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of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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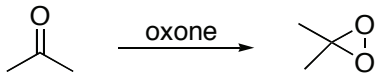
Simplified Preparation of Dimethyldioxirane (DMDO)



Submitted by Douglass F. Taber[1,]*, Peter W. DeMatteo and Rasha A. Hassan.
Checked by John L. Wood and John A. Enquist, Jr.

Caution! Reactions and subsequent operations involving peracids and peroxy compounds should be run behind a safety shield. For relatively fast reactions, the rate of addition of the peroxy compound should be slow enough so that it reacts rapidly and no significant unreacted excess is allowed to build up. The reaction mixture should be stirred efficiently while the peroxy compound is being added, and cooling should generally be provided since many reactions of peroxy compounds are exothermic. New or unfamiliar reactions, particularly those run at elevated temperatures, should be run first on a small scale. Reaction products should never be recovered from the final reaction mixture by distillation unless all residual active oxygen compounds (including unreacted peroxy compounds) have been destroyed. Decomposition of active oxygen compounds may be accomplished by the procedure described in Korach, M.; Nielsen, D. R.; Rideout, W. H. Org. Synth. ***1962****, 42, 50 (Org. Synth.* ***1973****, Coll. Vol. 5, 414).*
Dimethyldioxirane is a volatile peroxide and should be treated as such. The preparation and all reactions of the dioxirane should be carried out in a hood.

1. Procedure

A. *Dimethyldioxirane*. Distilled H_2O (20 mL), acetone (30 mL), and $NaHCO_3$ (24 g, 0.285 mol) are combined in a 1-L round-bottomed flask and chilled in an ice/water bath with magnetic stirring (oblong stirbar, 3 cm x 1 cm x 1.5 cm) for 20 min (Note 1). After 20 min, stirring is halted and Oxone (25 g, 0.0406 mol) is added in a single portion (Note 2). The flask is loosely covered and the slurry is stirred vigorously for 15 min while still submerged in the ice bath. After 15 min, the stir bar is removed from the reaction flask and rinsed with a small portion of distilled water.

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The flask containing the reaction slurry is then attached to a rotary evaporator with the bath at room temperature. The bump bulb (250 mL) (Note 3) is chilled in a dry ice/acetone bath and a vacuum of 155 mmHg is applied via a benchtop diaphragm pump and an accompanied in-line vacuum regulator. During this process, the flask is rotated vigorously (210 rpm) to prevent bumping of the slurry into the bump trap (Note 4). After 15 min, the bath temperature is raised to 40 °C over the course of 10 min. When the bath reaches 40 °C, the distillation is halted immediately via releasing the vacuum and raising the flask from the heated water bath.

The pale yellow acetone solution of DMDO is decanted from the bump bulb directly into a graduated cylinder to measure the total volume of the solution (an average of 25 mL) and then the solution is dried over Na_2SO_4. The Na_2SO_4 is removed by filtration and rinsed with 10 mL of acetone. Titration of the obtained DMDO solution is then performed according to the procedure of Adam, et al.[2] (Note 5). Results consistently show 2.1–2.3 mmol total DMDO in the solution, giving a final concentration typically in the range of 60–65 mM (Note 6). The DMDO solution was used immediately following titration.

