Synthesis of Macrocyclic Lactones and Dilactones Using Olive Oil

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ABSTRACT: Macrocyclic lactones have redolent characteristics of muscenes that originate from the rectal musk organs of the musk deer. These lactones are the primary raw material in the flavor and fragrance industry and are also found within the cyclic frameworks of various bioactive molecules. Due to great demand, many efforts have been made for their synthesis; however, strategies generating a large number of macrocyclic analogues from renewable resources have not been fully realized and are urgently required. Here, we outline a sustainable, straightforward, and eco-friendly approach to synthesize high-valued macrocyclic lactones utilizing olive oil under greener reaction conditions. The outlined method allows us to turn biomass into valuable 12- to 29-membered lactones and dilactones.

1. INTRODUCTION

Plant-based feedstocks have become an intriguing raw material for various industries in environment-friendly and economically sustainable processes.1−3 These feedstocks mainly include vegetable oils, which predominantly contain fatty acids. Olefinic bonds of (mono or poly) unsaturated fatty acids offer the inherent possibility for versatile chemical transformations, for example, oxidation,4 epoxidation,5,6 metathesis,7,8 hydroalkylation,9 and polymerization.10,11 They are renewable feedstocks for constructing high value-added products such as macrocycles via greener approaches.12,13 Also, there is a considerable demand for macrocyclic molecules in the fragrances and flavor industry, particularly for macrocyclic lactones, that is, musk lactones.7 Traditionally, musk lactone is obtained from the musk deer’s rectal musk gland and is one of the oldest ingredients in perfumery.7 In traditional Chinese medicine, musk is a sedative and stimulant to treat various sicknesses and is used in more than 300 medicines. Musk’s excellent olfactory properties and use in pharmaceutical formulations put the species in the endangered category due to overexploitation.14,15 Alternatively, these molecules can be obtained from plant sources; however, their low natural abundance makes them unsustainable.16

Olefin metathesis, a catalytic reaction, became a powerful tool for producing natural products, polymers, and fine chemicals from biomass valorization.17−21 This reaction frequently utilizes Ru- and Mo-based catalysts owing to their high activity, efficiency, and stability.22,23 In olefin metathesis, ring-closing metathesis (RCM) is often used to develop the cyclic framework, gaining importance in synthesizing varieties of macrocyclic cores.7,8,24 In 1996, Fürstner and Langemann reported conformationally unbiased macracyclization reactions for the synthesis of macrolacrones having musky odor using RCM for the first time.25 Thereafter, the same group utilized the RCM strategy to synthesize a range of olfactory macrocycles from terminal olefins.26 Matsuda et al. synthesized musk macrolides from β-butyrolactone utilizing Grignard reaction, esterification, and RCM reaction.27 Recently, in 2018, the Grela group employed the RCM strategy to synthesize musk-smelling macrolactones from the methyl/ethyl oleate (Figure 1I).7,17 The Spinella group described a non-RCM-based protocol to synthesize macrocyclic lactones from hydroxy fatty acids using Candida antarctica lipase B enzyme (Figure 1I).28

In the quest for a bioresource for sustainable chemistry to prepare high value-added macrocycles, we for the first time report olive oil utilization to synthesize high-valued macrocyclic lactones. The olive oil is obtained from the seeds of the plant Olea europaea that is cultivated worldwide.29 It produces seeds containing 20−30% oil30 with a massive quantity of unsaturated fatty acids (70−90%), mainly oleic acid (∼65−80%).31 The presence of enormous unsaturation in olive oil makes it possible to utilize for amalgamation into various value-added products.

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2. RESULTS AND DISCUSSION

To begin our studies, we have commercially purchased olive oil from TCI Chemicals (India). Olive oil was subjected to hydrolysis in the presence of aq sodium hydroxide solution to obtain hydrolyzed oil. Next, to remove saturated fatty acids, the hydrolyzed oil was subjected to winterization, that is, it was slowly cooled to 15−18 °C and stood for 2 h, resulting in saturated fatty acids to crystallize and unsaturated fatty acids to remain in the liquid state. The liquid part was collected by decantation to furnish an oleic acid-rich hydrolyzed olive oil fraction (HOL) that contains 91% oleic acid (Supporting Information, Figure S2). Further, oleic acid-rich HOL was condensed with various unsaturated alcohols to obtain corresponding esters (Scheme 1, 1a−1d).

