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A three-component reaction between benzynes, the enolate of acetaldehyde, and unsaturated esters and dihydroisoquinolines

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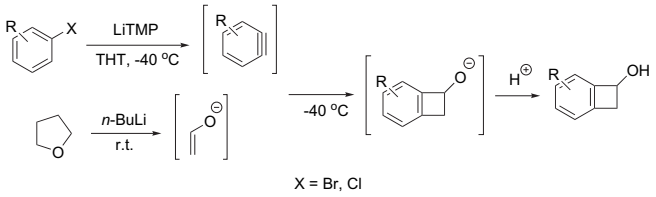
ABSTRACT

A three-component one-pot coupling between benzynes, the enolate of acetaldehyde and various electrophiles led to bicyclic and tetracyclic ring systems.

1. Introduction

The reactions of benzocyclobutenes with unsaturated carbonyl compounds have been widely studied.[1,2] A subset of these reactions, the reactions of benzocyclobutenols or their ethers, is particularly valuable because of the low temperature opening of the four-membered ring.[3] Notable studies include those of Danishefsky,[4] Inomata,[5] and Charlton.[6] In most cases the benzocyclobutenols are prepared and then reacted with dienophiles in a separate step. However, some preparations of benzocyclobutenols could permit in situ trapping with dienophiles. Benzocyclobutenols are made from substituted benzaldehydes via photoenolization,[7] from *ortho*-acyl benzylstannanes,[8] or from the reaction between benzynes and enolate derivatives. Both Fleming and Mah[9] and Olofson et al.[10] have reacted benzynes with the enolate of acetaldehyde[11] to produce benzocyclobutenoxides that open to produce *ortho*-quinodimethanes and undergo further reactions. The Durst group reported the generation of benzocyclobutenols in good yields using benzynes and ketone enolates.[11]

At the beginning of our study, we evaluated the feasibility of reacting the in situ generated enolate of acetaldehyde with benzynes to give benzocyclobutenols followed by an in situ trapping of the resulting *ortho*-quinodimethane with various dienophiles, a three-component reaction. We initially produced benzyne through the lithium tetramethylpiperidide-mediated elimination of halobenzenes. This method has been demonstrated by the Durst group to be a reliable way to generate benzynes at low temperatures (Scheme 1).



Scheme 1. One-pot benzocyclobutenol synthesis.

Formation of the enolate of acetaldehyde and the benzyne from chlorobenzene led to the production of benzocyclobutenol in 37% yield. When 2- or 3-haloanisoles were used as substrates, the addition of the acetaldehyde enolate to the benzynes was regioselective to give 6-methoxybenzocyclobutenol. In the benzyne formation step, the halogen group either *ortho* or *meta* to the methoxyl group afforded the same benzyne intermediate. In the enolate addition step, the enolate was directed by the methoxyl group to attack entirely from the *meta*-position. The yields for most of the reactions were only modest (37–50%). Although it has been reported that LiTMP has very low reactivity toward benzynes, we isolated a fair amount (22%–35%) of adducts containing the tetramethylpiperidine subunit (Fig. 1).

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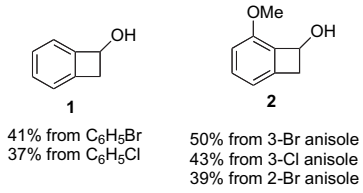
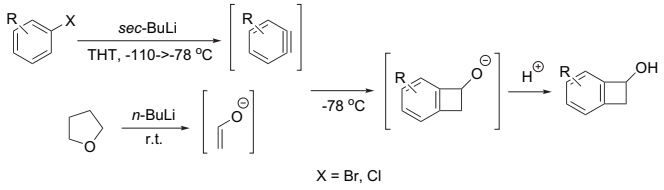


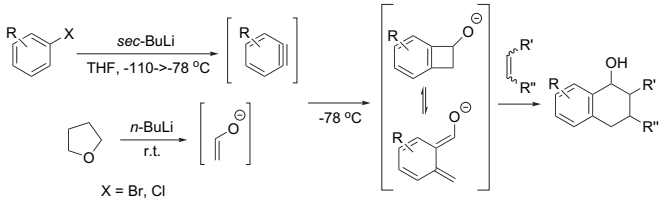
Figure 1. Benzocyclobutenols.

