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Direct Generation of Triketide Stereopolyads *via* Merged Redox-Construction Events: Total Synthesis of (+)-Zincophorin Methyl Ester

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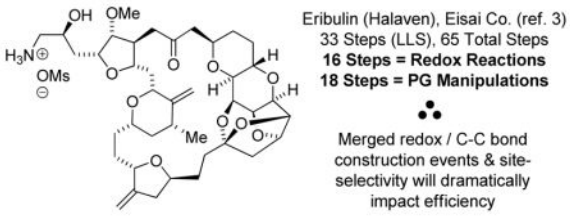
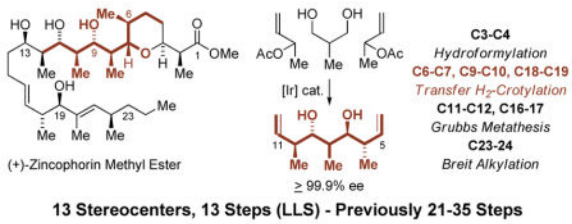
Abstract



(+)-Zincophorin methyl ester is prepared in 13 steps (longest linear sequence). A bidirectional redox-triggered double *anti*-crotylation of 2-methyl-1,3-propane diol directly assembles the triketide stereopolyad spanning C4-C12, significantly enhancing step-economy and enabling construction of (+)-zincophorin methyl ester in nearly half the steps previously required.

Polyketides derived from soil bacteria are estimated to account for roughly 20% of the top-selling small molecule drugs,[1] yet less than 5% of soil bacteria are amenable to culture.[2] As methods for bacterial culture improve, the use of polyketides in human medicine will surely increase, as will the need for concise manufacturing routes to these stereochemically complex structures and their functional analogues. Presently, all commercial polyketides, with the single exception of Eribulin,[3] are prepared by fermentation or semi-synthesis. Although *de novo* chemical synthesis can deliver otherwise inaccessible structural variants, routes that are reliant upon current technologies for acyclic stereocontrol *via* stepwise bond construction are especially lengthy, diminishing prospects for commercial application.



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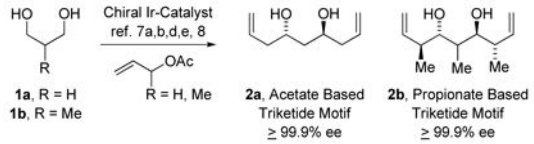
Supporting Information Available: Experimental procedures and spectral data. This material is available free of charge *via* the internet at http://pubs.acs.org.

We have developed a suite of catalytic methods for polyketide construction wherein lower alcohols are directly transformed to higher alcohols in a stereo- and site-selective fashion.[4] In such processes, hydrogen transfer from alcohols to π-unsaturated reactants triggers pairwise generation of carbonyl-organometal species *en route* to products of addition. These merged redox-construction events[5] bypass discrete alcohol-to-aldehyde redox reactions and, because they may be deployed in a site-selective manner,[6] streamline or eliminate the use of protecting groups. Most importantly, such redox-triggered carbonyl additions enable transformations and *strategies* beyond those accessible *via* conventional carbanion chemistry. Indeed, as borne out in total syntheses of roxaticin,[7a] bryostatin 7,[7b] trienomycins A and F,[7c] cyanolide A,[7d] and 6-deoxyerythronolide B,[7e] application of these methods have availed a "step-function increase" in efficiency – in each case, the synthetic route was significantly more concise than in any prior approach.[4b] These studies brought to light an especially powerful protocol for the direct assembly of acetate- or propionate-based triketide stereopolyads **2a** or **2b** involving the bidirectional enantioselective double allylation[8a] or *anti*-crotylation[8b] of 1,3-diols **1a** or **1b**, respectively (eq. 1).[8]



(eq. 1)

The iconic polyketide ionophore antibiotic (+)-zincophorin (Figure 1),[9] which possesses potent (≤ 1 ppm) *in vivo* activity against gram positive bacteria,[9c,10] including *Clostridium coelchii*, presented an opportunity to further assess the impact of direct triketide stereopolyad generation across diverse polyketide families. (+)-Zincophorin and its methyl ester have been the subject of five total syntheses.[11,12,13] The shortest route previously reported is 21 steps (LLS).[11g] Here, we report a "more ideal" total synthesis of (+)-zincophorin methyl ester in 13 steps (LLS) based on direct triketide stereopolyad generation *via* two-directional double *anti*-crotylation of 2-methyl-1,3-propane diol **1b**.

