The very low activation energies for the addition of carbenes to alkenes would seem to require an early transition state, but it is mute with respect to the degree of bonding. Clearly, a very early transition state might lead to relatively small activation volumes even if a two-bond-forming mechanism were involved.

Another aspect of our data which requires comment is the observation that for the faster reacting carbenes the plots of rate data vs. pressure are curved, whereas for the slower reacting carbenes the plots are linear in the pressure range investigated. We attribute at least part of the curvature for the more reactive carbenes to the influence of pressure on diffusion. The compression of MCH is such that over the pressure range 0.1 to 200 MPa, the rate of diffusion is expected to decrease by a factor of ca. 6. For the faster reacting carbenes this means that reactivity is becoming more and more controlled by diffusion as the pressure is increased. For the more slowly reacting carbenes the effect of pressure in this range does not introduce a significant contribution of diffusion-controlled quenching to the rate as a function of pressure. As further evidence for this conclusion, the slope of the rate constant/pressure curve for the reaction of phenylchlorocarbene with TME in acetonitrile is linear over the pressure range 0.1 to 203 MPa, whereas the analogous slope in MCH is sharply curved. The change to linearity is expected because the rate constant for diffusion, estimated from the viscosity in acetonitrile (1.9×10^{10} M^{-1} s^{-1} at 0.1 MPa), is larger than that in MCH (9.7×10^{9} M^{-1} s^{-1} at 0.1 MPa) and the pressure dependence of MCH on viscosity is larger than that of acetonitrile.[16] These observations suggest that the subtraction of the diffusion effects referred to above to obtain $\Delta\Delta V^{*}$ is valid. However, diffusion is probably not the only source of curvature in the plots of ln k_q vs. pressure; our upper limit for k_q for the reaction of PhCCl with TME is ca. 5×10^{8} M^{-1} s^{-1}.

Conclusions

The observed rate constants for the reactions of arylhalocarbenes with alkenes are accelerated by the application of moderate pressures. The magnitude of the activation volumes falls in the range −10 to −18 cm^3/mol for rate constants that vary from ca. 5×10^{8} to ca. 1×10^{6} M^{-1} s^{-1} and are not sensitive to solvent. These results appear to rule out a late, two-bond transition state and a bipolar single-bond transition state, but they are consistent with the reversible formation of a carbene–alkene complex or an early one- or two-bond transition state.

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Macrolide Formation by Free Radical Cyclization

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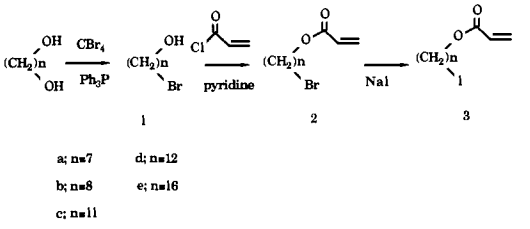
Abstract: A method for the synthesis of lactones with ring size greater than 11 members has been developed. The method involves intramolecular free radical addition to acrylate or fumarate esters. Thus, α,ω-halo alcohols are converted to the acrylate esters and the lactone is formed by treatment of the iodoalkyl acrylates with Bu_3SnH. Products formed are exclusively endocyclic. Yields of lactone are on the order of 55–88%, as analyzed by gas chromatography (45–78% isolated yields) for synthesis of rings greater than 15 members. Yields for 11–13 membered rings are lower and significantly more acrylic products are isolated for these systems. Cyclization to fumarate esters occurs in both the exo and endo mode, the endocyclic product being preferred by as much as 5/1 over the exocyclic compound. The ratio of endo/exo products is reduced to nearly 1/1 as the ring size is increased to 20. Rates of cyclization for the acrylate esters are on the order of 2×10^{4} s^{-1}.

Many natural products contain lactone substructures of 12 to 20 members, and these macrolides are of immense importance in the pharmaceutical industry.[1] Because of the importance of these compounds as antibiotics, an extensive effort has been made to develop methods for macrolide synthesis and highly successful approaches have been reported. Methods utilized from C—O, C=C, or C—C bonds in the crucial ring-making reactions with perhaps the most extensive literature involving formation of the lactone from acyclic ω-hydroxy acid derivatives.[2-4] More recent approaches utilize palladium coupling[5] or anionic cyclizations[6] to promote C–C bond formation.

Free radical methods are becoming increasingly important in organic synthesis, and successful methods for construction of 5- and 6-membered rings by radical cyclization are now an established part of the synthetic repertoire.[7,8] Thus, extensive investigations have focused on studies of the mechanism and synthetic applications of cyclopentane ring construction by radical intermediates. Intermolecular free radical addition reactions have also been studied extensively, and Giese's pioneering work has brought a new level of understanding to this field.[9,10] Steric and electronic effects dominate the mode of radical addition, and Giese's studies provide quantitative information about the nature of alkene substituents and how they influence radical additions to the double bond.

Scheme I



We reasoned that radical cyclization would be a potentially useful means of construction of large ring compounds. Our reasoning was based on the fact that $k_{intramolecular}/k_{intermolecular}$ values

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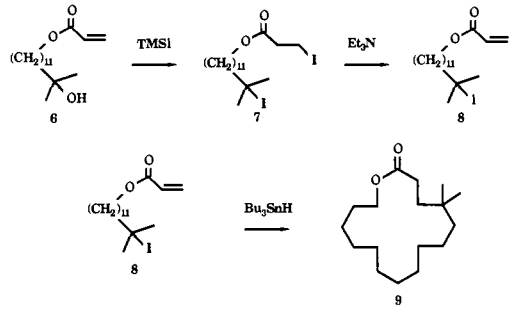
Table I. Products from Reactions of Iodo Acrylates **3** and Bu_3SnH

3 (concn)	ring size	4[a]	5[a]
a (6 mM)	11	(15–25)	(23–28)
b (6 mm)	12	(27–29)	(27–29)
c (6 mM)	15	(45)	(12)
d (3 mM)	16	63–67 (50–55)	18–24 (18–21)
e (3 mM)	20	68–76 (47–56)	17–19 (19)

[a] Yields by gas chromatography (isolated yields).

Scheme II

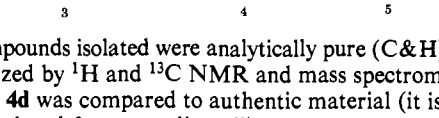


for large ring formation are typically between 10^{-1} and 10^{-2} M.[11,12] Said another way, the effective molarity of an ω-functional group is expected to be 0.1 to 0.01 M for chains greater than 12 members and radical reactions that propagate intermolecularly at these concentrations (~0.01 M) should therefore occur intramolecularly, as well. We thus predicted that macrocyclization of carbon radicals to terminal alkenes would be viable if the alkene is activated, according to Giese, by electron-withdrawing substituents. We report here the results of our studies on carbon radical macrocyclizations of acrylate and fumarate esters. Yields of macrolides formed by this approach range from 25 to 88%, depending on ring size and substitution.

