

# Continuous Flow Chemistry: A Discovery Tool for New Chemical Reactivity Patterns

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## Supporting Information

### General Information

Unless otherwise noted, all reactions were carried out under an argon atmosphere in flame-dried glassware. Reaction temperatures are reported as the temperature of the bath surrounding the vessel unless otherwise stated. All solvents were distilled prior to use and stored under argon.

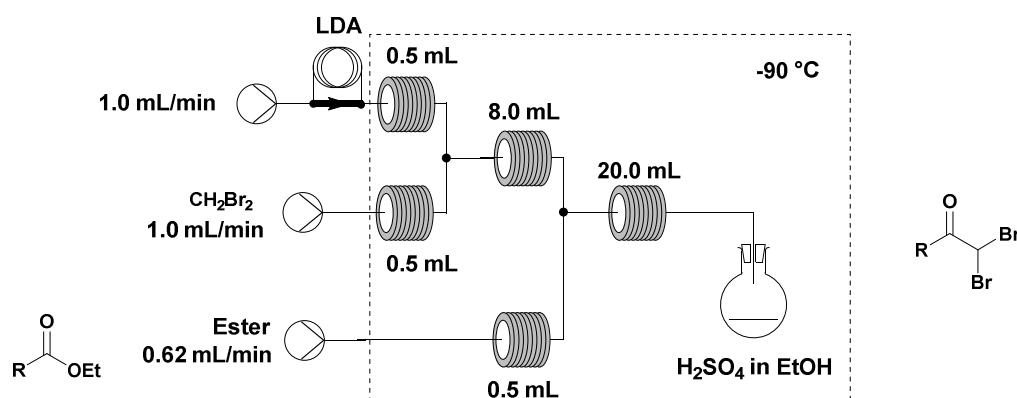
Commercially available starting materials were purchased from Sigma-Aldrich and Alfa Aesar. All flow reactions were performed on R-Series Flow equipment from Vapourtec.

<sup>1</sup>H- and <sup>13</sup>C-NMR spectra were recorded on a Bruker Avance DPX-400 spectrometer with residual solvent as the internal reference (CHCl<sub>3</sub> in CDCl<sub>3</sub>). LC/MS analysis was performed on an Agilent HP 1100 chromatograph (Luna Max RP column) attached to an HPLC/MSD massspectrometer. Elution was carried out using a reverse-phase gradient of MeCN/water with the water containing 0.1% formic acid. For HRMS an LCT Premier Micromass spectrometer was used. Flash purification was carried out on an Isolera<sup>TM</sup> Spektra Systems from Biotage using a gradient of ethylacetate/hexane.

### General procedure for the batch-synthesis of $\alpha$ -dibromoketones:

350  $\mu$ L (2.52 mmol, 2.4 eq.) diisopropylamine was dissolved in 3.0 mL THF and cooled to -78 °C. 1.44 mL (2.31 mmol, 2.2 eq., 1.6 mol/L in hexanes) *n*-BuLi was slowly added and the solution was allowed to warm up to 0°C. 170  $\mu$ L (2.31 mmol, 2.2 eq.) dibromomethane was dissolved in 3.0 mL THF in a second vessel and cooled to -90 °C. The resulted LDA solution was transferred via cannula and the mixture was stirred at -90 °C for 5 min. Next, 1.05 mmol ester (1.0 eq.) dissolved in 2.0 mL THF was added and stirred for additional 10 min. The solution was poured into 5% H<sub>2</sub>SO<sub>4</sub> in ethanol (10 mL) at -78 °C and diluted with 50 mL diethylether. The mixture was washed twice with HCl (1 mol/L, 30 mL), Sodium hydrogen carbonate (30 mL) and brine (30 mL). The organic phase was dried over magnesium sulfate, filtered and concentrated under reduced pressure. Purification by flash chromatography (Petroleum ether:ethyl acetate, 9:1) yielded the desired product.

