

Paths of analysis*

BMK1

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.

JSON Parameters: $\{\}$

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

Score: 269.29

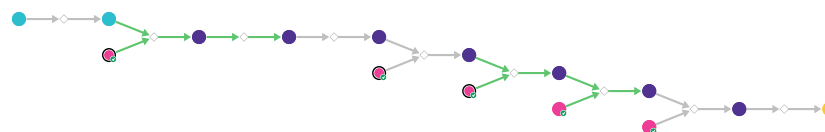


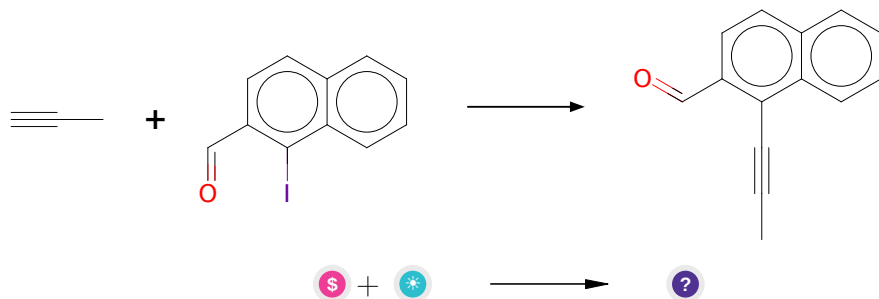
Figure 1: Outline of path 1

Protections: none

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

Retrosynthesis ID: 50426

2.1.2 Sonogashira Coupling



Substrates:

1. Propyne - [available at Sigma-Aldrich](#)
2. 1-iodo-2-naphthalenecarboxaldehyde

Products:

1. CC#Cc1c(C=O)ccc2ccccc12

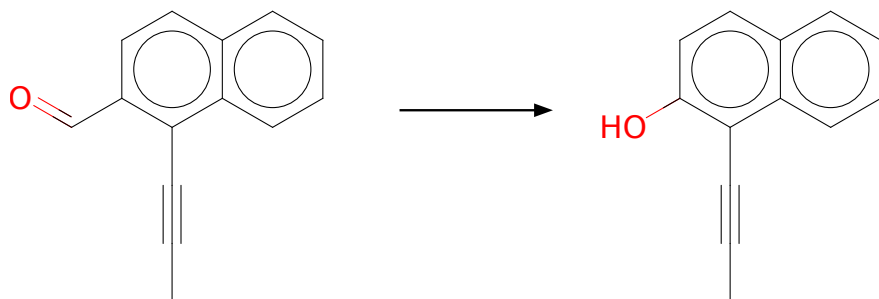
Typical conditions: [Pd] catalyst.CuI.R3N

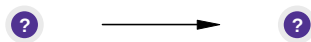
Protections: none

Reference: [10.1021/jo0057250](https://doi.org/10.1021/jo0057250) AND [10.1002/1521-3765\(20011203\)7:23<5118::AID-CHEM5118>3.0.CO;2-1](https://doi.org/10.1002/1521-3765(20011203)7:23<5118::AID-CHEM5118>3.0.CO;2-1) AND [10.1039/C3OB41798K](https://doi.org/10.1039/C3OB41798K) AND [10.1021/jm401395s](https://doi.org/10.1021/jm401395s)

Retrosynthesis ID: 10900

2.1.3 Oxidation of arylaldehydes to phenols/hydroxyheteroaryls via formates





Substrates:

1. CC#Cc1c(C=O)ccc2ccccc12

Products:

1. CC#Cc1c(O)ccc2ccccc12

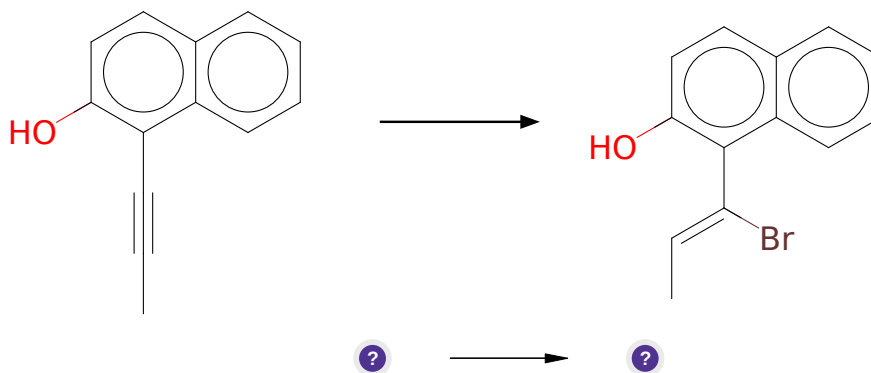
Typical conditions: H₂O₂ or mCPBA

Protections: none

Reference: [10.1021/jm034007d](#) and [10.1016/j.tet.2016.05.073](#) And [10.1039/b901358j](#) and [10.1039/c1cc11253h](#) and [10.1016/j.bmc.2012.02.005](#) And [10.1021/acs.jmedchem.5b00217](#) and [10.1248/cpb.c12-00725](#)

Retrosynthesis ID: 26287

2.1.4 Addition of HBr to alkynes



Substrates:

1. CC#Cc1c(O)ccc2ccccc12

Products:

1. C/C=C(\Br)c1c(O)ccc2ccccc12

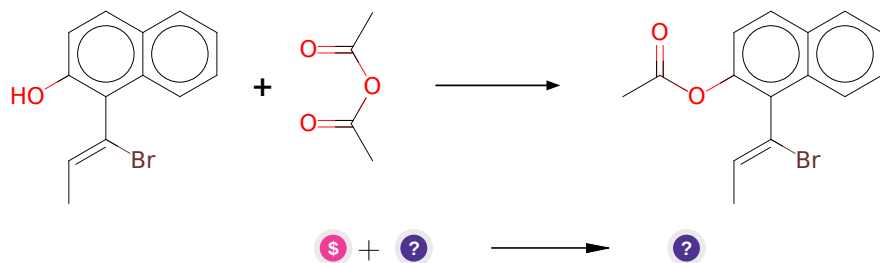
Typical conditions: HBr.Al₂O₃.DCM

Protections: none

Reference: [10.1021/ja00176a075](#)

Retrosynthesis ID: 7693

2.1.5 Cu(OTf)₂ catalyzed acylation of phenols



Substrates:

1. Acetic anhydride - *available at Sigma-Aldrich*
2. C/C=C(\Br)c1c(O)ccc2ccccc12

Products:

1. C/C=C(\Br)c1c(OC(C)=O)ccc2ccccc12

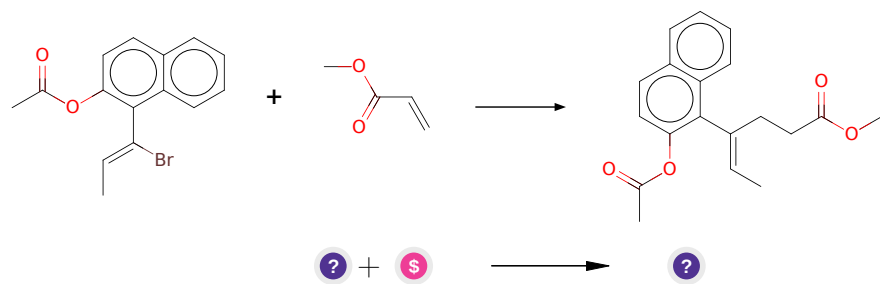
Typical conditions: Cu(II).triflate.DCM.RT

Protections: none

Reference: DOI: [10.1016/S0040-4020\(01\)01229-7](https://doi.org/10.1016/S0040-4020(01)01229-7)

Retrosynthesis ID: 11601

2.1.6 Suzuki alkyl-vinyl coupling



Substrates:

1. C/C=C(\Br)c1c(OC(C)=O)ccc2ccccc12
2. Methyl acrylate - *available at Sigma-Aldrich*

Products:

1. C/C=C(\CCC(=O)OC)c1c(OC(C)=O)ccc2ccccc12

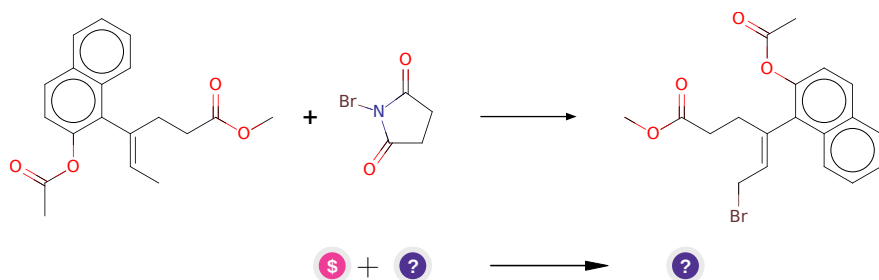
Typical conditions: 1. 9BBN-H. or. PinB-Bpin. Cu. 2. [Pd]. Ligand. Base

Protections: none

Reference: [10.1002/1521-3773\(20011217\)40:24<4544::AID-ANIE4544>3.0.CO;2-N](#) and [10.1021/ol300575d](#)

Retrosynthesis ID: 10034492

2.1.7 Wohl-Ziegler Bromination



Substrates:

1. N-Bromosuccinimide - [available at Sigma-Aldrich](#)
2. C/C=C(\CCC(=O)OC)c1c(OC(C)=O)ccc2ccccc12

Products:

1. COC(=O)CC/C(=C\CBr)c1c(OC(C)=O)ccc2ccccc12

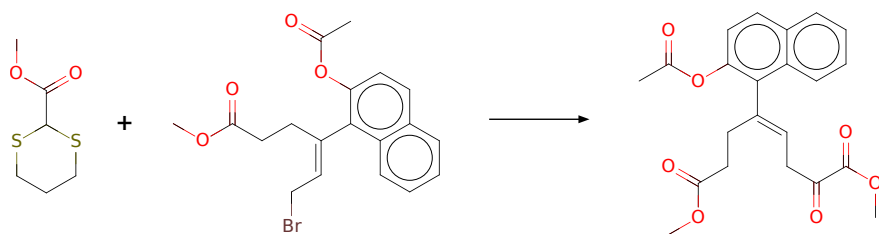
Typical conditions: NBS.AIBN or (BzO)₂ or heat

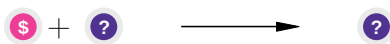
Protections: none

Reference: [10.1016/j.steroids.2018.10.005](#) (Scheme 1) and [10.1016/j.bmc.2010.06.075](#) (Scheme 2) and [10.1021/acs.orglett.9b03865](#) (p. SI 6)

Retrosynthesis ID: 245554

2.1.8 Corey-Seebach





Substrates:

1. methyl 1,3-dithiane-2-carboxylate - *available at Sigma-Aldrich*
2. COC(=O)CC/C(=C\CBr)c1c(OC(C)=O)ccc2ccccc12

Products:

1. COC(=O)CC/C(=C\CC(=O)C(=O)OC)c1c(OC(C)=O)ccc2ccccc12

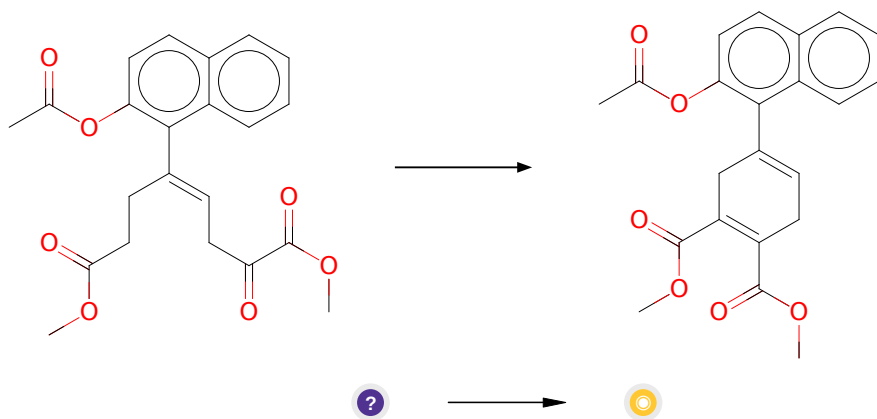
Typical conditions: 1.BuLi.TMEDA.2.TCCA

Protections: none

Reference: [10.1039/P19860000183](#) AND [10.1016/S0040-4020\(01\)85646-5](#) AND [10.1039/c5ob00638d](#) deprotection: [10.1016/j.tetlet.2006.06.131](#)

Retrosynthesis ID: 15272

2.1.9 Addition of enolate anion to 1,2-dicarbonyl compounds followed by dehydration



Substrates:

1. COC(=O)CC/C(=C\CC(=O)C(=O)OC)c1c(OC(C)=O)ccc2ccccc12

Products:

1. COC(=O)C1=C(C(=O)OC)CC(c2c(OC(C)=O)ccc3ccccc23)=CC1

Typical conditions: TiCl₄.NEt₃.

