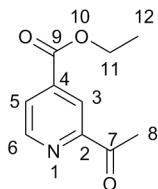


## Supplementary material

Synthetic procedures and detailed calculations for green metrics and cost.

NMR spectra were recorded on a Bruker AC 300 at 300 MHz for  $^1\text{H}$  and at 75 MHz for  $^{13}\text{C}$ . FTIR spectra were recorded on a Shimadzu IR-Affinity-1 spectrophotometer in Attenuated Total Reflectance Mode.

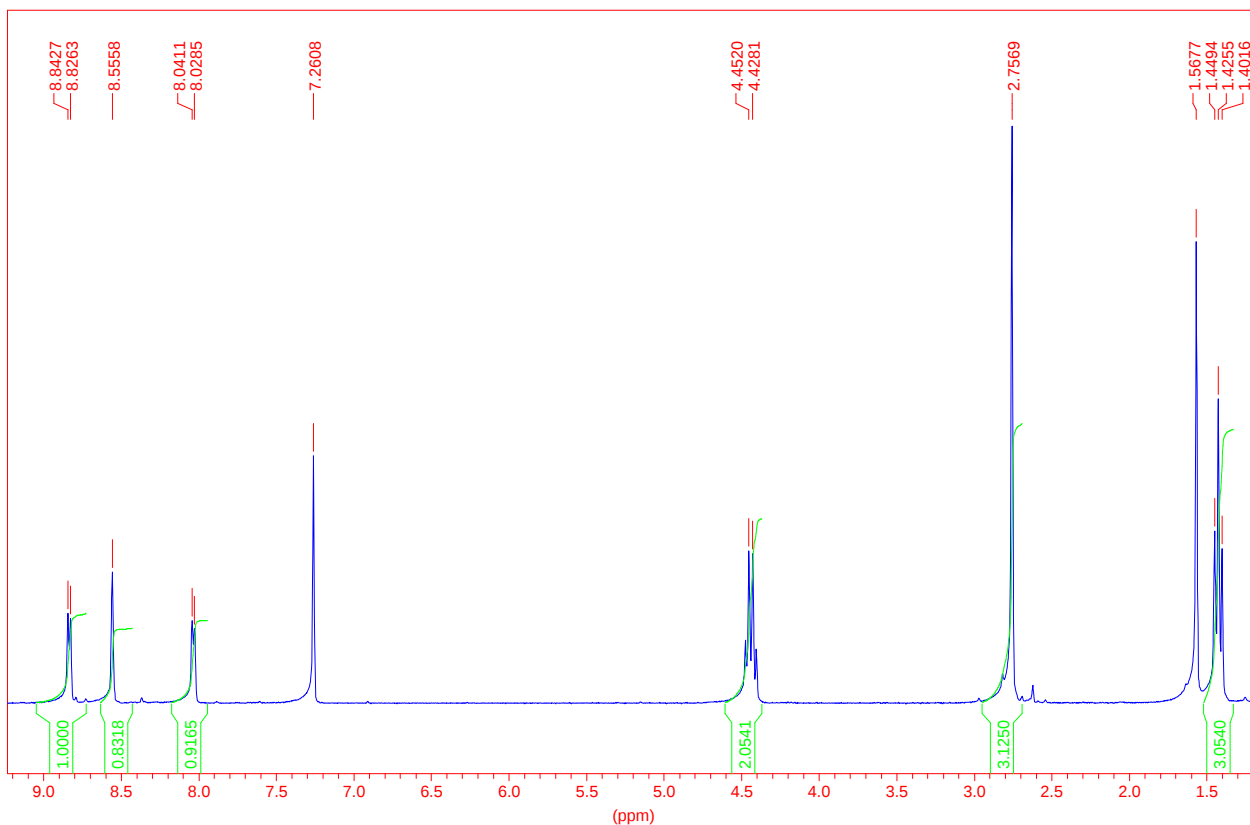
### Synthesis of ethyl 2-acetyl isonicotinate (2)



To a stirred solution of paraldehyde (82g, 620 mmol) and ethyl isonicotinate (19.2g, 127 mmol) in acetonitrile (260 mL) at ambient temperature,  $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$  (600 mg, 2.16 mmol), trifluoroacetic acid (14.86 g, 130 mmol) and 70% *t*-BuOOH (32 g, 252mmol) were added and the mixture was refluxed for 4 h. Solvent was removed under reduced pressure and the residue was taken up in a saturated sodium carbonate aqueous solution (100mL). Aqueous layer was extracted with toluene ( $3 \times 75\text{mL}$ ). The combined organic fractions were dried ( $\text{Na}_2\text{SO}_4$ ), filtered and solvent was removed under reduced pressure. The residue was then purified by bulb-to-bulb distillation, giving 15.02 g (61%) of pure **2** as white crystals (mp =  $56^\circ\text{C}$ ).

