



Total synthesis of a marine imidazole alkaloid, clathridine A

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Abstract

The first total synthesis of clathridine A (**8**), a marine imidazole alkaloid, was achieved by using a novel regioselective condensation as a key step, in which preclathridine A (**2**) was treated with 1-methylparabanic acid (**11**) in the presence of a silylating agent. © 2000 Elsevier Science Ltd. All rights reserved.

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Recently, many marine imidazole alkaloids such as **1–10** in Table 1 have been isolated from sponges, and their antitumor and antibacterial activities have also been found.^{1,2} Structural characteristics of these alkaloids are that one or two alkoxy benzyl group(s) locates at the 1-, 4- and/or 5-positions of the 1*H*-imidazole ring and the 2-position is substituted with a primary amino group or a (1-methyl-2,5-dioxo-3-imidazolin-4-yl)amino moiety² (Table 1).

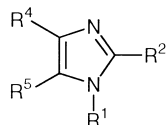
Hitherto, we have reported total synthesis of several marine imidazole alkaloids such as nortopsentin A–D,³ topsentin,⁴ kealiiquinone (**10**),⁵ and preclathridine A (**2**).⁶ In this paper, we would like to report the first total synthesis of clathridine A (**8**) starting from 1-methyl-1*H*-imidazole.

It is necessary for the conversion of preclathridine A (**2**) into clathridine A (**8**) to condense **2** with 1-methylparabanic acid (**11**) regioselectively at the 4-position of **11** (Scheme 2). We first examined the condensation of **11** with primary amines in the presence of water-soluble carbodiimide (WSC); however, the amines were incorporated into the heterocyclic ring to produce 3-substituted 1-methylparabanic acids (**12a–c**) (Scheme 1, Table 2).

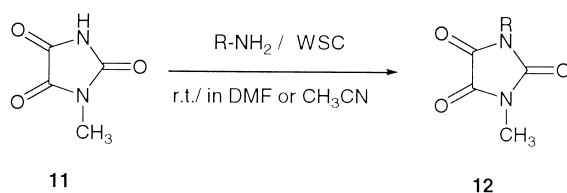
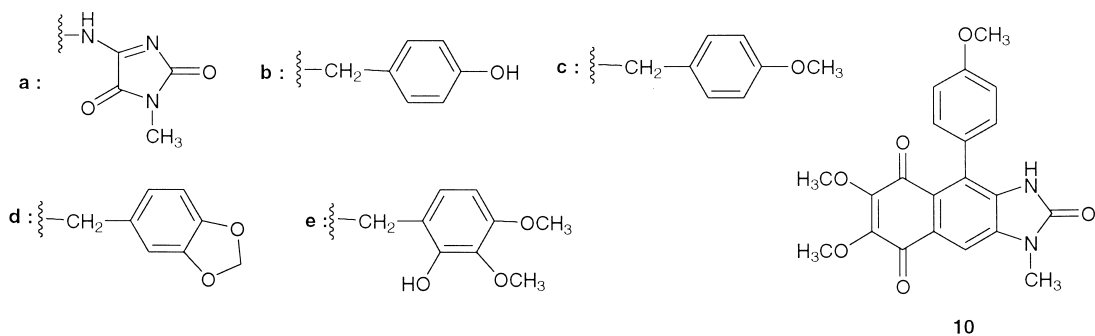
In order to change the reactivity of **11**, it was treated with trimethylsilyl chloride in the presence of triethylamine in chloroform, and then aniline was added to the reaction mixture to give, interestingly, the desired 4-phenylamino-1-methyl-2,5-dioxo-3-imidazoline (**15a**, mp 224–227°C). The structure of **15a** was finally determined by X-ray crystallographical analysis, by which intermolecular

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Table 1
Several marine imidazole alkaloids



Name	Compd. No.	R ¹	R ²	R ⁴	R ⁵
Dorimidazole	1	CH ₃	NH ₂	b	H
Preclathridine A	2	CH ₃	NH ₂	b	H
Isonaamine A	3	c	H	b	H
Naamine A	4	CH ₃	NH ₂	c	b
Naamidine A	5	CH ₃	a	c	b
Isonaamidine A	6	b	a	b	b
Pyrronaamidine A	7	CH ₃	a	c	e
Clathridine A	8	CH ₃	a	d	H
Clathridine B	9	CH ₃	a	d	d



Scheme 1.

