VIP Natural Product Synthesis

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Divergent Total Synthesis of the Antimitotic Agent Leiodermatolide**

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The development of drugs based on microtubule toxins marked major leaps forward in cancer chemotherapy.[1,2] All approved spindle poisons exert their primary function by interfering with tubulin dynamics upon binding to the protein. Cell-cycle arrest is the immediate biological response, which ultimately translates into cell death through a complex signaling cascade. In clinical settings, however, severe side effects as well as (multidrug) resistance set serious limitations to the use of such antimitotic agents, and make the search for more effective and selective drugs indispensable.[3]

It is against this backdrop that the recent discovery of leiodermatolide has to be seen.[4,5] This complex macrolide of marine origin exhibits remarkable, yet selective, cytotoxicity in vitro, with IC_{50} values for the most sensitive human cancer cell lines well below 10 nM.[6] This concentration also sufficed to effect cell-cycle arrest of the highly responsive A549 lung adenocarcinoma and PANC-1 pancreatic tumor cells at the G2M phase transition, accompanied by abnormal spindle formations in both cell types. Surprisingly though, leiodermatolide exerted no noticeable effect on purified tubulin even at much higher concentrations.[5] Therefore, this particular natural product seems to operate through a mechanism distinct from that of the established antimitotic agents such as vincristine, colchicine, paclitaxel, epothilone, and discodermolide, to mention only the most prominent ones,[1,2] and hence warrants close chemical, biochemical, and, possibly, pharmacological inspection.

Leiodermatolide was isolated from a lithistid *Leiodermatium* sponge collected by submersible in the deep waters off the Florida coastline (0.0011 % of the wet weight).[5] Approximately tenfold lower concentrations were detected in specimens harvested in the Bahamas,[7] whereas an earlier study on *Leiodermatium* sponges collected off Palau had only given structurally unrelated secondary metabolites of mixed polyketide/nonribosomal peptide synthetase origin ("leiotolides").[8,9]

A masterful investigation combining the predictive power of modern computational tools with advanced NMR spectroscopic techniques allowed the constitution and much of the stereostructure of leiodermatolide to be established.[5] However, the segregated stereoclusters within the macrolactone[10,11] and the δ-lactone terminus could not be correlated with each other, thus leaving it open as to whether structure **1** or **2** represents the natural product (Scheme 1). The absolute configuration of leiodermatolide also remained unknown. Moreover, Maier and co-workers cautiously questioned whether the unusual axial attachment of the side chain onto the δ-lactone at the tertiary alcohol site C21 had been correctly assigned by the isolation team.[12]

To resolve these open issues, we pursued an approach to this rewarding target that was programmed for late-stage divergence. If necessary for an unambiguous structure assignment, the retrosynthetic analysis outlined in Scheme 1 allows any conceivable stereoisomer of the terminal δ-lactone (fragment **E**) to be attached to a truncated macrolide synthon of type **A** while forming the *E*,*E* diene unit of the side chain.[10] Provided that **A** can be forged by ring-closing alkyne metathesis (RCAM) as envisaged,[13,14] the macrocyclization and the formation of the *Z*,*Z* diene become advantageously aligned. In this context, it is important to note that the stereo- and site-selective generation of *Z*,*Z*-configured 1,3-dienes by olefin metathesis seems currently impossible even with the most advanced catalysts.[15] The proposed strategic substitution of an alkene for an alkyne, as shown in Scheme 1, however, allows the orthogonal reactivity of the different π bonds through a metal alkylidyne catalyst to be harnessed, and hence the site of ring closure to be reliably determined. Moreover, as the configuration of the targeted alkene can be determined at will by stereoselective semireduction of the acetylene linkage, 1,3-dienes of any configuration—including the generally rather labile *Z*,*Z*-configured ones—seem within reach.[16]

In the leiodermatolide case, we opted to apply the RCAM/semireduction tactics at the C10–C11 bond rather than at the neighboring C12–C13 olefin, as this disconnection arguably leads to more manageable building blocks. The anticipated bonus of step economy aside, however, this strategic decision bore considerable risk at the stage of ring closure: in general, enynes tend to be less reactive than nonconjugated alkynes, and bulky[17] propargylic substrates have so far rarely succumbed to RCAM.[13] Both structural elements are present in the envisaged cyclization precursor **B**. At the outset of this project it was also unclear whether an alkenyl halide is compatible with the available alkyne metathesis catalysts, even though we were optimistic in view of the excellent tolerance of the latest generation of metal alkylidynes toward many different reactive functional groups.

