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# Palladium-Catalyzed Three-Component Tandem Cyclization Reaction of 2-(2,3-Allenyl)acylacetates, Organic Halides, and Amines: An Effective Protocol for the Synthesis of 4,5-Dihydro-1*H*-pyrrole Derivatives

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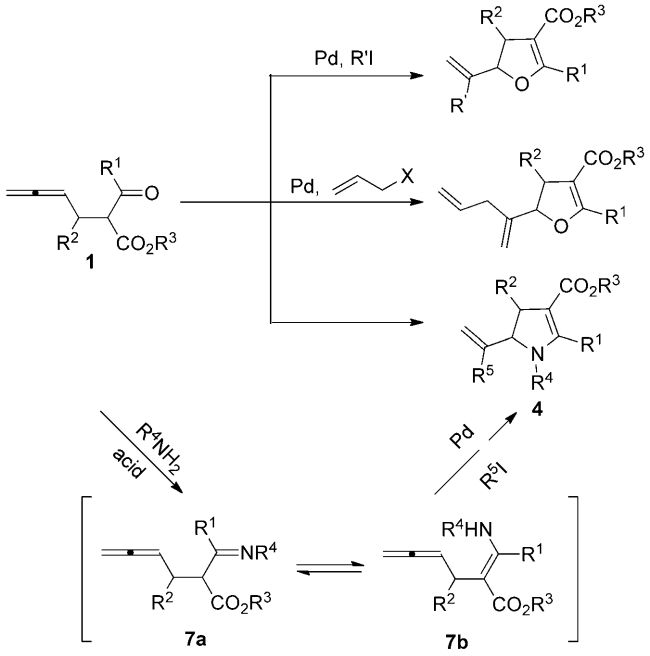
**Abstract:** A domino three-component reaction of 2-(2′,3′-allenyl)acylacetates with aryl or alkenyl halides and aryl- or benzylamines afforded 4,5-dihydro-1*H*-pyrrole derivatives highly chemo- and regioselectively in one pot through imine formation/imine-enamine tautomerization under the catalysis of palladium(0) and toluenesulfonic acid monohydrate. A high diastereoselectivity was observed.

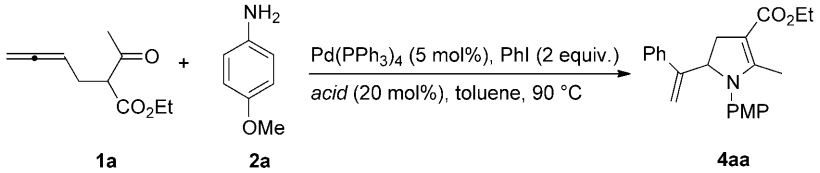
**Keywords:** allenes; cyclization; 4,5-dihydro-1*H*-pyrroles; three-component reactions

Multi-component reactions (MCRs) involving domino processes have emerged as powerful tools to synthesize molecules with efficiency and diversity from simple substrates and with atom-economy.[1,2] In this area, the development of new chemical processes producing elaborate and important hetereocyclic structures in an efficient manner has been catching the attention of synthetic organic chemists and medicinal chemists due to the importance of heterocyclic compounds.[3] As we know, pyrroles,[4] especially 4,5-dihydro-1*H*-pyrroles,[5] are common structural units in various biologically active natural compounds. On the other hand, functionalized allenes have been proven to be efficient starting materials for the synthesis of potentially useful carbo- and heterocycles.[6–8] Recently, we reported the highly selective synthesis of 4,5-dihydrofuran derivatives by Pd-catalyzed coupling-cyclization of 2-(2′,3′-allenyl)acetylacetates with organic halides.[7a,b] Based on these observations, we envisioned that the reaction of β-keto esters **1** with amines would provide imines **7a**, which would isomerize to enamines **7b**. Under the catalysis of Pd(0), organic halides would react with this class of enamines **7b** to provide 4,5-dihydro-1*H*-pyrroles. Due to the introduction of the three-component reaction concept here, the reaction would provide the azacyclic compounds with diversity. In this paper, we wish report such a concept for the efficient synthesis of 4,5-dihy-




**Scheme 1.**

**Table 1.** The effect of the amount of amine **2a** and Brønsted acid on the Pd(0)-catalyzed three-component tandem cyclization reaction of **1a**, **2a**, and phenyl iodide.