## General procedure for the flow-synthesis of $\alpha$ -dibromoketones:



3.0 mL LDA-stock solution in THF (0.83 mol/L, 2.2 eq.) was placed in an Vapourtec R2 Unit injection loop. The loop of the second R2 pump was filled with 3.0 mL dibromomethane solution in THF (0.83 mol/L, 2.2 eq.). Both streams were pumped at 1.0 mL/min and pre-cooled in 0.5 mL loops, which were placed in a cooling bath at  $-90\text{ }^\circ\text{C}$  together with the remaining reaction coils. A PEEK T-joint with 0.25 mm inner diameter was applied for mixing and deprotonation took place in an 8 mL coil. After 4 minutes, the third pump was started, infusing 1.05 mmol ester (1.0 eq.) dissolved in 2.0 mL THF. The ester was added using a third pump from a reservoir through a 0.5 mL pre-cooling coil at 0.62 mL/min via a second T-piece and the reaction took place in a 20 mL reaction coil. The reaction mixture was collected in a round bottom flask containing 5%  $\text{H}_2\text{SO}_4$  in ethanol (10 mL) at  $-90\text{ }^\circ\text{C}$ . 50 mL diethyl ether was added and the solution was washed with HCl (1 mol/L, 30 mL) twice, Sodium hydrogen carbonate (30 mL) and brine (30 mL). The organic phase was dried over magnesium sulfate, filtered and concentrated under reduced pressure. Purification by flash chromatography (PE:EE, 9:1) yielded the desired product.

## General procedure for the flow-synthesis of $\alpha$ -dibromoketones in large scale:

18.0 mL LDA-stock solution in THF (0.83 mol/L, 2.2 eq.) was placed in an Vapourtec R2 injection loop and cooled to  $0\text{ }^\circ\text{C}$ . The loop of the second R2 pump was filled with 18.0 mL dibromomethane solution in THF (0.83 mol/L, 2.2 eq.). Both streams were pumped at 1.0 mL/min and pre-cooled in 0.5 mL loops, which were placed in a cooling bath at  $-90\text{ }^\circ\text{C}$  together with the remaining reaction coils. A PEEK T-piece with 0.25 mm inner diameter was applied for mixing and deprotonation took place in an 8 mL coil. After 4 minutes the third pump was started, infusing 1.19 g (6.3 mmol, 1.0 eq.) ester dissolved in 12.0 mL THF. The ester was added through a 0.5 mL pre-cooling coil via a second T-piece and the reaction took place in a 20 mL reaction coil. The reaction mixture was collected in a round bottom flask containing 5%  $\text{H}_2\text{SO}_4$  in ethanol (60 mL) at  $-90\text{ }^\circ\text{C}$ . 300 mL diethyl ether was added and the solution was washed with HCl (1 mol/L, 150 mL) twice, Sodium hydrogen carbonate (150 mL) and brine (150 mL). The organic phase was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was taken up in  $\text{CH}_2\text{Cl}_2$ , slowly recrystallised and washed with 3.0 mL cold  $\text{CH}_2\text{Cl}_2$  to give the desired product as colourless crystals (1.74 g, 5.47 mmol, 87%).

## Synthetic procedures and characterisation

### (E)-1-bromo-3-methyl-4-phenylbut-3-en-2-one

200 mg (*E*)-1,1-dibromo-3-methyl-4-phenylbut-3-en-2-one (0.63 mmol, 1.0 eq.) was dissolved in 5.0 mL THF and cooled to -90 °C. Next 600  $\mu$ L (0.95 mmol, 1.5 eq.) *n*-BuLi was slowly added and stirred for 5 min. The solution was poured into 5% H<sub>2</sub>SO<sub>4</sub> in ethanol (5 mL) at -78 °C and diluted with 25 mL diethylether. The mixture was washed with HCl (1 mol/L, 10 mL) twice, Sodium hydrogen carbonate solution (sat., 10 mL) and brine (10 mL). The organic phase was dried over magnesium sulfate, filtered and concentrated under reduced pressure to give the desired product as a slightly yellow oil (140 mg, 0.59 mmol, 93%). <sup>1</sup>H-NMR: (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.59 (s, 1H), 7.50 – 7.33 (m, 5H), 4.34 (s, 2H), 2.13 (s, 3H) ppm; <sup>13</sup>C-NMR: (100 MHz, CDCl<sub>3</sub>)  $\delta$  193.5, 141.2, 135.23, 134.6, 129.9, 129.1, 128.6, 30.3, 12.4 ppm; HRMS (ESI): m/z calculated for C<sub>11</sub>H<sub>12</sub>OBr: 239.0072 [M+H<sup>+</sup>]; found: 239.0064 ( $\Delta$  = -3.3 ppm).