These reservations notwithstanding, we pursued the synthesis of the required building blocks as shown in Scheme 2. The cheap malonate derivative **3** served as the point of departure, which was advanced into 3-iodomethacrolein (**6**) by following a literature procedure.[18] A subsequent boron-mediated Masamune–Abiko reaction with donor **7**[19] fur-

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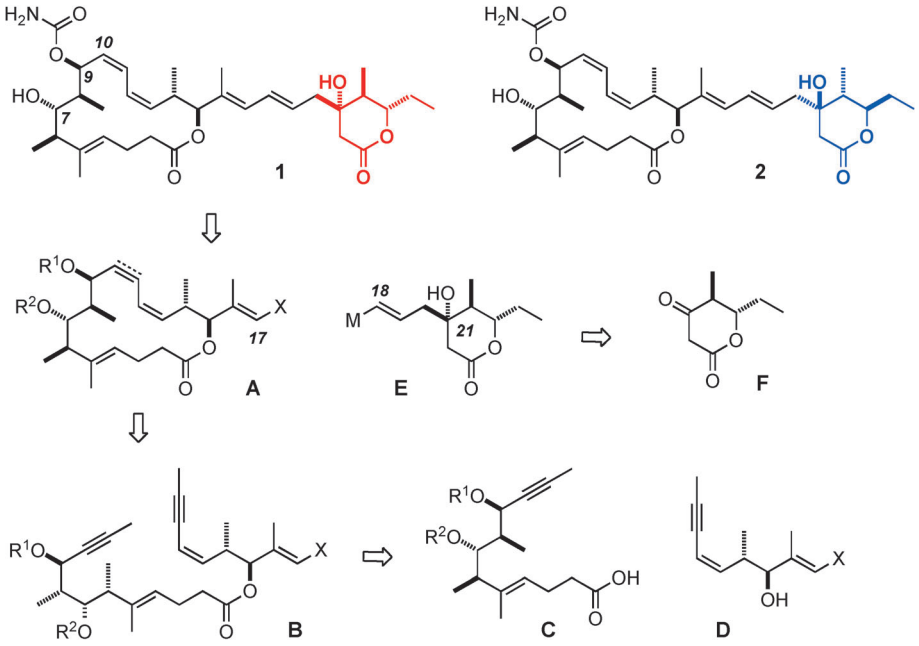
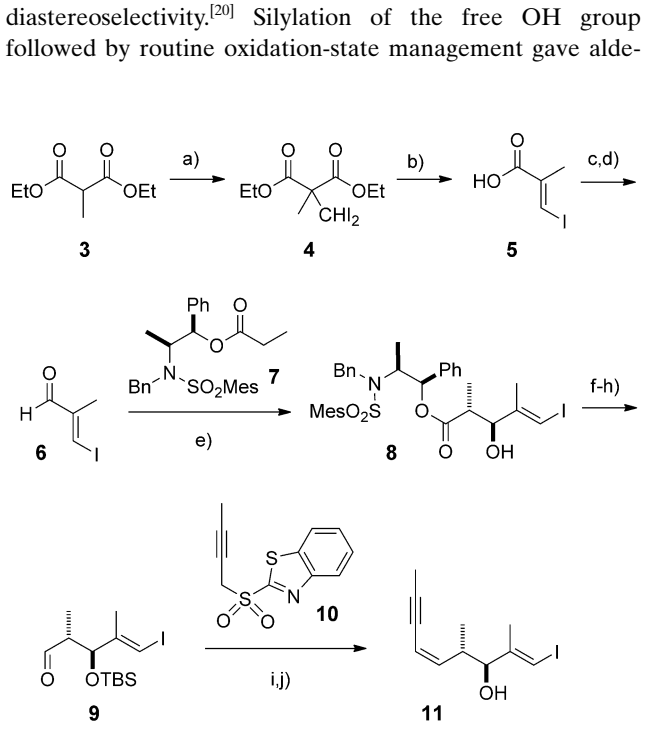


