

# Paths of analysis\*

Y7A

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

---

\*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:** 1000139.14

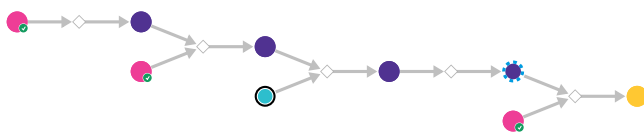
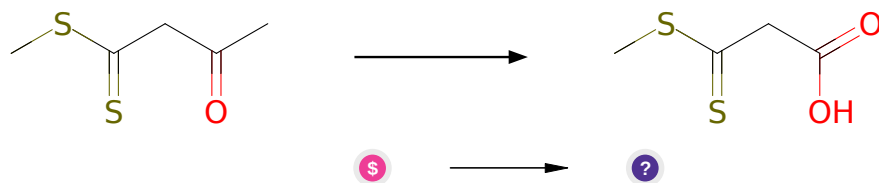


Figure 1: Outline of path 1

#### 2.1.1 Synthesis of Carboxylic Acids via Haloform Reaction



**Substrates:**

1. 4-(methylsulfanyl)-4-sulfanylidenebutan-2-one - *available at Sigma-Aldrich*

**Products:**

1. CSC(=S)CC(=O)O

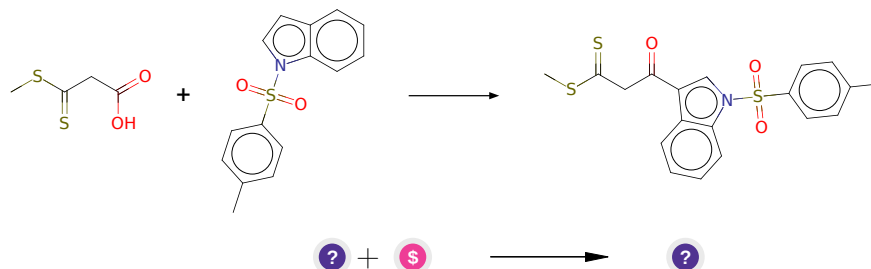
**Typical conditions:** I2.KI.KOH.H2O.dioxane

**Protections:** none

**Reference:** [10.1021/jacs.8b12242](https://doi.org/10.1021/jacs.8b12242) SI p. S25 and [10.1021/ol5025025](https://doi.org/10.1021/ol5025025) SI p. S27

**Retrosynthesis ID:** 10366

### 2.1.2 Friedel-Crafts Acylation



**Substrates:**

1. CSC(=S)CC(=O)O
2. 1-[(4-Methylphenyl)sulfonyl]-1H-indole - *available at Sigma-Aldrich*

**Products:**

1. CSC(=S)CC(=O)c1cn(S(=O)(=O)c2ccc(C)cc2)c2ccccc12

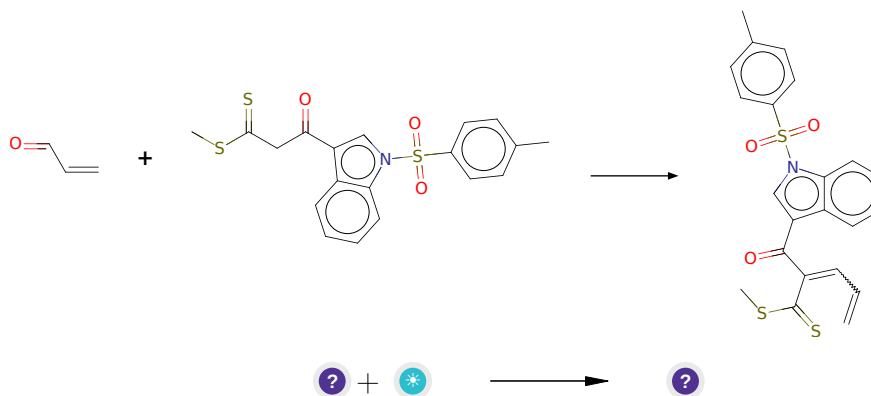
**Typical conditions:** 1.(COCl)<sub>2</sub>.Lewis Acid.solvent

