



# A short synthesis of 3-oxa- and 3-azabicyclo[3.1.0]hexanes from $\alpha,\beta$ -unsaturated esters based on the 1,5-CH insertion reaction of cyclopropylmagnesium carbenoids

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## ABSTRACT

1-Chlorocyclopropyl *p*-tolyl sulfoxides bearing an alkoxymethyl group at the 2-position were easily prepared from  $\alpha,\beta$ -unsaturated esters with dichloromethyl *p*-tolyl sulfoxide and alkylhalides in three steps in good overall yields. Treatment of the 1-chlorocyclopropyl *p*-tolyl sulfoxides with *i*-PrMgCl resulted in the formation of 3-oxabicyclo[3.1.0]hexanes in up to 89% yield as a single diastereomer via the 1,5-CH insertion reaction of the generated cyclopropylmagnesium carbenoid intermediates. This procedure provides a good way for the synthesis of 3-oxabicyclo[3.1.0]hexanes from  $\alpha,\beta$ -unsaturated esters in only four steps. 3-Aza- and 3-thiabicyclo[3.1.0]hexanes were also obtained from the corresponding precursors via the 1,5-CH insertion reaction of the cyclopropylmagnesium carbenoid intermediates, though the yields were low to moderate.

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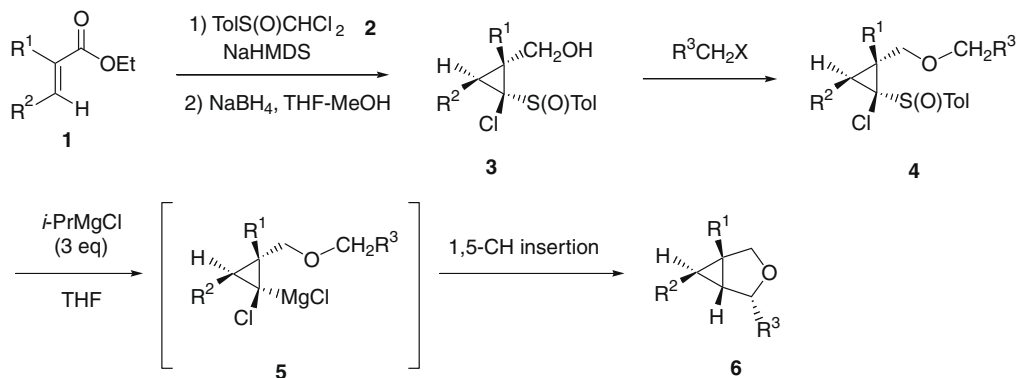
## 1. Introduction

Carbenes and carbenoids have long been recognized to be highly reactive carbon species and are frequently used as versatile intermediates in organic synthesis. They show a variety of distinctive reactions such as dimerization, addition to olefins to give cyclopropanes, ylide formation, and rearrangement.<sup>1</sup> The carbon–hydrogen insertion (CH insertion) reaction is also one of the most striking reactions of carbenes and carbenoids.<sup>2</sup> The CH insertion reaction is very interesting and highly important for the construction of molecules, because the reaction enables the formation of a carbon–carbon bond between a carbene (or carbenoid) carbon and an inactivated carbon.

Recently, we became interested in developing new reactions using magnesium carbenoids that are generated from 1-chloroalkyl *p*-tolyl sulfoxides via the sulfoxide–magnesium exchange reaction.<sup>3</sup> Previously, we found that the magnesium carbenoids, generated from aryl 1-chloroalkyl sulfoxides with Grignard reagents via the sulfoxide–magnesium exchange reaction, were stable at below  $-60\text{ }^{\circ}\text{C}$  for at least 30 min<sup>4</sup> and quite interestingly, when the carbon adjacent to the carbenoid carbon was quaternary, 1,3-CH insertion reaction took place to afford cyclopropanes in high to quantitative yields upon warming the reaction mixture to  $0\text{ }^{\circ}\text{C}$ .<sup>5</sup>