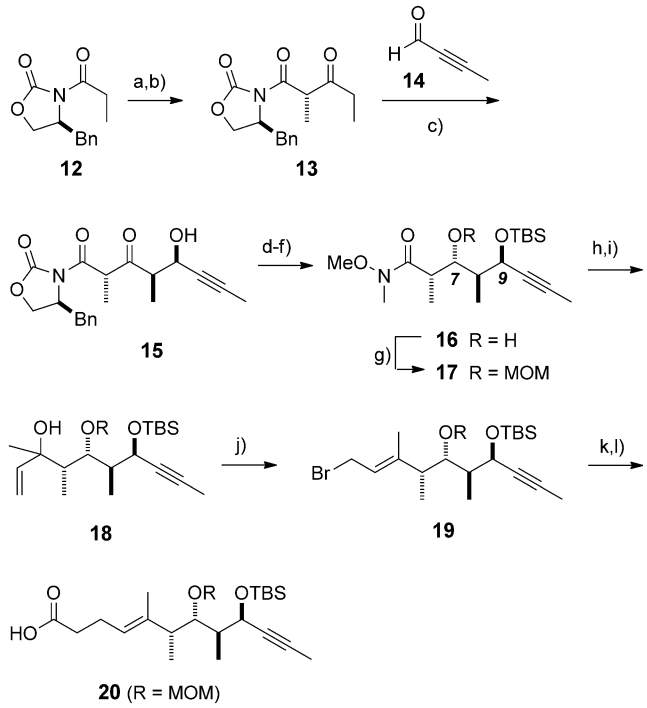
Scheme 1. The two possible stereostructures of leiodermatolide and our retrosynthetic analysis for isomer **1**.

nished the *anti*-aldol product **8** in good yield and respectable diastereoselectivity.[20] Silylation of the free OH group followed by routine oxidation-state management gave aldehyde **9**, which was immediately subjected to a Julia olefination with the known sulfone derivative **10**.[21] The enyne ($Z/E > 24{:}1$) thus obtained was finally deprotected with TBAF to give **11** in readiness for esterification with the acid sector **20**.

The preparation of this second key compound was also straightforward (Scheme 3). The necessary *syn*,*anti*,*syn*-configured stereotetrad was attained by a $Sn(OTf)_2$-mediated aldol reaction of the chiral ketone derivative **13**[22] with an excess of freshly prepared butynal (**14**)[23] followed by 1,3-*anti*-reduction of the resulting product **15**.[24] As expected, the subsequent O-silylation occurred regioselectively at the propargylic site, leaving the C7-OH group open for orthogonal protection as a MOM acetal. This pattern ensured that the distinctive carbamate group of leio-



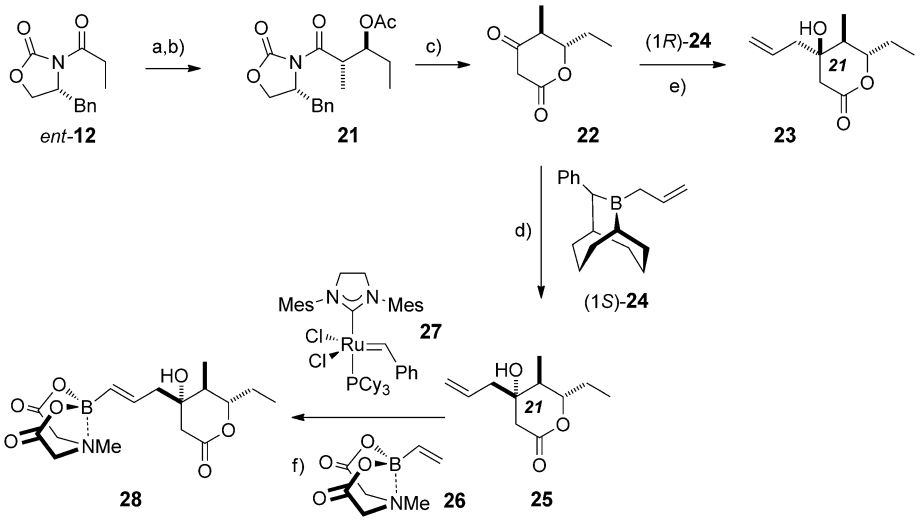
Scheme 2. a) CHI_3, NaH, Et_2O, reflux, 99%; b) KOH, EtOH/H_2O, reflux, 72%; c) $LiAlH_4$, Et_2O, 0°C→RT, 49%; d) MnO_2, CH_2Cl_2, 98%; e) **7**, Cy_2BOTf, Et_3N, CH_2Cl_2, −78°C→RT, 76%; f) TBSOTf, 2,6-dimethylpyridine, CH_2Cl_2, −10°C; g) DIBAl-H, toluene, −78°C, 83% (over two steps); h) Dess–Martin periodinane, CH_2Cl_2, 0°C; i) **10**, KHMDS, THF, −55°C, 56% (>24:1) (over two steps); j) TBAF, THF, 0°C, 99%. Bn = benzyl, Cy = cyclohexyl, DIBAl-H = diisobutylaluminum hydride, KHMDS = potassium hexamethyldisilazide, Mes = mesityl, TBAF = tetra-*n*-butylammonium fluoride, TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl.



