Synthesis and Characterization of Arsenolipids: Naturally Occurring Arsenic Compounds in Fish and Algae

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ABSTRACT: Arsenic-containing lipids (arsenolipids) are natural products present in fish and algae. Because these compounds occur in foods, there is considerable interest in their human toxicology. We report the synthesis and characterization of seven arsenic-containing lipids, including six natural products. The compounds comprise dimethylarsinyl groups attached to saturated long-chain hydrocarbons (three compounds), saturated long-chain fatty acids (two compounds), and monounsaturated long chain fatty acids (two compounds). The arsenic group was introduced through sodium dimethylarsenide or bis(dimethylarsenic) oxide. The latter route provided higher and more reproducible yields, and consequently, this pathway was followed to synthesize six of the seven compounds. Mass spectral properties are described to assist in the identification of these compounds in natural samples. The pure synthesized arsenolipids will be used for in vitro experiments with human cells to test their uptake, biotransformation, and possible toxic effects.

INTRODUCTION

The presence of arsenic in lipid extracts of fish and algae was first reported in the late 1960s, but their structures remained unknown. Subsequent biochemical studies in 1978 showed that arsenic-containing lipids (arsenolipids) in unicellular algae comprised three main lipid types, and the same compounds were then reported in clam tissues as a consequence of an algal–clam symbiosis. Enzymatic studies with phospholipases demonstrated that two of the three lipid types were arsenic-containing phospholipids, but a tentative structure proposed for the polar arsenic-containing head group was later shown to be incorrect. Although it was clear that the third lipid type was not a phospholipid, no additional information could be gleaned from the biochemical experiments.

In 1988, the major arsenolipid in the brown macroalga Undaria pinnatifida was purified and its structure established as a phospholipid with an arsenosugar head group. This structure seemed to fit the properties of two of the three lipid types described in the biochemical studies, and was consistent with the earlier observation that arsenosugars were the major watersoluble arsenical constituents of algae. In 2008, arsenolipids that were not based on phospholipids were first reported in fish oils, which contained arsenic bound directly to either a long chain fatty acid or a hydrocarbon, matched the properties of those compounds in the third lipid type, which were not changed by treatment with phospholipases. Subsequent work by several independent groups has extended the number of arsenolipids to more than 40 compounds. The structures of the arsenolipids have been proposed primarily on the basis of mass spectrometric data, and brief synthetic details were reported for one of the compounds. These compounds appear to be unrelated to the unique (lipid-soluble) polycyclic arsenic compound identified in a sponge and recently synthesized.

Because arsenolipids can occur at high levels in edible fish, and they had been shown to be bioavailable to humans and to be extensively degraded to small arsenic species, interest has turned to the possible toxic properties of these lipids. To address the ensuing human health concerns, we have undertaken a project employing human cells to investigate the bioavailability, toxicity, and biotransformation of arsenolipids. To perform these experiments, sufficient material of a range of arsenolipids was required to study their biological activity. We report the synthetic approaches to seven arsenolipids, including six naturally occurring compounds that will undergo toxicological testing. Moreover, we present a mass spectrometric analysis of the compounds to facilitate their detection in natural samples.

RESULTS AND DISCUSSION

Synthesis of Arsenolipids. Synthetic schemes for several water-soluble arsenic-containing natural products have been reported. Trimethylated quaternary arsonium compounds have usually been prepared by nucleophilic substitution, whereby trimethylarsine is heated with a brominated substrate.