The Iwao group reported a new method to generate *ortho*-chlorophenyl lithium through the direct lithiation of chlorobenzenes.[12] In their approach, the chlorine atom was used as an *ortho* directing group for the *ortho* lithiation at −105 °C. When 3-chloroanisole was lithiated at −78 °C and trapped with a Michael acceptor, only a biphenyl derived from aryl lithium attack on the benzyne was obtained. The low temperature is essential to prevent premature benzyne formation. This observation was used to our advantage.

A number of substrates were subjected to this new protocol to test its feasibility. As shown in Scheme 2, acetaldehyde enolate was first prepared and then halobenzene was lithiated by *sec*-BuLi at −110 °C, followed by warming to −78 °C to generate benzyne. The reaction between these two species subsequently afforded benzocyclobutenols. This new strategy permitted the synthesis of benzocyclobutenols with higher yields than those from the LiTMP procedure. The results are illustrated in Scheme 3.

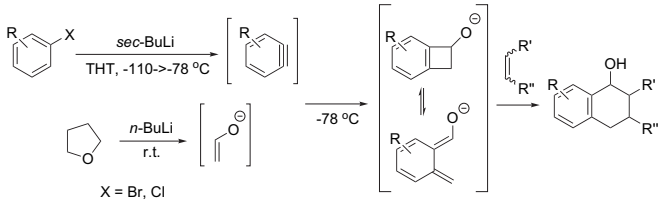


Scheme 2. Modified one-pot benzocyclobutenol synthesis.



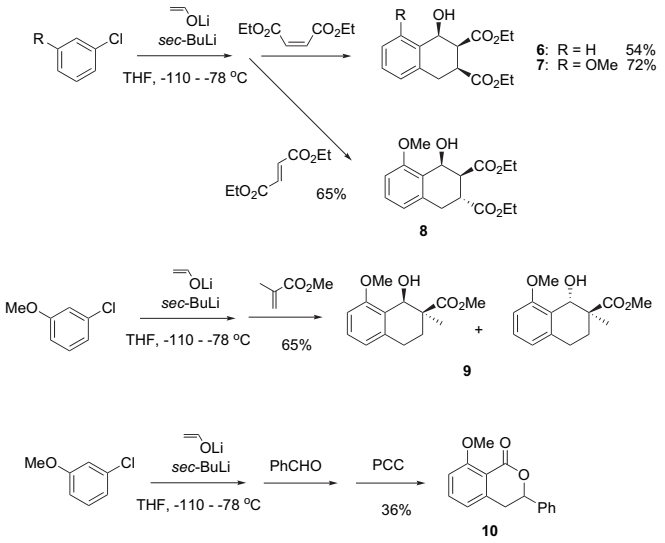
Scheme 3. In situ trapping of benzocyclobutenoxide intermediates.

Benzocyclobutenoxides were generated as precursors of the benzocyclobutenols. As benzocyclobutenoxides were in equilibrium with the corresponding *o*-quinodimethane intermediates, it is natural to explore the possibility of trapping them with dienophiles. Although the Olofson et al.[10] have studied the reactions between *o*-quinodimethanes and various dienophiles, they utilized pre-formed benzocyclobutenols. A reaction by way of this one-pot trapping (Scheme 4) has never been reported to the best of our knowledge.