**Scheme 1. Synthesis of Olive Oil-Derived Esters**

(i) NaOH, water

Olive oil 100 °C, 12 h

(ii) Winterization

Conditions

| R1 | R2 |
|----|----|
| 1a | 95% |
| 1b | 96% |
| 1c | 93% |
| 1d | 92% |

“Reaction conditions: (i) olive oil (1.0 g, 1.0 equiv), NaOH (1.1 equiv), water, 100 °C, 12 h. (ii) Winterization and decantation, 76% after two steps. (iii) HOL (1.0 g, 1.0 equiv), alkenol (1.1 equiv), EDC·HCl (1.5 equiv), dimethylaminopyridine (DMAP) (0.22 equiv), diisopropylethylamine (DIPEA) (3.0 equiv), DCM, r.t., 12 h. Isolated yield.

**Scheme 2. Synthesis of Azelaic Acid-Derived Esters**

(i) VO@TiO2

HOL 80 °C, 12 h

Condition

| R1 | R2 |
|----|----|
| 2a | 96% |
| 2b | 92% |
| 2c | 93% |
| 2d | 85% |

“Reaction conditions: (i) HOL (1.0 g, 1.0 equiv), VO@TiO2 (30 wt %), TBHP (20 vol), 80 °C, 12 h, 65%. (ii) Azelaic acid (376 mg, 1.0 equiv), alkenol (2.2 equiv), EDC·HCl (3.0 equiv), DMAP (0.44 equiv), DIPEA (6.0 equiv), DCM, r.t., 12 h. Isolated yield.

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Figure 1. (I) Previous approaches and (II) current approach for synthesizing macrocyclic lactones.
HOL-derived azelaic acid was coupled with di to furnish substrates for macrocyclization (Scheme 2, for the RCM, chlorinated and aromatic solvents such as DCM, their high reactivity and thermal stability over other catalysts. Generation (HG-2) catalysts were selected for RCM due to second generation (GB-2) and Hoveyda−Grubbs second generation (HG-2) catalysts were selected for RCM due to their high reactivity and thermal stability over other catalysts. For the RCM, chlorinated and aromatic solvents such as DCM, dichloroethane, toluene, benzene, and xylene were frequently employed. However, previously, we had performed the RCM reaction in ethyl acetate (EtOAc), a nonchlorinated, environmentally benign, and economical solvent due to health and environmental issues associated with these solvents.

In this context, to obtain the best reaction conditions for metathesis, various parameters such as the catalyst, reaction temperature, mode of catalyst addition, and additives were optimized, selecting compound 1a as a model substrate. Initially, a reaction in EtOAc at 70 °C without any catalyst resulted in no reaction, whereas reaction with the GB-2 catalyst resulted in reactant consumption, but no desired product was obtained (Table 1, entries 1 and 2). Next, reaction with portion-wise catalyst addition gave the desired product with poor selectivity (Table 1, entry 3). Interestingly, a decrease in the temperature from 70 to 50 °C resulted in no change in the product yield (Table 1, entry 4). Reaction with the TFBQ additive instead of BQ gave an excellent yield for the desired product (Table 1, entry 5). Another reaction with low catalyst loading leads to low conversion and poor yield even after 12 h (Table 1, entries 11 and 12) resulted in poor yields for the product. A reaction with low catalyst loading leads to low conversion and poor yield even after 12 h (Table 1, entries 13 and 17). When the reactions were performed with the HG-2 catalyst, a decreased yield under various conditions was obtained, and furnishing the desired ester 1a in excellent yield. To introduce further diversity, alcohols with varying alkyl chain lengths such as pent-4-en-1-ol and hex-5-en-1-ol were condensed with HOL to furnish corresponding esters (1b−1c) in 96 and 93% yields, respectively. Accordingly, an internal double bond containing alkeneol, that is, oleyl alcohol, was smoothly condensed with HOL to furnish the corresponding ester 1d in excellent yield.

In the quest for sustainable methods for active pharmaceutical ingredients and key starting materials, we recently reported a method for synthesizing azelaic acid utilizing renewable oils over the vanadia catalyst. Initially, we synthesized azelaic acid from the oleic acid-rich HOL. To continue our efforts, the HOL-derived azelaic acid was coupled with different alkenols to furnish substrates for macrocyclization (Scheme 2, 2a−2d). First, allyl alcohol was condensed with azelaic acid to provide the corresponding diester 2a in a 96% yield. Similarly, a terminal double bond containing but-3-en-1-ol and dec-9-en-1-ol was condensed with azelaic acid to deliver the corresponding diesters (2b−2c) in excellent yield. Finally, an internal double bond containing oleyl alcohol was coupled with azelaic acid to obtain dioleyl nonanedioate 2d in 85% yield.

