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Evolution of an Efficient and Scalable Nine-Step (LLS) Synthesis of Zincophorin Methyl Ester

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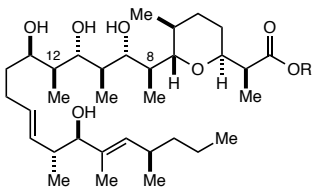
ABSTRACT: Due both to their synthetically challenging and stereochemically complex structures and their wide range of often clinically relevant biological activities, non-aromatic polyketide natural products have for decades attracted an enormous amount of attention from synthetic chemists and played an important role in the development of modern asymmetric synthesis. Often, such compounds are not available in quantity from natural sources, rendering analog synthesis and drug development efforts extremely resource-intensive and time-consuming. In this arena, the quest for ever more step-economical and efficient methods and strategies – useful and important goals in their own right – takes on added importance and the most useful syntheses will combine high levels of step-economy with efficiency and scalability. The non-aromatic polyketide natural product zincophorin methyl ester has attracted significant attention from synthetic chemists due primarily to the historically synthetically challenging C(8)-C(12) all-*anti* stereopentad. While great progress has been made in the development of new methodologies to more directly address this problem and as a result in the development of more highly step-economical syntheses, a synthesis that combines high levels of step economy with high levels of efficiency and scalability has remained elusive. To address this problem, we have devised a new synthesis of zincophorin methyl ester that proceeds in just nine steps in the longest linear sequence and proceeds in 10% overall yield. Additionally, the scalability and practicability of the route have been demonstrated by performing all of the steps on a meaningful scale. This synthesis thus represents by a significant margin the most step-economical, efficient, and practicable synthesis of this stereochemically complex natural product reported to date, and is well suited to facilitate the synthesis of analogs and medicinal chemistry development efforts in a time- and resource-efficient manner.

Introduction. Non-aromatic polyketide natural products have for the best part of half a century played an important and outsized role in the development of modern asymmetric synthesis. While ever-greater synthetic efficiency remains a worthy pursuit, the focus in this arena has in many labs expanded over the past ~20 years to include leveraging all of the highly enabling synthetic chemistry to develop the natural compounds as medicinal agents.[1,2] In many cases, total chemical synthesis is the only way to access significant quantities of the natural products and designed analogs thereof, and in this arena the quest for synthetic efficiency is not an abstract ideal, but rather an essential goal to render these development efforts practical in a time- and resource-efficient manner. In this light, the common academic practice of focusing primarily or even exclusively on step counts (typically expressed in terms of the longest linear sequence (LLS)) is inadequate as a measure of synthetic efficiency. Step-economy is an important component of synthetic efficiency, but the best and most useful syntheses combine step-economy with efficiency (yield), practicality, and scalability, attributes that might usefully be summarized as "practicability".

The non-aromatic polyketide natural products zincophorin (**1**)[3,4] and its methyl ester (**2**) have been popular synthetic targets[5] since Danishefsky's landmark synthesis 30 years ago (Figure 1).[6] Methodological investigations and fragment syntheses have followed from multiple laboratories,[7-14] and additional total syntheses have been reported by Cossy (2003),[15] Miyashita (2004),[16] Leighton (2011),[17] Krische (2015),[18] and Guindon (2015).[19] The enduring interest in these natural products derives at least in part from the historically challenging C(8)-C(12) all-*anti* stereopentad embedded within the C(6)-C(13) tetrapropionate with its densely packed array of 8 contiguous stereocenters. In part by designing new and more powerful reaction methodologies and strategies that more directly addressed this problem, first Leighton (21 steps, LLS),[17] and then Krische (13 steps, LLS),[18] achieved syntheses that in turn represented significant progress toward more highly step-economical syntheses of this target. Conversely, whereas the Leighton synthesis proceeded in 4.3% overall yield, the exceptionally concise Krische synthesis proceeded in 1.4% overall yield. Thus, while both syntheses indisputably represented significant advances, we were motivated to undertake a new synthesis of zincophorin methyl ester with the goal of achieving a synthesis that combines extraordinary step-economy with high levels of efficiency. As described herein, we have developed a synthesis of zincophorin methyl ester that proceeds in just nine steps (LLS) and in 10% overall yield, and demonstrated the practicability of the route by performing all of the steps on a significant scale.



