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Featured Article

Flow Chemistry under Extreme Conditions: Synthesis of Macrocycles with Musklike Olfactoric Properties

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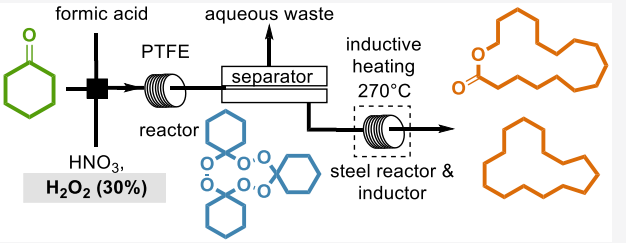
ABSTRACT: Starting from small cyclic ketones, continuous flow synthesis is used to produce medium-sized rings and macrocycles that are relevant for the fragrance industry. Triperoxides are important intermediates in this process and are pyrolyzed at temperatures above 250 °C. The synthesis is carried out in two continuously operated flow reactors connected by a membrane-operated separator. The practicality of flow chemistry is impressively demonstrated in this work by the use of hazardous reagent mixtures (30% H_2O_2, 65% HNO_3) and the pyrolysis of no less problematic peroxides. All new macrocycles were tested for their olfactory properties in relation to musk.



INTRODUCTION

The use of micro- or mesofluidic flow reactors has become a key enabling technology[1] often applied in the continuous preparation of drugs and pharmaceuticals.[2,3] It is very likely that the fragrance industry[4] could also benefit from these technological developments; only in selected cases have aroma molecules been produced on an industrial scale to date, and academic studies on this are rare.[5]

Typical examples include musklike scents that occupy a special place among fragrances, and (*R*)-muscone (**1**) is the most famous example secreted from a gland of the musk deer. Not only its animal origin but also its multifaceted scent makes musk one of the most important and expensive fragrances in the world. It is often used as a base note in perfumes due to its warm, animalic scent. However, (*R*)-muscone (**1**) is only present in it in small proportions (1−2%), but interestingly, the unnatural (+)-enantiomer exhibits the characteristic fragrance.[6] The few musk fragrances of plant origin are lactones, whose scent is very similar to that of musk but fresher. These include the plant-derived musk fragrances ambrettolide (**3**) from musk seed oil (*Hibiscus abelmoschus* L.) and oxacyclohexadecan-2-one (**5**, macrolide), from angelica root oil (*Archangelica officinalis* Hoffm.).[6] In 1999, the macrolides **3** and oxacycloheptadecan-2-one (**4**) were identified for the first time as components of a floral fragrance in the fragrance of orchids.[7] Macrolide (**5**) is also a component of oriental tobacco and responsible for its musky note (Figure 1).[8]

Ružička discovered the macrocyclic ring structures of the musk ketones, (*R*)-muscone (**1**) and civetone and also achieved the first total synthesis by pyrolysis of the corresponding dicarboxylic acids (also called Ružička cyclization), despite low yield (<10%).[9a,b] Later, in 1970, Story disclosed a remarkable synthetic approach to macrocyclic

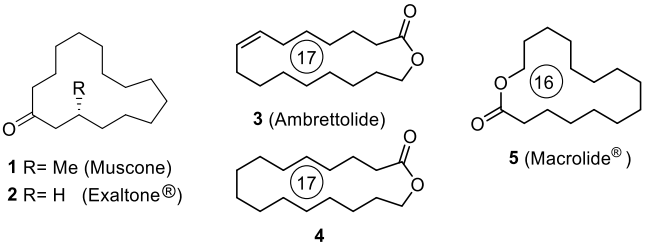


Figure 1. Examples of macrocyclic molecules **1**−**5** with musklike scents (the circled numbers refer to the ring size).

lactones and ketones wherein triperoxides act as key intermediates obtained by trimerization of readily available small cyclic ketones.[10,11]

Safety issues make Story's protocol unfavorable for large-scale production under batch conditions, since highly concentrated hydrogen peroxide is used and the intermediate triperoxide **7** must be exposed to pyrolytic conditions (Scheme 1). However, with modern flow chemistry, the safety problem is minimized because only small amounts of concentrated hydrogen peroxide and triperoxide **7** need to be exposed to the extreme conditions. In addition, extended operating times allow for large-scale production.[12] Here, we report the development of a complete flow protocol for the continuous synthesis of macrocycles with musklike properties. We also

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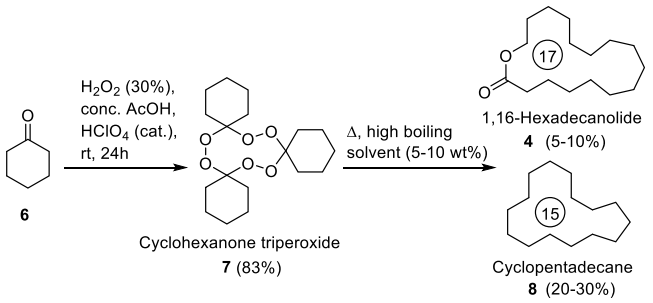
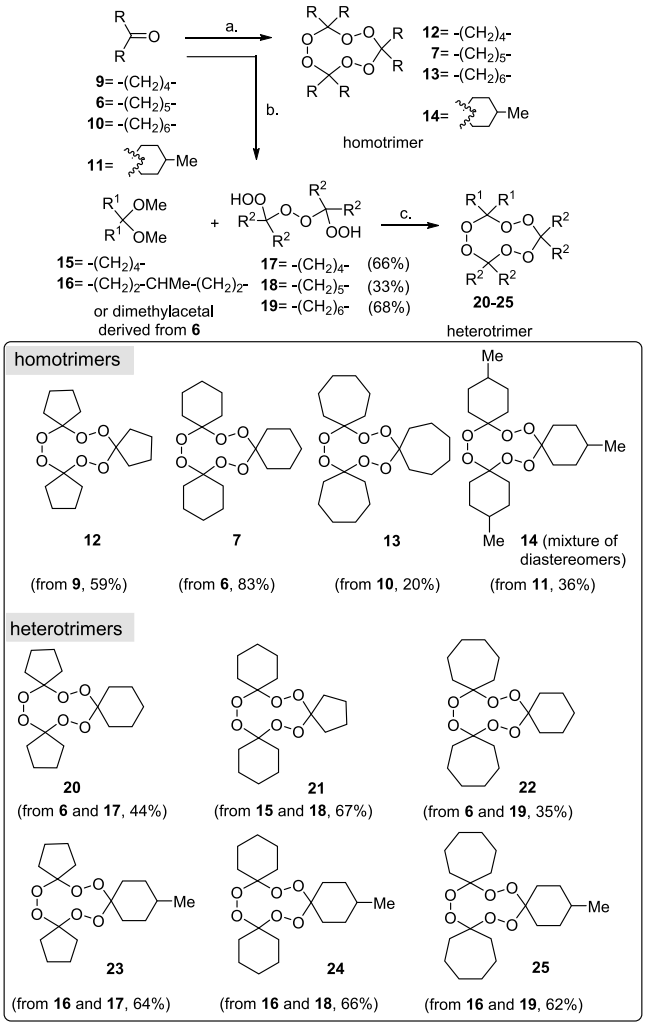
Scheme 1. Story's Two-Step Batch Synthesis of 1,16-Hexadecanolide (4) and Cyclopentadecane (8) from Cyclohexanone (6)[10]



Scheme 2. Synthesis of Triperoxides 7, 12−14 and 20−25 (I: Trimerization to Homotrimers; II: Formation of Heterotrimers, Yields Are Given)[a,b]



[a]Reagents and conditions: (a) 30% H_2O_2, $HICO_4$ (cat.), MeCN, 0 °C to rt, 24 h; (b) 30% H_2O_2, 34% HCl, H_2O, 5 °C to rt, 48 h (for **17**), 30% H_2O_2, 98% H_2SO_4, H_2O, 10 °C, 1 h (for **18**) and 30% H_2O_2, 34% HCl, −8 °C to rt, 1 h (for **19**); (c) $BF_3{\cdot}OEt_2$, Et_2O, 5 °C to rt, 16 h. [b]CAUTION: All of the described peroxides are considered to be shock sensitive to some degree. Proper precautions should be taken when working with them.[15]

expand the number of macrocycles accessible via the Story route. Our investigation was split into two optimization studies, starting with the second pyrolysis step, which is the more problematic of the two under large-scale batch conditions.