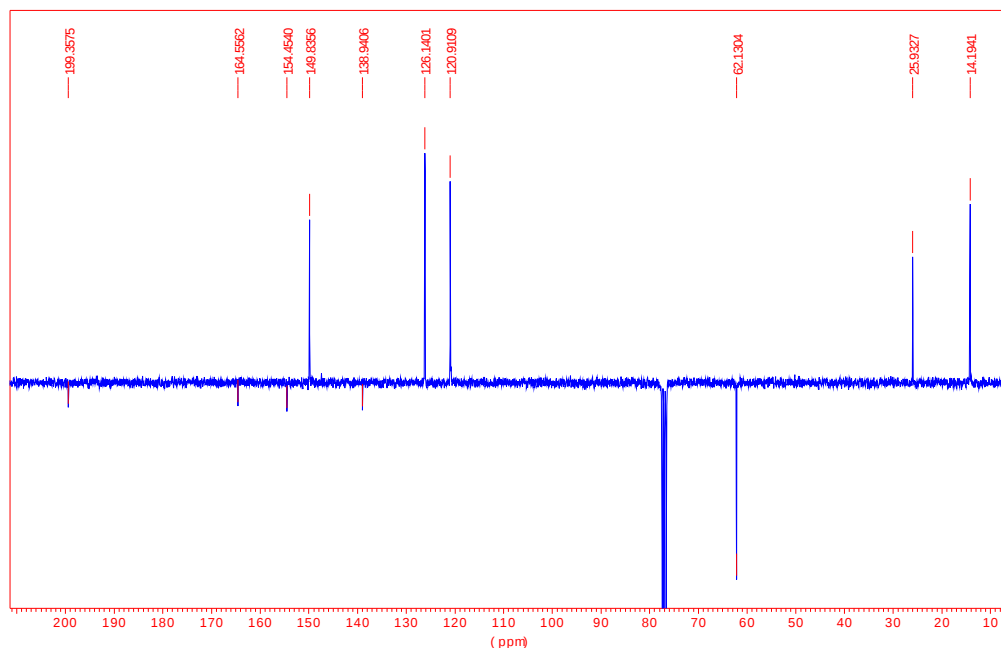
$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  ppm: 1.43 (t, 3H,  $J=7.18\text{Hz}$ , H12) , 2.76 (s, 3H, H8), 4.43 (q, 2H,  $J=7.18\text{Hz}$ , H11) 8.03 (d, 1H,  $J=3.78\text{Hz}$ , H5), 8.56 (s, 1H, H3), 8.83 (d, 1H,  $J=3.78\text{Hz}$ , H6).

JD016



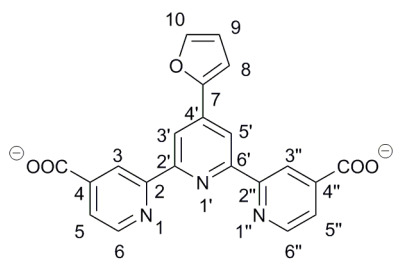
$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  ppm: 14.2, 25.9, 62.1, 120.9, 126.1, 138.9, 149.8, 154.5, 164.6, 199.4.

JD016



FT-IR ( $\text{cm}^{-1}$ ): 1718, 1700, 1653, 1558, 1507, 1307, 1236, 1132, 1017.

### Synthesis of potassium/ammonium 4'-furyl-2,2':6',2''-terpyridine-4,4''-dicarboxylate (3)

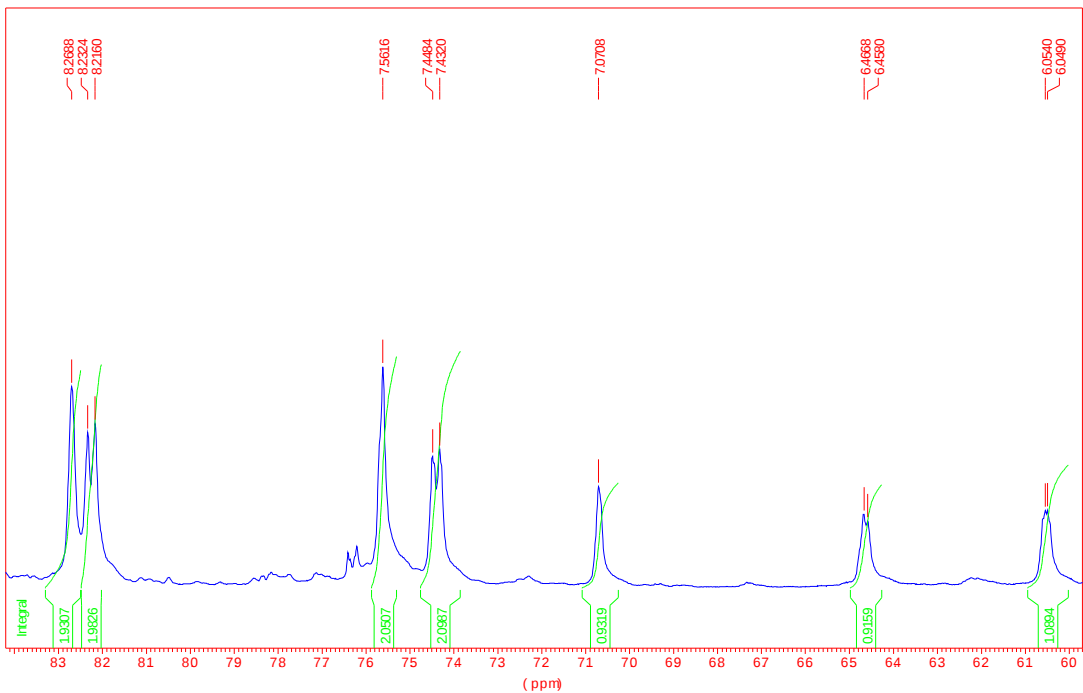


To a solution of **2** (4 g, 20.7 mmol), freshly distilled furfural (0.994g, 10.35mmol) and potassium hydroxide (2.748 g, 4.88 mmol) in 50 mL of absolute ethanol were added 22 mL of 25 % aqueous ammonia solution. The mixture was stirred for 24 h at room temperature.

