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

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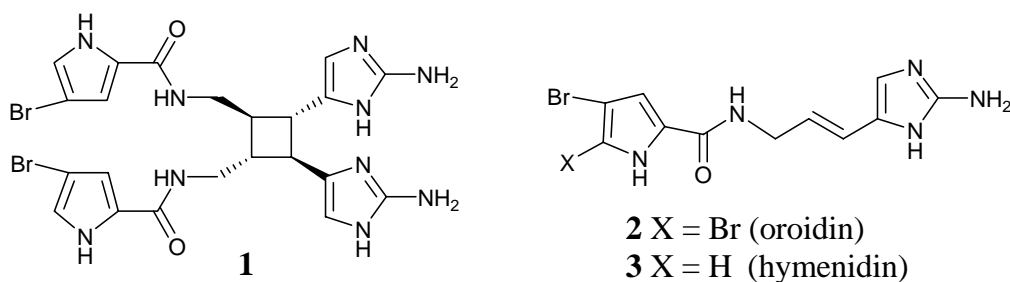
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**Abstract** – Head-to-head photo[2+2]cycloaddition of 1, -di[3-(1-methyl-2-phenylsulfanyl-1H-imidazol-5-yl)propenyloxy]alkylenes smoothly proceeded under irradiation of a high-pressure mercury lamp to give cyclobutane compounds regio- and stereoselectively. The stereochemistry of these cyclobutanes was determined as -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.<sup>1,2</sup> In 1981, sceptrin **1** was isolated from a sponge, *Agelas sceptrum*, as an antimicrobial agent by Faulkner and Clardy,<sup>3</sup> 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.<sup>4</sup>

**Figure 1**



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

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

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.<sup>9</sup>

**Table 1** Distribution of stereoisomers of [2+2]cycloadducts obtained from liquid ethyl cinnamate<sup>9</sup>

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

\*25 °C, liquid

A = Ph      B = CO<sub>2</sub>Et

We have investigated the total synthesis of several biologically active imidazole alkaloids<sup>10</sup> 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, -di[3-(1-methyl-2-phenylsulfanyl-1*H*-imidazol-5-yl)propenyloxy]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)<sup>11</sup>, 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.<sup>12</sup> 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**.<sup>13</sup> 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

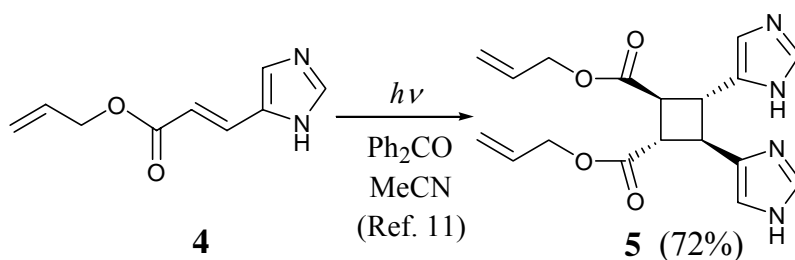
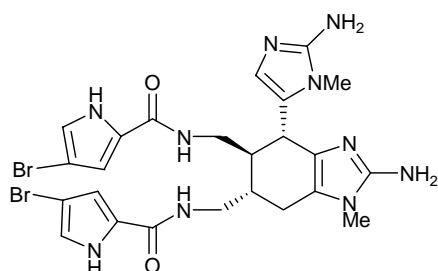


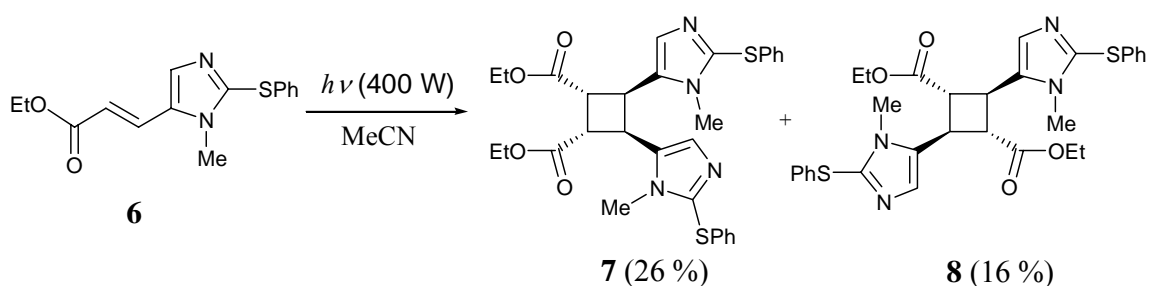
Figure 2



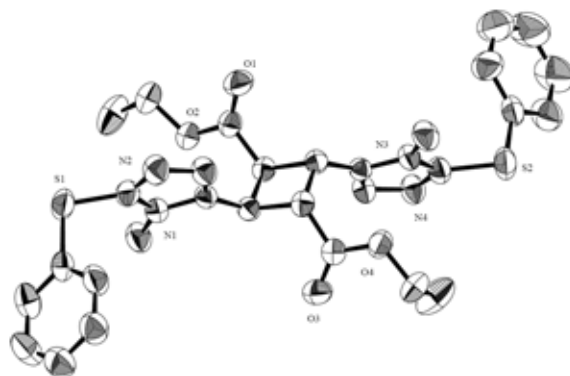
12,12'-dimethylageliferin

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-disubstituted 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.<sup>9</sup>

## Scheme 2

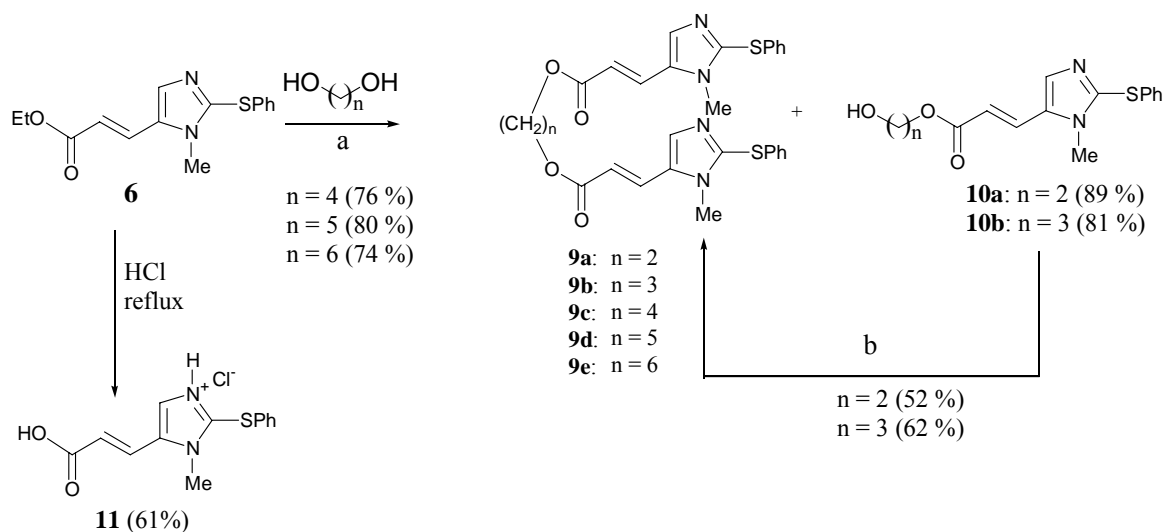


**Figure 3** ORTEP drawing of **8**



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.<sup>14</sup> Trans-esterification of the ethyl ester **6** with various 1, $\omega$ -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, $\omega$ -alkanediols in the presence of *p*-TsOH in good yields (74-80 %).<sup>15</sup> 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<sup>16</sup> from the alcohols **10a-b** and the imidazolylpropenoic acid hydrochloride **11**, prepared by acidic hydrolysis of **6**.

