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REGIO- AND STEREOSELECTIVE HEAD-TO-HEAD PHOTO[2+2]-CYCLOADDITION OF 3-(1-METHYL-2-PHENYLSULFANYL-1*H*-IMIDAZOL-5-YL)PROPENOATES

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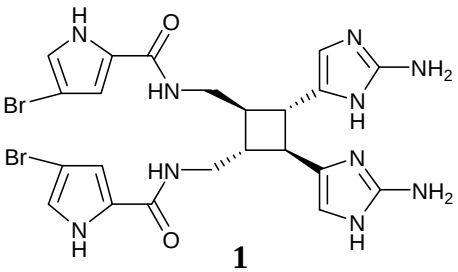
Abstract – Head-to-head photo[2+2]cycloaddition of 1, ω -di[3-(1-methyl-2-phenylsulfanyl-1*H*-imidazol-5-yl)propenoyloxy]alkylenes smoothly proceeded under irradiation of a high-pressure mercury lamp to give cyclobutane compounds regio- and stereoselectively. The stereochemistry of these cyclobutanes was determined as β-form.

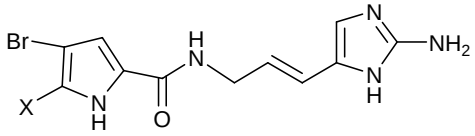
INTRODUCTION

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 1981, sceptrin **1** was isolated from a sponge, *Agelas sceptrum,* as an antimicrobial agent by Faulkner and Clardy,[3] and recently found to have various biological properties such as antiviral, antimuscarinic, antihistamic, inhibition of somatostatin and vasoactive intestinal peptide receptors. Use of **1** for a treatment of cystic fibrosis and Alzheimer's disease has also been tried.[4]

Figure 1



1



2 X = Br (oroidin)
3 X = H (hymenidin)

The structural skeleton of **1** has been considered to be biochemically synthesized through a formal head-to-head [2+2]cycloaddition[1b,3,4a] of the simplest pyrrole-imidazole alkaloids, oroidin **2**[5] or/and

hymenidin **3** (Figure 1).[6] Total synthesis of **1** was achieved first by Baran and his co-workers without [2+2]cycloaddition,[7] and next by Birman and his co-workers through the photo[2+2]cycloaddition of maleic anhydride with *trans*-1,4-dichloro-2-butene.[8]

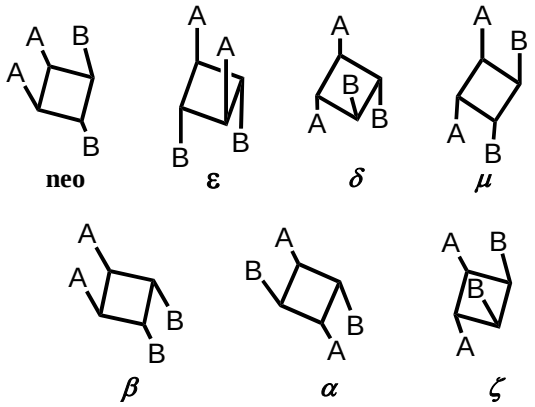
Formally, sceptrin is related to oroidin **(2)** by a head-to-head photo[2+2]cycloaddition, and it may be the first example of a biological [2+2]cycloaddition. The cyclodimerization of cinnamic acid is one of the oldest and best known reactions of photo[2+2]cycloaddition. In principle, ethyl cinnamate can form 11 cyclic dimers and the products distribution is shown in Table 1.[9]

Table 1 Distribution of stereoisomers of [2+2]cycloadducts obtained from liquid ethyl cinnamate [9]

Substitution pattern	Yield (%)*
neo	7.1
ε	2.5
δ	55.2
μ	0.5
β	24.0
α	6.3
ζ	4.4

*25 °C, liquid

Substitution patterns

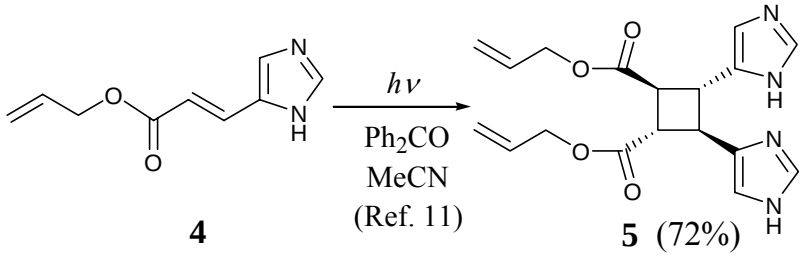


We have investigated the total synthesis of several biologically active imidazole alkaloids[10] and at this time our attention has been focused on the synthesis of sceptrin **1** *via* a biomimetic synthetic route. In this paper, we would like to report the first photo[2+2]cycloaddition of 1,ω-di[3-(1-methyl-2-phenyl-sulfanyl-1*H*-imidazol-5-yl)propenoyloxy]alkylenes to a cyclobutane derivative, which may be the key intermediate for the synthesis of **1.**

RESULTS AND DISCUSSION

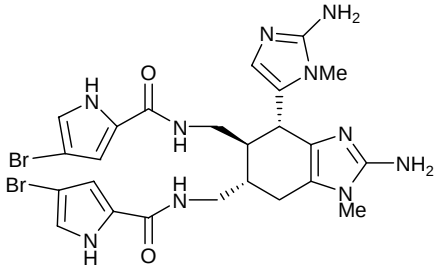
D'Auria reported photocycloaddition of allyl urocanate (**4**) to the head-to-head cyclobutane **5** (Scheme 1)[11], but in our hands, we obtained only a trace of **5** probably because of different reaction conditions such as the light source. Furthermore, *N*-unsubstituted imidazole seems to be not useful for synthesis of **1** because of difficulties relating to the tautomerism of the imidazole ring.[12] However, further conversion of **5** to sceptrin **1** has not yet been reported. On the other hand, we have demonstrated a synthesis of 12,12'-dimethylageliferin (Figure 2), which is an analogue of a member of the dimeric oroidin alkaloids, starting from the ethyl ester **6**.[13] Thus, we planned first to investigate the reactivity of the photo[2+2]cycloaddition of 3-(1-methyl-2-phenylsulfanyl-1*H*-imidazol-5-yl)propenonates **(6)**.

Scheme 1



4 **5** (72%)

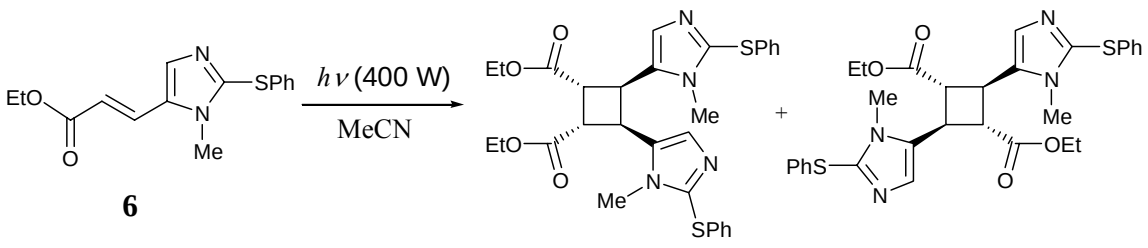
Figure 2



12,12'-dimethylageliferin

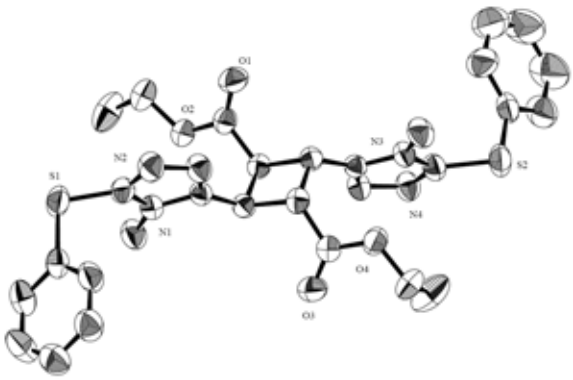
To examine the reactivity of the ethyl ester **6** under photocycloaddition reactions conditions, various [2+2]cycloaddition precursors, similar to Scheme 1, were prepared from 1, 2-disubsituted imidazoles. First, photo[2+2]cycloaddition of the ethyl ester **6** was attempted under irradiation with a 400-W high-pressure mercury lamp in MeCN, and two products could be isolated from the reaction mixture (Scheme 2). One of the products was head-to-head cycloadduct **7** (26%), whose structure was proven by further experiment described below, and the other product was the head-to-tail cycloadduct **8** (16 %), the structure of which was confirmed by X-ray crystallographic analysis as shown in Figure 3. This result shows that the tendency of the reactivity of ethyl 3-(1-methyl-2-phenylsulfanyl-1*H*-imidazol-5-yl)propenoate **6** under a photochemical reaction condition might be almost the same as that of the cinnamic acid derivatives.[9]

