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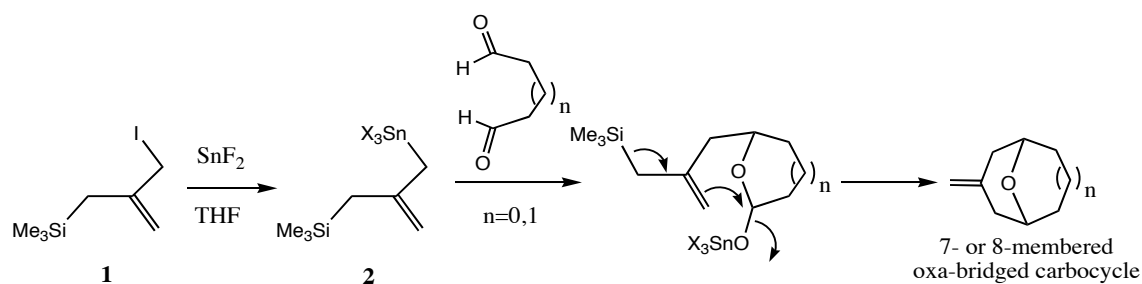
**SYNTHESIS OF OXA-BRIDGED 7- AND 8-MEMBERED RINGS VIA
INDIUM-MEDIATED ANNULATION OF 1,4- and 1,5-DICARBONYL
COMPOUNDS WITH
3-IODO-2-[(TRIMETHYLSILYL)METHYL]PROPENE**

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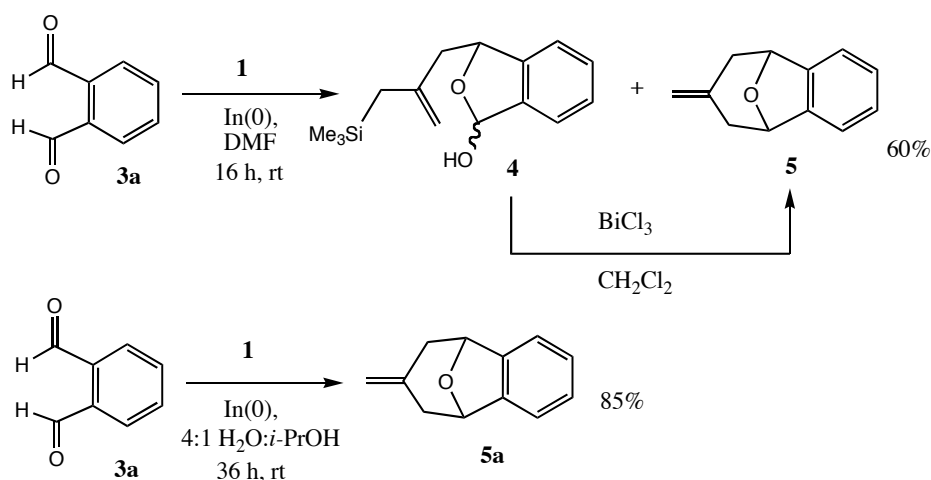
Abstract – A variety of 1,4- and 1,5-dicarbonyl compounds undergo reaction with 3-iodo-2-[(trimethylsilyl)methyl]propene in the presence of indium metal in aqueous media to produce oxa-bridged 7- and 8-membered rings in good yields. The reaction mechanism likely involves intermolecular indium allylation of one carbonyl of the substrate, followed by indium-halide promoted intramolecular allylsilane cyclization. This procedure offers an environmentally friendly alternative to the analogous tin-mediated annulation process.

The wide occurrence of seven and eight-membered carbocycles in natural products has stimulated numerous efforts on the part of synthetic chemists to develop a general method for the synthesis of medium rings akin to the Diels-Alder reaction employed for formation of six-membered rings.¹ The development of [m+n] annulation reactions, wherein a carbocycle is generated from two acyclic precursors in a single synthetic operation, remains an important focus of synthetic effort.² Molander has reported a successful [3+4] and [3+5] annulation approach to seven and eight membered rings involving combination of dicarbonyl compounds with 3-iodo-2-[(trimethylsilyl)methyl]propene (**1**) as a trimethylenemethane dianion synthon.³ The process is promoted by SnF₂, which serves to generate allylstannane (**2**) from **1** *in situ* (Scheme 1). Carbonyl allylation is then followed by hemiacetal formation and allylsilane cyclization, promoted by the presence of both Sn⁴⁺ and fluoride ions, to provide the oxa-bridged carbocycle in high yields. One undesirable aspect of this procedure is the necessity for use of stoichiometric amounts of a toxic tin reagent.

