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RESEARCH ARTICLE

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An efficient method for synthesizing dimethylsulfonio-^{34}S-propionate hydrochloride from $^{34}S_8$

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Dimethylsulfoniopropionate (DMSP, (2-carboxyethyl)dimethylsulfonium) is a highly abundant compound in marine environments. As a precursor to the climatically active gas, dimethylsulfide (DMS), DMSP connects the marine and terrestrial sulfur cycles. However, the fate of DMSP in microbial biomass is not well understood as only a few studies have performed isotopic labeling experiments. A previously published method synthesized ^{34}S-labeled DMSP from $^{34}S_8$, but the efficiency was only 26% and required five separate reactions, expensive reagents, and purification of the products of each reaction. In this study, a method of synthesizing ^{34}S-labeled DMSP from $^{34}S_8$ is described. Improvements include elemental steps, inexpensive reagents, purification of only one intermediate, and less time to complete. The efficiency of this method is 65% and results in pure DMSP with more than 98% isotope enrichment as determined by ^{1}H-nuclear magnetic resonance (NMR) and gas chromatography–mass spectrometry (GC–MS).

1 | INTRODUCTION

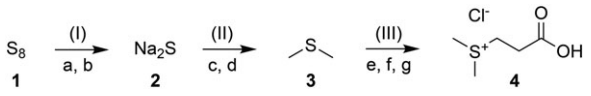
Dimethylsulfoniopropionate (4, DMSP, (2-carboxyethyl) dimethylsulfonium) is a highly abundant compound in marine surface waters. In the North Sea, the concentration of DMSP cycles seasonally from micromolar levels in the summer to picomolar levels in the spring and fall.[1,2] The majority of marine DMSP comes from halophytic plants and algae, where it is believed to regulate osmotic pressure in addition to antioxidant, predator deterrent, and/or cryoprotectant functions.[2] There is also evidence that at least 0.5% of marine bacteria are capable of producing DMSP, but this contribution to the global sulfur cycle is not yet fully understood.[3] Concurrent with its role as an osmoregulatory molecule, plants that produce the most DMSP are generally halotolerant and of marine origin, with sugarcane being the only nonmarine exception. During ^{35}S-labeling studies with bacterial cells, approximately 15% of added DMSP accumulated intracellularly but was not metabolized.[2] Molar levels of intracellular DMSP have been observed in some organisms, and it is estimated that up to 10% of the total fixed carbon in the oceans is in the form of DMSP.[4] Furthermore, DMSP released from phytoplankton blooms can satisfy up to 15% of the microbial carbon demand and 100% of the microbial sulfur demand.[4] DMSP is the precursor for the majority of atmospheric dimethylsulfide (3, DMS), which is a climatically active gas and connects the marine and terrestrial sulfur cycles.[5] It was previously believed that H_2S was responsible for the transfer of sulfur between marine and terrestrial environments but the necessary atmospheric concentrations were never detected and the surface layers of the ocean are too oxidizing to sustain equilibrium with the atmosphere.[5] However, the concentration of DMS in marine surface layers is sufficiently high, and DMS is resistant to oxidation in the lower atmosphere.[5] Its photooxidation in the upper atmosphere produces sulfur species that can be transferred to terrestrial environments via rain and promote the formation of cloud-condensation nuclei, resulting in an increased albedo effect and global cooling.[2,4,6,7]

Bacterial catabolism of DMSP proceeds through one of two known pathways. It can either undergo cleavage to form DMS and either acrylic acid or 3-hydroxypropionate or it can undergo demethylation to form methylmercaptopropionic acid, which can further be broken down into methanethiol, carbon dioxide, and acetaldehyde.[2] In both cases, the DMS and methanethiol can be metabolized further and assimilated into biomass. Because very few studies have performed isotope-labeling experiments with DMSP, the fate of DMSP in microbial biomass is not well understood.[8-11] DMSP hydrochloride can be easily synthesized via a Michael addition of DMS to acrylic acid under acidic conditions in methylene chloride.[12] Unfortunately, DMS enriched with a sulfur isotope is not commercially available, and the only commercially available form of isotopically labeled sulfur suitable for conversion to DMS is elemental sulfur (1, S_8). Thus, incorporation of a specific sulfur isotope requires a synthetic pathway to convert S_8 to DMSP.

