JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
pubs.acs.org/JACS
Communication

Total Synthesis of Limaol

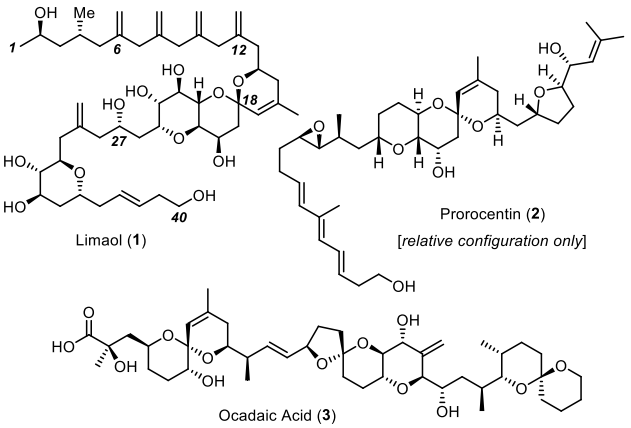
Stephan N. Hess, Xiaobin Mo, Conny Wirtz, and Alois Fürstner*

Cite This: J. Am. Chem. Soc. 2021, 143, 2464−2469
Read Online
ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: A nonthermodynamic array of four skipped methylene substituents on the hydrophobic tail renders limaol, a C40-polyketide of marine origin, unique in structural terms. This conspicuous segment was assembled by a two-directional approach and finally coupled to the polyether domain by an allyl/alkenyl Stille reaction under neutral conditions. The core region itself was prepared via a 3,3′-dibromo-BINOL-catalyzed asymmetric propargylation, a gold-catalyzed spirocyclization, and introduction of the southern sector via substrate-controlled allylation as the key steps.

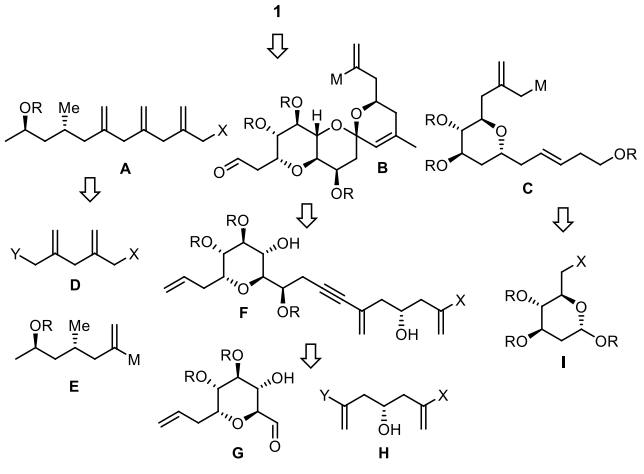
Like many other marine dinoflagellates of the genus *Prorocentrum*, *P. lima* species are toxigenic.[1,2] They were circumstantially associated with cases of diarrheic shellfish poisoning, likely caused by ocadaic acid (**3**) and analogues (Scheme 1). These intriguing polyether toxins produced by the benthic dinoflagellate occasionally accumulate in mussels, scallops, and sponges, and thus can reach the human food chain and cause severe ailment.[3] This discovery sparked considerable interest in the mode of action. Most importantly, **3** was recognized to be a highly potent and specific inhibitor of the Ser/Thr-protein phosphatases PP1 and PP2A; as such, it became an indispensable tool for the study of processes as fundamental as cell cycle control, apoptosis, and tumor promotion, to mention but a few.[3]

Scheme 1. Natural Products Derived from *P. lima*



The disproportionally large genome of many *Prorocentrum* species encodes numerous additional secondary metabolites of remarkable structural complexity, even though their biological role or physiological properties are often less clear.[4,5] A recent addition to this list is limaol (**1**) isolated from a *P. lima* strain collected in Korea.[6] **1** showed moderate cytotoxicity, but no further biological profiling beyond this standard assay was reported. This is all the more regrettable since **1** is arguably unique in structural terms: four of the five "*exo*"-methylene groups decorating the 40-carbon backbone are clustered in a skipped array; the resulting 1,3,5,7-tetra(methylene)heptane substructure is without precedent.[7] Although the isolation team did not mention any particular stability issues, it seemed prudent to bear the nonthermodynamic character of this peculiar motif in mind during retrosynthetic planning (Scheme 2). A late-stage attachment of the polyunsaturated side chain to the core region seemed advisible,[8−10] preferably by cross-coupling of an alkenyl nucleophile with an allylic electrophile under essentially neutral conditions to minimize the risk of deleterious rearrangement into a partly or fully conjugated tetraene. For the same reasons, it was planned to use only silyl

Scheme 2. Retrosynthetic Analysis



Received: December 14, 2020
Published: February 3, 2021

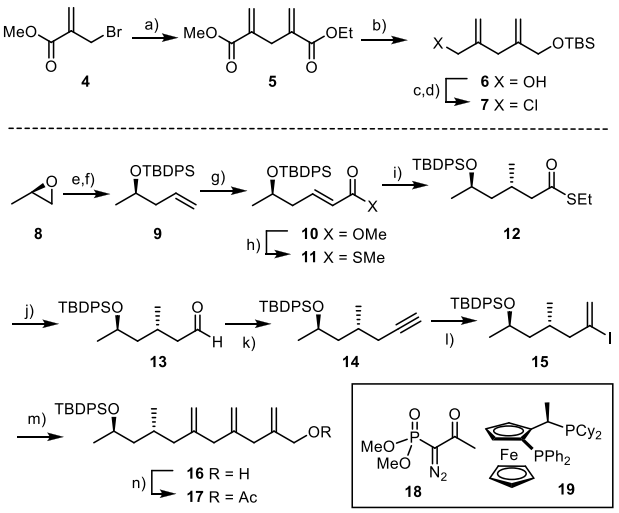
https://dx.doi.org/10.1021/jacs.0c12948
J. Am. Chem. Soc. 2021, 143, 2464−2469

protecting groups to avoid (strongly) acidic, basic, oxidative, or reductive conditions during global deprotection.