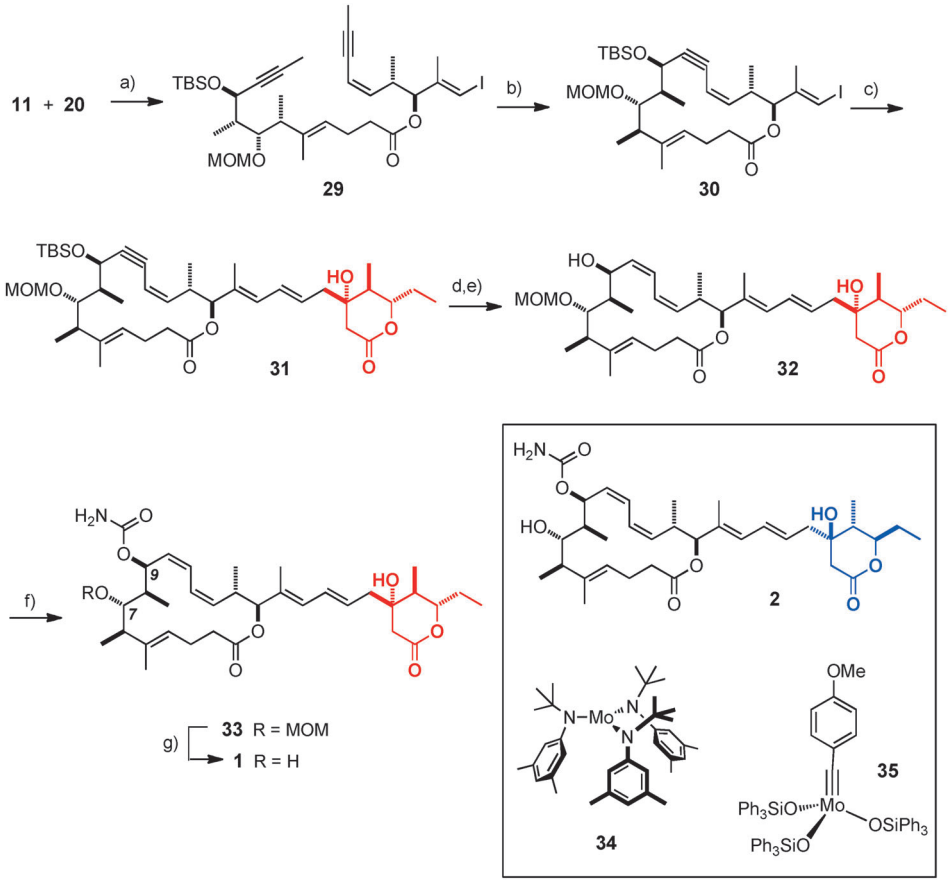
Scheme 3. a) Bu_2BOTf, Et_3N, propanal, 97%; b) SO_3·pyridine, CH_2Cl_2, DMSO, Et_3N, −15°C, 88%; c) **14** (5 equiv), $Sn(OTf)_2$, Et_3N, CH_2Cl_2, −20°C, 55% (88% brsm); d) $Me_4NBH(OAc)_3$, HOAc, MeCN, −50°C, 98%; e) TBSOTf, Et_3N, CH_2Cl_2, −78°C→0°C, 89%; f) (MeO)NH-Me·HCl, $AlMe_3$, THF, 0°C→RT, 90%; g) MOMCl, $(iPr)_2NEt$, DMF, 50°C, 89%; h) MeMgCl, Et_2O, 0°C, 97%; i) $CH_2{=}CHMgCl$, THF, −78°C→RT, 87%; j) PBr_3, pyridine, Et_2O, 0°C; k) EtOAc, LDA, CuI, THF, −110°C→−30°C, 63% (over two steps); l) Me_3SiOK, Et_2O, quant. brms = based on recovered starting material, LDA = lithium diisopropylamide, MOM = methoxymethyl.

