **20** and **12b** was treated under the standard reaction conditions. The anticipated tetrahydrofuran derivative **21** was obtained in 66% yield. The addition of α-iodo-γ-butyrolactone (**23**) or *N*,*N*-diethyl-2-iodoacetamide (**25**) to 4-penten-1-ol yielded the corresponding product **24** or **26** in excellent yield, respectively (Scheme 6). The addition of **20** to 4-pentenoic acid provided γ-lactone **27** in high yield. Furthermore, 5-hexen-1-ol reacted with **20** to give tetrahydropyran **28** in 40% yield, along with unsaturated ω-hydroxy nitriles. However, synthesis of pyrrolidine using the radical addition-ionic cyclization methodology seems difficult (Scheme 7). Treatment of *N*-(4-pentenyl)aniline (**29**) with **20** or **23** gave the corresponding pyrrolidine **30** or **31** in 22% or 41% yield, respectively.



Scheme 6.

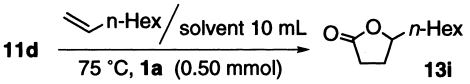
Iodide was liberated in the transformation of **16** into **13**. Thus, it was anticipated that, by adding a catalytic amount of sodium iodide, the use of 2-chloroacetamide instead of the iodo amide **11a** would provide **13**. We have indeed found that the radical-ionic tandem reaction of 2-chloroacetamide with 5-hexen-1-ol in the presence of a substoichiometric amount of NaI proceeds smoothly, as shown in Scheme 8. Heating a mixture of 2-chloroacetamide (1.0 mmol), 5-hexen-1-ol (1.5 mmol), and NaI (0.50 mmol)[19] in water (10 mL) at 75 °C for 16 h in the presence of **1a** (0.50 mmol) provided **13a** in 82% yield.

We have been interested in radical reactions in aqueous media and have disclosed the attractive solvent effect of water.[5a–5c] Accordingly, the solvent effect on the present reaction was examined (Scheme 9). The reaction of *N*-ethyl-2-iodoacetamide (**11d**) with 5-hexen-1-ol in water afforded **13a** in 75% yield. On the other hand, very interestingly, the reaction did not proceed at all in refluxing benzene, and **11d** was almost completely recovered. The results of further investigations are summarized in Table 2. Benzene, THF, CH_2Cl_2, and acetonitrile were completely ineffective for the synthesis of lactones.[20] In each case, **11d** was recovered, that is, the radical addition step itself did not take place. Employing protic solvents, such as ethanol and methanol, led to some conversion to give γ-decanolactone (**13i**) in 14 % and 26% yields, respectively. Water is the best for this reaction.



Scheme 9.

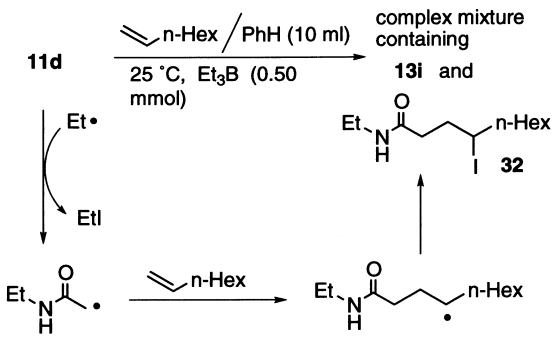
Table 2. Reaction in Various Solvents



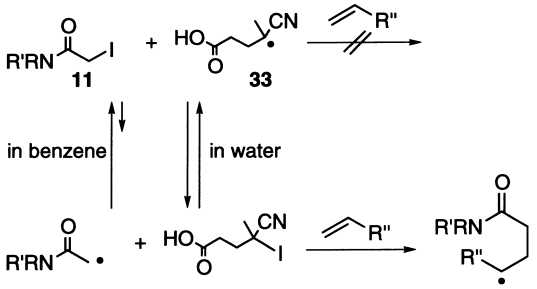
Solvent	Time /h	Yield of **13**/%	Recovered **11d**/%
benzene[1)]	16	0	97
THF[1)]	24	0	89
CH_2Cl_2[1)]	24	0	100
CH_3CN	24	0	100
MeOH[1)]	40	26	68
EtOH	40	14	77
H_2O[2)]	16	75	0

1) Reflux. 2) 5-Hexen-1-ol was used.

To get deeper insight into the solvent effect, the reaction was performed in benzene at room temperature in the presence of triethylborane[21] in place of **1a** (Scheme 10). A mixture of **11d** and 1-octene was treated with triethylborane in benzene at 25 °C. After 3 h, concentration of the reaction mixture yielded a complex mixture containing **13i** and the adduct **32**. The starting iodide **11d** was completely consumed. An ethyl radical, derived from triethylborane by the action of a trace of oxygen, is reactive enough to abstract iodine from iodo amide.[5e] Therefore, the reaction was initiated by triethylborane, and the products generated by the radical addition were obtained. Thus, the reason for the recovery or the poor conversion of **11d** in organic solvents in the presence of azo initiator **1a** is that the radical **33**, which is generated from **1a** and is stabilized by a cyano group, could not abstract iodine from iodo amide **11** (Scheme 11). The solvent effect of water works in the initiation step.



Scheme 10.

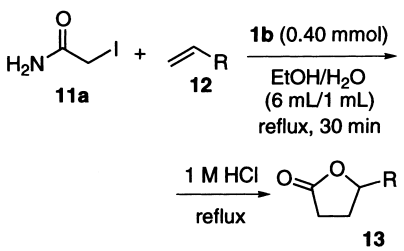


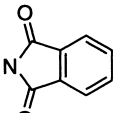
Scheme 11.

