Supporting Information

Integration of Solventless Reaction in Multi-Step Process.
Application to Efficient Synthesis of PA-824

Akihiro Orita, Kai Miwa, Genta Uehara, and Junzo Otera*
Department of Applied Chemistry, Okayama University of Science, Ridai-cho,
Okayama 700-0005, Japan
Fax: (+81)-86-256-4292; e-mail: otera@high.ous.ac.jp

Summary of reaction mass efficiencies (RMEs) and necessary solvents for PG, THP,
CIN and PG processes.
GL/SW

**2**

O₂N  

H  

NO₂

For workup
AcOEt 180.4 L
NaHCO₃aq, water and NaClaq 37.3 L
For column chromatography 12440 L

Total amount of solvents (12682.6 L)

**4b** 82% after c.c.

1.98 kg (5.10 mol)

**8b** 92% after c.c.

2.43 kg (4.69 mol)

Total amount of solvents (7806.2 L)

**8b** → OTIPS

O₂N  

H  

NO₂

For workup
AcOEt 140.7 L
NaHCO₃aq, water and NaClaq 140.7 L
For column chromatography 23450 L
Total amount of solvents (23758.6 L)

**6b** 91% after c.c.

1.35 kg (4.27 mol)

**7** 93% after filtration.

0.74 kg (3.97 mol)

Total amount of solvents (725.9 L)

**8b** → O₂N  

H  

NO₂

For workup
AcOEt 76.5 L
NaHCO₃aq and NaClaq 51.0 L
For column chromatography 7650 L
Total amount of solvents (8210.0 L)

RME = 0.98 + 0.60 + 0.094 + 1.27 + 3.00 + 0.23 + 0.91 + 1.05 + 0.12 + 1.35 + 0.012 + 1.22 + 0.0953 = 1.00/10.93 = 0.091

Solvent employed = 12682.6 + 7806.2 + 23758.6 + 725.9 + 8210.0 = 53183 L

Solvents for reaction = 24.9 + 25.5 + 3.2 + 23.5 + 3.7 + 170.8 + 19.9 = 272 L
For column chromatography 10905 L
Total amount of solvents (10905.0 L)

For workup
AcOEt 92.7 L
NaHCO₃aq and NaClaq 61.8 L
For column chromatography 12360 L
Total amount of solvents (12545.4 L)

For workup
CH₂Cl₂ 119.1 L
NaHCO₃aq, water and NaClaq 119.1 L
For column chromatography 7940 L
For recrystallization 11.9 L
Total amount of solvents (8210.0 L)

RME = \frac{1.00}{1.15 + 2.01 + 1.56 + 0.31 + 4.22 + 1.22 + 0.0953} = \frac{1.00}{10.56} = 0.094

Solvent employed = 10905.0 + 12545.4 + 27261.2 + 174.4 + 8210.0 = 59096 L

Solvents for reaction = 30.9 + 26.9 + 11.5 + 130.8 + 19.9 = 220 L
THP/IP-1

1.15 kg (7.28 mol)

For workup
AcOEt 109.2 L
NaHCO₃aq and NaCl 72.8 L
For column chromatography 18200 L
Total amount of solvents (18418.4 L)

2.72 kg (5.75 mol)

8a: 79% after c.c.

TBAF (4.51 kg, 3.0 equiv) 12N-HCl
THF (25.8 L) MeOH (172.5 L)
THF in TBAF/THF 12.2 L
For column chromatography 23000 L
For recrystallization 17.3 L
Total amount of solvents (23230.8 L)

0.74 kg (3.97 mol)

7: 69% after recrys.

Nah (95.3 g, 1.0 equiv)
DMF (19.9 L)
For workup
CH₂Cl₂ 119.1 L
NaHCO₃aq, water and NaCl 119.1 L
For column chromatography 7940 L
For recrystallization 11.9 L
Total amount of solvents (8210.0 L)

1.00 kg (2.78 mol)

1: 70% after recryst.

\[
\text{RME} = \frac{1.00}{1.15+2.01+1.84+0.37+4.51+1.22+0.0953} = \frac{1.00}{11.2} = 0.089
\]

Solvent employed = 18418.4 + 23230.8 + 8210.0 = 49859 L

Solvents for reaction = 36.4 + 28.8 + 12.2 + 172.5 + 19.9 = 270 L
THP/IP-2

1.35 kg
(8.55 mol)

O₂N

N

H

NO₂

2

O

N

H

O

N

H

O

N

H

O

N

H

O

6a: 51% after c.c.
1.17 kg
(4.36 mol)

O₂N

N

H

O

N

H

O

N

H

O

N

H

O

N

H

O

N

H

O

N

H

O

N

H

O

12N-HCl
MeOH (130.8 L)

