Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 62 (2006) 10182–10192

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

Ikuo Kawasaki, Norihiro Sakaguchi, Abdul Khadeer, Masayuki Yamashita and Shunsaku Ohta*

Department of Functional Molecular Chemistry, 21st Century COE Program, Kyoto Pharmaceutical University, Misasagi Yamashinaku, Kyoto 607-8414, Japan

Received 19 July 2006; revised 6 August 2006; accepted 8 August 2006
Available online 1 September 2006

Abstract—Homonuclear Diels–Alder 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, which is the basic skeleton of ageliferin, a biologically active pyrrole-imidazole marine alkaloid. The reaction was applied to the synthesis of 12,12′-dimethylageliferin.

1. Introduction

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.[1,2] In 1990, ageliferins **1**–**3** were isolated from *Agelas* sponges and found to have various biological properties such as actomyosin ATPase,[3] antiviral, antibacterial,[4] and several other interesting activities.[5] The structural skeleton of **1**–**3** in Figure 1 has been considered to be biochemically synthesized through [4π+2π] cycloaddition[1b,3,4] of the simplest pyrrole-imidazole alkaloids, oroidin **4**[6] or/and hymenidin **5**.[7] We have investigated the total synthesis of several biologically active imidazole marine alkaloids,[8] and at this time our attention was focused on the asymmetric total synthesis of ageliferins via a biomimetic synthetic route. In this paper, we would like to present a highly regio- and stereoselective homonuclear Diels–Alder (DA) dimerization of various 5-ethenyl-2-phenylsulfanyl-1*H*-imidazoles **8**, **9**, and the first synthesis of a 12,12′-dimethyl derivative of ageliferin **22**.[9] In 2004, Baran and co-workers reported the total synthesis of **1** by microwave heating of sceptrin,[10] a pyrrole-imidazole alkaloid.[11]

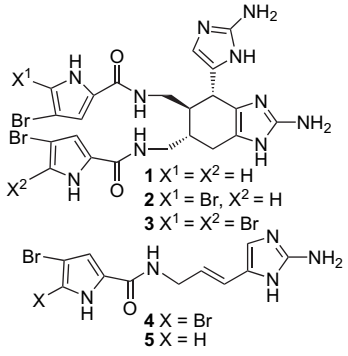


Figure 1.

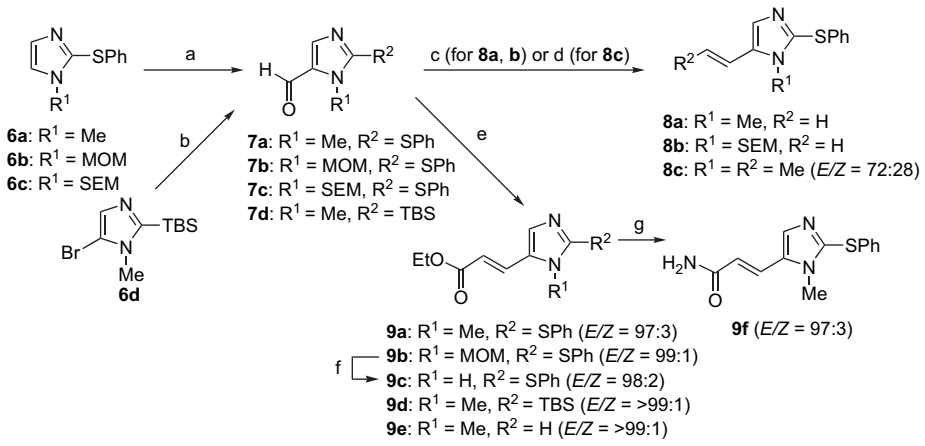
2. Results and discussion

To examine the reactivity of 5(4)-ethenylimidazoles under thermal reaction conditions, various DA dimerization precursors, **8a**–**c** and **9a**–**f**, were prepared from 1,2-disubstituted imidazoles **6** as shown in Scheme 1.[12] Formylimidazoles **7** were prepared through 5-lithioimidazoles[13] and then converted to vinylimidazoles, **8a**–**c**, by Wittig reaction. *E*-Acrylates **9a**–**e** were prepared from **7** by applying Horner–Wadsworth–Emmons reaction.[14] The amide **9f** was obtained from the ester **9a**.

The result of DA dimerization of **8a**–**c** and **9a**–**f** is summarized in Table 1. The desired homonuclear DA dimerization of **8a**–**c** and **9a**,**b** proceeded successfully (entries 1–5). Although there have been several examples of intermolecular 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,[15,16] homonuclear DA dimerization of imidazole derivatives has not been developed.

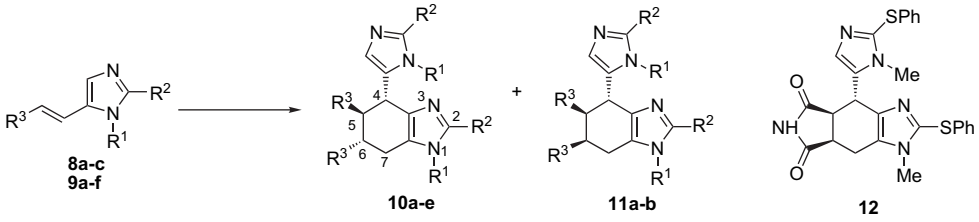
* Corresponding author. Tel.: +81 75 595 4703; fax: +81 75 595 4795; e-mail: sohta@mb.kyoto-phu.ac.jp

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.08.027



Scheme 1. Reagents and conditions: (a) LTMP, DMF, THF, DME, −78 °C, 98% (**7a**), 83% (**7b**), 95% (**7c**); (b) *n*-BuLi, DMF, THF, −78 °C, 58%; (c) *n*-BuLi, $Ph_3P^+MeBr^-$, THF, 0 °C to rt, 90% (**8a**), 77% (**8b**); (d) PhLi, $Ph_3P^+EtBr^-$, AcOH, *t*-BuOK, THF, Et_2O, −66 °C to rt, 92% (**8c**); (e) $(EtO)_2P(O)CH_2CO_2Et$, LiCl, DBU, MeCN, rt, 99% (**9a**), 100% (**9b**), 86% (**9d**); (f) 10% HCl aq, EtOH, 60 °C, 71% (from **9b**); (g) NH_3, MeOH, rt, 59% (from **9a**).

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



Entry	Starting Compd	Reaction condition[a]	Reaction time (h)	R^1	R^2	R^3	Yield (**10**+**11** or **12**) (%)[b]	Ratio (**10**/**11** or **12**)[c]	Product(s)
1	**8a**	A	30	Me	SPh	H	92	—	**10a**
2	**8b**	B	30	SEM	SPh	H	36	—	**10b**
3	**8c**	B	75	Me	SPh	Me	42	1:0	**10c**
4	**9a**	A	30	Me	SPh	CO_2Et	55	50:1	**10d**/**11a**
5	**9b**	C	60	MOM	SPh	CO_2Et	14[d]	4:1	**10e**/**11b**
6	**9c**	D	60	H	SPh	CO_2Et	0[e]	—	—
7	**9d**	D	60	Me	TBS	CO_2Et	0[e]	—	—
8	**9e**	D	60	Me	H	CO_2Et	0[d]	—	—
9	**9f**	D	30	Me	SPh	$CONH_2$	59	1:1.2	**10f**/**12**

[a] Reaction conditions: (A) refluxed in xylene at 140 °C; (B) neat in sealed tube at 150 °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] Decomposed.

Fortunately, we found that the plane and stereo structure of the major products **10c–e** were consistent with those of ageliferins.[17] Especially, the DA dimerization of **9a** proceeded in regio- and stereoselective fashion to give the multifunctionalized 4,5,6,7-tetrahydrobenzimidazole **10d** in 54% yield (entry 4). On the other hand, the reaction of **9c–e** gave no DA product (entries 6–8); this result shows that the presence of the alkyl group at the 1-position and the phenylsulfanyl group at the 2-position of the imidazole ring might be important for the DA dimerization of 5-ethenylimidazoles. The amide **9f** provided the DA dimerized product in relatively good yield (59%); however, the structure of the major product was imide **12** and unfortunately the undesired 5,6-*cis*-substituted 4,5,6,7-tetrahydrobenzimidazole.

We calculated the LUMO and HOMO energies and orbital coefficients of 5-[(2-methoxycarbonyl)ethenyl]-1-methyl-2-phenylsulfanyl-1*H*-imidazole **9g** as a model substrate using the MOPAC PM3 semiempirical method (Fig. 2, Table 2).[18] These results indicated that the ethyl acrylate **9a** might also react as both diene (C_4–C_5–C_6–C_7) and dienophile (C_6–C_7) in the homonuclear [4π+2π] cycloaddition to produce the desired product **10d**.

Next, we planned the synthesis of **16a**,**b** starting from diester **10d** as model compounds of the ageliferin analogue (Scheme 2). The diol **13** was obtained by $LiAlH_4$ reduction of the diester **10d** in 98% yield. Introduction of the nitrogen function into the side chain of the 5- and 6-position of the 4,5,6,7-tetrahydrobenzimidazole nucleus was achieved by Mitsunobu reaction, combination of DEAD, PPh_3, and phthalimide, to give the imide **14**. Removal of the phenylsulfanyl groups of **14** by desulfurization with a combination of $NiCl_2$ and $NaBH_4$[19] gave the 2,2′-unsubstituted derivative **15**

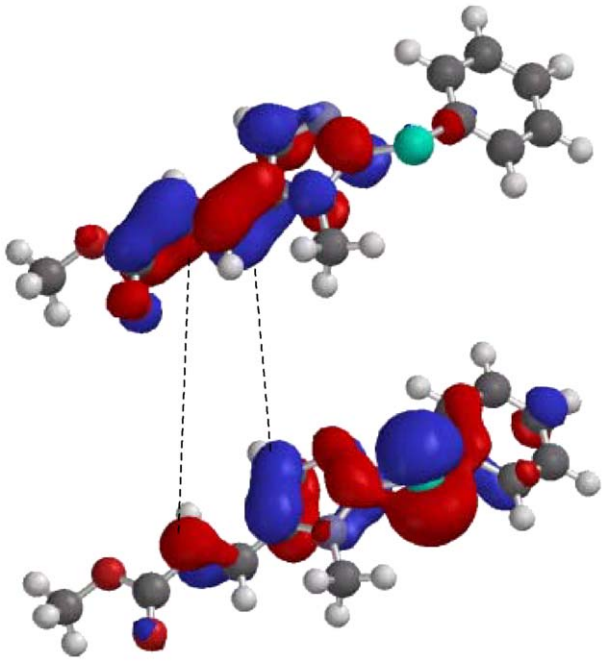


Figure 2. Approach of the LUMO (upper) to HOMO (lower) orbital of the methyl ester **9g**.

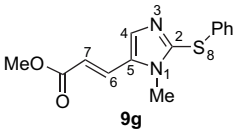
in 62% yield. Two-step conversion of **14** and **15** afforded the pyrrole-imidazole dimers **16a** and **b** in 49 and 72% yields, respectively.

Encouraged by this result, we then planned the synthesis of 12,12′-dimethylageliferin **24** (Scheme 3). The hydroxyl groups of **13** were protected by the TBDPS group to give the silyl ether **17** in 99% yield and the stereo structure of **17** was further confirmed by X-ray crystallographic analysis as shown in Figure 3.[20] After removal of the phenylsulfanyl groups of **17** by desulfurization with $NiCl_2$ and $NaBH_4$, introduction of azide groups into the 2- and 2′-position of the imidazole nucleus of **18** was achieved by lithiation with *sec*-BuLi followed by treatment with trisyl azide[21] to give the diazide **19** in 39% overall yield from **17**. The diazide **19** was hydrogenated over 5% Pd/C, and the resulting primary amino groups were protected with benzaldehyde to afford the diimine **20** followed by the removal of TBDPS groups by the action of CsF to give the diol **21** (42% in three steps). After several examinations for introduction of a nitrogen function by a substitution reaction of **21**, we found that the diazide compound **22** was obtained in excellent yield (95%) by the combination of DEAD, PPh_3, and DPPA.[22] The diazide **22** was converted to the corresponding diamine by selective reduction with PPh_3 in the presence of H_2O,[23] and then the diamine was acylated with 4-bromo-2-(trichloroacetyl)pyrrole[24] to give the protected ageliferin analogue **23** (21% yield in two steps). Finally, hydrolysis of the imino groups of **23** with dilute hydrochloric acid gave 12,12′-dimethylageliferin dihydrochloride **24** as powder.