2 | EXPERIMENTAL

Unless stated otherwise, all chemicals were purchased from commercial sources with American Chemical Society (ACS)-grade purity or higher and were used without further purification. Metallic sodium was provided by Dr Robert Phillips (Department of Chemistry, University of Georgia). The $^{34}S_8$ and $I^{13}CH_3$ were purchased from Sigma-Aldrich (St. Louis, MO) with 99% atom enrichment. The NH_3 (l) was generated by dripping 30% NH_4OH (aq) onto NaOH pellets, drying the NH_3 (g) by passing it over KOH pellets, and condensing the NH_3 (g) on a cold finger filled with dry ice and ethanol. Dry HCl (g) was generated by dripping concentrated HCl (aq) into concentrated H_2SO_4 and bubbling the resulting HCl (g) through concentrated H_2SO_4. All glassware used in the experiments was acid washed in 3% HCl (aq) for 24 hours to remove trace contaminants and then baked at 180°C for 24 hours to degrade any remaining organic compounds.

Because of the price of $^{34}S_8$, S_8 was used to determine the efficiency of reaction (I), Na_2S was used to determine the combined efficiency of reactions (II) and (III), and DMS was used to determine the efficiency of reaction (III) (Scheme 1). Because of the presence of excess Na and the potential for oxidation of Na_2S, a modified version of the methylene blue assay was used to calculate the amount of S^{2-} synthesized from reaction (I) and the amount of Na_2S used in reaction (II) (Scheme 1). The methylene blue assays were performed twice on a 10^{-5} dilution of each solution of Na_2S.[13-16] All reported efficiencies are relative to the amount of sulfur used.



SCHEME 1 Synthesis of 4. Reagents: a, Na; b, NH_3 (l); c, ICH_3; d, NaOH (aq); e, acrylic acid; f, CH_2Cl_2; g, HCl (g)

DMSP was analyzed via ^{1}H-nuclear magnetic resonance (NMR) by Dr Dongtao Cui (Chemical Sciences Magnetic Resonance Facility, University of Georgia). DMSP (5 mg) was dissolved in 600 μL of D_2O, and NMR spectra were obtained on a Bruker AVANCE III HD NMR spectrometer at a frequency of 400 MHz. NMR spectra were aligned by shifting the D_2O peak to the reference point of 4.790 ppm.[17]

DMS formed from DMSP by alkaline hydrolysis was analyzed via gas chromatography–mass spectrometry (GC–MS) at the Proteomics and Mass Spectrometry Facility (University of Georgia) with a modified version of the protocol described by Niki et al. (2004).[18] A 5-mL serum vial was charged with 4, 4A, or 4B (6 mg) dissolved in 100-μL water and crimp sealed with a teflon-coated butyl rubber stopper, and the headspace was flushed with N_2 for 10 minutes. A syringe was used to add 100 μL of 4 M NaOH (aq), and the vial was incubated at 30°C for 1 hour to convert 4, 4A, or 4B to equimolar amounts of 3, 3A, or 3B, respectively.[19] 500 μL of the headspace was applied to the injection port (heated at 150°C) of the GC (HP-5890A, Agilent) with a splitless duration of 2.75 minutes and an EC-5 (0.25-mm ID × 30 m × 0.25-μm film thickness, Alltech) column. The carrier gas was He with a head pressure capped at 12 psi. The GC oven was programmed to rise from 50°C to 150°C at a rate of 15°C min^{-1}. 3, 3A, and 3B were detected by a mass spectrometer (HP-5971A, Agilent) with an electron-ionization (EI) ion source running in scan mode (monitored m/z range was 45-67) with 12 scans per second and a detector temperature of 150°C.

2.1 | (2-Carboxyethyl)dimethylsulfonium-^{34}S chloride

$Na_2{}^{34}S$ (2A) was synthesized as previously described.[20,21] A 10-mL serum vial containing a teflon-coated stir bar was charged with $^{34}S_8$ (1A) (0.1071 g, 394 μmol) and freshly shaved, hexane-washed Na (0.1742 g, 7.577 mmol), flushed with N_2 for 1 hour, and then incubated at −78°C under a slow stream of nitrogen for the duration of the reaction. The vial was charged with approximately 8 mL of NH_3 (l), incubated with stirring until no yellow color could be seen, and then stirred for an additional 30 minutes. The vial was then flushed with a steady stream of N_2 until all NH_3 had evaporated, leaving

