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SPECIAL FEATURE: ARTICLE

Synthesis and biological evaluation of (±)-hippolachnin and analogs

Nils Winter[1] · Zeljka Rupcic[2] · Marc Stadler[2] · Dirk Trauner[1,3]

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Abstract

Due its unique structure and its reported potent antifungal activity, the marine polyketide hippolachnin A (**1**) has attracted much attention in the synthetic community. Herein, we describe the development of a concise, diversifiable and scalable synthesis of the racemic natural product, which serves as a platform for the generation of bioactive analogues. Biological testing of our synthetic material did not confirm the reported antifungal activity of hippolachnin A but unraveled moderate activity against nematodes and microbes.

Introduction

Opportunistic infections by ubiquitous fungi represent a major challenge to immunocompromised patients. The basidiomycete yeast *Cryptococcus neoformans*, for instance, can cause life-threatening meningitis and affect the lungs and skin of patients with advanced acquired immunodeficiency syndrome (AIDS) [1–6]. Hippolachnin A (**1**) was recently isolated from the South China Sea sponge *Hippospongia lachne*. The molecule features six contiguous stereocenters embedded in a bicyclo[3.2.0]heptane framework, four of which bear ethyl groups. Biochemical assays, reported in the initial study, revealed high potency against several pathogenic fungi, including *C. neoformans* (MIC = 0.41 μM) [7]. Biosynthetically, **1** is part of the plakortin family [8] and, more precisely, part of the gracilioether family (Fig. 1). This family also includes the unnamed compound **2**, the presumptive biosynthetic precursor of **1**, as well as the graciloethers (**3, 5, 6**), and plaktorin (**4**).

Attracted by its unusual structure combined with the potent bioactivity, numerous research groups, including ours, have developed unique synthetic solutions for this molecule. In the last three years, four total syntheses have been reported [9–13], including a recent biomimetic synthesis by Tang and Enders [14]. In 2014, we launched a program to develop a scalable and diversifiable approach to hippolachnin A (**1**). Herein, we show how our strategy evolved, discuss our studies on synthetic derivatives, and the results of our evaluation of their biological properties.

Results and discussion

As outlined in Scheme 1, we initially focused on a strategy based non-biomimetic [2 + 2]-cycloaddition of allylic ester **8**, to simultaneously form the cyclobutane and the tetrahydrofuran of the natural product. The vinylogous carbonate should then be installed by Peterson olefination. Even though the desired [2 + 2]-cycloaddition of an acyclic α,β-unsaturated ester was anticipated to be difficult, we envisioned that, conducting the reaction in an intramolecular fashion, might allow for efficient trapping of the photochemically formed triplet diradical.

The synthesis commenced with the preparation of tertiary alcohol **13** from dicyclopentadiene (**9**) (Scheme 2). Conjugate addition from the convex side of enone **10**, obtained from Alder-ene reaction of **9** with singlet oxygen, afforded ketone **11** [15]. Subsequent 1,2-addition of EtMgBr mediated by $LaCl_3.2LiCl$ yielded tertiary alcohol **12** as a single diastereoisomer [16]. While initial attempts to

Dedicated to Prof. Samuel J. Danishefsky with admiration and gratitude.

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✉ Dirk Trauner
dirktrauner@nyu.edu

[1] Department of Chemistry, Ludwig-Maximilians-Universität München, Butenandtstr. 5-13, 81377 Munich, Germany

[2] Helmholtz Centre for InfectionResearch, Inhoffenstr. 7, 38124 Braunschweig, Germany

[3] Department of Chemistry, New York University, Silver Center, 100 Washington Square East, Room 712, New York, NY, USA

effect thermolysis resulted in decomposition, flash vacuum pyrolysis (FVP) cleanly provided sensitive tertiary alcohol **13** in good yield [17].

With **13** in hand, we envisioned esterification with the known carboxylic acid **14** (Scheme 3) [18]. Standard esterification conditions utilizing the acid chloride only resulted in isolation of the free acid after work up. Attempts to generate the acylium ion only led to decomposition of the starting materials [19]. Anhydride **15** was found to be stable to column chromatography but could not be used for ester formation, even at elevated temperatures. Interestingly, both the acid chloride and the mixed anhydride were able to react with *t*-BuOK to form the corresponding *t*-butyl ester **16**.

Since the sterical hindrance of the tertiary alcohol could not be overcome, we decided to install the fourth ethyl group at a later stage of the synthesis. The revised retrosynthesis is shown in Scheme 4. We envisioned formation of **1** by ethyl Grignard addition to cyclopentenone **17**, followed by dehydration. The β-ketoester could be derived by Claisen condensation of methyl acetate with lactone **18**. Lactone **18** would be traced back to an intramolecular [2 + 2]-cycloaddition of ester **19**.

Epoxidation of cyclopentadiene [20] (**20**) followed by S_N2' displacement with ethylcyanocuprate [21] provided allylic alcohol **21** in moderate yield (Scheme 5). Quantitative formation of the lithium alkoxide and subsequent quenching with acid chloride **14** gave rise to allylic ester **19**.

With **19** in hand we investigated the key [2 + 2]-cycloaddition [22]. Unfortunately, irradiation of **19** with 310 nm LEDs in the presence of either acetone or benzophenone in various solvents (MeCN, CH_2Cl_2, benzene) did not result in the desired cycloadditon. Instead, we isolated starting material as a mixture with its (*E*)-configured diastereomer **22**. While excitation of the system proceeded smoothly as proved by the formation of **22**, we wondered whether π-bond rotation was too fast to allow for capture of the diradical by the tethered olefin.

To prevent isomerization we decided to incorporate the enone double bond into a ring by stitching the ends of the ethyl groups together using a sulfur bridge. Ring expansion of tetrahydrothiopyranone **23** using ethyl diazoacetate gave rise to thiepanone **24** which, after reduction, mesylation, and elimination provided ethyl ester **26** [23]. Saponification followed by activation of the carboxylic acid as the acid chloride and subsequent esterification accessed enoate **28** in moderate yields (Scheme 6). To investigate the cycloaddition, we submitted **28** to the same conditions used for **19**. After irradiation, the clear solution became cloudy and NMR analysis of the mixture indicated decomposition of the starting material.