Retrosynthetically, (+)-zincophorin methyl ester was envisioned to arise *via* convergent assembly of Fragments **A** and **B** *via* stereoselective carbonyl addition in accordance with the merged Felkin-Anh and Evans models,[14] followed by oxocarbenium ion addition to install the terminal monoketide Scheme 1. Retrosynthesis of (+)-Zincophorin Methyl Ester. moiety using a chiral propionate enolate.[11g,16] Fragment **A** is prepared in 8 steps from (+)-*tert*-butyl D-lactate **3**. Key C-C bond formations include Breit's method for the stereospecific substitution of α-hydroxy ester triflates with Grignard reagents to create the C22 stereocenter,[15] stereoselective Wittig olefination,[17] which defines the geometry of the trisubstituted olefin, and direct redox-triggered *anti*-crotylation of allylic alcohol **5** to form the C18-C19 stereodiad.[18] The synthesis of Fragment **B** takes advantage of the two-directional double *anti*-crotylation of 2-methyl-1,3-propane diol **1b** to form adduct **2b**,[7e,8b] which directly establishes the triketide stereopolyad spanning C6-C10. Cross-metathesis is

used to introduce the C12-C13 carbon atoms of allyl alcohol **8**, and hydroformylation is used to forge the C3-C4 bond of Fragment **B**.

The synthesis of Fragment **A** (Scheme 2) begins with the conversion of (+)-*tert*-butyl D-lactate **3** to the corresponding triflate, which upon exposure to *n*-propylmagnesium chloride in the presence of substoichiometric quantities of zinc chloride delivers the product of substitution with inversion of stereochemistry.[15] Reduction of the ester mediated by lithium aluminum hydride delivers alcohol **4**.[19] Swern oxidation of **4** followed by Wittig olefination of the chiral α-stereogenic aldehyde provides an α,β-unsaturated ester, which is subjected to DIBAL reduction to form the previously reported allylic alcohol **5**.[17] Direct redox-triggered *anti*-crotylation[18] of allylic alcohol **5** forms the C18-C19 bond, delivering the homoallylic alcohol **6** with good levels of catalyst-directed diastereoselectivity (5.5:1 dr). Cross-metathesis of compound **6** with 4-iodo-1-butene occurred uneventfully.[20] Minor diastereomers generated in the formation of compound **6** are easily separated at this stage. Conversion of the C19 hydroxyl to the TES-ether completes the synthesis of Fragment **A** in 8 steps from (+)-*tert*-butyl D-lactate.

To construct Fragment **B** (Scheme 3), diol **1b** is subjected to two-directional double *anti*-crotylation followed by iodoetherification to deliver **7**.[7e,8b] Iodoetherification defines the chirotopic nonstereogenic center of diol **2b** at C8, and serves to differentiate the terminal olefin moieties. The *pseudo-C* -symmetric diol **2b** is produced as a single enantiomer due to Horeau's principle,[21] that is, the minor enantiomer of the intervening mono-adduct is converted to the *pseudo-meso*-diastereomer.[22] In the conversion of diol **1b** to adduct **2b**, it was found that use of α-methyl allyl acetate prepared *via* acetylation of the corresponding alcohol using triethylamine rather than pyridine as base gave the best results. Whereas attempted cross-metatheses of **7** with allyl acetate or *cis*-butene diol di-acetate suffered from competing olefin isomerization, the Stewart-Grubbs catalyst enabled conversion of **7** to the allylic acetate in 81% yield.[23] Bernet-Vasella cleavage[24] of the iodoether in methanol solvent occurs with concomitant loss of the acetate. Subsequent formation of the acetonide delivers the allylic alcohol **8**, which is converted to a single diastereomeric epoxide using the Sharpless protocol.[25] Reaction of the epoxide with Gilman's reagent delivers compound **9**,[26] which incorporates the stereoheptad spanning C6-C12. Hydroformylation of **9** using a XantPhos modified rhodium catalyst[27] provides the linear aldehyde, which upon exposure to methanol in the presence of substoichiometric *p*-toluenesulfonic acid delivers the pyran **10** as a mixture of diastereomers at the anomeric position. The major diastereomeric pyran **10** could be separated by flash chromatography and was converted to the tris(triethylsilyl) ether. Exposure to Swern oxidation conditions results in cleavage of the primary TES-ether and formation of the aldehyde Fragment **B**.[28]