6a: 51% after c.c.
1.17 kg
(4.36 mol)

For recrystallization 43.6 L
Total amount of solvents
(174.4 L)

1.00 kg
(2.78 mol)

1.00
RME = = 0.070
1.35+2.36+2.16 + 0.43 +6.71+1.22+0.0953

Solvent employed = 21735.4 + 174.4 + 8210.0 = 30120 L

Solvents for reaction = 42.8 + 42.8 + 18.2 + 130.8 + 19.9 = 255 L
CIN/SW

**Diagram and Text:**

For column chromatography 9000 L
Total amount of solvents (9000.0 L)

**PhCH=CHCOOH (0.91 kg 1.2 equiv)**
**DCC (1.05 kg, 1.0 equiv)**
**DMAP (0.12 kg, 20 mol%)**
Toluene (25.5 L)
Pyridine in DCC/Pyridine 3.2 L
For workup
AcOEt 76.5 L
NaHCO₃aq and NaClaq 51.0 L
For column chromatography 7650 L
Total amount of solvents (7806.2 L)

**TBAF (1.35 kg, 1.1 equiv)**
THF (23.5 L)
THF in TBAF/THF 3.7 L
For workup
AcOEt 140.7 L
NaHCO₃aq, water and NaClaq 140.7 L
For column chromatography 23450 L
Total amount of solvents (23758.6 L)

**(−C₂H₅O)₂Ti (12.1 g, 1 mol%)**
MeOH (170.8 L)
For workup
MeOH 427.0 L
For filtration 128.1 L
Total amount of solvents (725.9 L)

**NaH (95.3 g, 1.0 equiv)**
DMF (19.9 L)
For workup
CH₂Cl₂ 119.1 L
NaHCO₃aq, water and NaClaq 119.1 L
For column chromatography 7940 L
For recrystallization 11.9 L
Total amount of solvents (8210.0 L)

**RME =**

\[
\frac{1.00}{0.95 + 1.66 + 0.91 + 1.05 + 0.12 + 1.35 + 0.012 + 1.22 + 0.0953} = \frac{1.00}{7.37} = 0.136
\]

Solvent employed = 9000.0 + 7806.2 + 23758.6 + 725.9 + 8210.0 = 49501 L

Solvents for reaction = 25.5 + 3.2 + 23.5 + 3.7 + 170.8 + 19.9 = 247 L
O2N
\[
\begin{align*}
\text{PhCH=CHCHOH} & \quad (0.88 \text{ kg} \ 1.02 \text{ equiv}) \\
\text{DCC} & \quad (1.03 \text{ kg} \ 0.85 \text{ equiv}) \\
\text{DMAP} & \quad (0.12 \text{ kg} \ 17 \text{ mol\%})
\end{align*}
\]

toluene (23.4 L)

Pyridine in DCC/Pyridine 3.1 L

For workup
AcOEt 87.8 L
NaHCO3aq and NaClaq 58.5 L

For column chromatography 14625 L

Total amount of solvents (14797.8 L)

O2N
\[
\begin{align*}
\text{TBAF} & \quad (1.33 \text{ kg} \ 1.1 \text{ equiv}) \\
\text{THF} & \quad (23.1 \text{ L})
\end{align*}
\]

THF in TBAF/THF 3.6 L

MeOH (184.8 L)

For column chromatography 23100 L

For reprecipitaion 13.9 L

Total amount of solvents (23325.4 L)

O2N
\[
\begin{align*}
\text{CF3O} & \quad (1.22 \text{ kg} \ 1.2 \text{ equiv}) \\
\text{NaH} & \quad (95.3 \text{ g} \ 1.0 \text{ equiv})
\end{align*}
\]

DMF (19.9 L)

For workup
CH2Cl2 119.1 L
NaHCO3aq, water and NaClaq 119.1 L

For column chromatography 7940 L

For recrystallization 11.9 L

Total amount of solvents (8210.0 L)

RME = \frac{1.00}{0.92 + 1.62 + 0.88 + 1.03 + 0.12 + 1.33 + 0.0122 + 1.22 + 0.0953} = \frac{1.00}{7.23} = 0.138

Solvent employed = 14797.8 + 23325.4 + 8210.0 = 46333 L

Solvents for reaction = 23.4 + 3.1 + 23.1 + 3.6 + 184.8 + 19.9 = 258 L
CIN/IP-2

1.05 kg (6.62 mol)

\[
\text{PhCH=CHCOOH (1.00 kg 1.02 equiv)} \quad \text{DCC (1.16 kg, 0.85 equiv)} \quad \text{DMAP (0.14 kg, 17 mol\%)}
\]

\[
\text{toluene (26.5 L)} \quad \text{Pyridine in DCC/Pyridine 3.5 L}
\]