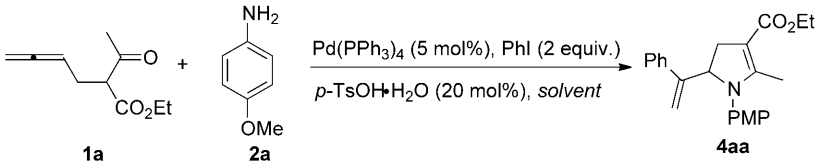



**1a** **2a** **4aa**

| Entry | **2a** (equiv.) | Brønsted acid | Time *t* [h] | Yield of **4aa** [%][a] |
|---|---|---|---|---|
| 1 | 1 | *p*-TsOH·$H_2O$ | 16 | 27 |
| 2 | 0.6 | *p*-TsOH·$H_2O$ | 9 | 22 |
| 3 | 2 | *p*-TsOH·$H_2O$ | 16 | 52 |
| **4** | **3** | *p*-TsOH·$H_2O$ | **10** | **72** |
| 5[b] | 3 | *p*-TsOH·$H_2O$ | 8 | 56 |
| 6 | 4 | *p*-TsOH·$H_2O$ | 10 | 60 |
| 7 | 5 | *p*-TsOH·$H_2O$ | 5 | 63 |
| 8 | 3 | – | 10 | 50 |
| 9 | 3 | TfOH | 10 | 56 |
| 10 | 3 | TFA | 6 | 54 |
| 11 | 3 | AcOH | 8 | 53 |

[a] Yield of isolated product.
[b] 1.0 equiv. of $MgSO_4$ was added.

**Table 2.** Solvent effect on the Pd(0)-catalyzed three-component tandem cyclization reaction of **1a**, **2a**, and phenyl iodide in the presence of *p*-TsOH·$H_2O$ (20 mol%).




**1a** **2a** (3 equiv.) **4aa**

| Entry | Solvent | Temperature [°C] | Time *t* [h] | Yield of **4aa** [%][a] |
|---|---|---|---|---|
| 1 | $MeNO_2$ | reflux | 7 | complicated |
| 2 | DMF | 90 | 8 | 57 |
| 3 | DCE | reflux | 7 | 64 |
| 4 | DME | reflux | 8 | 65 |
| **5** | **toluene** | **90** | **10** | **72** |
| 6 | PhCl | 90 | 8 | 73 |

[a] Yield of isolated product.

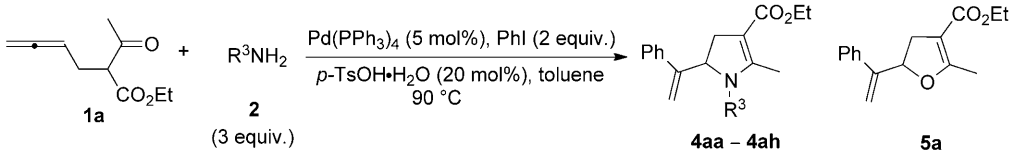
dropyrrole derivatives *via* imine-formation/imine-enamine tautomerization (Scheme 1).

As a first try, we were happy to notice that the reaction of ethyl 2-(2′,3′-allenyl)acetylacetate **1a** (1 equiv.), *p*-methoxyphenylamine **2a** (1 equiv.), $Pd(PPh_3)_4$ (5 mol%), PhI (2 equiv.), and *p*-TsOH·$H_2O$ (20 mol%) in toluene with stirring at 90 °C for 16 h afforded 4,5-dihydropyrrole **4aa** in 27% yield (Table 1, entry 1). Surprisingly, when 0.6 equiv. of **2a** were applied, the yield of **4aa** dropped to 22% (entry 2). When we increased the amount of the amine **2a**, the reaction became cleaner and higher-yielding with 3 equiv. of **2a** being the best (entries 3–7). Addition of anhydrous $MgSO_4$ for removal of the *in-situ* formed water seems useless (entry 5). Furthermore, the effect of Brønsted acids on this Pd(0)-catalyzed three-component tandem reaction was also studied. The yield of **4aa** was much lower when no *p*-TsOH·$H_2O$ was added (entry 8). Other Brønsted acids such as TfOH (entry 9), TFA (entry 10), or AcOH (entry 11) are not as efficient as TsOH·$H_2O$.

Studies on the solvent effect revealed that toluene (Table 2, entry 5) and PhCl (Table 2, entry 6) are the best solvents for this reaction, thus, toluene was chosen for further study.