Results

Cyclization of Iodoalkyl Acrylates. The substrate iodoalkyl acrylates **3a–e** were prepared as indicated in Scheme I. Isolated yields for formation of the bromo alcohol **1** were generally 35–45%, while formation of the acrylate ester and conversion of the bromide to the iodide occurs in 85–95% and quanitative yield. The substrates for cyclization are thus readily available from commercially available diols.

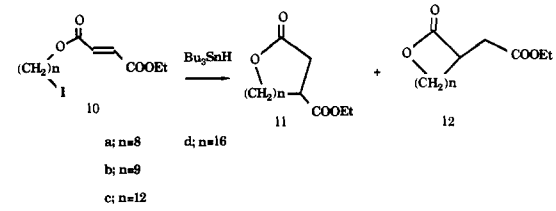
Cyclization of the substrates **3a–e** is carried out as follows. The iodide, **3** (3–6 mM) in dry benzene, along with 1.1 equiv of tributyltin hydride and 0.1 equiv of azobisisobutyrylnitrile (AIBN) initiator is refluxed for 3 h under argon.[13] Products isolated from these reactions are the macrolide **4** and acrylic acrylate **5** formed by simple reduction of the iodide. Yields of products **4** and **5** are given in Table I.



All compounds isolated were analytically pure (C&H) and were characterized by ^1H and ^{13}C NMR and mass spectrometry. The macrolide **4d** was compared to authentic material (it is a natural product isolated from angelica oil).

We have also examined cyclization with tertiary radicals and have prepared the required tertiary iodide by the route outlined in Scheme II. The compounds **7** and **8** were too unstable to be purified by chromatography, but examination of the crude reaction mixtures by NMR indicated that these compounds were essentially pure as prepared. The tertiary iodide undergoes cyclization to

Scheme III



give the dimethyl macrolide **9** in 88% yield as determined by gas chromatography (78% isolated) when the reaction is carried out at 0.7 mM iodide, 0.8 mM Bu_3SnH, and 0.1 equiv of AIBN. The acyclic reduction product was isolated in 6% yield under these cyclization conditions. It is of interest that this cyclization occurs at <1 mM concentrations, while the primary iodide systems **3** do not propagate well at this low concentration and these reactions must be carried out at concentrations ≥3 mM.[13]

Cyclization of Iodo Fumarates. Cyclization to acrylate esters occurs in an endocyclic mode in every case we have examined. We were interested in exploring the possibility of exocyclization in macrolide systems and for that reason we prepared the primary iodides **10a–d**. The synthesis of **10a–d** proceeds along the same lines as that for the iodide **3**. The bromo alcohols **1** are coupled to monoethyl fumaric anhydride to give the ω-bromo fumarates in high yield, and the conversion of the bromide to the primary iodide occurs in quantitative yield. All cyclization reactions were carried out with 1.1 equiv of tin hydride and 0.1 equiv of AIBN at iodide concentrations of 3–6 mM. Yields of macrolide products (**11** and **12**) range from 65 to 70% (50–55% isolated). Products **11** and **12** could be separated for systems **c–d** by HPLC or gas chromatography, while neither gas chromatography nor HPLC could be used to resolve the two macrolide products for system **a** and only gas chromatography was useful for resolving products in system **b**. The identification of products **11** and **12** was nontrivial, since ^1H and ^{13}C NMR did not distinguish between the two isomers. Mass spectrometry also did not provide data for unambiguous assignment, and alternate approaches for product structure proof were sought.

In the case of the **c** and **d** systems, we were able to selectively hydrolyze **11** and **12**, the isomeric products. Thus, the ethyl ester of the exocyclic product **12** hydrolyzes in $LiOD/C_2D_5OD$. This reaction was carried out in an NMR tube at room temperature and disappearance of the $-OCH_2-CH_3$ protons at δ 4.1 was complete after 8 h, while the ring $-CH_2-O-C-O-C$ protons remained intact. For the endocyclic products, **11**, the ethyl ester is unreactive, while the lactone ring is hydrolyzed by $LiOD/C_2D_5OD$. This differential hydrolytic behavior is expected on the basis of steric effects on the ester hydrolysis.[14] For the exocyclic product **12c**, the carbon α to the carboethoxy group is secondary, while the α carbon to the lactone is tertiary. The carboethoxy group thus undergoes hydrolysis more readily than the lactone for this system. In the endocyclic product **11**, the lactone is less hindered and more prone to hydrolysis than the carboethoxy group.

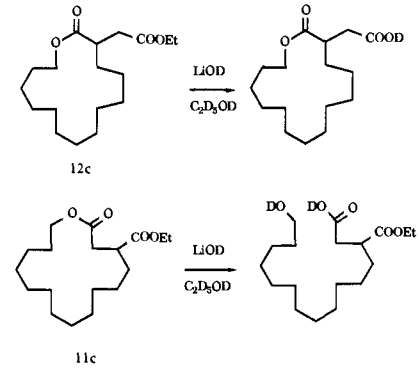


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Table II. Product Ratio for Cyclization of Iodo Fumarates **10a–d**

substrate	endo/exo ring size[a]	endo/exo product[b]
10a	12/11	5/1
10b	13/12	5/1
10c	16/15	2.5/1
10d	20/19	1.1/1

[a] Ring size of endocyclic and exocyclic products formed. [b] Ratio of endocyclic to exocyclic products.

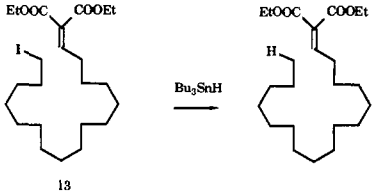
The exocyclic products could be independently prepared by alkylation of the corresponding macrolide with LDA/ethyliodoacetate. Thus, **4c** is converted to **12c** and the exocyclic **12a** and **12b** were also independently prepared by this approach. Since the exo- and endocyclic products could not be separated for **11a,b** and **12a,b**, the ratio of these two products formed in the cyclization was determined by integration of the protons α to the lactone for **11a,b** and comparison of this integrated area with protons α to the carboethoxy group for **12a,b**. These protons could be readily identified in the **11c,d** and **12c,d** pure compounds.

The exocyclic/endocyclic ratio for cyclization of **10a–d** is presented in Table II.