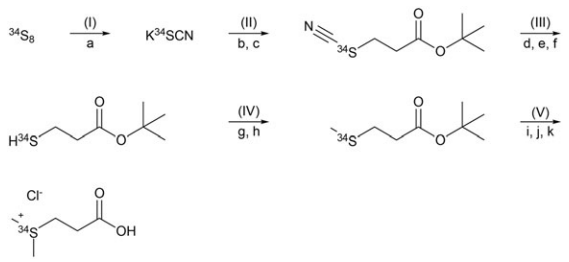
behind a white and silvery powder composed of excess Na and 2A. Dimethylsulfide-^{34}S (3A) was synthesized from the resulting 2A as previously described.[22] The vial containing 2A was crimp sealed with a teflon-coated butyl rubber stopper, and its headspace was replaced with N_2 and pressurized to 10 psi. The contents of the vial were dissolved in 3 mL of an anaerobic stock solution of 1.5 M NaOH (aq), and the vial was incubated on ice for 5 minutes. A glass syringe was used to add ICH_3 (470 μL, 1.0716 g, 7.550 mmol) to the vial, and the vial was incubated at 4°C with vigorous stirring for 4 hours. To stop the reaction, a syringe was used to add 2 mL of 3 M $Na_2S_2O_3$ (aq), and the vial was incubated at 4°C with vigorous stirring for 30 minutes. The vial was chilled to –196°C in N_2 (l) and connected to a receiving flask. The 3A was distilled from the solution by cooling the receiving flask in N_2 (l) while warming the vial to 40°C for 2.5 hours. (2-Carboxyethyl)dimethylsulfonium-^{34}S (4A) was synthesized as described previously.[12] The receiving flask containing distilled 3A was immediately charged with –80°C CH_2Cl_2 (12 mL). The receiving flask was removed from the N_2 (l) and was immediately charged with acrylic acid (260 μL, 0.2733 g, 3.792 mmol). Immediately afterwards, the solution was stirred vigorously at room temperature for 30 minutes while bubbling in dry HCl (g). The solution was dried at 50°C under a vacuum for 2.5 hours. The resulting white solids were washed with CH_2Cl_2 to yield white crystals composed of pure 4A (0.3551 g, 2.0578 mmol, 65.3%).

2.2 | (2-Carboxyethyl)di(methyl-^{13}C) sulfonium-^{34}S chloride

$Na_2{}^{34}S$ (2A) was synthesized from $^{34}S_8$ (1A) (0.1005 g, 370 μmol) and freshly shaved, hexane-washed Na (0.1564 g, 6.803 mmol) using the methods described above. Di(methyl-^{13}C)sulfide-^{34}S (3B) was synthesized from the resulting 2A and $I^{13}CH_3$ (450 μL, 1.0305 g, 7.210 mmol) using the method described above. (2-Carboxyethyl)di(methyl-^{13}C)sulfonium-^{34}S (4B) was synthesized from the resulting 3B and acrylic acid (250 μL, 0.2628 g, 3.646 mmol) using the method described above. This yielded white crystals composed of pure 4B (0.3307 g, 1.895 mmol, 64.0%).

3 | RESULTS AND DISCUSSION

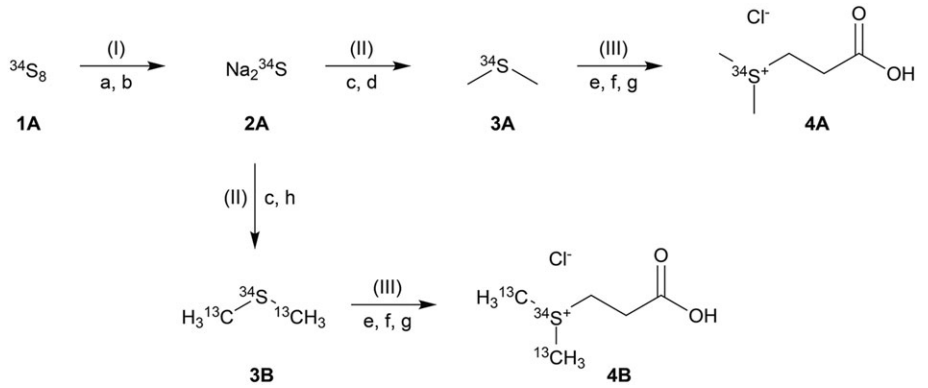
A previous study employed a strategy for the synthesis of 4A that avoided the production of volatile intermediates, but this approach required five separate reactions with purification of each intermediate and only produced an overall yield of 26% (Scheme 2).[23] In the approach



