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

Alejandra Cruz-Montañez^a, Keyla F. Morales-Rivera^a, Wildeliz Torres^b, Elizabeth M. Valentín^c, Jaileen Rentas^a, and José A. Prieto^{a,*}

^aDepartment of Chemistry, University of Puerto Rico, Río Piedras Campus. PO Box 23346 San Juan, PR 00931

^bDepartment of Chemistry, University of Puerto Rico, Mayagüez Campus, PO Box 9000, Mayagüez, PR 00681-9000

^cDepartment of Chemistry, Susquehanna University, 514 University Avenue, Selinsgrove, Pennsylvania 17870

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 an epoxide-based three-step reiterative 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 can be 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.

Graphical abstract

*Corresponding author: jose.prieto2@upr.edu.

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

Keywords

polypropionates; stereo-*n*-ads; asymmetric synthesis; epoxide-cleavage; organometallic-cleavage

1. Introduction

Polyketides are secondary metabolites that constitute 20% of the top-selling small-molecule drugs [1]. Due to insufficient quantities of these products recovered from nature, synthetic organic chemists play a fundamental role in the development and production of these drugs. Among the polyketides, the polypropionates are an abundant subclass that can be found as common products of metabolism in plants, bacteria, insects, fungi and marine organisms [2,3]. Some of these compounds are known to inhibit the growth of bacteria, viruses, fungi, parasites and human tumor cells. At least 1% of polypropionates possess drug-like activity, and although this may seem very low, it still represents five times the average found for natural products in general [4,5].

The polypropionate moiety is characterized by an aliphatic chain with alternating methyl and hydroxy groups with a specific absolute configuration at each carbon center. The number of consecutive stereocenters constitutes both a challenge and ideal targets for synthetic organic chemists. Their structure can be described in terms of the number of asymmetric carbons present within the chain. Stereotriads refer to three contiguous stereocenters, stereotetrads to four, stereopentads to five, and stereohexads to six, where the term “stereo-*n*-ad” refers to the number of asymmetric carbons in the chain (Figure 1) [6].

Numerous synthetic methodologies have been developed to accurately generate the polypropionate stereocenters, being aldol- and aldol-related strategies the most frequently utilized approaches [7,8]. While these present elegant solutions for polypropionate synthesis, double stereodifferentiation still represents a difficulty with these methods, together with the potential difficulties of dealing with highly reactive aldehydes. Several research groups have sought alternative methodologies for polypropionate construction [9]. Among the number of synthetic methodologies that have been developed to construct the different natural and non-natural stereochemical permutations [7,10–14], only few methods are known that use epoxides as building blocks for the iterative preparation of polypropionates [15–23]. Our laboratory has worked on the design and implementation of an epoxide-based methodology for the synthesis of these complex compounds, with the ultimate goal that our methodology can be adapted to the synthesis of any polypropionate fragment regardless of its configuration. This approach could then be extended to the total synthesis of polypropionate-containing natural product.

Our methodology consists on a three-step iterative sequence that involves epoxide cleavage with an appropriate organometallic reagent, *partial* reduction of the produced alkyne and further stereoselective epoxidation of the alkene, thus generating the next epoxide to which we apply another propionate-forming iteration (Scheme 1). This non-aldol methodology enables the preparation of polypropionate chains using substrate-control, since the absolute stereochemistry introduced in the first epoxidation step controls the relative stereochemistry of the rest of the molecule. Enantioselective epoxidation reactions such as the Sharpless

epoxidation allow access to the required absolute configuration[24,25]. These readily available epoxides can be regioselectively cleaved with a number of organometallic reagents [26,27]. Our reiterative methodology also allows the incorporation of functionalization at the methyl moiety to obtain hydromethyl groups that can be present within a target molecule [28]. Demethylated polyols, present in some polyketide fragments, can also be procured using this methodology.

Since epoxide cleavage with organometallic reagents behaves as a nucleophilic substitution process, our methodology can be systematically applied to the synthesis of polypropionate chains with the required configuration. Moreover, the different polypropionate permutations present can be obtained by selecting the correct combination of epoxide and nucleophile. This methodology was successfully applied to the synthesis of the all-*anti* C5–C10 polypropionate fragment of streptovaricin U and the C14–C25 bafilomycin A₁ polypropionate chain [29,30].