3. 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 dimerization reactions of 5-alkenyl imidazoles with high regio- and stereoselectivity. And the method could be applied to the first synthesis of an ageliferin derivative **24**. We are currently investigating the scope of this reaction with various

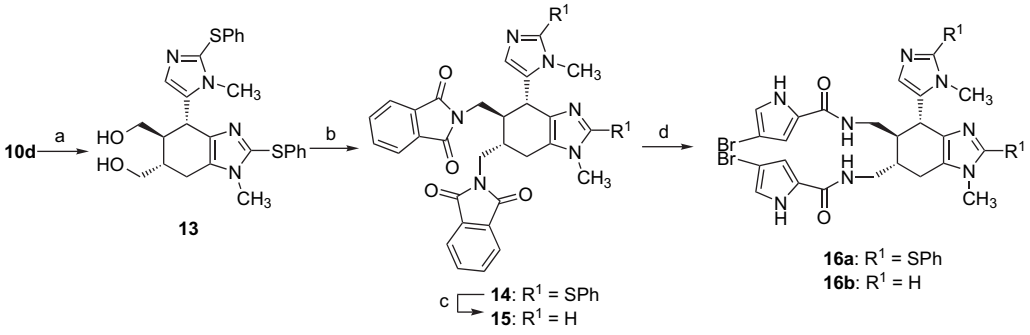
Table 2. The LUMO and HOMO energies and orbital coefficients of **9g**



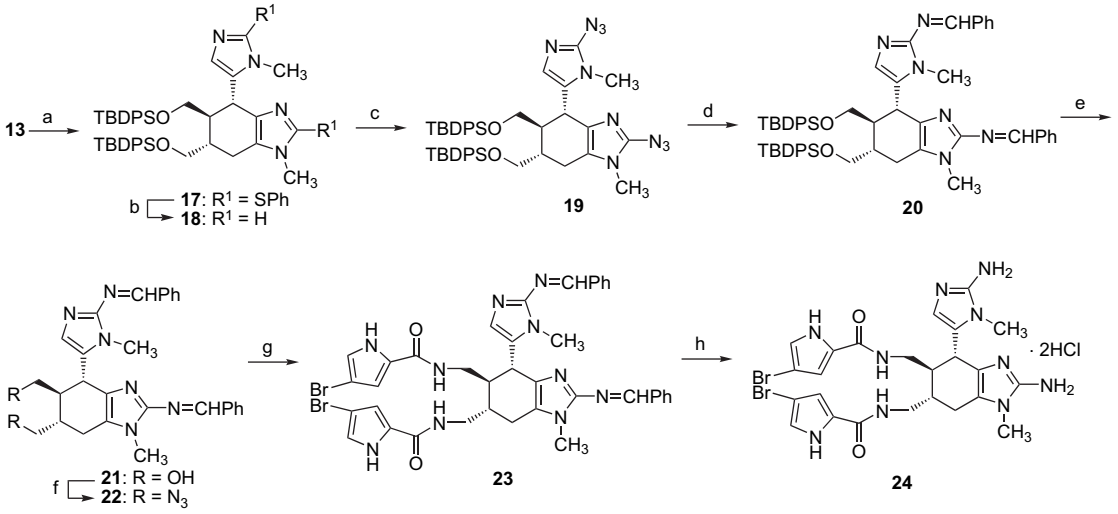
9g

		Coefficients of π-orbital at the atom positions							
	Energy (eV)	1[a]	2	3	4	5	6	7	8
LUMO	−0.9008	0.35	−0.34	0.08	0.31	−0.28	**−0.45**	**0.44**	0.12
HOMO	−8.7552	0.10	0.33	0.21	**−0.27**	−0.37	0.10	**0.27**	−0.49

[a] Position number.



Scheme 2. Reagents and conditions: (a) $LiAlH_4$, THF, rt, 98%; (b) DEAD, PPh_3, phthalimide, THF, 0 °C–rt, 63%; (c) $NiCl_2 \cdot 6H_2O$, $NaBH_4$, THF, MeOH, 0 °C–rt, 62%; (d) NH_2NH_2, 70 °C, then K_2CO_3, 4-bromo-2-(trichloroacetyl)pyrrole, DMAc, rt, 49% (**16a**), 72% (**16b**).



Scheme 3. Reagents and conditions: (a) TBDPSCl, imidazole, DMF, rt, 99%; (b) $NiCl_2 \cdot 6H_2O$, $NaBH_4$, THF, MeOH, 0 °C–rt, 70%; (c) *sec*-BuLi, trisyl azide, THF, DME, −40 °C to rt, 55%; (d) H_2, Pd/C, AcOEt, rt, then PhCHO, PhMe, reflux, 50%; (e) CsF, DMF, 100 °C, 83%; (f) DEAD, PPh_3, $(PhO)_2P(O)N_3$, THF, rt, 95%; (g) PPh_3, THF, H_2O, rt, then K_2CO_3, 4-bromo-2-(trichloroacetyl)pyrrole, DMAc, rt, 21%; (h) 0.5 M HCl aq, EtOH, rt, 76%.

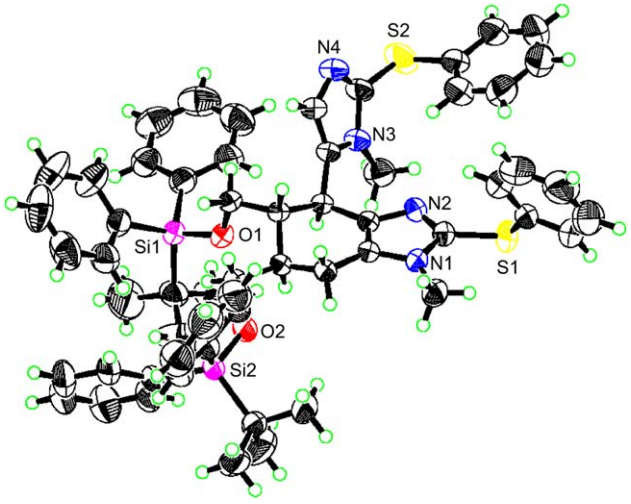


Figure 3. ORTEP plot of **17**.

imidazole substitution patterns and the asymmetric total synthesis of ageliferins (**1–3**) and their analogues.

4. Experimental

4.1. General

Melting points were measured with a Yanaco MP micro-melting point apparatus and are uncorrected. IR spectra were taken with Shimadzu IR-435 spectrophotometer. NMR (^1H, ^{13}C) spectra were measured on Varian UNITY INOVA 400NB (^1H: 400 MHz, ^{13}C: 100 MHz) and the chemical shifts were expressed in parts per million (ppm) downfield from tetramethylsilane as the internal standard (^1H) or referenced of solvent peak (^{13}C). MS and HRMS were measured on JEOL JMS BU-20 (EI) or JEOL JMS-SX 102A QQ (FAB) spectrometer. Silica gel (Merck Art. 7737) was used for column chromatography.

4.1.1. General procedure for 5-formylimidazoles (7a–c), synthesis of 5-formyl-1-methyl-2-phenylsulfanyl-1*H*-imidazole (7a) as an example. *n*-BuLi (1.6 M in *n*-hexane, 49.3 mL, 78.8 mmol) was added to a stirred solution of 2,2,6,6-tetramethylpiperidine (TMP) (13.3 mL, 78.8 mmol) in THF (50 mL) and DME (50 mL) under N_2 at −78 °C. After stirring for 30 min at the same temperature, a solution of **6a**[12a] (10.00 g, 52.56 mmol) in THF (50 mL) was added to the reaction mixture and the whole was stirred for 1 h at −78 °C. Then, DMF (6.10 mL, 78.8 mmol) was slowly added to the reaction mixture and the whole was stirred for 4 h at ambient temperature. H_2O (10 mL) was added to the mixture and after evaporation of the solvent the products were extracted with AcOEt (100 mL×2). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to give a crystalline residue, which was purified by recrystallization from AcOEt/*n*-hexane to give **7a** as yellow needles (11.184 g, 98%); mp 57–58 °C; ^1H NMR ($CDCl_3$): δ 3.91 (3H, s, NCH_3), 7.32–7.42 (5H, m, Ph), 7.78 (1H, s, 4-H), 9.66 (1H, s, CHO); ^{13}C NMR ($CDCl_3$): δ 33.3, 128.4, 129.5, 130.1, 131.5, 133.2, 143.4, 149.6, 178.4; IR ($CHCl_3$): ν_{max} 2961, 2807, 1664, 1457, 1325, 1154, 1079 cm^{-1}; MS (EI): *m/z* 218 (M^+, 100), 190 (24), 148 (19), 136 (13), 121 (33), 109 (20), 91 (59), 77 (27); HRMS (EI) *m/z* 218.0509 (M^+) (requires $C_{11}H_{10}N_2OS$: 218.0514). Found: C, 60.29; H, 4.59; N, 12.73; $C_{11}H_{10}N_2OS$ requires C, 60.53; H, 4.62; N, 12.83.

4.1.2. 5-Formyl-1-methoxymethyl-2-phenylsulfanyl-1*H*-imidazole (7b). Starting with **6b**[12b] (5.507 g, 25.00 mmol), *n*-BuLi (23.4 mL, 37.5 mmol), TMP (6.33 mL, 37.5 mmol), DMF (2.90 mL, 37.5 mmol), THF (48 mL), and DME (24 mL), **7b** was purified by column chromatography (AcOEt/*n*-hexane=1/3) and isolated as a yellow viscous oil (5.127 g, 83%); ^1H NMR ($CDCl_3$): δ 3.36 (3H, s, OCH_3), 5.78 (2H, s, NCH_2O), 7.38–7.55 (5H, m, Ph), 7.77 (1H, s, 4-H), 9.67 (1H, s, CHO); ^{13}C NMR ($CDCl_3$): δ 56.5, 75.5, 129.06, 129.13, 129.5, 132.85, 132.92, 144.2, 152.3, 178.2; IR ($CHCl_3$): ν_{max} 2972, 2807, 1663, 1473, 1439, 1333, 1149, 1116 cm^{-1}; MS (EI): *m/z* 248 (M^+, 100), 233 (31), 217 (43), 205 (72), 139 (33), 121 (82), 109 (31), 91 (41),

77 (43), 65 (29), 51 (37). HRMS (EI) *m/z* 248.0617 (M^+) (requires $C_{12}H_{12}N_2O_2S$: 248.0619).

4.1.3. 5-Formyl-1-1-[2-(trimethylsilyl)ethoxymethyl]-2-phenylsulfanyl-1*H*-imidazole (7c).[12e] Starting with **6c**[12c] (0.581 g, 1.90 mmol), *n*-BuLi (1.78 mL, 2.85 mmol), TMP (0.48 mL, 2.85 mmol), DMF (0.22 mL, 2.85 mmol), THF (3.6 mL), and DME (1.8 mL), **7c** was purified by column chromatography (AcOEt/*n*-hexane=1/3) and isolated as a yellow viscous oil (0.604 g, 95%); ^{1}H NMR ($CDCl_3$): δ −0.02 (9H, s, $SiMe_3$), 0.91 (2H, t, J=8.2 Hz, CH_2CH_2Si), 3.59 (2H, t, J=8.2 Hz, CH_2CH_2Si), 5.81 (2H, s, NCH_2O), 7.36–7.40 (3H, m, Ph), 7.52–7.54 (2H, m, Ph), 7.76 (1H, s, 4-H), 9.66 (1H, s, CHO).

4.1.4. 2-*tert*-Butyldimethylsilyl-5-formyl-1-methyl-1*H*-imidazole (7d). *n*-BuLi (3.13 mL, 5.00 mmol) was added to a stirred solution of **6d**[12d] (1.376 g, 5.00 mmol) in THF (5 mL) under N_2 at −78 °C. After stirring for 20 min at the same temperature, DMF (0.39 mL, 5.00 mmol) was added to the reaction mixture and the whole was stirred for 2 h at ambient temperature. H_2O (3 mL) was added to the mixture and after evaporation of the solvent the products were extracted with Et_2O (20 mL×2). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to give an oily residue, which was purified by column chromatography (AcOEt/*n*-hexane=1/3) to give **7d** as a yellow viscous oil (652 mg, 58%); ^{1}H NMR ($CDCl_3$): δ 0.44 (6H, s, $SiMe_2$), 0.98 (9H, s, CMe_3), 4.02 (3H, s, NMe), 7.89 (1H, s, 4-H), 9.77 (1H, s, CHO); ^{13}C NMR ($CDCl_3$): δ −4.9, 17.7, 26.4, 34.8, 133.4, 144.5, 159.2, 179.1; IR ($CHCl_3$): ν_{max} 2934, 2830, 1667, 1459, 1250, 1145, 837, 808 cm^{-1}; MS (EI): *m/z* 224 (M^+, 3), 209 (8), 167 (100), 140 (12), 113 (3); HRMS (EI) *m/z* 224.1340 (M^+) (requires $C_{11}H_{20}N_2OSi$: 224.1345).