While excitation of the molecule was possible, no productive pathways were observed, which might be attributed to a preferred conformation of the molecule where both olefins are pointing into opposite directions. In order to

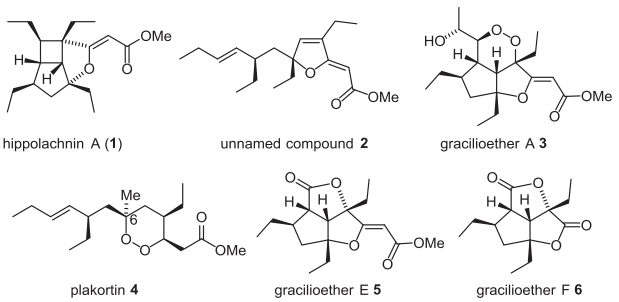
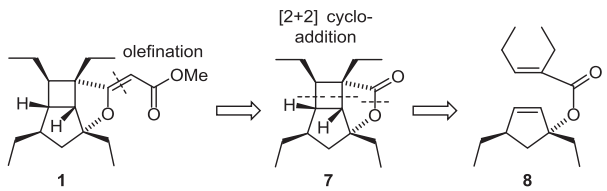
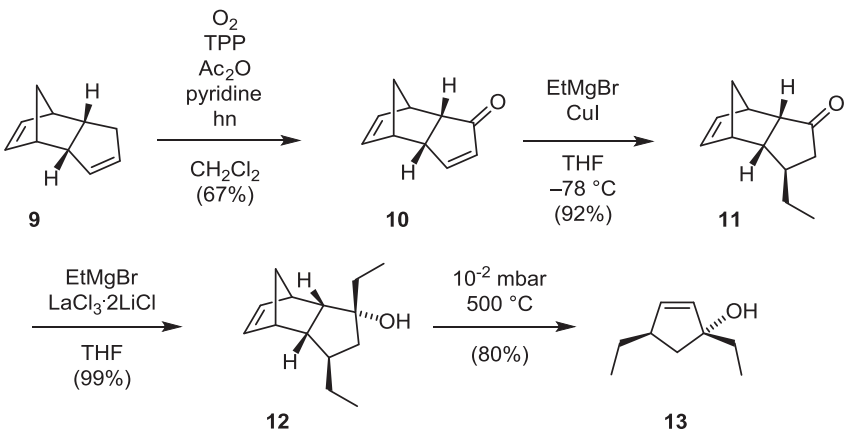


Fig. 1 Selected members of the plakortin family



Scheme 1 First generation retrosynthesis of hippolachnin A based on a [2 + 2]-cycloaddition

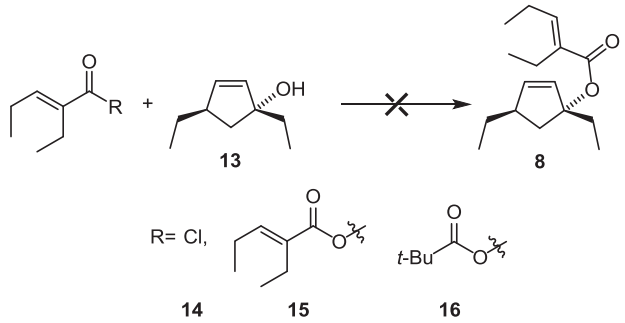
Scheme 2 Synthesis of allylic alcohol **13**



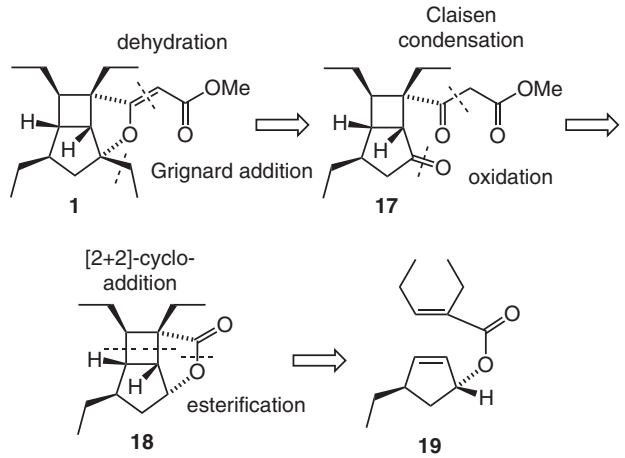
provide the molecule more flexibility, β-ketoester **32** was prepared (Scheme 7). Activation of acid **30** with CDI and subsequent Claisen condensation with *t*-BuOAc, followed by ketalization, gave dioxanone **31** [24]. Retro [4 + 2]-cycloaddition and trapping of the resulting ketene with alcohol **19** then afforded β-ketoester **32** [25]. Irradiation of **32** under the previously established conditions resulted in a complex mixture from which we were unable to isolate the desired bicyclo[3.2.0]heptane **33**.

Frustrated by our inability to effect (2 + 2) cycloadditons we decided to turn to a different type of photochemistry (Scheme 8). In our new retrosynthetic analysis, we planned to close the tetrahydofuran ring in **1** by *O*-alkylation of an enolized β-ketoester **34** [26]. The vicinal ethyl groups should be introduced by addition of an ethyl nucleophile and an ethyl electrophile to the Michael acceptor **35**. Compound **35** was derived from the known bicyclo[3.2.0] heptadiene **36**, which can be obtained from tropolone ether **37** (Scheme 8) [27].

