Published in final edited form as:

J Org Chem. 2009 March 20; 74(6): 2447–2451. doi:10.1021/jo8026966.

Stereoselective Construction of all-*anti* Polypropionate Modules: Synthesis of the C5-C10 Fragment of Streptovaricin U

Wildeliz Torres, Raúl R. Rodríguez, and José A. Prieto *

Department of Chemistry, University of Puerto Rico, Río Piedras Campus, PO Box 23346, San Juan, P.R. 00931-3346, USA

Abstract

A concise non-aldol approach for the stereoselective construction of all-*anti* polypropionate fragments was developed. The iterative epoxide-based methodology consists of the *syn*-selective epoxidation of cis homoallylic alcohols using the VO(acac)₂ catalyzed conditions followed by epoxide cleavage with a propynyl aluminum reagent as key steps. The methodology was applied to the synthesis of the all-*anti* C6-C10 fragment of streptovaricin U.

Introduction

Polypropionate chains are structural motifs consisting of alternating methyl and hydroxy groups within an aliphatic framework. These structures are found in many natural products having a wide range of biological and medicinal activity.¹ Their synthesis has attracted great interest among synthetic chemists due to the challenge represented by the stereoselective assembly of the contiguous stereogenic centers.² Among the diverse approaches that have been developed for the synthesis of polypropionates, aldol and aldol-related strategies are most prevalent, since these processes are well understood and their intricacies are well documented.³ Interestingly, the *anti,anti,anti*-stereotetrad **1** (Figure 1), found in many important natural products such as ionomycin, zincophorin, the streptovaricins, and others, has been the most difficult to construct when employing enantioselective aldol or crotylmatalation strategies.⁴ This is because the *anti,anti* relationship must arise from disfavored *anti*-Felkin transition states.⁵ This challenge has produced a number of ingenious *anti* selective aldol and crotylmatal strategies that have been very useful in polyketide synthesis.^{6,7}

While the alternative approaches present high diastereo- and enantioselectivities, efforts to develop efficient stereoselective non-aldol methods for the construction of *anti,anti* polypropionate subunits continue.⁸ These efforts become more evident when longer all-*anti* stereotetrad (**1**) or -pentad (**2**) subunits (such as the C18–C21 and the C6–C10 segments of ionomycin,⁹ and streptovaricin U,¹⁰ respectively) need to be elaborated.

E-mail: japrieto@uprrp.edu.

Supporting Information Available

NMR spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Epoxide-based approaches have also been used for the synthesis of polypropionates, albeit to a lesser extent. These versatile intermediates, which can be prepared stereoselectively by several methods,¹¹ were first considered for polypropionate synthesis by Kishi,¹² Corey¹³ and Bartlett,¹⁴ in studies related the synthesis of the rifamycin S ansa chain. During the mid eighties, Lipshutz developed a reiterative route for the preparation of all *syn*-1,3-polyols and polyketides, reacting optically active epoxides with higher order *cis*- or *trans*-propenyl cuprates.¹⁵ Later, Miyashita and co-workers developed a reiterative entry to polypropionates by means of a regio- and stereoselective methylation of γ,δ -epoxy acrylates with trimethylalane.¹⁶

Recently, we reported an epoxide-based methodology for the stereoselective construction of polypropionates (Scheme 1).¹⁷ Our reiterative approach includes a sequence of three reactions: stereoselective epoxidation of unsaturated alcohols, regioselective alkynyl alane cleavage of the epoxide, and *cis* or *trans* reduction of the incorporated alkyne to produce a new homoallylic alcohol. Each sequence incorporates a propionate fragment into the growing chain. The propionate unit formed during the epoxide cleavage step will have a *syn* relationship if the epoxide geometry is *trans* or an *anti* arrangement if a *cis* epoxide is used. The configuration of the resulting hydroxy groups is determined by the absolute configuration of the epoxide precursor, which results from a diastereoselective epoxidation of the alkenol precursor.¹⁸