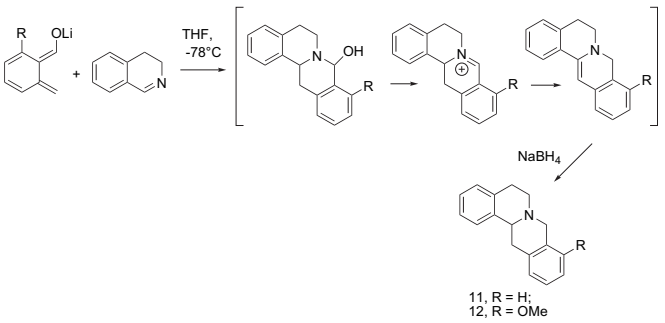
Scheme 4. In situ trapping of benzocyclobutenoxide intermediates.

When the new benzyne generation protocol was applied to the three-component reaction, better yields were obtained (Scheme 5). In the three-component reaction, diethyl maleate and diethyl fumarate were also used as dienophiles. In addition to diethyl maleate and diethyl fumarate, methyl methacrylate has also been used as a dienophile. The corresponding adducts were isolated. The adduct from methyl methacrylate was a 1:1 mixture of diastereomers.



Scheme 5. In situ trapping of benzocyclobutenoxides.

Berbines are biologically active alkaloids that possess a tetrahydroisoquinoline core.[13,14] Many studies have been directed toward this class of compounds owing to their synthetic and biological significance.[15,16] We envisioned that if cyclic imines could be used to trap the *o*-quinodimethane intermediates, the core structure of berbine derivatives could be constructed in one operation. The synthesis was initiated with 3,4-dihydroisoquinoline. Benzocyclobutenol was treated with *n*-BuLi at −78 °C, and the generated *o*-quinodimethide intermediate was trapped with 3,4-dihydroisoquinoline. After warming to 0 °C, a tetracyclic enamine was isolated in 40% yield (Scheme 6). We believe that the expected Diels–Alder adduct was first generated, followed by a series of base-mediated isomerizations to afford the tetracyclic enamine.[17]



Scheme 6. Expedient two-step synthesis of berbine derivatives.

Since a cyclic imine was proven to be an effective dienophile for *o*-quinodimethanes, a one-pot strategy was attempted. When chlorobenzene was used as a starting material, the *o*-quinodimethide was generated and reacted with 3,4-dihydroisoquinoline. The same enamine product was isolated in 32% yield. Similarly, 3-chloroanisole could also be converted to the methoxy-

substituted tetracyclic enamine in 28% yield. Berbine and 1-methyoxyberbine were then synthesized through sodium borohydride reduction of the enamine.

2. Experimental

2.1. General

Unless stated otherwise, all reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) using 0.25 mm precoated silica gel F_{254} plates (Sigma–Aldrich). Column or flash chromatography was performed with the indicated solvents using silica gel (230–400 mesh) purchased from Dynamic Adsorbents, LLC. All melting points were obtained on a Laboratory Devices capillary melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker VXR-400 (400 MHz) spectrometer. Chemical shifts are reported relative to internal chloroform (^{1}H, 7.26 ppm; ^{13}C, 77.23 ppm). High resolution mass spectra were performed at the Iowa State University Mass Spectrometry Laboratory.

2.1.1. First generation benzocyclobutenol synthesis representative procedure. To a 50 mL flame dried flask was added 12 mL of dry THF. *n*-BuLi (0.8 mL, 2.0 mmol) was added and stirred at rt for 16 h. Chlorobenzene or bromobenzene (4.0 mmol) was added, which was followed by dropwise addition of LiTMP (5.0 mmol) prepared in a separate flask at −40 °C. The reaction mixture was stirred at the same temperature for 5 h before it was quenched by slow addition of saturated NH_4Cl and allowed to warm to rt with stirring. The reaction mixture was extracted with ethyl acetate (30 mL×3) and the extracts were dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography to give the benzocyclobutenol compound.

Benzocyclobutenol **1**[18] was prepared by the first generation one-pot synthesis as a white solid. Mp: 62–63 °C.