Scheme 1. SnF_2 -promoted $[m+n]$ annulations.

The indium-mediated allylation of aldehydes and ketones in aqueous media is a powerful and stereoselective carbon-carbon bond-forming reaction that has been applied to the synthesis of a variety of complex natural products.⁴ In view of the environmentally benign characteristics of indium metal, we decided to explore the possibility of performing the above $[m+n]$ annulation process in aqueous solvent systems using indium as a mediator.

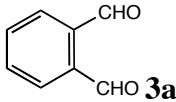
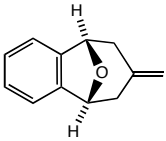
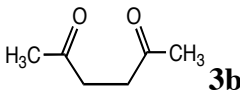
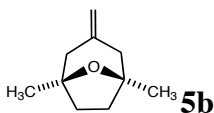
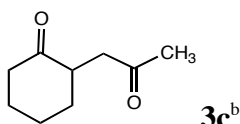
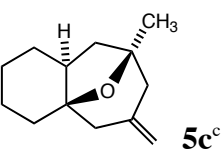
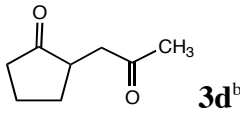
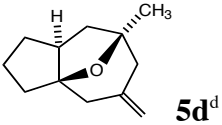
Combination of equimolar amounts of **1**,⁵ phthalic dicarboxaldehyde (**3a**), and indium powder in DMF ⁶ at room temperature for 16 hours gave rise to a 4:1 mixture of hemiacetal (**4**) (as a mixture of diastereomers) and methylene cycloheptane (**5**) (Scheme 2). Stirring the reaction mixture for an extended time period gave no further increase in the yield of **5**. Treatment of the isolated, crude reaction products⁷ with a catalytic amount of BiCl_3 ⁸ in CH_2Cl_2 at room temperature for 3 hours gave essentially complete conversion to **5** in 60% overall yield.

Scheme 2. An indium-mediated $[3+4]$ annulation reaction.

Although an alternative path to a seven-membered oxa-bridged carbocycle had been achieved, we desired a one-pot process that could furnish high yields of annulation products in the absence of halogenated

solvents. Gratifyingly, it was found that stirring equimolar amounts of **1**, phthalic dicarboxaldehyde and indium powder in 4:1 H₂O:*i*-PrOH at room temperature for 36 hours gave rise to carbocycle (**5**) exclusively in 85% yield (Scheme 2). Combination of **1** with diketone (**3b**) (Table 1, entry 2) similarly furnished **5b** in 60% yield. Substrates (**3c**)⁹ and (**3d**)¹⁰, with increased steric hindrance at the carbonyl groups and decreased solubility in the reaction medium, gave lower percent conversions (~15%) even after 48 hours of stirring. However, by simply increasing the proportion of isopropanol cosolvent (to 3:1 H₂O: *i*-PrOH), the yield of oxa-bridged cycloheptanes (**5c**) and (**5d**) increased, with optimal conversions (40% and 35%, respectively) achieved between 36 and 48 hours at room temperature. It is noteworthy that starting diketones (**3c**) and (**3d**) could be recovered in ~50% yield from these reactions.

Table 1. [3+4] annulation reactions of **1** with 1,4-dicarbonyl compounds in the presence of indium metal^a