RESULTS AND DISCUSSION

Thus, we first prepared a series of triperoxides **7**, **12**−**14**, and **20**−**25** according to established methods (Scheme 2).[10,12,13] The preparation of the heterotrimers **20**−**25** is based on a two-step procedure starting from the ketones **6**, **9** and **10** in acidic aqueous medium. Under these conditions, the dimeric triperoxides **17**−**19** are formed, and in combination with the corresponding dimethylacetals **15** and **16** or dimethylacetal of **6**, the heterotrimers **20**−**25** are formed.[14]

With these triperoxides in hand, their pyrolysis and macrocycle formation were studied under continuous flow conditions. The triperoxide **7** was chosen as the model compound (Scheme 3). In 2008, we introduced inductive heating as a new technology for organic synthesis and demonstrated in a number of applications that this technique is ideal for heating flow devices.[16] In this technique, an oscillating electromagnetic field (medium frequency 15−100 MHz or high frequency 100−800 MHz) induces heat in conductive materials or, alternatively, in nanostructured superparamagnetic particles.[17] Copper[18] or steel reactors[19] can be heated directly under these conditions. This very fast and efficient heating technique broadens the range of synthetic high-temperature applications since the residence times in flow devices and thus the duration of exposure to the high-temperature conditions can be controlled by the flow rate. In the present case, triperoxide **7** was dissolved in dodecane, added to a sample loop, introduced from the loop into the main flow of the dodecane, and finally pumped into the reactor. The reactor (V = 4.8 mL) was encased by an inductor driven by a generator. This in turn was equipped with a computer-controlled on/off switch. This device is thus able to flexibly control and determine the temperature at the reactor surface via the signal sent by an IR pyrometer.

The optimization of the flow processes was accelerated by utilizing the concept of Design of Experiments (DoE) (for details, see the Supporting Information). Pyrolysis of triperoxide **7** was carried out at temperatures between 180 °C and 330 °C. We tested copper and stainless steel as reactor materials as well as different reactor formats such as rod, loop, and serpentine reactors. Close examination of the gas chromatograms of the reaction solutions showed that oligomers are formed more frequently when copper is used as the reactor material, an observation that explains the low yields for the macrolactones and macrocyclic hydrocarbons. Therefore, stainless steel reactors were used in this study from then on. We also optimized the reactor temperature and residence time (see the Supporting Information for details).

According to GC analysis using eicosane as an internal standard, the highest yields were obtained in a 1/8 in. stainless steel loop reactor at 300 °C. The residence time was 5 min. Under these conditions, 1,16-hexadecanolide (**4**) and cyclopentadecane (**8**) are formed in nearly 60% combined yield. Both products can be separated by distillation. In the following, triperoxides **12**−**14** and **20**−**25** were also pyrolyzed under flow conditions. Again, the tool of DoE[20] in terms of solvent, temperature, and residence time served as a guide for the experimental design.

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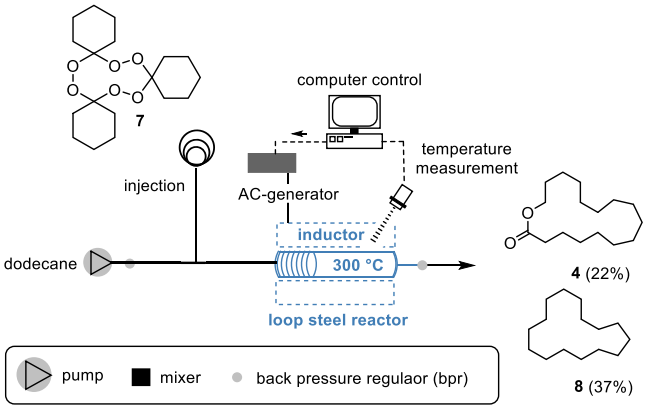
Scheme 3. Flow Setup for the Pyrolysis of Cyclohexanone Triperoxide (7)[a]



[a]Details of the technical setup are found in the accompanying text and the SI.

The macrolactones **26**, **28**, **30**, **32**, **34**, **36**, **38**, **40**, and **42** and the macrocyclic hydrocarbons **27**, **29**, **31**, **33**, **35**, **37**, **39**, **41**, and **43** produced are summarized in Table 1.[21] For a complete analytical evaluation, especially of the NMR spectroscopic data, we separated the lactones and macrocyclic hydrocarbons by preparative gas chromatography.[22] Essentially, pyrolytic decomposition of triperoxides using the enabling technology of inductive heating for the flow configuration developed here enables the continuous formation of industrially significant macrocyclic products.

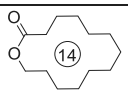
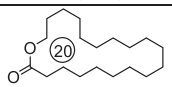
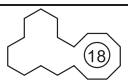
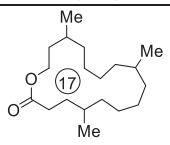
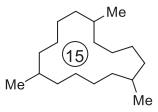
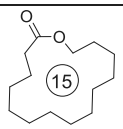
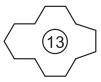
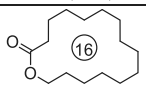
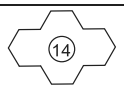
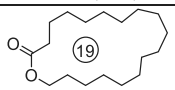
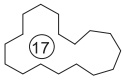
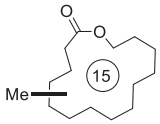
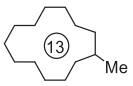
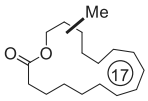
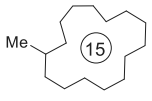
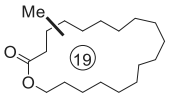
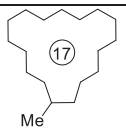
Next, we optimized the oxidative formation of cyclohexanone triperoxide (**7**) under flow conditions. The setup places the three components (cyclohexanone (**6**), 98% formic acid, and 30% hydrogen peroxide with 65% HNO_3) in three separate reservoirs (pumps 1−3, Scheme 4). To avoid contact of metal surfaces with potentially hazardous peroxides, PTFE was used as an inert reactor material and for piping. With a view to developing an industrially relevant protocol, we used formic acid rather the originally reported perchloric acid for safety and cost reasons. Formic acid and nitric acid have also been described as preferred acids for the process under flow conditions.[12]

The components were mixed in a small connector after being pumped through three separate HPLC pumps (pump 1: cyclohexanone (**6**) in dodecane, pump 2: 98% formic acid, pump 3: peroxide mixture; see also Table 2). The reaction mixture was then pumped through a PTFE reactor (V = 50 mL, ⌀ = 1.6 mm) at room temperature. The best homogeneity of the two-phase system was achieved when small inner diameter tubing was used or in the presence of a static mixer. However, to produce cyclohexanone triperoxide (**7**) in acceptable yield (Table 2), a considerable optimization effort was required.

Cyclohexanone triperoxide (**7**) was formed in a yield of 48%. It should be noted that the formation of the byproduct cyclohexanone diperoxide (**44**) could not be completely suppressed and was present in a yield of about 15%. It is noteworthy that conducting the reaction at higher temperatures (60 °C) under batch conditions favors the formation of DPO. We therefore chose room temperature as the reaction temperature under both batch and flow-through conditions to minimize DPO formation. Although reaction times (see also Scheme 1) and residence times are not quite comparable, the residence time found here is still practicable for continuous flow processes.