For workup
AcOEt 99.3 L
NaHCO₃aq , water and NaClaq 99.3 L

Total amount of solvents (13499.8 L)

\[
\text{O₂N} \quad \text{N} \quad \text{NO₂}
\]

3a (1.83 kg, 1.2 equiv)

\[
\text{O₂N} \quad \text{N} \quad \text{O}
\]

PhCH=CHCOOH (1.00 kg 1.02 equiv)
DCC (1.16 kg, 0.85 equiv)
DMAP (0.14 kg, 17 mol\%)

\[
\text{toluene (26.5 L)} \quad \text{Pyridine in DCC/Pyridine 3.5 L}
\]

For workup
AcOEt 99.3 L
NaHCO₃aq , water and NaClaq 99.3 L

Total amount of solvents (13499.8 L)

\[
\text{O₂N} \quad \text{N} \quad \text{NO₂}
\]

6b: 74% (mixture) after c.c.

1.54 kg (4.90 mol)

\[
\text{O₂N} \quad \text{N} \quad \text{O}
\]

(1.22 kg, 1.2 equiv)

For workup
CH₂Cl₂ 119.1 L
NaHCO₃aq , water and NaClaq 119.1 L

Total amount of solvents (7940 L)

For recrystallization 11.9 L

Total amount of solvents (8210.0 L)

\[
\text{O₂N} \quad \text{N} \quad \text{O}
\]

7: 81% after filtration

0.74 kg (3.97 mol)

\[
\text{O₂N} \quad \text{N} \quad \text{O}
\]

1: 70% after recryst.
GL/SW

O2
\[ \text{N} \]
\[ \text{N} \]
\[ \text{H} \]
\[ \text{NO}_2 \]
\[ \text{N} \]
\[ \text{N} \]
\[ \text{H} \]
\[ \text{NO}_2 \]

O2
\[ \text{N} \]
\[ \text{N} \]
\[ \text{H} \]
\[ \text{NO}_2 \]
\[ \text{N} \]
\[ \text{N} \]
\[ \text{H} \]
\[ \text{NO}_2 \]

\[ \text{PhCH}=\text{CHCOOH} \text{ (0.91 kg, 1.2 equiv)} \]
\[ \text{PhCH}=\text{CHCOOH} \text{ (0.91 kg, 1.2 equiv)} \]
\[ \text{DCC} \text{ (1.05 kg, 1.0 equiv)} \]
\[ \text{PhCl} \text{ (25.5 L)} \]

O2
\[ \text{N} \]
\[ \text{N} \]
\[ \text{H} \]
\[ \text{NO}_2 \]
\[ \text{N} \]
\[ \text{N} \]
\[ \text{H} \]
\[ \text{NO}_2 \]

\[ \text{OCON}=\text{CHPh} \text{ (24.9 L)} \]
\[ \text{Pyridine in DCC/Pyridine} \text{ 3.2 L} \]

O2
\[ \text{N} \]
\[ \text{N} \]
\[ \text{H} \]
\[ \text{NO}_2 \]
\[ \text{N} \]
\[ \text{N} \]
\[ \text{H} \]
\[ \text{NO}_2 \]

\[ \text{OCON}=\text{CHPh} \text{ (7806.2 L)} \]

\[ \text{OCON}=\text{CHPh} \text{ (8210.0 L)} \]

O2
\[ \text{N} \]
\[ \text{N} \]
\[ \text{H} \]
\[ \text{NO}_2 \]
\[ \text{N} \]
\[ \text{N} \]
\[ \text{H} \]
\[ \text{NO}_2 \]

O2
\[ \text{N} \]
\[ \text{N} \]
\[ \text{H} \]
\[ \text{NO}_2 \]
\[ \text{N} \]
\[ \text{N} \]
\[ \text{H} \]
\[ \text{NO}_2 \]

\[ \text{TBAF} (1.35 kg, 1.1 equiv) \]
\[ \text{THF} (23.5 L) \]

\[ \text{THF} \text{ in TBAF/THF} 3.7 L \]

\[ \text{OCON}=\text{CHPh} \text{ (23758.6 L)} \]

\[ \text{OCON}=\text{CHPh} \text{ (8210.0 L)} \]

\[ \text{TIPSCI} (3.00 kg, 2.5 equiv) \]
\[ \text{DMAP} (0.23 kg, 30 mol\% ) \]

\[ \text{DMF} (24.9 L) \]

For workup
\[ \text{AcOEt} 180.4 L \]
\[ \text{NaHCO}_3 \text{aq}, \text{ water and NaClaq} 37.3 L \]

For column chromatography 12440 L

Total amount of solvents
\[ (12682.6 L) \]

For workup
\[ \text{AcOEt} 76.5 L \]
\[ \text{NaHCO}_3 \text{aq} \text{ and NaClaq} 51.0 L \]

