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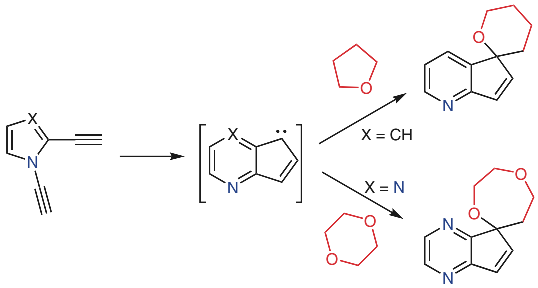
Spirocyclic Products via Carbene Intermediates from Thermolysis of 1,2-Dialkynylpyrrole and 1,2-Diethynylimidazole

Ashley L. Jewett[a]
Joshua A. Bondoc[b]
Bradford L. Gilbreath[a]
Brandon J. Reinus[c]
Sean M. Kerwin*[b]

[a] Division of Chemical Biology and Medicinal Chemistry, College of Pharmacy, University of Texas at Austin, Austin, TX 78712, USA
ajewe@utexas.edu
[b] Department of Chemistry and Biochemistry, Texas State University, San Marcos, TX 78666, USA
smk89@txstate.edu
[c] Department of Chemistry, University of Texas at Austin, Austin, TX 78712, USA
reinus@utexas.edu



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Abstract The thermal rearrangements of 1,2-dialkynylimidazoles have been shown to lead to trapping products of cyclopenta[*b*]pyrazine carbene intermediates. Here we show that a similar rearrangement also occurs in the case of 1,2-diethynyl-1*H*-pyrrole, and that trapping the intermediate cyclopenta[*b*]pyridine carbene with solvent THF affords an ylide that undergoes a Stevens rearrangement to a spirocyclic product. An analogous rearrangement and trapping is observed for thermolysis of 1,2-dialkynylimidazoles in THF or 1,4-dioxane.

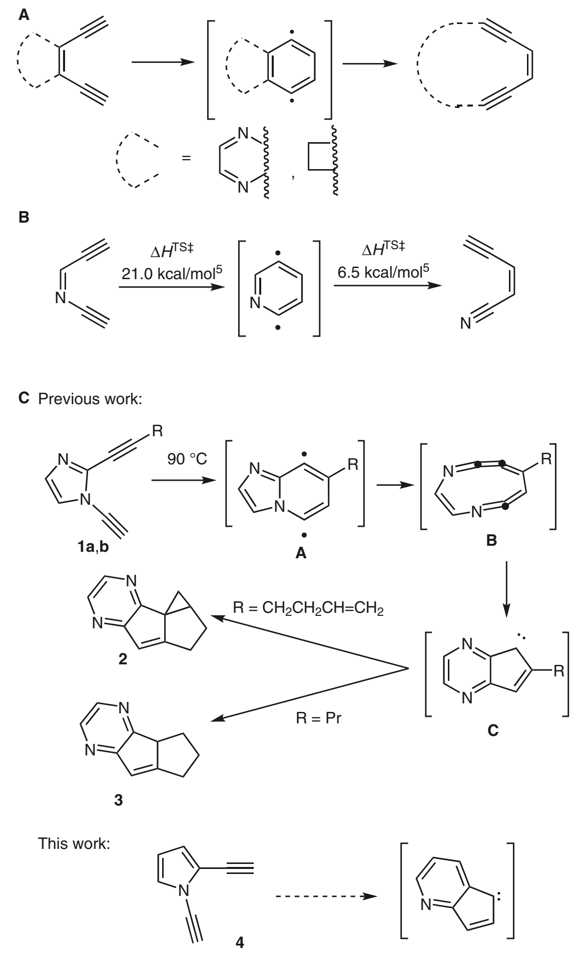
Key words azoles, carbenes, cycloaromatization, ylides, spiro compounds