Water could enhance the reactivity of radical **33** and/or activate the carbon-iodine bond in **11**. Other factors may work in this reaction. The exact role of water is not clear at present.[22]

Whereas hydrophilic olefins could be used in the present reaction, hydrophobic compounds such as 1-octene were not suitable. To extend the scope of this reaction, radical reaction in aqueous ethanol was studied. Radical addition-lactonization reaction proceeded less effectively in ethanol than in water in the presence of **1a**, as shown in Table 2. Thus, we tested **1b** as an initiator for the reaction in aqueous ethanol. A mixture of iodoacetamide (2.0 mmol) and 1-octene (10 mmol)[23] was heated in EtOH/H_2O (6 mL/1 mL) at reflux in the presence of **1b** (0.20 mmol) for 30 min. Usual workup followed by silica gel column purification provided **13i** in 80% yield in addition to ethyl 4-hydroxydecanoate (**13i′**, 6%), derived from solvolysis of the lactone. Hydroxy ester **13i′** could be easily converted into **13i**. Heating a crude mixture of **13i** and **13i′** in refluxing 1 M HCl for 20 min yielded **13i** in 83% yield after silica gel column purification. The reaction in aqueous ethanol is summarized in Table 3. Although excess of olefin was necessary,[24] good results were obtained compared with the reaction in water. Water as a cosolvent is essential to give a satisfactory result. For example, the yield of **13i** decreased to 47% on employing anhydrous ethanol (7 mL). The initiator **1b** proved to

Table 3. Synthesis of Lactones in Aqueous Ethanol



R	**13**/%
12i: n-C_6H_{13}	**13i**: 83 (0)
12j: $(CH_2)_8OH$	**13j**: 83 (31)
12k: $(CH_2)_3$ 	**13k**: 79 (0)
12l: $CH_2CH_2COCH_3$	**13l**: 72 (85)

The yields of **13** under the reaction conditions in Table 1 are in parentheses.

be more effective than **1a**, for which we assume the reason to be as follows. The radical, derived from **1b**, is stabilized with the amide group resulting from hydrolysis of the amidine group. The amide-stabilized radical would be less stable than the radicals produced from AIBN and **1a**, which the cyano groups stabilize,[25] and would be more reactive in iodine abstraction.

In summary, we have developed atom-transfer radical reactions in aqueous media, using a water-soluble azo initiator. Synthesis of γ-substituted γ-lactones has been accomplished by a radical addition-lactonization sequence in a nontoxic solvent. The reaction procedure is simple and safe, and no special technique is necessary. Similar to our previous reports, water as a solvent or a cosolvent accelerates the reaction.

Experimental

^{1}H NMR (300 MHz) and ^{13}C NMR (75.3 MHz) spectra were taken on a Varian GEMINI 300 spectrometer in $CDCl_3$ as a solvent, and chemical shifts are given in δ value with tetramethylsilane as an internal standard. IR spectra were determined on a JASCO IR-810 spectrometer. Mass spectra were recorded on a JEOL JMS-700 spectrometer. TLC analyses were performed on commercial glass plates bearing 0.25-mm layer of Merck Silica gel $60F_{254}$. Silica gel (Wakogel 200 mesh) was used for column chromatography. The analyses were carried out at the Elemental Analysis Center of Kyoto University. Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. Dichloromethane and acetonitrile were dried with molecular sieves 4A and 3A, respectively. Benzene was dried over slices of sodium. THF was freshly distilled from sodium benzophenone ketyl before use. Initiators **1a** and **1b** were purchased from Fluka. Et_3B was purchased from Aldrich Chemicals and was diluted to prepare a 1.0 M hexane solution, which was stored strictly under argon.

Typical Procedure for Synthesis of γ-Lactone in Water. A water-soluble radical initiator **1a** (0.14 g, 0.50 mmol) was added to a solution of 2-iodoacetamide (**11a**, 0.19 g, 1.0 mmol) and 5-hexen-1-ol (**12a**, 0.15 g, 1.5 mmol) in water (10 mL). After being flushed with argon, the mixture was heated at 75 °C for 16 h, and then cooled to 25 °C. Saturated $NaHCO_3$ (5 mL) was added, and the product was extracted with ethyl acetate (20 mL × 2). The combined organic layer was washed with water, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane : ethyl acetate = 1 : 2) to give 0.15 g of γ-lactone **13a** in 95% yield.

Synthesis of γ-Lactone in Aqueous Ethanol. Iodoacetamide (2.0 mmol) was placed in a round-bottomed flask, and ethanol (6 mL) and water (1 mL) were added to dissolve iodoacetoamide. 1-Octene (10 mmol) and **1b** (0.40 mmol) were added, and the whole mixture was heated at reflux (bath temp. 90 °C) for 30 min under argon. The product was extracted with ethyl acetate (20 mL × 2). The combined organic layer was dried and concentrated. 1 M HCl was added to the crude oil, and the mixture was heated at reflux for 20 min. Extraction and concentration followed by silica gel column purification provided 0.29 g (1.7 mmol) of γ-decanolactone in 83% yield.

Characterization Data. Compounds **2**,[26] **4**,[27] **9a**,[12h] and **10a**[12h] are found in the literature. Lactone **13i** is commercially available.

1-Acetyl-3-methyl-4-(phenylsulfanylmethyl)-1-pyrrolidine (3, 64/36 mixture of diastereomers. Two rotamers exist for each diastereomer.**):** Bp 240 °C/0.1 torr. IR (neat) 3432, 2920, 1657, 1464, 1359, 1205, 1088, 1025, 740, 691 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.00 (d, J = 6.6 Hz, 3H × 0.32), 1.02 (d, J = 6.6 Hz, 3H × 0.32), 1.06 (d, J = 6.6 Hz, 3H × 0.18), 1.07 (d, J = 6.6 Hz, 3H × 0.18), 1.93–2.53 (m, 2H), 2.01 (s, 3H × 0.64), 2.02 (s, 3H × 0.32), 2.71–2.89 (m, 1H), 2.92–3.11 (m, 1H), 3.14–3.40 (m, 2H), 3.48–3.60 (m, 1H), 3.62–3.93 (m, 1H), 7.18–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 12.92, 12.94, 15.96, 16.00, 21.83 (2C), 21.88, 21.92, 32.51, 32.60, 33.88, 35.01, 35.58, 35.75, 37.05, 38.38, 39.70, 41.50, 43.77, 45.55, 48.48, 50.30, 50.53, 51.97, 52.24, 52.32, 54.22, 54.25, 126.23, 126.25, 126.37, 126.39, 128.90 (4C), 128.99 (4C), 129.41 (2C), 129.51 (4C), 129.56 (2C), 135.56, 135.70, 135.74, 135.93, 168.95, 166.03, 169.32, 169.38. Found: C, 67.19; H, 7.75%. Calcd for $C_{14}H_{19}NOS$: C, 67.43; H, 7.68%.