Since both reaction steps were optimized under flow conditions, the next step was to telescope both steps with cyclohexanone (**6**) as starting material because products **4** and **8** are of commercial importance. This goal required the

Table 1. Products 26−43 Formed after the Pyrolysis of the Triperoxides 12−14 and 20−25 under Conditions Individually Optimized by DoE*

peroxide	macrolactone	macrocyclic hydrocarbon	comments (τ = res. time)[a]
12	 **26** (15%)[b]	 **27** (51%)	278 °C, τ = 48 min, dodecane
13	 **28** (16%)	 **29** (30%)	268 °C, τ = 7 min, dodecane
14	 **30** (21%)	 **31** (32%)[a]	330 °C, τ = 24 min, dodecane[c]
20	 **32** (10%)[b]	 **33** (21%)	260 °C, τ = 8 min, *n*-hexane
21	 **34** (10%)	 **35** (22%)	260 °C, τ = 8 min, *n*-hexane
22	 **36** (5%)	 **37** (29%)	270 °C, τ = 7 min, *n*-hexane
23	 *rac*-**38** (14%)	 **39** (56%)	270 °C, τ = 7 min, *n*-hexane
24	 *rac*-**40** (7%)	 **41** (43%)	270 °C, τ = 7 min, *n*-hexane
25	 *rac*-**42** (5%)	 **43** (28%)	270 °C, τ = 7 min, *n*-hexane

*The setup of the flow-through system is shown in Scheme 3, and further details can be found in the Supporting Information. [a]The macrolactones and macrocyclic hydrocarbons were separated by preparative gas chromatography and analyzed separately (see the SI). [b]Lactones **32** and **34** are known natural compounds isolated from the oil of angelica root (*A. officinalis* Hoffm.) in addition to **4**[7]. [c]Mixture of diastereoisomers in a 3:1 ratio formed.

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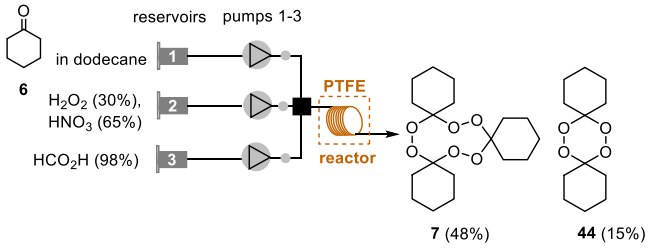
Scheme 4. Flow-Setup for the Oxidation of Cyclohexanone (6) to Cyclohexanone Triperoxide (7)[a]



[a]bpr = back pressure regulator.

Table 2. Optimized Conditions for the Oxidation of Cyclohexanone (6) to Triperoxide 7 at rt (Reactor Volume = 50 mL, ⌀ = 1.6 mm: τ = 39 min)[12]

pump 1 *c*-hexanone/dodecane	pump 2 H_2O_2/HNO_3	pump 3 HCO_2H
0.93 mL/min	0.2 mL/min	0.17 mL/min
1.61 mol/L	8.4/2.0 mol/L	25.9 mol/L
1.0 equiv	1.1/0.3 equiv	2.9 equiv

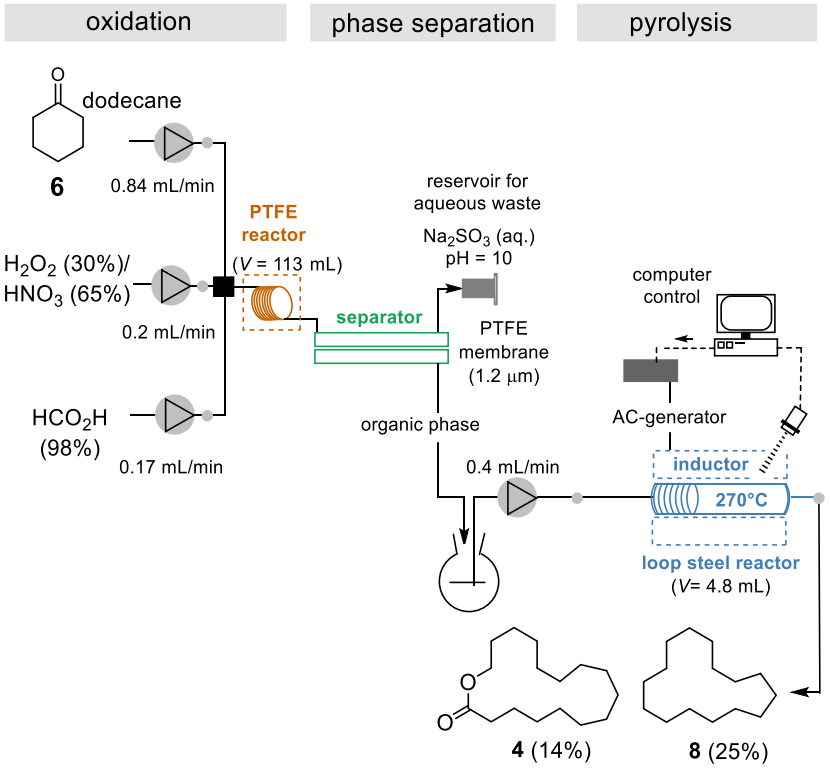
development and integration of an additional separation step into the flow system (Scheme 5). The aqueous phase containing hydrogen peroxide had to be removed from the product phase at the exit of reactor 1 to avoid exposing excess H_2O_2 to pyrolytic conditions in reactor 2. For that membrane separators consisting of two stainless steel plates containing a hydrophobic PTFE membrane with different pore sizes (0.1 μm, 0.2 μm, 0.45 μm, 1.2 and 5 μm) were investigated.[23] A pore size of 1.2 μm proved to be the most suitable for combining the two chemical processes. This separator could be operated continuously up to a flow rate of 5 mL/min.

The organic phase leaving the separator was collected in a flask, from where the reaction mixture was pumped without interruption directly into the stainless-steel reactor by another HPLC pump and subjected to pyrolysis by inductive heating. This setup allowed the whole process to be carried out more easily, since the second reaction is started under normal conditions and the two pressure regimes remain separate, so that the conditions of the first reaction cannot affect the second reaction.

Practically, the organic phase leaving the separator was collected in a flask and directly pumped via an HPLC pump into the stainless-steel loop reactor, which was inductively heated to 270 °C (high frequency IH: 500 kHz, 2.0 kWh). The initial oxidation was carried out in a PTFE-reactor (V = 113 mL, ⌀ = 2.4 mm) at room temperature. The residence time of the first step was 93 min, while the residence time of the second step was 12 min. Total yields over two steps were normalized to the additive eicosane by GC analysis (for **4**: 10%; for **8**: 25%). These yields are similar to the yields obtained under batch conditions (for **4**: 14%; for **8**: 23%).

Finally, GC-O (gas chromatography-olfactometry) odor analysis was performed with the aliphatic and lactonic macrocycles, which revealed that macrocyclic lactones with 16- and 17-membered ring sizes (**31**, **35**, **41**) exhibited strong muscone-like odors, while smaller as well as larger lactones, and all aliphatic macrocycles, showed only weakly pronounced or no olfactory effects.

Scheme 5. Flow Setup for Telescoping Oxidation−phase Separation−pyrolysis and Parameters for Pumps 1−3[a]



[a]Symbols for devices such as pumps are taken from Schemes 3 and 4.

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CONCLUSIONS

In summary, we have presented a three-step flow-through protocol (oxidation, separation, and pyrolysis under inductively heating conditions) for the production of macrocyclic 16-hexadecanolide (**4**) and cyclopentadecane (**8**) starting from cyclohexanone (**6**). The work demonstrates the performance of continuously operated processes with miniaturized flow-through devices when handling hazardous materials (in this case 30% H_2O_2 in 65% HNO_3) or under extreme conditions (>250 °C) for which the Story reaction is an illustrative example. In particular, large quantities and high concentrations of cyclohexane triperoxide (**7**) represent a potential safety hazard. The developed flow-through system avoids this potential hazard and enables the industrial application of this protocol. The work also shows that the fragrance industry can benefit from advanced flow chemistry, as it opens the doors to processes that are considered too unsafe in large-scale batch environments.[24]

EXPERIMENTAL SECTION

General Methods. Flash chromatography was performed using J. T. Baker silica gel (40−60 μm, 60 Å pores). Eluents used for flash chromatography were distilled before use. GC/MS analyses were performed on an Agilent 7890B GC with 5977B GC/MSD and Gerstel MPS Robotic XL with KAS 4C injector. An Optima 5HT column (30 m × 250 μm i.d. × 0.25 μm film thickness) was used for this purpose. Preparative GC (pGC) was performed using a nonpolar ZB-1 column (Phenomenex, 30 m × 0.53 mm i.d. × 3 μm film thickness) on an HP 6890 chromatograph with HP 7683 autosampler and hot injection. The products were isolated over a Gerstel PFC. The temperature program was modified for each individual isolation. **CAUTION:** Despite the fact that we found the procedures reported to be safe we stress that all discussed peroxides are considered to be shock sensitive if not handled properly. Precautions should be taken.

