JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

pubs.acs.org/JACS

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

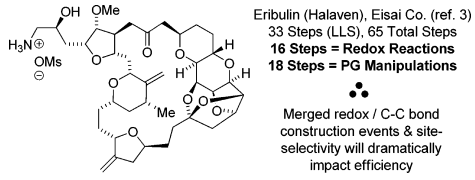
Zachary A. Kasun, Xin Gao, Radoslaw M. Lipinski, and Michael J. Krische*

University of Texas at Austin, Department of Chemistry, Austin, Texas 78712, United States

Supporting Information

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 semisynthesis. 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.



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

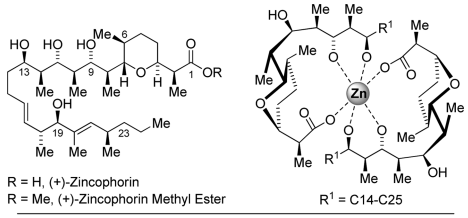
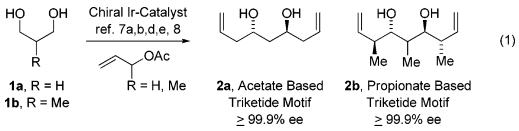


Figure 1. (+)-Zincophorin and (+)-zincophorin methyl ester and summary of prior total syntheses. For graphical summaries of prior total syntheses, see Supporting Information. Longest Linear Sequence (LLS); Total Steps (TS).

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]



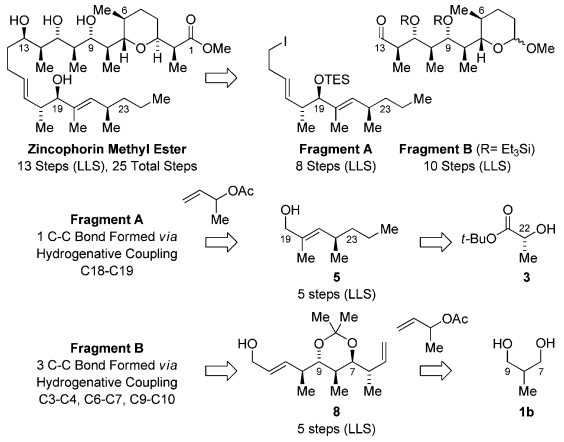
The iconic polyketide ionophore antibiotic (+)-zincophorin (Figure 1),[9] which possesses potent ($\leq$1 ppm) *in vivo* activity against Gram-positive bacteria,[9c,10] including *Clostridium coelchii*, presented an opportunity to further assess the impact of direct triketide stereopolyad generation across diverse polyketide families. (+)-Zincophorin and its methyl ester have been the subject of five total syntheses.[11−13] 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 through convergent assembly of Fragments **A** and **B** via stereoselective carbonyl addition in accordance with the merged Felkin−Anh and Evans models,[14] followed by

Received: May 23, 2015
Published: July 13, 2015

DOI: 10.1021/jacs.5b05296
J. Am. Chem. Soc. 2015, 137, 8900−8903

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

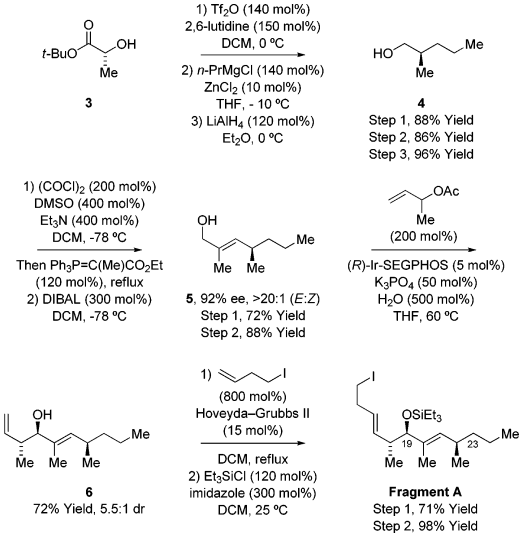


oxocarbenium ion addition to install the terminal monoketide moiety using a chiral propionate enolate (Scheme 1).[11g,16] Fragment **A** is prepared in 8 steps from (+)-*tert*-butyl D-lactate **3**. Key C−C bond formations include Breit's method for the stereospecific substitution of α-hydroxy ester 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.

