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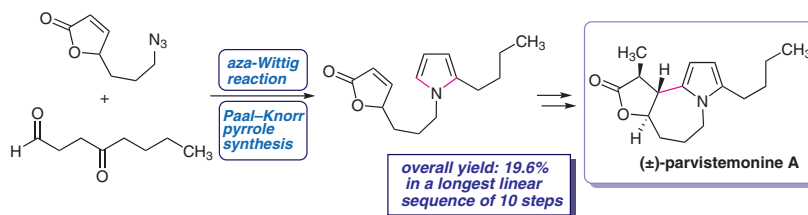# Concise Diastereoselective Total Synthesis of (±)-Parvistemonine A

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Abstract We have developed a concise diastereoselective total synthesis of (±)-parvistemonine A. By using a Mukaiyama–Michael addition, an aza-Wittig reaction, a Paal–Knorr pyrrole synthesis, an acid-mediated annulation, and a Mitsunobu reaction as key steps, we achieved a total synthesis in which the longest linear sequence was ten steps and the overall yield was 19.6%. Additionally, the relative stereochemistry of parvistemonine A was confirmed by X-ray crystallographic analysis for the first time.

Key words parvistemonine A, natural product, total synthesis, aza-Wittig reaction, Mitsunobu reaction

In 2016, Zhao and co-workers isolated a series of new alkaloids from the roots of *Stemona parviflora*. Parvistemonine A (**1**) was among them, and its structure was determined by NMR and MS analysis.[1] *Stemona parviflora* is a relatively small monocotyledonous plant of the Stemonaceae family. The roots of *Stemona* species have antitussive and insecticidal activities, and they have been used in folk medicine for thousands of years in East Asia. Antinematode activity has been identified for several isolated *Stemona* alkaloids.

As shown in Figure 1, the structure of parvistemonine A (**1**) is characterized by a fused tricyclic framework including a γ-lactone and a pyrrole, with a butyl side chain. For the total synthesis, three consecutive asymmetric centers and an acid-sensitive pyrrole ring bearing three electron-donating alkyl groups must be efficiently constructed at the appropriate times. From the viewpoint of medicinal chemistry, the functional groups on this framework could be arranged in various relative positions by introducing various substituents, because the central seven-membered ring

disrupts the planarity of the molecule. Therefore, a concise and effective route for the synthesis of **1** might serve as a useful access to drug-discovery leads and scaffolds.
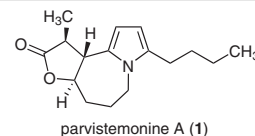

**Figure 1** Structure of parvistemonine A (**1**)

Because of the intriguing structures and the bioactivities of *Stemona* alkaloids, their total synthesis has been an intense area of research in recent decades.[2] To our knowledge, only one total synthesis has been reported to date. In 2019, Ma and co-workers reported the preparation of parvistemonine A in a racemic form by using a cross-metathesis, a Friedel–Crafts-type cyclization, a lactonization, a Vilsmeier–Haack formylation, and a Julia–Kocienski olefination. They obtained (±)-parvistemonine A in 11 steps and in 2.3% overall yield.[3]

Our retrosynthetic analysis of (±)-**1** is shown in Scheme 1. We planned to introduce the methyl group at the 1-position in the lactone ring at a late stage in the total synthesis by methylation of an ester enolate. We planned to construct the seven-membered ring by an intramolecular conjugated cycloaddition of an electron-rich pyrrole ring promoted by an acid. We assumed that the cyclization precursor **2** could be constructed by nucleophilic substitution with 2-butyl-1*H*-pyrrole (**3**) as the pyrrole moiety and iodide **4** as the butenolide moiety. Furthermore, iodide **4** could be synthesized by several functionalizations from the product of a Mukaiyama–Michael addition of commercially available 2-[(trimethylsilyl)oxy]furan (**5**) and acrolein (**6**).
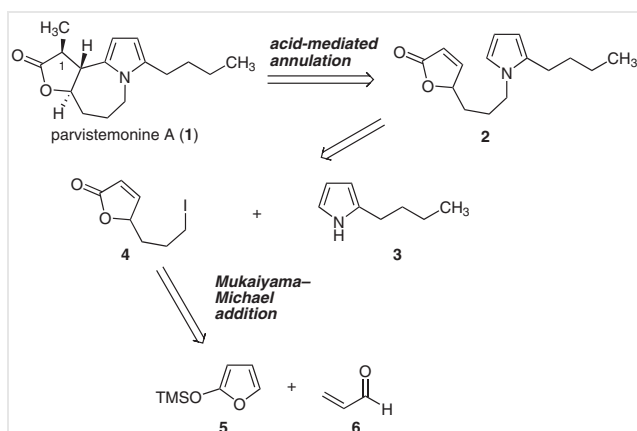
Scheme 1 Retrosynthetic analysis of parvistemonine A (**1**)