Components of Flow System. Solvent or reaction mixture pumping was performed using the HPLC pumps HPLC PUMP K-501, K-1001, Smartline Pump 100 and Azura P 4.1S (Knauer). Steel capillaries with 1/16″ outer diameter and 1.0 or 0.5 mm inner diameter made of stainless steel 316 from Techlab GmbH were employed in the systems. PTFE-tubing with 1.6 mm inner diameter from Bohlender GmbH was used in room pressured areas. Triperoxides were injected to the pressurized system via a Rheodyne 6-way valve from IDEX Corporation.

The temperature of the inductively heated system was measured with a digital IR pyrometer CTLLTCF3 with laser light tag from Optris GmbH. Pyrolysis in the range between 180 and 330 °C was realized via inductive heating. The high frequency generator HU 2000+ and the compatible inductor were acquired from Himmelwerk. Both devices are water cooled and allow a maximum power output of 2.0 kW. Power output is adjustable between 5 and 100% in 0.1% steps. Computer-assisted reaction control was done with LabView 2014 (14.0 32-bit) from National Instruments. Steel reactors and fittings made of stainless steel 316 were purchased from Swagelok. For pressure regulation in-line back pressure modules BPR Assembly from Upchurch Scientific with cartridges 100 psi (6.89 bar) were used.

The flow setups are graphically represented in Schemes 3−5, and a photograph can be found in the Supporting Information.

The Design of Experiment was performed using the commercial software Design-Expert (STAT-EASE). The variables specified were temperature (180−321 °C) and flow rate (0.1−1.15 mL/min). An experimental design was generated by the program using a Central Composite Design (CCD). The experiments were performed in the specified order of the experimental design and the data were analyzed using the response surface method (RSM) to determine a functional relationship between the influencing variables and the yields of the macrocycles.

General Information on the Synthesis under Flow Conditions. Cyclohexanone triperoxide (**7**) was continuously generated via an experimental setup consisting of three HPLC pumps (pump I: formic acid, pump II: H_2O_2/HNO_3 solution, pump III: cyclohexanone (**6**) in dodecane) which after a short section of tubing (PTFE) was mixed in a 4-port connector. The resulting mixture was then pumped through a PTFE reactor (V = 50 mL). The biphasic mixture was separated at the outlet of the reactor via a membrane reactor with PTFE membrane (pore size: 1.2 μm). Product formation was monitored by GC analysis of the organic phase.

For the telescoped process, the organic phase from the oxidation step, which contained cyclohexanone triperoxide (**7**) in dodecane, was collected in a flask and continuously pumped from there into a stainless-steel loop reactor (1/8″ outer diameter, V = 4.8 mL), which was inductively heated, using a fourth HPLC pump. The reaction mixture was collected at the outlet of the reactor and analyzed by GC or purified via pGC. The batch synthesis of homotrimers **7** and **12**−**14**, was achieved according to the method described by Ledaal.[25,26] This protocol actually reports the synthesis of dimers, although trimers are usually obtained by this method too. The heterotrimers **20**−**25** were prepared according to the literature.[14a] Among them, mixed triperoxides **22**−**25** are unknown. The synthesis of known dimers **17**−**19** is reported in ref 14.

*Syntheses of Peroxides **7**, **12**−**14**, and **17**−**19**. Cyclohexanone triperoxide (**7**).* A 30% hydrogen peroxide solution (1.0 mL, 9.98 mmol, 1.0 equiv) was slowly added to a mixture of cyclohexanone (1.0 mL, 9.98 mmol, 1.0 equiv) in acetonitrile (10 mL). Two drops of perchloric acid were added, and the reaction mixture was stirred for 15 min at room temperature and then left open in the fume hood. After 24 h, the resulting crude product was filtered, washed with water, and dried in vacuo. Cyclohexanone triperoxide (0.94 g, 2.79 mmol) was obtained as colorless crystals in 83% yield. ^{1}H NMR (400 MHz, $CDCl_3$, $CHCl_3$ = 7.26 ppm): δ = 1.88−1.73 (m, 12 H), 1.64−1.39 (m, 18 H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, $CDCl_3$ = 77.16 ppm): δ = 107.8, 30.8, 25.7, 22.9 ppm. HRMS (ESI) m/z calcd for $C_{18}H_{30}O_6Na$ $[M + Na]^+$ 365.1940, found: 365.1940. Mp: 90−91 °C.

*Cyclopentanone Triperoxide (**12**).* A 30% hydrogen peroxide solution (450 μL, 5.08 mmol, 1.0 equiv) was added slowly to a mixture of cyclopentanone (450 μL, 4.49 mmol, 0.9 equiv) in acetonitrile (10 mL). One drop of concd perchloric acid was added, and the reaction mixture was stirred at room temperature for 16 h and then left open in the fume hood. After several days, the resulting crude product was filtered, washed with water, and dried in vacuo. Cyclopentanone triperoxide (301 mg, 1.0 mmol) was obtained as colorless crystals in 59% yield. ^{1}H NMR (400 MHz, $CDCl_3$, $CHCl_3$ = 7.26 ppm): δ = 2.45−2.16 (m, 6 H), 1.82−1.61 (m, 18 H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, $CDCl_3$ = 77.16 ppm): δ = 119.4, 33.6, 24.7 ppm. HRMS (ESI) m/z calcd for $C_{15}H_{24}O_6Na$ $[M + Na]^+$ 323.1471, found: 323.1472. Mp: 171−172 °C.

*Cycloheptanone Triperoxide (**13**).* A 30% hydrogen peroxide solution (1.0 mL, 10.0 mmol, 1.0 equiv) was added slowly to a mixture of cycloheptanone (1.18 mL, 10.0 mmol, 1.0 equiv) in acetonitrile (10 mL). Two drops of concd perchloric acid were added, and the reaction mixture was stirred at room temperature for 16 h and then left open in the fume hood. After several days, the resulting crude product was filtered, washed with water, and recrystallized in methanol. After drying in vacuo, cycloheptanone triperoxide (250 mg, 0.65 mmol) was obtained as a solid material in 20% yield. ^{1}H NMR (400 MHz, $CDCl_3$, $CHCl_3$ = 7.26 ppm): δ = 2.22−2.10 (m, 6 H), 1.72−1.38 (m, 30 H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, $CDCl_3$ = 77.16 ppm): δ = 112.9, 33.0, 30.2, 22.9 ppm. HRMS (ESI) m/z calcd for $C_{21}H_{36}O_6Na$ $[M + Na]^+$ 407.2410, found: 407.2413. Mp: 108−109 °C.

*4-Methylcyclohexanone Triperoxide (**14**).* A 30% hydrogen peroxide solution (490 μL, 4.80 mmol, 0.96 equiv) was added slowly to a mixture of 4-methylcyclohexanone (613 μL, 5.0 mmol, 1.0 equiv) in acetonitrile (10 mL). Under cooling in an ice bath, one drop of concd perchloric acid was added, and the reaction mixture was stirred at room temperature for 16 h and then left open in the fume hood.

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The resulting crude product was filtered, washed with water and recrystallized in methanol. After drying in vacuo, 4-methylcyclohexanone triperoxide (230 mg, 0.60 mmol) was obtained as solid material in 36% yield. ^{1}H NMR (400 MHz, $CDCl_3$, $CHCl_3$ = 7.26 ppm): δ = 2.29−2.10 (m, 6 H), 1.67−1.09 (m, 21 H), 0.94−0.90 (m, 9 H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, $CDCl_3$ = 77.16 ppm): δ = 107.9, 107.8, 107.7, 32.0, 31.9, 31.8, 31.7, 31.3, 31.2, 31.1, 31.1, 31.0, 30.9, 28.8, 28.7, 21.8, 21.7, 21.6 ppm. HRMS (ESI) m/z calcd for $C_{21}H_{36}O_6Na$ $[M + Na]^+$ 407.2410, found: 407.2412. Mp: 104−106 °C.