The spirotricyclic core of **1** resembles that of prorocentin (**2**), yet another secondary metabolite derived from *P. lima*, of which only the relative configuration is known;[11] a closer look, however, also reveals subtle but important stereochemical differences. We recognized an opportunity to craft this substructure, which features a double anomeric effect, via π-acid catalysis.[12,13] This allows the masked C18-carbonyl group to be encoded as a triple bond, which, in turn, should facilitate the build-up of the carbon skeleton from smaller subunits. The homoallylic alcohol at C27 was deemed another privileged assembly point, given the huge repertoire of known asymmetric allylation reactions.[14] This analysis traces **1** back to three building blocks **A**–**C** of similar size and complexity and leaves a certain flexibility with regard to the exact implementation of the actual fragment coupling events.

In the forward sense, we were particularly keen on testing the access to and stability of the side chain segment bearing the unusual skipped array of methylene substituents. A two-directional approach was chosen that builds upon the latent symmetry of this sector (Scheme 3).[15] Specifically, a Baylis–

Scheme 3[a]



[a]Reagents and conditions: (a) (i) $H_2C{=}CHCOOMe$, DABCO; (ii) Dibal-H, THF, 57%; (b) TBSCl, NaH, THF, 0 °C → rt, 87%; (c) MsCl, Et_3N, THF, 88%; (d) LiCl, THF, 40 °C, 98%; (e) $H_2C{=}CHMgBr$, CuI (17 mol %), THF, −78 °C → 0 °C; (f) TBDPSCl, imidazole, CH_2Cl_2, 81%; (g) Grubbs II, $H_2C{=}CHCOOMe$, CH_2Cl_2, reflux, 86%; (h) TMS-SEt, $AlCl_3$, THF, reflux, 86%; (i) MeMgBr, CuBr·SMe_2 (2 mol %), **19** (2.4 mol %), *t*BuOMe, −78 °C, 90% (dr >20:1); (j) Et_3SiH, Pd/C (5 mol %), CH_2Cl_2, 85%; (k) **18**, K_2CO_3, MeOH, 94%; (l) 9-I-9-BBN, hexane, then HOAc, quant.; (m) (i) Zn, LiCl, THF, reflux; (ii) **17**, $Pd(PPh_3)_4$ (5 mol %), THF; (iii) TBAF, THF, 0 °C, 76% (over both steps); (n) Ac_2O, pyridine, DMAP (10 mol %), 96%.

Hillman reaction of bromomethacrylate **4** with excess methyl acrylate[16] followed by instant reduction of **5** and mono-silylation of the resulting diol paved the way to allylic chloride **7** in readiness for a first chain extension. The nucleophilic partner was prepared by copper-catalyzed opening of commercial **8** with vinylmagnesium bromide,[17] protection of the resulting alcohol, and cross metathesis of **9**[18] with methyl acrylate.[19] The projected asymmetric 1,4-addition to the resulting enoate **10** failed despite close literature precedent,[20] whereas the derived thiolester[21] **11** was compliant: on treatment with MeMgBr in the presence of CuI (2 mol %) and ligand **19** (2.4 mol %), adduct **12** was obtained in high yield and excellent diastereoselectivity (>3 g scale).[22] The thioester group then streamlined the reduction to the corresponding aldehyde **13**,[23] which was chain-extended to give alkyne **14**. Addition of 9-I-9-BBN followed by protolytic cleavage of the C–B bond furnished alkenyl iodide **15** quantitatively.[24,25] The derived organozinc reagent was coupled to allylic chloride **7** with the aid of catalytic Pd(0);[26,27] the resulting lipophilic compound was deprotected to render the purification more facile. This rewarding outcome together with the fact that product **16** and the derived allylic acetate **17** could be kept in a freezer for weeks made us confident that a similar allyl/alkenyl cross-coupling reaction would enable the projected late-stage fragment coupling.

For the synthesis of the central fragment, cheap **20** was subjected to C-glycosylation with allyltrimethylsilane on multigram scale[8] and the resulting primary product was elaborated into aldehyde **22** by standard protecting group and oxidation state management (Scheme 4). When reacted with allenylboronate **33** in the presence of catalytic (*R*)-3,3′-dibromo-BINOL (**32**), the desired homopropargyl alcohol **23** was obtained as a single diastereomer (96%, 1 mmol scale).[28−30] Adjustment of the protecting groups then set the stage for chain extension to be followed by the critical spirocyclization event.