dermatolide could later be installed at the correct position, which is not possible once the macrocycle has been formed.[25] Successive addition of MeMgCl and H_2C=CHMgCl at the Weinreb amide terminus of **17** furnished the tertiary alcohol **18**. Since the projected Claisen rearrangement of the derived acetate failed under a variety of conditions,[26] the rearrangement step and the necessary chain extension were dissected into two separate operations. To this end, **18** was first exposed to PBr_3 to give the rather labile allylic bromide **19**, which reacted cleanly with the lithium enolate of ethyl acetate in the presence of CuI at low temperature.[27] The saponification of the resulting ester by using TMSOK was slow but effective, and provided the required acid segment **20** in essentially quantitative yield.

The pseudoaxial orientation of the side chain actually makes the δ-lactone building block **E** more synthetically demanding than its size may suggest. Attempted intramolecular Reformatsky-type reactions had previously been shown to afford exclusively the wrong array, with the side chain in the equatorial position.[12] Therefore, we pursued a different and pleasingly short approach (Scheme 4). The chosen route was inspired by a literature report on the reduction of the readily available cyclic β-ketoester **22** with the borane adduct [(tBuNH$_2$)·BH$_3$] in acidic methanol, in which the incoming hydride was strictly delivered axially.[28] Attempts to translate this process to reactions of **22** with a variety of different carbon nucleophiles, however, originally met with limited success. In most cases, the product yields were zero or remained disappointingly low because of the pronounced enolization of the ketone group of **22**. Only an allylindium reagent generated in situ[29] as well as 9-allyl-9-BBN[30] gave good con-



Scheme 4. a) Bu_2BOTf (2 equiv), Et_3N, propanal, Et_2O, −78 °C, 74% (d.r. = 11:1); b) Ac_2O, Et_3N, DMAP cat., CH_2Cl_2, 0 °C, 82%; c) LiHMDS, THF, −78 °C, 83%; d) (1*S*)-**24**, THF, 0 °C, 86% combined yield (**23**/**25** = 1:5.5), 73% (pure **25**); e) (1*R*)-**24**, THF, −78 °C, 88% combined yield (**23**/**25** = 7.5:1); f) **26**, **27** (5 mol%), CH_2Cl_2, reflux, 81% (*E*/*Z* > 19:1). DMAP = 4-dimethylaminopyridine, LiHMDS = lithium hexamethyldisilazide.



Scheme 5. a) EDCI·HCl, DMAP, CH_2Cl_2, 0 °C, 89%; b) **34** (40 mol%), CH_2Cl_2/toluene, 100 °C, 72%; c) 1. **28**, [Pd(PPh$_3$)$_4$] (20 mol%), Tl(OEt), THF/H_2O (3:1); 2. aq HCl (0.5 M), *tert*-butyl methyl ether, 55%; d) TBAF, THF, 4 Å MS, 0 °C, 85%; e) Zn(Cu/Ag), THF/H_2O/MeOH, 50 °C, 89%; f) $Cl_3CC(O)NCO$, CH_2Cl_2, −78 °C, then Al_2O_3, 84%; g) Me_2BBr, CH_2Cl_2, −90 °C → −78 °C, 61%. EDCI = *N*′-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide, MS = molecular sieves.

versions, but afforded the wrong isomer **23** as the major product. All attempts to override this inherent bias of the indium reagent with the aid of chiral modifiers failed to afford a workable solution. Gratifyingly though, replacement of 9-allyl-9-BBN by its chiral relative **24** was more successful.[31] In this case, the addition is reagent-controlled, as evident from the data shown in Scheme 4. Specifically, (1*S*)-**24** afforded the required diastereomer **25** with appreciable selectivity (d.r. = 5.5:1) and good yield.[32] The terminal alkene of **25** participated well in a cross-metathesis reaction with the vinyl MIDA boronate ester **26** catalyzed by the second-generation Grubbs carbene **27**,[33] which provided the required Suzuki donor **28**, virtually as a single isomer ($E/Z > 19{:}1$).