In continuation of our interest in the CH insertion reaction of magnesium carbenoid, we recently investigated the reaction of 1-chlorocyclopropyl *p*-tolyl sulfoxides bearing an alkoxymethyl group at the 2-position **4** with Grignard reagents and found that the reaction resulted in the formation of 3-oxabicyclo[3.1.0]hexanes **6** in high yields via the 1,5-CH insertion reaction of the generated cyclopropylmagnesium carbenoid intermediates **5** (Scheme 1). As shown in Scheme 1, this procedure is very useful as a short synthesis of 3-oxabicyclo[3.1.0]hexanes **6** by assembly of three components,  $\alpha,\beta$ -unsaturated esters **1**, dichloromethyl *p*-tolyl sulfoxide **2**,<sup>6</sup> and alkylhalides. Thus,  $\alpha,\beta$ -unsaturated esters **1** were treated with dichloromethyl *p*-tolyl sulfoxide **2** in the presence of NaHMDS (giving 1-chlorocyclopropyl *p*-tolyl sulfoxides bearing an ethoxycarbonyl group at the 2-position)<sup>7</sup> and the products were reduced with  $\text{NaBH}_4$ <sup>8</sup> to give 1-chlorocyclopropyl *p*-tolyl sulfoxides bearing a hydroxymethyl group at the 2-position **3** in high overall yields. The hydroxyl group was alkylated with alkylhalides under the conventional conditions to afford 1-chlorocyclopropyl *p*-tolyl sulfoxides bearing an alkoxymethyl group at the 2-position **4** in good yields. Finally, **4** were treated with *i*-PrMgCl in THF to give 3-oxabicyclo[3.1.0]hexanes **6** as a single isomer in good to high yields via the 1,5-CH insertion reaction of cyclopropylmagnesium carbenoid intermediates **5**. Details of these reactions and extension of this procedure to the synthesis of 3-azabicyclo[3.1.0]hexanes and 3-thiabicyclo[3.1.0]hexanes are described.

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Scheme 1.

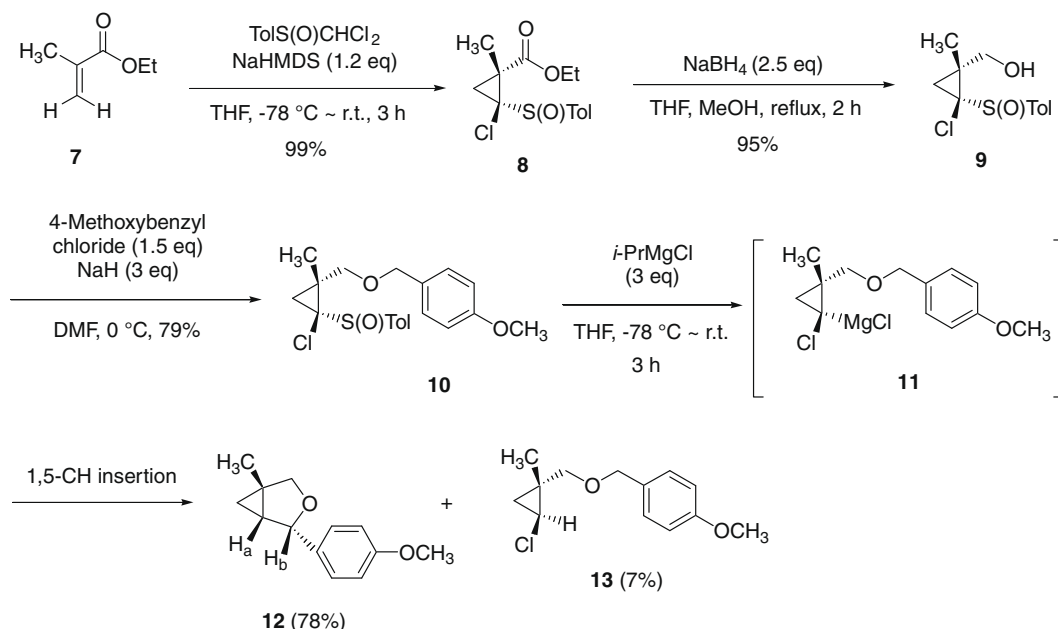
### 1.1. Synthesis of 3-oxabicyclo[3.1.0]hexanes from $\alpha,\beta$ -unsaturated esters with dichloromethyl *p*-tolyl sulfoxide and alkylhalides

At first, details of this procedure are reported using ethyl methacrylate as the representative example of the  $\alpha,\beta$ -unsaturated esters and 4-methoxybenzyl chloride as the alkylhalide (Scheme 2). Thus, to a mixture of ethyl methacrylate **7** and dichloromethyl *p*-tolyl sulfoxide at  $-78^\circ\text{C}$  was added NaHMDS and the reaction mixture was slowly allowed to warm to room temperature to afford 1-chlorocyclopropyl *p*-tolyl sulfoxide bearing an ethoxycarbonyl group at the 2-position **8** in a quantitative yield.<sup>7</sup> The ester group was reduced with  $\text{NaBH}_4$  in a refluxing mixture of THF–methanol<sup>8</sup> to give alcohol **9** in 95% yield. Finally, a solution of **9** and 4-methoxybenzyl chloride in DMF at  $0^\circ\text{C}$  was treated with NaH to give **10** in 79% yield.