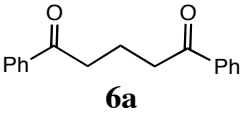
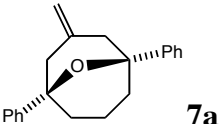
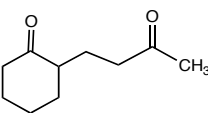
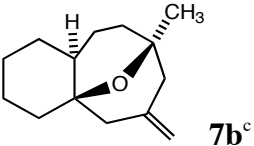
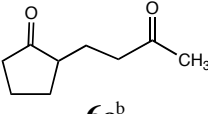
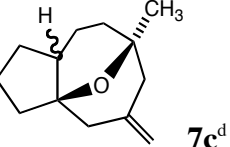
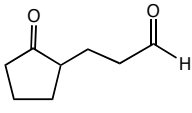
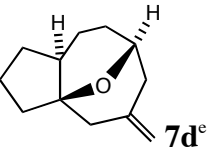
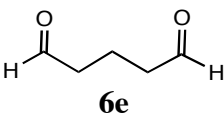
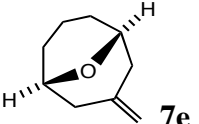
Entry	Dicarbonyl Substrate	Product	% Isolated Yield ^e
1	 3a	 5a	85
2	 3b	 5b	60
3	 3c^b	 5c^c	40
4	 3d^b	 5d^d	35

^a Reaction conditions: equimolar amounts of **1** + **3** + In(0) in 4:1 H₂O:*i*-PrOH, rt, 48 h. ^b Reaction performed in 3:1 H₂O:*i*-PrOH. ^c Isolated as a 3:1 mixture of diastereomers. ^d Isolated as a >10:1 mixture of diastereomers. ^e Refers to yields of chromatographically purified products

We next investigated [3+5] annulation reactions between **1** and 1,5-dicarbonyl compounds in the presence of indium metal. Treatment of 1,5-diphenylpentane-1,5-dione (**6a**) with one equivalent each of **1** and indium metal in 4:1 H₂O: *i*-PrOH gave, after 48 hours stirring, a 79% yield of the eight-membered oxa-bridged carbocycle (**7a**) (Table 2). Similarly, diones (**6b**)¹¹ and (**6c**)¹² furnished carbocycles (**7b**) and (**7c**) in 82 and 65% yields, respectively, each as a mixture of diastereomers. Keto-aldehyde (**6d**)¹³ also underwent smooth annulation with **1** in the presence of indium metal to provide **7d**¹⁴ in 60% yield. Subjection of glutaraldehyde (**7e**) to the reaction conditions, however, gave rise to a complex mixture of

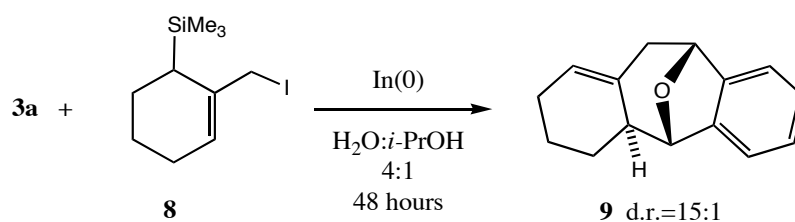
products with only trace amounts of cyclized material; Molander has also observed low yields for [m+n] annulations employing enolizable aldehydes.³

Table 2. [3+5] annulation reactions of **1** with 1,5-dicarbonyl compounds in the presence of indium metal^a

Entry	Dicarbonyl Substrate	Product	% Isolated Yield ^f
1	 6a	 7a	79
2	 6b^b	 7b^c	82
3	 6c^b	 7c^d	65
4	 6d	 7d^e	60
5	 6e	 7e	<10

