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Natural Products

A Modular Approach to the Antifungal Sphingofungin Family: Concise Total Synthesis of Sphingofungin A and C

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Abstract: *Sphingofungins are fungal natural products known to inhibit the biosynthesis of sphingolipids which play pivotal roles in various cell functions. Here, we report a short and flexible synthetic approach towards the sphingofungin family. Key step of the synthesis was a decarboxylative cross-coupling reaction of chiral sulfinyl imines with a functionalized tartaric acid derivative, which yielded the core motif of sphingofungins carrying four consecutive stereocenters and a terminal double bond. Subsequent metathesis reaction allowed for the introduction of different side chains of choice resulting in a total of eight sphingofungins, including for the first time sphingofungin C (eight steps from commercially available protected tartaric acid with an overall yield of 6 %) and sphingofungin A (ten steps). All newly synthesized derivatives were tested for their antifungal, cell-proliferative and antiparasitic activity unraveling their structure–activity relations.*

Introduction

Sphingolipids (SL) are integral parts of cell membranes and play a crucial role in a plethora of cell processes such as lipid raft stability, cell signaling and cell–cell recognition.[1,2] Disbalance in the sphingolipidome has been linked to various diseases (sphingolipidoses, cancer, immune and metabolic disorders), and there have been multiple attempts to hijack the biosynthesis of SL for therapeutic purposes.[3,4] Modulators of SL biosynthesis were identified as promising pharmaceutical leads with fingolimod as structural analog of sphingosine-1-phosphat, the first oral disease-modifying drug against multiple sclerosis.[5] Similarly, modulators of the de novo sphingolipid biosynthesis have been intensively investigated, such as inhibitors of the enzyme serine palmitoyltransferase (SPT), which catalyzes the condensation of the amino acid serine with palmitoyl-CoA to yield 3-ketodihydrosphingosine (Figure 1 A,B).[2] The most potent SPT inhibitors were isolated from different microbial sources, including the amino-acid-containing lipid lipoxamycin from *Streptomyces virginiae* (1971),[6] the fungal metabolite myriocin (1972),[7] and sphingofungins from *Aspergillus fumigatus* (1992) by VanMiddlesworth et al.[8,9] Later, several additional members of the sphingofungin family were reported from other fungal species, such as sphingofungin E and F (*Paecilomyces variotii*)[10] or the recently reported lactones sphingofungin G and H (*Aspergillus penicilliodes*).[11] Myriocin and sphingofungins are structurally related and composed of a hydrophilic part that contains an amino acid and a triol motif leading to four consecutive stereocenters, and a lipophilic aliphatic tail carrying a double bond at position C-6 and oxygen at position C-14 (Figure 1 A).[2] While sphingofungin A to D mainly differ in the position of the acetyl and guanin group, respectively, sphingofungins E and F contain a quaternary stereo center at the α-position, and a keto functionality at C-14. Due to their intriguing structural features and important pharmacological properties, sphingofungins became quickly popular total synthetic targets. Until today, 14 distinct synthetic strategies have been applied in the total synthesis of sphingofungins B, D, E, and F,[12–36] with the last syntheses of sphingofungin E and F being reported in 2017 by Noda et al.[35] and Sugai et al.[36] in 2018 (Figure 1 C). Despite these tremendous achievements, most synthetic routes require ten or more synthetic steps in the longest linear synthetic sequence and often require the preparation of elaborate starting materials as well as several protecting group transformation steps causing very low overall yields. In addition, the syntheses of sphingofungin A, C, G, and H remained elusive until today. Thus, access to material and derivatives for biological and biochemical studies has been a limiting factor and hampered further progress in understanding the biology and functions of this compound class.

