JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Radical Photocyclization Route for Macrocyclic Lactone Ring Expansion and Conversion to Macrocyclic Lactams and Ketones

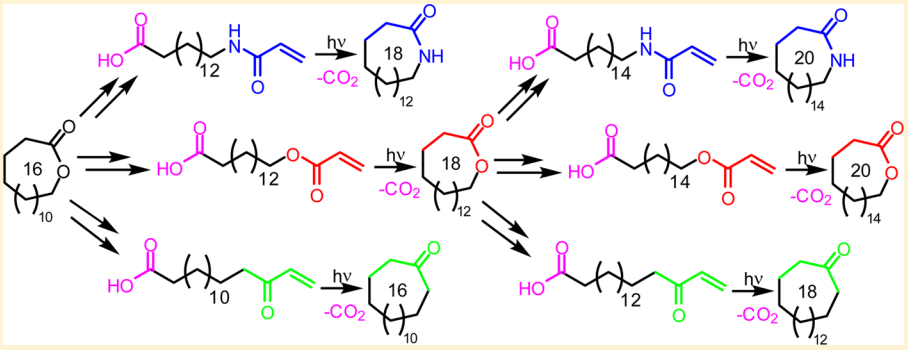
Keisuke Nishikawa,[†] Yasuharu Yoshimi,*[,†] Kousuke Maeda,[†] Toshio Morita,[†] Ichiro Takahashi,[†] Tatsuya Itou,[‡] Sho Inagaki,[§] and Minoru Hatanaka[§]

[†]Department of Applied Chemistry and Biotechnology, Graduate School of Engineering, University of Fukui, 3-9-1 Bunkyo, Fukui 910-8507, Japan

[‡]Graduate School of Pharmaceutical Sciences, University of Toyama, Sugitani 2630, Toyama 930-0194, Japan

[§]Department of Medicinal and Organic Chemistry, School of Pharmacy, Iwate Medical University, Yahaba, Iwate 028-3694, Japan

Supporting Information



ABSTRACT: A new method for the synthesis of macrocyclic lactones, lactams, and ketones, which utilizes photoinduced intramolecular radical cyclization reactions of substrates containing tethered carboxylic acids and α,β-unsaturated carbonyl moieties, has been uncovered. Photocyclization of the carboxylic acids tethered acrylate ester, which were prepared starting from the macrocyclic lactones, gave the two-carbon elongated macrocyclic lactones via decarboxylation. Similar photoreactions of carboxylic acid tethered acryl amide or α,β-unsaturated ketone moieties, which were also prepared starting from the macrocyclic lactones, produced macrocyclic lactams or ketones, respectively. The simple approach can be readily applied to the preparation of a variety of macrocyclic lactones, lactams, and ketones with tunable ring sizes.

INTRODUCTION

Because they are found in a variety of natural products and synthetic pharmaceuticals, many of which have strong antibacterial and antitumor activities, macrocyclic lactones, lactams, and ketones are fundamental substances that have served as targets of organic and medicinal chemistry investigations.[1] The efforts have uncovered a number of efficient methods for the synthesis of members of these macrocyclic compound families, including those that rely on transition-metal-catalyzed ring-closing methathesis,[2] Yamaguchi macrolactonization,[3] and AIBN/Bu_3SnH promoted intramolecular radical cyclization.[4] However, although being powerful, these synthetic methodologies suffer from one or more disadvantages associated with the use and/or production of potentially environmentally unfriendly substances and less than mild reaction conditions in macrocyclization.

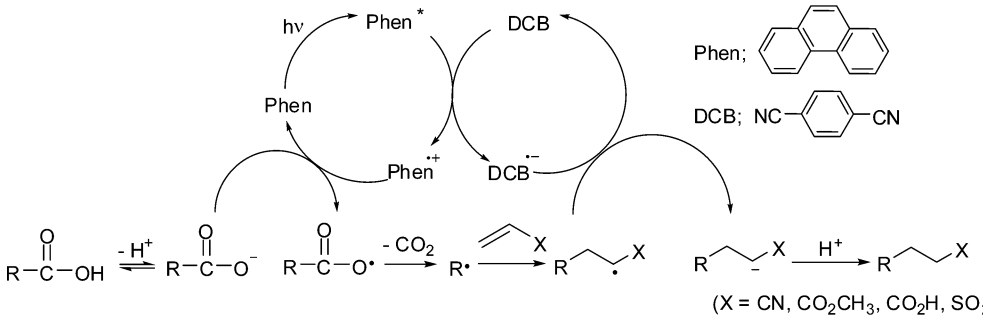
Photoinduced electron transfer (PET) reactions can serve as alternative methods to prepare macrocyclic compounds. Importantly, these processes utilize light as an environmentally clean and powerful reagent. Examples of this approach are found in PET-promoted macrocyclization reactions of phthalimides containing *N*-tethered carboxyl or trialkylsilyl groups.[5] While the reactions of the phthalimide derivatives take place efficiently under mild conditions, they are limited by the fact that products contain the 3-hydroxyphthalimidine moiety.

Recently, we reported that PET induced reactions of alphatic carboxylic acids, taking place through decarboxylation of radical cation intermediates, generate free alkyl radicals. The alkyl radicals, formed in this manner, were found to react with a variety of substrates to yield adducts in high yields.[6] Particularly instructive examples of this methodology are found in photodecarboxylative reactions of carboxylic acids in which carbon centered free radical intermediates undergo efficient intermolecular radical addition to electron-deficient alkenes even when only 1 equiv of the alkenes are used (Scheme 1).[6c]

These earlier observations led us to propose that PET-promoted reactions of substrate containing linked carboxylic acids and α,β-unsaturated carbonyl groups could be employed as part of concise sequences to prepare macrocyclic lactones,

Received: November 5, 2012
Published: December 19, 2012

Scheme 1. Decarboxylative Intermolecular Radical Addition of Carboxylic Acid to Alkene

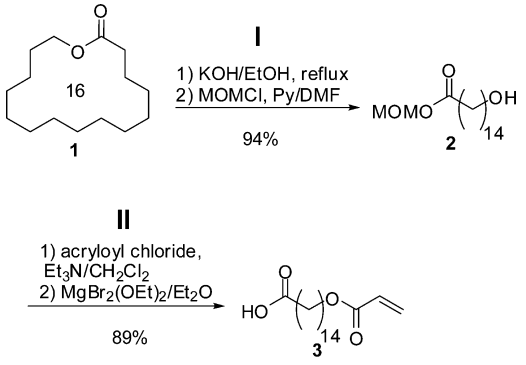


lactams, and ketones. As described below, studies aimed at assessing the validity of this proposal have demonstrated that the new photocyclization reactions, occurring under mild conditions, can be employed as key components of a general strategy for ring expansion of macrocyclic lactones and for conversions of macrocyclic lactones to macrocyclic lactams and ketones, although this method includes difficulties such as the requirement of some steps for the preparation of substrates containing tethered carboxylic acids and α,β-unsaturated carbonyl moieties.

RESULTS AND DISCUSSION

Synthesis of Macrocyclic Lactones by Route Involving PET-Promoted Cyclization of Carboxylic Acid Tethered Acrylate Ester. Initial studies directed at exploring the new PET-promoted cyclization strategy focused on the carboxylic acid tethered acrylate ester **3**. As previously reported by us,[6c] the ester **3** was prepared in 84% yield starting from the 16-membered macrocyclic lactone **1** through the formation of the alcohol **2** using the simple four-step route (**I** + **II**) displayed in Scheme 2.