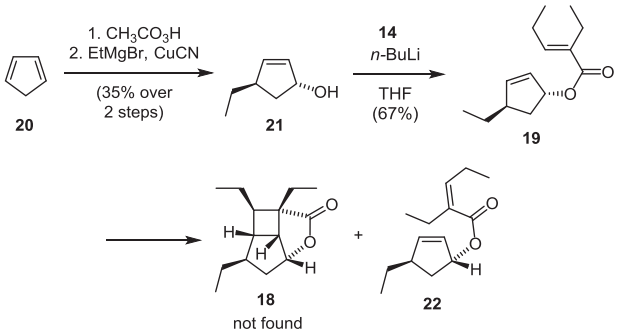
Our synthesis commences with the photochemical conversion of **37** into methoxy bicyclo[3.2.0]heptadienone **36**, which was originally reported by Dauben et. al [27]. Irradiation of **37** induced a disrotatory 4π-electrocyclization to



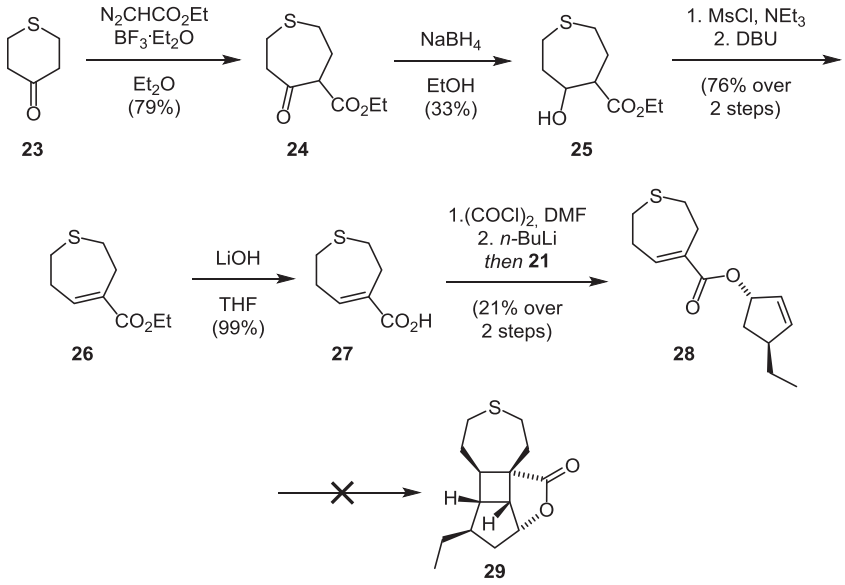
Scheme 3 Attempted esterification of **8**



Scheme 4 Revised retrosynthesis of **1**

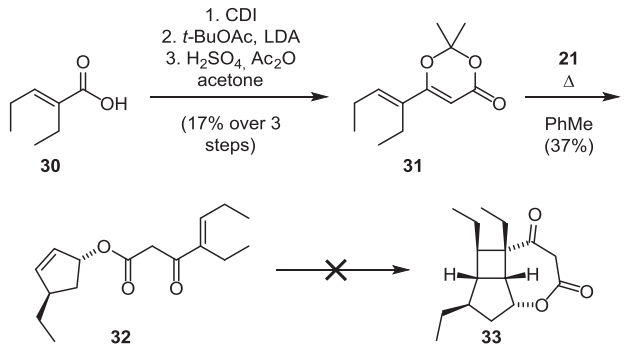


Scheme 5 Synthesis of allylic ester **19** and formation of ester **22**



Scheme 6 Synthesis of thiepan **28** and attempted [2 + 2]-cycloaddition

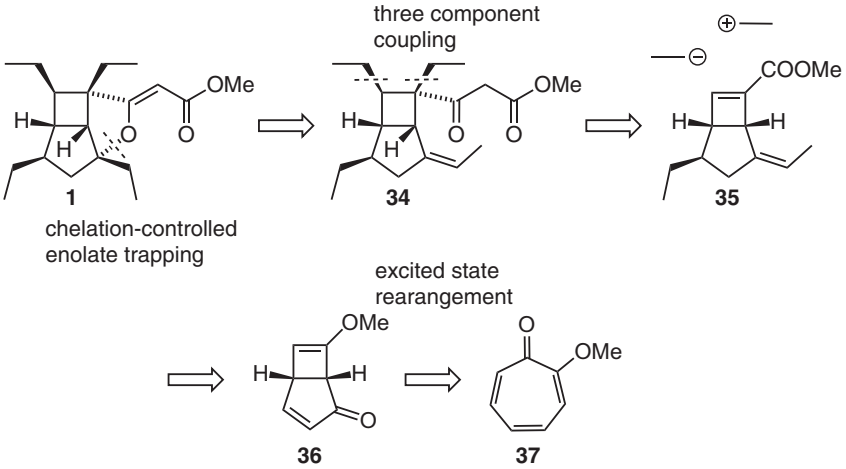
give **38**, which then undergoes an excited state rearrangement to yield **36**. Notably, even though **38** is an isolatable intermediate, **36** was the only product obtained after full conversion of **37**. Ethyl cuprate addition to **36** occurred exclusively from the convex side [15] of the molecule and gave, after Wittig olefination [28] and acid mediated cleavage of the enol ether [29] ketone **40** as a 10:1 mixture of *E*- and *Z*- isomers (major isomer shown). Formation of the vinyl triflate [30, 31] and subsequent carbomethoxylation [32] then gave methyl ester **41** (Scheme 9).