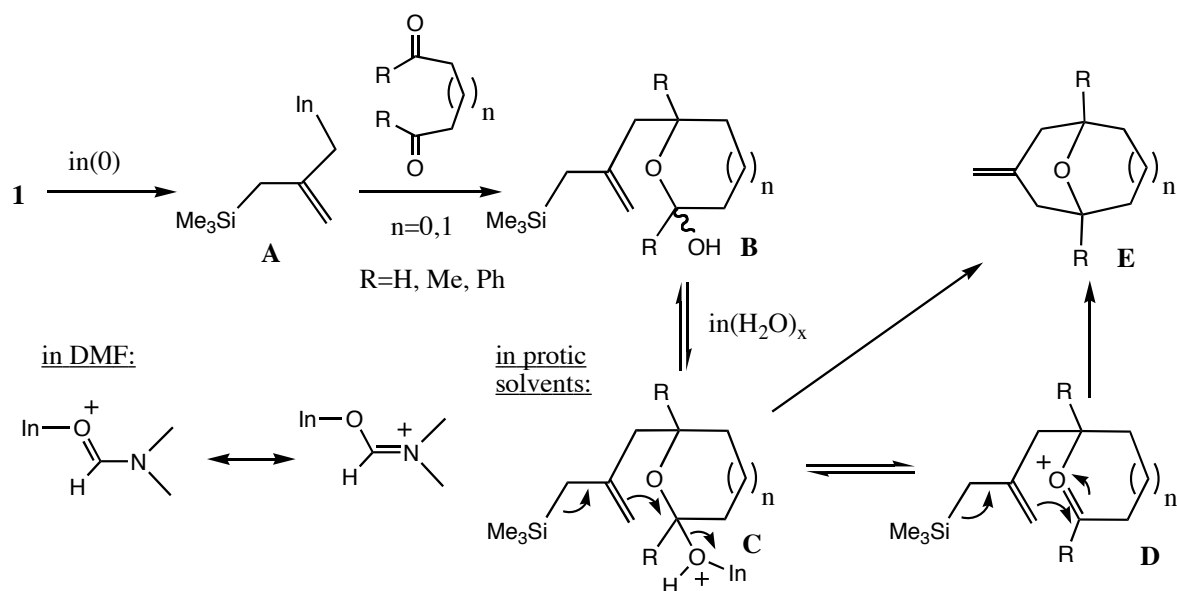
^a Reaction conditions: equimolar mounts of **1** + **6** + In(0) in 4:1 H₂O:*i*-PrOH, rt, 48 h. ^b Reaction performed in 3:1 H₂O:*i*-PrOH. ^c Isolated as a 3:1 mixture of diastereomers. ^d Isolated as a 1.1:1 mixture of diastereomers. ^e Isolated as a 6.5:1 mixture of diastereomers. ^f Refers to yields of chromatographically purified products

Finally, we combined cyclohexenyl iodide (**8**)¹⁵ with **3a** under our standard reaction conditions; after 48 hours, tricycle (**9**) was isolated in 55% yield as a 15:1 mixture of diastereomers (Scheme 3). This experiment demonstrates that more complex (silyl)allyl iodides may also be employed in aqueous [m+n] annulations.



Scheme 3. A [3+4] annulation reaction employing iodide (**8**).

Paralleling the SnF_2 -promoted process, the mechanism of this reaction likely involves *in situ* allylindium generation (furnishing **A**, scheme 4) followed by intermolecular carbonyl allylation, providing diastereomeric hemiacetals **B**; when the reactions are stopped after 5 hours, this is the main product obtained. The indium (I) and/or indium (III) halide salts produced in the initial steps then function in the capacity of a Lewis acid by slowly catalyzing an intramolecular allylsilane cyclization reaction (*via* structures **C** or **D**), furnishing product **E**. The indium salts also facilitate enolization of aldehydes such as **6e**, leading to numerous aldol-type side reactions for these substrates over the lengthy reaction period. Furthermore, it is possible that when the reaction is performed in DMF, the cyclization step is inhibited because the Lewis acidic indium species preferentially coordinate the electron-rich formamide carbonyl oxygen of the solvent.



Scheme 4. Mechanistic Proposal

In summary, we have established that [m+ n]-type annulation reactions can be carried out in aqueous media when indium metal is employed as a promoter of reactions between 2-[(trimethylsilyl)alkyl]allyl iodides and 1,4 or 1,5-dicarbonyl compounds.^{17,18} We anticipate that this environmentally benign methodology for constructing seven and eight-membered carbocycles may find broad applicability in natural products synthesis.

ACKNOWLEDGEMENTS

This paper is dedicated with great respect to Professor Yoshito Kishi on the occasion of his 70th birthday. We also thank the ACS Petroleum Research Fund (No. PRF 45277-B1) and Research Corporation (No. CC6343) for their generous support of our research program. We also thank Mr. Jesse Brister for initial preparations of compound **5a** in water.

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17. General Procedure: to a 10 mL round-bottom flask equipped with magnetic stirbar was added the dicarbonyl compound (**3** or **6**, 1.0 mmol). A 4:1 H₂O:*i*-PrOH solution (0.4 mL) was added and

stirred until a monophasic solution was obtained; if the dicarbonyl substrate did not completely dissolve, additional *i*-PrOH was added dropwise to effect a greater degree of homogeneity (~3:1 H₂O:*i*-PrOH). Then indium powder (1.0 mmol) was added in a single portion. To the stirring solution was added 3-iodo-2-[(trimethylsilyl)methyl]propene (**1**, 1.0 mmol), and the reaction flask was covered with a septum and shielded from light with aluminum foil. After stirring for 48 hours, the mixture was diluted with ether (2.0 mL) and washed with brine (2 x 2.0 mL). The organic extract was dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography (SiO₂, 98:2 hexanes:ether as eluant) afforded pure oxabicyclic products (**5**, **7**, or **9**).