Protections: none

Reference: [10.1016/j.tet.2014.12.099](https://doi.org/10.1016/j.tet.2014.12.099) AND [10.1021/ol403461b](https://doi.org/10.1021/ol403461b) AND [10.1016/0040-4039\(96\)01843-6](https://doi.org/10.1016/0040-4039(96)01843-6) AND [10.1016/S0968-0896\(99\)00312-0](https://doi.org/10.1016/S0968-0896(99)00312-0)

Retrosynthesis ID: 14990

2.2 Path 2

Score: 269.29

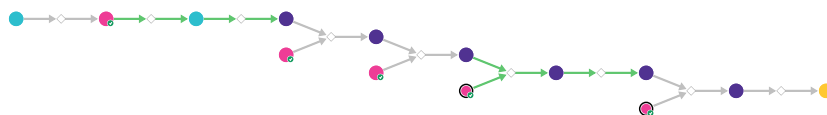
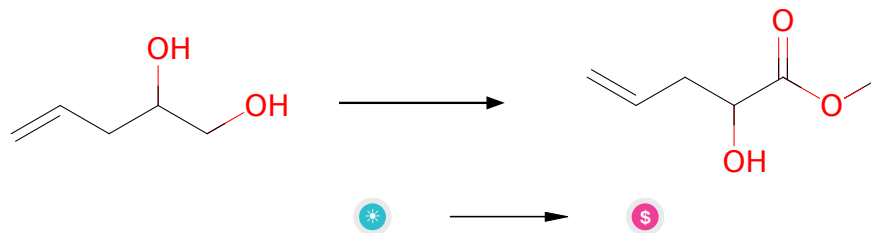


Figure 2: Outline of path 2

2.2.1 Tandem oxidation-esterification



Substrates:

1. 4-penten-1,2-diol

Products:

1. methyl 2-hydroxypent-4-enoate - *available at Sigma-Aldrich*

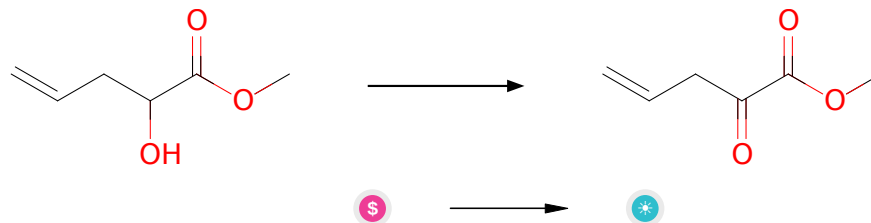
Typical conditions: Oxidant (eg. I2.K2CO3 or Ca(OCl)2).MeOH

Protections: none

Reference: [10.1016/S0040-4039\(00\)73550-7](https://doi.org/10.1016/S0040-4039(00)73550-7) and [10.1016/j.tet.2005.03.097](https://doi.org/10.1016/j.tet.2005.03.097) and [10.1021/ol062940f](https://doi.org/10.1021/ol062940f)

Retrosynthesis ID: 25234

2.2.2 PDC oxidation of secondary alcohols



Substrates:

1. methyl 2-hydroxypent-4-enoate - *available at Sigma-Aldrich*

Products:

1. C₆H₈O₃

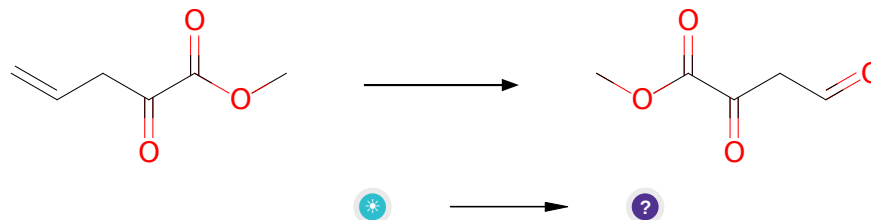
Typical conditions: PDC.DCM.0-25 C

Protections: none

Reference: [10.1016/j.bmc.2014.07.031](#) p. 5468, 5471 and [10.1016/j.bmc.2016.09.004](#) p. 5483, 5487

Retrosynthesis ID: 50447

2.2.3 Ozonolysis



Substrates:

1. C₆H₈O₃

Products:

1. COC(=O)C(=O)CC=O

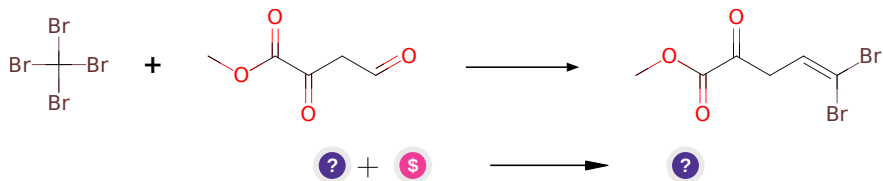
Typical conditions: O₃.MeOH.CH₂Cl₂.PPh₃ or Me₂S.low temperature

Protections: none

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

Retrosynthesis ID: 5074

2.2.4 Ramirez-Corey-Fuchs gem-dibromoolefination



Substrates:

1. COC(=O)C(=O)CC=O
2. Tetrabromomethane - *available at Sigma-Aldrich*

Products:

1. COC(=O)C(=O)CC=C(Br)Br

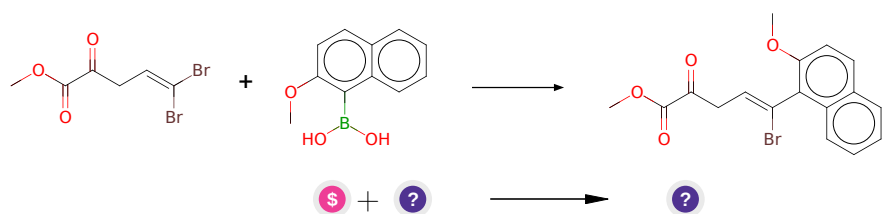
Typical conditions: PPh₃.DCM.0-20 C

Protections: none

Reference: [10.1016/j.bmc.2017.07.043](https://doi.org/10.1016/j.bmc.2017.07.043) p. 5315, 5323 and [10.1016/j.bmc.2014.05.011](https://doi.org/10.1016/j.bmc.2014.05.011) p. 3659, 3666

Retrosynthesis ID: 9900008

2.2.5 Suzuki coupling of arylboronic acids with 1,1-dibromoethenes



Substrates:

1. 1-(2-Methoxynaphthyl)boronic acid - *available at Sigma-Aldrich*
2. COC(=O)C(=O)CC=C(Br)Br

Products:

1. COC(=O)C(=O)C/C=C(\Br)c1c(OC)ccc2ccccc12

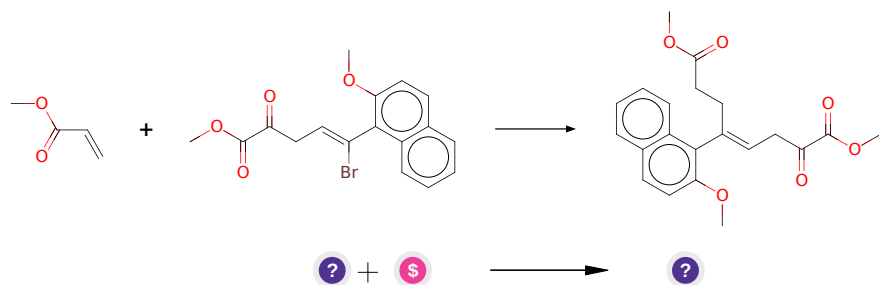
Typical conditions: Pd catalyst.base.solvent

Protections: none

Reference: [10.1055/s-0035-1561404](#) (SI) and [10.1002/ejoc.201100849](#) and [10.1039/c4cc00345d](#) and [10.1021/ol100844v](#) and [10.1039/c2ob06852d](#) and [10.1002/adsc.200505484](#)

