

# Paths of analysis\*

Y4

Synthia

October 10, 2022

## 1 Analysis parameters

**Analysis type:** Automatic Retrosynthesis

**Rules:** none selected

**Filters:** Exclude Diastereoselective reactions, Tunnels, FGI, FGI with protections

**Max. paths returned:** 50

**Max. iterations:** 2000

**Commercial:**

1. Max. molecular weight - 1000 g/mol
2. Max. price - 1500 \$/g

**Published:**

1. Max. molecular weight - 1000 g/mol
2. Popularity - 5

**My Stockroom:**

1. Max. molecular weight - 1000 g/mol

**Reaction scoring formula:**  $\text{TUNNEL\_COEF} * \text{FGI\_COEF} * \text{STEP} * 20 + 1000 * (\text{CONFLICT} + \text{NON\_SELECTIVITY} + \text{FILTERS} + \text{PROTECT})$

**Chemical scoring formula:**  $\text{SMALLER}^3, \text{SMALLER}^{1.5}$

**Min. search width:** 400

**Max. reactions per product:** 60

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\*The results stated herein were generated using the proprietary platform owned and maintained by Grzybowski Scientific Inventions, Inc., a subsidiary of Merck KGaA, Darmstadt Germany. The results are provided on an as is basis, and shall be used solely in connection with the rights afforded in the license agreement and for no other purpose.

**Strategies:** none selected

**FGI Coeff:** 0

**Tunnels Coeff:** 0

**JSON Parameters:** {}

## 2 Paths

5 paths found. *Paths are sorted by score. Reactions are sorted in appearance order for each path.*

### 2.1 Path 1

**Score:** 2250084.06

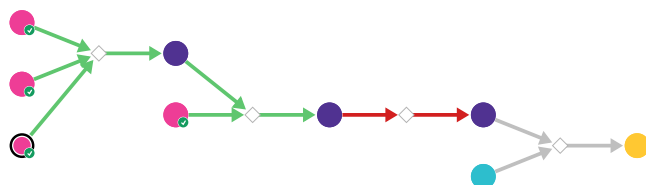
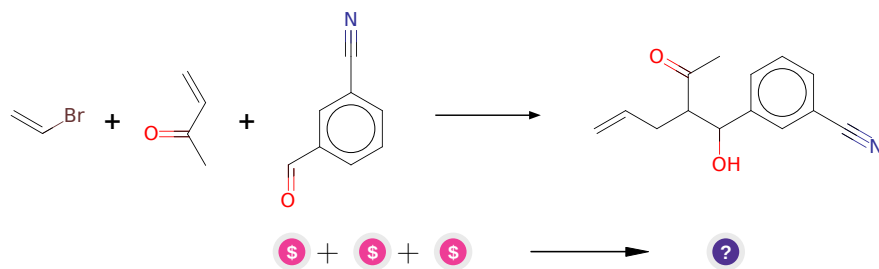


Figure 1: Outline of path 1

#### 2.1.1 Alkenylation-Aldol reaction of enones and enoate esters



**Substrates:**

1. 3-Cyanobenzaldehyde - *available at Sigma-Aldrich*
2. Bromoethylene - *available at Sigma-Aldrich*
3. 3-Buten-2-one - *available at Sigma-Aldrich*

**Products:**

1. C=CCC(C(C)=O)C(O)c1cccc(C#N)c1

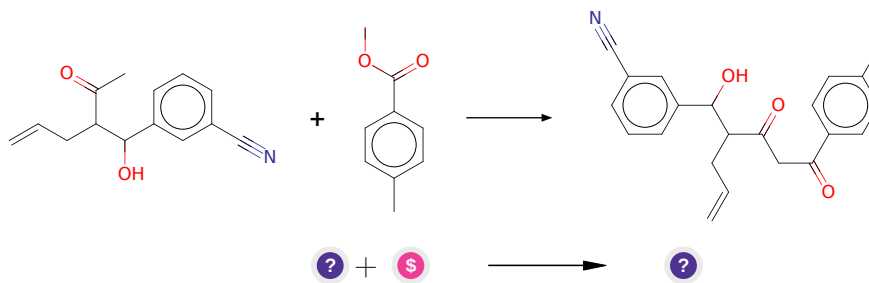
**Typical conditions:** 1.RCuLi.2.RCHO

**Protections:** none

**Reference:** [10.1016/S0040-4039\(01\)80891-1](#) AND [10.1016/S0040-4020\(01\)82115-3](#) AND [10.1021/jo2010186](#) AND [10.1021/jo101439h](#) AND [10.1021/ja906241w](#)