The precipitated  $\text{K}^+/\text{NH}_4^+$  salt was filtered and washed with ethanol (10 mL), and dried in an excicator over  $\text{P}_2\text{O}_5$  to give 3.05 g (64%) of a brown powder ( $\text{mp} > 300^\circ\text{C}$ ) which was used in next step without further purification.

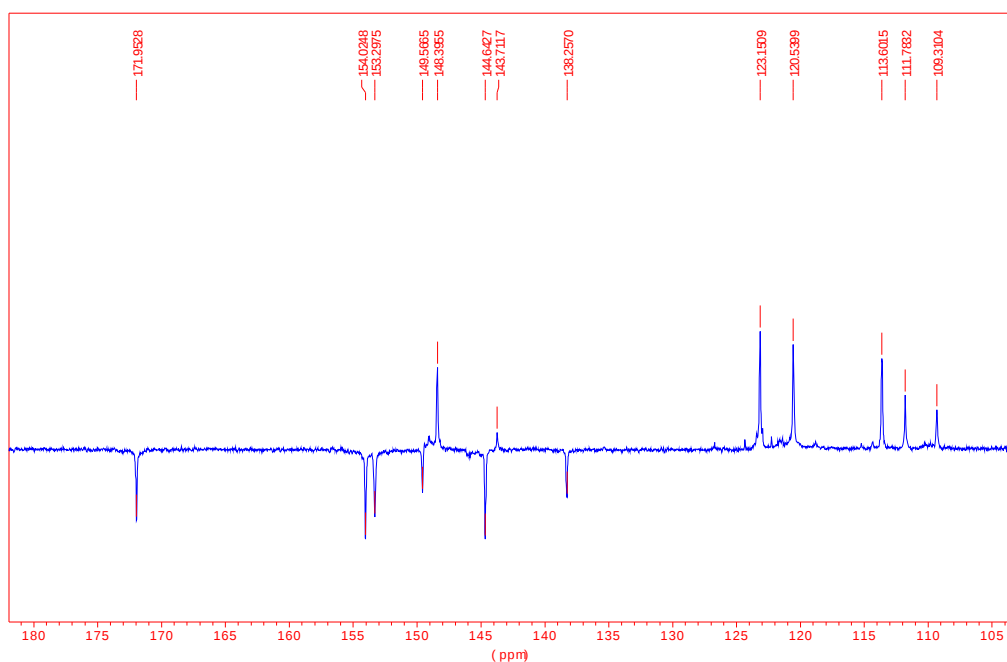
$^1\text{H}$  NMR ( $\text{D}_2\text{O}$ ):  $\delta$  ppm: 6.04 (dd, 1H,  $J=2.64\text{Hz}$ , 1.13Hz, H9), 6.46 (d, 1H,  $J=2.64\text{Hz}$ , H8), 7.07 (d, 1H,  $J=1.13\text{Hz}$ , H10), 7.44 (d, 2H,  $J=4.91\text{Hz}$ , H5, H5''), 7.56 (s, 2H, H3, H3'), 8.22 (d, 2H,  $J=4.91\text{Hz}$ , H6, H6''), 8.27 (s, 2H, H3', H5').

JD- 018- 6



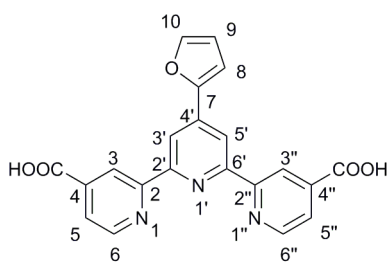
<sup>13</sup>C NMR (D<sub>2</sub>O): δ ppm: 109.3, 111.8, 113.6, 120.5, 123.2, 138.3, 143.7, 144.6, 148.4, 149.6, 153.3, 154.0, 172.0.

