TEMPO-Catalyzed Direct Conversion of Primary Alcohols to α-Chloroacetals with TCCA Both as an Oxidant and a Chlorination Reagent

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Supporting Information

ABSTRACT: Multistep reactions are often required for the transformation of alcohols to α-chloroacetals via the unstable intermediates aldehydes or α-halo aldehydes. Herein, we report a simplified procedure for practical synthesis of α-chloroacetals using 2,2,6,6-tetramethylpiperidine-1-oxyl as a catalyst and trichloroisocyanuric acid both as an oxidant and a chlorination reagent. The reaction is one-pot, solvent-free and high-yielding. In addition, the α-chloroacetals have been transformed to enol ethers through the elimination reaction in the presence of sodium.

INTRODUCTION

α-Chloroacetals act as significant intermediates in organic synthetic reactions and exhibit various bioactivities.1−4 In general, these compounds are prepared starting with alcohols by oxidation and subsequent α-halogenation in a two- or three-step sequence, in which the intermediates aldehydes, α-chloroaldehydes, or acetics are involved. For example, Ghelli’s group has reported the synthesis of α-chloroacetals through the chlorination of acetals derived from aldehydes and alcohols by MnO2-trimethylchlorosilane.5 In terms of process economy, one-pot oxidation with subsequent α-chlorination and acetalation is highly desirable, Nikishin’s group has reported the synthesis of α-chloroacetals through the oxidation of primary alkyl alcohols by Na2S2O8 in conjunction with an alkali metal chloride as a chlorination reagent in relatively low yields of 20−40%.6 However, all these reactions employed volatile organic solvents as reaction media.

Volatile organic solvents are consumed in large amounts in manufacturing of drugs, pesticides, dyes, and materials. In pharmaceutical industry alone, the cost of organic solvents has been estimated at four billion pounds annually.7 Because of the difficulties in 100% recovery of the volatile organic solvents, they have been one of the culprits for air pollution. There are various ways solving these problems. Our group has initiated the water/granular polytetrafluoroethylene methods conducting a series of organic reactions without using volatile organic solvents.8−11 In addition, large numbers of solvent-free organic synthesis reactions have been reported.12−14

Herein, we report the direct oxidation of primary alcohols in one pot to α-chloroacetals catalyzed by 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) with trichloroisocyanuric acid (TCCA) as an oxidant and a chlorination reagent under solvent-free conditions in the yields of 61−90%. TCCA is a commercially available and very cheap oxidant.15−17 The combination of TEMPO and TCCA has been used catalytically and stoichiometrically for the oxidation of primary alcohols to aldehydes,18 α-chloroaldehydes,19 carboxylic acids,20 esters,21 and so on.

RESULTS AND DISCUSSION

At the beginning of our study, we chose n-octanol (1) as the model substrate to optimize the reaction conditions (Table 1). Mixtures of n-octanol (1, 2.0 mmol, 260 mg), TEMPO, and TCCA in various ratios were stirred under solvent-free conditions at room temperature in air atmosphere. First, the amount of TEMPO was investigated. When the amount of TEMPO was 0.01 equiv, product 1a was obtained in a 25% yield (Table 1, entry 1). Along with the increasing amount of TEMPO from 0.01 to 0.10 equiv, the yields increased from 25 to 56% (Table 1, entries 1−5). Further increasing the amount of TEMPO to 0.15 equiv resulted in a lower yield of 1a (Table 1, entry 6). Then, the amount of TCCA was screened. When

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the amount of TCCA was reduced to 0.3 equiv, the conversion of this reaction was 84% with a 59% yield (Table 1, entry 7). With 0.5 equiv of TCCA, the conversion was 95% with the highest yield of 81%, and the reaction time increased from 2.0 to 3.0 h (Table 1, entry 8). Then, the yield decreased from 81 to 29% with further increasing amount of TCCA from 0.5 to 1.5 equiv (Table 1, entries 5 and 8–10). On the basis of these results, the optimized conditions were n-octanol (1, 2.0 mmol), TEMPO (0.1 equiv), and TCCA (0.5 equiv) at room temperature in air atmosphere (Table 1, entry 8).