**Retrosynthesis ID:** 20547

### 2.1.2 Condensation of methyl ketones with esters



**Substrates:**

1. C=CCC(C(C)=O)C(O)c1cccc(C#N)c1
2. Methyl p-toluate - *available at Sigma-Aldrich*

**Products:**

1. C=CCC(C(=O)CC(=O)c1ccc(C)cc1)C(O)c1cccc(C#N)c1

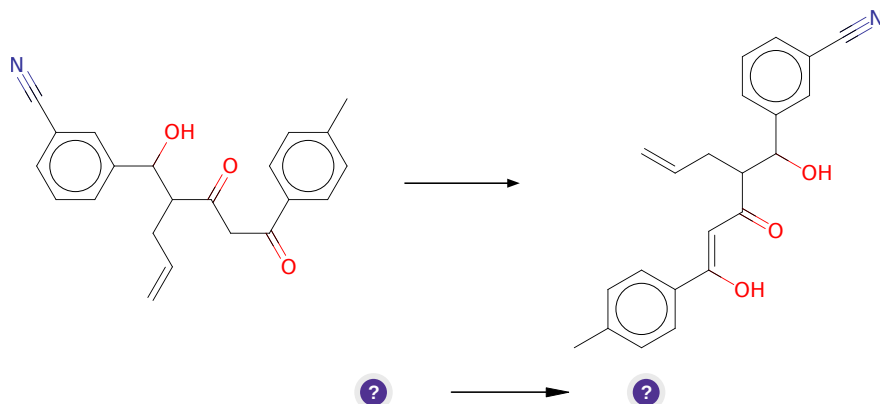
**Typical conditions:** NaOMe.MeOH

**Protections:** none

**Reference:** [10.1016/j.tetlet.2007.10.010](#) and [10.1016/j.tetlet.2013.09.025](#) and [10.1016/j.ejmech.2013.10.072](#) and [10.1002/ange.19921040631](#)