4.1.5. General procedure for 5-ethenylimidazoles (8a,b), synthesis of 1-methyl-2-phenylsulfanyl-5-ethenyl-1*H*-imidazole (8a) as an example. *n*-BuLi (3.13 mL, 5.00 mmol) was added to a stirred solution of methyltriphenylphosphonium bromide (1.79 g, 5.00 mmol) in THF (3 mL) under N_2 at 0 °C. After stirring for 1 h at the same temperature, a solution of **7a** (218 mg, 1.00 mmol) in THF (2 mL) was added to the reaction mixture and the whole was stirred for 6.5 h at ambient temperature. H_2O (3 mL) was added to the mixture and after evaporation of the solvent the products were extracted with AcOEt (20 mL×2). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to give an oily residue, which was purified by column chromatography (AcOEt) and recrystallized from AcOEt/*n*-hexane to give **8a** as yellow needles (195 mg, 90%); mp 59–62 °C; ^{1}H NMR ($CDCl_3$): δ 3.60 (3H, s, NCH_3), 5.30 (1H, dd, J=1.1, 11.4 Hz, C=C*H*H), 5.66 (1H, dd, J=1.1, 17.6 Hz, C=CH*H*), 6.48 (1H, ddd, J=0.7, 11.4, 17.6 Hz, *H*C=CH_2), 7.13–7.20 (3H, m, ArH), 7.23–7.28 (2H, m, ArH), 7.35 (1H, s, 4-H); ^{13}C NMR ($CDCl_3$): δ 31.6, 115.7, 123.2, 126.6, 127.9, 128.0, 129.2, 134.4, 134.8, 138.5; IR ($CHCl_3$): ν_{max} 2960, 1722, 1473, 1440, 1389, 1243, 1213, 1041 cm^{-1}; MS (EI): *m/z* 216 (M^+, 100), 183 (14), 91 (20), 80 (12), 68 (10); HRMS (EI) *m/z* 216.0714 (M^+) (requires $C_{12}H_{12}N_2S$: 216.0721). Found: C, 66.65; H, 5.65; N, 12.75; $C_{12}H_{12}N_2S$ requires C, 66.63; H, 5.59; N, 12.95.

4.1.6. 1-[2-(Trimethylsilyl)ethoxymethyl]-2-phenylsulfanyl-5-ethenyl-1*H*-imidazole (8b). Starting with **7c** (600 mg, 1.79 mmol), *n*-BuLi (5.59 mL, 8.95 mmol), methyltriphenylphosphonium bromide (3.20 g, 8.95 mmol), and THF (9 mL), **8b** was purified by column chromatography (AcOEt/*n*-hexane=1/1) and isolated as a yellow viscous oil (459 mg, 77%); ^{1}H NMR ($CDCl_3$): δ −0.07 (9H, s, $SiMe_3$), 0.82 (2H, t, J=8.2 Hz, CH_2CH_2Si), 3.40 (2H, t, J=8.2 Hz, CH_2CH_2Si), 5.32 (1H, dd, J=1.1, 11.4 Hz, C=C*H*H), 5.43 (2H, s, NCH_2O), 5.72 (1H, dd, J=1.1, 17.8 Hz, C=CH*H*), 6.64 (1H, ddd, J=0.7, 11.4, 17.8 Hz, *H*C=CH_2), 7.16–7.28 (5H, m, Ph), 7.38 (1H, s, 4-H); ^{13}C NMR ($CDCl_3$): δ −1.5, 17.4, 66.1, 73.3, 116.1, 123.1, 126.8, 128.1, 128.4, 129.2, 134.4, 134.7, 138.9; IR ($CHCl_3$): ν_{max} 2935, 1246, 1172, 1088, 856, 834 cm^{-1}; MS (EI): *m/z* 332 (M^+, 31), 237 (23), 259 (26), 73 (100); HRMS (EI) *m/z* 332.1378 (M^+) (requires $C_{17}H_{24}N_2OSSi$: 332.1379).

4.1.7. 1-Methyl-2-phenylsulfanyl-5-(1-propenyl)-1*H*-imidazole (8c). PhLi (0.97 M in Et_2O/cyclohexane, 27.6 mL, 26.8 mmol) was added to a stirred solution of ethyltriphenylphosphonium bromide (9.95 g, 26.8 mmol) in THF (22.5 mL) and Et_2O (15 mL) under N_2 at 0 °C. The reaction mixture was cooled to −70 °C, and a solution of **7a** (2.925 mg, 13.40 mmol) in THF (15 mL) and Et_2O (12 mL) was added to it. Then, PhLi (13.8 mL, 13.4 mmol) was added to the mixture at −40 °C and the reaction temperature was elevated to −20 °C. AcOH (0.77 mL, 13.4 mmol) and *t*-BuOK (2.26 g, 20.1 mmol) were added to the reaction mixture and the whole was stirred for 2 h at ambient temperature. H_2O (3 mL) was added to the mixture and after evaporation of the solvent the products were extracted with AcOEt (30 mL×2). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to give an oily residue, which was purified by column chromatography (AcOEt/*n*-hexane=1/1) to give **8c** (*E*/*Z*=72/28) as a yellow viscous oil (2.919 g, 95%). *E*-**8c**: ^{1}H NMR ($CDCl_3$): δ 1.89 (3H, t, J=2.8 Hz, C=CH*Me*), 3.56 (3H, s, NCH_3), 6.10–6.13 (1H, m, C=C*H*Me), 6.14–6.16 (1H, m, C*H*=CHMe), 7.11–7.27 (6H, m, Ph and 4-H); ^{13}C NMR ($CDCl_3$) δ: 18.7, 31.3, 117.4, 126.3, 126.7, 127.6, 128.6, 129.1, 134.6, 135.2, 137.1; IR ($CHCl_3$): ν_{max} 2934, 1579, 1474, 1478, 1395, 1097 cm^{-1}; MS (EI): *m/z* 230 (M^+, 100), 215 (52), 197 (11), 91 (13), 80 (15); HRMS (EI) *m/z* 230.0875 (M^+) (requires $C_{13}H_{14}N_2S$: 230.0878).

4.1.8. General procedure for 5-ethenylimidazoles (9a,b,d), synthesis of 5-[(2-ethoxycarbonyl)ethenyl]-1-methyl-2-phenylsulfanyl-1*H*-imidazole (9a) as an example. DBU (11.3 mL, 75.6 mmol) was added to a stirred solution of LiCl (3.20 g, 75.6 mmol) and triethyl phosphonoacetate (15.0 mL, 75.6 mmol) in CH_3CN (250 mL) under N_2 at 0 °C. After stirring for 10 min at the same temperature, **7a** (11.000 g, 50.39 mmol) was added to the reaction mixture and the whole was stirred for 5 h at ambient temperature. H_2O (10 mL) was added to the mixture and after evaporation of the solvent the products were extracted with AcOEt (100 mL×2). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to give a crystalline residue, which was purified by recrystallization from AcOEt/*n*-hexane to give **9a** (*E*/*Z*=97/3) as colorless needles (14.083 g, 97%); mp 64–66 °C. *E*-**9a**: ^{1}H NMR ($CDCl_3$): δ 1.33 (3H, t, J=7.1 Hz, CH_2CH_3), 3.69 (3H, s, NCH_3), 4.26 (2H, q,

J=7.1 Hz, CH_2CH$_3$), 6.31 (1H, d, J=15.9 Hz, C=CHCO), 7.13–7.20 (5H, m, Ph), 7.48 (1H, dd, J=0.5, 15.9 Hz, CH=CHCO), 7.58 (1H, s, 4-H); ^{13}C NMR ($CDCl_3$): δ 14.3, 32.0, 60.7, 117.2, 127.2, 129.0, 129.4, 129.5, 131.5, 132.2, 133.4, 142.5, 166.7; IR ($CHCl_3$): ν_{max} 2964, 1699, 1630, 1441, 1303, 1276, 1178, 1155 cm^{-1}; MS (EI): m/z 288 (M$^+$, 100), 259 (31), 243 (15), 215 (87), 121 (15), 109 (16), 91 (30), 80 (16), 65 (8), 51 (10); HRMS (EI) m/z 288.0930 (M$^+$) (requires $C_{15}H_{16}N_2O_2S$: 288.0932). Found: C, 62.66; H, 5.65; N, 9.69; $C_{15}H_{16}N_2O_2S$ requires C, 62.48; H, 5.59; N, 9.71.

4.1.9. 5-[(2-Ethoxycarbonyl)ethenyl]-1-methoxymethyl-2-phenylsulfanyl-1*H*-imidazole (9b). Starting with **7b** (4.924 g, 19.83 mmol), DBU (4.4 mL, 29.7 mmol), LiCl (1.26 g, 29.7 mmol), triethyl phosphonoacetate (5.9 mL, 29.7 mmol), and CH_3CN (100 mL), **9b** was purified by column chromatography (AcOEt/*n*-hexane=1/3) and recrystallized from AcOEt/*n*-hexane as colorless needles (6.301 g, 100%, *E*/*Z*=99/1); mp 71–73 °C. *E*-**9b**: ^{1}H NMR ($CDCl_3$): δ 1.32 (3H, t, J=7.1 Hz, CH_2CH_3), 3.22 (3H, s, OMe), 4.25 (q, 2H, J=7.1 Hz, CH_2CH$_3$), 5.47 (2H, s, NCH$_2$), 6.37 (1H, d, J=16.1 Hz, C=CHCO), 7.22–7.32 (5H, m, Ph), 7.58 (1H, dd, J=0.6, 15.9 Hz, CH=CHCO), 7.58 (1H, s, 4-H); ^{13}C NMR ($CDCl_3$): δ 14.2, 56.1, 60.6, 75.1, 118.1, 127.5, 129.0, 129.3, 129.4, 131.4, 132.8, 132.9, 143.3, 166.6; IR ($CHCl_3$): ν_{max} 2961, 1699, 1629, 1477, 1366, 1303, 1182, 1148, 1110 cm^{-1}; MS (EI): m/z 318 (M$^+$, 100), 275 (20), 227 (26), 121 (20), 91 (14); HRMS (EI) m/z 318.1027 (M$^+$) (requires $C_{16}H_{18}N_2O_3S$: 318.1038). Found: C, 60.11; H, 5.80; N, 8.71; $C_{16}H_{18}N_2O_3S$ requires C, 60.36; H, 5.70; N, 8.80.

4.1.10. 2-*tert*-Butyldimethylsilyl-5-(2-ethoxycarbonylethenyl)-1-methyl-1*H*-imidazole (9d). Starting with **7d** (449 mg, 2.00 mmol), DBU (0.45 mL, 3.00 mmol), LiCl (127 mg, 3.00 mmol), triethyl phosphonoacetate (0.60 mL, 3.00 mmol), and CH_3CN (15 mL), **9d** was purified by column chromatography (AcOEt/*n*-hexane=1/1) and isolated as a yellow viscous oil (507 mg, 86%, *E*/*Z*=99/1). *E*-**9d**: ^{1}H NMR ($CDCl_3$): δ 0.33 (6H, s, SiMe$_2$), 0.87 (9H, s, CMe$_3$), 1.23 (3H, t, J=7.1 Hz, CH_2CH_3), 3.67 (3H, s, NMe), 4.14 (2H, q, J=7.1 Hz, CH_2CH$_3$), 6.20 (1H, d, J=15.9 Hz, C=CHCO), 7.46 (1H, d, J=15.9 Hz, CH=CHCO), 7.54 (1H, s, 4-H); ^{13}C NMR ($CDCl_3$): δ −4.8, 14.2, 17.7, 26.4, 32.9, 60.4, 116.2, 129.6, 131.0, 132.8, 154.4, 167.0; IR ($CHCl_3$): ν_{max} 2928, 1694, 1627, 1303, 1271, 1250, 1201, 1147 cm^{-1}; MS (EI): m/z 294 (M$^+$, 11), 279 (5), 249 (7), 237 (100), 165 (37), 135 (6), 113 (10), 75 (41), 59 (8); HRMS (EI) m/z 294.1764 (M$^+$) (requires $C_{15}H_{26}N_2O_2Si$: 294.1763).