We began our synthesis from readily available pyrrole (**7**). 2-Butyl-1*H*-pyrrole (**3**) was prepared as follows. First, pyrrole (**7**) was converted into a magnesium reagent, which was treated with butanoyl chloride to give 1-(1*H*-pyrrol-2-yl)butan-1-one (**8**).[4] Reduction of **8** by NaBH$_4$ in refluxing propan-2-ol gave 2-butylpyrrole (**3**) (Scheme 2).[5]
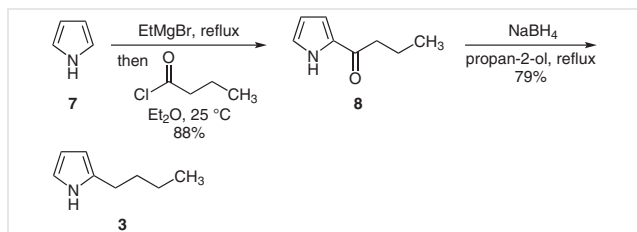

Scheme 2 Synthesis of 2-butylpyrrole (**3**)

A Mukaiyama–Michael addition of 2-[(trimethylsilyl)oxy]furan (**5**) to acrolein (**6**) at –60 °C gave aldehyde **9** in 87% yield.[6] However, when we attempted to reduce the aldehyde group in **9** with NaBH$_4$, the butenolide ring was also reduced. In contrast, reduction by borane at –20 °C afforded the desired alcohol **10** in good yield.[7] Next, sequential mesylation and iodination proceeded smoothly to give iodide **4** (Scheme 3).[8]
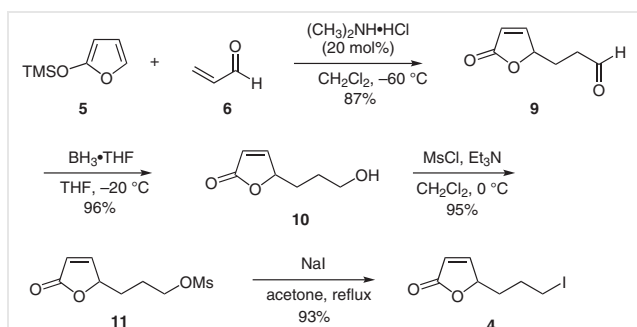

Scheme 3 Synthesis of iodide **4**

We then investigated the coupling reaction of 2-butyl-1*H*-pyrrole (**3**) and iodide **4**. In all our attempts using NaH, DBU, or LHMDS, the reaction was complicated, and the desired product **2** was not obtained. In most of these attempts, decomposition of the iodide **4** was observed, whereas the pyrrole **3** remained intact (Scheme 4).[9]
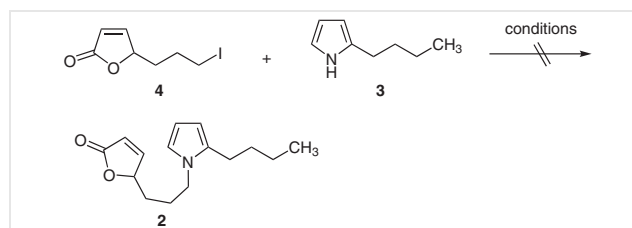
**Scheme 4** Attempted coupling reaction of pyrrole **3** and iodide **4**

