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 alkynyl silylformylation−crotylation/Tamao oxidation−diastereoselective tautomerization sequence (Figure 1C).8 For example, this sequence rapidly assembles stereotriads from simple starting materials, and it seemed plausible that we might adapt it for use in an intermolecular alkynyl silylformylation 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 oxidation,9 with concomitant diastereoselective enol tautomerization to deliver the target stereotriad building blocks. Such an approach would be conceptually attractive in that the α-stereocenter would be obtained for "free." Since first described by us around 1990,10 this "free" stereocenter approach has been adopted by several groups, as shown in Figure 1D.

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.
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 (R2SiH). 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 slow and highly enantioselective crotylation reactions while also being activated enough to participate in efficient Tamao oxidation reactions under both the “standard” and “aprotic” conditions that we have developed for diastereoccontrol in the tautomerization event. This last requirement is the most important and typically requires the use of an alkoxysilane. 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, 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 hydroxysilylation product 2a (Table 1, entry 1).

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 alkoxysilanes9b) 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.

An attempt to suppress the rearrangement product 3a, we employed the more sterically hindered isopropoxypophenylsilane and were delighted to find that this tactic was successful in producing 1b (R = i-Pr) unaccompanied by either 1b or 2b (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-BuNF·3H2O, which resulted in cyclization to 5, which was conveniently isolated by chromatography (Scheme 1). After optimization, 5 could be 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” and “aprotic,” 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-hydroxy 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 “aprotic” Tamao conditions (methylhydroquinone (MeHQ), 1 atm of O2, quinuclidine-HCl, AgF, PhCN, 60 °C) the reaction was sluggish, inefficient, and nonselective (<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

### Table 1. Optimization of the Silylformylation of 2-Butyne

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>X</th>
<th>solvent</th>
<th>t</th>
<th>i:2:3:4</th>
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<tr>
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<td>Et</td>
<td>5.0</td>
<td>PhH</td>
<td>24</td>
<td>1:0.7:0:0</td>
</tr>
<tr>
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<td>Et</td>
<td>2.5</td>
<td>CH3CN</td>
<td>14</td>
<td>1:0.5:0.3</td>
</tr>
<tr>
<td>3</td>
<td>i-Pr</td>
<td>2.5</td>
<td>CH3CN</td>
<td>20</td>
<td>1:0.0:0.7</td>
</tr>
<tr>
<td>4</td>
<td>i-Pr</td>
<td>2.0</td>
<td>PhCN</td>
<td>24</td>
<td>1:0.0:0.2</td>
</tr>
</tbody>
</table>

“The 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.”

### Scheme 1. Silylformylation—Crotylation of 2-Butyne

![Scheme 1](image)
was easily carried out with only 1 mol % of the Rh(acac)(CO)$_2$ffi. Indeed, the chemoselective silylformylation of propyne to give aldehyde $Bu_4NF$ requisite EZ-CrotylMix, and following quenching with $n$-Bu$_3NF-3H_2O$ cyclized crotylation products 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 was simply diluted with CH$_2$Cl$_2$ and then treated with the requisite EZ-CrotylMix, and following quenching with $n$-Bu$_3NF-3H_2O$ 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 (KHCO$_3$ 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 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$^d$ 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.$^c$ 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,$^c$ 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, 1182 dx.doi.org/10.1021/acs.orglett.4b00051 | Org. Lett. 2014, 16, 1180−1183
Ph₂Si(Oi-Pr)H, CO), and is characterized by 100% ideality. 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 approaches in which the Tamao oxidation conditions (curved arrows indicate minimization of A₁₃ 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.

**ACKNOWLEDGMENTS**

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**REFERENCES**


(2) For example, various versions of the Roche ester approach were employed (often more than once) in most of the total syntheses of discodermolide, as well as in the Novartis large-scale synthesis. See: Smith, A. B., III; Freeze, B. S. Tetrahedron 2008, 64, 261–298.

(3) The current Sigma Aldrich prices are ~$20/g for the S enantiomer and ~$52/g for the R enantiomer.


(7) Unfortunately, Sigma Aldrich recently discontinued the sale of the Landis ligand.


(12) It is our working assumption that most or all of the hydroxylation occurs rapidly upon venting of the Parr apparatus and release of the CO, giving an approximate indication of how much starting material remained at the time of venting.


(14) In their original report on the use of the O₂/hydroquinone system to generate dry H₂O₂ for carbon–silicon bond oxidation, Tamao, Hayashi, and Ito showed that 2,3-dimethylhydroquinone resulted in a higher rate of oxidation than did methylhydroquinone. See: Tamao, K.; Hayashi, T.; Ito, Y. Tetrahedron Lett. 1989, 30, 6533–6536.