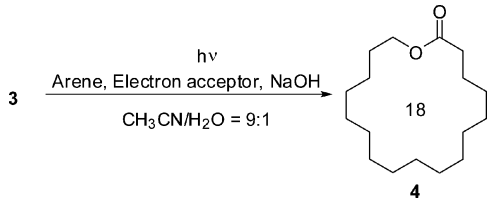
Scheme 2. Preparation of Carboxylic Acid Tethered Acrylate Ester 3



Irradiation (100 W high-pressure mercury lamp, Pyrex filter (λ > 280 nm), argon atmosphere, 6 h, room temperature) of an aqueous acetonitrile solution (CH_3CN/H_2O = 9:1) containing phenanthrene (Phen, 20 mM), 1,4-dicyanobenzene (DCB, 20 mM), substrate **3** (1 mM), and NaOH (1 mM) led to the formation of the18-membered macrocyclic lactone **4** in 84% yield (**III**, entry 1, Table 1). When NaOH was absent from the photoreaction mixture, a prolonged irradiation time was required, suggesting that the carboxylate ion undergoes the PET-promoted decarboxylation process more efficiently than does the corresponding carboxylic acid (entries 2–3). In addition, the utilization of higher concentrations of **3** (2, 3, 4, 5 mM) and 1 equiv of NaOH led to the generation of **4** in lower yields (73, 61, 51, 29%) along with polymeric materials (entries 4–7). These findings suggest that higher concentrations of **3** enhance competitive intermolecular radical addition reactions. The PET-promoted reactions of **3**, using either other arenes, such as biphenyl, and electron acceptors, such as 1,4-dicyanonaphthalene (DCN), or lower concentrations of Phen and DCB (1 mM), also generated **4** in similar yields (entries 8–11). Although use of catalytic amounts of Phen and DCB (0.5, 0.2 mM) in this photoreaction led to the formation of **4**, a prolonged irradiation time (10, 18 h) was required, and the yield of **4** decreased (entries 12–13).

In order to demonstrate the utility of this two-carbon ring expansion protocol for the preparation of macrocyclic lactones, repetitive carboxylic acid tethered acrylate ester forming and PET-promoted cyclization reactions (**I** + **II** + **III**) were

Table 1. PET-Promoted Cyclization of Carboxylic Acid 3 via Decarboxylation[a]



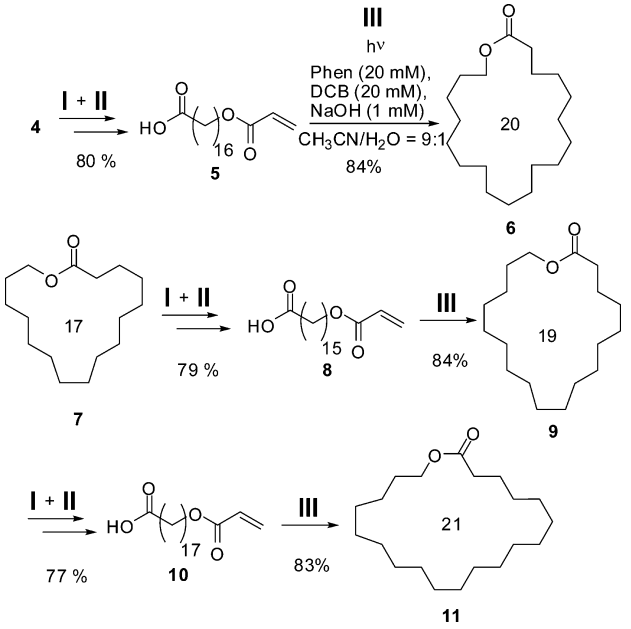
entry	3 (mM)	arene	electron acceptor	yield of 4 (%)[b]
1	1	Phen	DCB	84
2[c]	1			41
3[d]	1			69
4	2			73
5	3			61
6	4			51
7	5			29
8	1	Biphenyl		77
9	1	Phen	DCN	78
10	1	Biphenyl		75
11[e]	1	Phen	DCB	77
12[f]	1			69
13[g]	1			46

[a]The photoreaction of **3** was carried out in the presence of 1 equiv of NaOH, arene (20 mM), and electron acceptor (20 mM) using 100-W high-pressure mercury lamp under an argon atmosphere for 6 h. [b]Isolated yield. [c]In the absence of NaOH. [d]Irradiation time was 12 h in the absence of NaOH. [e]Concentrations of Phen and DCB were 1 mM. [f]Concentrations of Phen and DCB were 0.5 mM, and irradiation time was 10 h. [g]Concentrations of Phen and DCB were 0.2 mM, and irradiation time was 18 h.

dx.doi.org/10.1021/jo3024126 | J. Org. Chem. 2013, 78, 582–589

performed to transform the 18-membered macrocyclic lactone **4** to ring expanded 20-membered lactone **6** in a high yield (Scheme 3). Similarly, the respective 19- and 21-membered

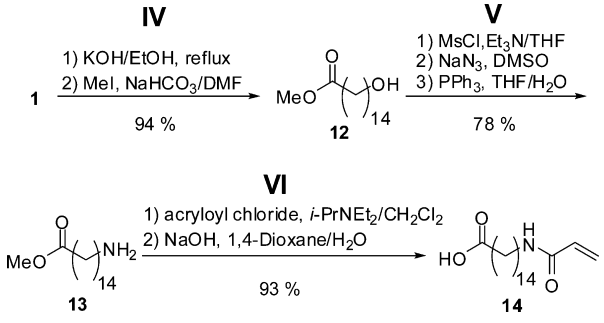
Scheme 3. Ring Expansion of Macrocyclic Lactones by the Photoreaction



macrocyclic lactones **9** and **11** were prepared starting with the 17-membered macrocyclic lactone **7** through a repetitive ring-opening radical-cyclization sequence. The observation made in the studies described above show that macrocyclic lactones having desired ring sizes can be efficiently prepared by employing the novel photochemical radical cyclization protocol.

Synthesis of Macrocyclic Lactams by Routes Involving PET-Promoted Cyclization of Carboxylic Acid Tethered Acryl Amides. The next phase of this investigation focused on applications of the general strategy to the synthesis of macrocyclic lactams. The key substrate **14**, containing tethered carboxylic acid and acryl amide moieties, used to probe this application was prepared from macrocyclic lactone **1** by a route featuring a Staudinger and amidation reaction sequence shown in Scheme 4. Accordingly, ring opening of **1** by treatment with KOH followed by methyl ester formation gave alcohol **12** (**IV**). Conversion of the hydroxyl group in **12** to the corresponding amine in **13** was performed by initial conversion to the mesylate followed by implementation of the Staudinger

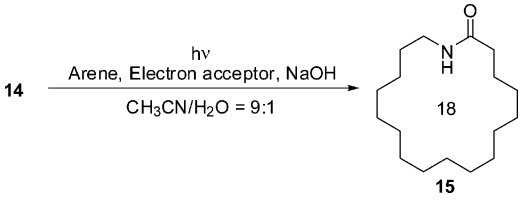
Scheme 4. Preparation of Carboxylic Acid Tethered Acryl Amide 14



conditions (NaN_3; Ph_3P) (**V**). Amidation of **13** with acryloyl chloride followed by saponification of the methyl ester with NaOH gave the desired carboxylic acid tethered acryl amide substrate **14** (**VI**) in an overall (7 steps, **IV** + **V** + **VI**) 68% yield.