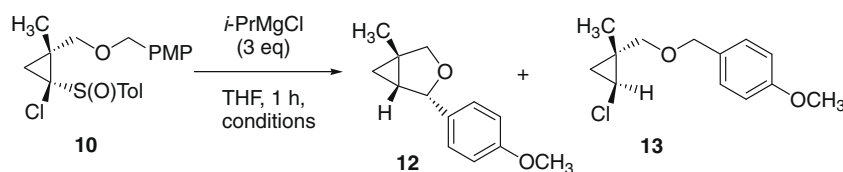
To a solution of **10** and  $i\text{-PrMgCl}$  (3 equiv) in THF at  $-78^\circ\text{C}$  was added a solution of **10** and the reaction mixture was slowly allowed to warm to room temperature for 3 h. All the starting material disappeared and 1-methyl-4-(4-methoxyphenyl)-3-oxabicyclo[3.1.0]hexane **12** was obtained as a single isomer in 78% yield along with chlorocyclopropane **13** (7% yield). The stereochemistry of the carbon bearing a 4-methoxyphenyl group of the product **12** was

determined from the vicinal coupling constant of the hydrogens  $\text{H}_a$  and  $\text{H}_b$  ( $J = 2.8\text{ Hz}$ ).<sup>9b,c</sup> The reaction mechanism and stereoselectivity of this reaction are discussed later (vide infra). Product **13** is, obviously, the protonated product of the cyclopropylmagnesium carbenoid intermediate **11**. This is the first example for the 1,5-CH insertion reaction of cyclopropylmagnesium carbenoids.

In order to understand the progress of this reaction, we carried out the reaction of **10** with  $i\text{-PrMgCl}$  under various conditions, and the results are summarized in Table 1. At first, sulfoxide **10** was treated with  $i\text{-PrMgCl}$  (3 equiv) in THF at  $-78^\circ\text{C}$ . The starting material immediately disappeared. The reaction mixture was stirred at  $-78^\circ\text{C}$  for 1 h and the reaction was quenched with water to afford only chlorocyclopropane **13** in 83% yield without any trace of **12** (entry 1). This result indicates that the sulfoxide–magnesium exchange reaction of **10** with  $i\text{-PrMgCl}$  proceeds rapidly even at  $-78^\circ\text{C}$ ; however, the 1,5-CH insertion reaction of the resulting cyclopropylmagnesium carbenoid **11** does not proceed at all at  $-78^\circ\text{C}$ . Temperature of the reaction mixture was slowly allowed to warm to  $-40^\circ\text{C}$  (entry 2). This result shows us that even under these conditions the 1,5-CH insertion reaction hardly takes place. When the reaction was allowed to warm to  $-20^\circ\text{C}$  for 1.5 h, product **12** was obtained in 42% yield along with chlorocyclopro-



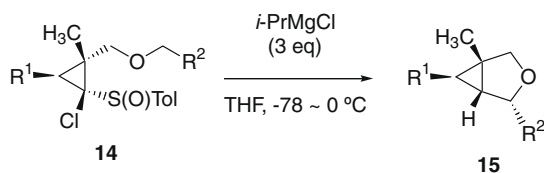
Scheme 2.

**Table 1**Treatment of 1-chlorocyclopropyl *p*-tolyl sulfoxide bearing an alkoxymethyl group at the 2-position **10** with *i*-PrMgCl under various conditions

Entry	Conditions			Yield (%)	
	Solvent	Temp (°C)	Time (h)	<b>12</b>	<b>13</b>
1	THF	-78	1	0	83
2	THF	-78 to -40	1.5	2	71
3	THF	-78 to -20	1.5	42	36
4	THF	-78 to 0	2	82	9
5	THF	-78 to rt	3	78	7
6	THF	0	1	61	23
7	Toluene	-78 to 0	2	31	49
8	Toluene	-78 to rt	3	74	9
9	Et <sub>2</sub> O	-78 to rt	3	54	28

pane **13** in 36% yield (entry 3). By raising the reaction temperature to 0 °C, we obtained the desired **12** in 82% yield (entry 4). When the reaction mixture was allowed to warm to room temperature, we obtained the same result compared with that in entry 4 within the experimental error (entry 5). From the results described above, it is now clear that the 1,5-CH insertion reaction of cyclopropylmagnesium carbenoid intermediate **11** starts to proceed at around -20 °C. Starting this reaction at 0 °C resulted in low yield (entry 6). Using toluene or diethyl ether as the solvent resulted in worse results (entries 7–9). We concluded that the conditions shown in entry 4 represent optimized conditions.<sup>10</sup>