The cycloaromatization of enediynes and related systems with trapping of the intermediate diradicals is well known.[1] In certain cases, a facile collapse (retro-Bergman cyclization) of diradical intermediates formed by cycloaromatization has been noted, for example in the case of dialkynylpyrazines and dialkynylcyclobutenes (Scheme 1A).[2] Even more extreme are the heteroatom-substituted 3-azahex-3-ene-1,5-diynes, which undergo cycloaromatization under very mild conditions[3] (below room temperature in some cases)[4] to form didehydropyridine diradicals that collapse with a barrier of ~6.5 kcal/mol[5] to the much more stable 1-azahex-3-ene-1,5-diynes (Scheme 1B). In the case of these azaenediynes, the diradical singlet state (S) is stabilized relative to the triplet (T), and the large difference in energy of these states (S–T gap = 11.6 kcal/mol) relative to the barrier to collapse further disfavors diradical trapping by hydrogen-atom abstraction. There is no evidence that the intermediate 2,5-didehydropyridine diradicals live long enough or are reactive enough to undergo hydrogen-atom abstraction trapping reactions.[6,7]

Efforts to mitigate this effect of the facile collapse of the diradicals derived from 3-aza-3-ene-1,5-diyne cycloaromatization led to the design of the 1,2-dialkynylimidazoles **1a** (R = $CH_2CH_2CH{=}CH_2$) and **1b** (R = Pr) (Scheme 1C). It was reasoned that the collapse of the cycloaromatization-derived diradical **A** would be disfavored due to the presumed instability of the resultant cyclic cumulene **B**. In fact, mild thermolysis (~90 °C) of such 1,2-dialkynylimidazoles affords good yields of trapping products derived from the carbene **C**.[8,9] Subsequent density functional theory (DFT) calculations demonstrated the carbene **C** is derived from the cyclic cumulene **B**, which is formed by a retro-aza-Bergman collapse of diradical **A**.[10] Surprisingly, the barrier for this collapse of **A** to **B** (~0.8 to 1.3 kcal/mol for substituted analogues)[10] is even lower than that for the collapse of parent 3-aza-3-ene-1,5-diyne-derived diradical.

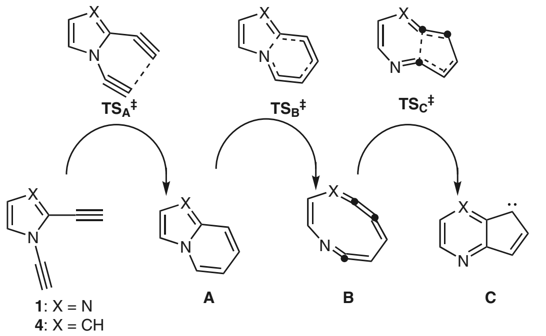
The rearrangement of **1a** or **1b** to **C** (Scheme 1C) provides a potential strategy to access carbenes under mild thermolysis conditions, but the generality of this rearrangement has not been explored. Here we report a DFT study of the rearrangement of 1,2-diethynyl-1*H*-pyrrole (**4**) and the synthesis and thermolysis of this 'azaenediyne', demonstrating the generality of this retro-aza-Bergman approach to reactive heterocyclic carbenes.

We carried out DFT calculations for the thermal rearrangement of 1,2-diethynyl-1*H*-imidazole (**1**) and 1,2-diethynyl-1*H*-pyrrole (**4**) by using the B3LYP functional[11] and a 6-31G(d,p) basis set (Table 1). For the singlet-state biradicals **A** and the transition states leading to these species ($\mathbf{TS_A}$ and $\mathbf{TS_B}$, respectively), the calculations employed the bro-



Scheme 1 (A) Retro-Bergman collapse of enediyne-derived diradicals and (B) azaenediyne-derived didehydropyridine, with computational barriers as reported in reference 5. (C) In the case of 1,2-dialkynylimidazoles, the diradicals **A** undergo collapse followed by cyclization to carbenes that efficiently undergo intramolecular trapping. Here we explore the potential of diethynylpyrrole **4** to serve as precursor to a cyclopenta[*b*]pyridine carbene.