4.1.11. 4-[(2-Ethoxycarbonyl)ethenyl]-2-phenylsulfanyl-1*H*-imidazole (9c). A solution of **9b** (200 mg, 0.63 mmol) in HCl aq (10%, 3 mL) and EtOH (3 mL) was heated at 60 °C for 2 h. The reaction mixture was basified by adding K_2CO_3 and the products were extracted with AcOEt (10 mL×2). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to give an oily residue, which was purified by column chromatography (AcOEt) to give **9c** as a yellow viscous oil (122 mg, 71%). *E*-**9c**: ^{1}H NMR ($CDCl_3$): δ 1.27 (3H, t, J=7.1 Hz, CH_2CH_3), 4.18 (2H, q, J=7.1 Hz, CH_2CH$_3$), 6.34 (1H, d, J=15.9 Hz, C=CHCO), 7.14 (1H, s, 5-H), 7.15–7.22 (5H, m, Ph), 7.46 (1H, d, J=15.9 Hz, CH=CHCO), 11.99 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 14.2, 60.4, 116.2, 126.0, 127.5, 129.3, 129.9, 132.9, 133.7, 136.1, 141.3, 167.4; IR ($CHCl_3$): ν_{max} 3115, 3013, 2832, 1689, 1635, 1472, 1295, 1255, 1170, 972 cm^{-1}; MS (EI): m/z 274 (M$^+$, 100), 227 (47), 201 (40), 109 (19), 66 (10); HRMS (EI) m/z 274.0775 (M$^+$) (requires $C_{14}H_{14}N_2O_2S$: 274.0776).

4.1.12. 5-[(2-Carbamoyl)ethenyl]-1-methyl-2-phenylsulfanyl-1*H*-imidazole (9f). A solution of **9a** (507 mg, 1.76 mmol) in MeOH (3 mL, saturated with NH_3 gas) was stirred for 3 days at room temperature. After evaporation of the solvent, a crystalline residue was purified by recrystallization from MeOH to give **9f** as colorless prisms (270 mg, 59%); mp 142–145 °C. *E*-**9f**: ^{1}H NMR ($CDCl_3$): δ 3.66 (3H, s, NMe), 5.99 (1H, br s, NH$_2$), 6.15 (1H, br s, NH$_2$), 6.41 (1H, d, J=15.4 Hz, C=CHCO), 7.15–7.30 (5H, m, Ph), 7.47 (1H, d, J=15.4 Hz, CH=CHCO), 7.54 (1H, s, 4-H); ^{13}C NMR ($CDCl_3$): δ 31.8, 119.1, 127.2, 127.4, 128.8, 129.4, 130.9, 131.9, 133.5, 141.7, 167.3; IR ($CHCl_3$): ν_{max} 3291, 2971, 1672, 1627, 1594, 1443, 1399, 1345, 1288 cm^{-1}; MS (EI): m/z 259 (M$^+$, 100), 241 (6), 215 (40), 150 (10), 121 (12), 109 (8), 91 (17), 80 (12), 66 (7), 51 (7); HRMS (EI) m/z 259.0783 (M$^+$) (requires $C_{13}H_{13}N_3OS$: 259.0779). Found: C, 59.97; H, 5.24; N, 15.95; $C_{13}H_{13}N_3OS$ requires C, 60.21; H, 5.05; N, 16.20.

4.1.13. General procedure for 5-ethenylimidazoles (10–12), synthesis of 1-methyl-4-(1-methyl-2-phenylsulfanyl-1*H*-imidazol-5-yl)-2-phenylsulfanyl-4,5,6,7-tetrahydro-1*H*-benzimidazole (10a) as an example (condition A in Table 1). A solution of **8a** (50 mg, 0.23 mmol) in xylene (1 mL) was refluxed under N_2 for 30 h. After evaporation of the solvent, the crystalline residue was purified by preparative TLC (PTLC) (AcOEt/*n*-hexane=1/1) to give **10a** as a yellow amorphous (46 mg, 92%); ^{1}H NMR ($CDCl_3$): δ 1.83–2.02 (3H, m, 6-CH$_2$ and 5-H), 2.04–2.13 (1H, m, 5-H), 2.51–2.65 (2H, m, 7-CH$_2$), 3.50 (3H, s, NMe), 3.66 (3H, s, NMe), 4.10 (1H, t, J=4.4 Hz, 4-H), 6.73 (1H, d, J=0.5 Hz, 4′-H), 7.10–7.29 (10H, m, Ph); ^{13}C NMR ($CDCl_3$): δ 19.6, 21.1, 29.2, 30.9, 31.5, 32.1, 126.1, 126.4, 127.4, 127.7, 128.6, 129.1, 129.2, 130.8, 135.3, 135.6, 135.9, 136.9, 137.1, 137.9; IR ($CHCl_3$): ν_{max} 2925, 1474, 1439, 1174, 1092 cm^{-1}; MS (EI): m/z 432 (M$^+$, 100), 417 (3), 404 (5), 374 (11), 355 (7), 341 (46), 323 (10), 295 (14), 243 (10), 110 (7), 91 (5); HRMS (EI) m/z 432.1436 (M$^+$) (requires $C_{24}H_{24}N_4S_2$: 432.1442).

4.1.14. 2-Phenylsulfanyl-4-{2-phenylsulfanyl-1-[2-(trimethylsilyl)ethoxymethyl]-1*H*-imidazol-5-yl}-4,5,6,7-tetrahydro-1*H*-benzimidazole (10b). Starting with **8b** (33 mg, 0.10 mmol) by the reaction condition B, **10b** was isolated as a colorless viscous oil (12 mg, 36%); ^{1}H NMR ($CDCl_3$): δ −0.09 (9H, s, SiMe$_3$), −0.06 (s, 9H, SiMe$_3$), 0.80 (4H, m, 2×CH$_2$CH_2Si), 1.82–1.88 (2H, m, 6-CH$_2$), 2.17–2.27 (2H, m, 5-CH$_2$), 2.61–2.70 (2H, m, 7-CH$_2$), 3.31–3.42 (4H, m, 2×CH_2CH$_2$Si), 4.18 (1H, br t, J=5.3 Hz, 4-H), 5.22, 5.28 (1H each, each d, J=10.6 Hz, NCH$_2$), 5.30, 5.35 (1H each, each d, J=10.6 Hz, NCH$_2$), 6.91 (1H, d, J=0.7 Hz, 4′-H), 7.10–7.26 (10H, m, Ph); ^{13}C NMR ($CDCl_3$): δ −1.5, −1.4, 17.7, 17.8, 19.9, 21.3, 30.1, 34.6, 66.1, 66.2, 73.3, 75.4, 122.3, 126.2, 126.3, 127.3, 127.5, 128.3, 129.1, 129.2, 135.7, 135.8, 136.0, 136.4, 139.4, 146.8;

IR ($CHCl_3$): ν_{max} 2930, 1244, 1220, 1170, 1086, 1023, 856, 834 cm^{-1}; MS (EI): *m/z* 664 (M^+, 100), 563 (15), 555 (25), 548 (21), 534 (11), 490 (13), 429 (10), 355 (9), 277 (6), 110 (25), 73 (46); HRMS (EI) *m/z* 664.2771 (M^+) (requires $C_{34}H_{48}N_4O_2S_2Si_2$: 664.2757).

4.1.15. (4*R,5*R**,6*R**)-1,5,6-Trimethyl-4-(1-methyl-2-phenylsulfanyl-1*H*-imidazol-5-yl)-2-phenylsulfanyl-4,5,6,7-tetrahydro-1*H*-benzimidazole (10c).** Starting with **8c** (23 mg, 0.10 mmol) by the reaction condition B, **10c** was isolated as a yellow viscous oil (10 mg, 43%); ^1H NMR ($CDCl_3$): δ 1.02 (3H, d, J=6.4 Hz, 5-Me), 1.16 (3H, d, J=6.4 Hz, 6-Me), 1.66–1.84 (2H, m, 5- and 6-H), 2.31 (1H, ddd, J=2.4, 10.4, 15.9 Hz, 7-H), 2.66 (1H, ddd, J=1.1, 5.1, 15.9 Hz, 7-H), 3.46 (3H, s, NMe), 3.52 (3H, s, NMe), 3.69 (1H, br d, J=10.1 Hz, 4-H), 7.00 (1H, s, 4′-H), 7.02–7.26 (10H, m, Ph); ^{13}C NMR ($CDCl_3$): δ 17.1, 19.9, 30.0, 30.9, 32.1, 35.7, 41.1, 41.2, 125.8, 126.3, 126.8, 127.7, 128.9, 129.1×2, 129.2, 135.3, 135.9, 136.1, 136.7, 136.8, 138.1; IR ($CHCl_3$): ν_{max} 3044, 1579, 1474, 1447, 1371, 1092 cm^{-1}; MS (EI): *m/z* 460 (M^+, 73), 445 (8), 404 (48), 369 (15), 327 (9), 295 (100), 230 (10), 202 (10), 150 (8), 109 (9), 91 (10), 77 (9); HRMS (EI) *m/z* 460.1764 (M^+) (requires $C_{26}H_{28}N_4S_2$: 460.1755).

4.1.16. (4*R,5*S**,6*S**)-5,6-Bis(ethoxycarbonyl)-1-methyl-4-(1-methyl-2-phenylsulfanyl-1*H*-imidazol-5-yl)-2-phenylsulfanyl-4,5,6,7-tetrahydro-1*H*-benzimidazole (10d) and (4*R**,5*S**,6*R**)-5,6-bis(ethoxycarbonyl)-1-methyl-4-(1-methyl-2-phenylsulfanyl-1*H*-imidazol-5-yl)-2-phenylsulfanyl-4,5,6,7-tetrahydro-1*H*-benzimidazole (11a).** Starting with **9a** (29 mg, 0.10 mmol) by the reaction condition A, a mixture of **10d** and **11a** (16 mg, 55%, **10d/11a**=50/1) was obtained and **10d** was isolated from the second fraction as a yellow amorphous and **11a** was isolated from the first fraction as a yellow viscous oil. Compound **10d**; ^1H NMR ($CDCl_3$): δ 1.15 (3H, t, J=7.1 Hz, CH_2CH_3), 1.20 (3H, t, J=7.1 Hz, CH_2CH_3), 2.94–3.04 (2H, m, 7-CH_2), 3.25–3.39 (2H, m, 5- and 6-H), 3.51 (3H, s, NMe), 3.57 (3H, s, NMe), 3.96–4.14 (4H, m, 2×CH_2CH_3), 4.49 (1H, br d, J=8.2 Hz, 4-H), 6.86 (1H, s, 4′-H), 7.09–7.24 (10H, m, Ph); ^{13}C NMR ($CDCl_3$): δ 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 ($CHCl_3$): ν_{max} 3017, 1725, 1474, 1447, 1368, 1266, 1229, 1177, 1091, 1032 cm^{-1}; MS (EI): *m/z* 576 (M^+, 100), 531 (7), 503 (93), 429 (20), 404 (47), 295 (61), 241 (12), 191 (9), 150 (8), 110 (12), 91 (12), 77 (12); HRMS (EI) *m/z* 576.1859 (M^+) (requires $C_{30}H_{32}N_4O_4S_2$: 576.1865). Compound **11a**: ^1H NMR ($CDCl_3$): δ 1.22 (3H, t, J=7.1 Hz, CH_2CH_3), 1.27 (3H, t, J=7.1 Hz, CH_2CH_3), 2.99 (1H, dd, J=5.0, 14.5 Hz, 7-H), 3.06–3.11 (1H, m, 6-H), 3.16 (1H, ddd, J=0.9, 10.4, 14.7 Hz, 7-H), 3.37 (1H, dd, J=2.0, 2.9 Hz, 5-H), 3.54 (3H, s, NMe), 3.75 (3H, s, NMe), 4.10–4.25 (4H, m, 2×CH_2CH_3), 4.71 (1H, br t, J=0.8 Hz, 4-H), 6.55 (1H, d, J=0.6 Hz, 4′-H), 7.10–7.29 (10H, m, Ph); ^{13}C NMR ($CDCl_3$): δ 14.0, 14.1, 20.8, 31.1, 31.3, 34.2, 36.9, 46.1, 61.2, 61.3, 126.5, 126.6, 127.81, 127.87, 129.19, 129.25, 129.27, 129.6, 134.2, 134.66, 134.68, 136.4, 137.8, 138.4, 170.9, 172.3; IR ($CHCl_3$): ν_{max} 2949, 1723, 1579, 1474, 1446, 1367, 1264, 1022 cm^{-1}; MS (EI): *m/z* 576 (M^+, 81), 503 (100), 429 (26), 404 (25), 295 (51), 241 (14), 217 (10), 191 (19), 110 (18), 91 (14), 77 (10), 57 (8); HRMS (EI) *m/z* 576.1866 (M^+) (requires $C_{30}H_{32}N_4O_4S_2$: 576.1865).