1,1′-Dihydroperoxydi(cyclopentyl)peroxide (17). To a mixture of cyclopentanone (860 μL, 9.70 mmol, 1.0 equiv) and water (1.5 mL) cooled to 0−5 °C was added a 30% hydrogen peroxide solution (3.0 mL, 29.4 mmol, 3.0 equiv) and concd hydrochloric acid (100 μL, 0.98 mmol, 0.1 equiv). The reaction mixture was stirred for 48 h at room temperature. The solid was filtered off, washed with distilled water, and dried under reduced pressure. Product **17** (764 mg, 3.26 mmol) was obtained as a colorless solid in 66% yield. ^{1}H NMR (400 MHz, $CDCl_3$, $CHCl_3$ = 7.26 ppm): δ = 9.93 (s, 2 H), 2.10−1.95 (m, 8 H), 1.80−1.73 (m, 8 H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, $CDCl_3$ = 77.16 ppm): δ = 122.7, 33.5, 24.7 ppm. HRMS (ESI) m/z calcd for $C_{10}H_{18}O_6Na$ $[M + Na]^+$ 257.1001, found: 257.0998. Mp: 63−65 °C.

1,1′-Dihydroperoxydi(cyclohexyl)peroxide (18). A mixture of cyclohexanone (2.1 mL, 20.3 mmol, 1.0 equiv) and water (2.0 mL) was added at 5 °C to a mixture of 30% hydrogen peroxide solution (6.2 mL, 29.4 mmol, 3.0 equiv) and concd sulfuric acid (100 μL, 60.8 mmol, 0.1 equiv). The reaction mixture was stirred for 1 h at a temperature of 5−10 °C. The solid was filtered off, mixed with distilled water, a saturated sodium hydrogen carbonate solution, and again distilled water, and then dried under reduced pressure. Product **18** (880 mg, 3.36 mmol) was obtained as a colorless solid in 33% yield. ^{1}H NMR (400 MHz, $CDCl_3$, $CHCl_3$ = 7.26 ppm): δ = 7.85 (s, 2 H), 1.85−1.81 (m, 8 H), 1.61−1.55 (m, 8 H), 1.49−1.43 (m, 4 H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, $CDCl_3$ = 77.16 ppm): δ = 110.6, 29.7, 25.5, 22.6 ppm. HRMS (ESI) m/z calcd for $C_{12}H_{22}O_6Na$ $[M + Na]^+$ 285.1314, found: 285.1314. Mp: 73−75 °C.

1,1′-Dihydroperoxydi(cycloheptyl)peroxide (19). Cycloheptanone (1.2 mL, 10 mmol, 1.0 equiv) was added to a mixture of 30% hydrogen peroxide solution (3.2 mL, 31.0 mmol, 3.0 equiv) and concd hydrochloric acid (720 μL, 7.99 mmol, 0.8 equiv) at a temperature of −8 °C. The reaction mixture was then stirred for 2 h at room temperature. The precipitate was filtered off, washed with distilled water, and dried under reduced pressure. A colorless solid was obtained as product **19** (990 mg, 3.10 mmol) in 68% yield. ^{1}H NMR (400 MHz, $CDCl_3$, $CHCl_3$ = 7.26 ppm): δ = 9.62 (s, 2 H), 2.00−1.98 (m, 8 H), 1.64−1.56 (m, 16 H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, $CDCl_3$ = 77.16 ppm): δ = 116.4, 33.1, 30.0, 22.9 ppm. HRMS (ESI) m/z calcd for $C_{14}H_{26}O_6Na$ $[M + Na]^+$ 313.1627, found: 313.1627. Mp: 69−72 °C.

Synthesis of Mixed Triperoxides 20−25. 6,7,13,14,21,22-Hexaoxatrispiro[4.2.4^8.2.5^{15}.2^5]docosane (20). 1,1′-Dihydroperoxydi(cyclopentyl)peroxide (**17**) (560 mg, 2.39 mmol, 1.0 equiv) and 1,1-dimethoxycyclohexane (473 μL, 3.10 mmol, 1.3 equiv) were dissolved in 2 mL of diethyl ether. Boron trifluoride etherate (60 μL, 0.48 mmol, 0.2 equiv) was added at a temperature of 0−5 °C. The reaction mixture was stirred for 16 h at room temperature, and then 30 mL of petroleum ether was added. The reaction mixture was washed with a 2% sodium hydroxide solution (20 mL), water (2 × 20 mL) at 40 °C and 50% aqueous methanol at 40 °C and dried over $MgSO_4$. After filtration, the solvent was evaporated, and the crude product was purified by column chromatography (PE/EE = 20:1). Triperoxide **20** (330 mg, 1.05 mmol) was obtained as solid material in 44% yield. ^{1}H NMR (400 MHz, $CDCl_3$, $CHCl_3$ = 7.26 ppm): δ = 2.26−2.16 (m, 4 H), 1.88−1.40 (m, 22 H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, $CDCl_3$ = 77.16 ppm): δ = 119.1, 108.5, 33.5, 30.8, 25.6, 24.7, 22.8 ppm. HRMS (ESI) m/z calcd for $C_{16}H_{26}O_6Na$ $[M + Na]^+$ 337.1627, found: 337.1624. Mp: 63−65 °C.

6,7,14,15,22,23-Hexaoxatrispiro[4.2.5^8.2.5^{16}.2^5]tricosane (21). 1,1′-Dihydroperoxydi(cyclohexyl)peroxide (**18**) (900 mg, 3.43 mmol, 1.0 equiv) and 1,1-dimethoxycyclopentane (620 μL, 4.46 mmol, 1.3 equiv) were dissolved in 3 mL of diethyl ether. Boron trifluoride etherate (130 μL, 1.03 mmol, 0.3 equiv) was added at 0−5 °C, and the reaction mixture was stirred for 16 h at room temperature. Then 30 mL of petroleum ether was added, and the mixture was washed with a 2% sodium hydroxide solution (20 mL), water (2 × 20 mL) at 40 °C, and 50% aqueous methanol at 40 °C and dried over $MgSO_4$. After filtration, the solvent was evaporated and the crude product was purified by column chromatography (PE/EE= 50:1). Heterotrimer **21** (752 mg, 2.29 mmol) was obtained as a solid material in 67% yield. ^{1}H NMR (400 MHz, $CDCl_3$, $CHCl_3$ = 7.26 ppm): δ = 2.24−2.17 (m, 2 H), 1.90−1.40 (m, 26 H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, $CDCl_3$ = 77.16 ppm): δ = 118.8, 108.1, 33.6, 30.8, 25.7, 24.7, 22.9 ppm. HRMS (ESI) m/z calcd for $C_{17}H_{28}O_6Na$ $[M + Na]^+$ 351.1784, found: 351.1798. Mp: 64−65 °C.

7,8,16,7,25,26-Hexaoxatrispiro[5.2.6^9.2.6^{18}.2^6]hexacosane (22). 1,1′-Dihydroperoxydi(cycloheptyl)peroxide (**19**) (800 mg, 2.76 mmol, 1.0 equiv) and 1,1-dimethoxycyclohexane(550 μL, 3.59 mmol, 1.3 equiv) were dissolved in 3 mL of diethyl ether. Boron trifluoride etherate (100 μL, 0.83 mmol, 0.3 equiv) was added, and the reaction mixture was stirred for 16 h at room temperature. Then 30 mL of petroleum ether was added, and the mixture was washed with a 2% sodium hydroxide solution (20 mL), water (2 × 20 mL) at 40 °C and 50% aqueous methanol at 40 °C and dried over $MgSO_4$. The solvent was removed, and the crude product purified by column chromatography (PE/EE= 90:1). Heterotrimer **22** (360 mg, 0.97 mmol) was obtained as solid material in 35% yield. ^{1}H NMR (600 MHz, $CDCl_3$, $CHCl_3$ = 7.26 ppm): δ = 2.20−2.12 (m, 4 H), 1.70−1.41 (m, 30 H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, $CDCl_3$ = 77.16 ppm): δ = 112.9, 107.8, 33.0, 32.9, 30.8, 30.2, 25.7, 22.9 ppm. HRMS (ESI) m/z calcd for $C_{20}H_{34}O_6Na$ $[M + Na]^+$ 393.2253, found: 393.2268. Mp: 79−82 °C.

