

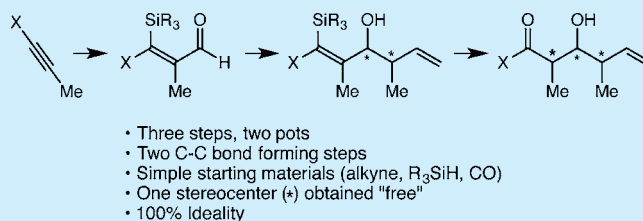
Beyond the Roche Ester: A New Approach to Polypropionate Stereotriad Synthesis

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Supporting Information

ABSTRACT: An efficient, step-economical, and scalable approach to the synthesis of polypropionate stereotriads has been developed. Either 2-butyne or propyne is subjected to rhodium-catalyzed silylformylation and in situ crotylation of the resulting aldehydes. Tamao oxidation under either “standard” conditions or “aprotic” conditions then delivers the completed stereotriads in a three-step, two-pot sequence. In contrast to the classical Roche ester approach, the α -stereocenter is obtained for “free.”

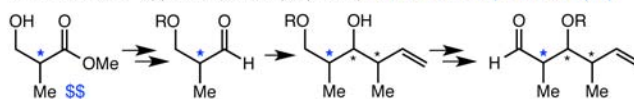


Since its full development by Roush almost 30 years ago,¹ the “Roche ester” approach to the construction of stereotriad building blocks for nonaromatic polyketide natural products synthesis has emerged as, and remains, one of the most widely employed.² In this approach, the Roche ester (and with it the α stereocenter) is purchased³ and converted in approximately six to seven steps into stereotriads with, for example, an aldehyde at one end and an alkene at the other (Figure 1A). Of those steps, only one is a carbon–carbon bond forming reaction (typically an asymmetric crotylation or aldol reaction) while the others all involve protecting group manipulations or oxidation state adjustments, leading to a particularly low “ideality” score.⁴

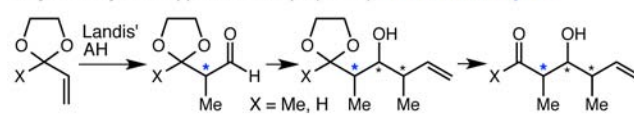
As recently reported by us as the centerpiece of our highly step-economical synthesis of dictyostatin,⁵ commercially available vinyl acetals may be transformed into fully functionalized stereotriads in an approximately three-step process entailing asymmetric hydroformylation (AH) using Landis’ method⁶ followed by crotylation (Figure 1B). Conceptually, this approach is attractive in that it entails a one-step synthesis of an α -methyl- β -ketoaldehyde or β -dialdehyde in configurationally stable form thus obviating most of the protecting group manipulations and oxidation state adjustments of the Roche ester approach. Conversely, it does suffer from some practical liabilities, principally the expense and inaccessibility of the Landis ligand⁷ that is used to set the α -stereocenter and the only moderate to poor regioselectivities of the AH reaction.

An alternative carbonylation-based approach is the tandem intramolecular alkyne silylformylation–crotylation/Tamao oxidation/diastereoselective tautomerization reaction (Figure 1C).⁸ This sequence rapidly assembles stereotriads from simple starting materials, and it seemed plausible that we might adapt it for use in an intermolecular alkyne silylformylation⁹ reaction using either propyne or 2-butyne as the starting material (Figure 1D). Crotylation of the resulting α -methyl- β -silyl- α,β -unsaturated aldehyde (an α -methyl- β -ketoaldehyde or β -dialdehyde in masked form) would be followed by Tamao

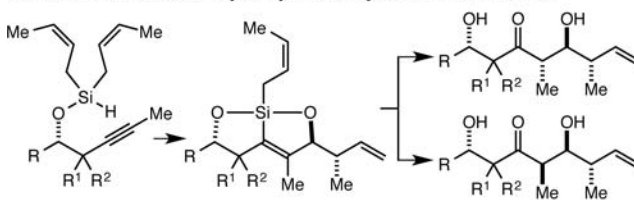
A “Roche ester” approach: 6–7 steps (1 C–C), α stereocenter purchased (\$\$)



B Hydroformylation approach: 3 steps (2 C–C), α stereocenter by AH



C Tandem intramolecular silylformylation–crotylation/Tamao oxidation



D Intermolecular silylformylation, crotylation, Tamao ox: α stereocenter “free”