### Phenylalanin ethyl ester

2.0 g (12.0 mmol) Phenylalanin was dissolved in 20 mL ethanol and 0.5 mL sulfuric acid was added. The esterification was carried out at 120 °C in a Biotage Initiator Microwave at normal absorption level over 2 h. The reaction mixture was diluted with 30 mL ethyl acetate and washed with 30 mL Sodium hydrogen carbonate solution (sat.) and 30 mL brine (sat.). The organic phase was dried over magnesium sulfate, filtered and concentrated under reduced pressure to give the desired product as a yellow liquid (1.17 g, 6.0 mmol, 50%). <sup>1</sup>H-NMR: (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.44 – 6.98 (m, 5H), 4.16 (q, 3J<sub>HH</sub> = 7.1 Hz, 2H), 3.71 (dd, 3J<sub>HH</sub> = 7.9, 5.3 Hz, 1H), 3.18 – 2.77 (m, 2H), 1.23 (t, 3J<sub>HH</sub> = 7.1 Hz) ppm; <sup>13</sup>C-NMR: (100 MHz, CDCl<sub>3</sub>)  $\delta$  174.8, 137.2, 129.3, 128.5, 126.7, 60.8, 55.8, 41.0, 14.1 ppm; HRMS (ESI): m/z calculated for C<sub>11</sub>H<sub>16</sub>NO<sub>2</sub>: 194.1181 [M+H<sup>+</sup>]; found: 194.1178 ( $\Delta$  = -1.5 ppm).

### *N,N*-dibenzyl phenylalanin ethyl ester

483 mg (2.5 mmol 1.0 eq.) phenylalanine ethyl ester, 1.28 g (7.5 mmol, 3.0 eq.) benzyl bromide and 1.05 g (12.5 mmol, 5 eq.) NaHCO<sub>3</sub> were dissolved in 10 mL THF and stirred at 100 °C in a Biotage Initiator Microwave at normal absorption level for 2 h. After cooling down the mixture was diluted with 20 mL H<sub>2</sub>O and 2.0 mL methanol. After extraction with ethyl acetate (3 x 30 mL) the organic phase was washed with brine (1 x 20 mL) and dried over sodium sulfate. Purification by flash chromatography (PE:EE, 1:0 to 7:3) yielded the desired product as a yellow oil (270 mg, 0.73 mmol, 29 %). <sup>1</sup>H-NMR: (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.36 – 7.14 (m, 13H), 7.02 (dd, 3J<sub>HH</sub> = 6.8, 2.7 Hz, 2H), 4.30 – 4.10 (m, 2H), 3.96 (d, 4J<sub>HH</sub> = 14.1 Hz, 2H), 3.66 (t, 3J<sub>HH</sub> = 7.7 Hz, 1H), 3.57 (d, 3J<sub>HH</sub> = 14.0 Hz, 2H), 3.06 (m, 2H), 1.30 (t, 3J<sub>HH</sub> = 7.1 Hz, 3H) ppm; <sup>13</sup>C-NMR: (100 MHz, CDCl<sub>3</sub>)  $\delta$  172.3, 139.4, 138.3, 129.5, 128.8, 128.2, 128.2, 127.0, 126.3, 62.4, 60.2, 54.5, 35.8, 14.6 ppm; HRMS (ESI): m/z calculated for C<sub>25</sub>H<sub>27</sub>NO<sub>2</sub>: 374.2120 [M+H<sup>+</sup>]; found: 374.2115.

**Following compounds were prepared using general procedure for the flow-synthesis):**

### 2,2-Dibromo-1-(4-fluorophenyl)ethan-1-one (table 1, entry 1)

<sup>1</sup>H-NMR: (400 MHz, CDCl<sub>3</sub>)  $\delta$  8,22 - 8.09 (m, 2H), 7.22 – 7.14 (m, 2H), 6.63 (s, 1H) ppm; <sup>13</sup>C-NMR: (100 MHz, CDCl<sub>3</sub>)  $\delta$  184,5, 167,6, 132,7, 127,1, 116,3, 39,4 ppm. HRMS (ESI): m/z calculated for C<sub>8</sub>H<sub>6</sub>O<sub>2</sub>Br<sub>2</sub>: 294.8769 [M+H<sup>+</sup>]; found: 294.8764 ( $\Delta$  = -1.7 ppm).