Scheme 2



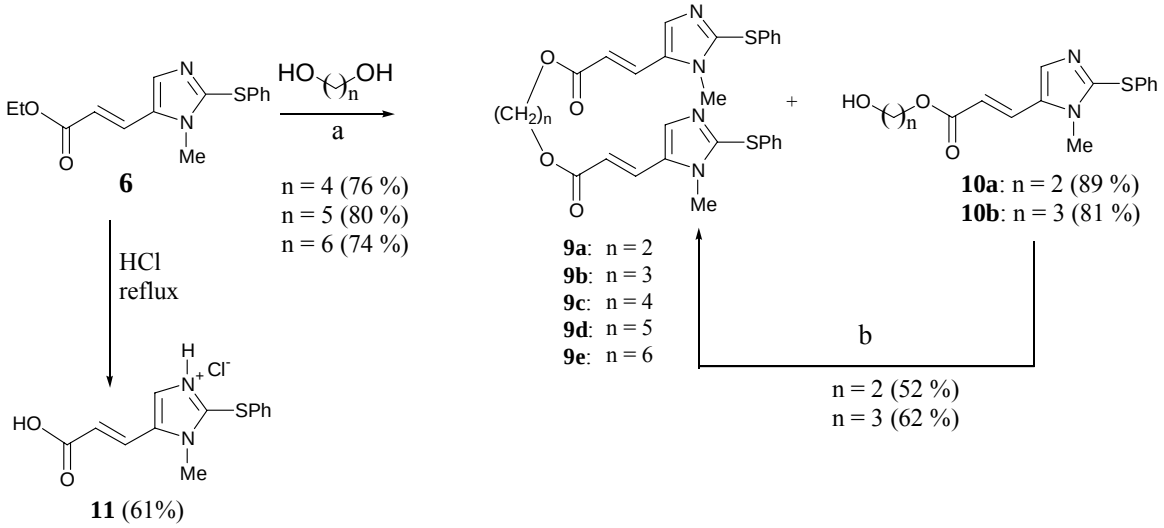
6 **7** (26 %) **8** (16 %)

Figure 3 ORTEP drawing of **8**



Then, we planned to prepare polymethylene-linked imidazolylpropenoate **9** expected to be a good precursor of an intramolecular head-to-head photo[2+2]cycloaddition.[14] Trans-esterification of the ethyl ester **6** with various 1,ω-alkanediols was performed in the presence of *p*-TsOH in refluxing benzene (Scheme 3). The diesters **9c-e** (n = 4 - 6) were provided by the reaction with the corresponding 1,ω-alkanediols in the presence of *p*-TsOH in good yields (74-80 %).[15] On the other hand, use of ethanediol or 1,3-propanediol gave monoesters **10a-b** and diesters **9a-b** (n = 2, 3) were not observed neither by prolongation of the reaction time nor by addition of a further amount of **6**. However, the diester imidazolylpropenonates **9a-b** could be obtained in moderate yields (52 - 62 %) by using Yamaguchi's method[16] from the alcohols **10a-b** and the imidazolylpropenoic acid hydrochloride **11,** prepared by acidic hydrolysis of **6**.

Scheme 3

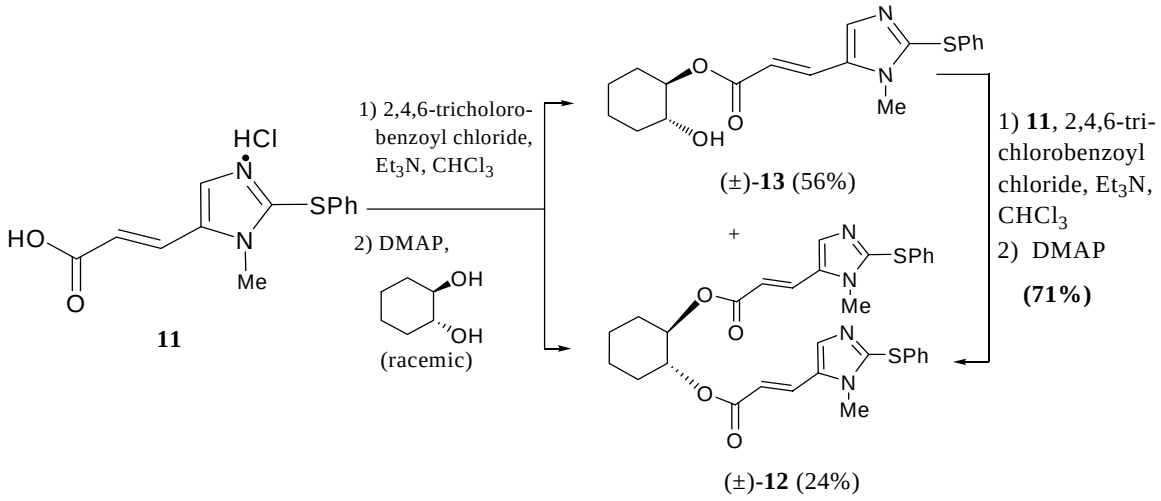


Reagents and conditions: (a) TsOH, PhH, reflux; (b) **11**, 2,4,6-trichlorobenzoyl chloride, DIEA, DMAP, DMF.

We also planned to prepare the cyclohexanediol-linked imidazolylpropenonates **12** expected to be a good precursor of the intramolecular head-to-head [2+2]cycloaddition by a photochemical reaction like the

above one. Also, asymmetric photo[2+2]cycloaddition may be expected by using chiral cyclohexanediol ester. These cyclohexanediol-linked esters were prepared by using Yamaguchi's method[16] of the (±)-*trans*-1,2-cyclohexanediols with the imidazolylpropenoic acid hydrochloride **11.** Here, once again monoester **13** was obtained in major yield (56%) compared to the diester **12** (24%), but upon subjection of the obtained monoester **13** to once again Yamaguchi's method, we could obtain the diesters **12** in 71% yield (Scheme 4).

Scheme 4



Photochemical reactions of **9a-e** were examined under several reaction conditions and the results are summarized in Table 2 as well as in Figure 4. The desired head-to-head cyclobutane compounds **14b-e** (n = 3 - 6) were only provided in 19 - 45 % yields under irradiation of a 400-W high-pressure mercury lamp in MeCN at room temperature (Entries 2-5). The reaction of **9a** (n = 2) did not give the corresponding [2+2]cycloadduct (Entry 1), because the length of two methylenes of the linker might not be enough to close both double bonds to form the cyclobutane ring. The **9d** (n = 5) gave the best result for the present photochemical reaction to afford the β-form product **14d** in 45 % isolated yield (Entry 4) and the structure of **14d** was determined by X-ray crystallographic analysis to be the β-form of the cyclobutane system as shown in Figure 5. Although some decomposed or polymerized products were observed in every reaction under the 400-W mercury lamp at room temperature, irradiation with a 100-W mercury lamp at lower temperature (10 °C) increased the yield of the β-form of the head-to-head cycloadduct **14d** to 52 % (Entry 6); when the reaction was carried out at 0° to -20 °C (Entry 7), the desired cyclobutane **14d** was obtained in lower yield (34 %) together with a small amount (1%) of the unexpected [2+2]cycloadduct **15,** whose structure was confirmed by X-ray crystallographic analysis as shown in Figure 6, and also a small amount (1.5%) of the δ-isomer **16** was obtained. The structure of **16** was determined by ^{1}HNMR and NOE (H_a-H_b and H_a-H_c) as shown below in Figure 7.

Figure 4

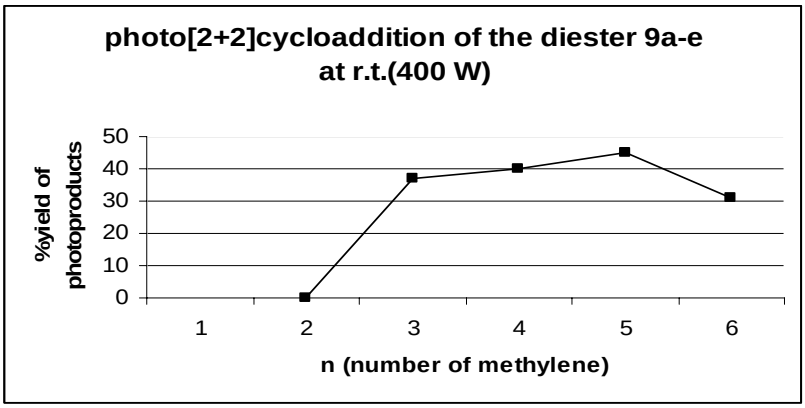
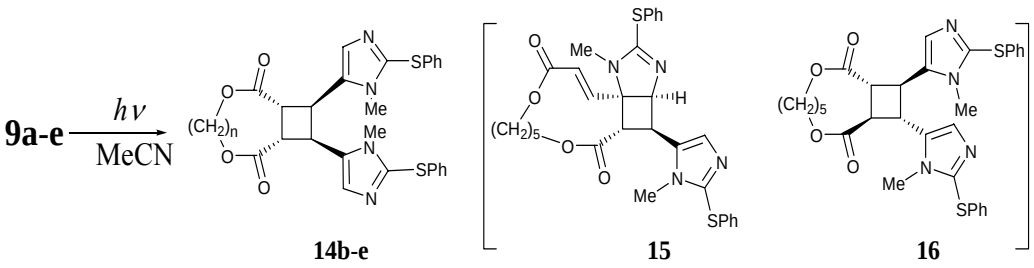


Table 2 Photochemical reaction of **9a-e.**[a]



Entry	n	Substrate	Light source (W)[b]	Temp. (°C) [c] /Time (h)	Product	Yield (%)
1	2	**9a**	400	rt/20	**14a**	0
2	3	**9b**	400	rt/20	**14b**	37
3	4	**9c**	400	rt/20	**14c**	39
4	5	**9d**	400	rt/20	**14d**	45
5	6	**9e**	400	rt/20	**14e**	19
6	5	**9d**	100	10/20	**14d**	52
7	5	**9d**	100	0 to -20/20	**14d**	34[d]

[a] All reactions were run in a Pyrex flask (>280 nm).

