# Synthesis of Bis (2, 6-dihydroxy-5-oxo-1, 3, 6-cycloheptatrienyl) methane from 2-Alkoxy-5-hydroxytropones and the Electrochemical Properties of Bis (3, 4, 7-trioxo-1, 5-cycloheptadienyl)- methane Derivatives

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# Synthesis of Bis(2, 6-dihydroxy-5-oxo-1, 3, 6-cycloheptatrienyl)-methane from 2-Alkoxy-5-hydroxytropones and the Electrochemical Properties of Bis(3, 4, 7-trioxo-1, 5-cycloheptadienyl)-methane Derivatives

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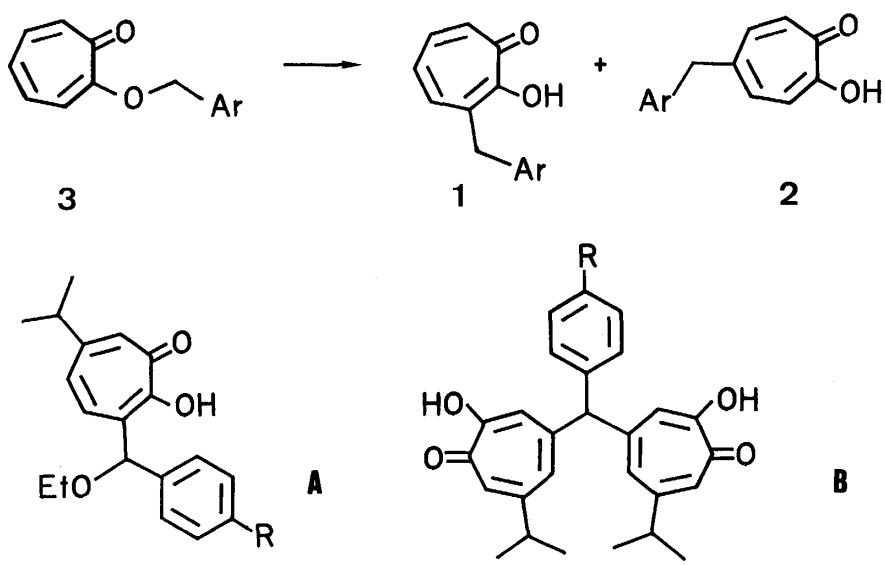
Bis(2-hydroxy-6-methoxy-5-oxo-1,3,6-cycloheptatrienyl)methane was prepared from 5-hydroxy-2-methoxytropone in a good yield. Its acid treatment gave a bis-demethylated derivative, bis(2,6-dihydroxy-5-oxo-1,3,6-cycloheptatrienyl)methane and a dehydration product, 2,10-dihydroxydicyclohepta[*b*, *e*]-pyran-3, 9-dione. By TTN- and CAN-oxidations, they yielded bis(3, 3-dimethoxy-4,7-dioxo-1,5-cycloheptadienyl)methane and bis(3,4,7-trioxo-1,5-cycloheptadienyl)methane acetal. This bisacetal was converted to 4-(3,3-dimethoxy-4,7-dioxo-1,5-cycloheptadienyl)methyl-*p*-tropoquinone by an acid treatment. The CV analysis of these *p*-tropoquinone derivatives disclosed a parallel substituent effect to that observed in the monofunctional *p*-tropoquinones.