ABSTRACT:
The dimethylated arsinyl compounds (Me₂As(O)−), however, are commonly prepared using the reactive sodium dimethylarsenide on the basis of the method of Feltham et al. Although this procedure has been successfully applied to the synthesis of dimethylarsinylribosides, the reaction is difficult to monitor and often suffers from low and variable yields. Nevertheless, we tried this approach for the synthesis of compound 5 (Figure 1; As-HC 332), whereby reaction of the tosylate of pentadecanol with sodium dimethylarsenide produced the arsine, which was oxidized without purification to the desired compound obtained in 15% overall yield. The final cleanup step involved the novel use of Dowex 50 (a cation-exchange polymer)/MeOH and elution with an ammonia/MeOH mixture, which takes advantage of the cationic properties of the easily protonated Me₂AsO− group. Although this approach with dimethylarsenide (Scheme 1) was successful for As-HC 332 (14 methylenes), attempts to perform the nucleophilic substitution by Me₂AsNa on increasingly longer carbon-chain analogues produced progressively lower yields. Hence, an alternative approach was investigated.

The second synthetic approach (Scheme 1) involved the simple reaction of iododimethylarsine in concentrated NaOH to form bis(dimethylarsenic) oxide ((Me₂As)₂O) and then addition of the brominated compound. This procedure gave consistent yields of the desired arsenic product. The mixture was stirred and heated overnight and then cooled and washed with ether. The aqueous layer was neutralized (As-hydroxycarbons) or acidified (As-fatty acids), and the arsonolipids were extracted into chloroform and crystallized from ethyl acetate. In this way, the saturated arsenic-containing hydrocarbons 6 and 7 (As-HC 360 and As-HC 444) and the saturated arsenic-containing fatty acids 1 and 2 (As-FA 362 and As-FA 418) were prepared in yields ranging from 37 to 88%.

The syntheses of the unsaturated arsenic fatty acids were more complex. Our initial aim was to prepare compound 4 (As-HC 374) as a model compound because it presented an easier synthetic target than the natural product 3 (As-HC 388). Furthermore, because As-HC 374 is not a natural product but differs by only one methylene group from a significant natural product, it could serve as a useful internal standard for performing checks on the various analytical steps needed to determine arsenolipids in natural samples. Thus, treatment of aleuritic acid (9,10,16-trihydroxypalmitic acid) with HBr in acetic acid gave the tribrominated carboxylic acid, which was esterified and selectively debrominated (Zn/methanol) to give the monounsaturated ester. Treatment with (Me₂As)₂O in the usual way gave the desired arsenic-containing carboxylic acid (4, As-FA 374) in 32% overall yield (Scheme 2).

The procedure employed for As-FA 374, however, was not feasible for As-FA 388 (compound 3) because there was no equivalent readily available starting material. Instead, esterification of the trihydroxy carboxylic acid (Scheme 3) followed by treatment with sodium periodate gave the aldehyde. Treatment of 1,8-dibromooctane with PPh₃ gave the phosphonium salt, which was reacted with the aldehyde to give 17-bromo-9-heptadecenoic acid methyl ester. Introduction of the Me₂As(O) group in the usual way yielded the desired monounsaturated arsenic-containing fatty acid 3 (As-FA 388) in 11% overall yield.

**HPLC/ICPMS and Molecular Mass Spectral Characterization of Arsenolipids.** The recent advance in our knowledge of arsenolipids has been provided primarily by HPLC/mass spectrometry measurements. The general approach is first to obtain an “arsenic profile” of the sample by using HPLC coupled to an elemental mass spectrometer such as an inductively coupled plasma mass spectrometer (ICPMS) and a molecular mass profile of the intact molecules by using HPLC/electrospray mass spectrometry. Often, both HPLC profiles are obtained simultaneously from the same chromatographic run by splitting the effluent flow from the HPLC column between the two mass spectrometers. High-resolution mass spectrometry can also be used to provide molecular formulas with high precision, opening the possibility of assigning a structure which can then be confirmed by synthesis. The mass deficiency of arsenic is an advantage because when one arsenic atom is included in possible formulas, the range of likely candidates is restricted, and often there is only one plausible formula. In this way, arsenolipids have been identified in fish oil, fish liver, sashimi tuna fillets, and algae. To assist with future determinations of...
arsenolipids, we report here results from some HPLC/ICPMS and tandem mass spectrometry measurements performed with a high-resolution mass analyzer.

