

Paths of analysis*

Y2A

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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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: 1000146.56

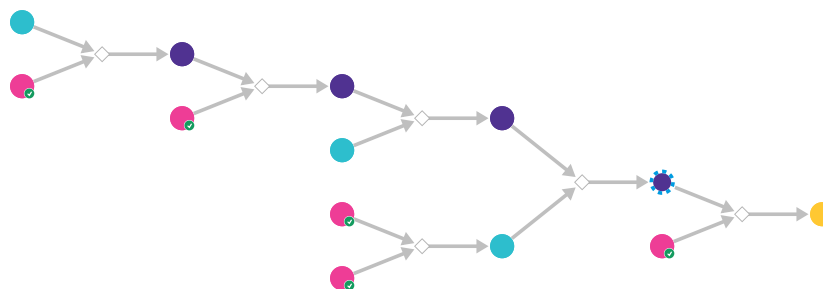
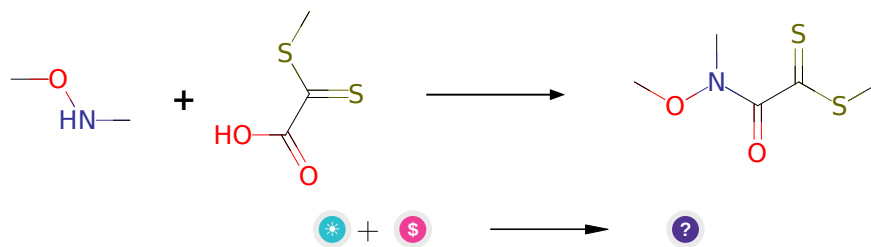


Figure 1: Outline of path 1

2.1.1 Synthesis of O-substituted N-substituted hydroxamic acids



Substrates:

- 1-methyl-1,1-dithiooxalacetic acid
- n-methoxymethylamine - *available at Sigma-Aldrich*

Products:

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

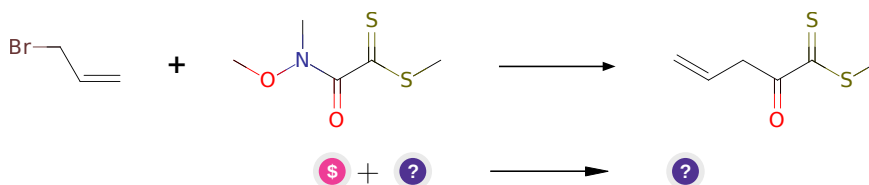
Typical conditions: DCC.DMAP or CDI.TEA.DCM

Protections: none

Reference: Patent: WO2007/67333A2, 2007 & [10.1016/j.bmcl.2008.09.100](#)

Retrosynthesis ID: 1152

2.1.2 Synthesis of ketones from Weinreb amides



Substrates:

1. Allyl bromide - [available at Sigma-Aldrich](#)
2. CON(C)C(=O)C(=S)SC

Products:

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

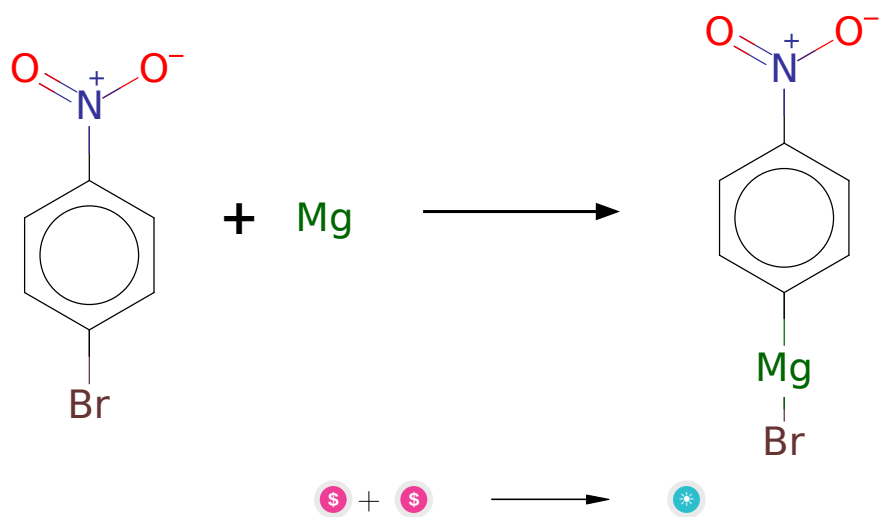
Typical conditions: 1.RmgBr.THF 2.TFA.DCM

Protections: none

Reference: [10.1021/jm051185t](#) and [10.1021/ol101021v](#) (supporting info)

Retrosynthesis ID: 6837

2.1.3 Synthesis of aryl Grignard reagents



Substrates:

1. Magnesium - *available at Sigma-Aldrich*
2. 1-Bromo-4-nitrobenzene - *available at Sigma-Aldrich*

Products:

1. $\text{C}_6\text{H}_4\text{BrMgNO}_2$

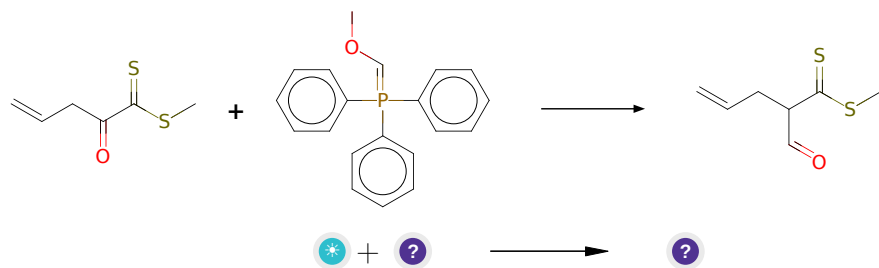
Typical conditions: $\text{iPrMgCl} \cdot \text{THF}$ or other conditions like $\text{BuLi} \cdot \text{MgBr}_2$ or $\text{Mg} \cdot \text{THF}$

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

2.1.4 Olefination of ketones followed by hydrolysis



Substrates:

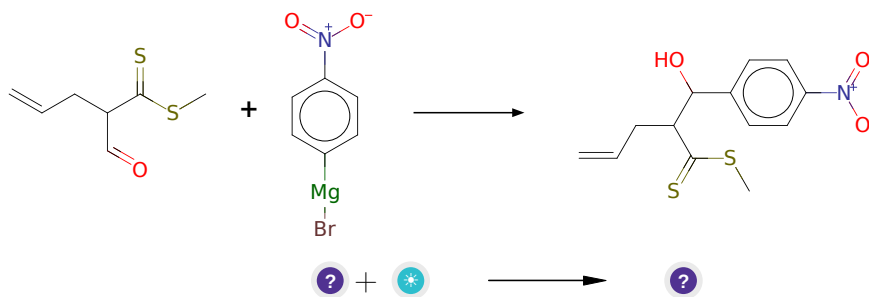
1. triphenylphosphonium methoxymethylide
2. C=CCC(=O)C(=S)SC

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**2.1.5 Grignard-Type Reaction****Substrates:**

1. C=CCC(C=O)C(=S)SC
2. C6H4BrMgNO2

Products:

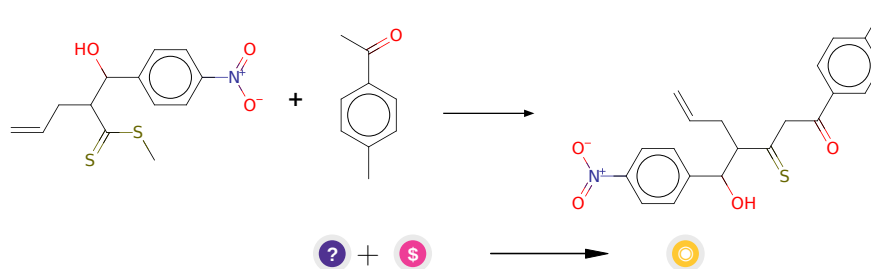
1. C=CCC(C(=S)SC)C(O)c1ccc([N+](=O)[O-])cc1

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

2.1.6 Condensation of ketones with dithioesters



Substrates:

1. C=CCC(C(=S)SC)C(O)c1ccc([N+](=O)[O-])cc1
2. Methyl p-tolyl ketone - *available at Sigma-Aldrich*

Products:

1. C=CCC(C(=S)CC(=O)c1ccc(C)cc1)C(O)c1ccc([N+](=O)[O-])cc1

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: 1000146.56

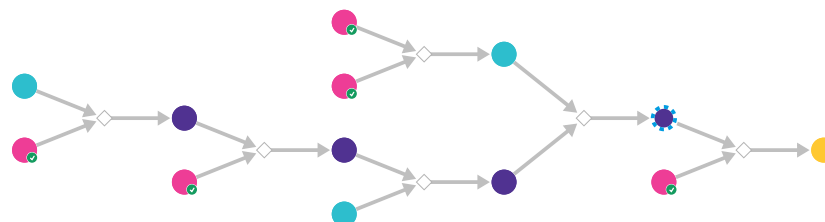
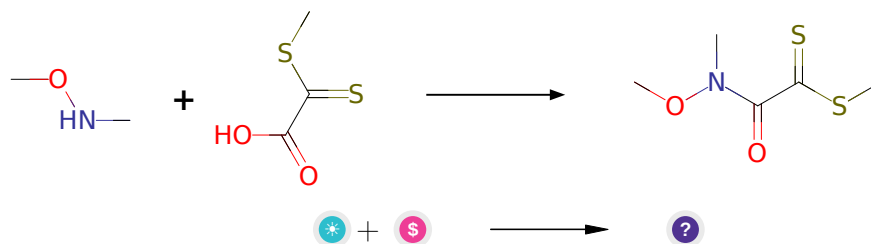