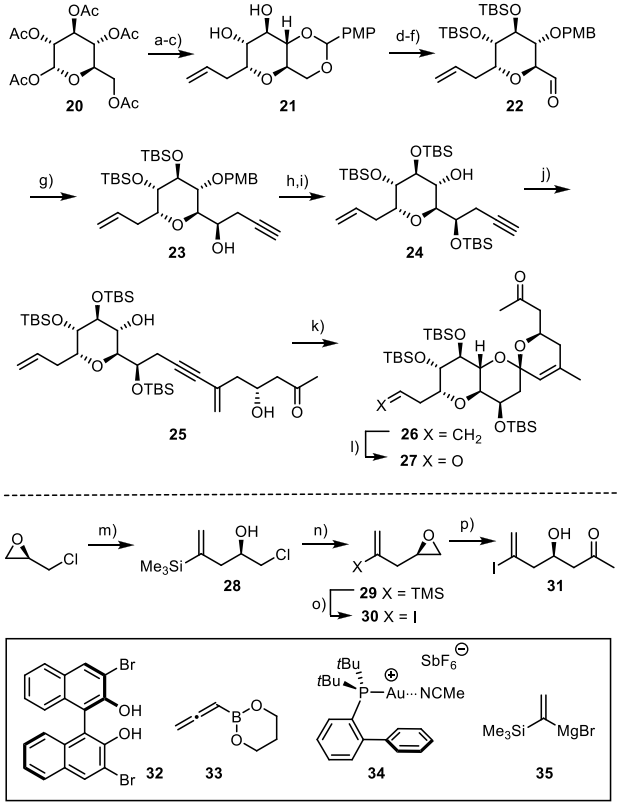
Of the different modules considered for this purpose,[31] ketone **31** proved most adequate; it was readily prepared from epichlorohydrin by copper-catalyzed ring opening with **35** and relocation of the epoxide.[32] Compound **29** was subjected to iododesilylation,[33] and the resulting oxirane **30** reacted with lithiated ethyl vinyl ether[34] and $BF_3{\cdot}OEt_2$ as promotor to give **31** after acidic workup. Sonogashira coupling with **24** furnished **25**.[35] Exposure of this compound to the gold catalyst **34** and cocatalytic PPTS entailed a remarkably clean spirocyclization to give **26** as a single isomer in 65–78% yield (1.7 mmol scale).[36] On account of the carbophilic complex, ketal formation occurred exclusively at the triple bond while leaving the peripheral ketone untouched; as expected, the reaction was accompanied by rearrangement of the *exo*-methylene group to the endocyclic position.[37] Selective cleavage of the terminal olefin furnished keto-aldehyde **27** in readiness for fragment coupling.

The third building block was derived from glucal **36**, which was transformed into the 2-deoxyglycoside **37** (Scheme 5).[38] Upon activation with TMSOTf, **37** reacted with allyltrimethylsilane to give **38** with >10:1 selectivity in favor of the required 2,6-*trans*-disubstitution. This favorable outcome is thought to reflect a Curtin–Hammett situation, whereby "inside attack" of the nucleophile to a $^4H_3$ half-chair oxocarbenium intermediate as shown in **J** is selectivity-determining.[39] After replacement of the acetyl groups by TBS-ethers, compound **39** was subjected to cross-metathesis with 3-buten-1-ol. Since both partners are "type I" olefins, this transformation was far from trivial.[19,40] Gratifyingly though, the crossed product **40** could be obtained in 75% yield when the tailored complex **47**[41] was used as catalyst and the conversion was driven with excess 3-buten-1-ol.

While the elaboration of **41** into tosylate **46** was straightforward, all attempts at reacting this product with appropriate C-nucleophiles essentially met with failure. This

https://dx.doi.org/10.1021/jacs.0c12948
J. Am. Chem. Soc. 2021, 143, 2464−2469

Scheme 4[a]

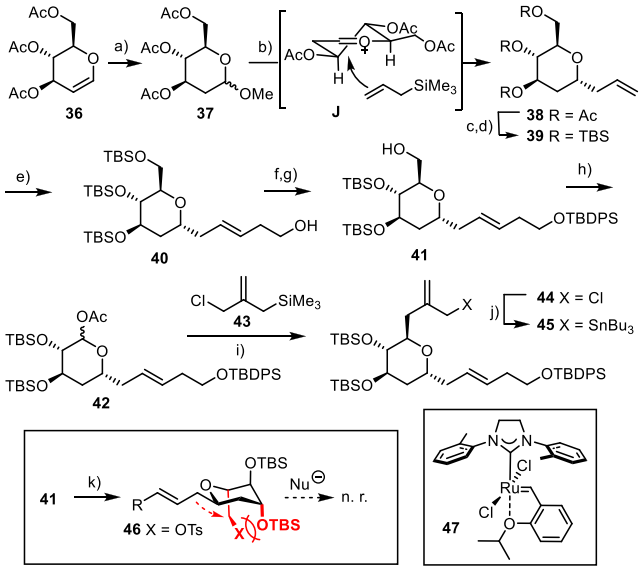


[a]Reagents and conditions: (a) allyltrimethylsilane, $BF_3{\cdot}OEt_2$, MeCN, 80 °C, 56%; (b) NaOMe, MeOH; (c) $MeOC_6H_4CH(OMe)_2$, *p*-TsOH cat., DMF, 79% (over two steps); (d) TBSOTf, 2,6-lutidine, CH_2Cl_2, −40 °C, 86%; (e) Dibal-H, CH_2Cl_2, −78 °C, quant.; (f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C → rt, 87%; (g) **33**, **32** (10 mol %), toluene, 96%; (h) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, quant.; (i) DDQ, aq. CH_2Cl_2, 0 °C → rt, 99%; (j) **31**, $Pd_2(dba)_3$ (5 mol %), PPh_3 (20 mol %), CuI (15 mol %), $HN(iPr)_2$, 93%; (k) **34** (10 mol %), PPTS (10 mol %), CH_2Cl_2, 65−78%; (l) OsO_4 (10 mol %), $NaIO_4$, 2,6-lutidine, 1,4-dioxane, H_2O, 87−93%; (m) **35**, CuCN (10 mol %), THF, −50 °C → −20 °C, quant.; (n) NaOH, Et_2O, quant.; (o) (i) ICl, CH_2Cl_2, −78 °C, (ii) TBAF, THF/Et_2O, 0 °C, 79%; (p) (i) *t*BuLi, ethyl vinyl ether, $BF_3{\cdot}OEt_2$, THF, −78 °C; (ii) aq. HCl, THF/H_2O, 63%.