Encouraged by today's high scientific interest in sphingolipid metabolism and bioactivities,[2] we started to investigate a new and flexible synthetic approach towards sphingofungins. Here, we report the successful implementation of a decarboxylative cross-coupling strategy in the total synthesis of sphingofungins, which resulted in one of the shortest and most flexible approaches towards sphingofungins yielding synthetic access to eight different sphingofungins including

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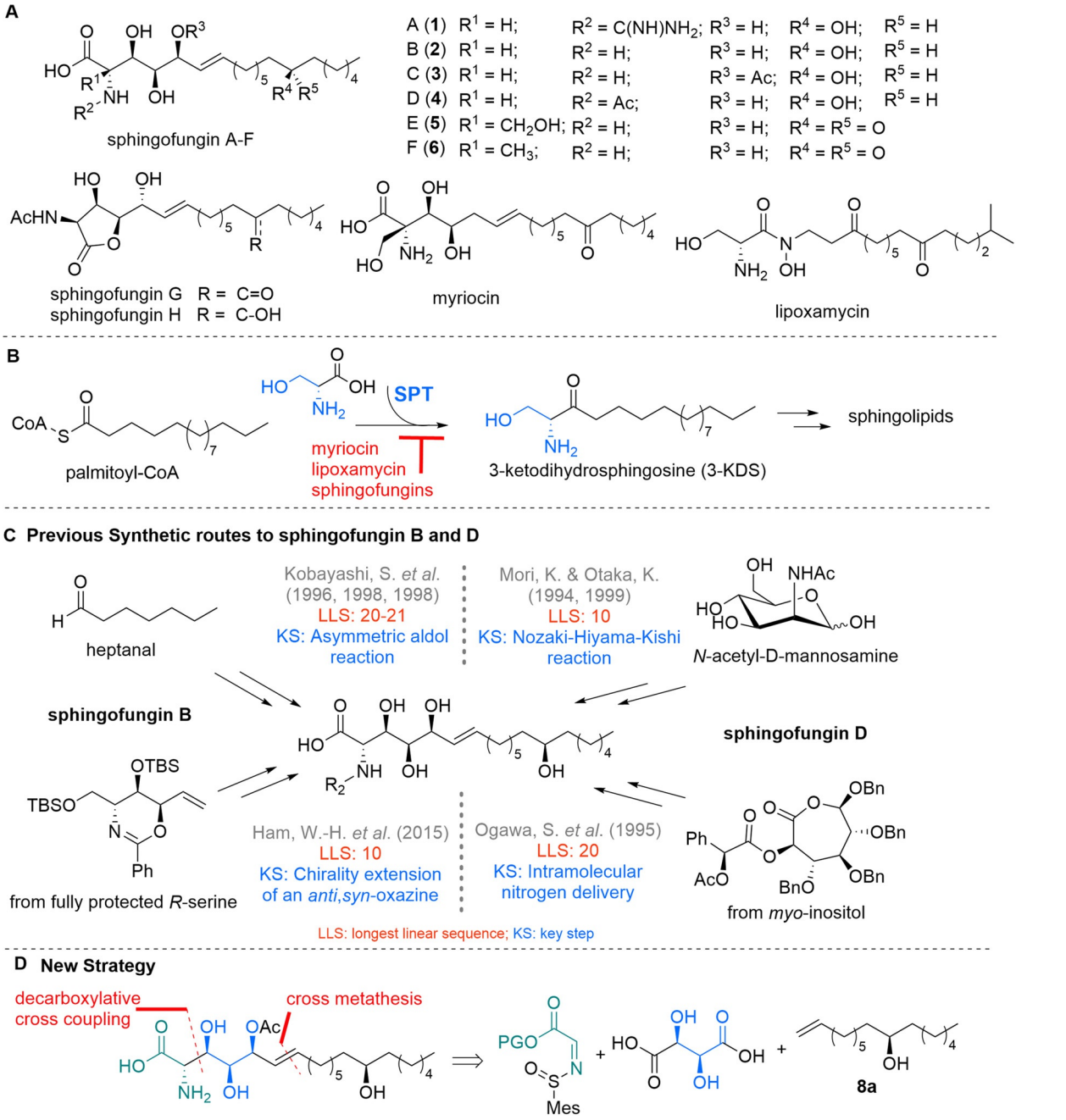