The application of our method to the preparation and cleavage of a series of diastereomeric 3,4-epoxy alcohols produced the corresponding stereotetrads with different degrees of regioselectivity and yield. Remarkably, the “arduously accessible”¹⁹ all-*anti* stereotetrad **9** was readily attained using this approach (Scheme 2). For this, the TIPS protected *cis* epoxy alcohol **6** was regioselectively cleaved with diethyl propynyl alane to yield the first *anti* unit. Hydrogenation of the incorporated alkyne produced alkenol **7** in good yield. An alternative copper catalyzed *cis*-propenylmagnesium bromide cleavage of epoxide **6** produced **7** in similar yield and regioselectivity with the convenient exclusion of the alkyne reduction step.²⁰ Alkenol **7** was converted to epoxide **8** using the VO(acac)₂ catalyzed epoxidation under microwave irradiation, which produced exclusively the desired *syn* epoxy alcohol in higher yield than the established iodocarbonation/methanolysis method.^{11b,c,18a} Finally, the propynyl alane cleavage of epoxide **8** produced the *anti,anti,anti* alkynyl diol **9** as the only regioisomer. These results prompted us to further elaborate on this approach with the intent to develop an effective methodology for the elaboration of all-*anti* polypropionate fragments, which could be incorporated as synthetic modules for the preparation of longer polypropionate chains. Herein, we report a highly stereo- and regioselective epoxide-based methodology for the synthesis of all-*anti* polypropionate units and its application to the synthesis of the all-*anti* C5–C10 segments of streptovaricin U.

Results and Discussion

For the elaboration of longer all-*anti* polypropionate fragments, we envisaged a linear progression that comprises a reiteration of our three-step reaction cycles (or a two-step sequence if the Grignard method is used) starting from alkynediol **9**. An advantage of employing epoxide chemistry in this fashion is the inherent S_N2 behavior of epoxides toward nucleophilic attack, providing stereodefined products. In addition, contrary to the generally more efficient convergent methodologies, a linear approach circumvents the setbacks associated with the coupling of advanced fragments that already contain stereogenic centers and are prone to mismatched interactions.²¹

In this regard, alkyne **9** was reduced to the *cis*-alkenediol **10** and subjected to an epoxidation using the microwave assisted VO(acac)₂ conditions, producing epoxide **11** as a single

diastereomer in 88% yield (Scheme 3). Epoxy diol **11** was protected as the acetonide **12** and reacted with the propynylalane reagent to produce the all-*anti,cis* epoxide **12**.

To evaluate the alternate epoxide cleavage manifold, epoxide **8** was subjected to the copper catalyzed *cis*-propenyl Grignard reaction conditions, with the expectation that diol **10** could be produced in one step. Instead of the alkenol product, a 1:1 mixture of ethyl ketone **17** and furan **18** were obtained as the major products (Scheme 4). The formation of ketone **17** is consistent with a MgBr_2 promoted epoxide to ketone rearrangement under the Grignard reaction conditions (Schlenk equilibrium).²² Furan **18** results from the intramolecular attack of the magnesium alkoxide to the external epoxide carbon. Both reactions occur because of the low reactivity of disubstituted epoxide **8** under the copper catalyzed Grignard reaction conditions. To test this assumption and suppress the formation of these side products, epoxy alcohol **9** was protected as the benzyl ether **19**. Although this strategy did curtail the formation of the unwanted products, only the starting benzyl ether **19** was recovered. The epoxidation of alkenediol **10** was also evaluated using the complementary iodocarbonation/methanolysis sequence. While the iodocarbonation reaction proceeded as expected, the methanolysis step produced epoxide **11**, together with a mixture of methyl carbonate products. The results establish the vanadium catalyzed epoxidation and the propynyl alane mediated epoxide cleavage, as the preferred reactions for the elaboration of *anti* propionate units.

To further extend the all-*anti* polypropionate fragment, another iteration was implemented. The reaction of epoxide **12** with diethylpropynylalane provided exclusively the desired external cleavage product in a 53% yield, however, a 2:1 mixture of acetonide **13** with the deprotected triol **14** was obtained. Thus, to complete the reaction sequence, compounds **13** and **14** were easily separated by chromatography and acetonide **13** was hydrogenated to produce alkenol **15**. Compounds **13** and **14** represent termini-differentiated all-*anti* stereohexad elaborated in a straightforward and highly stereoselective fashion. The all-*anti* stereohexad **15** corresponds to the C5–C10 fragment of streptovaricin U containing the five chiral centers (C6–C10) with the correct relative configuration, a homoallylic alkene for further epoxidation (an *anti* epoxidation is required at this point), and a masked aldehyde at C5.

