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Toward More "Ideal" Polyketide Natural Product Synthesis: A Step-Economical Synthesis of Zincophorin Methyl Ester

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Abstract

A highly efficient and step-economical synthesis of zincophorin methyl ester has been achieved. The unprecedented step-economy of this zincophorin synthesis is principally due to an application of the tandem silylformylation-crotylsilylation/Tamao oxidation-diastereoselective tautomerization reaction that achieves in a single step what would typically require a significant multi-step sequence.

Polyketide natural products continue to influence small molecule drug development efforts. Both natural products (*e.g.* discodermolide[1]) and designed analogs thereof (*e.g.* fludelone[2]) have progressed into clinical trials, and it seems reasonable to anticipate that it might only be a matter of time before approved drugs begin to emerge from such medicinal chemistry programs. It is equally reasonable to anticipate that most such compounds will have to be synthesized (as will, of course, most analogs), as was certainly the case for both discodermolide[3] and fludelone. It is for this reason that, despite decades of beautiful, powerful, and profoundly influential chemistry devoted to the synthesis of such structures, there remains a great need for creative new approaches that achieve significantly greater levels of "ideality."[4] Progress in this regard would be expected to have an impact on every aspect of polyketide natural product-based synthesis and drug development efforts.

Zincophorin (**1**) and its methyl ester (**2**)[5] have been popular targets for synthetic chemists ever since the groundbreaking synthesis by Danishefsky in 1987 (Figure 1).[6,7] Two additional total syntheses have been reported since then by Meyer and Cossy[8] and by Miyashita[9] (in addition to numerous reports of fragment syntheses[10]), and, interestingly, all three syntheses (of **2**) required ~47/~52 total steps[11] with longest linear sequences of 36, 28, and 37 steps resepectively. As part of a broad program devoted to the development of highly efficient and step-economical syntheses of polyketide structures of this type,[12] we decided to undertake a new synthesis of zincophorin methyl ester. Our primary motivation was to set for ourselves the goal of completing the synthesis in about half the number of total steps as the three previous syntheses, because we felt that achieving this would require a fresh approach and true methodological innovation (*i.e.* greater ideality). We report here the results of these efforts that have culminated in a 27/31 total step synthesis of **2**.

The synthesis commenced with an asymmetric epoxidation of alkene **3**[13] using Shi's catalyst[14] to provide **4** in 87% yield and 90% ee (Scheme 1). Epoxide opening using Pagenkopf's procedure[15] gave **5** in 43% yield.[16] NaH-catalyzed silane alcoholysis with di-*cis*-crotylsilane[12d] then provided **6** in 97% yield and set the stage for an application of the tandem silylformylation-crotylsilylation/Tamao oxidation-diastereoselective tautomerization reaction.[12k] Applied to **6**, this complex series of chemical events produced **7** in 67% yield

Supporting Information Available: Experimental procedures, characterization data, and complete refs. 3d and 3e. This material is available free of charge via the internet at http://pubs.acs.org.

with ≥15:1 overall diastereoselectivity. The transformation of **6** into **7** (which we have carried out on multi-gram scale) is remarkable not only for the direct installation of a ketone, three stereocenters, and an alkene, but also for the simplicity of the starting materials (a crotyl-SiH fragment, a propynyl fragment, CO, and H_2O_2). Overall, **7**, which contains five of the ten stereocenters of the C(1)–C(16) fragment, is accessed *in just four steps* from **3**, and this sequence is further noteworthy for what is *not* employed: protecting groups, non-strategic redox reactions, and chiral auxiliaries, controllers, and/or reagents. Using Baran's algorithm, this adds up to a four step sequence that delivers five stereocenters with 100% ideality.[4]

A series of straightforward steps (selective protection to give **8**, *syn*-selective β-hydroxy ketone reduction[17] to give **9**, diol protection to give **10**, and alkene oxidative cleavage) converted ketone **7** into aldehyde **11** and set up a crotylation reaction to establish the C(6) and C(7) stereocenters (Scheme 2). The desired product, **12**, is the result of Felkin addition of a Type I *trans*-crotylmetal reagent to aldehyde **11**, and this is a fully matched case[18] that should not require external asymmetric induction for very high levels of diastereoselectivity.[19] A survey of various Type I *trans*-crotylmetal reagents revealed that the potassium *trans*-crotyltrifluoroborate reagent introduced by Batey[20] was possessed of superior characteristics from the perspective of both efficiency and practicality/ease of use. In the present case its use led to the isolation of **12** in 85% yield (from **10**) with ≥20:1 diastereoselectivity.

