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Article

Scalable Flow Electrochemical Alcohol Oxidation: Maintaining High Stereochemical Fidelity in the Synthesis of Levetiracetam

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ABSTRACT: An electrochemical flow process has been developed for an alcohol oxidation step in the synthesis of the generic epilepsy drug levetiracetam. A crucial metric in this process is the retention of high enantiomeric purity as the oxidation of the primary alcohol to the carboxylic acid proceeds via an epimerizable aldehyde intermediate. Here, three different reactor configurations are compared: undivided batch, undivided flow, and divided flow cells. The divided flow cell accesses the highest rate, throughput, and enantiomeric fidelity among the three configurations. This approach is showcased in a 200-g scale process that retains \geq 97% enantiomeric purity and highlights a unique advantage of flow electrolysis.

KEYWORDS: alcohol oxidation, TEMPO, flow electrolysis, enantioselective, Pinnick

INTRODUCTION

Levetiracetam (LEV) is an important antiepileptic drug that has been used globally for more than two decades.¹ The ongoing demand for LEV and expiration of patents has contributed to exploration of improved synthetic protocols.² A particularly efficient route features a carboxylic acid intermediate (LEV-CO₂H) prepared via oxidation of a chiral primary alcohol precursor (LEV-CH₂OH) obtained by condensation of the corresponding chiral amino alcohol and butyrolactone (Figure 1a).⁴ A key challenge in this synthetic route is retention of the absolute (S) stereochemical configuration of the chiral alcohol. Basic reaction conditions commonly used in catalytic methods for the oxidation of primary alcohols to carboxylic acids⁵ can epimerize the basesensitive aldehyde intermediate in the reaction sequence. To address this limitation, we recently developed an electrochemical method for oxidation of LEV-CH2OH to LEV-CO2H using 4-acetamido-2,2,6,6-tetramethylpiperidin-1-oxyl (ACT) as a catalytic redox mediator (Figure 1b).^{6,7} The method has many appealing features, as it proceeds in water, uses a benign electrolyte (NaHCO₃/Na₂CO₃), and generates H_2 as the sole stoichiometric byproduct (via water/proton reduction at the counter electrode). Nevertheless, the batch reaction process exhibits low rates (elaborated below) and a drop in enantiomeric purity of the product becomes increasingly problematic at larger scale. Here, we develop a flow electrolysis process and analyze the comparative performance of batch and flow configurations for the alcohol oxidation step in the synthesis of Levetiracetam (Figure 1c). The data show that a divided-cell flow process exhibits the highest rates and leads to superior retention of enantiomeric purity in the reaction, nearly eliminating epimerization of the aldehyde intermediate. These results have important implications for other electrosynthetic methods and highlight the advantages of flow-based electrolysis for reactions that feature reactive intermediates.[®]



Figure 1. (a) Synthetic route for the preparation of Levetiracetam. (b) Stepwise sequence for oxidation of LEV-CH₂OH to LEV-CO₂H by ACT, highlighting the intermediacy of the epimerizable aldehyde. (c) Batch- versus flow-based electrochemical processes, considered herein.

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RESULTS AND DISCUSSION

Previous studies have shown that ACT is a very effective electrocatalytic mediator for oxidation of primary alcohols to carboxylic acids.^{6a,9} Chronoamperometry studies revealed that ACT exhibits turnover frequencies (TOFs) of 400–1900 h⁻¹ for primary aliphatic alcohols. Much slower rates are observed under bulk electrolysis conditions. The reaction rates observed when conducting ACT-mediated oxidation of LEV-CH₂OH under typical batch electrolysis conditions with reticulated vitreous carbon (RVC)^{6a} and graphite felt (GF) (see Table 1,

Table 1. Comparison of Batch and Flow Reaction Conditions

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|----------------|--|-----------------|--|----------------------------------|---|----------------------------|
| Entry | Format ^{<i>a</i>} | pH ^b | Time (h) | Yield ^c (%) | FE^d (%) | ee ret ^e (%) |
| 1 | Stirred batch | 9.0 | 11 | 92 | 89 | 92 |
| 2 | Flow, undivided | 9.0 | 1.2 | 91 | 81 | 97 |
| 3 | Flow, undivided | 8.0 | 1.2 | 50 | 44 | 98 |
| 4 | Flow, divided | 8.0 | 0.6 | 23 | N.D. | N.D. |
| 5 ^f | Flow, divided | 9.0 | 0.6 | 92 | 83 | >99 |