4.1.17. (4*R,5*S**,6*S**)-5,6-Bis(ethoxycarbonyl)-1-methoxymethyl-4-(1-methoxymethyl-2-phenylsulfanyl-1*H*-imidazol-5-yl)-2-phenylsulfanyl-4,5,6,7-tetrahydro-1*H*-benzimidazole (10e) and (4*R**,5*S**,6*R**)-5,6-bis(ethoxycarbonyl)-1-methoxymethyl-4-(1-methoxymethyl-2-phenylsulfanyl-1*H*-imidazol-5-yl)-2-phenylsulfanyl-4,5,6,7-tetrahydro-1*H*-benzimidazole (11b).** Starting with **9b** (57 mg, 0.18 mmol) by the reaction condition C, a mixture of **10e** and **11b** (8 mg, 14%, **10e/11b**=4/1) was obtained by PTLC ($CHCl_3$/MeOH=20/1) and **10e** was isolated from the second fraction as a yellow viscous oil and **11b** was isolated from the first fraction as a yellow viscous oil. Compound **10e**: ^1H NMR ($CDCl_3$): δ 1.16 (3H, t, J=7.1 Hz, CH_2CH_3), 1.20 (3H, t, J=7.1 Hz, CH_2CH_3), 3.05 (2H, dd, J=1.3, 7.5 Hz, 7-CH_2), 3.14 (3H, s, OMe), 3.19 (3H, s, OMe), 3.30–3.36 (1H, m, 6-H), 3.59 (1H, dd, J=8.4, 9.2 Hz, 5-H), 3.96–4.15 (4H, m, 2×CH_2CH_3), 4.67 (1H, d, J=8.4 Hz, 4-H), 5.19 (1H, br s, NC*H*H), 5.28 and 5.33 (1H each, each d, J=10.8 Hz, NCH_2O), 5.61 (1H, br d, J=10.8 Hz, NCH*H*), 6.93 (1H, s, 4′-H), 7.11–7.23 (10H, m, Ph); ^{13}C NMR ($CDCl_3$): δ 14.0, 14.1, 22.7, 35.4, 41.8, 47.4, 55.7, 56.0, 61.1, 61.3, 75.3, 75.7, 126.5, 126.9, 127.7, 127.9, 128.3, 129.18, 129.22, 130.5, 134.0, 134.6, 135.1, 136.2, 138.4, 139.0, 172.4, 172.7; MS (EI): *m/z* 636 (M^+, 100), 621 (20), 604 (91), 591 (50), 563 (43), 531 (30), 513 (13), 485 (27), 441 (12), 413 (23), 323 (9), 239 (8), 121 (9), 91 (7); HRMS (EI) *m/z* 636.2079 (M^+) (requires $C_{32}H_{36}N_4O_6S_2$: 636.2076). Compound **11b**: ^1H NMR ($CDCl_3$): δ 1.19 (3H, t, J=7.1 Hz, CH_2CH_3), 1.25 (3H, t, J=7.1 Hz, CH_2CH_3), 3.04–3.19 (3H, m, 6-H and 7-CH_2), 3.14 (3H, s, OMe), 3.33 (3H, s, OMe), 3.81 (1H, br t, J=2.2 Hz, 5-H), 4.09–4.24 (4H, m, 2×CH_2CH_3), 4.85 (1H, br t, J=0.9 Hz, 4-H), 5.30 and 5.35 (1H each, each d, J=10.6 Hz, NCH_2O), 5.51 and 5.57 (1H each, each d, J=11.1 Hz, NCH_2O), 6.55 (1H, s, 4′-H), 7.15–7.38 (10H, m, Ph).

4.1.18. (4*R,5*S**,6*S**)-5,6-Dicarbamoyl-1-methyl-4-(1-methyl-2-phenylsulfanyl-1*H*-imidazol-5-yl)-2-phenylsulfanyl-4,5,6,7-tetrahydro-1*H*-benzimidazole (10f) and (4*R**,5*S**,6*S**)-1-methyl-4-(1-methyl-2-phenylsulfanyl-1*H*-imidazol-5-yl)-2-phenylsulfanyl-4,5,6,7-tetrahydro-1*H*-benzimidazole-5,6-dicarboxamide (12).** Starting with **9f** (52 mg, 0.20 mmol) by the reaction condition D, **10f** was isolated from the second fraction as a yellow viscous oil (14 mg, 27%) and **12** was isolated from the first fraction as a yellow viscous oil (16 mg, 32%). Compound **10f**: ^1H NMR (CD_3OD): δ 2.94–2.98 (2H, m, 7-CH_2), 3.02 (1H, t, J=10.8 Hz, 5-H), 3.13 (1H, dt, J=5.9, 10.8 Hz, 6-H), 3.53 (3H, s, NMe), 3.56 (3H, s, NMe), 4.43 (1H, d, J=10.4 Hz, 4-H), 6.99 (1H, s, 4′-H), 7.06–7.28 (10H, m, Ph); ^{13}C NMR (CD_3OD): δ 18.2, 25.7, 31.7, 32.6, 37.3, 45.4, 115.3, 127.5, 128.0, 128.2, 129.1×2, 130.5, 130.6, 134.1, 135.9, 136.4, 137.7, 138.7, 141.6, 176.8, 177.5; IR (KBr): ν_{max} 3316, 3199, 2905, 1667, 1630, 1591, 1450 cm^{-1}; HRMS (FAB) *m/z* 519.1629 $(M+H)^+$ (requires $C_{26}H_{27}N_6O_2S_2$: 519.1637). Compound **12**: ^1H NMR ($CDCl_3$): δ 2.97 (1H, dd, J=7.4, 16.0 Hz, 7-H), 3.27 (1H, dd, J=1.4, 16.0 Hz, 7-H), 3.50 (3H, s, NCH_3), 3.52–3.62 (2H, m, 5- and 6-H), 3.80 (3H, s, NCH_3), 4.80 (1H, br s, 4-H), 6.71 (1H, d, J=0.6 Hz, 4′-H), 7.06–7.28 (10H, m, Ph), 8.51 (1H, br s, NH); ^{13}C NMR

($CDCl_3$): δ 20.6, 31.3, 31.9, 33.1, 40.5, 46.5, 126.1, 126.8, 126.9, 127.4, 128.1, 128.2, 129.3, 129.4, 134.3×2, 135.5, 135.8, 137.8, 156.5, 177.2, 178.6; IR ($CHCl_3$): ν_{max} 3126, 2928, 1776, 1714, 1578, 1473, 1437, 1347 cm^{-1}; MS (EI): *m/z* 501 (M^+, 100), 429 (10), 404 (27), 295 (27), 142 (25), 110 (16), 77 (6); HRMS (EI) *m/z* 501.1289 (M^+) (requires $C_{26}H_{23}N_5O_2S_2$: 501.1293).

4.1.19. (4*R,5*R**,6*S**)-5,6-Bis(hydroxymethyl)-1-methyl-4-(1-methyl-2-phenylsulfanyl-1*H*-imidazol-5-yl)-2-phenylsulfanyl-4,5,6,7-tetrahydro-1*H*-benzimidazole (13).** Lithium aluminum hydride (602 mg, 15.9 mmol) was added to a stirred solution of **10d** (3.000 g, 5.20 mmol) in THF (30 mL) under N_2 at 0 °C. After stirring for 21 min at ambient temperature, saturated $NaHCO_3$ aq (20 mL) was added to the mixture and after evaporation of the solvent the products were extracted with $CHCl_3$ (100 mL×3). The organic layer was dried over Na_2SO_4 and evaporated to give a crystalline residue, which was purified by recrystallization from EtOH/Et_2O to give **13** as colorless powder (2.522 g, 98%); mp 119–123 °C; ^1H NMR (DMSO-d_6): δ 1.93–2.00 (1H, m, 5-H), 2.07–2.15 (1H, m, 6-H), 2.59 (1H, ddd, *J*=2.0, 10.1, 16.3 Hz, 7-H), 2.74 (1H, dd, *J*=5.5, 15.6 Hz, 7-H), 3.30–3.35 (1H, m, C*H*$_2$OH), 3.48 (3H, s, NMe), 3.55 (3H, s, NMe), 3.62–3.65 (3H, m, C*H*$_2$OH), 4.15 (1H, br d, *J*=9.3 Hz, 4-H), 4.65 (1H, t, *J*=5.0 Hz, OH), 4.70 (1H, t, *J*=5.0 Hz, OH), 6.83 (1H, s, 4′-H), 6.97–7.28 (10H, m, Ph); ^{13}C NMR (DMSO-d_6): δ 23.3, 30.8, 31.7, 33.5, 37.3, 42.4, 58.9, 62.4, 126.0, 126.1, 126.3, 126.7, 128.1, 129.35, 129.40, 130.0, 133.9, 134.7, 135.6, 135.9, 137.3, 137.7; IR (KBr): ν_{max} 3371, 2874, 1474, 1448, 1386, 736 cm^{-1}; MS (EI): *m/z* 492 (M^+, 62), 461 (29), 404 (49), 295 (100), 241 (20), 191 (11), 150 (12), 109 (15), 77 (19), 51 (7); HRMS (EI) *m/z* 492.1667 (M^+) (requires $C_{26}H_{28}N_4O_2S_2$: 492.1653). Found: C, 63.11; H, 5.84; N, 11.16; $C_{26}H_{28}N_4O_2S_2$ requires C, 63.39; H, 5.73; N, 11.37.

4.1.20. (4*R,5*R**,6*S**)-5,6-Bis[(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)methyl]-1-methyl-4-(1-methyl-2-phenylsulfanyl-1*H*-imidazol-5-yl)-2-phenylsulfanyl-4,5,6,7-tetrahydro-1*H*-benzimidazole (14).** DEAD (40% in toluene, 1.28 mL, 2.94 mmol) was added to a stirred solution of **13** (181 mg, 0.37 mmol), triphenylphosphine (771 mg, 2.94 mmol), and phthalimide (433 mg, 2.94 mmol) in THF (2 mL) under N_2 at 0 °C. The reaction mixture was stirred for 18 h at ambient temperature. HCl aq (10%, 1 mL) was added to the mixture and the aqueous phase was washed with AcOEt (10 mL×2), basified by K_2CO_3, and extracted with AcOEt (10 mL×3). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to give an oily residue, which was purified by column chromatography (AcOEt/*n*-hexane=1/1) and recrystallization from AcOEt/*n*-hexane gave **14** as colorless needles (174 mg, 63%); mp 124–125 °C; ^1H NMR ($CDCl_3$): δ 2.30–2.35 (1H, m, 6-H), 2.58 (1H, dd, *J*=3.3, 16.5 Hz, 7-H), 2.73–2.78 (1H, m, 5-H), 2.95 (1H, dd, *J*=5.7, 16.5 Hz, 7-H), 3.23 (1H, dd, *J*=2.7, 13.8 Hz, NCH_2), 3.56 (3H, s, NMe), 3.79 (3H, s, NMe), 3.86 (1H, dd, *J*=5.3, 14.1 Hz, NCH_2), 3.94 (1H, dd, *J*=9.8, 14.1 Hz, NCH_2), 3.97 (1H, dd, *J*=11.0, 13.8 Hz, NCH_2), 4.10 (1H, d, *J*=1.5 Hz, 4-H), 6.76 (1H, d, *J*=0.9 Hz, 4′-H), 7.01–7.31 (10H, m, Ar), 7.67–7.84 (8H, m, Ar); ^{13}C NMR ($CDCl_3$): δ 20.8, 31.2, 31.6, 35.0, 35.2, 41.1×2, 41.2, 123.3, 123.4, 126.1, 126.4, 127.4, 127.6, 128.1, 129.2×2, 129.3, 131.6, 131.7, 133.7, 134.1, 134.3, 135.3×2, 136.9, 137.65, 137.69, 168.3, 168.5; IR ($CHCl_3$): ν_{max} 2919, 1708, 1375, 1354, 1174, 1092 cm^{-1}; MS (EI): *m/z* 750 (M^+, 14), 590 (100), 429 (21), 403 (6), 295 (16), 254 (9), 181 (13), 131 (15), 110 (38), 91 (14), 69 (42), 57 (19); HRMS (EI) *m/z* 750.2069 (M^+) (requires $C_{42}H_{34}N_6O_4S_2$: 750.2083). Found: C, 66.73; H, 4.82; N, 10.81; $C_{42}H_{34}N_6O_4S_2\cdot 1/3H_2O$ requires C, 66.65; H, 4.62; N, 11.10.