After successfully synthesizing a diverse range of olefins (1a−1d and 2a−2d), our subsequent attention turned toward identifying suitable reaction conditions for macrolactonization using the RCM protocol. Benzoquinone-based additives such as 1,4-benzoquinone (BQ) and 1,1,4,4-tetrafluorobenzoquinone (TFBQ) were also utilized to prevent oligomerization to a great extent by preventing undesirable reactions. Grubbs second generation (GB-2) and Hoveyda–Grubbs second generation (HG-2) catalysts were selected for RCM due to their high reactivity and thermal stability over other catalysts. For the RCM, chlorinated and aromatic solvents such as DCM, dichloroethane, toluene, benzene, and xylene were frequently employed. However, we had performed the RCM reaction in ethyl acetate (EtOAc), a nonchlorinated, environmentally benign, and economical solvent due to health and environmental issues associated with these solvents.

In this context, to obtain the best reaction conditions for metathesis, various parameters such as the catalyst, reaction temperature, mode of catalyst addition, and additives were optimized, selecting compound 1a as a model substrate. Initially, a reaction in EtOAc at 70 °C without any catalyst resulted in no reaction, whereas reaction with the GB-2 catalyst resulted in reactant consumption, but no desired product was obtained (Table 1, entries 1 and 2). Next, reaction with portion-wise catalyst addition gave the desired product with poor selectivity (Table 1, entry 3). Further, reaction with the TFBQ additive resulted in a relatively improved yield for the product (Table 1, entry 4). Reaction with the TFBQ additive instead of BQ gave an excellent yield for the desired product (Table 1, entry 5). Interestingly, a decrease in the temperature from 70 to 50 °C resulted in no change in the product yield (Table 1, entry 6). However, reactions with high olefinic concentrations (5 and 10 mM) furnished poor selectivity for the desired product (Table 1, entries 7 and 8). A reaction without the TFBQ additive resulted in a drastic decrease in the product yield (Table 1, entry 9). Reactions in DCM instead of EtOAc (Table 1, entry 10) at reduced temperature (Table 1, entries 11 and 12) resulted in poor yields for the product.

Table 1. Optimization of Reaction Conditions for RCM a

| entry | cat. (mol%) | additive (10 mol%) | solvent | temp (°C) | time (h) | yield (%) |
|-------|-------------|-------------------|---------|-----------|----------|-----------|
| 1     | GB-2 (5)    | TFBQ (10)         | EtOAc   | 70        | 1 + 24   | 10        |
| 2     | GB-2 (5)    | TFBQ (10)         | EtOAc   | 70        | 1 + 2    | 40        |
| 3     | GB-2 (5)    | TFBQ (10)         | EtOAc   | 70        | 1 + 2    | 90        |
| 4     | GB-2 (5)    | TFBQ (10)         | EtOAc   | 70        | 1 + 24   | 10        |
| 5     | GB-2 (5)    | TFBQ (10)         | EtOAc   | 70        | 1 + 2    | 40        |
| 6     | GB-2 (5)    | TFBQ (10)         | EtOAc   | 70        | 1 + 24   | 10        |
| 7     | GB-2 (5)    | TFBQ (10)         | EtOAc   | 70        | 1 + 2    | 40        |
| 8     | GB-2 (5)    | TFBQ (10)         | EtOAc   | 70        | 1 + 24   | 10        |
| 9     | GB-2 (5)    | TFBQ (10)         | EtOAc   | 70        | 1 + 2    | 40        |
| 10    | GB-2 (5)    | TFBQ (10)         | EtOAc   | 70        | 1 + 2    | 40        |
| 11    | GB-2 (5)    | TFBQ (10)         | EtOAc   | 70        | 1 + 24   | 10        |
| 12    | GB-2 (5)    | TFBQ (10)         | EtOAc   | 70        | 1 + 2    | 40        |
| 13    | GB-2 (5)    | TFBQ (10)         | EtOAc   | 70        | 1 + 24   | 10        |
| 14    | GB-2 (5)    | TFBQ (10)         | EtOAc   | 70        | 1 + 2    | 40        |
| 15    | GB-2 (5)    | TFBQ (10)         | EtOAc   | 70        | 1 + 24   | 10        |
| 16    | GB-2 (5)    | TFBQ (10)         | EtOAc   | 70        | 1 + 2    | 40        |
| 17    | GB-2 (5)    | TFBQ (10)         | EtOAc   | 70        | 1 + 24   | 10        |
| 18    | GB-2 (5)    | TFBQ (10)         | EtOAc   | 70        | 1 + 2    | 40        |