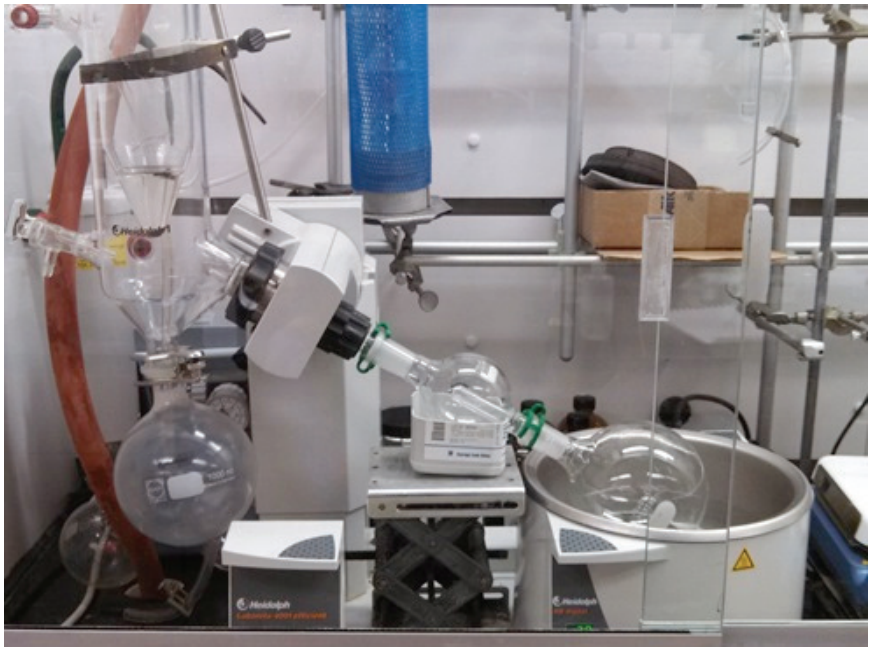
2. Notes

1. The checkers used distilled water obtained from Colorado State University's distilled water system. The checkers purchased acetone (purity of 99.7%) and $NaHCO_3$ (purity of 99.9%) from Fisher Scientific and used both directly without further purification.

2. The checkers employed oxone monopersulfate purchased from Aldrich, with purity unspecified, and used directly without further purification.

3. A standard rotary evaporator bump bulb like the one illustrated below was used.

4. The entire setup is illustrated in the accompanying photograph. The checkers found it necessary to constantly refresh the dry ice/acetone bath with additional dry ice and acetone throughout the distillation. Otherwise, cooling of the bump trap diminished significantly, and the desired DMDO solution was recovered in a much lower volume.



5. The following procedure is a representative example of the method employed by the checkers to assay the concentration of the obtained DMDO solution:[3c] In a 1 mL volumetric test tube, a 0.7 M solution of thioanisole in acetone-d_6 is prepared, to a total volume of 1 mL. A 0.6 mL portion of this solution is transferred to a 20 mL scintillation vial and chilled to ca. 10 °C in a 1,4-dioxane bath chilled with a small quantity of dry ice. Upon reaching 10 °C, 3.0 mL of the obtained DMDO solution is added to the thioanisole solution. The resulting solution is stirred for 10 min and then a portion of the solution is added directly to an NMR tube. Analysis of the ^{1}H NMR via signal integration of the sulfoxide phenyl protons at δ 7.6 – 7.9 ppm against the thioanisole phenyl protons at δ 7.1 – 7.3 ppm allows for determination of the ratio of oxidized product to excess thioanisole. From this data, concentration of the larger DMDO solution could be calculated.

The submitter's original procedure for assaying the concentration of the DMDO sample is as follows: The entire liquid collected in the bump bulb is transferred to a round-bottomed flask with CH_2Cl_2. A weighed excess amount of *trans*-stilbene is added. After 24 h, the solvent is removed under

high vacuum, and the ^{1}H NMR spectrum of the residue is recorded. All ten protons of *trans*-stilbene and the arene protons of the epoxide appear around δ 7.0, while the epoxide methine protons of the product appear at δ 3.95. Knowing how much *trans*-stilbene had been added, it is possible to calculate the amount of DMDO that had been generated.

6. In order to determine the efficacy of the prepared DMDO solution, the checkers performed a reaction wherein a sample of *trans*-stilbene was oxidized as follows: To a glass vial containing *trans*-stilbene (97.0 mg, 0.538 mmol, 1.0 equiv) is added 9.3 mL of a previously prepared and assayed solution of DMDO (65.6 mM in acetone, 0.610 mmol, 1.1 equiv). The resulting solution is stirred for 16 h, and then solvent is removed in *vacuo*. The resulting residue is dissolved in CH_2Cl_2 and dried over Na_2SO_4. After filtration and removal of solvent *in vacuo*, *trans*-stilbene oxide (104 mg, 98 %) is isolated in essentially pure form.

