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Asymmetric total syntheses of sarglamides A, C, D, E, and F†

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Sarglamides A–E were identified as a structurally new class of alkaloids with potential application for inflammation-associated diseases. Reported is the first asymmetric total synthesis of sarglamides A, C, D, E, and F within 7 steps, featuring an intermolecular Diels–Alder cycloaddition of (*S*)-phellandrene and 1,4-benzoquinone and intramolecular (*aza*-)Michael addition to construct the tetracyclic core of sarglamides. Importantly, our work demonstrated that the hypothetical Diels–Alder reaction of α -phellandrene with dienophile toussaintine C (or analogues) originally proposed as a biosynthetic pathway was not viable under non-enzymatic conditions. Additionally, we discovered novel and efficient double cyclization (cycloetherification and oxa-Michael cyclization) to construct the core framework of sarglamides E and D. Our concise synthetic strategy might allow rapid access to a library of sarglamide analogues for further evaluation of their bioactivity and mode of action.

Introduction

Sarglamides A–E¹ (Fig. 1a) were identified in 2023 by Yue *et al.* from the plants of genus *Sarcandra*, which have been used as traditional Chinese medicines for treatments of inflammation and physical injuries. Sarglamides C–E were found to inhibit NO production against lipopolysaccharide-induced inflammation in BV-2 microglial cells at 10–20 μ M concentrations without obvious cytotoxicity. Structurally, sarglamides are the first examples of natural products derived from heterodimerization of α -phellandrene and *trans*-*N*-cinnamoylindolinoids, which was suggested to be the biosynthetic pathway for the formation of sarglamides. The endo-selective intermolecular Diels–Alder (DA) reaction of α -phellandrene and toussaintine C² well rationalizes the tetracyclic core and relative stereochemistry of sarglamides (Fig. 1b). Sarglamides D and E might be biosynthetically derived from 1'',7- or 1'',4-cycloetherification of sarglamide C. The unprecedented caged pentacyclic skeleton of sarglamide E along with the inspirational biosynthetic hypothesis of sarglamides A–C prompted our interest in their total synthesis.

Inspired by the proposed biosynthetic hypothesis, we set out to investigate the “straightforward” intermolecular Diels–Alder reaction of α -phellandrene (6a) and *N*-tosyl-5,6-dehydro-4-hydroxyindolidin-7-one (7f, the analogue of toussaintine C) (Scheme 1a). Surprisingly, the Diels–Alder reaction did not

occur under either classical Lewis acid (Et₂AlCl or BF₃·Et₂O) or thermal conditions (200 °C). We suspected that the tertiary hydroxy group from 7f presented a significant steric interaction with the diene moiety of α -phellandrene (6a) as suggested in the transition state in Fig. 1b. Under harsh conditions, appreciable decomposition of 7f was observed. This unexpected failure drove us to re-examine this type of DA reaction more systematically. Literature survey revealed that only a few reports^{3–5} documented the intermolecular Diels–Alder reactions of cyclohexa-1,3-dienes and cyclohexenone derivatives (Scheme 1b) and the inherent challenge was uncovered with poor yield under thermal conditions (30% yield)⁴ or protic acid catalysis (0% yield).³ It was recognized that the reactivity of