Table 1. Optimization of the Reaction Conditions Using the Synthesis of 2-Chloro-1,1-bis(octyloxy)octane (1a) Starting from n-Octanol (1) under Solvent-Free Conditions as an Examplea

| entry | TEMPO (equiv) | TCCA (equiv) | t (h) | conversion (%) | yield (%)b |
|-------|---------------|--------------|------|----------------|------------|
| 1     | 0.01          | 1.0          | 2.0  | 100            | 25         |
| 2     | 0.03          | 1.0          | 2.0  | 100            | 32         |
| 3     | 0.05          | 1.0          | 2.0  | 100            | 46         |
| 4     | 0.08          | 1.0          | 2.0  | 100            | 54         |
| 5     | 0.10          | 1.0          | 2.0  | 100            | 56         |
| 6     | 0.15          | 1.0          | 2.0  | 100            | 52         |
| 7     | 0.10          | 0.3          | 3.0  | 84             | 59         |
| 8     | 0.10          | 0.5          | 3.0  | 95             | 81         |
| 9     | 0.10          | 0.8          | 3.0  | 100            | 63         |
| 10    | 0.10          | 1.5          | 1.0  | 100            | 29         |

Reactions conditions: n-octanol (1, 2 mmol, 260 mg), TEMPO, TCCA at rt. bAll yields are isolated yields.

Under the optimized reaction conditions, we sought to examine the scope and generality of this method. This method is applicable to a range of primary alcohols. As shown in Scheme 1, initially eight simple primary alcohols have been chosen (Scheme 1, 1a−1h), the yields ranged from 61 to 89% while the reaction times from 3 to 24 h. Both the yields and reaction rates decreased with the increase of the molecular weight of the alcohols (Scheme 1, 1a vs 1b vs 1c vs 1d vs 1e vs 1f). The fastest reaction rate and the highest yield was observed for the synthesis of 1b while the slowest reaction rate was observed for the formation of 1f, probably because of the better solubility of TEMPO and TCCA in n-hexanol than in n-octadecanol. In addition, under the solvent-free conditions, the higher molar concentration of n-hexanol than n-octadecanol is another possible reason for the higher reaction rate in n-hexanol. Furthermore, at room temperature, n-hexadecanol and n-octadecanol are solid, so heating is necessary in the synthesis of 1e and 1f. Then, this method was further applied to primary alcohols containing heteroatoms or aryl groups (Scheme 1, 1i−1m). The alcohols possessing heteroatoms

Scheme 1. Solvent-Free Direct Conversion of Primary Alcohols to α-Chloroacetalsa,b

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aReaction conditions: alcohols (2 mmol), TEMPO (0.1 equiv), TCCA (0.5 equiv) under solvent-free condition. bAll yields are isolated yields
such as Cl, Br gave \( \alpha \)-chloroacetals in excellent yields (90 and 84%; Scheme 1, 1i and 1j). Substrates with aryl groups also gave the products in moderate yields (Scheme 1, 1k−1m). Furthermore, the hindered primary alcohols yielded the products in high yields of 75−86% (Scheme 1, 1n−1p).

In the second stage of the research, the \( \alpha \)-chloroacetals were successfully transformed into enol ethers in the presence of sodium (Scheme 2). In the literature, there have been various methods\(^{22}\) for preparing enol ethers such as vinyl transfer to alcohols,\(^{23}\) reduction of vinyl phosphate ethers,\(^{24}\) functionalization of vinyl ethers,\(^{25}\) and so on. A method closely related to this work is the reaction between 3-chloro-2-methoxytetrahydropyran with sodium to yield chain enol ether with hydroxyl group.\(^{26}\) However, the starting material 3-chloro-2-methoxytetrahydropyran was synthesized from enol ether dihydropyran\(^{27}\) or from 1,2-dichlorotetrahydropyran.\(^{28}\) The starting materials are not as readily available and inexpensive as the primary alcohols used in this work. As shown in Scheme 2, \( \alpha \)-chloroacetals \( \mathbf{1b}, \mathbf{1c}, \mathbf{1d}, \) and \( \mathbf{1i} \) were treated with sodium to produce enol ethers \( \mathbf{2a}−\mathbf{2d} \) in good yields and at moderate reaction rates.