Figure 1. A) Chemical structures of all known members of the sphingofungin family, myriocin and lipoxamycin (inhibitors of the pyridoxal phosphate (PLP)-dependent serine palmitoyltransferase (SPT)). B) First step of sphingolipid biosynthesis: condensation of L-serine and palmitoyl-CoA mediated by a SPT homolog yielding 3-ketodihydrosphingosine (3-KDS). SPT activity is inhibited by fungal natural products such as myriocin and lipoxamycin. C) Previous synthetic approaches towards sphingofungin B and D showing key substrates, key steps, and summary of synthetic steps. D) New strategy showing retrosynthetic considerations and key synthetic building blocks. Mes-: mesityl-.

sphingofungin A and C for the first time. All synthesized sphingofungin derivatives were evaluated in antifungal, cell proliferative, and antiparasitic bioassays, unraveling their structure–activity relations.

Results and Discussion

We chose sphingofungin C (**3**) as the first synthetic target, which should then be transformed to other yet not synthesized sphingofungins A, B, and D. The synthesis of sphingofungin C itself requires not only the installation of four consecutive stereogenic centers but also the need to overcome the intrinsic reactivity of the polar sphingofungin head group and the introduction of acid-labile protecting groups to

avoid the migration of the acetyl ester of sphingofungin C (**3**) under basic conditions.[8,9] Inspired by seminal work reported by Weix[37] and Baran,[38–41] we envisaged to apply a decarboxylative cross-coupling strategy using sulfinyl imine **7** and D-tartaric acid to build the functionalized head group of sphingofungins (Figure 1D).

Subsequent introduction of the aliphatic tail (**8a**) via metathesis reaction[42] would allow the introduction of structural diversity at a late stage of the synthesis and afford sphingofungin C in less than ten synthetic steps.

Decarboxylative Cross-Coupling Reaction. We commenced our synthesis of sphingofungin C by preparing chiral sulfinyl imines (*R*)-**7** and (*S*)-**7** from freshly prepared *tert*-butyl glyoxylate **9**[43] and sulfinyl amines (*R*)-**10** and (*S*)-**10**[44] in 84% and 86% yield, respectively (Scheme 1A). Next, we focused on the preparation of the required coupling partner **13** carrying three out of the four stereogenic centers. Starting from literature-known Weinreb amide **11**, which was obtained in one step from commercially available fully protected D-tartaric acid, allyl alcohol **12** was prepared in only two steps and 61% yield using a modified procedure requiring only one purification step (Scheme 1B).[45,46] Here, it is noteworthy that the stereoselective reduction of the α,β-unsaturated ketone in the reaction sequence was achieved with high diastereoselectivity only if an excess of $NaBH_4$ was used, which contrasts previously reported conditions (excess of $CeCl_3$).[45] Next, the Weinreb amide of **12** was saponified and the secondary alcohol subjected to acetylation, which afforded acid **13** in almost quantitative yield after two steps (Scheme 1C). With both cross-coupling partners in hand, we explored different procedures to generate the required redox-active esters (RAE) in situ. As previous reports indicated that RAEs derived from tartaric acid are by nature intrinsically unstable,[38–41] we aimed for a one-pot procedure to optimize yields of the coupling reaction. Overall, the use of 1,1,3,3-tetramethyl-2-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)isouronium-hexafluorophosphate(V) (CITU) as an activating agent[47] and a specific addition sequence of reagents yielded (2*S*)-**14** and (2*R*)-**14**, respectively, as single diastereomer in good yields (52% and 54%, without detectable isomers).