The union of Fragments **A** and **B** is achieved through lithiation of the primary alkyl iodide Fragment **A** and subsequent addition to the aldehyde Fragment **B**.[29] Synergistic 1,2- and 1,3-stereoinduction effects[14] were anticipated to enforce highly diastereoselective addition. However, under standard reaction conditions using HMPA as additive, the adduct **11** formed as a 1:1 ratio of C13 diastereomers. HMPA was necessary to facilitate Li-halogen exchange of Fragment **A**, as its omission resulted in *tert*-butylation of Fragment **B**. This was not the

case using 4-iodo-1-butene, which underwent addition to Fragment **B** in ether in 70% yield to furnish 2:1 ratio of C13 diastereomers. The diastereomeric ratio did not change upon introduction of HMPA, suggesting chelation control was not operative, however, an improved 99% yield was observed. The Cram-Reetz and Evans polar models[14] assume the C11-$OSiEt_3$ moiety should predominantly populate a conformation wherein the C11-$OSiEt_3$ bond dipole cancels the C13 formyl bond dipole. It appears the negative inductive effect of the highly oxygenated C10-C3 moiety erodes this conformational bias, leading to diminished diastereoselectivities (Figure 2). Hence, modification of the organolithium reagent by chiral 1,2-diamines was investigated as a means of amplifying stereoselectivity.[30] Using tetramethylcyclohexane diamine, a 3:1 molar ratio of diastereomers was obtained, which could be separated by flash chromatography. With compound **11** in hand, installation of the terminal C3 monoketide moiety was achieved using a chiral propionate enolate,[11g,16] providing the *trans*-pyran as a single diastereomer. Subsequent methanolysis of the thiazole thione from the crude reaction mixture delivered (+)-zincophorin methyl ester, which was identical in all respects to literature. In this way, (+)-zincophorin methyl ester, which incorporates 13 stereocenters, was prepared 13 steps (LLS) with 4 C – C bonds formed using hydrogenative coupling protocols.

Despite enormous progress in synthetic methods development, the vast majority of *de novo* chemical syntheses remain distant from the Hendricksonian ideal.[31] This is principally due to (a) the separation of redox and skeletal construction events, and (b) the persistent requirement of protecting groups. Both deficiencies may be addressed through the design of catalytic methods that merge redox and C-C bond formation events,[5] especially transformations that may be deployed in a site-selective manner, and the new strategies that such methods evoke. In the present study, hydrogenative couplings that exploit alcohol-to-carbonyl oxidation as a driver for carbanion generation,[4] are used to directly generate triketide stereopoly-ads that would otherwise require lengthy multi-step syntheses. As demonstrated here and in prior work,[7] these methods have availed a “step-function” change in efficiency across diverse contexts, bringing us one step closer to the Hendricksonian ideal.[31] More immediately, the concise nature of the present route to (+)-zincophorin methyl ester will enable access to material that will allow for a more complete investigation into its biological properties; studies which are currently underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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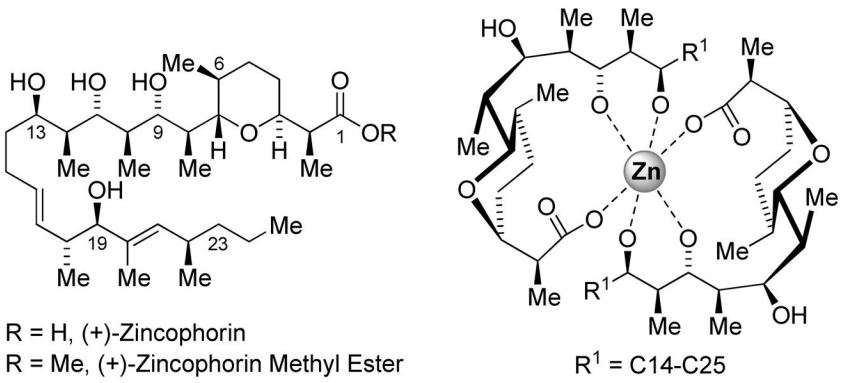