Trans-stilbene oxide has the following spectral properties: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.90 (s, 2 H), 7.42–7.37 (m, 10 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 62.96, 125.6, 128.4, 128.7, 137.3; IR (solid) cm^{-1}: 3036, 2989, 1603, 1493, 1461, 1285, 1072, 846, 795. Exact mass, Calculated for $C_{14}H_{13}O$ (M+H): 197.0966. Found: 197.0961. Anal. Calcd. for $C_{14}H_{12}O$: C, 85.68. H, 6.16. Found: C, 85.47. H, 6.24.

Handling and Disposal of Hazardous Chemicals

The procedures in this article are intended for use only by persons with prior training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011 www.nap.edu). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

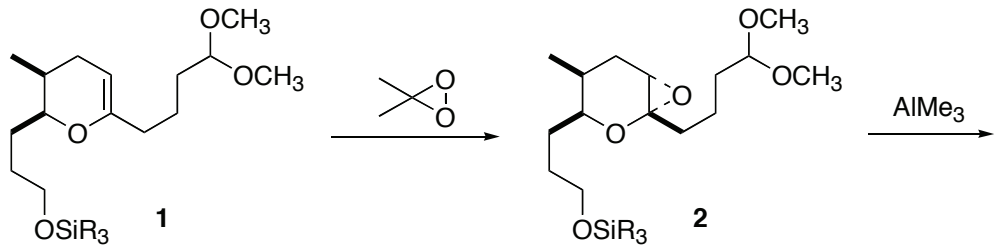
In the development and checking of these procedures, every effort has been made to identify and minimize potentially hazardous steps. The Editors believe that the procedures described in this article can be carried out with minimal risk if performed with the materials and equipment specified, and in careful accordance with the instructions provided. However, these procedures must be conducted at one's own risk. Organic Syntheses, Inc., its Editors, and its Board of Directors do not warrant or guarantee the safety of

individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

3. Discussion

Dimethyldioxirane (DMDO), easily prepared by the reaction of Oxone with acetone, has been used in organic synthesis for many years.[3] In particular, the "acetone free" form, prepared by partitioning the acetone solution of DMDO between CH_2Cl_2 and aqueous phosphate buffer, is prized for its ability to generate even very sensitive epoxides under neutral conditions.[4] This is clearly illustrated by the conversion of **1** to **3** by way of epoxide **2**, as reported by Rainer (Scheme 1).[5a]

Scheme 1. Preparation of a reactive epoxide with DMDO



Despite this utility, DMDO has not commonly been used for laboratory scale epoxidations, the commercial reagent MCPBA being widely preferred. The reluctance to employ DMDO may likely be due to the complicated cryogenic purification prescribed[3a] for the preparation of the reagent as a solution in acetone.

We have found that practical quantities of DMDO in acetone can be prepared by simple rotary evaporation of the Oxone/$NaHCO_3$/acetone slurry with collection of the distillate in the bump bulb of the rotary evaporator.

Using a 1-L round-bottomed flask, we could routinely prepare 2.1-2.3 mmol DMDO.

Titration was accomplished by the addition of a measured amount of the DMDO solution to a known quantity of thioanisole (Note 5), with ^{1}H NMR analysis of the resulting sulfide/sulfoxide ratio affording data on the concentration of the prepared solution. The DMDO solution prepared as described was used in the epoxidation of 100 mg of *trans*-stilbene in near quantitative yield.[6]

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2. Adam, W.; Chan, Y. Y.; Cremer, D.; Gauss, J.; Scheutzow, D.; Scheutzow, D.; Schindler, M. *J. Org. Chem.* **1987**, *52*, 2800–2803.

3. For current methods for the preparation of solutions of DMDO, see: a) Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847–2853. b) Adam. W.; Bialas, J.; Hadjiarapoglou, L. *Chem. Ber.* **1991**, *124*, 2377–2377. c) Murray, R. W.; Singh, M. *Org. Syn.* **1997**, *74*, 91; *Coll. Vol. 9*, **1998**, 288. c) Mikula, H.; Svatunek, D.; Lumpi, D.; Glöcklhofer, F.; Hametner, C.; Fröhlich, J. *Org. Process Res. Dev.* **2013**, *17*, 313–316.

