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A new synthesis of β,γ-unsaturated esters from three components, aldehydes, chloromethyl *p*-tolyl sulfoxide, and *tert*-butyl acetate, via magnesium carbenoid 1,2-CH and 1,2-CC insertion as the key reaction

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Abstract—Addition reaction of 1-chlorovinyl *p*-tolyl sulfoxides, which were derived from various aldehydes, with lithium enolate of *tert*-butyl acetate at −78 °C in THF gave adducts in high yields. Magnesium carbenoids were generated by treatment of these adducts with Grignard reagents via the sulfoxide–magnesium exchange reaction. When the adducts were derived from alkyl aldehydes or electron-deficient aromatic aldehydes, carbenoid 1,2-CH insertion reaction took place from the magnesium carbenoids to afford β,γ-unsaturated butyric esters having a substituent at the β-position. On the contrary, when the adducts were derived from electron-rich aromatic aldehydes, carbenoid 1,2-CC insertion reaction took place from the magnesium carbenoids to give β,γ-unsaturated butyric esters having the aromatic group at the γ-position. Highly stereospecific 1,2-CC insertion reactions were observed in the latter reactions. This procedure provides a good way for a synthesis of β,γ-unsaturated esters from aldehydes with two carbon–carbon bond-formations.

Carboxylic acids and their derivatives obviously are the most important and fundamental compounds in organic and synthetic organic chemistry.[1] Among the carboxylic acids, the unsaturated ones are even more versatile in synthetic organic chemistry. α,β-Unsaturated carboxylic acids and their derivatives are usually synthesized from saturated carboxylic acids[2] or from aldehydes and ketones by Horner–Wadsworth–Emmons reaction[3] with two-carbon elongation. Thus, the synthesis of α,β-unsaturated carboxylic acids and their derivatives is thought to be relatively easy.

Contrary to this, no universal method for the synthesis of β,γ-unsaturated carboxylic acids or esters has been reported. Methods so far reported for synthesis of β,γ-unsaturated carboxylic acids and their derivatives are as follows: one-carbon elongation of α,β-unsaturated esters or aldehydes,[4] deconjugative protonation of α,β-unsaturated esters,[5] photo deconjugation of α,β-unsaturated esters,[6] deconjugative alkylation of α,β-unsaturated esters,[7] reductive deconjugation of α-bromo α,β-unsaturated esters,[8] modified Knoevenagel condensation[9] and others.[10]

We previously reported a new method for synthesis of cyclopropanes utilizing the reaction of magnesium carbenoid 1,3-CH insertion as the key reaction.[11] In continuation of this chemistry, we recently investigated the property of magnesium carbenoid **3**, generated from 1-chloroalkyl *p*-tolyl sulfoxides **2**, which were derived from aldehydes via 1-chlorovinyl *p*-tolyl sulfoxide **1**, with a Grignard reagent (Scheme 1). Contrary to our expectation, magnesium carbenoids **3** gave β,γ-unsaturated esters **4** or **5**, instead of the cyclopropanes, depending on the nature of the substituent R, in moderate to high yields. This procedure offers a novel method for a synthesis of β,γ-unsaturated esters. Details of this study and mechanisms and stereochemistry of this reaction are described hereinafter.

At first, 1-chlorovinyl *p*-tolyl sulfoxide **6** was synthesized from 3-phenylpropanal in two steps in high overall yield