**Retrosynthesis ID:** 4792

### 2.1.3 Keto-enol Tautomerism



**Substrates:**

1. C=CCC(C(=O)CC(=O)c1ccc(C)cc1)C(O)c1cccc(C#N)c1

**Products:**

1. C=CCC(C(=O)/C=C(\O)c1ccc(C)cc1)C(O)c1cccc(C#N)c1

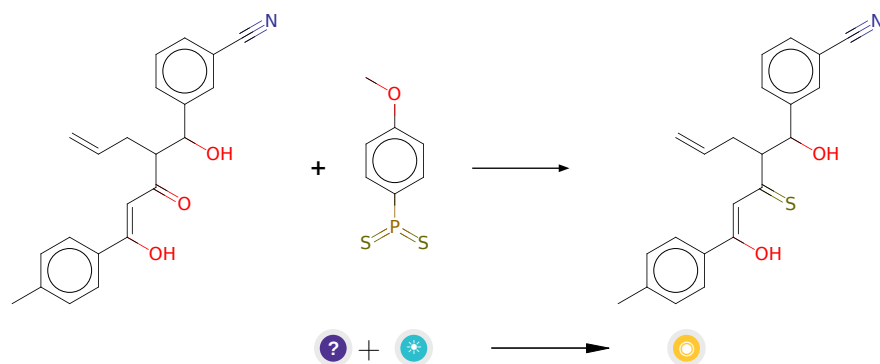
**Typical conditions:** solvent

**Protections:** none

**Reference:** [10.1021/ja01065a003](#) AND [10.1021/jo8012385](#)

**Retrosynthesis ID:** 7781

### 2.1.4 Synthesis of Thioketones using Lawesson's Reagent



**Substrates:**

1. C=CCC(C(=O)/C=C(\O)c1ccc(C)cc1)C(O)c1cccc(C#N)c1

2. 4-methoxyphenyl-dithiophosphonsaeureanhydrid

**Products:**

1. C=CCC(C(=S)/C=C(\O)c1ccc(C)cc1)C(O)c1cccc(C#N)c1

**Typical conditions:** Lawesson's Reagent.neat.microwave

**Protections:** none

**Reference:** DOI: [10.1021/ol990629a](https://doi.org/10.1021/ol990629a)

**Retrosynthesis ID:** 10798

## 2.2 Path 2

Score: 2250115.31

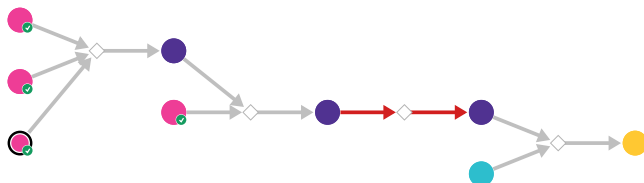
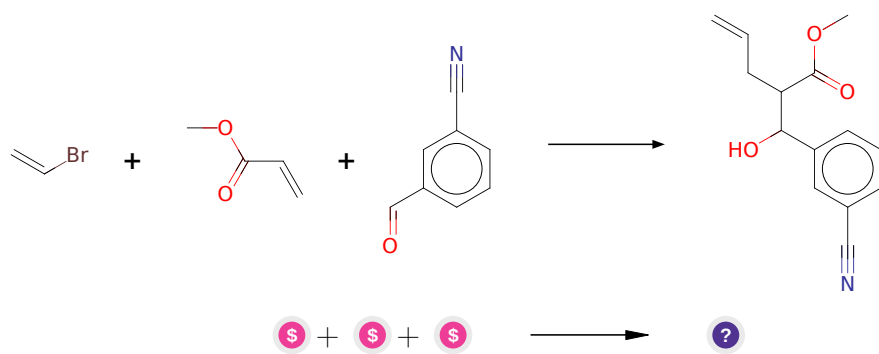


Figure 2: Outline of path 2

### 2.2.1 Alkenylation-Aldol reaction of enones and enoate esters



**Substrates:**

1. 3-Cyanobenzaldehyde - [available at Sigma-Aldrich](#)
2. Bromoethylene - [available at Sigma-Aldrich](#)

3. Methyl acrylate - *available at Sigma-Aldrich*

**Products:**

1. C=CCC(C(=O)OC)C(O)c1cccc(C#N)c1

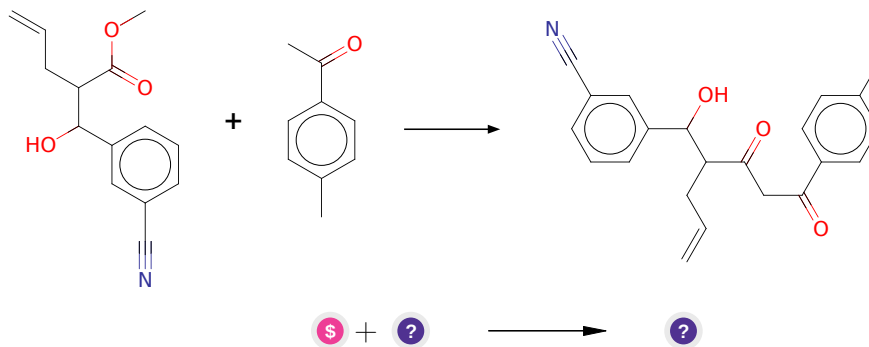
**Typical conditions:** 1.RCuLi.2.RCHO

**Protections:** none

**Reference:** [10.1021/jo2010186](#) AND [10.1021/jo101439h](#) AND [10.1021/ja906241w](#)  
AND [10.1016/S0040-4039\(01\)80891-1](#) AND [10.1016/S0040-4020\(01\)82115-3](#)

**Retrosynthesis ID:** 13048

**2.2.2 Condensation of methyl ketones with esters**



**Substrates:**

1. Methyl p-tolyl ketone - *available at Sigma-Aldrich*

2. C=CCC(C(=O)OC)C(O)c1cccc(C#N)c1

**Products:**

1. C=CCC(C(=O)CC(=O)c1ccc(C)cc1)C(O)c1cccc(C#N)c1

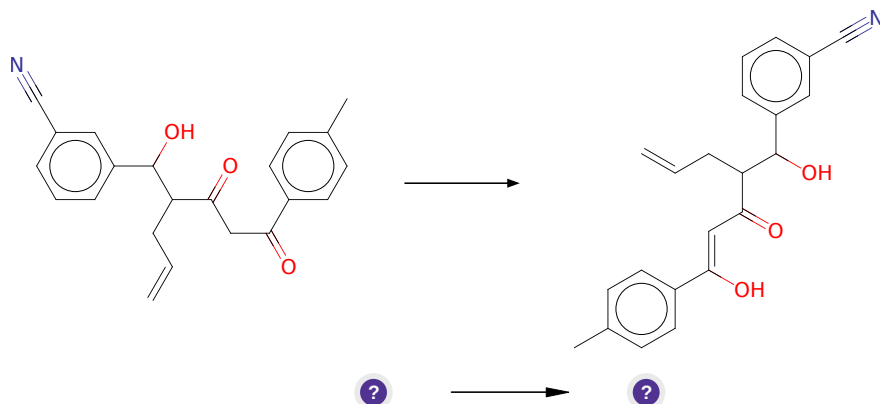
**Typical conditions:** NaOMe.MeOH

**Protections:** none

**Reference:** [10.1016/j.tetlet.2007.10.010](#) and [10.1016/j.tetlet.2013.09.025](#) and  
[10.1016/j.ejmech.2013.10.072](#) and [10.1002/ange.19921040631](#)