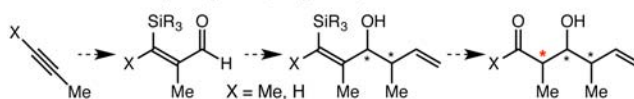


Figure 1. (A) The “Roche ester” approach to stereotriad synthesis. (B) The asymmetric hydroformylation (AH)/crotylation approach to stereotriad synthesis. (C) The tandem intramolecular silylformylation–crotylation/Tamao oxidation–diastereoselective tautomerization reaction. (D) The silylformylation, crotylation, Tamao oxidation approach to stereotriad synthesis.

oxidation¹⁰ with concomitant diastereoselective enol tautomerization to deliver the target stereotriad building blocks. Such an approach would be conceptually attractive in that the α -

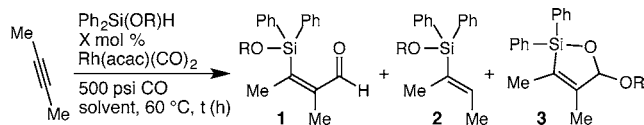
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stereocenter would be established after the crotylation event and would rely on the β -stereocenter to induce diastereoselectivity; in other words, the α -stereocenter would be established for “free”. In addition, the starting materials required for this approach would be 2-butyne or propyne, CO, and a silane (R_3SiH). Herein we describe the results of our efforts to develop the process described in Figure 1D for a sustainable, step-economical, and scalable approach to the synthesis of valuable polypropionate stereotriad building blocks.

At the outset, it was the choice of the silane component that was most critical, as the silane must facilitate efficient silylformylation reactions and allow for smooth and highly enantioselective crotylation reactions while also being activated enough to participate in efficient Tamao oxidation reactions under both the “standard”^{8a} and “aprotic”^{8c} conditions that we have developed for diastereocontrol in the tautomerization event. This last requirement is the most important and typically requires the use of an alkoxy silane. Thus, we prepared ethoxydiphenylsilane and investigated its performance in $Rh(acac)(CO)_2$ -catalyzed silylformylation reactions of 2-butyne. As we had feared based on Ojima’s observations,¹¹ the alkoxy group slowed the reaction and we had to use a high catalyst loading and high CO pressures to achieve high levels of conversion to desired product **1a** ($R = Et$). Thus, even with 5 mol % catalyst and 500 psi CO at 60 °C for 24 h, the reaction was incomplete as judged by the formation of substantial amounts of hydrosilylation product **2a** (Table 1, entry 1).¹²

Table 1. Optimization of the Silylformylation of 2-Butyne^a



entry	R	X	solvent	t	1:2:3:4
1	Et	5.0	PhH	24	1:0.7:0:0
2	Et	2.5	CH ₃ CN	14	1:0:0.5:0.3
3	<i>i</i> -Pr	2.5	CH ₃ CN	20	1:0:0:0.7
4	<i>i</i> -Pr	2.0	PhCN	24	1:0:0:0.2

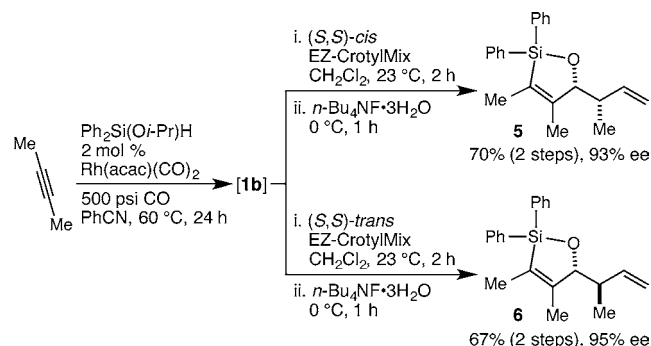
^aThe reactions were performed under the indicated conditions, and then the Parr apparatus was cooled and vented; analysis of an aliquot by ¹H NMR spectroscopy revealed the product ratio.