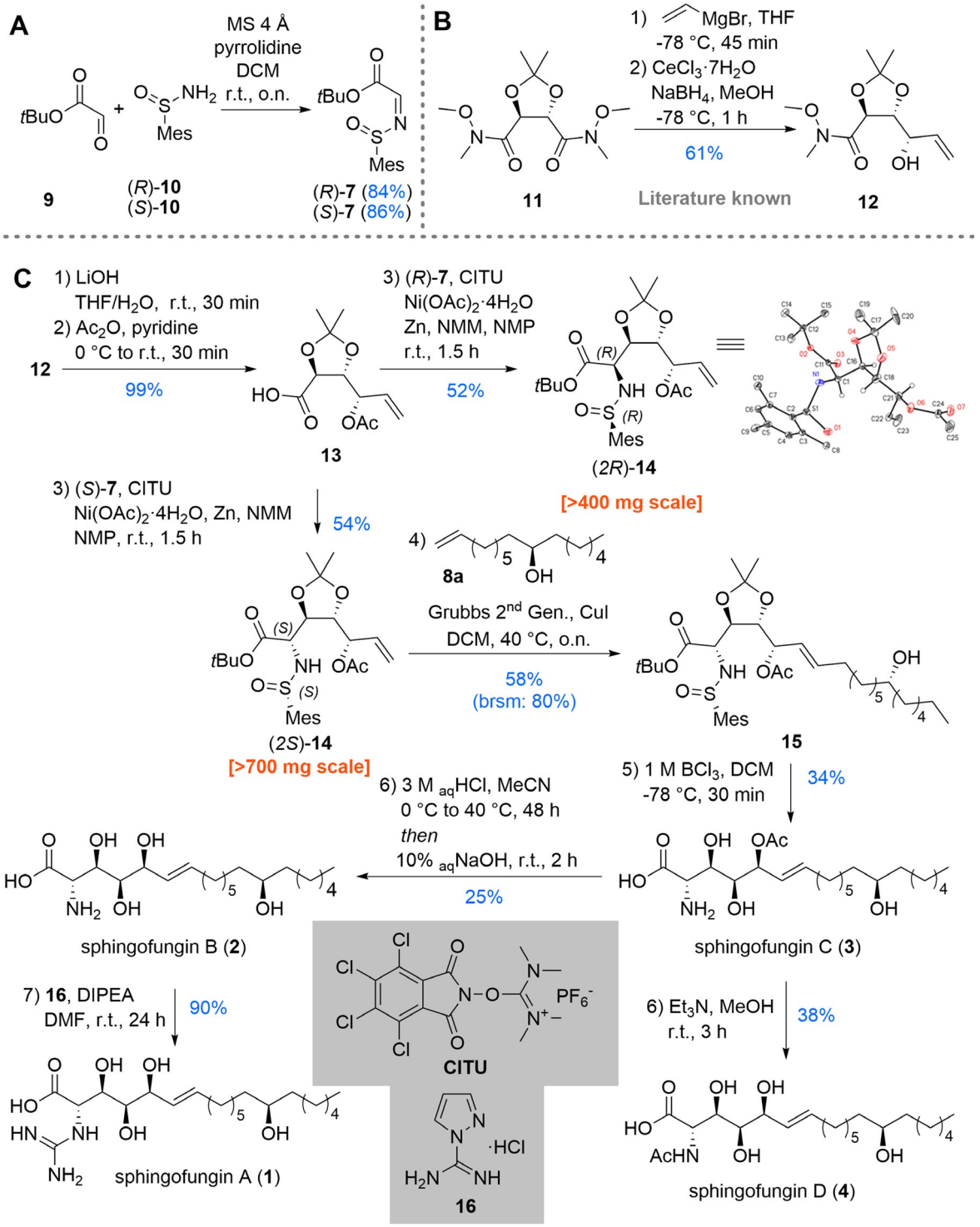
Using optimized reaction conditions, we were able to synthesize more than 400 mg of the coupling product in one batch ((2*R*)-**14**: 439 mg and (2*S*)-**14**: 774 mg). Although literature evidence suggested that the decarboxylative coupling of similar substrates proceeded under retention of the stereochemistry at the radical forming position,[39,40,48] we pursued the crystallization of diastereomers of **14** from a mixture of 2-propanol and water to prove that the stereochemistry at the 3-position remained unchanged in our reaction. While we were not able to obtain suitable single crystals of diastereomer (2*S*)-**14**, single-crystal diffraction of (2*R*)-**14** proved that indeed the proposed (2*R*,3*R*,4*R*,5*S*)-configuration was obtained (Scheme 1C).[49]