**Retrosynthesis ID:** 4792

### 2.2.3 Keto-enol Tautomerism



**Substrates:**

1. C=CCC(C(=O)CC(=O)c1ccc(C)cc1)C(O)c1cccc(C#N)c1

**Products:**

1. C=CCC(C(=O)/C=C(\O)c1ccc(C)cc1)C(O)c1cccc(C#N)c1

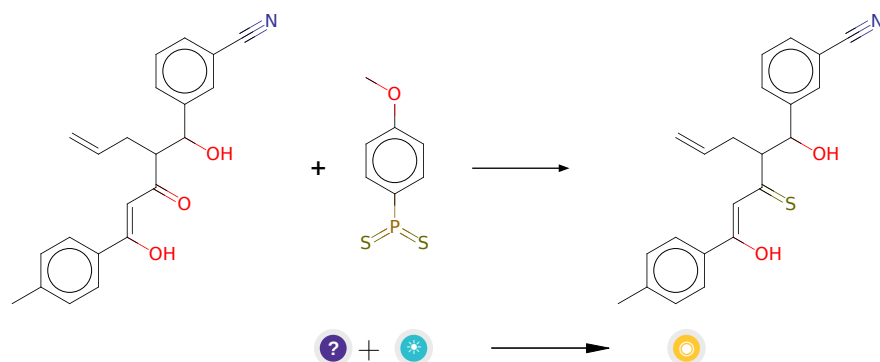
**Typical conditions:** solvent

**Protections:** none

**Reference:** [10.1021/ja01065a003](#) AND [10.1021/jo8012385](#)

**Retrosynthesis ID:** 7781

### 2.2.4 Synthesis of Thioketones using Lawesson's Reagent



**Substrates:**

1. C=CCC(C(=O)/C=C(\O)c1ccc(C)cc1)C(O)c1cccc(C#N)c1

2. 4-methoxyphenyl-dithiophosphonsaeureanhydrid

**Products:**

1. C=CCC(C(=S)/C=C(\O)c1ccc(C)cc1)C(O)c1cccc(C#N)c1

**Typical conditions:** Lawesson's Reagent.neat.microwave

**Protections:** none

**Reference:** DOI: [10.1021/ol990629a](https://doi.org/10.1021/ol990629a)

**Retrosynthesis ID:** 10798

## 2.3 Path 3

Score: 2250115.31

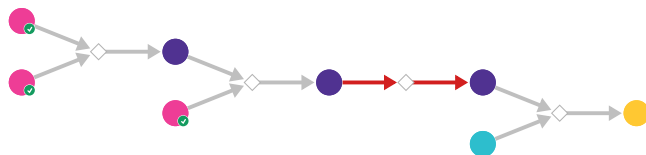
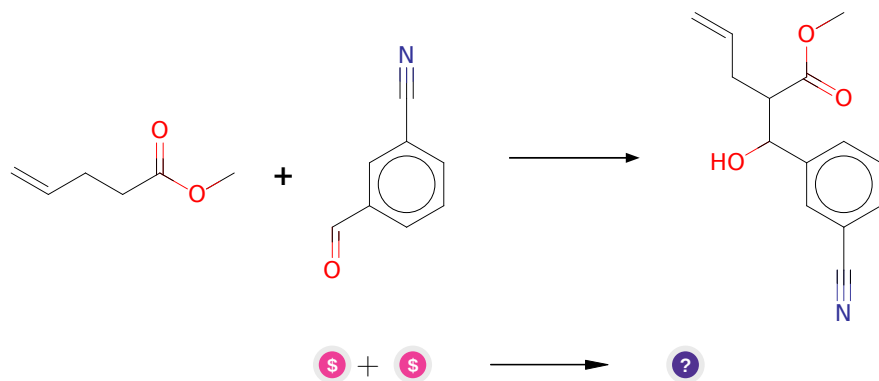