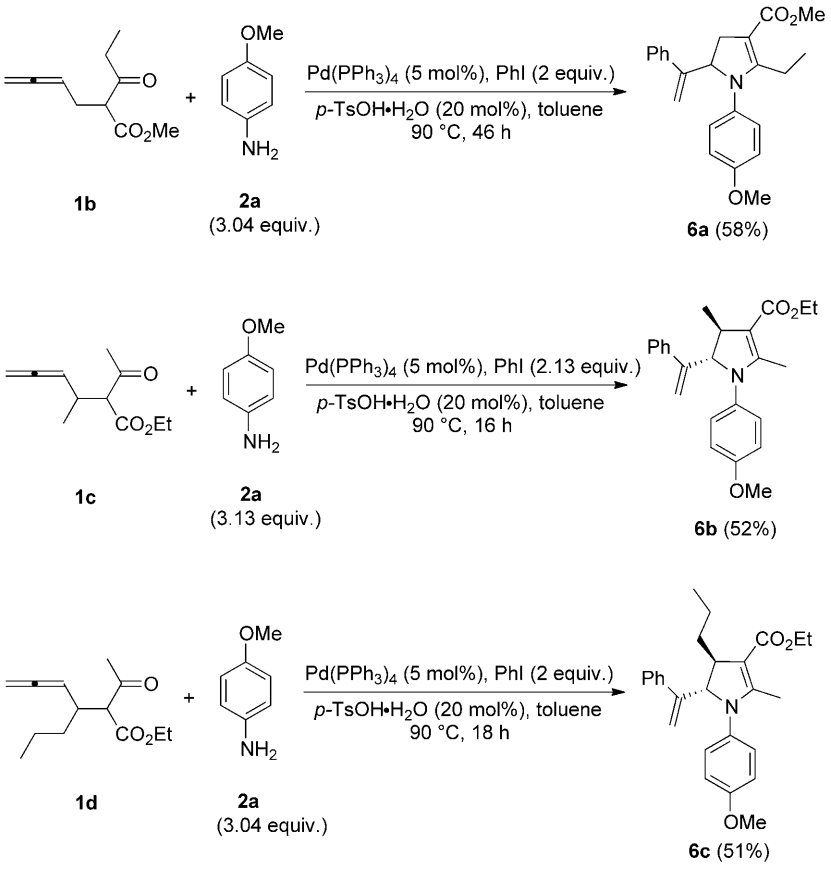
  

**Table 3.** The Pd(0)-catalyzed three-component tandem cyclization reaction of **1a** and PhI with different amines.




| Entry | $R^3NH_2$ | Time *t* [h] | Yield of **4** [%][a] |
|---|---|---|---|
| 1 | *p*-$MeOC_6H_4$ (**2a**) | 10 | 72 (**4aa**) |
| 2 | *p*-$MeC_6H_4$ (**2b**) | 10 | 60 (**4ab**) |
| 3 | Ph (**2c**) | 8 | 64 (**4ac**) |
| 4 | *p*-$MeOC_6H_4CH_2$ (**2d**) | 6 | 69 (**4ad**) |
| 5 | $PhCH_2$ (**2e**) | 8 | 67 (**4ae**) |
| 6 | *n*-Bu (**2f**) | 9 | 38 (**4af**) |
| 7 | allyl (**2g**) | 10 | 42 (**4ag**)[b] |

[a] Yield of isolated product.
[b] 34% of **5a** was also discovered.




**Scheme 2.** The Pd(0)-catalyzed diastereoselective cyclization of **1b**, **1c** or **1d** with *p*-methoxyphenylamine **2a** and phenyl iodide.

Thus, the reaction of **1a** with different amines was studied under the optimized reaction conditions (Table 3). Aromatic amines with electron-donating groups (Table 3, entries 1 and 2) afforded good yields of **4aa** and **4ab**. However, we found that **4ab** easily decomposed after being purified *via* silica-gel chromatography. The yield for the reaction with aniline (entry 3) is somewhat lower. Benzylamines (entries 4 and 5) could also afford the corresponding products in reasonable yields. However, the reaction with ali-

