

Total Synthesis of Limaol

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

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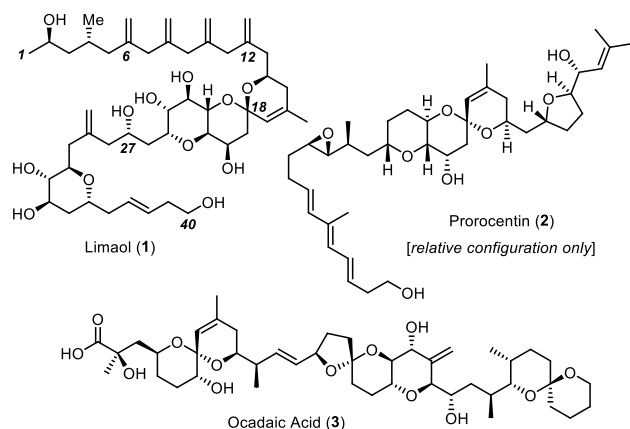


Supporting Information

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 toxicogenic.^{1,2} They were circumstantially associated with cases of diarrhetic shellfish poisoning, likely caused by ocaidaic acid (3) and analogues (Scheme 1). These intriguing polyether toxins produced by the

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

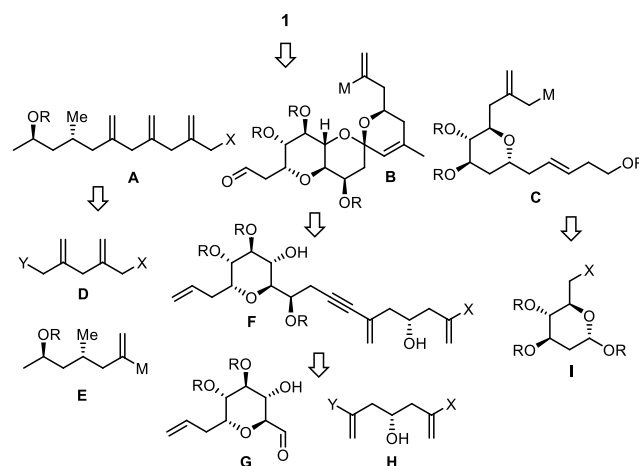


benthic dinoflagellate occasionally accumulate in mussels, scallops, and sponges, and thus can reach the human food chain and cause severe ailment.³ This discovery sparked considerable interest in the mode of action. Most importantly, 3 was recognized to be a highly potent and specific inhibitor of the 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

The disproportionately 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 advisable,^{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



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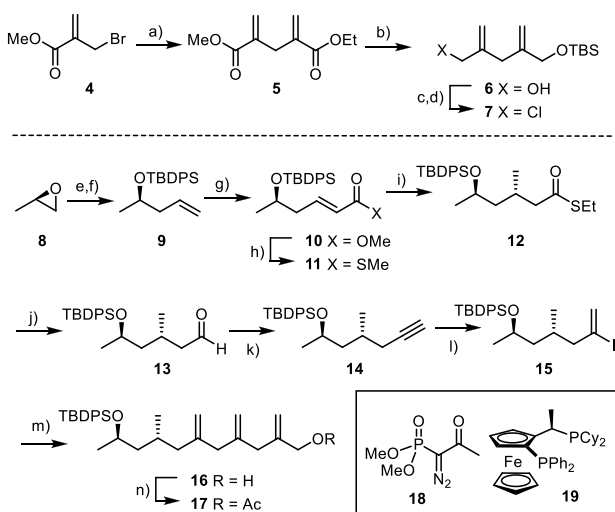
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protecting groups to avoid (strongly) acidic, basic, oxidative, or reductive conditions during global deprotection.

The spirotricyclic core of **1** resembles that of procofentoin (**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

^aReagents and conditions: (a) (i) $\text{H}_2\text{C}=\text{CHCOOMe}$, DABCO; (ii) Dibal-H, THF, 57%; (b) TBSCl, NaH, THF, 0 °C \rightarrow rt, 87%; (c) MsCl, Et_3N , THF, 88%; (d) LiCl, THF, 40 °C, 98%; (e) $\text{H}_2\text{C}=\text{CHMgBr}$, CuI (17 mol %), THF, -78 °C \rightarrow 0 °C; (f) TBDPSCI, imidazole, CH_2Cl_2 , 81%; (g) Grubbs II, $\text{H}_2\text{C}=\text{CHCOOMe}$, CH_2Cl_2 , reflux, 86%; (h) TMS-SEt, AlCl_3 , THF, reflux, 86%; (i) MeMgBr, CuBr-SMe₂ (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(PPh₃)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 acrylate¹⁶ followed by instant reduction of **5** and monosilylation 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