Figure 3: Outline of path 3

### 2.3.1 Condensation of esters with aldehydes



**Substrates:**

1. Methyl 4-pentenoate - *available at Sigma-Aldrich*
2. 3-Cyanobenzaldehyde - *available at Sigma-Aldrich*



**Products:**

1. C=CCC(C(=O)OC)C(O)c1cccc(C#N)c1

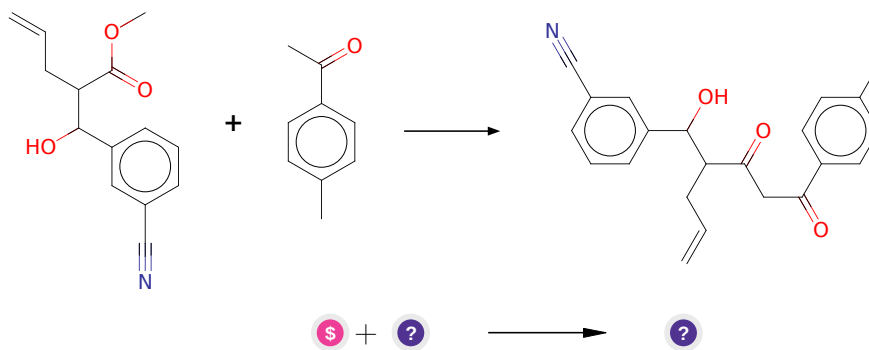
**Typical conditions:** LDA.THF

**Protections:** none

**Reference:** [10.1016/j.bmcl.2005.02.066](#) and [10.3762/bjoc.9.175](#) and [10.1021/ol1016178](#)

**Retrosynthesis ID:** 4788

**2.3.2 Condensation of methyl ketones with esters**



**Substrates:**

1. Methyl p-tolyl ketone - *available at Sigma-Aldrich*
2. C=CCC(C(=O)OC)C(O)c1cccc(C#N)c1

**Products:**

1. C=CCC(C(=O)CC(=O)c1ccc(C)cc1)C(O)c1cccc(C#N)c1

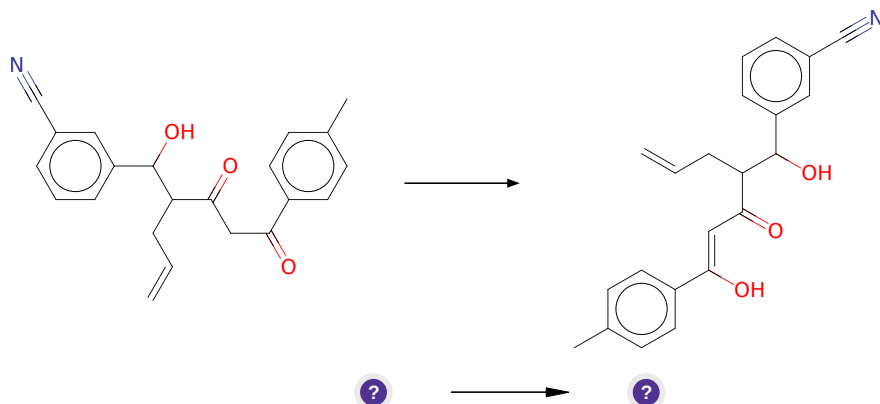
**Typical conditions:** NaOMe.MeOH

**Protections:** none

**Reference:** [10.1016/j.tetlet.2007.10.010](#) and [10.1016/j.tetlet.2013.09.025](#) and [10.1016/j.ejmech.2013.10.072](#) and [10.1002/ange.19921040631](#)