Keywords: Magnesium carbenoid; Sulfoxide–magnesium exchange reaction; β,γ-Unsaturated ester; 1,2-CH insertion; 1,2-CC insertion.
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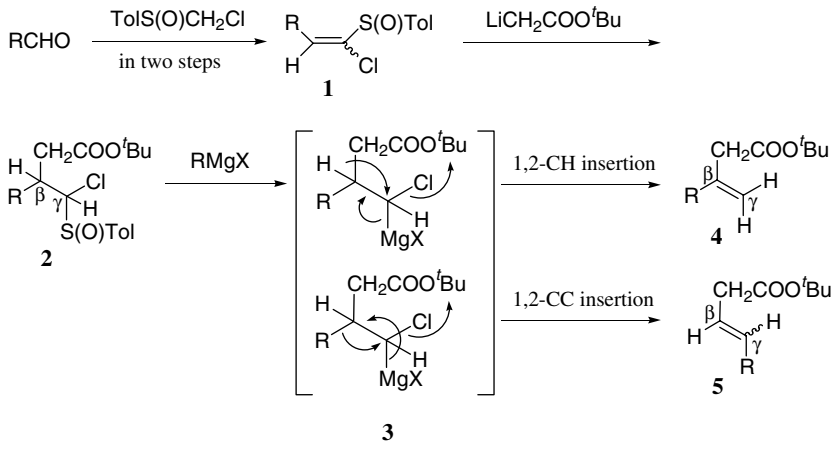
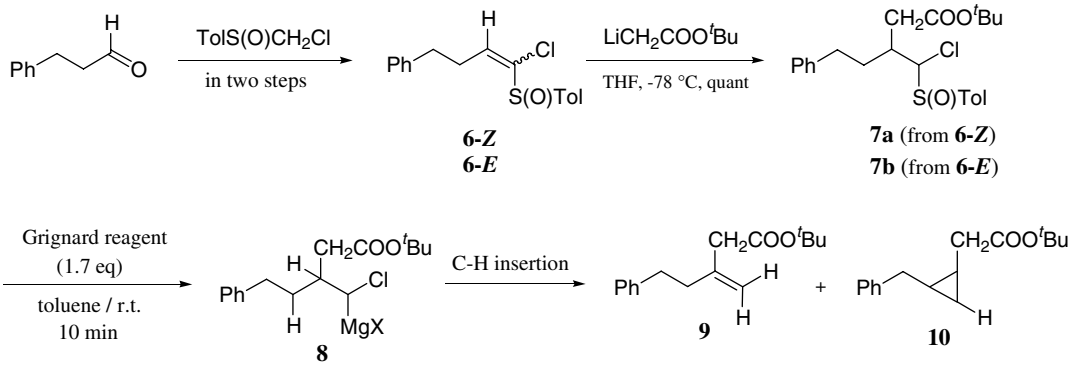


Scheme 1.



Adduct **7**	Grignard reagent	**9** / %	**10** / %
7a	*i*-PrMgCl	5	25
7b	*i*-PrMgCl	Complex mixture	
7a	*i*-PrMgBr	85	-[a)]
7b	*i*-PrMgBr	41	-[a)]

a) Trace of **10** was observed on the silica gel TLC.

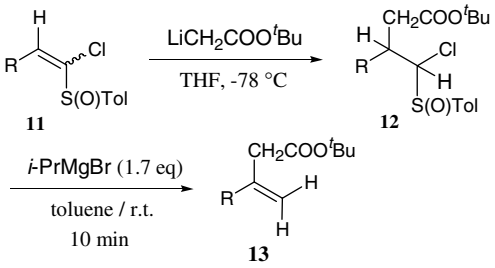
Scheme 2.

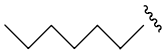
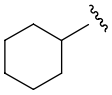
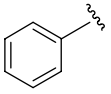
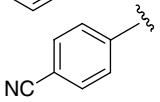
as two geometrical isomers (**6-*Z*** and **6-*E***) as shown in Scheme 2.[12] The two isomers were separated and treated with lithium enolate of *tert*-butyl acetate to afford adducts (**7a** and **7b**), each in quantitative yield as a single diastereomer. The addition reaction proceeded in a highly sterospecific manner, as reported in the previous Letter.[11c] The adducts were first treated with 1.7 equiv of *i*-PrMgCl in toluene at room temperature. The treatment of **7a** gave the expected cyclopropane **10**; however, the yield was poor (25%) and olefin **9** was obtained as a by-product in 5% yield. The treatment of **7b** with *i*-PrMgCl gave only a complex mixture.

Quite interestingly, treatment of adduct **7a** with *i*-PrMgBr gave olefin **9** (β,γ-unsaturated ester) in 85% yield. In this case, 1,2-CH insertion reaction of the generated magnesium carbenoid **8** was thought to be faster than 1,3-CH insertion reaction (giving cyclopropane **10**). The treatment of **7b** with *i*-PrMgBr also gave olefin **9** as the main product; however, the yield was not good compared with that from **7a**.