These findings raised again the intriguing question about the mechanism of the coupling reaction. Based on previous studies, we assume that after the formation of **A** the RAE is decarboxylated after single electron transfer (SET) from Ni^I species and/or Zn^0 (Figure 2).[39,40] Upon fragmentation (**B**) and release of tetrachlorophthalimide and CO_2, the carbon-centered dioxolane radical (**C**) formally loses its stereochemistry at the radical position. However, upon coupling with imine **7**, the previously lost stereochemistry is reinstated. We propose two main effects that might cause the *anti*-selective radical addition yielding **14** as similar selective reactivity of tartaric acid radicals has already been reported by Barton et al.[50,51] Firstly, orbital interactions of the singly occupied molecular orbital and the non-bonding electron pair of the neighboring oxygen likely stabilize conformations of the five-membered ring (Figure 2, red),[48] and secondly, the bulky substituent might direct the coupling reaction to the opposite side of the dioxolane ring (Figure 2, gray).[50,51] Here it should be mentioned that other studies involving different methods of radical formation (e.g. photochemically, transition-metal-mediated) and reactions with various radical acceptors (e.g. Giese-type reactions, organometals, phosphines) showed similar diastereoselective results.[50–53] In analogy to previous DFT calculations on similar substrates, we further assume that the conformation of the imine coupling partner is locked by hydrogen bonding (Figure 2, purple) between the sulfinyl oxygen and the imine hydrogen, which allows the radical to attack only from the more accessible side of the imine.[54,55] Finally, the reduction of the resulting nitrogen-centered radical leads to a single diastereomer of sulfinyl amine **14**.

Motivated by our findings, we finalized the synthesis of sphingofungin C. First, diastereomer (2*S*)-**14** was reacted with alkene **8a** using Grubbs 2nd generation catalyst[56] to afford fully protected sphingofungin C (**3**). To achieve a satisfying yield, the metathesis reaction required the addition of Grubbs catalysts in small portions over a period of eight hours and the presence of copper iodide as co-catalyst.[57] The last and critical step in the synthesis was the global deprotection of **15**. Here, numerous different conditions were tested (Table S1) and gratifyingly treatment of **15** with a BCl_3 solution at −78 °C yielded sphingofungin C with matching spectroscopic data. Overall, we accomplished the first synthesis of sphingofungin C (**3**) in five steps from literature-known Weinreb amide (**12**) in 11% yield.

Encouraged by these results, we then set out to synthesize other sphingofungin derivatives that are also likely biosynthetically derived from sphingofungin C. First, sphingofungin D (**4**) was obtained by treating sphingofungin C with triethylamine in 38% yield (an enzymatic deacetylation of sphingofungin D was previously reported by VanMiddlesworth et al.)[8,9] The synthesis of sphingofungin B from sphingofungin C was achieved in one-pot by first removal of the acetyl group under acidic conditions yielding a mixture of the lactone and methyl ester, which was then directly hydrolyzed with 10% $_{aq}$NaOH to yield sphingofungin B (**2**). Subsequent introduction of the guanylated amine using 1*H*-pyrazole-1-carboxamidine hydrochloride[58] **16** yielded sphingofungin A (**1**) in 90% yield.

A detailed literature survey revealed that none of the previous reports provided sufficient spectroscopic evidence of the claimed structure of sphingofungin A (**1**) making our report the first containing a full spectroscopic characterization of this derivative.[8,9] Finally, we exploited our modular synthetic approach and synthesized four additional sphingo-



Scheme 1. A) Synthesis of both sulfinyl imines enantiomers. B) Synthesis of Weinreb amide precursor. C) Total synthesis of sphingofungin A–D with ORTEP representation of (2*R*)-**14**. Mes-: mesityl-; Ac-: acetyl; MS: molecular sieves; DCM: dichloromethane; r.t.: room temperature; o.n.: overnight; THF: tetrahydrofuran; CITU: 1,1,3,3-tetramethyl-2-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)isouronium-hexafluorophosphate(V); NMM: *N*-methylmorpholine; NMP: *N*-methyl-2-pyrrolidon; Grubbs 2nd gen.: Grubbs 2nd generation catalyst (CAS: 246047-72-3); MeCN: acetonitrile; DIPEA: *N*,*N*-diisopropylethylamine; DMF: dimethylformamide.

fungin C derivatives (including 2-*epi* sphingofungin C (**18a**)) following the above-described procedure (Scheme 2).