Total Syntheses of (+)-Zincophorin Methyl Ester

Danishefsky 1987, 35 Steps (LLS), 61 Steps (TS), ref. 11a,b
Cossy 2003, 30 Steps (LLS), 56 Steps (TS), ref. 11c,d,e
Leighton 2011, 21 Steps (LLS), 33 Steps (TS), ref. 11g
Guindon 2015, 49 Steps (LLS), 70 Steps (TS), ref. 11h

Total Syntheses of (+)-Zincophorin

Miyashita 2004, 39 Steps (LLS), 54 Steps (TS), ref. 11f

Figure 1.

(+)-Zincophorin and (+)-Zincophorin Methyl Ester and Summary of Prior Total Syntheses.[a]

[a]For graphical summaries of prior total syntheses, see Supporting Information. Longest Linear Sequence (LLS); Total Steps (TS).

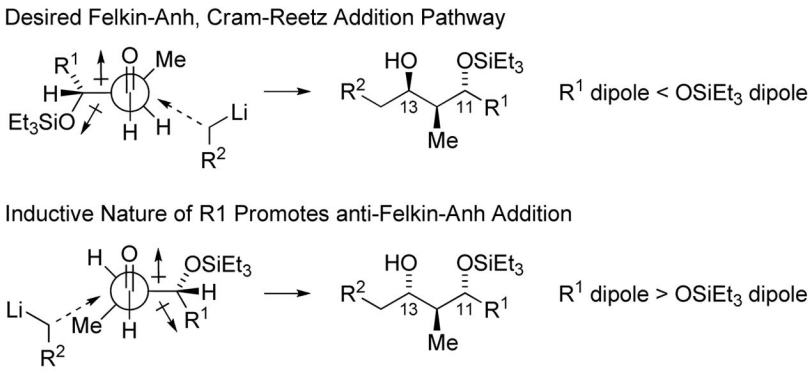
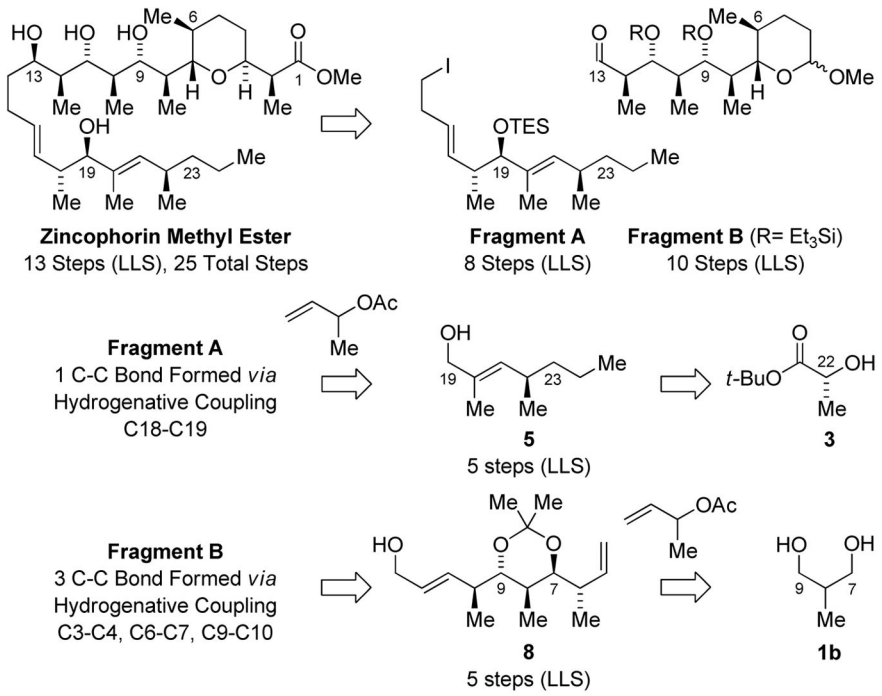