inertia is ascribed to the ring-flip enforced by the bulky −OTBS groups of **46**:[42] for an S_N2 reaction with an external nucleophile to take place, the tosylate would have to reside under the ring, where it clashes into one of the axially disposed protecting groups. Gratifyingly, this problem could be bypassed: treatment of **41** with $Pb(OAc)_4$ gave the "anomeric" acetate **42** by excising the C-atom carrying the primary alcohol.[43] On activation with $SnCl_4$, **42** reacted with the functionalized allylsilane **43** to give allyl chloride **44** with appreciable selectivity. Either this compound itself or the derived allylstannane **45**, formed on treatment of **44** with Bu_3SnLi, was deemed adequate to serve the projected coupling of this "southern" fragment to the core unit.

Indeed, addition of **45** to **27** mediated by $MgBr_2{\cdot}OEt_2$ furnished a single isomer in 88% yield; exclusive attack at the aldehyde was observed, whereas the ketone was a mere bystander. For the chelating Lewis acid promotor and the rigid *trans*-decaline-type scaffold, the Cram-chelate product should be formed, as necessary for the total synthesis of **1** (Scheme 6).[44,45] This expectation ultimately proved incorrect, but the mistake was recognized only after **48** had been elaborated into what was thought to be limaol. To this end, the ketone was transformed into alkenylstannane **49** via kinetic enolization with tritylpotassium as the base,[46] quenching with $PhNTf_2$, and instant reaction of the resulting alkenyl triflate with $(Bu_3Sn)_2CuCNLi_2$ at low temperature.[47] Stille coupling of **49** with **17** under conditions previously developed in our laboratory for exigent cases allowed the sensitive side chain to be attached without any scrambling of the olefins (which was inevitable under more conventional conditions).[48−50] This gratifying outcome is best assessed by comparison with the challenges encountered in the deprotection of product **50**: only HF·pyridine in THF/pyridine allowed the silyl groups to be cleaved without affecting the integrity of the compound.[31] Yet, the spectra of the resulting product did not match those of limaol;[6] the deviations were clustered about the C27-position,[31] suggesting that the substrate-controlled asymmetric allylation had given the wrong diastereomer and the formed product *epi*-**1** hence represents the C27-isomer of limaol.

Scheme 5[a]

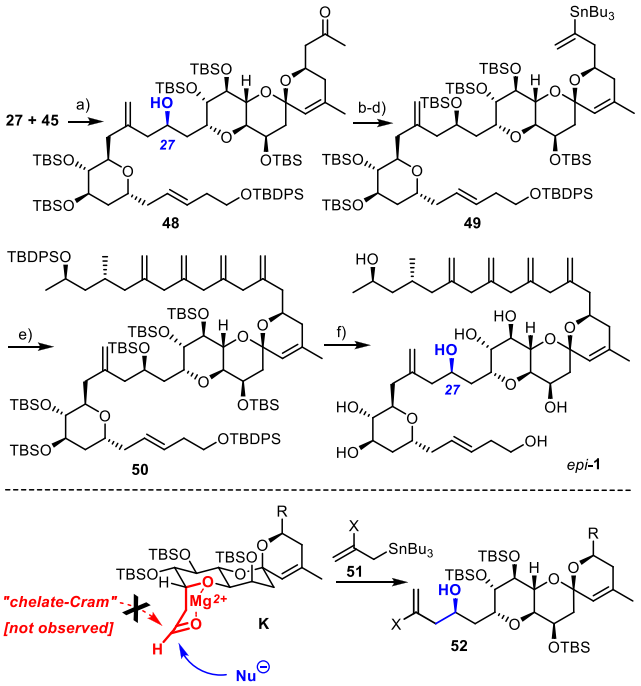


[a]Reagents and conditions: (a) $CeCl_3{\cdot}7H_2O$, NaI, MeOH, MeCN, reflux, 52%; (b) TMSOTf, allyltrimethylsilane, MeCN, 57% (dr >10:1); (c) K_2CO_3, MeOH; (d) TBSOTf, 2,6-lutidine, CH_2Cl_2, 95% (over two steps); (e) **47** (10 mol %), 1-buten-3-ol (excess), CH_2Cl_2, reflux, 75% (+7% of *Z*-isomer); (f) TBDPSCl, imidazole, CH_2Cl_2, quant.; (g) CSA (cat.), MeOH, CH_2Cl_2, −20 °C, 77%; (h) $Pb(OAc)_4$, THF, 61%; (i) $SnCl_4$, CH_2Cl_2, −78 °C, 83% (dr = 5:1); (j) Bu_3SnLi, THF, −78 °C, 91%; (k) TsCl, DMAP cat., pyridine, CH_2Cl_2, 69%.