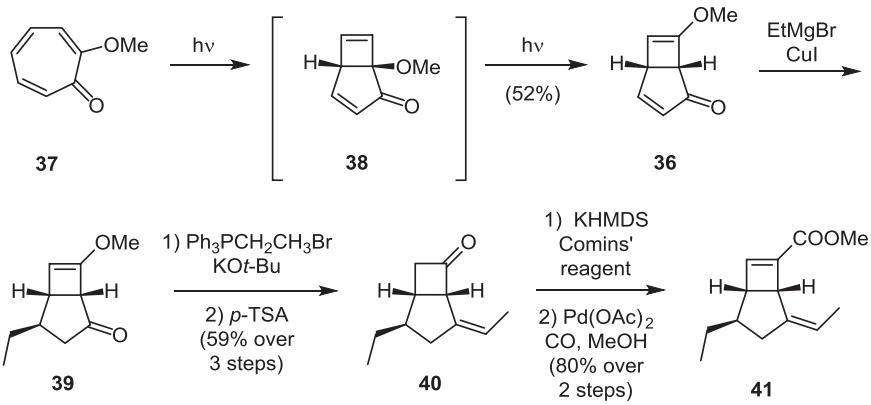
Scheme 7 Synthesis of β-ketoester **32** and attempted [2 + 2]-cycloaddition

With **41** in hand, the stage was set for the installation of the vicinal ethyl groups (Scheme 10). We first envisioned the conjugate addition of an ethyl cuprate and subsequent alkylation at the α-position of the ester. While the conjugate addition occurred solely from the convex side of the molecule, acidic quenching of the resulting ester enolate gave an inconsequential mixture of diastereomers with respect to the ester group. Reformation of the enolate using LDA and subsequent trapping with ethyl iodide resulted in 2:1 mixture of diastereomers [33], favoring the desired one. We attributed this result to the opposing stereochemical bias provided by the bicyclic core and the newly introduced ethyl group. Although, the major isomer could be converted into an advanced intermediate **44** of the Wood-Brown synthesis [10], we thought that this low level of selectivity was unacceptable for an efficient synthesis.

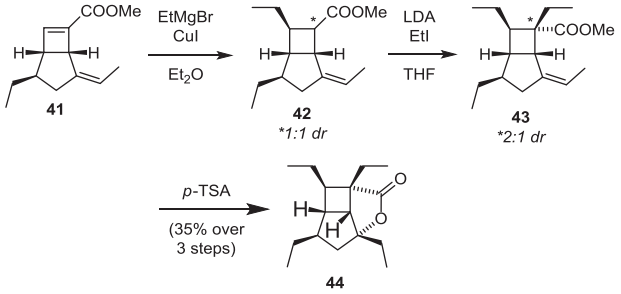
To overcome this problem, we turned toward the 1,3-dipolar cycloaddition of a thiocarbonyl ylide followed by reductive desulfurization to add, in effect, two ethyl radicals across the strained and electron poor double bond of **41** [34–38]. The requisite thiocarbonyl ylide **48** could be



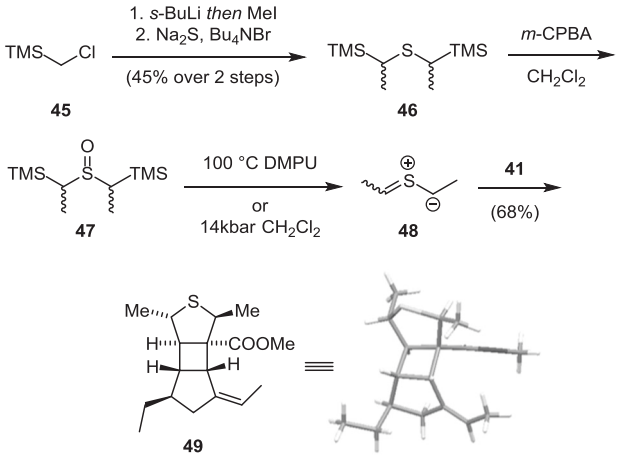
Scheme 8 Retrosynthetic analysis of **1** based on an excited state rearrangement



Scheme 9 Synthesis of methyl ester 41



Scheme 10 Synthesis of **44** via three component coupling



Scheme 11 Synthesis of thiocarbonylylide **48** and 1,3-cycloaddition to form **49**

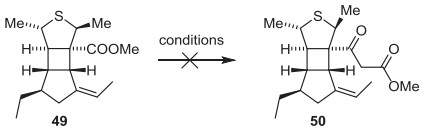
generated in situ from sulfoxide **47** following Achiwa's method [39–44]. Compound **47**, in turn, was derived from (chloromethyl)trimethylsilane **45** by alkylation with methyl iodide followed by nucleophilic displacement with sodium sulfide and subsequent oxidation (Scheme 11).

Dropwise addition of **48** to a hot solution of **41** indeed resulted in the clean formation of tetrahydrothiophen **49**, which was obtained as a single diastereosiomer. Single crystal X-ray structure analysis showed that the methyl groups adopt a *trans*-configuration with respect to the heterocyclic ring. Notably, the reaction also proceeds under high pressure conditions (12 kbar) at room temperature, albeit with slightly lower yield.

With the key intermediate in hand we turned our focus to the homologation of the ester group to the corresponding β-ketoester. Unfortunately, all attempts [45–48] to effect a Claisen condensation failed, presumably due to steric hinderance (Table 1).

We sought to overcome this problem by using a less hindered electrophile settling on the cyano group with its sp-hybridized carbon. To this end we prepared nitrile **52** from vinyl triflate **51** by Pd-catalyzed cross coupling with sodium cyanide [49] (Scheme 12). To our delight, the 1,3-

Table 1 Attempted Claisen condensation of **49**.



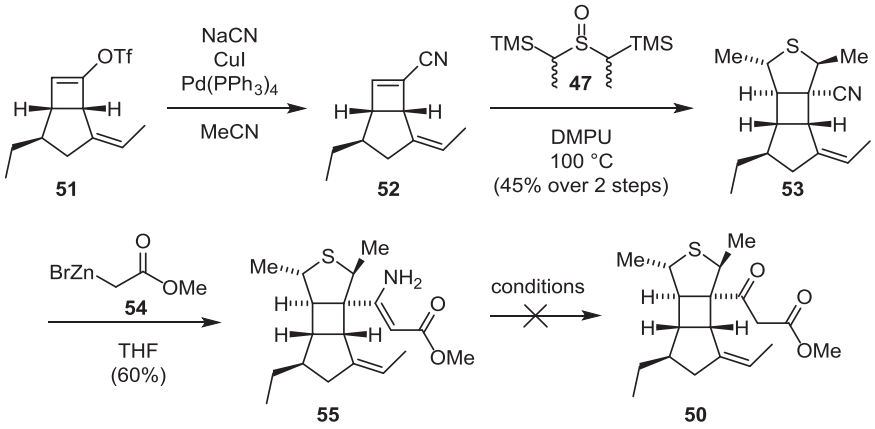
#	substrate	base	temp	result
1	MeOAc	LDA	–78 °C to RT	no reaction
2	MeOAc	MgDA	RT	no reaction
3	MeOAc	NaH	60 °C	no reaction
4	MeOAc	KO*t*-Bu	50 °C	no reaction
5	*t*-BuOAc	*t*-BuLi	–78 °C to RT	decomposition
6		*n*-BuLi	0 °C	decomposition