JD018



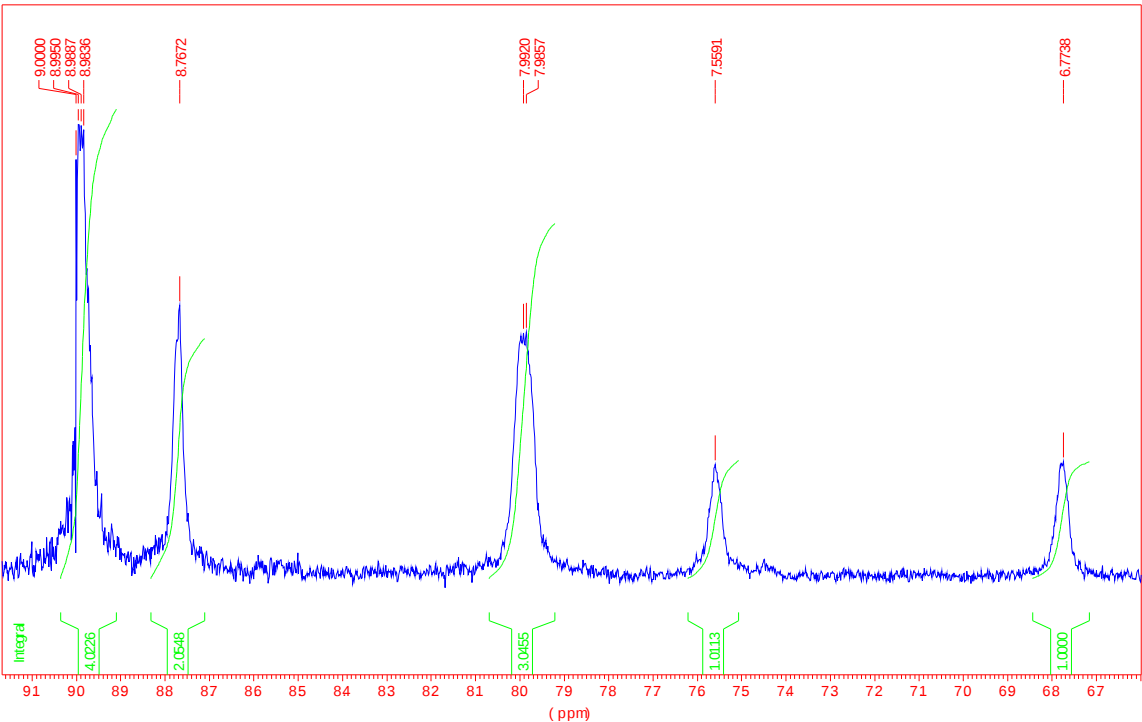
FTIR ( $\text{cm}^{-1}$ ): 2969, 2943, 2887, 2617, 2610, 1645, 1624, 1589, 1545, 1391, 1375, 1229, 1007, 978, 831, 787, 703.

For analytical purposes, diacid **4** was isolated by acidification of an aqueous solution of **3** with hydrochloric acid. This affords a precipitate ( $\text{mp} > 300^\circ\text{C}$ ) that was filtered, thoroughly washed with water and dried under vacuum over  $\text{P}_2\text{O}_5$ .



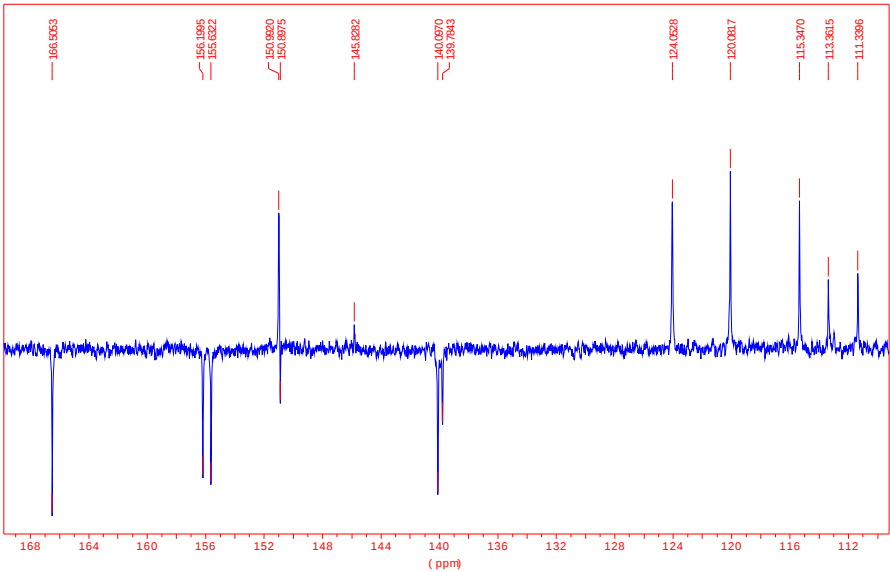
$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  ppm: 6.77 (m, 1H), 7.56 (m, 1H), 7.99 (m, 3H), 8.77 (s, 2H), 8.99 (m, 4H)

diacide (DMSO)



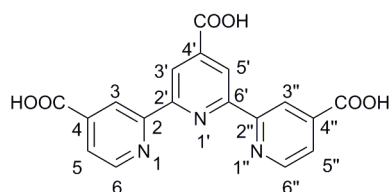
<sup>13</sup>C NMR (D<sub>2</sub>O): δ ppm: 111.3, 113.4, 115.3, 120.0, 124.1, 139.8, 140.1, 145.8, 150.9, 151.0, 155.6, 156.2, 166.5.

diacide (DMSO)



FT-IR (cm<sup>-1</sup>) : 1707, 1600, 1559, 1362, 1273, 1230, 1009.