[b] High-pressure mercury lamp was used.

[c] temperature of the reaction mixture: 20°-25° (rt)

[d] By-products **15** (1 %) and **16** (1.5 %) were also obtained (Figure 6 and Figure 7).

Figure 5 ORTEP drawing of **14d**

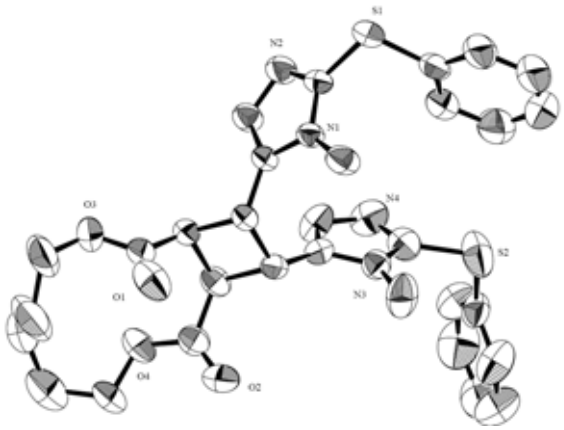
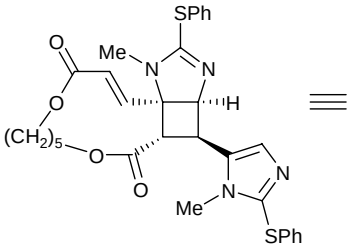


Figure 6 ORTEP drawing of **15**



15

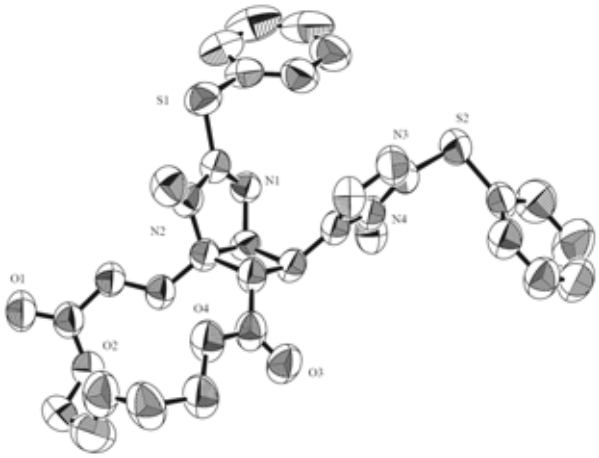
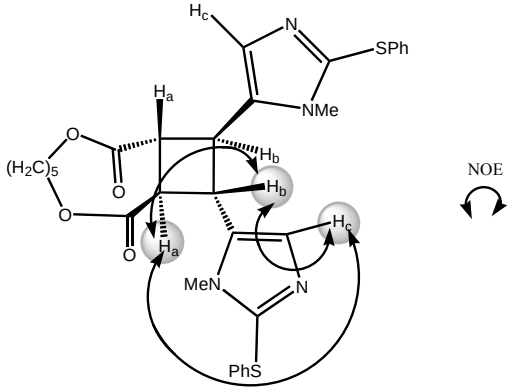


Figure 7 NOE co-relation of **16**



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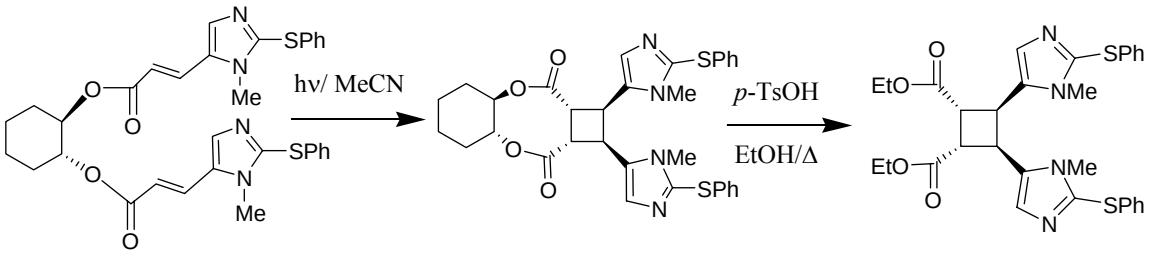
Photochemical reactions of the cyclohexanediol-linked imidazolylpropenonate **12** were also examined. The desired head-to-head cyclobutane compound **17** was provided in 38 % yield by irradiation with a 400-W high-pressure mercury lamp in MeCN at room temperature (Scheme 5).

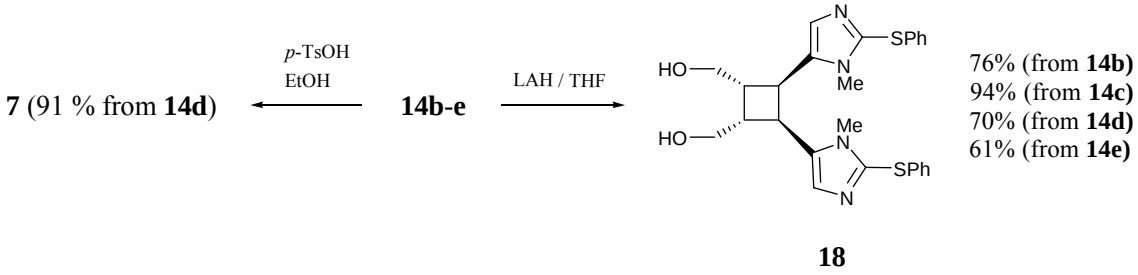
Scheme 5



12 **17** (38%) **7** (75%)

The cyclobutane **14d,** of which the structure was already confirmed by X-ray crystallographic analysis as *β*-form as shown above, was derived to **7** (91%) by acidic transesterification as shown in Scheme 6. Spectral data of this compound was compared with that of **7,** which was obtained by the photochemical reaction as shown in Scheme 2, to identify the structure of **7** as *β*-form. Compound **17** was also derived to **7** in order to confirm the structure of **17** as shown in Scheme 5.

Scheme 6



18

Furthermore, the cyclobutanes **14b-e** were all converted to the diol **18** by treatment with LAH as shown in Scheme 6. From these experiments, we could conclude that the structures of **7**, **14b-e** and **17** were all in the *β*-form.

At this stage, we decided to synthesize unnatural sceptrins or their analogs to examine their biological activities because MIC of natural sceptrin was reported to be not so high,[3] and further conversion of **14** to a *β*-sceptrin type derivative is currently under way.

In conclusion, we have developed the photo[2+2]cycloaddition of 1,ω-di-[3-(1-methyl-2-phenyl-sulfanyl-1*H*-imidazol-5-yl)propenoyloxy]alkylenes to obtain the head-to-head [2+2]cycloadducts regio- and stereoselectively.

EXPERIMENTAL

NMR were recorded on JEOL-AL 300 (^{1}H: 300 MHz, ^{13}C: 75 MHz) or Varian Inova-400 (^{1}H: 300 MHz, ^{13}C: 75 MHz) instruments at rt. Chemical shifts are given in δ relative to tetramethylsilane (TMS); TMS served as internal standard for ^{1}H-NMR, and solvent peak was referenced for ^{13}C-NMR. IR spectra were recorded on a Shimadzu IR-435 spectrometer. MS and HRMS were measured on JEOL JMS BU-20 (EI) or JEOL JMS-SX 102A QQ (FAB) spectrometer. Melting points were recorded on a Yanaco MPP－100 apparatus and uncorrected. X-ray crystallographic analysis was performed on a Rigaku RAXIS RAPID and AFC7R diffractometer with filtered Cu-Ka radiation and a rotating anode generator.