With alkenol **15** on hand, it was further *syn* epoxidized under the microwave assisted VO(acac)₂ catalyzed conditions to efficiently furnish the more advanced epoxide **16**. The resulting polypropionate chain has seven consecutive all-*anti* stereogenic centers assembled in a simple and highly stereoselective iterative fashion. In principle, another *anti* subunit could be further generated by cleavage of the epoxide moiety. Therefore, this epoxidation/cleavage sequence can be successfully applied for the preparation of advanced all-*anti* polypropionate fragments, which could be used as modules for chain elongation allowing further manipulations in both directions.

The regioselectivity of the epoxide cleavage reactions to produce the 1,3-diols resulting from the attack at the external epoxide carbon (C4) was confirmed by ¹³C NMR. For example, compound **13** showed diagnostic peaks at 38.9 ppm for the C2 methine and 30.1 ppm for the C4 propargyl carbon, compared to the 1,4-diols peaks at 34–37 and 41–46 ppm for the C2 and C3 carbon atoms, respectively (Figure 3). This was corroborated by the COSY spectra of **13** and **14**, showing cross peaks between the C4 methyl protons and the propargylic methines.

The *syn* 1,3-diol relationship in **11** was confirmed by its conversion to the corresponding 1,3-acetonide **12**, where the ¹³C NMR revealed peaks at 19.4 and 29.9 ppm for the *gem*-dimethyl carbon atoms.^{17,23} In addition, **12** showed coupling constants of $J_{ab} = 10.3$ Hz and $J_{bc} = 10.5$ Hz for the 6-membered ring vicinal protons corresponding to an axial-axial relationship, confirming the *anti,anti* stereotriad.²⁴ The *syn/anti* stereoselectivity of the epoxidation reaction was again established by ¹³C NMR using the diagnostic C2 methine and C3,C4

epoxide carbons. As previously reported,¹⁸ when an *anti* 2-methyl-3-epoxy relationship is present, the epoxide C3 and C4 carbons show signals near 52 and 58 ppm respectively, while a *syn* relationship displays higher values between 54 and 60 ppm. This tendency holds for the *cis*-2-methyl-3,4-epoxy alcohols **11**, **12** and **16**, thus establishing the required *syn* hydroxy-epoxide selectivity (Figure 3).

Conclusion

In summary, we have successfully devised a concise method for the stereo- and regioselective construction of all-*anti* termini-differentiated polypropionate modules. The microwave-assisted VO(acac)₂ catalyzed epoxidation of the *cis*-homoallylic alcohol precursors produced better yields than the iodocarbonation sequence and excellent *syn* diastereoselectivity. The diethylpropynylalane cleavage of the *anti,anti,cis*-3,4-epoxy alcohol systems showed to be more reliable than the copper catalyzed *cis*-propenyl Grignard conditions for the more advance all-*anti* systems. The simplicity of the chemical transformations and iterativity of the reaction sequence makes this method advantageous and practical. The methodology was applied to the synthesis of the all-*anti* C6–C10 fragment (**15**) of streptovaricin U.

Experimental Section

(±)-(2*S**, 3*S**, 4*S**, 5*S**, *Z*)-3,5-Dimethyl-1-[(triisopropylsilyl)oxy]-6-octene-2,4-diol. (**10**)

The alkyne diol **9** (3.0 g, 8.9 mmol) was hydrogenated^{18a} using 0.59 mL of freshly distilled dry quinoline, 0.58 g of Pd/C catalyst (10% Pd, 0.066 g/mmol) and 18.8 mL of dry hexane. After workup and solvent evaporation, 2.88 g (94%) of neat crude was obtained. The alkenediol **10** was used for the next step without further purification. ¹H NMR: TM 5.52 (dd, *J* = 10.5, 5.0 Hz, 1H), 5.50 (dd, *J* = 10.5, 7.1 Hz, 1H), 3.84 (dd, *J* = 9.7, 3.4 Hz, 1H), 3.70 (ddd, *J* = 7.8, 7.8, 3.4 Hz, 1H), 3.57 (dd, *J* = 9.7, 7.8 Hz, 1H), 3.47 (dd, *J* = 8.1, 3.6 Hz, 1H), 2.72 (ddq, *J* = 7.1, 6.6, 3.6 Hz, 1H), 1.66 (ddq, *J* = 8.1, 7.8, 6.9 Hz, 1H), 1.62 (d, *J* = 5.0 Hz, 3H), 1.06 (m, 21H), 1.06 (d, *J* = 6.6 Hz, 3H), 0.79 (d, *J* = 6.9 Hz, 3H). ¹³C NMR: δ 131.4, 124.1, 79.4, 76.2, 65.9, 38.6, 34.2, 18.1, 17.9, 13.0, 13.0, 12.1.

