

Paths of analysis*

L1_DIA

Synthia

October 11, 2022

1 Analysis parameters

Analysis type: Automatic Retrosynthesis

Rules: none selected

Filters: 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: $\text{TUNNEL_COEF} * \text{FGI_COEF} * \text{STEP} * 20 + 100000 * (\text{CONFLICT} + \text{NON_SELECTIVITY} + \text{FILTERS} + \text{PROTECT})$

Chemical scoring formula: $\text{SMALLER}^3, \text{SMALLER}^{1.5}$

Min. search width: 400

Max. reactions per product: 60

Strategies: none selected

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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: 84.06

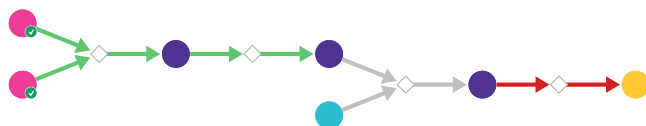
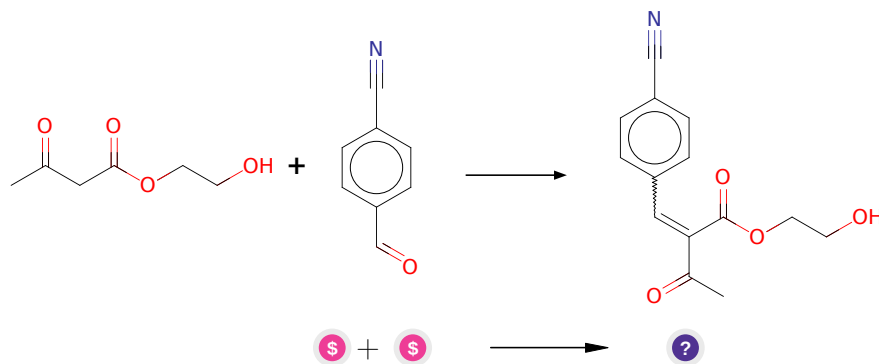


Figure 1: Outline of path 1

2.1.1 Knoevenagel Condensation



Substrates:

1. 4-Cyanobenzaldehyde - *available at Sigma-Aldrich*
2. 2-hydroxyethyl acetoacetate - *available at Sigma-Aldrich*

Products:

1. CC(=O)C(=Cc1ccc(C#N)cc1)C(=O)OCCO

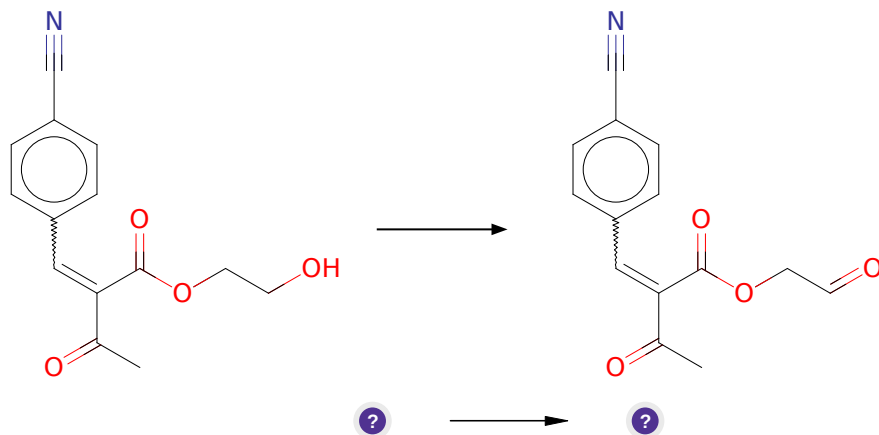
Typical conditions: base e.g.piperidine. solvent

Protections: none

Reference: [10.1002/0471264180.or015.02](#) and [10.13005/ojc/350154](#)

Retrosynthesis ID: 252

2.1.2 Oxidation of primary alcohols with DMP



Substrates:

1. CC(=O)C(=Cc1ccc(C#N)cc1)C(=O)OCCO

Products:

1. CC(=O)C(=Cc1ccc(C#N)cc1)C(=O)OCC=O

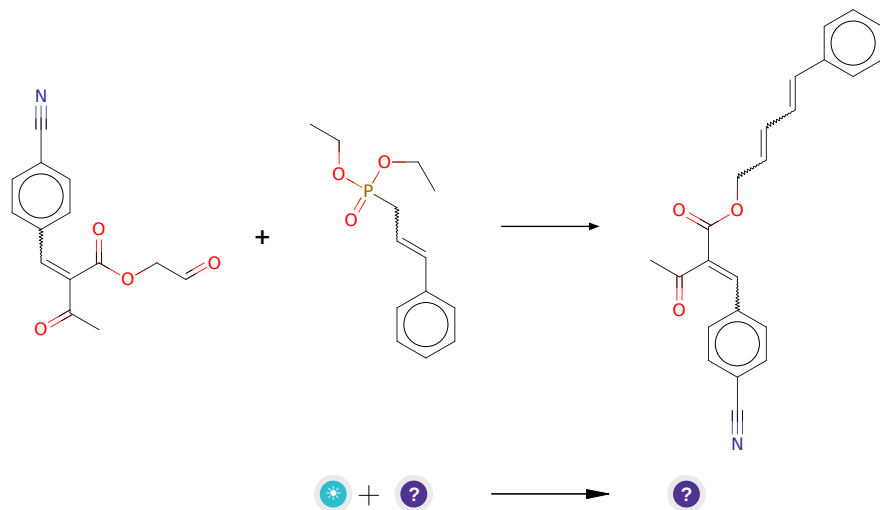
Typical conditions: DMP.DCM.0-25 C

Protections: none

Reference: [10.1016/j.bmc.2020.115469](#) p. 3, 9 and [10.1021/acs.jmedchem.8b01878](#) SI p. S43