The account is divided into four subsections describing how to apply our reiterative epoxide-based approach for the syntheses of different termini-differentiated stereotriads, stereotetrad, stereopentads and stereoheptads contained within selected polypropionate targets (Figure 2). The synthetic strategies with their challenges and solutions will be presented within each subsection.

2. Results and Discussion

2.1. Stereotriads

Bafilomycins, elaiophyllin, elaiolide, and formamicine (*among others*) are examples of plecomacrolides produced by different *Streptomyces* species [31]. They are characterized by a 16- or 18-membered macrolactone with two conjugated diene units and an hemiacetal side chain that is connected by a three-carbon linker. Many of these plecomacrolides act as selective inhibitors of ATPases (V-ATPases, and K-ATPases). The presence of these enzymes in proton-pump mechanisms that promote bone density loss in the body make V-ATPase inhibitors useful agents against bone-resorption diseases such as osteoporosis and arthritis [9].

Disconnection through the hemiacetal showcases how plecomacrolides can be constructed through a convergent approach (Scheme 2). Previous reported synthesis used aldol- or aldol-related methodologies to construct the propionate chain, where the usual starting material is a chiral ketone [32]. An approach similar to that used for the synthesis of the C14–C19 fragment of bafilomycin A₁ was envisioned for elaiolide, using dithiane **2** as the precursor of the C7–C11 fragment, and preparing alkyl iodide **3** as the hemiketal portion. Dithiane **2** was reported previously by us for the synthesis of the C14–C25 polypropionate fragment of bafilomycin A₁ [30]. Alkyl iodide **3** can be synthesized performing our established three-step methodology starting from known epoxide **4**. Using *trans*-pent-2-en-1-ol oxide as the starting material, we introduced the ethyl moiety at C14 from the beginning without making significant changes to the established methodology.

Cleavage of benzyl-protected epoxide **5** (obtained in 93% from **4** [33]) with the trimethylsilylacetylene aluminum and subsequent TMS removal provided alkyne **6** in 84% yield for two steps, with an 85:15 regioselectivity for the ring-opening step (Scheme 3).¹ Partial hydrogenation with Lindlar's catalyst and quinoline afforded 86% of allylic alcohol **7**. It is known that epoxidations with *m*-CPBA can be directed by adjacent hydroxy groups [17], therefore we predicted that the ethyl group would provide enough bias for the *anti*-epoxide **8** to be favored with *m*-CPBA. Stirring the reaction for more than 6 h resulted in unwanted side reactions. Fortunately, addition of 6 equiv of *m*-CPBA yielded, after 3 h, 53% of the desired *anti* epoxide **8**. Interestingly, we have found that *m*-CPBA does not provide useful diastereoselectivity with the methyl counterpart. Reduction of the terminal epoxide with LiAlH₄ furnished the expected diol and after acetonide protection, produced stereotriad **9** in 83% yield. This stereotriad corresponds to the C12–C16 polypropionate fragment of elaiolide, with the required *syn,anti* relationship as evidenced by the *J*-coupling analysis of acetonide **9** and analysis of the ¹³C NMR spectrum [34]. A formal synthesis can be completed using a reaction sequence analogous to the preparation of the C20–C25 fragment of bafilomycin A₁ [30].

2.2. Stereotetrads

Stereotetrads consist of two consecutive propionate units, and can have up to 16 different stereoisomers. Using our methodology, stereotetrads are obtained from the cleavage of 3,4-epoxy alcohols with the appropriate organometallic reagent (Scheme 1). A significant effort has been placed on the preparation of these important epoxy alcohol precursors, exploiting the capacity of hydroxyl groups to direct epoxidations.