Table 2
Reaction of 1-methylparabanic acid (**11**) with primary amines

Entry	RNH ₂	Product No.	Yield (%)
1	C ₆ H ₅ NH ₂	12a	43.1
2	2-Pyridyl-NH ₂	12b	43.0
3	C ₆ H ₅ CH ₂ CH ₂ NH ₂	12c	46.1 ^a
4	<i>c</i> -C ₆ H ₁₁ NH ₂	- ^b	-

a: By-product [(PhCH₂CH₂NHCO-)₂ (**13**)] was obtained in 12.8% yield.

b: (*c*-C₆H₁₁NHCO-)₂ (**14**) was obtained in 44.4% yield.

hydrogen bonds were observed between O2...H-N3' and N3-H...O2' as shown in Fig. 1. It was also clarified that the 4-amino form **15B** predominates rather than the 4-imino form **15A** in the crystalline state (Scheme 2).

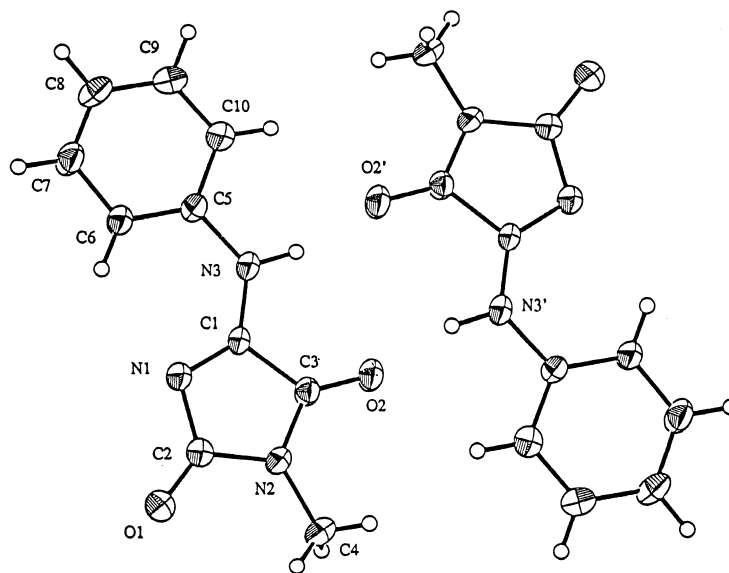
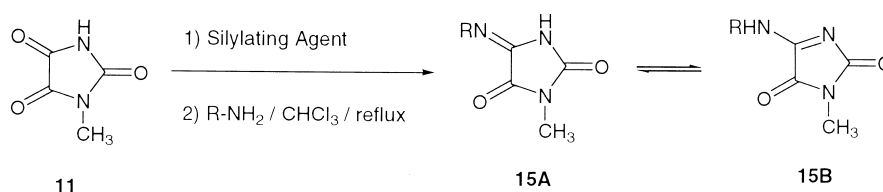


Figure 1.



Scheme 2.

Table 3 shows the results obtained by examining influences of the silylating agents and various primary amines on the condensation. In entry 13, the used primary amine is preclathridine A (**2**), and the product, clathridine A (**8**), was isolated as dark-red crystals, physical and spectral data of which were almost in agreement with those of the natural product (Scheme 3).[†] The present total synthesis of **8** is the first one in the series of imidazole alkaloids bearing a (1-methyl-2,5-dioxo-3-imidazolin-4-yl)amino moiety (Table 3).

[†] Data for the synthetic clathridine A (**8**): Dark-red granules (recryst. from CH₃OH), mp 233–235.6°C. IR (CHCl₃): 3315, 1784, 1732, 1716, 1672, 1611, 1439, 1392, 1300, 1093 cm⁻¹. ¹H NMR (400 MHz in CDCl₃) σ ppm: 3.19 (s, 3H, >N-CH₃), 3.71 (s, 3H, >N-CH₃), 3.81 (s, 2H, Ar-CH₂-Ar), 5.94 (s, 2H, O-CH₂-O), 6.53 (s, 1H, C5-H), 6.71 (dd, 1H, *J* = 1.7 and 7.7 Hz, Ar-H), 6.73 (dd, 1H, *J* = 0.6 and 1.7 Hz, Ar-H), 6.76 (dd, 1H, *J* = 0.6 and 7.7 Hz, Ar-H). ¹³C NMR (100 MHz in CDCl₃): 24.7, 32.2, 34.4, 100.9, 108.3, 109.2, 117.6, 121.6, 129.0, 132.6, 139.6, 144.2, 146.2, 147.8, 154.9, 162.0. HRMS *m/z*: calcd for C₁₆H₁₅N₅O₄: 341.1121. Found: 341.1119 (M⁺). Anal. calcd for C₁₆H₁₅N₅O₄: C, 56.30; H, 4.43; N, 20.52. Found: C, 56.42; H, 4.52; N, 20.13.