**Scheme 3**

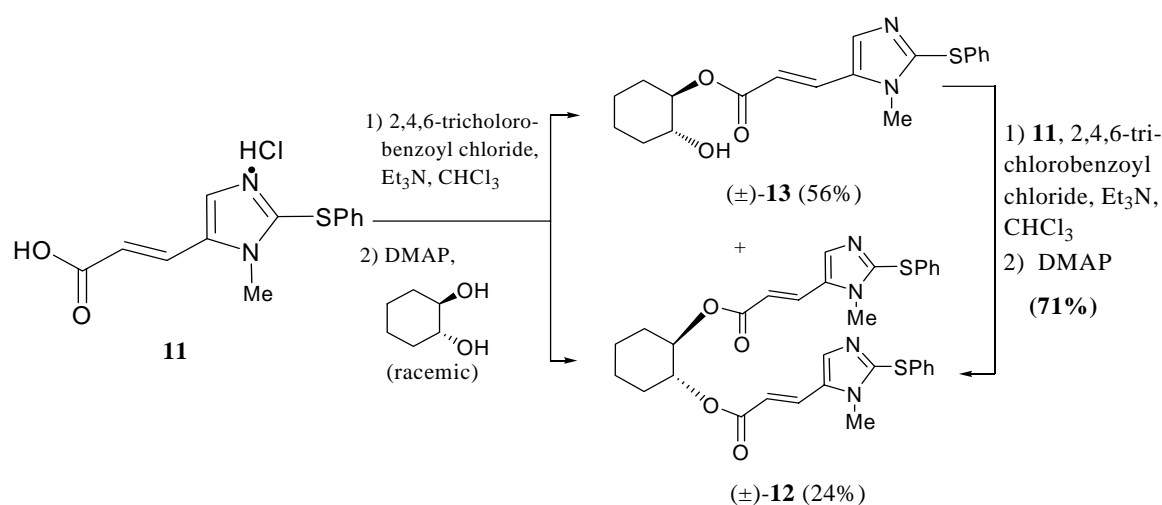


Reagents and conditions: (a) TsOH, PhH, reflux; (b) **11**, 2,4,6-trichlorobenzoyl chloride, DIEA, DMAP, DMF.

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

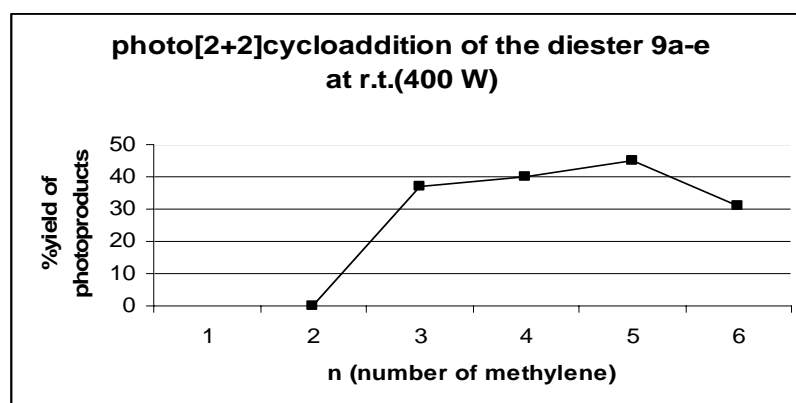
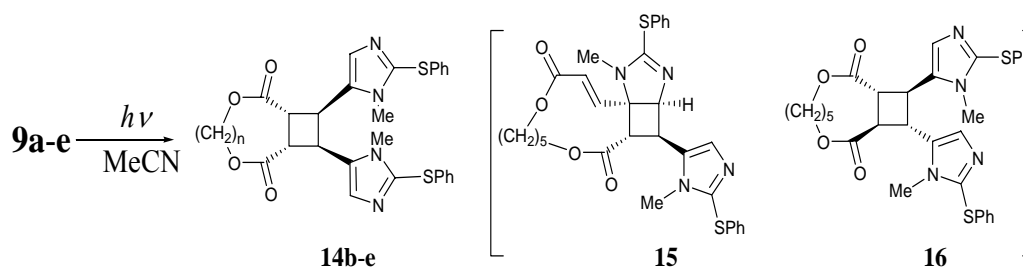
above one. Also, asymmetric photo[2+2]cycloaddition may be expected by using chiral cyclohexanediol ester. These cyclohexanediol-linked esters were prepared by using Yamaguchi's method<sup>16</sup> of the ( $\pm$ )-*trans*-1,2-cyclohexanediols with the imidazolylpropenoic acid hydrochloride **11**. Here, once again monoester **13** was obtained in major yield (56%) compared to the diester **12** (24%), but upon subsection 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  $\beta$ -form product **14d** in 45 % isolated yield (Entry 4) and the structure of **14d** was determined by X-ray crystallographic analysis to be the  $\beta$ -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  $\beta$ -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  $\alpha$ -isomer **16** was obtained. The structure of **16** was determined by <sup>1</sup>HNMR and NOE (H<sub>a</sub>-H<sub>b</sub> and H<sub>a</sub>-H<sub>c</sub>) as shown below in Figure 7.

Figure 4

Table 2 Photochemical reaction of **9a-e**.<sup>a</sup>

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

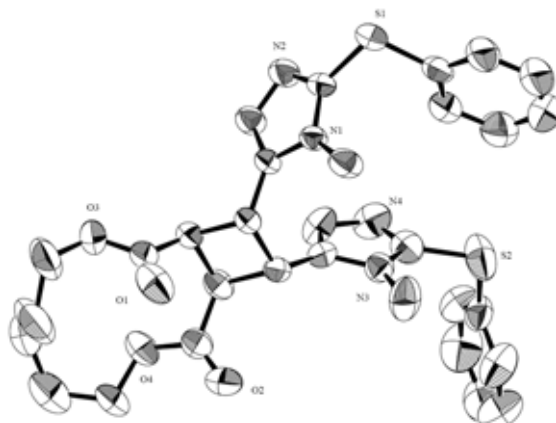
<sup>a</sup> All reactions were run in a Pyrex flask (>280 nm).

