Paths of analysis*

Y4A

Synthia

October 10, 2022

1 Analysis parameters

Analysis type: Automatic Retrosynthesis

Rules: none selected

Filters: Exclude Diastereoselecitve 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: TUNNEL_COEF*FGI_COEF*STEP*20+1000000*(CONFLICT+NON_SELECTIVITY+FILTERS+PROTECT)

Chemical scoring formula: SMALLER^ 3,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`

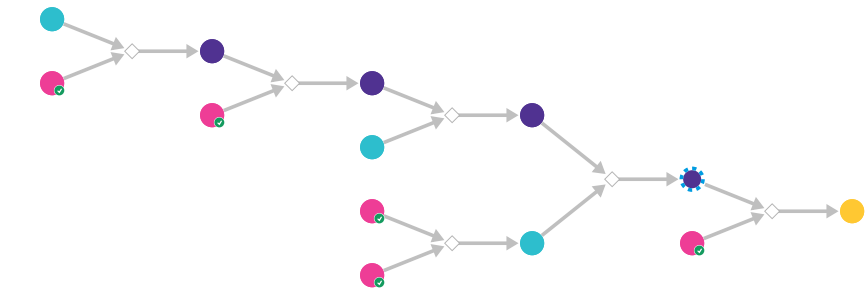
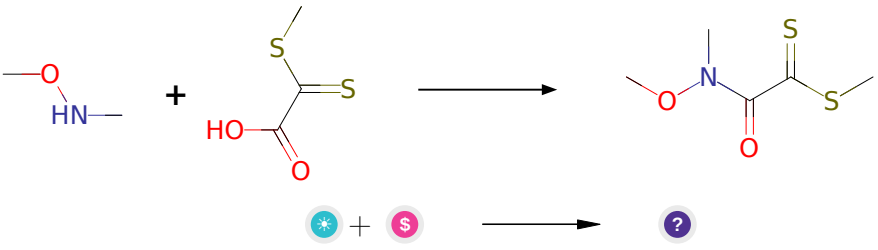


Figure 1: Outline of path 1

2.1.1 Synthesis of O-substituted N-substituted hydroxamic acids



Substrates:

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

Products:

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

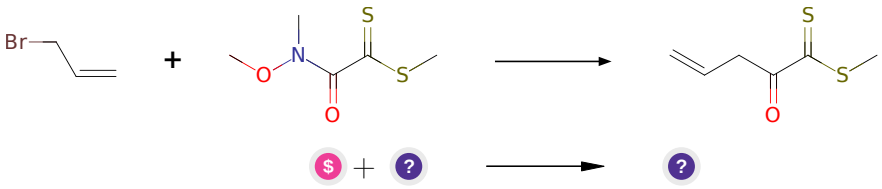
Typical conditions: DCC.DMAP or CDI.TEA.DCM

Protections: none

Reference: Patent: WO2007/67333A2, 2007 & *10.1016/j.bmcl.2008.09.100*

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

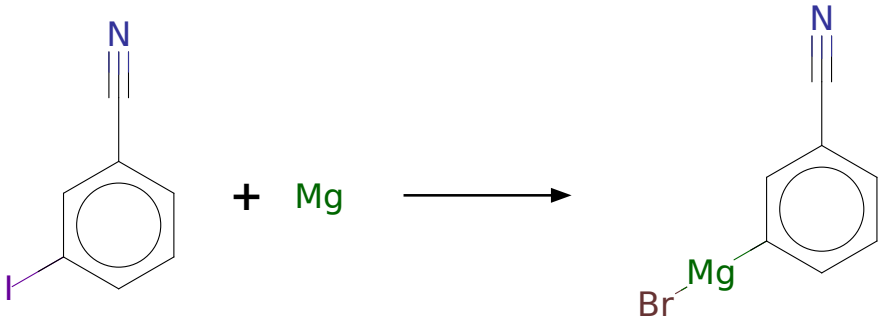
Typical conditions: 1.RmgBr.THF 2.TFA.DCM

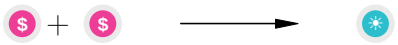
Protections: none

Reference: *10.1021/jm051185t* and *10.1021/ol101021v* (supporting info)

Retrosynthesis ID: 6837

2.1.3 Synthesis of aryl Grignard reagents





Substrates:

1. 3-Iodobenzonitrile - *available at Sigma-Aldrich*
2. Magnesium - *available at Sigma-Aldrich*

Products:

1. C7H4BrMgN

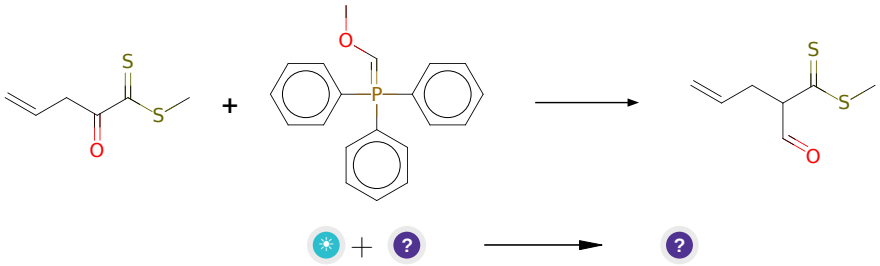
Typical conditions: iPrMgCl.LiCl.THF or other conditions Mg.THF or tBuLi.MgBr2