The assembly stage of the project commenced with the esterification of **11** and **20** to give the requisite cyclization precursor **29** (Scheme 5). Treatment of this substrate with the molybdenum alkylidyne complex **35**[34] endowed with bulky triphenylsilanolate ligands resulted only in the fast and clean formation of an acyclic dimer. This outcome was independent of whether the reaction was performed at ambient temperature or at 100 °C. Gratifyingly though, the catalyst formed in situ upon activation of complex **34** with CH_2Cl_2, as previously described by our research group,[35] furnished the desired cyclic monomer **30** in 72 % yield, with only traces of the dimer being detectable in the crude mixture.[36] The transformation required harsh conditions, a high catalyst loading, and an unusually long reaction time; this fact likely reflects the challenge derived—collectively—from the strain of the incipient polyunsaturated ring, the severe steric hindrance about the reacting propargylic site,[17] and the electronic toll to be paid for the enyne motif. However, the chemoselectivity was excellent, with the strict differentiation of the catalyst between the reactive π systems of the triple bonds and the inert π bonds of three different types of alkenes present in the substrate being remarkable and enabling at the same time.[13]

Since the alkenyl iodide had survived the metathesis step uncompromised, the stage was set for the attachment of the side chain by a Suzuki–Miyaura reaction with boronate **28**. Despite the outstanding track record of this venerable transformation,[37] this particular cross-coupling actually turned out to be challenging and required considerable optimization. Best results were obtained using Tl(OEt) in aqueous THF,[38] followed by an acidic work up to regenerate the δ-lactone ring, which was partly opened in the basic medium. Attempts to reduce the alkyne in the resulting polyunsaturated product **31** to the corresponding *Z* alkene failed under a variety of conditions as long as the TBS group on the C9-OH was present.[17] In contrast, the propargylic alcohol generated by cleavage of the silyl ether, despite being otherwise very unstable, could be cleanly converted into the 10*Z*-configured allylic congener **32** on exposure to Zn(Cu/Ag) as the preferred reducing agent.[39] This compound was treated with $Cl_3CC(O)NCO$, and the primary adduct hydrolyzed upon contact with alumina to release the still missing carbamate group.[40,41] After several unsuccessful attempts, we were pleased to find that the delicate final cleavage of the residual MOM group in the presence of the sensitive allylic carbamate could be accomplished with Me_2BBr at low temperature to give the targeted product **1** in good yield.[42,43]

To obtain the diastereomeric product **2**, the same end game was executed with similar yields but using the enantiomeric δ-lactone fragment *ent*-**28** (for details, see the Supporting Information). Interestingly, the ^{13}C NMR spectra (150 MHz, CD_2Cl_2) of **1** and **2** are almost indistinguishable and did not allow us to decide which of the two isomers represents leiodermatolide.[44] Likewise, their ^1H NMR spectra (600 MHz) are virtually identical, except for the region between 2.2 and 2.5 ppm, wherein subtle differences can be noticed that are deemed sufficiently characteristic (Figure 1).