dipolar cycloaddition gave tricycle **53** as a single diastereomer, albeit in slightly lower yield. Blaise reaction of **53** with zinc organyl **54** then yielded the desired en-amine **55** [50]. Unfortunately, the vinylogous carbamate **55** proved to be completely resistant to hydrolysis with starting material recovered under standard conditions [51, 52]. Harsher conditions led to decomposition of **55**.

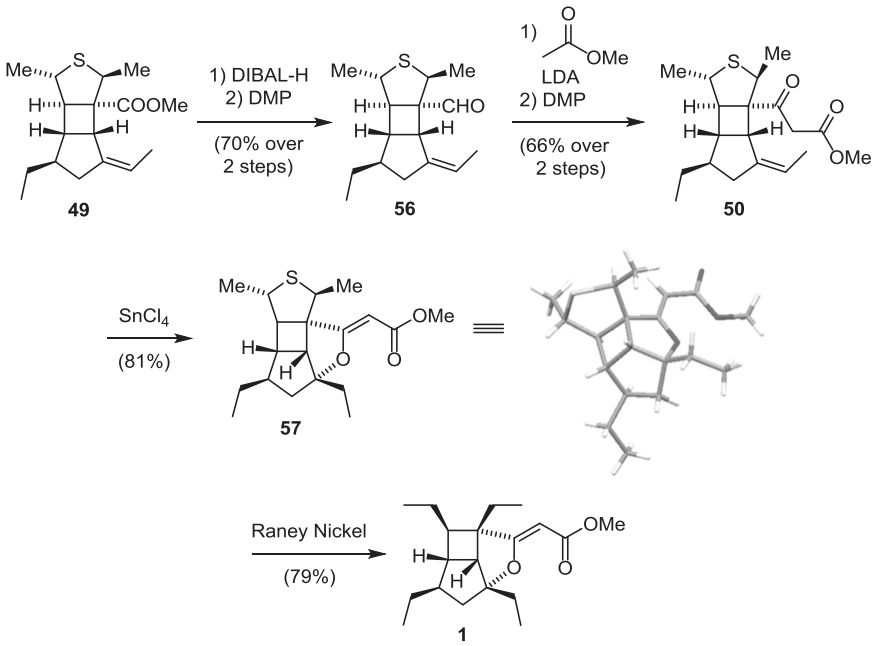
Although methyl ester **41** was resistant to a crossed-Claisen condensation, it could be reduced to the primary alcohol and mildly reoxidized. The resulting aldehyde **56** was able to undergo an aldol addition [53] with the enolate generated from methyl acetate and gave, after Dess Martin oxidaition, the desired β-ketoester **56**. Formation of the tin enolate followed by trapping of the simultaneously generated tertiary carbocation [26] gave rise to (*Z*)-configured vinylogous carbonate **57** [54]. Its structure could be confirmed by X-ray structure analysis. Reductive desulfurization with Raney nickel in THF [55–57] gave access to the natural product, hippolachnin A, as a racemate (Scheme 13).

Piao et. al. reported strong antifungal activity of hippolachnin A [7]. With a good synthetic entry at hand, we decided to develop analogues that would allow us to map structure-activity relationships and would show improved physicochemical properties. Since **1** is poorly soluble in aqueous solutions, we chose to synthesize more polar derivatives by oxidizing the sulfur of the advanced intermediate **57** to either the sulfoxide or the sulfone (Scheme 14). Notably, treatment of **57** with excess *m*-CPBA at room temperature led to partial isomerization of the double bond to afford a mixture of **58** and **59**. Partial oxidation of **57** gave sulfoxide **60** as a 5:1 mixture of

Scheme 12 Synthesis of enamine **55** and attempted hydrolysis



Scheme 13 Total synthesis of **1**



diastereomers. We also synthesized the butyrolactone **61** by acid mediated cyclization of **41**.

With the racemic natural product and several synthetic analogous in hand, we evaluated the antifungal, antimicrobial and the nematicidal activity of **1**, **57**, **44**, **61**, **59**, **58**, and **60**. We were surprised to find that (±)− **1** showed no antifungal activity, in particular against *C. neoformans* (Table 2). This observation was recently independently reported by Wood [58]. It seems unlikely that the unnatural enantiomer somehow neutralizes the biological effect of (+)-hippolachnin A. Our synthetic analogs of **1** were also inactive against the fungi listed in Table 2, except for butyrolactone **61**, which showed modest activity against *C. neoformans*. Compounds **1**, **57**, **44**, and **61** exhibited weak antimicrobial activity (Table 2 and supporting information) and no or very weak cytotoxicity (supporting information). Interestingly, all analogs, including the natural product, inhibited the growth of *Caenorhabditis elegans*, but again with weak potency (Table 2).