**Protections:** none

**Reference:** [10.1021/ol800752v](#)

**Retrosynthesis ID:** 13729

### 2.1.3 Aldol Condensation



**Substrates:**

1. CSC(=S)CC(=O)c1cn(S(=O)(=O)c2ccc(C)cc2)c2ccccc12
2. Acrolein

**Products:**

1. C=CC=C(C(=O)c1cn(S(=O)(=O)c2ccc(C)cc2)c2ccccc12)C(=S)SC

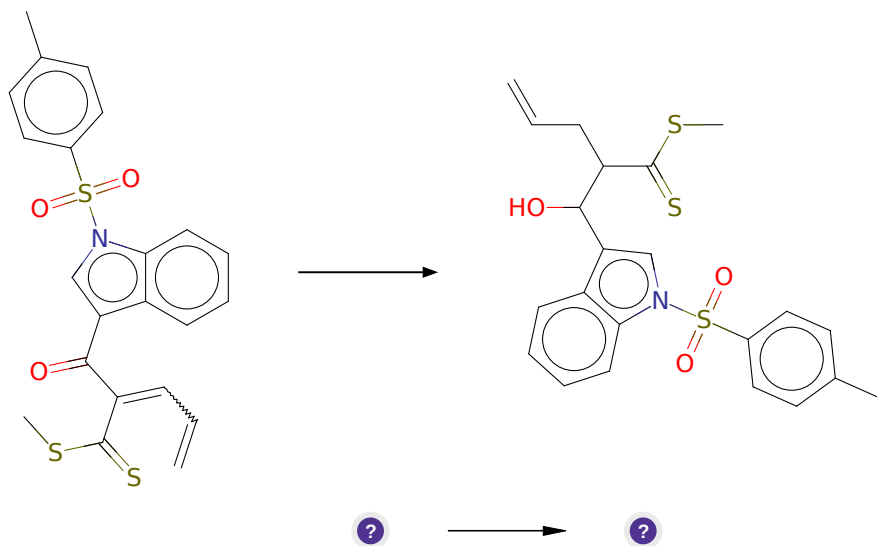
**Typical conditions:** NaOEt.base

**Protections:** none

**Reference:** [10.1080/00397911.2016.1206938](#)

**Retrosynthesis ID:** 10049

**2.1.4 Reduction of enones to saturated alcohols**



**Substrates:**

1. C=CC=C(C(=O)c1cn(S(=O)(=O)c2ccc(C)cc2)c2ccccc12)C(=S)SC

**Products:**

1. C=CCC(C(=S)SC)C(O)c1cn(S(=O)(=O)c2ccc(C)cc2)c2ccccc12

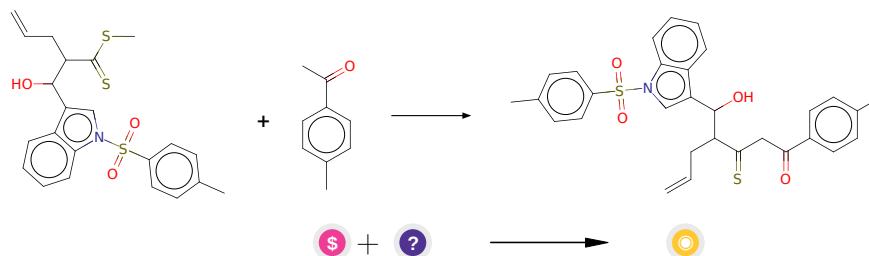
**Typical conditions:** NaBH<sub>4</sub>.transition.metal.salt.(eg.Pd(OAc)<sub>2</sub>.or.CeCl<sub>3</sub>)

**Protections:** none

**Reference:** [10.1080/00397910902788117](#) AND [10.1021/jo00235a009](#)  
AND [10.1016/0040-4020\(95\)00125-R](#) AND [10.1021/ja01327a041](#) AND  
[10.1021/jo00302a056](#) AND [10.1002/adsc.200900628](#)

**Retrosynthesis ID:** 15304

### 2.1.5 Condensation of ketones with dithioesters



#### Substrates:

1. Methyl p-tolyl ketone - *available at Sigma-Aldrich*
2. C=CCC(C(=S)SC)C(O)c1cn(S(=O)(=O)c2ccc(C)cc2)c2ccccc12

#### Products:

1. C=CCC(C(=S)CC(=O)c1ccc(C)cc1)C(O)c1cn(S(=O)(=O)c2ccc(C)cc2)c2ccccc12

**Typical conditions:** NaH.DMF

#### Protections:

Functional group SMARTS	Classification	Protecting groups
[#6][CH]([#6])[OH]	alcohols	Methoxymethyl Ether (MOM)
		2-Methoxyethoxymethyl Ether (MEM)
		Tetrahydropyranyl Ether (THP)
		Benzyl Ether (PMB)
		t-Butyldimethylsilyl Ether (TB-DMS)
		Methyl Ether

**Reference:** [10.1021/jo400599e](#) and [10.1002/ejoc.201301667](#)

**Retrosynthesis ID:** 9996413

## 2.2 Path 2

Score: 1000139.14

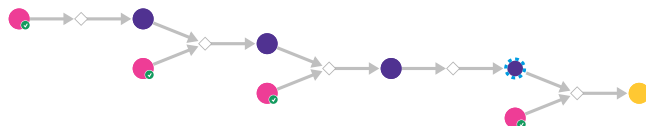
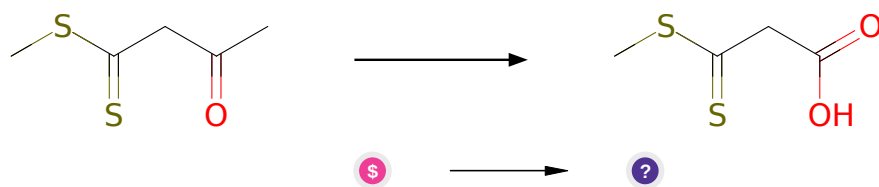


Figure 2: Outline of path 2

### 2.2.1 Synthesis of Carboxylic Acids via Haloform Reaction



**Substrates:**

1. 4-(methylsulfanyl)-4-sulfanylidenebutan-2-one - *available at Sigma-Aldrich*

**Products:**

1. CSC(=S)CC(=O)O

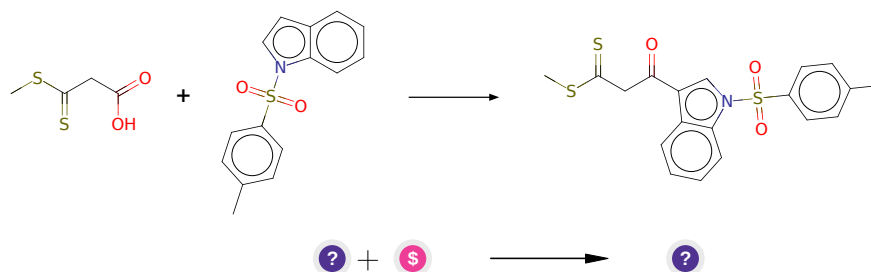
**Typical conditions:** I2.KI.KOH.H2O.dioxane