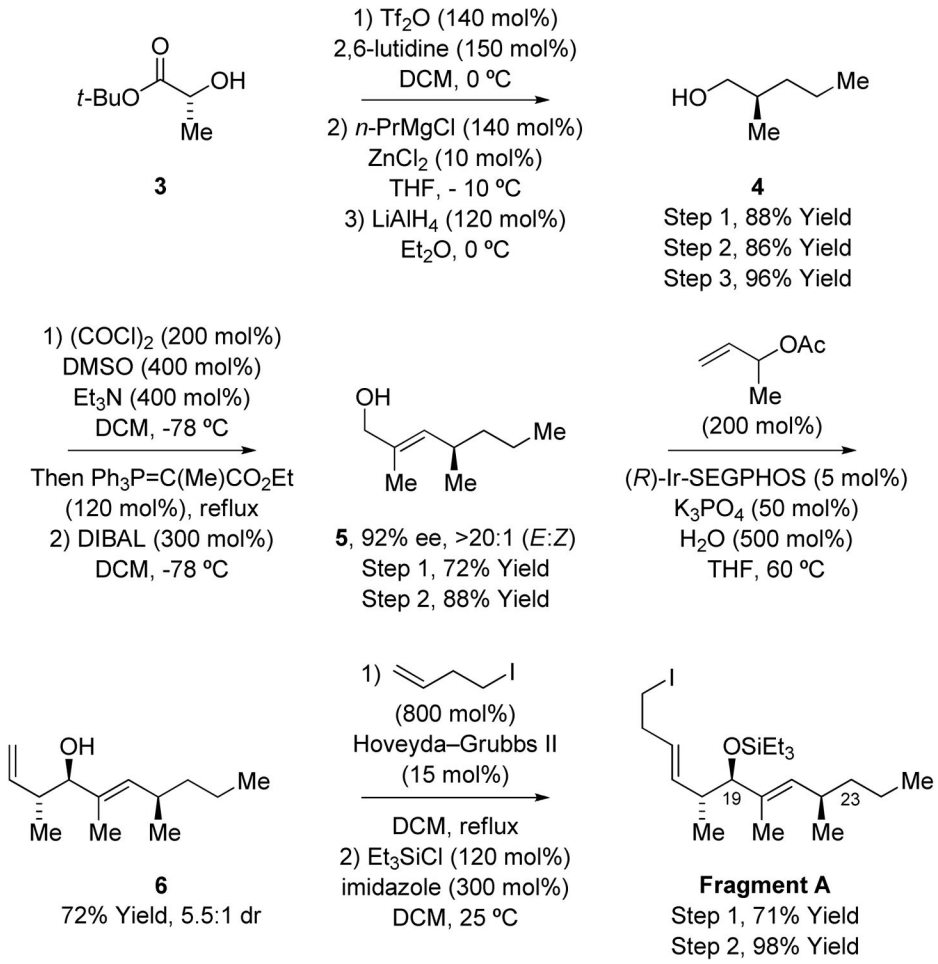
Figure 2.

Merged 1,2- and 1,3-Stereoinduction Model.[a]

[a]R^1 = C10-C3 of Fragment **B**, R^2 = C15-C25 of Fragment **A**.