## Introduction

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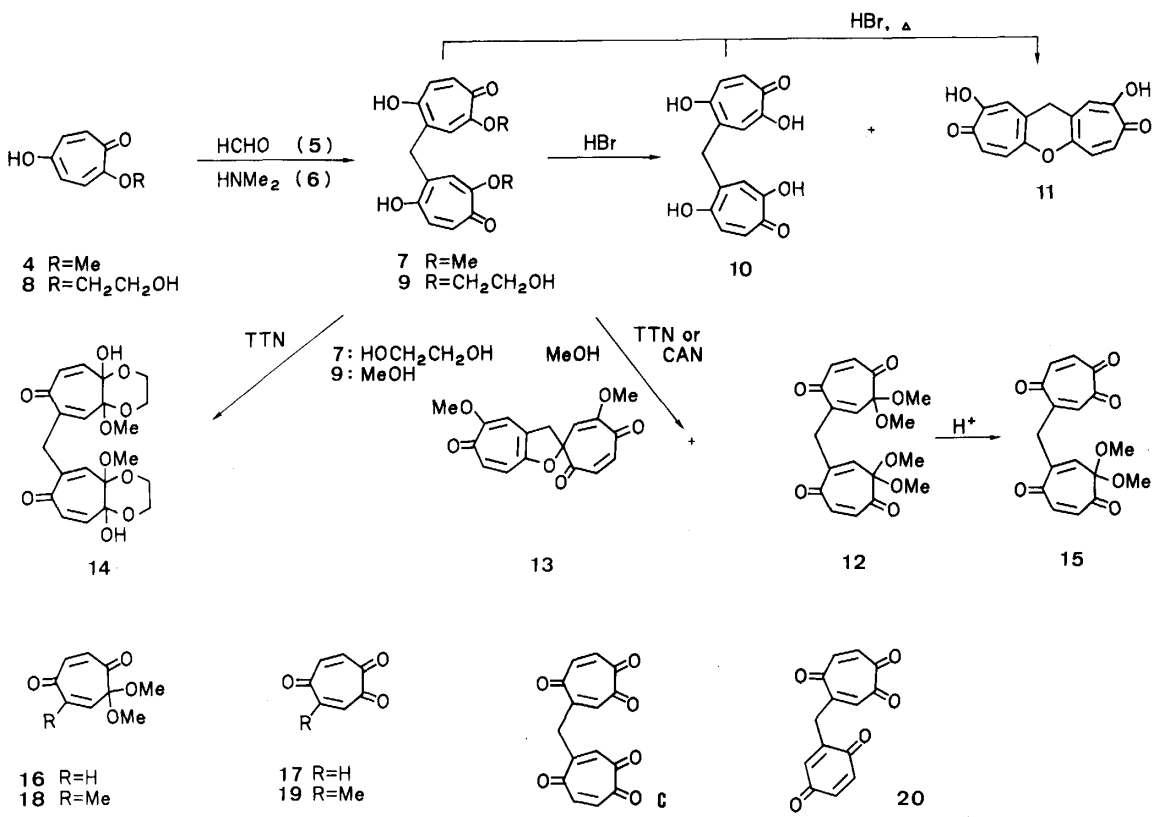
Recently, we have prepared several 3- and 5-arylmethyl tropolones (**1** and **2**)[1] by the thermal rearrangement of 2-benzyloxytropones (**3**) via a radical chain reaction. Meanwhile, we noticed a paper by Yamato et al[2]., who described a direct alkylation of tropolones with acetals to form mono- and ditropolonyl derivatives (**A** and **B**) which were subjects of their biological survey for anti-tumor drugs.[3] In this paper, we will report our own results on the similar C-C bond formation to obtain methylene-linked dimers of *p*-tropoquinone derivatives, together with their further transformations and cyclic voltammetric (CV) analysis of the electrochemical properties.

## Results and Discussion

**Preparation and Reactions of Bis(troponyl)methanes.** When 5-hydroxy-2-methoxytropone (**4**)[4] was heated at 60 °C with a mixture of formaldehyde (**5**), dimethylamine (**6**), and acetic acid[5] or with a mixture of **5** and aqueous potassium hydroxide,[6] yellow crystals (**7**) separated out from the mixture in 85 and 55%, respectively. Its $^1$H NMR spectrum showed only four singlets at $\delta$ = 4.41 (6H), 4.80 (2H), 8.16 (4H), and 8.76 (2H). The mass spectral determination of molecular weight, 316, deduced its structure to be a 2 : 1-condensate, bis(2-hydroxy-6-methoxy-5-oxo-1,3,6-cycloheptatrienyl)methane. Similarly, 5-hydroxy-2-(2-hydroxyethoxy)tropone (**8**) gave the corresponding ditropolonylmethane (**9**) in 27% yield. Structure of **9** was also clarified by NMR analysis.



