

Paths of analysis*

Y4A

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: $\text{TUNNEL_COEF} * \text{FGI_COEF} * \text{STEP} * 20 + 1000000 * (\text{CONFLICT} + \text{NON_SELECTIVITY} + \text{FILTERS} + \text{PROTECT})$

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: 2000051.25

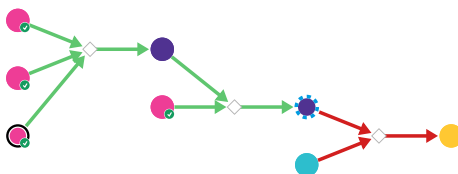
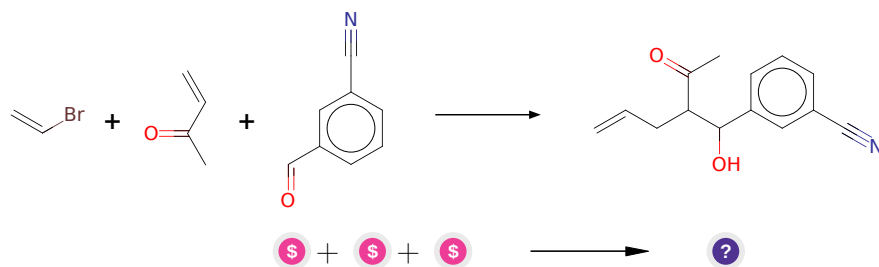


Figure 1: Outline of path 1

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

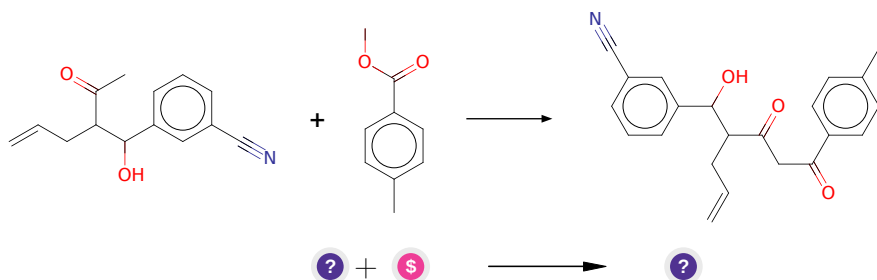
Typical conditions: 1.RCuLi.2.RCHO

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

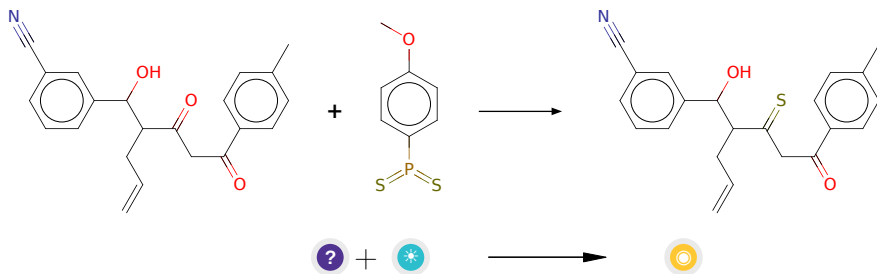
Typical conditions: NaOMe.MeOH

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 Synthesis of Thioketones using Lawesson's Reagent



Substrates:

1. C=CCC(C(=O)CC(=O)c1ccc(C)cc1)C(O)c1cccc(C#N)c1
2. 4-methoxyphenyl-dithiophosphonsaeureanhydrid

Products:

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

Typical conditions: Lawesson's Reagent.neat.microwave

Protections:

Functional group SMARTS	Classification	Protecting groups
[#6]C([#6])=O	carbonyls	1.3-Dioxanes
		1.3-Dioxolanes
		1.3-Dithianes
		1.3-Dithiolanes
		Dimethyl Acetals and Ketals
		N,N-Dimethylhydrazones