Sphingofungins are known for their high inhibitory activity against the eukaryotic enzyme SPT,[2,3] and we were able to verify the activity of all derivatives against *C. albicans* and *A. fumigatus* (Table S5, S6). We then evaluated if sphingofungins have antiproliferative and antiparasitic activity (Table 1) as most single-celled eukaryotic parasites that

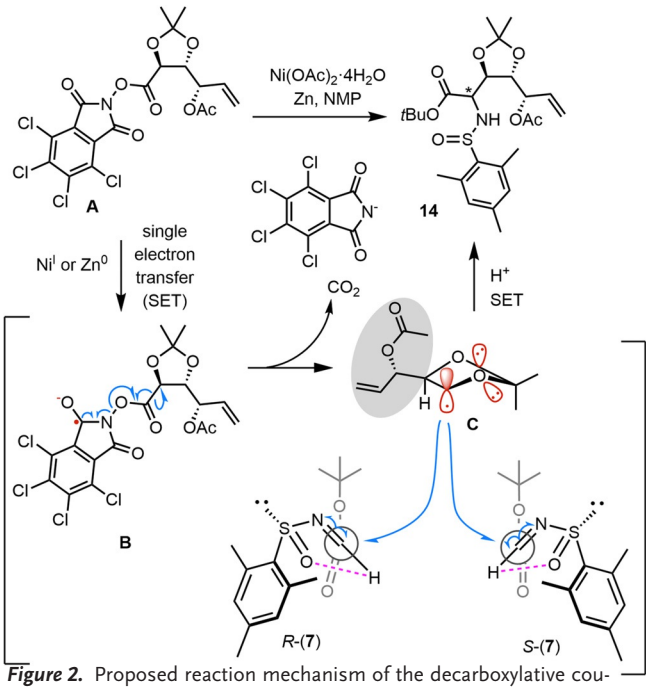
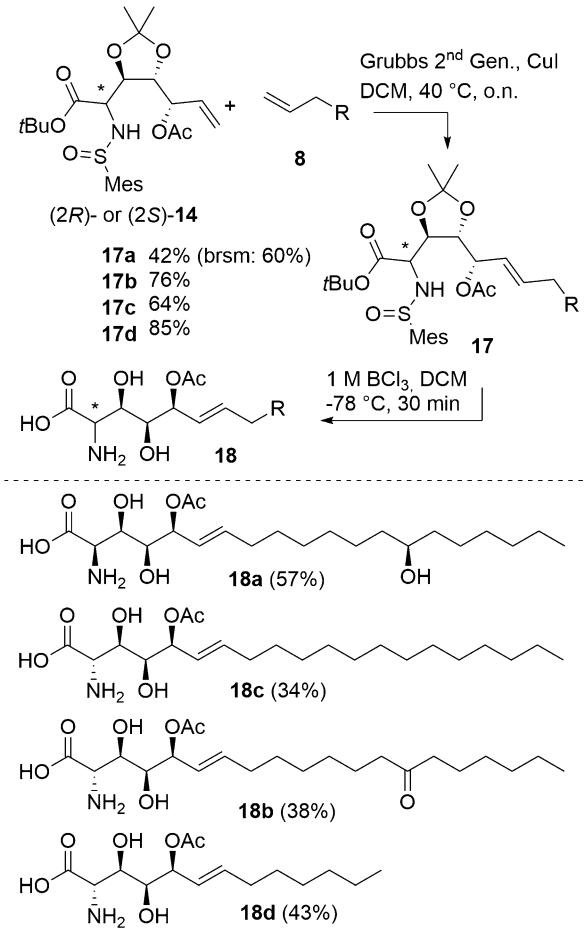


Figure 2. Proposed reaction mechanism of the decarboxylative coupling of activated form (**A**) of tartaric acid derivative **13** with sulfinyl imine **7**. SET: single electron transfer; NMP: *N*-methyl-2-pyrrolidon.