**Protections:** none

**Reference:** [10.1021/jacs.8b12242](#) SI p. S25 and [10.1021/ol5025025](#) SI p. S27

**Retrosynthesis ID:** 10366

### 2.2.2 Friedel-Crafts Acylation



**Substrates:**

1. CSC(=S)CC(=O)O
2. 1-[(4-Methylphenyl)sulfonyl]-1H-indole - *available at Sigma-Aldrich*

**Products:**

1. CSC(=S)CC(=O)c1cn(S(=O)(=O)c2ccc(C)cc2)c2ccccc12

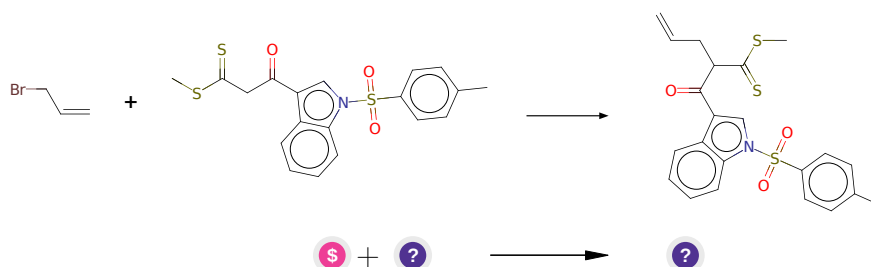
**Typical conditions:** 1.(COCl)<sub>2</sub>.Lewis Acid.solvent

**Protections:** none

**Reference:** [10.1021/ol800752v](#)

**Retrosynthesis ID:** 13729

### 2.2.3 Alkylation of ketones



**Substrates:**

1. Allyl bromide - *available at Sigma-Aldrich*
2. CSC(=S)CC(=O)c1cn(S(=O)(=O)c2ccc(C)cc2)c2ccccc12

**Products:**

1. C=CCC(C(=O)c1cn(S(=O)(=O)c2ccc(C)cc2)c2ccccc12)C(=S)SC

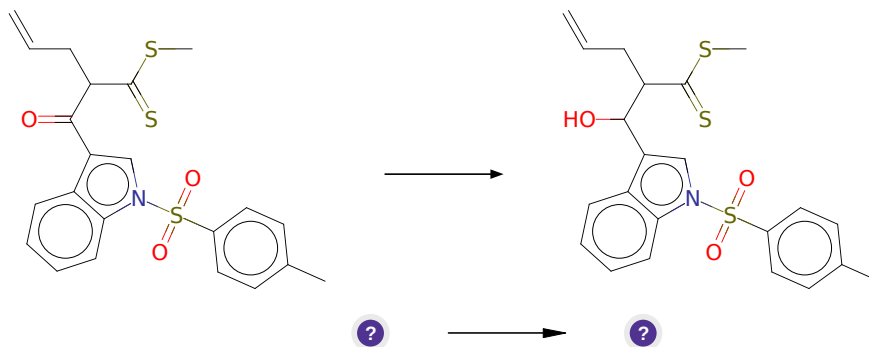
**Typical conditions:** LDA or other base.THF.-78C

**Protections:** none

**Reference:** DOI: [10.1021/jo1019738](#) OR DOI: [10.1021/jm00114a016](#)

**Retrosynthesis ID:** 1866

## 2.2.4 Reduction of ketones with NaBH<sub>4</sub>



**Substrates:**

1. C=CCC(C(=O)c1cn(S(=O)(=O)c2ccc(C)cc2)c2ccccc12)C(=S)SC

**Products:**

1. C=CCC(C(=S)SC)C(O)c1cn(S(=O)(=O)c2ccc(C)cc2)c2ccccc12

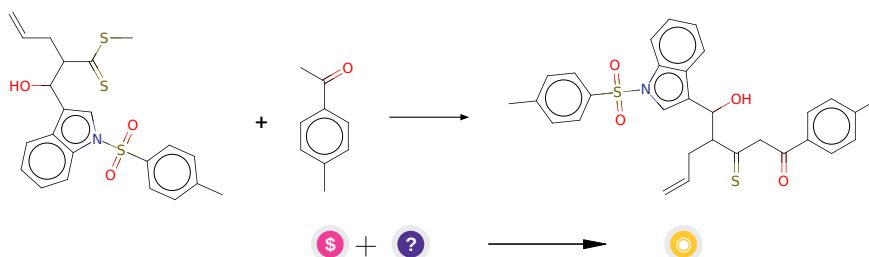
**Typical conditions:** NaBH<sub>4</sub>.EtOH.0-20 C

**Protections:** none

**Reference:** [10.1016/j.ejmech.2020.112360](https://doi.org/10.1016/j.ejmech.2020.112360) p. 3, 8 and [10.1016/j.ejmech.2010.10.012](https://doi.org/10.1016/j.ejmech.2010.10.012) p. 434, 436

**Retrosynthesis ID:** 50432

## 2.2.5 Condensation of ketones with dithioesters



**Substrates:**

1. Methyl p-tolyl ketone - [available at Sigma-Aldrich](#)
2. C=CCC(C(=S)SC)C(O)c1cn(S(=O)(=O)c2ccc(C)cc2)c2ccccc12

**Products:**

1. C=CCC(C(=S)CC(=O)c1ccc(C)cc1)C(O)c1cn(S(=O)(=O)c2ccc(C)cc2)c2ccccc12



**Typical conditions:** NaH.DMF

**Protections:**

Functional group SMARTS	Classification	Protecting groups
[#6][CH]([#6])[OH]	alcohols	Methoxymethyl Ether (MOM)
		2-Methoxyethoxymethyl Ether (MEM)
		Tetrahydropyranyl Ether (THP)
		Benzyl Ether (PMB)
		t-Butyldimethylsilyl Ether (TB-DMS)
		Methyl Ether