The general order of elution on reversed-phase HPLC of the three groups of arsenolipids is arsenic-containing fatty acids, arsenic-containing hydrocarbons, and arsenosugar phospholipids. Within each of these three groups, the compounds show increasing retention time with increasing C chain length and decreasing retention time with increasing number of double bonds (Figure 2).

High-resolution mass spectra of the synthesized compounds were recorded with external mass calibration of the mass spectrometer. The collision-induced fragmentation of the MH+ ions was recorded. Owing to the accuracy of the mass spectrometer, the compositions of fragments are easily determined; Table 1 summarizes fragmentation features, and spectra (MS and MSMS) are provided as Supporting Information.

The fragmentation patterns were similar for all compounds, although the carboxylic acids showed additional peaks because they readily lose water and the resulting acylium ion gives rise to a richer family of carboxocation fragments. Additionally, a small difference between the saturated and monounsaturated acid compounds can be seen as a general shift to a higher degree of unsaturation for carboxocation fragment ions.

**Concluding Comments.** The synthesis of seven arsenolipids reported here provides material for an evaluation of the bioavailability and toxicity of a novel group of arsenic-containing natural products that accumulate in fatty fish and algae.

**EXPERIMENTAL SECTION**

The 1H and 13C{1H} NMR spectra were recorded in CDCl3 or MeOH-d4 with a Bruker (360 MHz) instrument. ICPMS (inductively coupled plasma mass spectrometry) measurements were recorded on an Agilent 7500 cf instrument, and chromatographic separations were performed with an Agilent HPLC 1100 system (Agilent Technologies, Waldbronn). Mass spectra were recorded on a Q-Exactive hybrid quadrupole-Orbitrap mass spectrometer (Thermo Scientific). Acetonitrile solutions, approximately 10 μM in arsenolipid, were used for direct infusion at a flow rate of 10 μL/min. Spectra were recorded in the positive mode using the instrument’s HESI-2 source, a spray potential of 3.2 kV, a capillary temperature of 250 °C, and a sheath gas setting of 3 instrument units. The resolution was set to 140000, and full scans were obtained from m/z 50 to 400/500/750. MS/MS spectra were recorded with a parent ion isolation width of 0.4 Da. The collision energy (HCD) was adjusted to achieve the parent ion and largest fragment ion of similar intensity. For the reported MSMS results the HCD was 40 instrument units.