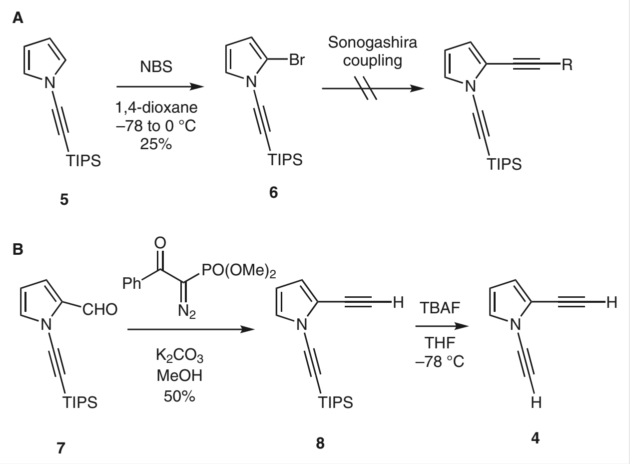
Table 1 DFT Energies for Rearrangements to Carbenes



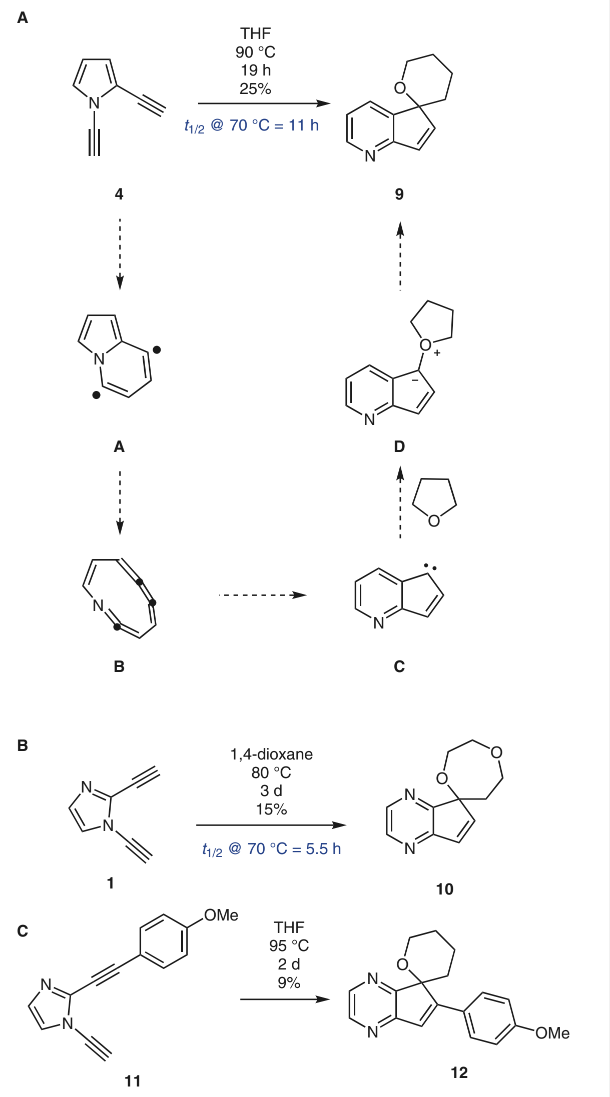
Molecule	B3LYP Relative Energy (kcal/mol)	Notes
1	0.0	
$\mathrm{TS_A}$ (1)‡	25.9	
A (1)	4.9	S–T gap = 10.5 kcal/mol
$\mathrm{TS_B}$ (1)‡	5.9	+1.0 relative to **A**
B (1)	−12.5	
$\mathrm{TS_C}$ (1)‡	3.8	+16.3 relative to **B**
C (1)	0.6	
4	0.0	
$\mathrm{TS_A}$ (4)‡	26.6	
A (4)	8.1	S–T gap = 10.5 kcal/mol
$\mathrm{TS_B}$ (4)‡	9.9	+1.8 kcal/mol relative to **A**
B (4)	−13.8	
$\mathrm{TS_C}$ (4)‡	4.5	+18.3 kcal/mol relative to **B**
C (4)	−8.1	

ken-spin unrestricted formalism, with sum correction for the effect of triplet-state contamination.[12] The calculated barriers for the initial aza-Bergman cyclization (**$\mathbf{TS_A}$**) of **1** and **4** are within 1 kcal/mol of each other, and the barriers for collapse of the diradicals **A** are small in both systems. In addition, the S–T gaps for these diradicals are identically high, indicating that they are unlikely to undergo hydrogen-atom-abstraction trapping before collapse. The cyclic cumulenes **B** are surprisingly stable in both systems, yet in both cases, the cyclization of **B** to carbene **C** (**$\mathbf{TS_C}$**) is energetically accessible. In fact, the two overall carbene-generating pathways are remarkably similar in their relative energies, with the exception of the carbene **C** derived from the diethynylpyrrole **4**, which is thermodynamically favored compared with the thermodynamically neutral rearrangement of **1** to carbene **C**.

