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**A HIGHLY EFFICIENT SYNTHESIS OF TRISPHERIDINE THROUGH
A CONSTRUCTION OF TETRAHYDROPHENANTHRIDINE BASED ON
A MICROWAVE-ASSISTED THERMAL ELECTROCYCLIC
REACTION OF AN AZA 6π -ELECTRON SYSTEM[†]**

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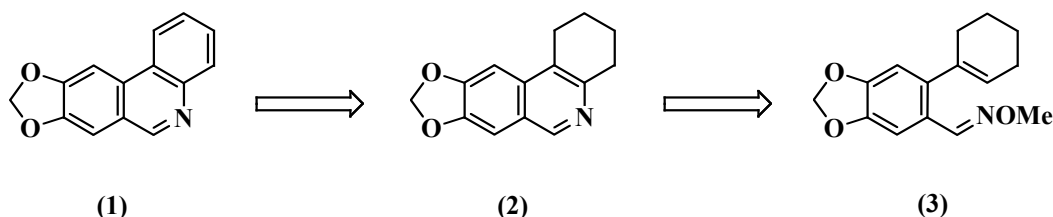
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Abstract— A highly efficient synthesis of a phenanthridine alkaloid, trispheridine (**1**) has been achieved in a 74% overall yield in a four-step sequence. The key step is the construction of a tetrahydrophenanthridine based on a microwave-assisted thermal electrocyclic reaction of an aza 6π -electron system including the benzene double bond.

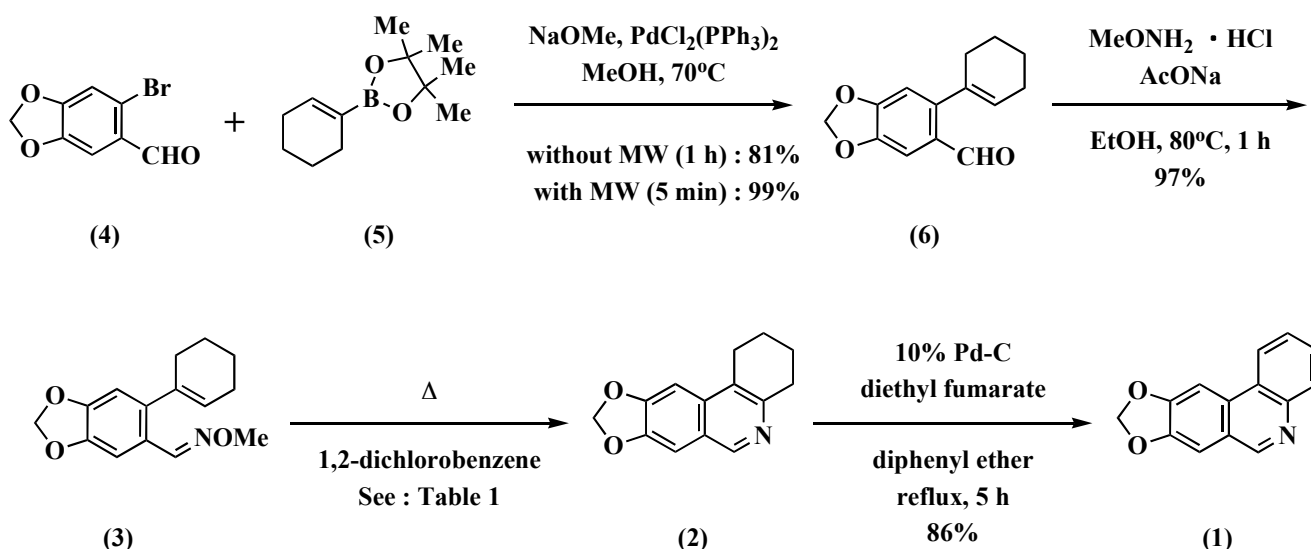
The development of a more convenient and efficient synthetic route to phenanthridine and benzo[*c*]phenanthridine alkaloids is still being continued due to the broad range of potent pharmacological activities.¹ On the other hand, it has been well known that microwave (MW) irradiation provides unique chemical processes with special attributes such as enhanced reaction rates, higher yields, greater selectivity and ease of manipulation.² We are currently developing the synthesis of a fused pyridine ring by means of the thermal electrocyclic reaction of an aza 6π -electron system incorporating one double bond of the aromatic or heteroaromatic moiety.³ We here describe a highly efficient and convenient synthetic route to phenanthridine alkaloid, trispheridine (**1**), which has been found in a member of the *Amaryllidaceae* plant family,^{4,5} via a construction of a tetrahydrophenanthridine (**2**) based on a MW assisted thermal electrocyclic reaction of an aza 6π -electron system (**3**)^{3f}, derived from a disconnection at N-2 and C-3 of the isoquinoline part, as depicted in a retro-synthetic analysis (Scheme 1).