Reactions run in acetonitrile were found to be substantially faster, and complete conversion could be obtained with 2.5 mol % catalyst in 14 h (entry 2). Unfortunately, however, these conditions led to the production of substantial amounts of rearranged silylformylation product **3a** (Matsuda observed similar products when using alkoxy silanes^{9b}) and a different side product, **4a**. Though we have been unable to isolate and characterize **4a**, it is clear that it is derived only from the silane. In an attempt to suppress the rearrangement product **3a**, we employed the more sterically hindered isopropoxydiphenylsilane and were delighted to find that this tactic was successful in producing **1b** ($R = i$ -Pr) unaccompanied by either **2b** or **3b** (entry 3). The silane-derived side product **4b** was still an issue that needed to be addressed, however, and extensive optimization eventually revealed that by switching to PhCN as the solvent, formation of **4b** could be minimized (entry 4). These conditions were selected for use in the proposed stereotriad synthesis.

Though it proved possible to isolate aldehyde **1b**, we hoped to develop crotylation conditions that could be used with the

unpurified product mixture from the silylformylation reaction. Indeed, when the PhCN solution containing **1b** was simply diluted with CH₂Cl₂ and treated with (*S,S*)-*cis* EZ-CrotylMix,¹³ crotylation proceeded smoothly. It proved most practical and effective to quench the reaction with *n*-Bu₄NF·3H₂O, which resulted in cyclization to **5**, which was conveniently isolated by chromatography (Scheme 1). After optimization, **5** could be

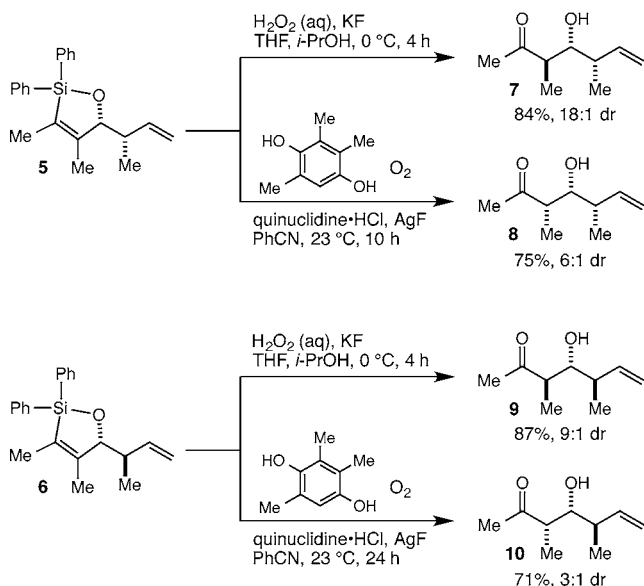
Scheme 1. Silylformylation–Crotylation of 2-Butyne



obtained in 70% overall yield and 93% ee. The same procedure using (*S,S*)-*trans* EZ-CrotylMix produced *anti* product **6** in 67% overall yield and 95% ee. Importantly, this one-pot two-step protocol scaled well and was used to produce **5** and **6** on an ~5 g scale in the indicated yields.

With direct, efficient, and highly enantioselective access to **5** and **6** secured, we turned our attention to the Tamao oxidation/diastereoselective tautomerization step to install the carbonyl and establish the α -methyl stereocenter. We have previously developed two sets of conditions, “standard”^{8a} and “aprotic,”^{8c} that allow access to the *anti* (with respect to the β -hydroxyl stereocenter) and *syn* products, respectively. Because they were derived from intramolecular silylformylation reactions (cf. Figure 1C), however, all previously examined substrates had β -hydroxyl groups on both sides of the enol, and the available evidence suggests that both groups contribute to the diastereoselectivity. It was thus an open question as to whether the enols derived from structurally simpler substrates **5** and **6** would undergo the tautomerization reactions with high levels of diastereoselectivity. Gratifyingly, subjection of **5** to the “standard” conditions (H₂O₂, KF, THF, *i*-PrOH, 0 °C) led to the isolation of **7** as the major product of an 18:1 mixture of diastereomers in 84% yield (Scheme 2). Conversely, when **5** was subjected to the previously reported^{8c} “aprotic” Tamao conditions (methylhydroquinone (MeHQ), 1 atm of O₂, quinuclidine-HCl, AgF, PhCN, 60 °C) the reaction was sluggish, inefficient, and nonselective ($\leq 2:1$ dr). Reasoning that we needed to boost the concentration of the active oxidant to increase the rate of the reaction in order to carry it out at lower temperatures to maximize diastereoselectivity, we switched to the use of trimethylhydroquinone in place of the MeHQ.¹⁴ In fact, this did lead to more efficient reactions that proceeded smoothly at ambient temperature, and upon optimization, *syn* product **8** was obtained as the major product of a 6:1 mixture of diastereomers in 75% yield. When the same two sets of Tamao oxidation conditions were applied to *anti* crotylation product **6**, **9** and **10** were obtained in good yields, albeit with diminished levels of diastereoselectivity. In the case of **9**, it should be noted that this approach represents an interesting and effective alternative for the traditionally difficult