**Reference:** [10.1021/jo400599e](#) and [10.1002/ejoc.201301667](#)

**Retrosynthesis ID:** 9996413

## 2.3 Path 3

**Score:** 1000139.14

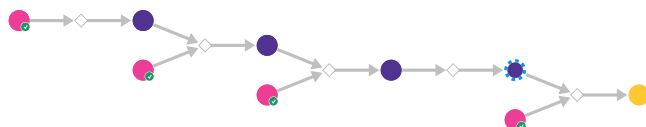
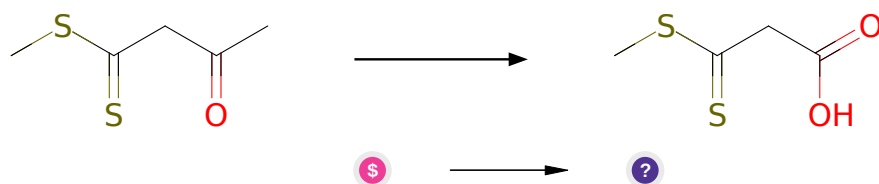


Figure 3: Outline of path 3

### 2.3.1 Synthesis of Carboxylic Acids via Haloform Reaction



**Substrates:**

1. 4-(methylsulfanyl)-4-sulfanylidenebutan-2-one - *available at Sigma-Aldrich*

**Products:**

1. CSC(=S)CC(=O)O

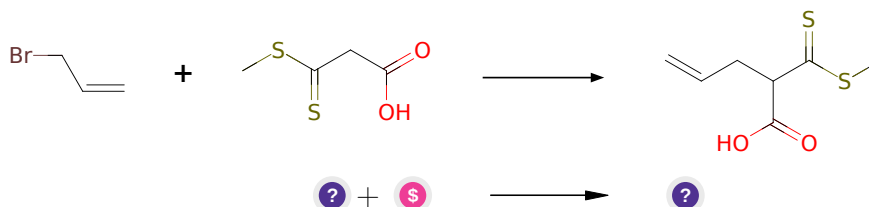
**Typical conditions:** I2.KI.KOH.H2O.dioxane

**Protections:** none

**Reference:** [10.1021/jacs.8b12242](#) SI p. S25 and [10.1021/ol5025025](#) SI p. S27

**Retrosynthesis ID:** 10366

### 2.3.2 Alkylation of carboxylic acids



**Substrates:**

1. CSC(=S)CC(=O)O
2. Allyl bromide - *available at Sigma-Aldrich*

**Products:**

1. C=CCC(C(=O)O)C(=S)SC

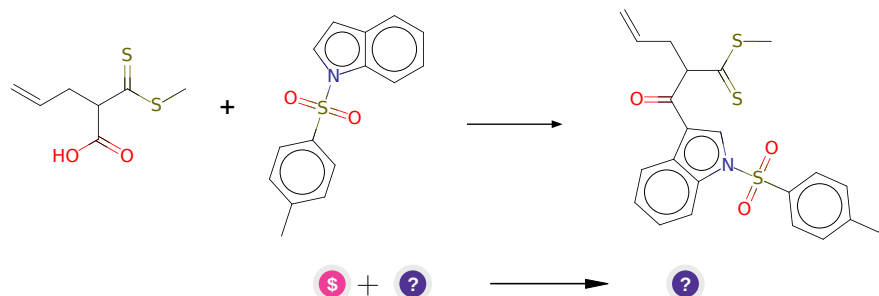
**Typical conditions:** nBuLi.THF.DIPEA

**Protections:** none

**Reference:** [10.1080/15257770.2013.820833](#) AND [10.1021/jm00078a017](#) AND [10.1016/j.bmc.2003.12.039](#) AND [10.1021/ml500411h](#)(SI,page 11) AND [10.1016/j.tet.2010.12.020](#) AND [10.1016/j.bmcl.2015.07.101](#)

**Retrosynthesis ID:** 28537

### 2.3.3 Friedel-Crafts Acylation



**Substrates:**

1. 1-[(4-Methylphenyl)sulfonyl]-1H-indole - *available at Sigma-Aldrich*
2. C=CCC(C(=O)O)C(=S)SC

**Products:**

1. C=CCC(C(=O)c1cn(S(=O)(=O)c2ccc(C)cc2)c2ccccc12)C(=S)SC

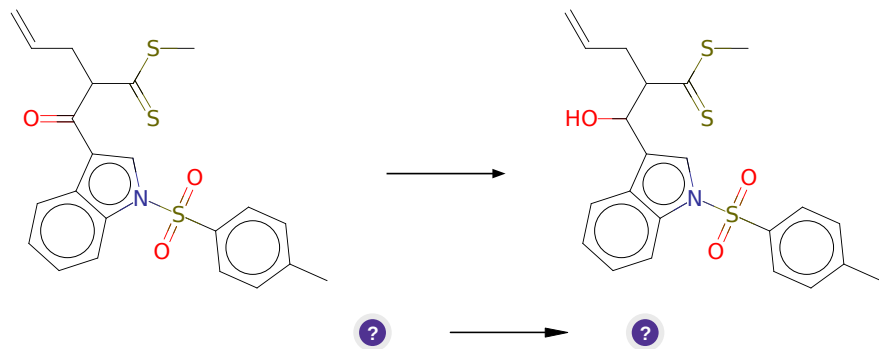
**Typical conditions:** 1.(COCl)<sub>2</sub> 2.Lewis Acid.solvent