Benzocyclobutenol **2**[19] was prepared by the first generation one-pot synthesis as a white solid. Mp: 67–68 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (t, J=7.4 Hz, 1H), 6.71 (d, J=7.4 Hz, 1H), 6.69 (d, J=8.7 Hz, 1H), 5.25 (s, 1H), 3.910 (s, 3H), 3.53 (dd, J=4.5, 14.5 Hz, 1H), 3.33 (d, J=7.4 Hz, 1H), 2.94 (d, J=14.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3, 144.2, 131.3, 131.1, 115.8, 113.9, 70.6, 56.9, 42.4; MS (*m*/*z*) 150, 149, 134, 132, 122, 119, 117, 91; HRMS calculated for $C_9H_{10}O_2$: 150.06808, found: 150.06832.

2.1.2. Second generation benzocyclobutenol synthesis representative procedure. To a 50 mL flame dried flask was added 12 mL of dry THF. *n*-BuLi (0.8 mL, 2.0 mmol) was added and stirred at rt for 16 h. Chlorobenzene (4.0 mmol) was added, which was followed by dropwise addition of 1.7 M *sec*-BuLi (2.47 mL, 4.2 mmol) at −110 °C. The reaction mixture was stirred at the same temperature for 1 h then slowly warmed to −78 °C. The reaction mixture was stirred for another 5 h before it was quenched by slow addition of saturated NH_4Cl and allowed to warm to rt with stirring. The reaction mixture was extracted with ethyl acetate (30 mL×3) and the extracts were dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography to give the benzocyclobutenol compound.

Benzocyclobutenol **3** was prepared by the second generation one-pot synthesis as a white solid. Mp: 95–97 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.75 (d, J=7.6 Hz, 1H), 6.57 (d, J=7.7 Hz, 1H), 5.17 (br s, 1H), 3.99 (s, 3H), 3.75 (s, 3H), 3.37–3.47 (m, 2H), 2.84 (dd, J=0.75, 14.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.5, 144.4, 134.8, 130.8, 115.4, 114.2, 70.1, 57.9, 56.5, 41.5; MS (*m*/*z*) 181, 180, 179, 165, 150, 122, 91; HRMS calculated for $C_{10}H_{12}O_3$: 180.07864, found: 180.07889.

Benzocyclobutenol **4** was prepared by the second generation one-pot synthesis as a white solid. Mp: 74–76 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.32 (s, 1H), 6.24 (s, 1H), 5.25 (d, J=2.7 Hz, 1H), 3.93 (s, 3H), 3.75 (s, 3H), 3.50 (dd, J=3.3, 10.9 Hz, 1H), 2.916 (d, J=10.9 Hz, 1H), 2.543 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.1, 155.8, 144.9, 123.3, 102.1, 100.4, 70.3, 57.3, 55.8, 42.4; MS (*m*/*z*) 181, 180, 179, 163, 162, 135, 120, 119, 91; HRMS calculated for $C_{10}H_{12}O_3$: 180.07864, found: 180.07890.

Benzocyclobutenol **5** was prepared by the second generation one-pot synthesis as a white solid. Mp: 81–83 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.69 (d, J=6.7 Hz, 1H), 6.63 (d, J=6.7 Hz, 1H), 5.28 (br s, 1H), 3.89 (s, 3H), 3.78 (s, 3H), 3.66 (dd, J=3.4, 10.4 Hz, 1H), 3.05 (dd, J=0.8, 10.4 Hz, 1H), 2.81 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.7, 148.5, 132.4, 126.7, 116.8, 115.2, 70.5, 57.1, 56.6, 41.9; MS (*m*/*z*) 181, 180, 165, 163, 150, 149, 134, 122, 91; HRMS calculated for $C_{10}H_{12}O_3$: 180.07864, found: 180.07889.

