

# Paths of analysis\*

L1

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

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

### 2.1 Path 1

**Score:** 185.63

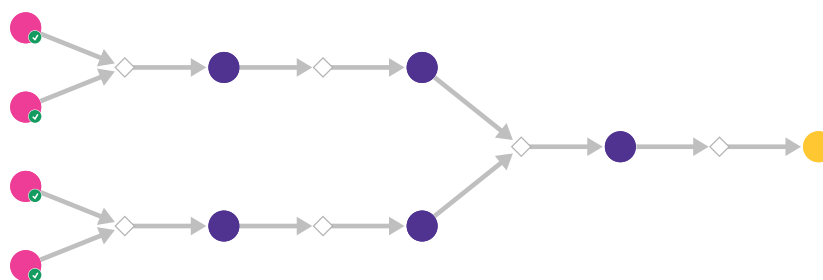
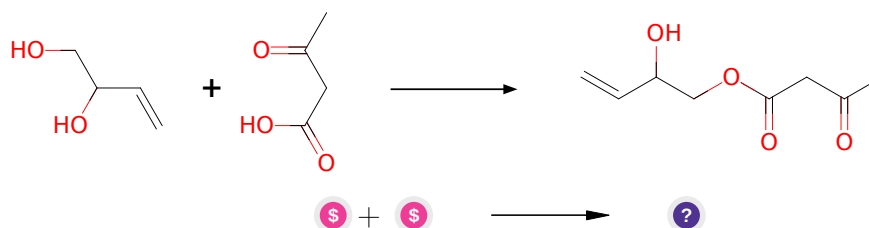


Figure 1: Outline of path 1

#### 2.1.1 Acylation of primary alcohols



**Substrates:**

1. 3-Butene-1,2-diol - *available at Sigma-Aldrich*
2. Lithium acetoacetate - *available at Sigma-Aldrich*

**Products:**

1. C=CC(O)COC(=O)CC(C)=O

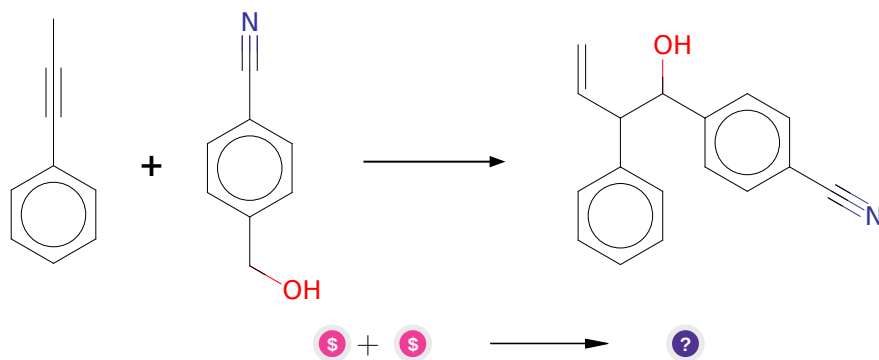
**Typical conditions:** DCC.DMAP.DCM

**Protections:** none

**Reference:** [10.1016/j.molstruc.2016.10.087](#) and [10.1016/j.bmc.2014.12.043](#) and [10.1016/j.steroids.2013.03.004](#) and [10.3390/molecules21091123](#)

**Retrosynthesis ID:** 9998689

### 2.1.2 Coupling of alkynes and alcohols



**Substrates:**

1. 4-Cyanobenzyl alcohol - [available at Sigma-Aldrich](#)
2. 1-Phenyl-1-propyne - [available at Sigma-Aldrich](#)

**Products:**

1. C=CC(c1ccccc1)C(O)c1ccc(C#N)cc1

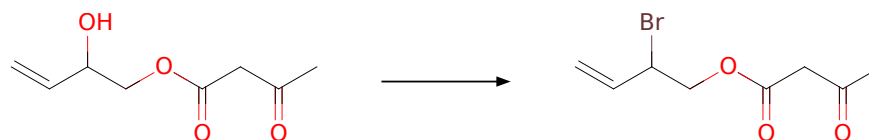
**Typical conditions:** H2Ru(CO)(PPh3)3.2,4,6-(iPr)<sub>3</sub>PhSO<sub>3</sub>H.SL-J009-1.TBAL.IPA.THF.95C

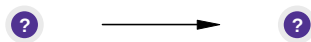
**Protections:** none

**Reference:** DOI: [10.1021/jacs.5b00747](#)

**Retrosynthesis ID:** 9894

### 2.1.3 Appel Reaction





**Substrates:**

1. C=CC(O)COC(=O)CC(C)=O

**Products:**

1. C=CC(Br)COC(=O)CC(C)=O

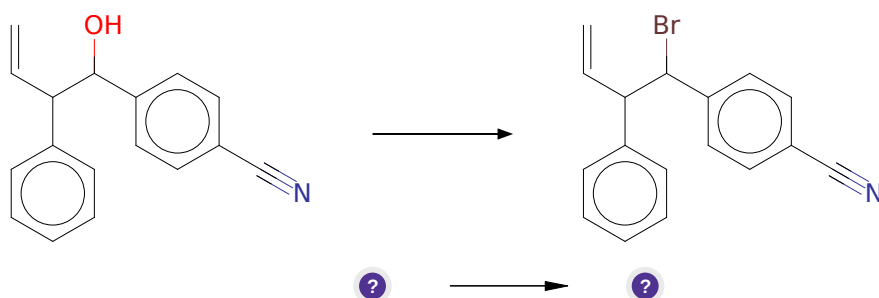
**Typical conditions:** PPh<sub>3</sub>.CBr<sub>4</sub>