(±)-(2*S**, 3*S**, 4*R**, 5*R**, 6*R**, 7*S**)-6,7-Epoxy-3,5-dimethyl-1-[(triisopropylsilyl) oxy]-2,4-octanediol. (**11**)

The alkene diol **10** (5.37 g, 15.60 mmol) was subjected to the vanadium catalyzed epoxidation under MW irradiation condition^{18b} using 0.058 g (0.014 equiv) of VO(acac)₂, 60 mL of toluene, and 4.1 mL of *t*-butyl hydroperoxide (4.24 M in toluene, 1.1 equiv). After workup and solvent evaporation, 5.63 g (100%) of epoxide **11** was obtained. The crude was used without further purification. ¹H NMR: δ 4.61 (s, 1H), 3.87 (dd, *J* = 9.6, 3.3 Hz, 1H), 3.68 (ddd, *J* = 8.3, 5.1, 3.3 Hz, 1H), 3.61 (dd, *J* = 8.3, 3.1 Hz, 1H), 3.57 (dd, *J* = 9.6, 8.3 Hz, 1H), 3.30 (s, 1H), 3.10 (dd, *J* = 9.2, 4.5 Hz, 1H), 2.99 (dq, *J* = 5.6, 4.5 Hz, 1H), 1.95 (ddq, *J* = 8.3, 6.8, 5.1 Hz, 1H), 1.70 (ddq, *J* = 9.3, 7.0, 3.1 Hz, 1H), 1.29 (d, *J* = 5.6 Hz, 3H), 1.06 (m, 21H), 1.06 (d, *J* = 7.0 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 3H). ¹³C NMR: δ 80.0, 76.7, 66.0, 57.1, 50.6, 38.6, 34.3, 17.9, 14.3, 13.4, 13.3, 11.8. Anal. Calcd for C₁₉H₄₀O₄Si: C, 63.28; H, 11.18. Found: C, 63.49; H, 11.32.

(±)-(4*R**, 5*S**, 6*S**)-4-[(1*R**, 2*R**, 3*S**)-(2,3-Epoxy-1-methyl butyl)]-2,2,5-trimethyl-6-[(triisopropyl silyl oxy) methyl]-1,3-dioxane. (**12**)

The crude epoxy diol **11** (2.0 g, 5.55 mmol) was converted to the acetone by adding 0.083 g of PPTS and 0.266 mL of 2-methoxypropene in 52.0 mL of CH₂Cl₂ at 0 °C. Workup, solvent evaporation and column chromatography (100:1 hexane/ether) yielded 1.31 g (59 % for the three-step sequence) of the expected product **12**. ¹H NMR: δ 3.82 (dd, *J* = 10.8, 3.5 Hz, 1H), 3.71 (dd, *J* = 10.8, 5.1 Hz, 1H), 3.52 (ddd, *J* = 10.3, 5.3, 3.5 Hz, 1H), 3.48 (dd, *J* = 10.5, 2.1

Hz, 1H), 3.09 (dd, $J = 9.2, 4.5$ Hz, 1H), 2.93 (dq, $J = 5.5, 4.5$ Hz, 1H), 1.86 (ddq, $J = 10.5, 10.3, 6.5$ Hz, 1H), 1.70 (ddq, $J = 9.2, 7.1, 2.1$ Hz, 1H), 1.41 (s, 3H), 1.36 (s, 3H), 1.27 (d, $J = 5.5$ Hz, 3H), 1.08 (m, 21H), 0.96 (d, $J = 7.1$ Hz, 3H), 0.85 (d, $J = 6.5$ Hz, 3H). ^{13}C NMR: δ 97.8, 77.4, 76.1, 66.3, 56.4, 50.3, 33.6, 33.0, 29.9, 19.4, 17.9, 13.9, 13.4, 12.1, 12.0. Anal. Calcd for $\text{C}_{22}\text{H}_{44}\text{O}_4\text{Si}$: C, 65.95; H, 11.07. Found: C, 65.87; H, 11.14.