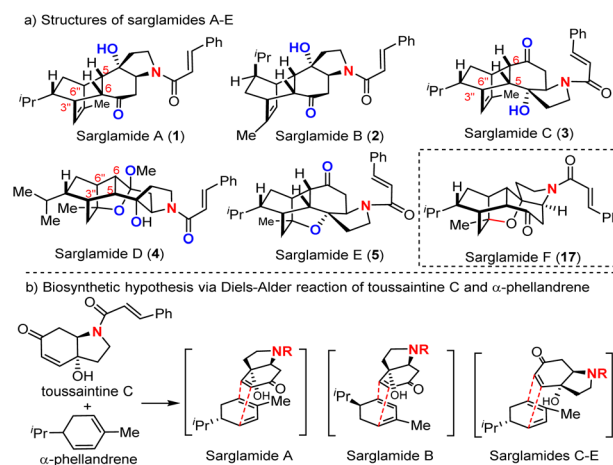
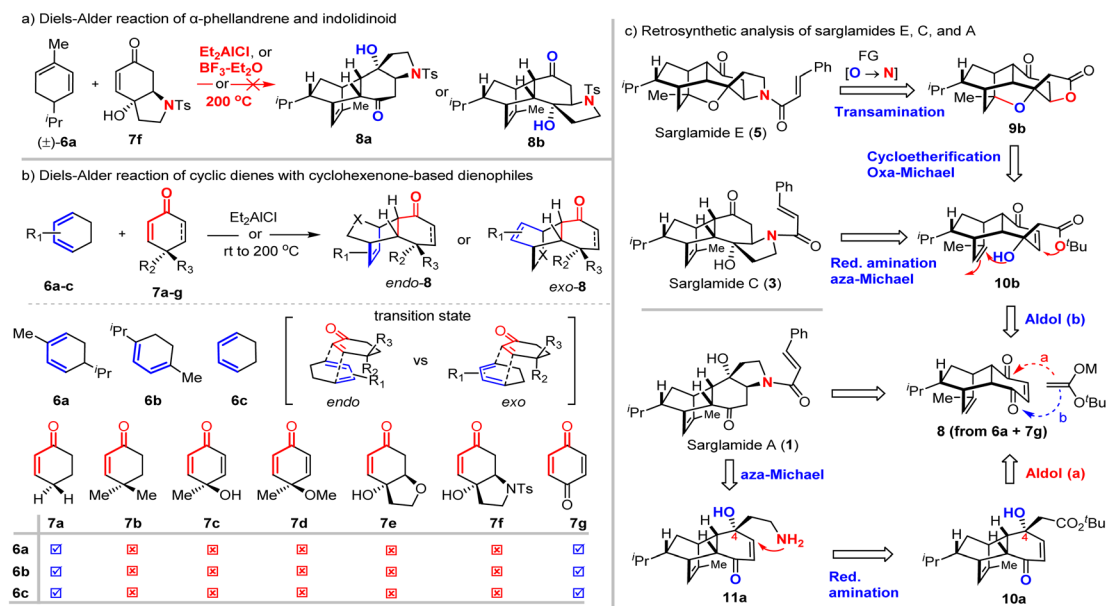


Fig. 1 (a) Molecular structures of sarglamides A–E and (b) their biosynthetic hypothesis involving the Diels–Alder reaction (transition states are provided).

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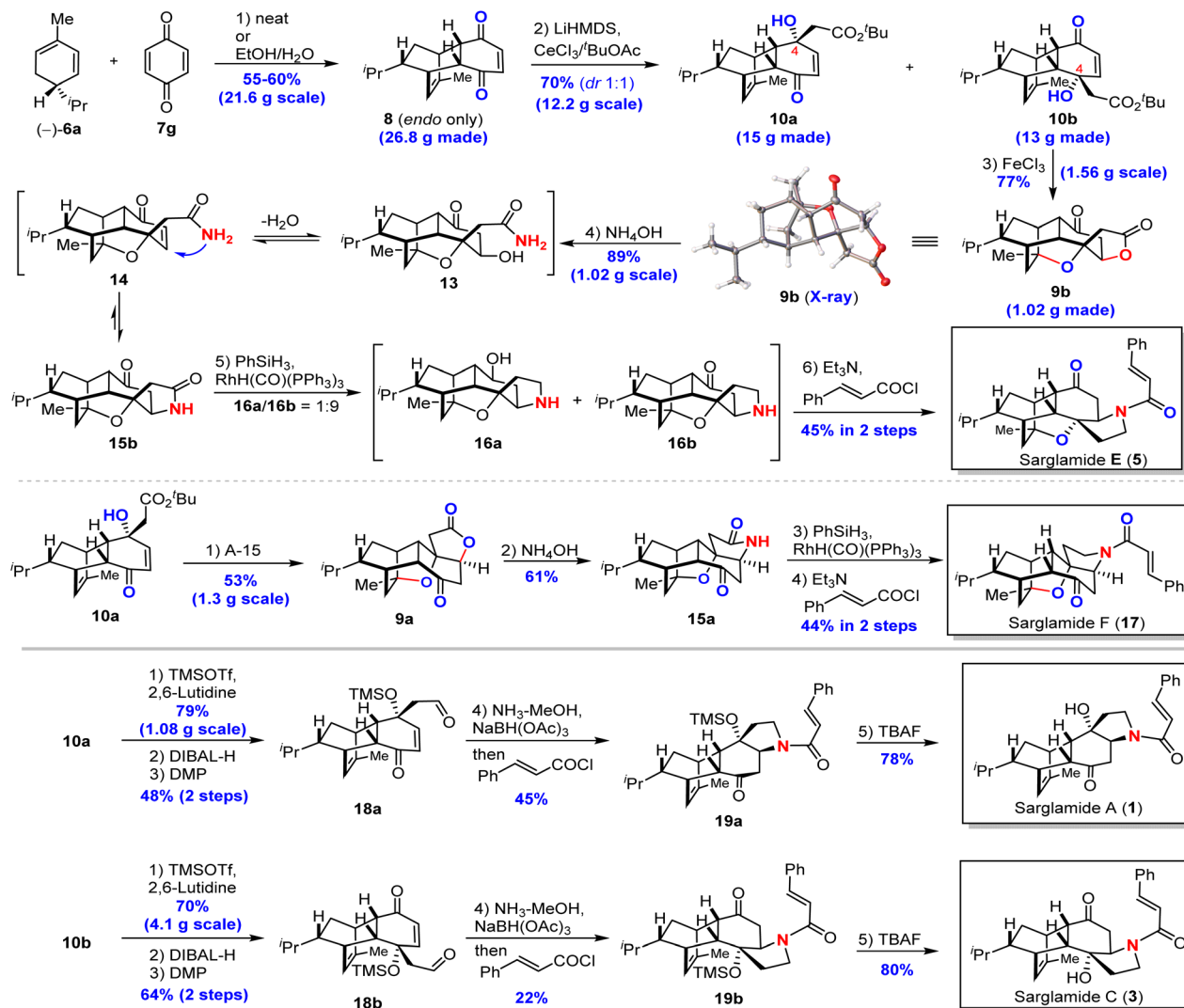