1-(Dimethylarsinyl)pentadecane (5, As-HC 332). 1-Pentadecyl tosylate was synthesized by the method described by Kazemi et al. Thus, KOH (2.7 g, 48 mmol), K2CO3 (5.0 g, 36 mmol), and 1-pentadecanol (2.28 g, 10.0 mmol) were combined and mixed in a mortar. Tosyl chloride (2.69 g, 14.1 mmol) was then added, and the mixture was mixed thoroughly with the pestle for 10 min. The reaction mixture was cooled to room temperature before excess tosyl chloride was destroyed by addition of tert-butyl alcohol (2 mL). The product was extracted from the resulting white powder with diethyl ether (3 × 25 mL); the ether layer was filtered and concentrated in vacuo, giving the product as a white crystalline solid. Yield: 3.24 g (8.47 mmol, 85%). 1H NMR (400 MHz, CDCl3): δ 0.88 (t, J = 7.5 Hz, 3H, CH3), 1.15–1.37 (m, 24 H, 12-CH2), 1.63 (quin, J = 7.5 Hz, 2H, CH2), 1.15–1.37 (m, 12 CH2), 1.63 (quin, J = 7.5 Hz, 2H, CH2), 1.45 (s, 3H, CH3), 4.02 (t, J = 7.5 Hz, 2H, CH2), 7.34 (d, J = 7.5 Hz, 2H, m-H), 7.79 (d, J = 7.5 Hz, 2H, e-H). 13C{1H} NMR (100 MHz, CDCl3): δ 14.1, 21.6, 22.7, 25.3, 28.8, 28.9, 29.4, 29.5, 29.6, 29.7 (2C), 29.7, 29.7, 31.9, 70.7, 127.9 (2C), 129.8 (2C), 133.3, 144.6.
With a syringe, a solution of sodium dimethylarsenide (4.9 g, 21 mmol), prepared from iododimethylarsine according to the method of Feltham et al., was transferred under argon to a two-necked round-bottom flask cooled to 0 °C and fitted with a reflux condenser and a dropping funnel. 1-Pentadecyl tosylate (1.6 g, 4.2 mmol) was dissolved in dry THF (20 mL) in the dropping funnel under argon, and this solution was added to the dimethylarsenide solution over 30 min. The solution was stirred overnight at room temperature and then refluxed for 6 h and cooled to room temperature. The reaction mixture was poured, under argon, into a separating funnel containing a mixture of water (25 mL) and ethyl acetate (25 mL), previously degassed with argon. The aqueous phase was removed and discarded, and the organic layer was washed with degassed water (2 × 25 mL). Hydrogen peroxide (30% H2O2, 4 × 2 mL) was added over 1 h and the mixture stirred for a further 2 h to convert the arsine to the oxide. The product was extracted from the reaction mixture with 0.1 M HCl (5 × 20 mL). The acidic aqueous phase was then adjusted to pH ~9 with 1 M NaOH, and dimethylarsinyl pentadecane was extracted back into ethyl acetate (5 × 20 mL). Removal of ethyl acetate in vacuo yielded the crude product as a waxy solid. The crude product was dissolved in methanol (5 mL) and loaded onto a column (2.5 × 15 cm) of cation-exchange polymer (DOWEX 50W-X8-200, Sigma Aldrich, in the H+ form). Impurities were eluted with methanol (150 mL) before the product was eluted with saturated NH3(aq)/methanol (1/9 by volume). The eluted fraction was then concentrated to dryness, dissolved in methanol (10 mL), and loaded onto a reverse-phase HPLC column (Zorbax SB C8, 1.8 μm, 1.0 × 50 mm) with a mobile phase of 10 mM NH4OAc pH 6.0 and ethanol with gradient elution (0–25 min, 35–95% ethanol); flow rate 0.2 mL min⁻¹. A small arsenic impurity eluting at the column void volume (retention time ca. 2 min) is dimethylarsinate (Me2As(O)O⁻), a degradation product of the arsenolipids.

### Table 1. Summary of MSMS Results

| compd code (no.) | MH⁺ | fragment ion MH⁺−H₂O | fragment ion C₂H₂OAs⁺123 | C₂H₂As⁺105 | C₂H₆As⁺57 | C₆H₇/CH₆/C₆H₉/C₆H₁₁/C₆H₁₃/ C₅H₁₁/C₅H₁₃/C₅H₁₇/ C₅H₁₁/C₅H₁₃/C₅H₁₇/ | C₆H₆/C₆H₈/C₆H₁₀/C₆H₁₂ | C₅H₁₁/C₅H₁₃/C₅H₁₇/ |
|-----------------|-----|---------------------|---------------------------|-------------|-----------|-----------------------------------|---------------------------|---------------------|
| As-FA 362 (1)   | 363.1870 | 54                | 100                        | 46          | 2         | 13                                | 18/62/12                  | 7/29/54/6           |
| As-FA 418 (2)   | 419.2496 | 52                | 65                         | 100         | 8         | 23                                | 13/57/20                  | 9/21/49/11          |
| As-FA 388 (3)   | 389.2023 | 63                | 57                         | 100         | 9         | 3                                  | 46/78/6                   | 14/84/48/6          |
| As-FA 374 (4)   | 375.1872 | 60                | 62                         | 100         | 9         | 3                                  | 52/95/7                   | 19/94/47/7          |
| As-HC 332 (5)   | 333.2128 | <1                | 58                         | 100         | 7         | 44                                | C₅H₁₁⁺71                  | C₅H₁₃⁺85            |
| As-HC 360 (6)   | 361.2440 | <1                | 59                         | 100         | 7         | 41                                | C₅H₁₁⁺71                  | C₅H₁₃⁺85            |
| As-HC 444 (7)   | 445.3384 | <1                | 100                        | 99          | 7         | 44                                | 41                        | 22                  |