Discussion

Endo vs. Exo Cyclization. Free radical cyclization is a useful method for construction of lactones of greater than 10 or 11 members. For simple acrylate systems, rings formed are exclusively endocyclic and the reaction is applicable for primary and tertiary radicals.[15] The endocyclic mode of cyclization observed for the systems **3a–e** is an interesting contrast to smaller systems where exocyclization is preferred. Thus, five exo and six exo modes of cyclization are preferred to the competing six endo and seven endo modes. In a system we have prepared to favor exocyclization, **13**, we observe no cyclization whatsoever under our standard conditions, but we isolated over 90% yield of the simple iodide reduction product.[15]

The preferential formation of endocyclic products **3a–e** may be understood if the macrocyclization process is viewed with reference to intermolecular addition of carbon radicals to olefins studied extensively by Giese.[9,10] Addition of carbon radicals to acrylate esters is favored, since (1) the alkene substituent (–COOR) is electron withdrawing and carbon radicals are thought to be nucleophilic and (2) the β carbon of acrylate esters is unsubstituted and no steric constraints to addition exist. Two factors, electronic and steric, dominate the rate of radical addition to olefins, and both of these factors are positive for simple acrylates. The systems **3a–e** offer simple intramolecular variants of this situation with favorable electronic and steric effects for endocyclization.



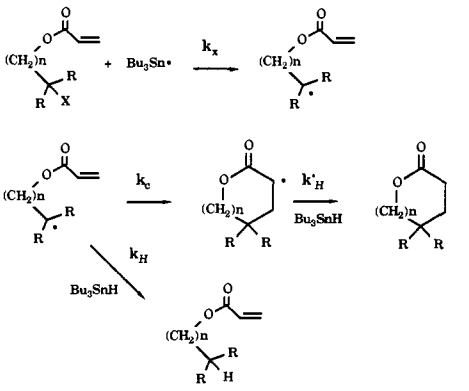
13

The malonate system **13** is electronically favorable for addition, but for exocyclization to occur, the carbon radical must add to an already substituted carbon. Steric factors reduce the rate of such additions. This problem will always exist for exocyclization and leads to the guideline for radical macrocyclization that "*endocyclization modes are favored*".

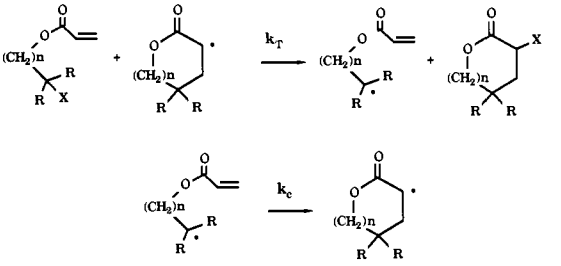
We examined the fumarate systems **10a–d**, since we view this system as being electronically and sterically unbiased. Even in these systems, the endocyclic product is generally preferred (by as much as 5/1 in the 13-endo/12-exo system). We interpret this bias for endocyclization as being due to the instability of intermediate size rings as compared to larger rings by virtue of enthalpic destabilization by transannular steric effects.[16] We reason

(15) We are currently investigating a series of other radicals such as 2° and vinyl radicals for cyclization.

Scheme IV



Scheme V



that the transition state for exocyclization has more transannular strain than the larger ring endocyclization transition state. This factor will also generally support the guideline that "*endocyclization modes are favored*" in radical macrocyclization. It seems reasonable to expect that exocyclization may become more competitive as unsaturation is increased in the tether linking the radical and olefin target.[17] This unsaturation reduces the unfavorable transannular interactions and the consequent increase in transition-state enthalpy.

Atom Transfer Chain Propagation and Rates of Cyclization. The established chain propagation for tin hydride mediated radical cyclization is shown in Scheme IV.[18] We have found in analogous systems[13] that the cyclization reaction does not propagate well at low concentrations if the halide is bromide. The iodide is the preferred radical precursor. Furthermore, the studies reported here indicate that tertiary iodides are preferred to primary iodides in that reactions can be carried out at concentrations as low as 0.07 mM for the iodide **8** (Scheme IV, X = I, R = CH_3), while the minimum concentrations possible for the iodides **3a–e** are about 3 mM (R = H). At the lower concentrations permitted for **8**, cyclization yields as high as 88% are observed.

Our observations that iodides are preferred to bromides and that tertiary iodides are preferred to primary iodides led us to consider an alternate mechanism for cyclization, namely atom transfer cyclization. This mechanism, shown in Scheme V, has recently been proposed by Curran in the cyclization of tertiary iodides in 5-exo systems.[19] The critical step in atom transfer cyclization is iodide atom transfer to the cyclized radical from the iodide substrate. This process is favored when the cyclized radical is destabilized (e.g., vinylic) and the iodide is tertiary. In the cases reported here, the atom transfer step would be endothermic and not expected to occur.

We have been unable to provide any evidence that the atom transfer mechanism is operable in our systems. Thus, reaction under any of the conditions of atom transfer cyclization described by Curran in 5-hexenyl systems failed to give any cyclic products with our substrates.[20] Furthermore, distribution for products

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(20) Crude reaction mixtures were analyzed by NMR, high-pressure liquid chromatography, and gas chromatography.

Table III. Product Distribution vs. Concentration

substrate	concn (Mm)[a]	cyclic[b]	acylic[c]
8	0.57	85	4
8	0.73	88	6
8	1.26	72	5
8	3.13	67	10
8	5.10	50	11
8	7.13	42	7
8	10.30	35	12

[a] Concentration of **8** in mM, 1.1 equiv of tin hydride. [b] GC yield of macrolide. [c] GC yields of acrylic reduced product.

formed from **8** depends on the concentration of tin hydride. Thus, reaction with higher concentrations of substrate and hydride gives more acyclic reduction product. Product distribution as a function of substrate concentration is presented in Table III for the substrate **8**. The yield of cyclic product increases at the expense of the reduction product as tin hydride concentration is reduced. We also note that product accountability is reduced at higher concentrations of substrate and tin hydride. While loss of product accountability at high concentrations is most likely the result of intermolecular additions competing with intramolecular cyclization, the variation in the ratio of cyclic to acyclic products is best understood by the normal cyclization mechanism outlined in Scheme IV.

The fact remains that the ease of macrocyclization is tertiary I > primary I > primary Br and this reactivity pattern must be interpreted within the Scheme IV format. At low halide and tin hydride concentrations, either the k_H or k_X step may cause propagation problems and our results suggest that the k_X step is the problem under macrocyclization conditions. Iodides are more reactive than bromides with $Bu_3Sn^\bullet$ and tertiary iodides are expected to be more reactive than primary iodides.[21] We note that the conclusion that the k_X step is rate determining at 80° is unanticipated, since at room temperture the H-atom transfer is the slow propagation step.

On the basis of the data presented in Table III for **8** and analogous data for **3**, the rates for cyclization of these systems may be calculated by using the integrated rate expression[22] or the "effective tin hydride" concentration proposed by Newcomb.[23] We find rate constants for cyclization of 2×10^4 s^{-1} at 80 °C for **3e** and $\sim 8 \times 10^3$ s^{-1} for **8** (80 °C). These slow unimolecular rates approach the limits for useful free radical reactions[24] and require the use of the dilute conditions developed here.