(1*R,2*S**,3*R**,4*S*)-3,4-Bis(1-methyl-2-phenylsulfanyl-1*H*-imidazol-5-yl)cyclobutane-1,2-dicarboxylic acid diethyl ester (7) and (1*R**,2*R**,3*S**,4*S**)-2,4-Bis(1-methyl-2-phenylsulfanyl-1*H*-imidazole-5-yl)cyclobutane-1,3-dicarboxylic acid diethyl ester (8):** N_2 gas was passed into a solution of **6** (288 mg, 1 mmol) in MeCN (0.5 mL) and the solution was irradiated by a 400-W mercury lamp through a Pyrex filter under N_2 at rt for 20 h. The solvent was evaporated and the crude product was purified by column chromatography ($CHCl_3$) and recrystallized from AcOEt-*n*-hexane. Yield of **7**; 75mg (26%) obtained from the second fraction. Yield of **8**; 46mg (16%) obtained from the first fraction.

7: White powder. Mp 157.5-160.0 °C (recrystallized from AcOEt-*n*-hexane). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.28 (t, 6H, J = 7.1 Hz, OCH_2CH_3 x 2), 3.26 (s, 6H, NCH_3 x 2), 3.73 (d, 2H, J = 5.9 Hz, $CHCO_2$ x 2), 4.17-4.22 (m, 6H, ImCH x 2 and OCH_2CH_3 x 2), 6.87 (s, 2H, ImH x 2), 6.98-7.25 (m, 10H, ArH). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 14.1, 31.1, 35.4, 44.2, 61.5, 126.6, 127.7, 128.2, 129.4, 132.8, 134.4, 138.8, 171.3. IR ($CHCl_3$) cm^{-1}: 2955, 1724, 1578, 1473, 1444, 1368, 1274, 1178, 1066, 1022. EI MS *m/z* (%): 576 (M^+, 2), 531 (1), 503 (2), 405 (2), 404 (2), 288 (100), 259 (9), 215 (43), 91 (24). HRMS (EI) *m/z* for $C_{30}H_{32}N_4O_4S_2$: requires M^+ 576.1865, found M^+ 576.1871. *Anal*. Calcd for $C_{30}H_{32}N_4O_4S_2$: C, 62.48; H, 5.59; N, 9.71. Found: C, 62.43; H, 5.73; N, 9.57.

8: Colorless prisms. Mp 154.0-158.5 °C (recrystallized from AcOEt-*n*-hexane).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 0.91 (t, 6H, J = 7.1 Hz, OCH_2CH_3 x 2), 3.62 (s, 6H, NCH_3 x 2), 3.72, 3.75 (q each, 2H, J = 7.1 Hz, OCH_2CH_3), 3.82 (dd, 2H, J = 7.0, 10.1, Hz, $CHCO_2$ x 2), 3.88, 3.91 (q each, 2H, J = 7.1 Hz, OCH_2CH_3), 4.33 (dd, 2H, J = 7.0, 9.8 Hz, ImC*H* x 2), 7.13 (s, 2H, ImH x 2), 7.16-7.28 (m, 10H, ArH). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 13.7, 31.5, 32.4, 45.1, 61.2, 126.8, 127.8, 128.3, 129.2, 132.8, 134.3, 139.0, 170.2. IR ($CHCl_3$) cm^{-1}: 2944, 1724, 1446, 1268, 1178, 1093. EI MS *m/z* (%): 576 (M^+, 5), 288 (100), 259 (7), 215 (31), 91 (9). HRMS (EI) *m/z* for $C_{30}H_{32}N_4O_4S_2$: requires M^+ 576.1865, found M^+ 576.1867. *Anal*. Calcd for $C_{30}H_{32}N_4O_4S_2$: C, 62.48; H, 5.59; N, 9.71. Found: C, 62.32; H, 5.75; N, 9.56. Crystal data for **8**: The crystal of **8** was obtained as space group P1 (#2), a = 11.364(1) Å, b = 17.267(1) Å, c = 7.7445(4) Å, α = 98.596(5)°, β = 104.633(5)°, γ = 90.965(6)°, V = 1451.5 (2) Å^3, Z = 2, D_{calc} = 1.319

g/cm^3, λ (CuKα) = 1.54178 Å, μ (CuKα) = 20.07 cm^{-1}, F_{000} = 608.00, T = 23±1°C, R1 = 0.0705 for 4428 reflections.

3-(1-Methyl-2-phenylsulfanyl-1*H*-imidazol-5-yl)acrylic acid 5-[3-(1-methyl-2-phenylsulfanyl-1*H*-imidazol-5-yl)acryloyloxy]alkyl ester; Synthesis of 9d (n = 5) as a General Procedure for compounds 9c-e from 6: A solution of **6** (5 g, 18.2 mmol), *p*-TsOH·H_2O (6.9 g, 36.5 mmol) and 1,5-pentanediol (1 mL, 14.5 mmol) of benzene (800 mL) was refluxed under N_2 equipped with Dean Stark condenser until no starting material **6** remained on TLC (16 h). The solvent was evaporated and the reaction mixture was neutralized with saturated aq.$NaHCO_3$ then the obtained yellow solid was filtered and to give pure **9d** (4.09 g, 80 %) as a white powder. Mp 134-136 °C (recrystallized from MeOH-Et_2O). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.48-1.79 (m, 6H, $OCH_2(CH_2)_3CH_2O$), 3.68 (s, 6H, NCH_3 x 2), 4.21 (t, 4H, J = 6.6 Hz, OCH_2 x 2), 6.33 (d, 2H, J = 15.7 Hz, $CHCO_2$ x 2), 7.19-7.35 (m, 10H, ArH), 7.50 (d, 2H, J = 15.7 Hz, ImCH x 2), 7.57 (s, 2H, ImH x 2). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 22.5, 28.3, 31.9, 64.4, 117.0, 127.3, 129.1, 129.4, 129.6, 131.6, 132.0, 133.2, 142.6, 166.7. IR ($CHCl_3$) cm^{-1}: 2934, 1698, 1627, 1275. EI MS *m/z* (%): 216 (43), 244 (20), 345 (49), 479 (100), 588 (46, M^+). HRMS (EI) *m/z* for $C_{31}H_{32}N_4O_4S_2$: requires M^+ 588.1865, found M^+ 588.1873. *Anal.* Calcd for $C_{31}H_{32}N_4O_4S_2$: C, 63.24; H, 5.48; N, 9.52. Found: C, 63.06; H, 5.50; N, 9.46.

3-(1-Methyl-2-phenylsulfanyl-1*H*-imidazol-5-yl)acrylic acid 4-[3-(1-methyl-2-phenylsulfanyl-1*H*-imidazol-5-yl)acryloyloxy]butyl ester (9c; n = 4): The title compound was prepared from the ethyl ester **6** (29.948 g, 103.9 mmol) and 1,4-butanediol (7.37 mL, 83.12 mmol) according to the general procedure **A**, and the obtained crude product was extracted AcOEt (200 mL x 3). The organic layer was dried over anhydrous sodium sulfate and evaporated to give an oily residue, which was purified by column chromatography ($CHCl_3$/MeOH = 100/1) to give **9c** (22.782 g, 76%) as white prisms. Mp 129-133 °C (recrystallized from AcOEt-*n*-hexane). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.82 (br t, 4H, J = 6.20 Hz, $CH_2(CH_2)_2CH_2$), 3.68 (s, 6H, NCH_3 x 2), 4.25 (br t, 4H, J = 5.6 Hz, OCH_2 x 2), 6.31 (d, 2H, J = 15.9 Hz, $CHCO_2$ x 2), 7.21-7.31 (m, 10H, ArH), 7.48 (dd, 2H, J = 0.6, 15.9 Hz, ImCH x 2), 7.58 (s, 2H, ImH x 2). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 25.3, 31.9, 64.0, 116.7, 127.2, 129.0, 129.4, 129.8, 131.4, 132.2, 133.3, 142.6, 166.6. IR ($CHCl_3$) cm^{-1}: 2950, 1701, 1628, 1441, 1302, 1275, 1176, 1155. EI MS *m/z* (%): 574 (M^+, 100), 465 (92), 331 (81), 259 (25), 243 (62), 215 (80). HRMS (EI) *m/z* for $C_{30}H_{30}N_4O_4S_2$: requires M^+ 574.1708, found M^+ 574.1701. *Anal*. Calcd for $C_{30}H_{30}N_4O_4S_2$: C, 62.70; H, 5.26; N, 9.75. Found: C, 62.75; H, 5.46; N, 9.77.

3-(1-Methyl-2-phenylsulfanyl-1*H*-imidazol-5-yl)acrylic acid 6-[3-(1-methyl-2-phenylsulfanyl-1*H*-imidazol-5-yl)acryloyloxy]hexyl ester (9e; n = 6): The title compound was prepared from the ethyl ester **6** (1.053 g, 3.65 mmol) and 1,6-hexanediol (0.34 mL, 2.92 mmol) according to the general procedure **A**, and obtained **9e** (814 mg, 74 %) as a white powder. Mp 133-134 °C (recrystallized from AcOEt).