We attributed these results to the low reactivity of the anion derived from pyrrole **3** and the labile nature of iodide **4** under basic conditions. We therefore planned a new synthetic route that avoided strongly basic reaction conditions. In the new synthetic strategy (Scheme 5), we envisioned that an in situ Paal–Knorr pyrrole synthesis using keto aldehyde **13** just after an aza-Wittig reaction of azide **12** might lead to the desired product **2**. Keto aldehyde **13** can be easily prepared from γ-lactone **14** in two steps.
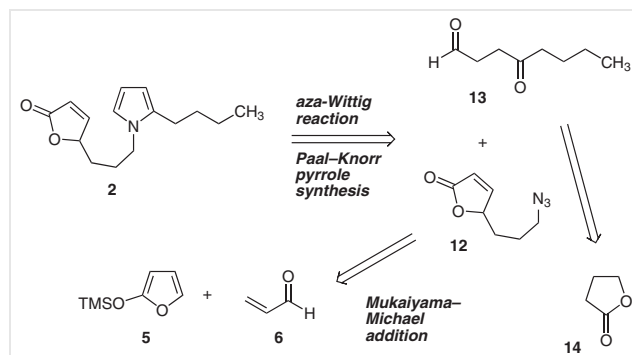
Scheme 5 Revised retrosynthetic analysis of compound **2**

First, keto aldehyde **13** for the Paal–Knorr pyrrole synthesis was prepared in two steps. Addition of butyllithium to γ-lactone **14** to form hydroxy ketone **15**[10] and subsequent IBX oxidation furnished **13** smoothly (Scheme 6).[11] For the butenolide moiety, treatment of iodide **4** with sodium azide in DMF gave azide **12** in 89% yield.[12] In this procedure, the formation of tricyclic compound **16** by an intramolecular [3 + 2]-pericyclic reaction of the azide moiety and the double bond in the butenolide was observed when the reaction temperature was increased. We therefore minimized the amount of time taken for reaction workup and column purification. The aza-Wittig reaction of azide **12** and keto aldehyde **13**, followed by the Paal–Knorr pyrrole synthesis in one pot gave the desired coupling product **2** in

65% yield.[13] In this step, we detected none of the desired primary amine when we attempted a selective reduction of the azide moiety in **12**.
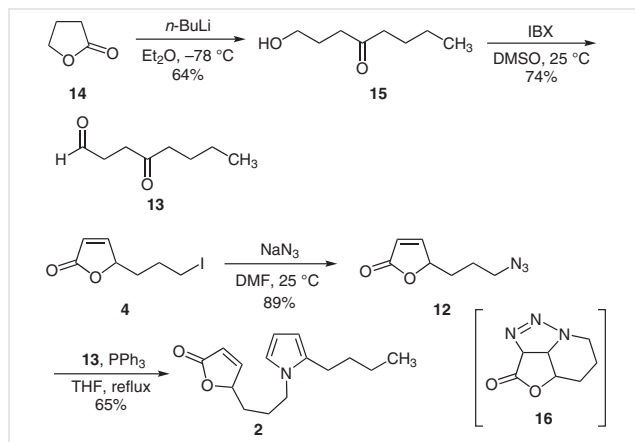

Scheme 6 Synthesis of compound **2**

Next, the intramolecular conjugated cycloaddition of **2** under acidic conditions to form tricyclic compound **17** was investigated (Table 1).[14] With Lewis acids, the reproducibility of the reaction yield was low, because the pyrrole ring bearing alkyl groups was not sufficiently stable under strongly acidic conditions. During optimization of the reaction conditions with various sulfonic acids, we predominantly obtained the *cis*-fused tricyclic compound **17** in 72%

yield when toluenesulfonic acid was employed in acetonitrile at 70 °C under dilute conditions. Moreover, the reaction did not proceed with PPTS.[15]