SCHEME 2 Published method for the synthesis of 4A.[23] Reported efficiencies: reaction (I), 99%; reaction (II), 92%; reaction (III), 87%; reaction (IV), 63%; reaction (V), 51%. Reagents: a, KCN (aq); b, acetonitrile; c, *tert*-butyl 3-bromopropionate; d, H_2O; e, THF; f, SmI_2; g, KOH in methanol; h, ICH_3; i, nitromethane; j, trimethyloxonium tetrafluoroborate; k, trifluoroacetic acid. The products of reactions (II), (III), and (IV) were purified by thin layer chromatography (TLC). The product of reaction (V) was purified with ion-exchange chromatography

utilized here, the loss of volatile intermediates, namely, H_2S (from aqueous 2, 2A, 2B) and DMS (3, 3A, 3B), was minimized by using a combination gas-tight reaction vessels and careful control of the temperature and pH. Loss of H_2S was reduced by using concentrated sodium hydroxide solutions.[24] Loss of DMS was reduced with low temperatures as it is a liquid below 38°C and a solid below –98°C. By taking advantage of these facts, a new method of producing 4A was developed (Schemes 1 and 3). However, because $^{34}S_8$ (1A) is quite expensive, the protocol was first optimized using S_8 (1), and the reactions were repeated multiple times to ensure reproducibility. 1 was first reduced to 2 via a Birch reduction[20,21] with Na in NH_3 (l). Subsequent evaporation of the NH_3 yielded a white powder primarily composed of anhydrous 2 with an efficiency of 78.0 ± 7.1%. The conversion of 2 to 3 was accomplished by the nucleophilic attack of S^{2-} on the methyl group of ICH_3 under anaerobic and basic conditions, and the resulting 3 was subsequently purified via distillation.[22] Finally, 3 was converted to 4 via Michael addition to acrylic acid in CH_2Cl_2 with an efficiency of 106.2 ± 13.7%.[12] The efficiency of the synthesis and purification of 3 was not determined because measurements of the amount of 3 required large dilutions of the headspace, which proved to be inaccurate (data not shown). However, the efficiency of the conversion of 2 to 4 was 75.5 ± 7.4%.

Because the boiling point of ICH_3 (43°C) is very close to that of DMS (38°C), there was a potential for unreacted ICH_3 to codistill, which would lower the purity of the final product. However, $S_2O_3{}^{2-}$ is capable of converting ICH_3 to nonvolatile compounds.[25] Thus, $Na_2S_2O_3$ was added in excess to ensure that all unreacted ICH_3 was consumed prior to distillation.



SCHEME 3 Synthesis of 4A and 4B. Reagents: a, Na; b, NH_3 (l); c, ICH_3; d, NaOH (aq); e, acrylic acid; f, CH_2Cl_2; g, HCl (g); h, $I^{13}CH_3$

To verify the purity of compounds 4A and 4B, ^{1}H-NMR was performed. The spectrum of 4A was nearly identical to that of a 4 standard (Figure 1). However, the spectrum for 4B was very different. The triplet at approximately 3.5 ppm was split into a triplet of triplets due to the isotopic coupling with the methyl-^{13}C atoms. The isotopic coupling also split the singlet indicative of the methyl protons into a doublet of doublets (Figure 1C). This complex splitting pattern has been observed in [$^{13}C_2$] DMSO (((methyl-^{13}C)sulfinyl)methane-^{13}C) and is