### 2,2-dibromo-1-(5-methylisoxazol-4-yl)ethan-1-one (table 1, entry 2)

<sup>1</sup>H-NMR: (400 MHz, CDCl<sub>3</sub>) δ 8.85 (s, 1H), 5.29 (s, 1H), 2.77 (s, 3H) ppm.

**2,2-Dibromo-1-(thiophen-2-yl)ethan-1-one (table 1, entry 3)**

<sup>1</sup>H-NMR: (400 MHz, CDCl<sub>3</sub>) δ 7.99 (d, 3J<sub>HH</sub> = 3.8 Hz, 1H), 7.77 (d, 3J<sub>HH</sub> = 5.0 Hz, 1H), 7.23 – 7.15 (dd, 3J<sub>HH</sub> = 5.0, 3.8 Hz, 1H), 6.50 (s, 1H) ppm; <sup>13</sup>C-NMR: (100 MHz, CDCl<sub>3</sub>) δ 179.7, 136.5, 134.7, 134.7, 128.5, 39.0 ppm; HRMS (ESI): m/z calculated for C<sub>6</sub>H<sub>5</sub>OSBr<sub>2</sub>: 282.8428 [M+H<sup>+</sup>]; found: 282.8419 (Δ = -3.2 ppm).

**2-Bromo-1-(thiophen-2-yl)ethan-1-one**

<sup>1</sup>H-NMR: (400 MHz, CDCl<sub>3</sub>) δ 7.80 (d, 3J<sub>HH</sub> = 3.8 Hz, 1H), 7.72 (d, 3J<sub>HH</sub> = 4.9 Hz, 1H), 7.17 (dd, 3J<sub>HH</sub> = 4.9, 3.8 Hz), 4.36 (s, 2H) ppm. <sup>13</sup>C-NMR: (100 MHz, CDCl<sub>3</sub>) δ 184.3, 140.7, 135.2, 133.5, 128.4, 30.6 ppm; HRMS (ESI): m/z calculated for C<sub>6</sub>H<sub>6</sub>OSBr 204.9323 [M+H<sup>+</sup>]; found 204.9323 (Δ = 0.0 ppm).

**2,2-Dibromo-1-(4-Methylphenyl)ethan-2-one (table 1, entry 4)**

<sup>1</sup>H-NMR: (400 MHz, CDCl<sub>3</sub>) δ 7.88 (d, 3J<sub>HH</sub> = 8.2 Hz, 2H), 7.28 (d, 3J<sub>HH</sub> = 7.9 Hz, 2H), 4.42 (s, 1H), 2.42 (s, 1H) ppm; <sup>13</sup>C-NMR: (100 MHz, CDCl<sub>3</sub>) δ 190.9, 145.0, 131.5, 129.5, 129.0, 30.9, 21.7 ppm; HRMS (ESI): m/z calculated for C<sub>19</sub>H<sub>8</sub>Br<sub>2</sub>ONa: 312.8834 [M+Na<sup>+</sup>]; found: 312.8827 (Δ = -2.36 ppm).

**(E)-1,1-dibromo-3-methyl-4-phenylbut-3-en-2-one (table 1, entry 5)**

<sup>1</sup>H-NMR: (400 MHz, CDCl<sub>3</sub>) δ 7.69 (s, 1H), 7.50 – 7.33 (m, 5H), 6.74 (s, 1H), 2.18 (s, 3H) ppm; <sup>13</sup>C-NMR: (100 MHz, CDCl<sub>3</sub>) δ 188.3, 141.9, 134.8, 131.4, 130.0, 129.5, 128.7, 39.5, 14.2 ppm; HRMS (ESI): m/z calculated for C<sub>11</sub>H<sub>10</sub>Br<sub>2</sub>ONa: 338.8991 [M+Na<sup>+</sup>]; found: 338.8978 (Δ = -3.83 ppm).