**Retrosynthesis ID:** 4792

### 2.3.3 Keto-enol Tautomerism



**Substrates:**

1. C=CCC(C(=O)CC(=O)c1ccc(C)cc1)C(O)c1cccc(C#N)c1

**Products:**

1. C=CCC(C(=O)/C=C(\O)c1ccc(C)cc1)C(O)c1cccc(C#N)c1

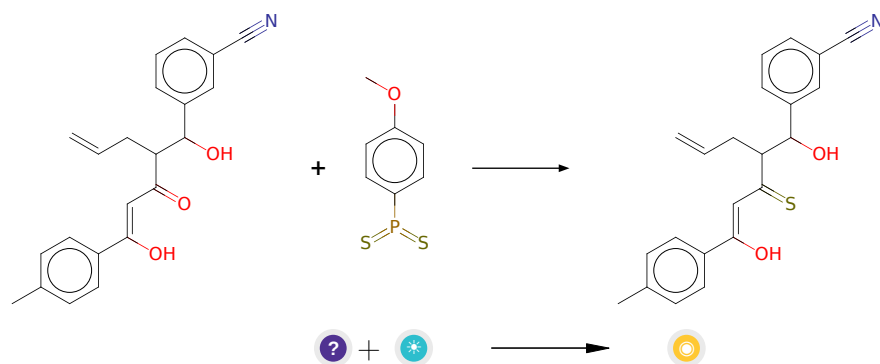
**Typical conditions:** solvent

**Protections:** none

**Reference:** [10.1021/ja01065a003](#) AND [10.1021/jo8012385](#)

**Retrosynthesis ID:** 7781

### 2.3.4 Synthesis of Thioketones using Lawesson's Reagent



**Substrates:**

1. C=CCC(C(=O)/C=C(\O)c1ccc(C)cc1)C(O)c1cccc(C#N)c1

2. 4-methoxyphenyl-dithiophosphonsaeureanhydrid

**Products:**

1. C=CCC(C(=S)/C=C(\O)c1ccc(C)cc1)C(O)c1cccc(C#N)c1

**Typical conditions:** Lawesson's Reagent.neat.microwave

**Protections:** none

**Reference:** DOI: [10.1021/ol990629a](https://doi.org/10.1021/ol990629a)

**Retrosynthesis ID:** 10798

## 2.4 Path 4

Score: 2250115.31

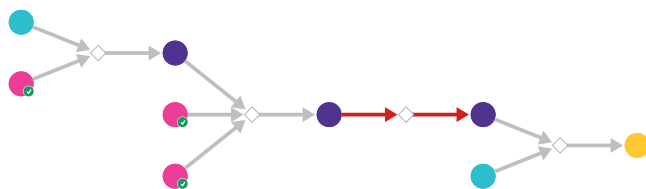
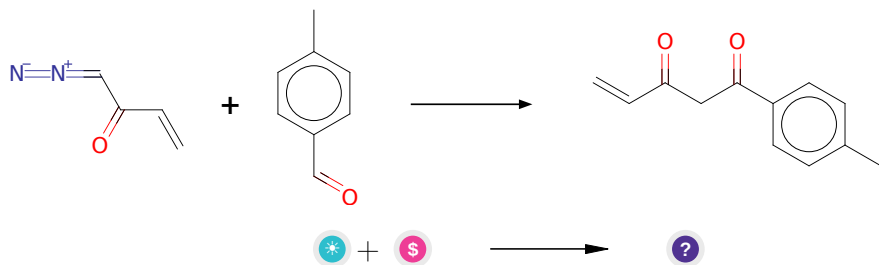


Figure 4: Outline of path 4

### 2.4.1 Homologation of aldehydes to ketones with diazoalkanes



**Substrates:**

1. 1-diazo-but-3-en-2-one
2. p-Tolualdehyde - *available at Sigma-Aldrich*

**Products:**

1. C=CC(=O)CC(=O)c1ccc(C)cc1

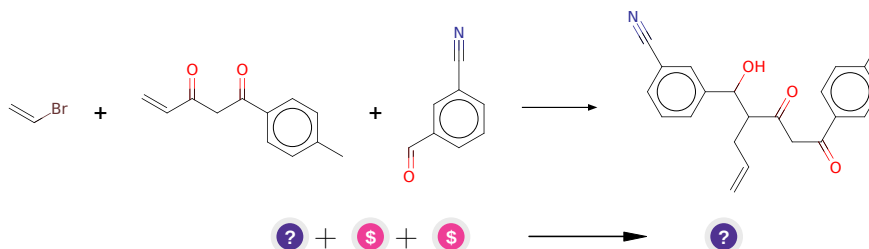
**Typical conditions:** Lewis.acid

**Protections:** none

**Reference:** [10.1021/jo00275a006](#) AND [10.1016/j.tet.2014.05.107](#) AND [10.1016/j.tet.2014.11.059](#) AND [10.1021/ol9010932](#)

**Retrosynthesis ID:** 15017

#### 2.4.2 Alkenylation-Aldol reaction of enones and enoate esters



**Substrates:**

1. C=CC(=O)CC(=O)c1ccc(C)cc1
2. 3-Cyanobenzaldehyde - *available at Sigma-Aldrich*
3. Bromoethylene - *available at Sigma-Aldrich*

**Products:**

1. C=CCC(C(=O)CC(=O)c1ccc(C)cc1)C(O)c1cccc(C#N)c1

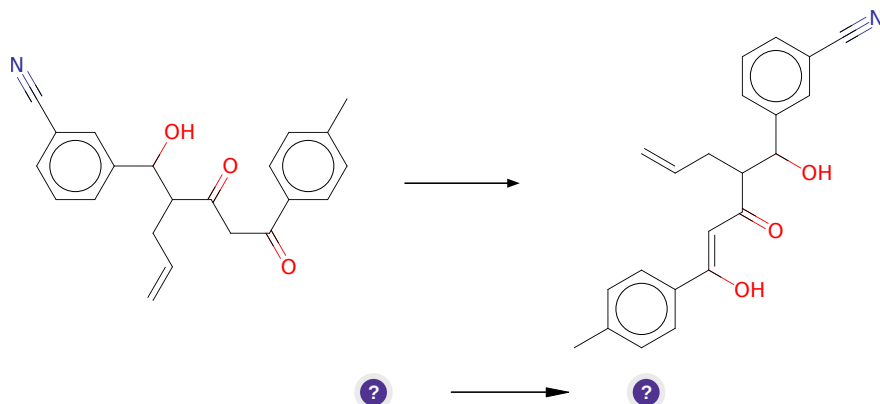
**Typical conditions:** 1.RCuLi.2.RCHO

**Protections:** none

**Reference:** [10.1021/jo2010186](#) AND [10.1021/jo101439h](#) AND [10.1021/ja906241w](#) AND [10.1016/S0040-4039\(01\)80891-1](#) AND [10.1016/S0040-4020\(01\)82115-3](#)