In this reaction, *cis*-fused **17** was obtained with high selectivity, as we had expected at the beginning of our synthetic plan. Furthermore, subsequent methylation of *cis*-fused **17** was expected to occur selectively from the convex face. On the other hand, Ma and co-workers obtained a mixture of diastereomeric methylated compounds when they methylated *trans*-fused **18**. They therefore synthesized (±)-parvistemonine A by isomerization of the resulting mixture of diastereomers under basic conditions (two steps; 49%).[2a,2b,2e,3]

After deprotonation by LHMDS, tricyclic compound **17** was treated with methyl iodide.[16] As expected, the methylation proceeded preferentially from the β-side (i.e., the convex face) and the desired methylated derivative **19** was obtained stereoselectively in 83% yield. Finally, to invert the stereochemistry at the 3a-position, the lactone ring of **19** was opened by alkaline hydrolysis and the product was rapidly subjected to a Mitsunobu reaction with di-2-methoxyethyl azodicarboxylate (DMEAD) and PPh₃ to give (±)-parvistemonine A[17] in 77% yield over the two steps (Scheme 7).[17] At this stage, precise pH control was essential during the hydrolysis workup procedure to suppress the reverse reaction to re-form *cis*-lactone **19**. Moreover, the Mitsunobu reaction was carried out at room temperature to accelerate the forward reaction and to prevent the reverse reaction. The ¹H NMR, ¹³C NMR, and HRMS of the synthetic samples

**Table 1** Optimization of the Acid-Mediated Annulation of Compound **2**[a]
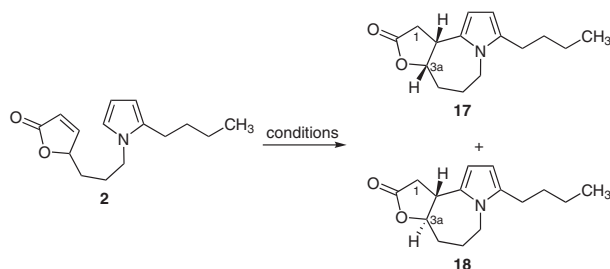
Entry	Acid (equiv)	Solvent	Temp. (°C)	Time (h)	Yield (%)		
					17	**18**	**2**[b]
1	BF₃·OEt₂ (10.0)	CH₂Cl₂	25	16	31	trace	69
2	AlCl₃ (15.0)	CH₂Cl₂	25	94	45	trace	trace
3	MsOH (15.0)	CH₂Cl₂	0–39	173	47	trace	10
4	CSA (10.0)	MeCN	50	19	39	trace	trace
5	TsOH·H₂O (2.1)	MeCN	55	15	46	trace	5
6[c]	TsOH·H₂O (10.5)	MeCN	70	18	72	6	–
7	PPTS (5.0)	MeCN	50	13	–	–	100

[a] Reaction conditions: **2** (10.0 mg, 40.5 μmol), solvent (810 μL).
[b] Recovered starting material.
[c] The reaction was performed under five-times diluted conditions.

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were in good agreement with those reported for natural parvistemonine A (**1**). Furthermore, recrystallization of (±)-**1** from hexane afforded single crystals suitable for X-ray crystallographic analysis, which confirmed the complete structure of (±)-**1**.[18]
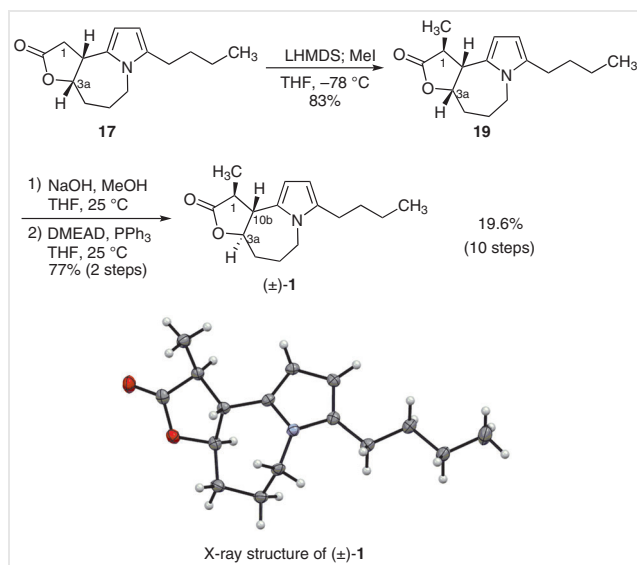
Scheme 7 Completion of the total synthesis of (±)-**1,** and the structure of (±)-**1** obtained by X-ray diffraction