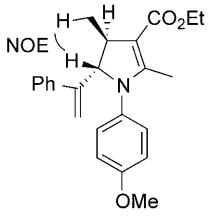


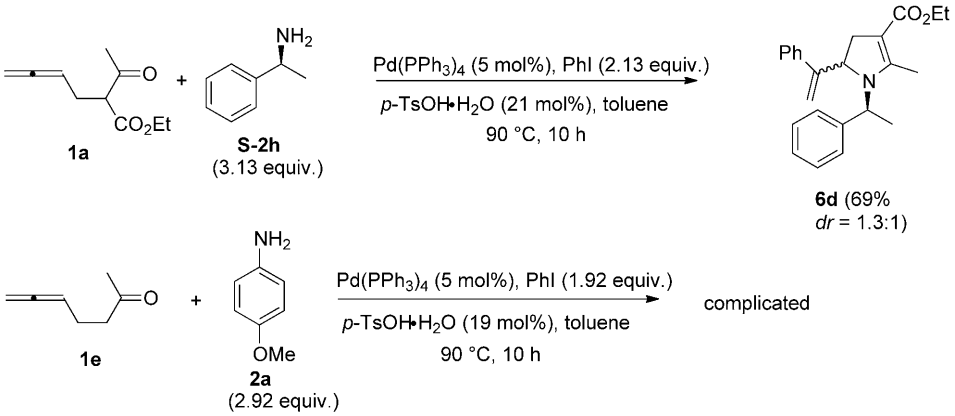

**Figure 1.** NOE study of **6b**.

phatic amines, such as *n*-butylamine (entry 6) and allylamine (entry 7), is low-yielding. For ethyl-substituted substrate **1b**, the desired product **6a** can also be obtained in moderate yield (Scheme 2).

The cyclization of polysubstituted 2-(1′-alkyl-2′,3′-allenyl)-β-keto esters **1c** or **1d** with *p*-methoxyphenylamine **2a** and phenyl iodide afforded 4,5-dihydro-1*H*-pyrrole derivatives *trans*-**6b** or *trans*-**6c** highly diastereoselectively (Scheme 2). The relative configuration here was established by its NOE study of **6b** (Figure 1).

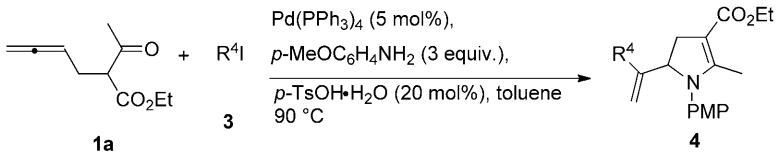
Then the scope of organic iodides has also been demonstrated (Table 4): The phenyl ring in the aryl iodide could be substituted by *p/m*-Me (Table 4, entries 2 and 3), OMe (entry 4), $CO_2Me$ (entry 5), Br (entry 6), F (entry 7), or an extra aryl group (entries 8 and 9). Furthermore, the reaction may be extended to 1-alkenyl iodides (entries 10 and 11). The reaction of 1-naphthyl iodide (entry 12) is also smooth.

The reaction of **1a** with (*S*)-(−)-α-phenylethylamine **2h** afforded a mixture of diastereoisomers with 69% yield in a ratio of 1.3:1. The starting allene without an ethoxycarbonyl moiety **1e** afforded an unidentified




**Scheme 3.** Further study of the scope of substrates.

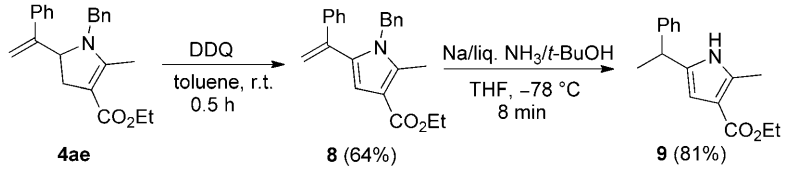
**Table 4.** The Pd(0)-catalyzed three-component tandem cyclization reaction of **1a**, *p*-methoxyphenylamine, and different organic iodides.