The bias inherent to this addition is so pronounced that various attempts to overturn it by means of reagent- or catalyst-controlled allylation reactions basically met with failure.[31] Additional control experiments showed that the outcome is not caused by any peculiarities of the chiral allylstannane **45** either: thus, Lewis acid mediated addition of simple **51a** (X = H) or **51b** (X = CH_2Cl) followed the same stereochemical course to give (27*R*)-configured products of type **52** exclusively.[30] Lewis acids other than $MgBr_2$ led to product mixtures in low yields.[31,51] Further investigations are necessary to clarify the origin of this peculiar steric preference.

https://dx.doi.org/10.1021/jacs.0c12948
J. Am. Chem. Soc. 2021, 143, 2464−2469

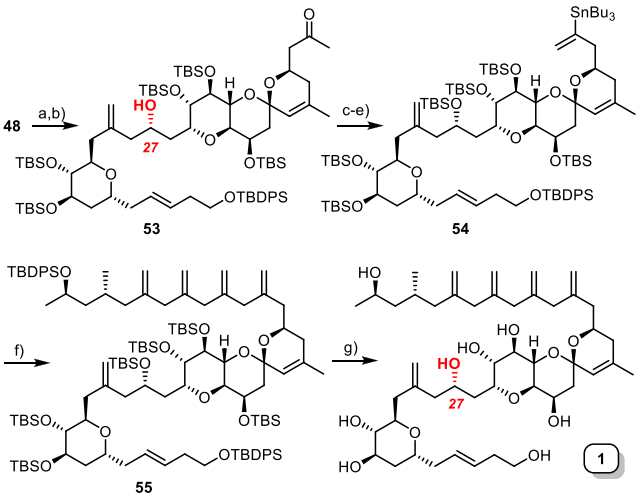
Scheme 6[a]



[a]Reagents and conditions: (a) $MgBr_2{\cdot}OEt_2$, CH_2Cl_2, −78 °C, 88%; (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 64%; (c) Ph_3CK, $PhNTf_2$, THF, −78 °C; (d) $(Bu_3Sn)_2CuCNLi_2$, THF, −55 °C, 77% (isomer ratio ≈ 4:1); (e) **17**, $Pd(PPh_3)_4$ (20 mol %), CuTC, $[Bu_4N][Ph_2P(=O)O]$, NMP, 77% (pure isomer); HF·pyridine, THF/pyridine, 37%.

Since all attempts to form the correct isomer directly failed, we resorted to an inversion of the secondary alcohol in **48** under Mitsunobu conditions (Scheme 7).[52] Thereon, the route to limaol was analogous to that pursued toward *epi*-**1**. Once again, kinetic enolization/stannylation of **53** followed by palladium catalyzed fragment coupling of **54** with **17** under notably mild conditions installed the tail region with the four skipped "*exo*"-methylene groups; equally critical were the conditions for the final deprotection of **55** thus formed. The analytical and spectral data of synthetic **1** matched those of natural limaol in all respects.[6,31] The acquired material can hence serve further biological profiling. The results of these studies and further investigations into the fascinating estate of dinoflagellate-derived metabolites will be reported in due course.

Scheme 7[a]



[a]Reagents and conditions: (a) PPh_3, 4-nitrobenzoic acid, DEAD, toluene, 0 °C → rt, 67%; (b) NaOH, MeOH, THF, 91%; (c) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 84%; (d) (i) Ph_3CK, $PhNTf_2$. THF, −78 °C; (e) $(Bu_3Sn)_2CuCNLi_2$, THF, −55 °C, 63% (isomer ratio ≈ 3:1); (f) **17**, $Pd(PPh_3)_4$ (20 mol %), CuTC, $[Bu_4N][Ph_2P(=O)O]$, DMF/THF, 60% (pure isomer); (g) HF·pyridine, THF/pyridine, 32%.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c12948.

Experimental Section including characterization data and NMR spectra of new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Alois Fürstner − *Max-Planck-Institut für Kohlenforschung, 45470 Mülheim/Ruhr, Germany*; orcid.org/0000-0003-0098-3417; Email: fuerstner@kofo.mpg.de

Authors

Stephan N. Hess − *Max-Planck-Institut für Kohlenforschung, 45470 Mülheim/Ruhr, Germany*

Xiaobin Mo − *Max-Planck-Institut für Kohlenforschung, 45470 Mülheim/Ruhr, Germany*

Conny Wirtz − *Max-Planck-Institut für Kohlenforschung, 45470 Mülheim/Ruhr, Germany*

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.0c12948

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Generous financial support by the Max-Planck-Gesellschaft is gratefully acknowledged. We thank Dr. G. Garivet for exploratory studies, Dr. M. Leutzsch for an independent confirmation of the assignment of the C27-stereochemistry, and the Analytical Departments of our Institute for excellent support.

■ REFERENCES

(1) Taylor, F. J. R., Ed. The Biology of Dinoflagellates, *Botanical Monographs*, Vol. *21*; Blackwell: Oxford, 1987.

(2) Nascimento, S. M.; Salgueiro, F.; Menezes, M.; de Andréa Oliveira, F.; Chiapetta Portella Magalhaes, V.; Campos de Paula, J.; Morris, S. *Prorocentrum lima* from the South Atlantic: Morphological, Molecular and Toxicological Characterization. *Harmful Algae* **2016**, *57*, 39−48.