2-[4-(Phenylsulfanylmethyl)tetrahydrofuran-3-yl]ethanol (5, 60/40 mixture of diastereomers**):** IR (neat) 3364, 2928, 2864, 1730, 1584, 1481, 1439, 1055, 898, 739, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.50–1.63 (m, 1H), 1.69–1.84 (m, 1H), 1.86–2.19 (m, 2H), 2.36–2.52 (m, 1H), 2.79 (dd, J = 12.6, 9.6 Hz, 0.6H), 2.92 (dd, J = 12.9, 8.1 Hz, 0.4H), 3.06–3.13 (m, 1H), 3.44 (dd, J = 8.4, 5.4 Hz, 0.4H), 3.54–3.74 (m, 3H), 3.79 (dd, J = 8.7, 4.8 Hz, 0.6H), 3.89–3.98 (m, 1.6H), 4.04 (dd, J = 8.7, 6.9 Hz, 0.4H), 7.17–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$) For major isomer: δ 29.98, 32.42, 38.77, 41.08, 61.40, 71.94, 71.97, 126.27, 128.98 (2C), 129.49 (2C), 135.96, for minor isomer, δ 35.77, 37.20, 41.80, 44.51, 61.02, 72.62, 73.53, 126.24, 129.00 (2C), 129.28 (2C), 135.93. Found: C, 65.23; H, 7.43%. Calcd for $C_{13}H_{18}O_2S$: C, 65.51; H, 7.61%.

4-(Phenylsulfanyl)-3-buten-1-ol (7, 50/50 mixture of diastereomers**):** IR (neat) 3335, 2930, 1583, 1479, 1439, 1047 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.61 (broad s, 1H), 2.43 (dt, J = 7.2, 7.2 Hz, 1H), 2.54 (dt, J = 7.2, 7.2 Hz, 1H), 3.65–3.80 (m, 2H), 5.85 (dt, J = 9.3, 7.2 Hz, 0.5H), 5.91 (dt, J = 15.3, 7.2 Hz, 0.5H), 6.28 (d, J = 15.3 Hz, 0.5H), 6.36 (d, J = 9.3 Hz, 0.5H), 7.17–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 32.34, 36.08, 61.38 (2C), 124.03, 125.43, 126.27 (2C), 128.67, 128.78 (2C), 128.84 (2C), 128.92 (4C), 131.70, 135.69, 135.82. HRMS Found: 180.0609. Calcd for $C_{10}H_{12}OS$: 180.0609.

3,4-Bis(phenylsulfanyl)-1-butanol (8): IR (neat) 3346, 2930, 1583, 1479, 1439, 1049, 741, 692 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.68–1.83 (m, 2H), 2.21–2.33 (m, 1H), 2.91 (dd, J = 14.4, 10.5 Hz, 1H), 3.25–3.35 (m, 2H), 3.87 (dt, J = 6.0, 5.4 Hz, 2H), 7.14–7.37 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 35.23, 39.48, 45.17, 60.34, 126.38, 127.49, 128.98 (2C), 129.05 (2C), 129.83 (2C), 132.67 (2C), 133.58, 135.47. Found: C, 66.42; H, 6.39%. Calcd for $C_{16}H_{18}OS_2$: C, 66.16; H, 6.25%.

***N*,*N*-Diallyl-2-iodopropanamide (9b)** was prepared as follows. Chloroacetyl chloride (16 mmol) was added dropwise to a dichloromethane solution (15 mL) of diallylamine (15 mmol) and pyridine (16 mmol) at −78 °C. The resulting mixture was warmed to room temperature and was stirred for 1 h. Usual workup gave a crude oil, which was dissolved in acetone (30 mL). Sodium iodide (30 mmol) was added to the solution at 25 °C. The mixture was stirred for 3 h. Extractive workup followed by silica gel column purification provided **9b** in 83% overall yield. IR (neat) 2976, 2914, 1655, 1459, 1224, 991, 923 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.96 (d, J = 6.6 Hz, 3H), 3.61 (dddd, J = 15.3, 6.3, 1.2, 1.2 Hz, 1H), 3.78 (dddd, J = 18.0, 4.5, 1.8, 1.8 Hz, 1H), 4.09 (dddd, J = 18.0, 4.8, 3.0, 1.8 Hz, 1H), 4.38 (dddd, J = 15.3, 4.8, 3.0, 1.8 Hz, 1H), 4.52 (q, J = 15.3 Hz, 1H), 5.10–5.26 (m, 4H), 5.74–5.92 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 13.40, 23.49, 48.16, 49.59, 116.12, 117.00, 132.04, 132.76, 170.85. Found: C, 38.89;

H, 5.05%. Calcd for $C_9H_{14}INO$: C, 38.73; H, 5.06%.

1-Allyl-4-iodomethyl-3-methylpyrrolidin-2-one (10b): For *trans* isomer (faster moving band, R_f = 0.40, hexane/ethyl acetate = 1/1) IR (Nujol) 2960, 2924, 1689, 1442, 1270, 1241, 1188, 920 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (d, J = 6.9 Hz, 3H), 2.08–2.27 (m, 2H), 3.00 (dd, J = 10.2, 7.8 Hz, 1H), 3.17 (dd, J = 10.2, 8.4 Hz, 1H), 3.41 (dd, J = 10.2, 4.5 Hz, 1H), 3.44 (dd, J = 10.2, 7.8 Hz, 1H), 3.57–3.99 (m, 2H), 5.16–5.24 (m, 2H), 5.66–5.80 (m,1H); ^{13}C NMR ($CDCl_3$) δ 8.01, 14.63, 42.56, 43.74, 45.02, 51.59, 118.09, 132.12, 175.47. Found: C, 38.88; H, 5.09%. Calcd for $C_9H_{14}INO$: C, 38.73; H, 5.06%. For *cis* isomer (slower moving band R_f = 0.34, hexane/ethyl acetate = 1/1) IR (Nujol) 2966, 2926, 1689, 1439, 1266, 1192, 930 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13 (d, J = 7.8 Hz, 3H), 2.62 (dq, J = 7.8, 7.8 Hz, 1H), 2.73–2.86 (m, 1H), 3.08 (dd, J = 9.9, 9.9 Hz, 1H), 3.11 (dd, J = 10.2, 6.6 Hz, 1H), 3.27 (dd, J = 9.9, 5.7 Hz, 1H), 3.46 (dd, J = 10.2, 7.2 Hz, 1H), 3.89 (ddd, J = 6.0, 1.5, 1.5 Hz, 2H), 5.20 (ddt, J = 18.3, 1.5, 1.5 Hz, 1H), 5.21 (ddt, J = 9.6, 1.5, 1.5 Hz, 1H), 3.89 (ddt, J = 18.3, 9.6, 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 4.22, 10.00, 39.15, 40.99, 45.09, 51.25, 118.29, 132.24, 176.09. Found: C, 38.89; H, 5.11%. Calcd for $C_9H_{14}INO$: C, 38.73; H, 5.06%.