Our initial studies towards the preparation of 3,4-epoxy alcohols were focused on using a iodocarbonation/methanolysis sequence [35]. Four propionate fragments were submitted to this two-step procedure, yielding epoxides **11** to **14** in good yields (Scheme 4). The study confirmed the prevalence of the 1,3-*syn* selectivity (relative to the C1 hydroxy group, also known as C1-*syn* selectivity). In the case of **13**, the C1-*anti* epoxide was the only observed product. In this system, the C2 methyl controlled the cyclic intermediate's conformation giving way to the *anti* epoxide. A microwave-assisted vanadium-catalyzed epoxidation was further developed to broaden the scope and applicability of homoallylic epoxidations [36]. Although the stereoselectivity of the epoxidation was the same as with the iodocyclization, vanadium epoxidation achieved higher yields and considerably lower reaction times for *cis* alkenols.

Both the iodocarbonation/methanolysis procedure and the vanadium epoxidation yielded primarily one major diastereoisomer, the C1-*syn* stereoisomer, except for epoxide **13** as previously discussed. A second-generation approach was developed in order to promote the opposite stereoselectivity. This methodology would allow for the stereoselective epoxidation of allylic alcohols not available with the conventional homoallylic epoxidation methods. The use of functionalized alkynes allowed access to allylic alcohols that, after some protecting group manipulation, enabled the synthesis of *syn,anti,trans* epoxide **17**, which could not be

¹Although cleavage with vinylmagnesium bromide would reduce the number of steps, a 50:50 mixture of regioisomers was obtained.

obtained with our first generation methodology (Scheme 5a) [28]. A variation of our second generation approach was also developed to reach the remaining epoxy alcohols, where a C2-hydroxymethyl was incorporated to enable *syn* selective epoxidations using the microwave-assisted VO(acac)₂ conditions [37]. Free and monoprotected 1,3-diols were stereoselectively epoxidized, and the directing effect was prompted by the C2-hydroxymethyl group, providing access to C2-*syn* epoxide **20** (Scheme 5b).

The developed methodologies were employed to obtain epoxides **11** through **14**, and **17**, which were used for the syntheses of crocacin, dolabriferol, and streptovaricin D polypropionate fragments discussed in the following sections. Epoxide **20** was developed as a precursor to the lankanolide polypropionate chain, not presented in this work.

2.2.1. Crocacin—The *syn,anti,anti* stereotetrad found in the crocacin family of natural products has captured the attention of a number of synthetic chemists. The crocacins are a class of antifungal and cytotoxic antibiotics isolated in 1994 from two different strains of myxobacteria, *Chondromyces crocatus* and *Chondromyces pediculatusi*. Crocacins were found to inhibit the electron transport chain in a beef heart mitochondrial respiratory assay, and they inhibited the growth of several fungi *in vitro*. They also have been identified as novel agricultural pesticide leads [38].

Retrosynthetic analysis of the crocacins revealed that they could be dissected into two halves, the polyketide fragment with the *syn,anti,anti* stereotetrad, and the acylenamine motif, the latter portion being specific to each crocacin (Scheme 6). Since the first total synthesis in 2000 [39], a plethora of formal and total syntheses of the crocacin family have been developed, most of them taking advantage of a chiral-auxiliary-based aldol reaction to install the first *syn* stereocenter (for recent total syntheses see [40–43]).

Our synthesis takes advantage of the copper-catalyzed Grignard addition studies for the cleavage of epoxide **22**, which eliminate the reduction step in the process. Epoxide **13** was obtained from chiral epoxide **22** using our reiterative approach previously discussed [26,36]. The resulting epoxide was cleaved with 1,3-dithiane using a modified Nakata procedure,[44] yielding 66% of diol **23** that contained the desired stereotetrad (Scheme 7). The absolute stereochemistry of the diol was confirmed by X-ray crystallography as being *2R,3S,4R,5R* [45]. A Stille coupling was envisioned to add the dienamide moiety present in crocacin C. Double methylation of the hydroxyl groups followed by Dess–Martin oxidation afforded aldehyde **21** quantitatively. This stereotetrad represents the *syn,anti,anti* C20–C15 polypropionate fragment of the crocacin family. Stereotetrad **23** was prepared in only 3 steps (5 steps starting from commercially available crotyl alcohol) in a 29% overall yield. Once completed, this example represents the “fastest” assembly of the crocacin stereotetrad to date.