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.43-1.72 (m, 8H, $CH_2(CH_2)_4CH_2$), 3.68 (s, 6H, NCH_3 x 2), 4.20 (t, 4H, J = 6.6 Hz, OCH_2 x 2), 6.31 (d, 2H, J = 16.0 Hz, $CHCO_2$ x 2), 7.20-7.28 (m, 10H, ArH), 7.47 (d, 2H, J = 16.0 Hz, ImCH x 2), 7.58 (s, 2H, ImH x 2). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 25.5, 28.5, 31.9, 64.6, 117.0, 127.2, 129.0, 129.4, 129.6, 131.5, 132.3, 133.4, 142.6, 166.8. IR ($CHCl_3$) cm^{-1}: 2928, 1698, 1629, 1276, 1178, 1157. EI MS *m/z* (%):602 (37, M^+), 494 (32), 493 (100), 359 (49), 243 (33), 216 (35), 215 (59). HRMS (EI) *m/z* for $C_{32}H_{34}N_4O_4S_2$: requires: M^+ 602.2021, found M^+ 602.2018. *Anal.* Calcd for $C_{32}H_{34}N_4O_4S_2$: C, 63.76; H, 5.69; N, 9.29. Found: C, 63.57; H, 5.83; N, 9.29.

3-(1-Methyl-2-phenylsulfanyl-1*H*-imidazol-5-yl)acrylic acid 2-hydroxyethyl ester (10a; n = 2): The title compound was prepared from the ethyl ester **6** (144mg, 0.50 mmol) and 1,2-ethanediol (0.014 mL, 0.25 mmol) according to the general procedure **A**, and the obtained crude product was extracted with AcOEt (50 mL x 3). The organic layer was dried over anhydrous sodium sulfate and evaporated to give an oily residue, which was purified by PTLC ($CHCl_3$/MeOH = 20/1) to give **10a** (68 mg, 89 %) as a white powder. Mp 127-128 °C (recrystallized from AcOEt-*n*-hexane). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 3.31 (t, 1H, J = 5.5 Hz, OH), 3.67 (s, 3H, NCH_3), 3.88 (brq, 2H, J = 4.7 Hz, OCH_2), 4.33 (t, 2H, J = 4.7 Hz, OCH_2), 6.34 (d, 1H, J = 15.9 Hz, $CHCO_2$), 7.20-7.31 (m, 5H, ArH), 7.50 (dd, 1H, J = 0.6, 15.9 Hz, ImCH), 7.57 (s, 1H, ImH). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 31.9, 60.8, 66.4, 116.6, 127.3, 129.0, 129.4, 130.0, 131.4, 132.1, 133.1, 142.7, 166.9. IR ($CHCl_3$) cm^{-1}: 2940, 1703, 1629, 1442, 1396, 1302, 1275, 1178, 1156, 1078. EI MS *m/z* (%): 304 (M^+, 100), 261 (18), 243 (17), 215 (42), 109 (11), 91 (20), 58 (10). HRMS (EI) *m/z* for $C_{15}H_{16}N_2O_3S$: requires M^+ 304.0882, found M^+ 304.0876. *Anal*. Calcd for $C_{15}H_{16}N_2O_3S$: C, 59.19; H, 5.30; N, 9.20. Found: C, 59.22; H, 5.56; N, 9.05.

3-(1-Methyl-2-phenylsulfanyl-1*H*-imidazol-5-yl)acrylic acid 3-hydroxypropyl ester (10b; n = 3): The title compound was prepared from the ethyl ester **6** (5.000 g, 17.34 mmol) and 1,3-propanediol (6.27 mL, 86.70 mmol) according to the general procedure **A**, and the obtained crude product was extracted AcOEt (200 mL x 3). The organic layer was dried over anhydrous sodium sulfate and evaporated to give an oily residue, which was purified by PTLC ($CHCl_3$/MeOH = 20/1) to give **10b** (4.457 g, 81 %) as a yellow powder. Mp 115-120 °C (recrystallized from AcOEt-*n*-hexane). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.94 (quintet, 2H, J = 6.0 Hz, $CH_2CH_2CH_2$), 3.69 (s, 3H, NCH_3), 3.73 (t, 2H, J = 6.0 Hz, CH_2OH), 4.37 (t, 2H, J = 6.0 Hz, $COOCH_2$), 6.32 (d, 1H, J = 15.9 Hz, $CHCO_2$), 7.21-7.30 (m, 5H, ArH), 7.50 (dd, 1H, J = 0.6, 15.9 Hz, ImCH), 7.59 (s, 1H, ImH). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 31.7, 31.9, 58.6, 61.6, 116.8, 127 .2, 128.9, 129.3, 129.7, 131.4, 132.0, 133.2, 142.4, 166.9. IR ($CHCl_3$) cm^{-1}: 2942, 1697, 1628, 1441, 1395, 1303, 1276, 1156. EI MS *m/z* (%): 318 (M^+, 100), 259 (18), 243 (17), 215 (44), 109 (11), 91 (22). HRMS (EI) *m/z* for $C_{16}H_{18}N_2O_3S$: requires M^+ 318.1038, found M^+ 318.1041. *Anal*. Calcd for $C_{16}H_{18}N_2O_3S$: C, 60.36; H, 5.70; N, 8.80. Found: C, 60.09; H, 5.83; N, 8.59.

3-(1-Methyl-2-phenylsulfanyl-1*H*-imidazol-5-yl)acrylic acid 2-[3-(1-methyl-2-phenylsulfanyl-1*H*-imidazol-5-yl)acryloyloxy]ethyl ester (9a; n = 2): DIEA (0.23 m1, 345 mmol) and 2,4,6-trichlorobenzoyl chloride (0.042 mL, 0.269 mmol) were added to a stirred solution of **11** (80 mg, 0.270 mmol) in DMF (1.3 mL) under N_2 at 0 °C. After stirring for 1.5 h at rt, a solution of **10a** (82 mg, 0.269 mmol) and DMAP (1 mg, 0.011 mmol) in DMF (2 mL) was added and the whole was stirred for 24 h at rt. The mixture was diluted with H_2O (1 mL) and the products were extracted with Et_2O (20 mL x 2). The organic layer was dried over anhydrous sodium sulfate and evaporated to give an oily residue, which was purified by PTLC ($CHCl_3$/MeOH = 20/1) to give **9a** (76 mg, 52 %) as a white powder. Mp 109-110 °C (recrystallized from AcOEt-*n*-hexane). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 3.68 (s, 6H, NCH_3 x 2), 4.46 (s, 4H, $O(CH_2)_2O$), 6.34 (d, 2H, J = 15.9 Hz, $CHCO_2$ x 2), 7.21-7.31 (m, 10H, ArH), 7.51 (d, 2H, J = 15.9 Hz, ImCH x 2), 7.59 (s, 2H, ImH x 2). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 31.9, 62.4, 116.1, 127.3, 129.1, 129.4, 130.3, 131.3, 132.5, 133.2, 142.9, 166.4. IR ($CHCl_3$) cm^{-1}: 2954, 1704, 1628, 1441, 1302, 1274, 1171, 1150. EI MS *m*/*z* (%): 546 (M^+, 100), 437 (69), 287 (59), 243 (63), 215 (83), 110 (62). HRMS (EI) *m*/*z* for $C_{28}H_{26}N_4O_4S_2$: requires M^+ 546.1395, found M^+ 546.1383. *Anal*. Calcd for $C_{28}H_{26}N_4O_4S_2$: C, 61.52; H, 4.79; N, 10.25. Found: C, 61.23; H, 4.93; N, 10.04.

3-(1-Methyl-2-phenylsulfanyl-1*H*-imidazol-5-yl)acrylic acid 3-[3-(1-methyl-2-phenylsulfanyl-1*H*-imidazol-5-yl)acryloyloxy]propyl ester (9b; n = 3): DIEA (0.25 m1, 1.41 mmol) and 2,4,6-trichlorobenzoyl chloride (0.044 mL, 0.283 mmol) were added to a stirred solution of **11** (84 mg, 0.283 mmol) in DMF (1.5 mL) under N_2 at 0 °C. After stirring for 1.5 h at rt, a solution of **10b** (90 mg, 0.283 mol) and DMAP (1 mg, 0.01 mmol) in DMF (2 mL) was added and the whole was stirred for 24 h at rt. The mixture was diluted with H_2O (1 mL) and the products were extracted with Et_2O (20 mL x 2). The organic layer was dried over anhydrous sodium sulfate and evaporated to give an oily residue which was purified by PTLC ($CHCl_3$/MeOH = 20/1) to give **9b** (98 mg, 62 %) as white prisms. Mp 132-134 °C (recrystallized from AcOEt-*n*-hexane). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 2.10 (quintet, 2H, J = 6.2 Hz, $OCH_2CH_2CH_2O$), 3.69 (s, 6H, NCH_3 x 2), 4.32 (t, 4H, J = 6.3 Hz, OCH_2 x 2), 6.31 (d, 2H, J = 15.9 Hz, $CHCO_2$ x 2), 7.21-7.31 (m, 10H, ArH), 7.49 (dd, 2H, J = 0.5, 15.9 Hz, ImCH x 2), 7.58 (s, 2H, ImH x 2). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 28.0, 31.9, 61.1, 116.5, 127.2, 129.0, 129.3, 129.9, 131.3, 132.4, 133.2, 142.7, 166.5. IR ($CHCl_3$) cm^{-1}: 2950, 1702, 1628, 1441, 1395, 1275, 1171. EI MS *m*/*z* (%): 560 (M^+, 100), 451 (72), 317 (57), 243 (44), 230 (28), 215 (63). HRMS (EI) *m*/*z* for $C_{29}H_{28}N_4O_4S_2$: requires M^+ 560.1552, found M^+ 560.1554. *Anal*. Calcd for $C_{29}H_{28}N_4O_4S_2$: C, 62.12; H, 5.03; N, 9.99. Found: C, 62.41; H, 5.20; N, 9.94