**Protections:** none

**Reference:** [10.1016/j.jfluchem.2015.03.009](https://doi.org/10.1016/j.jfluchem.2015.03.009) and [10.1016/j.tet.2005.12.006](https://doi.org/10.1016/j.tet.2005.12.006) and [10.1021/jm00161a029](https://doi.org/10.1021/jm00161a029) and [10.1055/s-1995-5215](https://doi.org/10.1055/s-1995-5215)

**Retrosynthesis ID:** 9990042

#### 2.1.4 Appel Reaction



**Substrates:**

1. C=CC(c1ccccc1)C(O)c1ccc(C#N)cc1

**Products:**

1. C=CC(c1ccccc1)C(Br)c1ccc(C#N)cc1

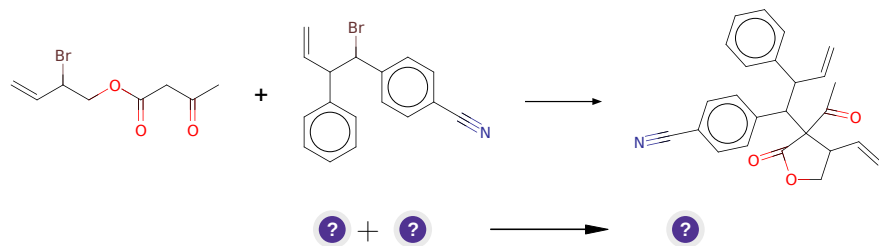
**Typical conditions:** PPh<sub>3</sub>.CBr<sub>4</sub>

**Protections:** none

**Reference:** [10.1016/j.jfluchem.2015.03.009](https://doi.org/10.1016/j.jfluchem.2015.03.009) and [10.1016/j.tet.2005.12.006](https://doi.org/10.1016/j.tet.2005.12.006) and [10.1021/jm00161a029](https://doi.org/10.1021/jm00161a029) and [10.1055/s-1995-5215](https://doi.org/10.1055/s-1995-5215)

**Retrosynthesis ID:** 9990042

### 2.1.5 Acetoacetic Ester Synthesis



**Substrates:**

1. C=CC(Br)COC(=O)CC(C)=O
2. C=CC(c1ccccc1)C(Br)c1ccc(C#N)cc1

**Products:**

1. C=CC(c1ccccc1)C(c1ccc(C#N)cc1)C1(C(C)=O)C(=O)OCC1C=C

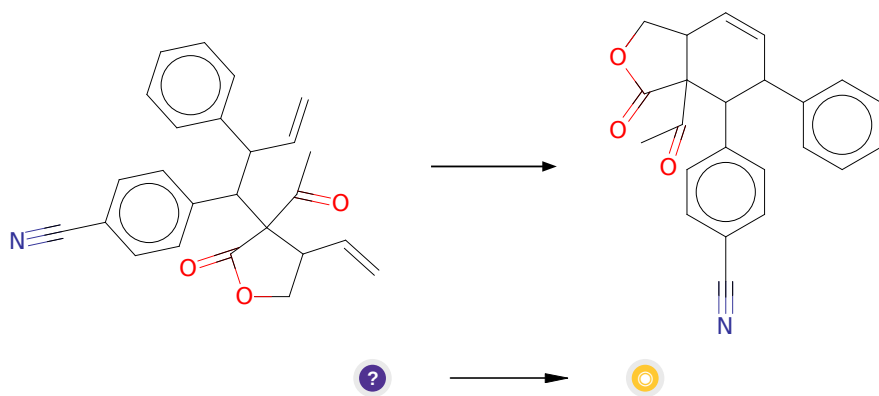
**Typical conditions:** Excess Typical bases LDA, NaHMDS, LiHMDS.THF

**Protections:** none

**Reference:** [10.1002/9780470638859.conrr003](https://doi.org/10.1002/9780470638859.conrr003)

**Retrosynthesis ID:** 5037

### 2.1.6 Ring-Closing Metathesis



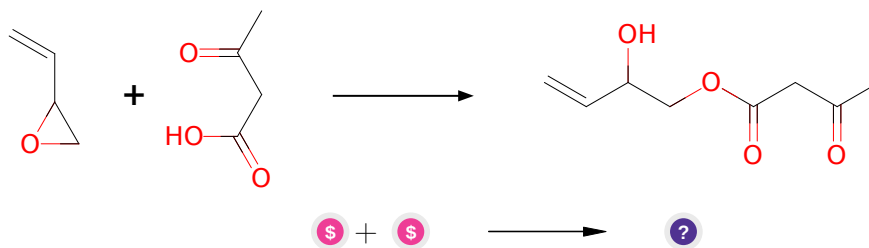
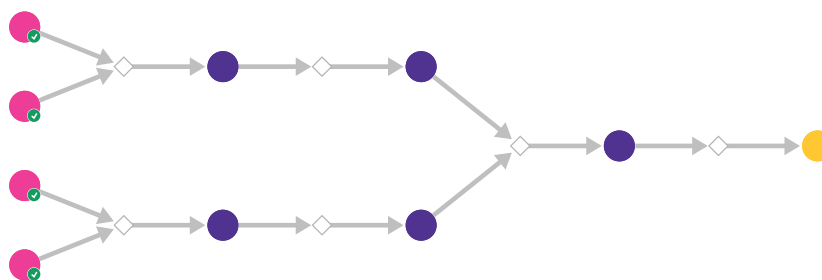
**Substrates:**