2.2.2. Dolabriferol—Dolabriferol was isolated in 1996, and belongs to a family of non-linear polypropionates [46]. Dolabriferols B and C are closely related structures, and were isolated more recently.⁴⁰ These two compounds show moderate activity against *Mycobacterium tuberculosis* H37Rv [47]. Some researchers believe that the dolabriferols are not really secondary metabolites, but are in fact artifacts of purification that occur via a

retro-Claisen fragmentation. The complexity of this non-linear polypropionate and how to approach this problem is what attracted us to the synthesis of this unusual metabolite.

A disconnection of the ester linkage at C15 and further ring opening of the cyclic hemiacetal generates acid **24** and ketone **25**, which contains an all-*anti* stereotriad and an all-*anti* stereotetrad respectively (Scheme 8). The close relationship between these two polyketides can be exploited by developing a divergent/convergent synthesis of these fragments from terminal epoxide **26**, itself derived from *anti,anti,cis* epoxide **14**. The synthesis of the *anti,anti* stereotetrads was extensively studied for the stereoselective synthesis of the streptovaricin U fragment [29].

The optically active stereotetrad **27** was prepared in 38% overall yield using two iterations of our *anti,anti* methodology [29]. Careful protecting group manipulation allowed the preparation of carbonate **28** with *N,N'*-carbonyldiimidazole (CDI), favoring formation of the 1,2-carbonate over the 1,3-carbonate. This was confirmed by IR spectroscopy (C=O: 1761.32 cm⁻¹, C-O: 1061.01 cm⁻¹). The remaining secondary alcohol was protected as silyl ether in 67% yield. Carbonate removal by hydrolysis under alkaline conditions, followed by selective tosylation using dibutyl tin oxide and TsCl yielded stereotetrad **29** [48]. Formation of the terminal epoxide was finally achieved using sodium methoxide in methanol, yielding 95% of the desired *anti,anti,anti*-epoxide **26**. This fragment corresponds to the C3–C9 and C12–C18 polypropionate fragments of dolabriferol and dolabriferol B. Some final manipulations would be needed in order to obtain the aforementioned fragments **24** and **25** to complete the total synthesis this peculiar metabolite.

2.3. Stereopentads

2.3.1. Mycalolide—Isolated in 1989, the mycalolides are a family of secondary metabolites produced by the *Mycale* sponge [49]. Mycalolide A is 25-membered macrolide ring that incorporates a tris-oxazole attached to a highly functionalized aliphatic polyketide side chain (Figure 2). It exhibits potent antifungal activity against a wide array of pathogenic fungi, and cytotoxicity against B-16 melanoma cells with IC₅₀ values of 0.5–1.0 ng/mL [50]. Its polyketide chain contains eight of the eleven stereogenic centers present in this compound. Only two total syntheses and two polypropionate fragments have been reported to date [51–53].

One interesting feature of this natural product is the C25-demethyl moiety contained within the polypropionate chain. To this end, a convergent synthesis was envisioned where the polypropionate fragment **30** is disconnected between carbons C29 and C30, yielding aldehyde **21** and terminal alkyne **31** (Scheme 10). Synthesis of aldehyde **21** was previously discussed in the synthesis of crocacin (Scheme 7). The demethyl moiety in alkyne **31** can in turn be prepared from reductive opening of terminal epoxide **32**.

Synthesis of epoxide **32** commenced with cleavage of chiral epoxide **33** with a functionalized aluminum reagent followed by partial hydrogenation, producing *cis*-alkene **34** in 77% yield (Scheme 11). The next *anti* epoxide was successfully introduced using the iodocarbonate/methanolysis procedure, yielding 89% of epoxide **35**.² The stereoselectivity of the epoxidation was confirmed via the NOESY NMR of the iodocarbonate intermediate.