[†]This paper is dedicated to the memory of Dr. Kenji Koga, Emeritus Professor of Tokyo University.



Scheme 1

For the synthesis of a key compound, tetrahydrophenanthridine (**2**), a 4,5-methylenedioxy-2-cyclohexenylbenzaldoxime methyl ether (**3**) as a precursor of **2** was prepared as follows (Scheme 2). Suzuki-Miyaura reaction of a readily available 2-bromopiperonal (**4**) with cyclohexenylboronic acid pinacol ester (**5**)⁶ was carried out in the presence of $\text{PdCl}_2(\text{PPh}_3)_2$ and NaOMe in MeOH at 70°C for 1 h to give cyclohexenylbenzaldehyde (**6**) (81% yield).⁷ In addition, this reaction was also attempted with MW irradiation for 5 min to produce the cyclohexenylbenzaldehyde (**6**) in a 99% yield. The effect of MW irradiation was reflected in the yield and the reaction rate.^{2c} Subsequent treatment of the aldehyde (**4**) with NH_2OMe afforded oxime ether (**3**) (97% yield) with a 6π -electron system. Oxime ether (**3**) was subjected to the thermal electrocyclic reaction at 180°C in 1,2-dichlorobenzene under both the MW assisted and conventional conditions. As shown in Table 1 run 3a and 4a with MW irradiation for 50-60 min provided excellent yields of **2** (86 and 90%, respectively). In contrast, although the yields of (**2**) with the conventional conditions (run 1b to run 4b) were gradually increased, the substrate **3** (14%) in run 4b still remained unchanged. In run 5b for 70 min, the substrate (**3**) disappeared and the yield reached 85%. Thus, it was found that the yield and the reaction rate of this type of thermal electrocyclic reaction were promoted by the MW irradiation.



Scheme 2

Table 1. Thermal electrocyclic ring-closure^{a)} from 3 to 2

run	time (min)	with MW ^{b)} : yield (%) ^{c)}	run	time (min)	without MW : yield (%) ^{c)}
1a	10	43 (53) ^{d)}	1b	10	37 (60) ^{d)}
2a	40	83 (7) ^{d)}	2b	40	47 (34) ^{d)}
3a	50	86	3b	50	53 (27) ^{d)}
4a	60	90	4b	60	73 (14) ^{d)}
5a	70	88	5b	70	85
6a	80	88	6b	80	84

a) heated at 180°C

b) 2450 MHz

c) isolated yield

d) recovered starting material 3

In the final stage, heating of tetrahydrophenanthridine (**2**) with 10% Pd-C in diphenyl ether in the presence of diethyl fumarate⁸ provided trispheridine (**1**) (86% yield). The physical and spectral data of synthetic trispheridine (**1**)⁹ were identical with those of natural and synthetic product^{4,5} in all respects.

In conclusion, a new total synthesis of trispheridine (**1**) has been established in a 74% overall yield in a four-step sequence. It was demonstrated that the MW irradiation of the thermal electrocyclic reaction of this aza 6 π -electron system provided a highly efficient procedure, which is applicable to other fused pyridine ring systems.

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- 9 Synthetic trispheridine, mp 138-140°C (*n*-hexane) (lit.,^{4e} mp 132-134°C, lit.,^{4f} 130-132°C, lit.,^{5c} mp 138-139°C, lit.,^{5h} mp 144.5-145°C, lit.,^{5k} mp 142.5-144°C). ¹H-NMR (300 MHz, CDCl₃) δ: 6.17 (2H, s), 7.34 (1H, s), 7.63 (1H, ddd, *J*=1.5, 6.9, 8.1 Hz), 7.70 (1H, ddd, *J*=1.5, 6.9, 8.1 Hz), 7.91 (1H, s), 8.14 (1H, dd, *J*=1.5, 8.1 Hz), 8.37 (1H, dd, *J*=1.5, 8.1 Hz), 9.10 (1H, s). ¹³C-NMR (75 MHz, CDCl₃) δ: 151.7, 151.5, 148.2, 143.9, 130.3, 129.9, 128.0, 126.7, 124.3, 123.0, 122.0, 105.5, 101.9, 99.9.