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

2.1.4 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

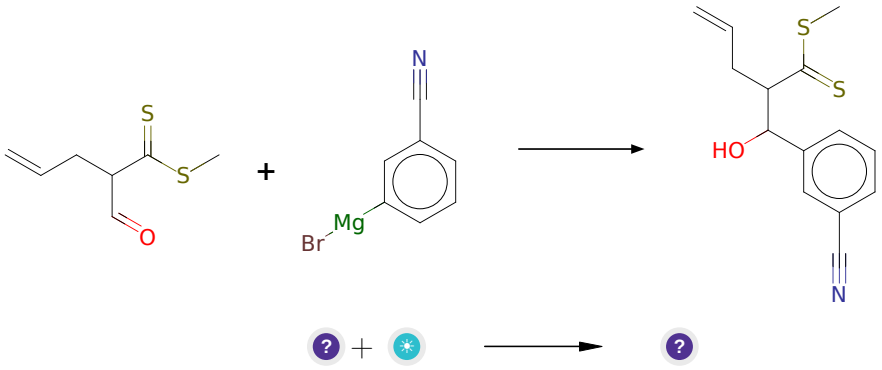
Typical conditions: KHMDS.THF hydrolysis: pTsOH.water.acetone

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. C7H4BrMgN

Products:

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

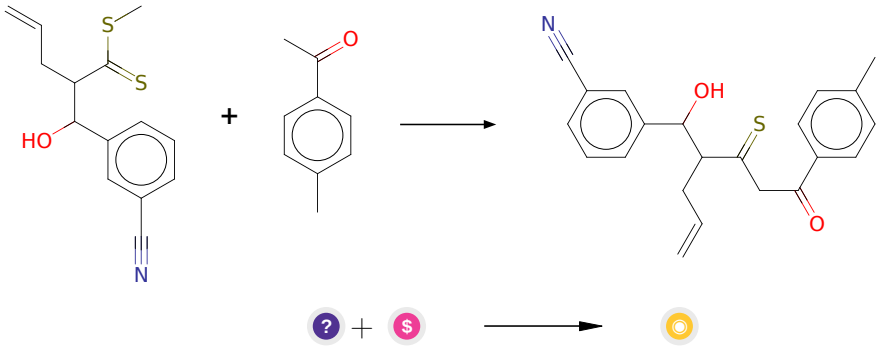
Typical conditions: Mg or Li.ether

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)c1cccc(C#N)c1

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

Products:

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

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 (TBDMS) Methyl Ether

Reference: *10.1021/jo400599e* and *10.1002/ejoc.201301667*

Retrosynthesis ID: 9996413

2.2 Path 2

Score: `1000151.35`

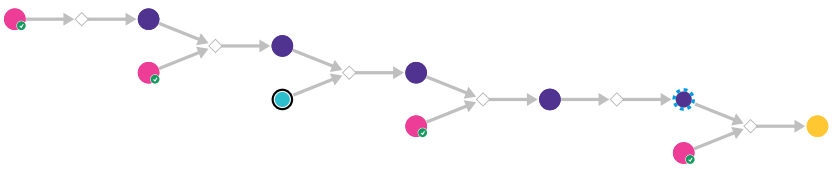
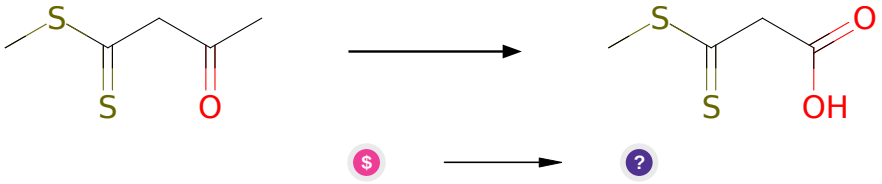


Figure 2: Outline of path 2

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

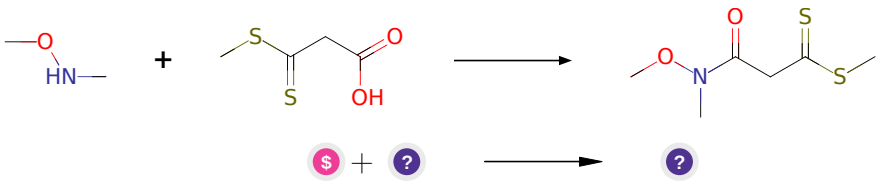
Typical conditions: I2.KI.KOH.H2O.dioxane

Protections: none

Reference: *10.1021/jacs.8b12242* SI p. S25 and *10.1021/ol5025025* SI p. S27

Retrosynthesis ID: 10366

2.2.2 Synthesis of O-substituted N-substituted hydroxamic acids



Substrates:

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

Products:

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

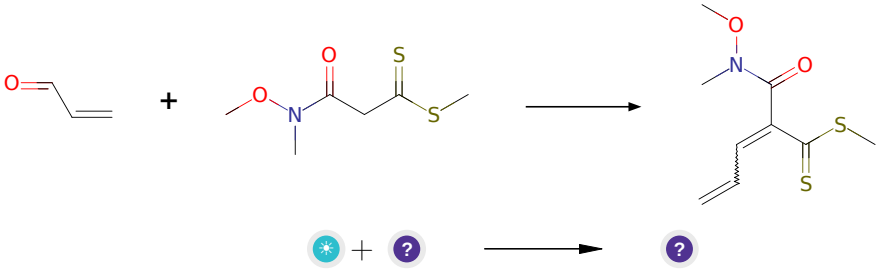
Typical conditions: DCC.DMAP or CDI.TEA.DCM

Protections: none

Reference: Patent: WO2007/67333A2, 2007 & *10.1016/j.bmcl.2008.09.100*

Retrosynthesis ID: 1152

2.2.3 Condensation of amides with aldehydes



Substrates:

1. Acrolein
2. CON(C)C(=O)CC(=S)SC

Products:

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

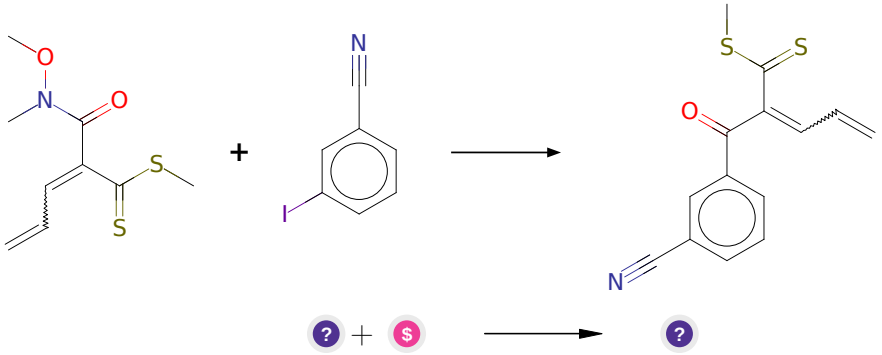
Typical conditions: piperidine.EtOH

Protections: none

Reference: *10.1021/ja075335w* (Si) AND *10.1016/j.bmcl.2012.10.016* AND *10.1016/j.tetlet.2013.12.097* AND *10.1021/ol303097j*

Retrosynthesis ID: 14975

2.2.4 Synthesis of ketones from Weinreb amides



Substrates:

1. C=CC=C(C(=O)N(C)OC)C(=S)SC
2. 3-Iodobenzonitrile - *available at Sigma-Aldrich*

Products:

1. C=CC=C(C(=O)c1cccc(C#N)c1)C(=S)SC

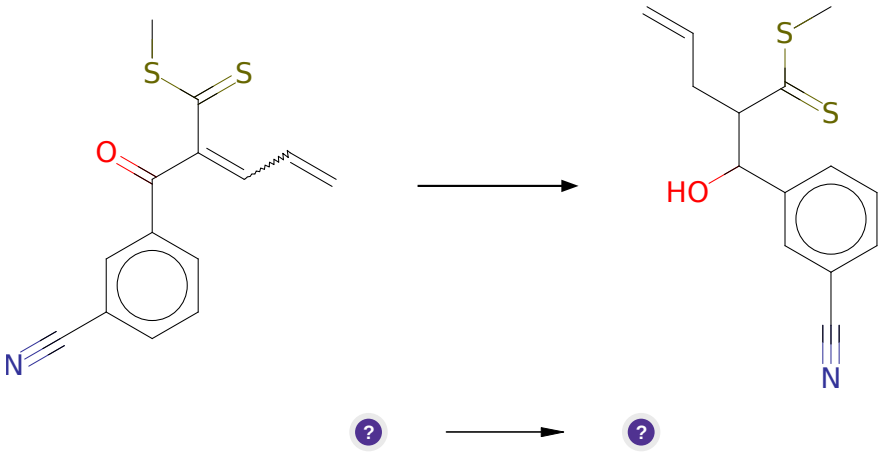
Typical conditions: 1.RmgBr.THF 2.TFA.DCM

Protections: none

Reference: *10.1021/jm051185t* and *10.1021/ol101021v* (supporting info)

Retrosynthesis ID: 5060

2.2.5 Reduction of enones to saturated alcohols



Substrates:

1. C=CC=C(C(=O)c1cccc(C#N)c1)C(=S)SC

Products:

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

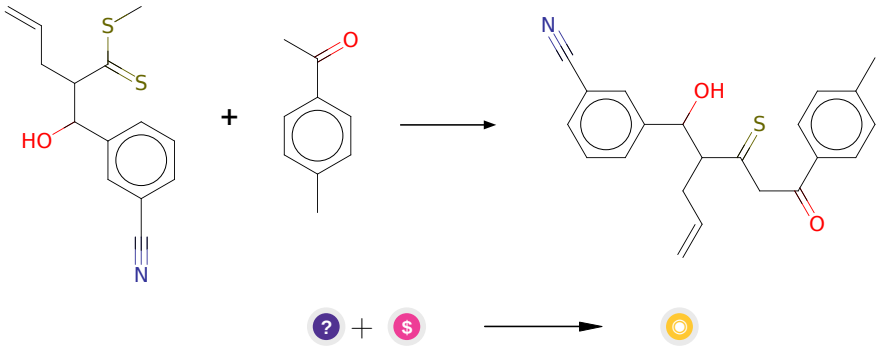
Typical conditions: NaBH4.transition.metal.salt.(eg.Pd(OAc)2.or.CeCl3)

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

2.2.6 Condensation of ketones with dithioesters



Substrates:

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

Products:

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

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: 1000161.11

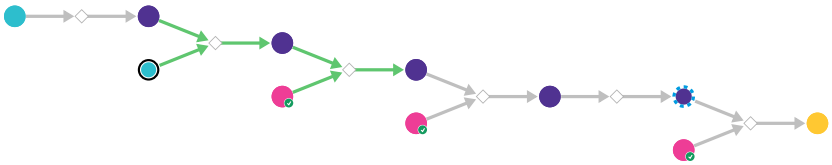
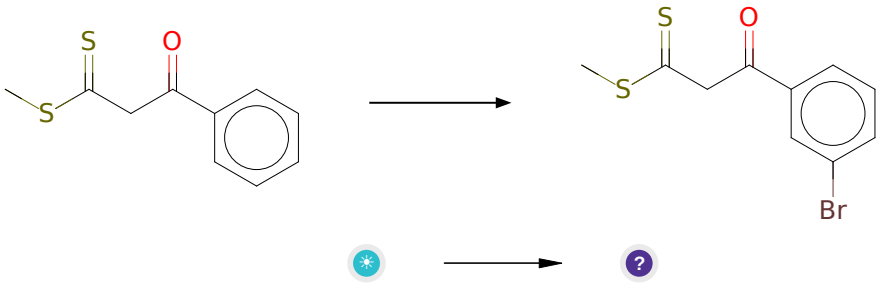


Figure 3: Outline of path 3

2.3.1 Bromination of aromatic compounds



Substrates:

1. methyl b-benzoyldithioacetate

Products:

1. CSC(=S)CC(=O)c1cccc(Br)c1

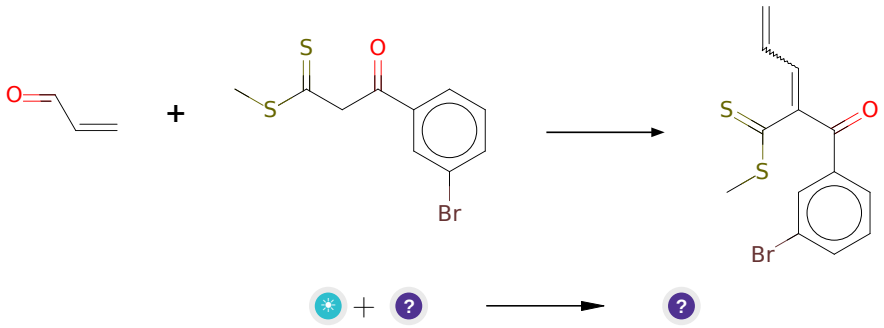
Typical conditions: Br2.Fe

Protections: none

Reference: *10.1021/acs.accounts.6b00120*

Retrosynthesis ID: 7777000

2.3.2 Aldol Condensation



Substrates:

1. Acrolein
2. CSC(=S)CC(=O)c1cccc(Br)c1

Products:

1. C=CC=C(C(=O)c1cccc(Br)c1)C(=S)SC

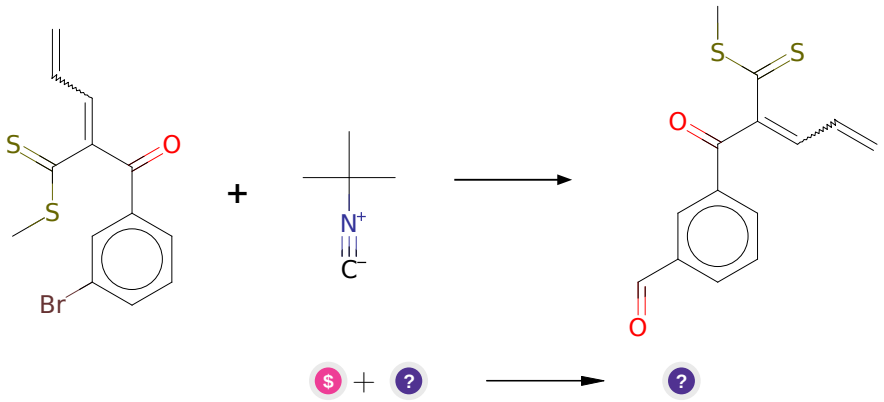
Typical conditions: NaOEt.base

Protections: none

Reference: *10.1080/00397911.2016.1206938*

Retrosynthesis ID: 10049

2.3.3 Pd-catalyzed formylation of aryl halides



Substrates:

1. tert-Butyl isocyanide - *available at Sigma-Aldrich*

2. C=CC=C(C(=O)c1cccc(Br)c1)C(=S)SC

Products:

1. C=CC=C(C(=O)c1cccc(C=O)c1)C(=S)SC

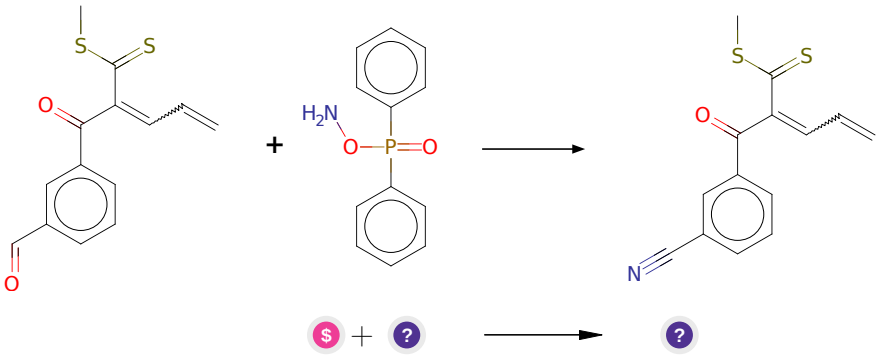
Typical conditions: Pd(OAc)2.JohnPhos.Na2CO3.H2O.Et3SiH.DMF.65C

Protections: none

Reference: DOI: *10.1021/ol5014262*

Retrosynthesis ID: 3103

2.3.4 Synthesis nitriles from aldehydes using DPPH



Substrates:

1. O-(Diphenylphosphinyl)hydroxylamine - *available at Sigma-Aldrich*
2. C=CC=C(C(=O)c1cccc(C=O)c1)C(=S)SC

Products:

1. C=CC=C(C(=O)c1cccc(C#N)c1)C(=S)SC

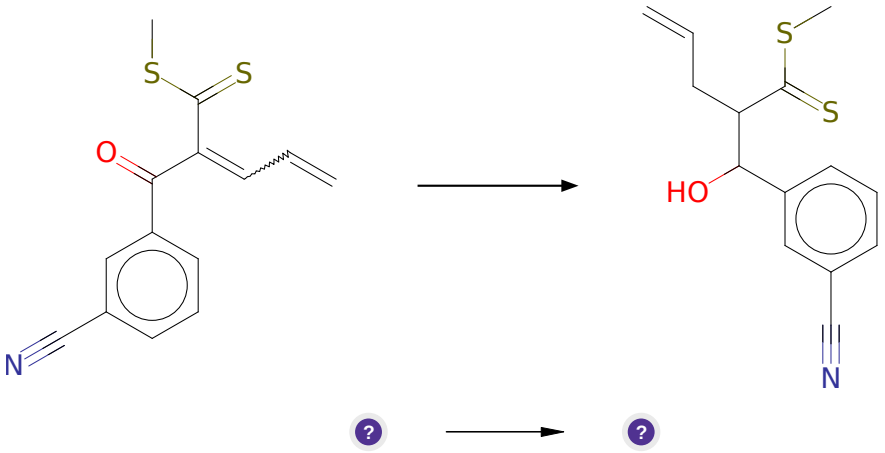
Typical conditions: DPPH.toluene.80C

Protections: none

Reference: DOI: *10.1021/jo301133y*

Retrosynthesis ID: 1175

2.3.5 Reduction of enones to saturated alcohols



Substrates:

1. C=CC=C(C(=O)c1cccc(C#N)c1)C(=S)SC

Products:

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

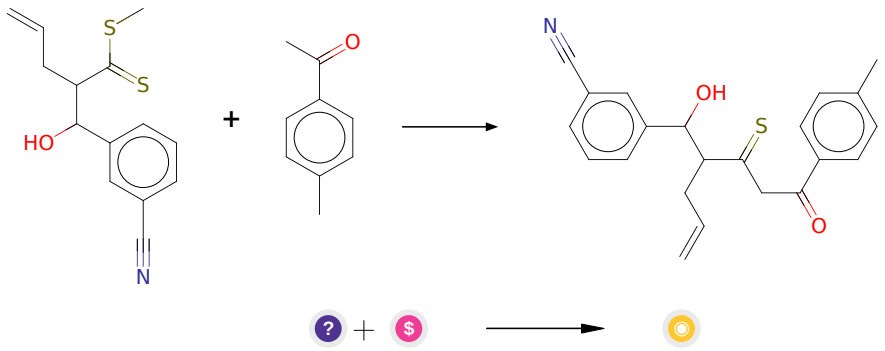
Typical conditions: NaBH4.transition.metal.salt.(eg.Pd(OAc)2.or.CeCl3)

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

2.3.6 Condensation of ketones with dithioesters



Substrates:

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

Products:

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

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 (TBDMS) Methyl Ether

Reference: *10.1021/jo400599e* and *10.1002/ejoc.201301667*

Retrosynthesis ID: 9996413

2.4 Path 4

Score: `1000161.11`

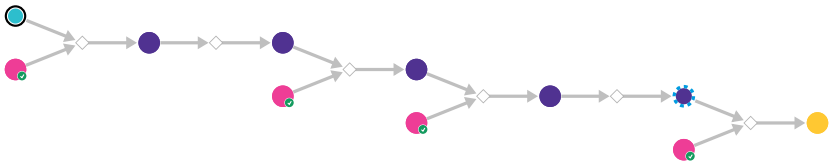
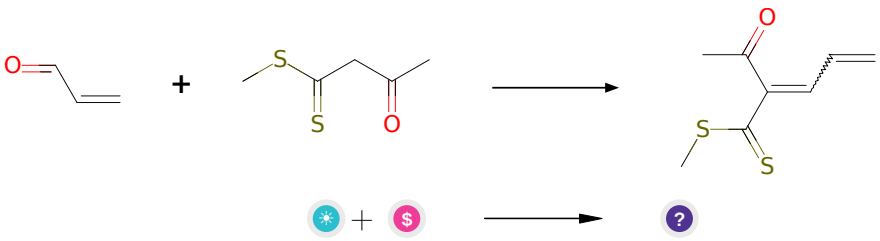


Figure 4: Outline of path 4

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

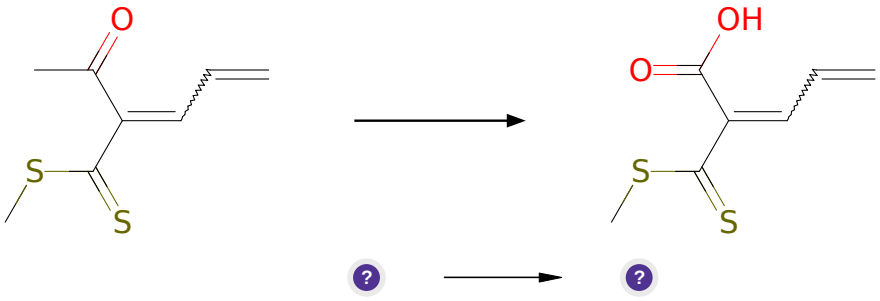
Typical conditions: NaOEt.base

Protections: none

Reference: *10.1080/00397911.2016.1206938*

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

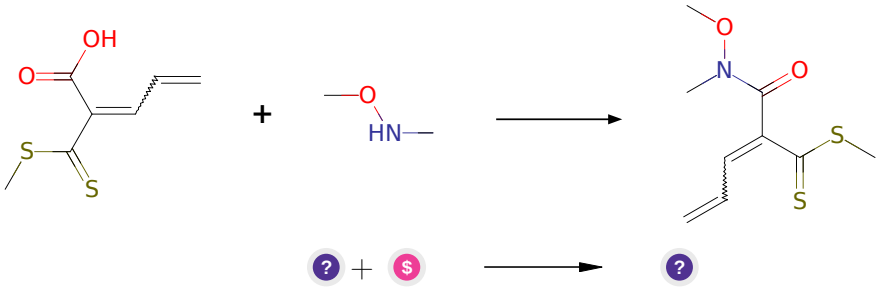
Typical conditions: NaClO.EtOH.0-20 C or Br2.NaOH.H2O.dioxane.0 C

Protections: none

Reference: *10.1016/j.ejmech.2015.06.037* p. 246, 247 and *10.1007/s00280-017-3265-1* p. 726, 728

Retrosynthesis ID: 10367

2.4.3 Synthesis of O-substituted N-substituted hydroxamic acids



Substrates:

1. C=CC=C(C(=O)O)C(=S)SC
2. n-methoxymethylamine - *available at Sigma-Aldrich*

Products:

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

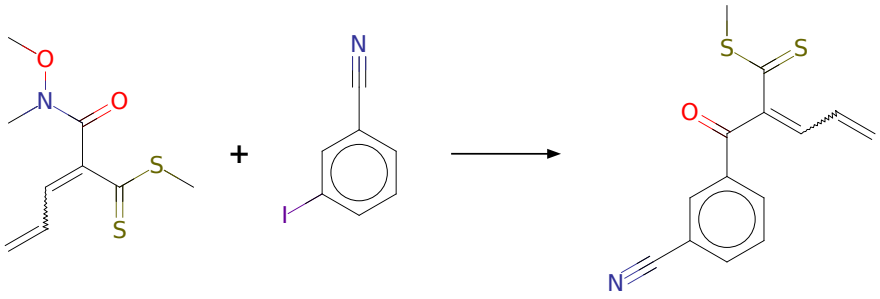
Typical conditions: DCC.DMAP or CDI.TEA.DCM

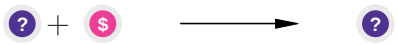
Protections: none

Reference: Patent: WO2007/67333A2, 2007 & *10.1016/j.bmcl.2008.09.100*

Retrosynthesis ID: 1152

2.4.4 Synthesis of ketones from Weinreb amides





Substrates:

1. C=CC=C(C(=O)N(C)OC)C(=S)SC
2. 3-Iodobenzonitrile - *available at Sigma-Aldrich*

Products:

1. C=CC=C(C(=O)c1cccc(C#N)c1)C(=S)SC

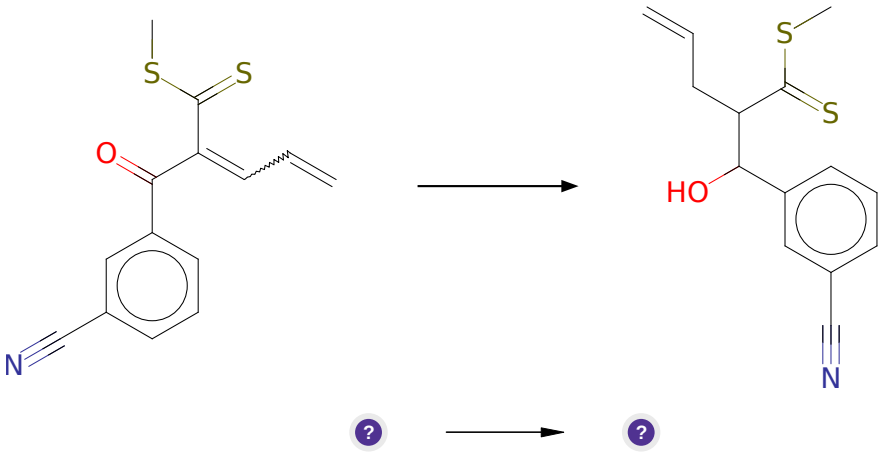
Typical conditions: 1.RmgBr.THF 2.TFA.DCM

Protections: none

Reference: *10.1021/jm051185t* and *10.1021/ol101021v* (supporting info)

Retrosynthesis ID: 5060

2.4.5 Reduction of enones to saturated alcohols



Substrates:

1. C=CC=C(C(=O)c1cccc(C#N)c1)C(=S)SC

Products:

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

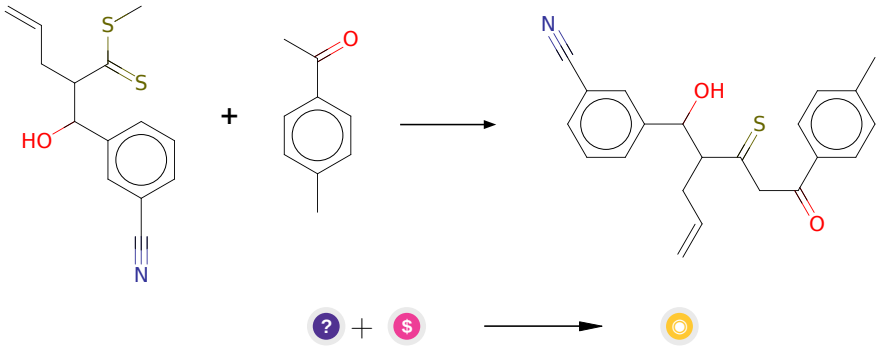
Typical conditions: NaBH4.transition.metal.salt.(eg.Pd(OAc)2.or.CeCl3)

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

2.4.6 Condensation of ketones with dithioesters



Substrates:

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

Products:

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

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: 1000164.14

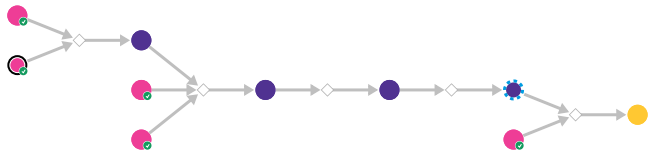
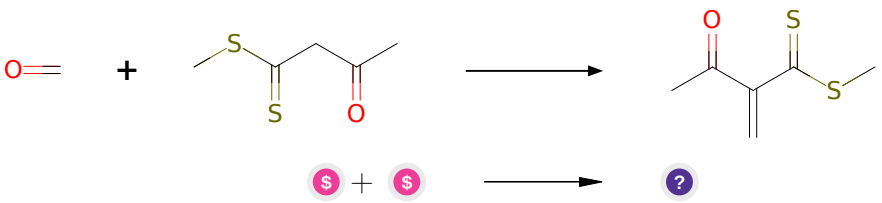


Figure 5: Outline of path 5

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

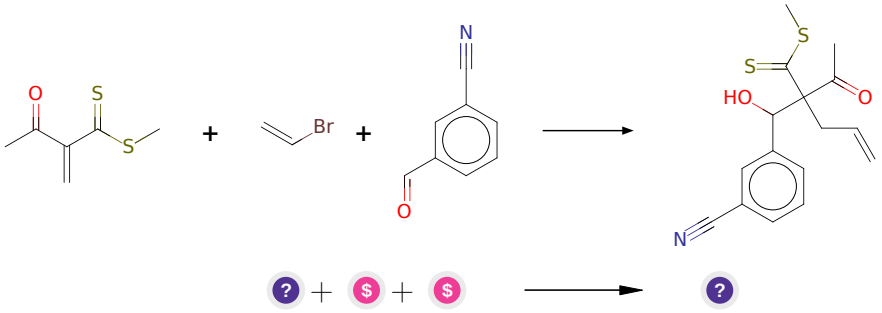
Typical conditions: iPr2NH.TFA.HCHO.or.organocatalyst