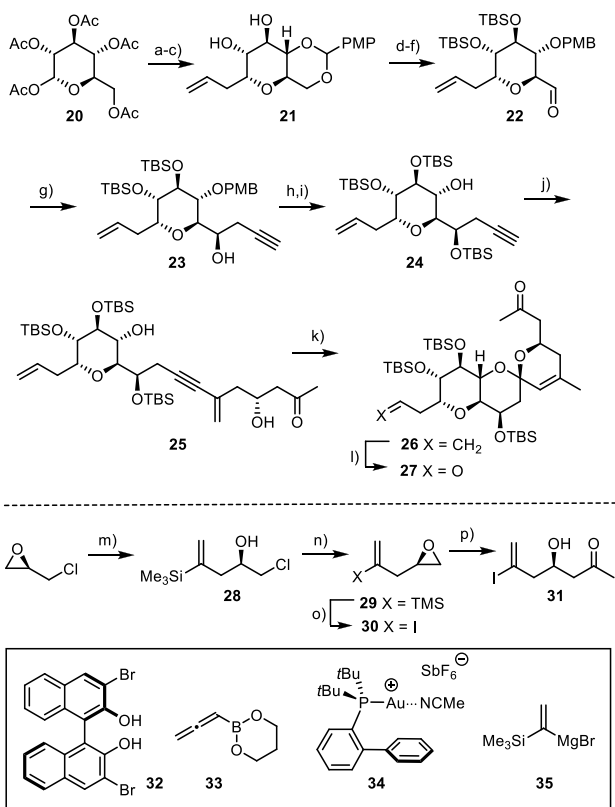
resulting enoate **10** failed despite close literature precedent,²⁰ whereas the derived thioester²¹ **11** was compliant: on treatment with MeMgBr in the presence of CuI (2 mol %) and ligand **19** (2.4 mol %), adduct **12** was obtained in high yield and excellent diastereoselectivity (>3 g scale).²² 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 scale⁸ 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 ether³⁴ and $\text{BF}_3\cdot\text{OEt}_2$ 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 ⁴H₃ 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.

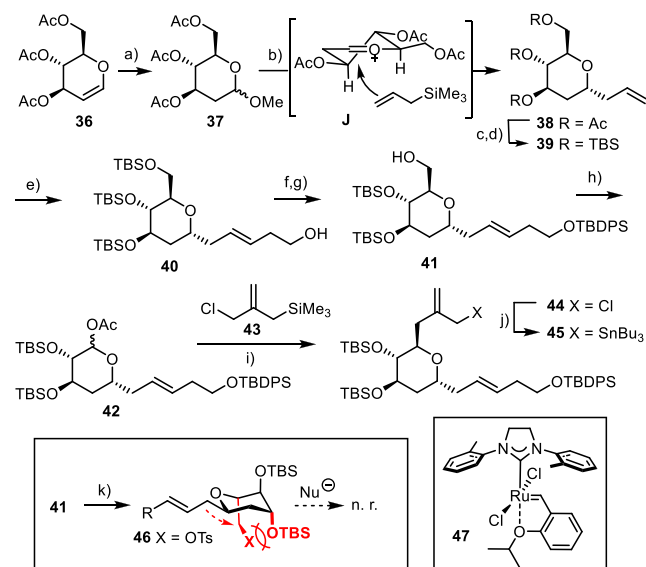
While the elaboration of **41** into tosylate **46** was straightforward, all attempts at reacting this product with appropriate C-nucleophiles essentially met with failure. This

Scheme 4^a

^aReagents and conditions: (a) allyltrimethylsilane, $\text{BF}_3 \cdot \text{OEt}_2$, MeCN, 80 °C, 56%; (b) NaOMe, MeOH; (c) $\text{MeOC}_6\text{H}_4\text{CH}(\text{OMe})_2$, *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) $(\text{COCl})_2$, 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, $\text{Pd}_2(\text{dba})_3$ (5 mol %), PPh_3 (20 mol %), CuI (15 mol %), $\text{HN}(\text{iPr})_2$, 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, $\text{BF}_3 \cdot \text{OEt}_2$, 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 $\text{S}_{\text{N}}2$ 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 $\text{Pb}(\text{OAc})_4$ 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.