($\pm$)-(4S*, 5S*, 6S*)-4-[(1S*, 2S*, 3S*)-1,3-Dimethyl-2-hydroxy-4-hexynyl]-6-[(triisopropyl silyl oxy)-methyl]-2,2,5-trimethyl-1,3-dioxane. (13)

Epoxide **12** (0.50 g, 1.25 mmol) was subjected to the propynylalane cleavage procedure¹¹ using 9.6 mL of dry toluene (0.13 M), 2.8 mL (6.2 mmol, 5 equiv) of *n*-BuLi (2.27 M in hexane), an excess of propyne gas, and 3.4 mL (6.2 mmol, 5 equiv) of diethylaluminum chloride (1.8 M in toluene). Work up, solvent evaporation and flash chromatography (12:1 Hex/EtOAc), yielded 0.195 g (35%) of pure product **13** and 0.089 g (18%) of the expected product **14** without the acetone moiety. ^1H NMR: δ 3.79 (dd, $J = 10.8, 3.5$ Hz, 1H), 3.72 (dd, $J = 10.8, 5.1$ Hz, 1H), 3.55 (dd, $J = 10.6, 1.7$ Hz, 1H), 3.52 (ddd, $J = 10.3, 5.1, 3.5$ Hz, 1H), 3.43 (ddd, $J = 8.5, 6.0, 2.4$ Hz, 1H), 2.72 (d, $J = 6.0$ Hz, 1H), 2.67 (dq, $J = 7.0, 2.4, 2.4$ Hz, 1H), 2.06 (ddq, $J = 8.5, 7.0, 1.7$ Hz, 1H), 1.94 (ddq, $J = 10.6, 10.3, 6.5$ Hz, 1H), 1.82 (d, $J = 2.4$, 3H), 1.42 (s, 3H), 1.38 (s, 3H), 1.25 (d, $J = 7.0$ Hz, 3H), 1.06 (m, 21H), 0.96 (d, $J = 7.0$ Hz, 3H), 0.90 (d, $J = 6.6$ Hz, 3H). ^{13}C NMR: δ 98.0, 79.6, 78.8, 78.1, 76.4, 76.3, 66.1, 38.9, 34.4, 30.4, 30.1, 19.2, 18.9, 18.0, 16.2, 12.5, 12.0, 3.7. Anal. Calcd for $\text{C}_{25}\text{H}_{48}\text{O}_4\text{Si}$: C, 68.13; H, 10.98. Found: C, 67.94; H, 11.08.

($\pm$)-(3S*, 4S*, 5S*, 6S*, 7S*, 8S*, Z)-3,5,7-trimethyl-1-[(triisopropylsilyl)oxy]-dec-8-ene-2,4,6-triol (14)

^1H NMR: δ 3.86 (dd, $J = 9.6, 3.8$ Hz, 1H), 3.76 (ddd, $J = 8.3, 7.4, 3.8$ Hz, 1H), 3.86 (dd, $J = 9.6, 3.6$ Hz, 1H), 3.58 (dd, $J = 5.4, 5.4$ Hz, 1H), 3.41 (dd, $J = 8.4, 2.2$ Hz, 1H), 2.72 (dq, $J = 7.8, 2.2, 1.8$ Hz, 1H), 2.08 (ddq, $J = 8.4, 6.9, 5.4$ Hz, 1H), 2.05 (ddq, $J = 7.4, 6.9, 5.4$ Hz, 1H), 1.81 (d, $J = 1.8$, 3H), 1.23 (d, $J = 7.8$ Hz, 3H), 1.06 (m, 21H), 0.95 (d, $J = 6.9$ Hz, 3H) and (d, $J = 6.9$ Hz, 3H). ^{13}C NMR: δ 81.6, 79.1, 78.6, 78.5, 75.2, 65.8, 40.3, 39.2, 30.4, 18.7, 17.9, 15.5, 14.3, 11.9, 3.6.

($\pm$)-(4S*, 5S*, 6S*)-4-[(1S*, 2S*, 3S*, Z)-1,3-Dimethyl-2-hydroxy-4-hexenyl]-6-[(triisopropylsilyloxy)-methyl]-2,2,5-trimethyl-1,3-dioxane (15)