Summary

Free radical macrolactonization is a suitable method for construction of saturated macrolides with ring size greater than 10 or 11 members. The guidelines for its application are as follows: (1) endocyclization modes are favored to electron deficient alkenes; and (2) yields are critically dependent on the radical precursor with iodides and tertiary precursors being preferred to bromides and primary systems. It seems likely that smaller ring products, as well as exocyclic systems, may result from this approach if unsaturation is introduced into the tether linking radical and target alkene and we are currently exploring this possibility.

Experimental Section

General. All reactions involving moisture-sensitive reagents were performed under a dry argon atmosphere. Benzene and THF were distilled from sodium/benzophenone. Methylene chloride was distilled from CaH_2.

Unless otherwise indicated, NMR data were obtained in $CDCl_3$ solution. The chemical shifts are reported relative to solvent $CDCl_3$ as δ 7.24 (^{1}H), δ 77.0 (^{13}C), respectively. ^{1}H NMR data (200 or 300 MHz) are reported as follows: chemical shift on the δ scale (multiplicity, number of hydrogens, coupling constant(s) in Hz).

The ^{1}H and ^{13}C spectra were obtained by Varian 200 or 300 Series. Elementary analyses were performed by Galbraith Laboratories, Inc. (Knoxville, TN), or Atlantic Microlab, Inc. (Atlanta, GA). Mass spectra were obtained by Oreida Research Services (New York, NY).

In general, reaction workups culminated in drying the organic phase over $MgSO_4$, filtering, and removing the solvent on a rotary evaporated under reduced pressure.

Gas chromatography was performed by HP5830 using capillary column SP2330 (column A), SPB-1 silica (column B), and carbowax (column C). All columns are 30 ft long. The temperature conditions were as indicated. The medium pressure liquid chromatograph was performed by a Waters pump (Model 6000A) with silica column (Dynamax, Rainin).

All chemicals were purchased from commercial sources without purification, except as indicated.

I.1. General Method for the Synthesis of α,ω-Bromoalkanol (1). To a solution of 20.2 g (0.1 mol) of 1,12-dodecanediol and 33.2 g (1 equiv) of carbon tetrabromide in 500 mL of anhydrous THF was dropwise added triphenylphosphine, 26.2 g (1 equiv), in 300 mL of THF over 1 h. The reaction mixture was stirred at room temperature for 20 h and then filtered. The filtrate was evaporated and the residue was placed on a silica gel column eluted with hexane/ethylacetate = 5/1 to give 9.9 g of product (38%).

I.2. General Method for the Synthesis of Iodoalkyl Acrylates (3). Acryloyl chloride, 0.78 mL (1.2 equiv), was added to 2 g (7.55 mmol) of 12-bromododecanol (**2d**) in 30 mL of dichloromethane, which was precooled in an ice bath. After triethylamine, 1.4 mL (1.2 equiv), was dropwise added, the reaction was stirred overnight at room temperature. The solvent was removed under reduced pressure, and the resulting residue was placed on a silica gel column and eluted with hexane/dichloromethane = 1/1 to yield the bromoalkyl acrylate, 2.3 g. The bromo acrylate was converted into iodoalkyl acrylate by refluxing the bromide (2.3 g) and 3.4 g of sodium iodide (3 equiv) in 40 mL of methyl ethyl ketone for 3 h. Chromatography (hexane/dichloromethane = 1/1) yielded 2.7 g (total yield 93%).

3a: ^{1}H NMR δ 1.30–1.45 (m, 6 H), 1.65 (m, 2 H), 1.81 (m, 2 H), 3.15 (t, 2 H, J = 6.3), 4.15 (t, 2 H, J = 8), 5.78 (dd, 1 H, J = 10, 1.5), 6.1 (dd, 1 H, J = 10, 16.5), 6.38 (dd, 1 H, J = 16.5, 1.5); ^{13}C NMR δ 7.08, 25.75, 28.14, 28.52, 30.33, 33.38, 64.39, 128.42, 130.24, and 165.98.

Anal. Calcd for $C_{10}H_{17}IO_2$: C, 40.54; H, 5.74. Found: C, 40.79; H, 5.66.

3b: ^{1}H NMR δ 1.25–1.50 (m, 8 H), 1.64 (m, 2 H), 1.80 (m, 2 H), 3.16 (t, 2 H, J = 6.3), 4.12 (t, 2 H, J = 8), 5.78 (dd, 1 H, J = 10, 1.5), 6.1 (dd, 1 H, J = 10, 16.5), 6.38 (dd, 1 H, J = 16.5, 1.5); ^{13}C NMR δ 7.40, 25.98, 28.54, 28.70, 29.16, 30.52, 33.60, 64.69, 128.59, 130.47, 166.25.

Anal. Calcd for $C_{11}H_{19}IO_2$: C, 42.58; H, 6.13. Found: C, 42.92; H, 6.12.

3c: ^{1}H NMR δ 1.20–1.40 (m, 14 H), 1.63 (m, 2 H), 1.80 (m, 2 H), 3.15 (t, 2 H, J = 6.3), 4.12 (t, 2 H, J = 8), 5.78 (dd, 1 H, J = 1.5), 6.10 (dd, 1 H, J = 10.8, 16.5), 6.38 (dd, 1 H, J = 16.5, 1.5); ^{13}C NMR δ 7.23, 25.84, 28.44, 28.53, 29.14, 29.29, 29.36, 30.41, 33.45, 64.49, 128.38, 130.30, 165.87.

Anal. Calcd for $C_{14}H_{25}IO_2$: C, 47.73; H, 7.10; I, 36.08. Found: C, 48.08; H, 7.28; I, 36.35.

3d: ^{1}H NMR δ 1.20–1.40 (m, 16 H), 1.64 (m, 2 H), 1.81 (m, 2 H), 3.15 (t, 2 H, J = 6.3), 4.13 (t, 2 H, J = 8), 5.78 (dd, 1 H, J = 10, 1.5), 6.10 (dd, 1 H, J = 10, 16.5), 6.38 (dd, 1 H, J = 16.5, 1.5); ^{13}C NMR δ 6.98, 25.67, 28.28, 28.35, 29.01, 29.16, 29.25, 30.25, 33.31, 64.36, 128.39, 130.09, 165.86.

Anal. Calcd for $C_{15}H_{27}IO_2$: C, 49.19; H, 7.38; I, 34.68. Found: C, 49.40; H, 7.45; I, 34.51. Mass (CI): 367 (M + 1).