Next, heating **7** in refluxing conc hydrobromic acid in acetic acid gave two hydrolyzed products (**10** and **11**) in 82 and 1% yields. The $^1$H NMR spectrum of each hydrolysate showed a methylene signal and a pair of *AB*-type signals in the aromatic region. From the mass spectra, **10** and **11** were concluded to be bis-demethyl derivatives of **7**, bis(2,6-dihydroxy-5-oxo-1,3,6-cycloheptatrienyl) methane and cyclized 2,10-dihydroxydicyclohepta[*b*, *e*]-pyran-3,9-dione. The latter **11** was also formed from either **7** or **10** by reflux in conc hydrobromic acid, in 40 and 72% yields, respectively. When **10** was oxidized in acetone with 2, 3-dichloro-5, 6-dicyano-*p*-benzoquinone (DDQ), the only product isolated in 29% yield was **11**, not bis(3,4,7-trioxo-1,5-cycloheptadienyl)methane (**C**). On the other hand, the thallium (III) nitrate (TTN)-oxidation[7] of **7** in anhydrous methanol gave two products (**12** and **13**) in 59 and 22% yields, respectively. The **12** was the desired bis(3,3-dimethoxy-4,7-dioxo-1,5-cycloheptadienyl)methane from the spectral evidence. That is, the $^1$H NMR spectrum showed four methoxyl groups on sp$^3$-carbons, a methylene signal, and six aromatic protons. The $^{13}$C NMR spectrum of **12** was consistent to its formulation. In the $^1$H NMR of **13**, two methoxyl groups on sp$^2$-carbons and a pair of *AB*-type signals appeared in the aliphatic region, and two pairs of *AB*-type signals and two singlets in the aromatic region.

Therefore, the structure of **13** was deduced to be a spiro derivative as shown in Scheme 1. These products (**12** and **13**) were also obtained from the cerium(IV) ammonium nitrate (CAN)-oxidation of **7** in methanol.[8] The TTN oxidation of **9** gave bis-diacetal (**14**) in 35% yield which was also obtained from the TTN-oxidation of **7** in 1, 2-ethanediol. Since its $^{13}$C NMR showed twelve lines, **14** must be a diastereomeric mixture.

Attempted hydrolysis of **12** with perchloric acid in aqueous acetone, however, led to 4-(3,3-dimethoxy-4,7-dioxo-1,5-cycloheptadienyl)methyl-*p*-tropoquinone (**15**), but no desired **C** at all. Probably, **C** is very reactive under the reaction conditions; this instability might be attributable to the low isolation yield of **15**.

**Cyclic Voltammetry Measurements.** The reduction peak potentials ($E_p$) of **12** and **15** were determined by cyclic voltammetry (CV). Table 1 summarizes the results together with several reference compounds, 7,7-dimethoxy-1,4-dioxo-2,5-cycloheptadiene (**16**),[7] *p*-tropoquinone (**17**),[9] and their methyl derivatives (**18**[4] and **19**[9]); the CV of **12** showed only two reduction peaks at −0.86 and −1.17 V as well as **16** and **18** did around −0.9 and −1.7 V.[10] The difference between the introduction potentials of the first and the second electrons and the difference between those of the third and the fourth electrons were both very small in **12**, resulting two peaks in the CV. Additionally, the second peak potential of **12** was more positive by ca. 0.5 to 0.7 V than those of **16** and **18**. On the other hand, three peaks ($E_p1$, $E_p2$, and $E_p3$) were observed in **15**; $E_p1$ and $E_p3$ (−0.27 and −1.23 V) were similar to the potentials of *p*-tropoquinone, **17** (−0.28 and −1.24 V), and $E_p2$ (−0.92 V) was similar to the first peak potential (−0.87 V) of *p*-tropoquinone dimethyl acetal (**16**). The enhancement and

the small difference of reduction potentials in the *p*-tropoquinone acetal moieties of **12** and **15** contrasted to the CV of 3-(3,6-dioxo-1,4-cyclohexadienyl)methyl-*p*-tropoquinone (**20**), which showed four peaks and no potential enhancement compared to **17** and *p*-benzoquinone.[11]

While the TTN- and CAN-oxidations of **7** gave a spirocyclic compound (**13**) due to an intramolecular interaction of two rings, similar interaction is conceivable to cause the enhancement of the reduction potentials in *p*-tropoquinone acetal moiety of **12** and **15**.

**Conclusion.** Consequently, the procedures described in this paper are evidently versatile, and could be employed for many other types of functionalized bis(troponyl)methane synthesis. Also noteworthy is analysis of the fundamental electrochemical properties of quinone acetals with CV method; this will help a molecular design for functional molecules in both engineering and physiological view points with this class of peculiar compounds.