Next, methylation of the free-hydroxy group with concomitant TMS removal using TBAF in DMF afforded terminal epoxide **32** in 80% yield. A Yamaguchi-Hirao protocol for primary epoxides [54] was used to open the epoxide, gratifyingly producing the expected external cleavage in 98%. Benzyl protection of the secondary alcohol then produced 83% of alkyne **36**. A *trans* reduction using LiAlH₄ provided allylic alcohol **37**, and a Sharpless epoxidation afforded epoxide **38** in 75% yield. This stereopentad represents the C22–C27 polypropionate fragment of mycalolide A, including a demethyl center dividing the pentad. Further synthetic manipulations would be required to complete stereopentad **31** so that fragment **30** can be achieved. However, this synthesis represents a practical example where epoxides were used to extend the length of a polypropionate precursor to yield the terminally-differentiated demethyl interrupted stereopentad feature found in the mycalolides A and B aliphatic chain.

2.4. Stereohexads

2.4.1. Lobophorolide—Extracted in 2003 from the brown algae *Lobophora variegata*, lobophorolide is a cytotoxic and antifungal marine macrolide that has shown sub- μ M activity against several pathogenic and saprophytic marine fungi [55,56]. It has shown a unique 2:2 stoichiometry as 2 molecules of lobophorolide cooperate to stabilize an actin dimer. Structurally, lobophorolide is a 22-membered macrolactone ring with a tetrahydropyran ring-terminated side chain (Figure 2). Its C24–C19 polypropionate fragment **39** contains a *syn,anti,syn,anti,anti* stereohehexad where the C19 hydroxyl is methylated. A number of other actin-binding marine macrolides, namely scytophycin C, preswinholide and swinholide, have the same polypropionate unit as lobophorolide, suggesting that they may have a genetic link of associated microorganisms as their origin [57].

A retrosynthetic analysis of the stereohehexad is presented in Scheme 12. Using our reiterative methodology, fragment **39** can be obtained from regioselective cleavage of *cis* epoxide **40** with the appropriate organometallic reagent, itself obtainable from *cis*-cleavage and *anti*-epoxidation of 3,4-epoxy alcohol **41**. Application of one iteration of our methodology led to the synthesis of **41**, starting from known epoxide **42** [28,30,35].

After methylation and epoxide cleavage of **41**, *anti* epoxidation of homoallylic alcohol **43** was accomplished using the microwave-assisted vanadium-catalyzed epoxidation [36] to yield 79% of epoxide **44** after TES protection (Scheme 13).³ Various reagents were unsuccessfully attempted for the cleavage of epoxide **44**, including aluminum and Grignard reagents. Therefore, a modified Pagenkopf procedure was envisioned where the epoxide was activated with TESOTf as the Lewis acid, and at the same time, *in situ* protection of the free hydroxy group was accomplished [58]. This stereospecific nucleophilic addition using an alkynyl aluminium ate complex was successful in the cleavage of *cis*-epoxide **44** with concomitant TES protection of the secondary alcohol and desilylation of the TMS, albeit in a low 25%. Nonetheless, the desired stereohehexad fragment corresponding to the C19–C24 of

²Different oxidizing agents were tried, including *m*-CPBA, VO(acac)₂ and iodocarbonation/methanolysis procedure. Epoxidation with *m*-CPBA slightly favored the desired *anti*-epoxide in a 60:40 ratio, albeit in a low 45%. The VO(acac)₂ epoxidation did not proceed under the studied conditions, possibly due to the steric hindrance offered by the TMS group.

³The iodocarbonation-methanolysis procedure was also investigated in this epoxidation step. Carbonate epoxidation followed by methanolysis using K₂CO₃ in methanol afforded the same *anti* epoxide as evidenced by NMR analysis of both fragments.

lobophorolide, scytophycin C and the swinholides was synthesized in only four steps starting from known epoxide **41**.