a Reaction conditions: 1a (50 mg, 1.0 equiv), GB-2 (5 mol%), TFBQ (10 mol%), EtOAc (1 mM), 50 °C, (1 + 2) h. Addition of the catalyst in six equal portions in intervals of 10 min that took 1 h for complete catalyst addition. Isolated yield. One portion catalyst addition. Olefin concentration in solvent = 10 mM. Olefin concentration in solvent = 5 mM. Reactions were performed at 1 mM concentration of olefin.
Scheme 3. (I) Synthesis of Macrolactones from Alkyl Oleate. (II) Synthesis of Macrolactones from Dialkyl Azelate

multiple spots were observed using thin-layer chromatography (TLC) (Table 1, entries 14–18).

After optimization, the best reaction conditions require portion-wise addition of 5 mol % of GB-2 and 10 mol % of TFBQ and maintaining a concentration of 1 mM concerning olefins in EtOAc at 50 °C for 2 h after complete addition of the catalyst. Having optimized reaction conditions in hand, we explored the substrate scope for the developed protocol. For this purpose, various synthesized olefinic (di)esters (1a–1d and 2a–2d) were tested for the RCM reaction.

The macrocyclization of olive oil-derived olefinic esters (1a–1d) was performed (Scheme 3I). First, homoallyl ester 1a was subjected to RCM, which resulted in industrially valuable 13-membered macrocyclic lactone 3a (yuju lactone) in 90% yield. Similarly, internal-terminal double bonds containing compounds 1b and 1c were cyclized smoothly to furnish respective macrocyclic lactones 3b (14-membered) and 3c (15-membered) in excellent yields. Further, terminal–terminal double bonds containing compound 1d was cyclized under the developed protocol to deliver the 19-membered macrocyclic lactone 3d in 94% yield. The result shows that long-chain alkenol-derived esters furnished the corresponding macro lactones in higher yield than the esters derived from small-chain alkenols.

Next, cyclization of diesters obtained from HOL-derived azelaic acid (2a–2d) was attempted (Scheme 3II). For this purpose, diallyl azelate (2a) containing terminal double bonds under RCM conditions yielded the desired 15-membered dilactone 4a in 88% yield. Similarly, 17- and 29-membered dilactones (4b–4c) were synthesized from their respective precursors (2b–2c) under the developed protocol in excellent yields. Interestingly, a cyclization reaction of dioleyl azelate (2d) containing the internal–internal double bond resulted in 29-membered dilactone 4c in excellent yield.

3. CONCLUSIONS

In summary, the work successfully demonstrates the first-time utilization of olive oil to synthesize high-valued macrocyclic lactones and dilactones. The hydrolyzed olive oil was successfully coupled with various unsaturated alcohols, including terminal and internal double bond containing alcohols, to produce eight olefinic (di)esters. These synthesized olefinic (di)esters were cyclized using the Grubbs catalyst under greener reaction conditions to furnish a range of macrocyclic products with diverse ring sizes varying from 12- to 29-membered. Utilizing natural resources made this strategy an efficient and proficient approach to deliver high-valued macrocycles, which has the potential for industrial application.
TOF LC/MS spectrometer. Gas chromatography–mass spectrometry (GC–MS) analysis was carried out on a Shimadzu QP 2010 GC–MS system with an AOC 5000 autoinjector equipped with a Zebon ZB-SMS capillary column (30 m x 0.25 mm, 0.25 mm film thickness); carrier gas: helium (flow: 1.0 mL/min); split ratio 1:50; ionization energy: 70 eV; ion source temperature: 250 °C; injector temperature: 240 °C. Oven temperature program: initially at 70 °C for 3 min, increased at 4 °C/min to 220 °C, and then held isothermal (5 min) at 220 °C. Full spectral data for all novel compounds are given; all previously characterized compounds gave spectra consistent with the literature.