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

Retrosynthesis ID: 11476

2.2 Path 2

Score: 2000076.25

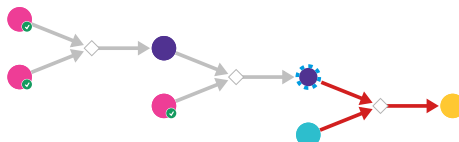
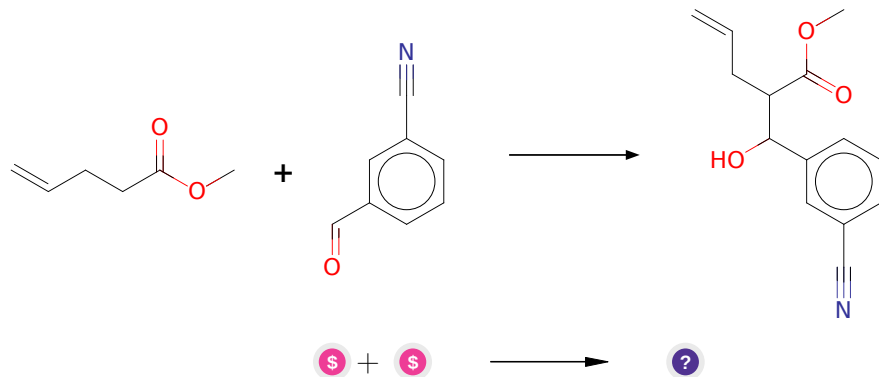


Figure 2: Outline of path 2

2.2.1 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

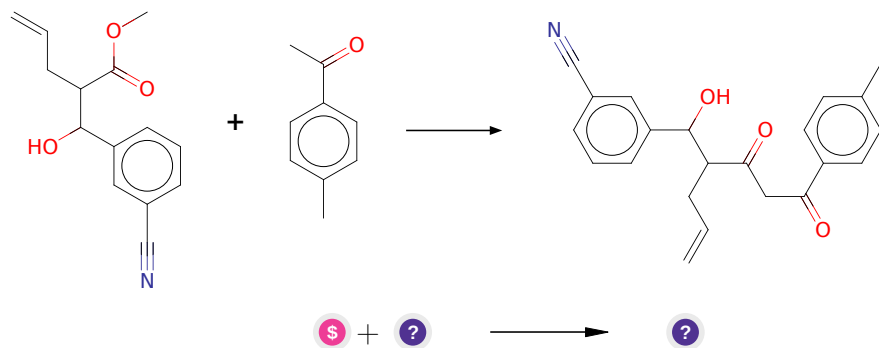
Typical conditions: LDA.THF

Protections: none

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

Retrosynthesis ID: 4788

2.2.2 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

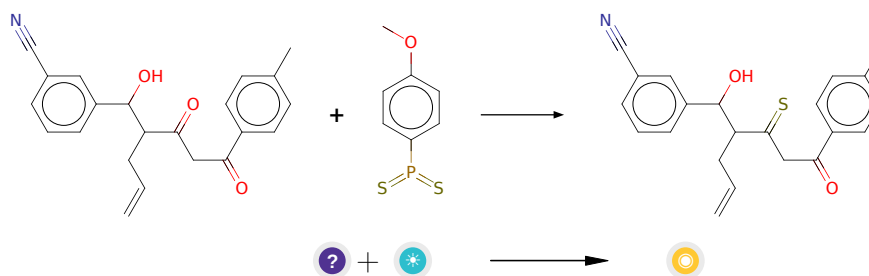
Typical conditions: NaOMe.MeOH

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 Synthesis of Thioketones using Lawesson's Reagent



Substrates:

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

2. 4-methoxyphenyl-dithiophosphonane

Products:

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

Typical conditions: Lawesson's Reagent.neat.microwave

Protections:

Functional group SMARTS	Classification	Protecting groups
<chem>[*]C([*])=O</chem>	carbonyls	1.3-Dioxanes 1.3-Dioxolanes 1.3-Dithianes 1.3-Dithiolanes Dimethyl Acetals and Ketals N,N-Dimethylhydrazones