The PET-promoted cyclization reaction was carried out by irradiation (see conditions above) of an aqueous acetonitrile solution (CH_3CN/H_2O = 9:1) of **14** (1 mM) containing NaOH (1 mM), Phen (20 mM), and DCB (20 mM). This process smoothly generated the corresponding 18-membered macrocyclic lactam **15** in 78% yield (entry 1, Table 2). In a

Table 2. PET-Promoted Cyclization of Carboxylic Acid 14 via Decarboxylation[a]



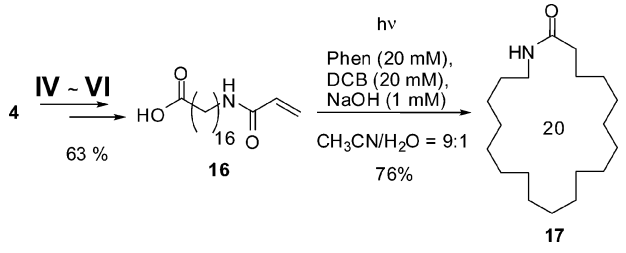
entry	**14** (mM)	arene	electron acceptor	yield of **15** (%)[b]
1	1	Phen	DCB	78
2	2			49
3	3			38
4	4			21
5	1	Biphenyl		75
6	1	Phen	DCB	76
7	1	Biphenyl		71
8[c]	1	Phen	DCB	69

[a]The photoreaction was carried out in the presence of 1 equiv of NaOH, arenes (20 mM), and electron acceptor (20 mM) using 100-W high-pressure mercury lamp under an argon atmosphere for 6 h. [b]Isolated yield. [c]Concentrations of Phen and DCB were 1 mM.

manner that is similar to the cyclization reactions of the corresponding carboxylic acid tethered acrylate ester substrate **3**, lower yields of **15** were obtained when higher concentrations of **14** (2, 3, 4, 5 mM) were employed (entries 2–4), but the efficiency of the process remained unchanged when either the biphenyl and DCN combination (entries 5–7) or lower concentrations of Phen and DCB (entry 8) were utilized. Finally, employment of a similar ring-opening radical-cyclization sequence (**IV**–**VI**) led to transformation of the 18-membered macrocyclic lactone **4** to the 20-membered macrocyclic lactam **17** in a high yield (Scheme 5).

Synthesis of Macrocyclic Ketones by Routes Involving PET-Promoted Cyclization of Carboxylic Acid Tethered *α,β*-Unsaturated Ketones. In order to expand the scope of the new method, an investigation was carried out to explore the

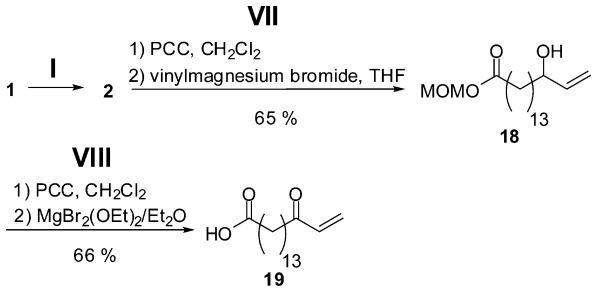
Scheme 5. Synthesis of 17 from 4 by Routes Involving PET-Promoted Cyclization



dx.doi.org/10.1021/jo3024126 | J. Org. Chem. 2013, 78, 582–589

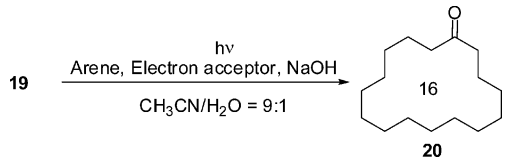
synthesis of macrocyclic ketones from macrocyclic lactones. Alcohol **2** was prepared from macrocyclic lactone **1** by using the procedure shown in Scheme 2 (**I**). PCC oxidation of **2** and subsequent Grignard reaction of the resulting aldehyde with vinylmagnesium bromide provided allyl alcohol **18** (**VII**). Oxidation of **18** with PCC followed by removal of the MOM protecting group gave the carboxylic acid tethered α,β-unsaturated ketone **19** in 42% yield from **1** (**I** + **VII** + **VIII**, Scheme 6).

Scheme 6. Preparation of Carboxylic Acid Tethered α,β-Unsaturated Ketone 19



Irradiation (see above) of an aqueous acetonitrile solution (CH_3CN/H_2O = 9:1) of **19** (1 mM) in the presence of NaOH (1 mM), Phen (20 mM), and DCB (20 mM) gave rise to the formation of the 16-membered macrocyclic ketone **20** in 52% yield (entry 1, Table 3). As observed before, when the

Table 3. PET-Promoted Cyclization of Carboxylic Acid 19 via Decarboxylation[a]



entry	**19** (mM)	arene	electron acceptor	yield of **20** (%)[b]
1	1	Phen	DCB	51
2	2			28
3	3			16
4	4			13
5	1	Biphenyl		42
6	1	Phen	DCN	76
7	1	Biphenyl		83
8[c]	1			77

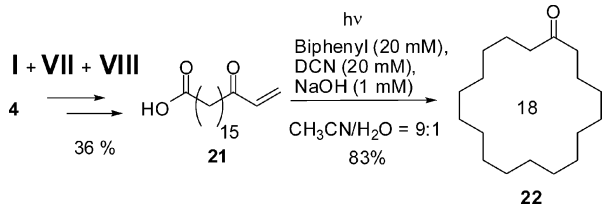
[a]The photoreaction was carried out in the presence of 1 equiv of NaOH, arenes (20 mM), and electron acceptor (20 mM) using 100-W high-pressure mercury lamp under an argon atmosphere for 6 h. [b]Isolated yield. [c]Concentrations of biphenyl and DCN were 1 mM.

photoreaction was carried out utilizing higher concentrations of **19** (2, 3, 4 mM), the yield of **20** decreased (28, 16, 13%) (entries 2–4). However, in contrast to photoreactions of **3** and **14**, the use of DCN instead of DCB led to an improved yield of **20** (entries 5–8).

In a similar manner, the 18-membered macrocyclic ketone **22** was produced from the 18-membered macrocyclic lactone **4** by using a seven-step route involving the key PET-promoted cyclization process (Scheme 7).

A Plausible Mechanism for PET-Promoted Decarboxylative Intramolecular Radical Cyclization. A plausible

Scheme 7. Synthesis of 22 from 4 by Routes Involving PET-Promoted Cyclization



mechanism for the PET-promoted decarboxylative intramolecular radical cyclization reaction is shown in Scheme 8. Decarboxylation of the carboxylate ion **23** through single-electron transfer with the photogenerated radical cation of Phen produces the alkyl radical **24**. When both biphenyl and DCN are used, the radical cation of biphenyl via PET between the excited state of DCN and biphenyl is formed, and the generated radical cation of biphenyl also oxidizes the carboxylate ion **23** to yield the radical **24** via decarboxylation. Intramolecular addition of the radical to the α,β-unsaturated carbonyl group in **24** leads to the formation of the α-carbonyl radical **25**, which subsequently participates in back electron transfer (BET) with the radical anion of the electron acceptor to yield the enolate ion precursor of the macrocyclic photoproduct. In the case of the photoreaction of the carboxylic acid tethered α,β-unsaturated ketone **19** (X = CH_2), DCN serves as a better electron acceptor than DCB (Table 3, entries 1, 5–7). The reason for this is likely associated with the fact that BET from the longer-lived radical anion of DCN (compared to that of DCB) to the α-carbonyl radical intermediate **25** occurs more efficiently.[7]

■ CONCLUSION

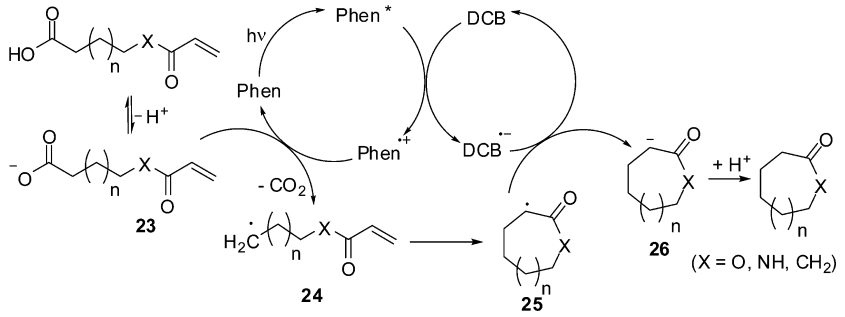
In summary, the study described above has led to the development of a general method for the preparation of macrocyclic lactones, lactams, and ketones that relies on cyclization reactions of radical intermediates derived by PET-promoted decarboxylation of carboxylic acid tethered α,β-unsaturated carbonyl compounds. The results show that, under dilute substrate conditions, these processes generate macrocyclic photoproducts in high yields. The yields of the macrocyclic lactone and lactam forming reactions are slightly dependent on the arene and electron acceptor employed to initiate the sequential SET pathway. The highest yield of the macrocyclic ketone forming reaction is achieved by using the biphenyl and DCN combination. In addition, by utilizing this method, a 16-membered macrocyclic lactone can be converted to an 18-membered macrocyclic lactone or lactam, or a 16-membered macrocyclic ketone, and an 18-membered macrocyclic lactone can be converted to a 20-membered macrocyclic lactone or lactam, or a 18-membered macrocyclic ketone, via carboxylic acid tethered α,β-unsaturated carbonyl moieties (Scheme 9). As a result, macrocyclic lactone, lactam, and ketone products can be prepared with desired ring sizes by using repetitive cycles of this method. Further investigation of applications to highly functionalized molecules such as erythromycin A is currently in progress.

