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Novel Diels–Alder-type dimerization of 5-ethenyl-2-phenylsulfanyl-1*H*-imidazoles and its application to biomimetic synthesis of 12,12′-dimethylageliferin

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Abstract—Diels–Alder-type dimerization of various 5-ethenyl-2-phenylsulfanyl-1*H*-imidazoles provided a novel highly regio- and stereoselective route to the preparation of multifunctionalized 4,5,6,7-tetrahydrobenzimidazoles, the basic skeleton of ageliferin, a biologically active pyrrole–imidazole marine alkaloid. The reaction was applied to the synthesis of 12,12′-dimethylageliferin.

Recently, many types of biologically active pyrrole–imidazole alkaloids have been isolated from marine lives such as sponges, and they have become an important focus of scientific attention.[1] In 1990, ageliferins **1**–**3**, were isolated from *Agelas* sponges and found to have various biological properties such as actomyosin ATPase,[2] antiviral, antibacterial[3] and several other interesting activities.[4] The structural skeleton of **1**–**3** in Fig. 1 has been considered to be biochemically synthesized through [4π+2π] cycloaddition[1e,2,3] of the simplest pyrrole–imidazole alkaloids,[1a] oroidin **4**[5] or/and hymenidin **5**.[6] We have investigated total syntheses of several biologically active imidazole alkaloids,[7] and at this time our attention was focused on the first total synthesis of ageliferins via a biomimetic synthetic route. In this paper, we would like to report the first synthesis of 12,12′-dimethylageliferin **20**.

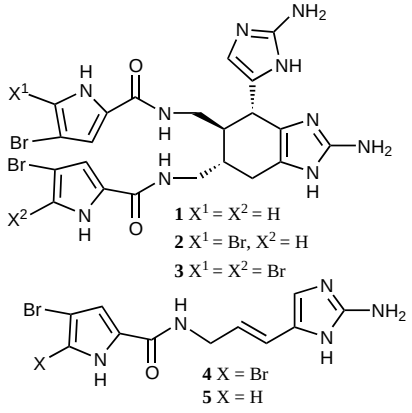

Figure 1.

Although there are several examples of Diels–Alder (DA) reactions of 4- or 5-ethenylimidazole derivatives as the diene component with active dienophiles such as *N*-phenylmaleimide or 4-phenyl-1,2,4-triazoline-3,5-dione,[8] homonuclear DA-type dimerization of 5-alkenylimidazole compounds **8** and **9** has remained unknown.

First, we examined the reactivity of various 5(4)-ethenylimidazole under thermal reaction conditions. The DA-type dimerization precursors **8** and **9** were prepared from 1,2-substituted imidazoles **6** (Scheme 1). The desired homonuclear DA-type dimerization of **8a**, **8b**, **8c**, **9a** and **9b** successfully proceeded as shown in Table 1.[9] Fortunately, we found that the plane and stereo structure of the major products (**10c**–**e**) were consistent with those of ageliferins. The structure of **10a** was confirmed by HMBC experiment, and the regio- and stereochemistry of **10c**–**d** and **11a** was determined by HMBC and NOESY experiments. These correlations of **10d** and **11a** were observed as shown in Fig. 2.[10]

Next, we planned a synthesis of 12,12′-dimethylageliferin **20** from the DA product **10d** (Scheme 2). The

