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Total Synthesis of (+)-Perophoramidine and Determination of the Absolute Configuration

Haoxing Wu,† Fei Xue,† Xue Xiao, and Yong Qin*

Department of Medicinal Natural Products and Key Laboratory of Drug Targeting and Drug Delivery Systems of the Ministry of Education and State Key Laboratory of Biotherapy, West China School of Pharmacy, Sichuan University, Chengdu 610041, P. R. China

Received August 5, 2010; E-mail: yongqin@scu.edu.cn

Abstract: The first asymmetric total synthesis of (+)-perophoramidine has been achieved in 17 steps with ~11% overall yield. The key step relies on an asymmetric biomimetic Diels−Alder reaction between the in situ-generated chiral diene **T-24** and the substituted tryptamine **23** to assemble the core structure **27a** in a highly efficient way. An acid-catalyzed thermodynamic equilibrium results in C=N double-bond migration of the amidine moiety in **37**, which guarantees a regioselective methylation on N_1 at the end of the synthesis. The absolute configuration of (+)-perophoramidine was determined by X-ray crystallographic analysis of the chiral intermediate **32** and comparison of the rotation of synthetic (+)-perophoramidine with that of the natural product.

(+)-Perophoramidine[1] and (−)-communesins[2] are structurally related indole alkaloids (Figure 1). These indole alkaloids have architectures that are unique among known indole alkaloids. They possess a complex multiring system, bisamidine or bisaminal functionality, and two vicinal quaternary carbon centers between the two ethylene groups. The two ethylene groups are trans to each other in perophoramidine and cis in communesins. The challenging structures and interesting cytotoxic activities of these indole alkaloids have attracted substantial interest from synthetic chemists in recent years.[3] Method development[4] for construction of the core structure has led to the total syntheses of (±)-perophoramidine by Funk[5a] and (±)-dehaloperophoramidine by Rainier[5b] as well as two total syntheses of (±)-communesin F, one by us and the other by Weinreb,[6] but syntheses of enantiomerically pure perophoramidine and communesins have not been achieved. Thus, the absolute configurations of the natural products are unknown.

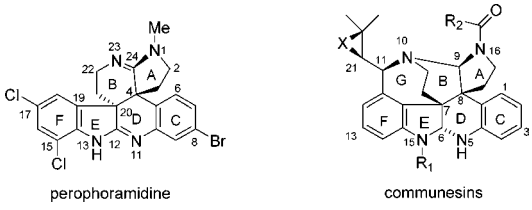
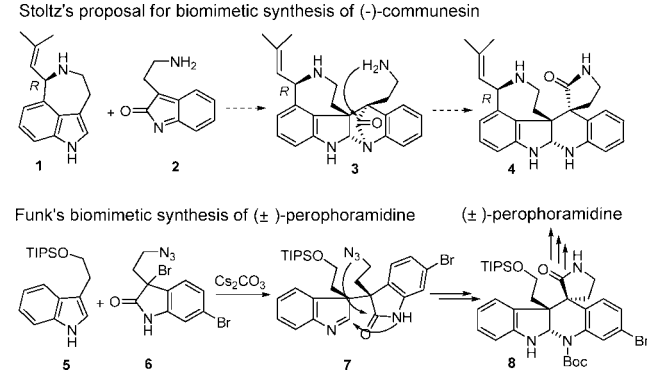


Figure 1. Structures of perophoramidine and communesins (communesin F: $R_1 = R_2 = Me$; X = double bond).