■ EXPERIMENTAL SECTION

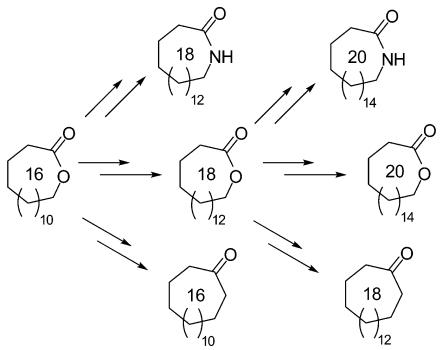
General Experimental. All reagents and solvents were used as supplied commercially. ^{1}H NMR spectra were recorded in $CDCl_3$ containing tetramethylsilane as an internal standard, and were acquired

dx.doi.org/10.1021/jo3024126 | J. Org. Chem. 2013, 78, 582–589

Scheme 8. Plausible Mechanism for Photodecarboxylative Intramolecular Radical Cyclization



Scheme 9. Ring Expansion of Macrocyclic Lactone and Conversion to Macrocyclic Lactam and Ketone from Macrocyclic Lactone



on either a 300 or a 500 MHz spectrometer. ^{13}C NMR spectra were acquired on either a 75 or 125 MHz spectrometer. High resolution mass spectra were obtained using a time-of-flight mass spectrometer with a Fourier transform ion cyclotron resonance mass spectrometer with an ESI positive mode. The light source was a high-pressure mercury arc.

General Procedure for Synthesis of Macrocyclic Lactones by Route Involving PET-Promoted Cyclization. *Preparation of Methoxymethyl 15-Hydroxypentadecanate (**2**).* Pentadecalactone **1** (4.81 g, 20 mmol) was added to a solution of KOH (1.68 g, 30 mmol) in EtOH (80 mL), and the mixture was refluxed for 2 h. The mixture was evaporated, and the residue was added by hexane and filtered. The filtrate was dried in vacuo to afford the ring-opening potassium carboxylate as a white solid in a quantitative yield. ^{1}H NMR (300 MHz, CD_3OD) δ 3.52 (t, J = 6.6 Hz, 2H), 2.13 (t, J = 7.5 Hz, 2H), 1.58−1.49 (m, 4H), 1.28 (m, 20H).

MOMCl (1.47 mL, 19.5 mmol) was added dropwise to a solution of the potassium carboxylate (4.44 g, 15 mmol) and pyridine (8 mL) in DMF (80 mL) at 0 °C under an argon atmosphere. The mixture was stirred overnight at room temperature, and then water (100 mL) was added. The product was extracted with EtOAc (30 mL × 3), dried over Na_2SO_4, and concentrated under reduced pressure. Purification by column chromatography on silica gel using hexane and EtOAc as eluents gave the alcohol **2** as a white solid in 94% yield (4.27 g, 14.1 mmol). Mp 57 °C; IR (KBr, cm^{-1}) 3274, 2915, 1724; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.23 (s, 2H), 3.67−3.61 (m, 2H), 3.46 (s, 3H), 2.35 (t, J = 7.3 Hz, 2H), 1.64−1.56 (m, 4H), 1.25 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 90.2, 63.1, 57.6, 34.4, 32.8, 29.6, 29.5, 29.4, 29.3, 29.1, 25.7, 24.8; HRMS (ESI, m/z) calcd for (M + Na)$^+$ $C_{17}H_{34}NaO_4$, 325.2355; found, 325.2355.

*Preparation of 15-Acryloxylpentadecanoic Acid (**3**).* Acryloyl chloride (0.98 mL, 12 mmol) was added dropwise to a solution of the alcohol **2** (3.03 g, 10 mmol) and Et_3N (5 mL) in CH_2Cl_2 (50 mL) at 0 °C under an argon atmosphere. The mixture was stirred for 2 h at room temperature, and water (50 mL) was added. The product was extracted with CH_2Cl_2 (30 mL × 2), dried over Na_2SO_4, and concentrated under reduced pressure. Purification by column chromatography on silica gel using hexane and EtOAc as eluents gave the desired MOM-protected compound as a white solid in 92% yield (3.28 g, 9.2 mmol). Mp 37−38 °C; IR (KBr, cm^{-1}) 2916, 1727; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.37 (d, J = 17.2 Hz, 1H), 6.09 (dd, J = 17.2, 10.3 Hz, 1H), 5.78 (d, J = 10.3 Hz, 1H), 5.20 (s, 2H), 4.11 (t, J = 6.8 Hz, 2H), 3.43 (s, 3H), 2.32 (t, J = 7.3 Hz, 2H), 1.66−1.57 (m, 4H), 1.23 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 166.3, 130.3, 128.6, 90.1, 64.6, 57.5, 34.3, 29.5, 29.5, 29.5, 29.4, 29.4, 29.2, 29.0, 28.5, 25.8, 24.7; HRMS (ESI, m/z) calcd for (M + Na)$^+$ $C_{20}H_{36}NaO_5$, 379.2460; found, 379.2460.

The MOM-protected compound (3.57 g, 10 mmol) was added to a solution of $MgBr_2(Et_2O)$ (6.46 g, 25 mmol) in Et_2O (50 mL). The mixture was stirred for 2 h at room temperature and then quenched by water (50 mL). The product was extracted with Et_2O (30 mL × 2), dried over Na_2SO_4, and concentrated under reduced pressure. Purification by column chromatography on silica gel using hexane and EtOAc as eluents gave the carboxylic acid **3** as a white solid in 97% yield (3.03 g, 9.7 mmol). Mp 56−57 °C; IR (KBr, cm^{-1}) 3105, 2918, 1723, 1699; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.38 (d, J = 17.2 Hz, 1H), 6.10 (dd, J = 17.2, 10.3 Hz, 1H), 5.79 (d, J = 10.3 Hz, 1H), 4.13 (t, J = 6.8 Hz, 2H), 2.33 (t, J = 7.3 Hz, 2H), 1.66−1.57 (m, 4H), 1.24 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.9, 166.3, 130.4, 128.6, 64.7, 34.0, 29.5, 29.5, 29.5, 29.4, 29.3, 29.2, 29.2, 29.0, 28.5, 25.8, 24.6; HRMS (ESI, m/z) calcd for (M+Na)$^+$ $C_{18}H_{32}NaO_4$, 335.2198; found, 335.2198.

*17-Acryloxylheptadecanoic Acid (**5**).* White solid, mp 64−65 °C; IR (KBr, cm^{-1}) 3103, 2920, 1724, 1699; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.39 (d, J = 17.2 Hz, 1H), 6.11 (dd, J = 17.2, 10.3 Hz, 1H), 5.80 (d, J = 10.3 Hz, 1H), 4.14 (t, J = 6.8 Hz, 2H), 2.35 (t, J = 7.3 Hz, 2H), 1.68−1.58 (m, 4H), 1.25 (m, 24H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.5, 166.3, 130.4, 128.6, 64.7, 33.9, 29.6, 29.6, 29.5, 29.5, 29.4, 29.4, 29.2, 29.2, 29.0, 28.5, 25.9, 24.6; HRMS (ESI, m/z) calcd for (M + Na)$^+$ $C_{20}H_{36}NaO_4$, 363.2511; found, 363.2511.