1-Allyloxy-2-isopropoxyethane (12e) was prepared from commercially available 2-isopropoxyethanol and allyl bromide by the action of stoichiometric sodium hydride in refluxing THF. Bp 125 °C/50 torr. IR (neat) 2966, 2852, 1648, 1468, 1368, 1080, 995, 920 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (d, J = 6.0 Hz, 6H), 3.59 (s, 4H), 3.62 (septet, J = 6.0 Hz, 1H), 4.04 (ddd, J = 6.0 , 1.5, 1.5, Hz, 2H), 5.18 (ddt, J = 10.5, 1.8, 1.5 Hz, 1H), 5.28 (ddt, J = 17.1, 1.8, 1.5 Hz, 1H), 5.93 (ddt, J = 17.1, 10.5, 6.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.83 (2C), 67.30, 69.62, 71.77, 72.11, 116.86, 134.87. HRMS Found: m/z 129.0911. Calcd for $C_8H_{16}O_2 - CH_3$: 129.0916.

***N*-(4-Pentenyl)phthalimide (12k)** was synthesized by treatment of 1-bromo-4-pentene with an equimolar amount of potassium phthalimide in DMF at 90 °C overnight. IR (neat) 2939, 1771, 1713, 1641, 1396, 1371, 1188, 1072, 993, 719 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.79 (tt, J = 7.2, 7.2 Hz, 2H), 2.13 (dt, J = 7.2, 7.2 Hz, 2H), 3.71 (t, J = 7.2 Hz, 2H), 4.99 (dd, J = 9.9, 1.2 Hz, 1H), 5.06 (dd, J = 17.1, 1.2 Hz, 1H), 5.82 (ddt, J = 17.1, 9.9, 7.2 Hz, 1H), 7.69–7.74 (m, 2H), 7.82–7.88 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 27.43, 30.78, 37.37, 115.25, 123.12 (2C), 132.13, 133.85 (2C), 137.30 (2C), 168.42 (2C). Found: C, 72.60; H, 6.07%. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09%.

Hydroxy lactones **13** were silylated with *t*-butyldimethylsilyl chloride in the presence of imidazole in DMF in more than 90% yield to afford analytically pure material.

5-(4-Hydroxybutyl)dihydrofuran-2(3*H*)-one (13a): IR (neat) 3346, 2922, 1752, 1180 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40–1.94 (m, 9H), 2.34 (sextet, $J \approx$ 7 Hz, 1H), 2.54 (dd, J = 9.3, 6.9 Hz, 2H), 3.67 (t, J = 6.0 Hz, 2H), 4.51 (quintet, $J \approx$ 7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.25, 27.55, 28.52, 31.84, 34.93, 61.87, 80.92, 177.65; MS m/z (rel intensity) 157 (M−1, 1), 140 (3), 128 (25), 110 (22), 85 (100).

5-[4-(*t*-Butyldimethylsiloxy)butyl]dihydrofuran-2(3*H*)-one (13a′): IR (neat) 2926, 1777, 1460, 1255, 1180, 1098, 836, 775 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.04 (s, 6H), 0.88 (s, 9H), 1.41–1.67 (m, 5H), 1.70–1.91 (m, 2H), 2.31 (sextet, $J \approx$ 7 Hz, 1H), 2.52 (dd, J = 9.3, 6.9 Hz, 2H), 3.61 (t, J = 6.0 Hz, 2H), 4.48 (quintet, $J \approx$ 7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ −5.58 (2C), 18.09, 21.45, 25.74 (3C), 27.76, 28.62, 32.21, 35.15, 62.63, 80.83, 177.26. Found: C, 62.01; H, 10.44%. Calcd for $C_{14}H_{28}O_3Si$: C, 61.72; H, 10.36%.

5-(3-Hydroxypropyl)dihydrofuran-2(3*H*)-one (13b): IR (neat) 3380, 2938, 1749, 1183 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.60–2.05 (m, 6H), 2.36 (sextet, $J \approx$ 7 Hz, 1H), 2.55 (dd, J = 9.3, 6.9 Hz, 2H), 3.70 (t, J = 6.3 Hz, 3H), 4.55 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 27.70, 28.10, 28.59, 31.72, 61.69, 80.91, 177.66.

5-[3-(*t*-Butyldimethylsiloxy)propyl]dihydrofuran-2(3*H*)-one (13b′): IR (neat) 2926, 1768, 1463, 1255, 1181, 1097, 834, 774 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.04 (s, 6H), 0.88 (s, 9H), 1.53–1.92 (m, 5H), 2.33 (sextet, $J \approx$ 7 Hz, 1H), 2.53 (dd, J = 9.3, 6.3 Hz, 2H), 3.62–3.67 (m, 2H), 4.52 (quintet, $J \approx$ 7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ −5.58 (2C), 18.08, 25.73 (3C), 27.83, 28.27, 28.67, 31.98, 62.33, 80.80, 177.28. Found: C, 60.15; H, 10.10%. Calcd for $C_{13}H_{26}O_3Si$: C, 60.42; H, 10.14%.

5-(2-Hydroxyethyl)dihydrofuran-2(3*H*)-one (13c): IR (neat) 3184, 2926, 1753, 1180, 1045 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.78–1.86 (broad, 1H), 1.87–2.00 (m, 3H), 2.39 (sextet, $J \approx$ 7 Hz, 1H), 2.56 (dd, J = 9.3, 6.6 Hz, 2H), 3.83 (t, J = 6.0 Hz, 2H), 4.71 (quintet, $J \approx$ 7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 28.06, 28.57, 38.06, 59.12, 78.50, 177.30.