^{*a*}Conditions: 0.1 M (5 mmol) LEV-CH₂OH, 5 mol % ACT, 50 mL of carbonate buffer electrolyte (0.5 M; pH adjusted by varying the ratio of Na₂CO₃/NaHCO₃), flow rate = 50 mL min⁻¹, rt. Variable constant currents, set according to the current recorded at 0.7 V vs Ag/AgCl during CV measurement at scan rate of 50 mV/s, corresponded to the following values: batch, $I_{app} = 50$ mA; undivided flow, $I_{app} = 500$ mA; divided flow, $I_{app} = 500$ mA; electrode dimensions = 10 cm² × 0.5 cm. ^bpH controlled by using different ratios of NaHCO₃ and Na₂CO₃. ^{c1}H NMR yields with DMSO as the internal standard. ^dFaradaic Efficiency. ^e% ee ret = (ee of LEV-CO₂H/ee of LEV-CH₂OH)*100; enantiomeric excess (ee) determined by HPLC. ^fThe pH of the anode solution maintained by titration with 1.0 M NaOH using a pH controller.

entry 1) electrodes correspond to an "effective TOF" of only $0.6-7 h^{-1}$, drawing attention to the influence of mass transport on the reaction rate. Postulating that the longer reaction times imposed by the batch reaction format contributes to the loss of enantiomeric purity during the oxidation of LEV-CH₂OH, we initiated an effort to explore flow electrolysis conditions. Single-pass flow conditions have been reported previously for TEMPO-mediated alcohol oxidation;¹⁰ however, this approach requires slow flow rates to ensure complete conversion in a single pass and negates many of the beneficial mass transport contribution of flow-based electrolysis.

As an alternative, we considered a recirculating flow process that would be compatible with high flow rates. A commercially available parallel-plate electrolysis cell (Micro Flow Cell from ElectroCell¹¹) was selected for these studies, owing to their modular construction and availability of larger-scale reactor formats. Three-dimensional (3D) porous graphite felt (GF; 10 cm² geometric surface area with a 0.5 cm thickness) was integrated in the anode compartment. GF has been commonly used in redox flow batteries due to its wide operating potential range, good electrical conductivity, high specific surface area, and chemical and mechanical stability¹² and recently has begun to be used in organic electrochemistry applications.¹³ This electrode material has a high surface-to-volume ratio, and the three-dimensional porosity promotes turbulent mixing and efficient mass transport. A recent study by Weber and co-workers analyzed the flow behavior through GF electrodes and showed that this material serves as a static mixer that supports plug-flow behavior.^{13b}

The GF anode was paired with a stainless-steel plate cathode (10 cm^2) , and a PTFE static mixing spacer was included in the cathode compartment of the flow cell (see Figures S1-S3 in the Supporting Information for details of the reactor construction). The cell was tested with and without a sulfonated fluoropolymer membrane between the anode and cathode compartments. Finally, a Ag/AgCl reference electrode was interfaced with the inlet tube of the anodic chamber to allow the anode potential to be monitored while performing flow electrolysis at constant current. Prior to each electrolysis experiment, the flow was initiated and a voltammogram was recorded in order to measure the current at 0.7 V (i.e., just beyond ACT/ACT⁺ potential: $E_{1/2}(ACT) = 0.63$ V vs Ag/ AgCl). This current value was used to conduct the ensuing constant current electrolysis. The anode potential was stable throughout the electrolytic oxidation of LEV-CH2OH (detailed below) until substrate was consumed, and the reaction was terminated when the anode potential rose to 1.0 V.