1. C=CC(c1ccccc1)C(c1ccc(C#N)cc1)C1(C(C)=O)C(=O)OCC1C=C

**Products:**

1. CC(=O)C12C(=O)OCC1C=CC(c1ccccc1)C2c1ccc(C#N)cc1

Retrosynthesis ID: 31014187



1. C=CC(O)COC(=O)CC(C)=O

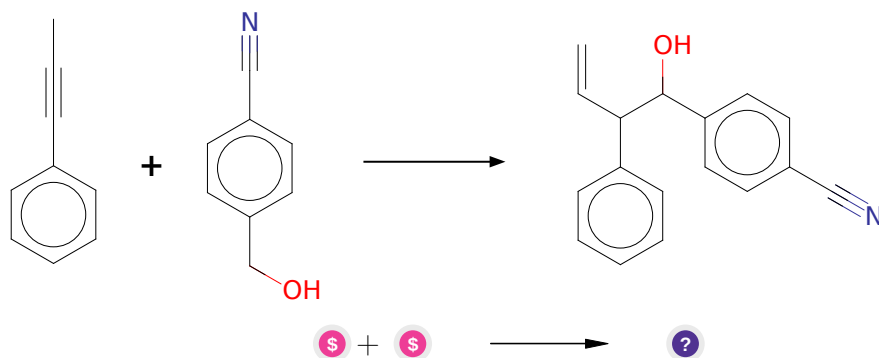
**Typical conditions:** RCOOH.catalyst

**Protections:** none

**Reference:** [10.1021/ol051051+](#) AND [10.1016/j.tet.2005.05.050](#)  
and US2011/86912 A1 (P.13) and [10.1055/s-2003-42416](#) and  
[10.5012/bkcs.2013.34.8.2286](#)

**Retrosynthesis ID:** 15151

### 2.2.2 Coupling of alkynes and alcohols



**Substrates:**

1. 4-Cyanobenzyl alcohol - [available at Sigma-Aldrich](#)
2. 1-Phenyl-1-propyne - [available at Sigma-Aldrich](#)

**Products:**

1. C=CC(c1ccccc1)C(O)c1ccc(C#N)cc1

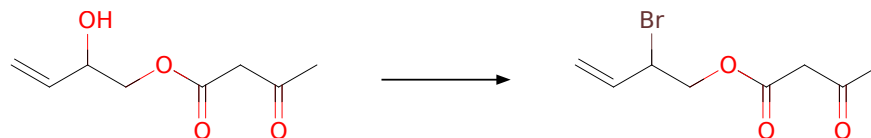
**Typical conditions:**  $\text{H}_2\text{Ru}(\text{CO})(\text{PPh}_3)_3$ .2,4,6-(iPr) $_3$ PhSO $_3$ H.SL-J009-1.TBALIPA.THF.95C

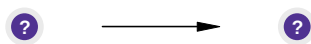
**Protections:** none

**Reference:** DOI: [10.1021/jacs.5b00747](#)

**Retrosynthesis ID:** 9894

### 2.2.3 Appel Reaction





**Substrates:**

1. C=CC(O)COC(=O)CC(C)=O

**Products:**

1. C=CC(Br)COC(=O)CC(C)=O

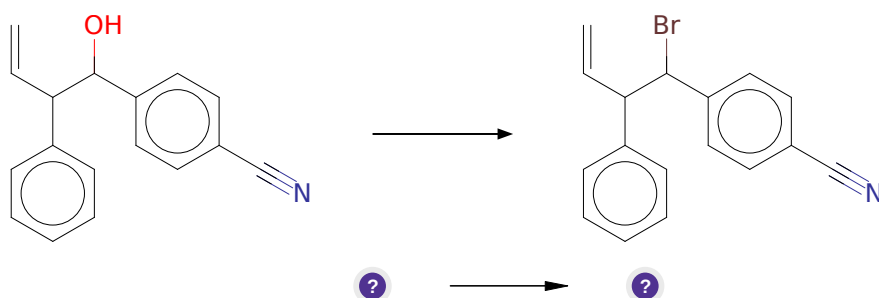
**Typical conditions:** PPh<sub>3</sub>.CBr<sub>4</sub>

**Protections:** none

**Reference:** [10.1016/j.jfluchem.2015.03.009](https://doi.org/10.1016/j.jfluchem.2015.03.009) and [10.1016/j.tet.2005.12.006](https://doi.org/10.1016/j.tet.2005.12.006) and [10.1021/jm00161a029](https://doi.org/10.1021/jm00161a029) and [10.1055/s-1995-5215](https://doi.org/10.1055/s-1995-5215)