Conclusion

Herein, we have presented the evolution of our campaign for the total synthesis of hippolachnin A. Starting from tropolone methyl ether **37**, we developed a robust and scalable synthetic route which enabled us to synthesize not only more than 100 mg of the natural product but also a variety of synthetic derivatives. The bicyclic carbon core was constructed by photoisomerization of **37**. The four ethyl groups were introduced by diastereoselective cuprate addition, Wittig olefination, and the 1,3-dipolar cycloaddition of a thiocarbonyl ylide. The latter represents a rarely used method to overcome steric hindrance and, in effect, link a

Scheme 14 Synthesis of synthetic analogs of **1**

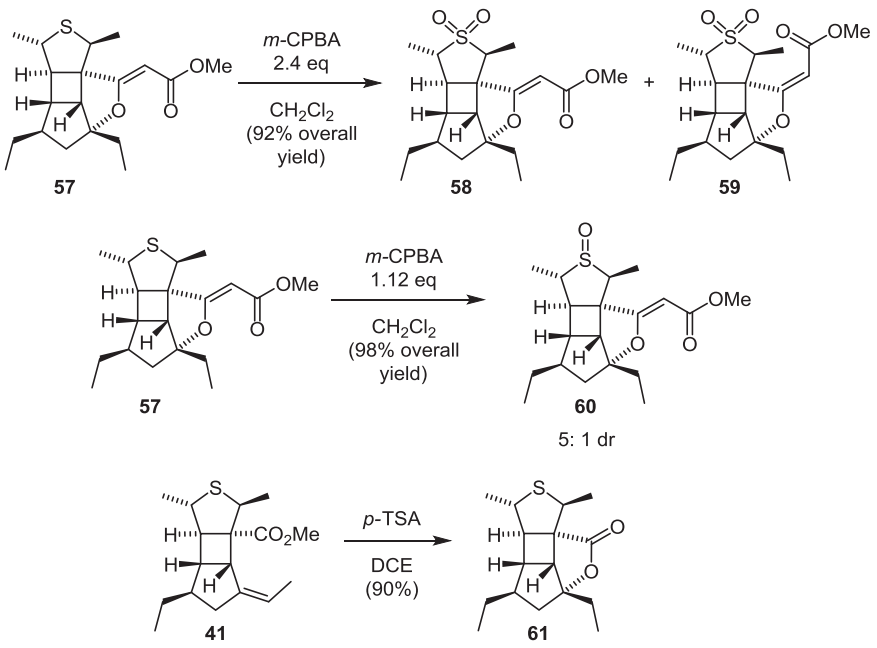


Table 2 Antifungal, antimicrobial, and nematicidal activity activity of **1** and its analogs

Test organism	DSM	**1**	**57**	**44**	**61**	**59**	**58**	**60**	Reference (μg/ml)
Fungi									
Alternaria solani	2947	/	/	/	/	/	/	/	16.6[c]
Aspergillus fumigatus	819	/	/	/	/	/	/	/	67.0-33.3[c]
Botrytis cinerea	877	/	/	/	/	/	/	/	67.0[c]
Candida albicans	1665	/	/	/	/	/	/	/	4.2[c]
Cryptococcus neoformans	15466	/	/	/	67.0	/	/	/	8.3[c]
Fusarium oxysporum	62297	/	/	/	/	/	/	/	67.0[c]
Phytophthora drechsleri[f]	62679								[c]
Sclerotinia sclerotiorum	1946								[c]
Bacteria									
Staphylococcus aureus	346	8.3	33.3	/	33.3	/	/	/	0.21-0.1[a]
Staphylococcus aureus MRSA	11822	33.3	/	/	/	/	/	/	0.83[b]
Bacillus subtilis	10	8.3	33.3	8.3	/	/	/	/	4.2[a]
Escherichia coli	1116	/	/	/	/	/	/	/	3.3-0.83[a]
Nematode									
Caenorhabditis elegans	–	12.5	10	10	50	10	10	25	1.0[e]

In vitro antibacterial, anti-oomycete nematicidal activity of substances **1**, **57**, **44**, **61**, **59**, **58**, **60** and our control drugs. For determination of antibacterial and antifungal activity, substances were dissolved in MeOH (10 mg/ml) and then further diluted to a final concentration of 1 mg/ml. 2 and 20 μl of this solution was tested against different test organisms (67.0-0.052 μg/ml final concentration). Alternatively, for determination of nematicidal activity, substances were dissolved in MeOH (1.5 mg/mL) and an aliquot thereof transferred to 24 well plate, where each well contained 1 mL of M9 buffer, to reach final concentrations in a range from 100–1 μg/mL [61]. For all assays MeOH was used as negative control and showed no activity against the selected test strains. Results of antibacterial and antifungal assays were expressed as MIC: Minimum inhibitory concentration μg/ml, while nematicidal activity was assessed as LD_{50}: lethal dose (concentration) causing over 50 % immobility of nematodes. The cell density was adjusted to 8×10^6 cells/ml

N.I. no inhibition, *DSMZ* German collection of microorganisms and cell cultures, Braunschweig