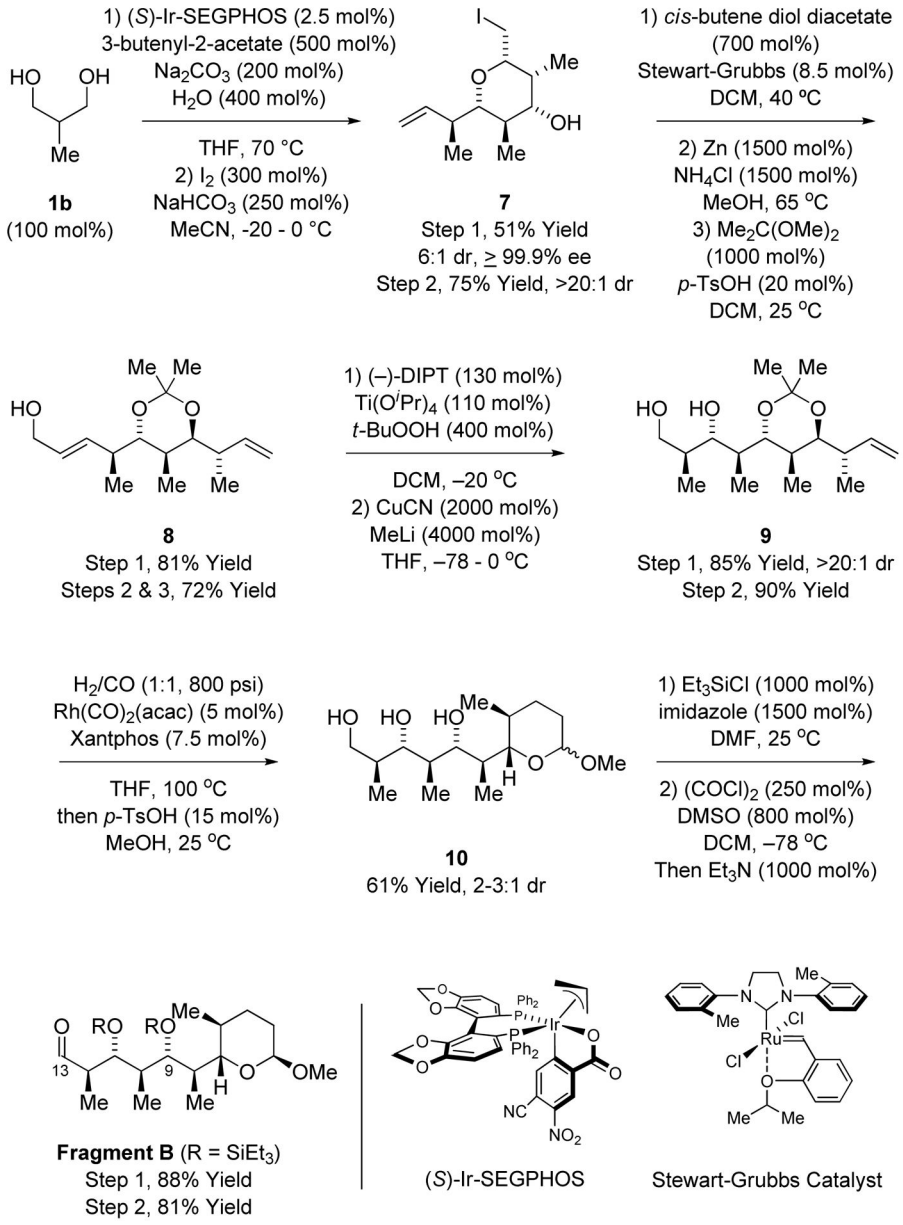
Scheme 1.
Retrosynthesis of (+)-Zincophorin Methyl Ester.



Scheme 2.

Synthesis of Fragment **A** *via* Direct *anti*-Crotylation of Allylic Alcohol **5**.[a]

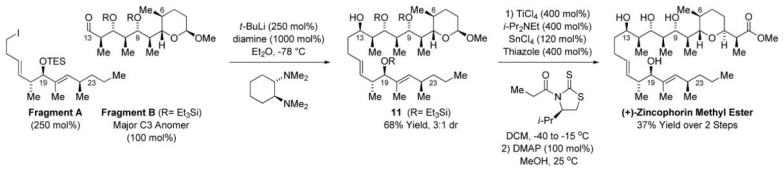
[a]Yields are of material isolated by silica gel chromatography. Enantiomeric excess was determined by chiral GLC. See Supporting Information for further experimental details.



Scheme 3.

Synthesis of Fragment **B** *via* Two-Directional Double *anti*-Crotylation of 2-Methyl-1,3-Propane Diol **1b**.[a]

[a]Yields are of material isolated by silica gel chromatography. See Supporting Information for further experimental details.



Scheme 4.

Union of Fragment **A** and Fragment **B** and Total Synthesis of (+)-Zincophorin Methyl Ester.[a]

[a]Yields are of material isolated by silica gel chromatography. See Supporting Information for further experimental details.