The final stereochemical challenges in the synthesis of the C(1)–C(16) fragment were the C(2) and C(3) stereocenters that would accompany tetrahydropyran ring synthesis. It was clear that the most direct way to accomplish those goals in a single step would be the addition of a propionate enolate to an oxocarbenium ion at C(3). To set up such a reaction, **12** was subjected to hydroformylation to give hemiacetal **13** which was acetylated to give **14** in 94% overall yield (Scheme 3). While the well-established preference for axial attack on the oxocarbenium ion generated from **14** would give the desired outcome at C(3), control of the C(2) center was much more speculative. Extensive experimentation with various achiral propionate enolate species failed to reveal an adequate solution, and we therefore turned to the use of chiral enolates that would allow for control of enolate face selectivity. Romea and Urpí have developed a protocol for the highly stereoselective addition of the titanium enolate derived from **15** to oxocarbenium ions derived from acetals, glycals, and pseudoglycals,[21] and this appeared to be a highly relevant precedent. Indeed, the titanium enolate derived from **15** was treated with **14** and $SnCl_4$ to produce **16** in 91% yield as a single diastereomer. Methanolysis proceeded exceptionally smoothly to give **17** and this was followed by a three-step conversion of the benzyl ether into the *N*-phenyltetrazolylsulfone **20**.

The synthesis of the (17)-C(25) fragment commenced with a $Sc(OTf)_3$-catalyzed crotylation of propionaldehyde using *cis*-crotylsilane **21**[22] (Scheme 4).[23] This reaction proceeded smoothly at ambient temperature to provide **22** in 97% yield (based on the use of **21** as the limiting reagent) and 93% ee. Highly *trans*-selective (>20:1) cross-metathesis with excess methacrolein and the second generation Hoveyda-Grubbs catalyst[24] was followed without purification by alcohol tosylation using the Tanabe protocol[25] to provide **23** in 79% yield. A second application of the $Sc(OTf)_3$-catalyzed crotylation reaction with *trans*-crotylsilane **24** then gave **25** in 81% yield with excellent (19:1) diastereoselectivity. Protection of the alcohol as its *para*-methoxy benzyl (PMB) ether was followed in the same pot by tosylate reduction with $LiBEt_3H$ to give **26** in 86% yield. Finally, one pot oxidative cleavage produced aldehyde **27** in 87% yield. The synthesis of **27** thus proceeded in just five steps and 46% overall yield from **21** and relied on two applications of the operationally attractive $Sc(OTf)_3$-catalyzed crotylation methodology.

Julia-Kociensky olefination[26] with sulfone **20** and aldehyde **27** proceeded smoothly and with excellent *trans* selectivity to provide **28** in 69% yield (Scheme 5).[27] Three sequential deprotection steps (oxidative PMB removal, basic carbonate methanolysis, and TBS deprotection) then completed the synthesis of zincophorin methyl ester **2** in 60% overall yield. Full spectral comparison to the data provided by Cossy[8b] and Miyashita[9] confirmed the identity of our synthetic material.