To gain insights into the mechanism in the synthesis of \( \alpha \)-chloroacetals, several control experiments were carried out (Scheme 3). In the synthesis of \( \mathbf{1a}, \) 0.1 equiv of \( \alpha \)-chlorodecanal (4) was added, product \( \mathbf{3a} \) was generated which indicated that maybe \( \alpha \)-chloroaldehydes are the reaction intermediates (Scheme 3, reaction 2). Subsequently, under the optimized reaction conditions, using acetal 5 as the starting material, no reaction occurred, excluding acetals as the reaction intermediates (Scheme 3, reaction 3).

On the basis of the control experiments and according to that reported for similar cases,\(^{18−21}\) the probable reaction pathway is put forward, as shown in Scheme 4. First, TCCA reacts with TEMPO to form \( \text{N-oxoammonium ion I} \), which oxidizes the primary alcohol through intermediate II to the corresponding aldehyde IV, giving hydroxylamine III. Then, intermediate III is in turn oxidized to I by TCCA. In the meantime, aldehyde IV is turned into enol V through a keto enol tautomerism equilibrium which reacts with the chloronium ion from TCCA, giving VI. Then, intermediate VI reacts with the primary alcohol to give final \( \alpha \)-chloroacetal IX.

\section*{CONCLUSION}

In conclusion, we have for the first time realizing the oxidation and chlorination in one pot for the synthesis of \( \alpha \)-chloroacetals from alcohols under solvent-free conditions using the combination of TEMPO and TCCA. In comparison to all methods documented in the literature, this method offered several advantages including readily available starting materials and reagents, solvent-free conditions. In addition, we have realized the transformation of \( \alpha \)-chloroacetals to enol ethers in presence of sodium which provides a simple method for the synthesis of enol ethers.

\section*{EXPERIMENTAL SECTION}

\textbf{General Information.} Commercially available reagents were used without further purification. \(^1\)H NMR and \(^13\)C NMR spectra were recorded with a 400 or 600 MHz spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts (\( \delta \)) are reported relative to TMS (\(^1\)H) or CDCl\(_3\) (\(^13\)C). High-resolution mass spectra (HRMS) were recorded on a QTOF mass analyzer using electrospray ionization (ESI).
Scheme 4. Possible Pathway for the Synthesis of α-Chloroacetals

General Procedure for Preparation of α-Chloroacetals Using the Synthesis of 2-Chloro-1,1-bis(octyloxy)octane (1a) as an Example. A mixture of n-octanol (2 mmol, 260 mg) and TEMPO (0.10 equiv) was stirred for 15 min at 25 °C in a 10 mL tube. Then, TCCA (0.5 equiv) was added in portions under stirring for another 3 h at 25 °C. Thin-layer chromatography (TLC) indicated the completion of the reaction. Then, to the mixture, petroleum ether (5 mL) was added. The mixture was filtered, and the cake was washed with petroleum ether (5 mL × 2). The combined organic phase was washed with water (5 mL), dried over Na2SO4, filtered, and the cake was washed with petroleum ether (5 mL). The filtrate was concentrated to give the crude product which was purified by column chromatography to give 1a as a colorless oil (219 mg, 81%); 1H NMR (400 MHz, CDCl3): δ 4.45 (d, J = 5.7 Hz, 1H), 3.95–3.84 (m, 1H), 3.70–3.63 (m, 2H), 3.58–3.44 (m, 2H), 1.99–1.84 (m, 1H), 1.66–1.58 (m, 9H), 1.46–1.17 (m, 28H), 0.90 (t, J = 6.7 Hz, 9H); 13C NMR (101 MHz, CDCl3): δ 104.6, 68.3, 67.3, 62.3, 32.4, 31.8, 31.7, 29.8, 29.7, 29.40, 29.38, 29.3, 28.8, 26.14, 26.08, 22.7, 22.6, 14.0. HRMS (ESI) found m/z: 427.3317 [M + Na]+; calcd for C24H49ClO2Na+, 427.3313.