[a]Oxytetracyclin hydrochloride

[b]Vancomycin

[c]Nystatin

[d]Kanamycin

[e]Ivermecitin

[f]spores from agar plates were applied without justification

nucleophile to an electrophile. The heterocyclic ring was closed via trapping of carbocation generated in situ by a tin enolate. Reports about the antifungal activity of hippolachnin A could not be confirmed. This is in keeping with several other recent cases where the purported bioactivity of natural products did not match the activity of their synthetic versions [59, 60]. Of course, this serves as yet another justification for total synthesis, which often provides material in purer form and on a larger scale than isolation from natural sources.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Kauffman CA. Cryptococcosis. In: Goldman L, Schafer AI, editors. Goldman-Cecil Medicine. 25th ed. Philadelphia: Elsevier Saunders; 2016: chap 336.
2. Govender NP, Patel J, van Wyk M, Chiller TM, Lockhart SR. Trends in antifungal drug susceptibility of *Cryptococcus neoformans* isolates obtained through population-based surveillance in South Africa in 2002–3 and 2007–8. Antimicrob Agents Chemother. 2011;55:2606–11.
3. Loyse A, et al. Cryptococcal meningitis: improving access to essential antifungal medicines in resource-poor countries. Lancet Infect Dis. 2013;13:629–37.
4. Sabiiti W, et al. Efficient phagocytosis and laccase activity affect the outcome of HIV-associated cryptococcosis. J Clin Invest. 2014;124:2000–8.
5. Li SS, Mody CH. *Cryptococcus*. Ann Am Thorac Soc. 2010;7:186–96.
6. Hyde KD, Al-Hatmi A, Andersen B, Boekhout T, Buzina W, Dawson Jr TL, et al. The world's ten most feared fungi. Fungal Divers 2018;93:161–94.
7. Piao SJ, et al. Hippolachnin A, a new antifungal polyketide from the South China Sea sponge *Hippospongia lachne*. Org Lett. 2013;15:3526–3529.
8. Rahm F, Harges PY, Kitching W. Metabolites from marine sponges of the genus *Plakortis*. Heterocycles. 2004;64:523–575.
9. Ruider SA, Sandmeier T, Carreira E-M. Total synthesis of (±)-Hippolachnin A. Angew Chem Int Ed. 2015;54:2378–82.
10. McCallum ME, Rasik CM, Wood JL, Brown M-K. Collaborative Total synthesis: routes to (±)-Hippolachnin A enabled by quadricyclane cycloaddition and late-stage C–H oxidation. J Am Chem Soc. 2016;7:2437–42.
11. Datta R, Dixon RJ, Ghosh S. A convenient access to the tricyclic core structure of hippolachnin A. Tetrahedron Lett. 2016;57:29–31.
12. Xu ZJ, Wu Y. Efficient synthetic routes to (±)-Hippolachnin A, (±)-Gracilioethers E and F and the alleged structure of (±)-Gracilioether I. Chem Eur J. 2017;23:2026–30.
13. Winter N, Trauner D. Thiocarbonyl Ylide chemistry enables a concise synthesis of (±)-Hippolachnin A. J Am Chem Soc. 2017;139:11706–9.
14. Li Q, et al. Enantioselective total syntheses of (+)-Hippolachnin A, (+)-Gracilioether A, (−)-Gracilioether E, and (−)-Gracilioether F. J Am Chem Soc. 2018;140:1937–44.
15. Demuynck ALW, et al. Retro-diels–alder reactions of masked cyclopentadienones catalyzed by heterogeneous brønsted acids. Adv Synth Catal. 2010;352:3419–30.
16. Krasovskiy A, Kopp F, Knochel P. Soluble lanthanide salts (LnCl3·2 LiCl) for the Improved addition of organomagnesium reagents to carbonyl compounds. Angew Chem Int Ed Engl. 2006;45:497–500.
17. Zhu J, Yang J-Y, Klunder AJH, Liu Z-Y, Zwanenburg B. A stereo- and enantioselective approach to clavulones from tricyclodecadienone using flash vacuum thermolysis. Tetrahedron. 1995;51:5847–70.
18. Zweifel G, Steele RB. A new and convenient method for the preparation of isomerically pure alpha-beta-unsaturated derivatives via hydroalumination of alkynes. J Am Chem Soc. 1967;89:2754–5.
19. Effenberger F, Epple F, Eberhard JK, Bühler U, Sohn E. Carbonsäure-trifluormethansulfonsäure- und -methansultonsäure-anhydride, Darstellung und Dissoziationstendenz. Chem Ber. 1983;116:1183–94.
20. M Korach, DR Nielsen, WH Rideout, Cyclopentenediol. Org Synth. 1962,42:50.
21. Kobayashi Y, Ito M, Igarashi J. Alkylation of 4-substituted 1-acetoxy-2-cyclopentenes by using copper reagents derived from alkylmagnesium halides and copper(I) cyanide. Tetrahedron Lett. 2002;43:4829–32.
22. Reichardt C. Solvents and Solvent Effects in Organic Chemistry. Weinheim: VCH; 1988.
23. Zhou T, Peters B, Maldonado MF, Govender T, Andersson PG. Enantioselective synthesis of chiral sulfones by ir-catalyzed asymmetric hydrogenation: a facile approach to the preparation of chiral allylic and homoallylic compounds. J Am Chem Soc. 2012;134:13592–5.
24. Chen J, Chen J, Xie Y, Zhang H. Enantioselective total synthesis of (−)-stenine. Angew Chem Int Ed. 2012;51:1024–7.
25. Palma A, Serginson JM, Barrett AG. Synthesis of poly β ketoesters via double acylketene trapping. Tetrahedron Lett. 2015;56:674–6.
26. Reetz MT, Chatziiosifidis I, Schwellnus K. Allgemeines Verfahren zur intramolekularen α-tert-Alkylierung von Carbonylverbindungen. Angew Chem. 1981;93:716–17.
27. Dauben W-G, Koch K, Smith S-L-, Chapman O-L. Photoisomerizations in the α-tropolone series: the mechanistic path of the α-tropolone methyl ether to methyl 4-Oxo-2-cyclopentenylacetate Conversion. J Am Chem Soc. 1963;85:2616–21.
28. Barbasiewicz M, Michalak M, Grela K. A new family of halogen-chelated Hoveyda–Grubbs-type metathesis. Catal Chem Eur J. 2012;18:14237–41.
29. Stille JR, Santarsiero BD, Grubbs RH. Rearrangement of bicyclo [2.2.1]heptane ring systems by titanocene alkylidene complexes to bicyclo[3.2.0]heptane enol ethers. Total synthesis of (. + −)-. DELTA.9(12)-capnellene. J Org Chem. 1990;55:843–62.
30. Bonnaud B, Mariet N, Vacher B. Preparation of conformationally constrained α2-antagonists: the bicyclo[3.2.0]heptane approach. Eur J Org Chem. 2006; 246–56.
31. Molander GA, Carey JS. Total synthesis of furanether B. An application of a [3 + 4] annulation strategy. J Org Chem. 1995;60:4845–9.
32. Magauer T, Mulzer J, Tiefenbacher K. Total syntheses of (+)-echinopine A and B: determination of absolute stereochemistry. Org Lett. 2009;11:5306–9.