“15-dimethylarsinyl pentadecanoic acid
(1, As-FA 362)

1-dimethylarsinyl-pentadecane
(5, As-HC 360)

17-dimethylarsinyl-9-heptadecanoic acid
(2, As-FA 388)

17-dimethylarsinyl-9-heptadecane
(6, As-HC 360)

As-HC 332 (5)
As-HC 360 (6)
As-HC 444 (7)

The intensities of MH⁺−H₂O ions are given in percentages of MH⁺. Intensities of other fragments are percentages of the base peak.

With a syringe, a solution of sodium dimethylarsenide (4.9 g, 21 mmol), prepared from iododimethylarsine according to the method of Feltham et al., was transferred under argon to a two-necked round-bottom flask cooled to 0 °C and fitted with a reflux condenser and a dropping funnel. 1-Pentadecyl tosylate (1.6 g, 4.2 mmol) was dissolved in dry THF (20 mL) in the dropping funnel under argon, and this solution was added to the dimethylarsenide solution over 30 min. The solution was stirred overnight at room temperature and then refluxed for 6 h and cooled to room temperature. The reaction mixture was poured, under argon, into a separating funnel containing a mixture of water (25 mL) and ethyl acetate (25 mL), previously degassed with argon. The aqueous phase was removed and discarded, and the organic layer was washed with degassed water (2 × 25 mL). Hydrogen peroxide (30% H₂O₂, 4 × 2 mL) was added over 1 h and the mixture stirred for a further 2 h to convert the arsine to the oxide. The product was extracted from the reaction mixture with 0.1 M HCl (5 × 20 mL). The acidic aqueous phase was then adjusted to pH ~9 with 1 M NaOH, and dimethylarsinyl pentadecane was extracted back into ethyl acetate (5 × 20 mL). Removal of ethyl acetate in vacuo yielded the crude product as a waxy solid. The crude product was dissolved in methanol (5 mL) and loaded onto a column (2.5 × 15 cm) of cation-exchange polymer (DOWEX 50W-X8-200, Sigma Aldrich, in the H⁺ form). Impurities were eluted with methanol (150 mL) before the product was eluted with saturated NH₃(aq)/methanol (1/9 by volume).
volume). The eluent was concentrated in vacuo and the product recrystallized twice from acetone, giving needles of 1-(dimethylarsinyl)pentadecane (5, As-HC 332), which were dried in small portions on a piece of filter paper under a stream of argon. Yield: 212 mg (0.638 mmol, 15%). Melting point: 91–92 °C. 1H NMR (MeOH-d₄, 300 MHz): δ 0.9 (t, J = 6.9 Hz, 3H, −CH₃), 1.2–1.5 (m, 24H, 12-CH₂), 1.5 (m, 2H, −CH₂), 1.7 (s, 6H, −As(CH₃)₂), 2.1 (m, 2H, −As(CH₃)₂), 2.7 (m, 2H, −CH₂), 1.7 (m, 2H, −CH₂), 1.75 (s, 6H, −As(CH₃)₂), 2.20 (m, 2H, −AsCH₂), 2.28 (t, J = 7.5 Hz, 2H, −CH₂COOH). 13C{1H} NMR (MeOH-d₄, 75 MHz): δ 12.2, 13.0, 21.7, 22.3, 28.7, 29.1, 29.3, 29.4, 31.6. ESI-HRMS: m/z [M + H]+ calculated for M = C₁₇H₃₇AsO 333.2139, found 333.2126 (Δm = −3.9 ppm).