For column chromatography 7650 L

Total amount of solvents
\[ (7806.2 L) \]

For workup
\[ \text{MeOH} 427.0 L \]
For filtration 128.1 L

Total amount of solvents
\[ (7259.1 L) \]

O2
\[ \text{N} \]
\[ \text{N} \]
\[ \text{H} \]
\[ \text{NO}_2 \]
\[ \text{N} \]
\[ \text{N} \]
\[ \text{H} \]
\[ \text{NO}_2 \]

\[ \text{NaH} (95.3 g, 1.0 equiv) \]
\[ \text{DMF} (19.9 L) \]

\[ \text{CF}_3 \text{OCF}_3 \]

\[ \text{CF}_3 \text{OCF}_3 \]

\[ \text{H}_2 \text{O} \text{ (2.76 mol)} \]

\[ \text{CH}_2\text{Cl}_2 119.1 L \]
\[ \text{NaHCO}_3 \text{aq}, \text{ water and NaClaq} 119.1 L \]

For column chromatography 7940 L
For recrystallization 11.9 L

Total amount of solvents
\[ (8210.0 L) \]

RME = \[ 0.091 \]

Solvent employed = 12682.6 + 7806.2 + 23758.6 + 725.9 + 8210.0 = 53183 L

Solvents for reaction = 24.9 + 25.5 + 3.2 + 23.5 + 3.7 + 170.8 + 19.9 = 272 L
GL/IP-1

2

For workup
AcOEt 177.5 L
NaHCO₃aq, water and NaClaq 36.7 L
For column chromatography 12240 L
Total amount of solvents (12478.7 L)

0.97 kg (6.12 mol)

PhCH=CHCOOH (0.89 kg, 1.2 equiv)
DCC (1.04 kg, 1.0 equiv)
DMAP (0.12 kg, 20 mol%)

4b: 82% after c.c.
1.95 kg (5.02 mol)

8b: 92% after c.c.
2.40 kg (4.62 mol)

TBAF (1.33 kg, 1.1 equiv)
(1-C₃H₇O)₂Ti (12.2 g, 0.93 mol%)

THF (23.1 L)
THF in TBAF/THF 3.6 L
MeOH (184.8 L)

7: 86% after reprecip.
0.74 kg (3.97 mol)

CF₃O

1: 70% after recryst.
1.00 kg (2.78 mol)

\[
\text{RME} = \frac{1.00}{0.97 + 0.59 + 0.093 + 1.25 + 2.95 + 0.22 + 0.89 + 1.04 + 0.12 + 1.33 + 0.0122 + 1.22 + 0.0953} = 1.00 = 0.093 \div 10.78
\]

Solvent employed = 12478.7 + 7683.8 + 23235.4 + 8210.0 = 51698 L

Solvents for reaction = 24.5 + 25.1 + 3.2 + 23.1 + 3.6 + 184.8 + 19.9 = 284 L
GL/IP-2

\[
\begin{align*}
\text{O}_2\text{N} & \quad \text{N} \\
\text{H} & \quad \text{N} \\
\text{NO}_2 & \quad \text{NO}_2
\end{align*}
\]

2

1.06 kg

(6.72 mol)

\[
\begin{align*}
\text{CsF} (0.10 \text{ kg, 0.1 equiv}) & \quad \text{TIPSCI} (3.24 \text{ kg, 2.5 equiv}) \\
\text{DMAP} (0.25 \text{ kg, 30 mol%}) & \quad \text{DMF} (26.9 \text{ L})
\end{align*}
\]

For workup
AcOEt 194.9 L
\(\text{NaHCO}_3\text{aq, water and NaClaq 40.3 L}\)

For column chromatography 13440 L

Total amount of solvents

(13702.1 L)

\[
\begin{align*}
\text{PhCH} = \text{CHCOOH} (0.98 \text{ kg, 1.2 equiv}) & \quad \text{DCC} (1.14 \text{ kg, 1.0 equiv}) \\
\text{DMAP} (0.13 \text{ kg, 20 mol%}) & \quad \text{TBAF} (1.44 \text{ kg, 1.1 equiv}) \\
\text{\{C}_2\text{H}_5\text{O}\}_3\text{Ti} (14.56 \text{ g, 0.93 mol%}) & \quad \text{THF} (22.0 \text{ L}) \\
\text{THF in TBAF/THF 3.91 L} & \quad \text{MeOH} (220.4 \text{ L})
\end{align*}
\]

4b: 82% after c.c.

2.14 kg

(5.51 mol)

\[
\begin{align*}
\text{toluene (27.5 L)} & \quad \text{Pyridine in DCC/Pyridine 3.5 L}
\end{align*}
\]

For column chromatography 16530 L

For reprecipitation 8.3 L

Total amount of solvents

(16815.7 L)

7: 72% after reprecip.