(3) (a) Valdiglesias, V.; Prego-Faraldo, M. V.; Pásaro, E.; Méndez, J.; Laffon, B. Okadaic Acid: More than a Diarrheic Toxin. *Mar. Drugs* **2013**, *11*, 4328−4349. (b) Hu, W.; Xu, J.; Sinkkonen, J.; Wu, J. Polyketides from Marine Dinoflagellates of the Genus *Prorocentrum*, Biosynthetic Origin and Bioactivity of Their Okadaic Acid Analogues. *Mini-Rev. Med. Chem.* **2010**, *10*, 51−61.

(4) Van Wagoner, R. M.; Satake, M.; Wright, J. L. C. Polyketide Biosynthesis in Dinoflagellates: What Makes it Different? *Nat. Prod. Rep.* **2014**, *31*, 1101−1137.
(5) For a very recent example and a literature survey, see: Dominguez, H. J.; Cabrera-Garcia, D.; Cuadrado, C.; Novelli, A.; Fernández-Sánchez, T.; Fernández, J. J.; Hernández Daranas, A. Prorocentroic Acid, A Neuroactive Super-Carbon-Chain Compound from the Dinoflagellate *Prorocentrum hoffmannianum*. *Org. Lett.* **2021**, *23*, 13−18.
(6) Yang, A. R.; Lee, S.; Yoo, Y. D.; Kim, H. S.; Jeong, E. J.; Rho, J.-R. Limaol: A Polyketide from the Benthic Marine Dinoflagellate *Prorocentrum lima*. *J. Nat. Prod.* **2017**, *80*, 1688−1692.
(7) Some other *Prorocentrum*-derived secondary metabolites such as the complex macrolide belizanolide show skipped "*exo*"-methylene groups, but in no case is the array as extended as in the C6-C12 region of limaol; cf.: Napolitano, J. G.; Norte, M.; Padrón, J. M.; Fernández, J. J.; Daranas, A. H. Belizeanolide, a Cytotoxic Macrolide from the Dinoflagellate *Prorocentrum belizeanum*. *Angew. Chem., Int. Ed.* **2009**, *48*, 796−799.
(8) For the massive problems caused by the instability of a skipped array of olefins comprising one "*exo*"-methylene unit in the total synthesis of the dinoflagellate-derived compound belizentrin, see: Anderl, F.; Größl, S.; Wirtz, C.; Fürstner, A. Total Synthesis of Belizentrin Methyl Ester: Report on a Likely Conquest. *Angew. Chem., Int. Ed.* **2018**, *57*, 10712−10717.
(9) Schulthoff, S.; Hamilton, J. Y.; Heinrich, M.; Kwon, Y.; Wirtz, C.; Fürstner, A. The Formosalides: Structure Determination by Total Synthesis. *Angew. Chem., Int. Ed.* **2021**, *60*, 446−454.
(10) For other selected total syntheses of natural products containing highly sensitive skipped polyenes from this laboratory, see: (a) Fürstner, A.; Nevado, C.; Waser, M.; Tremblay, M.; Chevrier, C.; Tepý, F.; Aissa, C.; Moulin, E.; Müller, O. Total Synthesis of Iejimalide A-D and Assessment of the Remarkable Actin-Depolymerizing Capacity of the Polyene Macrolides. *J. Am. Chem. Soc.* **2007**, *129*, 9150−9161. (b) Chaladaj, W.; Corbet, M.; Fürstner, A. Total Synthesis of Neurymenolide A Based on a Gold-Catalyzed Synthesis of 4-Hydroxy-2-pyrones. *Angew. Chem., Int. Ed.* **2012**, *51*, 6929−6933. (c) Hoffmeister, L.; Fukuda, T.; Pototschnig, G.; Fürstner, A. Total Syntheis of an Exceptioal Brominated 4-Pyrone Derivative of Algal Origin: An Exercise in Gold Catalysis and Alkyne Metathesis. *Chem. - Eur. J.* **2015**, *21*, 4529−4533. (d) Hickmann, V.; Kondoh, A.; Gabor, B.; Alcarazo, M.; Fürstner, A. Catalysis-based and Protecting-Group-free Total Syntheses of the Marine Oxylipins Hybridalactone and the Ecklonialactones A, B, and C. *J. Am. Chem. Soc.* **2011**, *133*, 13471−13480.
(11) Lu, C.-K.; Chou, H.-N.; Lee, C.-K.; Lee, T.-H. Prorocentin, a New Polyketide from the Marine Dinoflagellate *Prorocentrum lima*. *Org. Lett.* **2005**, *7*, 3893−3896.
(12) Fürstner, A.; Davies, P. W. Catalytic Carbophilic Activation: Catalysis by Platinum and Gold π-Acids. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410−3449.
(13) (a) Pflästerer, D.; Rudolph, M.; Hashmi, A. S. K. Gold-Catalyzed Hydrofunctionalizations and Spiroketalizations of Alkynes as Key Steps in Total Synthesis. *Isr. J. Chem.* **2018**, *58*, 622−638. (b) Quach, R.; Furkert, D. P.; Brimble, M. A. Gold Catalysis: Synthesis of Spiro, Bridged, and Fused Ketal Natural Products. *Org. Biomol. Chem.* **2017**, *15*, 3098−3104. (c) Fürstner, A. From Understanding to Prediction: Gold and Platinum-Based π-Acid Catalysis in Target Oriented Synthesis. *Acc. Chem. Res.* **2014**, *47*, 925−938.
(14) Knochel, P., Molander, G. A., Eds. *Comprehensive Organic Synthesis*, 2nd ed., Vol. *2*; Elsevier: 2014.