4.2. Hydrolysis of Olive Oil. The olive oil was subjected to hydrolysis under basic conditions to obtain free fatty acids. For this purpose, in a 250 mL round-bottom flask was added 5 g of olive oil and 800 mg of NaOH in 30 mL of water. The resultant reaction mixture was refluxed for 24 h, and water (30 mL) was added in intervals of 3 h (3 × 10 mL) to ensure complete hydrolysis. After completion (TLC monitoring), the reaction mixture was quenched with water (30 vol) and extracted with DCM (3 × 50 mL). The combined organic fractions were dried over anhydrous Na2SO4, the solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography to afford the desired product.37

4.4.1. But-3-en-1-yl Oleate (1a). Colorless oil, (1.13 g, 3.36 mmol, yield 95%).1H NMR (300 MHz, CDCl3): δ 5.77–5.72 (m, 1H), 5.31–5.29 (m, 2H), 5.07 (d, J = 17.1 Hz, 1H), 5.03 (d, J = 10.2 Hz, 1H), 4.09 (t, J = 6.7 Hz, 2H), 2.34 (q, J = 6.7 Hz, 2H), 2.25 (t, J = 7.5 Hz, 2H), 1.99–1.96 (m, 4H), 1.59–1.57 (m, 2H), 1.27–1.22 (m, 20H), 0.85 (t, J = 6.9 Hz, 3H).13C{1H} NMR (151 MHz, CDCl3): δ 173.6, 134.0, 129.9, 129.9, 117.0, 63.1, 34.2, 33.1, 31.9, 29.7, 29.6, 29.5, 29.3, 29.1, 29.0, 27.1, 27.1, 24.9, 24.9, 22.6, 14.0. ESI-HRMS m/z: calcld for C15H26O2 [M + H]+, 225.2042; found, 225.2055.

4.4.2. Pent-4-en-1-yl Oleate (1b). Colorless oil, (1.19 g, 3.398 mmol, yield 96%).1H NMR (300 MHz, CDCl3): δ 5.86–5.76 (m, 1H), 5.39–5.28 (m, 2H), 5.03 (d, J = 17.1 Hz, 1H), 4.98 (d, J = 10.0 Hz, 1H), 4.07 (t, J = 6.6 Hz, 2H), 2.28 (t, J = 7.5 Hz, 2H), 2.16–1.99 (m, 6H), 1.76–1.67 (m, 5H), δ = 7.0 Hz, 2H), 1.61 (t, J = 6.4 Hz, 2H), 1.29–1.25 (m, 20H), 0.87 (t, J = 6.3 Hz, 3H).13C{1H} NMR (151 MHz, CDCl3): δ 173.9, 137.4, 129.9, 129.7, 115.2, 63.6, 34.3, 31.9, 30.0, 29.7, 29.6, 29.5, 29.3, 29.1, 29.1, 27.1, 27.8, 27.2, 27.1, 25.0, 22.6, 14.1. ESI-HRMS m/z: calcld for C21H38O2 [M + H]+, 351.3258; found, 351.3260.

4.4.3. Hex-5-en-1-yl Oleate (1c). Colorless oil, (1.198 g, 3.398 mmol, yield 93%).1H NMR (300 MHz, CDCl3): δ 5.86–5.73 (m, 1H), 5.40–5.29 (m, 2H), 5.05–4.95 (m, 2H), 4.07 (t, J = 6.5 Hz, 2H), 2.29 (t, J = 7.5 Hz, 2H), 2.12–2.01 (m, 6H), 1.67–1.60 (m, 4H), 1.51–1.41 (m, 2H), 1.31–1.26 (m, 24H), 0.88 (t, J = 6.4 Hz, 3H).13C{1H} NMR (151 MHz, CDCl3): δ 173.7, 134.0, 129.9, 129.7, 117.1, 63.2, 34.2, 33.1, 31.9, 29.7, 29.6, 29.5, 29.3, 29.1, 29.0, 27.1, 27.2, 24.9, 22.6, 14.0. ESI-HRMS m/z: calcld for C22H39O2 [M + H]+, 365.3414; found, 365.3400.