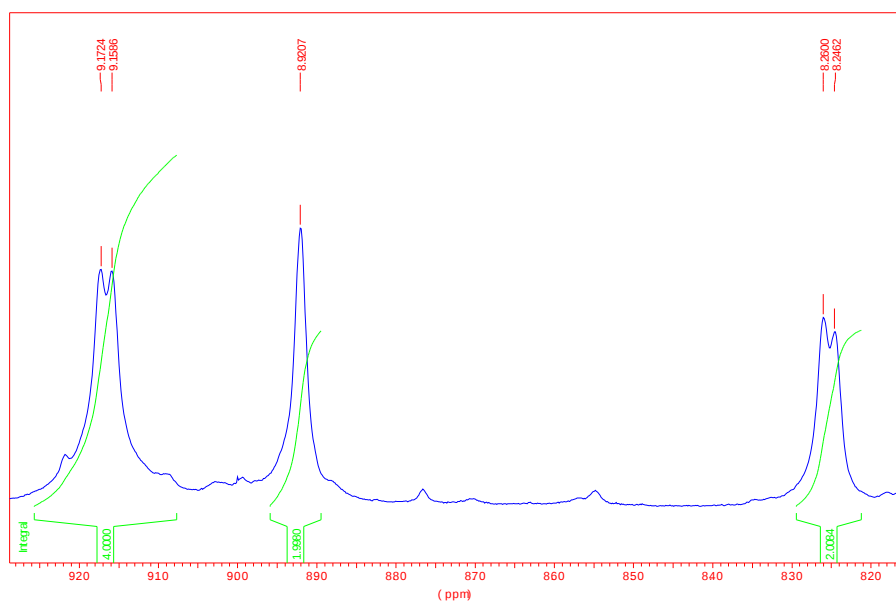
## Synthesis of 4,4',4''-tricarboxy-2,2':6',2''-terpyridine (1)



Compound **3** (2.456 g, 5.3 mmol) and  $\text{KMnO}_4$  (4 g, 25.3 mmol) were mixed in water (100 mL). The solution was adjusted to pH= 10 with potassium hydroxide (40 mg). The resulting mixture was stirred at room temperature for 24 h.  $\text{Na}_2\text{S}_2\text{O}_3$  (4 g, 25.3 mmol) in water (80 mL) was added.  $\text{MnO}_2$  was filtered on a bed of celite (2g) and the filtrate was acidified to pH =4 with 37 % HCl (1.15 g). The obtained precipitate was filtered, thoroughly washed with ethanol and  $\text{H}_2\text{O}$ . The product was dried over  $\text{P}_2\text{O}_5$ . 4,4',4''-Tricarboxy-2,2':6',2''-terpyridine was obtained (1.8g, 93%) as a white solid (mp>300°C).

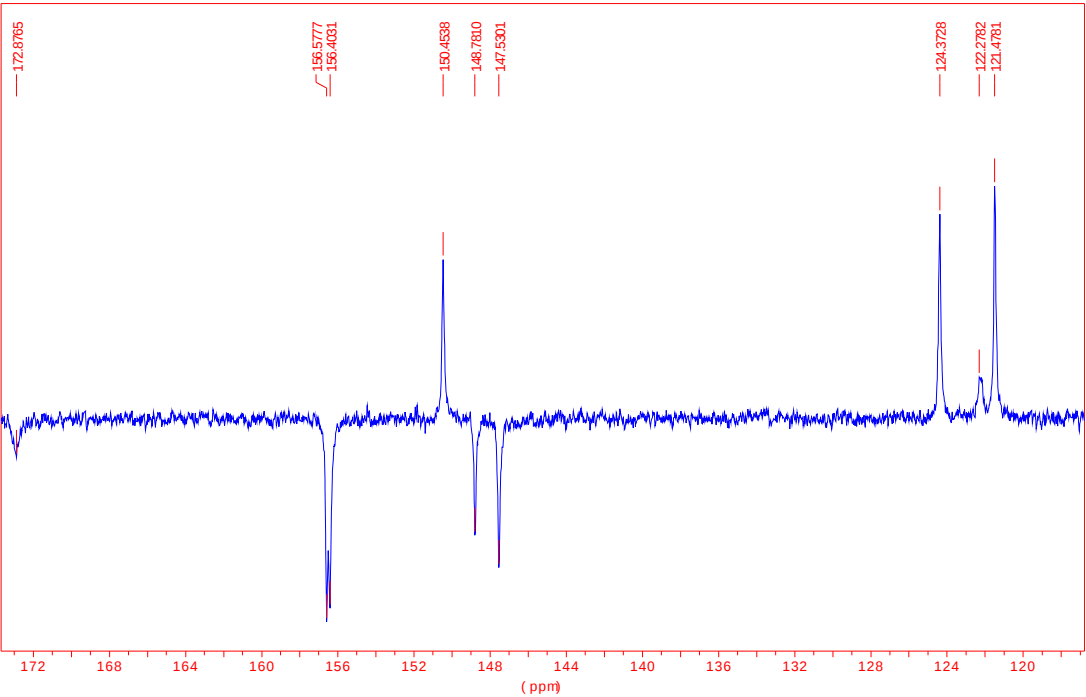
$^1\text{H}$  NMR ( $\text{ND}_3/\text{D}_2\text{O}$ ):  $\delta$  ppm: 8.25 (d, 2H,  $J=4.14\text{Hz}$ , H5, H5''), 8.92 (s, 2H, H3, H3''), 9.17 (d, 2H,  $J=4.14\text{Hz}$ , H6, H6''), 9.18 (s, 2H, H3', H5').

H3tcterpy



<sup>13</sup>C NMR (ND<sub>3</sub>/D<sub>2</sub>O): δ ppm: 121.5, 122.3, 124.4, 147.5, 148.8, 150.5, 156.4, 156.6, 172.9.