**(E)-1,1-Dibromo-4-phenylbut-3-en-2-one (table 1, entry 6)**

<sup>1</sup>H-NMR: (400 MHz, CDCl<sub>3</sub>) δ 7.88 (d, 3J<sub>HH</sub> = 15.8 Hz, 1H), 7.65 (m, 2H), 7.45 (d, 3J<sub>HH</sub> = 2.2 Hz, 2H), 7.30 (d, 3J<sub>HH</sub> = 15.8 Hz, 1H), 7.26 (s, 1H), 5.94 (s, 1H) ppm; <sup>13</sup>C-NMR: (100 MHz, CDCl<sub>3</sub>) δ 185.5, 147.7, 133.9, 131.5, 129.0, 128.9, 117.8, 42.69 ppm; HRMS (ESI): m/z calculated for C<sub>10</sub>H<sub>8</sub>Br<sub>2</sub>ONa: 324.8834 [M+Na<sup>+</sup>]; found: 324.8828 (Δ = -1.97 ppm).

**2,2-Dibromo-1-(6-chloropyridin-3-yl)ethan-1-one (table 1, entry 7)**

<sup>1</sup>H-NMR: (400 MHz, CDCl<sub>3</sub>) δ 9.13 (d, 3J<sub>HH</sub> = 2.6 Hz, 1H), 8.37 (dd, 3J<sub>HH</sub> = 8.3, 2.6 Hz, 1H), 7.49 (d, 3J<sub>HH</sub> = 8.3 Hz, 1H), 6.48 (s, 1H) ppm; <sup>13</sup>C-NMR: (100 MHz, CDCl<sub>3</sub>) δ 183.9, 156.7, 151.3, 139.8, 125.5, 124.7, 53.4 ppm; HRMS (ESI): m/z calculated for C<sub>7</sub>H<sub>5</sub>NOCIBr<sub>2</sub>: 311.8426 [M+H<sup>+</sup>]; found: 311.8415 (Δ = -3.5 ppm).

**2,2-Dibromo-1-(4-nitrophenyl)ethan-1-one (table 1, entry 8)**

<sup>1</sup>H-NMR: (400 MHz, CDCl<sub>3</sub>) δ 8.38 – 8.28 (m, 4H), 6.60 (s, 1H) ppm; <sup>13</sup>C-NMR: (100 MHz, CDCl<sub>3</sub>) δ 184.5, 150.8, 135.6, 130.7, 123.9, 38.8 ppm.

**1,1-Dibromo-3-phenylpentan-2-one (table 2)**

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ 7.40 – 7.21 (m, 5H), 5.87 (s, 1H), 4.16 (t, 3J<sub>HH</sub> = 7.4 Hz, 1H), 2.14 (m, 1H), 1.90 – 1.75 (m, 1H), 0.89 (td, 3J<sub>HH</sub> = 7.3, 1.9 Hz, 3H) ppm; <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) δ

195.3, 137.9, 129.1, 128.3, 127.9, 54.7, 42.6, 27.3, 11.9 ppm; HRMS (ESI): m/z calculated for  $C_{11}H_{12}Br_2ONa$ : 340.9147 [ $M+Na^+$ ]; found: 340.9137 ( $\Delta = -2.87$  ppm).

**1,1-Dibromohex-3-yn-2-one (table 3, entry 1)**

$^1H$ -NMR: (400 MHz,  $CDCl_3$ )  $\delta$  5.84 (s, 1H), 2.59 – 2.40 (q,  $3J_{HH} = 7.29$  Hz, 2H), 1.38 – 1.15 (t,  $3J_{HH} = 6.93$  Hz, 3H) ppm;  $^{13}C$ -NMR: (100 MHz,  $CDCl_3$ )  $\delta$  173.5, 102.5, 75.0, 42.6, 13.0, 12.4 ppm; HRMS (ESI): m/z calculated for  $C_6H_7Br_2O$ : 252.8864 [ $M+H^+$ ]; found: 252.8867 ( $\Delta = 1.2$  ppm).