Other examples for the synthesis of 3-oxabicyclo[3.1.0]hexanes **15** starting from 1-chlorocyclopropyl *p*-tolyl sulfoxides bearing an alkoxymethyl group at the 2-position **14** under the best conditions described above are summarized in Table 2. As shown in entries 1 and 2, it is apparent that the presence of a strong electron-withdrawing group, fluorine, on the aromatic ring does not affect at all in this reaction. 1-Methyl-4-(2-phenylethyl)-3-oxabicyclo[3.1.0]hexane **15c** was obtained in 89% yield (entry 3). This result shows that the aromatic group as R is not essential to this reaction. As shown in entry 4, 1,6-dimethyl-4-(4-methoxyphenyl)-3-oxabicyclo[3.1.0]hexane **15d** was synthesized starting from *trans*-2,3-dimethylacrylic acid ethyl ester in good overall yield.

**Table 2**Synthesis of 3-oxabicyclo[3.1.0]hexane **15** by treatment of **14** with *i*-PrMgCl

Entry	<b>14</b>		<b>15</b> /Yield (%)
	R <sup>1</sup>	R <sup>2</sup>	
1	H	F-	<b>15a</b> 78
2	H		<b>15b</b> 79
3	H		<b>15c</b> 89
4	CH <sub>3</sub>	H <sub>3</sub> CO-	<b>15d</b> 81

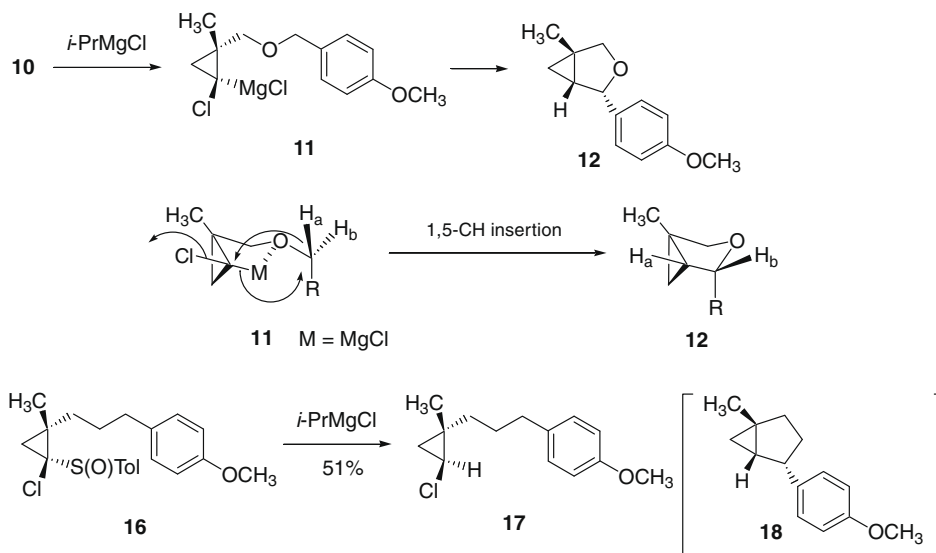
Mechanism and the stereoselectivity of these reactions are proposed in Scheme 3. Thus, as the sulfoxide–magnesium exchange reaction is known to take place with retention of the configuration of the carbon bearing the sulfinyl group,<sup>11</sup> the reaction of **10** with *i*-PrMgCl gives cyclopropylmagnesium carbenoid intermediate **11**. The magnesium and oxygen of the ether group must interact to generate five-membered intermediate as shown in Scheme 3. Deduced from the configuration of the product **12**, the carbon–H<sub>a</sub> bond attacks from the backside of the carbon–chlorine bond to afford 3-oxabicyclo[3.1.0]hexane **12**. The interaction of the oxygen with the magnesium appeared to be essential to this 1,5-CH insertion reaction. When 1-chlorocyclopropyl *p*-tolyl sulfoxide bearing 3-(4-methoxyphenyl)propyl group at the 2-position **16** was treated with *i*-PrMgCl, chlorocyclopropane **17** was obtained in 51% yield and no expected bicyclo[3.1.0]hexane **18** was observed. This result indicates that the interaction of the oxygen with the magnesium is essential to this 1,5-CH insertion reaction.