JD019 ND<sub>3</sub>



FT-IR (cm<sup>-1</sup>): 2361, 1736, 1717, 1616, 1553, 1369, 1229, 1128, 1001.

## Atom Economy

### Pathway A

|        | Reagent                     | Formula                                       | FW (g/mol) | Stoichiometry |
|--------|-----------------------------|-----------------------------------------------|------------|---------------|
| Step 1 | Ethyl isonicotinate         | C <sub>8</sub> H <sub>9</sub> NO <sub>2</sub> | 151,16     | 2             |
|        | Paraldehyde                 | C <sub>6</sub> H <sub>12</sub> O <sub>3</sub> | 132,16     | 0,7           |
|        | <i>t</i> Butylhydroperoxide | C <sub>4</sub> H <sub>10</sub> O <sub>2</sub> | 90,12      | 2             |
|        | iron (II) sulfate           | FeSO <sub>4</sub>                             | 278,01     | 2             |
|        | Trifluoroacetic acid        | C <sub>2</sub> HF <sub>3</sub> O <sub>2</sub> | 114,02     | 2             |
| Step 2 | Furfuraldehyde              | C <sub>5</sub> H <sub>4</sub> O <sub>2</sub>  | 96,09      | 1             |
|        | Potassium hydroxide         | KOH                                           | 56,11      | 2             |
|        | Ammonia                     | NH <sub>3</sub>                               | 17,00      | 1             |
| Step 3 | Potassium hydroxide         | KOH                                           | 56,11      | 1             |
|        | Potassium permanganate      | KMnO <sub>4</sub>                             | 158,03     | 5,3           |
|        | Hydrochloric acid           | HCl                                           | 36,46      | 3             |

|         |                                            |                                                               |        |
|---------|--------------------------------------------|---------------------------------------------------------------|--------|
| Product | 4,4',4''-tricarboxy-,2':6',2''-terpyridine | C <sub>18</sub> N <sub>11</sub> N <sub>3</sub> O <sub>6</sub> | 365,30 |
|---------|--------------------------------------------|---------------------------------------------------------------|--------|

|              |       |
|--------------|-------|
| Atom Economy | 14,12 |
|--------------|-------|

### Pathway B

|        | Reagent              | Formula                                       | FW (g/mol) | Stoichiometry |
|--------|----------------------|-----------------------------------------------|------------|---------------|
| Step 1 | 4-Ethylpyridine      | C <sub>7</sub> H <sub>9</sub> N               | 107,16     | 3             |
| Step 2 | Sulfuric acid        | H <sub>2</sub> SO <sub>4</sub>                | 98,07      | 24            |
|        | potassium dichromate | K <sub>2</sub> Cr <sub>2</sub> O <sub>7</sub> | 294,18     | 6             |

|         |                                            |                                                               |        |
|---------|--------------------------------------------|---------------------------------------------------------------|--------|
| Product | 4,4',4''-tricarboxy-,2':6',2''-terpyridine | C <sub>18</sub> N <sub>11</sub> N <sub>3</sub> O <sub>6</sub> | 365,30 |
|---------|--------------------------------------------|---------------------------------------------------------------|--------|

|              |      |
|--------------|------|
| Atom Economy | 8,23 |
|--------------|------|

**E factor :**

Pathway A

Step 1

| Reagent                      | Amount (g) | Amount (mL) | Density | TOTAL mass (g) |
|------------------------------|------------|-------------|---------|----------------|
| Ethyl isonicotinate          | 19,200     |             |         | 19,20          |
| Paraldehyde                  | 82,000     |             |         | 82,00          |
| Iron sulfate heptahydrate    | 0,330      |             |         | 0,33           |
| Trifluoroacetic acid         | 14,860     |             |         | 14,86          |
| <i>t</i> Butyl hydroperoxide | 22,690     |             |         | 22,69          |
| Acetonitrile                 |            | 260         | 0,78    | 203,06         |
| Calcium carbonate            | 30,000     |             |         | 30,00          |
| Toluene                      |            | 225         | 0,87    | 194,85         |
| Sodium sulfate               | 25,000     |             |         | 25,00          |

Amount intermediate 2 (g)

15,02

Amount wastes (g)

576,97

E factor for step 1

38,41

Step 2

| Reagent                    | Amount (g) | Amount (mL) | Density | TOTAL mass (g) |
|----------------------------|------------|-------------|---------|----------------|
| Wastes from previous step  | 153,654    |             |         | 153,65         |
| Intermediate 2             | 4,000      |             |         | 4,00           |
| Furfuraldehyde             | 0,994      |             |         | 0,99           |
| Potassium hydroxide        | 2,748      |             |         | 2,75           |
| Aqueous NH <sub>4</sub> OH | 5,005      |             |         | 5,01           |
| Ethanol                    |            | 60          | 0,78    | 46,80          |

Amount intermediate 3 (g)

3,05

Amount wastes (g)

210,15

E factor for step 2

68,90

Step 3

| Reagent                   | Amount (g) | Amount (mL) | Density | TOTAL mass (g) |
|---------------------------|------------|-------------|---------|----------------|
| Wastes from previous step | 169,223    |             |         | 169,22         |
| Intermediate 3            | 2,456      |             |         | 2,46           |
| Potassium permanganate    | 4,000      |             |         | 4,00           |
| Potassium hydroxide       | 0,040      |             |         | 0,04           |
| Celite                    | 2,000      |             |         | 2,00           |
| Conc. Hydrochloric acid   | 0,368      |             |         | 0,37           |
| Ethanol                   |            | 20          | 0,78    | 15,60          |