1 R = H, zincophorin
2 R = Me, zincophorin methyl ester

Previous synthesis of **1**:
Miyashita, 39 steps (LLS), ref. 16

Previous syntheses of **2**:
Danishefsky, 35 steps (LLS), ref. 6
Cossy, 30 steps (LLS), ref. 15
Guindon, 49 steps (LLS), ref. 19

Leighton, 21 steps (LLS),
4.3 % overall yield, ref. 17

Krische, 13 steps (LLS),
1.4% overall yield, ref. 18

Figure 1. Summary of previous total syntheses of zincophorin (**1**) and zincophorin methyl ester (**2**).

Strategic Considerations. The most fundamental strategic challenge posed by zincophorin is how to divide the structure into two fragments of roughly equivalent complexity in order to maximize convergency, while the main methodological/tactical challenges are the C(8)-C(12) all-*anti* stereopentad embedded within the C(6)-C(13) tetrapropionate, and the construction of the tetrahydropyran ring and the associated C(2) and C(3) stereocenters. In our first-generation synthesis, we devised highly step-economical and efficient methods to address the latter challenges, and the result was the conversion of alcohol **3** into fragment **4** in 14 steps and 12% overall yield (Figure 2a). This efficiency came at a significant cost, however, in that it dictated a fragment coupling strategy that entailed a Julia-Kociensky olefination[20] to form the C(16)-C(17) *E*-alkene from aldehyde **5** and tetrazolylsulfone **6**. While this fragment coupling and end game strategy proved reasonably efficient and practicable, it was not at all convergent and also unexpectedly required a convoluted protecting group scheme that necessitated three separate deprotection steps. Combined with the fact that three steps were required just to install the tetrazolylsulfone, it was the decision to pursue this non-convergent Julia-Kociensky fragment coupling approach that more than any other factor resulted in significantly reduced step-economy in our first-generation synthesis. By contrast, and uniquely among the reported total syntheses, the Krische disconnection did result in two fragments (**7** and **8**) of similar complexity that were prepared in highly efficient eight and ten step sequences, respectively, and which were converted into zincophorin methyl ester in just three additional steps (Figure 2b).[18] One of the major benefits of this convergent strategy was a vastly simplified protecting group strategy as well as

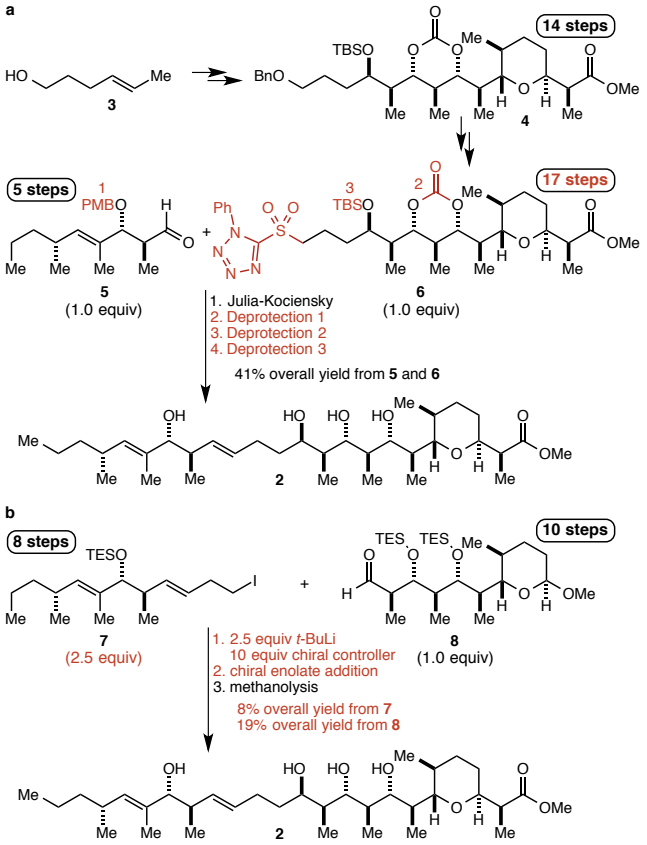


Figure 2. (a) Leighton's fragment coupling and end game strategy. (b) Krische's fragment coupling and end game strategy.