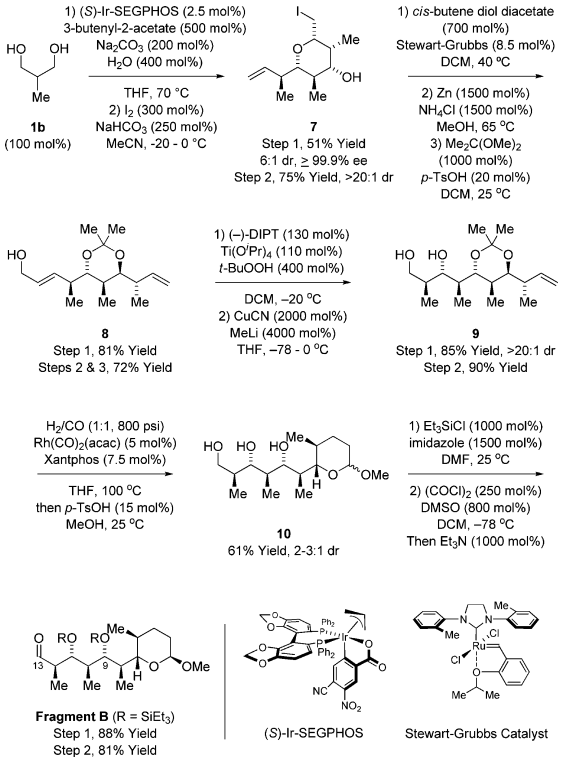
To construct Fragment **B** (Scheme 3), diol **1b** is subjected to two-directional double *anti*-crotylation followed by iodoetherification to deliver **7**.[7e,8b] Iodoetherification defines the chirotopic nonstereogenic center of diol **2b** at C8 and serves to differentiate the terminal olefin moieties. The *pseudo*-C_2-symmetric diol **2b** is produced as a single enantiomer due to Horeau's principle;[21] that is, the minor enantiomer of the intervening monoadduct 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 a base gave the best results. Whereas

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]

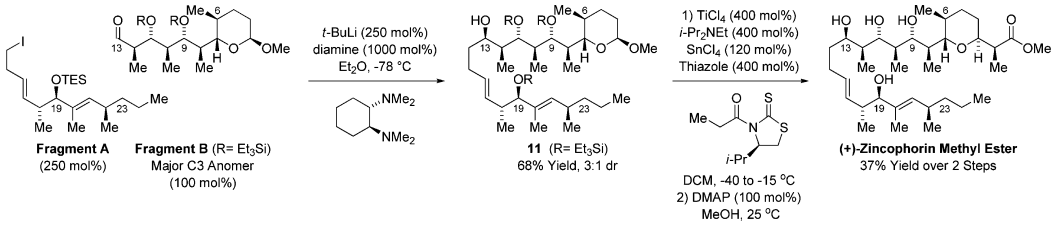


[a]Yields are of material isolated by silica gel chromatography. See Supporting Information for further experimental details.

attempted cross-metatheses of **7** with allyl acetate or *cis*-butene diol diacetate 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

DOI: 10.1021/jacs.5b05296
J. Am. Chem. Soc. 2015, 137, 8900−8903

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.

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** (Scheme 4).[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 an 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 a 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

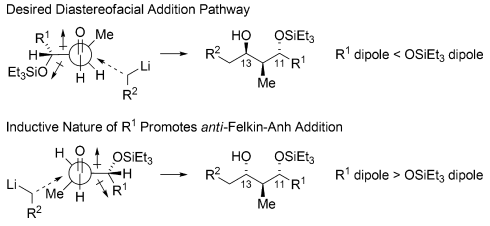


Figure 2. Merged 1,2- and 1,3-stereoinduction model. R^1 = C10−C3 of Fragment **B**; R^2 = C15−C25 of Fragment **A**.

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 the reported literature material.[9] In this way, (+)-zincophorin methyl ester, which incorporates 13 stereocenters, was prepared in 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,[6] and the new strategies that such methods evoke. In the present study, transfer hydrogenative couplings that directly convert lower alcohols to higher alcohols[4] are used to generate triketide stereopolyads that would otherwise require lengthy multistep syntheses. As demonstrated across diverse contexts,[7] these methods consistenly and significantly enhance efficiency, 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.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b05296.