<sup>b</sup> High-pressure mercury lamp was used.

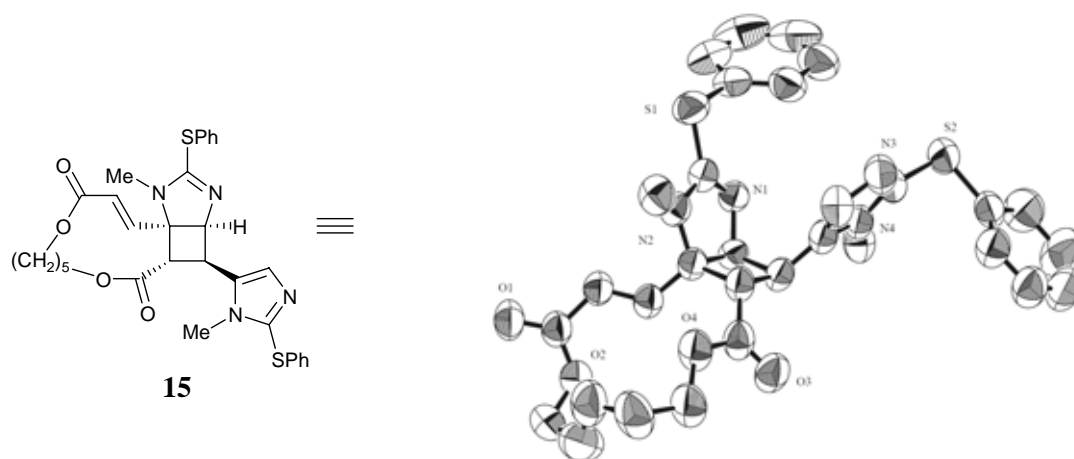
<sup>c</sup> temperature of the reaction mixture: 20°-25° (rt)

<sup>d</sup> By-products **15** (1 %) and **16** (1.5 %) were also obtained (Figure 6 and Figure 7).

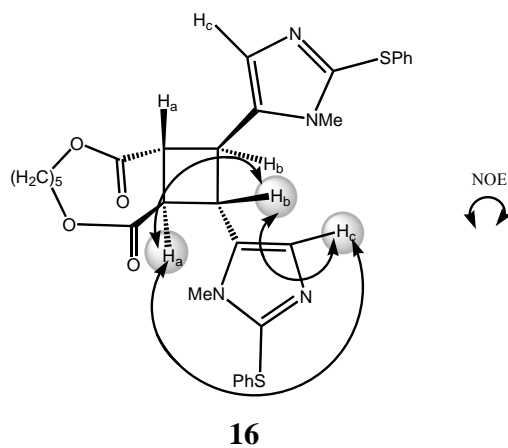
**Figure 5** ORTEP drawing of **14d**



**Figure 6** ORTEP drawing of **15**

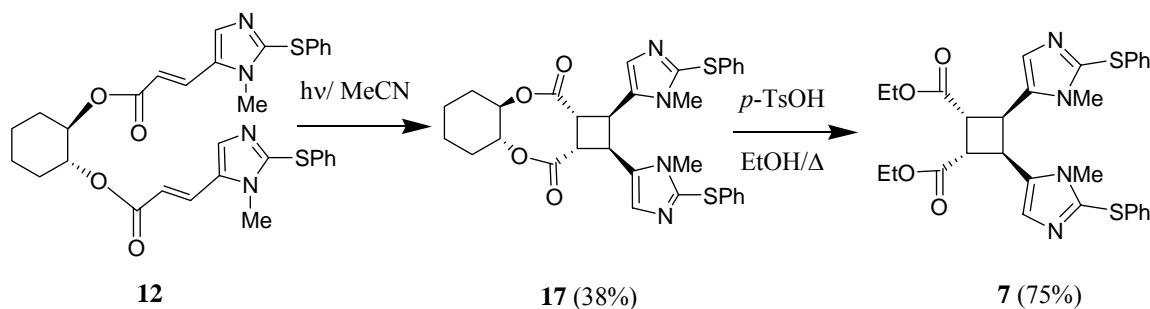


**Figure 7** NOE co-relation of **16**



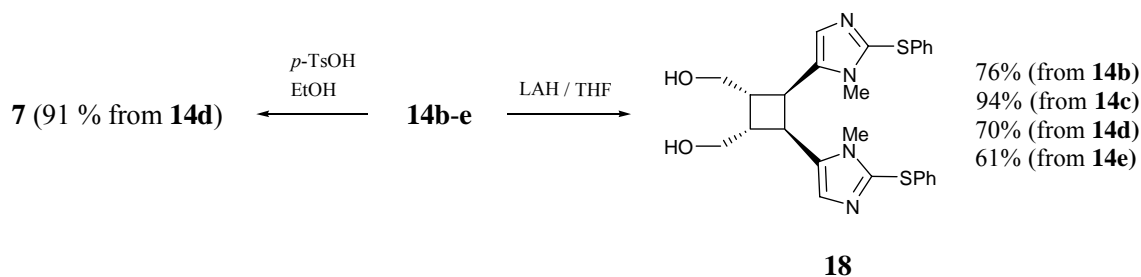
Photochemical reactions of the cyclohexanediol-linked imidazolylpropenonate **12** were also examined. The desired head-to-head cyclobutane compound **17** was provided in 38 % yield by irradiation with a 400-W high-pressure mercury lamp in MeCN at room temperature (Scheme 5).

### Scheme 5



The cyclobutane **14d**, of which the structure was already confirmed by X-ray crystallographic analysis as  $\beta$ -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  $\beta$ -form. Compound **17** was also derived to **7** in order to confirm the structure of **17** as shown in Scheme 5.

### Scheme 6



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  $\beta$ -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,<sup>3</sup> and further conversion of **14** to a  $\beta$ -sceptrin type derivative is currently under way.

In conclusion, we have developed the photo[2+2]cycloaddition of 1, $\omega$ -di-[3-(1-methyl-2-phenylsulfanyl-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 ( $^1\text{H}$ : 300 MHz,  $^{13}\text{C}$ : 75 MHz) or Varian Inova-400 ( $^1\text{H}$ : 300 MHz,  $^{13}\text{C}$ : 75 MHz) instruments at rt. Chemical shifts are given in  $\delta$  relative to tetramethylsilane (TMS); TMS served as internal standard for  $^1\text{H}$ -NMR, and solvent peak was referenced for  $^{13}\text{C}$ -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-K $\alpha$  radiation and a rotating anode generator.