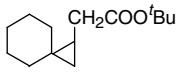
As we recognized that this might be a useful method for a synthesis of β,γ-unsaturated esters, we studied generality of this reaction starting from various aldehydes and the results are summarized in Table 1. *n*-Heptanal, cyclohexanecarboxaldehyde, pivalaldehyde, benzaldehyde, and 4-cyanobenzaldehyde were selected as the representative aldehydes. 1-Chlorovinyl *p*-tolyl sulfoxides **11** were synthesized from the aldehydes in two steps in high overall yields. Addition reaction of vinyl sulfoxides **11** with lithium enolate of *tert*-butyl acetate gave almost

Table 1. Synthesis of β,γ-unsaturated ester **13** from 1-chlorovinyl *p*-tolyl sulfoxide **11** via adduct **12**



Entry	13		
	R		Yield[a] (%)
1		From **11a-*Z***	65
2		From **11a-*E***	50
3		From **11b-*Z***	56[b]
4		From **11b-*E***	44
5		From **11c-*Z***	70
6		From **11c-*E***	64
7		From **11d-*Z***	88
8		From **11d-*E***	50
9		From **11e-*Z***	47
10		From **11e-*E***	40

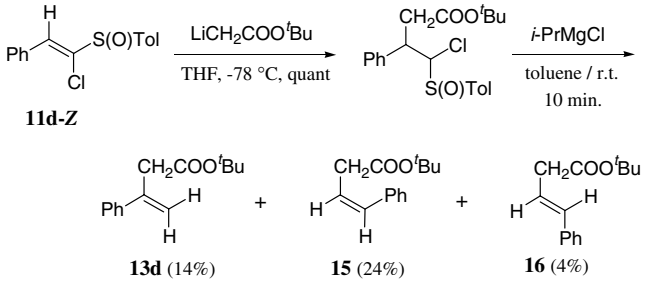
[a] The yield of the reaction of adduct **12** with *i*-PrMgBr.
[b] Cyclopropane **14** was obtained as a by-product in 35% yield.



14

quantitative yields of adducts **12**. Finally, treatment of **12** with *i*-PrMgBr (1.7 equiv) in toluene at room temperature for 10 min gave moderate to good yields of the desired β,γ-unsaturated esters **13a** to **13e** having a substituent R at the β-position. Only the case of cyclohexyl group as R gave cyclopropane **14** as a by-product (entry 3). It is worth noting that isomerization of β,γ-unsaturated esters to α,β-unsaturated esters under these conditions was never observed throughout this study.

Very interestingly, as shown in Scheme 3, treatment of the adduct derived from **11d-Z** with *i*-PrMgCl (instead of *i*-PrMgBr) gave three olefins **13d**, **15**, and **16**. Olefin **13d** is the 1,2-CH insertion product of the magnesium carbenoid intermediate. Olefins **15** and **16** are expected



Scheme 3.

to be the products from 1,2-CC insertion reaction of the carbenoid intermediate. This result suggested that if we used aromatic aldehydes, we could obtain the β,γ-unsaturated esters having the aromatic group at the γ-position. We investigated the substrate scope of aromatic aldehydes and the results are summarized in Table 2.

At first, 1-chlorovinyl *p*-tolyl sulfoxide **17a-*Z*** (Ar = *p*-methoxyphenyl) was synthesized from *p*-anisaldehyde and the addition reaction of **17a-*Z*** with lithium enolate of *tert*-butyl acetate gave adduct **18a** in quantitative yield. Treatment of **18a** with *i*-PrMgBr or *i*-PrMgCl was investigated and indeed when *i*-PrMgCl was used a mixture of the expected olefins **19a** and **20a** were obtained in 64% and 5% yields, respectively. As these yields were not acceptable, we further investigated to improve the yield and finally EtMgCl was found to be the Grignard reagent of choice. When adduct **18a** was treated with EtMgCl (Table 2, entry 1) β,γ-unsaturated esters bearing the aromatic group at the γ-position, **19a** and **20a**, were obtained in 80% and 6% yields, respectively.