(15) Poss, C. S.; Schreiber, S. L. Two-directional Chain Synthesis and Terminus Differentiation. *Acc. Chem. Res.* **1994**, *27*, 9−17.
(16) Basavaiah, D.; Sharada, D. S.; Kumaragurubaran, N.; Reddy, R. M. The Baylis−Hillman Reaction: One-Pot Facile Synthesis of 2,4-Functionalized 1,4-Pentadienes. *J. Org. Chem.* **2002**, *67*, 7135−7137.
(17) The fairly low yield of this step is due to competing bromohydrin formation; no attempt was undertaken to optimize the results.
(18) Thirupathi, B.; Gundapaneni, R. R.; Mohapatra, D. K. First Total Syntheses of (3R,5R)-Sonnerlactone and (3R,5S)-Sonnerlactone. *Synlett* **2011**, *2011*, 2667−2670.
(19) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. A General Model for Selectivity in Olefin Cross Metathesis. *J. Am. Chem. Soc.* **2003**, *125*, 11360−11370.
(20) Lum, T.-K.; Wang, S.-Y.; Loh, T.-P. A Highly Catalytic Asymmetric Conjugate Addition: Synthesis of the C14-C20 Fragment of Antibiotic TMS-151A, Siphonarienal and Siphonarienone. *Org. Lett.* **2008**, *10*, 761−764.
(21) Mukaiyama, T.; Takeda, T.; Atsumi, K. The Reaction of Trimethylsilyl Sulfides with Carboxylic Esters. A Convenient Method for the Preparation of Thiolesters. *Chem. Lett.* **1974**, *3*, 187−188.
(22) Des Mazery, R.; Pullez, M.; Lopez, F.; Harutyunyan, S. R.; Minnaard, A. J.; Feringa, B. L. An Iterative Catalytic Route to Enantiopure Deoxypropionate Subunits: Asymmetric Conjugate Addition of Grignard Reagents to α,β-Unsaturated Thioesters. *J. Am. Chem. Soc.* **2005**, *127*, 9966−9967.
(23) Fukuyama, T.; Tokuyama, H. Palladium-Mediated Synthesis of Aldehydes and Ketones from Thiol Esters. *Aldrichimica Acta* **2004**, *37*, 87−96.
(24) Hara, S.; Dojo, H.; Takinami, S.; Suzuki, A. Organic Synthesis Using Haloboration Reaction. I. A Simple and Selective Synthesis of 2-Bromo- and 2-Iodo-1-Alkenes. *Tetrahedron Lett.* **1983**, *24*, 731−734.
(25) For an advanced application, see: MacMillan, D. W. C.; Overman, L. E.; Pennington, L. D. A General Strategy for the Synthesis of Cladiellin Diterpenes: Enantioselective Total Syntheses of 6-Acetoxycladiell-7(16),11-dien-3-ol (Deacetoxyalcyonin Acetate), Cladiell-11-ene-3,6,7-triol, Sclerophytin A, and the Initially Purported Structure of Sclerophytin A. *J. Am. Chem. Soc.* **2001**, *123*, 9033−9044.
(26) Negishi, E. Transition Metal-Catalyzed Organometallic Reactions that Have Revolutionized Organic Synthesis. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 233−257.
(27) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. Palladium-Catalyzed Cross-Coupling Reactions in Total Synthesis. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442−4489.
(28) Barnett, D. S.; Schaus, S. E. Asymmetric Propargylation of Ketones Using Allenylboronates Catalyzed by Chiral Biphenols. *Org. Lett.* **2011**, *13*, 4020−4023.
(29) For an application in total synthesis, see: Mailhol, D.; Willwacher, J.; Kausch-Busies, N.; Rubitski, E. E.; Sobol, Z.; Schuler, M.; Lam, M.-H.; Musto, S.; Loganzo, F.; Maderna, A.; Fürstner, A. Synthesis, Molecular Editing and Biological Assessment of the Potent Cytotoxin Leiodermatolide. *J. Am. Chem. Soc.* **2014**, *136*, 15719−15729.
(30) The configuration was ascertained by Mosher ester analysis; for details, see the Supporting Information (SI).
(31) For details, see the SI.
(32) Fürstner, A.; Flügge, S.; Larionov, O.; Takahashi, Y.; Kubota, T.; Kobayashi, J. Total Synthesis and Biological Evaluation of Amphidinolide V and Analogues. *Chem. - Eur. J.* **2009**, *15*, 4011−4029.
(33) Miller, R. B.; McGarvey, G. Addition of ICI to Vinylsilanes. *Synth. Commun.* **1978**, *8*, 291−299.
(34) Boeckman, R. K.; Bruza, K. J. Chemistry of Diorganocuprates Containing Functionalized Ligands. 2. Methodology for Conjugate Addition of Synthetic Equivalents of Enolates and Acyl Anions. *J. Org. Chem.* **1979**, *44*, 4781−4788.
(35) Chinchilla, R.; Najera, C. Recent Advances in Sonogashira Reactions. *Chem. Soc. Rev.* **2011**, *40*, 5084−5121.
(36) For a very advanced spirocyclization catalyzed by the same complex, see: Benson, S.; Collin, M.-P.; Arlt, A.; Gabor, B.; Goddard, R.; Fürstner, A. Second-Generation Total Synthesis of Spirastrellolide F Methyl Ester: The Alkyne Route. *Angew. Chem., Int. Ed.* **2011**, *50*, 8739−8744.