Figure 2: Outline of path 2

2.2.1 Synthesis of O-substituted N-substituted hydroxamic acids



Substrates:

1. 1-methyl-1,1-dithiooxalsaeure
2. n-methoxymethylamine - *available at Sigma-Aldrich*

Products:

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

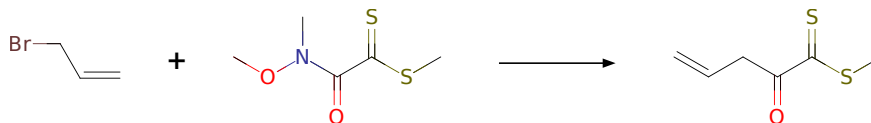
Typical conditions: DCC.DMAP or CDI.TEA.DCM

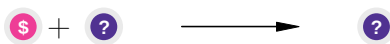
Protections: none

Reference: Patent: WO2007/67333A2, 2007 & [10.1016/j.bmcl.2008.09.100](https://doi.org/10.1016/j.bmcl.2008.09.100)

Retrosynthesis ID: 1152

2.2.2 Synthesis of ketones from Weinreb amides





Substrates:

1. Allyl bromide - *available at Sigma-Aldrich*
2. CON(C)C(=O)C(=S)SC

Products:

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

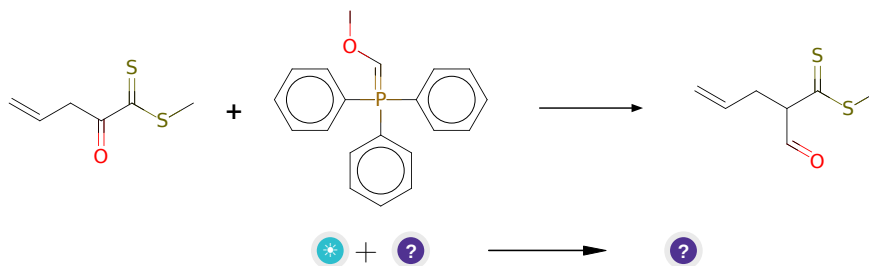
Typical conditions: 1.RmgBr.THF 2.TFA.DCM

Protections: none

Reference: [10.1021/jm051185t](#) and [10.1021/ol101021v](#) (supporting info)

Retrosynthesis ID: 6837

2.2.3 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

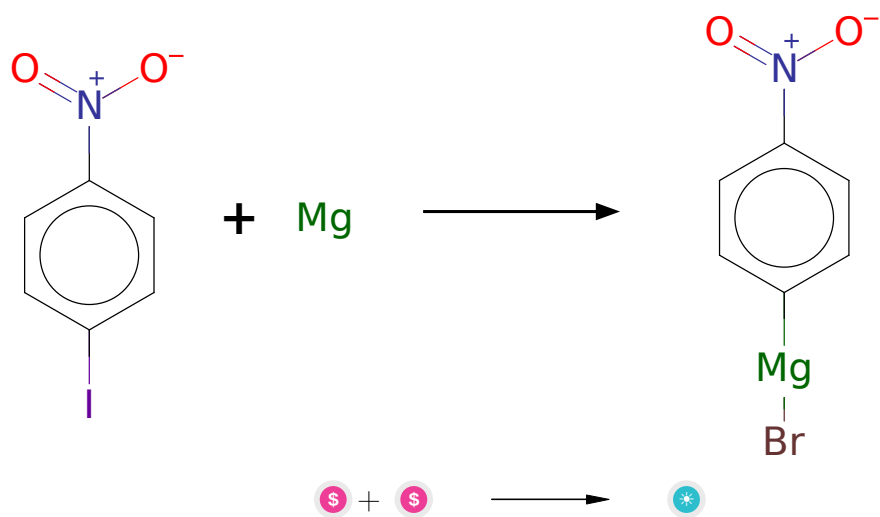
Typical conditions: KHMDS.THF hydrolysis: pTsOH.water.acetone

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

2.2.4 Synthesis of aryl Grignard reagents



Substrates:

1. Magnesium - *available at Sigma-Aldrich*
2. 1-Iodo-4-nitrobenzene - *available at Sigma-Aldrich*

Products:

1. $\text{C}_6\text{H}_4\text{BrMgNO}_2$

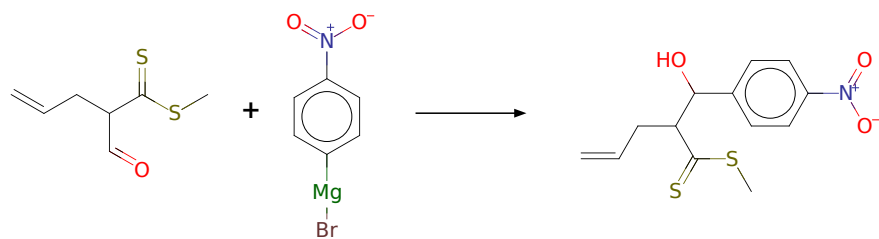
Typical conditions: $\text{iPrMgCl} \cdot \text{LiCl} \cdot \text{THF}$ or other conditions $\text{Mg} \cdot \text{THF}$ or $\text{tBuLi} \cdot \text{MgBr}_2$

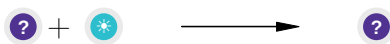
Protections: none

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 WO2014123793 p.137 and [10.1021/jm400491x](https://doi.org/10.1021/jm400491x) and [10.3762/bjoc.12.36](https://doi.org/10.3762/bjoc.12.36)

Retrosynthesis ID: 10011460

2.2.5 Grignard-Type Reaction





Substrates:

1. C=CCC(C=O)C(=S)SC
2. C6H4BrMgNO2

Products:

1. C=CCC(C(=S)SC)C(O)c1ccc([N+](=O)[O-])cc1

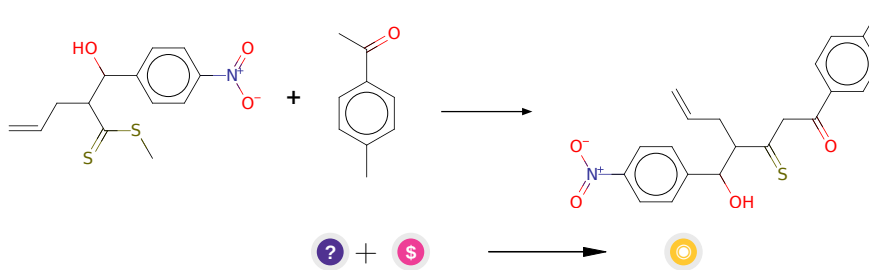
Typical conditions: Mg or Li.ether

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

2.2.6 Condensation of ketones with dithioesters



Substrates:

1. C=CCC(C(=S)SC)C(O)c1ccc([N+](=O)[O-])cc1
2. Methyl p-tolyl ketone - *available at Sigma-Aldrich*

Products:

1. C=CCC(C(=S)CC(=O)c1ccc(C)cc1)C(O)c1ccc([N+](=O)[O-])cc1

Typical conditions: NaH.DMF

Protections:

Functional group SMARTS	Classification	Protecting groups
<chem>[*6][CH]([*6])[OH]</chem>	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: 1000146.56

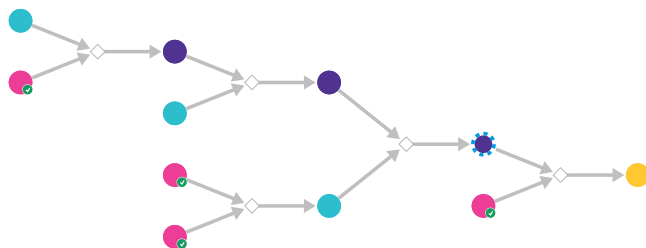
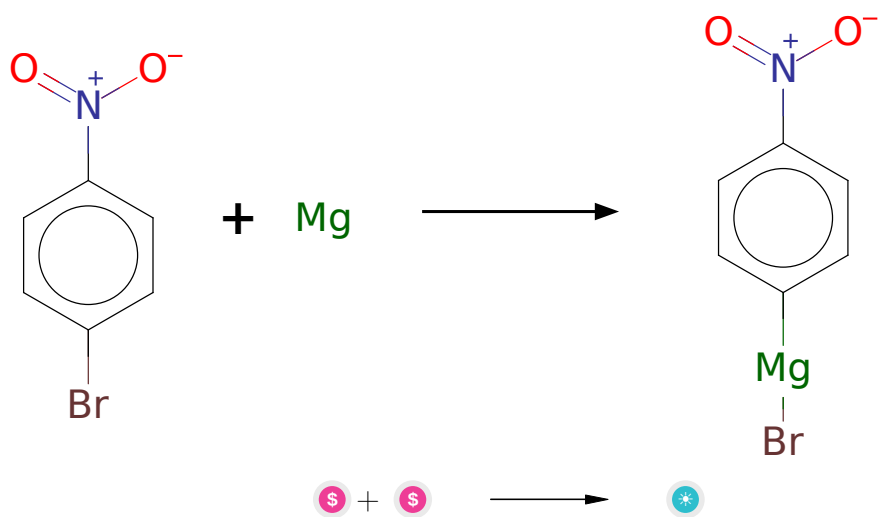


Figure 3: Outline of path 3

2.3.1 Synthesis of aryl Grignard reagents



Substrates:

1. Magnesium - *available at Sigma-Aldrich*
2. 1-Bromo-4-nitrobenzene - *available at Sigma-Aldrich*

Products:

1. $\text{C}_6\text{H}_4\text{BrMgNO}_2$

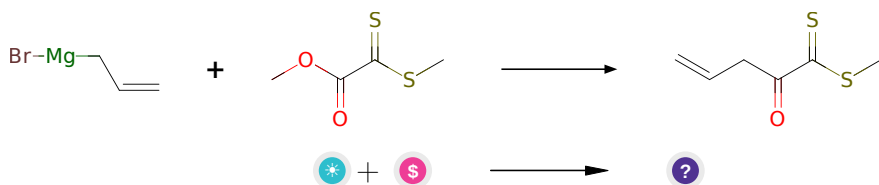
Typical conditions: $\text{iPrMgCl} \cdot \text{THF}$ or other conditions like $\text{BuLi} \cdot \text{MgBr}_2$ or $\text{Mg} \cdot \text{THF}$

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

2.3.2 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

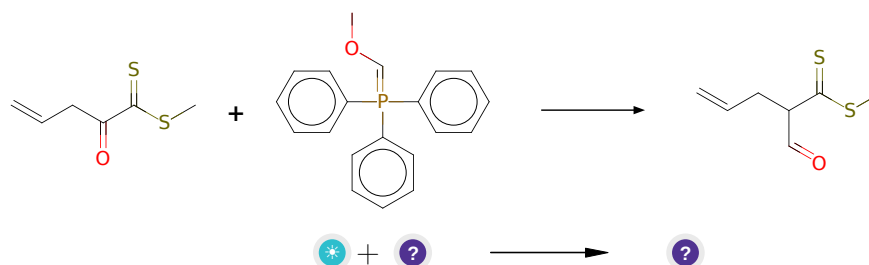
Typical conditions: THF. Low temp

Protections: none

Reference: [10.1021/jm800136b](#) and [10.1021/ol402802g](#)

Retrosynthesis ID: 10011836

2.3.3 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

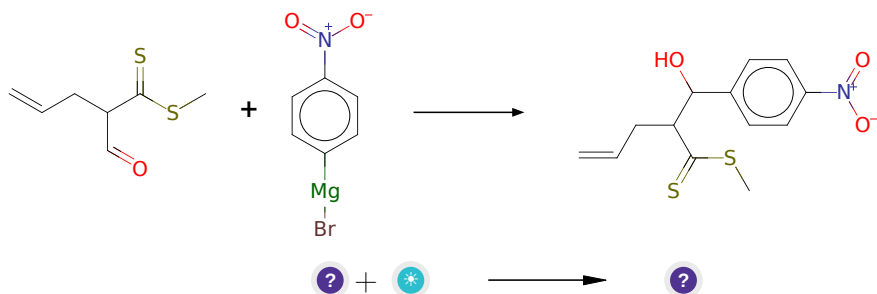
Typical conditions: KHMDs.THF hydrolysis: pTsOH.water.acetone

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

2.3.4 Grignard-Type Reaction



Substrates:

1. C=CCC(C=O)C(=S)SC
2. C6H4BrMgNO2

Products:

1. C=CCC(C(=S)SC)C(O)c1ccc([N+](=O)[O-])cc1

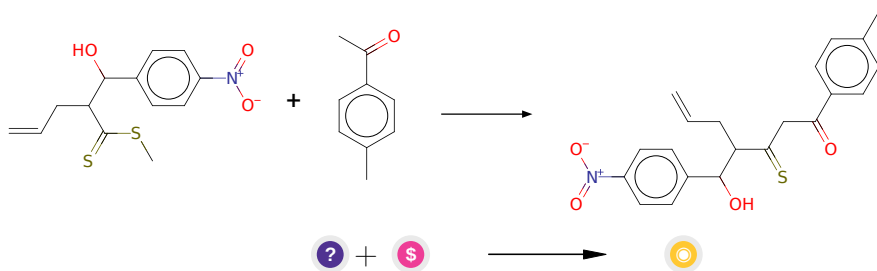
Typical conditions: Mg or Li.ether

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

2.3.5 Condensation of ketones with dithioesters



Substrates:

1. C=CCC(C(=S)SC)C(O)c1ccc([N+](=O)[O-])cc1
2. Methyl p-tolyl ketone - *available at Sigma-Aldrich*

Products:

1. C=CCC(C(=S)CC(=O)c1ccc(C)cc1)C(O)c1ccc([N+](=O)[O-])cc1

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

2.4 Path 4

Score: 1000146.56

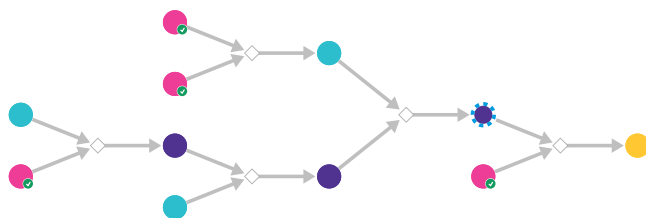
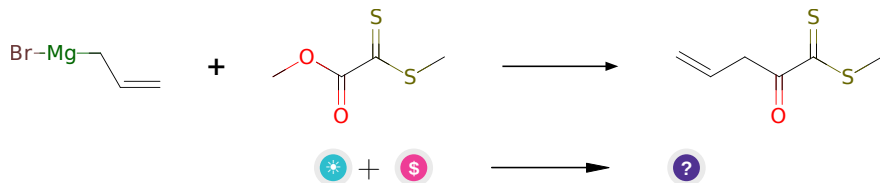


Figure 4: Outline of path 4

2.4.1 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

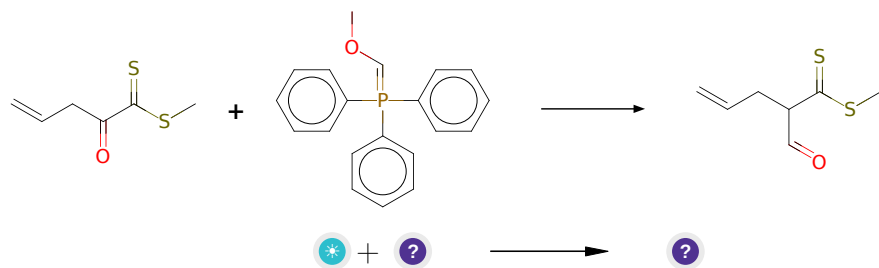
Typical conditions: THF. Low temp

Protections: none

Reference: [10.1021/jm800136b](#) and [10.1021/ol402802g](#)

Retrosynthesis ID: 10011836

2.4.2 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

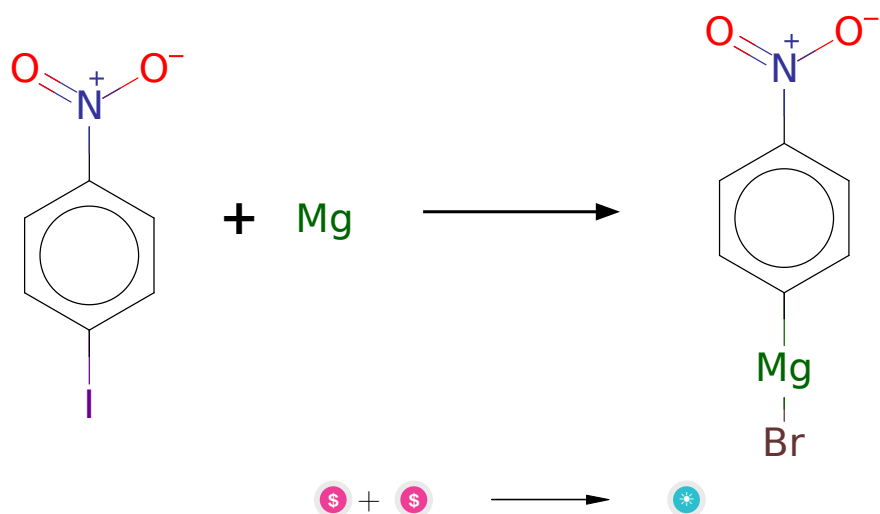
Typical conditions: KHMDS. THF hydrolysis: pTsOH. water. acetone

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

2.4.3 Synthesis of aryl Grignard reagents



Substrates:

1. Magnesium - [available at Sigma-Aldrich](#)
2. 1-Iodo-4-nitrobenzene - [available at Sigma-Aldrich](#)

Products:

1. C₆H₄BrMgNO₂

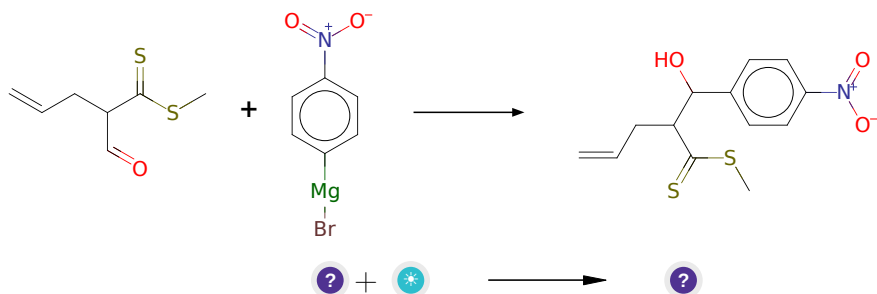
Typical conditions: iPrMgCl.LiCl.THF or other conditions Mg.THF or tBuLi.MgBr₂