Alkynol **13** (0.34 g, 0.77 mmol) was hydrogenated^{18a} using 0.05 mL of freshly distilled dry quinoline, 0.05 g of Pd/C catalyst (10% Pd, 0.066 g/mmol) and dry hexane. After workup and solvent evaporation, column chromatography (50:1 HexEtAc), yielded 0.24 g (71%) of pure product **15**. ^1H NMR: δ 5.52 (dq, $J = 11.0, 5.0$ Hz, 1H), 5.49 (dd, $J = 11.0, 8.9$ Hz, 1H), 3.77 (dd, $J = 10.9, 3.2$ Hz, 1H), 3.72 (dd, $J = 10.9, 5.0$ Hz, 1H), 3.49 (ddd, $J = 10.5, 5.0, 3.2$ Hz, 1H), 3.49 (dd, $J = 8.3, 3.4$ Hz, 1H), 3.48 (dd, $J = 10.5, 1.7$ Hz, 1H), 3.10 (bs, 1H), 2.70 (ddq, $J = 8.9, 6.8, 3.4$ Hz, 1H), 1.93 (ddq, $J = 10.5, 10.5, 6.5$ Hz, 1H), 1.83 (ddq, $J = 8.3, 7.1, 1.7$ Hz, 1H), 1.62 (d, $J = 5.0$, 3H), 1.42 (s, 3H), 1.38 (s, 3H), 1.06 (m, 21H), 1.05 (d, $J = 6.8$ Hz, 3H), 0.94 (d, $J = 7.1$ Hz, 3H), 0.86 (d, $J = 6.5$ Hz, 3H). ^{13}C NMR: δ 132.1, 123.7, 98.1, 80.0, 78.7, 76.4, 65.9, 36.9, 34.6, 34.2, 30.2, 19.1, 18.4, 18.0, 13.0, 12.6, 12.0. Anal. Calcd. for $\text{C}_{25}\text{H}_{50}\text{O}_4\text{Si}$: C, 67.82; H 11.38. Found: C, 67.55; H, 11.42.

($\pm$)-(4S*, 5S*, 6S*)-4-[(1S*, 2S*, 3R*, 4R*, 5S*)-1,3-Dimethyl-2-hydroxy-4,5-epoxyhexyl]-6-[(triisopropylsilyloxy)-methyl]-2,2,5-trimethyl-1,3-dioxane. (16)

Alkenol **15** (0.21 g, 0.47 mmol) was subjected to the vanadium catalyzed epoxidation under MW irradiation conditions^{18b} using 0.0017 g (0.014 equiv) of $\text{VO}(\text{acac})_2$, 10 mL of toluene, and 0.13 mL of *t*-butyl hydroperoxide (3.85 M in toluene, 1.1 equiv). After column chromatography (9:1 hexane/ethyl acetate), 0.176 g (87%) of the epoxide **16** was

obtained. ^1H NMR: δ 3.77 (dd, J = 10.9, 3.3 Hz, 1H), 3.71 (dd, J = 10.9, 5.1 Hz, 1H), 3.60 (ddd, J = 6.3, 2.6, 2.7 Hz, 1H), 3.51 (ddd, J = 10.3, 5.1, 3.3 Hz, 1H), 3.48 (dd, J = 10.8, 1.0 Hz, 1H), 3.38 (d, J = 2.7 Hz, 1H), 3.11 (dd, J = 9.2, 4.6 Hz, 1H), 2.98 (dq, J = 5.4, 4.6 Hz, 1H), 2.28 (ddq, J = 7.0, 6.3, 1.0 Hz, 1H), 1.95 (ddq, J = 10.8, 10.3, 6.5 Hz, 1H), 1.61 (ddq, J = 9.2, 6.9, 2.6 Hz, 1H), 1.42 (s, 3H), 1.39 (s, 3H), 1.28 (d, J = 5.4 Hz, 3H), 1.05 (m, 24H), 0.96 (d, J = 7.0 Hz, 3H), 0.91 (d, J = 6.5 Hz, 3H). ^{13}C NMR: δ 98.1, 80.2, 78.3, 76.5, 65.8, 56.9, 50.3, 36.6, 35.1, 34.5, 30.2, 19.0, 18.2, 17.9, 14.7, 13.4, 12.6, 12.0. Anal. Calcd for $\text{C}_{25}\text{H}_{50}\text{O}_5\text{Si}$: C, 65.45; H, 10.99. Found: C, 65.72; H, 11.22.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This work was supported by NIH RISE (1R25-GM-61151-01A1) and NIH SCORE (2S06GM-08102-29) programs.