0.74 kg

(3.97 mol)

\[
\begin{align*}
\text{NaH} (95.3 \text{ g, 1.0 equiv}) & \quad \text{DMF} (19.9 \text{ L})
\end{align*}
\]

For workup
\(\text{CH}_2\text{Cl}_2 119.1 \text{ L}\)
\(\text{NaHCO}_3\text{aq, water and NaClaq 119.1 L}\)

For column chromatography 7940 L

For recrystallization 11.9 L

Total amount of solvents

(8210.0 L)

\[
\begin{align*}
\text{RME} = \frac{1.00}{1.06 + 0.65 + 0.10 + 1.37 + 3.24 + 0.25 + 0.98 + 1.14 + 0.13 + 1.44 + 0.01456 + 1.22 + 0.0953} &= \frac{1.00}{11.69} = 0.086
\end{align*}
\]

Solvent employed = 13702.1 + 16815.7 + 8210.0 = 38728 L

Solvents for reaction = 26.9 + 27.6 + 3.5 + 22.0 + 3.91 + 220.4 + 19.9 = 324 L
**PG process/SW (stepwise)**

1. **Reaction 3a**
   - Reagents: O3N (0.96 kg, 6.45 mmol), TBS (1.54 kg, 1.5 equiv) in EtOH (0.545 L)
   - Solvent employed: 8175 L
   - Total amount of solvents: 8175.5 L

2. **Reaction 4a**
   - Reagents: O3N (1.02 kg, 2.94 mmol), TBS (1.11 kg, 1.5 equiv) in CH2Cl2 (14.7 L)
   - For workup: CH2Cl2 44.1 L, NaHCO3aq, water and NaClaq 44.1 L
   - For column chromatography: 5880 L
   - Total amount of solvents: 5882.9 L

3. **Reaction 5**
   - Reagents: O3N (2.19 kg, 5.08 mmol), TBAF (3.98 kg, 3.0 equiv) in THF (25.4 L)
   - For workup: CHCl3 152.4 L, NaHCO3aq, water and NaClaq 152.4 L
   - For column chromatography: 20320 L
   - Total amount of solvents: 20661.0 L

4. **Reaction 6a**
   - Reagents: CH3OH/THF/H2O (35.9 L)
   - For recrystallization: 17.1 L
   - Total amount of solvents: 53.0 L

5. **Reaction 7**
   - Reagents: CH2Br (1.22 kg, 1.2 equiv) in DMF (19.9 L)
   - For workup: CH2Cl2 119.1 L, NaHCO3aq, water and NaClaq 119.1 L
   - For column chromatography: 7940 L
   - For recrystallization: 11.9 L
   - Total amount of solvents: 8210.0 L

**RME Calculations**
- **Reaction 3a**: 
  \[ RME = \frac{1}{0.86 + 1.54} = \frac{1}{2.4} = 0.417 \]
  Solvent employed = 8175 L
  Solvents for reaction = 0.545 L

- **Reaction 4a**: 
  \[ RME = \frac{1}{1.02 + 0.49 + 1.11} = \frac{1}{2.62} = 0.382 \]
  Solvent employed = 5983 L
  Solvents for reaction = 14.7 L

- **Reaction 5**: 
  \[ RME = \frac{1}{2.19 + 3.98} = \frac{1}{6.17} = 0.162 \]
  Solvent employed = 20661 L
  Solvents for reaction = 25.4 + 10.8 = 36.2 L

- **Reaction 6a**: 
  \[ RME = \frac{1}{1.84} = 0.543 \]
  Solvent employed = 53 L
  Solvents for reaction = 35.9 L

- **Reaction 7**: 
  \[ RME = \frac{1}{0.74 + 1.22 + 0.0953} = \frac{1}{2.06} = 0.485 \]
  Solvent employed = 8210 L
  Solvents for reaction = 19.9 L
### THP/SW (stepwise)

#### 2
- **O<sub>2</sub>N<sub>2</sub>N<sub>2</sub>OH<sub>2</sub>O<sub>2</sub>N<sub>2</sub>OH**
- **3b (835 g, 1.2 equiv)**
- **For column chromatography 4530 L**
- **Total amount of solvents (4530 L)**
- **4b: 85% after c.c.**
- **1.00 kg (2.57 mol)**

**RME = \( \frac{1000}{477+835} \approx 0.762 \)**
- **Solvent employed = 4530 L**

#### 4b
- **948 g (2.44 mol)**
- **DHP (616 g, 3.0 equiv)**
- **PPTS (123 g, 20 mol%)**
- **Toluene (12.2 L)**
- **For workup:**
  - AcOEt 36.6 L
  - NaHCO<sub>3</sub>aq and NaClaq 24.4 L
- **For column chromatography 4880 L**
- **Total amount of solvents (4953.2 L)**
- **8a: 87% after c.c.**
- **1.00 kg (2.12 mol)**