(2*E*)-3-(1-Methyl-2-phenylsulfanyl-1*H*-imidazol-5-yl)acrylic acid hydrochloride (11): A solution of the ethyl ester **6** (2.00 g, 6.94 mmol) in HCl (10 %, 30 mL) aq. was refluxed for 2h. Then toluene (30 mL) was added to the reaction mixture and the solvent was evaporated to give crystalline residue **11** (1.263 g,

61 %) as a white powder. Mp 158-162 °C (recrystallized from MeOH-Et_2O). ^{1}H-NMR (CD_3OD, 400 MHz) δ: 3.96 (s, 3H, NCH_3), 6.66 (d, 1H, J = 16.1 Hz, C*H*CO_2), 7.46-7.57 (m, 5H, ArH), 7.56 (dd, 1H, J = 0.5, 16.3 Hz, ImC*H*), 8.21 (s, 1H, ImH). ^{13}C-NMR (CD_3OD, 100 MHz) δ: 33.9, 122.1, 125.8, 128.2, 129.2, 131.3, 131.7, 133.2, 134.7, 142.5, 168.3. IR (KBr) cm^{-1}: 3865, 2672, 1809, 1692, 1635, 1469, 1388, 1260, 1187, 966, 847. EI MS *m*/*z* (%): 260 (M^+, 100), 215 (66), 156 (9), 112 (12), 91 (35), 80 (25). HRMS (EI) *m*/*z* for $C_{13}H_{12}N_2O_2S$: requires M^+ 260.0619, found M^+ 260.0611. *Anal*. Calcd for $C_{13}H_{13}N_2O_2ClS$: C, 52.61; H, 4.42; N, 9.44. Found: C, 52.52; H, 4.49; N, 9.38.

(±)-*(E)*-1,2-Di[(2*E*)-3-(1-Methyl-2-phenylsulfanyl-1*H*-imidazol-5-yl)acrylic acid 2-[3-(1-methyl-2-phenylsulfanyl-1*H*-imidazol-5-yl)acryloyloxy]cyclohexyl ester (12) and 3-(1-Methyl-2-phenylsulfanyl-1*H*-imidazol-5-yl)acrylic acid 2-hydroxycyclohexyl ester (13): DIEA (1.70 m1, 10 mmol) and 2,4,6-trichlorobenzoyl chloride (0.31 mL, 2 mmol) were added to a stirred solution of **11** (594 mg, 2 mmol) in $CHCl_3$ (6 mL) under N_2 at 0 °C. After stirring for 1.5 h at rt, a solution of (±)–*trans*-1,2-cyclohexanediol (279 mg, 2.4 mmol) and DMAP (9 mg, 0.080 mmol) in $CHCl_3$ (3 mL) was added and the whole was stirred for 24 h at rt. The mixture was diluted with H_2O (1 mL) and the products were extracted with EtOAc (50 mL x 2). The organic layer was dried over anhydrous sodium sulfate and evaporated to give an oily residue, which was purified by PTLC (AcOEt/*n*-hexane = 2/1) to give **12** (176mg, 24%) and **13** (404 mg, 56%) as white prisms. **12**: Mp 129-132 °C (recrystallized from AcOEt-*n*-hexane). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.38-1.51 (m, 4H, $CH_2(CH_2)_2CH_2$), 1.78-17.9 (m, 2H, C*H*HCHO x 2), 2.12-2.15 (m, 2H, C*H*HCHO x 2), 3.65(s, 6H, NCH_3 x 2), 4.96-5.03 (m, 2H, CHO x 2), 6.24 (d, 2H, J = 15.9 Hz, $CHCO_2$ x 2), 7.18-7.30 (m, 10H, ArH), 7.43 (dd, 2H, J = 0.4, 15.9 Hz, ImCH x 2), 7.55 (s, 2H, ImH x 2). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 23.5, 30.3, 31.9, 74.1, 116.9, 127.3, 129.0, 129.4, 129.9, 131.4, 132.4, 133.3, 142.7, 166.0. IR ($CHCl_3$) cm^{-1}: 2929, 1699, 1628, 1440, 1275, 1177, 1157, 1022. EI MS *m*/*z* (%): 600 (M^+, 44), 491 (40), 357 (23), 243 (100), 215 (62), 91 (75), 81 (41). HRMS (EI) *m*/*z* for $C_{32}H_{32}N_4O_4S_2$: requires M^+ 600.1865, found M^+ 600.1858. *Anal*. Calcd for $C_{32}H_{32}N_4O_4S_2$: C, 63.98; H, 5.37; N, 9.33. Found: C, 63.72; H, 5.22; N, 9.29.

13: Mp 153-155 °C (recrystallized from AcOEt-*n*-hexane). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.26-1.44 (m, 4H, $CH_2(CH_2)_2CH_2$), 1.73-1.75 (m, 2H, CH_2CHO), 2.04-2.10 (m, 2H, CH_2CHO), 3.61-3.66 (m, 1H, -C*H*(OH)), 3.67 (s, 3H, NCH_3), 4.68-4.74 (m, 1H, -CH(OCO)), 6.32 (d, 1H, J = 16.1 Hz, $CHCO_2$), 7.19-7.31 (m, 5H, ArH), 7.49 (dd, 1H, J = 0.6, 15.9 Hz, ImCH), 7.57 (s, 1H, ImH). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 23.7, 23.9, 30.0, 32.0, 33.1, 72.6, 78.5, 117.1, 127.2, 129.0, 129.4, 129.9, 131.5, 132.3, 133.3, 142.6, 166.9. IR ($CHCl_3$) cm^{-1}: 2924, 1697, 1628, 1443, 1274, 1181, 1156, 1019. EI MS *m*/*z* (%): 358 (M^+, 100), 259 (55), 243 (56), 215 (77), 133 (15), 109 (30). HRMS (EI) *m*/*z* for $C_{19}H_{22}N_2O_3S$: requires M^+ 358.1351, found M^+ 358.1347. *Anal*. Calcd for $C_{19}H_{22}N_2O_3S$: C, 63.66; H, 6.19; N, 7.82. Found: C, 63.67; H, 6.26; N, 7.89.

(±)-(*E*)-1,2-Di[(2*E*)-3-(1-Methyl-2-phenylsulfanyl-1*H*-imidazol-5-yl)acrylic acid 2-[3-(1-methyl-2-phenylsulfanyl-1*H*-imidazol-5-yl)acryloyloxy]cyclohexyl ester (12) from 13: DIEA (0.73 m1, 4.19 mmol) and 2,4,6-trichlorobenzoyl chloride (0.13 mL, 0.83 mmol) were added to a stirred solution of **11** (248 mg, 0.83 mmol) in $CHCl_3$ (2.5 mL) under N_2 at 0 °C. After stirring for 1.5 h at rt, a solution of **13** (300 mg, 0.83 mol) and DMAP (4 mg, 0.033 mmol) in DMF (2 mL) was added and the whole was stirred for 24 h at rt. The mixture was diluted with H_2O (1 mL) and the products were extracted with Et_2O (50 mL x 2). The organic layer was dried over anhydrous sodium sulfate and evaporated to give an oily residue, which was purified by PTLC (AcOEt/*n*-hexane = 2/1) and to give **12** (358 mg, 71 %) as white prisms. Spectral data was matched with the above prepared compound **12**.