This synthesis of zincophorin methyl ester proceeds in 27/31 total steps,[11] with a longest linear sequence of 22 steps from (*E*)-4-hexen-1-ol in 4.2% overall yield.[28] Another useful measure of efficiency is steps/stereocenter,[29] and in this regard it is noteworthy that the synthesis of the C(1)–C(16) fragment **20** – which contains 10 stereocenters – required just 1.8 steps/stereocenter. Regardless of the metrics used to guage efficiency, it is clear that much of the effciency and step-economy of the route derives from the four-step transformation of **3** to **7**. The “ideality” of that sequence is without precedent and we remain committed to the further development of these and related transformations for application to the synthesis of important and complex polyketide natural products and analogs thereof.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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11. In all of these syntheses, as well as our own, reagents that had to be synthesized are employed (see **15** in Scheme 3, *e.g.*). These syntheses can often be performed once on a large scale, and the reagents are typically reacted with vastly more precious material. In a very real sense, therefore, these steps have essentially no impact on the overall efficiency of the synthesis. The first number given for total steps does not count these steps, whereas the second number counts every step from commercially available materials.
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28. The 43% yield for the conversion of **4** to **5** has, of course, a large impact on the overall yield. Because it comes very near the beginning of the sequence, however, it has less of an impact in terms of the loss of valuable material. In that regard, it is worth noting that the overall yield of the 19-step sequence from **5** to **2** is 12%
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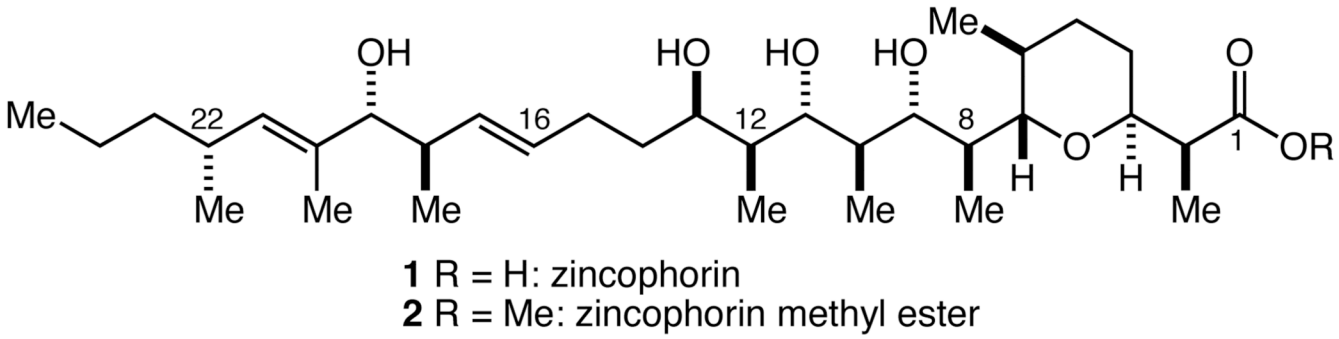
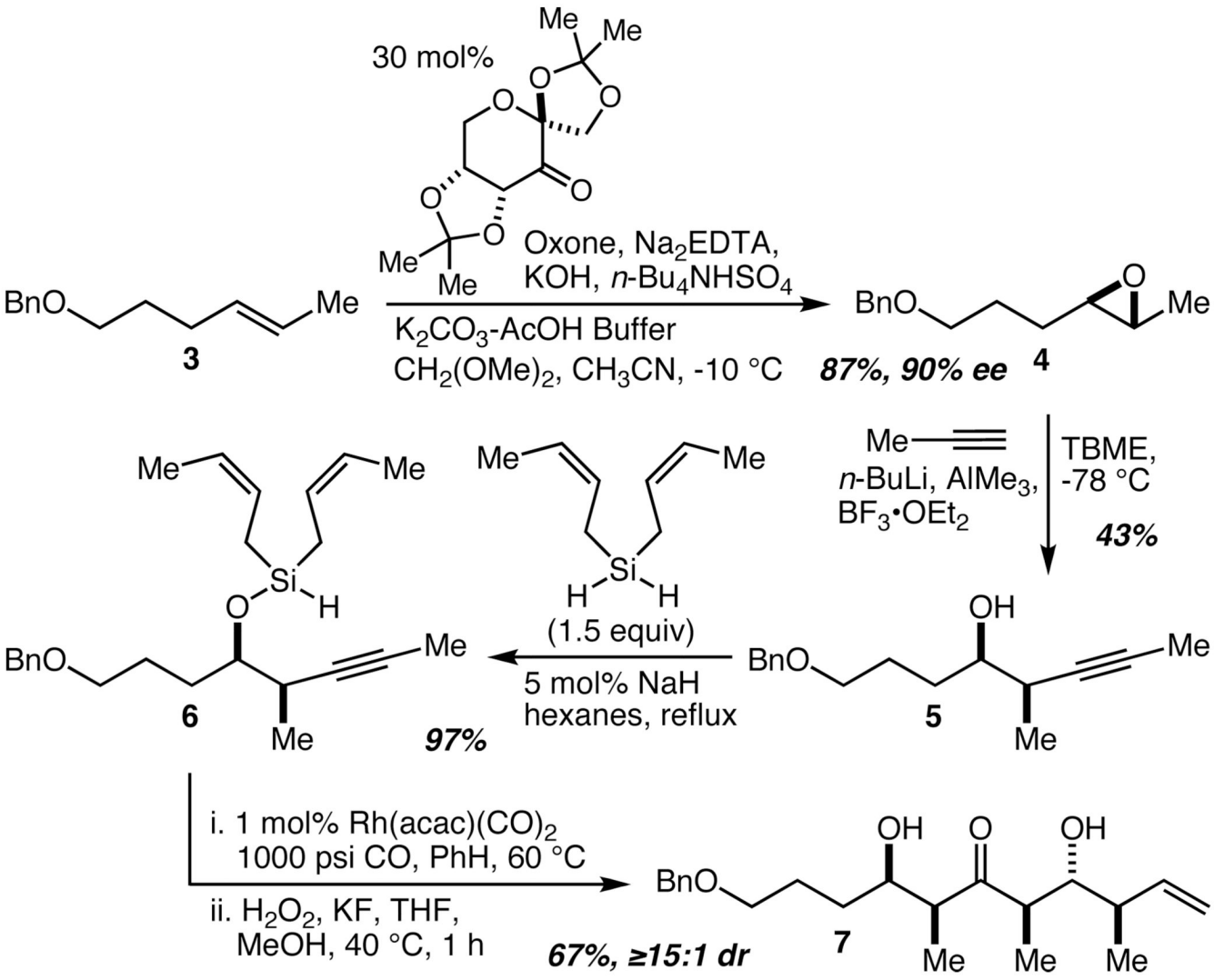
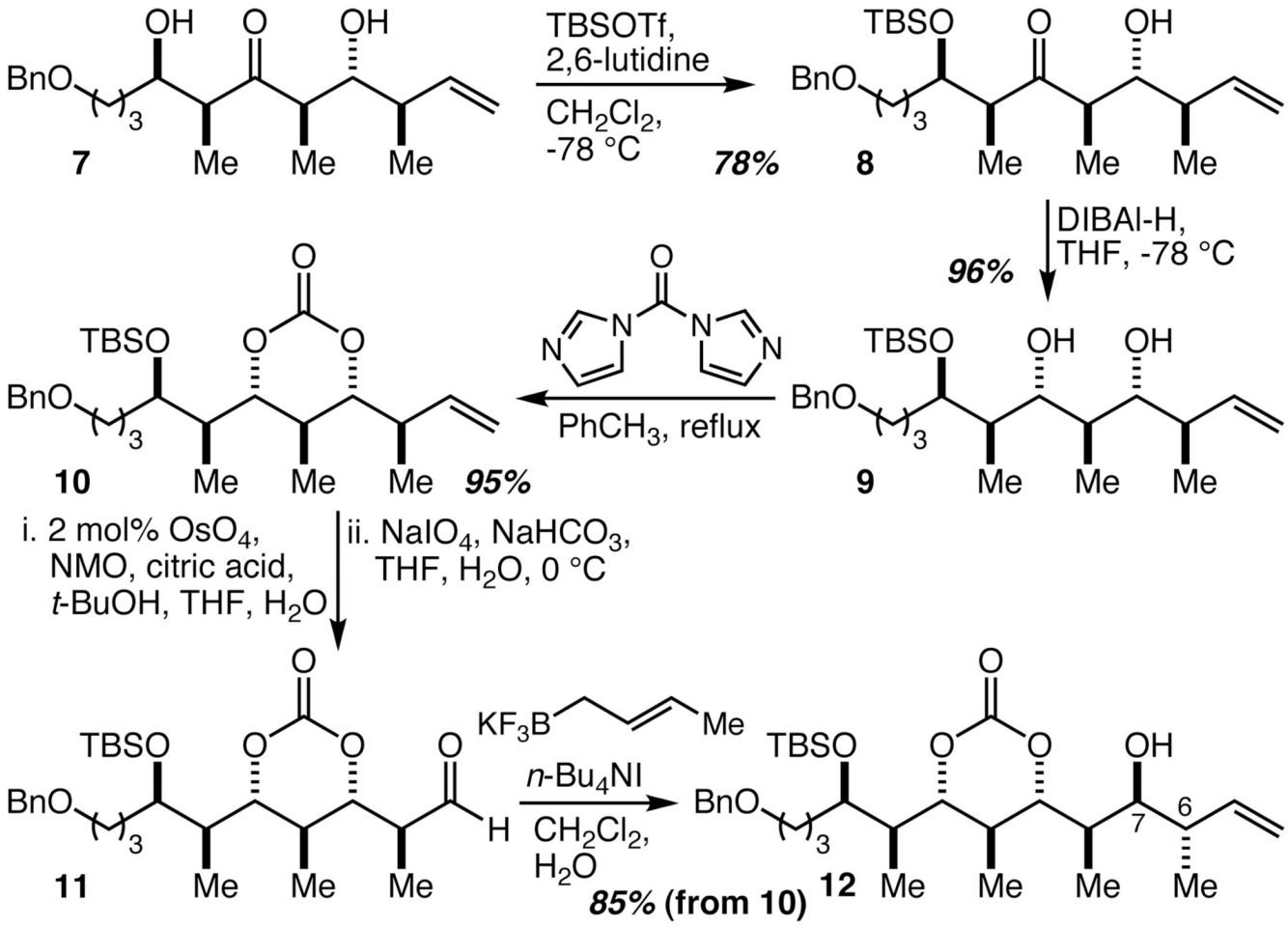