■ AUTHOR INFORMATION

Corresponding Author

*mkrische@mail.utexas.edu

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The Robert A. Welch Foundation (F-0038), the NIH-NIGMS (RO1-GM093905), and the University of Texas Center for Green Chemistry and Catalysis are acknowledged for partial support of this research.

■ REFERENCES

(1) Reviews: (a) O'Hagan, D. *The Polyketide Metabolites*; Ellis Horwood: Chichester, U.K., 1991. (b) Rohr, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 2847. (c) *Polyketides: Biosynthesis, Biological Activity, and Genetic Engineering*; Rimando, A. M., Baerson, S. R., Eds.; ACS

DOI: 10.1021/jacs.5b05296
J. Am. Chem. Soc. 2015, 137, 8900−8903

Symposium Series 955; American Chemical Society: Washington, DC, 2007. (d) Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2007**, *70*, 461. (e) Cragg, G. M.; Grothaus, P. G.; Newman, D. J. *Chem. Rev.* **2009**, *109*, 3012.

(2) Sait, M.; Hugenholtz, P.; Janssen, P. H. *Environ. Microbiol.* **2002**, *4*, 654 and references cited therein. .

(3) Eribulin (halaven), a truncated analogue of the marine polyketide halichondrin B and FDA approved treatment for metastatic breast cancer, requires 65 steps for its preparation. Over half these steps are protecting group (PG) manipulations and redox reactions. Eribulin is 200 times more potent than taxol, which compensates for its relatively high manufacturing costs. Yu, M. J.; Zheng, W.; Seletsky, B. M. *Nat. Prod. Rep.* **2013**, *30*, 1158.

(4) For selected reviews on enantioselective redox-triggered carbonyl addition from the alcohol oxidation level, see: (a) Ketcham, J. M.; Shin, I.; Montgomery, T. P.; Krische, M. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 9142. (b) Dechert-Schmitt, A.-M. R.; Schmitt, D. C.; Gao, X.; Itoh, T.; Krische, M. J. *Nat. Prod. Rep.* **2014**, *31*, 504.

(5) For a review on redox economy, see: Burns, N. Z.; Baran, P. S.; Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2009**, *48*, 2854.

(6) For site-selective C−C coupling of unprotected diols and higher polyols, see: (a) Dechert-Schmitt, A.-M. R.; Schmitt, D. C.; Krische, M. J. *Angew. Chem., Int. Ed.* **2013**, *52*, 3195. (b) Shin, I.; Wang, G.; Krische, M. J. *Chem. - Eur. J.* **2014**, *20*, 13382. (c) Wang, G.; Franke, J.; Ngo, C. Q.; Krische, M. J. *J. Am. Chem. Soc.* **2015**, *137*, 7915.

(7) (a) Han, S. B.; Hassan, A.; Kim, I. S.; Krische, M. J. *J. Am. Chem. Soc.* **2010**, *132*, 15559. (b) Lu, Y.; Woo, S. K.; Krische, M. J. *J. Am. Chem. Soc.* **2011**, *133*, 13876. (c) Del Valle, D. J.; Krische, M. J. *J. Am. Chem. Soc.* **2013**, *135*, 10986. (d) Waldeck, A. R.; Krische, M. J. *Angew. Chem., Int. Ed.* **2013**, *52*, 4470. (e) Gao, X.; Woo, S. K.; Krische, M. J. *J. Am. Chem. Soc.* **2013**, *135*, 4223.

(8) (a) Lu, Y.; Kim, I. S.; Hassan, A.; Del Valle, D. J.; Krische, M. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 5018. (b) Gao, X.; Han, H.; Krische, M. J. *J. Am. Chem. Soc.* **2011**, *133*, 12795.

(9) For the isolation and structure determination of (+)-zincophorin, also known as M144255 or griseocholin, see: (a) Gräfe, U.; Schade, W.; Roth, M.; Radics, L.; Incze, M.; Ujszászy, K. *J. Antibiot.* **1984**, *37*, 836. (b) Radics, L. *J. Chem. Soc., Chem. Commun.* **1984**, 599. (c) Brooks, H. A.; Gardner, D.; Poyser, J. P.; King, T. J. *J. Antibiot.* **1984**, *37*, 1501. (d) Radics, L.; Kajtár-Peredy, M. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1471. (e) Tonew, E.; Tonew, M.; Graefe, U.; Zopel, P. *Pharmazie* **1988**, *43*, 717. (f) Scharfenberg-Pfeiffer, D.; Czugler, M. *Pharmazie* **1991**, *46*, 781.