**Retrosynthesis ID:** 9990042

#### 2.2.4 Appel Reaction



**Substrates:**

1. C=CC(c1ccccc1)C(O)c1ccc(C#N)cc1

**Products:**

1. C=CC(c1ccccc1)C(Br)c1ccc(C#N)cc1

**Typical conditions:** PPh<sub>3</sub>.CBr<sub>4</sub>

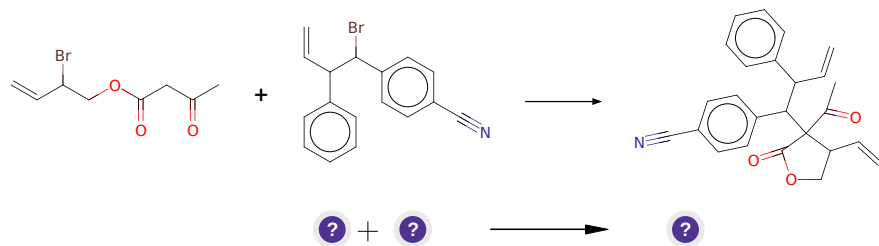
**Protections:** none

**Reference:** [10.1016/j.jfluchem.2015.03.009](https://doi.org/10.1016/j.jfluchem.2015.03.009) and [10.1016/j.tet.2005.12.006](https://doi.org/10.1016/j.tet.2005.12.006) and [10.1021/jm00161a029](https://doi.org/10.1021/jm00161a029) and [10.1055/s-1995-5215](https://doi.org/10.1055/s-1995-5215)

**Retrosynthesis ID:** 9990042



### 2.2.5 Acetoacetic Ester Synthesis



**Substrates:**

1. C=CC(Br)COC(=O)CC(C)=O
2. C=CC(c1ccccc1)C(Br)c1ccc(C#N)cc1

**Products:**

1. C=CC(c1ccccc1)C(c1ccc(C#N)cc1)C1(C(C)=O)C(=O)OCC1C=C

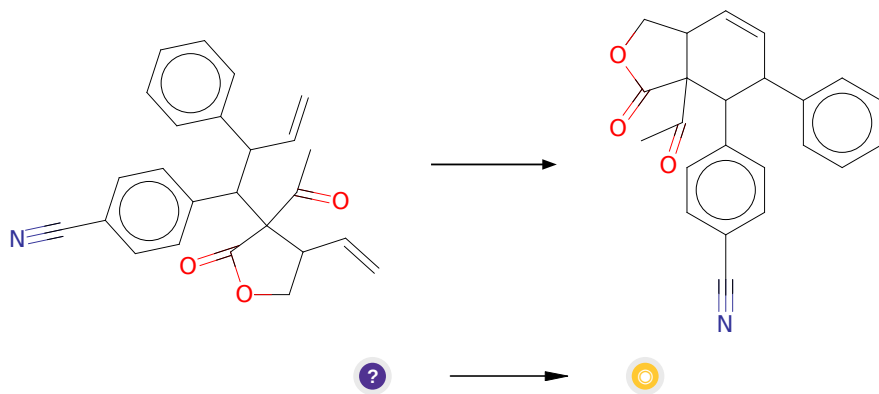
**Typical conditions:** Excess Typical bases LDA, NaHMDS, LiHMDS.THF

**Protections:** none

**Reference:** [10.1002/9780470638859.conrr003](https://doi.org/10.1002/9780470638859.conrr003)

**Retrosynthesis ID:** 5037

### 2.2.6 Ring-Closing Metathesis



**Substrates:**

1. C=CC(c1ccccc1)C(c1ccc(C#N)cc1)C1(C(C)=O)C(=O)OCC1C=C

**Products:**

1. CC(=O)C12C(=O)OCC1C=CC(c1ccccc1)C2c1ccc(C#N)cc1

**Typical conditions:** catalyst e.g. Hoveyda-Grubbs . solvent e.g. CH<sub>2</sub>Cl<sub>2</sub>

**Protections:** none

**Reference:** DOI: [10.1002/anie.200800693](https://doi.org/10.1002/anie.200800693) and [10.1021/acs.orglett.8b04003](https://doi.org/10.1021/acs.orglett.8b04003) and [10.1021/jo0264729](https://doi.org/10.1021/jo0264729) and [10.1021/ja072334v](https://doi.org/10.1021/ja072334v) and [10.1002/ejoc.201001102](https://doi.org/10.1002/ejoc.201001102)

**Retrosynthesis ID:** 31014187

## 2.3 Path 3

Score: 195.39

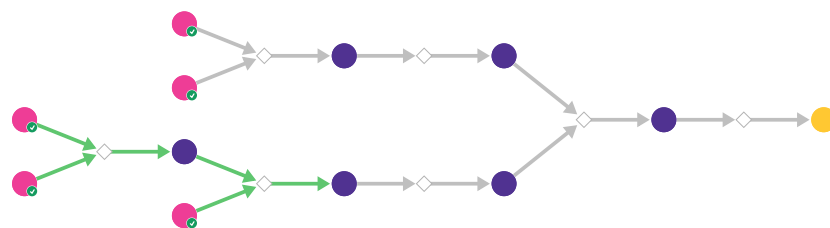
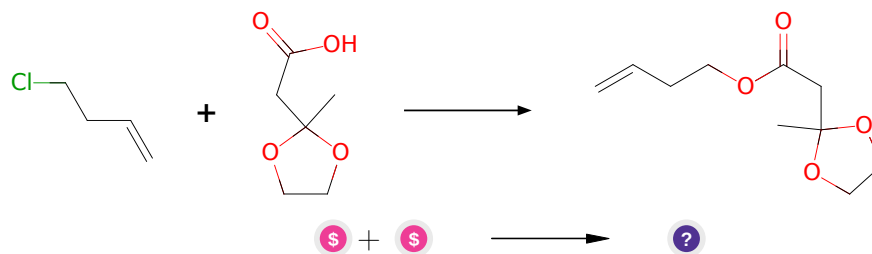


Figure 3: Outline of path 3

### 2.3.1 Synthesis of esters from alkyl chlorides and carboxylic acids or thioacids



**Substrates:**

1. 4-chlorobut-1-ene - *available at Sigma-Aldrich*
2. 2-(2-methyl-1,3-dioxolan-2-yl)acetic acid - *available at Sigma-Aldrich*