References

- Omura, S., editor. *Macrolide Antibiotics. Chemistry, Biology, and Practice*. Vol. 2. Academic Press; New York: 2002. (b) Davies-Coleman MT, Garson MJ. *Nat Prod Rep* 1998;15:477–493. [PubMed: 9807811] O'Hagan, D. *The Polyketide Metabolites*. Ellis Harwood; Chichester: 1991. (d) O'Hagan D. *Nat Prod Rep* 1995;12:1–32.
- For recent reviews see: (a) Koskinen AMP, Karisalmi K. *Chem Soc Rev* 2005;34:677–690.690 [PubMed: 16186897] (b) Faul MM, Huff BE. *Chem Rev* 2000;100:2407–2474.2474 [PubMed: 11749289]
- For reviews see: (a) Schetter B, Mahrwald R. *Angew Chem Int Ed* 2006;45:7506–7525.7525(b) Mahrwald R. *Modern Aldol Reactions*. Wiley-VCH New York 2004 (c) Paterson I, Cowden CJ, Wallace DJ, Otera J. *Modern Carbonyl Chemistry* Wiley-VCH New York 2000:249. (d) Carreira EM, Otera J. *Modern Carbonyl Chemistry* Wiley-VCH New York 2000:279.
- For reviews see: (a) Chemler SR, Roush WR, Otera J. *Modern Carbonyl Chemistry* Wiley-VCH New York 2000:403. (b) Denmark SE, Almstead MG, Otera J. *Modern Carbonyl Chemistry* Wiley-VCH New York 2000:299.
- (a) Roush WR, Palkowitz AD, Ando K. *J Am Chem Soc* 1990;112:6348–6359. (b) Roush WR. *J Org Chem* 1991;56:4151–4157. (c) Hoffmann RW, Dahmann G, Andersen MW. *Synthesis* 1994:629–638.
- For reviews see: (a) Ramachandran PV. *Aldrichimica Acta* 2002;35:23–35.35 (b) Mahrwald R. *Chem Rev* 1999;99:1095–1120.1120 [PubMed: 11749441] (c) Brown HC, Ramachandran PV. *J Organometal Chem* 1995;500:1–19.19 (d) Duthaler RO, Hafner A. *Chem Rev* 1992;92:807–832.832 (e) Hoffmann RW. *Angew Chem Int Ed Engl* 1982;21:555–566.566
- For recent examples: (a) Karisalmi K, Koskinen AMP. *Synthesis* 2004:1331–1342.1342 (b) Calter MA, Song W, Zhou JG. *J Org Chem* 2004;69:1270–1275.1275 [PubMed: 14961680] (c) Kiyooka S. *Tetrahedron: Asymm* 2003;14:2897–2910.2910 (d) Guindon Y, Brazeau JF. *Organic Lett* 2004;6:2599–2602.2602 (e) Chemler SR, Roush WR. *J Org Chem* 2002;68:1319–1333.1333 [PubMed: 12585871] (f) Hassfeld J, Christmann M, Kalesse M. *Org Lett* 2001;3:3561–3564.3564 [PubMed: 11678708]
- For recent non-aldol methods see (a) Sarabia F, Martín-Gálvez F, García-Castro M, Chammaa S, Sánchez-Ruiz A, Tejón-Blanco JF. *J Org Chem* 2008;73:8979–8986.8986 [PubMed: 18855458] (b) Parker K, Xie Q. *Org Lett* 2008;10:1349–1352.1352 [PubMed: 18314993] (c) El-Awa A, du Jourdin XM, Fuchs PL. *J Am Chem Soc* 2007;129:9086–9093.9093 [PubMed: 17567130] (d) Defosseux M, Blanchard N, Meyer C, Cossy J. *Tetrahedron* 2005;61:7632–7653.7653 (e) Breit B, Zahn SK. *J Org Chem* 2001;66:4870–4877.4877 [PubMed: 11442419] (f) Arjona O, Menchaca R, Plumet J. *J Org Chem* 2001;66:2400–2413.2413 [PubMed: 11281781]
- Structure: (a) Toeplitz BK, Cohen AI, Funke PT, Parker WL, Gougoutas JZ. *J Am Chem Soc* 1979;101:3344–3353.3353 Total synthesis: (b) Evans DA, Dow RL, Shih TL, Takacs JM, Zahler R. *J Am Chem Soc* 1990;112:5290–5313.5313 (c) Hanessian S, Cooke NG, Dehoff B, Sakito Y. *J Am Chem*