**(1R\*,2S\*,3R\*,4S)-3,4-Bis(1-methyl-2-phenylsulfanyl-1H-imidazol-5-yl)cyclobutane-1,2-dicarboxylic acid diethyl ester (7) and (1R\*,2R\*,3S\*,4S\*)-2,4-Bis(1-methyl-2-phenylsulfanyl-1H-imidazole-5-yl)cyclobutane-1,3-dicarboxylic acid diethyl ester (8):** N<sub>2</sub> 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<sub>2</sub> at rt for 20 h. The solvent was evaporated and the crude product was purified by column chromatography (CHCl<sub>3</sub>) 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).  $^1\text{H}$ -NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$ : 1.28 (t, 6H,  $J = 7.1$  Hz, OCH<sub>2</sub>CH<sub>3</sub> x 2), 3.26 (s, 6H, NCH<sub>3</sub> x 2), 3.73 (d, 2H,  $J = 5.9$  Hz, CHCO<sub>2</sub> x 2), 4.17-4.22 (m, 6H, ImCH x 2 and OCH<sub>2</sub>CH<sub>3</sub> x 2), 6.87 (s, 2H, ImH x 2), 6.98-7.25 (m, 10H, ArH).  $^{13}\text{C}$ -NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$ : 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<sub>3</sub>) cm<sup>-1</sup>: 2955, 1724, 1578, 1473, 1444, 1368, 1274, 1178, 1066, 1022. EI MS  $m/z$  (%): 576 (M<sup>+</sup>, 2), 531 (1), 503 (2), 405 (2), 404 (2), 288 (100), 259 (9), 215 (43), 91 (24). HRMS (EI)  $m/z$  for C<sub>30</sub>H<sub>32</sub>N<sub>4</sub>O<sub>4</sub>S<sub>2</sub>: requires M<sup>+</sup> 576.1865, found M<sup>+</sup> 576.1871. *Anal.* Calcd for C<sub>30</sub>H<sub>32</sub>N<sub>4</sub>O<sub>4</sub>S<sub>2</sub>: 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).

$^1\text{H}$ -NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$ : 0.91 (t, 6H,  $J = 7.1$  Hz, OCH<sub>2</sub>CH<sub>3</sub> x 2), 3.62 (s, 6H, NCH<sub>3</sub> x 2), 3.72, 3.75 (q each, 2H,  $J = 7.1$  Hz, OCH<sub>2</sub>CH<sub>3</sub>), 3.82 (dd, 2H,  $J = 7.0, 10.1$ , Hz, CHCO<sub>2</sub> x 2), 3.88, 3.91 (q each, 2H,  $J = 7.1$  Hz, OCH<sub>2</sub>CH<sub>3</sub>), 4.33 (dd, 2H,  $J = 7.0, 9.8$  Hz, ImCH x 2), 7.13 (s, 2H, ImH x 2), 7.16-7.28 (m, 10H, ArH).  $^{13}\text{C}$ -NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$ : 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<sub>3</sub>) cm<sup>-1</sup>: 2944, 1724, 1446, 1268, 1178, 1093. EI MS  $m/z$  (%): 576 (M<sup>+</sup>, 5), 288 (100), 259 (7), 215 (31), 91 (9). HRMS (EI)  $m/z$  for C<sub>30</sub>H<sub>32</sub>N<sub>4</sub>O<sub>4</sub>S<sub>2</sub>: requires M<sup>+</sup> 576.1865, found M<sup>+</sup> 576.1867. *Anal.* Calcd for C<sub>30</sub>H<sub>32</sub>N<sub>4</sub>O<sub>4</sub>S<sub>2</sub>: 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,  $\alpha = 98.596(5)^\circ$ ,  $\beta = 104.633(5)^\circ$ ,  $\gamma = 90.965(6)^\circ$ ,  $V = 1451.5(2)$  Å<sup>3</sup>,  $Z = 2$ ,  $D_{\text{calc}} = 1.319$

$\text{g/cm}^3$ ,  $\lambda$  (CuK $\alpha$ ) = 1.54178 Å,  $\mu$  (CuK $\alpha$ ) = 20.07  $\text{cm}^{-1}$ ,  $F_{000}$  = 608.00,  $T = 23 \pm 1^\circ\text{C}$ ,  $R_1 = 0.0705$  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<sub>2</sub>O (6.9 g, 36.5 mmol) and 1,5-pentanediol (1 mL, 14.5 mmol) of benzene (800 mL) was refluxed under N<sub>2</sub> 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<sub>3</sub> 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<sub>2</sub>O). <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$ : 1.48-1.79 (m, 6H, OCH<sub>2</sub>(CH<sub>2</sub>)<sub>3</sub>CH<sub>2</sub>O), 3.68 (s, 6H, NCH<sub>3</sub> x 2), 4.21 (t, 4H,  $J = 6.6$  Hz, OCH<sub>2</sub> x 2), 6.33 (d, 2H,  $J = 15.7$  Hz, CHCO<sub>2</sub> 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). <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$ : 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<sub>3</sub>)  $\text{cm}^{-1}$ : 2934, 1698, 1627, 1275. EI MS  $m/z$  (%): 216 (43), 244 (20), 345 (49), 479 (100), 588 (46, M<sup>+</sup>). HRMS (EI)  $m/z$  for C<sub>31</sub>H<sub>32</sub>N<sub>4</sub>O<sub>4</sub>S<sub>2</sub>: requires M<sup>+</sup> 588.1865, found M<sup>+</sup> 588.1873. *Anal.* Calcd for C<sub>31</sub>H<sub>32</sub>N<sub>4</sub>O<sub>4</sub>S<sub>2</sub>: 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<sub>3</sub>/MeOH = 100/1) to give **9c** (22.782 g, 76%) as white prisms. Mp 129-133 °C (recrystallized from AcOEt-*n*-hexane). <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$ : 1.82 (br t, 4H,  $J = 6.20$  Hz, CH<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub>CH<sub>2</sub>), 3.68 (s, 6H, NCH<sub>3</sub> x 2), 4.25 (br t, 4H,  $J = 5.6$  Hz, OCH<sub>2</sub> x 2), 6.31 (d, 2H,  $J = 15.9$  Hz, CHCO<sub>2</sub> 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). <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$ : 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<sub>3</sub>)  $\text{cm}^{-1}$ : 2950, 1701, 1628, 1441, 1302, 1275, 1176, 1155. EI MS  $m/z$  (%): 574 (M<sup>+</sup>, 100), 465 (92), 331 (81), 259 (25), 243 (62), 215 (80). HRMS (EI)  $m/z$  for C<sub>30</sub>H<sub>30</sub>N<sub>4</sub>O<sub>4</sub>S<sub>2</sub>: requires M<sup>+</sup> 574.1708, found M<sup>+</sup> 574.1701. *Anal.* Calcd for C<sub>30</sub>H<sub>30</sub>N<sub>4</sub>O<sub>4</sub>S<sub>2</sub>: 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).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 300 MHz)  $\delta$ : 1.43-1.72 (m, 8H,  $\text{CH}_2(\text{CH}_2)_4\text{CH}_2$ ), 3.68 (s, 6H,  $\text{NCH}_3 \times 2$ ), 4.20 (t, 4H,  $J = 6.6$  Hz,  $\text{OCH}_2 \times 2$ ), 6.31 (d, 2H,  $J = 16.0$  Hz,  $\text{CHCO}_2 \times 2$ ), 7.20-7.28 (m, 10H, ArH), 7.47 (d, 2H,  $J = 16.0$  Hz, ImCH  $\times 2$ ), 7.58 (s, 2H, ImH  $\times 2$ ).  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 75 MHz)  $\delta$ : 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 ( $\text{CHCl}_3$ )  $\text{cm}^{-1}$ : 2928, 1698, 1629, 1276, 1178, 1157. EI MS  $m/z$  (%): 602 (37,  $\text{M}^+$ ), 494 (32), 493 (100), 359 (49), 243 (33), 216 (35), 215 (59). HRMS (EI)  $m/z$  for  $\text{C}_{32}\text{H}_{34}\text{N}_4\text{O}_4\text{S}_2$ : requires:  $\text{M}^+$  602.2021, found  $\text{M}^+$  602.2018. *Anal.* Calcd for  $\text{C}_{32}\text{H}_{34}\text{N}_4\text{O}_4\text{S}_2$ : C, 63.76; H, 5.69; N, 9.29. Found: C, 63.57; H, 5.83; N, 9.29.