18-Methyl-6,7,13,14,21,22-hexaoxatrispiro[4.2.4^8.2.5^{15}.2^5] docosane (23). 1,1′-Dihydroperoxydi(cyclopentyl)peroxide (**17**) (700 mg, 2.98 mmol, 1.0 equiv) and 1,1-dimethoxy-4-methylcyclohexane **16** (680 μL, 3.88 mmol, 1.3 equiv) were dissolved in 3 mL of diethyl ether. Boron trifluoride etherate (130 μL, 1.03 mmol, 0.3 equiv) was added, and the reaction mixture was stirred for 16 h at room temperature. Then 30 mL of petroleum ether was added, and the mixture was washed with a 2% sodium hydroxide solution (20 mL), water (2 × 20 mL) at 40 °C, and 50% aqueous methanol at 40 °C and dried over $MgSO_4$. The solvent was evaporated, and the crude product purified by column chromatography (PE/EE = 50:1). Heterotrimer **23** (752 mg, 2.29 mmol) was obtained as a colorless oil in 64% yield. ^{1}H NMR (400 MHz, $CDCl_3$, $CHCl_3$ = 7.26 ppm): δ = 2.27−2.15 (m, 4 H), 1.74−1.12 (m, 21 H), 0.94−0.90 (m, 3 H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, $CDCl_3$ = 77.16 ppm): δ = 119.2, 108.4, 33.6, 31.8, 31.2, 30.9, 28.7, 24.7, 21.7 ppm. HRMS (ESI) m/z calcd for $C_{17}H_{28}O_6Na$ $[M + Na]^+$ 351.1784, found: 351.1809.

3-Methyl-7,8,15,16,23,24-hexaoxatrispiro[5.2.5^9.2.5^{17}.2^6]-tetracosane (24). 1,1′-Dihydroperoxydi(cyclohexyl)peroxide (**18**) (813 mg, 3.10 mmol, 1.0 equiv) and 1,1-dimethoxy-4-methylcyclohexane **16** (700 μL, 4.03 mmol, 1.3 equiv) were dissolved in 3 mL of diethyl ether. Boron trifluoride etherate (120 μL, 0.92 mmol, 0.3 equiv) was added, and the reaction mixture was stirred for 16 h at room temperature. Then 30 mL of petroleum ether was added, and the mixture was washed with a 2% sodium hydroxide solution (20 mL) and water (2 × 20 mL) at 40 °C and 50% aqueous methanol at 40 °C and dried over $MgSO_4$. The solvent was evaporated, and the crude product purified by column chromatography (PE/EE = 90:1). Heterotrimer **24** (734 mg, 2.06 mmol) was obtained as colorless oil in 66% yield. ^{1}H NMR (400 MHz, $CDCl_3$, $CHCl_3$ = 7.26 ppm): δ = 2.27−2.11 (m, 2 H), 1.91−1.12 (m, 27 H), 0.93−0.90 (m, 3 H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, $CDCl_3$ = 77.16 ppm) δ = 107.9, 107.8, 31.9, 31.9, 31.3, 31.0, 30.9, 30.8, 30.7, 30.7, 28.7, 25.7, 22.9, 21.7 ppm. HRMS (ESI) m/z calcd for $C_{19}H_{32}O_6Na$ $[M + Na]^+$ 379.2097, found: 379.2112.

3-Methyl-7,8,16,17,25,26-hexaoxatrispiro[5.2.6^9.2.6^{18}.2^6] hexacosane (25). 1,1′-Dihydroperoxydi(cycloheptyl)peroxide (**19**) (580 mg, 2.0 mmol, 1.0 equiv) and 1,1-dimethoxy-4-methylcyclohexane **16**

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(452 μL, 2.60 mmol, 1.3 equiv) were dissolved in 2 mL of diethyl ether. Boron trifluoride etherate (76 μL, 0.60 mmol, 0.3 equiv) was added and the reaction mixture was stirred for 16 h at room temperature. Then 30 mL of petroleum ether was added, and the mixture was washed with a 2% sodium hydroxide solution (20 mL) and water (2 × 20 mL) at 40 °C and 50% aqueous methanol at 40 °C and dried over $MgSO_4$. The solvent was evaporated, and the crude product purified by column chromatography (PE/EE= 90:1). Heterotrimer **25** (482 mg, 1.25 mmol) was obtained as solid material in 62% yield. ^{1}H NMR (400 MHz, $CDCl_3$, $CHCl_3$ = 7.26 ppm): δ = 2.22−2.11 (m, 6 H), 1.69−1.30 (m, 27 H), 0.93−0.82 (m, 3 H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, $CDCl_3$ = 77.16 ppm): δ = 113.1, 112.8, 107.7, 33.1, 33.0, 32.9, 32.7, 31.9, 31.3, 31.0, 30.3, 30.3, 30.2, 28.7, 23.0, 22.9, 21.7 ppm. HRMS (ESI) m/z calcd for $C_{21}H_{36}O_6Na$ $[M + Na]^+$ 407.2410, found: 407.2414. Mp: 75−80 °C.

*Pyrolysis of Triperoxides under Flow Conditions. Oxacycloheptadecan-2-one (**4**) and Cyclopentadecane (**8**).* Synthesis under flow conditions: Cyclohexanone triperoxide (**7**) (25.0 mg, 0.07 mmol) and an internal standard were dissolved in 3.5 mL of dodecane and injected via a sample loop into the system. From there, the mixture was pumped into a 1/8′′-loop reactor (ss, V = 4.8 mL). The reactor was heated inductively to 250 °C, and the reaction mixture was analyzed by GC using eicosane as internal standard for determining the yield. Both products are commercially available.

*Oxacyclotetradecan-2-one (**26**)[27] and Cyclododecane (**27**).[28]* Synthesis under flow conditions: Cyclopentanone triperoxide (**12**) (127 mg, 0.42 mmol) was dissolved in 16 mL of a hexane/MTBE mixture. The mixture was injected via a sample loop into the main stream through a 1/8′′-loop reactor (ss, V = 4.8 mL) with hexane and a flow rate of 0.69 mL/min. The reactor was inductively heated to 270 °C. The reaction mixture was collected and the solvent was removed under reduced pressure. The isolation of the two main products was achieved by preparative gas chromatography. **26**: ^{1}H NMR (400 MHz, $CDCl_3$, $CHCl_3$ = 7.26 ppm): δ = 4.15 (t, J = 5.3 Hz, 2 H), 2.38 (t, J = 6.3 Hz, 2 H), 1.65 (q, 4 H), 1.44−1.25 (m, 16 H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, $CDCl_3$ = 77.16 ppm): δ = 174.1, 63.4, 34.5, 27.8, 26.4, 26.2, 26.0, 25.8, 24.9, 24.8, 24.2, 23.9, 23.8, 22.9 ppm. HRMS (EI) m/z calcd for $C_{13}H_{24}O_2$ 212.1776, found: 212.1773. **27**: ^{1}H NMR (400 MHz, $CDCl_3$, $CHCl_3$ = 7.26 ppm): δ = 1.34 (br s, 24 H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, $CDCl_3$ = 77.16 ppm): δ = 23.8 ppm. HRMS (EI) m/z calcd for $C_{12}H_{24}$ 168.1878, found: 168.1878.

*Oxacycloicosan-2-one (**28**)[29] and Cyclooctadecane (**29**).[28]* Synthesis under flow conditions: Cycloheptanone triperoxide (**13**) (102 mg, 0.27 mmol) was dissolved in 14 mL of a hexane/MTBE mixture. The mixture was injected via a sample loop into the main stream through a 1/8′′-loop reactor (ss, V = 4.8 mL) with hexane and a flow rate of 1.10 mL/min. The reactor was inductively heated to 281 °C. The reaction mixture was collected and the solvent was removed under reduced pressure. The isolation of the two main products was achieved by preparative gas chromatography. **28**: ^{1}H NMR (400 MHz, $CDCl_3$, $CHCl_3$ = 7.26 ppm): δ = 4.10 (t, J = 5.9 Hz, 2 H), 2.31 (t, J = 7.2 Hz, 2 H), 1.68−1.59 (m, 4 H), 1.40−1.25 (m, 28 H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, $CDCl_3$ = 77.16 ppm): δ = 174.2, 64.4, 34.8, 28.8, 28.7, 28.7, 28.6, 28.6, 28.4, 28.2, 28.0, 28.0, 27.8, 27.5, 27.4, 27.3, 27.3, 25.9, 25.2 ppm. HRMS (EI) m/z calcd for $C_{19}H_{36}O_2$ 296.2715, found: 296.2711. **29**: ^{1}H NMR (400 MHz, $CDCl_3$, $CHCl_3$ = 7.26 ppm): δ = 1.30 (br s, 36 H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, $CDCl_3$ = 77.16 ppm): δ = 27.5 ppm. HRMS (EI) m/z calcd for $C_{18}H_{36}$ 252.2814, found: 252.2814.