4.1.21. General procedure for 15 and 18 by desulfurization, synthesis of (4*R,5*R**,6*S**)-5,6-bis[(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)methyl]-1-methyl-4-(1-methyl-1*H*-imidazol-5-yl)-4,5,6,7-tetrahydro-1*H*-benzimidazole (15) as an example.** $NaBH_4$ (45 mg, 1.18 mmol) was added to a stirred solution of **14** (45 mg, 0.060 mmol) and $NiCl_2\cdot 6H_2O$ (21 mg, 0.89 mmol) in THF (2 mL) and MeOH (6 mL) under N_2 at 0 °C. The reaction mixture was stirred for 1 h at ambient temperature. HCl aq (36%, 2 mL) was added to the mixture and the whole was stirred for 10 min and was basified by 28% NH_3 aq. The products were extracted with AcOEt (20 mL×5). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to give an oily residue, which was purified by PTLC ($CHCl_3$/MeOH=5/1) to give **15** as a colorless amorphous (20 mg, 62%); ^1H NMR (CD_3OD): δ 2.38–2.46 (1H, m, 6-H), 2.55 (1H, dd, *J*=3.6, 16.4 Hz, 7-H), 2.72–2.78 (1H, m, 5-H), 2.90 (1H, dd, *J*=5.8, 16.6 Hz, 7-H), 3.23 (1H, dd, *J*=3.6, 13.8 Hz, NCH_2), 3.60 (3H, s, NMe), 3.79 (3H, s, NMe), 3.81–3.89 (3H, m, NCH_2), 4.06 (1H, br s, 4-H), 6.44 (1H, s, 4′-H), 7.54 (1H, s, 2′-H), 7.62 (1H, s, 2-H), 7.71–7.80 (8H, m, Ar). ^{13}C NMR (CD_3OD): δ 30.1, 31.5, 32.4, 34.9, 36.3, 41.8, 41.9, 42.3, 124.1, 124.2, 126.4, 127.1, 128.2, 128.5, 130.5, 133.1, 135.4, 135.5, 138.9, 139.3, 169.87, 169.93; IR (KBr): ν_{max} 3365, 2908, 1763, 1702, 1395, 1357, 715 cm^{-1}; MS (EI): *m/z* 534 (M^+, 12), 374 (100), 213 (11), 187 (21), 160 (12), 132 (9), 104 (7), 77 (7); HRMS (EI) *m/z* 534.2027 (M^+) (requires $C_{30}H_{26}N_6O_4$: 534.2015).

4.1.22. General procedure for pyrrole-imidazole dimmers (16a,b), synthesis of (4*R,5*R**,6*S**)-5,6-bis[(4-bromo-1*H*-pyrrol-2-yl)-carbonylaminomethyl]-1-methyl-4-(1-methyl-2-phenylsulfanyl-1*H*-imidazol-5-yl)-2-phenylsulfanyl-4,5,6,7-tetrahydro-1*H*-benzimidazole (16a) as an example.** A solution of **14** (57 mg, 0.08 mmol) in hydrazine monohydrate (3 mL) was heated at 70 °C under N_2 for 9 h. After evaporation of the solvent, the residue was dissolved in DMAc (3 mL). 4-Bromo-2-(trichloroacetyl)pyrrole[24] (177 mg, 0.61 mmol) and K_2CO_3 (84 mg, 0.61 mmol) were added to the reaction mixture and the whole was stirred for 3 h at room temperature. After evaporation of the solvent, H_2O (1 mL) was added and the products were extracted with $CHCl_3$ (20 mL×2). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to give an oily residue, which was purified by column chromatography ($CHCl_3$/MeOH=10/1) to give **16a** as a yellow amorphous (31 mg, 49%); ^1H NMR (CD_3OD): δ 2.35–2.43 (2H, m, 5- and 6-H), 2.61 (1H, dd, *J*=4.5, 16.5 Hz, 7-H), 2.84 (1H, dd, *J*=5.2, 16.4 Hz, 7-H), 3.29–3.34 (2H, m, NCH_2), 3.39 (1H, dd, *J*=5.9, 14.1 Hz, NCH_2), 3.53 (3H, s, NMe), 3.55 (3H, s, NMe), 3.66 (1H, dd, *J*=4.8, 14.1 Hz, NCH_2), 4.08 (1H, d, *J*=4.6 Hz, 4-H), 6.76 (1H, d, *J*=1.5 Hz, pyrrole), 6.82 (1H, d, *J*=1.5 Hz, pyrrole), 6.83 (1H, s, 4′-H), 6.90 (1H, d, *J*=1.5 Hz, pyrrole), 6.91 (1H, d, *J*=1.6 Hz,

pyrrole), 7.04–7.25 (m, 10H, Ph); ^{13}C NMR (CD_3OD): δ 23.0, 31.6, 32.5, 35.7, 37.8, 41.9, 43.0, 43.6, 97.5, 97.6, 113.3, 113.7, 114.1, 122.9, 123.1, 127.3, 127.4, 127.6, 127.9, 128.4, 128.8, 129.7, 130.5×2, 131.1, 135.7, 136.1, 136.3, 138.4, 139.0, 162.7, 162.8; IR (KBr): ν_{max} 3392, 2973, 1629, 1577, 1449, 1380, 1318, 919 cm^{-1}; HRMS (FAB) *m/z* 833.0703 (M+H)$^+$ (requires $C_{36}H_{35}Br_2N_8O_2S_2$: 833.0691).

4.1.23. (4*R,5*R**,6*S**)-5,6-Bis[(4-bromo-1*H*-pyrrol-2-yl)-carbonylaminomethyl]-1-methyl-4-(1-methyl-1*H*-imidazol-5-yl)-4,5,6,7-tetrahydro-1*H*-benzimidazole (16b).** Starting with **15** (49 mg, 0.09 mmol), hydrazine monohydrate (3 mL), DMAc (3 mL), 4-bromo-2-(trichloroacetyl)-pyrrole[24] (213 mg, 0.73 mmol), and K_2CO_3 (101 mg, 0.73 mmol), **16b** was purified by column chromatography ($CHCl_3$/MeOH=5/1) and isolated as a colorless amorphous (41 mg, 72%); ^{1}H NMR (CD_3OD): δ 2.29–2.36 (2H, m, 5- and 6-H), 2.57 (1H, dd, *J*=4.6, 16.7 Hz, 7-H), 2.82 (1H, dd, *J*=4.2, 13.6 Hz, 7-H), 3.34–3.40 (3H, m, NCH_2), 3.55 (3H, s, NMe), 3.57 (3H, s, NMe), 3.65 (1H, dd, *J*=4.0, 13.9 Hz, NCH_2), 3.98 (1H, d, *J*=4.2 Hz, 4-H), 6.61 (1H, s, 4′-H), 6.77 (1H, d, *J*=1.5 Hz, pyrrole), 6.84 (1H, d, *J*=1.6 Hz, pyrrole), 6.91 (1H, d, *J*=1.6 Hz, pyrrole), 6.93 (1H, d, *J*=1.5 Hz, pyrrole), 7.50 (2H, s, 2- and 2′-H); ^{13}C NMR (CD_3OD): δ 21.3, 31.4, 32.2, 35.5, 38.4, 41.8, 43.4, 43.5, 97.47, 97.54, 113.3, 113.7, 122.9, 123.0, 126.7, 127.40, 127.43, 128.1, 134.7, 135.1, 138.5, 139.4, 162.7, 162.8; IR (KBr): ν_{max} 3371, 3262, 2937, 1723, 1622, 1271, 1119 cm^{-1}; HRMS (FAB) *m/z* 617.0627 (M+H)$^+$ (requires $C_{24}H_{27}Br_2N_8O_2$: 617.0624).

4.1.24. (4*R,5*R**,6*S**)-5,6-Bis[(*tert*-butyldiphenylsiloxy)-methyl]-1-methyl-4-(1-methyl-2-phenylsulfanyl-1*H*-imidazol-5-yl)-2-phenylsulfanyl-4,5,6,7-tetrahydro-1*H*-benzimidazole (17).** TBDPSCl (2.54 mL, 9.76 mmol) was added to a solution of **12** (2.186 g, 4.44 mmol) and imidazole (1.51 g, 22.19 mmol) in DMF (5 mL). After stirring for 7 h at room temperature, saturated $NaHCO_3$ aq (3 mL) was added to the reaction mixture and the products were extracted with Et_2O (20 mL×2). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to give an oily residue, which was purified by column chromatography (AcOEt/*n*-hexane=1/3) to give **17** as a colorless amorphous (4.261 g, 99%); ^{1}H NMR ($CDCl_3$): δ 0.99 (9H, s, CMe_3), 1.02 (9H, s, CMe_3), 2.17–2.23 (1H, m, 5- or 6-H), 2.39–2.47 (1H, m, 5- or 6-H), 2.55 (2H, br d, *J*=6.6 Hz, 7-CH_2), 3.40 (3H, s, NMe), 3.46 (3H, s, NMe), 3.69–3.84 (4H, m, 2×OCH_2), 4.31 (1H, br d, *J*=6.2 Hz, 4-H), 6.65 (1H, s, 4′-H), 7.01–7.42 (22H, m, Ph), 7.44–7.61 (8H, m, Ph); ^{13}C NMR ($CDCl_3$) δ: 19.28, 19.32, 23.0, 26.9×2, 30.8, 31.8, 33.6, 37.4, 42.0, 62.2, 65.1, 125.8, 126.4, 126.8, 127.7, 127.9, 128.6, 128.9, 129.10, 129.13, 129.69, 129.74, 129.8, 133.07, 133.12, 133.4, 133.5, 135.2, 135.4, 135.51, 135.53, 135.9, 136.3, 136.6, 136.8, 136.9; IR ($CHCl_3$): ν_{max} 2916, 1467, 1437, 1100 cm^{-1}; HRMS (FAB) *m/z* 969.4097 (M+H)$^+$ (requires $C_{58}H_{65}N_4O_2S_2Si_2$: 969.4087).

4.1.25. (4*R,5*R**,6*S**)-5,6-Bis[(*tert*-butyldiphenylsiloxy)-methyl]-1-methyl-4-(1-methyl-1*H*-imidazol-5-yl)-4,5,6,7-tetrahydro-1*H*-benzimidazole (18).** Starting with **17** (485 mg, 0.50 mmol), $NiCl_2\cdot 6H_2O$ (1.663 g, 7.00 mmol), $NaBH_4$ (794 mg, 21.00 mmol), THF (15 mL), and MeOH (45 mL), **18** was purified by PTLC ($CHCl_3$/MeOH=20/1) and isolated as a colorless amorphous (263 mg, 70%); ^{1}H NMR ($CDCl_3$): δ 0.99 (9H, s, CMe_3), 1.04 (9H, s, CMe_3), 2.11 (1H, br t, *J*=9.9 Hz, 5-H), 2.38–2.47 (1H, m, 6-H), 2.53 (1H, dd, *J*=1.8, 15.4 Hz, 7-H), 2.60 (1H, dd, *J*=5.9, 15.2 Hz, 7-H), 3.44 (3H, s, NMe), 3.46 (3H, s, NMe), 3.76 (2H, d, *J*=2.6 Hz, 5-CH_2O), 3.84 (1H, dd, *J*=4.9, 10.3 Hz, 6-CH_2O), 3.88 (1H, dd, *J*=3.3, 10.4 Hz, 6-CH_2O), 4.24 (1H, br d, *J*=9.7 Hz, 4-H), 6.55 (1H, s, 4′-H), 7.19–7.55 (18H, m, Ph), 7.57–7.62 (4H, m, Ph); ^{13}C NMR ($CDCl_3$): δ 19.28, 19.30, 22.7, 26.7, 26.9, 30.8, 31.8, 32.6, 37.5, 42.2, 61.3, 65.0, 125.0, 126.4, 127.56, 127.59, 127.62, 129.6, 129.7, 132.7, 133.19, 133.22, 133.4, 133.6, 135.4, 135.5, 135.6, 136.4, 136.7, 137.8; IR (KBr): ν_{max} 3339, 2908, 1498, 1466, 1445, 1105, 820 cm^{-1}; MS (EI): *m/z* 752 (M$^+$, 53), 695 (8), 483 (100), 319 (7), 263 (10), 213 (17), 159 (9), 135 (33), 95 (10), 57 (6); HRMS (EI) *m/z* 752.3941 (M$^+$) (requires $C_{46}H_{56}N_4O_2Si_2$: 752.3941).