**RME = \( \frac{1000}{948+616+123} \approx 0.593 \)**
- **Solvent employed = 4953 L**
- **Solvents for reaction = 12.2 L**

#### 5a
- **O<sub>2</sub>N<sub>2</sub>N<sub>2</sub>OH<sub>2</sub>O<sub>2</sub>N<sub>2</sub>OH**
- **TBAF (3.59 kg, 3.0 equiv)**
- **THF (22.9 L)**
- **THF in TBAF/THF 9.76 L**
- **For workup:**
  - CH<sub>2</sub>Cl<sub>2</sub> 137.4 L
  - NaHCO<sub>3</sub>aq, water and NaClaq 137.4 L
- **For column chromatography 22900 L**
- **Total amount of solvents (23207.5 L)**
- **6a: 81% after c.c.**
- **1.00 kg (3.71 mol)**

**RME = \( \frac{1}{2.16+3.59} = \frac{1}{5.75} = 0.174 \)**
- **Solvent employed = 23208 L**
- **Solvents for reaction = 22.9 + 9.76 = 32.7 L**

#### 6a
- **1.60 kg (5.93 mol)**
- **12N-HCl**
- **MeOH (177.9 L)**
- **For recrystallization 59.3 L**
- **7: 91% after recryst.**
- **1.00 kg (5.40 mol)**

**RME = \( \frac{1}{1.60} = 0.625 \)**
- **Solvent employed = 237 L**
- **Solvents for reaction = 177.9 L**

#### 7
- **O<sub>2</sub>N<sub>2</sub>N<sub>2</sub>OH<sub>2</sub>O<sub>2</sub>N<sub>2</sub>OH**
- **CF<sub>3</sub>O<sub>2</sub>N**
- **Br (1.22 kg, 1.2 equiv)**
- **NaH (95.3 g, 1.0 equiv)**
- **DMF (19.9 L)**
- **For workup:**
  - CH<sub>2</sub>Cl<sub>2</sub> 119.1 L
  - NaHCO<sub>3</sub>aq, water and NaClaq 119.1 L
- **For column chromatography 7940 L**
- **For recrystallization 11.9 L**
- **Total amount of solvents (8210.0 L)**
- **1: 70% after recryst.**
- **1.00 kg (2.78 mol)**

**RME = \( \frac{1}{0.74+1.22+0.0953} = \frac{1}{2.06} = 0.485 \)**
- **Solvent employed = 8210 L**
- **Solvents for reaction = 19.9 L**
THP/IP-1 (stepwise)

For workup
AcOEt 40.2 L
NaHCO₃aq and NaClq 26.8 L
For column chromatography 6700 L
Total amount of solvents (6780.4 L)

Solvent employed = 6780 L
Solvents for reaction = 13.4 L

For column chromatography 31320 L
For recrystallization 23.5 L
Total amount of solvents (31634.3 L)

Solvent employed = 31634 L
Solvents for reaction = 39.2 + 16.7 + 234.9 = 290.8 L

For workup
CH₂Cl₂ 119.1 L
NaHCO₃aq, water and NaClq 119.1 L
For column chromatography 7940 L
For recrystallization 11.9 L
Total amount of solvents (8210.0 L)

Solvent employed = 8210 L
Solvents for reaction = 19.9 L
THPSP-2 (stepwise)

**Reaction 1: 6b**

1.60 kg (5.93 mol)

12N-HCl
MaOH (177.9 L)

For recrystallization 59.3 L

Total amount of solvents (237.2 L)

RME = \frac{1}{1.60} = 0.625

Solvent employed = 237 L

Solvents for reaction = 177.9 L

**Reaction 2: 10**

0.74 kg (3.97 mol)

NaH (95.3 g, 1.0 equiv)
DMF (19.9 L)

For workup
CH₂Cl₂, 119.1 L NaHCO₃, water and NaClaq 119.1 L

For column chromatography 7940 L
For recrystallization 11.9 L

Total amount of solvents (8210.0 L)

RME = \frac{1}{0.74 \times 1.22 + 0.6953} = \frac{1}{2.06} = 0.485

Solvent employed = 8210 L

Solvents for reaction = 19.9 L

**Reaction 3: 6a**

1.15 kg (7.27 mol)

OTIPS (2.01 kg, 1.2 equiv)
PPTS (0.365 kg, 20 mol %)
TBAF (5.70 kg, 3.0 equiv)

toluene (36.4 L)
THF (36.4 L)
THF in TBAF/THF 15.5 L

For workup
CH₂Cl₂, 109.1 L NaHCO₃, water and NaClaq 109.1 L

For column chromatography 18175 L

Total amount of solvents (18461.5 L)