2-Chloro-1,1-bis(hexyloxy)hexane (1b). n-Hexanol (2.0 mmol) reacted with TCCA (1.0 mmol) in the presence of TEMPO (0.2 mmol) according to the general procedure. The mixture was stirred for another 3 h at 25 °C. After column chromatography, α-chloroacetal 1b was obtained as a colorless oil (190 mg, 89% yield); 1H NMR (400 MHz, CDCl3): δ 4.46 (d, J = 5.7 Hz, 1H), 3.98–3.84 (m, 1H), 3.71–3.63 (m, 2H), 3.60–3.45 (m, 2H), 1.96–1.90 (m, 1H), 1.69–1.56 (m, 6H), 1.40–1.28 (m, 15H), 0.95–0.87 (m, 9H); 13C NMR (101 MHz, CDCl3): δ 104.6, 68.4, 67.5, 62.4, 32.2, 31.6, 31.6, 29.7, 29.7, 28.3, 25.8, 22.6, 22.2, 14.0, 13.9.

2-Chloro-1,1-bis(hexyloxy)hexadecane (1d). n-Hexadecanol (2.0 mmol) reacted with TCCA (1.0 mmol) in the presence of TEMPO (0.2 mmol) according to the general procedure. The mixture was stirred for another 3 h at 25 °C. After column chromatography, α-chloroacetal 1d was obtained as a colorless oil (268 mg, 70% yield); 1H NMR (400 MHz, CDCl3): δ 4.46 (d, J = 5.7 Hz, 1H), 3.96–3.84 (m, 1H), 3.71–3.63 (m, 2H), 3.56–3.50 (m, 2H), 1.99–1.87 (m, 1H), 1.80–1.46 (m, 7H), 1.28 (s, 50H), 0.91 (t, J = 6.5 Hz, 9H); 13C NMR (151 MHz, CDCl3): δ 104.6, 68.4, 67.5, 62.5, 32.5, 31.9, 29.78, 29.76, 29.75, 29.68, 29.6, 29.51, 29.50, 29.44, 29.38, 29.31, 26.1, 22.7, 14.1. HRMS (ESI) found m/z: 595.5196 [M + Na]+; calcd for C51H105ClO2Na+, 595.5191.

2-Chloro-1,1-bis(dodecyloxy)dodecane (1e). n-Hexadecanol (2.0 mmol) reacted with TCCA (1.0 mmol) in the presence of TEMPO (0.2 mmol) according to the general procedure under stirring for 24 h at 60 °C. After column chromatography, α-chloroacetal 1e was obtained as a colorless oil (286 mg, 70% yield); 1H NMR (400 MHz, CDCl3): δ 4.46 (d, J = 5.7 Hz, 1H), 3.91–3.88 (m, 1H), 3.69–3.63 (m, 2H), 3.56–3.49 (m, 2H), 1.98–1.86 (m, 1H), 1.71–1.57 (m, 7H), 1.28 (s, 74H), 0.91 (t, J = 6.7 Hz, 9H); 13C NMR (151 MHz, CDCl3): δ 104.6, 68.4, 67.5, 62.5, 32.5, 32.0, 29.80, 29.76, 29.72, 29.68, 29.65, 29.5, 29.45, 29.42, 29.2, 26.2, 22.7, 14.1. HRMS (ESI) found m/z: 763.7069 [M + Na]+; calcd for C91H186ClO2Na+, 763.7069.

2-Chloro-1,1-bis(octadeoxyl)octadecane (1f). n-Octadecanol (2.0 mmol) reacted with TCCA (1.0 mmol) in the presence of TEMPO (0.2 mmol) according to the general procedure under stirring for 24 h at 90 °C. After column chromatography, α-chloroacetal 1f was obtained as a colorless oil (336 mg, 64% yield); 1H NMR (400 MHz, CDCl3): δ 4.45 (d, J = 5.7 Hz, 1H), 3.96–3.81 (m, 1H), 3.70–3.63 (m, 2H), 3.58–3.42 (m, 2H), 1.94–1.88 (m, 1H), 1.71–1.54 (m, 7H), 1.27 (s, 86H), 0.90 (t, J = 6.8 Hz, 9H); 13C NMR (101 MHz, CDCl3): δ 104.6, 68.3, 67.4, 62.4, 32.5, 32.0, 29.8, 29.7, 29.5.
29.4, 29.2, 26.2, 22.7, 14.1. HRMS (ESI) found m/z: 847.8008 [M + Na]+; calcld for C₁₉H₂₉ClO₄Na⁺, 847.8008.