**Protections:** none

**Reference:** [10.1021/ol800752v](#)

**Retrosynthesis ID:** 13729

### 2.3.4 Reduction of ketones with NaBH<sub>4</sub>



**Substrates:**

1. C=CCC(C(=O)c1cn(S(=O)(=O)c2ccc(C)cc2)c2ccccc12)C(=S)SC

**Products:**

1. C=CCC(C(=S)SC)C(O)c1cn(S(=O)(=O)c2ccc(C)cc2)c2ccccc12

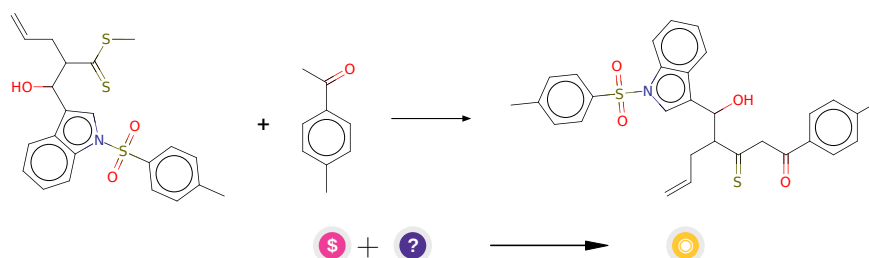
**Typical conditions:** NaBH<sub>4</sub>.EtOH.0-20 C

**Protections:** none

**Reference:** [10.1016/j.ejmech.2020.112360](https://doi.org/10.1016/j.ejmech.2020.112360) p. 3, 8 and [10.1016/j.ejmech.2010.10.012](https://doi.org/10.1016/j.ejmech.2010.10.012) p. 434, 436

**Retrosynthesis ID:** 50432

### 2.3.5 Condensation of ketones with dithioesters



**Substrates:**

1. Methyl p-tolyl ketone - [available at Sigma-Aldrich](#)
2. C=CCC(C(=S)SC)C(O)c1cn(S(=O)(=O)c2ccc(C)cc2)c2ccccc12

**Products:**

1. C=CCC(C(=S)CC(=O)c1ccc(C)cc1)C(O)c1cn(S(=O)(=O)c2ccc(C)cc2)c2ccccc12

**Typical conditions:** NaH.DMF

**Protections:**

Functional group SMARTS	Classification	Protecting groups
[#6][CH]([#6])[OH]	alcohols	Methoxymethyl Ether (MOM)
		2-Methoxyethoxymethyl Ether (MEM)
		Tetrahydropyranyl Ether (THP)
		Benzyl Ether (PMB)
		t-Butyldimethylsilyl Ether (TB-DMS)
		Methyl Ether

Reference: [10.1021/jo400599e](https://doi.org/10.1021/jo400599e) and [10.1002/ejoc.201301667](https://doi.org/10.1002/ejoc.201301667)

Retrosynthesis ID: 9996413

## 2.4 Path 4

Score: 1000139.14

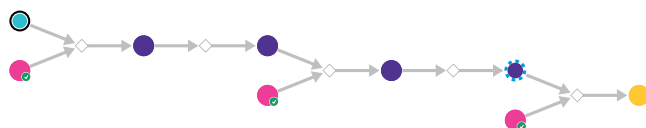
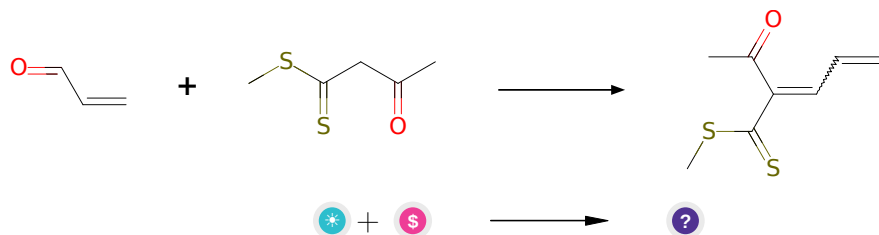


Figure 4: Outline of path 4

### 2.4.1 Aldol Condensation



Substrates:

1. Acrolein
2. 4-(methylsulfanyl)-4-sulfanylidenebutan-2-one - *available at Sigma-Aldrich*

Products:

1. C=CC=C(C(C)=O)C(=S)SC

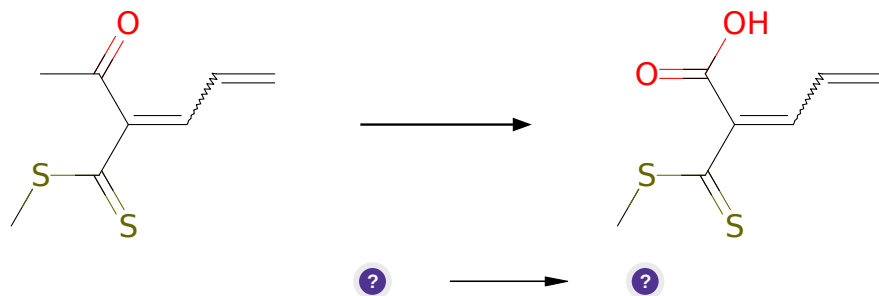
Typical conditions: NaOEt.base

Protections: none

Reference: [10.1080/00397911.2016.1206938](https://doi.org/10.1080/00397911.2016.1206938)