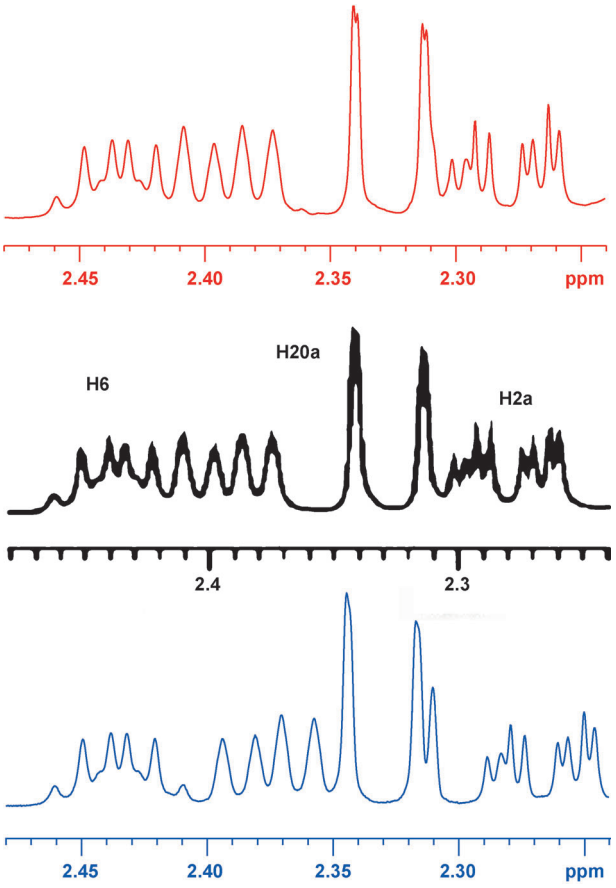


Figure 1. Region of the ^1H NMR spectra (600 MHz, CD_2Cl_2) that shows subtle, but distinctive, differences for the isomers **1** (red) and **2** (blue), and allows for a correlation with the published spectrum of the natural product (black).

Direct comparison of the published spectrum of leiodermatolide (black)[5] with that of compound **1** (red) shows a perfect match, whereas the pattern of **2** (blue) is slightly dissimilar.[45] The recorded optical rotation of **1** ($[\alpha]_D^{24} = -74.3$, $c = 0.41$, MeOH) implies that the absolute configuration of leiodermatolide ($[\alpha]_D^{24} = -84.2$, $c = 0.34$, MeOH)[5] must be as drawn. Although we have no authentic sample of the natural product at our disposal, we believe that formula **1** properly depicts the molecular structure of leiodermatolide.

In summary, we accomplished the first total synthesis of the structurally challenging and biologically highly promising

antimitotic agent leiodermatolide by pushing the limits of alkyne metathesis to new frontiers. The chosen approach is short, efficient, and flexible, and should hence qualify for a synthesis-driven mapping of the pharmacophore of this lead compound. In chemical terms, this case study corroborates our previous conclusion that RCAM is particularly well-suited for applications to polyunsaturated targets, where olefin metathesis often finds its limits.[46] At the same time, this investigation shows that total synthesis remains an indispensable tool for structure elucidation, even in the age of spectroscopy, when dealing with compounds that contain spatially segregated stereoclusters.[47]

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[43] In contrast, a variety of commonly used reagents for the cleavage of MOM acetals gave complex mixtures, containing significant amounts of products formed by elimination of the carbamate

moiety (anhydr. HCl, TMSCl/$(n\text{Bu})_4$NBr, $BF_3{\cdot}Et_2O$, $[Ph_3C]BF_4$ (with and without 2,6-di-*tert*-butylpyridine), $ZnBr_2$/BuSH, (catechol)BX (X = Cl, Br), 9-I-9-BBN).

[44] The NMR spectra of both isomers are contained in the Supporting Information.

[45] The spectra of synthetic **1** were recorded at different molarities to make sure that these delicate differences are not caused by concentration effects.

[46] For other instructive cases, see a) W. Chaładaj, M. Corbet, A. Fürstner, *Angew. Chem.* **2012**, *124*, 7035 – 7039; *Angew. Chem. Int. Ed.* **2012**, *51*, 6929 – 6933; b) V. Hickmann, A. Kondoh, B. Gabor, M. Alcarazo, A. Fürstner, *J. Am. Chem. Soc.* **2011**, *133*, 13471 – 13480; c) K. Lehr, R. Mariz, L. Leseurre, B. Gabor, A. Fürstner, *Angew. Chem.* **2011**, *123*, 11575 – 11579; *Angew. Chem. Int. Ed.* **2011**, *50*, 11373 – 11377.

[47] For another study from our research group illustrating this notion, see A. Fürstner, M. Albert, J. Mlynarski, M. Matheu, E. DeClercq, *J. Am. Chem. Soc.* **2003**, *125*, 13132 – 13142.