**Table 1.** Reduction Peak Potentials (V) of **12, 15,** and the Reference *p*-Tropoquinones[a]

| compd. | $E_{p1}$ | $E_{p2}$ | $E_{p3}$ | $E_{p4}$ |
|---|---|---|---|---|
| **15** | −0.27 | −0.92 | −1.23 | −1.23 |
| **12** | | −0.86 | | −1.17 |
| **16**[b] | | −0.87 | | −1.68 |
| **18**[b] | | −0.93 | | −1.88 |
| **17** | −0.28 | | −1.24 | |
| **19** | −0.32 | | −1.22 | |

a) The CV was measured in anhydrous DMF with 0.1 M TBAF using Pyrex glass-sealed Pt-wire as working and counter electrodes, and the standard Ag/AgCl as reference electrode at 22-23 °C under $N_2$ with scan rate of 100 mV/s.
b) Additional oxidation peaks; at 0.16 V for and **16** and 0.09 V for **18**.

## Experimental

The elemental analyses were carried out by Miss S. Hirashima, of Institute of Advanced Material Study, Kyushu University. The NMR spectra were measured by a JEOL FX 100 Spectrometer in $CDCl_3$ solution, unless otherwise specified, and the chemical shifts expressed were in $\delta$ unit. The mass spectra were measured with a JEOL OISG-2 Spectrometer. The IR spectra were taken as KBr disks or as a liquid film inserted between NaCl plates using a Jasco IR-A 102 Spectrometer.

**Preparation of 7.** **a**) Glacial AcOH solution (1 $cm^3$) of **4** (162.6 mg) and **6** (50%, 0.2 $cm^3$) was treated with **5** (37%, 0.8 $cm^3$) at 60 °C for 2.5 h under $N_2$ atmosphere. The resultant crystals were collected by filtration, washed with MeOH to give **7** [yellow crystals, mp 191 -194°C (decomp), 135.1 mg; 80%. Found: $m/z$, 316.0945 ($M^+$). Calcd for $C_{17}H_{16}O_6$: 316.0945. $^1H$ NMR ($CF_3COOD$) $\delta$ = 4.41 (6H, s), 4.80 (2H, s), 8.16 (4H, s), and 8.76 (2H, s). $^{13}C$ NMR

($CF_3COOD$) $\delta$ = 45.6, 59.8 (2C), 135.6 (4C), 143.7 (4C), 159.9 (2C), 165.2 (2C), and 169.5 (2C). IR $\nu$ : 1625, 1521, 1394, 1255, and 1162 $cm^{-1}$] .

**b**) A 50%-aqueous KOH solution (0.4 $cm^3$) of **4** (197 mg) and **5** (37%, 0.4 $cm^3$) was stirred at 60 °C for 45 min under $N_2$ atmosphere. After an addition of water, the mixture was acidified with dil $H_2SO_4$ to precipitate yellow crystalline **7** [111.7 mg ; 55%] .

**Preparation of 9.** Glacial AcOH solution (1 $cm^3$) of **8** (100.7 mg) and **6** (50%, 0.2 $cm^3$) was treated with **5** (37%, 0.8 $cm^3$) at 60 °C for 6 h under $N_2$ atmosphere. The mixture was heated in vacuo to remove the solvent, and the residue was again diluted with water, and the resultant precipitates were collected by filtration, washed with MeOH to give **9** [yellow crystals, mp 135.5 °C (decomp), 27.9 mg ; 27%. Found : $m/z$, 376.1111 ($M^+$). Calcd for $C_{19}H_{20}O_8$ : 376.1156. $^1H$ NMR ($CD_3OD$) $\delta$ = 3.8−3.9 (2H, m), 4.0−4.1 (8H, m), 7.25 (4H, s), and 7.66 (2H, s). $^{13}C$ NMR (DMSO−$d_6$ at 100 °C) $\delta$ = 38.2, 59.5 (2C),79.2 (2C), 128.4 (2C), 132.8 (2C), 133.5 (2C), 133.8 (2C), 151.5 (2C), 164.6 (2C), and 168.7 (2C). IR $\nu$ : 1621, 1520, 1258, and 1155 $cm^{-1}$] .