Retrosynthesis ID: 10049

## 2.4.2 Synthesis of Carboxylic Acids via Haloform Reaction



**Substrates:**

1. C=CC=C(C(C)=O)C(=S)SC

**Products:**

1. C=CC=C(C(=O)O)C(=S)SC

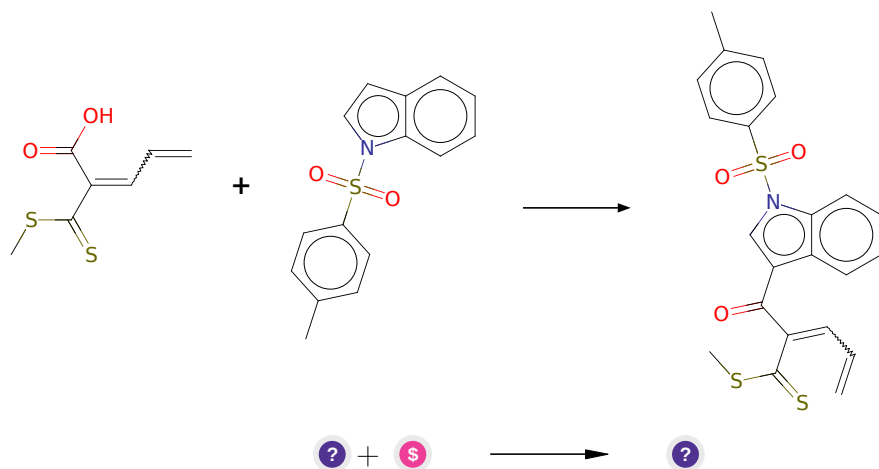
**Typical conditions:** NaClO.EtOH.0-20 C or Br<sub>2</sub>.NaOH.H<sub>2</sub>O.dioxane.0 C

**Protections:** none

**Reference:** [10.1016/j.ejmech.2015.06.037](https://doi.org/10.1016/j.ejmech.2015.06.037) p. 246, 247 and [10.1007/s00280-017-3265-1](https://doi.org/10.1007/s00280-017-3265-1) p. 726, 728

**Retrosynthesis ID:** 10367

## 2.4.3 Friedel-Crafts Acylation



**Substrates:**

1. C=CC=C(C(=O)O)C(=S)SC

2. 1-[(4-Methylphenyl)sulfonyl]-1H-indole - *available at Sigma-Aldrich*

**Products:**

1. C=CC=C(C(=O)c1cn(S(=O)(=O)c2ccc(C)cc2)c2ccccc12)C(=S)SC

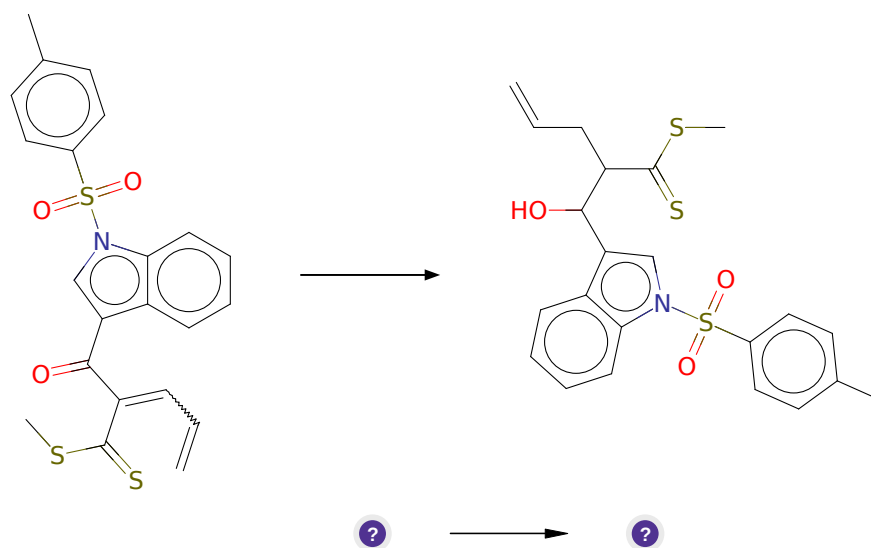
**Typical conditions:** 1.(COCl)<sub>2</sub>.Lewis Acid.solvent

**Protections:** none

**Reference:** *10.1021/ol800752v*

**Retrosynthesis ID:** 13729

#### 2.4.4 Reduction of enones to saturated alcohols



**Substrates:**

1. C=CC=C(C(=O)c1cn(S(=O)(=O)c2ccc(C)cc2)c2ccccc12)C(=S)SC

**Products:**

1. C=CCC(C(=S)SC)C(O)c1cn(S(=O)(=O)c2ccc(C)cc2)c2ccccc12

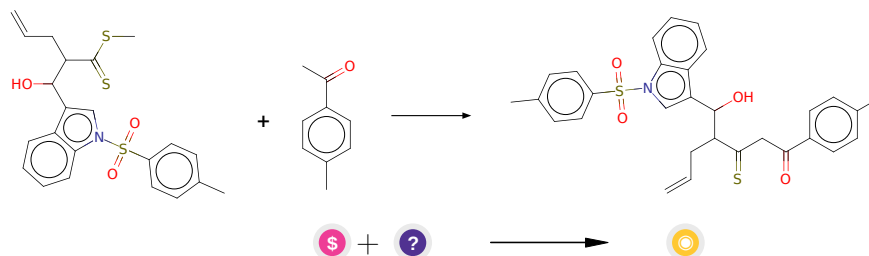
**Typical conditions:** NaBH<sub>4</sub>.transition.metal.salt.(eg.Pd(OAc)<sub>2</sub>.or.CeCl<sub>3</sub>)