((2-Chloro-2-cyclohexylethane-1,1-diyl)bis(oxy))bis(ethane-2,1-diyl)dicyclohexane (1g). 2-Cyclohexylethanol (2.0 mmol) reacted with TCCA (1.0 mmol) in the presence of TEMPO (0.2 mmol) according to the general procedure. After column chromatography, α-chloroacetal 1g was obtained as a colorless oil (194 mg, 73% yield); ¹H NMR (600 MHz, CDCl₃): δ 4.52 (d, J = 7.1 Hz, 1H), 3.82 (d, J = 6.2 Hz, 1H), 3.72–3.62 (m, 2H), 3.61–3.56 (m, 1H), 3.52–3.47 (m, 1H), 1.90 (s, 1H), 1.77–1.65 (m, 14H), 1.56–1.40 (m, 8H), 1.31–1.14 (m, 10H), 0.97–0.85 (m, 4H); ¹³C NMR (101 MHz, CDCl₃): δ 102.7, 67.7, 65.3, 64.7, 46.8, 39.5, 37.2, 37.1, 34.4, 34.3, 33.5, 33.4, 33.1, 30.9, 27.6, 26.6, 26.3, 26.2, 25.8, 25.6. HRMS (ESI) found m/z: 421.2843 [M + Na]+; calcld for C₂₄H₄₃ClO₂Na⁺, 421.2844.

(((2-Chloro-2-cyclohexylethane-1,1-diyl)bis(oxy))bis(propane-3,1-diyl))dicyclohexane (1h). 3-Cyclohexylenanol (2.0 mmol) reacted with TCCA (1.0 mmol) in the presence of TEMPO (0.2 mmol) according to the general procedure. After column chromatography, α-chloroacetal 1h was obtained as a colorless oil (209 mg, 74% yield); ¹H NMR (400 MHz, CDCl₃): δ 1.88–1.86 (m, 2H), 3.45–3.40 (m, 6H), 1.98–1.86 (m, 7H), 1.77–1.57 (m, 7H), 1.51–1.40 (m, 8H); ¹³C NMR (101 MHz, CDCl₃): δ 104.6, 68.5, 67.5, 62.0, 45.2, 44.7, 32.52, 32.51, 32.1, 31.6, 29.60, 29.58, 26.62, 26.61, 25.4, 23.6. HRMS (ESI) found m/z: 447.1177 [M + Na]+; calcld for C₃₃H₄₃ClO₄Na⁺, 447.1177.

6-Bromo-1,1-bis(6-bromohexyl)oxy)-2-chloroacetal (1j). 6-Bromohexanol (2.0 mmol) reacted with TCCA (1.0 mmol) in the presence of TEMPO (0.2 mmol) according to the general procedure. After column chromatography, α-chloroacetal 1j was obtained as a colorless oil (312 mg, 84% yield); ¹H NMR (400 MHz, CDCl₃): δ 4.46 (d, J = 5.4 Hz, 1H), 3.90–3.86 (m, 1H), 3.73–3.64 (m, 2H), 3.58–3.51 (m, 8H), 1.99–1.91 (m, 1H), 1.88–1.71 (m, 8H), 1.70–1.59 (m, 5H), 1.52–1.39 (m, 8H); ¹³C NMR (101 MHz, CDCl₃): δ 104.6, 68.5, 67.5, 62.0, 45.2, 44.7, 32.52, 32.51, 32.1, 31.6, 29.60, 29.58, 26.62, 26.61, 25.4, 23.6. HRMS (ESI) found m/z: 547.0738 [M + Na]+; calcld for C₃₈H₄₄BrClO₄Na⁺, 547.0736.

(((1-Chlorocyclopentyl)methylene)bis(oxy))bis-(methylenedioxy)cyclopentane (1n). Cyclopentylmethanol (2.0 mmol) reacted with TCCA (1.0 mmol) in the presence of TEMPO (0.2 mmol) according to the general procedure. After column chromatography, α-chloroacetal 1n was obtained as a colorless oil (157 mg, 75% yield); ¹H NMR (400 MHz, CDCl₃): δ 4.53 (s, 1H), 3.71 (dd, J = 8.7, 6.7 Hz, 2H), 3.45 (dd, J = 8.5, 7.6 Hz, 2H), 2.27–2.15 (m, 2H), 2.13–2.03 (m, 2H), 2.01–1.85 (m, 4H), 1.77–1.68 (m, 6H), 1.66–1.48 (m, 8H), 1.37–1.20 (m, 4H); ¹³C NMR (101 MHz, CDCl₃): δ 106.7, 82.5, 74.8, 39.7, 37.8, 29.7, 29.4, 25.4, 24.9. HRMS (ESI) found m/z: 337.1910 [M + Na]+; calcld for C₁₉H₂₆BrClO₄Na⁺, 337.1905.