**3-(1-Methyl-2-phenylsulfanyl-1H-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  $\times 3$ ). The organic layer was dried over anhydrous sodium sulfate and evaporated to give an oily residue, which was purified by PTLC ( $\text{CHCl}_3/\text{MeOH} = 20/1$ ) to give **10a** (68 mg, 89 %) as a white powder. Mp 127-128 °C (recrystallized from AcOEt-*n*-hexane).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 400 MHz)  $\delta$ : 3.31 (t, 1H,  $J = 5.5$  Hz, OH), 3.67 (s, 3H,  $\text{NCH}_3$ ), 3.88 (brq, 2H,  $J = 4.7$  Hz,  $\text{OCH}_2$ ), 4.33 (t, 2H,  $J = 4.7$  Hz,  $\text{OCH}_2$ ), 6.34 (d, 1H,  $J = 15.9$  Hz,  $\text{CHCO}_2$ ), 7.20-7.31 (m, 5H, ArH), 7.50 (dd, 1H,  $J = 0.6, 15.9$  Hz, ImCH), 7.57 (s, 1H, ImH).  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 100 MHz)  $\delta$ : 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 ( $\text{CHCl}_3$ )  $\text{cm}^{-1}$ : 2940, 1703, 1629, 1442, 1396, 1302, 1275, 1178, 1156, 1078. EI MS  $m/z$  (%): 304 ( $\text{M}^+$ , 100), 261 (18), 243 (17), 215 (42), 109 (11), 91 (20), 58 (10). HRMS (EI)  $m/z$  for  $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}_3\text{S}$ : requires  $\text{M}^+$  304.0882, found  $\text{M}^+$  304.0876. *Anal.* Calcd for  $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}_3\text{S}$ : C, 59.19; H, 5.30; N, 9.20. Found: C, 59.22; H, 5.56; N, 9.05.

**3-(1-Methyl-2-phenylsulfanyl-1H-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  $\times 3$ ). The organic layer was dried over anhydrous sodium sulfate and evaporated to give an oily residue, which was purified by PTLC ( $\text{CHCl}_3/\text{MeOH} = 20/1$ ) to give **10b** (4.457 g, 81 %) as a yellow powder. Mp 115-120 °C (recrystallized from AcOEt-*n*-hexane).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 400 MHz)  $\delta$ : 1.94 (quintet, 2H,  $J = 6.0$  Hz,  $\text{CH}_2\text{CH}_2\text{CH}_2$ ), 3.69 (s, 3H,  $\text{NCH}_3$ ), 3.73 (t, 2H,  $J = 6.0$  Hz,  $\text{CH}_2\text{OH}$ ), 4.37 (t, 2H,  $J = 6.0$  Hz,  $\text{COOCH}_2$ ), 6.32 (d, 1H,  $J = 15.9$  Hz,  $\text{CHCO}_2$ ), 7.21-7.30 (m, 5H, ArH), 7.50 (dd, 1H,  $J = 0.6, 15.9$  Hz, ImCH), 7.59 (s, 1H, ImH).  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 100 MHz)  $\delta$ : 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 ( $\text{CHCl}_3$ )  $\text{cm}^{-1}$ : 2942, 1697, 1628, 1441, 1395, 1303, 1276, 1156. EI MS  $m/z$  (%): 318 ( $\text{M}^+$ , 100), 259 (18), 243 (17), 215 (44), 109 (11), 91 (22). HRMS (EI)  $m/z$  for  $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}_3\text{S}$ : requires  $\text{M}^+$  318.1038, found  $\text{M}^+$  318.1041. *Anal.* Calcd for  $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}_3\text{S}$ : 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 mL, 345  $\mu\text{mol}$ ) 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<sub>2</sub> 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<sub>2</sub>O (1 mL) and the products were extracted with Et<sub>2</sub>O (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<sub>3</sub>/MeOH = 20/1) to give **9a** (76 mg, 52 %) as a white powder. Mp 109-110 °C (recrystallized from AcOEt-*n*-hexane). <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$ : 3.68 (s, 6H, NCH<sub>3</sub> x 2), 4.46 (s, 4H, O(CH<sub>2</sub>)<sub>2</sub>O), 6.34 (d, 2H, *J* = 15.9 Hz, CHCO<sub>2</sub> 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). <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$ : 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<sub>3</sub>) cm<sup>-1</sup>: 2954, 1704, 1628, 1441, 1302, 1274, 1171, 1150. EI MS *m/z* (%): 546 (M<sup>+</sup>, 100), 437 (69), 287 (59), 243 (63), 215 (83), 110 (62). HRMS (EI) *m/z* for C<sub>28</sub>H<sub>26</sub>N<sub>4</sub>O<sub>4</sub>S<sub>2</sub>: requires M<sup>+</sup> 546.1395, found M<sup>+</sup> 546.1383. *Anal.* Calcd for C<sub>28</sub>H<sub>26</sub>N<sub>4</sub>O<sub>4</sub>S<sub>2</sub>: 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 mL, 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<sub>2</sub> at 0 °C. After stirring for 1.5 h at rt, a solution of **10b** (90 mg, 0.283 mmol) 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<sub>2</sub>O (1 mL) and the products were extracted with Et<sub>2</sub>O (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<sub>3</sub>/MeOH = 20/1) to give **9b** (98 mg, 62 %) as white prisms. Mp 132-134 °C (recrystallized from AcOEt-*n*-hexane). <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$ : 2.10 (quintet, 2H, *J* = 6.2 Hz, OCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>O), 3.69 (s, 6H, NCH<sub>3</sub> x 2), 4.32 (t, 4H, *J* = 6.3 Hz, OCH<sub>2</sub> x 2), 6.31 (d, 2H, *J* = 15.9 Hz, CHCO<sub>2</sub> 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). <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$ : 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<sub>3</sub>) cm<sup>-1</sup>: 2950, 1702, 1628, 1441, 1395, 1275, 1171. EI MS *m/z* (%): 560 (M<sup>+</sup>, 100), 451 (72), 317 (57), 243 (44), 230 (28), 215 (63). HRMS (EI) *m/z* for C<sub>29</sub>H<sub>28</sub>N<sub>4</sub>O<sub>4</sub>S<sub>2</sub>: requires M<sup>+</sup> 560.1552, found M<sup>+</sup> 560.1554. *Anal.* Calcd for C<sub>29</sub>H<sub>28</sub>N<sub>4</sub>O<sub>4</sub>S<sub>2</sub>: 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<sub>2</sub>O). <sup>1</sup>H-NMR (CD<sub>3</sub>OD, 400 MHz) δ: 3.96 (s, 3H, NCH<sub>3</sub>), 6.66 (d, 1H, *J* = 16.1 Hz, CHCO<sub>2</sub>), 7.46-7.57 (m, 5H, ArH), 7.56 (dd, 1H, *J* = 0.5, 16.3 Hz, ImCH), 8.21 (s, 1H, ImH). <sup>13</sup>C-NMR (CD<sub>3</sub>OD, 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<sup>-1</sup>: 3865, 2672, 1809, 1692, 1635, 1469, 1388, 1260, 1187, 966, 847. EI MS *m/z* (%): 260 (M<sup>+</sup>, 100), 215 (66), 156 (9), 112 (12), 91 (35), 80 (25). HRMS (EI) *m/z* for C<sub>13</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub>S: requires M<sup>+</sup> 260.0619, found M<sup>+</sup> 260.0611. *Anal.* Calcd for C<sub>13</sub>H<sub>13</sub>N<sub>2</sub>O<sub>2</sub>ClS: C, 52.61; H, 4.42; N, 9.44. Found: C, 52.52; H, 4.49; N, 9.38.