*16-Acryloxylhexadecanoic Acid (**8**).* White solid, mp 62−63 °C; IR (KBr, cm^{-1}) 3105, 2917, 1723, 1699; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.39 (d, J = 17.2 Hz, 1H), 6.11 (dd, J = 17.2, 10.3 Hz, 1H), 5.80 (d, J = 10.3 Hz, 1H), 4.14 (t, J = 6.8 Hz, 2H), 2.34 (t, J = 7.3 Hz, 2H), 1.68−1.58 (m, 4H), 1.25 (m, 22H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.2, 166.4, 130.4, 128.6, 64.7, 34.1, 29.6, 29.5, 29.5, 29.5, 29.4, 29.2, 29.0, 28.6, 25.9, 24.6; HRMS (ESI, m/z) calcd for (M + Na)$^+$ $C_{19}H_{34}NaO_4$, 349.2355; found, 349.2355.

*18-Acryloxyloctadecanoic Acid (**10**).* White solid, mp 68 °C; IR (KBr, cm^{-1}) 3103, 2917, 1724, 1699; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.38 (d, J = 17.2 Hz, 1H), 6.11 (dd, J = 17.2, 10.3 Hz, 1H), 5.80 (d, J = 10.3 Hz, 1H), 4.14 (t, J = 6.8 Hz, 2H), 2.34 (t, J = 7.3 Hz, 2H), 1.68−1.58 (m, 4H), 1.24 (m, 26H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.0, 166.4, 130.4, 128.6, 64.7, 33.9, 29.6, 29.6, 29.5, 29.5, 29.5, 29.4, 29.2, 29.2, 29.0, 28.6, 25.9, 24.7; HRMS (ESI, m/z) calcd for (M + Na)$^+$ $C_{21}H_{38}NaO_4$, 377.2668; found, 377.2668.

Photoreaction of Carboxylic Acid Tethered Acrylate Ester. An aqueous solution (CH_3CN 360 mL, H_2O 40 mL) of carboxylic acid **3** (125 mg, 1 mM), NaOH (16 mg, 1 mM), Phen (1.43 g, 20 mM), and DCB (1.28 g, 20 mM) in Pyrex vessels (18 mm × 180 mm) was purged with argon for 10 min. The mixture was irradiated with a 100-W high-pressure mercury lamp for 6 h. Then CH_3CN was removed

dx.doi.org/10.1021/jo3024126 | J. Org. Chem. 2013, 78, 582−589

under reduced pressure, and the resulting aqueous solution was extracted with EtOAc, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by silica gel column chromatography using hexane and EtOAc as eluents gave macrocyclic lactone **4** as a colorless oil in 84% yield. Compound **4** has been previously reported.[8] IR (neat, cm^{-1}) 2925, 1734; ^1H NMR (300 MHz, $CDCl_3$) δ 4.10 (t, J = 6.3 Hz, 2H), 2.31 (t, J = 7.1 Hz, 2H), 1.65−1.60 (m, 4H), 1.24 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 64.1, 34.7, 28.5, 28.2, 28.2, 28.1, 27.7, 27.2, 27.1, 26.8, 26.6, 26.2, 25.3, 25.0; GC-MS m/z 268 (M^+).

*Oxacycloeicosan-2-one (**6**).* Compound **6** has been previously reported.[9] Colorless oil; IR (neat, cm^{-1}) 2925, 1734; ^1H NMR (300 MHz, $CDCl_3$) δ 4.09 (t, J = 6.2 Hz, 2H), 2.30 (t, J = 7.1 Hz, 2H), 1.64−1.59 (m, 4H), 1.29 (m, 24H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 64.2, 34.6, 28.5, 28.5, 28.4, 28.4, 28.4, 28.2, 28.0, 27.8, 27.8, 27.5, 27.3, 27.2, 27.1, 27.0, 25.7, 25.0; GC-MS m/z 296 (M^+).

*Oxacyclononadecan-2-one (**9**).* Compound **9** has been previously reported.[4b] Colorless oil; IR (neat, cm^{-1}) 2925, 1734; ^1H NMR (300 MHz, $CDCl_3$) δ 4.11 (t, J = 6.3 Hz, 2H), 2.31 (t, J = 7.1 Hz, 2H), 1.67−1.60 (m, 4H), 1.30 (m, 22H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 64.3, 34.6, 28.7, 28.6, 28.6, 28.5, 28.5, 28.3, 27.7, 27.7, 27.6, 27.5, 27.5, 27.4, 26.7, 25.8, 25.0; GC-MS m/z 282 (M^+).

*Oxacycloheneicosan-2-one (**11**).* Compound **11** has been previously reported.[2d] Colorless oil; IR (neat, cm^{-1}) 2925, 1734; ^1H NMR (300 MHz, $CDCl_3$) δ 4.10 (t, J = 6.3 Hz, 2H), 2.30 (t, J = 7.1 Hz, 2H), 1.66−1.58 (m, 4H), 1.29 (m, 26H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 64.3, 34.6, 28.9, 28.8, 28.7, 28.6, 28.6, 28.3, 28.3, 28.2, 27.8, 27.7, 27.7, 27.6, 27.5, 25.9, 25.0; GC-MS m/z 310 (M^+).

General Procedure for Synthesis of Macrocyclic Lactams by Route Involving PET-Promoted Cyclization. *Preparation of Methyl 15-Hydroxypentadecanate (**12**).* Pentadecalactone **1** (4.81 g, 20 mmol) was added to a solution of KOH (1.68 g, 30 mmol) in EtOH (80 mL), and the mixture was refluxed for 2 h. After removal of solvent in vacuo, the residue was added by hexane and filtered. The filtrate was dried in vacuo to give the ring-opening potassium carboxylate as a white solid in a quantitative yield.

Methyl iodide (6.2 mL, 100 mmol) and sodium bicarbonate (3.36 g, 40 mmol) were added to a solution of the potassium carboxylate (5.92 g, 20 mmol) in DMF (200 mL) at 0 °C under an argon atmosphere. After stirring at room temperature for 12 h, the mixture was quenched by water (100 mL), and the product was extracted with EtOAc (50 mL × 3). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography on silica gel using hexane and EtOAc as eluents gave **12** as a white solid in 94% yield (5.12 g, 18.8 mmol). Mp 52 °C; IR (KBr, cm^{-1}) 3291, 2918, 2849, 1741; ^1H NMR (500 MHz, $CDCl_3$) δ 3.66 (s, 3H), 3.65−3.60 (m, 2H), 2.30 (t, J = 7.6 Hz, 2H), 1.62−1.55 (m, 4H), 1.25 (m, 20H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.4, 63.0, 51.4, 34.2, 34.1, 32.8, 29.7, 29.6, 29.6, 29.5, 29.5, 29.4, 29.3, 29.3, 29.2, 25.8, 25.1, 25.0; HRMS (ESI, m/z) calcd for $(M+Na)^+$ $C_{16}H_{32}NaO_3$, 295.2249; found, 295.2249.

*Preparation of Methyl 15-Aminopentadecanate (**13**).* Methanesulfonyl chloride (1.6 mL, 20 mmol) was added dropwise to a solution of the alcohol **12** (2.72 g, 10 mmol) and Et_3N (2.8 mL, 20 mmol) in THF (50 mL) at 0 °C under an argon atmosphere. The mixture was stirred for 12 h at room temperature and quenched by water (50 mL). The product was extracted with EtOAc (30 mL × 3), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by column chromatography on silica gel using hexane and EtOAc as eluents gave mesyl ether as a white solid in 97% yield (3.40 g, 9.7 mmol). Mp 72 °C; IR (KBr, cm^{-1}) 3017, 2915, 2848, 1738, 1343, 1175, 986, 948, 856; ^1H NMR (500 MHz, $CDCl_3$) δ 4.23 (t, J = 6.7 Hz, 2H), 3.67 (s, 3H), 3.01 (s, 3H), 2.30 (t, J = 7.6 Hz, 2H), 1.76−1.72 (m, 2H), 1.62 (m, 2H), 1.25 (m, 18H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.4, 70.2, 51.4, 37.4, 34.1, 29.6, 29.6, 29.5, 29.4, 29.4, 29.3, 29.1, 29.0, 25.4, 25.0; HRMS (ESI, m/z) calcd for $(M + Na)^+$ $C_{17}H_{34}NaO_5S$, 373.2025; found, 373.2025.