5-[2-(*t*-Butyldimethylsiloxy)ethyl]dihydrofuran-2(3*H*)-one (13c′): IR (neat) 2928, 1774, 1458, 1255, 1179, 1092, 836, 775 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (s, 6H), 0.88 (s, 9H), 1.76–1.99 (m, 3H), 2.35 (sextet, $J \approx$ 7 Hz, 1H), 2.53 (dd, J = 9.3, 6.9 Hz, 2H), 3.75 (t, J = 6.0 Hz, 2H), 4.67 (quintet, $J \approx$ 7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ −5.67 (2C), 18.06, 25.72 (3C), 27.98, 28.63, 38.43, 59.05, 78.06, 177.30. Found: C, 58.74; H, 9.98%. Calcd for $C_{12}H_{24}O_3Si$: C, 58.97; H, 9.90%.

5-(6-Methyl-2,5-dioxaheptyl)dihydrofuran-2(3*H*)-one (13e): Bp 155 °C/0.1 torr. IR (neat) 2968, 2868, 1778, 1369, 1128, 1087 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16 (d, J = 6.0 Hz, 6H), 2.08–2.79 (m, 4H), 3.54–3.75 (m, 7H), 4.62–4.70 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 21.86 (2C), 23.90, 28.22, 67.30, 71.35, 71.86, 72.67, 79.08, 177.52. HRMS Found: m/z 187.0966. Calcd for $C_{10}H_{18}O_4-CH_3$: 187.0970.

Lactone **13f** was quantitatively converted into allyl ester by treatment with allyl bromide (1.5 eq.) and K_2CO_3 (1.5 eq.) in refluxing acetone for 3 h.

5-[2-(Allyloxycarbonyl)ethyl]dihydrofuran-2(3*H*)-one (13f′): IR (neat) 2942, 1774, 1739, 1650, 1439, 1376, 1345, 1264, 1141, 1044, 990, 926 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.81–2.10 (m, 3H), 2.37 (sextet, $J \approx$ 7 Hz, 1H), 2.45–2.63 (m, 4H), 4.50–4.61 (m, 3H), 5.25 (ddt, J = 10.5, 1.2, 1.2 Hz, 1H), 5.32 (ddt, $J \approx$ 17.4, 1.2, 1.2 Hz, 1H), 5.92 (ddt, J = 17.4, 10.5, 5.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 27.62, 28.44, 29.85, 30.44, 65.13, 79.46, 118.32, 131.97, 172.29, 176.79. Found: C, 60.61; H, 7.12%. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12%.

5-(4-Hydroxybutyl)-3-methyldihydrofuran-2(3*H*)-one (13h, 1/1 mixture of diastereomers**):** IR (neat) 3347, 2925, 1755, 1180 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (d, J = 6.9 Hz, 1.5H), 1.28 (d, J = 7.2 Hz, 1.5H), 1.42–1.84 (m, 6.5H), 1.96–2.18 (m, 1H), 2.50 (ddd, J = 12.6, 8.4, 5.4 Hz, 0.5H), 2.61–2.90 (m, 2H), 3.67 (t, J = 5.7 Hz, 2H), 4.30–4.40 (m, 0.5H), 4.48–4.57 (m, 0.5H); ^{13}C NMR ($CDCl_3$) δ 14.75, 15.50, 21.35, 21.40, 31.82, 31.87, 33.80, 34.84, 34.92, 35.07, 35.66, 36.96, 62.05 (2C), 78.41, 78.62, 179.99, 180.50.

5-[4-(*t*-Butyldimethylsiloxy)butyl]-3-methyldihydrofuran-2(3*H*)-one (13h′, 1/1 mixture of diastereomers**):** IR (neat) 2928, 2856, 1775, 1460, 1250, 1188, 1166, 1097, 1002, 835, 773 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (s, 6H), 0.89 (s, 9H), 1.27 (d, J = 6.9 Hz, 1.5H), 1.28 (d, J = 7.2 Hz, 1.5H), 1.39–1.84 (m, 6.5H), 1.95–2.18 (m, 1H), 2.48 (ddd, J = 12.3, 9.0, 5.4 Hz, 0.5H), 2.59–2.73 (m, 1H), 3.62 (t, J = 6.0 Hz, 2H), 4.29–4.39 (m, 0.5H), 4.46–4.55 (m, 0.5H); ^{13}C NMR ($CDCl_3$) δ −5.55 (4C), 14.92, 15.69, 18.12,

21.53, 21.60, 25.76 (7C), 32.21, 32.27, 33.84, 35.03, 35.13, 35.25, 35.74, 37.16, 62.68 (2C), 78.28, 78.52, 179.64, 180.12. Found: C, 62.84; H, 10.48%. Calcd for $C_{15}H_{30}O_3Si$: C, 62.89; H, 10.55%.

5-(1-Hydroxyethyl)dihydrofuran-2(3*H*)-one (13g, 54/46 mixture of diastereomers**):** IR (neat) 3342, 2974, 1753, 1191, 1139, 1021, 986, 918 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.19 (d, J = 6.3 Hz, 3H $\times$ 0.46), 1.27 (d, J = 6.3 Hz, 3H $\times$ 0.54), 2.00–2.69 (m, 5H), 3.79 (dq, J = 6.3, 6.3 Hz, 0.5H), 4.08–4.17 (m, 0.5H), 4.32–4.45 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 17.58, 18.28, 20.79, 23.82, 28.44, 28.52, 67.23, 69.60, 83.65, 84.23, 177.71, 178.05.

Acetylation of **13g** (acetic anhydride, pyridine, overnight, 95% yield) provided analytically pure sample **13g′**.

5-[1-(Acetoxy)ethyl]dihydrofuran-2(3*H*)-one (13g′, 50/50 mixture of diastereomers**):** IR (neat) 2940, 1780, 1739, 1374, 1242, 1180, 1137, 1074, 1048, 981, 941 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (d, J = 6.6 Hz, 1.5H), 1.31 (d, J = 6.6 Hz, 1.5H), 1.92–2.20 (m, 1H), 2.06 (s, 1.5H), 2.08 (s, 1.5H), 2.24–2.36 (m, 1H), 2.46–2.64 (m, 2H), 4.51 (septet, $J \approx$ 4 Hz, 1H), 4.96–5.04 (m, 0.5H), 5.04–5.13 (m, 0.5H); ^{13}C NMR ($CDCl_3$) δ 15.02, 15.72, 20.84 (2C), 22.46, 23.78, 27.81, 28.00, 70.44, 71.13, 80.67, 80.92, 170.09, 170.24, 176.66 (2C). Found: C, 55.79; H, 6.94%. Calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.02%.