4.1.26. (4*R,5*R**,6*S**)-2-Azido-4-(2-azido-1-methyl-1*H*-imidazol-5-yl)-5,6-bis[(*tert*-butyldiphenylsiloxy)methyl]-1-methyl-4,5,6,7-tetrahydro-1*H*-benzimidazole (19).** *sec*-BuLi (1.0 M in cyclohexane, 3.4 mL, 3.4 mmol) was added to a stirred solution of **18** (855 mg, 1.14 mmol) in THF (6 mL) and DME (6 mL) under N_2 at −40 °C. After stirring for 10 min at the same temperature, trisyl azide (738 mg, 2.39 mmol) was added to the reaction mixture and the whole was stirred for 30 min at −40 °C. H_2O (1 mL) was added to the mixture and after evaporation of the solvent the products were extracted with $CHCl_3$ (20 mL×3). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to give a crystalline residue, which was purified by column chromatography ($CHCl_3$/MeOH=50/1) to give **19** as a yellow amorphous (521 mg, 55%); ^{1}H NMR ($CDCl_3$): δ 0.99 (9H, s, CMe_3), 1.02 (9H, s, CMe_3), 2.11–2.17 (1H, m, 5-H), 2.34–2.40 (1H, m, 6-H), 2.45–2.48 (2H, m, 7-CH_2), 3.21 (3H, s, NMe), 3.23 (3H, s, NMe), 3.72 (2H, d, *J*=2.6 Hz, 5-CH_2O), 3.78 (1H, dd, *J*=5.9, 10.3 Hz, 6-CH_2O), 3.83 (1H, dd, *J*=3.9, 10.2 Hz, 6-CH_2O), 4.07 (1H, br d, *J*=8.6 Hz, 4-H), 6.35 (1H, d, *J*=0.5 Hz, 4′-H), 7.24–7.44 (12H, m, Ph), 7.46–7.49 (4H, m, Ph), 7.56–7.59 (4H, m, Ph); IR ($CHCl_3$): ν_{max} 2933, 2126, 1482, 1108 cm^{-1}; HRMS (FAB) *m/z* 835.4042 (M+H)$^+$ (requires $C_{46}H_{55}N_{10}O_2Si_2$: 835.4048).

4.1.27. (4*R,5*R**,6*S**)-2-Benzylidenamino-4-(2-benzylidenamino-1-methyl-1*H*-imidazol-5-yl)-5,6-bis[(*tert*-butyldiphenylsiloxy)methyl]-1-methyl-4,5,6,7-tetrahydro-1*H*-benzimidazole (20).** A mixture of **19** (142 mg, 0.17 mmol) and Pd/C (10%, 100 mg) in AcOEt (3 mL) was stirred under H_2 (1 atm) for 12 h at room temperature. Pd/C was removed by filtration, the filtrate was evaporated, and the residue was dissolved in toluene (1 mL). Benzaldehyde (0.04 mL, 0.42 mmol) was added to the mixture and the whole was refluxed for 8 h. After evaporation of the solvent, the residue was purified by column chromatography (AcOEt/*n*-hexane=1/3) to give **20** as a yellow amorphous (81 mg, 50%); ^{1}H NMR ($CDCl_3$): δ 1.02 (9H, s, CMe_3), 1.03 (9H, s, CMe_3), 2.26–2.32 (1H, m, 5-H), 2.42–2.51 (1H, m, 6-H), 2.63 (2H, d, *J*=7.0 Hz, 7-CH_2), 3.61 (3H, s, NMe), 3.63 (3H, s, NMe), 3.78–3.85 (4H, m, 2×CH_2O), 4.34 (1H, d, *J*=8.2 Hz, 4-H), 6.54 (1H, s, 4′-H), 7.23–7.61 (26H, m, Ph), 7.89–7.96 (4H, m, Ph), 9.09 (1H, s, NC*H*Ph), 9.19 (1H, s, NC*H*Ph); ^{13}C NMR ($CDCl_3$): δ 19.31, 19.34, 22.6, 26.9, 27.0, 28.8, 29.8, 33.4, 37.4, 42.1, 62.3, 65.2, 125.75,

125.81, 127.6, 128.6, 128.7, 128.81, 128.83, 129.65, 129.68, 129.70, 131.19, 131.22, 133.2, 133.4, 133.5, 133.7, 134.0, 135.50, 135.58, 135.60, 136.3, 136.4, 149.4, 150.0, 158.1, 158.2; IR ($CHCl_3$): ν_{max} 2910, 1606, 1468, 1423, 1108 cm^{-1}; HRMS (FAB) *m/z* 959.4860 $(M+H)^+$ (requires $C_{60}H_{67}N_6O_2Si_2$: 959.4864).

4.1.28. (4*R,5*R**,6*S**)-2-Benzylidenamino-4-(2-benzylidenamino-1-methyl-1*H*-imidazol-5-yl)-5,6-bis(hydroxymethyl)-1-methyl-4,5,6,7-tetrahydro-1*H*-benzimidazole (21).** CsF (16 mg, 0.11 mmol) was added to a solution of **20** (10 mg, 0.01 mmol) in DMF (0.1 mL) and the whole was stirred at 80 °C for 9 h. After evaporation of the solvent, the residue was purified by PTLC ($CHCl_3$/MeOH=5/1) and recrystallization from MeOH gave **21** as yellow powder (4 mg, 83%); mp 273–274 °C; ^1H NMR ($CDCl_3$, CD_3OD): δ 1.99–2.05 (1H, m, 5-H), 2.26 (1H, ddd, *J*=4.8, 9.5, 14.5 Hz, 6-H), 2.67–2.82 (2H, m, 7-CH_2), 3.59 (1H, dd, *J*=3.7, 11.5 Hz, CH_2O), 3.69 (3H, s, NMe), 3.71 (3H, s, NMe), 3.77–3.87 (3H, m, CH_2O), 4.20 (1H, d, *J*=9.3 Hz, 4-H), 6.77 (1H, s, 4′-H), 7.42–7.53 (6H, m, Ph), 7.83–7.98 (4H, m, Ph), 8.94 (1H, s, NC*H*Ph), 9.04 (1H, s, NC*H*Ph); ^{13}C NMR ($CDCl_3$, CD_3OD): δ 22.6, 28.3, 29.2, 33.3, 37.8, 44.6, 60.0, 63.6, 125.0, 126.1, 128.18, 128.22, 128.36, 128.42, 131.2, 131.3, 133.1, 133.2, 135.5×2, 149.1, 149.4, 158.8, 159.0; IR ($CHCl_3$): ν_{max} 2909, 1722, 1369, 1239, 1209, 1041 cm^{-1}; HRMS (FAB) *m/z* 483.2513 $(M+H)^+$ (requires $C_{28}H_{31}N_6O_2$: 483.2508). Found: C, 69.46; H, 6.41; N, 17.24; $C_{28}H_{30}N_6O_2$ requires C, 69.69; H, 6.27; N, 17.41.

4.1.29. (4*R,5*R**,6*S**)-5,6-Bis(azidomethyl)-2-benzylidenamino-4-(2-benzylidenamino-1-methyl-1*H*-imidazol-5-yl)-1-methyl-4,5,6,7-tetrahydro-1*H*-benzimidazole (22).** DEAD (40% in toluene, 0.18 mL, 0.42 mmol) was added to a stirred solution of **21** (48 mg, 0.10 mmol), triphenylphosphine (107 mg, 0.41 mmol), and DPPA (0.107 mL, 0.50 mmol) in THF (1 mL) under N_2 at 0 °C. After stirring for 1.5 h, the solvent was evaporated and saturated $NaHCO_3$ aq (1 mL) was added to the residue, the products were extracted with $CHCl_3$ (10 mL×3). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to give an oily residue, which was purified by PTLC (AcOEt) to give **22** as a yellow amorphous (50 mg, 95%); ^1H NMR ($CDCl_3$): δ 2.13–2.19 (1H, m, 5- or 6-H), 2.27–2.36 (1H, m, 5- or 6-H), 2.69 (1H, ddd, *J*=1.8, 9.0, 15.9 Hz, 7-H), 2.77 (1H, ddd, *J*=1.1, 5.7, 16.1 Hz, 7-H), 3.58–3.65 (4H, m, 2×CH_2N_3), 3.67 (3H, s, NMe), 3.70 (3H, s, NMe), 4.17 (1H, d, *J*=8.4 Hz, 4-H), 6.81 (1H, s, 4′-H), 7.39–7.58 (6H, m, Ph), 7.88–7.97 (4H, m, Ph), 9.08 (1H, s, NC*H*Ph), 9.23 (1H, s, NC*H*Ph); ^{13}C NMR ($CDCl_3$): δ 23.8, 29.0, 30.0, 34.7, 35.9, 41.2, 51.0, 54.1, 125.5, 126.3, 128.6, 128.7, 128.87, 128.92, 131.4, 131.5, 131.9, 133.4, 136.0, 136.1, 149.9, 150.6, 158.9, 159.0; IR ($CHCl_3$): ν_{max} 2916, 2089, 1476, 1420, 1266, 961 cm^{-1}; MS (EI): *m/z* 532 (M^+, 63), 504 (17), 490 (21), 419 (50), 394 (39), 292 (31), 250 (60), 236 (100), 170 (31), 145 (29), 94 (59), 77 (46); HRMS (EI) *m/z* 532.2573 (M^+) (requires $C_{28}H_{28}N_{12}$: 532.2559).

4.1.30. (4*R,5*R**,6*S**)-2-Benzylidenamino-4-(2-benzylidenamino-1-methyl-1*H*-imidazol-5-yl)-5,6-bis[(4-bromo-1*H*-pyrrol-2-yl)-carbonylaminomethyl]-1-methyl-4,5,6,7-tetrahydro-1*H*-benzimidazole (23).** Triphenylphosphine (56 mg, 0.21 mmol) and 1 drop of H_2O were added to a stirred solution of **22** (50 mg, 0.09 mmol) in THF (0.5 mL) and the whole was stirred for 1.5 h at room temperature. After evaporation of the solvent, the residue was dissolved in DMAc (0.5 mL). 4-Bromo-2-(trichloroacetyl)pyrrole[24] (164 mg, 0.56 mmol) and K_2CO_3 (78 mg, 0.56 mmol) were added to the reaction mixture and the whole was stirred for 3 h at room temperature. K_2CO_3 was removed by filtration and the filtrate was evaporated to give an oily residue, which was purified by PTLC ($CHCl_3$/MeOH=10/1) to give **23** as a yellow amorphous (16 mg, 21%); ^1H NMR (CD_3OD): δ 2.37–2.42 (1H, m, 5- or 6-H), 2.46–2.52 (1H, m, 5- or 6-H), 2.66 (1H, dd, *J*=6.0, 17.2 Hz, 7-H), 2.89–2.94 (1H, m, 7-H), 3.42–3.47 (3H, m, NCH_2), 3.65–3.71 (1H, m, NCH_2), 3.68 (3H, s, NMe), 3.70 (3H, s, NMe), 4.06 (1H, br d, *J*=5.3 Hz, 4-H), 6.70 (1H, s, 4′-H), 6.77 (1H, d, *J*=1.5 Hz, pyrrole), 6.81 (1H, d, *J*=1.5 Hz, pyrrole), 6.86 (1H, d, *J*=1.5 Hz, pyrrole), 6.90 (1H, d, *J*=1.5 Hz, pyrrole), 7.43–7.53 (6H, m, Ph), 7.89–7.95 (4H, m, Ph), 8.94 (2H, s, NC*H*Ph); ^{13}C NMR (CD_3OD): δ 21.3, 29.5, 30.3, 35.5, 37.8, 38.4, 42.9, 43.4, 97.5×2, 113.3, 113.6, 122.9, 123.0, 127.3, 127.4, 127.5, 129.88, 129.93, 129.97, 130.08, 130.17, 130.21, 132.9, 133.1, 135.4, 137.36, 137.40, 151.2×2, 160.9×2, 162.7, 162.8; IR (KBr): ν_{max} 3340, 2903, 1617, 1583, 1317 cm^{-1}; HRMS (FAB) *m/z* 823.1465 $(M+H)^+$ (requires $C_{38}H_{37}Br_2N_{10}O_2$: 823.1468).