**Retrosynthesis ID:** 13048

### 2.4.3 Keto-enol Tautomerism



**Substrates:**

1. C=CCC(C(=O)CC(=O)c1ccc(C)cc1)C(O)c1cccc(C#N)c1

**Products:**

1. C=CCC(C(=O)/C=C(\O)c1ccc(C)cc1)C(O)c1cccc(C#N)c1

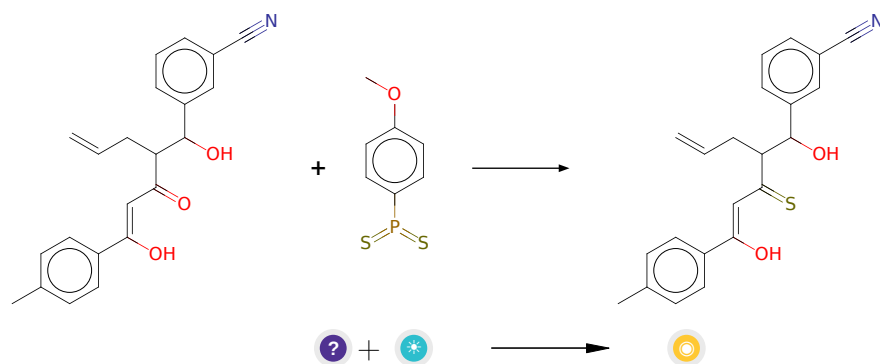
**Typical conditions:** solvent

**Protections:** none

**Reference:** [10.1021/ja01065a003](#) AND [10.1021/jo8012385](#)

**Retrosynthesis ID:** 7781

### 2.4.4 Synthesis of Thioketones using Lawesson's Reagent



**Substrates:**

1. C=CCC(C(=O)/C=C(\O)c1ccc(C)cc1)C(O)c1cccc(C#N)c1

2. 4-methoxyphenyl-dithiophosphonsaeureanhydrid

**Products:**

1. C=CCC(C(=S)/C=C(\O)c1ccc(C)cc1)C(O)c1cccc(C#N)c1

**Typical conditions:** Lawesson's Reagent.neat.microwave

**Protections:** none

**Reference:** DOI: [10.1021/ol990629a](https://doi.org/10.1021/ol990629a)

**Retrosynthesis ID:** 10798

## 2.5 Path 5

Score: 2250115.31

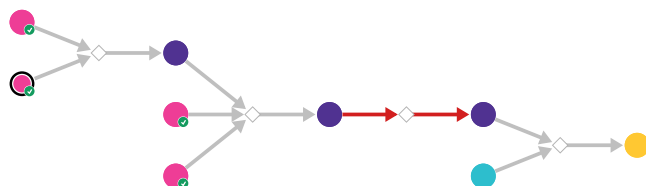
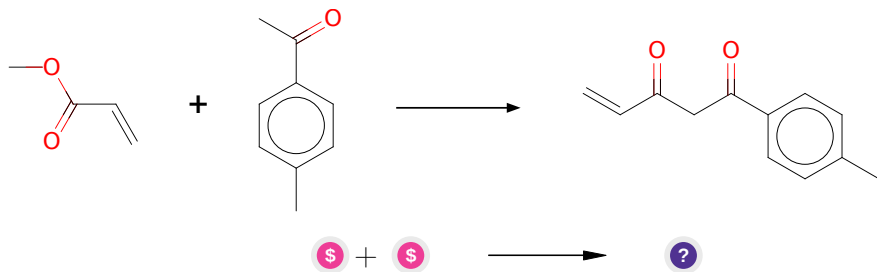


Figure 5: Outline of path 5

### 2.5.1 Condensation of methyl ketones with esters



**Substrates:**

1. Methyl p-tolyl ketone - *available at Sigma-Aldrich*
2. Methyl acrylate - *available at Sigma-Aldrich*

**Products:**

1. C=CC(=O)CC(=O)c1ccc(C)cc1

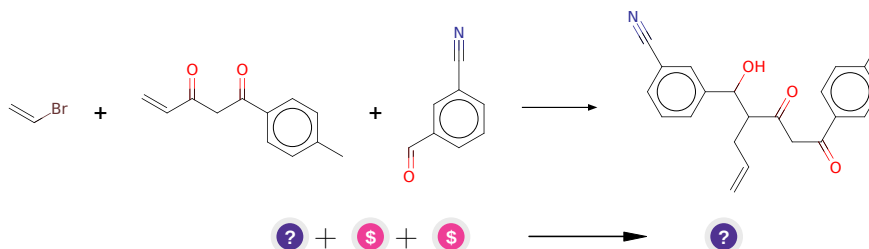
**Typical conditions:** NaOMe.MeOH

**Protections:** none

**Reference:** [10.1016/j.tetlet.2007.10.010](#) and [10.1016/j.tetlet.2013.09.025](#) and [10.1016/j.ejmech.2013.10.072](#) and [10.1002/ange.19921040631](#)