*rac-5,10,15-Trimethyloxacycloheptadecan-2-one (**30**) and 1,6,11-Trimethylcyclopentadecan (**31**).* Synthesis under flow conditions: 4-Methylcyclohexanone triperoxide (**14**) (140 mg, 0.36 mmol) was dissolved in 14 mL of MTBE. The mixture was injected via a sample loop into the main stream through a 1/8′′-loop reactor (ss, V = 4.8 mL) with hexane and a flow rate of 0.68 mL/min. The reactor was inductively heated to 300 °C. The reaction mixture was collected, and the solvent was removed under reduced pressure. The isolation of the two main products was achieved by preparative gas chromatography. **30**: ^{1}H NMR (400 MHz, $CDCl_3$, $CHCl_3$ = 7.26 ppm): δ = 4.26−4.02 (m, 2 H), 2.42−2.21 (m, 2 H), 1.71−1.03 (m, 23 H), 0.92−0.82 (m, 9 H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, $CDCl_3$ = 77.16 ppm) δ = 174.4−174.3, 62.6, 62.5, 62.4, 36.1−35.9, 34.9−34.8, 32.6−32.4, 32.0−31.7, 31.5−31.0, 26.4−26.0, 25.6−25.3, 21.3-21.1, 20.2−19.9 ppm. HRMS (EI) m/z calcd for $C_{19}H_{36}O_2$ 296.2715, found: 296.2713. **31**: ^{1}H NMR (400 MHz, $CDCl_3$, $CHCl_3$ = 7.26 ppm): δ = 1.53−1.16 (m, 24 H), 1.13−0.94 (m, 3 H), 0.85 (d, J = 6.6 Hz, 9 H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, $CDCl_3$ = 77.16 ppm): δ = 35.4−34.1, 30.9−30.3, 25.8−24.8, 21.2−20.9 ppm. HRMS (EI) m/z calcd for $C_{18}H_{36}$ 252.2817, found: 252.2815.

*Oxacyclopentadecan-2-one (**32**) and Cyclotridecane (**33**).[28]* Synthesis under flow conditions: Triperoxide **20** (128 mg, 0.41 mmol) was dissolved in 14 mL of hexane. The mixture was injected via a sample loop into the main stream through a 1/8′′-loop reactor (ss, V = 4.8 mL) with hexane and a flow rate of 0.70 mL/min. The reactor was inductively heated to 270 °C. The reaction mixture was collected and the solvent was removed under reduced pressure. The isolation of the two main products was achieved by preparative gas chromatography. **32**: ^{1}H NMR (400 MHz, $CDCl_3$, $CHCl_3$ = 7.26 ppm): δ = 4.15−4.12 (m, 2 H), 2.37−2.33 (m, 2 H), 1.71−1.62 (m, 4 H), 1.41−1.25 (m, 18 H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, $CDCl_3$ = 77.16 ppm): δ = 174.5, 64.2, 34.3, 28.5, 28.0, 26.9, 26.9, 26.7, 26.7, 26.6, 26.2, 25.4, 25.1, 25.0 ppm. HRMS (EI) m/z calcd for $C_{14}H_{26}O_2$ 226.1933, found: 226.1932. **33**: ^{1}H NMR (400 MHz, $CDCl_3$, $CHCl_3$ = 7.26 ppm): δ = 1.34 (br s, 26 H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, $CDCl_3$ = 77.16 ppm): δ = 26.2 ppm. HRMS (EI) m/z calcd for $C_{13}H_{26}$ 182.2035, found: 182.2034.

*Oxacyclohexadecan-2-one (**34**)[30] and Cyclotetradecane (**35**).[28]* Synthesis under flow conditions: Triperoxide **21** (161 mg, 0.49 mmol) was dissolved in 14 mL of hexane. The mixture was injected via a sample loop into the main stream through a 1/8′′-loop reactor (ss, V = 4.8 mL) with hexane and a flow rate of 0.70 mL/min. The reactor was inductively heated to 270 °C. The reaction mixture was collected, and the solvent was removed under reduced pressure. The isolation of the two main products was achieved by preparative gas chromatography. **34**: ^{1}H NMR (600 MHz, $CDCl_3$, $CHCl_3$ = 7.26 ppm): δ = 4.13 (t, J = 5.4 Hz, 2 H), 2.33 (t, J = 6.5 Hz, 2 H), 1.69−1.60 (m, 4 H), 1.44−1.26 (m, 20 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, $CDCl_3$ = 77.16 ppm) δ = 174.2, 64.1, 34.6, 28.5, 27.9, 27.3, 27.3, 27.1, 26.8, 26.5, 26.2, 26.1, 26.0, 25.3, 25.1 ppm. HRMS (EI) m/z calcd for $C_{15}H_{28}O_2$ 240.2089, found: 240.2085. **35**: ^{1}H NMR (400 MHz, $CDCl_3$, $CHCl_3$ = 7.26 ppm) δ = 1.32 (br s, 28 H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, $CDCl_3$ = 77.16 ppm): δ = 25.2 ppm. HRMS (EI) m/z calcd for $C_{14}H_{28}$ 196.2191, found: 196.2196.

*Oxacyclononadecan-2-one (**36**)[31] and Cycloheptadecane (**37**).[32]* Synthesis under flow conditions: Triperoxide 22 (127 mg, 0.34 mmol) was dissolved in 14 mL hexane. The mixture was injected via a sample loop into the main stream through a 1/8′′-loop reactor (ss, V = 4.8 mL) with hexane and a flow rate of 0.70 mL/min. The reactor was inductively heated to 270 °C. The reaction mixture was collected and the solvent was removed under reduced pressure. The isolation of the two main products was achieved by preparative gas chromatography. **36**: ^{1}H NMR (600 MHz, $CDCl_3$, $CHCl_3$ = 7.26 ppm): δ = 4.11 (t, J = 5.6 Hz, 2 H), 2.32 (t, J = 6.8 Hz, 2 H), 1.67−1.60 (m, 4 H), 1.31 (br s, 26 H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, $CDCl_3$ = 77.16 ppm) δ = 174.3, 64.5, 34.8, 28.8, 28.8, 28.8, 28.7, 28.7, 28.5, 27.9, 27.9, 27.8, 27.7, 27.7, 27.7, 27.6, 27.5, 26.9, 25.9, 25.2; HRMS (EI) m/z calcd for $C_{18}H_{34}O_2$ 282.2559, found: 282.2563. **37**: ^{1}H NMR (400 MHz, $CDCl_3$, $CHCl_3$ = 7.26 ppm): δ = 1.31 (br s, 34 H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, $CDCl_3$ = 77.16 ppm): δ = 27.7 ppm. HRMS (EI) m/z calcd for $C_{17}H_{34}$ 238.2661, found: 238.2666.