Representative electrolysis data obtained under different conditions are provided in Table 1. The reaction time, product yield, and faradaic efficiency were determined, together with the extent of epimerization, defined according to the % ee retained in the product [i.e., (ee of LEV-CO₂H/ee of LEV- CH_2OH * 100]. An initial batch experiment was conducted as a benchmark, using the same electrode materials used for the flow electrolysis methods (see Supporting Information for details). This reaction exhibits a comparatively long reaction time (11 h) and a notable drop in ee, from 95.2% ee in the alcohol to 87.5% ee in the LEV-CO₂H product (92% ee ret) (Table 1, entry 1). Flow conditions were initially tested using an undivided flow cell (UDFC), which avoids the need for a membrane and uses a single reservoir for the reaction solution. Flow electrolysis under conditions otherwise identical to the batch reaction (pH 9, 0.5 M Na₂CO₃/NaHCO₃ electrolyte, rt, 10 cm^2 GF electrode) led to a much faster rate, reaching completion in only 1.2 h, and exhibited a significant improvement in enantiomeric retention (97% ee ret, entry 2). Lowering the pH led to a slight improvement in enantiomeric retention (98% ee ret at pH 8) but a significantly lower rate, resulting in only 50% yield of product over the same 1.2 h time period (entry 3). A divided flow cell (DFC) was also tested by incorporating a Nafion 324 membrane between the anode and cathode compartments and using separate feed solutions for each electrode. A preliminary experiment at pH 8 revealed very poor reaction performance (entry 4). This outcome was traced to acidification of the anodic reaction solution during electrolysis (a solution pH of 6-7 was measure after 0.6 h). It was possible to maintain the pH by use of a pH controller that titrated 1 M NaOH solution into solution (Figure 2). Optimization of this approach (see Supporting Information for further details) led to an excellent yield (92%) within 0.6 h and near-perfect enantiomeric retention (entry 5).

Analysis of the reaction time course provided valuable insights into the reaction performance during the DFC electrolysis conditions (cf. Table 1, entry 5). The anode potential was monitored relative to the Ag/AgCl reference

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Figure 2. Schematic diagram of the divided flow cell with graphite felt anode, stainless steel plate cathode, and Nafion N324 membrane. A pH meter/controller maintains the pH of the anode reservoir solution (for details, see Figures S1–S3 in the Supporting Information).

electrode (Figure 3a), and aliquots of the reaction mixture were analyzed by ¹H NMR spectroscopy throughout the time course (Figure 3b). The aldehyde hydrate LEV-CH(OH)₂ is detected as an intermediate during the course of the reaction, rising to a steady-state concentration of ~14 mM. Full conversion of the alcohol to LEV-CO₂H after ~30 min coincides with a rise in anode potential (cf. Figure 3a).

Further studies were conducted to probe the performance of the different reactor configurations (batch, UDFC, and DFC; Figure 4). The same electrode size (10 cm^2) and composition (GF/stainless steel) were used in each case. Voltammetry data highlight the different current response in the different reactors (Figure 4a). The DFC accessed a current density of 250 mA cm^{-2} at 0.8 V vs Ag/AgCl, 2-fold higher than that observed in the UDFC and 20-fold higher than that in the batch reactor. The difference between the DFC and UDFC reactors is rationalized by the presence of the membrane in the DFC, which ensures that the reaction solution is forced to flow through the GF working electrode. In the UDFC, approximately half of the reactor volume is not in contact with the GF and will not support electrolysis (see Figure S8). The current density observed at 0.7 V in the voltammetry experiments (cf. Figure 4a) was used to define the current for bulk electrolysis reactions. The reaction time-course data reveal significant differences in rate and mass throughput for the three different reactors (Figure 4b and 4c). Each reactor was then used to perform the bulk electrolysis at different pH values. The data show evidence for significant epimerization in the batch reaction format (Figure 4d, blue data), with progressively worse retention of ee as the pH is raised from 8 to 11.5. The drop in product ee is rationalized by equilibration of the LEV- $CH(OH)_2$ intermediate (cf. Figure 3b) with the aldehyde (cf. Figure 1b), which can undergo base-promoted epimerization during the oxidation process. Significantly improved retention of ee is observed with the UDFC and DFC reactors (Figure 4d, red and black data, respectively), with virtually no loss of enantiopurity in the DFC from pH 8-9.

The improved retention of ee in the flow cells is attributed to the faster rates in these reactors, which reduce the time available for the aldehyde to epimerize. Support for this hypothesis was obtained by testing the relationship between reaction time and ee retention. A series of electrolysis experiments were performed using the DFC Micro Flow Cell, varying the amount of LEV-CH₂OH from 2 to 20 g



Figure 3. (a) Anode potential and charge passed during the electrochemical ACT-mediated oxidation of LEV-CH₂OH in a DFC. (b) Time course for the conversion of 0.1 M LEV-CH₂OH during electrocatalytic oxidation. Reaction conditions: 5 mmol of LEV-CH₂OH and 5 mol % ACT in 50 mL of aqueous carbonate buffer, NaHCO₃ (1.0 M)/Na₂CO₃ (1.0 M) with pH 9.0, constant current = 100 mA/cm², flow rate = 50 mL/min, rt. Yields determined using ¹H NMR spectroscopy with DMSO as the internal standard.

