

Paths of analysis*

L4

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

*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

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

2.1 Path 1

Score: 115.31

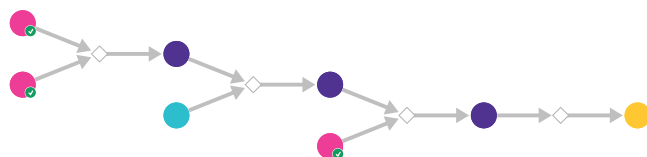
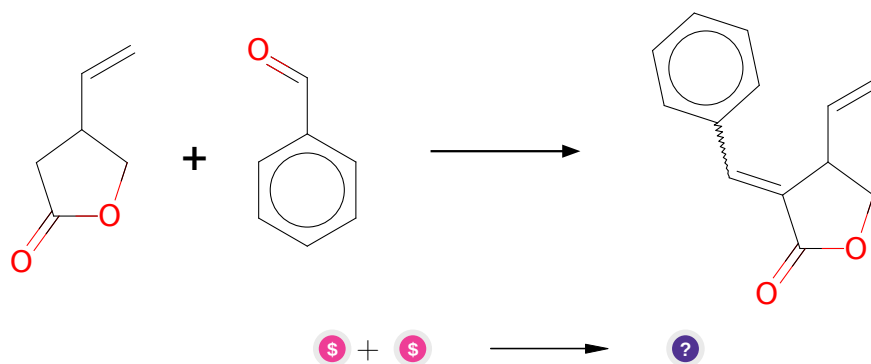


Figure 1: Outline of path 1

2.1.1 Condensation of esters with aldehydes/ketones



Substrates:

1. Benzaldehyde - *available at Sigma-Aldrich*
2. 4-ethenyloxolan-2-one - *available at Sigma-Aldrich*

Products:

1. C=CC1COC(=O)C1=Cc1ccccc1

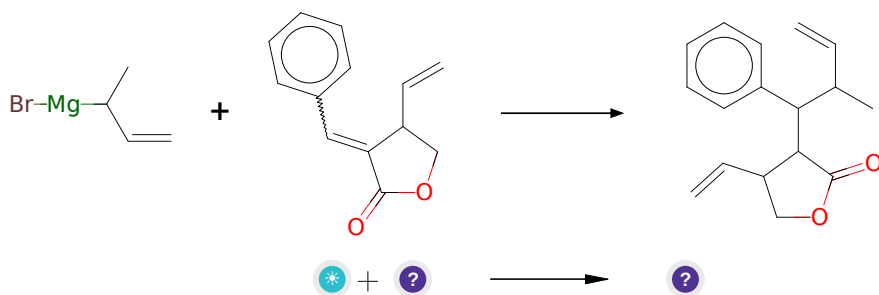
Typical conditions: LDA.THF

Protections: none

Reference: [10.1021/op040006z](#) AND [10.1016/j.bmcl.2005.10.104](#) AND

Retrosynthesis ID: 14983

2.1.2 Conjugate addition of organocuprate



Substrates:

1. 3-butenylmagnesium bromide
2. C=CC1COC(=O)C1=Cc1ccccc1

Products:

1. C=CC(C)C(c1ccccc1)C1C(=O)OCC1C=C

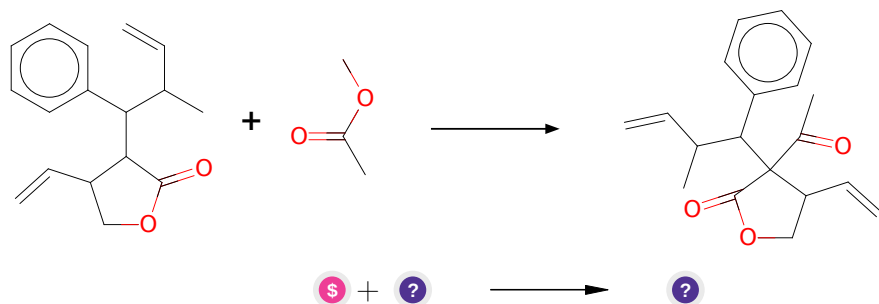
Typical conditions: 1.CuCN.LiCl.2.Eletrophile.3.NH4Cl

Protections: none

Reference: [10.3891/acta.chem.scand.24-3490](#) AND [10.1016/S0040-4020\(01\)92354-3](#) AND [10.1016/j.tet.2011.12.046](#) AND [10.1016/S0040-4039\(02\)01713-6](#)

Retrosynthesis ID: 10003575

2.1.3 Claisen Condensation



Substrates:

1. Methyl acetate - *available at Sigma-Aldrich*
2. C=CC(C)C(c1ccccc1)C1C(=O)OCC1C=C

Products:

1. C=CC(C)C(c1ccccc1)C1(C(C)=O)C(=O)OCC1C=C

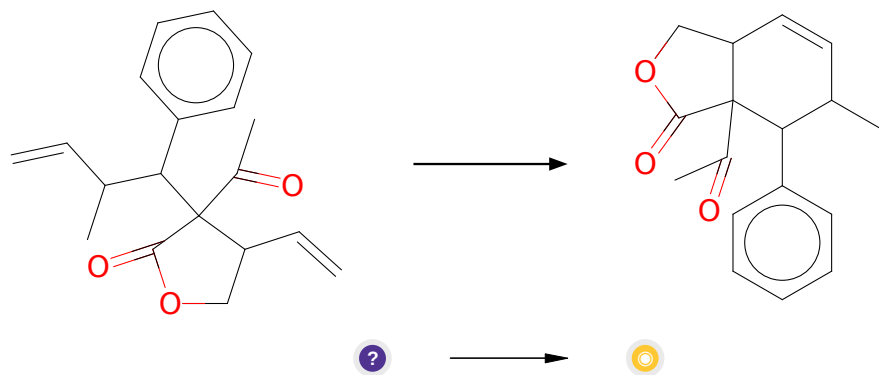
Typical conditions: Base.Solvent

Protections: none

Reference: *10.1021/cr020703u* and *10.1021/cr60088a002*

Retrosynthesis ID: 5015

2.1.4 Ring-Closing Metathesis



Substrates:

1. C=CC(C)C(c1ccccc1)C1(C(C)=O)C(=O)OCC1C=C

Products:

1. CC(=O)C12C(=O)OCC1C=CC(C)C2c1ccccc1

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

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

2.2 Path 2

Score: 125.08

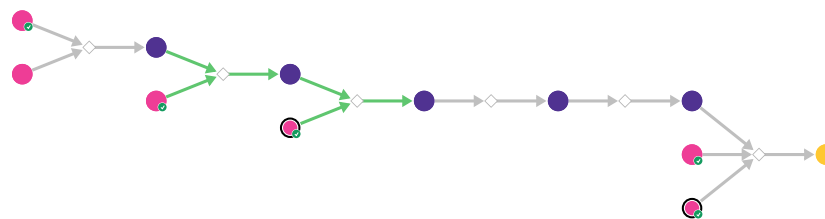
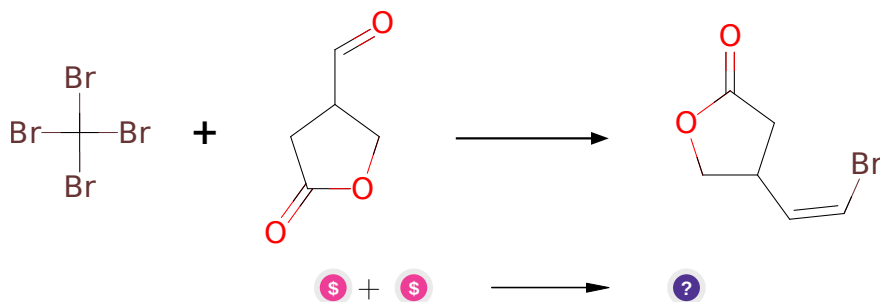


Figure 2: Outline of path 2

2.2.1 Synthesis of Z-bromoalkenes



Substrates:

1. Tetrabromomethane - [available at Sigma-Aldrich](#)
2. 5-oxotetrahydrofuran-3-carbaldehyde - [A1BioChemLabs](#)

Products:

1. O=C1CC(/C=C\Br)CO1

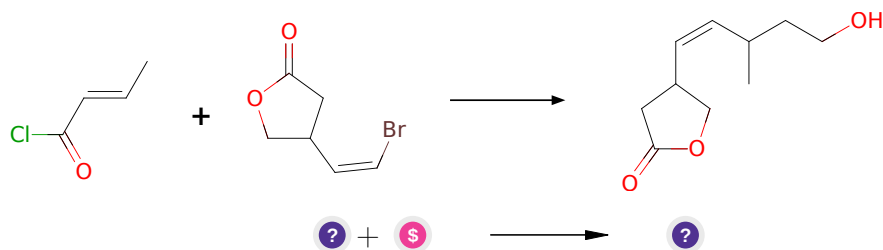
Typical conditions: 1.CBr₄.Ph₃P.TEA.THF.cooling to rt.2. nBu₃SnH.Pd(PPh₃)₄.toluene.rt

Protections: none

Reference: [10.1002/chem.201101630](#) (SI p.13) and [10.1021/jo0498157](#) and [10.1016/j.tetlet.2004.01.151](#) and [10.1021/ol035127i](#)

Retrosynthesis ID: 10001762

2.2.2 Chiral auxiliary directed enantioselective Micheal addition



Substrates:

1. O=C1CC(/C=C\Br)CO1
2. Crotonoyl chloride - *available at Sigma-Aldrich*

Products:

1. CC(/C=C\C1COC(=O)C1)CCO

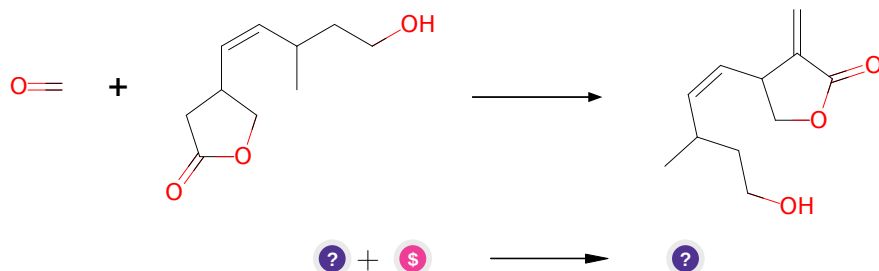
Typical conditions: 1.Chiral auxiliary(Oppolzer's,Evans' or Seebach's).or.ephedrine.2.RMgX.3.LAH