Mesyl ether (3.51 g, 10 mmol) and NaN_3 (0.85 g, 13 mmol) in DMSO (50 mL) were stirred for 12 h at 80 °C. After the mixture cooled to room temperature, DMSO was removed by distillation under high vacuum with heating (water bath, 60 °C). Purification by column chromatography on silica gel using hexane and EtOAc as eluents gave azide as a colorless oil in 90% yield (2.68 g, 9.0 mmol). IR (KBr, cm^{-1}) 2926, 2854, 2096, 1742; ^1H NMR (500 MHz, $CDCl_3$) δ 3.67 (s, 3H), 3.25 (t, J = 7.0 Hz, 2H), 2.30 (t, J = 7.6 Hz, 2H), 1.65−1.57 (m, 4H), 1.25 (m, 20H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.3, 51.4, 34.1, 29.6, 29.6, 29.5, 29.5, 29.4, 29.3, 29.2, 28.9, 26.7, 25.0.

Azide (1.49 g, 5.0 mmol) was added to a solution of PPh_3 (1.70 g, 6.5 mmol) in THF (50 mL) under an argon atmosphere, and the mixture was stirred at room temperature. After 1 day of stirring, water (10 mL) was added to the solution, and the mixture was stirred for 1 day at room temperature under an argon atmosphere. Then a 1% HCl aqueous solution (25 mL) was added to the resulting mixture, and THF and H_2O were removed by distillation under high vacuum with heating (water bath, 40 °C). Purification by column chromatography on silica gel using CH_2Cl_2 and MeOH as eluents gave the amine hydrochloride of **13** as a white solid in 89% yield (1.37 g, 4.9 mmol). Mp 163−164 °C; IR (KBr, cm^{-1}) 3303, 2916, 2849, 2096, 1732, 1655, 1558; ^1H NMR (500 MHz, $CDCl_3$) δ 8.28 (m, 3H), 3.67 (s, 3H), 2.97 (t, J = 7.6 Hz, 2H), 2.30 (t, J = 7.6 Hz, 2H), 1.76 (m, 2H), 1.61 (m, 4H), 1.25 (m, 18H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.3, 51.4, 40.0, 34.1, 29.6, 29.6, 29.5, 29.4, 29.3, 29.2, 29.0, 27.7, 26.5, 25.0; HRMS (ESI, m/z) calcd for $(M + H)^+$ $C_{16}H_{34}NO_2$, 272.2590; found, 272.2591.

*Preparation of 15-Acrylamidepentadecanoic Acid (**14**).* Acryloyl chloride (0.53 mL, 6.5 mmol) was added dropwise to a solution of amine hydrochloride of **13** (1.54 g, 5.0 mmol) and ethyldiisopropylamine (2.4 mL, 15 mmol) in CH_2Cl_2 (40 mL) at 0 °C under an argon atmosphere. The mixture was stirred for 4 h at 0 °C and quenched by a 1% HCl aqueous solution (50 mL). The product was extracted with CH_2Cl_2 (30 mL × 3), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by column chromatography on silica gel using CH_2Cl_2 and MeOH as eluents gave the acryl amide as a white solid in 93% yield (1.51 g, 4.65 mmol). Mp 80−81 °C; IR (KBr, cm^{-1}) 3039, 2915, 2850, 1732, 1726; ^1H NMR (500 MHz, $CDCl_3$) δ 6.28 (d, J = 15.6 Hz, 1H), 6.08 (dd, J = 17.0, 10.5 Hz, 1H), 5.64 (d, J = 10.3 Hz, 1H), 5.53 (m, 1H), 3.67 (s, 3H), 3.32 (m, 2H), 2.30 (t, J = 7.6 Hz, 2H), 1.60 (m, 2H), 1.53 (m, 2H), 1.25 (m, 20H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.4, 165.5, 131.1, 126.0, 51.4, 39.7, 34.2, 29.6, 29.6, 29.5, 29.4, 29.3, 29.3, 29.2, 27.0, 25.0; HRMS (ESI, m/z) calcd for $(M + Na)^+$ $C_{19}H_{35}NNaO_3$, 348.2515; found, 348.2515.

Acryl amide (1.63 g, 5.0 mmol) was dissolved in 3 M NaOH aqueous solution (1,4-dioxane 50 mL, H_2O 20 mL). The mixture was stirred overnight at room temperature and neutralized by a 10% HCl aqueous solution. The mixture was evaporated, and the residual aqueous phase was extracted with EtOAc (30 mL × 3), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by column chromatography on silica gel using CH_2Cl_2 and MeOH as eluents gave carboxylic acid **14** as a white solid in a quantitative yield (1.56 g, 5.0 mmol). Mp 103−104 °C; IR (KBr, cm^{-1}) 3305, 3052, 2920, 2850, 1699, 1654, 1624, 1539, 1474; ^1H NMR (500 MHz, $CDCl_3$) δ 6.27 (d, J = 15.6 Hz, 1H), 6.08 (dd, J = 17.1, 10.4 Hz, 1H), 5.65 (m, 1H), 5.64 (d, J = 10.3 Hz, 1H), 3.33 (m, 2H), 2.35 (t, J = 7.5 Hz, 2H), 1.65 (m, 2H), 1.53 (m, 2H), 1.28 (m, 20H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.7, 165.7, 130.9, 126.3, 39.7, 34.0, 29.6, 29.5, 29.5, 29.3, 29.3, 29.2, 29.0, 26.9, 24.7. HRMS (ESI, m/z) calcd for $(M + Na)^+$ $C_{18}H_{33}NNaO_3$, 334.2358; found, 334.2358.

*17-Acrylamideheptadecanoic Acid (**16**).* White solid, mp 109−110 °C; IR (KBr, cm^{-1}) 3305, 3055, 2919, 2850, 1697, 1654, 1623, 1539, 1472; ^1H NMR (500 MHz, $CDCl_3$) δ 6.28 (d, J = 15.6 Hz, 1H), 6.08 (dd, J = 17.1, 10.3 Hz, 1H), 5.63 (d, J = 10.3 Hz, 1H), 5.53 (m, 1H), 3.33 (m, 2H), 2.35 (t, J = 7.6 Hz, 2H), 1.64 (m, 2H), 1.54 (m, 2H), 1.28 (m, 24H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.7, 165.7, 130.9, 126.3, 39.7, 34.0, 29.6, 29.4, 29.3, 29.3, 29.2, 29.0, 26.9, 24.7; HRMS (ESI, m/z) calcd for $(M + Na)^+$ $C_{20}H_{37}NNaO_3$, 362.2671; found, 362.2671.