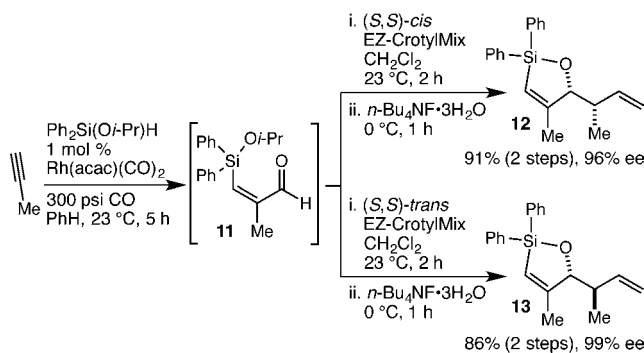
Scheme 2. "Standard" and "Aprotic" Tamao Oxidation



problem of establishing all-*anti* stereochemistry in polypropionate building blocks of this type.

In order to access the perhaps even more generally useful corresponding aldehyde stereotriads we turned next to an examination of the use of propyne in the three-step, two-pot sequence. The desired regioselectivity in the silylformylation reaction was well-precedented,^{9,11} and we were optimistic that the reaction would be significantly more efficient due to reduced steric hindrance. Indeed, efficient and regio- and chemoselective silylformylation of propyne to give aldehyde **11** was easily carried out with only 1 mol % of the Rh(acac)(CO)₂ catalyst and 300 psi CO at room temperature in just 5 h (Scheme 3). As above, the silylformylation reaction solution

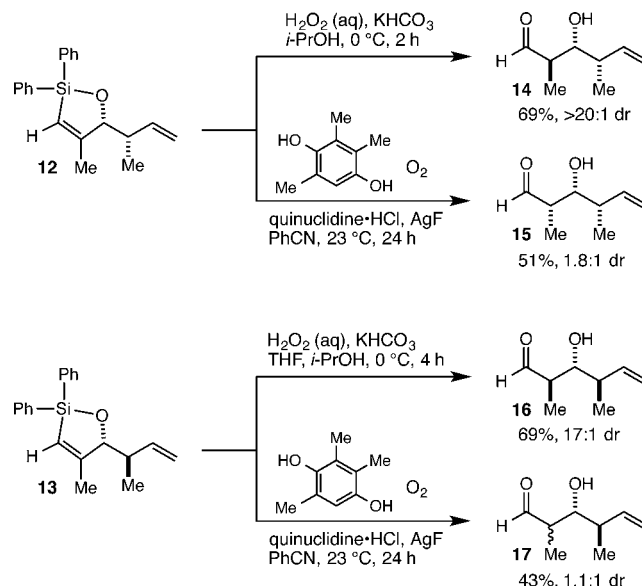
Scheme 3. Silylformylation–Crotylation of Propyne



was simply diluted with CH₂Cl₂ and then treated with the requisite EZ-CrotylMix, and following quenching with *n*-Bu₄NF·3H₂O cyclized crotylation products **12** and **13** could be isolated in excellent overall yields and enantioselectivities. These reactions too scaled well and were carried out on gram scale in the indicated yields.

After some minor tweaking of the "standard" Tamao oxidation conditions (KHCO₃ instead of KF, no THF), **14** could be obtained as a single diastereomer in 69% yield from **12** (Scheme 4). Unfortunately, the moderate success we had achieved using the "aprotic" conditions with substrate **5** did not translate to substrate **12**, as **15** was produced in only moderate

Scheme 4. "Standard" and "Aprotic" Tamao Oxidation



yield and with poor diastereoselectivity. The general reliability of the "standard" conditions was confirmed by the conversion of **13** to all-*anti* product **16** in 69% yield and with 17:1 diastereoselectivity, while the "aprotic" conditions applied to **13** resulted in an inefficient and nonselective reaction.