2.4.2. Streptovaricin D—Streptovaricins are ansamycin antibiotics whose structure consists of a naphthoquinoid core and a polypropionate ansa bridge (Figure 2). They are a family of related structures that differ only in the degree of oxidation and acetylation of the ansa chain. They were first isolated from *Streptomyces spectabilis* in 1957, and reported activity against *Mycobacterium tuberculosis* [59]. Of all the streptovaricins, streptovaricin D is the most active against reverse transcriptase (0.25 $\mu\text{mol/mL}$ for 70% inhibition) [60]. Its polypropionate fragment consists of nine stereocenters, with a carbomethoxy functionality at C10. The polypropionate fragment of streptovaricin U replaces the C10 carbomethoxy for a methyl group, and its synthesis was reported by us using our reiterative methodology [29]. The ansa chain of streptovaricin D has yet to see a synthesis. Since this methodology offers termini differentiated fragments that can be manipulated on each end, the retrosynthesis of streptovaricin D exposes two different pathways that can be explored, the C5 to C15 route and C15 to C5 path, where the difference is the absolute configuration of the starting 3,4-epoxy alcohol (Scheme 14). The C5 to C15 pathway starts with *anti,anti,cis*-3,4-epoxy alcohol **14**, whereas the C15 to C5 route begins with *syn,anti,trans*-3,4-epoxy alcohol **41**. Both routes were studied and are summarized herein.

2.4.2.1. The C5–C15 pathway: Addition of the C10 carbomethoxy functionality required for streptovaricin D was approached using a functionalized alkyne epoxide cleavage as developed in our second generation approach [28]. *Cis* reduction then afforded epoxy diol **47** in 93% yield with the correct stereochemistry. Vanadium-catalyzed epoxidation followed by acetonide protection produced epoxide **48** in a moderate 42% yield. Attempts at the regioselective cleavage of this epoxide with diethylpropynyl aluminum occurred in moderate yield and showed mixture of regioisomeric products **49–52** with poor selectivity. Also, the acetonide moiety was partially removed under the cleavage conditions. The undesired internal attack could be attributed to the chelating ability of the methoxy group that causes it to behave not only as a 3,4-epoxy alcohol, but also as a C1-protected 2,3-epoxy alcohol derivative. *Cis* reduction and *anti* epoxidation of alkyne **49** then proceeded in good yield and excellent diastereoselectivity (>95:5), producing the advanced epoxide **53** that comprises an all-*anti* stereohexad. However, the last epoxide has the wrong relative stereochemistry, and would have to be inverted in order to complete the synthesis of the targeted polypropionate chain [61,62]. Several unsuccessful attempts were made in a similar substrate model, but starting material was generally recovered. Regardless of this outcome, compound **53** is an advanced polypropionate systems that proved the feasibility of the strategic introduction of the C10 variation required for the synthesis of streptovaricin D.

2.4.2.2. The C15–C5 pathway: The C15–C5 route takes advantage of the stereoselectivity obtained for the cleavage of epoxide **41** with the 2-TMS-ethynyl alane, which serves to implement the allylic alcohol-directed epoxidation needed in the next iteration, and also satisfies the streptovaricin D requirement for the C10 oxygenated functionality. Epoxide **54** was obtained starting from the known *syn,anti,trans*-3,4-epoxy alcohol **41** (Scheme 16). Copper-catalyzed cleavage of **54** produced alkene **55** with excellent regioselectivity (>95:5)

and good yield. The geometrical purity of the *cis* alkene was addressed by IR analysis, where the *cis* out-of-plane bending vibration band was located at 684 cm^{-1} .⁴ Monoprotection of the primary alcohol followed by iodocarbonatation produced single iodocarbonate stereoisomer **56** in 66% yield after purification. 2D NOESY analysis revealed a cross peak between the C8 methyl and C11 proton, in addition to a correlation between the C10 methylene substituent and the C9 proton, confirming the *anti* selectivity. Methanolysis with K_2CO_3 in MeOH then produced 14% of the desired *anti* epoxide **57** and 74% of the methyl carbonate **58**. Further acetonide protection of **57** provided epoxide **59** in 79%. Stereohexads **57** through **59** corresponds to the C15–C8 polypropionate fragment of streptovaricin D with the correct stereochemistry in all the stereocenters, including the C10 carbomethoxy functionality needed. The elaboration of this advanced termini-differentiated stereoheptad with the correct relative configuration and the C10 methyl variation demonstrates the flexibility and utility of our second-generation epoxide-based approach to polypropionate systems.