**Products:**

1. C=CCCOC(=O)CC1(C)OCCO1

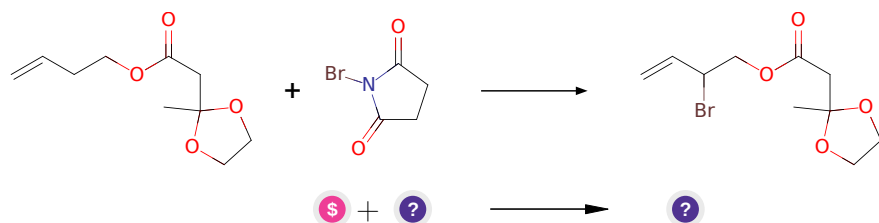
**Typical conditions:** K<sub>2</sub>CO<sub>3</sub>.DMF

**Protections:** none

**Reference:** [10.1016/j.bmcl.2005.08.026](#) AND [10.1021/ol034655r](#) (SI) AND [10.1039/C3RA41967C](#) AND [10.1016/j.bmcl.2012.03.093](#)

**Retrosynthesis ID:** 14684

### 2.3.2 Wohl-Ziegler Bromination



**Substrates:**

1. N-Bromosuccinimide - [available at Sigma-Aldrich](#)
2. C=CCCOC(=O)CC1(C)OCCO1

**Products:**

1. C=CC(Br)COC(=O)CC1(C)OCCO1

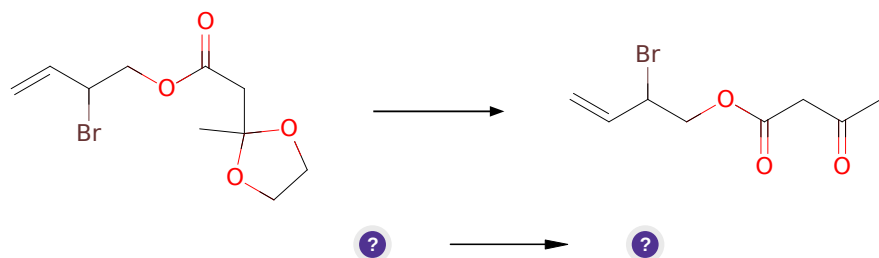
**Typical conditions:** NBS.AIBN or (BzO)<sub>2</sub> or heat

**Protections:** none

**Reference:** [10.1002/bscb.19830920407](#) and [10.1002/prac.19813230417](#) and [10.1002/cbic.201402000](#)

**Retrosynthesis ID:** 245553

### 2.3.3 Hydrolysis of ketals



**Substrates:**

1. C=CC(Br)COC(=O)CC1(C)OCCO1

**Products:**

1. C=CC(Br)COC(=O)CC(C)=O

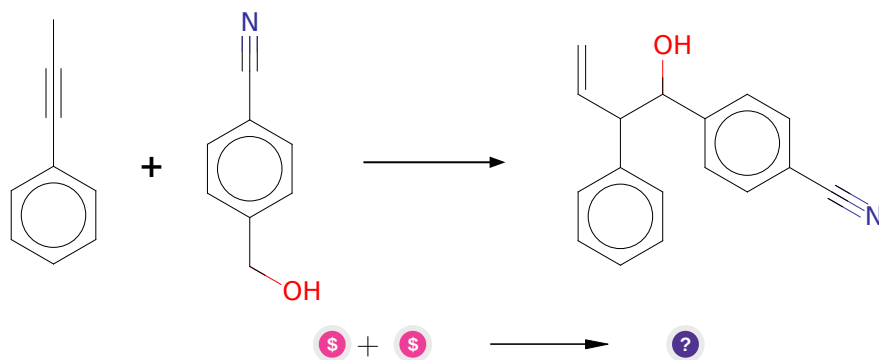
**Typical conditions:** H<sub>2</sub>O.HCl

**Protections:** none

**Reference:** [10.1021/jo0159035](https://doi.org/10.1021/jo0159035) and [10.1021/jo00194a003](https://doi.org/10.1021/jo00194a003) and

**Retrosynthesis ID:** 31013139

### 2.3.4 Coupling of alkynes and alcohols



**Substrates:**

1. 4-Cyanobenzyl alcohol - *available at Sigma-Aldrich*
2. 1-Phenyl-1-propyne - *available at Sigma-Aldrich*

**Products:**

1. C=CC(c1ccccc1)C(O)c1ccc(C#N)cc1

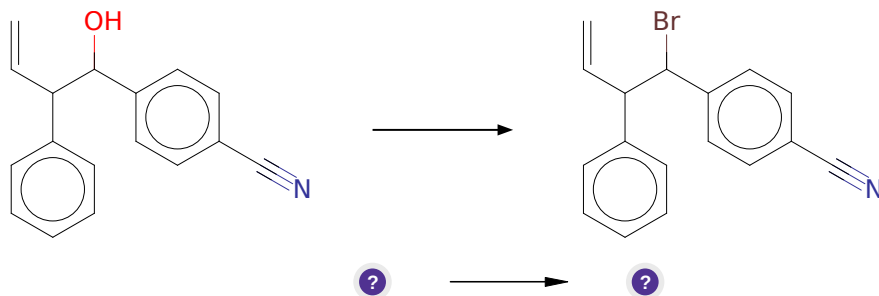
**Typical conditions:** H<sub>2</sub>Ru(CO)(PPh<sub>3</sub>)<sub>3</sub>.2,4,6-(iPr)<sub>3</sub>PhSO<sub>3</sub>H.SL-J009-1.TBAL.IPA.THF.95C