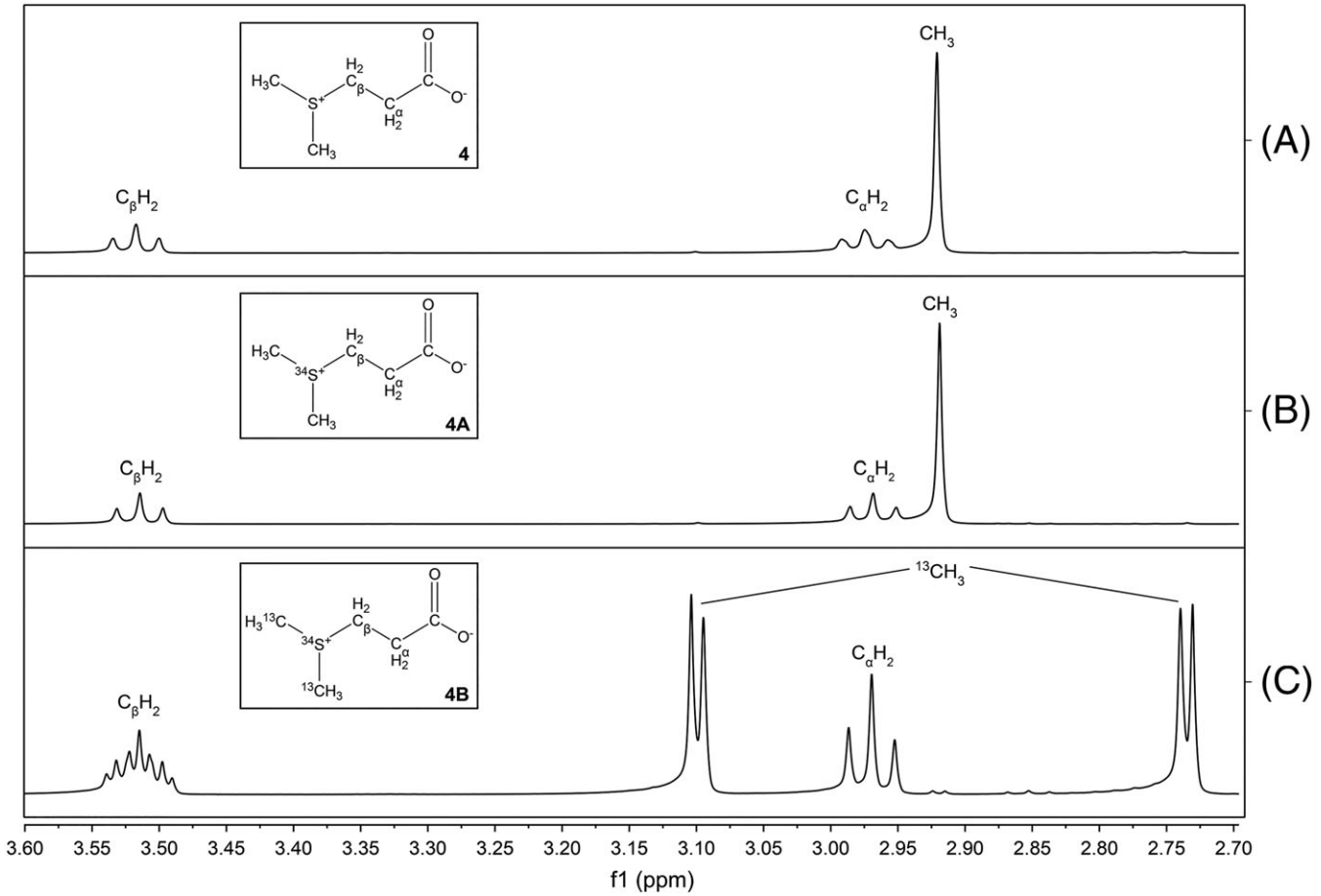
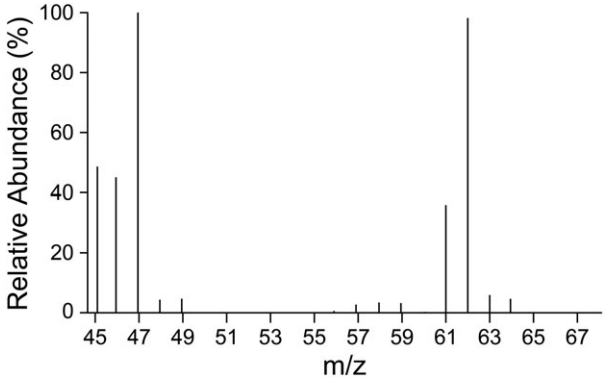