more direct access to the functionalities (iodide, aldehyde) necessary to execute the fragment coupling strategy by aldehyde alkylation. Unfortunately, this three-step fragment coupling and end game sequence proved inefficient and less than readily practicable, and as this sequence comes at the end of the synthesis with valuable late-stage intermediates, the overall efficiency of the synthesis is significantly diminished.

With these considerations in mind, we sought to identify a new fragment coupling and end game strategy that would both lead to a highly convergent (and therefore highly step-economical) synthesis and proceed in an efficient and practicable fashion. Retrosynthetic oxidation of the C(9)-hydroxyl group gives β-hyxdroxyketone **9**, the product of a double diastereodifferentiating *anti*-aldol addition reaction between aldehyde **10** and ethyl ketone **11** to form the C(10)-C(11) bond and the C(10) and C(11) stereocenters (Figure 3a). In deciding to pursue this strategy, we were cognizant of Evans' demonstration that this particular stereochemical array represents a partially matched case that resulted in 81:19 diastereoselectivity in a closely related model system (Figure 3b).[21] We were hopeful that this approach would lead not only to a much more highly convergent approach, but also to a vastly simplified protecting group strategy relative to our first-generation synthesis.

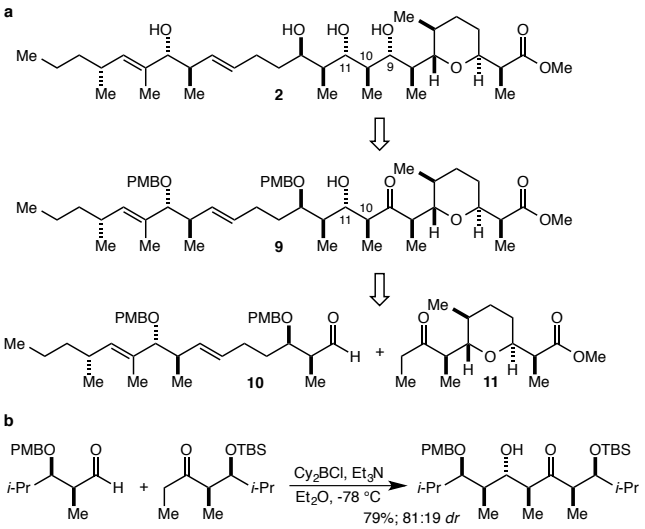


Figure 3. (a) A new disconnection for a convergent and step-economical fragment coupling and end-game strategy. (b) Evans' precedent for the proposed *anti* aldol fragment coupling strategy.

Results. Our synthesis of aldehyde **10** began from **12**, which was an intermediate in our first-generation synthesis that was prepared in 4 steps and 53% overall yield (Figure 4a).[17] Cross metathesis with vinylBPin using the 2nd generation Hoveyda-Grubbs catalyst[22] (HG-II) gave **13** (≥20:1 *E*:*Z*) in 68% yield and set up a cross-coupling reaction. The requisite bromide cross-coupling partner was prepared as outlined in Figure 4b. Based on our demonstration of a one-pot hydroformylation-crotylation reaction with 2-vinyl-1,3-dioxolane in our dictyostatin synthesis,[23] we envisioned that the C(12) and C(13) stereocenters could be established using this strategy and employed (*S*,*S*)-Ph-BPE as the ligand for the asymmetric hydroformylation following Morken's demonstration that this ligand leads to improved levels of regioselectivity.[24] Using these conditions and our one-pot asymmetric allylation method with diaminophenol **14**,[25] we isolated **15** (≥20:1 *dr*) in 81%