**Protections:** none

**Reference:** *10.1080/00397910902788117* AND *10.1021/jo00235a009*  
 AND *10.1016/0040-4020(95)00125-R* AND *10.1021/ja01327a041* AND  
*10.1021/jo00302a056* AND *10.1002/adsc.200900628*

**Retrosynthesis ID:** 15304

## 2.4.5 Condensation of ketones with dithioesters



### Substrates:

1. Methyl p-tolyl ketone - *available at Sigma-Aldrich*
2. C=CCC(C(=S)SC)C(O)c1cn(S(=O)(=O)c2ccc(C)cc2)c2ccccc12

### Products:

1. C=CCC(C(=S)CC(=O)c1ccc(C)cc1)C(O)c1cn(S(=O)(=O)c2ccc(C)cc2)c2ccccc12

**Typical conditions:** NaH.DMF

### Protections:

Functional group SMARTS	Classification	Protecting groups
[#6][CH]([#6])[OH]	alcohols	Methoxymethyl Ether (MOM)
		2-Methoxyethoxymethyl Ether (MEM)
		Tetrahydropyranyl Ether (THP)
		Benzyl Ether (PMB)
		t-Butyldimethylsilyl Ether (TB-DMS)
		Methyl Ether

**Reference:** [10.1021/jo400599e](#) and [10.1002/ejoc.201301667](#)

**Retrosynthesis ID:** 9996413



## 2.5 Path 5

Score: 1000146.56

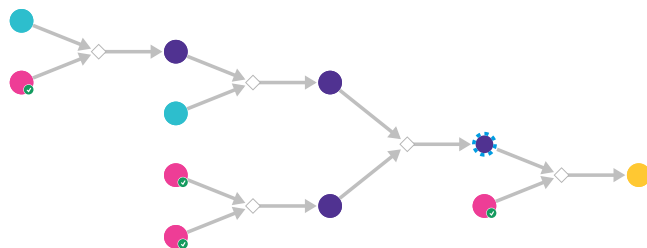
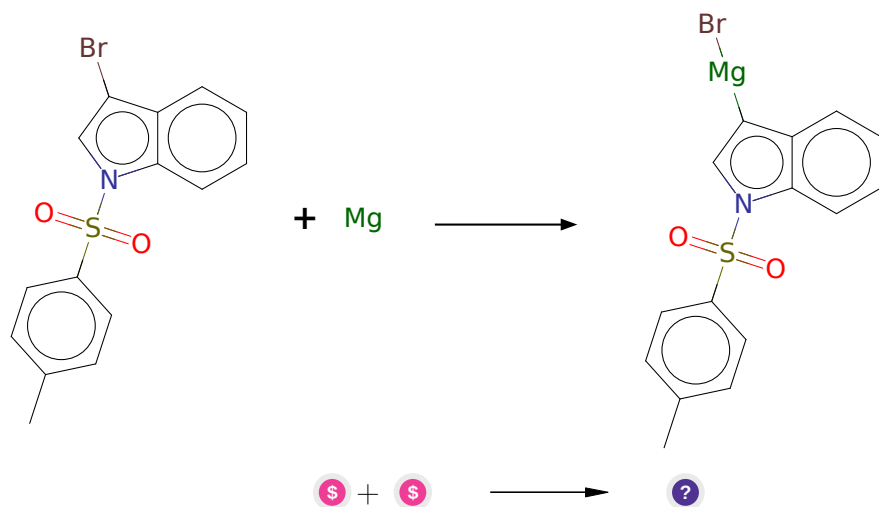


Figure 5: Outline of path 5

### 2.5.1 Synthesis of aryl Grignard reagents



#### Substrates:

1. Magnesium - *available at Sigma-Aldrich*
2. 3-Bromo-1-(p-toluenesulfonyl)indole - *available at Sigma-Aldrich*

#### Products:

1. Cc1ccc(S(=O)(=O)n2cc([Mg]Br)c3ccccc32)cc1

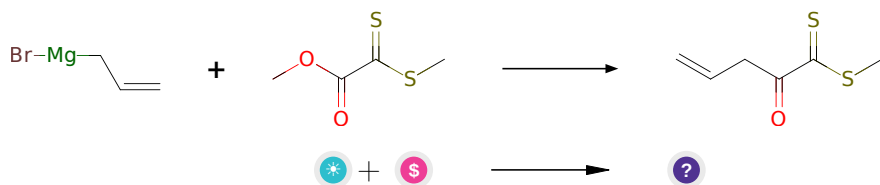
**Typical conditions:** iPrMgCl.THF or other conditions like BuLi.MgBr<sub>2</sub> or Mg.THF

**Protections:** none

**Reference:** DOI: [10.1016/S0040-4039\(99\)01404-5](https://doi.org/10.1016/S0040-4039(99)01404-5) and [10.1021/jo0000574](https://doi.org/10.1021/jo0000574) and [10.1002/anie.200454084](https://doi.org/10.1002/anie.200454084) and [10.1021/ol400150z](https://doi.org/10.1021/ol400150z)

**Retrosynthesis ID:** 10011461

### 2.5.2 Synthesis of ketones from esters via Grignard addition



**Substrates:**

1. dimethyl-1,1-dithiooxalat
2. Allylmagnesium bromide solution - *available at Sigma-Aldrich*