In summary, we have described a total synthesis of (±)-parvistemonine A. From the commercially available furan **5**, this synthesis proceeded with a longest linear sequence of ten steps and in 19.6% overall yield. The synthesis included a Mukaiyama–Michael addition, an aza-Wittig reaction, a Paal–Knorr pyrrole synthesis, an acid-mediated annulation, and a Mitsunobu reaction as key steps. X-ray crystallographic analysis of (±)-**1** clearly confirmed the relative stereochemistry of parvistemonine A (**1**). This concise synthesis might be useful in syntheses of derivatives of (±)-**1** or the purpose of medicinal chemistry and for providing drug-discovery scaffolds.

Funding Information

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707283.

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(15) In a TLC analysis of the products of this reaction, no other conspicuous spots were detected other than those for the starting material **2**, product **17**, and a trace amount of *trans*-fused **18**. We have not yet isolated any other byproducts.

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(17) No epimerization at the 1-position was observed after the last two steps.

(18) CCDC 2015461 contains the supplementary crystallographic data for (±)-parvistemonine A [(±)-(**1**)]. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures. A summary of the crystallographic analysis and the crystal structure are provided in the Supporting Information.

(19) **(±)-Parvistemonine A [(±)-1)]**
A 1 M solution of NaOH in MeOH (527 μL) was added to a stirred solution of lactone **19** (13.8 mg, 52.7 μmol) in THF (5.3 mL) at 25 °C, and the mixture was stirred for 1 h at 25 °C. The pH of the

reaction mixture was adjusted to 4–5 by addition of 1 M aq HCl, and the resulting mixture was diluted with EtOAc/H$_2$O and extracted with EtOAc (×6). The combined organic layer was dried (Na$_2$SO$_4$), filtered, and concentrated. The residue was treated at 25 °C with a second reaction mixture separately prepared in advance from bis(2-methoxyethyl) azodicarboxylate (185 mg, 791 µmol) and PPh$_3$ (207 mg, 791 µmol). The resulting mixture was stirred for 1 h at 25 °C, and the reaction was then quenched by addition of sat. aq NaHCO$_3$. The mixture was diluted with EtOAc/H$_2$O and extracted with EtOAc (×3). The combined organic layer was dried (Na$_2$SO$_4$), filtered, and concentrated. The residue was purified by flash column chromatog-raphy [silica gel, hexane–Et$_2$O (100:0 to 3:1)] to give a colorless oil; yield: 10.6 mg (40.6 µmol, 77%).

^{1}H NMR (600 MHz, CDCl$_3$): d = 5.85 (d, J = 3.6 Hz, 1 H), 5.82 (d, J = 3.6 Hz, 1 H), 4.19 (dd, J = 14.4, 5.4 Hz, 1 H), 3.89 (ddd, J = 11.4, 9.6, 3.6 Hz, 1 H), 3.63 (dd, J = 14.4, 11.4 Hz, 1 H), 3.03–2.93 (m, 2 H), 2.57–2.48 (m, 3 H), 2.14–2.10 (m, 1 H), 1.80–1.73 (m, 1 H), 1.61–1.54 (m, 3 H), 1.45–1.37 (m, 5 H), 0.94 (t, J = 7.2 Hz, 3 H).

^{13}C NMR (151 MHz, CDCl$_3$): d = 178.44, 134.27, 128.06, 104.32, 102.98, 81.75, 49.42, 44.12, 39.41, 34.34, 31.53, 26.30, 25.98, 22.51, 13.90, 13.83. HRMS (ESI) m/z [M + Na]$^+$calcd for C$_{16}$H$_{23}$NNaO$_2$: 284.1621; found: 284.1646.