4.4.4. (Z)-Octadec-9-en-1-yl Oleate (1d). Colorless oil (1.73 g, 3.26 mmol, yield 92%).1H NMR (300 MHz, CDCl3): δ 5.40–5.28 (m, 4H), 4.04 (t, J = 6.6 Hz, 2H), 2.27 (t, J = 7.4 Hz, 2H), 2.16 (s, 4H), 2.03–1.94 (m, 7H), 1.65–1.55 (m, 4H), 1.36–1.21 (m, 43H), 0.89–0.84 (m, 6H).13C{1H} NMR (75 MHz, CDCl3): δ 173.9, 129.9, 129.7, 64.3, 34.3, 32.5, 31.8, 30.8, 29.6, 29.5, 29.3, 29.1, 29.0, 27.1, 25.9, 25.0, 22.6, 14.0. ESI-HRMS m/z: calcld for C36H72O2 [M + H]+, 533.5292; found, 533.5281.

4.5. General Procedure for the Synthesis of Olive Oil-Derived Olefinic Ester (1a–1d). To a stirred solution of oleic acid-rich HOL (1.0 g, 1.0 equiv) in DCM (10 vol) at 0 °C was added EDC–HCl (1.7 equiv) and DMAP (0.22 equiv). After 10 min at 0 °C, alcohol (1.1 equiv) and DIPEA (6.0 equiv) were added, and the reaction mixture was stirred at room temperature for 12 h. After completion (TLC monitoring), the reaction mixture was quenched with water (30 vol) and extracted with DCM (3 × 50 vol). The combined organic fractions were dried over anhydrous Na2SO4, the solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography to afford the desired product.37
pressure, and the residue was purified by silica gel column chromatography to afford the desired product.37

4.5.1. Diallyl Nonanedioate (2a). Colorless oil (514.6 mg, 1.92 mmol, yield 96%).1 H NMR (600 MHz, CDCl3): δ 5.92–5.87 (m, 2H), 5.29 (dd, J = 17.1, 1.4 Hz, 2H), 5.21 (dd, J = 10.4, 1.2 Hz, 2H), 4.55 (d, J = 5.7 Hz, 4H), 2.30 (t, J = 7.5 Hz, 2H), 1.61 (t, J = 7.1 Hz, 4H), 1.30 (m, 6H).13C{1H} NMR (151 MHz, CDCl3): δ 173.3, 132.3, 118.0, 64.9, 34.1, 28.8, 28.8, 24.8. ESI-HRMS m/z: calcd for C18H32O4 [M + H]+, 269.1747; found, 269.1730.

4.5.2. Di(but-3-en-1-yl) Nonanedioate (2b). Colorless oil (568.3 mg, 1.92 mmol, yield 96%).1 H NMR (300 MHz, CDCl3): δ 5.81–5.74 (m, 2H), 5.10 (qd, J = 17.6, 1.5 Hz, 2H), 5.06 (dd, J = 10.2, 1.0 Hz, 2H), 4.11 (t, J = 6.7 Hz, 4H), 2.39–2.35 (m, 4H), 2.30–2.27 (m, 4H), 1.65–1.59 (m, 4H), 1.34–1.30 (m, 6H).13C{1H} NMR (75 MHz, CDCl3): δ 173.7, 173.5, 134.0, 117.1, 102.2, 63.2, 34.2, 34.0, 33.5, 29.6, 28.9, 28.8, 28.7, 28.5, 24.8, 24.7, 24.5. ESI-HRMS m/z: calcd for C20H36O4 [M + H]+, 297.2060; found, 297.2066.

4.5.3. Di(dec-9-en-1-yl) Nonanedioate (2c). Colorless oil (863 mg, 1.86 mmol, yield 93%).1 H NMR (600 MHz, CDCl3): δ 5.81–5.76 (m, 2H), 4.98 (t, J = 17.1 Hz, 2H), 4.91 (t, J = 10.1 Hz, 2H), 4.04 (t, J = 6.6 Hz, 4H), 2.29–2.26 (m, 4H), 2.02 (q, J = 7.0 Hz, 4H), 1.61–1.59 (m, 8H), 1.38–1.35 (m, 4H), 1.30–1.28 (m, 2H).13C{1H} NMR (151 MHz, CDCl3): δ 173.9, 139.1, 114.1, 64.4, 34.3, 33.8, 29.3, 29.2, 29.0, 28.9, 28.9, 28.8, 28.6, 25.9, 24.9, 24.6. ESI-HRMS m/z: calcd for C22H40O4 [M + H]+, 465.3938; found, 465.3946.