Retrosynthesis ID: 50426

2.1.3 Olefination of aldehydes



Substrates:

1. 1-diaethylphosphono-3-phenyl-propen-(2)
2. CC(=O)C(=Cc1ccc(C#N)cc1)C(=O)OCC=O

Products:

1. CC(=O)C(=Cc1ccc(C#N)cc1)C(=O)OCC=CC=Cc1ccccc1

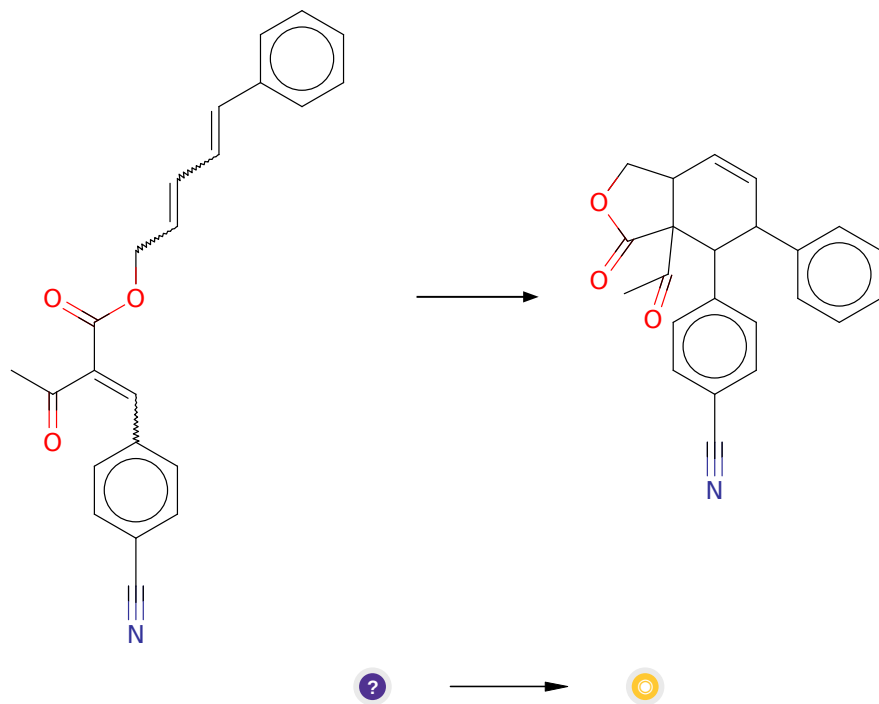
Typical conditions: KHMDS.THF

Protections: none

Reference: [10.1016/j.tetlet.2010.11.090](https://doi.org/10.1016/j.tetlet.2010.11.090) and [10.1021/acs.jmedchem.6b01329](https://doi.org/10.1021/acs.jmedchem.6b01329) and [10.1016/j.tet.2018.04.046](https://doi.org/10.1016/j.tet.2018.04.046) and [10.1021/ja00093a065](https://doi.org/10.1021/ja00093a065) and [10.1055/s-0035-1561580](https://doi.org/10.1055/s-0035-1561580)

Retrosynthesis ID: 31014852

2.1.4 Diels-Alder



Substrates:

1. CC(=O)C(=Cc1ccc(C#N)cc1)C(=O)OCC=CC=Cc1ccccc1

Products:

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

Typical conditions: Lewis acid or chiral Lewis acid. Solvent.

Protections: none

Reference: DOI: [10.1002/1521-3773\(20020517\)41:10<1668::AID-ANIE1668>3.0.CO;2-Z](https://doi.org/10.1002/1521-3773(20020517)41:10<1668::AID-ANIE1668>3.0.CO;2-Z) AND [10.1021/ja062508t](https://doi.org/10.1021/ja062508t)

Retrosynthesis ID: 18116

2.2 Path 2

Score: 93.83

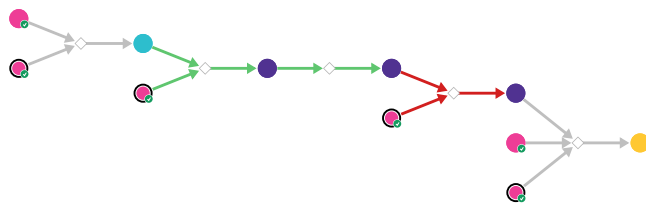
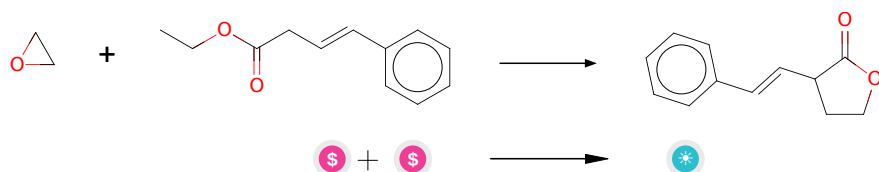


Figure 2: Outline of path 2

2.2.1 Synthesis of lactones from epoxides



Substrates:

1. Ethyl trans-4-phenyl-3-buten-2-ynoate - *available at Sigma-Aldrich*
2. Oxirane - *available at Sigma-Aldrich*

Products:

1. 2-[(E)-2-phenylethenyl]-4-butan-2-olide

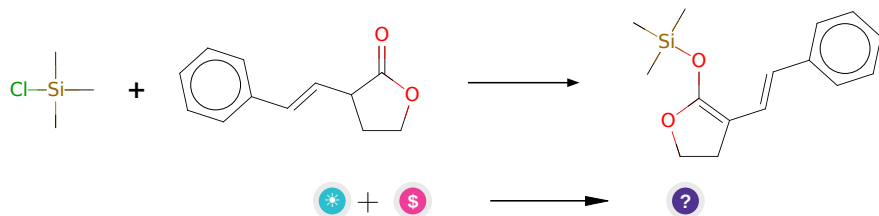
Typical conditions: EtONa.EtOH.r.t

Protections: none

Reference: [10.1021/ja9049959](https://doi.org/10.1021/ja9049959) and [10.1016/j.tetlet.2014.12.024](https://doi.org/10.1016/j.tetlet.2014.12.024)
and [10.1021/jo00077a012](https://doi.org/10.1021/jo00077a012) and [10.1016/0040-4039\(96\)00494-7](https://doi.org/10.1016/0040-4039(96)00494-7) and [10.1002/chem.201403294](https://doi.org/10.1002/chem.201403294)

Retrosynthesis ID: 21258

2.2.2 Enol esters and ethers synthesis



Substrates:

1. 2-[(e)-2-phenylethenyl]-4-butanolide
2. TMSCl - *available at Sigma-Aldrich*

Products:

1. C[Si](C)(C)OC1=C(/C=C/c2ccccc2)CCO1

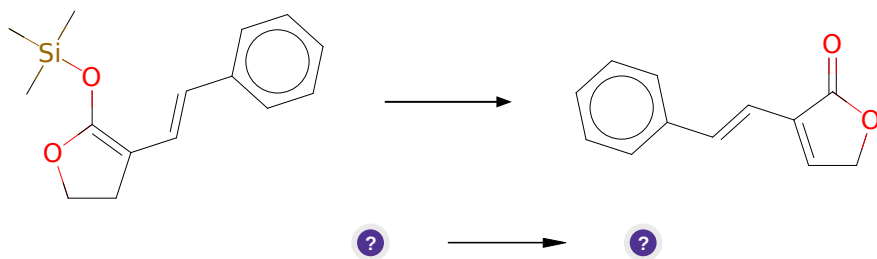
Typical conditions: 1. Et3N.Electrophile

Protections: none

Reference: *10.1016/S0040-4020(03)00977-3* AND *10.1021/ja00056a002*

Retrosynthesis ID: 7799

2.2.3 Dehydrogenation of silyl enol ethers



Substrates:

1. C[Si](C)(C)OC1=C(/C=C/c2ccccc2)CCO1

Products:

1. O=C1OCC=C1/C=C/c1ccccc1

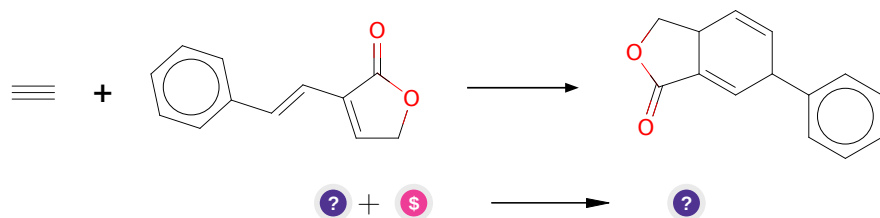
Typical conditions: Pd(OAc)2.Cu(OAc)2.O2.MeCN

Protections: none

Reference: *10.1271/bbb.60.405* and *10.1039/C3CC46778C* and US2015284405 p.40 and *10.1016/S0040-4039(01)81518-5* and US2010204477 p. 15-16 and *10.1016/0040-4039(95)00694-8* and *10.1021/jo00089a034* and *10.1016/S0040-4020(01)90587-3* and *10.1080/00397919008052802* and *10.1021/ja00218a060*

Retrosynthesis ID: 9999877

2.2.4 Diels-Alder



Substrates:

1. O=C1OCC=C1/C=C/c1ccccc1
2. Calcium carbide - *available at Sigma-Aldrich*

Products:

1. O=C1OCC2C=CC(c3ccccc3)C=C12

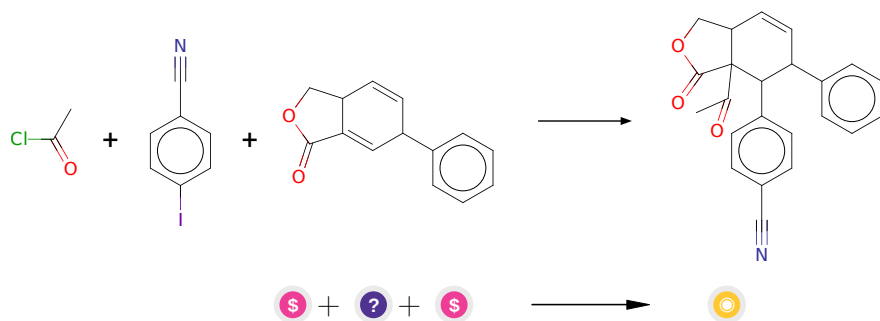
Typical conditions: H₂O.MeOH.EtOH.isooctane

Protections: none

Reference: [10.1002/1521-3773\(20020517\)41:10<1668::AID-ANIE1668>3.0.CO;2-Z](#)

Retrosynthesis ID: 10557

2.2.5 Conjugated addition of organocuprate-acylation of enones and enoate esters



Substrates:

1. 4-Iodobenzonitrile - *available at Sigma-Aldrich*
2. O=C1OCC2C=CC(c3ccccc3)C=C12
3. Acetyl chloride - *available at Sigma-Aldrich*

Products:

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

Typical conditions: 1.RCuLi.2.AcCl.HMPA

Protections: none

Reference: [10.3987/COM-99-S143](#) AND [10.1021/ja00148a023](#) AND [10.1016/S0040-4039\(01\)80891-1](#)

Retrosynthesis ID: 12521

2.3 Path 3

Score: 106.04

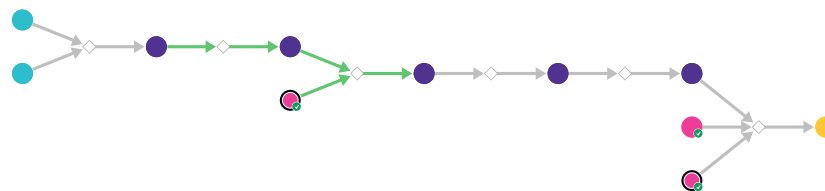
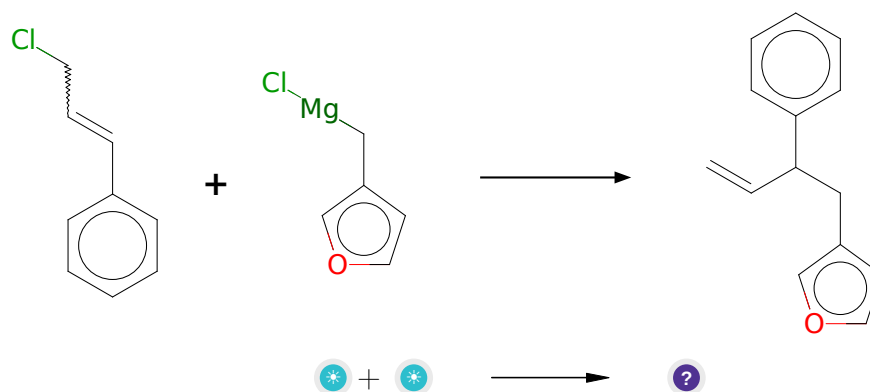


Figure 3: Outline of path 3

2.3.1 NHC-catalyzed Grignard allylic substitution



Substrates:

1. cinnamyl chloride

2. (furan-3-ylmethyl)magnesium chloride

Products:

1. C=CC(Cc1ccoc1)c1ccccc1

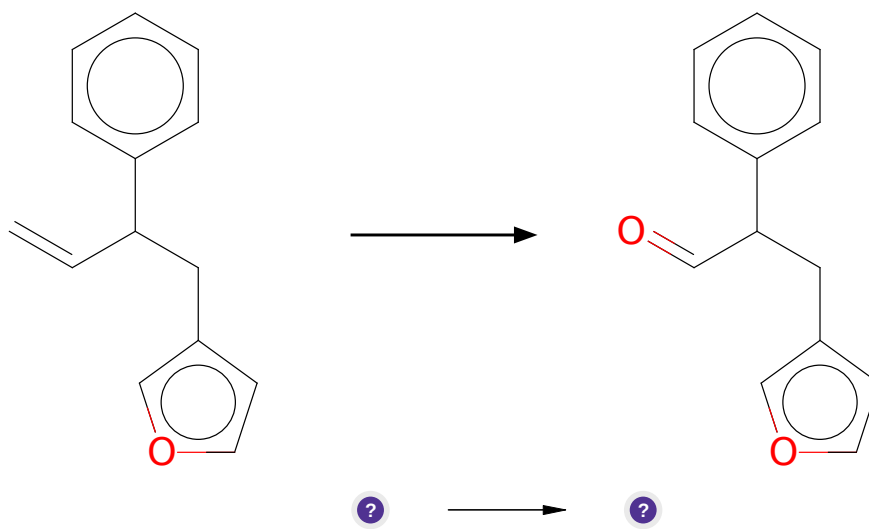
Typical conditions: RMgCl.THF.NHC-complex

Protections: none

Reference: [10.1016/j.tetlet.2012.12.124](#)

Retrosynthesis ID: 1171

2.3.2 Ozonolysis



Substrates:

1. C=CC(Cc1ccoc1)c1ccccc1

Products:

1. O=CC(Cc1ccoc1)c1ccccc1

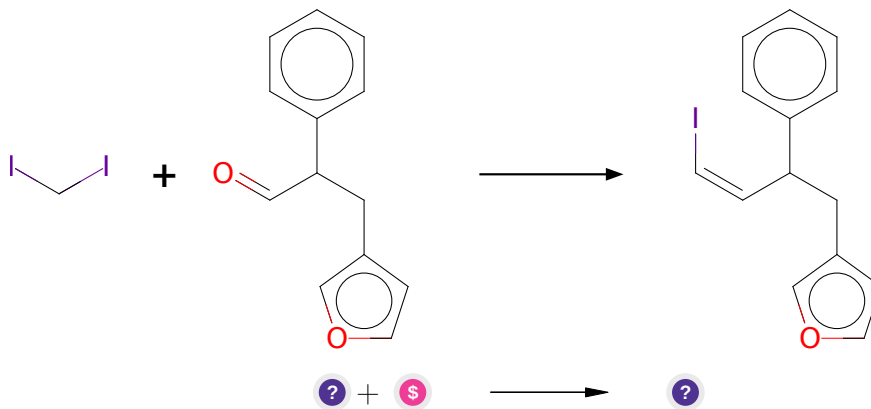
Typical conditions: O₃.MeOH.CH₂Cl₂.PPh₃ or Me₂S.low temperature

