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Review article

Reiterative epoxide-based strategies for the synthesis of stereo-*n*-ads and application to polypropionate synthesis. A personal account

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This paper is dedicated to Professor Luis Echegoyen, a mentor, a colleague and a friend.

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ABSTRACT

The enantioselective synthesis of polypropionates continues to be an attractive realm for the synthetic chemists, mostly due to the challenges presented by the number of consecutive stereogenic centers contained within the aliphatic chain. Over the years, our laboratory has developed a reiterative epoxide-based methodology for the construction of these targets, with the ultimate goal that the approach could be extended to the synthesis of polypropionate-containing natural products. The key steps include the diastereoselective epoxidation of allylic and homoallylic alcohols, and the regioselective cleavage of 2-methyl-3,4-epoxy alcohols. The choice of the organometallic reagent, and the cis/trans geometry of the chiral epoxide are used to control both the relative and absolute configuration of the resulting propionate unit, allowing our approach to be applied in the synthesis of advanced fragments. Additionally, the combination of our first- and second-generation methodologies permits the incorporation of different variations at the methyl moiety.

Contents

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José A. Prieto received his B.S (1973) in Chemistry and Ph.D. (1981) in Organic Chemistry at the University of Puerto Rico-Río Piedras under the guidance of Professor Gerald Larson (organoboranes and organosilanes). He continued as a postdoctoral fellow at UC-Berkeley with Professor Paul Bartlett (organic synthesis). In 1984, he joined de Department of Chemistry at UPR-RP were he is currently a Professor of Chemistry. His research interests include organic and organometallic synthesis, mainly synthesis of bioactive compounds. He is the Director of the UPR-RP and the Molecular Sciences Center NMR facilities. Dr. Prieto has receive several awards including the Puerto Rico Chemist Association Osvaldo Ramírez Torres Award, the UPR Academic Excellence and Productivity Award and the ACS, Puerto Rico Section, Leonardo Igaravídez Award.

Alejandra Cruz-Montañez obtained her B.S. in Chemistry from the University of Puerto Rico – Rio Piedras, in 2007. During her undergraduate education she explored chemical education and Green Chemistry research with Dr. Ingrid Montes, and a summer internship in synthetic chemistry with Dr. Alex Deiters at North Carolina State University. She is pursuing her Ph.D. in Dr. José A. Prieto's research group, focusing her efforts in developing a revised-second generation approach for the synthesis of stereotetrads and its application to interesting polypropionate-containing fragments. Her efforts have been rewarded with a fellowship from the Research Initiative for Scientific Enhancement (RISE). Her scientific curiosity has led to collaborations in the fields of biochemistry, crystallography and science education.

Keyla F. Morales-Rivera received her B.S. degree in Chemistry from University of Puerto Rico-Río Piedras Campus in 2009. In that same year, she began her graduate studies at the Chemistry Graduate Program at University of Puerto Rico-Río Piedras Campus under the guidance of Dr. José A. Prieto working on the epoxide-based approach towards the total synthesis of (−)-dolabriferol and (−)-dolabriferol B. She is recipient of Alfred P. Sloan Fellowship (2011–2013), and Research Initiative for Scientific Enhancement (RISE) Fellowship (2013–present). Her research interests include organic and organometallic synthesis, multi step synthesis of natural products.

Wildeliz Torres received her B.S. degree in Chemistry from University of Puerto Rico-Cayey Campus in 1999. In 2007, she obtained her PhD in Chemistry from University of Puerto Rico-Río Piedras Campus, developing elegant termini-differentiated syntheses of Streptovaricins D and U using Prieto's epoxide-based methodology. She received numerous accolades as a graduate student, including RISE, AGEP, and PRIDCO fellowships. Wildeliz continued as a NIH postdoctoral fellow at Stanford University with Professor Bary M. Trost, developing new transition-metal catalysis reactions. From 2014 she serves as Assistant Professor of Chemistry at the University of Puerto Rico in Mayagüez. Her research is focused on the development of metal-catalyzed step and atom economical methods toward *N*-, *O*-, and *S*-heterocycles.

Elizabeth M. Valentín received her B.S. degree in Chemistry from University of Puerto Rico at Rio Piedras in 2003, and her Ph.D. in 2013. Her dissertation focused on the convergent epoxide-based synthesis of bafilomycin A_1 and other plecomacrolide compounds in Jose A Prieto's research laboratory. During this period, she received fellowships from the Alfred P. Sloan Foundation, the IDeA Network for Biomedical Research Excellence, and the Research Initiative for Scientific Enhancement. She worked as a postdoctoral researcher at New York University with Dr. K. A. Woerpel, studying the selectivity and reactivity of highly reactive oxocarbenium intermediates. Elizabeth is currently an Assistant Professor of Chemistry at Susquehanna University in Selinsgrove, Pennsylvania. Her research interests include development of environmentally friendly methods for total synthesis of small molecules, and chemical education.

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