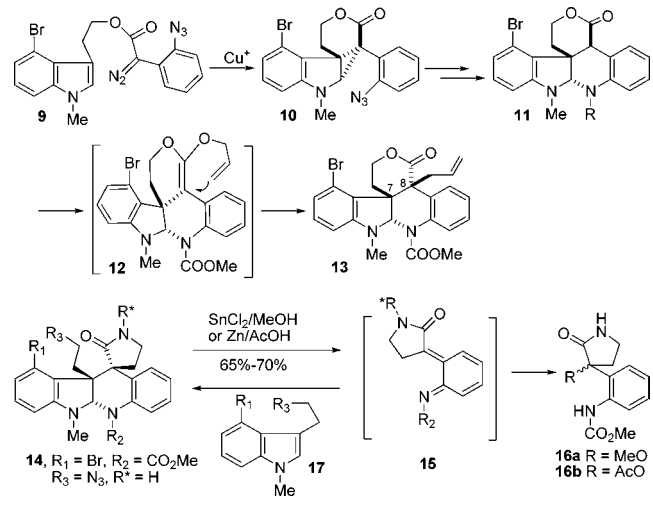
In view of the possible biosynthetic pathway of perophoramidine and communesins based on a model reaction, Stoltz first proposed that the architecture of these indole alkaloids might be biosynthetically produced through a hetero-Diels−Alder reaction of the ergot alkaloid (*R*)-aurantioclavine (**1**) with oxidized tryptamine **2** (Scheme 1).[4f,i] Following his own model reaction,[4g] Funk completed a biomimetic total synthesis of (±)-perophoramidine.[5a] The key reactions were a stepwise formal Diels−Alder reaction of tryptamine derivative **5** with bromo-substituted oxindole **6**, protection of the amide nitrogen with Boc, reductive opening of the lactam ring, and simultaneous cyclization (Scheme 1).[5a]

Scheme 1. Previous Biomimetic Approaches to the Core Structures



We previously reported a total synthesis of (±)-communesin F that uses a synthetic strategy of intramolecular cyclopropanation (**9** to **10**), reductive ring opening and ring closure (**10** to **11**), and α-allylation via Johnson−Claisen rearrangement (**12**) to provide the pentacyclic intermediate **13** having the two ethylene groups at C7 and C8 in a cis relationship (Scheme 2).[6a] Such a cis relationship occurs in communesins. During the total synthesis, while we were trying to reduce an

Scheme 2. Asymmetric Biomimetic Approach to the Core Structure



† These authors contributed equally.

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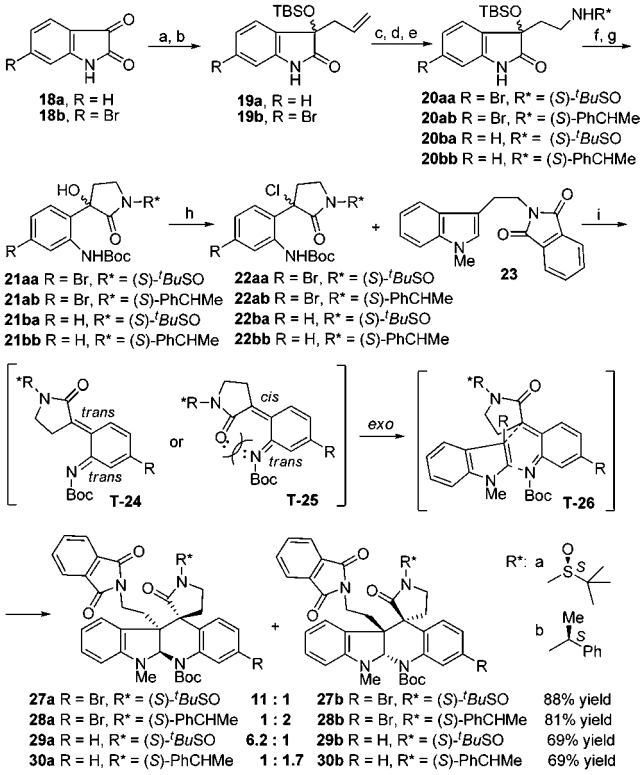
azide group in **14** to an amine group with a reductive Lewis acid (Zn dust or $SnCl_2$) on heating, a retro-Diels−Alder reaction unexpectedly occurred, leading to the stable compound **16** (Scheme 2).[7] Most likely, **16** was generated by solvent capture of the unstable diene **15**. This observation encouraged us to explore a new biomimetic approach for the synthesis of the core skeleton by applying a reverse procedure from a diene such as **15** and tryptamine derivatives such as **17** via an intermolecular hetero-Diels−Alder reaction. The major challenge in this designed Diels−Alder reaction is achieving the correct stereochemistry of the adducts, since perophoramidine and communesins have the opposite stereochemistry at the two vicinal quaternary carbon centers. An advantage of this approach is that it readily allows an asymmetric reaction induced by a preexisting chiral auxiliary (R*) on the amide nitrogen. In this communication, we report the first asymmetric total synthesis of (+)-perophoramidine, in which the key reaction is an intermolecular hetero-Diels−Alder reaction that assembles the core structure. We also report the determination of the absolute configuration of the natural product.