(10) For a review of the antibacterial properties of polyether ionophores, see: Kevin, D. A., II; Meujo, D. A. F.; Hamann, M. T. *Expert Opin. Drug Discovery* **2009**, *4*, 109.

(11) For total syntheses of (+)-zincophorin and its methyl ester, see: (a) Danishefsky, S. J.; Selnick, H. G.; DeNinno, M. P.; Zelle, R. E. *J. Am. Chem. Soc.* **1987**, *109*, 1572. (b) Danishefsky, S. J.; Selnick, H. G.; Zelle, R. E.; DeNinno, M. P. *J. Am. Chem. Soc.* **1988**, *110*, 4368. (c) Defosseux, M.; Blanchard, N.; Meyer, C.; Cossy, J. *Org. Lett.* **2003**, *5*, 4037. (d) Defosseux, M.; Blanchard, N.; Meyer, C.; Cossy, J. *J. Org. Chem.* **2004**, *69*, 4626. (e) Cossy, J.; Meyer, C.; Defosseux, M.; Blanchard, N. *Pure Appl. Chem.* **2005**, *77*, 1131. (f) Komatsu, K.; Tanino, K.; Miyashita, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4341. (g) Harrison, T. J.; Ho, S.; Leighton, J. L. *J. Am. Chem. Soc.* **2011**, *133*, 7308. (h) Godin, F.; Mochirian, P.; St-Pierre, G.; Guindon, Y. *Tetrahedron* **2015**, *71*, 709.

(12) For a review highlighting synthetic approaches to (+)-zincophorin and its methyl ester, see: Song, Z.; Lohse, A. G.; Hsung, R. P. *Nat. Prod. Rep.* **2009**, *26*, 560.

(13) For selected formal syntheses and fragment syntheses, see: (a) Balestra, M.; Wittman, M. D.; Kallmerten, J. *Tetrahedron Lett.* **1988**, *29*, 6905. (b) Cywin, C. L.; Kallmerten, J. *Tetrahedron Lett.* **1993**, *34*, 1103. (c) Marshall, J. A.; Palovich, M. R. *J. Org. Chem.* **1998**, *63*, 3701. (d) Chemler, S. R.; Roush, W. R. *J. Org. Chem.* **1998**, *63*, 3800. (e) Song, Z.; Hsung, R. P. *Org. Lett.* **2007**, *9*, 2199. (f) Sabitha, G.; Srinivas, R.; Yadav, J. S. *Synthesis* **2011**, *2011*, 1484. (g) Cooksey, J. P. *Org. Biomol. Chem.* **2013**, *11*, 5117. (h) Yadav, J. S.; Gyanchander, E.; Das, S. *Tetrahedron Lett.* **2014**, *55*, 3996.

(14) (a) Leitereg, T. J.; Cram, D. J. *J. Am. Chem. Soc.* **1968**, *90*, 4011. (b) Nguyen Trong Anh; Eisenstein, O.; Lefour, J.-M.; Tran Huu Dau, M.-E. *J. Am. Chem. Soc.* **1973**, *95*, 6146. (c) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61. (d) Reetz, M. T.; Kesseler, K.; Jung, A. *Tetrahedron Lett.* **1984**, *25*, 729. (e) Evans, D. A.; Duffy, J. L.; Dart, M. J. *Tetrahedron Lett.* **1994**, *35*, 8537. (f) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G.; Livingston, A. B. *J. Am. Chem. Soc.* **1995**, *117*, 6619. (g) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322.

(15) Studte, C.; Breit, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 5451.

(16) (a) Cosp, A.; Romea, P.; Talavera, P.; Urpí, F.; Vilarrasa, J.; Font-Bardia, M.; Solans, X. *Org. Lett.* **2001**, *3*, 615. (b) Larrosa, I.; Romea, P.; Urpí, F.; Balsells, D.; Vilarrasa, J.; Font-Bardia, M.; Solans, X. *Org. Lett.* **2002**, *4*, 4651. (c) Larrosa, I.; Romea, P.; Urpí, F. *Org. Lett.* **2006**, *8*, 527.