5-(8-Hydroxyoctyl)dihydrofuran-2(3*H*)-one (13j): Mp 57–59 °C. IR (Nujol) 3402, 3335, 2856, 1747, 1198, 1182, 970 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26–1.66 (m, 14H), 1.68–1.92 (m, 2H), 2.33 (sextet, $J \approx$ 7 Hz, 1H), 2.54 (dd, J = 9.6, 6.6 Hz, 2H), 3.64 (t, J = 6.6 Hz, 2H), 4.49 (quintet, $J \approx$ 7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 24.93, 25.42, 27.72, 28.61, 28.96, 29.00, 29.11, 32.43, 35.27, 62.57, 80.99, 177.54. Found: C, 66.99; H, 10.61%. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35%.

5-(3-Phthalimidopropyl)dihydrofuran-2(3*H*)-one (13k): Mp 76–79 °C. IR (Nujol) 2941, 1767, 1715, 1398, 1180, 1047, 721 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.61–1.98 (m, 5H), 2.34 (sextet, $J \approx$ 7 Hz, 1H), 2.54 (dd, J = 9.3, 7.2 Hz, 2H), 3.75 (t, $J \approx$ 6 Hz, 2H), 4.55 (quintet, $J \approx$ 7 Hz, 1H), 7.70–7.67 (m, 2H), 7.81–7.88 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 24.30, 27.53, 28.35, 32.41, 36.96, 79.87, 122.98 (2C), 131.74 (2C), 133.84 (2C), 168.14 (2C), 176.86. Found: C, 65.87; H, 5.53%. Calcd for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53%.

5-(3-Oxobutyl)dihydrofuran-2(3*H*)-one (13l): IR (neat) 2936, 1771, 1715, 1423, 1358, 1180, 980, 916 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.76–1.93 (m, 2H), 1.96–2.08 (m, 1H), 2.18 (s, 3H), 2.37 (sextet, $J \approx$ 7 Hz, 1H), 2.55 (dd, J = 9.6, 6.9 Hz, 2H), 2.67 (t, $J \approx$ 7 Hz, 2H), 4.52 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 27.68, 28.40, 29.02, 29.71, 38.85, 79.64, 176.91, 207.46. Found: C, 61.58; H, 7.84%. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74%.

3-(Tetrahydrofuran-2-yl)propanoic acid (19) was isolated as allyl ester after treatment with allyl bromide in the presence of K_2CO_3 in refluxing acetone.

Allyl 3-(Tetrahydrofuran-2-yl)propanoate (19′): IR (neat) 2932, 2862, 1737, 1648, 1376, 1236, 1158, 1066, 988, 927 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.48 (ddt, J = 10.5, 7.5, 7.5 Hz, 1H), 1.77–2.05 (m, 5H), 2.36–2.56 (m, 2H), 3.71 (q, $J \approx$ 7 Hz, 1H), 3.80–3.90 (m, 2H), 4.58 (ddd, J = 5.7, 0.9, 0.9 Hz, 2H), 5.23 (ddt, J = 10.5, 1.5, 0.9 Hz, 1H), 5.31 (ddt, J = 16.5, 1.5, 0.9 Hz, 1H), 5.93 (ddt, J = 16.5, 10.5, 5.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 25.49, 30.48, 30.86, 30.98, 64.87, 67.54, 78.01, 117.99, 132.30, 173.24. Found: C, 64.93; H, 8.94%. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75%.

3-(Tetrahydrofuran-2-yl)propanenitrile (21): IR (neat) 2953, 2872, 2245, 1445, 1427, 1074, 1024, 910 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44–1.57 (m, 1H), 1.72–1.97 (m, 4H), 2.00–2.11 (m, 1H), 2.46 (dd, J = 7.5, 3.6 Hz, 1H), 2.48 (dd, J = 7.8, 2.7 Hz, 1H), 3.74 (dt, J = 8.4, 6.9 Hz, 1H), 3.82–3.96 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.11, 25.54, 30.95, 31.18, 67.80, 76.98, 119.77. Found: C, 66.99; H, 9.00%. Calcd for $C_7H_{11}NO$: C, 67.17; H, 8.86%.

3-(Tetrahydrofuran-2-ylmethyl)dihydrofuran-2(3*H*)-one (24, 1/1 mixture of diastereomers**):** IR (neat) 2941, 1767, 1715, 1398, 1373, 1180, 1047, 721 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43–1.70 (m, 2H), 1.80–2.15 (m, 5H), 2.44–2.54 (m, 1H), 2.58–2.69 (m, 0.5H), 2.75–2.87 (m, 0.5H), 3.68–3.78 (m, 1H), 3.81–3.96 (m, 1.5H), 3.98–4.08 (m, 0.5H), 4.14–4.24 (m, 1H), 4.32–4.41 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 25.25, 25.39, 28.58, 29.27, 31.33, 31.43, 35.86, 36.03, 36.65, 37.60, 66.48, 66.53, 67.52, 67.54, 76.20, 77.56, 179.57, 179.72. Found: C, 63.52; H, 8.47%. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29%.

***N*,*N*-Diethyl-3-(tetrahydrofuran-2-yl)propanamide (26):** IR (neat) 2966, 2928, 1640, 1629, 1459, 1380, 1096, 1066, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.11 (t, J = 4.2 Hz, 3H), 1.17 (t, J = 4.2 Hz, 3H), 1.44–1.56 (m, 1H), 1.70–2.07 (m, 5H), 2.32–2.54 (m, 2H), 3.33 (q, J = 4.2 Hz, 2H), 3.37 (q, J = 4.2 Hz, 2H), 3.72 (q, $J \approx$ 7 Hz, 1H), 3.80–3.89 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 12.96, 14.20, 25.59, 29.82, 31.17, 31.33, 40.01, 41.83, 67.61, 78.68, 172.04. Found: C, 66.25; H, 10.67%. Calcd for $C_{11}H_{21}NO_2$: C, 66.29; H, 10.62%.