3e: ^{1}H NMR δ 1.10–1.35 (m, 24 H), 1.58 (m, 2 H), 1.75 (m, 2 H), 3.11 (t, 2 H, J = 7.2), 4.07 (t, 2 H, J = 6.9), 5.73 (dd, 1 H, J = 10, 1.5), 6.05 (dd, 1 H, J = 10, 16.5), 6.34 (dd, 1 H, J = 16.5, 1.5); ^{13}C NMR δ 7.06, 25.91, 28.54, 28.61, 29.25, 29.32, 29.42, 29.50, 29.56, 29.64, 30.51, 33.57, 64.57, 128.63, 130.26, 166.05.

Anal. Calcd for $C_{19}H_{35}IO_2$: C, 54.04; H, 3.80. Found: C, 54.31; H, 8.39. Mass (CI): 423 (M + 1).

I.3. General Method for the Cyclization of Iodoalkyl Acrylate (3). To the refluxing solution (94 mg, 0.26 mmol) of the iodide **3d** in 43 mL of anhydrous benzene, tributyltin hydride (78 μL, 1.1 equiv) was added, followed by the addition of 4 mg (0.1 equiv) of AIBN. The reaction was stirred under reflux for 3 h. After the solvent was removed, the resulting residue was placed on a silica gel column and eluted with hexane/dichloromethane = 2/1. The faster elutant was the reduced product (11 mg, 18%); the slower eluent was the cyclized product (33 mg, 54%).

4a: ^{1}H NMR δ 1.22–1.55 (m, 10 H), 1.63–1.78 (m, 4 H), 2.32 (m, 2 H), 4.15 (m, 2 H); ^{13}C NMR δ 21.43, 22.49, 24.19, 24.81, 25.41, 25.50, 26.30, 35.34, 64.79, 174.01.

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Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.59; H, 10.59. Found: C, 70.76; H, 10.40.

4b: ^{1}H NMR δ 1.20–1.70 (m, 16 H), 2.30 (m, 2 H), 4.15 (m, 2 H); ^{13}C NMR δ 23.35, 23.52, 23.89, 24.07, 24.53, 24.90, 26.13, 34.40, 64.53, 173.71.

Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.74; H, 10.87. Found: C, 71.58; H, 10.88.

4c: ^{1}H NMR δ 1.20–1.40 (m, 18 H), 1.55–1.70 (m, 4 H), 2.32 (m, 2 H), 4.11 (m, 2 H); ^{13}C NMR δ 24.84, 24.94, 25.18, 26.09, 26.45, 26.59, 26.81, 27.83, 28.33, 34.07, 63.92, 173.97.

4d: ^{1}H NMR δ 1.31–1.43 (m, 20 H), 1.58–1.68 (m, 4 H), 2.33 (t, 2 H, J = 6.9), 4.13 (t, 2 H, J = 6.3); ^{13}C NMR δ 24.91, 25.08, 25.77, 25.86, 25.98, 26.28, 26.61, 26.87, 27.08, 27.16, 27.72, 28.34, 34.42, 63.97, 174.07.

Mass (CI): 241 (M + 1).

4e: ^{1}H NMR δ 1.2–1.4 (m, 28 H), 1.62 (m, 4 H), 2.30 (t, 2 H, J = 6.6), 4.09 (t, 2 H, J = 5.7); ^{13}C NMR δ 25.03, 25.72, 27.01, 27.08, 27.18, 27.31, 27.54, 27.75, 27.83, 27.97, 28.17, 28.43, 28.47, 28.57, 34.59, 64.17, 173.96.

Anal. Calcd for $C_{19}H_{36}O_2$: C, 77.03; H, 12.16. Found: C, 76.97; H, 12.28. Mass (CI): 297 (M + 1).

5a: ^{1}H NMR δ 0.88 (t, 3 H, J = 6.9), 1.2–1.4 (m, 8 H), 1.65 (m, 2 H), 4.12 (t, 2 H, J = 6.3), 5.78 (dd, 1 H, J = 10.3, 1.5), 6.10 (dd, 1 H, J = 10.3, 16.5), 6.38 (dd, 1 H, J = 16.5, 1.5); ^{13}C NMR δ 14.14, 22.65, 25.96, 28.69, 28.98, 31.77, 64.72, 128.56, 130.24, 166.15.

5b: ^{1}H NMR δ 0.87 (t, 3 H, J = 6.6), 1.16–1.40 (m, 10 H), 1.62 (m, 2 H), 4.11 (t, 2 H, J = 6.3), 5.78 (dd, 1 H, J = 10.2, 1.5), 6.10 (dd, 1 H, J = 10.2, 16.5), 6.38 (dd, 1 H, J = 16.5, 1.5); ^{13}C NMR δ 14.14, 22.68, 25.97, 28.66, 29.21, 31.81, 64.69, 128.53, 130.22, 166.11.

Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.74; H, 10.87. Found: C, 71.92; H, 10.97.

5c: ^{1}H NMR δ 0.88 (t, 3 H, J = 6.6), 1.18–1.40 (m, 16 H), 1.65 (m, 2 H), 4.12 (t, 2 H, J = 6.3), 5.78 (dd, 1 H, J = 10.3, 1.5), 6.10 (dd, 1 H, J = 10.3, 16.5), 6.38 (dd, 1 H, J = 16.5, 1.5); ^{13}C NMR δ 14.21, 22.77, 25.99, 28.68, 29.39, 29.67, 31.97, 64.73, 128.53, 130.28, 166.16.

Anal. Calcd for $C_{14}H_{26}O_2$: C, 74.34; H, 11.50. Found: C, 74.52; H, 11.67.

5d: ^{1}H NMR δ 0.87 (t, 3 H, J = 6.6), 1.25–1.38 (m, 18 H), 1.66 (m, 2 H), 4.14 (t, 2 H, J = 6.9), 5.80 (dd, 1 H, J = 10.38, 1.5), 6.10 (dd, 1 H, J = 10.3, 16.5), 6.39 (dd, 1 H, J = 16.5, 1.5); ^{13}C NMR δ 14.12, 22.70, 25.93, 28.61, 29.27, 29.36, 29.52, 29.57, 29.64, 31.92, 64.74, 128.66, 130.40, 166.36.

Anal. Calcd for $C_{15}H_{28}O_2$: C, 75.00; H, 11.67. Found: C, 74.91; H, 11.75. Mass (CI): 241 (M + 1).

5e: ^{1}H NMR δ 0.88 (t, 3 H, J = 6.9), 1.18–1.38 (m, 26 H), 1.60–1.72 (m, 2 H), 4.15 (t, 2 H, J = 6.9), 5.80 (dd, 1 H, J = 10.2, 1.5), 6.10 (dd, 1 H, J = 10.2, 16.5), 6.38 (dd, 1 H, J = 16.5, 1.5); ^{13}C NMR δ 14.12, 22.67, 22.72, 25.90, 28.58, 29.30, 29.35, 29.49, 29.56, 29.67, 31.92, 64.71, 76.59, 76.66, 77.01, 77.43, 128.63, 130.39, 166.33.