**(±)-(E)-1,2-Di[(2E)-3-(1-Methyl-2-phenylsulfanyl-1H-imidazol-5-yl)acrylic acid 2-[3-(1-methyl-2-phenylsulfanyl-1H-imidazol-5-yl)acryloyloxy]cyclohexyl ester (12) and 3-(1-Methyl-2-phenylsulfanyl-1H-imidazol-5-yl)acrylic acid 2-hydroxycyclohexyl ester (13):** DIEA (1.70 mL, 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<sub>3</sub> (6 mL) under N<sub>2</sub> 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<sub>3</sub> (3 mL) was added and the whole was stirred for 24 h at rt. The mixture was diluted with H<sub>2</sub>O (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). <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz) δ: 1.38-1.51 (m, 4H, CH<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub>CH<sub>2</sub>), 1.78-17.9 (m, 2H, CHHCHO x 2), 2.12-2.15 (m, 2H, CHHCHO x 2), 3.65(s, 6H, NCH<sub>3</sub> x 2), 4.96-5.03 (m, 2H, CHO x 2), 6.24 (d, 2H, *J* = 15.9 Hz, CHCO<sub>2</sub> 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). <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 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<sub>3</sub>) cm<sup>-1</sup>: 2929, 1699, 1628, 1440, 1275, 1177, 1157, 1022. EI MS *m/z* (%): 600 (M<sup>+</sup>, 44), 491 (40), 357 (23), 243 (100), 215 (62), 91 (75), 81 (41). HRMS (EI) *m/z* for C<sub>32</sub>H<sub>32</sub>N<sub>4</sub>O<sub>4</sub>S<sub>2</sub>: requires M<sup>+</sup> 600.1865, found M<sup>+</sup> 600.1858. *Anal.* Calcd for C<sub>32</sub>H<sub>32</sub>N<sub>4</sub>O<sub>4</sub>S<sub>2</sub>: 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). <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz) δ: 1.26-1.44 (m, 4H, CH<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub>CH<sub>2</sub>), 1.73-1.75 (m, 2H, CH<sub>2</sub>CHO), 2.04-2.10 (m, 2H, CH<sub>2</sub>CHO), 3.61-3.66 (m, 1H, -CH(OH)), 3.67 (s, 3H, NCH<sub>3</sub>), 4.68-4.74 (m, 1H, -CH(OCO)), 6.32 (d, 1H, *J* = 16.1 Hz, CHCO<sub>2</sub>), 7.19-7.31 (m, 5H, ArH), 7.49 (dd, 1H, *J* = 0.6, 15.9 Hz, ImCH), 7.57 (s, 1H, ImH). <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 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<sub>3</sub>) cm<sup>-1</sup>: 2924, 1697, 1628, 1443, 1274, 1181, 1156, 1019. EI MS *m/z* (%): 358 (M<sup>+</sup>, 100), 259 (55), 243 (56), 215 (77), 133 (15), 109 (30). HRMS (EI) *m/z* for C<sub>19</sub>H<sub>22</sub>N<sub>2</sub>O<sub>3</sub>S: requires M<sup>+</sup> 358.1351, found M<sup>+</sup> 358.1347. *Anal.* Calcd for C<sub>19</sub>H<sub>22</sub>N<sub>2</sub>O<sub>3</sub>S: 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 mL, 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<sub>3</sub> (2.5 mL) under N<sub>2</sub> at 0 °C. After stirring for 1.5 h at rt, a solution of **13** (300 mg, 0.83 mmol) 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<sub>2</sub>O (1 mL) and the products were extracted with Et<sub>2</sub>O (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<sub>2</sub> 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<sub>2</sub> at rt for 12 h. The solvent was evaporated and the crude product was purified by PTLC (CHCl<sub>3</sub>/MeOH = 20/1) to give the cyclobutane **14e** (44 mg, 31 %) as a viscous oil. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz) δ: 1.40-1.80 (m, 8H, OCH<sub>2</sub>(CH<sub>2</sub>)<sub>4</sub>CH<sub>2</sub>O), 3.27 (s, 6H, NCH<sub>3</sub> x 2), 3.78 (d, 2H, *J* = 5.9 Hz, CHCO<sub>2</sub> x 2), 3.92-3.96 (m, 2H, OCH<sub>2</sub>), 4.25 (d, 2H, *J* = 6.0 Hz, ImCH x 2), 4.57-4.59 (m, 2H, OCH<sub>2</sub>), 6.87 (s, 2H, ImH x 2), 6.97-7.24 (m, 10H, ArH). <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 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<sub>3</sub>) cm<sup>-1</sup>: 2911, 1723, 1473, 1446, 1274. FAB MS *m/z* (%): 603 [78, (M+H)<sup>+</sup>]. HRMS (FAB) *m/z* for C<sub>32</sub>H<sub>35</sub>N<sub>4</sub>O<sub>4</sub>S<sub>2</sub>: requires (M+H)<sup>+</sup> 603.2100, found (M+H)<sup>+</sup> 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). <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz) δ: 1.99-2.08 (m, 1H, one of CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 2.14-2.24 (m, 1H, one of CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 3.25 (s, 6H, NCH<sub>3</sub> x 2), 3.72 (d, 2H, *J* = 5.7 Hz, CHCO<sub>2</sub> x 2), 4.26 (d, 2H, *J* = 5.7 Hz, ImCH x 2), 4.46-4.51 (m, 2H, OCH<sub>2</sub>), 4.56-4.62 (m, 2H, OCH<sub>2</sub>), 6.90 (s, 2H, ImH x 2), 6.96-7.25 (m, 10H, ArH). <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 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<sub>3</sub>) cm<sup>-1</sup>: 2945, 1735, 1474, 1444, 1272, 1250, 1218, 1172. EI MS *m/z* (%): 560 (M<sup>+</sup>, 38), 451 (24), 317 (15), 260 (22), 215 (34), 110 (100), 78 (49). HRMS (EI) *m/z* for C<sub>29</sub>H<sub>28</sub>N<sub>4</sub>O<sub>4</sub>S<sub>2</sub>: requires M<sup>+</sup> 560.1552, found M<sup>+</sup> 560.1563. *Anal.* Calcd for C<sub>29</sub>H<sub>28</sub>N<sub>4</sub>O<sub>4</sub>S<sub>2</sub>: 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<sub>3</sub>/MeOH = 100/1) to give **14c** (46 mg, 40 %) as white needles. Mp 204-206 °C (recrystallized from AcOEt-*n*-hexane). <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz) δ: 1.90-1.92 (m, 4H, OCH<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub>CH<sub>2</sub>O), 3.26 (s, 6H, NCH<sub>3</sub> x 2), 3.78 (d, 2H, *J* = 5.9 Hz, CHCO<sub>2</sub> x 2), 4.12-4.16 (m, 2H, OCH<sub>2</sub>), 4.28 (d, 2H, *J* = 6.0 Hz, ImCH x 2), 4.38-4.41 (m, 2H, OCH<sub>2</sub>), 6.89 (s, 2H, ImH x 2), 6.96-7.24 (m, 10H, ArH). <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 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<sub>3</sub>) cm<sup>-1</sup>: 2939, 1728, 1445, 1286, 1251, 1227, 1202, 1175, 1079. EI MS *m/z* (%): 574 (M<sup>+</sup>, 67), 465 (100), 331 (85), 259 (21), 243 (45), 215 (79), 109 (17), 91 (39). HRMS (EI) *m/z* for C<sub>30</sub>H<sub>30</sub>N<sub>4</sub>O<sub>4</sub>S<sub>2</sub>: requires M<sup>+</sup> 574.1708, found M<sup>+</sup> 574.1703. *Anal.* Calcd for C<sub>30</sub>H<sub>30</sub>N<sub>4</sub>O<sub>4</sub>S<sub>2</sub>: C, 62.70; H, 5.26; N, 9.75. Found: C, 62.51; H, 5.35; N, 9.67.

