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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.

Keywords: clathridine A; preclathridine A; marine alkaloid; total synthesis; parabanic acid; regioselective condensation; imidazole.

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 moiety[2] (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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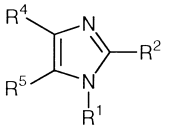
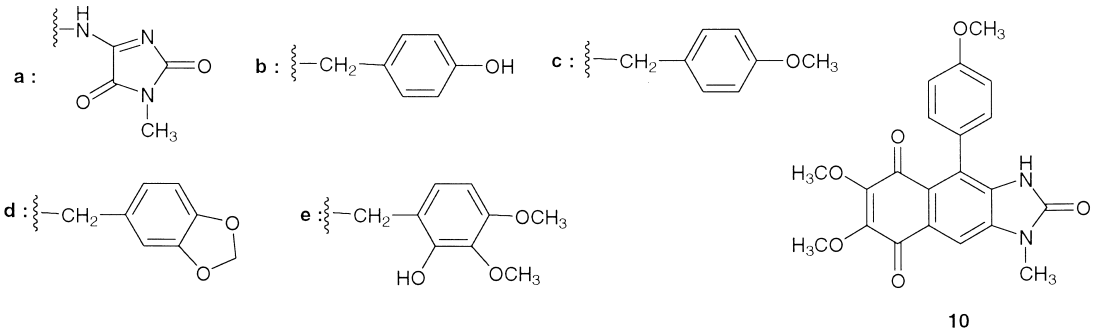
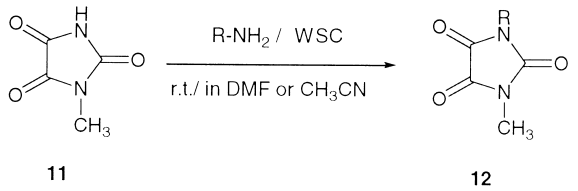
Table 1
Several marine imidazole alkaloids



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	$C_6H_5NH_2$	**12a**	43.1
2	2-Pyridyl-NH_2	**12b**	43.0
3	$C_6H_5CH_2CH_2NH_2$	**12c**	46.1[a]
4	*c*-$C_6H_{11}NH_2$	-[b]	-

a: By-product [$(PhCH_2CH_2NHCO\text{-})_2$ (**13**)] was obtained in 12.8% yield.

b: $(c\text{-}C_6H_{11}NHCO\text{-})_2$ (**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).

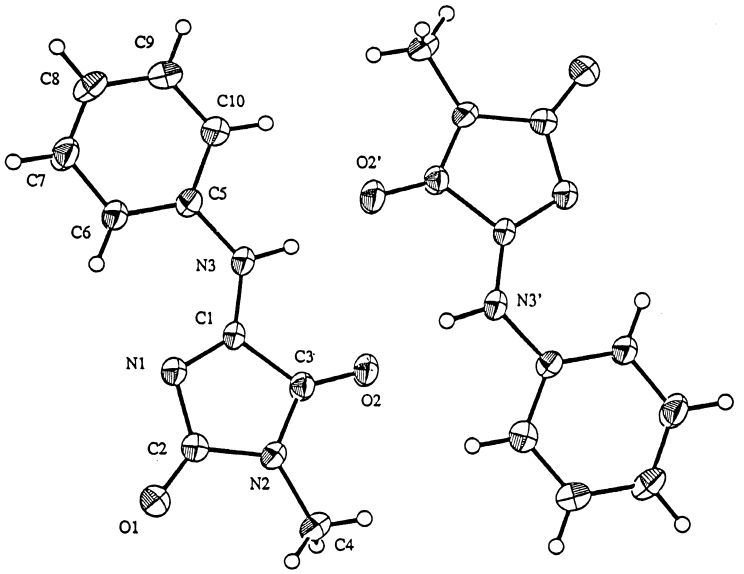
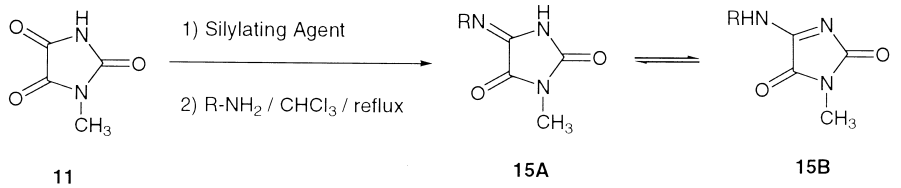


Figure 1.



Scheme 2.

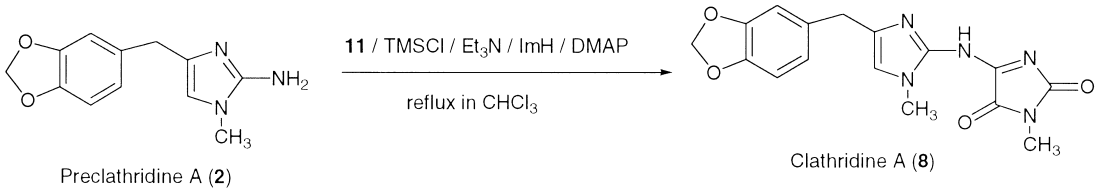
Table 3 shows the results obtained by examining influences of the silylating agents and various primary amines on the condensation. In entry 13, the used primary amine is preclathridine A (**2**), and the product, clathridine A (**8**), was isolated as dark-red crystals, physical and spectral data of 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 CH_3OH), mp 233–235.6°C. IR ($CHCl_3$): 3315, 1784, 1732, 1716, 1672, 1611, 1439, 1392, 1300, 1093 cm^{-1}. ^1H NMR (400 MHz in $CDCl_3$) σ ppm: 3.19 (s, 3H, >N-CH_3), 3.71 (s, 3H, >N-CH_3), 3.81 (s, 2H, Ar-CH_2-Ar), 5.94 (s, 2H, O-CH_2-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). ^{13}C NMR (100 MHz in $CDCl_3$): 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 $C_{16}H_{15}N_5O_4$: 341.1121. Found: 341.1119 (M^+). Anal. calcd for $C_{16}H_{15}N_5O_4$: 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 (%)[e]
1	$C_6H_5NH_2$	TMSCl	**15a**	63.8
2	$C_6H_5NH_2$	TBDMSCl	**15a**	35.0
3	$C_6H_5NH_2$	TMSOTf	**15a**	51.7
4	$C_6H_5NH_2$	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-Et$C_6H_4NH_2$	TMSCl	**15d**	84.3
9	4-Br$C_6H_4NH_2$	TMSCl	**15e**	20.9
10	4-$CH_3OC_6H_4NH_2$	TMSCl	**15f**	82.9
11	2-$CH_3OC_6H_4NH_2$	TMSCl	**15g**	64.9
12	*n*-$C_3H_7NH_2$	TMSCl	**15h**	92.3
13	preclathridine A (**2**)	TMSCl	**8**	73.3

a: 2-amino-1-methylbenzimidazole; b: 2-aminopyridine; c: $TMSO(CH_3O)C{=}CHCH_3$
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 $CHCl_3$ (2.0 ml) was stirred for 2 h at room temperature under an N_2 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 $CHCl_3$ (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 ($CHCl_3$: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-CH_3), 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). ^{13}C 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 $C_{10}H_9N_3O_2$: 203.0695. Found: 203.0691 (M^+). Anal. calcd for $C_{10}H_9N_3O_2$: C, 59.11; H, 4.46; N, 20.68. Found: C, 58.90; H, 4.55; N, 20.43.

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