https://dx.doi.org/10.1021/jacs.0c12948
J. Am. Chem. Soc. 2021, 143, 2464−2469

(37) For a related example, see: Joung, S.; Kim, R.; Lee, H.-Y. Total Synthesis of (−)-Phorbaketal A. *Org. Lett.* **2017**, *19*, 3903−3906.
(38) Ghosh, A. K.; Veitschegger, A. M.; Nie, S.; Relitti, N.; MacRae, A. J.; Jurica, M. S. Enantioselective Synthesis of Thailanstatin A Methyl Ester and Evaluation of *in Vitro* Splicing Inhibition. *J. Org. Chem.* **2018**, *83*, 5187−5198.
(39) Krumper, J. R.; Salamant, W. A.; Woerpel, K. A. Correlations Between Nucleophilicities and Selectivities in the Substitution of Tetrahydropyran Acetals. *J. Org. Chem.* **2009**, *74*, 8039−8050.
(40) Different protecting groups on both partners were screened but found less adequate.
(41) Stewart, I. C.; Douglas, C. J.; Grubbs, R. H. Increased Efficiency in Cross-Metathesis Reactions of Sterically Hindered Olefins. *Org. Lett.* **2008**, *10*, 441−444.
(42) This conformational change is manifested in the $^{3}J_{H,H}$ coupling constants; for details, see the SI.
(43) Alvarez-Manzaneda, E.; Chahboun, R.; Alvarez, E.; Alvarez-Manzaneda, R.; Munoz, P. E.; Jimenez, F.; Bouanou, H. Lead(IV) Acetate Mediated Cleavage of β-Hydroxy Ethers: Enantioselective Synthesis of α-Acetoxy Carbonyl Compounds. *Tetrahedron* **2011**, *67*, 8910−8917.
(44) (a) Keck, G. E.; Castellino, S.; Wiley, M. R. Dramatic Effects of Oxygen Substituents on 1,3-Asymmetric Induction in Additions of Allyltriphenylstannanes to β-Alkoxy Aldehydes: A Chemical and Spectroscopic Investigation. *J. Org. Chem.* **1986**, *51*, 5478−5480. (b) Keck, G. E.; Castellino, S. On the Origins of Stereoselectivity in "Chelation Controlled" Nucleophilic Additions to β-Alkoxy Aldehydes: Solution Structures of Lewis Acid Complexes via NMR Spectroscopy. *J. Am. Chem. Soc.* **1986**, *108*, 3847−3849.
(45) See also: Trost, B. M.; Rey, J. Diastereoselective Formation of Tetrahydrofurans via Pd-Catalyzed Asymmetric Allylic Alkylation: Synthesis of the C13-C29 Subunit of Amphidinolide N. *Org. Lett.* **2012**, *14*, 5632−5635.
(46) Huffman, J. W.; Harris, P. G. Potassium Triphenylmethide. A Strong Base for Organic Synthesis. *Synth. Commun.* **1977**, *7*, 137−141.
(47) Gilbertson, S. R.; Challener, C. A.; Bos, M. E.; Wulff, W. D. An Examination of the Coupling of Vinyl and Aryl Triflates with Stannyl Cuprates for the Purpose of Providing Regioselective Access to Vinyl Lithiums. *Tetrahedron Lett.* **1988**, *29*, 4795−4798.
(48) Fürstner, A.; Funel, J.-A.; Tremblay, M.; Bouchez, L. C.; Nevado, C.; Waser, M.; Ackerstaff, J.; Stimson, C. C. A Versatile Protocol for Stille-Migita Coupling Reactions. *Chem. Commun.* **2008**, 2873−2875.
(49) For selected applications, see: (a) Fürstner, A.; Bouchez, L. C.; Funel, J.-A.; Liepins, V.; Porée, F.-H.; Gilmour, R.; Beaufils, F.; Laurich, D.; Tamiya, M. Total Synthesis of Amphidinolide H and G. *Angew. Chem., Int. Ed.* **2007**, *46*, 9265−9270. (b) Larivée, A.; Unger, J. B.; Thomas, M.; Wirtz, C.; Dubost, C.; Handa, S.; Fürstner, A. The Leiodolide B Puzzle. *Angew. Chem., Int. Ed.* **2011**, *50*, 304−309. (c) Preindl, J.; Schulthoff, S.; Wirtz, C.; Lingnau, J.; Fürstner, A. Polyunsaturated C-Glycosidic 4-Hydroxy-2-Pyrone Derivatives: Total Synthesis Shows that Putative Orevactaene is Likely Identical with Epipyrone A. *Angew. Chem., Int. Ed.* **2017**, *56*, 7525−7530. (d) Zhuo, C.-X.; Fürstner, A. Catalysis-Based Total Synthesis of Pateamine A and DMDA-Pat A. *J. Am. Chem. Soc.* **2018**, *140*, 10514−10523.
(50) At this stage, small amounts of a regioisomer could be separated, which derived from thermodynamic enolization of ketone **48**.
(51) According to ref 44, the formation of isomer mixtures is actually more in line with a chelate transition state such as **K** in which the β-substituent is equatorially disposed; hence, the course and the level of induction are striking.
(52) Hughes, D. L. The Mitsunobu Reaction. *Org. React.* **1992**, *42*, 335−656.

https://dx.doi.org/10.1021/jacs.0c12948
J. Am. Chem. Soc. 2021, 143, 2464−2469