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

Retrosynthesis ID: 11476

2.3 Path 3

Score: 2000090.31

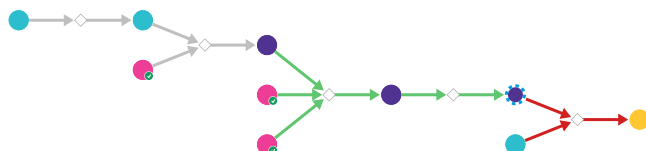
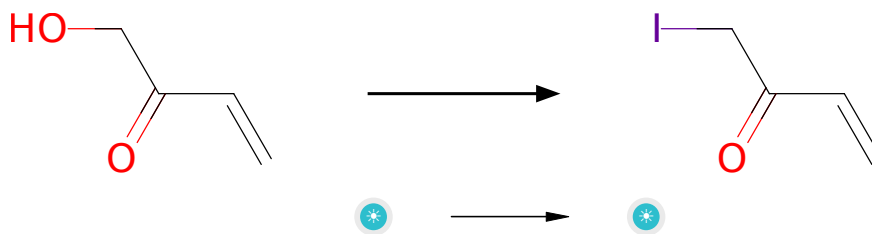


Figure 3: Outline of path 3

2.3.1 Synthesis Of Alkyl Iodides Via Appel Reaction



Substrates:

- 1-hydroxy-but-3-en-2-one

Products:

- 1-iodo-but-3-en-2-one

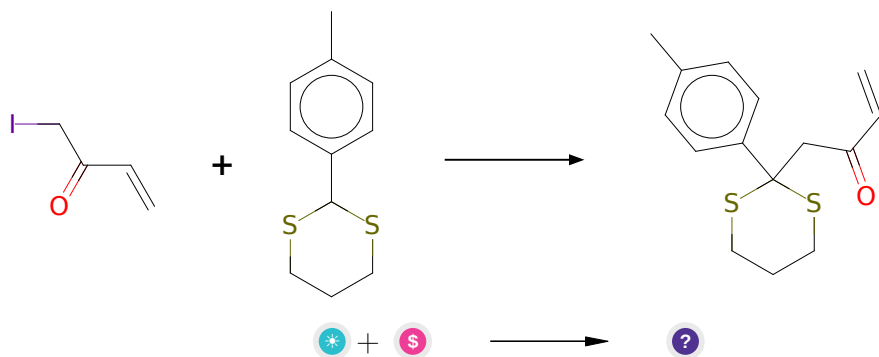
Typical conditions: Imidazole.PPh₃.I₂

Protections: none

Reference: [10.1002/1099-0690\(200102\)2001:3<493::AID-EJOC493>3.0.CO2-B](#) (compound 20) and [10.1016/j.tet.2014.09.030](#)

Retrosynthesis ID: 9990040

2.3.2 Alkylation of dithianes



Substrates:

- 1-iodo-but-3-en-2-one
- 2-p-tolyl-[1,3]dithiane - *available at Sigma-Aldrich*

Products:

- C=CC(=O)CC1(c2ccc(C)cc2)SCCS1

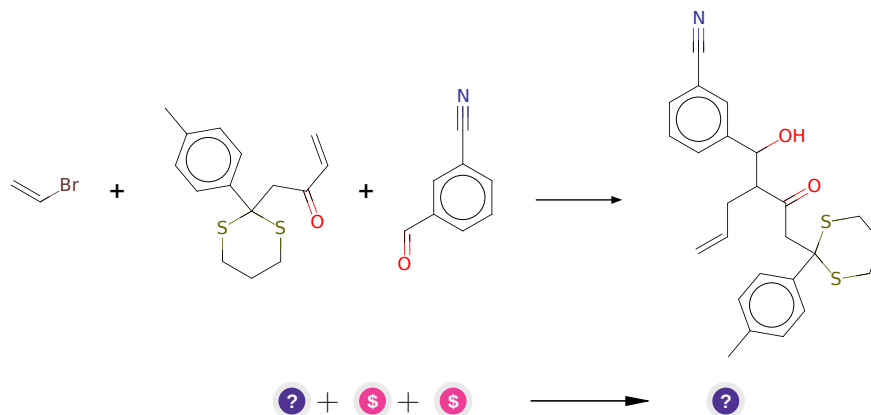
Typical conditions: LDA.THF

Protections: none

Reference: [10.1021/ja055740s](#) (SI) and [10.1016/S0008-6215\(99\)00275-X](#) and [10.1021/ja0618954](#)

Retrosynthesis ID: 34220

2.3.3 Alkenylation-Aldol reaction of enones and enoate esters



Substrates:

1. C=CC(=O)CC1(c2ccc(C)cc2)SCCCS1
2. 3-Cyanobenzaldehyde - *available at Sigma-Aldrich*
3. Bromoethylene - *available at Sigma-Aldrich*

Products:

1. C=CCC(C(=O)CC1(c2ccc(C)cc2)SCCCS1)C(O)c1cccc(C#N)c1

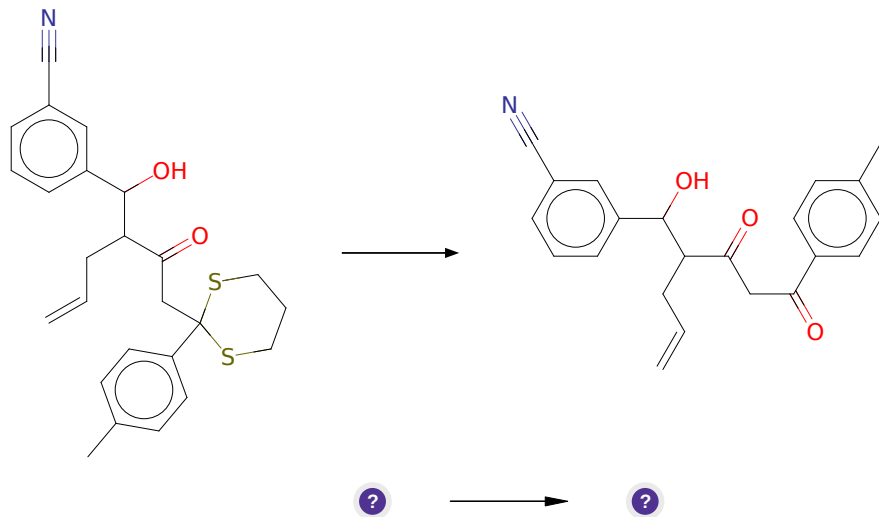
Typical conditions: 1. RCuLi . 2. RCHO

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

2.3.4 Synthesis of ketones from dithianes



Substrates:

1. C=CCC(C(=O)CC1(c2ccc(C)cc2)SCCS1)C(O)c1ccc(C#N)c1

Products:

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

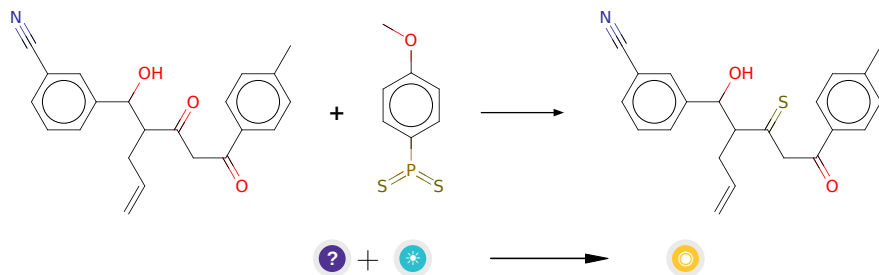
Typical conditions: MeI.CaCO₃

Protections: none

Reference: [10.1016/j.tet.2013.09.075](https://doi.org/10.1016/j.tet.2013.09.075) and [10.1021/jo00007a015](https://doi.org/10.1021/jo00007a015) and [10.1021/jo0610412](https://doi.org/10.1021/jo0610412) and [10.1021/ol901024t](https://doi.org/10.1021/ol901024t) and [10.1021/ol500553x](https://doi.org/10.1021/ol500553x) and [10.1021/jo0626459](https://doi.org/10.1021/jo0626459)

Retrosynthesis ID: 31724

2.3.5 Synthesis of Thioketones using Lawesson's Reagent



Substrates:

1. C=CCC(C(=O)CC(=O)c1ccc(C)cc1)C(O)c1cccc(C#N)c1
2. 4-methoxyphenyl-dithiophosphonsaeureanhydrid

Products:

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

Typical conditions: Lawesson's Reagent.neat.microwave

Protections:

Functional group SMARTS	Classification	Protecting groups
<chem>[*]C([*])=O</chem>	carbonyls	1.3-Dioxanes 1.3-Dioxolanes 1.3-Dithianes 1.3-Dithiolanes Dimethyl Acetals and Ketals N,N-Dimethylhydrazones