**Retrosynthesis ID:** 4792

## 2.5.2 Alkenylation-Aldol reaction of enones and enoate esters



**Substrates:**

1. C=CC(=O)CC(=O)c1ccc(C)cc1
2. 3-Cyanobenzaldehyde - *available at Sigma-Aldrich*
3. Bromoethylene - *available at Sigma-Aldrich*

**Products:**

1. C=CCC(C(=O)CC(=O)c1ccc(C)cc1)C(O)c1cccc(C#N)c1

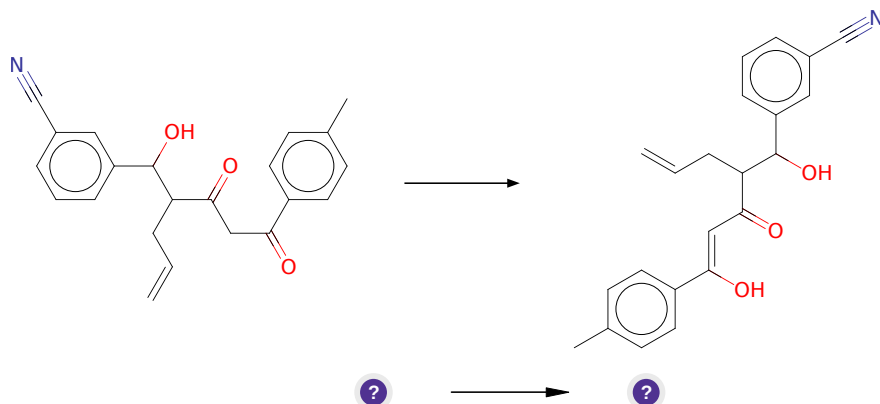
**Typical conditions:** 1.RCuLi.2.RCHO

**Protections:** none

**Reference:** [10.1021/jo2010186](#) AND [10.1021/jo101439h](#) AND [10.1021/ja906241w](#) AND [10.1016/S0040-4039\(01\)80891-1](#) AND [10.1016/S0040-4020\(01\)82115-3](#)

**Retrosynthesis ID:** 13048

### 2.5.3 Keto-enol Tautomerism



**Substrates:**

1. C=CCC(C(=O)CC(=O)c1ccc(C)cc1)C(O)c1cccc(C#N)c1

**Products:**

1. C=CCC(C(=O)/C=C(\O)c1ccc(C)cc1)C(O)c1cccc(C#N)c1

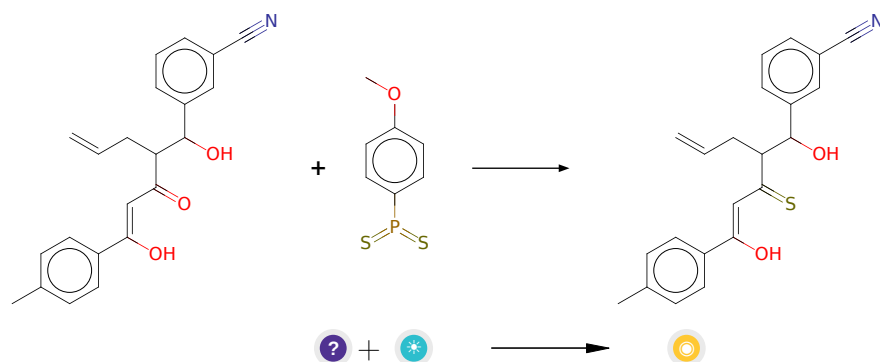
**Typical conditions:** solvent

**Protections:** none

**Reference:** [10.1021/ja01065a003](#) AND [10.1021/jo8012385](#)

**Retrosynthesis ID:** 7781

### 2.5.4 Synthesis of Thioketones using Lawesson's Reagent



**Substrates:**

1. C=CCC(C(=O)/C=C(\O)c1ccc(C)cc1)C(O)c1cccc(C#N)c1



2. 4-methoxyphenyl-dithiophosphonsaeureanhydrid

**Products:**

1. C=CCC(C(=S)/C=C(\O)c1ccc(C)cc1)C(O)c1cccc(C#N)c1

**Typical conditions:** Lawesson's Reagent.neat.microwave

**Protections:** none

**Reference:** DOI: [10.1021/ol990629a](https://doi.org/10.1021/ol990629a)

**Retrosynthesis ID:** 10798