**(1R\*,11S\*,12R\*,13S\*)-12,13-Bis(1-methyl-2-phenylsulfanyl-1H-imidazol-5-yl)-3,9-dioxabicyclo[9.2.0]tridecane-2,10-dione (14d):** N<sub>2</sub> 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<sub>2</sub> 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). <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz) δ: 1.76-1.81 (m, 6H, CH<sub>2</sub>(CH<sub>2</sub>)<sub>3</sub>CH<sub>2</sub>), 3.33 (s, 6H, NCH<sub>3</sub> x 2), 3.80 (d, 2H, *J* = 5.8 Hz, CHCO<sub>2</sub> x 2), 3.95-3.97 (m, 2H, OCH<sub>2</sub>), 4.27 (d, 2H, *J* = 6.1 Hz, ImCH x 2), 4.53-4.56 (m, 2H, OCH<sub>2</sub>), 6.89 (s, 2H, ImH x 2), 6.96-7.25 (m, 10H, ArH). <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 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<sub>3</sub>) cm<sup>-1</sup>: 2937, 1726, 1627, 1578, 1473, 1445, 1392, 1275, 1176. FAB MS *m/z* (%): 589 [100, (M+H)<sup>+</sup>]. HRMS (FAB) *m/z* for C<sub>31</sub>H<sub>33</sub>N<sub>4</sub>O<sub>4</sub>S<sub>2</sub>: requires (M+H)<sup>+</sup> 589.1943, found (M+H)<sup>+</sup> 589.1950. *Anal.* Calcd for C<sub>31</sub>H<sub>33</sub>N<sub>4</sub>O<sub>4</sub>S<sub>2</sub>: 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<sub>1</sub>/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<sup>3</sup>, Z = 4, D<sub>calc</sub> = 1.297 g/cm<sup>3</sup>, λ (CuKα) = 1.54187 Å, μ (CuKα) = 19.452 cm<sup>-1</sup>, F<sub>000</sub> = 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.

**(1R\*,2E,13S\*,14S\*,15S\*)-18-Methyl-14-(1-methyl-2-phenylsulfanyl-1H-imidazol-5-yl)-17-phenylsulfanyl-5,11-dioxa-16,18-diazatricyclo[13.3.0.0<sup>1,13</sup>]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). <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz) δ: 1.52-1.91 (m, 6H, CH<sub>2</sub>(CH<sub>2</sub>)<sub>3</sub>CH<sub>2</sub>), 2.97 (s, 3H, NCH<sub>3</sub>), 3.38 (s, 3H, NCH<sub>3</sub>), 3.76(d, 1H, *J* = 7.1 Hz, CHCO<sub>2</sub>), 3.87-3.94 (m, 1H, OCHH), 4.17-4.24 (m, 2H, OCHH and CHIm), 4.35-4.42 (m, 1H, OCHH), 4.55-4.62 (m, 1H,