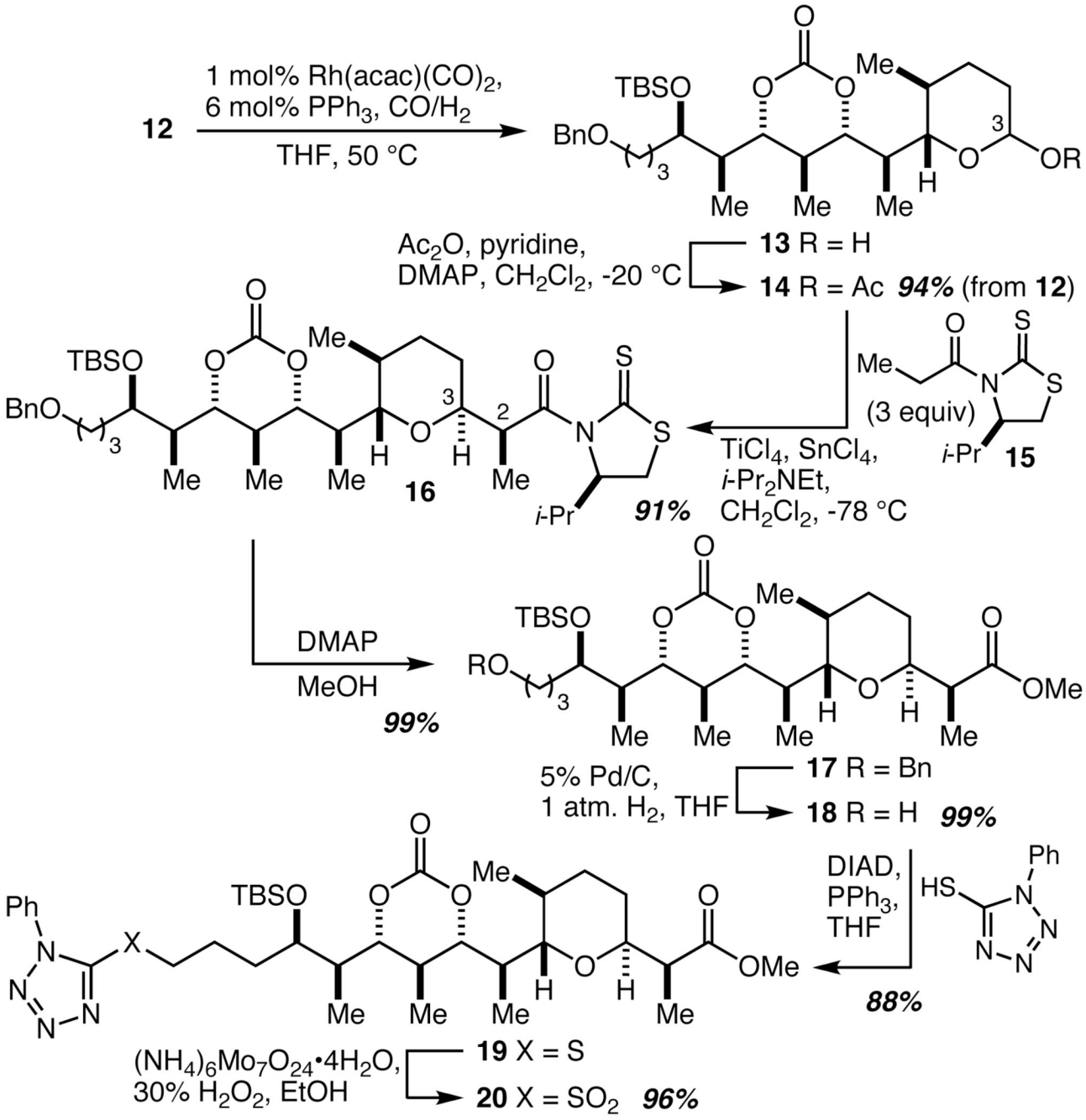
Figure 1.
Zincophorin and zincophorin methyl ester.