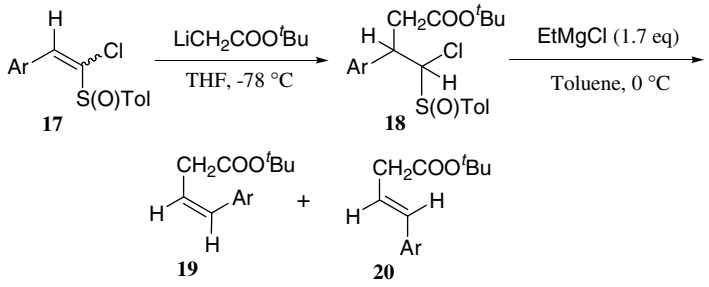
Generality of this reaction was investigated using 4-methylthiobenzaldehyde, piperonal, furfural, and 2-formylthiophene and the results are summarized in Table 2. Geometrical isomers of the 1-chlorovinyl *p*-tolyl sulfoxides (**17b-*Z*** and **17b-*E***) were synthesized from 4-methylthiobenzaldehyde and they were separated. The addition reaction of these geometrical isomers with lithium enolate of *tert*-butyl acetate gave adducts **18b** as a single diastereomer to each other. When the adduct **18b** derived from **17b-*Z*** was treated with EtMgCl (entry 2), a similar result was obtained compared with that shown in entry 1. Quite interestingly, the reaction with the adduct derived from **17b-*E*** gave the geometrical isomer of olefin **20b** as a main product, though the yield was lower (entry 3). From these two reactions, it was suggested that this magnesium carbenoid 1,2-CC insertion reaction is a highly stereospecific reaction.

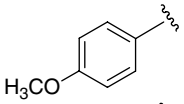
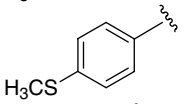
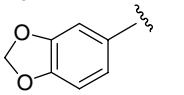
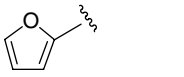
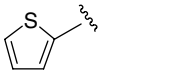
Very interestingly, when the adduct **18c** derived from **17c-*Z*** was treated with EtMgCl, *Z*-β,γ-unsaturated ester **19c** was obtained as a single isomer in 95% yield without any formation of isomer **20c** (entry 4).[13] On the other hand, when the adduct derived from **17c-*E*** was treated with EtMgCl, *E*-β,γ-unsaturated ester **20c** was obtained as a single isomer in 83% yield (entry 5).[13] It is worth noting that the reaction mentioned above is the first example of highly stereospecific magnesium carbenoid 1,2-CC insertion.

In addition, the reactions starting from furfural, and 2-formylthiophene gave completely stereospecific reactions to afford β,γ-unsaturated esters **19d**, **20d** and **19e**, **20e**, respectively, each in high yields (entries 6–9). In these reactions (entries 2–9), it was found that the yields were always better when the adducts derived from **17-*Z*** isomers were treated with EtMgCl.

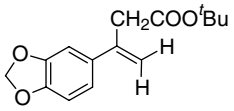
A plausible mechanism (Scheme 4) for this highly stereospecific magnesium carbenoid 1,2-CC insertion is

Table 2. Synthesis of β,γ-unsaturated esters **19** or **20** by treatment of adducts **18**, which were derived from aromatic aldehydes via 1-chlorovinyl *p*-tolyl sulfoxides **17**, with EtMgCl

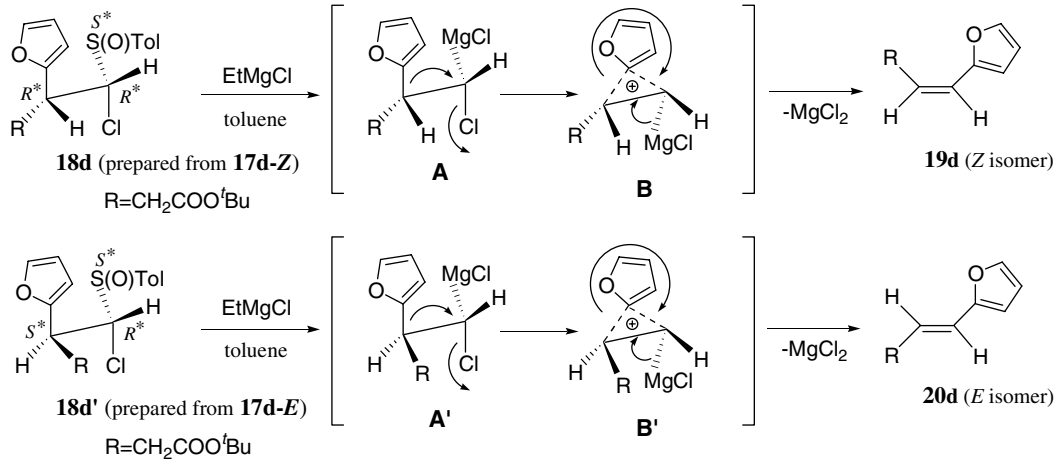


Entry	**18** Ar		**19**[a] (%)	**20**[a] (%)
1		From **17a-*Z***[b]	80	6
2		From **17b-*Z***	80	8
3		From **17b-*E***	8	42
4		From **17c-*Z***	95	0
5		From **17c-*E***	0	83[c]
6		From **17d-*Z***	92	0
7		From **17d-*E***	0	75
8		From **17e-*Z***	92	0
9		From **17e-*E***	0	72