Anal. Calcd for $C_{19}H_{36}O_2$: C, 77.03; H, 12.16. Found: C, 76.87; H, 12.24. Mass (CI): 297 (M + 1).

I.4. General Method for Determination of Maximum Yield and k_c Value from Iodoalkyl Acrylates (3). The reactions were carried out as described above. Instead of purifying through flash column, the reactions were monitored by GC (column A, temperature 180 °C) directly, using methyl stearate (for 15-pentadecanolide) and methyl eicosanoate (for 19-nonadecanolide) as the internal standards.

II.1. Prepration of Compounds 6–9. 12-Hydroxydodecanoic acid (5 g, 23.1 mmol) in 70 mL of MeOH and 4 mL of concentrated hydrochloric solution were heated to reflux overnight. After evaporation of solvent, the residue was taken up in ethyl acetate and washed with saturated $NaHCO_3$ (×2) and saturated NaCl (×1). The organic layer was dried ($MgSO_4$) and concentrated to give 5.2 g of methyl ester (TLC dichloromethane/methanol = 20/1 one spot).

The methyl ester (5.2 g) was dissolved in THF (100 mL) precooled in an ice bath, and methylmagnesium bromide (3 M) (25 mL, 3 equiv) was added dropwise. After addition, the bath was removed and the reaction stirred at room temperature for 2 h. Saturated NH_4Cl solution was carefully added to quench the reaction. The mixture was partitioned between H_2O and ethyl acetate, while the aqueous layer was adjusted to be acidic with 1 N HCl. The organic layer was dried and evaporated to afford 4.8 g (90%) of product. ^{1}H NMR δ 1.99 (s, 6 H), 1.23–1.61 (m, 20 H), 3.53 (t, 2 H, J = 6.9); ^{13}C NMR δ 17.41, 18.80, 22.26, 22.47, 22.61, 23.22, 25.85, 37.02, 56.00, 64.06.

Anal. Calcd for $C_{14}H_{30}O_2$: C, 73.04; H, 13.04. Found: C, 72.95; H, 13.03.

II.2. 12-Hydroxy-12-methyltridecyl Acrylate (6). To the solution of 1.7 g (7.4 mmol) of diol in 50 mL of dry THF, which was cooled in an ice bath, was added acryloyl chloride (1 mL, 1.44 equiv), followed by pyridine (1 mL). The ice bath was removed and the reaction stirred at room temperature for 20 min. TLC (hexane/ethyl acetate = 4/1) indicated no more starting material was left. The reaction was extracted with ethyl ether/H_2O (×3). The organic layer was separated, dried ($MgSO_4$), and concentrated. The product, **6**, was purified by flash column (silica gel, eluted with hexane/ethyl acetate = 4/1) to give 1 g of colorless oil (50%). ^{1}H NMR δ 1.18–1.70 (m, 26 H), 4.13 (t, 2 H, J = 7.0), 5.80 (dd, 1 H, J = 1.02, 1.5), 6.10 (dd, 1 H, J = 10.2, 17.9), 6.40 (dd, 1 H, J = 17.9, 1.5); ^{13}C NMR δ 24.40, 25.95, 28.64, 29.13, 29.24, 29.35, 29.57, 29.79, 29.89, 30.90, 30.22, 44.01, 64.69, 70.96, 76.61, 128.50, 130.28, 166.14.

Anal. Calcd for $C_{17}H_{32}O_3$: C, 71.83; H, 11.27. Found: C, 71.56; H, 10.87.

II.3. 12-Iodo-12-methyltridecyl Acrylate (8). To the solution of alcohol, **6** (157 mg, 0.55 mmol) in 30 mL of dry dichloromethane cooled in an ice bath, was added dropwise 250 μL (3 equiv) of trimethylsilyl iodide. After a 10 min stirring period, TLC (hexane/ethyl acetate = 4/1) indicated the reaction was complete. Triethylamine (400 μL, 5 equiv) was carefully added to the reaction, which was still stirred on an ice bath. The reaction was stirred in an ice bath for 1 h. Workup involved extracting with dichloromethane/H_2O. Dichloromethane was separated and dried ($MgSO_4$) and the solution concentrated. The resulting residue was treated with ethyl ether (5 mL) and the white precipitate filtered. The filtrate was concentrated to give 210 mg (96%) of oil, which was used without further purification. NMR indicated that the solution contained essentially pure **8**. ^{1}H NMR δ 1.20–1.72 (m, 20 H), 1.92 (s, 6 H), 4.24 (t, 2 H, J = 7.2), 5.80 (dd, 1 H, J = 10.5, 1.5), 6.10 (dd, 1 H, J = 10.5, 17.5), 6.40 (dd, 1 H, J = 17.5, 1.5); ^{13}C NMR δ 25.96, 28.52, 28.66, 29.28, 29.43, 29.54, 38.07, 50.56, 53.02, 64.68, 128.53, 130.25, 166.11.

II.4. 4,4-Dimethyl-15-pentadecanolide (9). The solution of freshly prepared iodide, **8** (105 mg, 0.266 mmol), tributyltin hydride (79 μL, 1.1 equiv), and AIBN (5 mg, 0.1 equiv) in 360 mL of dry benzene was stirred under reflux for 3 h. The reaction was evaporated and residue was placed on the top of a silica gel column eluted with hexane/dichloromethane = 3/1 and then changed to hexane/dichloromethane = 1/1. The first elutant was the reduced product (5 mg, 6%). The later fractions gave (56 mg, 78%) cyclized product, and the analytical samples were purified by medium pressure LC (1% ethyl acetate in hexane).

Reduced product: ^{1}H NMR δ 0.84 (d, 6 H, J = 6.6), 1.08–1.67 (m, 21 H), 4.13 (t, 2 H, J = 6.6), 5.79 (dd, 1 H, J = 1.5, 10.2), 6.13 (dd, 1 H, J = 10.2, 17.4), 6.35 (dd, 1 H, J = 1.5, 17.14); ^{13}C NMR δ 22.74, 26.00, 27.50, 28.05, 28.69, 29.33, 29.58, 29.64, 29.72, 29.76, 30.01, 39.12, 64.74, 128.55, 130.28, 166.18.

Anal. Calcd for $C_{17}H_{32}O_2$: C, 76.12; H, 11.94. Found: C, 76.09; H, 11.87.

Cyclized product (9): ^{1}H NMR δ 0.84 (s, 6 H), 1.13–1.42 (m, 18 H), 1.51–1.63 (m, 4 H), 2.19 (m, 2 H), 4.09 (t, 2 H, J = 5.7); ^{13}C NMR δ 21.54, 24.76, 26.05, 26.39, 26.90, 27.40, 27.74, 27.82, 28.01, 28.09, 30.22, 32.46, 34.93, 39.90, 64.15, 174.31.