4.5.4. Di(Z)-octadec-9-en-1-yl) Nonanedioate (2d). Colorless oil (1.17 g, 1.70 mmol, yield 88%).1 H NMR (600 MHz, CDCl3): δ 5.40–5.31 (m, 4H), 4.06 (t, J = 6.7 Hz, 4H), 2.29 (t, J = 7.5 Hz, 4H), 2.05–2.00 (m, 6H), 1.64–1.60 (m, 8H), 1.36–1.27 (m, 5H), 0.89 (t, J = 6.9 Hz, 6H).13C{1H} NMR (151 MHz, CDCl3): δ 173.8, 130.4, 130.2, 129.9, 129.7, 64.3, 34.3, 32.5, 32.5, 31.9, 29.7, 29.6, 29.6, 29.6, 29.5, 29.4, 29.4, 29.3, 29.3, 29.2, 29.2, 29.1, 29.0, 28.9, 28.9, 28.6, 27.2, 27.2, 25.9, 24.9, 22.6, 21.4, 14.0. ESI-HRMS m/z: calcd for C24H44O4 [M + H]+, 689.6642; found, 689.6620.

4.6. General Procedure for Macrocyclization of Synthesized Olefinic (Di)ester (1a–1d & 2a–2d)

4.6.2.1. (3E/Z)-1,6-Dioxacyclopentadec-3-ene-7,15-dione (4a). Colorless oil with musky odor (52.4 mg, 0.27 mmol, 90%). Rf = 0.50 (1:19, diethyl ether/n-hexane).1 H NMR (300 MHz, CDCl3): δ 5.88–5.88 (m, 2H), 4.61–4.57 (m, 4H), 2.35–2.29 (m, 4H), 1.63–1.57 (m, 4H), 1.30–1.27 (m, 6H).13C{1H} NMR (75 MHz, CDCl3): δ 173.3, 128.9, 62.5, 34.6, 28.3, 27.6, 24.9. ESI-HRMS m/z: calcd for C13H20O2 [M + H]+, 231.1434; found, 231.1430.

4.6.2.2. (4E/Z)-1,8-Dioxacycloheptadec-4-ene-9,17-dione (4b). Colorless oil with musky odor (87.3 mg, 0.27 mmol, 95%). Rf = 0.48 (1:19, diethyl ether/n-hexane).1 H NMR (300 MHz, CDCl3): δ 5.56–5.49 (m, 2H), 4.19–4.14 (m, 4H), 2.41–2.28 (m, 8H), 1.65–1.59 (m, 4H), 1.34–1.28 (m, 6H).13C NMR shows the presence of geometrical isomers in the
ratio of Z/E = 1:4). $^{13}$C{1H} NMR (151 MHz, CDCl$_3$): $\delta$ 173.9, 128.9, 128.4, 63.5, 34.4, 34.2, 31.9, 27.9, 27.7, 27.5, 27.3, 24.7, 24.6. ESI-HRMS m/z: calc'd for C$_{14}$H$_{20}$O$_4$ [M + H]$^+$, 269.1747; found, 269.1740.

4.6.2.3. (20E/Z)-1,11-Dioxacyclonacos-20-ene-2,10-dione (4c). From compound 2c. Colorless oil with musky odor (84.7 mg, 0.19 mmol, 90%). $R_f$ = 0.50 (1:19, diethyl ether/n-hexane). From compound 2d. Colorless oil with musky odor (84.7 mg, 0.19 mmol, 90%). $R_f$ = 0.50 (1:19, diethyl ether/n-hexane). 1H NMR (300 MHz, CDCl$_3$): $\delta$ 5.41–5.35 (m, 2H), 4.07 (d, $J$ = 6.7 Hz, 4H), 2.30 (d, $J$ = 7.5 Hz, 4H), 2.03–1.96 (m, 4H), 1.64–1.60 (m, 10H), 1.31–1.27 (m, 24H). $^{13}$C{1H} NMR (75 MHz, CDCl$_3$): $\delta$ 173.9, 130.3, 64.4, 34.3, 32.5, 31.9, 29.7, 29.6, 29.3, 29.2, 29.1, 28.9, 28.6, 25.9, 24.9, 22.6. ESI-HRMS m/z: calc'd for C$_{27}$H$_{48}$O$_4$ [M + H$^+$]$^+$, 438.3698; found, 438.3695.

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R.R. contributed to the optimization, synthesis of substrate scope, data analysis, and manuscript writing. Shreya contributed to the synthesis of building blocks and substrate scope. R.U. contributed to the substrate scope. S.K.M. conceived and supervised the experiments, contributed to data analysis and editing of the manuscript, and provided overall guidance.

**Notes**

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