(((1-Chlorocyclohexyl)methylene)bis(oxy))bis-(methylenedioxy)cyclohexane (1o). Cyclohexylmethanol (2.0 mmol) reacted with TCCA (1.0 mmol) in the presence of TEMPO (0.2 mmol) according to the general procedure. After column chromatography, α-chloroacetal 1o was obtained as a colorless oil (188 mg, 79% yield); ¹H NMR (600 MHz, CDCl₃): δ 4.25 (s, 1H), 3.60 (t, J = 6.9 Hz, 2H), 3.34 (t, J = 7.4 Hz, 2H), 1.99–1.52 (m, 20H), 1.35–1.12 (m, 8H), 0.98–0.92 (m, 4H); ¹³C NMR (151 MHz, CDCl₃): δ 108.6, 77.4,
was obtained as a colorless oil (232 mg, 86% yield); 1H NMR

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Ethylhexanol (2.0 mmol) reacted with TCCA (1.0 mmol) in

raphy, enol ether

according to the general procedure. After column chromatography, enol ether 1p was obtained as a colorless oil (232 mg, 86% yield); 1H NMR (400 MHz, CDCl3): δ 4.43 (s, 1H), 3.71–3.68 (m, 2H), 3.53–3.36 (m, 2H), 1.99–1.77 (m, 4H), 1.54–1.28 (m, 22H), 1.01 (t, J = 7.4 Hz, 0.97–0.87 (m, 0.15H); 13C NMR (151 MHz, CDCl3): δ 106.9, 79.8, 73.3, 73.1, 41.0, 40.0, 36.72, 36.71, 36.69, 30.64, 30.57, 30.5, 30.4, 30.0, 29.9, 29.2, 29.14, 29.05, 29.0, 26.2, 23.9, 23.2, 23.1, 14.1, 14.09, 11.26, 11.25, 11.03, 11.01, 8.6. HRMS (ESI) found m/z: 427.3316 [M + Na]+; calc for C21H37ClO2Na+: 427.3313.

**General Procedure for Preparation of Enol Ether Using the Synthesis of 1-(Hexyloxy)hex-1-ene (2a) as an Example.** A mixture of 2-chloro-1,1-bis(hexyloxy)hexane (1b, 1 mmol) and sodium (2.0 mmol) in 1,4-dioxane (5 mL) was stirred for 2 h at 100 °C under N2. TLC indicated the completion of the reaction. Then, the mixture was cooled to 25 °C, quenched by addition of methanol (2 mL), poured into water (5 mL), and extracted with CH2Cl2 (10 mL × 2). The combined organic phase was washed with brine (5 mL), dried over Na2SO4, and kept under N2. TLC indicated the completion of the reaction. After column chromatography, enol ether 2b was obtained as a colorless oil (218 mg, 86% yield; E/Z = 77:23); 1H NMR (400 MHz, CDCl3): δ 6.24 (d, J = 12.6 Hz, 0.72H), 5.93 (d, J = 6.2 Hz, 0.23H), 4.78 (dt, J = 12.6, 7.3 Hz, 0.72H), 0.36–4.31 (m, 0.23H), 3.72 (t, J = 6.7 Hz, 0.46H), 3.64 (t, J = 6.6 Hz, 1.54H), 2.12–2.07 (m, 0.46H), 1.93 (q, J = 6.9 Hz, 1.54H), 1.68–1.60 (m, 0.2H), 1.37–1.31 (m, 8H), 0.93–0.89 (m, 6H).

**ASSOCIATED CONTENT**

**Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.8b01501.

**Copies of 1H NMR and 13C NMR spectra (PDF)**

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**Notes**

The authors declare no competing financial interest.

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