Protections: none

Reference: [10.1016/j.tetlet.2010.11.083](#) AND [10.1039/B404205K](#) AND [10.1021/ol006410+](#) AND [10.1002/anie.199702741](#) AND [10.1016/j.tet.2015.05.023](#) AND [10.1021/jm9005302](#) AND [10.1016/j.tet.2011.12.046](#)

Retrosynthesis ID: 15874

2.2.3 Eschenmoser methenylation



Substrates:

1. CC(/C=C\C1COC(=O)C1)CCO
2. Formalin - *available at Sigma-Aldrich*

Products:

1. C=C1C(=O)OCC1/C=C\C(C)CCO

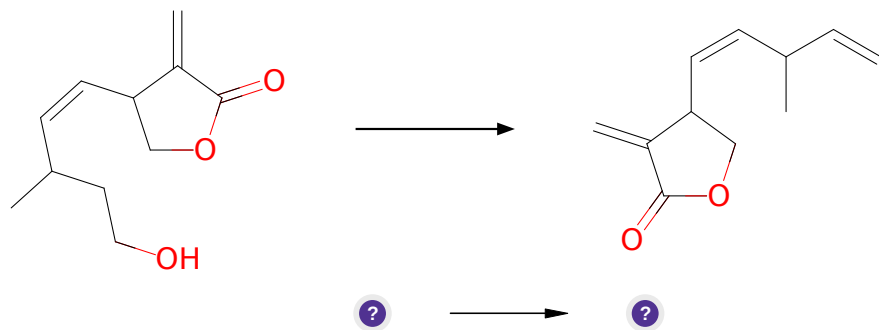
Typical conditions: iPr₂NH.TFA.HCHO.or.organocatalyst

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

2.2.4 Synthesis of alkenes from alcohols



Substrates:

1. C=C1C(=O)OCC1/C=C\C(C)CCO

Products:

1. C=CC(C)/C=C\C1COC(=O)C1=C

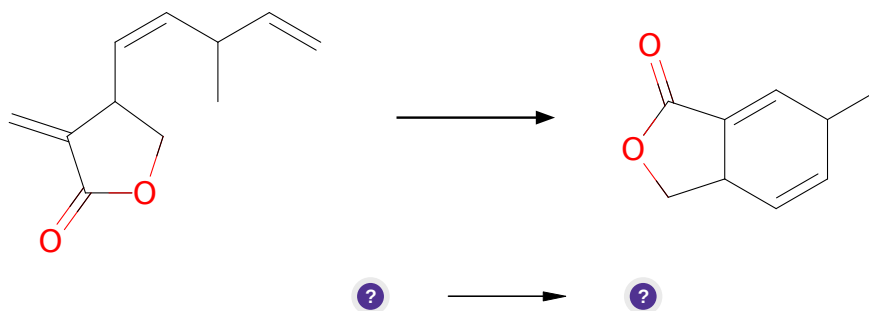
Typical conditions: PhSeCN.PBu3.THF then H2O2.THF.H2O

Protections: none

Reference: [10.1016/j.tet.2011.05.034](#) and [10.1055/s-0036-1588104](#) and [10.1002/anie.200501760](#) and [10.1002/anie.200700854](#) and [10.1002/asia.201301248](#) and [10.1021/ol501095w](#)

Retrosynthesis ID: 31010457

2.2.5 Ring-Closing Metathesis



Substrates:

1. C=CC(C)/C=C\C1COC(=O)C1=C

Products:

1. CC1C=CC2COC(=O)C2=C1

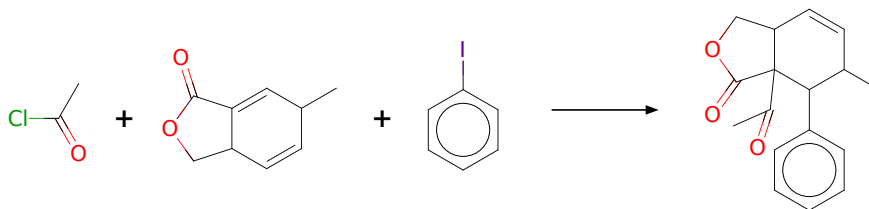
Typical conditions: catalyst e.g. Hoveyda-Grubbs . solvent e.g. CH2Cl2

Protections: none

Reference: DOI: [10.1021/jo202073n](#) and [10.1021/jm060486f](#) and [10.1039/B801206G](#) and [10.1021/ol052856k](#)

Retrosynthesis ID: 31014201

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





Substrates:

1. Iodobenzene - *available at Sigma-Aldrich*
2. CC1C=CC2COC(=O)C2=C1
3. Acetyl chloride - *available at Sigma-Aldrich*

Products:

1. CC(=O)C12C(=O)OCC1C=CC(C)C2c1ccccc1

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: 125.08

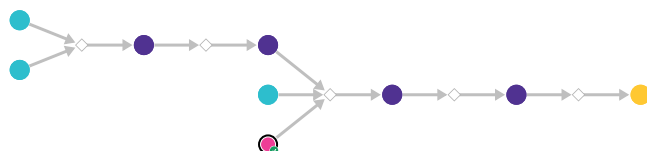
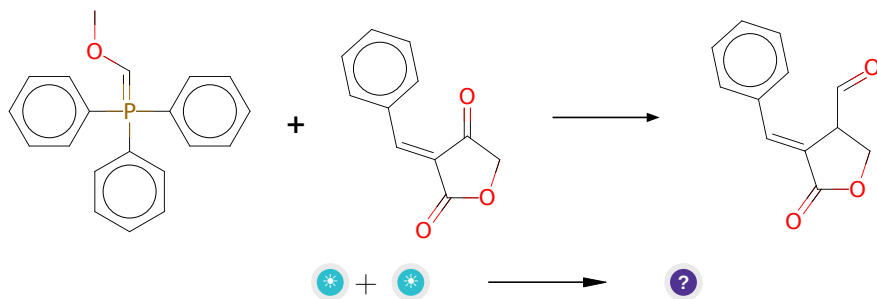


Figure 3: Outline of path 3

2.3.1 Olefination of ketones followed by hydrolysis



Substrates:

1. triphenylphosphonium methoxymethylide
2. C₁₁H₈O₃

Products:

1. O=CC1COC(=O)/C1=C/c1ccccc1

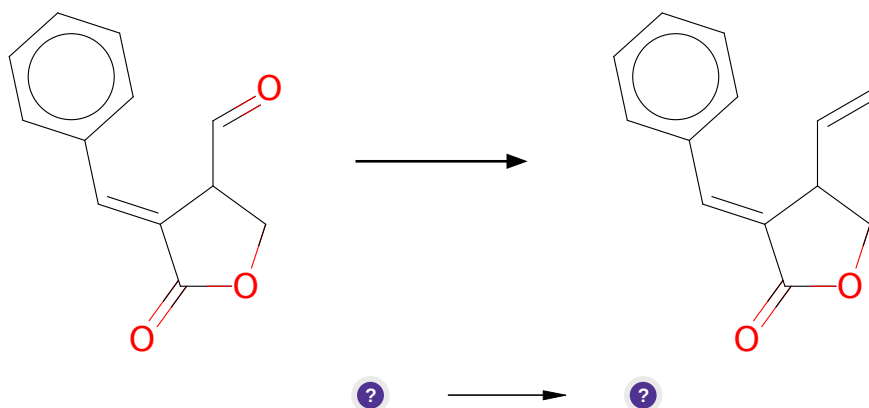
Typical conditions: KHMDS.THF hydrolysis: pTsOH.water.acetone

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

2.3.2 Tebbe Olefination



Substrates:

1. O=CC1COC(=O)/C1=C/c1ccccc1

Products:

1. C=CC1COC(=O)/C1=C/c1ccccc1

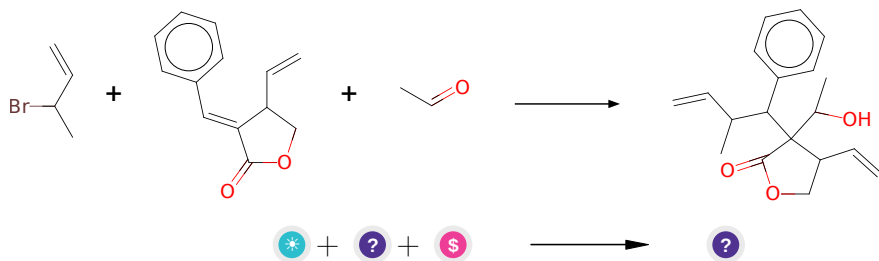
Typical conditions: Cp₂TiCl₂.AlMe₃.toluene

Protections: none

Reference: [10.1016/j.tet.2007.03.015](#) and [10.1002/9780470638859.conrr617](#)

Retrosynthesis ID: 11714

2.3.3 Conjugated addition of cuprate-aldol sequence



Substrates:

1. 3-brom-but-1-en
2. C=CC1COC(=O)/C1=C/c1ccccc1
3. Ethanal - *available at Sigma-Aldrich*

Products:

1. C=CC(C)C(c1ccccc1)C1(C(C)O)C(=O)OCC1C=C

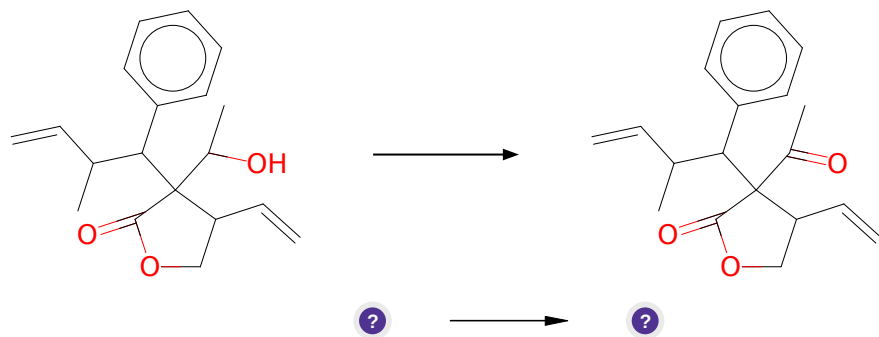
Typical conditions: 1.RCuLi.2.RCHO

Protections: none

Reference: [10.1021/jo9905672](#) AND [10.1021/ja0320018](#) AND [10.1021/ja015900+](#) AND [10.3987/COM-99-S143](#) AND [10.1021/ja00148a023](#) AND [10.1016/S0040-4039\(01\)80891-1](#) AND [10.1271/bbb.69.391](#) AND [10.1039/b612593j](#)