*rac-Methyloxacyclopentadecan-2-one (**38**) and Methylcyclotridecane (**39**).* Synthesis under flow conditions: Triperoxide **23** (150 mg, 0.46 mmol) was dissolved in 14 mL of hexane. The mixture was injected via a sample loop into the main stream through a 1/8′′-loop reactor (ss, V = 4.8 mL) with hexane and a flow rate of 0.70 mL/min. The reactor was inductively heated to 270 °C. The reaction mixture was collected, and the solvent was removed under reduced pressure. The isolation of the two main products was realized by preparative gas

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chromatography. **38**: ^{1}H NMR (400 MHz, $CDCl_3$, $CHCl_3$ = 7.26 ppm): δ = 4.26−4.00 (m, 2 H), 2.46−2.26 (m, 2 H), 1.75−1.56 (m, 4 H), 1.52−0.96 (m, 17 H), [0.90 (d, J = 6.5 Hz, 3 d), 0.88 (d, J = 6.5 Hz, 3 H), 0.85 (d, J = 6.5 Hz, 3 H), 0.84 (d, J = 6.6 Hz, 3 H), 0.82 (d, J = 6.6 Hz, 3 H)] ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, $CDCl_3$ = 77.16 ppm): δ = 174.5, 174.4, 174.4, 64.2, 64.1, 62.5, 36.4, 35.5, 35.2, 35.1, 34.9, 34.3, 34.2, 34.1, 33.9, 33.8, 33.7, 32.5, 32.2, 31.2, 31.1, 30.8, 30.5, 28.5, 28.3, 28.2, 28.0, 27.8, 27.7, 27.1, 27.0, 27.0, 26.8, 26.5, 26.5, 26.4, 26.3, 25.9, 25.9, 25.7, 25.6, 25.5, 25.3, 25.1, 24.9, 24.9, 24.8, 24.8, 24.7, 21.1, 20.1, 19.8, 19.8 ppm. HRMS (EI) m/z calcd for $C_{15}H_{28}O_2$ 240.2089, found: 240.2083. **39**: ^{1}H NMR (400 MHz, $CDCl_3$, $CHCl_3$ = 7.26 ppm): δ = 1.53−1.11 (m, 25 H), 0.85 (d, J = 6.5 Hz, 3 H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, $CDCl_3$ = 77.16 ppm): δ = 34.3, 30.6, 26.7, 26.2, 26.0, 24.4, 21.4 ppm. HRMS (EI) m/z calcd for $C_{14}H_{28}$ 196.2191, found: 196.2189.

*rac-Methyloxacycloheptadecan-2-one (**40**) and Methylcyclopentadecane (**41**).* Synthesis under flow conditions: Triperoxide **24** (160 mg, 0.45 mmol) was dissolved in 14 mL of hexane. The mixture was injected via a sample loop into the main stream through a 1/8″-loop reactor (ss, V = 4.8 mL) with hexane and a flow rate of 0.70 mL/min. The reactor was inductively heated to 270 °C. The reaction mixture was collected, and the solvent was removed under reduced pressure. The isolation of the two main products was achieved by preparative gas chromatography. **40**: ^{1}H NMR (600 MHz, $CDCl_3$, $CHCl_3$ = 7.26 ppm): δ = 4.23−4.07 (m, 2 H), 2.41−2.24 (m, 2 H), 1.71−1.59 (m, 4 H), 1.50−1.12 (m, 21 H), [0.90 (d, J = 6.8 Hz, 3 H), 0.89 (d, J = 6.5 Hz, 3 H), 0.86 (d, J = 6.7 Hz, 3 H), 0.85 (d, J = 6.9 Hz, 3 H)] ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, $CDCl_3$ = 77.16 ppm): δ = 174.4, 174.3, 174.2, 64.6, 64.5, 62.5, 35.9, 35.8, 35.6, 35.0, 34.9, 34.7, 32.5, 31.7, 31.6, 31.4, 28.9, 28.6, 28.5, 28.4, 28.3, 28.1, 28.0, 27.8, 27.7, 27.6, 27.4, 27.3, 27.2, 27.2, 27.1, 27.0, 26.9, 25.9, 25.8, 25.7, 25.4, 25.3, 25.2, 25.0, 24.9, 21.5, 19.9, 19.8 ppm. HRMS (EI) m/z calcd for $C_{17}H_{32}O_2$ 268.2402, found: 268.2403. **41**: ^{1}H NMR (400 MHz, $CDCl_3$, $CHCl_3$ = 7.26 ppm): δ = 1.53−1.10 (m, 29 H), 0.85 (d, J = 6.7 Hz, 3 H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, $CDCl_3$ = 77.16 ppm): δ = 34.9, 30.9, 27.5, 27.1, 27.0, 26.8, 24.9, 21.2 ppm. HRMS (EI) m/z calcd for $C_{16}H_{32}$ 224.2504, found: 224.2509.

*rac-Methyloxacyclononadecan-2-one (**42**) and Methylcycloheptadecane(**43**).* Synthesis under flow conditions: Triperoxide **25** (150 mg, 0.39 mmol) was dissolved in 14 mL of hexane. The mixture was injected via a sample loop into the main stream through a 1/8″-loop reactor (ss, V = 4.8 mL) with hexane and a flow rate of 0.70 mL/min. The reactor was inductively heated to 270 °C. The reaction mixture was collected and the solvent was removed under reduced pressure. The isolation of the two main products was achieved by preparative gas chromatography. **42**: ^{1}H NMR (600 MHz, $CDCl_3$, $CHCl_3$ = 7.26 ppm): δ = 4.21−4.06 (m, 2 H), 2.40−2.21 (m, 2 H), 1.70−1.58 (m, 4 H), 1.51−1.09 (m, 24 H), [0.90 (d, J = 6.4 Hz, 3 H), 0.88 (d, J = 6.6 Hz, 3 H), 0.83 (d, J = 6.3 Hz, 3 H)] ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, $CDCl_3$ = 77.16 ppm): δ = 174.4, 174.3, 174.2, 64.5, 64.4, 62.6, 36.5, 36.2, 35.6, 35.4, 35.2, 35.1, 34.8, 34.7, 32.5, 32.1, 32.0, 31.8, 30.0, 29.9, 29.8, 29.5, 29.2, 28.9−28.5, 28.3−28.0, 27.8−27.6, 26.3, 26.0, 25.9, 25.8, 25.5, 25.2, 25.0, 20.5, 19.9 ppm. HRMS (EI) m/z calcd for $C_{19}H_{36}O_2$ 296.2715, found: 296.2720. **43**: ^{1}H NMR (400 MHz, $CDCl_3$, $CHCl_3$ = 7.26 ppm): δ = 1.31 (br s, 33 H), 0.85 (d, J = 6.7 Hz, 3 H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, $CDCl_3$ = 77.16 ppm): δ = 35.4, 31.4, 28.3, 28.0, 27.7, 27.4, 25.5, 21.0 ppm. HRMS (EI) m/z calcd for $C_{18}H_{36}$ 252.2817, found: 252.2812.

Telescoped Synthesis for Oxacycloheptadecan-2-one (4) and Cyclopentadecane (8). *Long-Term Experiment.* Cyclohexanone triperoxide (7) was continuously generated via an experimental setup consisting of three HPLC pumps (pump I: formic acid, 0.17 mL/min, 25.9 mol/L, 2.7 equiv; pump II: H_2O_2 (30%)/HNO_3 (65%) solution, 8.4 mol/L/0.2 mol/L, 1.0 equiv/0.2 equiv; pump III: cyclohexanone in dodecane, 0.84 mL/min, 1.94 mol/L, 1.0 equiv) which after a short section of tubing (PTFE) was mixed in a 4-port connector. The resulting mixture was then pumped through a PTFE reactor (V = 113 mL, 2.4 mm, τ = 93 min). The biphasic mixture was separated at the outlet of the reactor via a membrane reactor with PTFE membrane (pore size: 1.2 μm). The organic phase from the oxidation step, which contained cyclohexanone triperoxide (7) in dodecane, was collected in a flask and without interruption continuously pumped via an HPLC-pump (0.4 mL/min) into a stainless-steel loop reactor (1/8″ outer diameter, V = 4.8 mL, τ = 12 min), which was inductively heated to 270 °C. The reaction mixture was collected at the outlet of the reactor and analyzed by GC. Yields of the commercial products were calculated using eicosane as internal standard (cyclohexanone triperoxide (7): 30%, cyclohexanone diperoxide: 10%, oxacycloheptadecan-2-one (4): 10%, cyclopentadecane (8): 19%). The synthesis was performed continuously over a period of 4 h.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00663.

Flow setup, the Design of Experiment (DoE), and covers copies of ^{1}H- and ^{13}C{^{1}H}-NMR spectra (PDF)

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Author Contributions

A.K. supervised the research. A.S. developed the complete flow process, while J.P. was responsible for evaluating the suitability of the protocol for the development of an industrial process which also included safety issues. A.K., A.S., and J.P. wrote the paper.

Notes

The authors declare no competing financial interest.

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