18. Spectroscopic data (GCMS: Agilent 6890 (injector 250°C, 10.5 psi, column gradient 100°C for 2 minutes, 25°C/min to 320°C, 320°C for 10 minutes). ¹H- and ¹³C NMR spectra were recorded on a Bruker 400MHz spectrometer using Me₄Si as internal standard.):

5a: GCMS: t_R=5.77 min; calculated for C₁₀H₁₆O 172.0888, found m/z=172 (M⁺). ¹H NMR: 7.20 (m, 5H); 5.25 (d, *J*=4.4 Hz, 2H); 4.49 (m, 2H); 2.84 (dd, *J*=14.4, 2.4 Hz, 2H); 2.24 (d, *J*=14.8 Hz, 2H). ¹³C NMR: 143.3; 139.9; 127.3; 119.9; 113.7; 78.8; 39.8. Previous preparation: references 3 and 15.

5b: GCMS: t_R=3.01 min; calculated for C₁₀H₁₆O 152.1201, found m/z=152 (M⁺). ¹H NMR: 4.76 (t, *J*=2.0 Hz, 2H); 2.22 (d, *J*= 13.0 Hz, 2H); 2.08 (d, *J*= 13.8 Hz); 1.63 (m, 4H); 1.34 (s, 6H). ¹³C NMR: 143.8; 96.1; 81.4; 46.6; 36.6; 26.3. Previous preparation: references 3 and 16.

5c: A 3:1 mixture of diastereomers was obtained. GCMS: t_R=5.51 min (major), calculated for C₁₃H₂₀O 192.1514, found m/z=192 (M⁺); t_R=5.74 min (minor), calculated for C₁₃H₂₀O 192.1514, found m/z=192 (M⁺). ¹H NMR (major): 4.68 (q, *J*=2.4 Hz, 1H); 4.63 (q, *J*=2.0 Hz, 1H); 2.15-1.84 (m, 4H); 1.75-1.25 (m, 11H); 1.31 (s, 3H). ¹H NMR (minor): 4.73 (q, *J*=2.1 Hz, 1H); 4.61 (q, *J*=2.3Hz, 1H); 2.28-1.80 (m, 4H); 1.75-1.34 (m, 11H); 1.32 (s, 3H) ¹³C NMR (major): 144.2; 110.4; 96.1; 79.8; 47.2; 46.0; 44.4; 42.1; 34.0; 32.8; 26.9; 23.9; 21.0. ¹³C NMR (minor): 142.9; 110.5; 96.0; 81.5; 50.0; 47.6; 46.9; 40.1; 38.3; 26.6; 26.3; 23.8; 22.7. Previous preparation: reference 3.

5d: Isolated as a >10:1 mixture of diastereomers. Major diastereomer: GCMS: t_R=4.68 min; calculated for C₁₂H₁₈O 178.1358, found m/z=178 (M⁺). ¹H NMR: 4.74 (m, 2H); 2.51 (dd, *J*=13.6, 1.6 Hz, 1H); 2.16 (m, 2H); 2.05 (m, 3H); 1.92-1.74 (m, 3H); 1.62-1.54 (m, 2H); 1.48-1.26 (m, 2H); 1.32 (s, 3H). ¹³C NMR: 144.6; 110.2; 93.2; 83.0; 46.9; 46.2; 45.9; 43.5; 36.9; 34.9; 26.4; 25.8. Previous preparation: reference 3.