Scheme 3. Construction of the Core Structure[a]



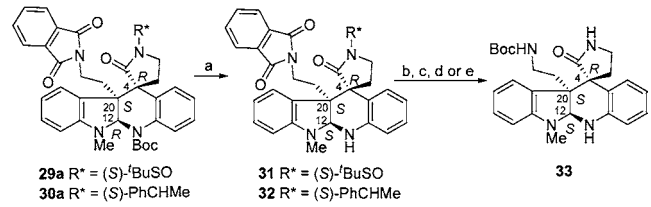
[a] Reagents and conditions: (a) allylMgBr, Et_2O, 25 °C, 2 h, 85−88%; (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 25 °C, 20 h, 95−97%; (c) O_3/Me_2S, CH_2Cl_2, −78 to 25 °C, 30 h, 76−84%; (d) R^*NH_2, $KHSO_4$, toluene, 50 °C, 2 h, or 4 Å molecular sieves, CH_2Cl_2, 25 °C; (e) $NaBH_4$, MeOH, 0 °C, 30 min, 81−85% over two steps; (f) Boc_2O, NaOH, CH_2Cl_2, 25 °C, 2 h, 87−93%; (g) TBAF, THF, 25 °C, 1 h, 89−90%; (h) $SOCl_2$, pyridine, CH_2Cl_2, 0 °C, 15 min; (i) 4.5 equiv of $AgClO_4$, 1 equiv of **23**, 3 equiv of **22**, toluene, −78 °C, 17−43 h.

On the basis of the above hypothesis, our first task was to prepare chiral diene precursor **22** (Scheme 3). Starting from isatins **18a** and **18b**, a parallel synthesis of **22aa**−**bb** with different chiral substituents was conducted using a similar procedure. Thus, Grignard addition followed by protection of the resulting tertiary hydroxyl group with TBS provided oxindole **19** in high yield. Ozonolysis of the double bond in **19**, condensation of the resulting aldehyde with (*S*)-α-methylbenzylamine[8a] or (*S*)-*tert*-butylsulfinamide,[8b,c] and reduction of the imine afforded chiral amine **20**. Lactam ring opening by activation with a Boc group and deprotection of TBS with TBAF gave alcohol **21**. The hydroxyl group in **21** was replaced with chloride by treating **21** with $SOCl_2$ and pyridine in CH_2Cl_2 at 0 °C, affording **22**.

Initial attempts to carry out the Diels−Alder reaction with **22aa** gave promising results. Without purification, the unstable **22aa** (1.2 equiv) was directly treated with **23** (1 equiv) and anhydrous $AgBF_4$ (2 equiv) at −78 °C in dry CH_2Cl_2 for 2 h to afford the separable major adduct **27a** and minor adduct **27b** in a 5.9:1 ratio with a combined yield of 74%. A variety of silver salts were screened, and $AgClO_4$ was found to catalyze the reaction smoothly for 30 h to give the highest ratio of 6.8:1 with a combined yield of 76%. Under the same conditions, replacing the CH_2Cl_2 solvent with toluene increased the ratio from 6.8:1 to 11:1 with 77% yield. The reaction yield was further enhanced to 88% when 3 equiv of **22aa** and 4.5 equiv of $AgClO_4$ were used. Under the optimal conditions (3 equiv of **22** and 4.5 equiv of $AgClO_4$ at −78 °C in toluene), reactions with compounds **22ab**, **22ba**, and **22bb** provided adducts **28**, **29**, and **30**, respectively, in ratios of 1.7:1 to 6.2:1 with yields of 69−81% (Scheme 3).