**Protections:** none

**Reference:** DOI: [10.1021/jacs.5b00747](https://doi.org/10.1021/jacs.5b00747)

**Retrosynthesis ID:** 9894

### 2.3.5 Appel Reaction



**Substrates:**

1. C=CC(c1ccccc1)C(O)c1ccc(C#N)cc1

**Products:**

1. C=CC(c1ccccc1)C(Br)c1ccc(C#N)cc1

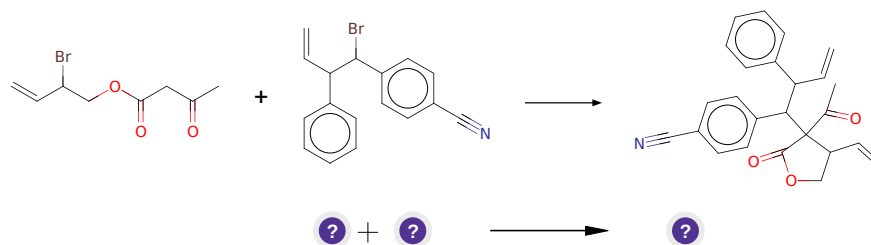
**Typical conditions:** PPh<sub>3</sub>.CBr<sub>4</sub>

**Protections:** none

**Reference:** [10.1016/j.jfluchem.2015.03.009](https://doi.org/10.1016/j.jfluchem.2015.03.009) and [10.1016/j.tet.2005.12.006](https://doi.org/10.1016/j.tet.2005.12.006) and [10.1021/jm00161a029](https://doi.org/10.1021/jm00161a029) and [10.1055/s-1995-5215](https://doi.org/10.1055/s-1995-5215)

**Retrosynthesis ID:** 9990042

### 2.3.6 Acetoacetic Ester Synthesis



**Substrates:**

1. C=CC(Br)COC(=O)CC(C)=O
2. C=CC(c1ccccc1)C(Br)c1ccc(C#N)cc1

**Products:**

1. C=CC(c1ccccc1)C(c1ccc(C#N)cc1)C1(C(C)=O)C(=O)OCC1C=C

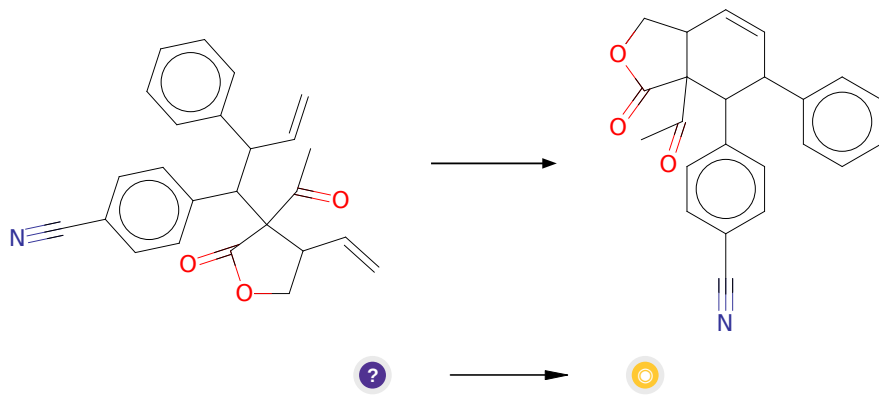
**Typical conditions:** Excess Typical bases LDA, NaHMDS, LiHMDS.THF

**Protections:** none

**Reference:** [10.1002/9780470638859.conrr003](https://doi.org/10.1002/9780470638859.conrr003)

**Retrosynthesis ID:** 5037

### 2.3.7 Ring-Closing Metathesis



**Substrates:**

1. C=CC(c1ccccc1)C(c1ccc(C#N)cc1)C1(C(C)=O)C(=O)OCC1C=C

**Products:**

1. CC(=O)C12C(=O)OCC1C=CC(c1ccccc1)C2c1ccc(C#N)cc1

**Typical conditions:** catalyst e.g. Hoveyda-Grubbs . solvent e.g. CH<sub>2</sub>Cl<sub>2</sub>

**Protections:** none

**Reference:** DOI: [10.1002/anie.200800693](https://doi.org/10.1002/anie.200800693) and [10.1021/acs.orglett.8b04003](https://doi.org/10.1021/acs.orglett.8b04003) and [10.1021/jo0264729](https://doi.org/10.1021/jo0264729) and [10.1021/ja072334v](https://doi.org/10.1021/ja072334v) and [10.1002/ejoc.201001102](https://doi.org/10.1002/ejoc.201001102)