Protections: none

Reference: [10.1016/j.tet.2017.03.039](#)

Retrosynthesis ID: 5074

2.3.3 Iodoolefination of aldehydes



Substrates:

1. O=CC(Cc1ccoc1)c1ccccc1
2. Diiodomethane - *available at Sigma-Aldrich*

Products:

1. I/C=C\C(Cc1ccoc1)c1ccccc1

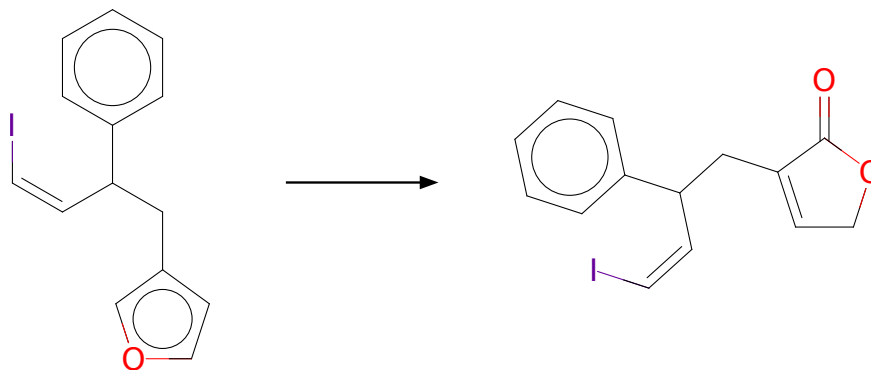
Typical conditions: 1. PPh_3 2. $\text{NaN}(\text{TMS})_2$ 3. HMPA. THF

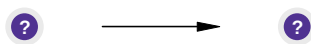
Protections: none

Reference: [10.1021/ja00171a035](#) and [10.1039/C0OB00977F](#) and WO2009033499 (p.25)

Retrosynthesis ID: 10001773

2.3.4 NBS-promoted oxidation of furans to lactones





Substrates:

1. I/C=C\C(Cc1ccoc1)c1ccccc1

Products:

1. O=C1OCC=C1CC(/C=C\I)c1ccccc1

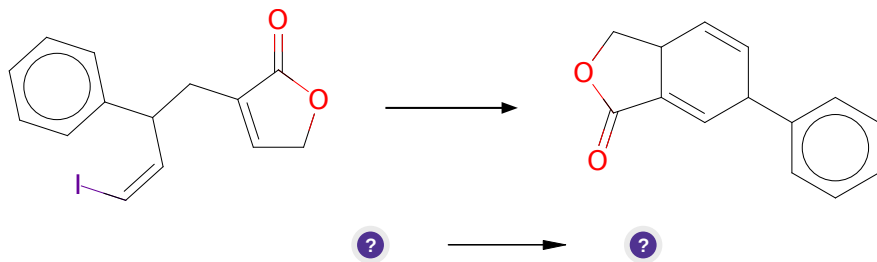
Typical conditions: NBS.MW.MeOH

Protections: none

Reference: DOI: [10.1016/S0040-4039\(01\)01261-8](https://doi.org/10.1016/S0040-4039(01)01261-8)

Retrosynthesis ID: 49766

2.3.5 Heck Reaction



Substrates:

1. O=C1OCC=C1CC(/C=C\I)c1ccccc1

Products:

1. O=C1OCC2C=CC(c3ccccc3)C=C12

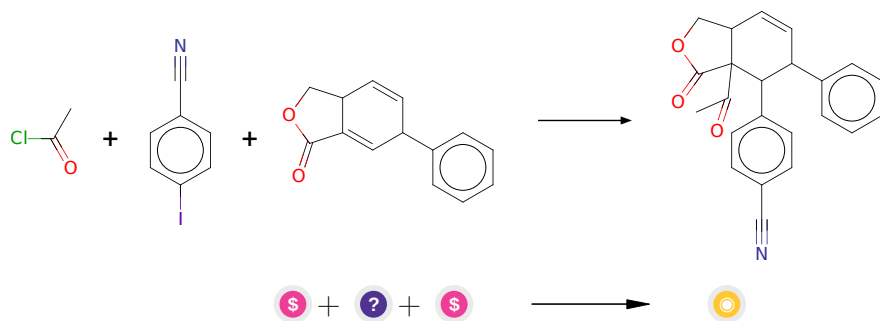
Typical conditions: Pd (cat). ligand. base e.g DIPEA.solvent

Protections: none

Reference: DOI: [10.1021/jo00270a011](https://doi.org/10.1021/jo00270a011) or DOI: [10.1021/ar00049a001](https://doi.org/10.1021/ar00049a001) or DOI: [10.1021/ja00206a034](https://doi.org/10.1021/ja00206a034) or DOI: [10.1021/cr020039h](https://doi.org/10.1021/cr020039h) or DOI: [10.1039/C1CS15101K](https://doi.org/10.1039/C1CS15101K) or DOI: [10.1002/9780470716076](https://doi.org/10.1002/9780470716076)

Retrosynthesis ID: 8584

2.3.6 Conjugated addition of organocuprate-acylation of enones and enoate esters



Substrates:

1. 4-Iodobenzonitrile - *available at Sigma-Aldrich*
2. O=C1OCC2C=CC(c3ccccc3)C=C12
3. Acetyl chloride - *available at Sigma-Aldrich*

Products:

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

Typical conditions: 1.RCuLi.2.AcCl.HMPA

Protections: none

Reference: [10.3987/COM-99-S143](#) AND [10.1021/ja00148a023](#) AND [10.1016/S0040-4039\(01\)80891-1](#)

Retrosynthesis ID: 12521

2.4 Path 4

Score: 107.50

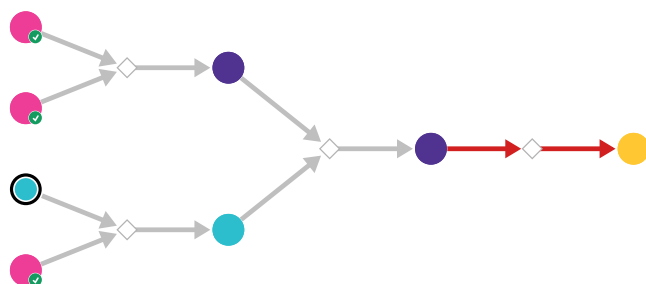
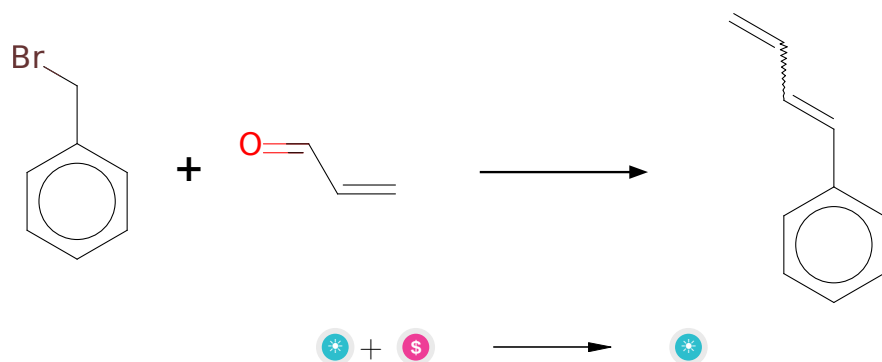


Figure 4: Outline of path 4

2.4.1 Wittig olefination



Substrates:

1. Acrolein
2. α -Bromotoluene - *available at Sigma-Aldrich*

Products:

1. buta-1,3-dienyl-benzol

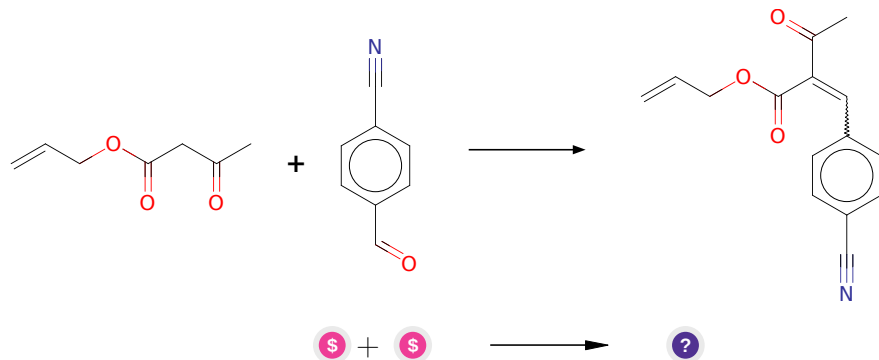
Typical conditions: 1.PPh₃ or trialkylphosphite.2.base.aldehyde

Protections: none

Reference: [10.1021/ja0015287](#) and [10.1021/ja404673s](#) and [10.1021/ol901979x](#)

Retrosynthesis ID: 9545

2.4.2 Knoevenagel Condensation



Substrates:

- 4-Cyanobenzaldehyde - *available at Sigma-Aldrich*
- Allyl Acetoacetate - *available at Sigma-Aldrich*

Products:

- C=CCOC(=O)C(=Cc1ccc(C#N)cc1)C(C)=O

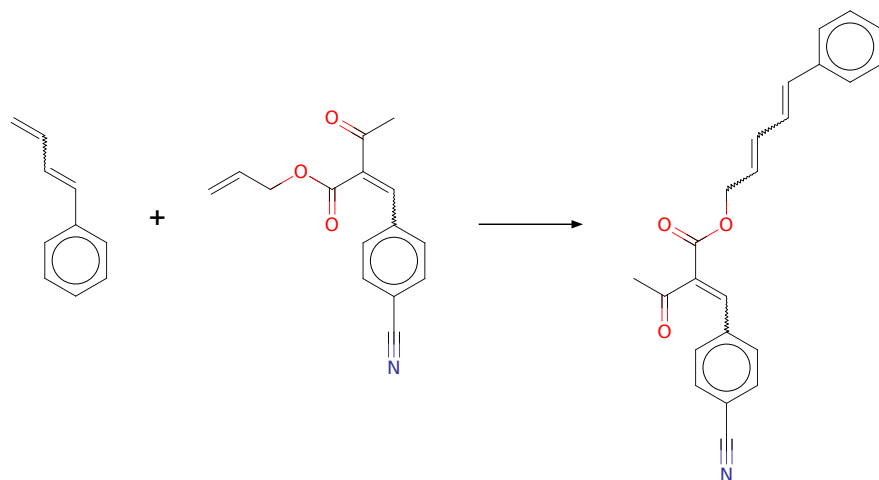
Typical conditions: base e.g.piperidine. solvent

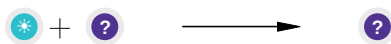
Protections: none

Reference: [10.1002/0471264180.or015.02](#) and [10.13005/ojc/350154](#)

Retrosynthesis ID: 252

2.4.3 Cross-Metathesis





Substrates:

1. buta-1,3-dienyl-benzol
2. C=CCOC(=O)C(=Cc1ccc(C#N)cc1)C(C)=O

Products:

1. CC(=O)C(=Cc1ccc(C#N)cc1)C(=O)OCC=CC=Cc1ccccc1

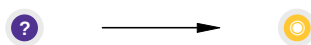
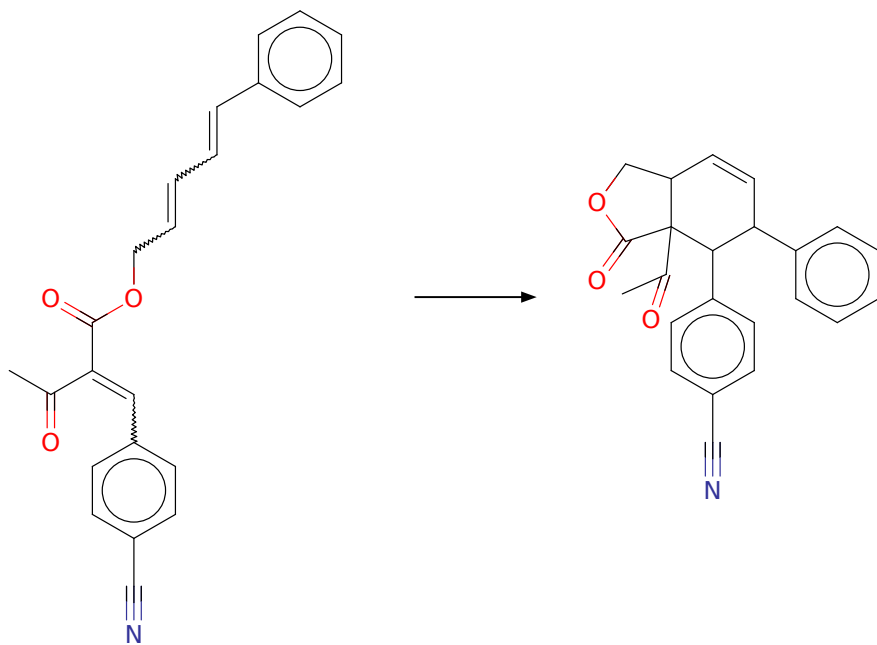
Typical conditions: catalyst e.g. Hoveyda-Grubbs . solvent e.g. CH₂Cl₂

Protections: none

Reference: DOI: [10.1002/anie.200602601](https://doi.org/10.1002/anie.200602601) and [10.1021/acs.orglett.7b00920](https://doi.org/10.1021/acs.orglett.7b00920) and [10.1021/acs.joc.9b02268](https://doi.org/10.1021/acs.joc.9b02268)

Retrosynthesis ID: 31014172

2.4.4 Diels-Alder



Substrates:

1. CC(=O)C(=Cc1ccc(C#N)cc1)C(=O)OCC=CC=Cc1ccccc1

Products:

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

Typical conditions: Lewis acid or chiral Lewis acid. Solvent.

Protections: none

Reference: DOI: [10.1002/1521-3773\(20020517\)41:10<1668::AID-ANIE1668>3.0.CO;2-Z](https://doi.org/10.1002/1521-3773(20020517)41:10<1668::AID-ANIE1668>3.0.CO;2-Z) AND [10.1021/ja062508t](https://doi.org/10.1021/ja062508t)

Retrosynthesis ID: 18116

2.5 Path 5

Score: 115.31

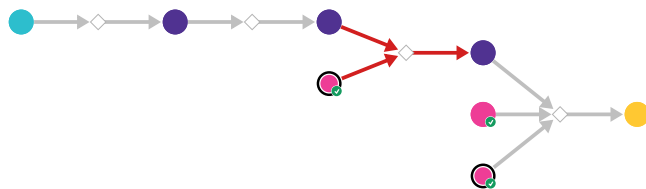
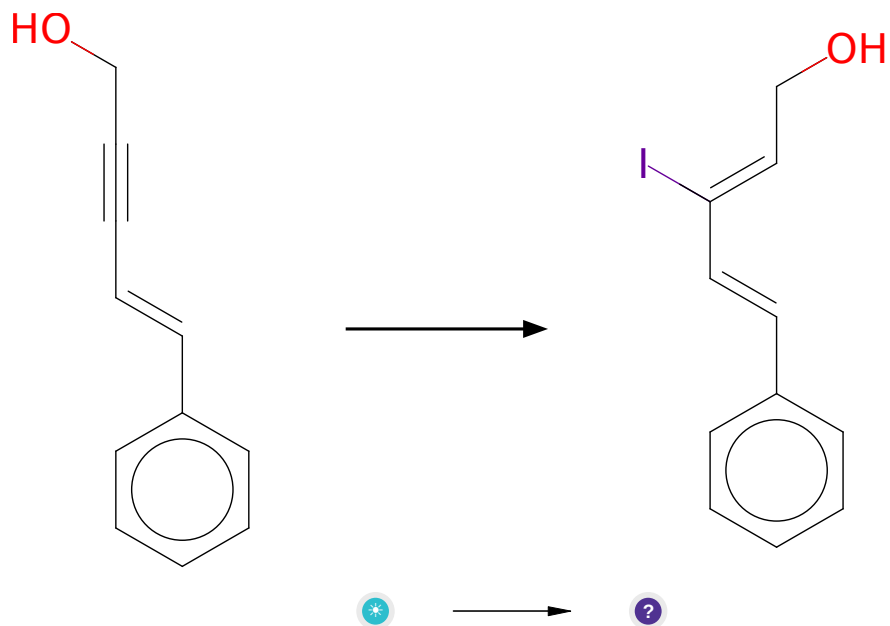