[different volumes of 0.5 M substrate solution in the anode reservoir; 1 M NaHCO₃/Na₂CO₃, (pH 8.5)]. Each electrolysis used an identical current density (200 mA/cm²) and solution flow rate (100 mL/min). The results in Figure 5 (see Experimental Section and Table S6 for details) show that retention of ee correlates with the overall reaction time, which directly correlates with the scale of the reaction (top *x*-axis in Figure 5).

The results above suggest that good overall reaction performance should be possible on any scale by properly matching the reaction scale with the electrolysis cell and operational parameters (e.g., current density). This conclusion was tested with a 200 g scale reaction using the Electro MP Cell,¹¹ which accommodates a GF electrode area of 100 cm² (Figure 6; see Figures S5 and S6).



Figure 4. Comparison of the electrochemical behavior of DFC, UDFC, and batch reactors for the ACT-mediated oxidation of LEV- CH_2OH (0.1 M, 5 mmol). (a) Voltammetric analysis of ACT-mediated electrocatalytic LEV- CH_2OH oxidation; scan rate: 50 mV/s. (b) Product yield time course during constant-current electrolysis (the current density observed at 0.7 V in Figure 4a was used to define the applied current). (c) Reaction throughput of LEV- CO_2H obtained from constant-current electrolysis. (d) Retention of enantiomeric excess for electrolysis reactions at different pH.



Figure 5. Relationship between enantiomeric excess retention (ee ret), scale and reaction time in the DFC (Micro Cell). Reaction conditions: 0.5 M of LEV-CH₂OH, 5 mol % ACT, 1.0 M NaHCO₃/Na₂CO₃ electrolyte, pH 8.5, constant current = 200 mA/cm², flow rate = 100 mL/min, rt. See Supporting Information for details.

The oxidation of LEV-CH₂OH (200 g, 1272 mmol, 0.5 M, pH 8.5) was conducted with a current density of 300 mA/cm², and a stable anode potential of ~1.2 V vs Ag/AgCl was observed during the reaction (Figures 6b). These conditions, together with a high faradaic efficiency (97%), allowed the

reaction to reach completion within 4.5 h (Figure 6c), affording LEV-CO₂H in 91% isolated yield with 97.3% retention of ee. No evidence for product degradation was observed during the reaction. The high faradaic efficiency suggests the carbon electrode maintains good stability throughout the experiment, although systematic efforts were not undertaken to explore the material stability limits. The 44.5 g/h throughput in this demonstration may be compared to the 1.4 g/h throughput achieved in the previously reported 40 g scale batch reaction. The principles established here are readily adapted to larger scale applications.^{6a}

CONCLUSIONS

The results of this study showcase the efficient electrochemical oxidation of an important pharmaceutical intermediate using mediated electrocatalysis. The high rates accessed by the DFC play a crucial role in maintaining high enantiomeric purity by minimizing the residence time of a sensitive reaction intermediate. This phenomenon has important implications for other reactions that proceed via metastable intermediates susceptible to unwanted side reactions. More generally, the systematic performance comparison of three electrochemical reactor configurations establishes an important foundation for scalable application of electrochemical methods to organic synthesis.



Figure 6. Scale up of constant-current electrochemical oxidation of LEV-CH₂OH. (a) Size comparison of the Micro flow cell and MP Cell; (b) observed potential over time during the 200 g constant current electrochemical oxidation of LEV-CH₂OH in the divided MP flow cell; and (c) constant current time course of 0.5 M LEV-CH₂OH electrocatalytic oxidation. Reaction conditions: 1272 mmol of LEV-CH₂OH and 5 mol % ACT in 2540 mL of aqueous carbonate buffer, NaHCO₃ (1.0 M)/Na₂CO₃ (1.0 M), pH 8.5, at an applied current density of 300 mA/cm², flow rate = 1000 mL/min, rt. Yield determined by HPLC analysis.