Based on these promising computational results, we set out to synthesize 1,2-diethynyl-1*H*-pyrrole (**4**) to study its thermolysis (Scheme 2). Our first attempt to prepare **4** began with bromination of the previously reported *N*-alkynylpyrrole **5**[13] (Scheme 2A). Unfortunately, all attempts to carry out Sonogashira couplings of the 2-bromopyrrole **6** met with failure, possibly due to reaction at the *N*-alkynyl group.[14] In an alternative approach, the previously reported *N*-alkynyl-2-formylpyrrole **7**[13] was prepared in high yield and then treated with Bestmann–Ohira reagent to afford the silyl-protected 1,2-diethynylpyrrole **8**[15] (Scheme 2B). Although **8** could be easily deprotected, the volatile nature of **4** complicated its isolation. For NMR characterization, **4** was purified of tetraalkylammonium byproducts by chromatography and elution with THF-d_8.[16]



Scheme 2 Preparation of 1,2-diethynyl-1*H*-pyrrole (**4**)



Scheme 3 (A) Thermolysis of the 1,2-dialkynylpyrrole **5** in THF affords spirocycle **9** by a Stevens rearrangement of the ylide formed by trapping carbene **C**. (B) A similar process leads to the spirocycle **10** from thermolysis of **1** in 1,4-dioxane.

Mild thermolysis of solutions of **4** in THF afforded somewhat complex mixtures of products [see the Supporting Information (SI)], from which the spirocycle **9**[17] could be isolated (Scheme 3A).[18] The structure of **9** was established by COSY and NOESY NMR analyses (see SI). We propose that **9** is derived from the ylide **D**, formed by interception of the carbene **C** by THF (Scheme 3A). A Stevens rearrangement[19] of ylide **D** under the reaction conditions affords the spirocycle **9**.[20] The conversion of **1** into **9** at 70 °C was monitored by GC/MS; the reaction followed first-order kinetics (see SI) with a half-life of 11 hours.

Further support for the proposed carbene trapping and Stevens rearrangement of carbene **C** derived from **4** comes from a similar thermolysis of 1,2-diethynyl-1*H*-imidazole (**1**) in 1,4-dioxane, which afforded the spirocycle **10** (Scheme 3B).[18,20] Interestingly, this reaction is faster than the conversion of **4** into **9**, with a half-life of only 5.5 hours at 70 °C. Although this might reflect the lower initial aza-Bergman barrier **TS**$_{\mathbf{A}}$ for **1** (25.9 kcal/mol) relative to **4** (26.6 kcal/mol) (Table 1), it is not clear if this represents the rate-limiting step in the overall transformation. Indeed, an Arrhenius plot of the thermolysis of 1,2-diethynyl-1*H*-pyrrole (**4**) in THF at temperatures between 50 and 90 °C gives an activation energy (E_a) of 34.4 kcal/mol (see SI), which is significantly higher that the barrier calculated for aza-Bergman cyclization (26.6 kcal/mol). This might indicate that steps following the initial aza-Bergman cyclization contribute to the observed rate, but this will require further investigation, as the mechanism for the Stevens rearrangement in this case is not clear.

To further establish the generality of this approach, we carried out the thermolysis of the previously reported[10] substituted 1,2-dialkynylimidazole **11** in THF, and we isolated the spirocycle **12** in low yield.[18,21] This indicates that carbenes derived from 1,2-dialkynylimidazoles react similarly to those derived from 1,2-dialkynylpyrroles in the presence of THF, leading to ylide formation and Stevens rearrangement to spiropyrans, and that ylide formation followed by Stevens rearrangement occurs for substituted 1,2-dialkynylimidazoles in addition to the parent 1,2-diethynyl-1*H*-imidazole (**1**).