Protections: none

Reference: DOI: [10.1016/S0040-4039\(99\)01404-5](#) and [10.1021/jo0000574](#) and WO2014123793 p.137 and [10.1021/jm400491x](#) and [10.3762/bjoc.12.36](#)

Retrosynthesis ID: 10011460

2.4.4 Grignard-Type Reaction



Substrates:

1. C=CCC(C=O)C(=S)SC
2. C6H4BrMgNO2

Products:

1. C=CCC(C(=S)SC)C(O)c1ccc([N+](=O)[O-])cc1

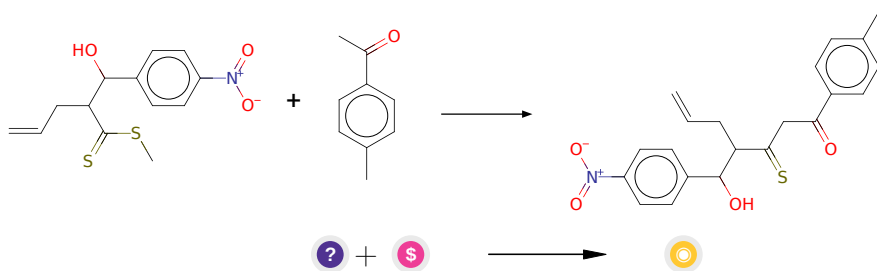
Typical conditions: Mg or Li.ether

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

2.4.5 Condensation of ketones with dithioesters



Substrates:

1. C=CCC(C(=S)SC)C(O)c1ccc([N+](=O)[O-])cc1
2. Methyl p-tolyl ketone - *available at Sigma-Aldrich*

Products:

1. C=CCC(C(=S)CC(=O)c1ccc(C)cc1)C(O)c1ccc([N+](=O)[O-])cc1

Typical conditions: NaH.DMF

Protections:

Functional group SMARTS	Classification	Protecting groups
<chem>[*6][CH]([*6])[OH]</chem>	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: 1000164.14

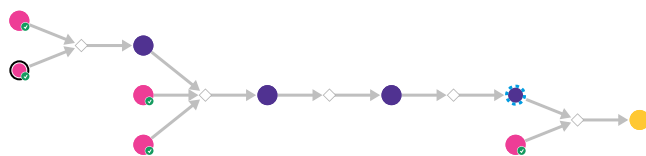
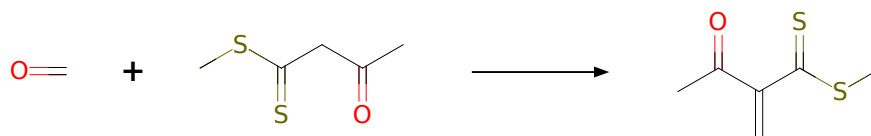
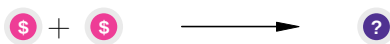


Figure 5: Outline of path 5

2.5.1 Eschenmoser methenylation





Substrates:

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

Products:

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

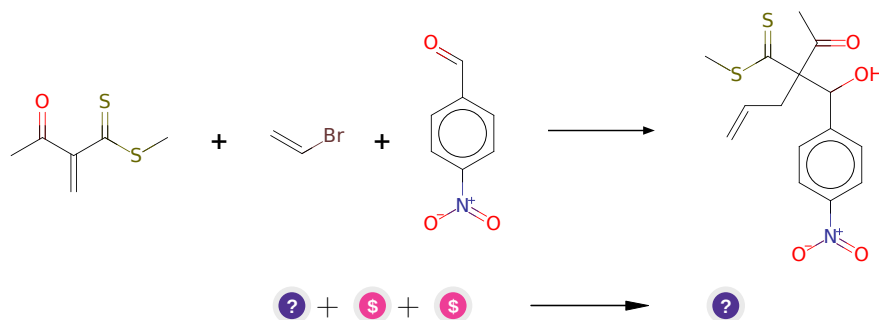
Typical conditions: iPr₂NH.TFA.HCHO.or.organocatalyst

Protections: none

Reference: DOI:[10.1016/S0040-4039\(00\)82176-0](https://doi.org/10.1016/S0040-4039(00)82176-0) AND DOI:[10.1021/jo052529q](https://doi.org/10.1021/jo052529q)
AND DOI:[10.1039/b924577d](https://doi.org/10.1039/b924577d)

Retrosynthesis ID: 7270

2.5.2 Alkenylation-Aldol reaction of enones and enoate esters



Substrates:

1. C=C(C(C)=O)C(=S)SC
2. Bromoethylene - *available at Sigma-Aldrich*
3. 4-Nitrobenzaldehyde - *available at Sigma-Aldrich*

Products:

1. C=CCC(C(C)=O)(C(=S)SC)C(O)c1ccc([N+](=O)[O-])cc1

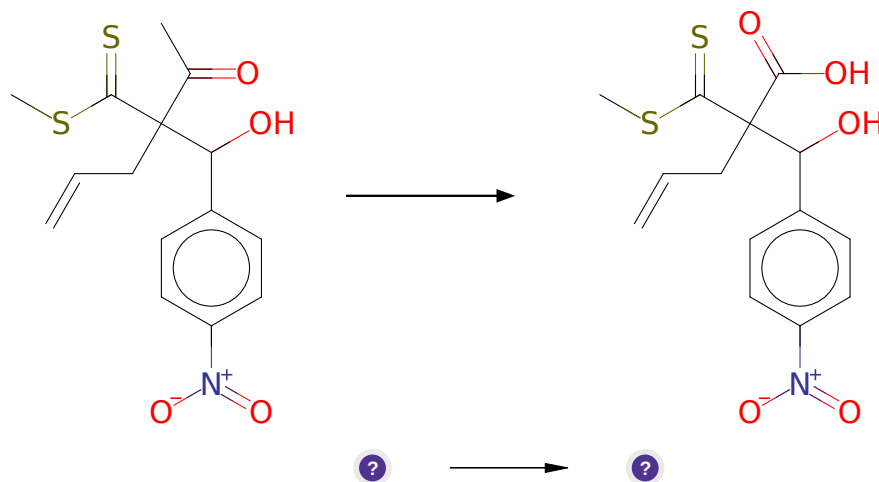
Typical conditions: 1.RCuLi.2.RCHO

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 Synthesis of Carboxylic Acids via Haloform Reaction



Substrates:

1. C=CCC(C(C)=O)(C(=S)SC)C(O)c1ccc([N+](=O)[O-])cc1

Products:

1. C=CCC(C(=O)O)(C(=S)SC)C(O)c1ccc([N+](=O)[O-])cc1

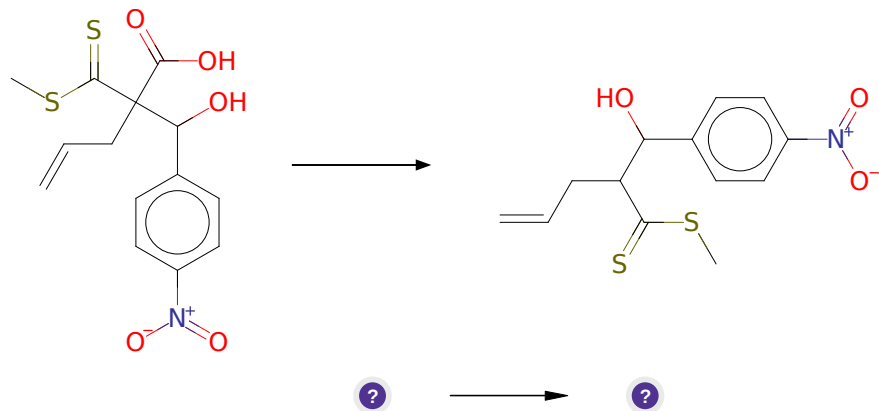
Typical conditions: I2.KI.KOH.H2O.dioxane

Protections: none

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

Retrosynthesis ID: 10366

2.5.4 Decarboxylation of tertiary carboxylic acids



Substrates:

1. C=CCC(C(=O)O)(C(=S)SC)C(O)c1ccc([N+](=O)[O-])cc1

Products:

1. C=CCC(C(=S)SC)C(O)c1ccc([N+](=O)[O-])cc1

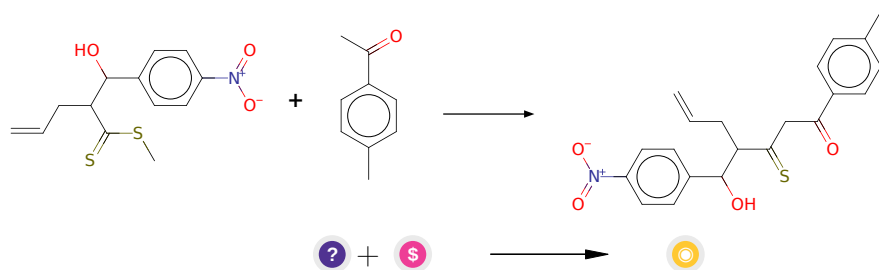
Typical conditions: DMSO, 135°C

Protections: none

Reference: DOI: [10.1021/jm990630f](https://doi.org/10.1021/jm990630f) AND [10.1016/S0040-4039\(99\)02191-7](https://doi.org/10.1016/S0040-4039(99)02191-7)

Retrosynthesis ID: 7791

2.5.5 Condensation of ketones with dithioesters



Substrates:

1. C=CCC(C(=S)SC)C(O)c1ccc([N+](=O)[O-])cc1
2. Methyl p-tolyl ketone - [available at Sigma-Aldrich](#)

Products:

1. C=CCC(C(=S)CC(=O)c1ccc(C)cc1)C(O)c1ccc([N+](=O)[O-])cc1

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