Figure 5: Outline of path 5

2.5.1 Hydroalumination-iodination of alkynes



Substrates:

1. 5-phenylpent-4-en-2-yn-1-ol

Products:

1. OC/C=C(I)/C=C/c1ccccc1

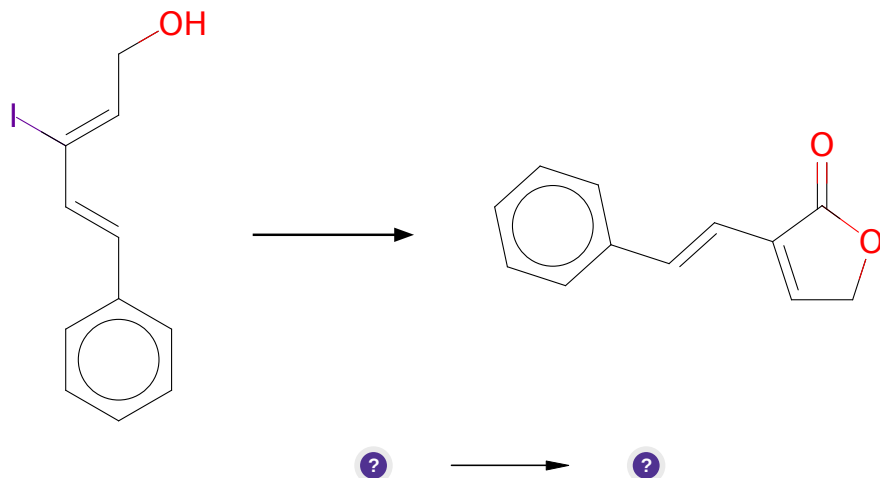
Typical conditions: DIBAL-H then I₂

Protections: none

Reference: [10.1002/anie.200500088](https://doi.org/10.1002/anie.200500088) and [10.1016/j.ejmech.2016.01.027](https://doi.org/10.1016/j.ejmech.2016.01.027) and [10.1002/ejoc.201300870](https://doi.org/10.1002/ejoc.201300870)

Retrosynthesis ID: 9993055

2.5.2 Synthesis of lactones from vinyl halides



Substrates:

1. OC/C=C(I)/C=C/c1ccccc1

Products:

1. O=C1OCC=C1/C=C/c1ccccc1

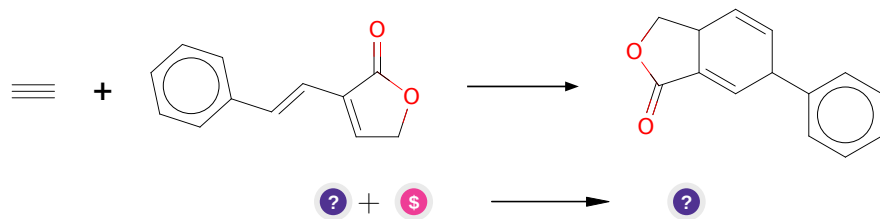
Typical conditions: BuLi.THF then CO₂ then HCl

Protections: none

Reference: [10.1002/anie.200702637](#) and [10.1016/0040-4020\(95\)00003-Q](#) and [10.1021/jo00219a022](#) and [10.1021/ja00258a077](#)

Retrosynthesis ID: 31005638

2.5.3 Diels-Alder



Substrates:

1. O=C1OCC=C1/C=C/c1ccccc1
2. Calcium carbide - [available at Sigma-Aldrich](#)

Products:

1. O=C1OCC2C=CC(c3ccccc3)C=C12

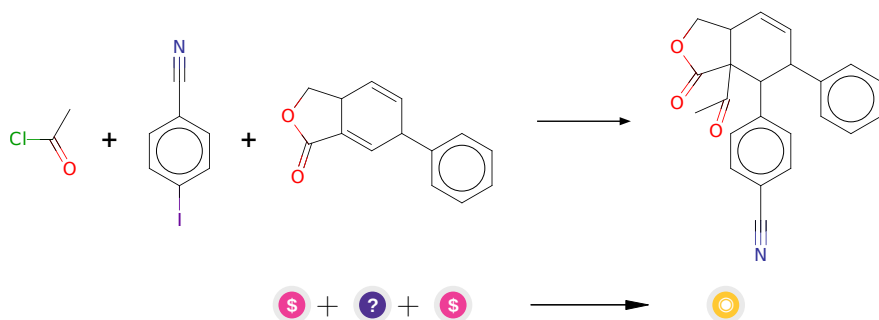
Typical conditions: H₂O.MeOH.EtOH.isooctane

Protections: none

Reference: [10.1002/1521-3773\(20020517\)41:10<1668::AID-ANIE1668>3.0.CO;2-Z](#)

Retrosynthesis ID: 10557

2.5.4 Conjugated addition of organocuprate-acylation of enones and enoate esters



Substrates:

1. 4-Iodobenzonitrile - *available at Sigma-Aldrich*
2. O=C1OCC2C=CC(c3ccccc3)C=C12
3. Acetyl chloride - *available at Sigma-Aldrich*

Products:

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

Typical conditions: 1.RCuLi.2.AcCl.HMPA

Protections: none

Reference: [10.3987/COM-99-S143](#) AND [10.1021/ja00148a023](#) AND [10.1016/S0040-4039\(01\)80891-1](#)

Retrosynthesis ID: 12521