4. For the preparation of "acetone free" DMDO, see Gilbert, M.; Ferrer, M.; Sánchez-Baez, F.; Messeguer, A. *Tetrahedron* **1997**, *53*, 8643-8650.

5. For applications of "acetone free" DMDO, see: a) Zhang, Y.; Rohanna, J.; Zhou, J.; Iyer, K.; Rainier, J. D. *J. Am. Chem. Soc.* **2011**, *133*, 3208–3216. b) Alberch, L.; Cheng, G.; Seo, S.-K.; LI, X.; Boulineau, F., Wei, A. *J. Org. Chem.* **2011**, *76*, 2532–-2547. c) Ghosh, P.; Lotesta, S. D.; Williams, L. J. *J. Am. Chem. Soc.* **2007**, *129*, 2438–2439. d) Crimmins, M. T.; McDougall, P. J.; Emmitte, K. A. *Org. Lett.* **2005**, *7*, 4033–4036. e) Bach, R. D.; Dmitrenko, O.; Adam, W.; Schambony, S. *J. Am. Chem. Soc.* **2003**, *125*, 924–934. f) Ndakala, A. J.; Howell, A. R. *J. Org. Chem.* **1998**, *63*, 6098–6099.

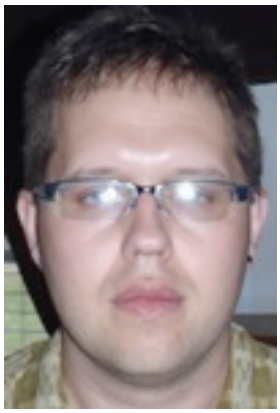
6. For a recent preparation and characterization of *trans*-stilbene oxide, see Mercier, E. A.; Smith, C. D., Parvez, M.; Back, T. G. *J. Org. Chem.* **2012**, *77*, 3508–3517.

Appendix
Chemical Abstracts Nomenclature; (Registry Number)

DMDO; dimethyldioxirane (74087-85-7)
Oxone; (70693-62-8)