Protections: none

Reference: DOI:*10.1016/S0040-4039(00)82176-0* AND DOI:*10.1021/jo052529q* AND DOI:*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. 3-Cyanobenzaldehyde - *available at Sigma-Aldrich*
3. Bromoethylene - *available at Sigma-Aldrich*

Products:

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

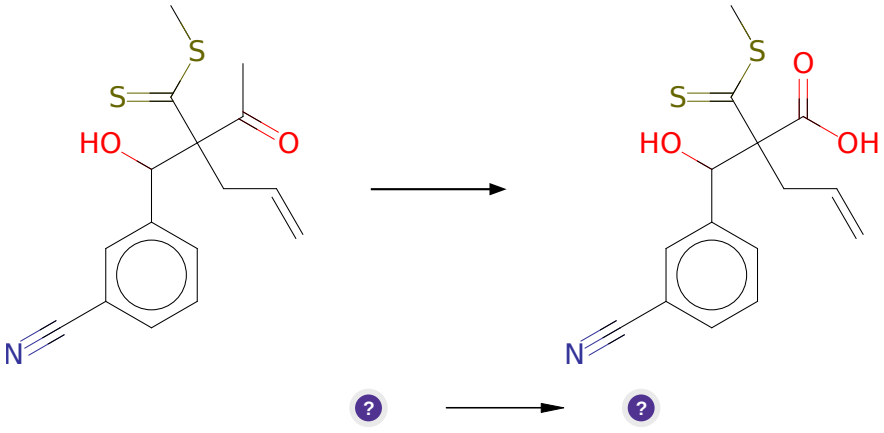
Typical conditions: 1.RCuLi.2.RCHO

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 Synthesis of Carboxylic Acids via Haloform Reaction



Substrates:

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

Products:

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

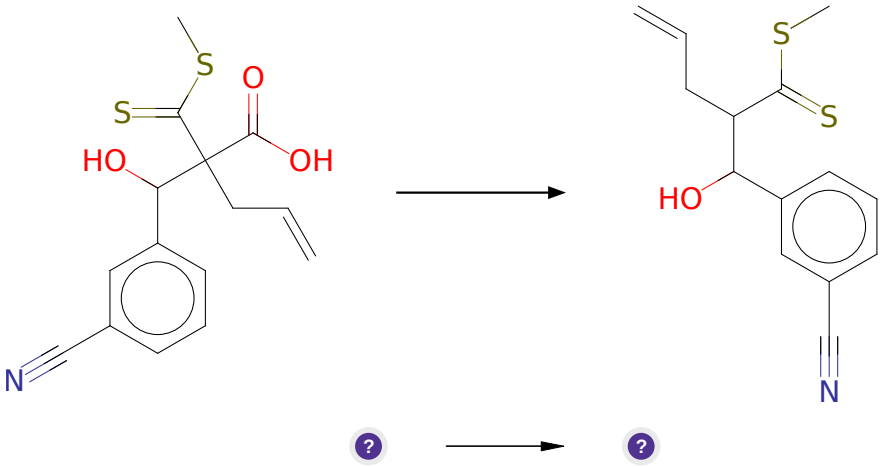
Typical conditions: I2.KI.KOH.H2O.dioxane

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)c1cccc(C#N)c1

Products:

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

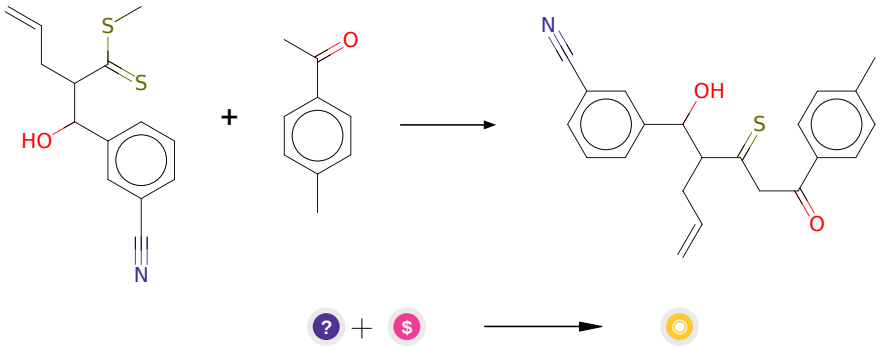
Typical conditions: DMSO.135C

Protections: none

Reference: DOI: *10.1021/jm990630f* AND *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)c1cccc(C#N)c1
2. Methyl p-tolyl ketone - *available at Sigma-Aldrich*

Products:

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

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 (TBDMS) Methyl Ether

Reference: *10.1021/jo400599e* and *10.1002/ejoc.201301667*

Retrosynthesis ID: 9996413