RME = \frac{1}{1.15 + 2.01 + 1.83 + 0.365 + 5.70} = \frac{1}{11.06} = 0.090

Solvent employed = 18462 L

Solvents for reaction = 36.4 + 36.4 + 15.5 = 88.3 L
CIN/SW (stepwise)

**Step 1**

\[
\text{N}^2\text{O}^2\text{O}^2\text{N}^2\text{O}^2\text{N}^2\text{O}^2\text{N}^2\text{O}^2\text{N}^2\text{O}^2
\]

\[\text{OTIPS}\]

\[\text{3b (835 g, 1.2 equiv)}\]

For column chromatography 4530 L

Total amount of solvents (4530 L)

**Step 2**

\[
\text{PhCH=CHCOOH (373 g, 1.2 equiv)}
\]

DCC (433 g, 1.0 equiv)

DMAP (51.3 g, 20 mol%)

**Note:**

*To be continued...*
CINIP-1 (stepwise)

For workup
AcOEt 36.6 L
NaHCO₃aq and NaCl 24.4 L

For column chromatography 6100 L
Total amount of solvents (6172.1 L)

For workup
AcOEt 36.6 L
NaHCO₃aq and NaCl 24.4 L

For column chromatography 31400 L
For reprecipitation 18.8 L
Total amount of solvents (31706.3 L)

For workup
CH₂Cl₂ 119.1 L
NaHCO₃aq, water and NaCl 119.1 L
For column chromatography 7540 L
For recrystallization 11.9 L
Total amount of solvents (8210.0 L)
**IN/IP-2 (stepwise)**

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**3a** (1.18 kg, 1.2 equiv)

- **DITPS**
- ** benchmark**
- **PHCl-CHCOOH (647 g, 1.02 equiv)**
- **DCC (751 g, 0.95 equiv)**
- **DMAP (85.9 g, 17 mol%)**
- **toluene (17.1 L)**
- **Pyridine in DCC/Pyridine 2.3 L**
- **For workup**
  - AcOEt 64.2 L
  - NaHCO₃, water and NaCl 64.2 L
- **For column chromatography 8580 L**

**TBAF (1.12 kg, 1.0 equiv)**

**THF (17.1 L)**

**THF in TBAF/THF 3.0 L**

**Total amount of solvents**

**8727.9 L**

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**6b: mixture**

- **2.10 kg**
  - **(6.67 mol)**

**(-C=H)O₂Ti (19.0 g, 1 mol%)**

- **MeOH**
  - **(266.8 L)**

**For workup**

**MeOH-697.0 L**

**For filtration 200.1 L**

**Total amount of solvents**

**1133.9 L**

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**7**: 81% after filtration.

**1.00 kg**

**(5.46 mol)**

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**0.74 kg**

**(3.97 mol)**

**NaH (95.3 g, 1.0 equiv)**

- **DMF (19.0 L)**

**For workup**

**CH₂Cl₂ 119.1 L**

**NaHCO₃, water and NaCl 119.1 L**

**For column chromatography 7940 L**

**For recrystallization 11.9 L**

**Total amount of solvents**

**8210.0 L**

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**RME = \frac{1}{1.12 + 0.0190} = \frac{1}{1.21} \approx 0.472**

**Solvent employed = 1134 L**

**Solvents for reaction = 266.8 L**

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**RME = \frac{1}{0.74 + 1.22 + 0.0953} = \frac{1}{2.05} \approx 0.485**

**Solvent employed = 8210 L**

**Solvents for reaction = 19.9 L**
GL/SW (stepwise)

**O2N**

2

For workup
AcOEt 90.8 L
NaHCO₃aq, water and NaClaq 18.8 L
For column chromatography 6260 L
Total amount of solvents (6382.1 L)

**O2N**

4b

For workup
AcOEt 31.5 L
NaHCO₃aq and NaClaq 21.0 L
For column chromatography 3150 L
Total amount of solvents (3214.3 L)

**O2N**

8b

For workup
AcOEt 104.4 L
NaHCO₃aq, water and NaClaq 104.4 L
For column chromatography 17400 L
Total amount of solvents (17628.9 L)

**O2N**

6b

For workup
MeOH 581.0 L
For filtration 174.3 L
Total amount of solvents (987.7 L)

**O2N**

7

For workup
CH₂Cl₂ 119.1 L
NaHCO₃aq, water and NaClaq 119.1 L
For column chromatography 7940 L
For recrystallization 11.9 L
Total amount of solvents (8210.0 L)
GL/JP-1 (stepwise)