**Preparation of 10 and 11 from 7.** An AcOH solution (5 $cm^3$) of **7** (514.6 mg) and 48% HBr (20 $cm^3$) was refluxed for 1 h. The mixture was then diluted with water, and the precipitates were collected by filtration to give, after silica-gel column chromatography, **10** [yellow crystals, mp 186-189 °C (decomp), 383.9 mg ; 82%. Found : C, 62.22 ; H, 4.14 %. Calcd for $C_{15}H_{12}O_6$ : C, 62.50 ; H, 4.20%. $^1H$ NMR ($CF_3COOD$) $\delta$ = 4.65 (2H, s), 8.00 (2H, d, $J$ = 12 Hz), 8.20 (2H, d, $J$ = 12 Hz), and 8.63 (2H, s). $^{13}C$ NMR ($CF_3COOD$) $\delta$ = 43.7, 132.8 (2C), 135.5 (2C), 140.0 (2C), 145.2 (2C), 160.8 (2C), 161.7 (2C), and 169.4 (2C). IR $\nu$ : 1620, 1378, 1268, and 1200 $cm^{-1}$] and **11** [greenish yellow crystals, mp 179-182 °C (decomp), 6.2 mg ; 1%. Found : $m/z$, 270.0493 ($M^+$). Calcd for $C_{15}H_{10}O_5$ : 270.0528. $^1H$ NMR ($CF_3COOD$) $\delta$ = 4.66 (2H, s), 8.02 (2H, d, $J$ = 12.5 Hz), 8.26 (2H, d, $J$ = 12.5 Hz), and 8.67 (2H, s). $^{13}C$ NMR ($CF_3COOD$) $\delta$ = 37.6, 133.0 (2C), 135.9 (2C), 139.1 (2C), 157.0 (2C), 159.5 (2C), 166.0 (2C), and 168.7 (2C). IR $\nu$ : 1618, 1548, 1460, 1418, and 1262 $cm^{-1}$] .

**An HBr-Treatment of 7.** A 48%-HBr solution (5 $cm^3$) of **7** (109.6 mg) was refluxed for 8 h to give **11** [37.5 mg ; 40%] .

**An HBr-Dehydration of 10 to 11.** A suspension of **10** (32.9 mg) in conc HBr (48%, 2 $cm^3$) was refluxed for 4 h. The mixture was diluted with water, and the resultant crystals were collected by filtration to give **11** [22.3 mg ; 72%] .

**The DDQ-Oxidation of 10.** An acetone suspension (3 $cm^3$) of **10** (35.2 mg) and DDQ (60 mg) was stirred for 20 h at room temperature. The resultant precipitates were collected by filtration to give **11** [9.6 mg ; 29%] .

**TTN-Oxidation of 7 in MeOH.** To a suspension of **7** (101 mg) in anhydrous MeOH (3 $cm^3$) was added TTN (300.6 mg) at −20 °C. The mixture was stirred at −20 °C for 10 min, then at room temperature for 1 h. The mixture was diluted with water and extracted with

$CHCl_3$. The organic extract was washed with aq $NaHCO_3$, and evaporated in vacuo, and chromatographed on a silica-gel column to give **12** [yellow crystals, mp 114 °C (decomp), 70.2 mg ; 59%. Found : C, 60.35 ; H, 5.37%. Calcd for $C_{19}H_{20}O_8$ : C, 60.63 ; H, 5.36%. $^1$H NMR $\delta$ = 3.24 (12H, s), 3.34 (2H, t, $J$ = 1.5 Hz), 6.08 (2H, t, $J$ = 1.5 Hz), 6.34 (2H, d, $J$ = 12.5 Hz), and 6.52 (2H, d, $J$ = 12.5 Hz). $^{13}$C NMR $\delta$ = 36.9, 50.6 (4C), 102.9 (2C), 132.3 (2C), 134.4 (2C), 138.3 (2C), 148.0 (2C), 192.3 (2C), and 192.8 (2C). IR $\nu$ : 1712, 1665, and 1065 $cm^{-1}$] and **13** [yellow crystals, mp 123 °C (decomp), 22 mg ; 22%. Found : C, 64.82 ; H, 4.54%. Calcd for $C_{17}H_{14}O_6$ : C, 64.96 ; H, 4.49%. $^1$H NMR $\delta$ = 3.28 (1H, d, $J$ = 17 Hz), 3.68 (3H, s), 3.88 (3H, s), 4.24 (1H,d, $J$ = 17 Hz), 5.47 (1H, s), 6.52 (1H, d, $J$ = 13 Hz), 6.61 (1H, s), 6.70 (1H, d, $J$ = 13 Hz), 6.98 (1H, d, $J$ = 13 Hz), and 7.18 (1H, d, $J$ = 13 Hz). $^{13}$C NMR $\delta$ = 43.7, 56.2, 56.3, 89.1, 107.2, 109.8, 121.5, 124.9, 133.0, 137.2, 137.8, 153.9, 156.9, 161.5, 178.5, 186.2, and 192.2. IR $\nu$ : 1700, 1628, 1565, 1555, and 1510 $cm^{-1}$] .