(17) The conversion of alcohol **4** to allylic alcohol **5** *via* Swern oxidation followed by Wittig olefination has been described: Lister, T.; Perkins, M. V. *Aust. J. Chem.* **2004**, *57*, 787.

(18) For iridium catalyzed carbonyl crotylation from the alcohol oxidation level employing α-methyl allyl acetate as the crotyl donor, see: (a) Kim, I. S.; Han, S. B.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 2514. (b) Gao, X.; Townsend, I. A.; Krische, M. J. *J. Org. Chem.* **2011**, *76*, 2350.

(19) Alcohol **4** is a known compound: Chen, H.-Y.; McDonald, F. E. *J. Am. Chem. Soc.* **2006**, *128*, 4568 and ref 17. .

(20) (a) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490. (b) Fürstner, A. *Chem. Commun.* **2011**, *47*, 6505.

(21) (a) Vigneron, J. P.; Dhaenens, M.; Horeau, A. *Tetrahedron* **1973**, *29*, 1055. (b) For a historical review, see: Heller, D.; Drexler, H.-J.; Fischer, C.; Buschmann, H.; Baumann, W.; Heller, B. *Angew. Chem., Int. Ed.* **2000**, *39*, 495.

(22) (a) Kogure, T.; Eliel, E. L. *J. Org. Chem.* **1984**, *49*, 576. (b) Midland, M. M.; Gabriel, J. *J. Org. Chem.* **1985**, *50*, 1143. (c) Poss, C. S.; Schreiber, S. L. *Acc. Chem. Res.* **1994**, *27*, 9.

(23) (a) Stewart, I. C.; Ung, T.; Pletnev, A. A.; Berlin, J. M.; Grubbs, R. H.; Schrodi, Y. *Org. Lett.* **2007**, *9*, 1589. (b) Stewart, I. C.; Douglas, C. J.; Grubbs, R. H. *Org. Lett.* **2008**, *10*, 441.

(24) (a) Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1979**, *62*, 1990. (b) Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1979**, *62*, 2400. (c) Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1984**, *67*, 1328.

(25) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.

(26) (a) Gilman, H.; Jones, R. G.; Woods, L. A. *J. Org. Chem.* **1952**, *17*, 1630. (b) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873.

(27) For impact of large bite-angle ligands on regioselectivity in hydroformylation, see citation (a). For seminal use of XantPhos in linear regioselective hydroformylation, see citation (b): (a) Casey, C. P.; Whiteker, G. T.; Melville, M. G.; Petrovich, L. M.; Gavney, J. A., Jr.; Powel, D. R. *J. Am. Chem. Soc.* **1992**, *114*, 5535. (b) Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Goubitz, K. G.; Fraanje, J. *Organometallics* **1995**, *14*, 3081.

(28) Rodríguez, A.; Nomen, M.; Spur, B. W.; Godfroid, J. J. *Tetrahedron Lett.* **1999**, *40*, 5161.

(29) (a) Wittig, G.; Pockels, U.; Dröge, H. *Ber. Dtsch. Chem. Ges. B* **1938**, *71*, 1903. (b) Gilman, H.; Langham, W.; Jacoby, A. L. *J. Am. Chem. Soc.* **1939**, *61*, 106. (c) Bailey, W. F.; Punzalan, E. R. *J. Org. Chem.* **1990**, *55*, 5404.

(30) Goldfuss, B. *Top. Organomet. Chem.* **2003**, *5*, 21.

(31) "*The ideal synthesis creates a complex skeleton...in a sequence only of successive construction reactions involving no intermediary refunctionalizations, and leading directly to the structure of the target, not only its skeleton but also its correctly placed functionality.*" (a) Hendrickson, J. B. *J. Am. Chem. Soc.* **1975**, *97*, 5784. (b) Shin, I.; Montgomery, T. P.; Krische, M. J. *Aldrichimica Acta* **2015**, *48*, 15.

DOI: 10.1021/jacs.5b05296
J. Am. Chem. Soc. 2015, 137, 8900−8903