yield (and recovered **14** in 92% yield). A series of standard operations (protection of the alcohol as its *p*-methoxybenzyl (PMB) ether, oxidative cleavage of the alkene, reduction, and bromination) proceeded smoothly and delivered, by way of **16**, **17**, and **18**, bromide **19** in 76% overall yield from **15**. Vinyl boronate-alkyl bromide cross-coupling of **13** and **19** using Nishihara's modification[26] to the original Fu conditions[27] proceeded smoothly and produced **20** in 82% yield (Figure 4c). Finally, acetal deprotection was, to avoid epimerization at C(12), best carried out with TMSOTf and 2,2'-bipyridine,[28] and this produced aldehyde **10** in 81% yield. As evidence of the robustness and practicability of these reactions, we note that all of the reactions in Figure 4 were carried out on a ≥1-g scale. This route to aldehyde **10** thus comprises seven steps in the longest linear sequence and may be used to rapidly generate significant quantities of material in a single run.

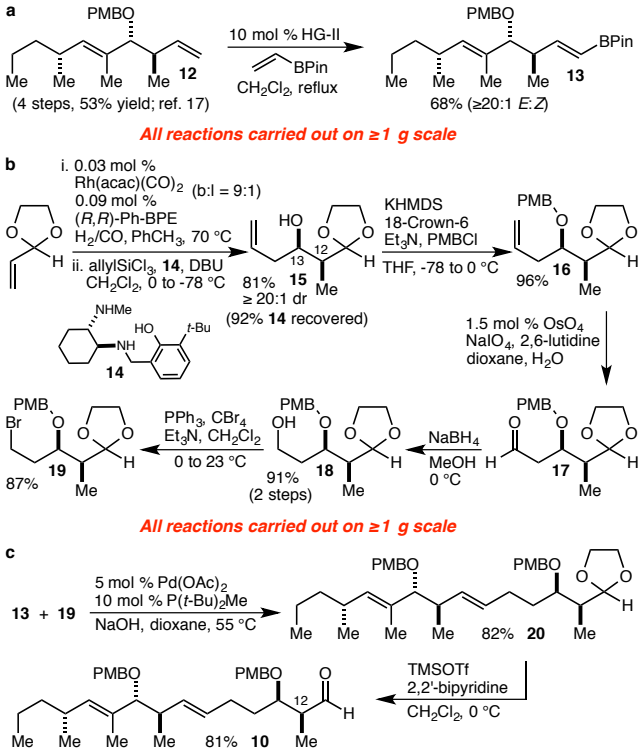


Figure 4. (a) Preparation of vinylboronate **13**. (b) Synthesis of bromide **19**. (c) Completion of the seven-step (LLS) synthesis of aldehyde **10**.

Ketone **11** was prepared as described in Figure 5. Asymmetric hydroformylation of 2-ethyl-2-vinyl-1,3-dioxolane using (*S*,*S*)-Ph-BPE[24] proceeded with 2:1 branched:linear (b:l) regioselectivity, and the branched isomer **21** was isolated in 53% yield and 81% ee on a 7-g scale. The low regioselectivity and the resulting moderate yield are of little practical consequence as this is the first step in the fragment synthesis and the starting material is inexpensive. A more informative measure of efficiency is how much product can be produced per unit of the more expensive and resource-intensive catalyst and ligand, and in this reaction we isolated 4.6 g of **21** using just 13 mg of $Rh(acac)(CO)_2$ and 125 mg of (*S*,*S*)-Ph-BPE. Crotylation of **21** with *trans*-crotylpinacolboronate was highly diastereoselective (≥20:1 *dr*), and led, after *in situ* hydrolysis of the acetal, to the isolation of ketone **22** in 80% yield. Though the hydroformylation and crotylation reactions may also be conducted as a one-pot procedure, we have found that in cases where the b:l ratio is low, the sequence is more easily practicable with isolation of the desired branched aldehyde. Linear selective hydroformylation of **22** gave hemiacetal **23** as a mixture of diastereomers in 91% yield, and acetylation produced **24** in 96% yield, thus setting the stage for the critical introduction of the C(2) and C(3) stereocenters. As we had done in our first-generation synthesis,[17] we adapted the method of Romea and Urpí,[29] adding the titanium enolate derived from **25** to the oxocarbenium ion derived from acetate **24**. This reaction proceeded smoothly and led to the isolation of **26** in 68% yield. We observed no other diastereomeric products, suggesting that the minor enantiomer of **24** (81% ee) does not successfully undergo the reaction. This helped render the isolation straightforward, and indicates that that the true efficiency of the reaction is somewhat higher than 68%. Finally, the chiral auxiliary was removed by methanolysis to give ketone **11** in 91% yield. This synthesis of **11** thus comprises just six steps, and as above, all of the reactions in this sequence were demonstrated on ≥1-g scale, and all proved robust and readily practicable.