In 1971, Baird<sup>9a</sup> and in 1987, Oku and Harada<sup>9b</sup> reported a similar 1,5-CH insertion reaction from 1,1-dibromocyclopropanes bearing an alkoxymethyl group at the 2-position with methyllithium. In their reaction, they obtained 3-oxabicyclo[3.1.0]hexanes as a mixture of two diastereomers and allenes, and the yields were moderate. In contrast to this, our reaction presented herein gave 3-oxabicyclo[3.1.0]hexanes in good yields (up to 89% yield) as a single diastereomer and the reaction conditions are quite mild.

## 1.2. Synthesis of 3-thiabicyclo[3.1.0]hexanes and 3-azabicyclo[3.1.0]hexanes

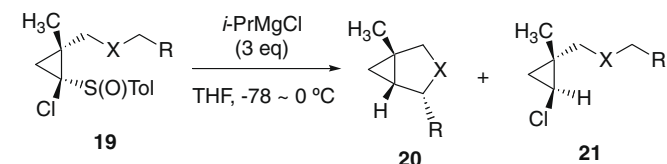
Extension of the above-mentioned chemistry to a synthesis of 3-thiabicyclo[3.1.0]hexanes and 3-azabicyclo[3.1.0]hexanes was investigated, and the results are summarized in Table 3. Starting materials **19** were synthesized from **9** via the corresponding iodides with thiols and amines.

As shown in entries 1 and 2, treatment of the sulfides **19a** and **19b** with *i*-PrMgCl under the conditions mentioned above gave the desired 3-thiabicyclo[3.1.0]hexanes, **20a** and **20b**, in low yields. In these cases, the products were found to be unstable and decomposed slowly at room temperature. One reason for the low yields must be attributed to the unstable nature of these products. The results for the treatment of 1-chlorocyclopropyl *p*-tolyl sulfoxides bearing a nitrogen atom, **19c–e**, with *i*-PrMgCl are summarized in entries 3–5. The reaction of **19** bearing N-alkylated functional groups, **19c** and **19d**, gave the desired 3-azabicyclo[3.1.0]hexanes **20c** and **20d**, respectively, in moderate yields; however, **19** bearing



Scheme 3.

**Table 3**  
Synthesis of 3-thia- and 3-azabicyclo[3.1.0]hexanes **20** by treatment of **19** with *i*-PrMgCl



Entry	19		20	21	
	X	R			Yield (%)
1	19a	S		20a 19 <sup>a</sup>	21a 29
2	19b	S		20b 27 <sup>a</sup>	21b 15
3	19c	NBn		20c 43	21c 15
4	19d	NCH <sub>3</sub>		20d 42	21d 14
5	19e	N-Boc		20e 17	21e 14

<sup>a</sup> The product was unstable and decomposed slowly.

*N*-Boc functional group gave the desired product **20e** in only 17% yield.<sup>12</sup> These results implied again that the interaction of the magnesium to the heteroatom, in other words, Lewis basicity of the heteroatom, is very important to this 1,5-CH insertion reaction.

In conclusion, we have developed a new procedure for a short synthesis of 3-oxabicyclo[3.1.0]hexanes from  $\alpha,\beta$ -unsaturated ketones with dichloromethyl *p*-tolyl sulfoxide and alkylhalides with 1,5-CH insertion of cyclopropylmagnesium carbenoid as the key reaction in four steps. We believe that the chemistry presented in this Letter contributes to the synthesis of bicyclo[3.1.0]hexanes having a heteroatom at the 3-position and also to the chemistry of magnesium carbenoids.

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Sports, Science and Technology, Japan, and TUS Grant for Research Promotion from Tokyo University of Science, which are gratefully acknowledged.