FIGURE 1 ^{1}H- nuclear magnetic resonance (NMR) spectra. All spectra have been aligned by shifting the D_2O peak to 4.790 ppm.[17] Peak heights have been adjusted for clarity. The molecule corresponding to each spectrum is shown inside the box. Peaks have been labeled with their corresponding atoms. A, ^{1}H-NMR spectrum of 4 (400 MHz, D_2O). ^{1}H-NMR δ 3.52 (t, 2H, $C_\beta H_2$, J = 6.9 Hz), δ 2.98 (t, 2H, $C_\alpha H_2$, J = 6.9 Hz), δ 2.92 (s, 6H, CH_3). B, ^{1}H-NMR spectrum of 4A (400 MHz, D_2O). ^{1}H-NMR δ 3.51 (t, 2H, $C_\beta H_2$, J = 6.9 Hz), δ 2.97 (t, 2H, $C_\alpha H_2$, J = 6.9 Hz), δ 2.92 (s, 3H). C, ^{1}H-NMR spectrum of 4B. ^{1}H-NMR δ 3.51 (tt, 2H, $C_\beta H_2$, J = 6.8, 2.9 Hz), δ 2.97 (t, 2H, $C_\alpha H_2$, J = 6.9 Hz), δ 2.92 (dd, 6H, $^{13}CH_3$, J = 145.7, 3.6 Hz)

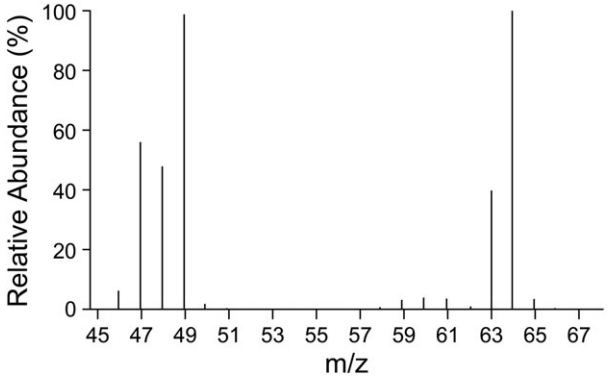
due to the $AX_3A'X'_3$ spin system.[22] On the basis of the isotopic coupling observed in the ^{1}H-NMR, there was more than or equal to 99% enrichment of the methyl-^{13}C atoms in 4B. Furthermore, ^{1}H-NMR showed that the resulting compounds were contaminated with less than 1% 3-hydroxypropionate.

In order to determine the enrichment of the ^{34}S atoms, GC–MS analyses were performed on DMS formed from DMSP. Alkaline hydrolysis converted 4, 4A, and 4B into equimolar amounts of 3, 3A, and 3B, respectively,[19] which were then analyzed via GC–MS. The relative abundance of the peaks at m/z 62, 64, and 66 was examined for 4, 4A, and 4B, respectively (Figures 2–4). For 4A, the ratio of the m/z values at 62 and 64 indicated that there was a more than or equal to 99% enrichment of the ^{34}S atom (Figure 3). For 4B, the peak at m/z equal to 66 could not be directly compared with the peak at m/z equal to 62 because the three minor peaks corresponding to m/z equal to 57 to 59 (Figure 2) were shifted to 61 to 63, respectively (Figure 4). However, the peak at m/z equal to 66 showed a 98.9% relative enrichment as compared with the peak at m/z equal to 64. This value agreed with the value determined by integrating the peaks in the ^{1}H-NMR spectrum, which qualitatively suggested that $^{13}CH_3$ was enriched by more than or equal to 99% in 4B as compared with $^{12}CH_3$ (Figure 1C). Taken together, with



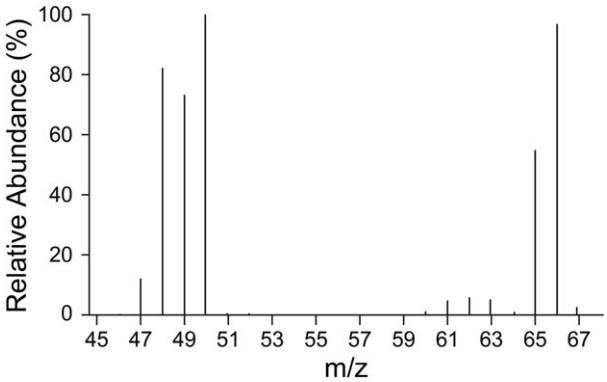
m/z	Intensity	Relative
45.10	2729515	48.64
45.95	2527357	45.03
46.95	5612041	100.00
47.95	244298	4.35
48.95	262760	4.68
55.90	34217	0.61
56.90	151226	2.69
57.95	191645	3.41
58.95	181407	3.23
60.05	15372	0.27
61.00	2013908	35.89
62.00	5510967	98.20
63.00	330274	5.89
63.95	260473	4.64
64.95	9010	0.16