2.1.3. Three-component reaction via in situ trapping of benzocyclobutenoxide intermediates representative procedure. To a 50 mL flame dried flask was added 12 mL of dry THF. *n*-BuLi (0.8 mL, 2.0 mmol) was added and stirred at rt for 16 h. Chlorobenzene (4.0 mmol) was added, which was followed by dropwise addition of 1.7 M *sec*-BuLi (2.47 mL, 4.2 mmol) at −110 °C. The reaction mixture was stirred at the same temperature for 1 h then slowly warmed to −78 °C. The reaction mixture was stirred at the same temperature for another 5 h before it was quenched by slow addition of dienophiles (4.0 mmol) and allowed to warm to rt with stirring. The reaction mixture was extracted with ethyl acetate and the extracts were dried and concentrated. The crude product was purified by flash chromatography to give the three component adduct.

Benzocyclohexenol **6** was prepared by the three-component reaction as yellow oil.

(Major isomer) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.37 (m, 1H), 7.24–7.26 (m, 1H), 7.12–7.14 (m, 1H), 5.10 (d, J=2.7 Hz, 1H), 4.17–4.25 (m, 4H), 3.35 (ddd, J=5.6, 11.8, 17.4 Hz, 1H), 3.19 (dd, J=5.5, 16.8 Hz, 1H), 3.09 (dd, J=3.4, 11.7 Hz, 1H), 2.87 (dd, J=11.9, 16.7 Hz, 1H), 2.40 (br s 1H), 1.28–1.32 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 172.7, 136.1, 134.1, 129.8, 128.9, 128.9, 127.1, 68.4, 61.3, 61.1, 48.2, 37.2, 32.2, 14.4, 14.4; MS (*m*/*z*) 292, 291, 275, 274, 229, 227; HRMS calculated for $C_{16}H_{20}O_5$: 292.13107, found: 292.13107.

Benzocyclohexenol **7** was prepared by the three-component reaction as yellow oil.

(Major isomer) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (t, J=7.8 Hz, 1H), 6.77 (d, J=8.4 Hz, 1H), 6.75 (d, J=7.4 Hz, 1H), 5.43 (d, J=3.9 Hz, 1H), 4.18–4.28 (m, 4H), 3.88 (s, 1H), 3.29 (ddd, J=5.0, 12.2, 17.2 Hz, 1H), 3.15 (dd, J=5.0, 16.6 Hz, 1H), 2.99 (dd, J=4.0, 12.1 Hz, 1H), 2.82 (dd, J=12.7, 16.4 Hz, 1H), 1.28–1.33 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 172.2, 157.6, 135.4, 129.2, 125.1, 121.0, 108.2, 63.1, 61.0, 60.8, 55.6, 48.2, 37.0, 32.9, 14.3; MS (*m*/*z*) 322, 304, 259, 248, 231, 230, 203; HRMS calculated for $C_{17}H_{22}O_6$: 322.14164, found: 322.14202.

Benzocyclohexenol **8** was prepared by the three-component reaction as yellow oil.

(Major isomer) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (t, J=8.0 Hz, 1H), 6.75 (d, J=8.2 Hz, 1H), 6.74 (d, J=7.7 Hz, 1H), 5.42 (d, J=4.1 Hz, 1H), 4.18–4.27 (m, 4H), 3.87 (s, 1H), 3.28 (ddd, J=7.3, 12.4, 17.4 Hz, 1H), 3.14 (dd, J=5.1, 16.8 Hz, 1H), 2.99 (dd, J=4.1, 12.1 Hz, 1H), 2.81 (dd, J=12.6, 16.6 Hz, 1H), 2.50 (br s 1H), 1.28–1.32 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 172.2, 157.6, 135.4, 129.2, 125.1, 121.0, 108.2, 63.0, 61.0, 60.8, 55.5, 48.1, 36.9, 32.9, 14.3; MS (*m*/*z*) 322, 321, 305, 304, 303, 259, 258, 248, 247, 231, 230, 229; HRMS calculated for $C_{17}H_{22}O_6$: 322.14164, found: 322.14202.

Benzocyclohexenol **9** was prepared by the three-component reaction as yellow oil.