EXPERIMENTAL SECTION

General Considerations. Chemicals and solvents were purchased from commercially available sources and used without purification. 1-[(2S)-1-Hydroxy-2-butanyl]-2-pyrrolidinone (LEV-CH₂OH, 95.2% ee) was prepared according to a literature protocol.4b Pyrene-TEMPO was synthesized according to a previously reported protocol.^{9b} Deionized water was used for making all the solutions for voltammetric studies, and electrolysis reactions. The aqueous buffered solutions were made based on standard tables reported online.¹⁴ For the desired pH values in this work, sodium hydrogen carbonate/ sodium carbonate buffer were used. The total concentration of buffers was 0.1 to 1 M. Graphite felt (GF065) and Nafion N324 membrane were purchased from Fuel Cell Store. ¹H and ¹³C NMR spectra were obtained with Bruker Avance-400 MHz with residual solvent peaks or tetramethylsilane as the internal reference. Multiplicities are described using the following abbreviations: s = singlet, bs = broad singlet, d = doublet, dd = doublet of doublet, t = triplet, m = multiplet. Chiral HPLC experiments were performed using a Shimadzu 1260 Series HPLC equipped with a Chiralpak ID column. High-resolution mass spectra were obtained using a Thermo Q Exactive Plus via (ASAP-MS) by the mass spectrometry facility at the University of Wisconsin-Madison. The structural images were obtained by scanning electron microscopy (SEM) using a Hitachi FE-SEM S-4700 operated at 15.0 kV.

Flow Electrochemical Oxidation Experimental Procedure. Small-Scale Electrochemical Flow Setup. For the small-scale electrochemical flow reactions, a commercial Micro Flow Cell (purchased from ElectroCell) with an electrode area of 10 cm^2 was used, the active reactor volume is 5 mL, and the Bipotentiostat BP-300 was used as power supply. For the divided flow cell, consisting of PTFE end frames, a stainless steel plate (316L) as the cathode, a stainless steel plate, and a graphite plate overlay together as the anode, the Nafion N324 membrane was used to separate the anode and cathode. The flow cell also contains the flow frames and gaskets. Graphite felt (0.6 g, BET surface area = 0.66 m^2) with approximately dimensions = $3.5 \times 3.0 \times 0.5$ cm³ (Brunner–Emmet–Teller (BET) surface area is $1.1 \text{ m}^2 \text{ g}^{-1}$) was used to increase the surface area of the electrode, and PTFE mesh was used as turbulence material for diffusion. The interelectrode distance between the anode and cathode is 3.5 mm as shown in Figure S1 where the anode is separated from the cathode with a nafion membrane, two gaskets, and a PTFE frame. All electrolysis reactions were performed in aqueous solutions. The working electrode potential during constant current electrolysis was monitored versus Ag/AgCl. A magnetic stir bar (1 cm) was used in the reservoirs, and the reaction mixture was stirred (300 rpm) during the course of flow electrolysis reactions. The aqueous carbonate buffer/reaction mixture in the anodic reservoir and the aqueous carbonate buffered solution in the cathodic reservoir were each pumped through the system using peristaltic pumps with flow rates of 50 mL/ min. The undivided cell is identical to the divided flow cell, but without the Nafion N324 membrane using one reservoir with a

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Large-Scale Electrochemical Flow Setup. A commercial MP Flow Cell (purchased from ElectroCell) with an electrode area of 100 cm² was used for the large-scale demonstration. The divided flow cell utilized a nickel plate cathode with a graphite felt and plate anode. A Nafion N324 membrane was used to separate the anodic and cathodic compartments. The reactor was assembled following the manufacturer's instructions and illustrated in Figure S5. The input and output ports corresponding to the anodic and cathodic chambers were equipped with PVDF hose barb adapters (3/8'' ID × 1/2'' NPT(M); Cole-Palmer #EW-30704-18). The unused ports were plugged with HDPE threaded plugs (1/2'' NPT(M); Cole-Palmer #EW-30401-39).