**(S)-1,1-dibromo-3-(dibenzylamino)-4-phenylbutan-2-one (table 3, entry 2)**

$^1H$ -NMR: (400 MHz,  $CDCl_3$ )  $\delta$  7.61 – 7.01 (m, 15H), 6.10 (s, 1H), 4.00 (dd,  $3J_{HH} = 3.9$  Hz  $4J_{HH} = 9.7$  Hz, 1H), 3.69 (m, 4H), 3.37 – 2.84 (m, 2H) ppm;  $^{13}C$ -NMR: (100 MHz,  $CDCl_3$ )  $\delta$  222.5, 138.3, 137.8, 129.3, 129.1, 128.9, 128.7, 128.5, 127.7, 126.4, 63.6, 54.4, 41.8, 29.0 ppm; HRMS (ESI): m/z calculated for  $C_{24}H_{24}NOBr_2$ : 500.0225 [ $M+H^+$ ]; found: 500.0228 ( $\Delta = 0.6$  ppm).

**(S)-2-(dibenzylamino)-1-phenylpentan-3-one**

$^1H$ -NMR: (400 MHz,  $CDCl_3$ )  $\delta$  7.81 – 6.71 (m, 15H), 4.19 – 4.02 (m, 1H), 3.89 – 3.81 (d,  $3J_{HH} = 13.2$  Hz, 2H), 3.86 – 3.78 (m, 2H), 3.65 – 3.56 (d,  $3J_{HH} = 13.2$  Hz, 2H), 3.30 – 2.95 (m, 2H) ppm;  $^{13}C$ -NMR: (100 MHz,  $CDCl_3$ )  $\delta$  200.0, 138.6, 138.6, 129.4, 128.9, 128.6, 128.5, 127.5, 126.3, 66.3, 54.65, 34.18, 29.05 ppm; HRMS (ESI): m/z calculated for  $C_{24}H_{25}NOBr$ : 422.1120 [ $M+H^+$ ]; found: 422.1114 ( $\Delta = -1.2$  ppm).

**(R)-6,6-dibromo-3-hydroxy-5-oxohexanenitrile (table 3, entry 3)**

$^1H$  NMR: (400 MHz,  $CDCl_3$ )  $\delta$  5.82 (s, 1H), 4.53 – 4.39 (p,  $3J_{HH} = 5.78$  Hz, 1H), 3.37 – 3.22 (m, 2H), 3.12 - 2.82 (s, 1H), 2.74 - 2.59 (dd,  $3J_{HH} = 5.78$  Hz,  $4J_{HH} = 1.65$  Hz, 2H) ppm ;  $^{13}C$ -NMR: (100 MHz,  $CDCl_3$ )  $\delta$  195.6, 116.6, 64.2, 41.8, 40.5, 25.2 ppm. HRMS (ESI): m/z calculated for  $C_6H_7NO_2Br_2Na$ : 305.8736 [ $M+Na^+$ ]; found: 305.8731 ( $\Delta = -1.6$  ppm), calcd. for  $C_6H_6NO_2Br_2$  281.8771 [ $M-H$ ], found 281.8773 ( $\Delta = 0.8$  ppm).

**Methyl (Z)-5,5-dibromo-4-oxopent-2-enoate (table 3, entry 4)**

$^1H$ -NMR: (400 MHz,  $CDCl_3$ )  $\delta$  6.97 (d,  $3J_{HH} = 11.8$  Hz, 1H), 6.27 (dd,  $3J_{HH} = 11.8$ ,  $4J_{HH} = 1.2$  Hz, 1H), 6.22 (d,  $4J_{HH} = 1.8$  Hz, 1H), 3.79 (s, 3H) ppm;  $^{13}C$ -NMR: (100 MHz,  $CDCl_3$ )  $\delta$  187.2, 165.6, 153.2, 128.8, 52.6, 42.7 ppm; HRMS (ESI): m/z calculated for  $C_6H_7O_3Br_2$ : 284.8762 [ $M+H^+$ ]; found: 284.8771 ( $\Delta = 3.2$  ppm).

**2,2-Dibromo-1-(3-methyl-3-phenyloxiran-2-yl)ethan-1-one (table 3, entry 5)**

$^1H$ -NMR: (400 MHz,  $CDCl_3$ )  $\delta$  7.49 – 7.24 (m, 5H), 5.95 (s, 1H), 4.14 (s, 1H), 1.68 (s, 3H) ppm;  $^{13}C$ -NMR: (100 MHz,  $CDCl_3$ )  $\delta$  222.52, 140.0, 128.7, 128.6, 126.5, 66.5, 62.8, 39.5, 25.0.