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- A synthesis of 1-methyl-4-(4-methoxyphenyl)-3-oxabicyclo[3.1.0]hexane **12** from ethyl methacrylate is reported as a representative example of this procedure. To a solution of ethyl methacrylate **7** (0.14 mL; 1.1 mmol) and dichloromethyl *p*-tolyl sulfoxide (223 mg; 1.0 mmol) in 10 mL of dry THF at  $-78^\circ\text{C}$  was added a solution of NaHMDS (1.9 M solution in THF; 0.63 mL; 1.2 mmol) dropwise with stirring. The temperature of the reaction mixture was slowly allowed to warm to room temperature for 3 h. The reaction was quenched with satd aq NH<sub>4</sub>Cl and the whole was extracted with CHCl<sub>3</sub>. The product was purified by silica gel column chromatography to give

cyclopropane bearing an ethoxycarbonyl group at the 2-position **8** (298 mg; 99%) as colorless crystals.<sup>7</sup> To a solution of ester **8** (150 mg; 0.5 mmol) in 5 mL of THF was added NaBH<sub>4</sub> (56.7 mg; 1.5 mmol) and the reaction mixture was refluxed for 5 min. To this reaction mixture was added methanol (0.5 mL) dropwise with stirring and the reaction mixture was refluxed for 2 h. The reaction was quenched with satd aq NH<sub>4</sub>Cl and the whole was extracted with CHCl<sub>3</sub>. The product was purified by silica gel column chromatography to afford alcohol **9** as colorless crystals. IR (KBr) 3325 (OH), 2901, 1499, 1438, 1074, 1030, 812 cm<sup>-1</sup>; <sup>1</sup>H NMR δ 1.18 (1H, d, *J* = 7.3 Hz), 1.47 (3H, s), 1.95 (1H, d, *J* = 7.3 Hz), 2.43 (3H, s), 2.75 (1H, m), 3.82 (1H, dd, *J* = 12.0, 5.8 Hz), 4.06 (1H, dd, *J* = 12.0, 3.8 Hz), 7.32 (2H, d, *J* = 8.2 Hz), 7.68 (2H, d, *J* = 8.2 Hz). To a solution of alcohol **9** (52 mg; 0.2 mmol) and 4-methoxybenzyl chloride (1.5 mmol) in 2 mL of DMF was added NaH (60% oil suspension; 24 mg; 0.4 mmol) at 0 °C and the reaction mixture was stirred at 0 °C for 30 min. The reaction was quenched by satd aq NH<sub>4</sub>Cl and the whole was extracted with CHCl<sub>3</sub>. The product was purified by silica gel column chromatography to give **10** (60 mg; 79%) as pale yellow oil. IR (neat) 2933, 2862, 1612, 1514, 1248, 1086, 813 cm<sup>-1</sup>; <sup>1</sup>H NMR δ 1.30 (1H, d, *J* = 7.2 Hz), 1.45 (3H, s), 1.95 (1H, d, *J* = 7.2 Hz), 2.40 (3H, s), 3.67 (1H, d, *J* = 9.8 Hz), 3.82 (1H, d, *J* = 9.8 Hz), 3.82 (3H, s), 4.49, 4.51 (each 1H, d,

*J* = 11.6 Hz), 6.88 (2H, d, *J* = 8.7 Hz), 7.27 (4H, m), 7.68 (2H, d, *J* = 8.7 Hz). To a solution of *i*-PrMgCl (2.0 M solution in THF; 0.15 mL; 0.3 mmol) in 1 mL of THF at -78 °C was added a solution of **10** (38 mg; 0.1 mmol) in dry THF dropwise with stirring. Temperature of the reaction mixture was slowly allowed to warm to 0 °C for 2 h and the reaction was quenched by satd aq NH<sub>4</sub>Cl. The whole was extracted with CHCl<sub>3</sub>. The product was purified by silica gel column chromatography to give **12** (17 mg; 82%) as colorless oil. IR (neat) 2956, 2836, 1614, 1513, 1247, 1173, 1087, 1034, 819 cm<sup>-1</sup>; <sup>1</sup>H NMR δ 0.42 (1H, m), 0.74 (1H, m), 1.30 (3H, s), 1.47 (1H, m), 3.71 (1H, d, *J* = 8.1 Hz), 3.81 (3H, s), 3.92 (1H, d, *J* = 8.1 Hz), 5.00 (1H, d, *J* = 2.8 Hz), 6.86, 7.31 (each 2H, d, *J* = 8.8 Hz). MS *m/z* (%) 204 (M<sup>+</sup>, 48), 175 (100), 149 (36), 147 (14), 135 (53), 121 (27), 108 (17). Calcd for C<sub>13</sub>H<sub>16</sub>O<sub>2</sub>: *M*, 204.1150. Found: *m/z* 204.1150.

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