In diastereomers **27a** and **27b**, the ethylene groups on the two quaternary carbon centers are trans to each other, consistent with the geometry in perophoramidine but not in communesins. Although multiple modes of addition are possible in the Diels−Alder reaction, the stereochemistry of adducts **27a** and **27b** indicates that the Diels−Alder reaction proceeds through an exo addition (**T-26**) with an in situ-generated trans/trans diene **T-24** rather than with the trans/cis diene **T-25**. **T-25** may not be produced during the reaction, perhaps because of strong electron-pair repulsion in **T-25** (Scheme 3).[6]

Scheme 4. Determination of the Absolute Configurations of the Major Adducts[a]



[a] Reagents and conditions: (a) TMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 2 h, 82−85%; (b) $MeNH_2$/MeOH, 25 °C, 12 h; (c) Boc_2O, Na_2CO_3, CH_2Cl_2, 25 °C, 2 h, 78−80% over two steps; (d) Li/NH_3, THF, −78 °C, 30 min, 83%; (e) NaOH, CH_2Cl_2, 25 °C, 12 h, 81%.

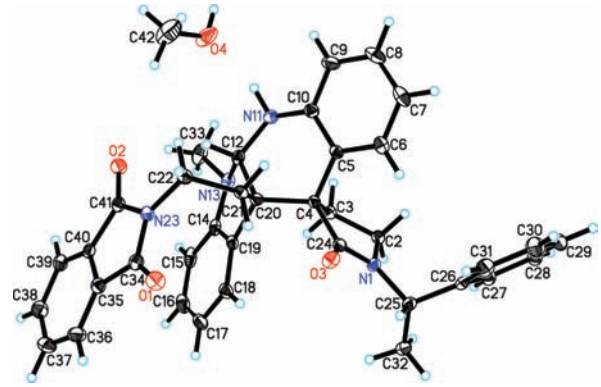


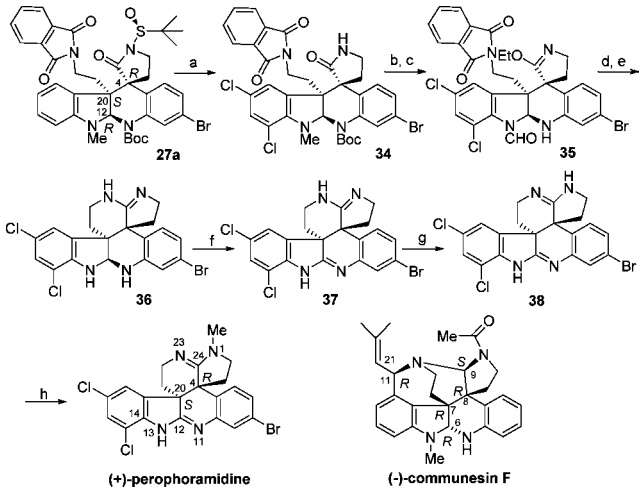
Figure 2. ORTEP diagram of **32**.

In order to determine the absolute configurations of the major adducts, **29a** and **30a** were converted to **31** and **32** by removal of the Boc protecting group with TMSOTf (Scheme 4). Fortunately, compound **32** was easily recrystallized from MeOH to form a solvated single crystal, X-ray analysis of which revealed a 4*R*,12*S*,20*S* configuration (Figure 2).[9] The absolute configuration

of **29a** and **30a** was determined to be 4*R*,12*R*,20*S* by comparison with the rotation of compound **33**, which was prepared from **31** and **32** by a three-step conversion involving removal of the phthaloyl group, protection of the amine, and removal of the chiral auxiliary (Scheme 4). In view of the absolute configuration of **29a**, the absolute configuration of **27a** with a bromo substituent was deduced to be 4*R*,12*R*,20*S* by comparison of its rotation and NMR spectra with those of **29a**. This deduction was reasonable because both **27a** and **29a** containing the same (*S*)-*tert*-butylsulfinyl group were generated under the same conditions.