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

Retrosynthesis ID: 11476

2.4 Path 4

Score: 2000115.31

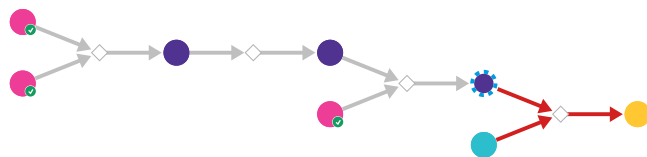
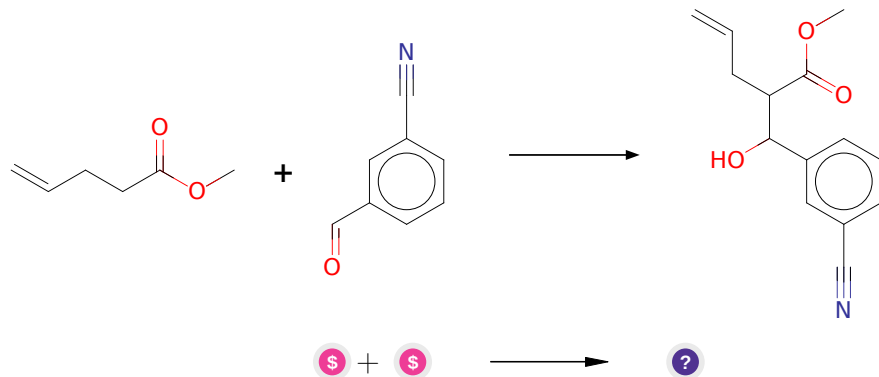


Figure 4: Outline of path 4

2.4.1 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

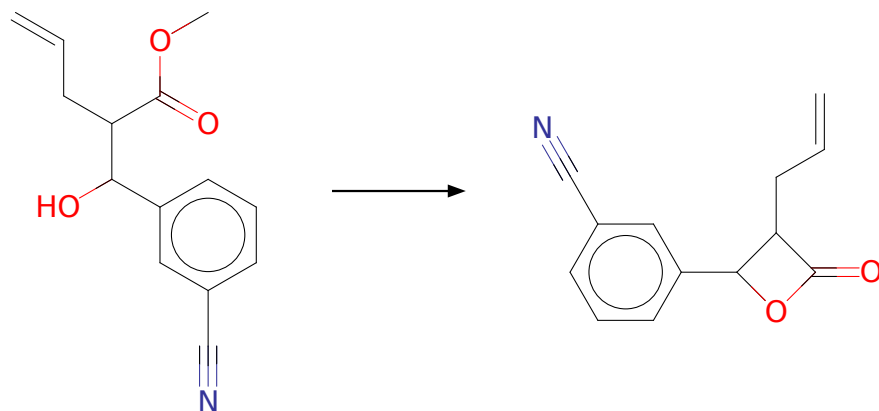
Typical conditions: LDA.THF

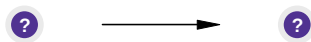
Protections: none

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

Retrosynthesis ID: 4788

2.4.2 Acid catalyzed transesterification





Substrates:

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

Products:

1. C=CCC1C(=O)OC1c1cccc(C#N)c1

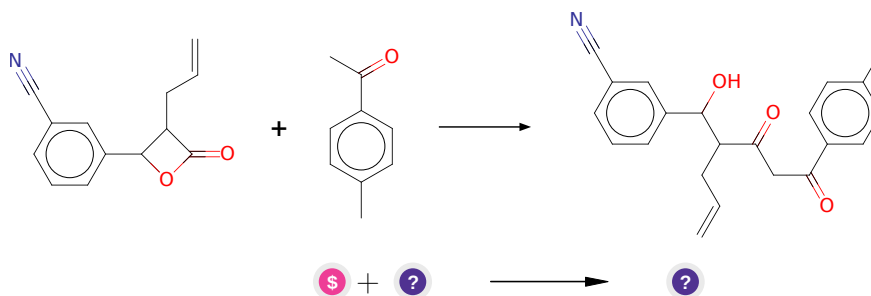
Typical conditions: H+

Protections: none

Reference: [10.1021/cr00020a004](#)

Retrosynthesis ID: 50438

2.4.3 Ring opening of lactones with enolates



Substrates:

1. Methyl p-tolyl ketone - [available at Sigma-Aldrich](#)
2. C=CCC1C(=O)OC1c1cccc(C#N)c1

Products:

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

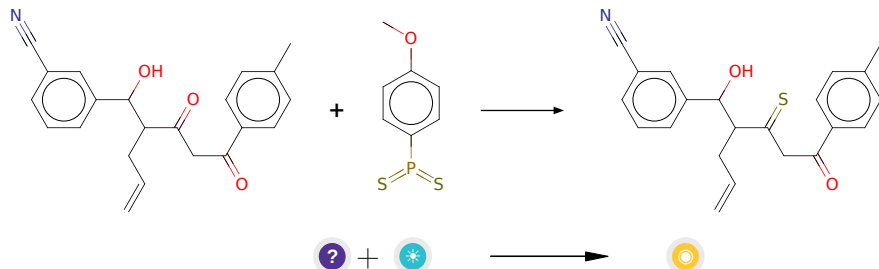
Typical conditions: LiHMDS.THF

Protections: none

Reference: [10.1021/ol801493w](#) and [10.1021/ol403423r](#) and [10.1021/ja061938g](#) and [10.1021/ja036521e](#)

Retrosynthesis ID: 24105

2.4.4 Synthesis of Thioketones using Lawesson's Reagent



Substrates:

1. C=CCC(C(=O)CC(=O)c1ccc(C)cc1)C(O)c1cccc(C#N)c1
2. 4-methoxyphenyl-dithiophosphonane

Products:

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

Typical conditions: Lawesson's Reagent.neat.microwave

Protections:

Functional group SMARTS	Classification	Protecting groups
[#6]C([#6])=O	carbonyls	1.3-Dioxanes
		1.3-Dioxolanes
		1.3-Dithianes
		1.3-Dithiolanes
		Dimethyl Acetals and Ketals
		N,N-Dimethylhydrazones

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

Retrosynthesis ID: 11476

2.5 Path 5

Score: 2000115.31

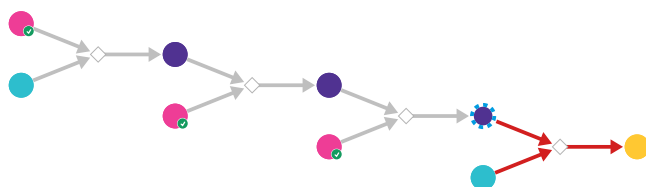
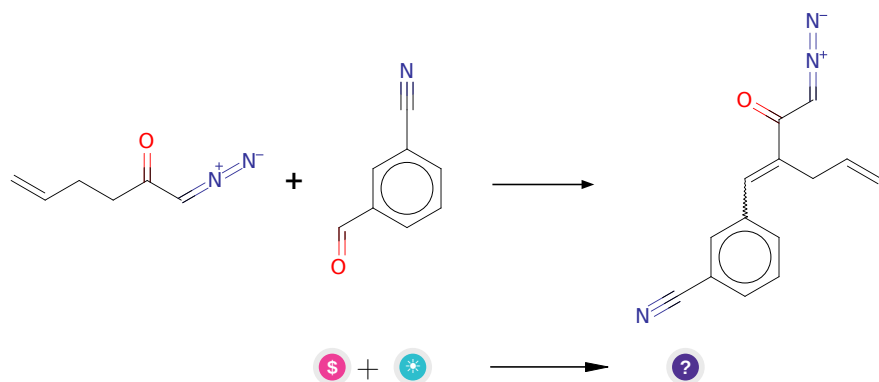


Figure 5: Outline of path 5

2.5.1 Aldol Condensation



Substrates:

1. 3-Cyanobenzaldehyde - *available at Sigma-Aldrich*
2. 1-diazo-hex-5-en-2-one

Products:

1. C=CCC(=Cc1cccc(C#N)c1)C(=O)C=[N+]=[N-]

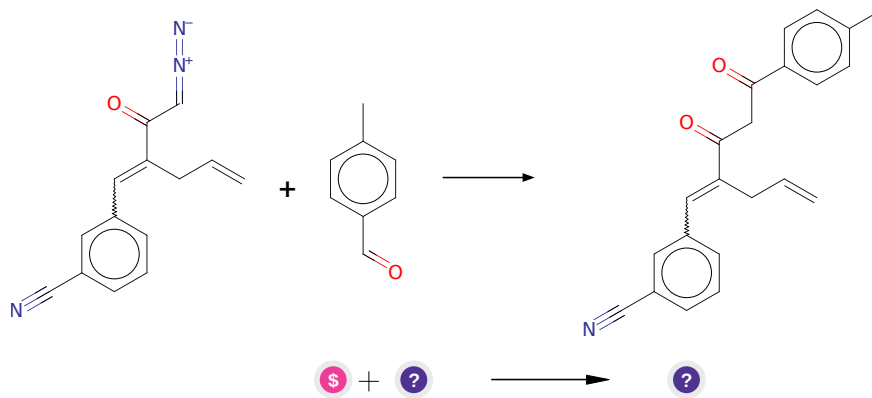
Typical conditions: NaOEt.base

Protections: none

Reference: *10.1080/00397911.2016.1206938*

Retrosynthesis ID: 10049

2.5.2 Homologation of aldehydes to ketones with diazoalkanes



Substrates:

1. p-Tolualdehyde - *available at Sigma-Aldrich*
2. C=CCC(=Cc1cccc(C#N)c1)C(=O)C=[N+]=[N-]

Products:

1. C=CCC(=Cc1cccc(C#N)c1)C(=O)CC(=O)c1ccc(C)cc1

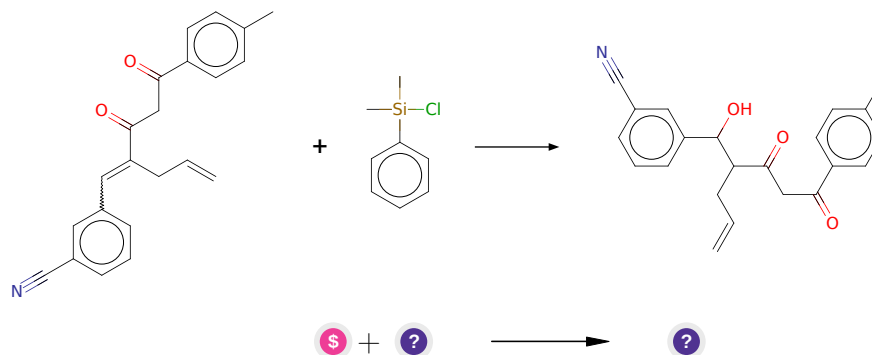
Typical conditions: Lewis.acid

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

2.5.3 Addition of silanes to Michael acceptors followed by oxidation



Substrates:

1. DMPSCl - *available at Sigma-Aldrich*
2. C=CCC(=Cc1cccc(C#N)c1)C(=O)CC(=O)c1ccc(C)cc1

Products:

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

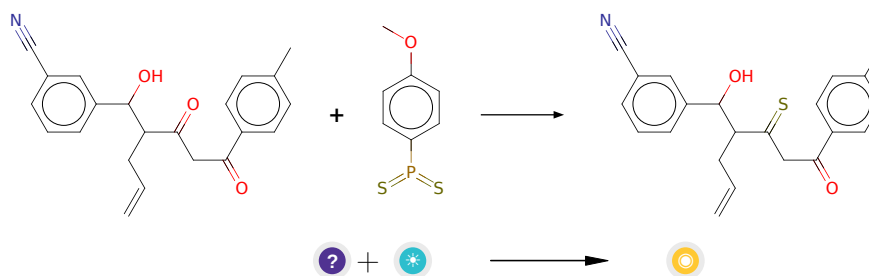
Typical conditions: 1.nBuLi.2.CuCN.3.electrophile.4.H2O2

Protections: none

Reference: [10.1021/ja058370g](#) AND (Oxidation) [10.1021/jo9905672](#) or [10.1021/ol300832f](#)

Retrosynthesis ID: 20301

2.5.4 Synthesis of Thioketones using Lawesson's Reagent



Substrates:

1. C=CCC(C(=O)CC(=O)c1ccc(C)cc1)C(O)c1cccc(C#N)c1
2. 4-methoxyphenyl-dithiophosphonane

Products:

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

Typical conditions: Lawesson's Reagent.neat.microwave

Protections:

Functional group SMARTS	Classification	Protecting groups
<chem>[*]C([*])=O</chem>	carbonyls	1.3-Dioxanes 1.3-Dioxolanes 1.3-Dithianes 1.3-Dithiolanes Dimethyl Acetals and Ketals N,N-Dimethylhydrazones

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

Retrosynthesis ID: 11476