1. **Structure 7**
   - Reactants: CF₃O⌢CBr
   - Base: NaH (96.3 g, 1.0 equiv)
   - Solvent: DMF (19.9 L)
   - For workup: CH₂Cl₂ 119.1 L, NaHCO₃aq, and NaClaq 119.1 L
   - For column chromatography: 7940 L
   - Total amount of solvents: 8210.0 L

2. **Structure 4b**
   - Reaction: O₂N ● N ● NO₂
   - Catalyst: CsF (48 g, 0.1 equiv)
   - Solvent: DMF (12.5 L)
   - For workup: AcOEt 90.8 L, NaHCO₃aq, and NaClaq 18.8 L
   - For column chromatography: 6260 L
   - Total amount of solvents: 6382.1 L

3. **Structure 8b**
   - Reaction: O₂N ● N ● NO₂
   - Catalyst: PhCH=CHCOOH (373 g, 1.2 equiv)
   - Solvent: DCC (433 g, 1.0 equiv)
   - For workup: AcOEt 31.5 L, NaHCO₃aq, and NaClaq 21.0 L
   - For column chromatography: 3150 L
   - Total amount of solvents: 3214.3 L

4. **Structure 4b**
   - Reaction: O₂N ● N ● NO₂
   - Catalyst: TBAF (1.81 kg, 1.1 equiv)
   - Solvent: THF in TBAF/THF 4.9 L
   - For workup: AcOEt 31.4 L, NaHCO₃aq, and NaClaq 21.0 L
   - For column chromatography: 31400 L
   - Total amount of solvents: 31708.3 L

RME calculations:

- **Structure 2**: RME = \( \frac{1000}{495 + 301 + 48 + 639 + 1510 + 115} = \frac{1000}{3108} = 0.322 \) Solvent employed = 6382 L
- **Structure 4b**: RME = \( \frac{1000}{816 + 373 + 433 + 51.3} = \frac{1000}{1673} = 0.598 \) Solvent employed = 3214 L
- **Structure 8b**: RME = \( \frac{1}{3.26 + 1.81 + 0.0166} = \frac{1}{5.09} = 0.196 \) Solvent employed = 31706 L
- **Structure 7**: RME = \( \frac{1}{0.74 + 1.22 + 0.0953} = \frac{1}{2.06} = 0.485 \) Solvent employed = 8210 L
- **Structure 1**: RME = \( \frac{1}{0.74 + 1.22 + 0.0953} = \frac{1}{2.06} = 0.485 \) Solvent employed = 8210 L

Solvents for reaction:

- **Structure 2**: Solvents for reaction = 12.5 L
- **Structure 4b**: Solvents for reaction = 10.5 + 1.3 = 11.8 L
- **Structure 8b**: Solvents for reaction = 31.4 + 4.9 + 251.2 = 287.5 L
- **Structure 7**: Solvents for reaction = 19.9 L
GLIP-2 (stepwise)

2

405 g
(3.13 mol)

For workup
AcOH 90.9 L
NaHCO₃, water and NaClaq 18.8 L
For column chromatography 6280 L
Total amount of solvents
(6382.1 L)

4b: 82% after c.c.
1.00 g
(2.57 mol)

RME = 1000
495 + 301 + 48 + 639 + 1510 + 115 = 3018
Solvent employed = 6382 L
Solvents for reaction = 12.5 L

3

2.91 kg
(7.50 mol)

PhCH=CHCOOH (1.33 kg 1.2 equiv)
DCC (1.55 kg 1.0 equiv)
DMAP (0.153 kg 20 mol%)
TBAF (1.96 kg 1.0 equiv)
(C₂H₅O)₂Ti (19.8 g 0.93 mol%)
Methanol (37.5 L)
Toluene (30.0 L)
Pyridine in DCC-Pyridine 4.7 L

For column chromatography 22500 L
For reprecipitation 11.3 L
Total amount of solvents
(22888.8 L)

7: 86% after reprecip.
1.00 kg
(5.40 mol)

RME = \frac{1}{2.91 + 1.33 + 1.55 + 0.183 + 1.96 + 0.0198} = \frac{1}{7.96} = 0.126
Solvent employed = 22889 L
Solvents for reaction = 37.5 + 4.7 + 30.0 + 5.3 + 300.0 = 377.5 L

6

0.74 kg
(3.97 mol)

NalH (95.3 g 1.0 equiv)

For workup
CH₂Cl₂ 116.1 L
NaHCO₃, water and NaClaq 119.1 L
For column chromatography 7940 L
For recrystallization 11.0 L
Total amount of solvents
(8210.0 L)

1: 70% after recryst.
1.00 kg
(2.78 mol)

RME = \frac{1}{0.74 + 1.22 + 0.0953 - 0.06} = \frac{1}{2.06} = 0.485
Solvent employed = 8210 L
Solvents for reaction = 19.9 L