Photoreaction of Carboxylic Acids Tethered Acryl Amide. An aqueous solution (CH_3CN 360 mL, H_2O 40 mL) of carboxylic acid **14** (125 mg, 1 mM), NaOH (16 mg, 1 mM), Phen (1.43 g, 20 mM), and DCB (1.28 g, 20 mM) in Pyrex vessels (18 mm × 180 mm) was

dx.doi.org/10.1021/jo3024126 | J. Org. Chem. 2013, 78, 582−589

purged with argon for 10 min. The mixture was irradiated with a 100-W high-pressure mercury lamp for 6 h. Then CH_3CN was removed under reduced pressure, and the resulting aqueous solution was extracted with EtOAc, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by silica gel column chromatography using hexane and EtOAc as eluents gave macrocyclic lactam **15** as a white solid in 78% yield (80.2 mg, 0.3 mmol). Mp 118 °C; IR (KBr, cm^{-1}) 3308, 2929, 2851, 1646, 1559, 1459, 722; ^1H NMR (500 MHz, $CDCl_3$) δ 5.65 (m, 1H), 3.30 (m, 2H), 2.16 (t, J = 6.8 Hz, 2H), 1.64 (m, 2H), 1.50 (m, 2H), 1.25 (m, 20H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1, 39.2, 37.0, 29.4, 29.0, 28.8, 28.8, 28.6, 28.5, 28.3, 28.1, 28.0, 27.9, 27.4, 27.3, 27.1, 27.1, 26.4, 25.9; HRMS (ESI, m/z) calcd for $(M + Na)^+$ $C_{17}H_{33}NNaO$, 290.2460; found, 290.2460.

*Azacycloeicosan-2-one (**17**).* White solid, mp 101 °C; IR (KBr, cm^{-1}) 3305, 2932, 2851, 1646, 1559, 1460, 724; ^1H NMR (500 MHz, $CDCl_3$) δ 5.41 (m, 1H), 3.29 (m, 2H), 2.17 (t, J = 6.7 Hz, 2H), 1.64 (m, 2H), 1.50 (m, 2H), 1.25 (m, 24H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1, 39.2, 37.0, 29.4, 28.8, 28.8, 28.6, 28.5, 28.3, 28.1, 28.0, 27.9, 27.9, 27.4, 27.3, 27.1, 27.1, 26.4, 25.9; HRMS (ESI, m/z) calcd for $(M + Na)^+$ $C_{19}H_{37}NNaO$, 318.2773; found, 318.2773.

General Procedure for Synthesis of Macrocyclic Ketones by Route Involving PET-Promoted Cyclization. *Preparation of Methoxymethyl 15-Hydroxy-heptadec-16-enate (**18**).* Alcohol **2** (1.51 g, 5.0 mmol) was added to a solution of pyridium chlorochromate (PCC, 1.51 g, 7 mmol) in CH_2Cl_2 (20 mL) at 0 °C under an argon atmosphere. The mixture was stirred for 4 h at 0 °C, diluted with CH_2Cl_2, and decanted off three times. The resulting solution was concentrated under reduced pressure. Purification by silica gel column chromatography on silica gel using hexane and EtOAc as eluents gave aldehyde as a white solid in 87% yield (1.31 g, 4.35 mmol). Mp 58−59 °C; IR (KBr, cm^{-1}) 2913, 2849, 1738; ^1H NMR (500 MHz, $CDCl_3$) δ 9.77 (s, 1H), 5.23 (s, 2H), 3.47 (s, 3H), 2.43 (t, J = 7.1 Hz, 2H), 2.36 (t, J = 7.5 Hz, 2H), 1.63 (m, 4H), 1.26 (m, 18H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.9, 173.4, 90.1, 57.5, 43.9, 34.3, 29.5, 29.5, 29.4, 29.4, 29.3, 29.2, 29.1, 24.8, 22.1; HRMS (ESI, m/z) calcd for $(M + Na)^+$ $C_{17}H_{32}NaO_4$, 323.2198; found, 323.2199.

Vinylmagnesium bromide (6.5 mL, 1 M in THF solution) was added dropwise to a solution of aldehyde (1.51 g, 5.0 mmol) in THF (50 mL) at 0 °C under an argon atmosphere. The mixture was stirred for 2 h at 0 °C and quenched by a sat. NH_4Cl aqueous solution (50 mL). The product was extracted with EtOAc (30 mL × 3), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by column chromatography on silica gel using hexane and EtOAc as eluents gave allyl alcolol **18** as a white solid in 75% yield (1.23 g, 3.75 mmol). Mp 33 °C; IR (KBr, cm^{-1}) 3447, 2931, 2853, 1747, 1646, 1466; ^1H NMR (500 MHz, $CDCl_3$) δ 5.93−5.82 (m, 1H), 5.24 (s, 2H), 5.22 (d, J = 17.2 Hz, 1H), 5.10 (d, J = 10.3 Hz, 1H), 4.09 (m, 1H), 3.46 (s, 3H), 2.35 (t, J = 7.3 Hz, 2H), 1.67−1.47 (m, 4H), 1.25 (m, 20H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 141.4, 114.5, 90.2, 73.3, 57.5, 37.1, 34.4, 29.6, 29.6, 29.6, 29.4, 29.3, 29.1, 25.3, 25.0, 24.8; HRMS (ESI, m/z) calcd for $(M + Na)^+$ $C_{19}H_{36}NaO_4$, 351.2511; found, 351.2511.

*Preparation of 15-Oxo-heptadec-16-enoic acid (**19**).* Alcohol **18** (0.66 g, 2.0 mmol) was added to a solution of PCC (1.51 g, 7 mmol) in CH_2Cl_2 (5 mL) at 0 °C under an argon atmosphere. The mixture was stirred for 4 h at 0 °C, diluted with CH_2Cl_2, and decanted off three times. The resulting solution was concentrated under reduced pressure. Purification by silica gel column chromatography using hexane and EtOAc as eluents gave α,β-unsaturated ketone as a white solid in 70% yield (0.46 g, 1.40 mmol). Mp 42−43 °C; IR (KBr, cm^{-1}) 2926, 2854, 1743, 1712; ^1H NMR (500 MHz, $CDCl_3$) δ 6.36 (dd, J = 17.7, 10.3 Hz, 1H), 6.21 (d, J = 17.6 Hz, 1H), 5.81 (d, J = 10.3 Hz, 1H), 5.23 (s, 2H), 3.46 (s, 3H), 2.58 (t, J = 7.3 Hz, 2H), 2.35 (t, J = 7.5 Hz, 2H), 1.67−1.58 (m, 4H), 1.25 (m, 18H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.0, 173.3, 136.5, 127.7, 90.1, 57.4, 39.6, 34.2, 29.5, 29.4, 29.3, 29.3, 29.2, 29.0, 24.7, 23.9; HRMS (ESI, m/z) calcd for $(M + Na)^+$ $C_{19}H_{34}NaO_4$, 349.2355; found, 349.2354.

α,β-Unsaturated ketone (0.33 g, 1.0 mmol) was added to a solution of $MgBr_2(EtO_2)$ (0.65 g, 2.5 mmol) in EtO_2 (50 mL). The mixture was stirred for 2 h at room temperature and quenched by water (50 mL). The product was extracted with EtOAc (30 mL × 3), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by column chromatography on silica gel using hexane and EtOAc as eluents gave carboxylic acid **19** as a white solid in 97% yield (0.28 g, 0.97 mmol). Mp 63−64 °C; IR (KBr, cm^{-1}) 3049, 2912, 2850, 1712, 1696, 1472; ^1H NMR (500 MHz, $CDCl_3$) δ 6.36 (dd, J = 17.6, 10.3 Hz, 1H), 6.21 (d, J = 17.6 Hz, 1H), 5.82 (d, J = 10.3 Hz, 1H), 2.58 (t, J = 7.3 Hz, 2H), 2.35 (t, J = 7.3 Hz, 2H), 1.61 (m, 4H), 1.26 (m, 18H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.2, 179.5, 136.6, 127.9, 39.7, 34.0, 29.5, 29.4, 29.4, 29.2, 29.2, 29.0, 24.7, 24.0; HRMS (ESI, m/z) calcd for $(M + Na)^+$ $C_{17}H_{30}NaO_3$, 305.2093; found, 305.2093.