Scheme 1 (a) Diels-Alder reaction of α -phellandrene (**6a**) and *N*-tosyl-5,6-dehydro-4-hydroxyindolidin-7-one (**7f**), (b) Diels-Alder reaction of cyclohexadienes and cyclic dienophiles, and (c) our synthetic strategy towards sarglamides A, C and E.

cyclopentadiene as a diene for the DA reaction was much higher than that of cyclohexadiene: TfOH promoted the reaction of cyclopentadiene and cyclohexanone in 65% yield while no reaction occurred under identical conditions for cyclohexadiene.³ Since our targets (sarglamides) required the use of cyclohexadiene (α -phellandrene) as the diene for the DA reaction, we sought appropriate cyclohexene-containing dienophiles. We performed a study of the DA reaction of cyclohexadiene **6a-c** and dienophiles **7a-7g** under either Lewis acid or heating conditions (Scheme 1b). It was found that only **7a** (cyclohexenone) and **7g** (*p*-benzoquinone) could react with cyclohexadienes **6a-c**. This success might be attributed to an effective minimization of the steric repulsion between R_2 and diene in the transition state when R_2 was hydrogen (**7a**) or R_2/R_3 were ketonic oxygen (**7g**). In the case of R_2 being a methyl (**7b-d**) or hydroxyl (**7c**, **7e** and **7f**) group, the severe steric repulsion between R_2 and diene prevented the Diels-Alder reaction. Notably, *p*-benzoquinone (**7g**) as the dienophile for the Diels-Alder reaction was historically significant as the very first example investigated by Diels and Alder.^{6,7} On the basis of these preliminary results, we re-designed our synthetic strategy towards sarglamides and focused on the most structurally complex E by exploiting the Diels-Alder reaction of α -phellandrene (**6a**)⁸ and the structurally planar *p*-benzoquinone (**7g**) as depicted in Scheme 1c. Sarglamide E could be synthesized from pentacyclic compound **9b**. Transamination⁹ or aminolysis¹⁰⁻¹⁶ of lactone **9b** followed through a late-stage amidation with cinnamoyl chloride. We envisioned that acid promoted cycloetherification¹⁷⁻²³ and *cis*-selective *oxa*-Michael cyclization²⁴⁻²⁸ of **10b** might occur to provide the key pentacyclic lactone **9b**. The substrate for such cascade double cyclization could be obtained by the acetate aldol reaction of **8** (path b) that was readily available from the Diels-Alder reaction of α -