**Retrosynthesis ID:** 31014187

## 2.4 Path 4

**Score:** 195.39

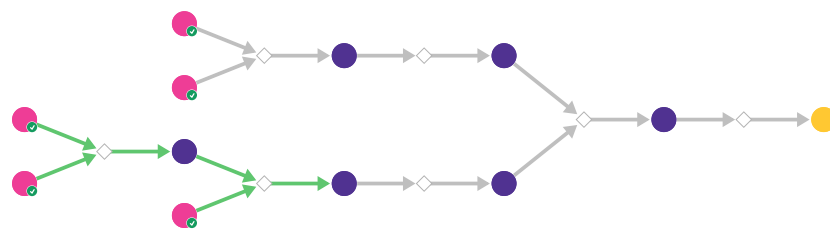
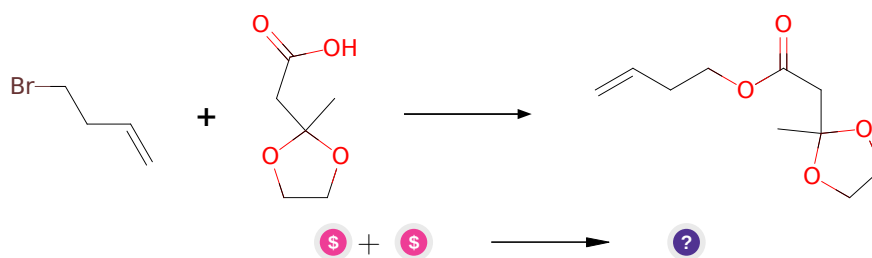


Figure 4: Outline of path 4

#### 2.4.1 Synthesis of esters from alkyl chlorides and carboxylic acids or thioacids



##### Substrates:

1. 4-Bromo-1-butene - *available at Sigma-Aldrich*
2. 2-(2-methyl-1,3-dioxolan-2-yl)acetic acid - *available at Sigma-Aldrich*

##### Products:

1. C=CCCOC(=O)CC1(C)OCCO1

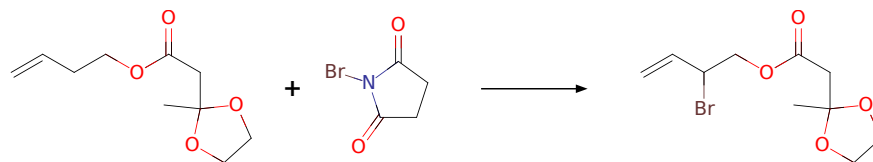
**Typical conditions:** K<sub>2</sub>CO<sub>3</sub>.DMF

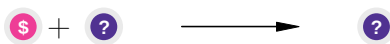
**Protections:** none

**Reference:** [10.1016/j.bmcl.2005.08.026](#) AND [10.1021/ol034655r](#) (SI) AND [10.1039/C3RA41967C](#) AND [10.1016/j.bmcl.2012.03.093](#)

**Retrosynthesis ID:** 14685

#### 2.4.2 Wohl-Ziegler Bromination





**Substrates:**

1. N-Bromosuccinimide - *available at Sigma-Aldrich*
2. C=CCCOC(=O)CC1(C)OCCO1

**Products:**

1. C=CC(Br)COC(=O)CC1(C)OCCO1

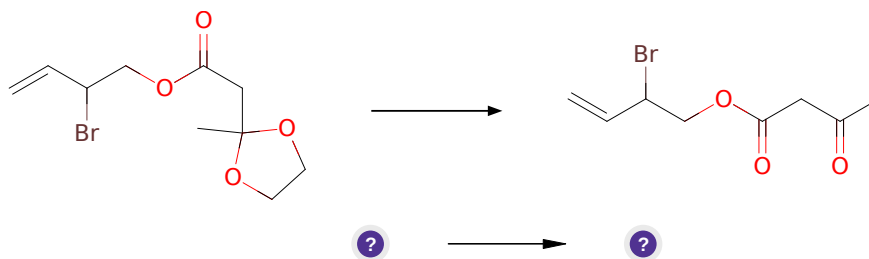
**Typical conditions:** NBS.AIBN or (BzO)<sub>2</sub> or heat

**Protections:** none

**Reference:** [10.1002/bscb.19830920407](#) and [10.1002/prac.19813230417](#) and [10.1002/cbic.201402000](#)

**Retrosynthesis ID:** 245553

### 2.4.3 Hydrolysis of ketals



**Substrates:**

1. C=CC(Br)COC(=O)CC1(C)OCCO1

**Products:**

1. C=CC(Br)COC(=O)CC(C)=O

**Typical conditions:** H<sub>2</sub>O.HCl

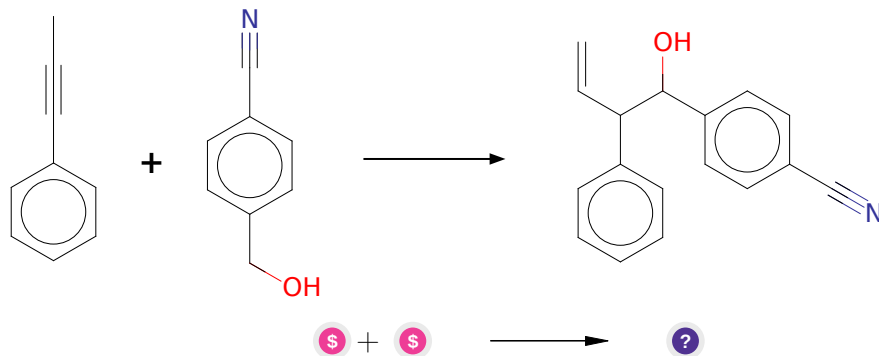
**Protections:** none

**Reference:** [10.1021/jo0159035](#) and [10.1021/jo00194a003](#) and

**Retrosynthesis ID:** 31013139



#### 2.4.4 Coupling of alkynes and alcohols



##### Substrates:

1. 4-Cyanobenzyl alcohol - *available at Sigma-Aldrich*
2. 1-Phenyl-1-propyne - *available at Sigma-Aldrich*