Scheme 2. Synthesis of unnatural sphingofungin derivatives. Grubbs 2nd gen.: Grubbs 2nd generation catalyst (CAS: 246047-72-3); Mes-: mesityl-; DCM: dichloromethane.

are responsible for several neglected tropical diseases such as malaria (*Plasmodium falciparum*), chagas (*Trypanosoma cruzi*), sleeping sickness (*Trypanosoma brucei rhodesiense*), or leishmaniasis (*Leishmania* spp.) carry SPT homologs.[59] To our delight, moderate antiprotozoal activity was observed against *T. b. rhodienses* in case of sphingofungin B (entry 2). Even more promising results were obtained against *P. falciparum* with **2** being the most active compound (1.6 μg mL^{-1}) followed by sphingofungin A (entry 1, 3.7 μg mL^{-1}), C (entry 3, 4.2 μg mL^{-1}), and D (entry 4, 8.6 μg mL^{-1}). Interestingly, epimer **18a** (entry 5, 2.4 μg mL^{-1}) exhibited higher inhibitory activity than the natural diastereomer (entry 3). Furthermore, unnatural derivatives lacking the hydroxy group (**18b** and **18d**, entry 6 and 7) showed the overall lowest activity, indicating that the hydroxy group at C-14 is likely a crucial component for the activity against *P. falciparum*. In all cases none of the compounds exhibited cell-proliferative or cytotoxic activity.

Table 1: Evaluation of antiparasitic activity of sphingofungins. IC_{50} in μg mL^{-1}.

Entry	Compound	IC_{50} *T. b. rhodesiense*[a]	IC_{50} *T. cruzi*[b]	IC_{50} *L. donovani*[b]	IC_{50} *P. falciparum*[c]
1	**1**	22.9	35.7	17.4	3.7
2	**2**	5.95	41.9	32.5	1.6
3	**3**	66	63.8	>100	4.2
4	**4**	58.3	55.7	65.6	8.6
5	**18a**	58.5	53.7	>100	2.4
6	**18b**	33.3	62.4	>100	13.0
7	**18d**	66.8	66.5	>100	10.1
8	**pc**	0.006[d]	0.484[e]	0.469[f]	0.004[g]

[a] Trypomastigotes. [b] Amastigotes. [c] Intraerythrocytic forms. [d] Melarsoprol. [e] Benznidazole. [f] Miltefosine. [g] Chloroquine.

Conclusion

In summary, we developed a short and flexible synthesis of sphingofungins A–D and derivatives thereof by combining a versatile decarboxylative coupling reaction and a cross-metathesis protocol to quickly establish the demanding stereochemistry of sphingofungins and introduce structural diversity at a late stage. The flexible approach led to the first total synthesis of sphingofungin C (**3**) in five steps from literature-known Weinreb amide **12** (overall yield of 11%), thus requiring in total only eight synthetic steps (overall yield of 6%) when starting from commercial building blocks. Furthermore, our concise route also allowed for the shortest synthesis of sphingofungin B and D (**2** and **4**) yet reported requiring only nine synthetic steps from commercially available starting material with overall yields of 1–2%. The first synthesis of sphingofungin A (**1**) was accomplished in ten steps and also allowed for the first complete spectroscopic characterization of this compound. All sphingofungin derivatives were verified to have the expected antifungal proper-

ties and we demonstrated for the first time their antiparasitic properties. Our synthetic strategy exemplifies the power and flexibility of decarboxylative coupling reactions and the applicability in natural product chemistry.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: antiparasitic activity · cross coupling · natural products · sphingofungins · total synthesis

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