- Soc 1990;112:5276–5290.5290(d)Lautens M, Colucci JT, Hiebert S, Smith ND, Bouchain G. *Org Lett* 2002;4:1879–1882.1882 [PubMed: 12027637]
10. Structure: (a)Knoll WMJ, Rinehart KL, Wiley PF, Li LH. *J Antibiot* 1980;33:249–251.251 [PubMed: 6103894] Total synthesis: (b)Miyashita M, Yamasaki T, Shiratani T, Hatakeyama S, Miyazawa M, Irie H. *Chem Commun* 1997:1787–1788.1788(c)Miyashita M, Shiratani T, Kawamine K, Hatakeyama S, Irie H. *Chem Commun* 1996:1027–1028.1028
11. (a) Rao AS, Paknicar SK, Kirtane JG. *Tetrahedron* 1983;39:2367–2370. (b) Cardillo G, Orena M. *Tetrahedron* 1990;46:3321–3408. (c) Bongini A, Cardillo G, Orena M, Porzi G, Sandri S. *J Org Chem* 1982;47:4626–4633. (d) Fleming PR, Sharpless KB. *J Org Chem* 1991;56:2869–2875. (e) Sharpless KB, Woodward SS, Finn MG. *Pure and Appl Chem* 1983;55:1823–1836.
12. (a) Nagaoka H, Rutsch W, Schmid G, Lio H, Johnson MR, Kishi Y. *J Am Chem Soc* 1980;102:7962–7965. (b) Nagaoka H, Kishi Y. *Tetrahedron* 1981;37:3873–3888.
13. Corey EJ, Hase T. *Tetrahedron Lett* 1979;20:335–338.
14. (a) Bartlett PA, Meadows JD, Brown EG, Morimoto A, Junstedt KK. *J Org Chem* 1982;47:4013–4018. (b) Bartlett PA, Myerson J. *J Am Chem Soc* 1978;100:3950–3952.
15. (a) Lipshutz BH, Kozlowski JA. *J Org Chem* 1984;49:1147–1149. (b) Lipshutz BH, Barton JC. *J Org Chem* 1988;53:4495–4499. (c) Lipshutz BH, Kotsuki H, Lew W. *Tetrahedron Lett* 1986;27:4825–4828. (d) Lipshutz BH, Moretti R, Crow R. *Tetrahedron Lett* 1989;30:15–18.
16. (a) Miyashita M, Hoshino M, Yoshikoshi A. *J Org Chem* 1991;56:6483–6485. (b) Miyashita M, Yoshihara K, Kawamine K, Hoshino M, Irie H. *Tetrahedron Lett* 1993;34:6285–6288.
17. Tirado R, Torres G, Torres W, Prieto JA. *Tetrahedron Lett* 2005;46:797–801.
18. (a) Tirado R, Prieto JA. *J Org Chem* 1993;58:5666–5673. (b) Torres G, Torres W, Prieto JA. *Tetrahedron* 2004;60:10245–10251.
19. Marshall JA, Perkins JF, Wolf MA. *J Org Chem* 1995;60:5556–5559.
20. Rodríguez D, Mulero M, Prieto JA. *J Org Chem* 2006;71:5826–5829. [PubMed: 16839177]
21. (a) Hoffmann RW, Dresely S. *Chem Ber* 1989;122:903–909. (b) Short RP, Masamune S. *Tetrahedron Lett* 1987;28:2841–2844. (c) Tanimoto N, Gerritz SW, Sawabe A, Noda T, Filla SA, Masamune S. *Angew Chem Int Ed* 1994;33:673–675. (d) Andersen MW, Hildebrandt B, Dahmann G, Hoffmann RW. *Chem Berichte* 1991;124:2127–2139.
22. Schlenk W, Schlenk W Jr. *Ber Dtsch Chem Ges* 1929;62:920–924.
23. (a) Rychnovsky SD, Skalitzky DJ. *Tetrahedron Lett* 1990;31:945. (b) Evans DA, Rieger DL, Gage JR. *Tetrahedron Lett* 1990;31:7099–7100.
24. Wang Z, Schreiber SL. *Tetrahedron Lett* 1990;31:31–34.

Figure 1.
The all-*anti* stereotetrad 1, -pentad 2, and -hexad 3

Figure 2.
Ionomycin (4) and streptovaricin U (5) and their all-*anti,anti* C18–C21 and C6–C10
stereotetrad and -pentad

Figure 3.
Selected ^{13}C NMR data for the regio- and stereoselectivity determination

Scheme 1.

General reiterative epoxide-based approach for polypropionate synthesis

Scheme 2.
Preparation of the *anti,anti,anti* stereotetrad 9

Scheme 3.

Synthesis of the all-*anti* stereohexads 13, 14 and the streptovaricin U C5–C10 fragment 15

Scheme 4.

Epoxide cleavage attempts using the copper catalyzed *cis*-propenylmagnesium bromide conditions