Synthesis of (1*R,12*S**,13*R**,14*S**)-13,14-Bis(1-methyl-2-phenylsulfanyl-1*H*-imidazol-5-yl)-3,10-dioxabicyclo[10.2.0]tetradecane-2,11-dione (14e) as a General Procedure for the cyclobutane derivatives from 9:** N_2 gas was passed into a solution of the alkene **9e** (141 mg, 0.23 mmol), in MeCN (11.6 mL) and the solution was irradiated by a 400-W mercury lamp through a Pyrex filter under N_2 at rt for 12 h. The solvent was evaporated and the crude product was purified by PTLC ($CHCl_3$/MeOH = 20/1) to give the cyclobutane **14e** (44 mg, 31 %) as a viscous oil. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.40-1.80 (m, 8H, $OCH_2(CH_2)_4CH_2O$), 3.27 (s, 6H, NCH_3 x 2), 3.78 (d, 2H, J = 5.9 Hz, $CHCO_2$ x 2), 3.92-3.96 (m, 2H, OCH_2), 4.25 (d, 2H, J = 6.0 Hz, ImCH x 2), 4.57-4.59 (m, 2H, OCH_2), 6.87 (s, 2H, ImH x 2), 6.97-7.24 (m, 10H, ArH). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 24.3, 26.4, 31.2, 35.0, 44.5, 65.7, 126.6, 127.7, 128.2, 129.4, 132.8, 134.4, 138.8, 171.3. IR ($CHCl_3$) cm^{-1}: 2911, 1723, 1473, 1446, 1274. FAB MS *m/z* (%): 603 [78, $(M+H)^+$]. HRMS (FAB) *m/z* for $C_{32}H_{35}N_4O_4S_2$: requires $(M+H)^+$ 603.2100, found $(M+H)^+$ 603.2107.

(1*R,9*S**,10*R**,11*S**)-10,11-Bis(1-methyl-2-phenylsulfanyl-1*H*-imidazol-5-yl)-3,7-dioxabicyclo-[7.2.0]undecane-2,8-dione (14b):** The title compound was prepared from the ester **9b** (96 mg, 0.171 mmol) according to the general procedure **B**, and the obtained crude product was purified by column chromatography (AcOEt/*n*-hexane = 2/1) to give **14b** (35 mg, 37 %) as colorless needles. Mp 211-214 °C (recrystallized from AcOEt-*n*-hexane). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.99-2.08 (m, 1H, one of $CH_2CH_2CH_2$), 2.14-2.24 (m, 1H, one of $CH_2CH_2CH_2$), 3.25 (s, 6H, NCH_3 x 2), 3.72 (d, 2H, J = 5.7 Hz, $CHCO_2$ x 2), 4.26 (d, 2H, J = 5.7 Hz, ImCH x 2), 4.46-4.51 (m, 2H, OCH_2), 4.56-4.62 (m, 2H, OCH_2), 6.90 (s, 2H, ImH x 2), 6.96-7.25 (m, 10H, ArH). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 25.8, 31.3, 35.2, 44.5, 65.7, 126.9, 128.0, 128.6, 129.7, 132.4, 134.5, 139.2, 170.3. IR ($CHCl_3$) cm^{-1}: 2945, 1735, 1474, 1444, 1272, 1250, 1218, 1172. EI MS *m/z* (%): 560 (M^+, 38), 451 (24), 317 (15), 260 (22), 215 (34), 110 (100), 78 (49). HRMS (EI) *m/z* for $C_{29}H_{28}N_4O_4S_2$: requires M^+ 560.1552, found M^+ 560.1563. *Anal*. Calcd for $C_{29}H_{28}N_4O_4S_2$: C, 62.12; H, 5.03; N, 9.99. Found: C, 62.32; H, 5.19; N, 10.02.

(1*R,10*S**,11*R**,12*S**)-11,12-Bis(1-methyl-2-phenylsulfanyl-1*H*-imidazol-5-yl)-3,8-dioxabicyclo-**

[8.2.0]dodecane-2,9-dione (14c): The title compound was prepared from the ester **9c** (115 mg, 0.20 mmol) according to the general procedure **B**, and the obtained crude product was purified by PTLC ($CHCl_3$/MeOH = 100/1) to give **14c** (46 mg, 40 %) as white needles. Mp 204-206 °C (recrystallized from AcOEt-*n*-hexane). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.90-1.92 (m, 4H, $OCH_2(CH_2)_2CH_2O$), 3.26 (s, 6H, NCH_3 x 2), 3.78 (d, 2H, J = 5.9 Hz, $CHCO_2$ x 2), 4.12-4.16 (m, 2H, OCH_2), 4.28 (d, 2H, J = 6.0 Hz, ImCH x 2), 4.38-4.41 (m, 2H, OCH_2), 6.89 (s, 2H, ImH x 2), 6.96-7.24 (m, 10H, ArH). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 25.5, 31.1, 34.8, 44.9, 65.7, 126.5, 127.6, 128.3, 129.4, 132.5, 134.3, 138.8, 170.2. IR ($CHCl_3$) cm^{-1}: 2939, 1728, 1445, 1286, 1251, 1227, 1202, 1175, 1079. EI MS *m*/*z* (%): 574 (M^+, 67), 465 (100), 331 (85), 259 (21), 243 (45), 215 (79), 109 (17), 91 (39). HRMS (EI) *m*/*z* for $C_{30}H_{30}N_4O_4S_2$: requires M^+ 574.1708, found M^+ 574.1703. *Anal*. Calcd for $C_{30}H_{30}N_4O_4S_2$: C, 62.70; H, 5.26; N, 9.75. Found: C, 62.51; H, 5.35; N, 9.67.

(1*R,11*S**,12*R**,13*S**)-12,13-Bis(1-methyl-2-phenylsulfanyl-1*H*-imidazol-5-yl)-3,9-dioxabicyclo-[9.2.0]tridecane-2,10-dione (14d):** N_2 gas was passed into a solution of **9d** (1.5 g, 2.5 mmol), in MeCN (900 mL) and the solution was irradiated by a 100-W mercury lamp through a Pyrex filter under N_2 at 10 °C for 20 h. The solvent was evaporated and the crude product was purified by column chromatography (AcOEt) to give pure **14d** (780 mg, 52 %) as white needles. Mp 160-162 °C (recrystallized from AcOEt-*n*-hexane). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.76-1.81 (m, 6H, $CH_2(CH_2)_3CH_2$), 3.33 (s, 6H, NCH_3 x 2), 3.80 (d, 2H, J = 5.8 Hz, $CHCO_2$ x 2), 3.95-3.97 (m, 2H, OCH_2), 4.27 (d, 2H, J = 6.1 Hz, ImCH x 2), 4.53-4.56 (m, 2H, OCH_2), 6.89 (s, 2H, ImH x 2), 6.96-7.25 (m, 10H, ArH). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 19.3, 24.1, 31.1, 34.5, 44.7, 64.0, 126.5, 127.7, 128.2, 129.3, 132.7, 134.4, 138.0, 170.9. IR ($CHCl_3$) cm^{-1}: 2937, 1726, 1627, 1578, 1473, 1445, 1392, 1275, 1176. FAB MS *m*/*z* (%): 589 [100, $(M+H)^+$]. HRMS (FAB) *m*/*z* for $C_{31}H_{33}N_4O_4S_2$: requires $(M+H)^+$ 589.1943, found $(M+H)^+$ 589.1950. *Anal.* Calcd for $C_{31}H_{32}N_4O_4S_2$: C, 63.24; H, 5.48; N, 9.52. Found: C, 63.03; H, 5.34; N, 9.51. Crystal data for **14d** (n=5): The crystal of **14d** was obtained as space group $P2_1/n$ (#14), a = 19.2833(9) Å, b = 6.4736(3) Å, c = 24.3370(11) Å, β = 97.223(3)°, V = 3013.9 (2) Å^3, Z = 4, D_{calc} = 1.297 g/cm^3, λ (CuKα) = 1.54187 Å, μ (CuKα) = 19.452 cm^{-1}, F_{000} = 1240.00, T = 22 ± 1°C, R1 = 0.0542 for 5456 reflections. When this same reaction was carried out at 0 to -20 °C for 20hr, the product **(14d)** was obtained in 34% yield.