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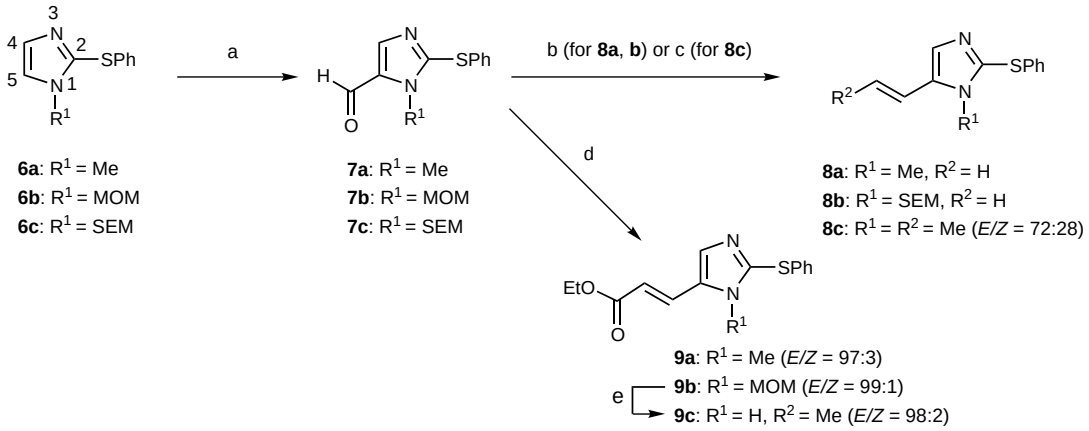
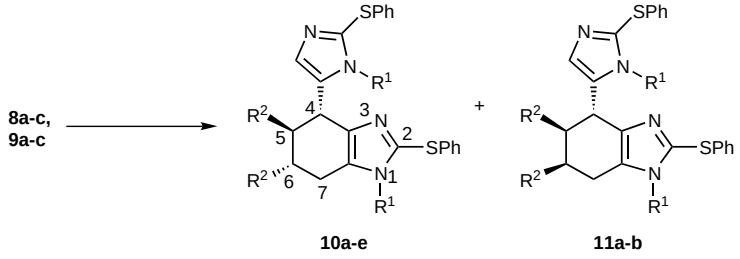


Scheme 1. *Regents and conditions*: (a) LTMP, DMF, THF, DME, −78°C, 98% (**7a**), 83% (**7b**), 95% (**7c**); (b) *n*-BuLi, $Ph_3P^+MeBr^-$, THF, 0°C to rt, 90% (**8a**), 77% (**8b**); (c) PhLi, $Ph_3P^+EtBr^-$, AcOH, *t*-BuOK, THF, Et_2O, −66°C to rt, 92% (**8c**); (d) $(EtO)_2P(O)CH_2CO_2Et$, LiCl, DBU, MeCN, rt, 99% (**9a**), 100% (**9b**); (e) 10% HCl aq., EtOH, 60°C, 71% (from **9b**).

Table 1. DA dimerizations of the alkenyl imidazoles **8** and **9**



Entry	Starting compd.	Reaction condition[a]	Reaction time (h)	R^1	R^2	Yield (**10**+**11**) (%)[b]	Ratio (**10**/**11**)[c]	Product(s)
1	**8a**	A	30	Me	H	93	–	**10a**
2	**8b**	A	30	SEM	H	36	–	**10b**
3	**8c**	A	75	Me	Me	42	1:0	**10c**
4	**9a**	B	30	Me	CO_2Et	55	50:1	**10d**/**11a**
5	**9b**	C	60	MOM	CO_2Et	14[d]	4:1	**10e**/**11b**
6	**9c**	D	60	H	CO_2Et	0[e]	–	–

[a] Reaction condition: (A) neat in sealed tube at 150°C; (B) refluxed in xylene at 140°C; (C) neat in sealed tube at 100°C; (D) neat in sealed tube at 120°C.
[b] Isolated yield.
[c] Determined by ^1H NMR.
[d] Starting material was mainly recovered.
[e] Resinous product was formed.

ester **10d** was reduced with $LiAlH_4$ to give the diol **12** in 98% yield. Protection of the hydroxy groups of **12** followed by desulfurization with a combination of NiCl and $NaBH_4$[11] gave the silyl ether **14** in 69% yield from **12**. Introduction of azide groups into the 2- and 2′-positions of the imidazole nucleus of **14** was achieved by lithiation with *sec*-BuLi followed by treatment with trisyl azide[1b] to give the diazide **15a** in 55% yield accompanied with mono azides **15b** and **15c** (total 30% yield). The diazide **15a** was hydrogenated in the presence of 5% Pd–C, and the resulting primary amino groups were protected with benzaldehyde to afford the diimine **16** (50% in two steps). The TBDPS groups of **16** were removed by the action of CsF, and the resultant diol **17** was subjected the Mitsunobu reaction conditions[12] to give the diazide **18** in 79% yield in two steps. The diazide **18** was converted into the corresponding diamine by selective reduction with PPh_3 in the presence of H_2O,[13] and then the diamine was acylated with 4-bromo-2-(trichloroacetyl)pyrrole[14] to give the protected ageliferin analogue **19** (21% yield in two steps). Finally, hydrolysis of the imino groups of **19** with diluted hydrochloric acid gave 12,12′-dimethylageliferin dihydrochloride **20** as a powdered material, spectral data of which fully supported its structure.[15]