OCHH), 4.71 (d, 1H,  $J = 7.9$  Hz, CHN), 5.86 (d, 1H,  $J = 15.7$  Hz, =CHCO), 7.07-7.37 (m, 12H, ArH and CH=CHCO).  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 75 MHz)  $\delta$ : 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 ( $\text{CHCl}_3$ )  $\text{cm}^{-1}$ : 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  $\text{C}_{31}\text{H}_{33}\text{N}_4\text{O}_4\text{S}_2$ : requires (M $^+$ +H) 589.1943, found (M+H) $^+$  589.1951. *Anal.* Calcd for  $\text{C}_{31}\text{H}_{32}\text{N}_4\text{O}_4\text{S}_2$ : 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  $\text{P2}_1/\text{n}$  (#14),  $a = 10.602(2)$  Å,  $b = 13.901(3)$  Å,  $c = 20.2778(14)$  Å,  $\beta = 92.555(10)^\circ$ ,  $V = 2985.4(9)$  Å $^3$ ,  $Z = 4$ ,  $D_{\text{calc}} = 1.310$  g/cm $^3$ ,  $\lambda$  (CuK $\alpha$ ) = 1.54178 Å,  $\mu$  (CuK $\alpha$ ) = 19.638 cm $^{-1}$ ,  $F_{000} = 1240.00$ ,  $T = 23 \pm 1^\circ\text{C}$ ,  $R_1 = 0.0924$  for 5633 reflections.

**(1R\*,11R\*,12S\*,13S\*)-12,13-Bis(1-methyl-2-phenylthio-1H-imidazole-5-yl)-3,9-dioxabicyclo[9,2,0]-tridecane-2,10-dione (16)**: This compound was obtained when **9d** was irradiated at 0 $^\circ$  C to -20 $^\circ$  C in yield of 1.5 % as a viscous oil.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 300 MHz)  $\delta$ : 1.62-1.72 (m, 6H,  $\text{CH}_2(\text{CH}_2)_3\text{CH}_2$ ), 3.10 (d, 2H,  $J = 9.7$  Hz,  $\text{CHCO}_2 \times 2$ ), 3.46 (s, 6H,  $\text{NCH}_3 \times 2$ ), 3.72 (d, 2H,  $J = 9.9$  Hz, ImCH  $\times 2$ ), 3.74-3.78 (m, 2H,  $\text{OCH}_2$ ), 4.71-4.76 (m, 2H,  $\text{OCH}_2$ ), 7.12 (s, 2H, ImH  $\times 2$ ), 7.13-7.27 (m, 10H, ArH).  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 75 MHz,)  $\delta$ : 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 ( $\text{CHCl}_3$ )  $\text{cm}^{-1}$ : 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  $\text{C}_{31}\text{H}_{33}\text{N}_4\text{O}_4\text{S}_2$ : requires (M $^+$ +H) 589.1943, found (M+H) $^+$  589.1947.

**(1R\*,2S\*,3S\*,4R\*)-1,2-Bis(1-methyl-2-phenylsulfanyl-1H-imidazol-5-yl)-decahydro-4,9-dioxabenzocyclobuta[e]cyclooctene-3,10-dione (17)**:  $\text{N}_2$  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  $\text{N}_2$  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  $^\circ\text{C}$  (recrystallized from MeOH-*n*-hexane).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 300 MHz)  $\delta$ : 1.36-1.48 (m, 2H, ( $\text{CH}_2$  in  $\text{C}_6\text{H}_{10}$ ), 1.58-1.69 (m, 2H,  $\text{CH}_2$  in  $\text{C}_6\text{H}_{10}$ ), 1.82-1.92 (m, 2H,  $\text{CH}_2$  in  $\text{C}_6\text{H}_{10}$ ), 2.15 (br t, 2H,  $J = 13.2$  Hz, ( $\text{CH}_2\text{CHO}$ ), 3.02 (s, 3H,  $\text{NCH}_3$ ), 3.47 (s, 3H,  $\text{NCH}_3$ ) 3.68 (dd, 1H,  $J = 9.4, 2.0$  Hz,  $\text{CHCO}_2$ ), 4.11 (t, 1H,  $J = 10.1$  Hz,  $\text{CHCO}_2$ ), 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, ( $\text{CH}_2\text{CHO}$ ), 4.98 (ddd, 1H,  $J = 4.0$  Hz, ( $\text{CH}_2\text{CHO}$ ), 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).  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 75 MHz,)  $\delta$ : 24.3  $\times 2$ , 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 ( $\text{CHCl}_3$ )  $\text{cm}^{-1}$ : 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  $\cdot$  H<sub>2</sub>O (10 mg, 0.05 mmol) in EtOH (4 mL) was refluxed under N<sub>2</sub> for 48 h. The reaction mixture was neutralized with saturated NaHCO<sub>3</sub> aq (5 mL), then the product was extracted with AcOEt (15 mL  $\times$  3). The organic layer was dried over anhydrous sodium sulfate and evaporated to give an oily residue, which was purified by PTLC (CHCl<sub>3</sub>/MeOH = 20/1) to give **7** (21 mg, 91 %) as a colorless solid. <sup>1</sup>H- and <sup>13</sup>C-NMR of the product was identified with **7 $\beta$** .

**(1R\*,2S\*,3S\*,4R\*)-[2-Hydroxymethyl-3,4-bis(1-methyl-2-phenylsulfanyl-1H-imidazol-5-yl)cyclobutyl]methanol (18) from 14d; General Procedure:** A THF (10mL) solution of LiAlH<sub>4</sub> (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<sub>4</sub> was quenched with sat. aq NaHCO<sub>3</sub> 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<sub>3</sub>/MeOH = 100/1 ) to give pure diol **18** (460mg, 70%) as white needles. Mp 193.8-197.3°C (recrystallized from MeOH-Et<sub>2</sub>O). <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>, 300 MHz)  $\delta$ : 2.80-2.88 (m, 2H, CHCH<sub>2</sub>OH  $\times$  2), 3.36 (s, 6H, NCH<sub>3</sub>  $\times$  2), 3.64 (br d, 2H, *J* = 5.5 Hz, ImCH  $\times$  2), 3.71-3.72 (m, 4H, CH<sub>2</sub>OH  $\times$  2), 4.69 (t, 2H, *J* = 5.1 Hz, OH  $\times$  2); 6.80-6.83 (m, 4H, ArH), 7.12-7.25 (m, 6H, ArH), 7.40 (s, 2H, ImH). <sup>13</sup>C-NMR (DMSO, 75 MHz)  $\delta$ : 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<sup>-1</sup>: 3193, 2896, 1576, 1473, 1436, 1414, 1269, 1019. FAB MS  $m/z$  (%): 493 [46, (M+H)<sup>+</sup>], 246 (70). HRMS (FAB)  $m/z$  for  $C_{26}H_{29}N_4O_2S_2$ : requires (M+H)<sup>+</sup> 493.1732, found [M+H]<sup>+</sup> 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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