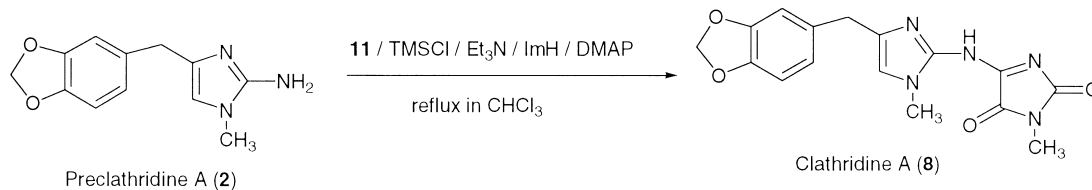
Table 3
Condensation of **11** with primary amines in the presence of silylating agent^d

Entry	R-NH ₂	Silylating Agent	Product No.	Yield (%) ^c
1	C ₆ H ₅ NH ₂	TMSCl	15a	63.8
2	C ₆ H ₅ NH ₂	TBDMSCl	15a	35.0
3	C ₆ H ₅ NH ₂	TMSOTf	15a	51.7
4	C ₆ H ₅ NH ₂	HMDS	15a	11.9
5	2-BzIm-NH ₂ ^a	TMSCl	15b	24.7
6	2-BzIm-NH ₂ ^a	MSMKA ^c	15b	40.4
7	2-Pyr-NH ₂ ^b	TMSCl	15c	40.4
8	4-EtC ₆ H ₄ NH ₂	TMSCl	15d	84.3
9	4-BrC ₆ H ₄ NH ₂	TMSCl	15e	20.9
10	4-CH ₃ OC ₆ H ₄ NH ₂	TMSCl	15f	82.9
11	2-CH ₃ OC ₆ H ₄ NH ₂	TMSCl	15g	64.9
12	<i>n</i> -C ₃ H ₇ NH ₂	TMSCl	15h	92.3
13	preclathridine A (2)	TMSCl	8	73.3

a: 2-amino-1-methylbenzimidazole; b: 2-aminopyridine; c: TMSO(CH₃O)C=CHCH₃

d: Example for the reaction conditions: see the typical procedure described below.

e: Entry 1 -7, 12, and 13 : isolated yields; Entry 8 - 11: yields obtained by UV method.



Scheme 3.

Synthesis 15a as a typical procedure: A solution of 1-methylparabanic acid (**11**; 256 mg, 2.0 mmol), DMAP (2 mg), triethylamine (0.59 ml, 4.2 mmol), imidazole (150 mg, 2.2 mmol) and TMSCl (0.54 ml, 4.2 mmol) in CHCl₃ (2.0 ml) was stirred for 2 h at room temperature under an N₂ atmosphere. Aniline (0.83 ml, 2.0 mmol) was added to the mixture, and the whole was refluxed at 78°C for 24 h. After cooling, water (2.0 ml) and CHCl₃ (20 ml) were added to the reaction mixture. The organic layer was dried over anhydrous sodium sulfate and evaporated to give a colorless solid mass. The crude product was purified by column chromatography (CHCl₃:MeOH = 10:1 in volume) and the crystalline main fraction was recrystallized from MeOH to give colorless needles, mp 224–227°C. Yield, 259 mg (63.8%); IR (KBr): 3252, 1729, 1639, 1587, 1495, 1446, 1128 cm⁻¹. ¹H NMR (300 MHz in DMSO-*d*₆) σ 2.95 (s, 3H, N-CH₃), 7.20 (t, 1H, *J* = 7.4 Hz, Ar-H), 7.41 (t, 2H, *J* = 7.6 Hz, Ar-H), 7.83–7.92 (m, 2H, Ar-H). ¹³C NMR (75 MHz in DMSO-*d*₆): 24.9, 121.6, 125.7, 129.3, 138.4, 162.8, 163.0. HRMS *m/z*: calcd for C₁₀H₉N₃O₂: 203.0695. Found: 203.0691 (M⁺). Anal. calcd for C₁₀H₉N₃O₂: C, 59.11; H, 4.46; N, 20.68. Found: C, 58.90; H, 4.55; N, 20.43.

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