Amount final product 1 (g) 1,80

Amount wastes (g) 191,89

E factor for process 106,60

Pathway B : “Worst” scenario : No recycling

Step 1

| Reagent | Amount (g) | Amount (mL) | Density | TOTAL mass (g) |
|---------|------------|-------------|---------|----------------|
|---------|------------|-------------|---------|----------------|

|                 |      |        |      |        |
|-----------------|------|--------|------|--------|
| 4-Ethylpyridine |      | 50,00  | 0,94 | 47,10  |
| 10% Pd on C     | 4,00 |        |      | 4,00   |
| Dichloromethane |      | 600,00 | 1,33 | 795,00 |

|                           |      |                   |        |
|---------------------------|------|-------------------|--------|
| Amount intermediate 5 (g) | 9,50 | Amount wastes (g) | 836,60 |
|---------------------------|------|-------------------|--------|

|                     |       |
|---------------------|-------|
| E factor for step 1 | 88,06 |
|---------------------|-------|

Step 2 (final step of process)

| Reagent | Amount (g) | Amount (mL) | Density | TOTAL mass (g) |
|---------|------------|-------------|---------|----------------|
|---------|------------|-------------|---------|----------------|

|                           |        |       |      |        |
|---------------------------|--------|-------|------|--------|
| Wastes from previous step | 792,57 |       |      | 792,57 |
| Intermediate 5            | 9,00   |       |      | 9,00   |
| Sulfuric acid 98%         | 504,89 |       |      | 504,89 |
| Potassium dichromate      | 54,00  |       |      | 54,00  |
| Nitric acid 65%           | 86,45  |       |      | 86,45  |
| Diethyl ether             |        | 60,00 | 0,71 | 42,84  |

|                            |      |                   |         |
|----------------------------|------|-------------------|---------|
| Amount final product 1 (g) | 4,30 | Amount wastes (g) | 1485,45 |
|----------------------------|------|-------------------|---------|

|                      |        |
|----------------------|--------|
| E factor for process | 345,45 |
|----------------------|--------|

Pathway B : “Best” scenario with recycling of catalyst and 4-ethylpyridine

Step 1

| Reagent         | Amount (g) | Amount (mL) | Density | TOTAL mass (g) |
|-----------------|------------|-------------|---------|----------------|
| 4-Ethylpyridine |            | 10,21       | 0,94    | 9,62           |
| 10% Pd on C     | 0,20       |             |         | 0,20           |
| Dichloromethane |            | 600,00      | 1,33    | 795,00         |

Amount intermediate 5 (g) 9,50

Amount wastes (g) 795,32

E factor for step 1 83,72

Step 2 (final step of process)

| Reagent                   | Amount (g) | Amount (mL) | Density | TOTAL mass (g) |
|---------------------------|------------|-------------|---------|----------------|
| Wastes from previous step | 753,46     |             |         | 753,46         |
| Intermediate 5            | 9,00       |             |         | 9,00           |
| Sulfuric acid 98%         | 504,89     |             |         | 504,89         |
| Potassium dichromate      | 54,00      |             |         | 54,00          |
| Nitric acid 65%           | 86,45      |             |         | 86,45          |
| Diethyl ether             |            | 60,00       | 0,71    | 42,84          |

Amount final product 1 (g) 4,30

Amount wastes (g) 1446,34

E factor for process 336,36

**Cost**

Pathway A

Step 1

| Reagent                      | Amount (g) | Amount (mL) | Price (€/g or ml) | TOTAL reagent (€) |
|------------------------------|------------|-------------|-------------------|-------------------|
| Ethyl isonicotinate          | 19,2       |             | 0,380             | 7,296             |
| Paraldehyde                  | 82         |             | 0,037             | 3,034             |
| Iron sulfate heptahydrate    | 0,6        |             | 0,022             | 0,013             |
| Trifluoroacetic acid         | 14,86      |             | 0,200             | 2,972             |
| <i>t</i> Butyl hydroperoxide | 32,42      |             | 0,050             | 1,621             |
| Acetonitrile                 |            | 260         | 0,048             | 12,480            |
| Calcium carbonate            | 30         |             | 0,020             | 0,600             |
| Toluene                      |            | 225         | 0,022             | 4,950             |
| Sodium sulfate               | 25         |             | 0,008             | 0,200             |

Amount intermediate 2 (g) 15,02

Cost intermediate 2 (€/g) 2,21

## Step 2

| Reagent                    | Amount (g) | Amount (mL) | Price (€/g or ml) | TOTAL reagent (€) |
|----------------------------|------------|-------------|-------------------|-------------------|
| intermediate 2             | 4          |             | 2,210             | 8,840             |
| Furfuraldehyde             | 0,994      |             | 0,039             | 0,039             |
| Potassium hydroxide        | 2,748      |             | 0,017             | 0,047             |
| Aqueous NH <sub>4</sub> OH |            | 22          | 0,012             | 0,264             |
| Ethanol                    |            | 60          | 0,011             | 0,660             |

Amount intermediate 3 (g)

Cost intermediate 3 (€/g)