7a: GCMS: t_R=10.08 min; calculated for C₂₁H₂₂O 290.1671, found m/z=290 (M⁺). ¹H NMR: 7.64 (dd, *J*=1.2, 8.4 Hz, 4H); 7.39 (t, *J*=7.2 Hz, 4H); 7.25 (m, 2H); 4.88 (t, *J*= 2.0 Hz, 2H); 2.88 (d, *J*=15.2 Hz, 2H); 2.55 (d, *J*=14.4 Hz, 2H); 2.15 (dd, *J*=2.8, 14.0 Hz, 2H); 1.76 (td, *J*=5.6, 13.6 Hz, 2H); 1.61 (m, 2H). ¹³C NMR: 149.7; 145.3; 128.1; 126.4; 123.7; 108.5; 75.0; 44.9; 37.2; 19.4.

7b: Isolated as a 3:1 mixture of diastereomers. GCMS: $t_R=6.20$ min (major), calculated for $C_{14}H_{22}O$ 206.1671, found $m/z=206$ (M^+); $t_R=6.33$ min (minor), calculated for $C_{14}H_{22}O$ 206.1671, found $m/z=206$ (M^+). 1H NMR: 4.68 (s, 2H); 4.65 (s, 2H); 2.85 (d, $J=14.4$ Hz, 1H); 2.57 (ddd, $J=5.6, 13.6, 19.2$ Hz, 1H); 2.28–2.21(m, 5H); 1.99 (m, 3H); 1.78-1.04 (m, 24H); 1.20 (s, 3H); 1.19 (s, 3H); ^{13}C NMR: 146.8; 145.6; 107.3; 106.8; 74.5; 72.3; 71.8; 46.3; 45.5; 45.4; 45.0; 41.4; 40.3; 38.7; 37.8; 37.7; 31.7; 31.4; 31.3; 30.2; 28.2; 26.4; 25.9; 25.8; 25.0; 22.9; 21.5. Previous preparation: reference 3.

7c: Isolated as a 1.1:1 mixture of diastereomers. GCMS: $t_R=5.51$ min (major), calculated for $C_{10}H_{16}O$ 192.1514, found $m/z=192$ (M^+); $t_R=5.74$ min (minor), calculated for $C_{10}H_{16}O$ 192.1514, found $m/z=192$ (M^+). 1H NMR: 4.70 (m, 2H); 4.63 (m, 2H); 2.49 (d, $J=14.8$ Hz, 2H); 2.39 (d, $J=13.6$ Hz, 2H); 2.28 (m, 2H); 2.14 (s, 1H); 2.00 (m, 2H); 1.76-1.33 (m, 20H); 1.23 (s, 3H); 1.18 (s, 3H). ^{13}C NMR: 145.6; 144.9; 108.8; 107.2; 81.1; 73.7; 71.5; 46.7; 45.6; 43.7; 41.2; 38.3; 37.5; 31.5; 30.9; 26.2; 23.4; 21.9; 18.4.

7d: Isolated as a 6.5:1 mixture of diastereomers. Major diastereomer: GCMS: $t_R=5.66$ min; calculated for $C_{12}H_{18}O$ 178.1358, found $m/z=178$ (M^+). 1H NMR: 4.77 (m, 1H); 4.75 (m, 1H); 4.17 (m, 2H); 2.61-2.54 (m, 1H); 2.53-2.46 (m, 1H), 2.16-2.09 (dd, $J=14.0, 7.2$ Hz, 1H); 2.06-1.94 (m, 2H); 1.78-1.65 (m, 5H); 1.64-1.49 (m, 2H); 1.36-1.25 (m, 2H). ^{13}C NMR: 144.3; 109.3; 80.0; 69.0; 44.1; 41.9; 41.1; 39.0; 30.9; 25.1; 21.6; 20.9. Previous preparation: reference 13.

9: Isolated as a 15:1 mixture of diastereomers. Major diastereomer: GCMS: $t_R=7.85$ min; calculated for $C_{15}H_{16}O$ 212.1201, found $m/z=212$ (M^+). 1H NMR: 7.18 (m, 4H); 5.18 (m, 2H); 4.90 (d, $J=4.4$ Hz, 1H); 2.79 (m, 2H); 2.09 (d, $J=14.4$ Hz, 1H); 1.81 (dt, $J=4.0, 12.4$ Hz, 2H); 1.72-1.19 (m, 5H); 1.10 (qd, $J=2.4, 12.8$ Hz, 1H). ^{13}C NMR: 144.1; 141.7; 132.3; 127.0; 126.2; 125.5; 121.7; 119.9; 82.0; 79.3; 41.7; 38.9; 24.9; 24.7; 21.5.