Having developed an efficient hetero-Diels−Alder reaction for assembly of the core structure of perophoramidine and determined the absolute configuration of the major adduct **27a** (4*R*,12*R*,20*S*), we then began to synthesize (+)-perophoramidine from **27a**. As shown in Scheme 5, chlorination of **27a** on the indoline ring with NaClO in AcOH at −40 °C resulted in removal of the *tert*-butylsulfinyl group, providing amide **34** in high yield. After oxidation of the methyl group to a formyl group, the resulting compound was treated with excess Et_3OBF_4 and DIPEA at 25 °C in CH_2Cl_2, which converted the amide bond to an imidate bond and simultaneously removed the Boc protecting group, giving compound **35**. After removal of both the formyl and phthaloyl protecting groups in **35** with $MeNH_2$ without purification, the resulting intermediate was heated at reflux for 10 h in $CHCl_3$ to give amidine **36** in 73% yield over two steps. The aminal group in **36** was oxidized with MnO_2 as an amidine group to give kinetic product **37** in 76% yield. In order to selectively add a methyl group at N1, compound **37** was subsequently converted to its thermodynamic product **38** in quantitative yield by heating with 0.5 equiv of PPTs in $CHCl_3$. The final step of selective methylation of **38** with MeOTf and NaHMDS in THF at −78 °C completed the total synthesis of (+)-perophoramidine in 76% yield.

Scheme 5. Completion of the Synthesis of (+)-Perophoramidine[a]



[a] Reagents and conditions: (a) NaClO, HOAc, MeOH, −40 °C, 0.5 h, 91%; (b) PCC, CH_2Cl_2, 25 °C, 12 h, 89%; (c) Et_3OBF_4, DIPEA, CH_2Cl_2, 25 °C, 12 h, 85%; (d) $MeNH_2$/MeOH, 25 °C, 2 h; (e) $CHCl_3$, reflux, 10 h, 77% over two steps; (f) MnO_2, CH_2Cl_2, 25 °C, 3 h, 76%; (g) PPTs, $CHCl_3$, reflux, 2 h, quantitative; (h) MeOTf, NaHMDS, THF, −78 °C, 73%.

The synthetic sample showed NMR spectra identical to those of natural product, and its rotation $\{[\alpha]_D^{25} = +3.9$ (*c* 0.5, $CHCl_3)\}$ was consistent with that of the natural compound $\{[\alpha]_D^{25}$ +3.8 (*c* 0.73, $CHCl_3)$[1]$\}$. These results unambiguously indicate that the natural (+)-perophoramidine possesses a 4*R*,20*S* configuration. Because (+)-perophoramidine and (−)-communesin F have opposite configurations at the vicinal quaternary carbon centers, the absolute configuration of (−)-communesin F can be inferred to be 6*R*,7*R*,8*R*,9*S*,11*R* on the basis of the relative stereochemistry of natural (−)-communesins reported in the literature[2a,b] and the proposed biosynthetic pathway in which (−)-communesins are generated from the ergot alkaloid (*R*)-aurantioclavine **1**.[4f,i]

In summary, the first asymmetric total synthesis of (+)-perophoramidine has been accomplished in 17 steps in ∼11% overall yield. The key step for diastereoselective assembly of the core structure is a chiral-auxiliary-induced hetero-Diels−Alder reaction that is efficiently catalyzed by $AgClO_4$. The absolute configuration of (+)-perophoramidine has been determined to be 4*R*,20*S* by X-ray analysis of a synthetic intermediate and comparison of the rotation of the synthetic sample with that of the natural product.

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Supporting Information Available: Experimental details, NMR spectra of all new compounds, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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