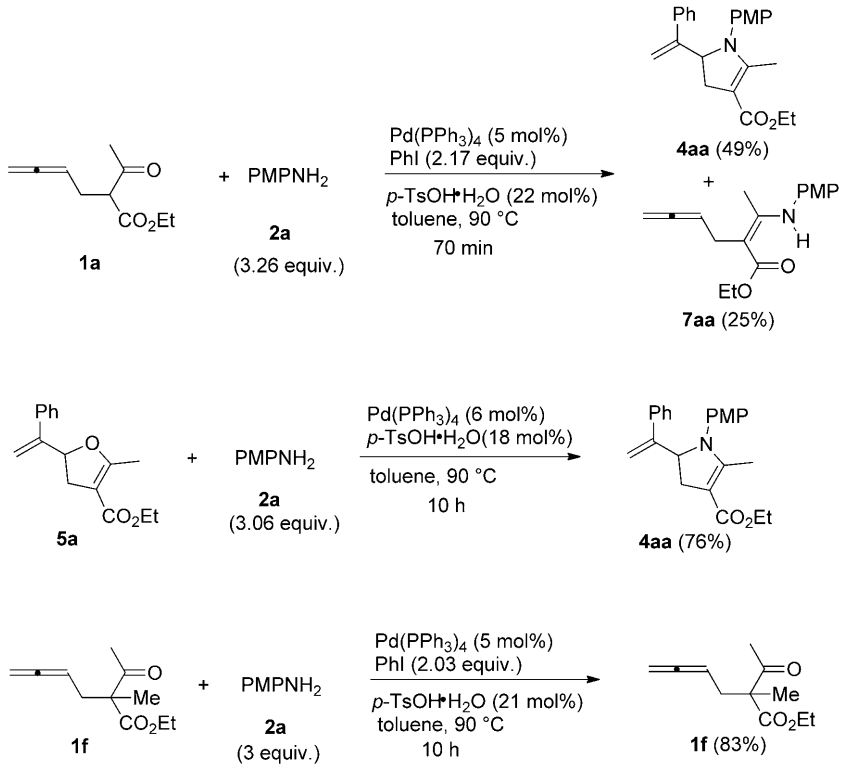

| Entry | $R^4$ | Time *t* [h] | Yield of **4** [%][a] |
|---|---|---|---|
| 1 | Ph (**3a**) | 10 | 72 (**4aa**) |
| 2 | *p*-$MeC_6H_4$ (**3b**) | 10 | 57 (**4ba**) |
| 3 | *m*-$MeC_6H_4$ (**3c**) | 10 | 59 (**4ca**) |
| 4 | *p*-$MeOC_6H_4$ (**3d**) | 9 | 46 (**4da**) |
| 5 | *p*-$MeO_2CC_6H_4$ (**3e**) | 10 | 67 (**4ea**) |
| 6 | *p*-$BrC_6H_4$ (**3f**) | 10 | 74 (**4fa**) |
| 7 | *p*-$FC_6H_4$ (**3g**) | 10 | 58 (**4ga**) |
| 8 | *p*-$PhC_6H_4$ (**3h**) | 10 | 78 (**4ha**) |
| 9 | *p*-(*p*-$BrC_6H_4$)$C_6H_4$ (**3i**) | 10 | 64 (**4ia**) |
| 10 | hex-1(*E*)-enyl (**3j**) | 10 | 66 (**4ja**) |
| 11 | (*E*)-2-phenylvinyl (**3k**) | 10 | 48 (**4ka**) |
| 12 | 1-naphthyl (**3l**) | 10 | 54 (**4la**) |

[a] Yield of isolated product.




**Scheme 4.** Synthetic application of 4,5-dihydro-1*H*-pyrrole **4ae**.




**Scheme 5.** Control experiments for the mechanistic study.

mixture, suggesting that the ethoxycarbonyl moiety is necessary for this reaction (Scheme 3).

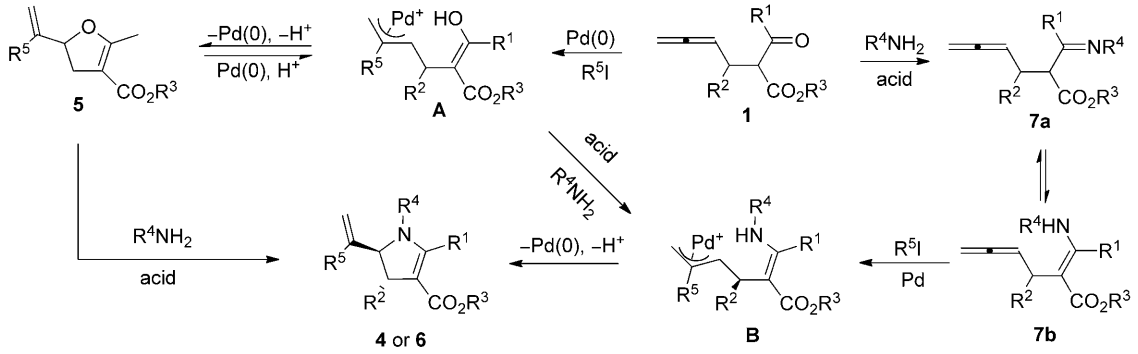
In order to show the utility of our method, 4,5-dihydro-1*H*-pyrrole **4ae** was transformed to the *N*-Bn-pyrrole **8** with DDQ in toluene at room temperature (Scheme 4). The subsequent deprotection of the Bn group was also achieved with Na/liquid $NH_3$/*t*-BuOH at −78 °C to afford the NH pyrrole derivative **9**.