Anal. Calcd for $C_{17}H_{32}O_2$: C, 76.12; H, 11.94. Found: C, 76.28; H, 12.10.

II.5. General Method for the Study of Tertiary Iodide k_c Cyclization. The solution of freshly prepared iodide (20.0–48.7 mg), 1.1 equiv of tributyltin hydride, and 0.1 equiv of AIBN in a corresponding amount of dry benzene (12–40 mL) was refluxed for 3 h. The reduced and cyclized products were determined by GC (column B, temperature 200 °C) with methyl palmitate as the internal standard. Burning ratio – reference (weight)/% reference × product (weight)/% product = 1.0421.

III. General Method for Atom Transfer Experiment. The solution of iodide in a corresponding amount of benzene with 10% hexabutyltin was stirred under a lamp (250 W). No reaction was observed under any conditions.

The tertiary iodide reaction was carried out at 0.73 mM for 30 min and at 0.3 M for 30 min plus 3 h.

The primary iodide reaction was carried out at 2.8 mM for 3 h and 0.3 M for 30 min. The starting iodide was recovered in 80–82% after column chromatography.

IV.1. Bromoalkyl Fumarate. Fumaric monoethyl ester anhydride was prepared by mixing 2.5 g (2 equiv) of fumaric acid monomethyl ester (Aldrich) and 1.79 g (1 equiv) of DCC in 50 mL of dichloromethane at 0 °C for 15 min. After filtration, the anhydride solution was added to 2.8 g (8.7 mmol) of 16-bromohexadecanol in 100 mL of dichloromethane with 0.1 g (0.1 equiv) of dimethylaminopyridine, which was also cooled in an ice bath. The reaction was stirred for 10 h, during which time it was allowed to warm to room temperature. After evaporation and chromatography (hexane/ethyl acetate = 10/1), it yielded 3.3 g (89%) of bromoalkyl fumarate.

IV.2. Iodoalkyl Fumarate (10). The mixture of the preceeding bromide, 1.7 g (3.3 mmol), and 1.5 g (3 equiv) of NaI in 50 mL of methyl ethyl ketone was stirred under reflux for 1 h. The solvent was removed and the residue slurried in 200 mL of hexane/dichloromethane = 1/1. The slurried solution was filtered through a funnel containing silica gel. The filtrate was concentrated to give the desired product, 1.8 g (100%).

10a: ^{1}H NMR δ 1.21–1.43 (m, 11 H), 1.65 (m, 2 H), 1.80 (m, 2 H), 3.15 (t, 2 H, J = 7.0), 4.13–4.30 (m, 4 H), 6.83 (s, 2 H); ^{13}C NMR δ 7.10, 14.06, 25.70, 28.29, 28.35, 28.95, 29.12, 30.29, 33.36, 61.08, 65.17, 133.28, 164.50, 164.56.

Anal. Calcd for $C_{14}H_{23}IO_4$: C, 43.98; H, 6.02; I, 33.25. Found: C, 44.08; H, 6.08; I, 33.14.

10b: ^{1}H NMR δ 1.20–1.41 (m, 13 H), 1.65 (m, 2 H), 1.80 (m, 2 H), 3.17 (t, 2 H, J = 7.0), 4.18 (t, 2 H, J = 6.8), 4.24 (q, 2 H, J = 7.0), 6.82 (s, 2 H); ^{13}C NMR δ 7.11, 14.06, 25.70, 28.29, 28.35, 28.95, 29.12, 30.29, 33.36, 61.08, 65.17, 133.28, 164.50, 164.57.

Anal. Calcd for $C_{15}H_{25}IO_4$: C, 45.45; H, 6.13. Found: C, 45.36; H, 6.45.

10c: ^{1}H NMR δ 1.13–1.88 (m, 23 H), 3.15 (t, 2 H, J = 7.0), 4.15 (t, 2 H, J = 6.4), 4.23 (q, 2 H, J = 7.0), 6.81 (s, 2 H); ^{13}C NMR δ 7.41, 14.19, 25.90, 28.53, 28.67, 29.24, 29.43, 29.53, 30.63, 33.68, 61.33, 65.48, 133.52, 133.60, 164.91.

Anal. Calcd for $C_{18}H_{31}IO_4$: C, 49.32; H, 7.08; I, 28.99. Found: C, 49.42; H, 7.15; I, 29.06. Mass (CI): 439 (M + 1).

10d: ^{1}H NMR δ 1.10–1.45 (m, 27 H), 1.58–1.88 (m, 4 H), 3.15 (t, 2 H, J = 7.0), 4.15 (t, 2 H, J = 6.4), 4.23 (q, 2 H, J = 7.0), 6.81 (s, 2 H); ^{13}C NMR δ 7.42, 14.21, 25.93, 28.53, 28.59, 29.29, 29.48, 29.60, 29.69, 30.57, 33.63, 61.33, 65.50, 133.52, 133.61, 164.90, 164.98.

Anal. Calcd for $C_{22}H_{39}IO_4$: C, 53.44; H, 7.89. Found: C, 53.54; H, 7.98. Mass (CI): 495 (M + 1).

IV.3. Cyclization of Iodoalkyl Fumarate (10). To the refluxing solutions of iodide (154 mg, 0.27 mmol), prepared as described above, 75 μL (1.1 equiv) of Bu_3SnH and 5 mg (0.1 equiv) of AIBN were added. The solution was stirred under reflux for 4 h. The solvent was removed and the residue placed on a silica gel column eluted with hexane/dichloromethane = 3/1. The reduced product (14.6 mg, 12%) eluted first. The later eluting endo- and exocyclization products were obtained as a mixture (66 mg, 56%). The endo and exo products (**11c**, **12c**, **11d**, and **12d**) could be separated by medium-pressure LC (Dynamax, 3% ethyl acetate in hexane) to give the endo cyclization product as the faster elutant.

The purity and product ratio were monitored by GC: column C for **11a** and **12a** (temperature 175 °C); column A for **11b** and **12b** (temperature 180 °C), **11c** and **12c** (temperature 200 °C), **11d** and **12d** (temperature 220 °C). In **10a** cyclization, the ratio of **11a** and **12a** was determined by ^{1}H NMR.

11c: ^{1}H NMR δ 1.14–1.80 (m, 25 H), 2.53 (dd, 1 H, J = 8.3, 15.5), 2.67 (dd, 1 H, J = 5.7, 15.5), 2.89 (m, 1 H), 4.13 (m, 4 H); ^{13}C NMR δ 14.33, 24.83, 24.87, 25.62, 25.97, 26.33, 26.35, 26.47, 26.57, 27.13, 28.29, 30.26, 35.83, 40.79, 60.64, 64.34, 171.88, 174.68. Anal. Calcd for $C_{18}H_{32}O_4$: C, 69.23; H, 10.26. Found: C, 68.96; H, 10.13. Mass (CI): 313 (M + 1).