In conclusion, we have successfully developed a convenient and efficient preparation method for the highly functionalized 4,5,6,7-tetrahydrobenzimidazole derivatives by novel homonuclear DA-type dimerization reactions of 5-alkenyl imidazoles with high regio- and stereoselectivity. We are currently investigating the

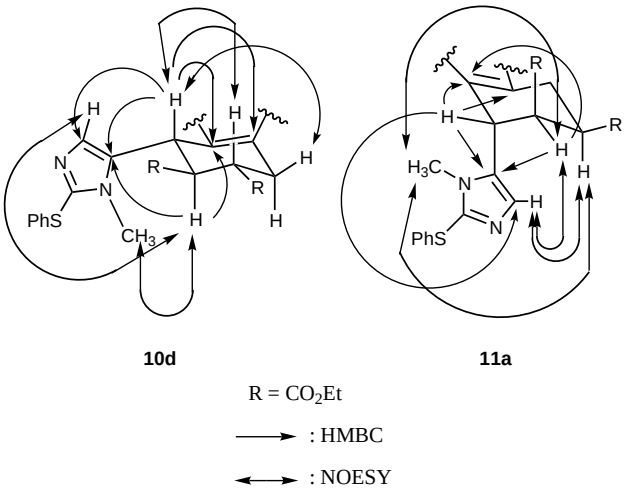


Figure 2. HMBC and NOESY correlations of **10d** and **11a**.

scope of this reaction with various imidazole substitution patterns and the asymmetric total synthesis of ageliferins (**1**–**3**). The results of these studies will be reported in due course.

Acknowledgements

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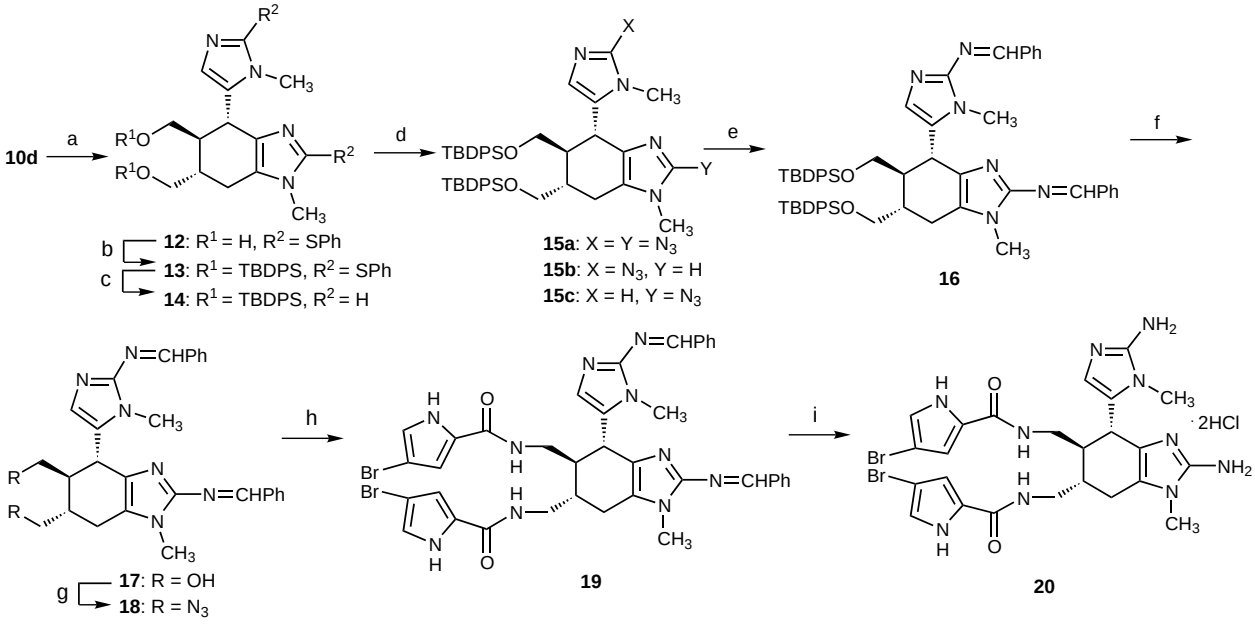