Although the yields for these spirocycle-forming reactions are low, they permit access to previously unknown 6,9-dioxaspiro[4,6]undecane-containing compounds and they represent a single-step approach to 6-oxaspiro[4.5]decane-containing compounds, which have previously only been prepared by multistep methods.[22] The optimization of the cascade aza-Bergman cyclization–diradical collapse–carbene formation–ylide trapping–Stevens rearrangement process described here might further improve the synthetic utility of this method. Currently, these efforts are focused on improving the ylide trapping–Stevens rearrangement components, as our previous work has demonstrated the efficiency of carbene generation from 1,2-dialkynylimidazoles and trapping by intermolecular cyclopropanation and intramolecular C–H insertion reactions.

In conclusion, we have demonstrated that the remarkable thermal rearrangements of 1,2-dialkynylimidazoles to carbene intermediates might be a general reaction of 1,*x*-dialkynylazoles by showing that 1,2-diethynyl-1*H*-pyrrole also undergoes this rearrangement. No evidence for trapping by hydrogen-atom abstraction of diradical intermediates derived from aza-Bergman cyclization is found in either the 1,2-dialkynylimidazole or 1,2-diethynylpyrrole cases, in accord with the computational predictions of a facile collapse of these diradicals having large S–T gaps. The carbenes that form from the products of diradical collapse can participate in a variety of reactions. Here, we show that these carbenes can form ylides that undergo a subsequent Stevens rearrangement to afford spirocyclic products. This represents a novel process to rapidly access complex spirocyclic heterocycles. Further explorations of the thermal rearrangements of related 1,*x*-dialkynylazoles are currently underway.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0041-1737937.

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(15) **2-Ethynyl-1-[(triisopropylsilyl)ethynyl]-1*H*-pyrrole (8)**
Oven-dried K_2CO_3 (524 mg, 3.8 mmol), pyrrole **7** (513 mg, 1.9 mmol), and 60–70% pure dimethyl (1-diazo-2-oxo-2-phenylethyl)phosphonate (1.11g 2.6–3.0 mmol) were added to MeOH (10 mL, 0.2 M) dried over MS, and the mixture was stirred at rt overnight. H_2O (10 mL) was added and the mixture was extracted by $CHCl_3$ (6 × 10 mL). The organics were dried ($NaSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 100% hexanes) to give a yellow oil; yield: 256 mg (50%).
^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.87 (dd, *J* = 3.0, 1.5 Hz, 1 H), 6.45 (dd, *J* = 3.7, 1.5 Hz, 1 H), 6.10 (dd, *J* = 3.7, 3.0 Hz, 1 H), 3.33 (s, 1 H), 1.12 (s, 21 H). ^{13}C{^{1}H} NMR (100 MHz, THF-*d*$_8$): δ = 127.0, 120.2, 117.2, 111.1, 95.8, 84.4, 74.9, 68.7, 19.2, 12.4. HRMS (CI): *m/z* [M + H]$^+$ calcd for $C_{17}H_{26}NSi$: 272.1835; found: 272.1830.

(16) **1,2-Diethynyl-1H-pyrrole (4)**
CAUTION: All steps should be performed in a well-ventilated environment: inhalation of **4** has been found to induce severe headaches, and should be avoided.
Deprotection of **8** (46 mg, 0.17 mmol) with TBAF (0.2 mL, 0.20 mmol, 1 M) in THF (0.9 mL, 0.2 M) at –78 °C for 10 min afforded near-complete conversion into **4** (TLC). Due to the volatility of the product, the entire mixture, was subjected to flash chromatography (silica gel, anhyd THF). Fractions were collected on ice and then analyzed for purity (TLC) and subsequently used in the thermolysis experiments. For spectral analysis, the deprotection and purification were performed with THF-d$_8$.
^{1}H NMR (400 MHz, THF-d$_8$): δ = 6.98 (dd, J = 3.0, 1.5 Hz, 1 H), 6.41 (dd, J = 3.8, 1.5 Hz, 1 H), 6.12 (dd,J = 3.7, 3.0 Hz, 1 H), 4.43 (s, 1 H), 3.90 (s, 1 H). ^{13}C{^{1}H} NMR (100 MHz, THF-d$_8$): δ = 127.2, 119.9, 117.3, 111.2, 84.3, 74.8, 74.6, 59.7. HRMS (CI): m/z [M$^+$] calcd for C_8H_5N: 115.0422; found: 115.0422.