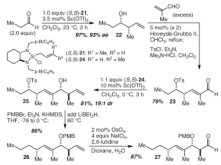
Scheme 1.
A four-step synthesis of **7** from **3**.



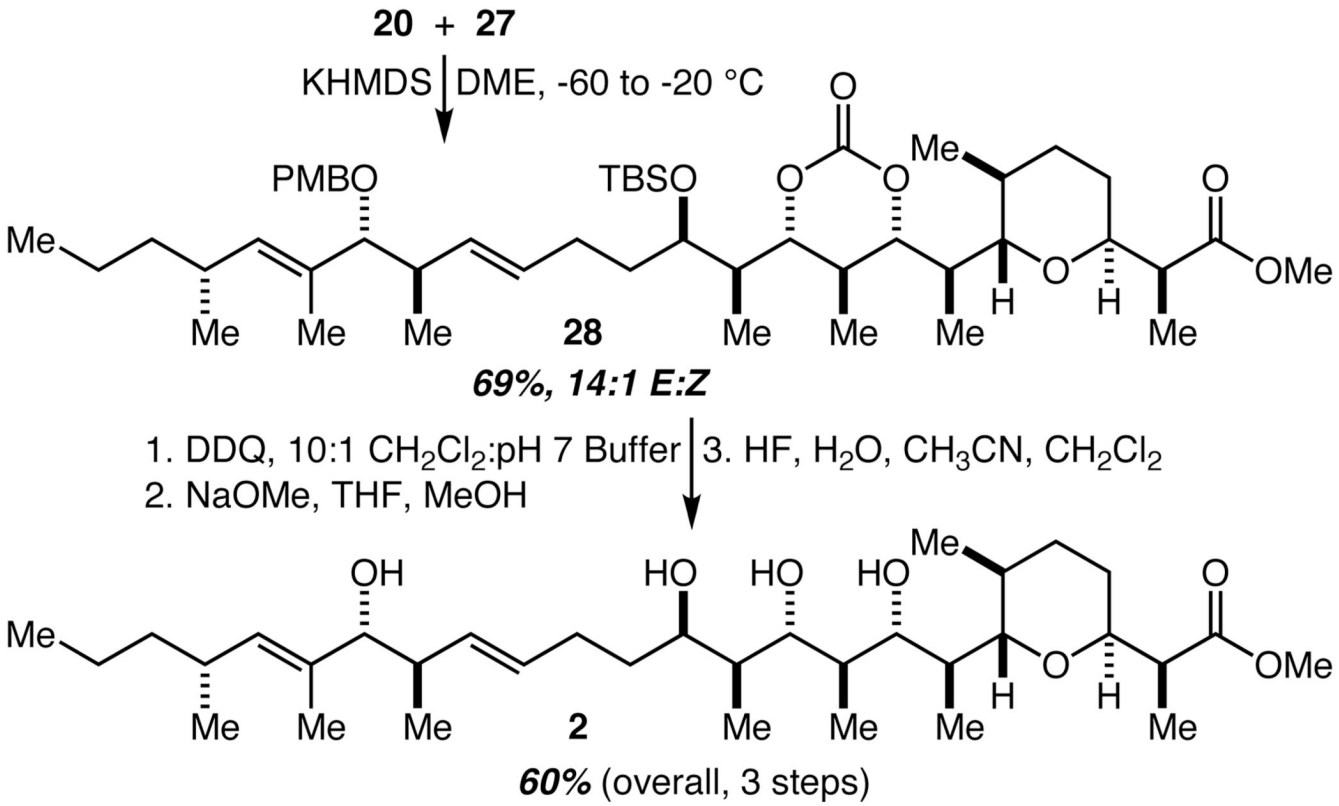
Scheme 2.
Synthesis of the C(11), C(7), and C(6) stereocenters.



Scheme 3.
Completion of the C(1)–C(16) fragment.



Scheme 4.
Synthesis of the C(17)–C(25) fragment.



Scheme 5.
Completion of the synthesis.