The arsenolipids 1–4, 6 and 7 (Figure 1) were prepared by the following general procedure using bis(dimethylarsine) oxide. Thus, iododimethylarsine (3.0 mmol) was added dropwise to a stirred and cooled (2 °C) solution of sodium hydroxide (0.3 mL of 10 M, 3.0 mmol) under argon. After the mixture was stirred for 10 min, the bis(dimethylarsine) oxide (top layer) was separated from the aqueous layer, and the clear solution was concentrated in vacuo. A solution of crude 1,10-dibromo-10-undecanoic acid (140 mg, 0.79 mmol) at 0 °C was quenched with saturated aqueous NaHCO₃, and the aqueous layer was extracted with CH₂Cl₂. The organic layer was dried (Na₂SO₄), quenched with saturated aqueous NaHCO₃, and then saturated brine, dried (Na₂SO₄), and evaporated in vacuo. The residue was purified by column chromatography (silica gel, 20% ethyl acetate in hexane) to give 1-(dimethylarsinyl)undecanoic acid (140 mg, 0.79 mmol) at 0 °C. The resulting solution was stirred under argon at room temperature until TLC analysis showed no remaining starting material. The reaction mixture was quenched with saturated aqueous NaHCO₃, and the aqueous layer was extracted with dichloromethane (10 mL) followed by N-bromosuccinimide (140 mg, 0.79 mmol) at 0 °C. The resulting solution was stirred under argon at room temperature until TLC analysis showed no remaining starting material. The reaction mixture was redistributed with saturated aqueous NaHCO₃, and the aqueous layer was extracted with dichloromethane. The organic layer was washed with Na₂SO₄ and the aqueous layer was extracted with dichloromethane. The organic layer was washed with Na₂SO₄ (10% v/v) and then saturated brine, dried (Na₂SO₄), filtered, and evaporated. The resulting solid was brown in n-pentane and filtered, and the filtrate was evaporated to give 1-bromoundecanoic acid (180 mg, 80%) as a white solid. 1H NMR (CDCl₃, 300 MHz): δ 0.89 (t, J = 6.9 Hz, 3H, −CH₃), 1.2–1.5 (m, 40H, 20-CH₂), 1.87 (m, 2H, −CH₂CH₂Br), 3.42 (t, J = 6.6 Hz, 2H, -CH₂Br). 13C{1H} NMR (CDCl₃, 75 MHz): δ 14.1, 22.7, 28.1, 29.3, 29.4, 29.5, 29.6, 29.7, 31.9, 32.8, 34.0.