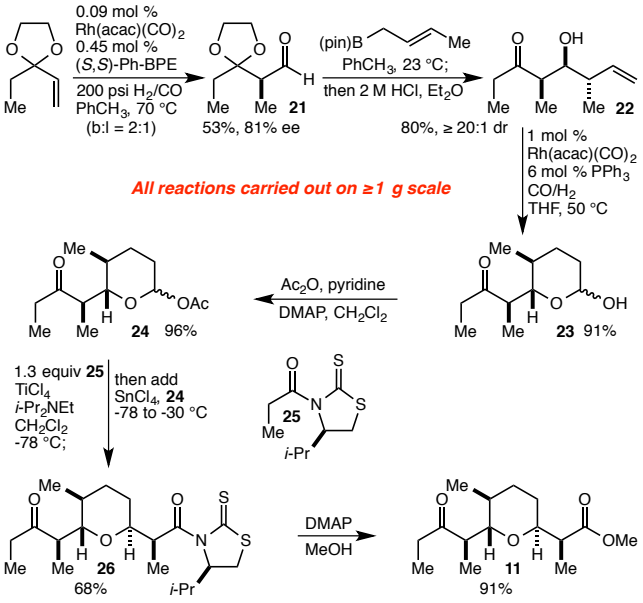


Figure 5. An efficient and practicable six-step synthesis of ethyl ketone **11**.

A comment about the chiral enolate addition reaction (**24** + **25** → **26**) is warranted, both because it is a key step in the synthesis that delivers the tetrahydropyran ring along with the C(2) and C(3) stereocenters, and because in the course of our development of our two syntheses of zincophorin methyl ester we have documented some unexpected and interesting remote effects that dramatically and directly impact on the success of this critically important reaction. In our first-generation synthesis we employed triethylsilyl (TES) protecting groups for the C(9) and C(11) alcohols, so as to have a unified protecting group strategy, but were surprised and disappointed to find that this substrate (**27a**) failed completely in the enolate addition process (Figure 6a). The illustrated conformation of the oxocarbenium ion was derived from first principles and represents the only available conformation which does not suffer from costly *syn*-pentane interactions, and it provides a plausible rationalization of our results in that the highlighted **TES** group appears to block access to the reactive disastereoface of the oxocarbenium ion. It was this analysis that led to the switch to a carbonate protecting group for the C(9) and C(11)

alcohols (**27b**) to achieve a successful enolate addition, which in turn necessitated an additional deprotection step (*cf.* Figure 2a). In the present work, we ultimately required a ketone at C(9), and the question we faced was whether to leave the C(9) ketal protecting group in place for the chiral enolate addition reaction or attempt the reaction with the unprotected ketone at C(9). Consistent with – and guided by – the analysis presented here, we were delighted to find that the unprotected ketone-bearing substrate (**24**) performs well in the reaction (*cf.* Figure 5), and further confirmed that the analogous ketal protected substrate (**29**) – whether due to a similar steric effect or simply to the instability of the ketal to the strongly Lewis acidic conditions of the reaction – performs poorly (Figure 6b).