phellandrene (**6a**) and *p*-benzoquinone (**7g**). We also recognized that the structurally less complex sarglamide C could be obtained from **10b** if the alcohol was protected to thwart cycloetherification. Reduction of the ester **10b** into aldehyde followed by reductive amination²⁹⁻³² might trigger the intramolecular *aza*-Michael addition³³⁻³⁷ to afford the tetracyclic framework of sarglamide C. If the acetate aldol reaction of **8** proceeded through pathway a or in a nonselective fashion, **10a** might be obtained and elaborated to sarglamide A through similar reductive amination (**11a**), *aza*-Michael addition, and amidation with cinnamoyl chloride. Our synthesis started with the intermolecular Diels-Alder reaction of enantio-enriched (*S*)-(+)- α -phellandrene (**6a**) and 1,4-benzoquinone (Scheme 2). Since (*S*)-(+)- α -phellandrene (**6a**) was expected to deliver the corresponding correct stereochemistry of sarglamides but was not commercially available, it was prepared from (*R*)-(-)-carvone through selective hydrogenation and the Shapiro reaction^{38,39} (see the ESI† for details). The Diels-Alder reaction of sublimated 1,4-benzoquinone occurred smoothly under solvent-free conditions at room temperature to provide the desired cyclization adduct **8** in 60% yield (gram scale, >4.9 g obtained) with exclusive *endo* selectivity. For the reaction at a larger scale (200 mmol), the reaction needed to be carried out in reflux EtOH/H₂O to afford comparable yields. The aldol reaction of **8** and ^tbutyl acetate/LiHMDS was achieved with 70% yield in a non-regioselective manner with the assistance of CeCl₃, which was believed to improve the nucleophilicity of lithium enolate.^{40,41} Due to the poor solubility of CeCl₃ in THF, the maximum scale for this aldol reaction was 12.2 g of **8**. The resulting stereoisomers **10a** and **10b** were separated by column chromatography on silica gel, determined at the late stage, and used for the synthesis of sarglamides A/F and C/E, respectively. The stereoisomer **10b** was subjected to the conditions optimized for



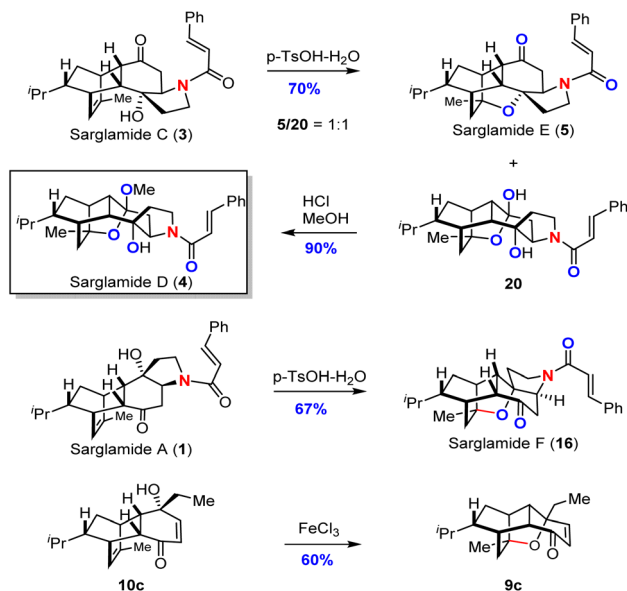


Scheme 2 Asymmetric total syntheses of sarglamides A, C, E, and F.

double cyclization (cycloetherification^{42,43} and *oxa*-Michael cyclization⁴⁴). Examination of different acid promoters led to the identification of iron(III) chloride (FeCl₃) as the optimal acid for the double cyclization to provide pentacyclic **9b** in 77% yield. Other acid promoters including Amberlyst-15, BF₃·Et₂O, TMSOTf, and TBSOTf gave similar results (see the ESI† for details). The relative and absolute configuration of pentacyclic **9b** was confirmed by X-ray diffraction analysis (CCDC 2358359). Transamination of lactone **9b**: replacement of “O” with “NH” was successfully achieved with 89% yield by using ammonium hydroxide (NH₄OH) at room temperature, which was believed to involve aminolysis^{45,46} of lactone (**13a**), dehydration (**14**) and intramolecular *cis*-selective *aza*-Michael addition (**15b**). Reductive deoxygenation of lactam **15b** with silane could be achieved with rhodium catalysis^{47–49} when the reaction time was well controlled to minimize the competing reduction of the ketonic group into alcohol (**16a**). Subsequent amidation completed the total synthesis of sarglamide E in only 6 steps with 14.38% overall yield. The spectroscopic data of our synthetic sample