The assembled MP Cell was inserted into the flow setup diagramed in Figure S6. The analyte and catholyte solutions were held in jacketed cylindrical reactors equipped with overhead stirrers and connected to a Huber Ministat 230 chiller (Figure S6, 1). J-Kem temperature probes were inserted into the reactors to monitor the internal temperature (Figure S6, 1). A Mettler-Toledo InLab Micro Pro-ISM pH Probe (#51344163) was inserted into the analyte solution to monitor the pH (Figure S6, 2). A 1/4" stainless steel dip tube was inserted to withdraw the solutions from the bottom of the reactors before transitioning to Tygon 3/8" tubing (E-LFL L/ S 35, Cole-Palmer #EW-06440-35). The solutions were recirculated via a Cole-Palmer Masterflex L/S Digital Drive (#EW-075220-20) equipped with two Easy-Load II Pump Heads (#EW-77200-62) at a flow rate of 1000 mL/min (Figure S6, 4). The sodium hydroxide buffering solution was pumped via a single-channel Cole-Palmer Masterflex L/S Digital Miniflex Pump (#EW-07525-20) with 1/8" ID Tygon E-LFL L/S 16 tubing (Cole-Palmer #EW-06440-16; Figure S6, 5), through a McMaster-Carr 0.33PSI opening pressure checkvalve (#45385K53; Figure S6, 6). The buffering solution, through 1/8" tubing transitioned to 3/8", was combined with the anolyte solution stream in a Cole-Palmer 3/8 in. compression tee (#EW-06386-30) and flowed through a Koflo 3/8" static mixer (#3/8-40-3-6-2; Figure S6, 7). The anolyte was passed through an Evsco 443-PV PVDF Three-Way valve (1/2" NPT(F); Cole-Palmer #EW-06472-47) with an Oakton In-Line pH meter (Cole-Palmer #EW-27001-90) inserted into one of the ports (Figure S6, 8). Two polypropylene compression adapters $(1/2'' \text{ OD } \times 1/2'')$ NPT(M); Cole-Palmer #EW-06385-70) were used to connect the 3/8" ID Tygon tubing to the valve. The anolyte stream continued through another 3/8'' compression tee with a Pine Research Ag/AgCl reference electrode (#RREF0021; Figure S6, 9) before entering the electrolysis cell with a flow rate of 1000 mL/min. The catholyte solution was pumped directly into the cell with the same flow rate. Both solutions were immediately returned to the respective vessels upon exiting the cell.

A Biologic VMP-300 potentiostat equipped with four 10-Amp booster boards was used as the power supply. The individual boards were connected to a Biologic CC8 current collector. The power and sensory cables from the current collector were attached to the MP cell with the provided hardware. The cell potential was monitored versus the in-line Ag/AgCl reference electrode.

Epimerization Time-Dependence Experiment. A 0.5 M solution of LEV-CH₂OH was prepared with 1.95 equiv of sodium bicarbonate, 0.05 equiv of sodium carbonate, and 5 mol % ACT, consistent with section 2.4 in the Supporting Information, and agitated until homogeneous. The flow electrolysis was conducted in the microcell reactor with a 10 cm² graphite felt anode as outlined in the previous section (Figures S1-S3). The reaction solution was recirculated at 100 mL/min, and a constant current electrolysis was performed at 2000 mA. A 4 M sodium hydroxide solution was used to maintain a pH of 8.5 in the anodic reaction solution. Upon completion, a sample of the reaction solution was acidified with HCl and extracted with EtOAc. The organic layer was concentrated and analyzed for product enantiopurity. This process was performed on 2, 5, 10, 15, and 20 g scales. The chiral purities of the resulting products are outlined in Table S6.

Characterization Data for Product. (2S)-2-(2-Oxopyrrolidin-1-yl) Butanoic Acid (S-LEV-CO₂H): The ¹H and ¹³C NMR data match those reported in the literature.^{6b} ¹H NMR (500 MHz, D₂O, δ (ppm)): 4.43 (dd, J = 10.9, 4.8 Hz, 1H), 3.45 (m, 2H), 2.45 (td, J = 8.0, 7.3, 5.1 Hz, 2H), 2.06 (m, 2H), 1.95 (td, J = 14.5, 7.9 Hz, 1H), 1.74 (ddd, J = 14.4, 11.0, 7.2 Hz, 1H), 0.83 (t, J = 7.4 Hz, 3H). ¹³C NMR (126 MHz, D₂O): 179.5, 174.5, 56.2, 44.7, 30.9, 21.3, 17.5, 9.9. HRMS (ESI) Calculated for [M+H⁺], 172.0968; measured, 172.0966.

ASSOCIATED CONTENT

1 Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.1c00036.

Experimental details and compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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