*17-Oxo-nonadec-18-enoic Acid (**21**).* White solid, mp 70−71 °C; IR (KBr, cm^{-1}) 3075, 2912, 2852, 1716, 1695, 1471; ^1H NMR (500 MHz, $CDCl_3$) δ 6.35 (dd, J = 17.6, 10.3 Hz, 1H), 6.22 (d, J = 17.6 Hz, 1H), 5.81 (d, J = 10.3 Hz, 1H), 2.58 (t, J = 7.3 Hz, 2H), 2.35 (t, J = 7.3 Hz, 2H), 1.62 (m, 4H), 1.26 (m, 22H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.3, 179.8, 136.6, 127.9, 39.6, 34.0, 29.5, 29.5, 29.5, 29.4, 29.4, 29.3, 29.2, 29.2, 29.1, 29.0, 24.6, 24.0; HRMS (ESI, m/z) calcd for $(M + Na)^+$ $C_{19}H_{34}NaO_3$, 333.2406; found, 333.2406.

Photoreaction of Carboxylic Acid Tethered α,β-Unsaturated Ketone. An aqueous solution (CH_3CN 360 mL, H_2O 40 mL) of carboxylic acid **19** (113 mg, 1 mM), NaOH (16 mg, 1 mM), biphenyl (1.43 g, 20 mM), and DCN (1.43 g, 20 mM) in Pyrex vessels (18 mm × 180 mm) was purged with argon for 10 min. The mixture was irradiated with a 100-W high-pressure mercury lamp for 6 h. Then CH_3CN was removed under reduced pressure, and the resulting aqueous solution was extracted with EtOAc, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by silica gel column chromatography using hexane and EtOAc as eluents gave macrocyclic ketone **20** as a colorless oil in 83% yield (95.4 mg, 0.33 mmol). Compound **20** has been previously reported.[2d] IR (neat, cm^{-1}) 2927, 2856, 1714; ^1H NMR (500 MHz, $CDCl_3$) δ 2.41 (t, J = 6.7 Hz, 4H), 1.64−1.61 (m, 4H), 1.30 (m, 22H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.5, 42.0, 27.6, 27.2, 27.0, 26.5, 26.5, 23.4; GC-MS m/z 239 (M^+).

*Cyclooctadecanone (**22**).* Compound **22** has been previously reported.[4a] Colorless oil; IR (neat, cm^{-1}) 2925, 2854, 1714; ^1H NMR (500 MHz, $CDCl_3$) δ 2.41 (t, J = 6.8 Hz, 4H), 1.64−1.61 (m, 4H), 1.31 (m, 26H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.2, 42.3, 28.2, 28.1, 28.0, 27.9, 27.9, 27.8, 27.7, 27.6, 27.2, 27.0, 26.5, 26.7, 23.5; GC-MS m/z 267 (M^+).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H and ^{13}C NMR spectra data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: yyoshimi@u-fukui.ac.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by Takahashi Industrial and Economic Research Foundation, Japan, and the Sasagawa Scientific Research Grant from the Japan Science Society.

■ REFERENCES

(1) (a) Roxburgh, C. J. *Tetrahedron* **1995**, *51*, 9767−9822. (b) Parenty, A.; Moreau, X.; Campagne, J.-M. *Chem. Rev.* **2006**, *106*, 911−939. (c) Parenty, A.; Moreau, X.; Niel, G.; Campagne, J.-M. *Chem. Rev.* **2012**, DOI: 10.1021/cr300129n.

(2) (a) Houri, A. F.; Xu, Z.; Cogen, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1995**, *117*, 2943−2944. (b) Miller, S. J.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 5855−5856. (c) Fürstner, A.; Langemann,

K. *J. Org. Chem.* **1996**, *61*, 3942−3943. (d) Hon, Y.-S.; Wong, Y.-C.; Chang, C.-P.; Hsieh, C.-H. *Tetrahedron* **2007**, *63*, 11325−11340. (e) Wadsworth, A. D.; Furkert, D. P.; Sperr, J.; Brimble, M. A. *Org. Lett.* **2012**, *14*, 5374−5377.

(3) (a) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989−1993. (b) Hikota, M.; Tone, H.; Horita, K.; Yonemitsu, O. *J. Org. Chem.* **1990**, *55*, 7−9.

(4) (a) Porter, N. A.; Magnin, D. R.; Wright, B. T. *J. Am. Chem. Soc.* **1986**, *108*, 2787−2788. (b) Porter, N. A.; Chang, V. H. T. *J. Am. Chem. Soc.* **1987**, *109*, 4976−4981. (c) Porter, N. A.; Chang, V. H. T.; Magnin, D. R.; Wright, B. T. *J. Am. Chem. Soc.* **1988**, *110*, 3554−3560. (d) Porter, N. A.; Lacker, B.; Chang, V. H. T.; Magnin, D. R. *J. Am. Chem. Soc.* **1989**, *111*, 8309−8310. (e) Nagahara, K.; Ryu, I.; Yamazaki, H.; Kambe, N.; Komatsu, M.; Sonoda, N.; Baba, A. *Tetrahedron* **1997**, *53*, 14615−14626. (f) Philippon, A.; Degueil-Castaing, M.; Beckwith, A. L. J.; Maillard, B. *J. Org. Chem.* **1998**, *63*, 6814−6819.

(5) (a) Griesbeck, A. G.; Heinrich, T.; Olegemöller, M.; Lex, J.; Molis, A. *J. Am. Chem. Soc.* **2002**, *124*, 10972−10973. (b) Yoon, U. C.; Jin, Y. X.; Oh, S. W.; Park, C. H.; Park, J. H.; Campana, C. F.; Cai, X.; Dueslar, E. N.; Mariano, P. S. *J. Am. Chem. Soc.* **2003**, *125*, 10664−10671. (c) Griesbeck, A. G.; Hoffmann, N.; Warzecha, K.-D. *Acc. Chem. Res.* **2007**, *40*, 128−140. (d) Cho, D. W.; Yoon, U. C.; Mariano, P. S. *Acc. Chem. Res.* **2011**, *44*, 204−215.

(6) (a) Yoshimi, Y.; Itou, T.; Hatanaka, M. *Chem. Commun.* **2007**, 5244−5246. (b) Itou, T.; Yoshimi, Y.; Morita, T.; Tokunaga, Y.; Hatanaka, M. *Tetrahedron* **2009**, *65*, 263−269. (c) Yoshimi, Y.; Masuda, M.; Mizunashi, T.; Nishikawa, K.; Maeda, K.; Koshida, N.; Itou, T.; Morita, T.; Hatanaka, M. *Org. Lett.* **2009**, *11*, 4652−4655. (d) Yoshimi, Y.; Hayashi, S.; Nishikawa, K.; Haga, Y.; Maeda, K.; Morita, T.; Itou, T.; Okada, Y.; Hatanaka, M. *Molecules* **2010**, *15*, 2623−2630. (e) Yoshimi, Y.; Kobayashi, K.; Kamakura, H.; Nishikawa, K.; Haga, Y.; Maeda, K.; Morita, T.; Itou, T.; Okada, Y.; Hatanaka, M. *Tetrahedron Lett.* **2010**, *51*, 2332−2334. (f) Itou, T.; Yoshimi, Y.; Nishikawa, K.; Morita, T.; Okada, Y.; Ichinose, N.; Hatanaka, M. *Chem. Commun.* **2010**, 6177−6179. (g) Yoshimi, Y.; Hayashi, S.; Nishikawa, N.; Okita, Y.; Maeda, K.; Morita, T.; Itou, T. *Res. Chem. Intermed.* **2013**, *39*, 397−402.

(7) (a) Das, P. K.; Muller, A. J.; Griffin, G. W. *J. Org. Chem.* **1984**, *49*, 1977−1985. (b) Ichinose, N.; Tanaka, T.; Kawanishi, S.; Majima, T. *Chem. Phys. Lett.* **2000**, *326*, 293−298. (c) Lund, T.; Christensen, P.; Wilbrandt, R. *Org. Biomol. Chem.* **2003**, *1*, 1020−1025.

(8) Hunsdiecker, H.; Erlbach, H. *Eur. J. Inorg. Chem.* **1947**, *80*, 129.

(9) Venkataraman, K.; Wagle, D. R. *Tetrahedron Lett.* **1980**, *21*, 1893.