3-(5-Oxotetrahydrofuran-2-yl)propionitrile (27): IR (neat) 2939, 2247, 1771, 1423, 1157 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.83–2.09 (m, 3H), 2.36–2.48 (m, 1H), 2.53–2.62 (m, 4H), 4.54–4.64 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 13.85, 27.42, 28.33, 31.23, 78.09, 118.62, 176.24. Found: C, 60.27; H, 6.67%. Calcd for $C_7H_9NO_2$: C, 60.42; H, 6.52%.

3-(Tetrahydropyran-2-yl)propionitrile (28): IR (neat) 2936, 2849, 2245, 1443, 1090, 1049, 880 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22–1.35 (m, 1H), 1.42–1.64 (m, 4H), 1.71–1.88 (m, 3H), 2.44–2.51 (m, 2H), 3.31–3.47 (m, 2H), 3.94–4.00 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 13.32, 23.11, 25.79, 31.48, 31.86, 68.44, 75.32, 119.98. Found: C, 68.78; H, 9.15%. Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.41%.

***N*-(4-Pentenyl)aniline (29)** was prepared by treating a mixture of aniline (20 mmol) and 1-bromo-4-pentene (10 mmol) with potassium carbonate (20 mmol) in acetone at reflux (32% yield). IR (neat) 3410, 2932, 1603, 1506, 1321, 1259, 912, 748, 692 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.72 (tt, J = 7.5, 6.9 Hz, 2H), 2.17 (dt, J = 6.9, 6.6 Hz, 2H), 3.13 (t, J = 7.5 Hz, 2H), 3.50–3.80 (broad s, 1H), 4.97–5.10 (m, 2H), 5.84 (ddt, J = 16.8, 9.9, 6.6 Hz, 1H), 6.60 (dd, J = 8.7, 0.9 Hz, 2H), 6.69 (tt, J = 7.5, 0.9 Hz, 1H), 7.17 (dd, J = 8.7, 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 28.53, 31.19, 43.29, 112.73 (2C), 115.12, 117.19, 129.29 (2C), 138.13, 148.47. Found: C, 81.88; H, 9.55%. Calcd for $C_{11}H_{15}N$: C, 81.94; H, 9.38%.

3-(1-Phenyl-2-pyrrolidinyl)propanenitrile (30): IR (neat) 2936, 2245, 1599, 1504, 1367, 1159 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.63–1.76 (m, 1H), 1.79–1.86 (m, 1H), 1.95–2.12 (m, 4H), 2.28–2.46 (m, 2H), 3.17 (dt, J = 8.7, 8.1 Hz, 1H), 3.44–3.51 (m, 1H), 3.79–3.87 (m, 1H), 6.60 (d, J = 8.1 Hz, 2H), 6.70 (t, J = 7.5 Hz, 1H), 7.21–7.28 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 13.95, 23.26, 28.51, 29.93, 48.54, 56.86, 112.01 (2C), 116.26, 119.56, 129.42 (2C), 147.00. Found: C, 78.08; H, 8.33%. Calcd for $C_{13}H_{16}N_2$: C, 77.96; H, 8.05%.

3-(1-Phenyl-2-pyrrolidinylmethyl)dihydrofuran-2(3*H*)-one (31, 1/1 mixture of diastereomers**):** IR (neat) 2932, 1771, 1599, 1373, 1157, 1024 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.74–2.26 (m, 7H), 2.36–2.47 (m, 0.5H), 2.48–2.60 (m, 1.5H), 3.13–3.24 (m, 1H),

3.42-3.50 (m, 1H), 3.79–3.88 (m, 0.5H), 4.14–4.53 (m, 2.5H), 6.57 (d, J = 8.1 Hz, 1H), 6.64–6.70 (m, 2H), 7.19–7.26 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 22.95, 23.26, 29.10, 29.71, 29.91, 30.08, 33.60, 33.78, 36.49, 37.14, 48.07, 48.40, 55.87, 56.43, 66.43, 66.51, 111.67 (2C), 112.09 (2C), 115.72 (2C), 129.27 (2C), 129.30 (2C), 147.17 (2C), 179.31, 179.50. HRMS Found: *m*/*z* 245.1414. Calcd for $C_{15}H_{18}NO$: 245.1416.

This work was supported by Grants-in-Aid for Scientific Research (Nos. 12305058 and 10208208) from the Ministry of Education, Culture, Sports, Science and Technology. H. Y. acknowledges JSPS for financial support. H. S. also thanks Banyu Pharmaceutical Co., Ltd.

References

1 a) C.-J. Li and T.-H. Chan, "Organic Reactions in Aqueous Media," John Wiley & Sons, Inc., New York (1997). b) P. A. Grieco, "Organic Synthesis in Water," Blackie Academic & Professional, London (1998). c) A. Lubineau and J. Auge, in "Modern Solvents in Organic Synthesis," ed by P. Knochel, Springer-Verlag, Berlin/Heidelberg (1999).

2 D. C. Rideout and R. Breslow, *J. Am. Chem. Soc.*, **102**, 7816 (1980).

3 C.-J. Li and T.-H. Chan, *Tetrahedron Lett.*, **32**, 7017 (1991).

4 a) F. Minisci, *Synthesis*, **1973**, 1. b) O. Yamazaki, H. Togo, G. Nogami, and M. Yokoyama, *Bull. Chem. Soc. Jpn.*, **70**, 2519 (1997). c) R. Breslow and J. Light, *Tetrahedron Lett.*, **31**, 2957 (1990). d) D. O. Jang, *Tetrahedron Lett.*, **39**, 2957 (1998). e) U. Maitra and K. D. Sarma, *Tetrahedron Lett.*, **35**, 7861 (1994). f) M. Bietti, E. Baciocchi, and J. B. F. N. Engberts, *J. Chem. Soc., Chem. Commun.*, **1996**, 1307. g) H. Miyabe, M. Ueda, and T. Naito, *J. Org. Chem.*, **65**, 5043 (2000). h) C. Petrier, C. Dupuy, and J. L. Luche, *Tetrahedron Lett.*, **27**, 3149 (1986). i) B. Giese, W. Damm, M. Roth, and M. Zehnder, *Synlett*, **1992**, 441.