were well in agreement with those reported for the natural sarglamide E.¹ The isomer **10a** was found to undergo similar cycloetherification/*oxa*-Michael cyclization under protic acid conditions (Amberlyst-15) to provide pentacyclic **9a** in 53% yield, which was elaborated in an identical 3-step sequence to sarglamide F (**17**), a compound that has not yet been identified from the natural source but shares the pentacyclic structural framework of sarglamide E. Next, we set out to elaborate the acetate aldol product **10a/b** into sarglamides A/C, respectively. Our strategy was exploiting cascade reductive amination and intramolecular *aza*-Michael addition⁵⁰ to construct the pyrrolidine moiety (**18a/b** → **19a/b**). To this end, the tertiary alcohol of **10a/b** was protected as trimethylsilyl ether (without the protection, the *retro*-aldol reaction occurred during the reduction) and DIBAL-H reduction and Dess–Martin periodinane⁵¹ (DMP) oxidation delivered the desired aldehyde **18a/b**. The cascade reductive amination/intramolecular *aza*-Michael addition⁵⁰ was successful but low yields were obtained (45% and 22% yield, respectively). Attempts to improve the yield of this





Scheme 3 Cycloetherification of sarglamides A and C and compound 10c.

cascade reaction proved fruitless. A major side-product was isolated, but its structure could not be fully determined. We suspected that the ammonia mediated (*aza*-)Morita–Baylis–Hillman reaction^{52–54} might effectively compete with reductive amination/*aza*-Michael addition. The resulting pyrrolidine was unstable and used without purification for subsequent amidation with cinnamoyl chloride (**18a/b** → **19a/b**). Desilylation of **19a/b** could afford sarglamides A and C, respectively. All spectroscopic data of our synthetic samples were in good agreement with those of natural sarglamides A and C.¹

It was noted that sarglamide C could be converted into sarglamides E and D under acidic conditions through cycloetherification,¹ which implied their possible biosynthetic relationship or artifact of sarglamides E/D. We were intrigued by such transformation and performed the cycloetherification of sarglamide C with *p*-TsOH and isolated sarglamide E (35% yield) and compound **20** (35% yield), which upon treatment with HCl/MeOH resulted in production of sarglamide D (90% yield) (Scheme 3). Similarly, *p*-TsOH triggered the cycloetherification of sarglamide A to furnish sarglamide F (67% yield). When **10c** was treated with FeCl₃, cycloetherification occurred to provide **9c** in 60% yield. These findings unveiled that the pyrrolidine moiety as a *cis*-fused ring was not essential for the cycloetherification and the caged conformation of the tricyclic framework might be responsible for the high efficiency of the cycloetherification.^{17–23}

Conclusion

In summary, we have accomplished the first asymmetric total syntheses of sarglamides A, C, D, E, and F in 6 or 7 steps. Our study revealed that the straightforward biosynthetic hypothesis involving the Diels–Alder reaction of α -phellandrene and tous-saintine C (*N*-cinnamoyl-5,6-dehydro-4-hydroxyindolidin-7-one)

did not occur under either acid catalysis or thermal conditions. We strategically designed the Diels–Alder reaction of α -phellandrene and planar 1,4-benzoquinone and one-pot sequential reductive amination/*aza*-Michael cyclization/amidation to construct the tetracyclic core of sarglamides. Importantly, new cascade cyclization involving cycloetherification and *oxa*-Michael cyclization is developed, which enables the 6-step total synthesis of sarglamides E and F. The biomimetic cycloetherification of sarglamide C to sarglamides D and E as well as sarglamide A to F is successfully achieved with biosynthetic implications. We believe that our concise synthetic strategy might be applicable to the facile synthesis of a library of structurally related compounds for bioactivity evaluation.

Data availability

Experimental procedures and characterization data are available within this article and its ESI.† Data are also available from the corresponding author on request.

Author contributions

R. K. and Y. W. performed the synthetic experiments. R. T. conceptualized and directed the project and drafted the manuscript with the assistance from all co-authors.

Conflicts of interest

There are no conflicts to declare.

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