11d: ^{1}H NMR δ 1.10–1.75 (m, 33 H), 2.43 (dd, 1 H, J = 7.0, 15.8), 2.64 (dd, 1 H, J = 7.2, 15.8), 2.82 (m, 1 H), 3.92–4.23 (m, 4 H); ^{13}C NMR δ 14.33, 25.65, 26.14, 27.19, 27.30, 27.47, 27.54, 27.60, 27.60, 27.72, 27.98, 28.04, 28.22, 28.35, 28.47, 31.11, 36.06, 41.02, 60.60, 64.69, 171.88, 174.80.

Anal. Calcd for $C_{22}H_{40}O_4$: C, 71.74; H, 10.87. Found: C, 71.61; H, 10.96. Mass (CI): 369 (M + 1).

12c: ^{1}H NMR δ 1.00–1.80 (m, 25H), 2.37 (dd, 1 H, J = 5.4, 16.2), 2.74 (dd, 1 H, J = 9.3, 16.2), 2.88 (m, 1 H), 4.01 (m, 1 H), 4.12 (q, 2 H, J = 7.2), 4.28 (m, 1 H); ^{13}C NMR δ 14.24, 24.94, 25.46, 26.03, 26.16, 26.50, 26.59, 26.75, 27.19, 28.40, 32.37, 36.87, 41.15, 60.58, 64.52, 171.93, 175.51.

Anal. Calcd for $C_{18}H_{32}O_4$: C, 69.23; H, 10.26. Found: C, 69.25; H, 10.38. Mass (CI): 313 (M + 1).

12d: ^{1}H NMR δ 1.16–1.75 (m, 33 H), 2.36 (dd, 1 H, J = 15.8, 4.8), 2.74 (dd, 1 H, J = 9.2, 25.0), 2.84 (m, 1 H), 3.90–4.24 (m, 4 H); ^{13}C NMR δ 14.24, 25.65, 25.83, 26.13, 26.54, 26.74, 27.07, 27.16, 27.35, 27.50, 27.61, 27.77, 27.98, 28.36, 28.49, 28.68, 28.75, 28.80, 29.27, 32.45, 36.51, 41.33, 60.58, 64.84, 172.01, 175.39.

Anal. Calcd for $C_{22}H_{40}O_4$: C, 71.74; H, 10.87. Found: C, 71.83; H, 10.95. Mass (CI): 369 (M + 1).

Mixtures of **11a**/**12a** and **11b**/**12b** gave correct C&H analyses and spectroscopic data (^{1}H and ^{13}C) consistent with the mixture based on **11c,d** and **12c,d**.

IV.4. Independent Synthesis of Exo Cyclization Product (12b). Lithium diisopropylamine (prepared fresh from diisopropylamine and *n*-BuLi in THF), 380 μL (1 M, 2 equiv), was added to the solution of 11-dodecanolide **4b** (35 mg, 0.2 mmol) in 1 mL of THF, which was precooled in a dry ice/2-propanol bath. After being stirred for 20 min, this lithiated solution was transferred to a flask containing 70 μL (3 equiv) of ethyl iodoacetate in 1 mL of HMPA, which was cooled in an ice bath. The reaction mixture was stirred at 0 °C for 20 min and quenched with NH_4Cl salt. The mixture was partitioned between ethyl acetate and saturated NH_4Cl solution and the organic layer washed with H_2O (×3). After evaporation and chromatography (silica gel, 5% ethyl acetate in hexane), it afforded the desired alkylation product (21 mg, 40%). The products were homogeneous, and coeluted with **12b** on TLC and GC.

12a: ^{1}H NMR δ 1.18–1.83 (m, 17 H), 2.31 (dd, 1 H, J = 6.3, 16.5), 2.74 (dd, 1 H, J = 8.4, 16.2), 2.90 (m, 1 H), 3.93 (m, 1 H), 4.12 (q, 2 H, J = 7.5), 4.43 (m, 1 H); ^{13}C NMR δ 14.23, 22.97, 23.11, 23.72, 24.54, 24.96, 25.21, 28.42, 36.32, 41.40, 60.56, 64.79, 171.98, 175.15.

12b: ^{1}H NMR δ 1.20–1.75 (m, 19 H), 2.32 (dd, 1 H, J = 5.4, 16.8), 2.75 (dd, 1 H, J = 9.6, 16.2), 2.98 (m, 1 H), 3.85 (m, 1 H), 4.12 (q, 2 H, J = 6.9), 4.52 (m, 1 H); ^{13}C NMR δ 14.23, 22.81, 23.13, 23.96, 24.84, 24.97, 26.33, 30.26, 36.35, 40.76, 60.55, 65.00, 171.92, 174.81.

Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.67, H, 9.63. Found: C, 66.73; H, 9.62.

12c: ^{1}H NMR δ 1.00–1.80 (m, 25 H), 2.37 (dd, 1 H, J = 5.4, 15.9), 2.74 (dd, 1 H, J = 9.3, 16.5), 2.88 (m, 1 H), 4.01 (m, 1 H), 412 (q, 2 H, J = 7.2), 4.28 (m, 1 H); ^{13}C NMR δ 14.31, 25.00, 25.44, 26.07, 26.19, 26.78, 27.34, 28.44, 32.45, 36.91, 41.17, 60.62, 64.56, 171.91, 175.50.

Anal. Calcd for $C_{18}H_{32}O_4$: C, 69.23; H, 10.26. Found: C, 69.65; H, 10.33.

IV.5. General Method for Selective Hydrolysis. The preceding endo cyclized **11c,d** (3.1 mg) and exo cyclized **12c,d** lactones (2.9 mg) were dissolved in NMR tubes containing 0.8 mL of EtOH-d_6, respectively. Two drops of LiOD/D_2O (15 mg, Li metal in 2 mL of D_2O) were added to the NMR tubes. After 8 h, the individual reaction was partitioned between ethyl ether and H_2O, while the aqueous solution was adjusted to pH 6 with 1 N HCl. The ether layers were mixed with excess CH_2N_2 and the mixture evaporated. NMR indicated the exo cyclized product was converted to a methyl ester lactone from an ethyl ester lactone. The endo cyclized lactone was converted to linear hydroxyl methyl ester.

11c hydrolysis product: (^{1}H NMR δ between 3.50 and 4.50) ^{1}H NMR δ 3.62 (t, 2 H, J = 7.2), 3.65 (s, 3 H), 4.12 (q, 2 H, J = 6.9).

12c hydrolysis product: (^{1}H NMR δ between 3.50 and 4.50) ^{1}H NMR δ 3.64 (s, 3 H), 3.98 (m, 1 H), 4.25 (m, 1 H).

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