##### Products:

1. C=CC(c1ccccc1)C(O)c1ccc(C#N)cc1

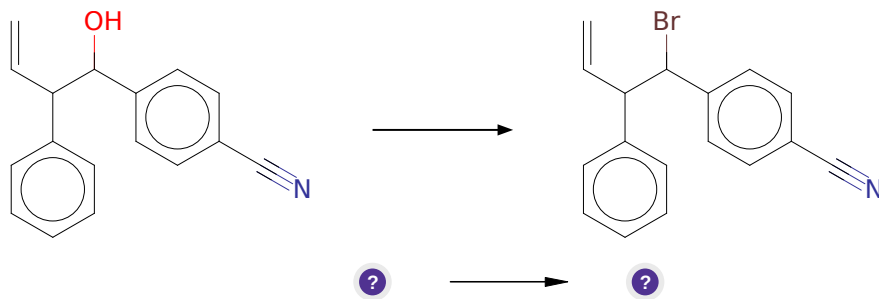
**Typical conditions:** H2Ru(CO)(PPh3)3.2,4,6-(iPr)<sub>3</sub>PhSO<sub>3</sub>H.SL-J009-1.TBAL.IPA.THF.95C

**Protections:** none

**Reference:** DOI: [10.1021/jacs.5b00747](https://doi.org/10.1021/jacs.5b00747)

**Retrosynthesis ID:** 9894

#### 2.4.5 Appel Reaction



##### Substrates:

1. C=CC(c1ccccc1)C(O)c1ccc(C#N)cc1

##### Products:

1. C=CC(c1ccccc1)C(Br)c1ccc(C#N)cc1

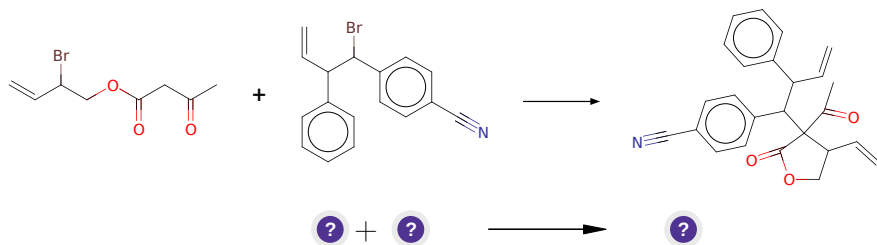
**Typical conditions:** PPh<sub>3</sub>.CBr<sub>4</sub>

**Protections:** none

**Reference:** [10.1016/j.jfluchem.2015.03.009](#) and [10.1016/j.tet.2005.12.006](#) and [10.1021/jm00161a029](#) and [10.1055/s-1995-5215](#)

**Retrosynthesis ID:** 9990042

#### 2.4.6 Acetoacetic Ester Synthesis



**Substrates:**

1. C=CC(Br)COC(=O)CC(C)=O
2. C=CC(c1ccccc1)C(Br)c1ccc(C#N)cc1

**Products:**

1. C=CC(c1ccccc1)C(c1ccc(C#N)cc1)C1(C(C)=O)C(=O)OCC1C=C

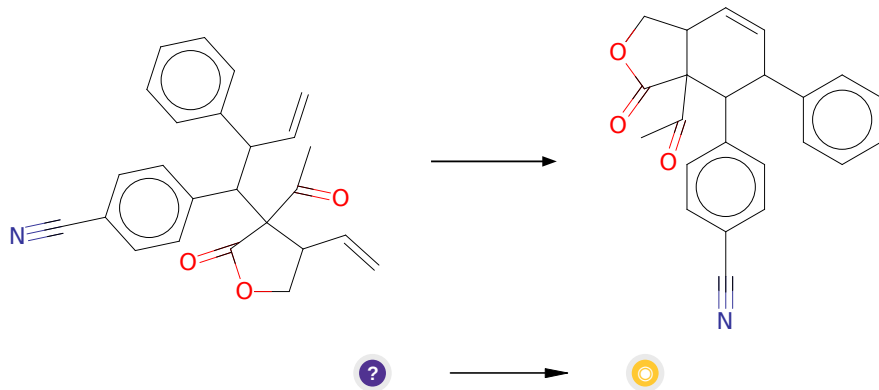
**Typical conditions:** Excess Typical bases LDA, NaHMDS, LiHMDS.THF

**Protections:** none

**Reference:** [10.1002/9780470638859.conrr003](#)

**Retrosynthesis ID:** 5037

### 2.4.7 Ring-Closing Metathesis



**Substrates:**

1. C=CC(c1ccccc1)C(c1ccc(C#N)cc1)C1(C(C)=O)C(=O)OCC1C=C

**Products:**

1. CC(=O)C12C(=O)OCC1C=CC(c1ccccc1)C2c1ccc(C#N)cc1

**Typical conditions:** catalyst e.g. Hoveyda-Grubbs . solvent e.g. CH<sub>2</sub>Cl<sub>2</sub>

**Protections:** none

**Reference:** DOI: [10.1002/anie.200800693](https://doi.org/10.1002/anie.200800693) and [10.1021/acs.orglett.8b04003](https://doi.org/10.1021/acs.orglett.8b04003) and [10.1021/jo0264729](https://doi.org/10.1021/jo0264729) and [10.1021/ja072334v](https://doi.org/10.1021/ja072334v) and [10.1002/ejoc.201001102](https://doi.org/10.1002/ejoc.201001102)

**Retrosynthesis ID:** 31014187