3. Conclusions

We have presented a unique non-aldol approach to the synthesis of polypropionate units using epoxides as building blocks. This approach is a flexible alternative, allowing the formation of a number of stereochemical permutations and structural variations, including the incorporation of demethyl, hydroxymethyl or ethyl, as required by some target molecules. We have extensively studied a number of epoxidation and cleavage combinations that can be applied to both simple and advanced polypropionate targets, showing that this methodology can be used in a systematic synthesis of advanced polypropionate targets.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Biographies

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 the Department of Chemistry at UPR-RP where 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 received several awards including the Puerto Rico Chemist Association Osvaldo Ramírez

⁴The cleavage was also attempted using *alane* and *alanate* conditions, but only SM was recovered in both cases, probably due to the sterically demanding TES groups.

Torres Award, the UPR Academic Excellence and Productivity Award and the ACS, Puerto Rico Section, Leonardo Igaravidez Award.

Alejandra Cruz-Montañez obtained her B.S. in Chemistry from the University of Puerto Rico – Río 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 fellowships and awards 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 Río Piedras in 2003, and her Ph.D. in 2013. Her dissertation focused on the convergent epoxide-based synthesis of bafilomycin A1 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.

Jaileen Rentas received her B.S. degree in Chemistry from University of Puerto Rico-Cayey Campus in 2004. In 2013, she obtained her PhD in Chemistry from University of Puerto Rico-Río Piedras Campus, working on the preparation of the polypropionate segments of scytophycin C and mycalolide A under the supervision José A. Prieto. She received fellowships from AGEP, RISE and PRIDCO (Puerto Rico industrial development corporation). Her research career was continued with a postdoctoral fellow at Eli Lilly Pharmaceutical Company.

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Highlights

- Stereoselective synthesis of stereo-*n*-ads using epoxide cleavage strategy.
- Termini-differentiated methodology allows for a linear or convergent synthesis.
- Diastereoselective approach for the reiterative construction of polypropionates.
- Organometallic reagent aids in assembling different structural variations within the target.

Figure 1.
Examples of stereo- n -ads where $n = 3, 4, 5, 6$

Figure 2.
Examples of selected polypropionate-containing natural products

Scheme 1.

Prieto's three-step reiterative sequence for the synthesis of polypropionates

Scheme 2.

Elaiolide's convergent retrosynthesis of the C7–C11 and C12–C16 polypropionate chain

Scheme 3.

Synthesis of stereotriad **9** corresponding to the C12–C16 polypropionate fragment of elaiolide

Scheme 4.

Epoxidation study of homoallylic alcohol **10** using the iodocarbonation/methanolysis procedure and the vanadium epoxidation

Scheme 5.

Second-generation approach for the stereoselective epoxidation of allylic and homoallylic alcohols

Scheme 6.

Crocacin's stereotetrad epoxide-based retrosynthesis

Scheme 7.

Synthesis of the chiral *syn,anti,anti* stereotetrad of the crocacin family

Scheme 8.

Divergent/convergent retrosynthesis of dolabriferol and dolabriferol B

Scheme 9.

Synthesis of key precursor **26** for the divergent/convergent synthesis of dolabriferol

Scheme 10.

Convergent retrosynthesis of mycalolide's C34–C22 polypropionate chain

Scheme 11.

Synthesis of the C22–C27 polypropionate fragment of mycalolide A

Scheme 12.

Retrosynthetic analysis of the C19–C24 polypropionate fragment of lobophorolide

Scheme 13.

Synthesis of C19–C24 stereohexad **45** starting from *syn,anti,trans*-3,4-epoxy alcohol **41**

Scheme 14. Retrosynthetic analysis of the streptovaricin D ansa chain **46**

Scheme 15.

Synthesis of the all-*anti* C5–C12 stereohexad **53** starting from *anti,anti,cis*-3,4-epoxy alcohol **14**

Scheme 16.

Synthesis of the C15–C8 stereohexad of streptovaricin D