5 a) T. Nakamura, H. Yorimitsu, H. Shinokubo, and K. Oshima, *Synlett*, **1998**, 1351. b) H. Yorimitsu, T. Nakamura, H. Shinokubo, and K. Oshima, *J. Org. Chem.*, **63**, 8604 (1998). c) H. Yorimitsu, T. Nakamura, H. Shinokubo, K. Oshima, K. Omoto, and H. Fujimoto, *J. Am. Chem. Soc.*, **122**, 11041 (2000). d) H. Yorimitsu, H. Shinokubo, and K. Oshima, *Chem. Lett.*, **2000**, 104. e) K. Wakabayashi, H. Yorimitsu, H. Shinokubo, and K. Oshima, *Bull. Chem. Soc. Jpn.*, **73**, 2377 (2000). f) H. Yorimitsu, H. Shinokubo, and K. Oshima, *Bull. Chem. Soc. Jpn.*, **74**, 225 (2001).

6 Recent example using a water-soluble initiator: A. E. Graham, A. V. Thomas, and R. Yang, *J. Org. Chem.*, **65**, 2583 (2000). Also see Ref. 4c.

7 A part of this work was reported: H. Yorimitsu, K. Wakabayashi, H. Shinokubo, and K. Oshima, *Tetrahedron Lett.*, **40**, 519 (1999).

8 M. S. Kharasch, P. S. Skell, and P. Fisher, *J. Am. Chem. Soc.*, **70**, 1055 (1948).

9 a) G. A. Kraus and K. Landgrebe, *Tetrahedron*, **41**, 4039 (1985). b) M. Degueil-Castaing, B. De Jeso, G. A. Kraus, K. Landgrebe, and B. Maillard, *Tetrahedron Lett.*, **27**, 5927 (1986).

10 Radical additions of alkyl 2-haloalkanoates to alkenes initiated by electron transfer from copper in solvent-free systems to give γ-lactones have been reported. J. O. Metzger, R. Mahler, and G. Francke, *Liebigs. Ann./Recueil*, **1997**, 2303.

11 a) K. Griesbaum, *Angew. Chem., Int. Ed. Engl.*, **9**, 273 (1970). b) Y. Ichinose, K. Wakamatsu, K. Nozaki, J.-L. Birbaum, K. Oshima, and K. Utimoto, *Chem. Lett.*, **1987**, 1647. c) T. Naito, Y. Honda, O. Miyata, and I. Ninomiya, *J. Chem. Soc., Perkin Trans. 1*, **1995**, 19.

12 Selected examples of atom transfer radical cyclization for the synthesis of lactams in an organic solvent: a) M. Beneditti, L. Forti, F. Chelfi, U. M. Pagnoni, and R. Ronzoni, *Tetrahedron*, **53**, 14031 (1997). b) M. Mori, N. Kanda, I. Oda, and Y. Ban, *Tetrahedron*, **41**, 5465 (1985). c) J. Boivin, M. Yousfi, and S. Z. Zard, *Tetrahedron Lett.*, **35**, 5629 (1994). d) R. S. Jolly and T. Livinghouse, *J. Am. Chem. Soc.*, **110**, 7536 (1989). e) F. Barth and C. O-Yang, *Tetrahedron Lett.*, **31**, 1121 (1990). f) A. J. Clark, D. J. Duncalf, R. P. Filik, D. M. Haddleton, G. H. Thomas, and H. Wongtap, *Tetrahedron Lett.*, **40**, 3807 (1999). g) M. Ikeda, H. Teranishi, N. Iwamura, and H. Ishibashi, *Heterocycles*, **45**, 863 (1997). h) D. P. Curran and J. Tamine, *J. Org. Chem.*, **56**, 2746 (1991). Also see Ref. 5e.

13 Allyl 2-iodoacetate gave the desired γ-lactone in only 38% yield upon heating at 60 °C in H_2O for 10 h in the presence of **1b**. In addition to the γ-lactone, a complex mixture containing acids, which were generated by hydrolysis of the ester group, was obtained.

14 The solution became acidic as the reaction proceeded. A base is not necessary in this system. Addition of a base resulted in lower yield.

15 a) C. J. M. Stirling, *J. Chem. Soc.*, **1960**, 255. b) H. E. Zaugg and R. J. Michaels, *J. Org. Chem.*, **28**, 1801 (1963).

16 Radical atom transfer reactions followed by irreversible ionic reactions have been reported. Whereas the radical addition step in these reactions is reversible, our reaction would involve irreversible addition: a) D. P. Curran and S.-B. Ko, *Tetrahedron Lett.*, **39**, 6629 (1998). b) M. J. Joung, J. H. Ahn, D. W. Lee, and N. M. Yoon, *J. Org. Chem.*, **63**, 2755 (1998). c) K. Nagahara, I. Ryu, M. Komatsu, and N. Sonoda, *J. Am. Chem. Soc.*, **119**, 5465 (1997). d) S. Kreimerman, I. Ryu, S. Minakata, and M. Komatsu, *Org. Lett.*, **2**, 389 (2000).

17 The use of **1b**, instead of **1a**, also gave the corresponding lactone in good yield. Treating a mixture of iodoacetamide (1.0 mmol), 5-hexen-1-ol (1.5 mmol), and **1b** (0.5 mmol) at 75 °C for 5 h provided **13a** in 96% yield. However, the product was contaminated with residues derived from **1b** even after silica gel column purification.

18 Reaction in refluxing water lowered the yield of lactone (70% yield in the case of **13a**).

19 Reducing the amount of NaI (0.20 mmol) resulted in formation of **13a** in only 39% yield.

20 The use of AIBN, instead of **1a**, also led to recovery of iodo amide.

21 K. Nozaki, K. Oshima, and K. Utimoto, *J. Am. Chem. Soc.*, **109**, 2547 (1987).

22 Water may act as an acid to promote the radical reaction. For a review of use of a Lewis acid in radical reaction, see: P. Renaud and M. Gerster, *Angew. Chem., Int. Ed.*, **37**, 2562 (1998).

23 When 4 mmol or 6 mmol of 1-octene was employed, the lactone was obtained in 66% or 76% yield, respectively.

24 Non-volatile olefins could be recovered easily.

25 A. Luedtke, K. Meng, and J. W. Timberlake, *Tetrahedron Lett.*, **28**, 4255 (1987).

26 N. O. Brace, *J. Org. Chem.*, **36**, 3187 (1971).

27 S. Ghosh, S. R. Raychaudhuri, R. G. Salomon, *J. Org. Chem.*, **52**, 83 (1987).