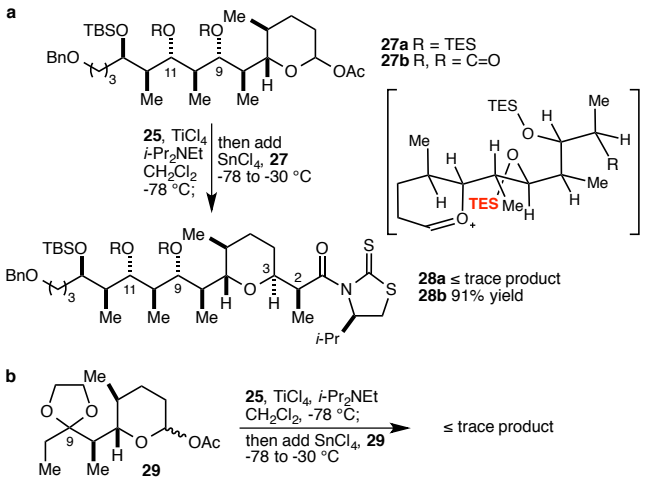


Figure 6. (a) The C(9) and C(11) OH protecting groups dramatically impacted on the success of the chiral enolate addition reaction in our first-generation synthesis. (b) In the present work, C(9)-protected substrate **29** was found to perform poorly in the enolate addition reaction, consistent with the results from our first-generation synthesis.

As described above, our plan for a fragment coupling of **10** and **11** by way of an *anti*-aldol addition reaction was predicated on Evans' demonstration that this particular stereochemical permutation represents a partially matched case that provides for ~4:1 diastereoselectivity (Figure 3b).[21] Unfortunately, (*E*)-selective enolization of ketone **11** using Brown's method[30] and addition of 1.0 equiv of aldehyde **10** led to an aldol reaction that unexpectedly proceeded with only 1.7:1 diastereoselectivity (Figure 7a). Despite this lower selectivity, the reaction did prove robust and reliable and the products easily separable, and in one representative reaction conducted with 500 mg of **10** and 237 mg of **11**, we isolated the major product **9** in 53% yield. While in practical terms this constitutes a useful reaction (especially a reaction that couples the two major fragments, forges a C-C bond, and establishes two stereocenters), we were nevertheless curious about the origin of the discrepancy between the Evans reaction (Figure 3b) and our own. To shed light on this, we repeated the aldol reaction with model aldehyde **30** in place of aldehyde **10**, and found that the reaction proceeded to give **31** with 4:1 diastereoselectivity (Figure 7b). A further reaction with model aldehyde **32** gave **33** with only 1.6:1 diastereoselectivity (Figure 7c), implicating the remote alkene in aldehydes **10** and **32**, but not the alkene in aldehyde **30**, as the origin of the reduced diastereoselectivity. Though it is difficult to rationalize these effects with any authority, we note that they are reminiscent of an effect documented by Danishefsky in *syn*-selective lithium enolate aldol addition reactions,[31] in which properly positioned alkenes and arenes on the aldehyde component had a small but significant impact on the aldehyde's diastereofacial bias, as appears to be the case in the *anti*-aldol reactions reported here.