FIGURE 2 Gas chromatography–mass spectrometry (GC–MS) spectrum of dimethylsulfide produced by the alkaline hydrolysis of 4. Peaks with less than 0.1% relative abundance were omitted from the table



m/z	Intensity	Relative
45.95	325631	6.23
46.95	2924768	55.98
47.95	2501316	47.88
48.95	5162289	98.81
49.90	93377	1.79
50.90	19647	0.38
57.90	37487	0.72
58.90	164444	3.15
59.90	204001	3.90
60.95	187106	3.58
62.05	49390	0.95
63.00	2078325	39.78
63.95	5224674	100.00
64.95	179914	3.44
65.90	21834	0.42

FIGURE 3 Gas chromatography–mass spectrometry (GC–MS) spectrum of dimethylsulfide produced by the alkaline hydrolysis of 4A. Peaks with less than 0.1% relative abundance were omitted from the table



m/z	Intensity	Relative
46.05	17956	0.34
47.00	638249	12.10
48.00	4338070	82.25
49.00	3864464	73.27
49.95	5274039	100.00
50.95	30698	0.58
51.95	28416	0.54
60.00	62569	1.19
61.00	252671	4.79
62.00	307792	5.84
62.95	273197	5.18
64.05	52790	1.00
65.00	2896262	54.92
66.00	5109027	96.87
66.90	137835	2.61

FIGURE 4 Gas chromatography–mass spectrometry (GC-MS) spectrum of dimethylsulfide produced by the alkaline hydrolysis of 4B. Peaks with less than 0.1% relative abundance were omitted from the table

the high atom enrichment of 4A, these data indicated that it was very likely that there was a more than 98% enrichment of the ^{13}C- and ^{34}S-atoms in 4B (Figure 4).

Because this method uses ICH_3 and acrylic acid, it allows for isotopic labeling at one or more of the atoms in 4. Acrylic-1-^{13}C acid, acrylic-$^{13}C_3$ acid, $I^{13}CH_3$, and ICD_3 are commercially available and can be used in place of unlabeled acrylic acid or ICH_3, respectively. Supporting this claim, 4B was synthesized from 1A and $I^{13}CH_3$ with an overall yield of 64.0%. This indicated that the use of ^{13}C-labeled reactants has little effect on the overall efficiency and supports the claim that this synthetic method facilitates complex labeling experiments in DMSP-utilizing organisms. Furthermore, the products of reactions (I) and/or (II) (Scheme 3) could be applied in other syntheses to generate a variety of ^{34}S-labeled compounds.

4 | CONCLUSIONS

A straight-forward method for the synthesis of a variety of dimethylsulfoniopropionate hydrochloride ((2-carboxyethyl)dimethylsulfonium hydochloride) isotopomers was developed and possessed a 250% increase in efficiency as compared with the previously published method.[23] This method is simpler, uses fewer purification steps, uses fewer and less expensive reagents, and can be completed within 2 days. The resulting DMSP is more than or equal to 99% pure and possesses more than 98% atom enrichment. Furthermore, the simplicity of this method allows for its adaptation to produce other ^{34}S-labeled compounds.

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Dr Robert Phillips (Department of Chemistry, University of Georgia) generously provided the metallic sodium used in the experiment and demonstrated how to produce liquid ammonia from ammonium hydroxide. The specialty glassware needed for performing the Birch reduction was produced by Kyle Meyer (Chemistry Glass Shop, University of Georgia). ^1H-NMR spectra were obtained by Dr Dongtao Cui (Chemical Sciences Magnetic Resonance Facility, University of Georgia), who also helped in the interpretation. Dr Dennis R. Phillips (Proteomics and Mass Spectrometry Facility, University of Georgia) provided access to a GC–MS and helped optimize the GC–MS method. This research was supported in part by a National Science Foundation Dimensions of Biodiversity grant OCE-1342694.

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