Supporting Information

1. The reaction condition screening of compound 3.

1.1 The reaction solvent screening.

| Lot number | Solvent | Reaction temperature | Yield | HPLC purity of reaction solvent |
|---|---|---|---|---|
| 1 | Toluene | 100 $^0$C | The reaction does not work | |
| 2 | Ethanol | 75 $^0$C | The reaction does not work | |
| 3 | 1-Pentanol | 130-132 $^0$C | 68% | 97.94% |
| 4 | Isopentanol | 130-135 $^0$C | 71% | 97.23% |

1.2 The base screening of the reaction.

| Lot number | Base | Mol eq. | Reaction temperature | Results |
|---|---|---|---|---|
| 1 | $K_2CO_3$ | 0.5 | 130-135$^0$C | Starting materials totally consumed |
| 2 | $Et_3N$ | 0.5 | 130-135$^0$C | Reaction does not work |
| 3 | $K_2CO_3$ | 1.0 | 130-135$^0$C | Starting materials totally consumed |
| 4 | NaOH | 0.5 | 130-135$^0$C | Lots of starting materials remained |
| 5 | NaOH | 1.0 | 130-135$^0$C | Lots of starting materials remained |

1.3 The results of three validation batches.

| Lot number | Yield | HPLC purity |
|---|---|---|
| 1 | 82.50% | 97.86% |
| 2 | 83.10% | 97.45% |
| 3 | 82.30% | 97.25% |

2. The reaction condition screening of compound 4.

2.1 $POCl_3$ used as the solvent and chlorination reagent.

| Lot number | Mole eq. of $POCl_3$ | Reaction time | Impurity IV | Impurity V | Compound 4 | Isolated yield |
|---|---|---|---|---|---|---|
| 1 | 4 | 6h | 21.83% | 3.21% | 72.52% | 65.0% |
| 2 | 6 | 3h | 10.72% | 2.28% | 85.02% | 78.0% |
| 3 | 8 | 7h | 17.25% | 4.83% | 71.92% | 62.35% |
| 4 | 10 | 6.5h | 12.62% | 3.08% | 82.30% | 79.75% |
| 5 | 20 | 2.5h | 3.63% | 0.43% | 95.85% | 78.67% |
| 6 | 20 | 2h | 2.56% | 2.23% | 93.21% | 85.0% |

2.2 Reaction solvent screening.

| Lot number | Solvent | Volume of solvent | Mole eq. of $POCl_3$ | Reaction temperature | Reaction results |
|---|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| 1 | DCM | 10 V | 5 | $45^0$C | Little product formed |
| 2 | Toluene | 10 V | 5 | $95^0$C | Lots of starting materials remained |
| 3 | $POCl_3$ | 20 V | -- | $95^0$C | Product and impurity IV produced at the same time |
| 4 | Toluene | 10 V | 4+ 4.4 eq. $Et_3N$ | 95 $^0$C | Starting materials totally consumed and no impurity IV formed |

2.3 The results of three validation batches.

| | Yield | Purity |
|---|---|---|
| 1 | 95.5% | 99.15%* |
| 2 | 96.4% | 99.00% |
| 3 | 95.8% | 99.10% |

3 The reaction condition screening of compound 11.

3.1 The purification process of compound 11

| Lot number | Impurity II | Impurity III | Compound 11 | Note |
|---|---|---|---|---|
| 1 | ND | 1.25 % | 93.12 % | The HPLC report of the reaction solvent |
| 2 | ND | 0.76 % | 96.78 % | The HPLC report of the HCl salt |
| 3 | ND | ND | 99.88 % | The HPLC report after recrystallization in methanlol |

3.2 The results of three validation batches, compound 11.

| Lot number | Yield | Purity |
|---|---|---|
| 1 | 82.0% | 99.88% |
| 2 | 83.1% | 99.88% |
| 3 | 83.5% | 100.0% |

4 The results of three validation batches, compound 12.

| Lot number | Yield | Purity |
|---|---|---|
| 1 | 97.3% | 98.68% |
| 2 | 96.7% | 98.46% |
| 3 | 97.9% | 97.94% |

5 The results of three validation batches, final product compound 1.

| Lot number | Yield | Purity |
|---|---|---|
| 1 | 86.93%* | 99.80% |

| | | |
|---|---|---|
| 2 | 86.65% | 99.68% |
| 3 | 86.99% | 99.76% |

6 The formation, purge and fate of the impurity in the process.