(1*R,2*E*,13*S**,14*S**,15*S**)-18-Methyl-14-(1-methyl-2-phenylsulfanyl-1*H*-imidazol-5-yl)-17-phenyl-sulfanyl-5,11-dioxa-16,18-diazatricyclo[13.3.0.0^{1,13}]octadeca-2,16-diene-4,12-dione (15):** This compound was obtained when **9d** was irradiated at 0 to -20 °C in yield of 1 % as white needles. Mp 198-200 °C (recrystallized from AcOEt-*n*-hexane). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.52-1.91 (m, 6H, $CH_2(CH_2)_3CH_2$), 2.97 (s, 3H, NCH_3), 3.38 (s, 3H, NCH_3), 3.76(d, 1H, J = 7.1 Hz, $CHCO_2$), 3.87-3.94 (m, 1H, OC*H*H), 4.17-4.24 (m, 2H, OC*H*H and CHIm), 4.35-4.42 (m, 1H, OC*H*H), 4.55-4.62 (m, 1H,

OC*H*H), 4.71 (d, 1H, *J* = 7.9 Hz, CHN), 5.86 (d, 1H, *J* = 15.7Hz, =CHCO), 7.07-7.37 (m, 12H, ArH and C*H*=CHCO).^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 21.3, 26.0, 27.3, 28.8, 31.5, 35.5, 51.1, 63.4, 65.1, 69.4, 72.0, 121.9, 126.4, 127.4, 127.7, 128.3, 129.1, 129.2, 129.3, 132.8, 134.6, 134.8, 138.2, 142.9, 165.5, 167.5, 170.3. IR ($CHCl_3$) cm^{-1}: 2934, 1713, 1578, 1541, 1473, 1472, 1327, 1245, 1222, 1165, 1091, 1050. FAB MS *m/z* (%): 589 [100, $(M+H)^+$]. HRMS (FAB) *m/z* for $C_{31}H_{33}N_4O_4S_2$: requires (M^++H) 589.1943, found $(M+H)^+$ 589.1951. *Anal.* Calcd for $C_{31}H_{32}N_4O_4S_2$: C, 63.24; H, 5.48; N, 9.52. Found: C, 63.05; H, 5.35; N, 9.44. Crystal data for **15:** The crystal of **15** was obtained as space group $P2_1/n$ (#14), a = 10.602(2) Å, b = 13.901(3) Å, c = 20.2778(14) Å, β = 92.555(10)°, V = 2985.4(9) $Å^3$, Z = 4, D_{calc} = 1.310 g/cm^3, λ (CuKα) = 1.54178 Å, μ (CuKα) = 19.638 cm^{-1}, F_{000} = 1240.00, T = 23±1°C, R1 = 0.0924 for 5633 reflections.

(1*R,11*R**,12*S**,13*S**)-12,13-Bis(1-methyl-2-phenylthio-1*H*-imidazole-5-yl)-3,9-dioxabicyclo[9,2,0]-tridecane-2,10-dione (16):** This compound was obtained when **9d** was irradiated at 0° C to -20° C in yield of 1.5 % as a viscous oil.^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.62-1.72 (m, 6H, $CH_2(CH_2)_3CH_2$), 3.10 (d, 2H, *J* = 9.7 Hz, $CHCO_2$ x 2), 3.46 (s, 6H, NCH_3 x 2), 3.72 (d, 2H, *J* = 9.9 Hz, ImCH x 2), 3.74-3.78 (m, 2H, OCH_2), 4.71-4.76 (m, 2H, OCH_2), 7.12 (s, 2H, ImH x 2), 7.13-7.27 (m, 10H, ArH). ^{13}C-NMR ($CDCl_3$, 75 MHz,) δ: 24.2, 28.3, 31.6, 35.7, 48.5, 66.4, 126.9, 127.9, 128.5, 129.3, 133.74, 134.4, 158.0, 170.9. IR ($CHCl_3$) cm^{-1}: 2925, 1698, 1627, 1473, 1439, 1391, 1274, 1174. FAB MS *m/z* (%): 589 [7, $(M+H)^+$], 307 (25), 154 (100), 136 (70). HRMS (FAB) *m/z* for $C_{31}H_{33}N_4O_4S_2$: requires (M^++H) 589.1943, found $(M+H)^+$ 589.1947.

(1*R,2*S**,3*S**,4*R**)-1,2-Bis(1-methyl-2-phenylsulfanyl-1*H*-imidazol-5-yl)-decahydro-4,9-dioxabenzo-[*a*]cyclobuta[*e*]cyclooctene-3,10-dione (17):** N_2 gas was passed into a solution of the **12** (540 mg, 0.90 mmol) in MeCN (90.0 mL) and the solution was irradiated by a 400W mercury lamp through a Pyrex filter under N_2 at rt for 16 h. The solvent was evaporated and the crude product was purified by column chromatography (AcOEt), to give pure **17** (205 mg, 38 %) as a white needles. Mp 164-167 °C (recrystallized from MeOH-*n*-hexane). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.36-1.48 (m, 2H, (CH_2 in C_6H_{10}), 1.58-1.69 (m, 2H, CH_2 in C_6H_{10}), 1.82-1.92 (m, 2H, CH_2 in C_6H_{10}), 2.15 (br t, 2H, *J* = 13.2 Hz, (CH_2CHO), 3.02 (s, 3H, NCH_3), 3.47 (s, 3H, NCH_3) 3.68 (dd, 1H, *J* = 9.4, 2.0 Hz, $CHCO_2$), 4.11 (t, 1H, *J* = 10.1 Hz, $CHCO_2$), 4.26 (t, 1H, *J* = 9.3 Hz, ImCH), 4.32 (dd, 1H, *J* = 8.2, 2.0 Hz, ImCH), 4.70 (ddd, 1H, *J* = 4.0 Hz, (CH_2CHO), 4.98 (ddd, 1H, *J* = 4.0 Hz, (CH_2CHO), 6.68 (d, 1H, *J* = 0.5 Hz, ImH), 6.93-7.30 (m, 10H, ArH), 7.12 (d, 1H, *J* = 0.5 Hz, ImH). ^{13}C-NMR ($CDCl_3$, 75 MHz,) δ: 24.3 x 2, 30.4, 30.7, 31.0, 31.6, 34.2, 37.7, 46.9, 49.9, 85.6, 85.7, 126.8, 127.0, 128.1, 128.6, 129.1, 129.5, 129.8, 131.8, 132.0, 134.3, 134.6, 139.3, 139.5, 172.7, 175.6. IR ($CHCl_3$) cm^{-1}: 2928, 1730, 1473, 1444, 1578, 1340, 1231, 1161, 1079. EI MS *m/z* (%): 600 (M^+, 62), 491 (61), 358 (38), 261 (79), 243 (100), 215 (65).

HRMS (EI) *m/z* for $C_{32}H_{32}N_4O_4S_2$: requires M^+ 600.1865, found M^+ 600.1866. *Anal.* Calcd for $C_{32}H_{32}N_4O_4S_2$: C, 63.98; H, 5.37; N, 9.33. Found: C, 63.76; H, 5.30; N, 9.26.

7 Obtained by the Transesterification of the Linked Cyclobutane 14d: A solution of **14d** (25 mg, 0.04 mmol) and *p*-TsOH • H_2O (10 mg, 0.05 mmol) in EtOH (4 mL) was refluxed under N_2 for 48 h. The reaction mixture was neutralized with saturated $NaHCO_3$ aq (5 mL), then the product was extracted with AcOEt (15 mL x 3). The organic layer was dried over anhydrous sodium sulfate and evaporated to give an oily residue, which was purified by PTLC ($CHCl_3$/MeOH = 20/1) to give **7** (21 mg, 91 %) as a colorless solid. ^{1}H- and ^{13}C-NMR of the product was identified with **7***β*.

(1R*,2S*,3S*,4R*)-[2-Hydroxymethyl-3,4-bis(1-methyl-2-phenylsulfanyl-1*H*-imidazol-5-yl)cyclobutyl]methanol (18) from 14d; General Procedure: A THF (10mL) solution of $LiAlH_4$ (200mg, 5.3mmol) was cooled to 0 °C and to this a solution of **14d** (780mg, 1.32 mmol) in THF (10mL) was added and stirred at rt. After completion of the reaction, as indicated by TLC (30 min), the reaction mixture was cooled to 0 °C and the remaining $LiAlH_4$ was quenched with sat. aq $NaHCO_3$ and stirred for 1h at rt. After filtration the reaction mixture washed with MeOH. The solvent was evaporated to give an oily residue which was purified by column chromatography ($CHCl_3$/MeOH = 100/1) to give pure diol **18** (460mg, 70%) as white needles. Mp 193.8-197.3°C (recrystallized from MeOH-Et_2O)**.** ^{1}H-NMR (DMSO-d_6, 300 MHz) *δ*: 2.80-2.88 (m, 2H, C*H*CH_2OH x 2), 3.36 (s, 6H, NCH_3 x 2), 3.64 (br d, 2H, *J* = 5.5 Hz, ImCH x 2), 3.71-3.72 (m, 4H, C*H*$_2$OH x 2), 4.69 (t, 2H, *J* = 5.1 Hz, OH x 2); 6.80-6.83 (m, 4H, ArH), 7.12-7.25 (m, 6H, ArH), 7.40 (s, 2H, ImH).^{13}C-NMR (DMSO, 75 MHz) *δ*: 30.8, 34.5, 41.3, 60.2, 126.1, 126.3, 127.9, 129.5, 135.0, 135.3, 136.0. IR (KBr) cm^{-1}: 3193, 2896, 1576, 1473, 1436, 1414, 1269, 1019. FAB MS *m/z* (%):493 [46, $(M+H)^+$], 246 (70). HRMS (FAB) *m/z* for $C_{26}H_{29}N_4O_2S_2$: requires $(M+H)^+$ 493.1732, found $[M+H]^+$ 493.1735. *Anal.* Calcd for $C_{26}H_{28}N_4O_2S_2$: C, 63.39; H, 5.73; N, 11.37. Found: C, 63.19; H, 5.92; N, 11.21.

14b, c and **14e** were converted to **18** in the similar manner in 76, 94 and 61 % yields, respectively.

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