[a] The yield of the reaction of **18** with EtMgCl.
[b] Only *Z*-isomer could be synthesized from *p*-anisaldehyde.
[c] Olefin **21** was obtained as a by-product in 12% yield.



21



Scheme 4. A proposed mechanism for the stereospecific magnesium carbenoid 1,2-CC insertion reaction.

explained as follows using the reaction from 1-chlorovinyl *p*-tolyl sulfoxides **17d-*Z*** and **17d-*E*** (Table 2, entries 6 and 7) as representative examples. As described above, the addition reaction of lithium enolate of *tert*-butyl

acetate to 1-chlorovinyl *p*-tolyl sulfoxides is highly stereospecific.[11c] Thus, the addition reaction of **17d-*Z*** and **17d-*E*** gave the adduct (3*R**,4*R**,S*s**)-*tert*-butyl 4-chloro-3-furyl-4-(*p*-tolylsulfinyl)butyrate **18d** and (3*S**,4*R**,S*s**)-*tert*-butyl 4-chloro-3-furyl-4-(*p*-tolylsulfinyl)butyrate **18d′**, respectively. Because the sulfoxide–magnesium exchange reaction is known to proceed with retention of configuration of the carbon bearing the sulfinyl group,[14] treatment of **18d** with EtMgCl should afford the magnesium carbenoid intermediate **A** as shown in Scheme 4. In this magnesium carbenoid intermediate, the carbon–carbon bond between the furyl group and the carbon at the 3-position will attack to the carbon bearing the chlorine atom from backside of the chlorine atom. This reaction gives *Z*-olefin **19d** via transition state **B**. By the same mechanism, **18d′** will give *E*-olefin **20d** via transition state **B′**.

In conclusion, we found that magnesium carbenoids **3**, derived from 1-chlorovinyl *p*-tolyl sulfoxides **2**, take place 1,2-CH or 1,2-CC insertion reaction to give β,γ-unsaturated esters **4** or **5** depending on the nature of the substituent R. It was also found that the 1,2-CC insertion reaction is highly stereospecific. The reactions mentioned above contribute to a synthesis of various β,γ-unsaturated esters.