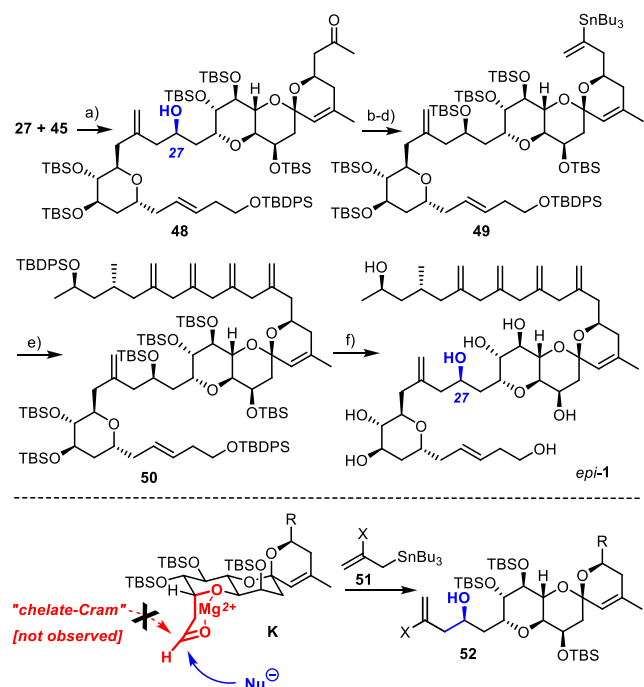
Indeed, addition of 45 to 27 mediated by $\text{MgBr}_2 \cdot \text{OEt}_2$ furnished a single isomer in 88% yield; exclusive attack at the aldehyde was observed, whereas the ketone was a mere bystander. For the chelating Lewis acid promotor and the rigid *trans*-decaline-type scaffold, the Cram-chelate product should be formed, as necessary for the total synthesis of 1 (Scheme

Scheme 5^a

^aReagents and conditions: (a) $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$, 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) $\text{Pb}(\text{OAc})_4$, 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%.

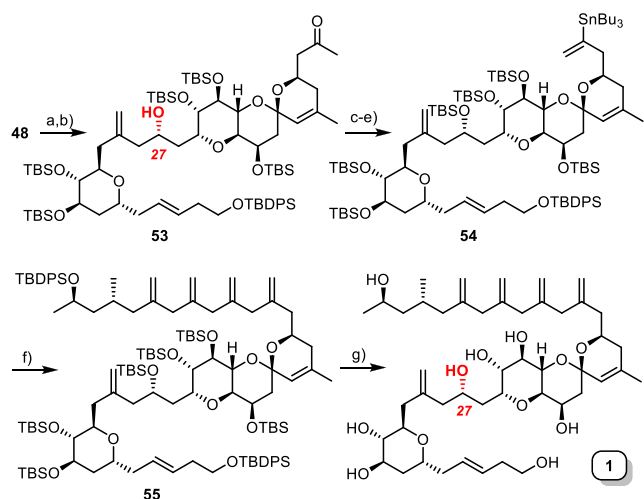
6).^{44,45} This expectation ultimately proved incorrect, but the mistake was recognized only after 48 had been elaborated into what was thought to be limaol. To this end, the ketone was transformed into alkenylstannane 49 via kinetic enolization with tritylpotassium as the base,⁴⁶ quenching with PhNTf_2 , and instant reaction of the resulting alkenyl triflate with $(\text{Bu}_3\text{Sn})_2\text{CuCNLi}_2$ 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.

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.

Scheme 6^a

^aReagents and conditions: (a) MgBr₂·OEt₂, CH₂Cl₂, −78 °C, 88%; (b) TBSOTf, 2,6-lutidine, CH₂Cl₂, −78 °C, 64%; (c) Ph₃CK, PhNTf₂, THF, −78 °C; (d) (Bu₃Sn)₂CuCNLi₂, THF, −55 °C, 77% (isomer ratio ≈ 4:1); (e) **17**, Pd(PPh₃)₄ (20 mol %), CuTC, [Bu₄N][Ph₂P(=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

Scheme 7^a

^aReagents and conditions: (a) PPh₃, 4-nitrobenzoic acid, DEAD, toluene, 0 °C → rt, 67%; (b) NaOH, MeOH, THF, 91%; (c) TBSOTf, 2,6-lutidine, CH₂Cl₂, −78 °C, 84%; (d) (i) Ph₃CK, PhNTf₂, THF, −78 °C; (e) (Bu₃Sn)₂CuCNLi₂, THF, −55 °C, 63% (isomer ratio ≈ 3:1); (f) **17**, Pd(PPh₃)₄ (20 mol %), CuTC, [Bu₄N][Ph₂P(=O)O], DMF/THF, 60% (pure isomer); (g) HF·pyridine, THF/pyridine, 32%.

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.

■ 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/doi/10.1021/jacs.0c12948>

Notes

The authors declare no competing financial interest.

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