There are two discernible trends from the oxidation results described in Schemes 2 and 4 that merit further comment. The first is the observation that the *syn* crotylation products **5** and **12** consistently give higher diastereoselectivities than do the *anti* substrates **6** and **13**, especially under the "standard" conditions. This observation is consistent with the model we have advanced^{8a} for the *anti*-diastereoselectivity under the "standard" conditions in that substrates **5** and **12** are geared such that the vinyl group is blocking the approach of the proton to the front face of the enol, while for substrates **6** and **13** it is the smaller methyl group that performs this function (Figure 2A). In the case of the "aprotic" Tamao oxidation reactions, the origins of the *syn*-selectivity are far murkier, and we have shown that the structure of the amine in the amine·HF salt has a direct and dramatic impact on the diastereoselectivity.^{8c} Thus, although we cannot advance a simple model for this selectivity, we do note the second discernible trend that the steric size of R in the enol intermediate **18** is critical. Thus, in the originally reported substrate,^{8c} R was a quaternary carbon center and the selectivity was 14:1 (Figure 2B). When R = Me (**5** and **6**), the selectivity drops to 6:1 and 3:1 respectively, and when R = H (**12** and **13**), there is little to no selectivity at all. The bottom line is that the "standard" conditions quite reliably lead to usefully high levels of *anti*-diastereoselectivity, while the "aprotic" conditions are less general and reliable and more substrate-dependent. The development of more general and reliable *syn*-selective Tamao oxidation/tautomerization conditions thus remains an important long-term goal of this program.

We have developed a new synthesis of polypropionate stereotriad building blocks that we contend represents a significant conceptual and practical advance relative to the now classical and still widely used Roche ester strategy. The synthesis proceeds in just three steps and two pots, employs exceedingly simple starting materials (2-butyne or propyne,

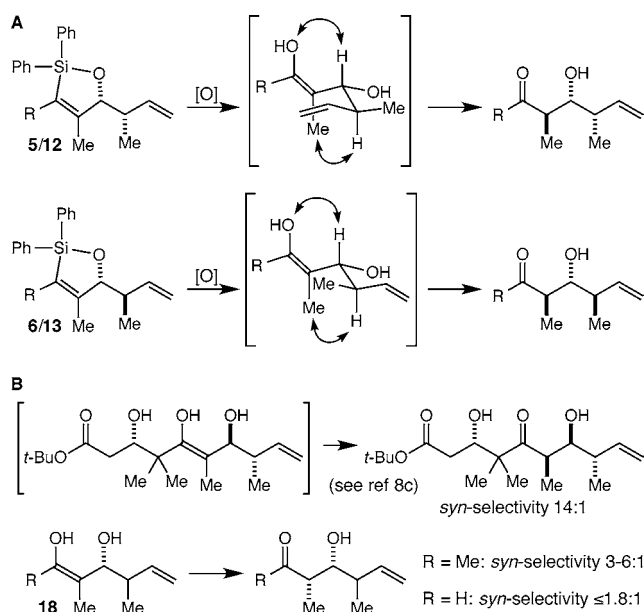


Figure 2. (A) Our model to explain the *anti*-diastereoselectivity under the “standard” Tamao oxidation conditions (curved arrows indicate minimization of $A_{1,3}$ strain and *syn*-pentane like interactions) is consistent with the observation that substrates **5/12** give higher selectivity than do **6/13**. (B) The size of the R group in the enol intermediate (**18**) correlates to the tautomerization diastereoselectivity under the “aprotic” Tamao oxidation conditions.

$\text{Ph}_2\text{Si}(\text{Oi-Pr})\text{H}$, CO), and is characterized by 100% ideality.⁴ In contrast to the Roche ester approach and all other related approaches in which the α -methyl stereocenter is either purchased or synthesized by external asymmetric induction (thereby adding steps and expense), the α -methyl stereocenter is established after the crotylation event using internal diastereochemical control and is therefore obtained for “free.” The method is not yet comprehensive in terms of the diastereomers that are accessible, but does provide access to three of the four possible products in the methyl ketone series (**7–9**) and two of the four possible products in the aldehyde series (**14** and **16**) with moderately good to excellent diastereoselectivities (6 to >20:1). The sequences have been demonstrated on gram or multigram scale, and the overall yields for products **7**, **8**, **9**, **14**, and **16** are all in the range of 53–63%. Attempts to identify a more generally useful set of conditions for a *syn*-selective Tamao oxidation/diastereoselective tautomerization reaction and the application of this method to the synthesis of important polyketide natural products and analogs thereof are ongoing.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, spectroscopic and analytical data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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