33. Meier R, Trauner D. A synthesis of (±)-plydactone. Angew Chem Int Ed. 2016;55:11251–5.
34. Huisgen R, Mloston G, Polborn K, Sustmann R. 1,3-dithiolanes from cycloadditions of alicyclic and aliphatic thiocarbonyl ylides with thiones: regioselectivity. Chem Eur J. 2003;9:2256–63.
35. Huisgen R, Kalvinsch I, Li X, Mloston, G. The formation of 1,3-dithiolanes from aromatic thioketones and diazomethane—the mechanism of the schönberg reaction. Eur J Org Chem. 2000; 1685–94.
36. Kellogg RM. The molecules R2CXCR2 including azomethine, carbonyl and thiocarbonyl ylides. Their syntheses, properties and reactions. Tetrahedron. 1976;32:2165–84.
37. Hosomi A, Matsuyama Y, Sakurai H. Chloromethyl trimethylsilylmethyl sulphide as a parent thiocarbonyl ylide synthon. A simple synthesis of dihydro- and tetrahydro-thiophenes. J Chem Soc, Chem Commun. 1986; 1073–4.
38. Lan Y, Houk KN. Mechanism and stereoselectivity of the stepwise 1,3-dipolar cycloadditions between a thiocarbonyl ylide and electron-deficient dipolarophiles: a computational investigation. J Am Chem Soc. 2010;132:17921–7.
39. Terao Y, Tanaka M, Imai N, Achiwa K. New generation of thiocarbonyl ylide and its 1,3-cycloaddition leading to tetrahydrothiophene derivatives. Tetrahedron Lett. 1985;25:3011–4.
40. Terao Y, Aono M, Imai N, Achiwa K. Thiocarbonyl ylides. VI. New generation of thiocarbonyl ylides from organosilicon compounds containing sulfur and their 1,3-cycloadditions. Chem Pharm Bull. 1987;35:1734–40.
41. Terao Y, Aono I, Takahashi I, Achiwa K. Generation of Thioketene s-methylides and their 1,3-cycloadditions. Chem Lett. 1986;15:2089–92.
42. Aono M, Terao Y, Achiwa K. New method for generation of Thiocarbonyl Ylides from Bis(trimethylsilylmethyl)sulfoxides and their application to cycloadditions. Heterocycles . 1995;40:249–60.
43. Cherney RJ, et al. Conversion of potent MMP inhibitors into selective TACE inhibitors. Bioorg Med Chem Lett. 2006;16:1028–31.
44. Aono M, Hyodo C, Terao Y, Achiwa K. Generation of thiocarbonyl ylides with release of disiloxane from bis(trimethylsilylmethyl) sulfoxides. Tetrahedron Lett. 1986;27:4039–42.
45. Frostic FF Jr, Hauser C. Condensations of Esters by Diisopropylaminomagnesium Bromide and Certain Related Reagents. J Am Chem Soc. 1949;71:1350–2.
46. Stoll I, Flament M. Synthèse du « Propylure », phéromone sexuelle de Pectinophora gossypiella SAUNDERS. Helv Chim Acta. 1969;52:1996–2003.
47. Lehmann F, Holm M, Laufer S. Three-component combinatorial synthesis of novel dihydropyrano[2,3-c]pyrazoles. J Comb Chem. 2008;10:364–7.
48. Komine K, Nomura Y, Ishihara J, Hatakeyama S. Total synthesis of (−)-N-Methylwelwitindolinone C isothiocyanate based on a Pd-catalyzed tandem enolate coupling strategy. Org Lett. 2015;17:3918–21.
49. Kou KGM, et al. Syntheses of denudatine diterpenoid alkaloids: cochlearenine, N-Ethyl-1α-hydroxy-17-veratroyldictyzine, and paniculamine. J Am Chem Soc. 2016;138:10830–3.
50. Mineno M, Sawai Y, Kanno K, Sawada N, Mizufune H. Double reformatsky reaction: divergent synthesis of δ-hydroxy-β-ketoesters. J Org Chem. 2013;78:5843–5850.
51. Stamhuis EJ, Maas W. Mechanism of enamine reactions. II.[1] The hydrolysis of tertiary enamines. J Org Chem. 1965;30:2156–60.
52. Maas W, Janssen MJ, Stamhuis EJ, Wynberg H. Mechanism of enamine reactions. IV. The hydrolysis of tertiary enamines in acidic medium. J Org Chem. 1967;32:1111–5.
53. Van der Veen R-H, Geenevasen J-A-J, Cerfontain H. Reactions of α-aryl carbonyl compounds with lithium ester enolates. Can J Chem. 1984;62:2202–5.
54. Hanquet G, Salom-Roig XJ, Lemeitour S, Solladie G. Isomerisation of (E)-2-tetrahydrofurylidenealkanecarboxylic Esters and amides into their (Z) isomers by chelation control with metallated bases or Lewis acids. Eur J Org Chem. 2002; 2112–9.
55. Lin R, Cao L, West FG. Medium-sized cyclic ethers via stevens [1,2]-shift of mixed monothioacetal-derived sulfonium ylides: application to formal synthesis of (+)-laurencin. Org Lett. 2017;19:552–5.
56. Hauptmann H, Walter WF. The action of raney nickel on organic sulfur compounds. Chem Rev. 1962;62:347–404.
57. Rentner J, Kljajic M, Offner L, Breinbauer R. Recent advances and applications of reductive desulfurization in organic synthesis. Tetrahedron 2014;70:8983–9027.
58. Timmerman JC, Wood JL. Synthesis and biological evaluation of hippolachnin A analogues. Org Lett. 2018;20:3788–92.
59. Cernijenko A, Risgaard R, Baran PS. 11-step total synthesis of (−)-maoecrystal V. J Am Chem Soc. 2016;138:9425–9428.
60. Tian M, Yan M, Baran PS. 11-step total synthesis of araiosamines. J Am Chem Soc. 2016;138:14234–14237.
61. Rupcic Z, Chepkirui C, Hernández-Restrepo M, Crous PW, Luangsa-ard JJ, Stadler M. New nematicidal and antimicrobial secondary metabolites from a new species in the new genus, *Pseudobambusicola thailandica*. MycoKeys. 2018;33:1–23.