Three control experiments were conducted to reveal the mechanism of this reaction (Scheme 5): when the reaction was stopped right after the disappearance of the allene substrate **1a**, besides 4,5-dihydro-1*H*-pyrrole **4aa**, the enamine intermediate **7aa** was isolated in 25% yield, which indicates the enamine **7aa** is the intermediate for the reaction; furthermore, it was observed that the reaction of 4,5-dihydrofuran derivative **5a** under the same conditions also afforded **4aa** smoothly; finally, it should be noted that **1f** with an extra methyl group at the 2-position failed to afford any product.

Based on these results, a mechanism was proposed to explain the regio- and stereoselectivity of this transformation (Scheme 6). Condensation of allene **1** with an amine in the presence of Brønsted acid would form imine intermediate **7a**, which could isomerize to enmine **7b**. Oxidative addition of the organic halide with Pd(0), followed by carbopallation with **7b** would afford the $\eta^3$-allyl complex **B**. Finally, a nucleophilic attack by the nitrogen atom would provide **4** or **6** highly regioselectively. The stereoselectivity may be explained by the 1,2-chiral induction. On the other hand, allene **1** may also afford **A** in the presence of Pd(0) and the organic halide first. The intermediate **A** would react with amine to afford the intermediate **B** in the presence of acid, finally providing the 4,5-dihydro-1*H*-pyrrole **4** or **6**.

In conclusion, we have developed a highly efficient Pd(0)-catalyzed one-pot protocol for the synthesis of 4,5-dihydro-1*H*-pyrroles from 2-(2′,3′-allenyl)acetylacetates, organic halides, and amines. The utilization




**Scheme 6.** Proposed catalytic cycle.

of 20 mol% of $TsOH{\cdot}H_2O$ is required for the formation of the imine and enamine intermediate between the carbonyl of the ketone moiety and the amine. Because of the introduction of the three-component reaction concept, this cyclization could provide multiple points for the diversity and affords only single diastereoisomers with α-(1′-alkyl-2′,3′-allenyl)-β-keto esters **1c** and **1d**. Further studies in this area including the enatioselective cyclization are currently being carried out in our laboratory.

## Experimental Section

### Typical Procedure

In a flame-dried Schlenk tube, a mixture of ethyl 2-(2′,3′-allenyl)acetylacetate **1a** (42 mg, 0.23 mmol), 4-methoxyaniline **2a** (94 mg, 0.76 mmol), $Pd(PPh_3)_4$ (14 mg, 0.0125 mmol), phenyl iodide **3a** (107 mg, 0.52 mmol), and *p*-$TsOH{\cdot}H_2O$ (11 mg, 0.06 mmol) in 2 mL of toluene was stirred under argon at 90 °C for 10 h. After the reaction was complete as monitored by TLC (petroleum ether:ethyl acetate = 15:1), the reaction mixture was evaporated and purified *via* flash chromatography on silica gel (eluent: petroleum ether:ethyl acetate = 20:1) to afford **4aa** as a liquid; yield: 60 mg (72%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.42–7.20 (m, 5H), 6.98 (d, $J$ = 8.7 Hz, 2H), 6.82 (d, $J$ = 9.0 Hz, 2H), 5.40 (s, 1H), 5.19 (s, 1H), 4.89 (dd, $J$ = 11.4, 9.0 Hz, 1H), 4.22–4.08 (m, 2H), 3.77 (s , 3H), 3.24 (t, $J$ = 13.8 Hz, 1H), 2.73 (dd, $J$ = 14.7, 8.7 Hz, 1H), 2.16 (s, 3H), 1.25 (d, $J$ = 7.5 Hz, 3H); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta$ = 167.2, 159.6, 157.5, 147.8, 139.1, 134.6, 128.3, 127.7, 127.4, 126.7, 115.0, 114.2, 98.5, 69.6, 58.7, 55.3, 35.8, 14.6, 14.0; MS (EI): *m/z* (%) = 363 ($M^+$, 22.95), 290 (100); IR (neat): ν = 3055, 2978, 2933, 1677, 1598, 1511, 1391, 1290, 1232, 1085, 1033 cm$^{-1}$; HR-MS (EI): *m/z* = 363.1827, calcd. for $C_{23}H_{25}NO_3$ ($M^+$) 363.1834.

## Acknowledgements

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