**Products:**

1. C=CCC(=O)C(=S)SC

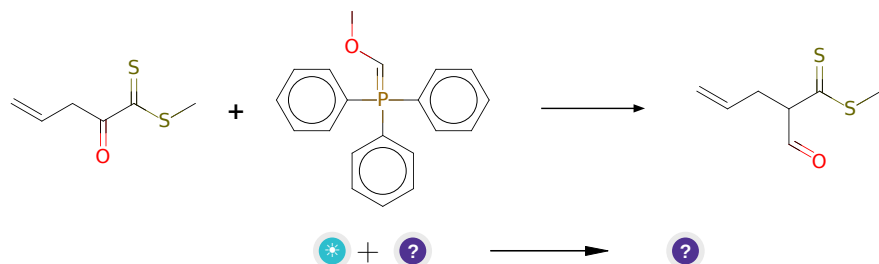
**Typical conditions:** THF. Low temp

**Protections:** none

**Reference:** [10.1021/jm800136b](https://doi.org/10.1021/jm800136b) and [10.1021/ol402802g](https://doi.org/10.1021/ol402802g)

**Retrosynthesis ID:** 10011836

### 2.5.3 Olefination of ketones followed by hydrolysis



**Substrates:**

1. triphenylphosphonium methoxymethylide
2. C=CCC(=O)C(=S)SC

**Products:**

1. C=CCC(C=O)C(=S)SC

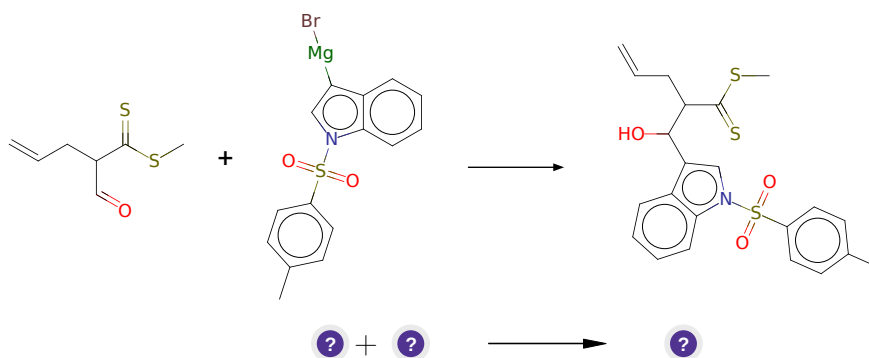
**Typical conditions:** KHMDs.THF hydrolysis: pTsOH.water.acetone

**Protections:** none

**Reference:** [10.1002/anie.201811403](#) and [10.1002/anie.201809130](#) and [10.1002/anie.201705809](#) and [10.1002/anie.201409038](#) and [10.1021/ol3028994](#) (SI)

**Retrosynthesis ID:** 31014861

#### 2.5.4 Grignard-Type Reaction



**Substrates:**

1. C=CCC(C=O)C(=S)SC
2. Cc1ccc(S(=O)(=O)n2cc([Mg]Br)c3ccccc32)cc1

**Products:**

1. C=CCC(C(=S)SC)C(O)c1cn(S(=O)(=O)c2ccc(C)cc2)c2ccccc12

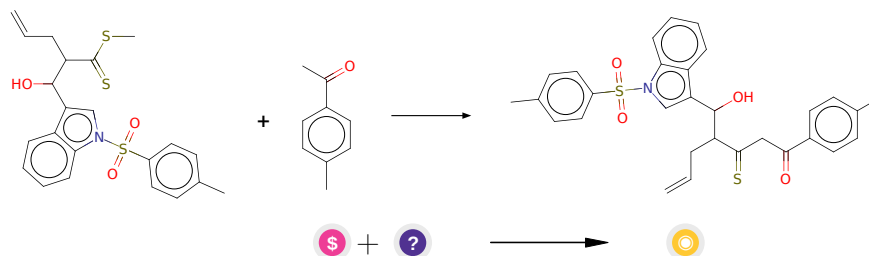
**Typical conditions:** Mg or Li.ether

**Protections:** none

**Reference:** [10.1055/s-0030-1260809](#) or [10.1021/jm061429p](#) or [10.1021/jo0621423](#) or [10.1021/ja00373a036](#) or [10.1016/S0040-4020\(01\)00457-4](#)

**Retrosynthesis ID:** 25123

### 2.5.5 Condensation of ketones with dithioesters



#### Substrates:

1. Methyl p-tolyl ketone - *available at Sigma-Aldrich*
2. C=CCC(C(=S)SC)C(O)c1cn(S(=O)(=O)c2ccc(C)cc2)c2ccccc12

#### Products:

1. C=CCC(C(=S)CC(=O)c1ccc(C)cc1)C(O)c1cn(S(=O)(=O)c2ccc(C)cc2)c2ccccc12

**Typical conditions:** NaH.DMF

#### Protections:

Functional group SMARTS	Classification	Protecting groups
[#6][CH]([#6])[OH]	alcohols	Methoxymethyl Ether (MOM)
		2-Methoxyethoxymethyl Ether (MEM)
		Tetrahydropyranyl Ether (THP)
		Benzyl Ether (PMB)
		t-Butyldimethylsilyl Ether (TB-DMS)
		Methyl Ether

**Reference:** [10.1021/jo400599e](#) and [10.1002/ejoc.201301667](#)

**Retrosynthesis ID:** 9996413