## Step 3

| Reagent                 | Amount (g) | Amount (mL) | Price (€/g or ml) | TOTAL reagent (€) |
|-------------------------|------------|-------------|-------------------|-------------------|
| intermediate 3          | 2,456      |             | 3,230             | 7,93288           |
| Potassium permanganate  | 4          |             | 0,039             | 0,156             |
| Potassium hydroxide     | 0,04       |             | 0,017             | 0,00068           |
| Celite                  | 2          |             | 0,037             | 0,074             |
| Conc. Hydrochloric acid | 1,15       |             | 0,004             | 0,0046            |
| Ethanol                 |            | 20          | 0,011             | 0,22              |

Amount final product 1 (g)

Cost final product 1 (€/g)

## Pathway B : only “best” scenario

### Step 1

| Reagent         | Amount (g) | Amount (mL) | Price (€/g or ml) | TOTAL reagent (€) |
|-----------------|------------|-------------|-------------------|-------------------|
| 4-Ethylpyridine |            | 10,21       | 1,06              | 10,8226           |
| 10% Pd on C     | 0,2        |             | 10,18             | 2,036             |
| Dichloromethane |            | 600         | 0,01              | 6                 |

Amount intermediate 5 (g)

Cost intermediate 5 (€/g)

### Step 2

| Reagent              | Amount (g) | Amount (mL) | Price (€/g or ml) | TOTAL reagent (€) |
|----------------------|------------|-------------|-------------------|-------------------|
| intermediate 5       | 9          |             | 1,99              | 17,91             |
| Sulfuric acid 98%    |            | 280         | 0,006             | 1,68              |
| Potassium dichromate | 54         |             | 0,03              | 1,62              |
| Nitric acid 65%      |            | 95          | 0,02              | 1,9               |
| Diethyl ether        |            | 60          | 0,017             | 1,02              |

Amount final product 1 (g)

Cost final product 1 (€/g)

EcoScale parameter

Pathway A

| Parameter                                  | Penalty points |
|--------------------------------------------|----------------|
| Overall yield : 36,3 %                     | 31,85          |
| Price for 10 mmol (3,65 g) : 17,01 €       | 3              |
| Safety : ethyl isonicotinate : Xi          | 0              |
| Safety : paraldehyde : F                   | 5              |
| Safety : iron sulfate : Xn                 | 0              |
| Safety : trifluoroacetic acid : C          | 0              |
| Safety : tbutylhydroperoxide : O,C         | 0              |
| Safety : acetonitrile : F, Xn              | 5              |
| Safety : calcium carbonate : Xi            | 0              |
| Safety : toluene : F, Xn                   | 5              |
| Safety : sodium sulfate                    | 0              |
| Safety : furfuraldehyde : T                | 5              |
| Safety : potassium hydroxide : C           | 0              |
| Safety : aqueous ammonia : C,N             | 5              |
| Safety : ethanol : F                       | 5              |
| Safety : potassium permanganate : O, Xn, N | 5              |
| Safety : hydrochloric acid : C             | 0              |
| Safety : Celite                            | 0              |
| Common setup (step 1)                      | 0              |
| Heating > 1 h (step 1)                     | 3              |
| Removal of acetonitrile (step 1)           | 0              |
| Liquid-liquid extraction (step 1)          | 3              |
| Drying + filtration (step 1)               | 0              |
| Removal of toluene (step 1)                | 0              |
| Distillation (step 1)                      | 3              |
| Common setup (step 2)                      | 0              |
| Stirring at room temperature 24 h (step 2) | 1              |
| Filtration (step 2)                        | 0              |
| Common setup (step 3)                      | 0              |
| Stirring at room temperature 24 h (step 3) | 1              |
| Filtration (step 3)                        | 0              |
| Adding hydrochloric acid (step 3)          | 0              |
| Filtration (step 3)                        | 0              |

EcoScale parameter : 19,15

## Pathway B : “Best” scenario

| Parameter                                  | Penalty points |
|--------------------------------------------|----------------|
| Overall yield : 7,2 %                      | 46,4           |
| Price for 10 mmol (3,65 g) : 20,48 €       | 3              |
| Safety : 4-ethylpyridine : F               | 5              |
| Safety : palladium on carbon : F           | 5              |
| Safety : dichloromethane : T               | 5              |
| Safety : sulfuric acid : C                 | 0              |
| Safety : potassium dichromate : T+         | 10             |
| Safety : nitric acid : C                   | 0              |
| Safety : diethyl ether : F+                | 10             |
| Common setup (step 1)                      | 0              |
| Heating > 1 h (step 1)                     | 3              |
| Cooling to room temperature (step 1)       | 0              |
| Filtration (step 1)                        | 0              |
| Removal of dichloromethane (step 1)        | 0              |
| Distillation 4-ethylpyridine (step 1)      | 3              |
| Sublimation bipyridine by-product (step 1) | 3              |
| Common setup (step 2)                      | 0              |
| Cooling to 5°C (step 2)                    | 0              |
| Filtration (step 2)                        | 0              |
| Heating > 1 h (step 2)                     | 3              |
| Cooling to room temperature (step 2)       | 0              |
| Cooling to 5°C (step 2)                    | 0              |
| Filtration (step 2)                        | 0              |

EcoScale parameter : 3,6