4.1.31. (4*R,5*R**,6*S**)-2-Amino-4-(2-amino-1-methyl-1*H*-imidazol-5-yl)-5,6-bis[(4-bromo-1*H*-pyrrol-2-yl)-carbonylaminomethyl]-1-methyl-4,5,6,7-tetrahydro-1*H*-benzimidazole (24) (12,12′-dimethylageliferin).** A solution of **23** (6 mg, 0.007 mmol) in EtOH (0.5 mL) and HCl (0.5 M, 0.5 mL) was stirred for 30 min at room temperature. After evaporation of the solvent, the residue was washed with AcOEt (10 mL) and dried to give **24** as a yellow amorphous (4 mg, 76%); ^1H NMR (CD_3OD): δ 2.37–2.44 (1H, m, 5- or 6-H), 2.44–2.50 (1H, m, 5- or 6-H), 2.55 (1H, br d, *J*=17.0 Hz, 7-H), 2.75 (1H, dd, *J*=17.0, 5.0 Hz, 7-H), 3.406 (3H, s, NMe), 3.414 (3H, s, NMe), 3.42–3.49 (2H, m, NCH_2), 3.56 (1H, dd, *J*=9.5, 5.1 Hz, NCH_2), 3.67 (1H, dd, *J*=9.5, 4.2 Hz, NCH_2), 3.95 (1H, br s, 4-H), 6.73 (1H, br s, 4′-H), 6.83 (1H, d, *J*=1.5 Hz, pyrrole), 6.90 (1H, d, *J*=1.5 Hz, pyrrole), 6.92 (1H, d, *J*=1.5 Hz, pyrrole), 6.95 (1H, d, *J*=1.5 Hz, pyrrole); IR (KBr): ν_{max} 3285, 2993, 1659, 1634 cm^{-1}; HRMS (FAB) *m/z* 647.0839 $(M+H)^+$ (requires $C_{24}H_{29}Br_2N_{10}O_2$: 647.0842).

4.2. X-ray crystallography

4.2.1. Compound 17. *Crystal data*: $C_{58}H_{64}N_4O_2S_2Si_2$, *M*=969.46, triclinic, *a*=14.419(7), *b*=14.670(3), *c*=13.487(5) Å, α=101.91(2)°, β=102.32(4)°, γ=82.14(2)°; *V*=2714(1) Å^3; *Z*=2, μ(Cu Kα)=16.53 cm^{-1}; *T*=296 K; *R*1=0.075 for 8620 observations, space group *P*-1(#2).

Acknowledgements

We are grateful for financial support in part by the Frontier Research Program and the 21st Century COE Program 'Development of Drug Discovery Frontier Integrated from Traditional to Proteome′ from the Ministry of Education, Culture, Sports, Science, and Technology (MEXT) of Japan, and a Grant-In-Aid for the promotion of the advancement of

education and research in graduate schools in subsidies for ordinary expenses of private schools from the Promotion and Mutual Aid Corporation for Private Schools.

References and notes

1. For reviews, see: (a) Hoffmann, H.; Lindel, T. *Synthesis* **2003**, 1753; (b) Mourabit, A. A.; Potier, P. *Eur. J. Org. Chem.* **2001**, 237; (c) Lewis, J. R. *Nat. Prod. Rep.* **1998**, *15*, 417.
2. (a) Jacquot, D. E. N.; Zoellinger, M.; Lindel, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 2295; (b) Travert, N.; Martin, M.-T.; Bourguet-Kondracki, M.-L.; Al-Mourabit, A. *Tetrahedron Lett.* **2005**, *46*, 249; (c) Lindel, T.; Breckle, G.; Hochgürtel, M.; Volk, C.; Grube, A.; Köck, M. *Tetrahedron Lett.* **2004**, *45*, 8149; (d) Travert, N.; Al-Mourabit, A. *J. Am. Chem. Soc.* **2004**, *126*, 10252; (e) He, Y.; Chen, Y.; Wu, H.; Lovely, C. J. *Org. Lett.* **2003**, *5*, 3623; (f) Poullennec, K. G.; Kelly, A. T.; Romo, D. *Org. Lett.* **2002**, *4*, 2645; (g) Feldman, K. S.; Saunders, J. C. *J. Am. Chem. Soc.* **2002**, *124*, 9060; (h) Jacquot, D. E. N.; Hoffmann, H.; Polborn, K.; Lindel, T. *Tetrahedron Lett.* **2002**, *43*, 3699; (i) Wiese, K. J.; Yakushijin, K.; Horne, D. A. *Tetrahedron Lett.* **2002**, *43*, 5135; (j) Fresneda, P. M.; Molina, P.; Sanz, M. A. *Tetrahedron Lett.* **2001**, *42*, 851; (k) Stien, D.; Anderson, G. T.; Chase, C. E.; Koh, Y.; Weinreb, S. M. *J. Am. Chem. Soc.* **1999**, *121*, 9574.
3. Kobayashi, J.; Tsuda, M.; Murayama, T.; Nakamura, H.; Ohizumi, Y.; Ishibashi, M.; Iwamura, M.; Ohta, T.; Nozoe, S. *Tetrahedron* **1990**, *46*, 5579.
4. Keifer, P. A.; Schwartz, R. E.; Koker, M. E. S.; Hughes, R. G., Jr.; Rittechof, D.; Rinehart, K. L. *J. Org. Chem.* **1991**, *56*, 2965.
5. (a) Assmann, M.; Lichte, E.; Pawlik, J. R.; Köck, M. *Mar. Ecol.: Prog. Ser.* **2000**, *207*, 255; (b) Eder, C.; Proksch, P.; Wray, V.; van Soest, R. W. M.; Ferdinandus, E.; Pattisina, L. A.; Sudarsono. *J. Nat. Prod.* **1999**, *62*, 1295; (c) Vassas, A.; Bourdy, G.; Paillard, J. J.; Lavayre, J.; Païs, M.; Quirion, J. C.; Debitus, C. *Planta Med.* **1996**, *62*, 28.
6. Forenza, S.; Minale, L.; Riccio, R.; Fattorusso, E. *J. Chem. Soc., Chem. Commun.* **1971**, 1129.
7. Kobayashi, J.; Ohizumi, Y.; Nakamura, H.; Hirata, Y. *Experientia* **1986**, *42*, 1176.
8. (a) Nakamura, S.; Kawasaki, I.; Yamashita, M.; Ohta, S. *Heterocycles* **2003**, *60*, 583; (b) Nakamura, S.; Kawasaki, I.; Kunimura, M.; Matsui, M.; Noma, Y.; Yamashita, M.; Ohta, S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1061; (c) Kawasaki, I.; Nakamura, S.; Yanagitani, S.; Kakuno, A.; Yamashita, M.; Ohta, S. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3095; (d) Ohta, S.; Tsuno, N.; Nakamura, S.; Taguchi, N.; Yamashita, M.; Kawasaki, I.; Fujieda, M. *Heterocycles* **2000**, *53*, 1939; (e) Ohta, S.; Tsuno, N.; Maeda, K.; Nakamura, S.; Taguchi, N.; Yamashita, M.; Kawasaki, I. *Tetrahedron Lett.* **2000**, *41*, 4623; (f) Kawasaki, I.; Katsuma, H.; Nakayama, Y.; Yamashita, M.; Ohta, S. *Heterocycles* **1998**, *48*, 1887; (g) Kawasaki, I.; Taguchi, N.; Yamashita, M.; Ohta, S. *Chem. Pharm. Bull.* **1997**, *45*, 1393; (h) Kawasaki, I.; Yamashita, M.; Ohta, S. *Chem. Pharm. Bull.* **1996**, *44*, 1831; (i) Kawasaki, I.; Katsuma, H.; Nakayama, Y.; Yamashita, M.; Ohta, S. *Heterocycl. Commun.* **1996**, *2*, 189; (j) Kawasaki, I.; Taguchi, N.; Yoneda, Y.; Yamashita, M.; Ohta, S. *Heterocycles* **1996**, *43*, 1375; (k) Kawasaki, I.; Taguchi, N.; Yamamoto, T.; Yamashita, M.; Ohta, S. *Tetrahedron Lett.* **1995**, *36*, 8251; (l) Kawasaki, I.; Yamashita, M.; Ohta, S. *J. Chem. Soc., Chem. Commun.* **1994**, 2085.
9. Kawasaki, I.; Sakaguchi, N.; Fukushima, N.; Fujioka, N.; Nikaido, F.; Yamashita, M.; Ohta, S. *Tetrahedron Lett.* **2002**, *43*, 4377.
10. (a) Baran, P. S.; O'Malley, D. P.; Mitsos, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 249; (b) Baran, P. S.; O'Malley, D. P.; Zografos, A. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 2674.
11. Walker, R. P.; Faulkner, D. J.; Van Engen, D.; Clardy, J. *J. Am. Chem. Soc.* **1981**, *103*, 6772.
12. Compound **6a** (a), **6b** (b), **6c** (c), **6d** (d), **7c** (e), and **9e** (f) were known compounds. See: (a) Ohta, S.; Yamamoto, T.; Kawasaki, I.; Yamashita, M.; Katsuma, H.; Nasako, R.; Kobayashi, K.; Ogawa, K. *Chem. Pharm. Bull.* **1992**, *40*, 2681; (b) Tang, C. C.; Davalian, D.; Huang, P.; Breslow, R. *J. Am. Chem. Soc.* **1978**, *100*, 3918; (c) Nakamura, S.; Tsuno, N.; Yamashita, M.; Kawasaki, I.; Ohta, S.; Ohishi, Y. *J. Chem. Soc., Perkin Trans. 1* **2001**, 429; (d) Azami, H.; Barrett, D.; Tanaka, A.; Sasaki, H.; Matsuda, K.; Sakurai, M.; Matsumoto, Y.; Tawara, S.; Chiba, T.; Sakane, K. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1409; (e) Lipshutz, B. H.; Huff, B.; Hagen, W. T. *Tetrahedron Lett.* **1988**, *29*, 3411; (f) Sakamoto, T.; Nagata, H.; Kondo, Y.; Shiraiwa, M.; Yamanaka, H. *Chem. Pharm. Bull.* **1987**, *35*, 823.
13. Ohta, S.; Yamamoto, T.; Kawasaki, I.; Yamashita, M.; Nagashima, Y.; Yoshikawa, T. *Chem. Pharm. Bull.* **1994**, *42*, 821.
14. Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1995**, *36*, 8251.
15. (a) Lovely, C. J.; Du, H.; Dias, H. V. R. *Org. Lett.* **2001**, *3*, 1319; (b) Deghati, P. Y. F.; Wanner, M. J.; Koomen, G. J. *Tetrahedron Lett.* **1998**, *39*, 4561; (c) Walters, M. A.; Lee, M. D. *Tetrahedron Lett.* **1994**, *35*, 8307.
16. Intramolecular DA reaction of 4-vinylimidazoles was reported, Ref. 2e.
17. The structure of **10a** was confirmed by HMBC experiment, and the regio- and stereochemistry of **10c–d** and **11a** were determined by HMBC and NOESY experiments.
18. Hehre, W. J. *SPARTAN, version 2.0*; Wavefunction: Irvine, CA, 1999.
19. Back, T. G.; Baron, D. L.; Yang, K. *J. Org. Chem.* **1993**, *58*, 2407.
20. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited at the Cambridge Crystallographic Data Centre as a supplementary number CCDC 616563. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
21. Lindel, T.; Hochgürtel, M. *J. Org. Chem.* **2000**, *65*, 2806.
22. Lal, B.; Pramanik, B. N.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1977**, 1977.
23. Knouzi, N.; Vaultier, M.; Carrié, R. *Bull. Soc. Chim. Fr.* **1985**, 815.
24. Bélanger, P. *Tetrahedron Lett.* **1979**, 2505.