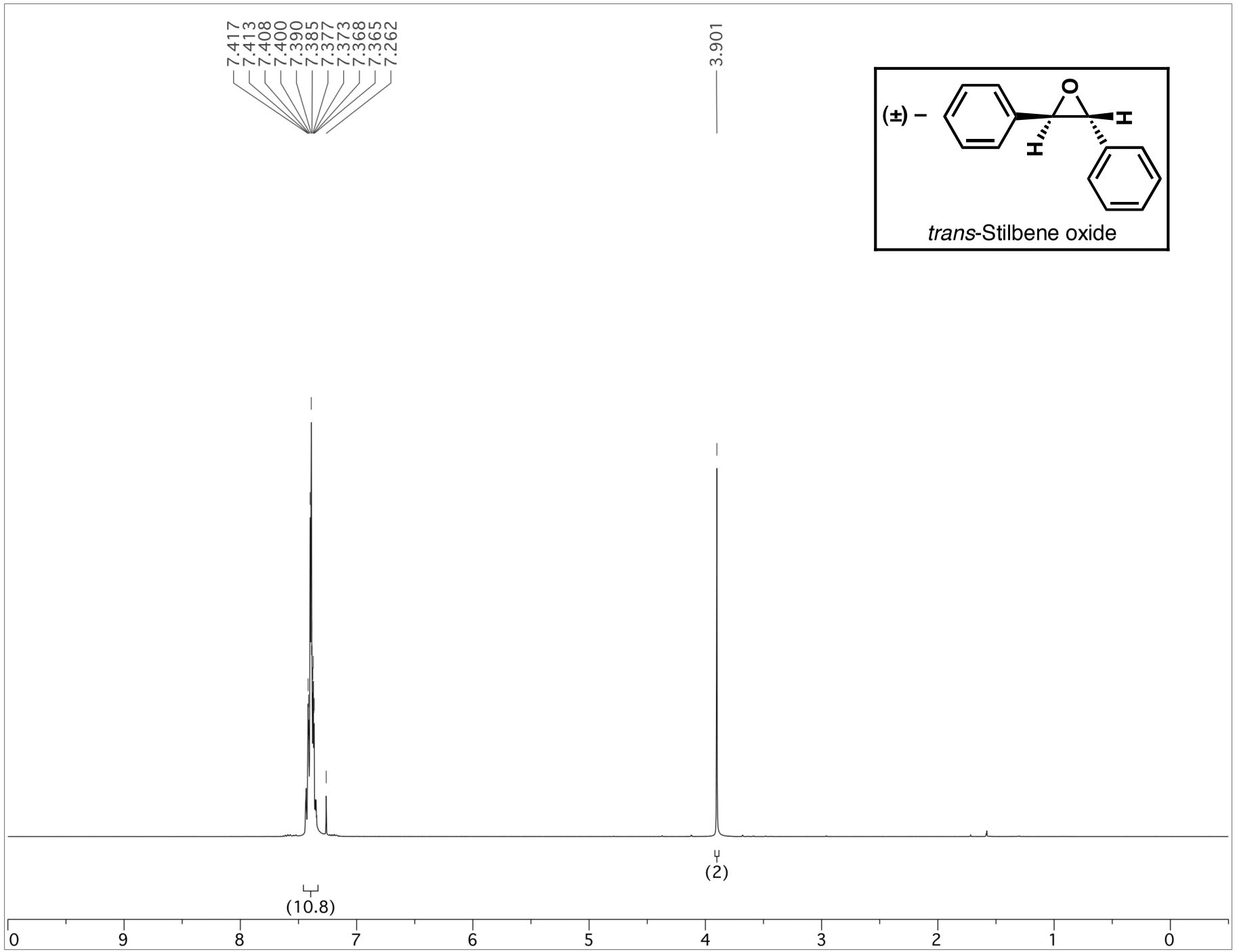
Douglass F. Taber was born in 1948 in Berkeley, California. He earned a B.S. in Chemistry with Honors from Stanford University in 1970, and a Ph.D. in Organic Chemistry from Columbia University in 1974 (G. Stork). After a postdoctoral year at the University of Wisconsin (B.M. Trost), Taber accepted a faculty position at Vanderbilt University. He moved to the University of Delaware in 1982, where he is currently Professor of Chemistry. Taber is the author of more than 200 research papers on organic synthesis and organometallic chemistry. He is also the author of the weekly Organic Highlights published at http://www.organic-chemistry.org/

Rasha Hassan was born on June 12, 1978 in Egypt. On 1995, she joined the Faculty of Pharmacy, Cairo University for college study. In May 2000, she graduated with an excellent honors grade, ranked 13th out of 1400 student in her class. Based on these accomplishments, Rasha joined the faculty of the Organic Chemistry department as a lecturer assistant, teaching laboratory Organic Chemistry to the pharmacy students. Simultaneously, she carried out research in organic synthesis to earn her Master's degree, awarded in May 2005. Since May 2011 she has continued her research toward a Ph.D. as a visiting scholar in the laboratory of Professor Douglass F. Taber at the University of Delaware.



Peter W. DeMatteo received a dual B.S. in Chemical Engineering and Chemistry from Lehigh University in 2002. He continued his chemistry studies under Ned Heindel and received his M.S. In Chemistry in 2004. He then transferred into the natural products lab of Douglass F. Taber, receiving his Ph.D. in 2011. He is currently employed as an IRTA postdoc at the National Institute for Drug Abuse where he synthesizes opioid analogs under the supervision of Dr. Kenner C. Rice.

John A. Enquist, Jr. received a B.S. in Chemistry from the University of California at San Diego in 2004. Later, he received a Ph.D. in Chemistry from the California Institute of Technology under the direction of Professor Brian M. Stoltz. He is currently a post-doctoral fellow in the laboratories of Professor John L. Wood, at the Colorado State University.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