**TTN-Oxidation of 7 in 1,2-Ethanediol.** To a suspension of **7** (97.1 mg) in 1,2-ethanediol (3 $cm^3$) was added TTN (608.7 mg) at −20 °C. After stirring at room temperature for 30 min, the mixture was diluted with water, and extracted with AcOEt, washed with aq $NaHCO_3$, and evaporated in vacuo. The residue was purified with silica-gel column chromatography to give **14** [colorless crystals, mp 175-176 °C, 44.5 mg ; 33%. Found : C, 57.71 ; H, 5.51%. Calcd for $C_{21}H_{24}O_{10}$ : C, 57.79 ; H, 5.54%. $^1$H NMR ($CD_3OD$) $\delta$ = 3.10 (6H, s), 3.4-3.6 (4H, m), 3.8-4.5 (6H, m), 5.88 (2H, d, $J$ = 13 Hz). 6.14 (2 H, t, J = 1.5 Hz), and 6.22 (2 H, d, J = 13 Hz). $^{13}$C NMR ($CD_3OD$) $\delta$ = 36.5, 59.6 (2C), 59.9 (2C), 93.9 (2C), 98.9 (2C), 130.2 (2C), 140.6, 140.8, 141.1 (2C), 145.5 (2C), 192.2, and 193.1. IR $\nu$ : 3600−3200, 1625, 1150, 1085, and 1002 $cm^{-1}$] and **13** [8.2mg ; 8%] .

**CAN-Oxidation of 7.** To a suspension of **7** (74.3 mg) in anhydrous MeOH (2 $cm^3$) was added CAN (280 mg) at 0 °C. The mixture was stirred for 20 min at 0 °C and at room temperature for 1 h. The mixture was then diluted with water, extracted with $CHCl_3$, washed with aq $NaHCO_3$, and evaporated in vacuo. The residue was purified with silica-gel column chromatography to give **12** [30.7 mg ; 35%] and **13** [19.6 mg ; 27%] .

**TTN-Oxidation of 9.** To an anhydrous MeOH solution (2 $cm^3$) of **9** (41.3 mg) was added TTN (205.7 mg) at −20 °C. The mixture was stirred at −20 °C for 10 min, then at room temperature for 1.5 h. The mixture was then diluted with water, extracted with $CHCl_3$ and AcOEt, washed with aq $NaHCO_3$, and exaporated in vacuo. Preparative thin-layer (silica-gel) chromatography of the residue yielded **14** [16.8 mg ; 85%] .

**Acid-Hydrolysis of 12. Formation of 15.** An MeOH solution (8 $cm^3$) of **12** (107.9 mg) and aq $HClO_4$ (2 M, 8 $cm^3$) was stirred at room temperature for 2 h. The mixture was diluted with water and extracted with $CHCl_3$. The organic extract was evaporated in vacuo and the residue was chromatographed on a silica-gel column to give **15** [a yellow oil, 15.9 mg ; 24%. Found : $m/z$, 330.0746 ($M^+$). Calcd for $C_{17}H_{14}O_7$ : 330.0739. $^1$H NMR $\delta$ = 3.26 (6H, s), 3.56

(2H, t, $J$ = 1.5 Hz), 6.24 (1H, t, $J$ = 1.5 Hz), 6.38 (1H, d, $J$ = 13 Hz), 6.56 (1H, d, $J$ = 13 Hz), 6.74 (1H, d, $J$ = 13 Hz), 6.76 (1H, t, $J$ = 1.5 Hz), and 6.90 (1H, d, $J$ = 13 Hz). $^{13}$C NMR $\delta$ = 37.4, 50.8 (2C), 103.0, 133.0, 133.5, 134.1, 136.5, 138.4, 140.2, 142,2, 148.7, 185.4, 186.1, 187.4, 192.5, and 192.8] along with the recovered **12** [33.7 mg ; 31%]

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