Retrosynthesis ID: 20521

2.3.4 Swern Oxidation



Substrates:

1. C=CC(C)C(c1ccccc1)C1(C(C)O)C(=O)OCC1C=C

Products:

1. C=CC(C)C(c1ccccc1)C1(C(C)=O)C(=O)OCC1C=C

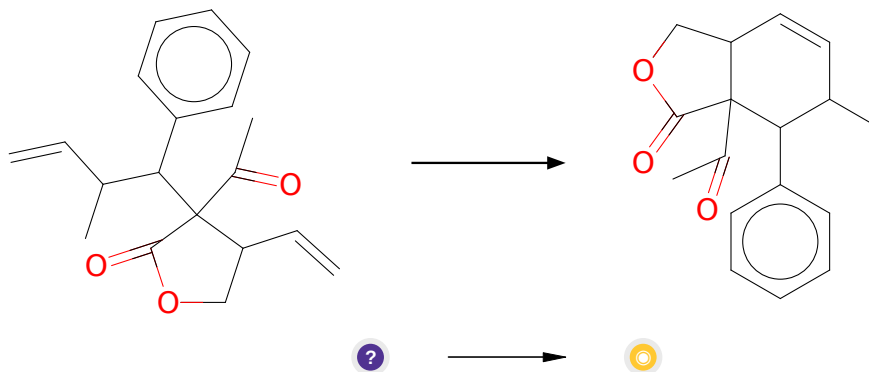
Typical conditions: oxalyl chloride.DMSO.DCM.NMe3.-40C

Protections: none

Reference: [10.1055/s-1990-27036](#)

Retrosynthesis ID: 11163

2.3.5 Ring-Closing Metathesis



Substrates:

1. C=CC(C)C(c1ccccc1)C1(C(C)=O)C(=O)OCC1C=C

Products:

1. CC(=O)C12C(=O)OCC1C=CC(C)C2c1ccccc1

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

Protections: none

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

Retrosynthesis ID: 31014187

2.4 Path 4

Score: 164.14

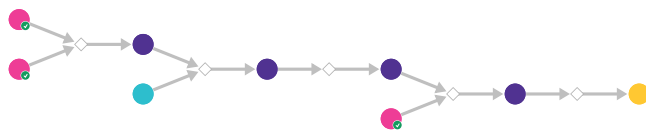
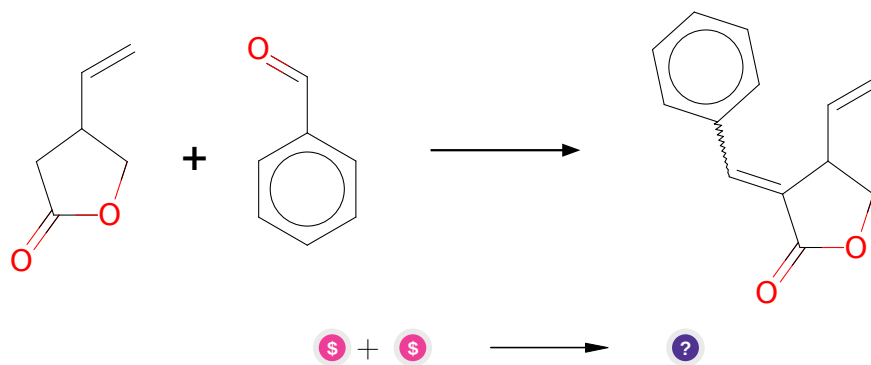


Figure 4: Outline of path 4

2.4.1 Condensation of esters with aldehydes/ketones



Substrates:

1. Benzaldehyde - *available at Sigma-Aldrich*
2. 4-ethenyloxolan-2-one - *available at Sigma-Aldrich*

Products:

1. C=CC1COC(=O)C1=Cc1ccccc1

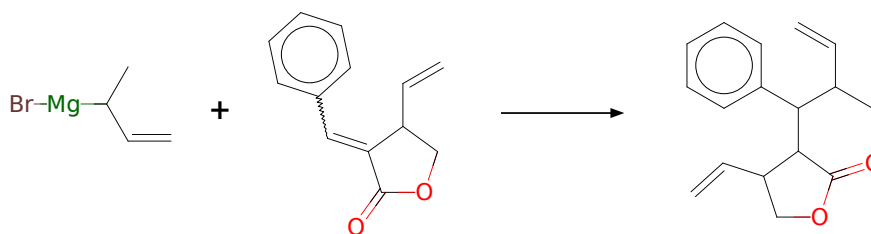
Typical conditions: LDA.THF

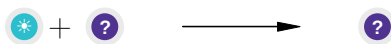
Protections: none

Reference: [10.1021/op040006z](#) AND [10.1016/j.bmcl.2005.10.104](#) AND

Retrosynthesis ID: 14983

2.4.2 Conjugate addition of organocuprate





Substrates:

1. 3-butenylmagnesium bromide
2. C=CC1COC(=O)C1=Cc1ccccc1

Products:

1. C=CC(C)C(c1ccccc1)C1C(=O)OCC1C=C

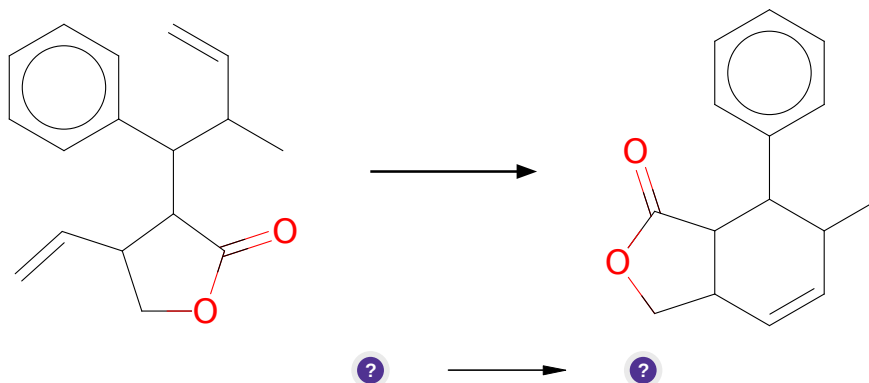
Typical conditions: 1.CuCN.LiCl.2.Eletrophile.3.NH₄Cl

Protections: none

Reference: [10.3891/acta.chem.scand.24-3490](#) AND [10.1016/S0040-4020\(01\)92354-3](#) AND [10.1016/j.tet.2011.12.046](#) AND [10.1016/S0040-4039\(02\)01713-6](#)

Retrosynthesis ID: 10003575

2.4.3 Ring-Closing Metathesis



Substrates:

1. C=CC(C)C(c1ccccc1)C1C(=O)OCC1C=C

Products:

1. CC1C=CC2COC(=O)C2C1c1ccccc1

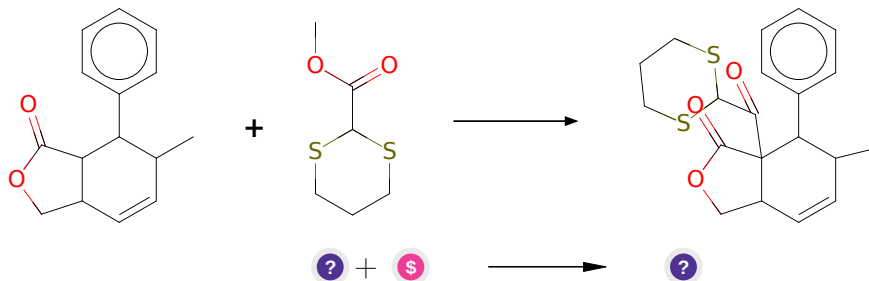
Typical conditions: catalyst e.g. Hoveyda-Grubbs . solvent e.g. CH₂Cl₂

Protections: none

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

Retrosynthesis ID: 31014187

2.4.4 Claisen Condensation



Substrates:

1. CC1C=CC2COC(=O)C2C1c1ccccc1
2. methyl 1,3-dithiane-2-carboxylate - *available at Sigma-Aldrich*

Products:

1. CC1C=CC2COC(=O)C2(C(=O)C2SCCSCS2)C1c1ccccc1

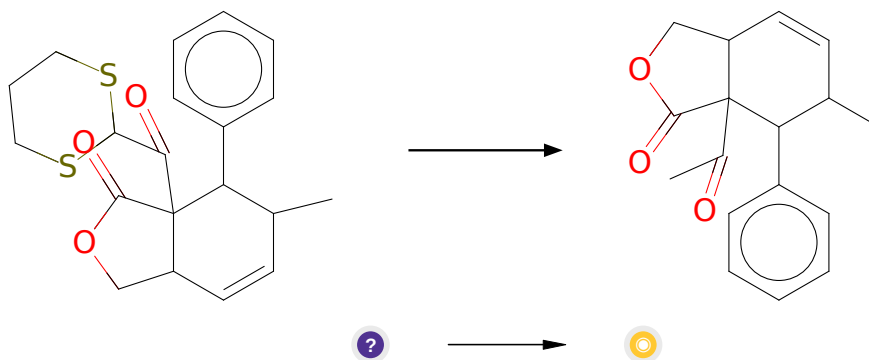
Typical conditions: Base.Solvent

Protections: none

Reference: [10.1021/cr020703u](#) and [10.1021/cr60088a002](#)

Retrosynthesis ID: 5015

2.4.5 Reductive cleavage of dithianes



Substrates:

1. CC1C=CC2COC(=O)C2(C(=O)C2SCCSCS2)C1c1ccccc1

Products:

1. CC(=O)C12C(=O)OCC1C=CC(C)C2c1ccccc1

Typical conditions: H₂.Ra-Ni or NiCl₂.NaBH₄

Protections: none

Reference: [10.1021/jo701885n](#) and [10.1002/ejoc.201201128](#) and [10.1002/ejoc.201201184](#)

Retrosynthesis ID: 31726

2.5 Path 5

Score: 225.18

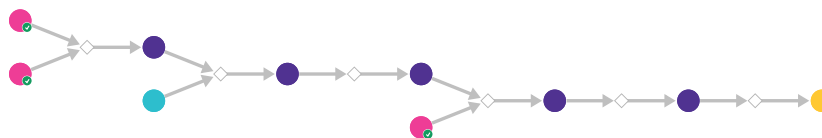
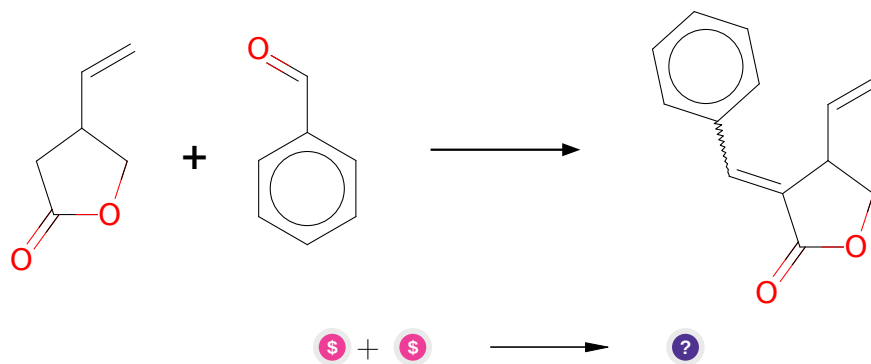


Figure 5: Outline of path 5

2.5.1 Condensation of esters with aldehydes/ketones



Substrates:

1. Benzaldehyde - [available at Sigma-Aldrich](#)
2. 4-ethenyloxolan-2-one - [available at Sigma-Aldrich](#)

Products:

1. C=CC1COC(=O)C1=Cc1ccccc1

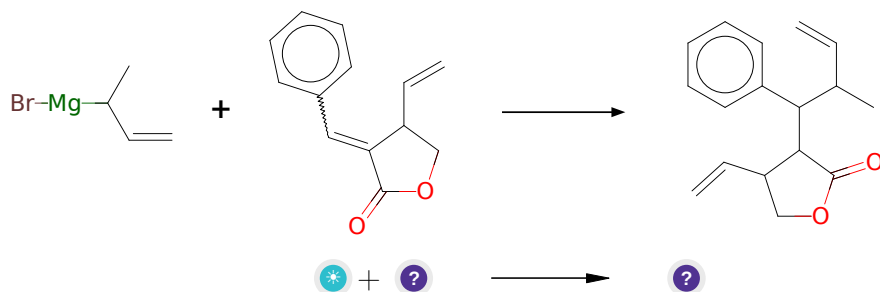
Typical conditions: LDA.THF

Protections: none

Reference: [10.1021/op040006z](#) AND [10.1016/j.bmcl.2005.10.104](#) AND

Retrosynthesis ID: 14983

2.5.2 Conjugate addition of organocuprate



Substrates:

1. 3-butenylmagnesium bromide
2. C=CC1COC(=O)C1=Cc1cccc1

Products:

1. C=CC(C)C(c1cccc1)C1C(=O)OCC1C=C

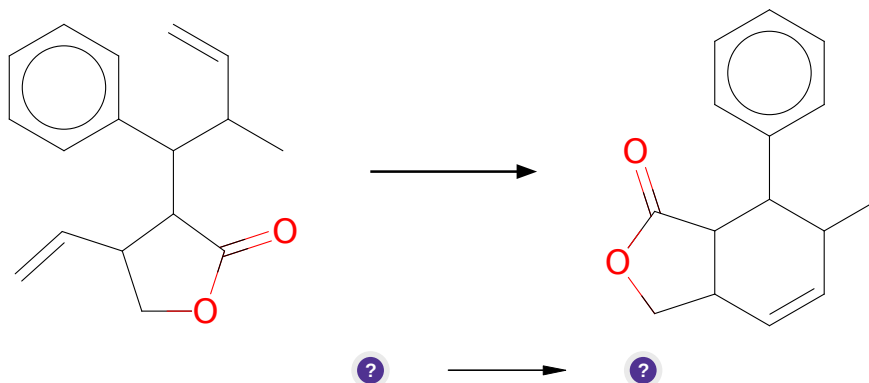
Typical conditions: 1.CuCN.LiCl.2.Eletrophile.3.NH₄Cl

Protections: none

Reference: [10.3891/acta.chem.scand.24-3490](#) AND [10.1016/S0040-4020\(01\)92354-3](#) AND [10.1016/j.tet.2011.12.046](#) AND [10.1016/S0040-4039\(02\)01713-6](#)

Retrosynthesis ID: 10003575

2.5.3 Ring-Closing Metathesis



Substrates:

1. C=CC(C)C(c1ccccc1)C1C(=O)OCC1C=C

Products:

1. CC1C=CC2COC(=O)C2C1c1ccccc1

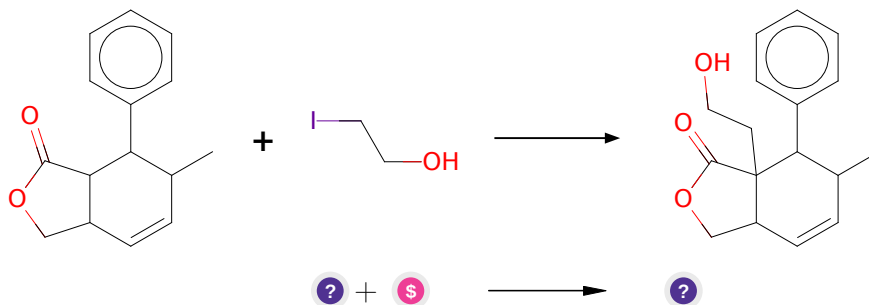
Typical conditions: catalyst e.g. Hoveyda-Grubbs . solvent e.g. CH₂Cl₂

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

2.5.4 Alkylation of Esters



Substrates:

1. CC1C=CC2COC(=O)C2C1c1ccccc1
2. 2-Iodoethanol - *available at Sigma-Aldrich*

Products:

1. CC1C=CC2COC(=O)C2(CCO)C1c1ccccc1

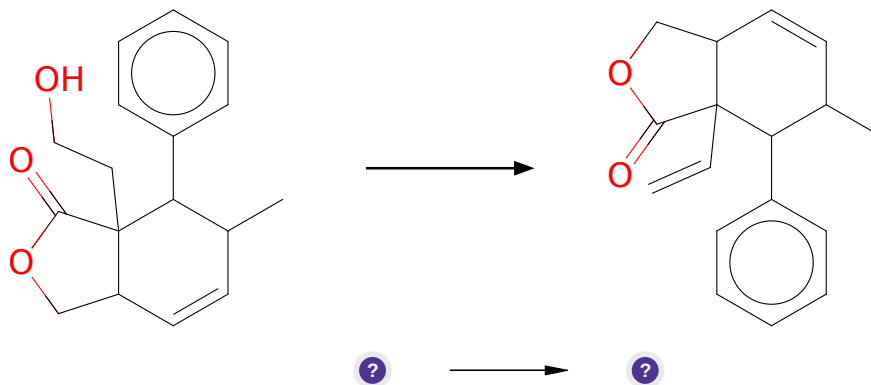
Typical conditions: base e.g. BuLi.THF

Protections: none

Reference: [10.1021/ja065404r](#) and [10.1016/S0040-4020\(01\)88337-X](#)

Retrosynthesis ID: 31017056

2.5.5 Synthesis of alkenes from alcohols



Substrates:

1. CC1C=CC2COC(=O)C2(CCO)C1c1ccccc1

Products:

1. C=CC12C(=O)OCC1C=CC(C)C2c1ccccc1

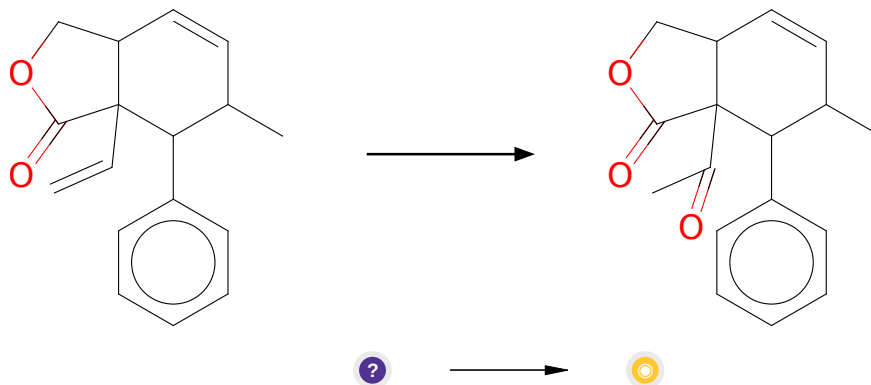
Typical conditions: PhSeCN.PBu3.THF then H2O2.THF.H2O

Protections: none

Reference: [10.1016/j.tet.2011.05.034](#) and [10.1055/s-0036-1588104](#) and [10.1002/anie.200501760](#) and [10.1002/anie.200700854](#) and [10.1002/asia.201301248](#) and [10.1021/ol501095w](#)

Retrosynthesis ID: 31010457

2.5.6 Wacker-Tsuji Olefin oxidation



Substrates:

1. C=CC12C(=O)OCC1C=CC(C)C2c1ccccc1

Products:

1. CC(=O)C12C(=O)OCC1C=CC(C)C2c1ccccc1

Typical conditions: PdCl₂.CuCl₂.H₂O.DMSO.O₂

Protections: none

Reference: [10.1021/ja043203m](#) and [10.1002/anie.200502886](#)
and [10.1021/acs.joc.6b00137](#) and [10.1016/j.tet.2013.07.048](#) and
[10.1002/1521-3773\(20011001\)40:19<3675::AID-ANIE3675>3.0.CO;2-G](#) and
[10.1002/cctc.201500241](#) and [10.1016/j.tetlet.2013.01.082](#)

Retrosynthesis ID: 26291