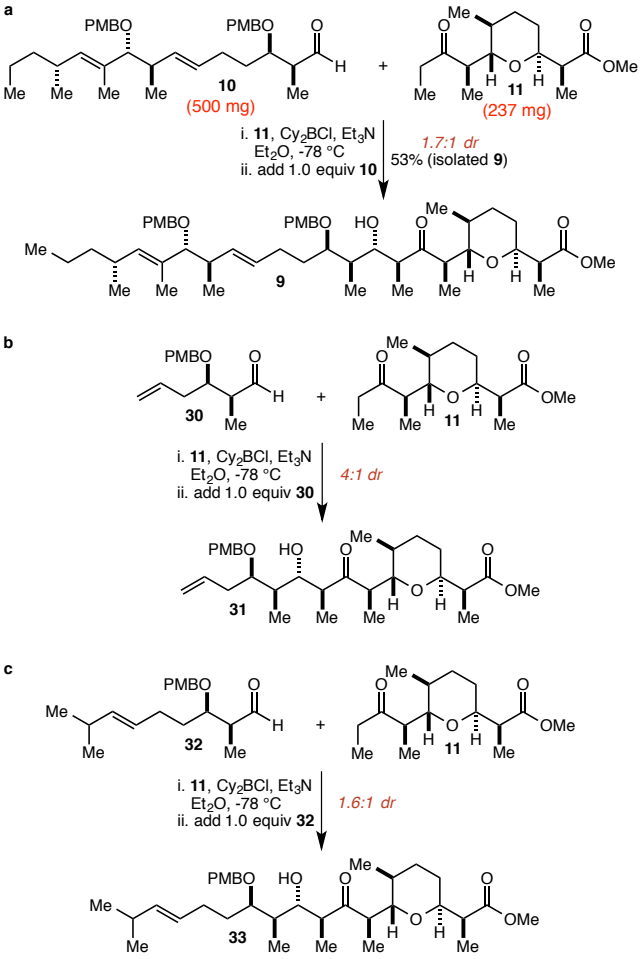


Figure 7. (a) The fragment coupling *anti* aldol addition reaction. (b) The aldol reaction with aldehyde **30** proceeds with the same 4:1 diastereoselectivity as observed by Evans.[21] (c) The aldol reaction with aldehyde **32** proceeds with just 1.6:1 diastereoselectivity, implicating the remote alkene in aldehydes **10** and **32** as the source of the compromised selectivity.

To complete the synthesis it remained only to reduce the C(9) ketone and deprotect the PMB ethers. After screening several known methods for *syn*-selective β-hydroxy ketone reduction, we settled on the use of catecholborane following the method of Evans[32] as it provided the cleanest reactions (Figure 8a). With access to diol **34** secured (87%, ≥ 20:1 dr), we turned our attention to what we assumed would be a routine deprotection of the two PMB ethers with DDQ.[33] Unfortunately, acetal and orthoester formation – which typically happens only under strictly anhydrous conditions – with the C(11)- and C(9)-OH groups (multiple acetal and orthoester products were observed) could not be avoided even using excess water or methanol as co-solvent. Faced with the unpleasant prospect of having to protect diol **34** prior to PMB deprotection, it occurred to us that in the initial product of the reduction reaction prior to hydrolytic work-up, the C(9) and C(11) alcohols would be "protected" as their catecholboronates, and we might be able to perform the ketone reduction and PMB

ether deprotection as a simple one-pot procedure. Indeed, this proved feasible, and, upon optimization, delivered zincophorin methyl ester (**2**) in 78% yield in a reaction conducted with 316 mg of **9** (Figure 8b). Thus, despite the unexpectedly low diastereoselectivity of the aldol reaction, the fragment coupling and end game sequence described here comprises just two readily practicable steps that establish three stereocenters and convert fragments **10** and **11** into zincophorin methyl ester (**2**) in 41% overall yield.