Isomer (*I*): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (t, J=7.8 Hz, 1H), 6.71 (d, J=7.9 Hz, 2H), 5.32 (s, 1H), 3.87 (s, 3H), 3.62 (s, 3H), 2.77–2.83 (m, 1H), 2.74–2.75 (m, 1H), 1.99–2.07 (m, 1H), 1.87–1.96 (m, 1H), 1.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.7, 158.1, 137.1, 128.3, 126.9, 121.6, 107.9, 66.2, 55.6, 52.0, 46.4, 27.6, 26.6, 21.3; MS (*m*/*z*) 250, 232, 191, 190, 175, 173, 172, 149, 132; HRMS calculated for $C_{14}H_{18}O_4$: 250.12051, found: 250.12087.

Isomer (*II*): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (t, J=7.9 Hz, 1H), 6.75 (d, J=7.7 Hz, 1H), 6.73 (d, J=8.0 Hz, 1H), 5.07 (s, 1H), 3.86 (s, 3H), 3.78 (s, 3H), 2.72–2.89 (m, 2H), 2.57 (br s, 1H), 2.25–2.36 (m, 1H), 1.86–1.92 (m, 1H), 1.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.4, 158.5, 136.9, 128.7, 124.8, 121.4, 107.9, 67.2, 55.5, 52.1, 46.1, 25.3, 23.6, 19.2; MS (*m*/*z*) 250, 249, 232, 191, 190, 188, 175, 174, 173, 172; HRMS calculated for $C_{14}H_{18}O_4$: 250.12051, found: 250.12087.

3,4-Dihydroisocoumarin **10** was prepared by the three-component reaction followed by PCC oxidation as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.50(m, 3H), 7.33–7.36 (m, 3H), 6.94 (d, J=8.6 Hz, 1H), 6.83 (d, J=7.4 Hz, 1H), 5.41 (dd, J=3.0, 11.9 Hz, 1H), 3.95 (s, 3H), 3.23 (dd, J=12.0, 16.1 Hz, 1H), 3.04 (dd, J=2.7, 16.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5, 161.5, 141.9, 138.7, 134.9, 128.8, 128.8, 126.5, 119.5, 114.0, 111.3, 79.3, 56.5, 40.0; MS (*m*/*z*) 255, 254, 236, 148, 146, 106, 105, 104, 91, 90; HRMS calculated for $C_{16}H_{14}O_3$: 254.09429, found: 254.09464.

Berbine **11** was prepared by the three-component reaction followed by $NaBH_4$ reduction as yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09–7.31 (m, 8H), 4.05 (d, J=14.9 Hz, 1H), 3.69–3.78 (m, 2H), 3.35 (dd, J=3.9, 16.4 Hz, 1H), 3.15–3.23 (m, 2H), 2.90–2.99 (m, 1H), 2.62–2.71 (m, 2H); MS (*m*/*z*) 235, 234, 130, 105, 104, 86, 84; HRMS calculated for $C_{17}H_{17}N$: 235.13610, found: 235.13648.

Berbine **12** was prepared by the three-component reaction followed by $NaBH_4$ reduction as yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12–7.30 (m, 5H), 6.79 (d, J=7.7 Hz, 1H), 6.70 (d, J=8.2 Hz, 1H), 4.21 (d, J=15.9 Hz, 1H), 3.84 (s, 1H), 3.68 (dd, J=3.3, 11.3 Hz, 1H), 4.48 (d, J=15.9 Hz, 1H), 3.36 (dd, J=3.3, 16.4 Hz, 1H), 3.17–3.25 (m, 2H), 2.91 (dd, J=11.4, 16.1 Hz, 1H), 2.64–2.80 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.1, 138.1, 136.2, 134.9, 129.1, 129.1, 127.0, 126.3, 126.2, 126.2, 125.8, 125.8, 123.6, 121.1, 121.1, 121.1, 107.3, 76.9, 59.5, 55.5, 54.0, 51.5, 37.0, 29.8; MS (*m*/*z*) 266, 265, 264, 234, 157, 136, 135, 134; HRMS calculated for $C_{18}H_{19}NO$: 265.14666, found: 265.14703.

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