The bromoundecanoic acid was reacted with bis(dimethylarsine) oxide in the usual way to give 1-[(dimethylarsinyl)undecanoyl]arsinic acid (2, 1401). Bromoplastoenoic acid was reacted with bis(dimethylarsine) oxide in the usual way to give 1-[(dimethylarsinyl)pentadecanoyl]arsinic acid (288 mg, 0.86 mmol) in 88% yield (167 mg, 0.46 mmol). Melting point: 138–140 °C. 1H NMR (MeOH-d₄, 300 MHz): 1.2–1.5 (m, 20H, 10-CH₂), 1.6 (m, 4H, 2-CH₂), 1.7 (s, 6H, −As(CH₃)₂), 2.1 (m, 2H, −As(CH₃)₂), 2.3 (t, J = 7.5 Hz, 2H, −CH₂COOH). 13C{1H} NMR (MeOH-d₄, 75 MHz): δ 12.1, 21.6, 24.7, 28.7, 29.0, 29.1, 29.2, 30.2, 30.3, 176.6. ESI-HRMS: m/z [M + H]+ calculated for M = C₁₅H₃₇AsO 315.1930, found 315.1933 (Δm = +0.3 ppm).
g) was refluxed for 10 h. The solution was concentrated in vacuo, the residue was taken up in ether, and the ether layer washed with water and brine and then dried and concentrated to give the methyl ester. Yield: 13 g (83%). 1H NMR (CDCl3, 300 MHz): δ 1.3–1.6 (m, 2H, −CH2), 2.3 (t, J = 7.5 Hz, 2H, −CH2COOCH3), 3.4 (bs, 2H, −COOCH3), 3.6 (t, J = 2H, −CH2COOCH3), 3.7 (s, 3H, −COOCH3), 9.7 (s, 1H). 13C{1H} NMR (CDCl3, 75 MHz): δ 24.8, 25.5, 25.6, 29.1, 29.3, 29.4, 32.4, 33.4, 34.0, 51.5, 62.8, 74.4, 174.4. After the method of Ames,34 to a cooled (0 °C) and stirred solution of the methyl ester (10 g, 31 mmol) in a mixture of CH2CN and H2O (3/2, 130 mL) was added NaIO4 (8.5 g, 40 mmol) in a stirred solution at room temperature for 6 h. The mixture was stirred for 10 h. The solution was concentrated in vacuo, the residue was dissolved in chloroform (15 mL) and the mixture added to dry diethyl ether (100 mL) to precipitate the product, which was washed with ether and dried to give 8-bromo(9-heptadecenoic acid methyl ester (4.9 g, 3.6 mmol, 84%). 1H NMR (CDCl3, 300 MHz): δ 0.8–1.46 (m, 16H, 8-CH2), 1.5 (m, 4H, 2-CH2), 1.7 (s, 6H, 3-CH2), 1.90 (m, 4H, 2-CH2), 2.57 ppm).

Following the method of Hill,35 a mixture of 1,8-dibromooctane (15 g, 55 mmol) and triphenylphosphine (2.9 g, 11 mmol) was heated in an oil bath at 90 °C for 6 h. The flask was then cooled, and the excess 1,8-dibromooctane was decanted off, leaving the monophosphonium salt as a sticky solid, which was washed with dry toluene (2 × 40 mL). The residue was dissolved in chloroform (15 mL) and the mixture added to dry diethyl ether (100 mL) to precipitate the product, which was washed with more diethyl ether and dried in vacuo to give 8-(bromoctyl)triphenylphosphonium bromide as a white solid (5.3 g, 11 mmol). 1H NMR (CDCl3, 300 MHz): δ 1.2–1.8 (m, 12H, 6-CH3), 3.3 (t, J = 6.8 Hz, 2H, −CH2Br), 3.7 (m, 2H, −CH2PPh3Br), 7.6–7.9 (m, 15H, 3-C6H5). 13C{1H} NMR (CDCl3, 75 MHz): δ 22.1, 24.7, 28.9, 29.0, 33.4, 43.9, 51.5, 113.7, 135.0. After the method of Shi,36 a mixture of phosphonium salt (2.3 g, 3.7 mmol), 9-oxononanoic acid methyl ester (0.6 g, 3.2 mmol), anhydrous potassium carbonate (1.7 g, 13 mmol), and triethylamine (5.3 mL) in dry CH2Cl2 (30 mL) was added NaH (0.5 g, 13 mmol) in a dry diethyl ether (100 mL) and stirred until the pink color of NaH disappeared. The reaction mixture was cooled to 0 °C, 8-oxononanoic acid methyl ester as a colorless oil. Yield: 4.9 g (84%). 1H NMR (CDCl3, 300 MHz): δ 1.3 (m, 6H, 2-CH3), 1.6 (m, 4H, 2-CH2), 2.3 (t, J = 7.5 Hz, 2H, −CH2COOCH3), 2.4 (dt, J = 7.3, 1.9 Hz, 2H, CH2CHO), 3.6 (s, 3H, −COOCH3), 9.7 (s, 1H, −CHO). 13C{1H} NMR (CDCl3, 75 MHz): δ 22.1, 24.7, 28.9, 29.0, 33.4, 43.9, 51.5, 113.7, 174.3, 202.9.

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