(17) **3′,4′,5′,6′-Tetrahydrospiro[cyclopenta[*b*]pyridine-5,2′-pyran] (9)**
Pyrrole **4** (estimated 0.17 mmol after deprotection of **8**) was subjected to thermolysis in THF at 90 °C for 19 h in a sealed tube. The solvent was then evaporated and the crude mixture was subjected purified by flash chromatography (silica gel, 25% EtOAc–hexanes) to give a yellow oil; yield: 8 mg (25%).
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.39 (dd, *J* = 5.2, 1.5 Hz, 1 H), 7.71 (ddd, *J* = 7.4, 1.5, 0.7 Hz, 1 H), 7.21 (d, *J* = 6.0 Hz, 1 H), 7.09 (dd, *J* = 7.5, 5.1 Hz, 1 H), 6.88 (dd, *J* = 6.0, 0.7 Hz, 1 H), 4.05–3.99 (m, 1 H), 3.88–3.81 (m, 1 H), 2.09–1.95 (m, 2 H), 1.89–1.72 (m, 3 H), 1.61–1.54 (m, 1 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 162.2,

149.2, 142.0, 141.8, 133.7, 129.6, 120.7, 84.0, 65.8, 32.3, 25.8, 21.8. HRMS (CI): *m/z* [M$^+$] calcd for $C_{12}H_{13}NO$: 187.0997; found: 187.0992.

(18) In all cases, thermolysis reactions in 1,4-dioxane and THF afforded complex mixtures of highly colored polar byproducts in addition to the spirocycles. Thermolyses carried out for shorter reaction times or at lower temperatures also afforded the starting material, but in these cases, the yield of the spirocycle corrected for the recovered starting material was not significantly higher than for reactions that ran to completion.

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(20) **Spiro[cyclopenta[*b*]pyrazine-5,5′-[1,4]dioxepane] (10)**
Thermolysis of **1** in 1,4-dioxane afforded a red oil; yield: 20 mg (15%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 2.9 Hz, 1 H), 8.20 (d, *J* = 3.1 Hz, 1 H), 6.93 (d, *J* = 6.3 Hz, 1 H), 6.85 (d, *J* = 6.3 Hz, 1 H), 4.45 (ddd, *J* = 13.4, 7.3, 1.0 Hz, 1 H), 4.24 (ddd, *J* = 12.5, 7.0, 1.3 Hz, 1 H), 3.98–3.90 (m, 3 H), 3.88–3.79 (m, 1 H), 2.64 (ddd, *J* = 16.2, 8.8, 1.5 Hz, 1 H), 2.12 (ddd, *J* = 16.2, 7.0, 1.3 Hz, 1 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 162.7, 156.4, 143.4, 139.7, 83.6, 72.4, 69.9, 66.9, 36.8. HRMS (CI): *m/z* [M + H]$^+$ calcd for $C_{11}H_{13}N_2O_2$: 205.09715; found: 205.09698.

(21) **6-(4-Methoxyphenyl)-3′,4′,5′,6′-tetrahydrospiro[cyclopenta[*b*]pyridine-5,2′-pyran] (12)**
Thermolysis of **11** in THF gave a red oil; yield: 9 mg (9%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.28 (d, *J* = 3.0 Hz, 1 H), 8.12 (d, *J* = 3.0 Hz, 1 H), 7.94 (d, *J* = 9.0 Hz, 2 H), 7.02 (s, 1 H), 6.97 (d, *J* = 9.0 Hz, 2 H), 4.83–4.76 (m, 1 H), 4.06–4.02 (m, 1 H), 3.86 (s, 3 H), 2.68–2.57 (m, 1 H), 2.26–2.18 (m, 1 H), 1.95–1.81 (m, 3 H), 1.44–1.40 (m, 1 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 163.6, 160.5, 156.6, 156.4, 142.9, 137.5, 129.4, 126.0, 124.4, 114.1, 82.0, 64.9, 55.5, 30.2, 25.9, 19.0. MS (ESI, +): *m/z* (%) = 295 (48) [M + H]$^+$, 223 (30), 199 (12).

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