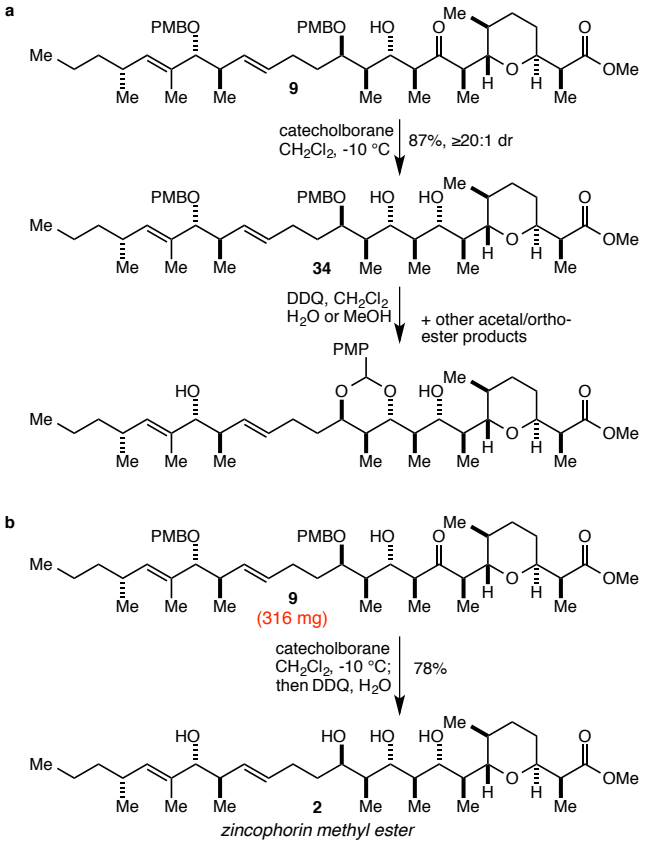


Figure 8. (a) Stepwise ketone reduction and PMB ether deprotection was unsuccessful due to acetal formation. (b) One-pot sequential ketone reduction and PMB ether deprotection delivers zincophorin methyl ester in a single step from aldol product **9**.

Conclusion. We have developed a new synthesis of zincophorin methyl ester that proceeds in nine steps (LLS) and 17% overall yield from 2-vinyl-1,3-dioxolane, nine steps (LLS) and 10% overall yield from propionaldehyde (the starting material for the preparation of **12**), and eight steps (LLS) and 10% overall yield from 2-ethyl-2-vinyl-1,3-dioxolane. Though by no means perfected (*e.g.* the unexpectedly low diastereoselectivity of the fragment coupling aldol reaction), this work consititutes by a significant margin the most step-economical and efficient synthesis of zincophorin methyl ester yet reported, and represents significant progress toward more step-economical[34] and ideal[35,36] syntheses of non-aromatic polyketide natural products. In more practical terms, we have demonstrated the practicability of the route by performing most of the steps on a ≥1-g scale and all of the steps on a meaningful scale, and should one be interested in exploring in greater detail the biological activity of zincophorin and in its development as a medicinal agent, our synthesis would enable such studies with significantly reduced expenditures of time, effort, and resources.

Strategically, the remarkable step-economy of this new synthesis derives in part from the identification of a convergent strategy that divides the target into two fragments of similar complexity, and the development of a novel single step reduction/deprotection reaction. The result is a fragment coupling and end game sequence that couples the two fragments, establishes three stereocenters, and removes the two protecting groups in just two steps. The step-economy as well as the practicability of the synthesis also derive in part from the asymmetric hydroformylation-allylation/crotylation of commercially available vinyl acetals,[23] an approach which obviates most of the protecting group and oxidation state manipulations that have historically reduced step-economy in non-aromatic polyketide natural product syntheses, delivers polypropionate stereodiads and stereotriads in one or two steps, and which was used to establish five of the 13 asymmetric centers in zincophorin methyl ester in just three total steps. The extraordinary power of this methodology is most clearly evident in the development of a synthesis of ketone **11** comprising five stereocenters in just six steps. We expect that this methodology will find applicability in other related contexts, particularly where step-economy and practicability are critically important as facilitators of non-aromatic polyketide natural product-based drug development efforts.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures and compound characterization data. 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 interests.

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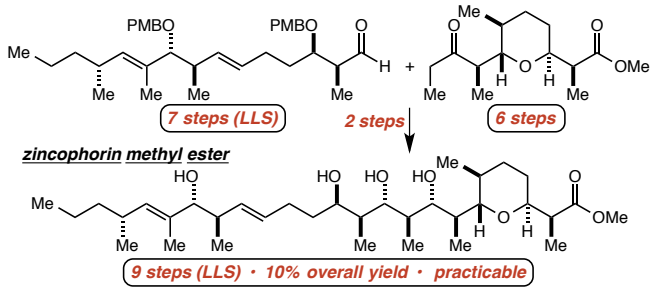
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