Scheme 2. *Regents and conditions*: (a) $LiAlH_4$, THF, rt, 98%; (b) TBDPSCl, imidazole, DMF, rt, 99%; (c) $NiCl{\cdot}6H_2O$, $NaBH_4$, THF, MeOH, 0°C to rt, 70%; (d) *sec*-BuLi, trisyl azide, THF, DME, −40°C to rt, 55% (**15a**), 30% (**15b**+**15c**); (e) H_2, Pd–C, AcOEt, rt, then PhPHO, PhMe, reflux, 50% (from **15a**); (f) CsF, DMF, 100°C, 83%; (g) DEAD, PPh_3, $(PhO)_2P(O)N_3$, THF, rt, 95%; (h) PPh_3, THF, H_2O, rt, then K_2CO_3, 4-bromo-2-(trichloroacetyl)pyrrole, DMAc, rt, 21%; (i) 0.5 M HCl aq., EtOH, rt, 76%.

M.; Kawasaki, I.; Ohta, S.; Ohishi, Y. *J. Chem. Soc., Perkin Trans. 1* **2001**, 429; (c) Ohta, S.; Tsuno, N.; Nakamura, S.; Taguchi, N.; Yamashita, M.; Kawasaki, I.; Fujieda, M. *Heterocycles* **2000**, *53*, 1939; (d) Ohta, S.; Tsuno, N.; Maeda, K.; Nakamura, S.; Taguchi, N.; Yamashita, M.; Kawasaki, I. *Tetrahedron Lett*. **2000**, *41*, 4623; (e) Kawasaki, I.; Katsuma, H.; Nakayama, Y.; Yamashita, M.; Ohta, S. *Heterocycles* **1998**, *48*, 1887; (f) Kawasaki, I.; Taguchi, N.; Yamashita, M.; Ohta, S. *Chem. Pharm. Bull*. **1997**, *45*, 1393; (g) Kawasaki, I.; Yamashita, M.; Ohta, S. *Chem. Pharm. Bull*. **1996**, *44*, 1831; (h) Kawasaki, I.; Katsuma, H.; Nakayama, Y.; Yamashita, M.; Ohta, S. *Heterocycl. Commun*. **1996**, *2*, 189; (i) Kawasaki, I.; Taguchi, N.; Yoneda, Y.; Yamashita, M.; Ohta, S. *Heterocycles* **1996**, *43*, 1375; (j) Kawasaki, I.; Taguchi, N.; Yamamoto, T.; Yamashita, M.; Ohta, S. *Tetrahedron Lett*. **1995**, *36*, 8251; (k) Kawasaki, I.; Yamashita, M.; Ohta, S. *Chem. Commun*. **1994**, 2085.

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9. Compound **10d**: ^{1}H NMR (δ, ppm in $CDCl_3$): 1.15 (t, $J=7.1$ Hz, 3H), 1.20 (t, $J=7.1$ Hz, 3H), 2.94–3.04 (m, 2H), 3.25–3.39 (m, 2H), 3.51 (s, 3H), 3.57 (s, 3H), 3.96–4.14 (m, 4H), 4.49 (br d, $J=8.2$ Hz, 1H), 6.86 (s, 1H), 7.09–7.24 (m, 10H); ^{13}C NMR (δ, ppm): 13.95, 14.01, 22.9, 31.2, 31.9, 35.9, 41.8, 47.8, 61.2, 61.4, 126.1, 126.6, 127.3, 127.6, 128.0, 129.1, 129.2, 129.7, 133.8, 134.6, 135.4, 135.5, 137.7, 137.8, 172.3, 172.6; IR: 3017, 1725, 1474, 1447, 1368, 1266, 1229, 1177, 1091, 1032; HRMS (EI+): m/z, calcd: 576.1865 M^+; found: 576.1859.
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15. Compound **20**: ^{1}H NMR (δ, ppm in CD_3OD): 2.40 (m, 1H), 2.47 (m, 1H), 2.55 (br d, $J=17.0$, 1H), 2.75 (dd, $J=17.0$, 5.0, 1H), 3.41 (s, 3H), 3.41 (s, 3H), 3.42–3.49 (m, 2H), 3.56 (dd, $J=9.5$, 5.1, 1H), 3.67 (dd, $J=9.5$, 4.2, 1H), 3.95 (br s, 1H), 6.73 (br s, 1H), 6.83 (d, $J=1.5$, 1H), 6.90 (d, $J=1.5$, 1H), 6.92 (d, $J=1.5$, 1H), 6.95 (d, $J=1.5$, 1H); HRMS (FAB+): m/z, calcd: 647.0842 $(M+H)^+$; found: 647.0839.