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13. *tert*-Butyl acetate (0.85 mL; 6.23 mmol) was added to a solution of LDA (6.23 mmol) in 26 mL of dry THF at −78 °C with stirring. The solution was stirred for 10 min and then a solution of **17c-*Z*** (500 mg; 1.56 mmol) in THF (5 mL) was added. The solution was stirred for 5 min and the reaction was quenched by adding satd aq NH_4Cl. The whole was extracted with $CHCl_3$. The extract was washed with brine and the organic layer was dried over $MgSO_4$. The solvent was evaporated to give a residue, which was purified by silica gel column chromatography to give 670 mg (98%) of **18c-*Z*** as colorless amorphous powder. IR (neat) 2979, 1727 (CO), 1491, 1368, 1253 (COC), 1151, 1042 (SO), 934 cm^{-1}; ^1H NMR δ 1.34 (9H, s), 2.42 (3H, s), 2.78 (1H, dd, $J = 16.0$, 8.0 Hz), 2.79 (1H, dd, $J = 16.0$, 8.0 Hz), 4.34 (1H, dt, $J = 7.8$, 2.9 Hz), 4.63 (1H, d, $J = 3.0$ Hz), 5.98 (2H, s), 6.83 (1H, dd, $J = 7.2$, 1.4 Hz), 7.01 (1H, s), 7.02 (1H, dd, $J = 7.2$, 1.8 Hz), 7.30 (2H, d, $J = 8.2$ Hz), 7.63 (2H, d, $J = 8.2$ Hz).
In a similar way **18c-*E*** was synthesized from **17c-*E*** in 95% yield as colorless amorphous powder. IR (neat) 2977, 2929, 1733 (CO), 1504, 1488, 1368, 1242 (COC), 1149, 1040 (SO), 935 cm^{-1}; ^1H NMR δ 1.30 (9H, s), 2.42 (3H, s), 2.92 (1H, dd, $J = 16.0$, 10.8 Hz), 3.04 (1H, dd, $J = 16.0$, 4.7 Hz), 4.12 (1H, ddd, $J = 7.6$, 4.5, 3.1 Hz), 4.48 (1H, d, $J = 2.9$ Hz), 5.94 (2H, s), 6.76 (1H, d, $J = 8.0$ Hz), 6.81 (1H, dd, $J = 8.1$, 1.7 Hz), 6.85 (1H, d, $J = 1.7$ Hz), 7.32 (2H, d, $J = 8.3$ Hz), 7.64 (2H, d, $J = 8.3$ Hz).
EtMgCl (2.0 M solution in diethyl ether; 0.1 mL; 0.21 mmol) was added to dry toluene (1.8 mL) at 0 °C, and then a solution of **18c-*Z*** (50 mg 0.114 mmol) in toluene (0.5 mL) was added dropwise to the solution of EtMgCl. The reaction mixture was stirred at 0 °C for 30 min. The reaction was quenched by adding satd aq NH_4Cl. The whole was extracted with $CHCl_3$. The extract was washed with brine and the organic layer was dried over $MgSO_4$ and the solvent was evaporated. The residue was purified by silica gel column chromatography to give 28.5 mg (95%) of **19c** as colorless oil. IR (neat) 2978, 1731(CO), 1490, 1442, 1368, 1237 (COC), 1147, 1040, 846, 820 cm^{-1}; ^1H NMR δ 1.47 (9H, s), 3.23 (2H, dd, $J = 7.3$, 1.9 Hz), 5.79 (1H, dt, $J = 11.6$, 7.3 Hz), 5.96 (2H, s),6.50 (1H, dt, $J = 11.5$, 1.8 Hz), 6.75 (1H, dd, $J = 8.1$, 1.5 Hz), 6.78 (1H, d, $J = 7.4$ Hz), 6.80 (1H, d, $J = 1.9$ Hz). MS *m/z* (%) 262 (M^+, 100), 189 (55), 161 (77), 131 (90), 103 (40), 57 (86). Calcd for $C_{15}H_{18}O_4$: M, 262.1205. Found: *m/z* 262.1207.
A similar treatment of **18c-*E*** with EtMgCl afforded 25 mg (83%) of **20c** as colorless oil and 3.5 mg (12%) of **21** as colorless oil. **20c**: IR (neat) 2978, 1731 (CO), 1490, 1446, 1368, 1250 (COC), 1147, 1040, 964, 937, 801 cm^{-1}; ^1H NMR δ 1.47 (9H, s), 3.12 (2H, dd, $J = 7.2$, 1.5 Hz), 5.95 (2H, s), 6.11 (1H, dt, $J = 15.8$, 7.2 Hz), 6.37 (1H, d, $J = 15.8$ Hz), 6.73 (1H, d, $J = 8.0$ Hz), 6.78 (1H, dd, $J = 8.0$, 1.6 Hz), 6.92 (1H, d, $J = 1.6$ Hz). MS *m/z* (%) 262 (M^+, 88), 206 (54), 161 (100), 131 (93), 103 (44), 57 (93). Calcd for $C_{15}H_{18}O_4$: M, 262.1205. Found: *m/z* 262.1207. **21**: IR (neat) 2922, 1732 (CO), 1505, 1493, 1445, 1368, 1235 (COC), 1146, 1040, 937, 813 cm^{-1}; ^1H NMR δ 1.38

(9H, s) 3.37 (2H, d, $J = 1.0$ Hz), 5.12 (1H, d, $J = 0.9$ Hz), 5.40 (1H, d, $J = 0.9$ Hz), 5.95 (2H, s), 6.76 (1H, d, $J = 8.1$ Hz), 6.90 (1H, dd, $J = 8.1$, 1.8 Hz), 6.95 (1H, d, $J = 1.8$ Hz). MS *m*/*z* (%) 262 (M^+, 17), 206 (100), 189 (16), 178 (16), 103 (14), 57 (26). Calcd for $C_{15}H_{18}O_4$: M, 262.1205. Found: *m*/*z* 262.1204.

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