Retrosynthesis ID: 25114

2.2.6 Suzuki alkyl-vinyl coupling



Substrates:

1. COC(=O)C(=O)C/C=C(\Br)c1c(OC)ccc2ccccc12
2. Methyl acrylate - *available at Sigma-Aldrich*

Products:

1. COC(=O)CC/C(=C\CC(=O)C(=O)OC)c1c(OC)ccc2ccccc12

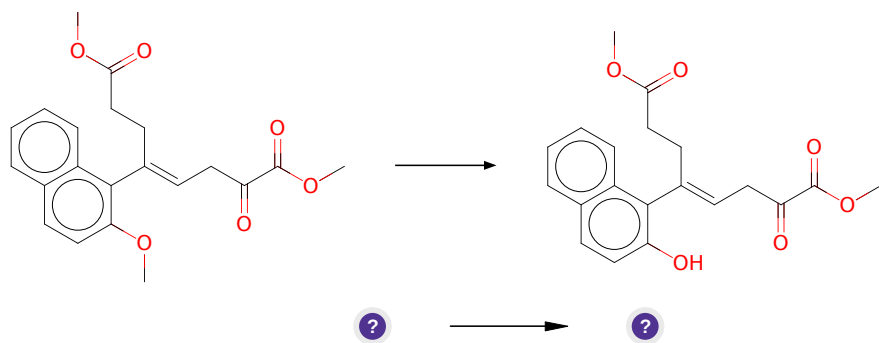
Typical conditions: 1. 9BBN-H. or. PinB-Bpin. Cu. 2. [Pd]. Ligand. Base

Protections: none

Reference: [10.1002/1521-3773\(20011217\)40:24<4544::AID-ANIE4544>3.0.CO;2-N](#) and [10.1021/ol300575d](#)

Retrosynthesis ID: 10034492

2.2.7 Demethylation of Phenols



Substrates:

1. COC(=O)CC/C(=C\CC(=O)C(=O)OC)c1c(OC)ccc2ccccc12

Products:

1. COC(=O)CC/C(=C\CC(=O)C(=O)OC)c1c(O)ccc2ccccc12

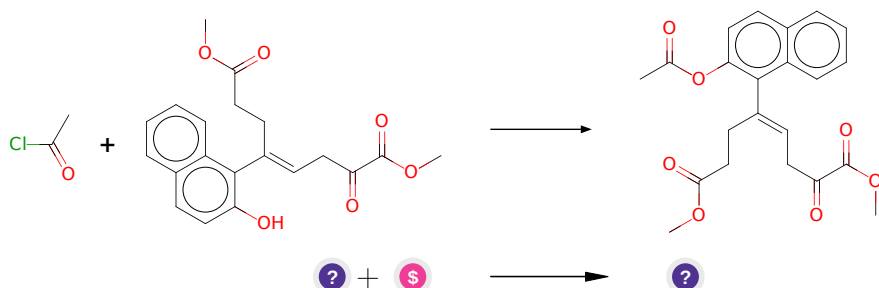
Typical conditions: BBr₃.CH₂Cl₂

Protections: none

Reference: DOI: [10.1021/ja00105a021](https://doi.org/10.1021/ja00105a021) and [10.1021/jm00176a011](https://doi.org/10.1021/jm00176a011) and [10.1021/jm970277i](https://doi.org/10.1021/jm970277i) and [10.1021/ja0106164](https://doi.org/10.1021/ja0106164) and Patent: US2010/16298, 2010, A1, page 185

Retrosynthesis ID: 10011837

2.2.8 Reaction of acyl chlorides with alcohols and phenols



Substrates:

1. COC(=O)CC/C(=C\CC(=O)C(=O)OC)c1c(O)ccc2ccccc12
2. Acetyl chloride - [available at Sigma-Aldrich](#)

Products:

1. COC(=O)CC/C(=C\CC(=O)C(=O)OC)c1c(OC(C)=O)ccc2ccccc12

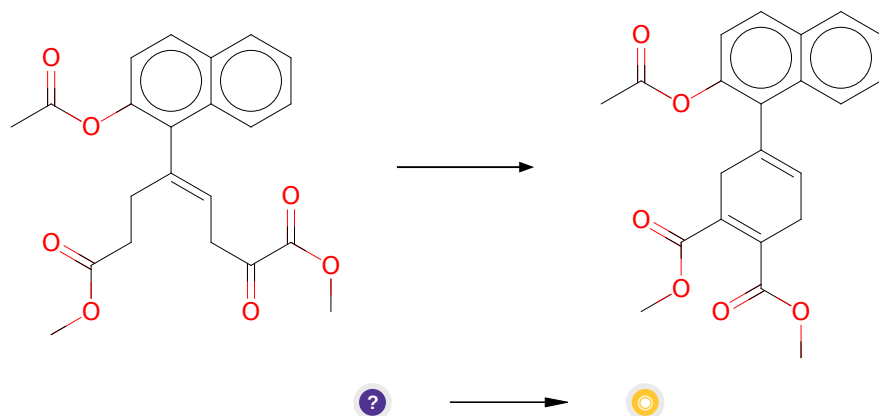
Typical conditions: base.DCM

Protections: none

Reference: [10.1016/j.bmcl.2012.03.021](https://doi.org/10.1016/j.bmcl.2012.03.021) AND [10.1021/ja026266i](https://doi.org/10.1021/ja026266i) (SI, hydroperoxides) AND [10.1016/j.tetasy.2004.07.044](https://doi.org/10.1016/j.tetasy.2004.07.044) AND [10.1021/jm1006929](https://doi.org/10.1021/jm1006929) (SI) AND [10.1016/j.tet.2011.05.017](https://doi.org/10.1016/j.tet.2011.05.017) AND [10.1016/j.tetasy.2012.09.002](https://doi.org/10.1016/j.tetasy.2012.09.002) AND [10.1021/ol016268s](https://doi.org/10.1021/ol016268s) (SI) AND [10.1021/jo801116n](https://doi.org/10.1021/jo801116n) AND [10.1021/jo00279a041](https://doi.org/10.1021/jo00279a041) AND WO2013/64518 A1, 2013 (page 102)

Retrosynthesis ID: 28549

2.2.9 Addition of enolate anion to 1,2-dicarbonyl compounds followed by dehydration



Substrates:

1. COC(=O)CC/C(=C\CC(=O)C(=O)OC)c1c(OC(C)=O)ccc2ccccc12

Products:

1. COC(=O)C1=C(C(=O)OC)CC(c2c(OC(C)=O)ccc3ccccc23)=CC1

Typical conditions: TiCl₄.NEt₃.

Protections: none

Reference: [10.1016/j.tet.2014.12.099](#) AND [10.1021/ol403461b](#) AND [10.1016/0040-4039\(96\)01843-6](#) AND [10.1016/S0968-0896\(99\)00312-0](#)

Retrosynthesis ID: 14990

2.3 Path 3

Score: 272.19

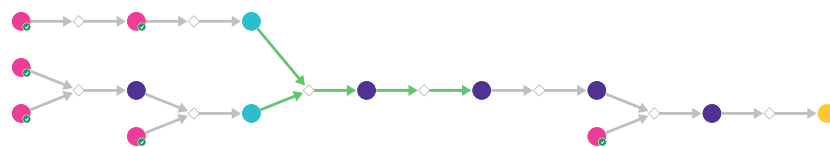
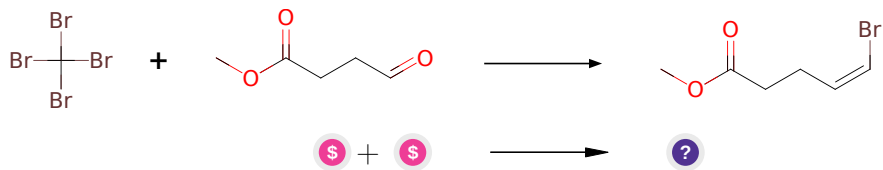


Figure 3: Outline of path 3

2.3.1 Synthesis of Z-bromoalkenes



Substrates:

1. Methyl 4-oxobutanoate - *available at Sigma-Aldrich*
2. Tetrabromomethane - *available at Sigma-Aldrich*

Products:

1. COC(=O)CC/C=C\Br

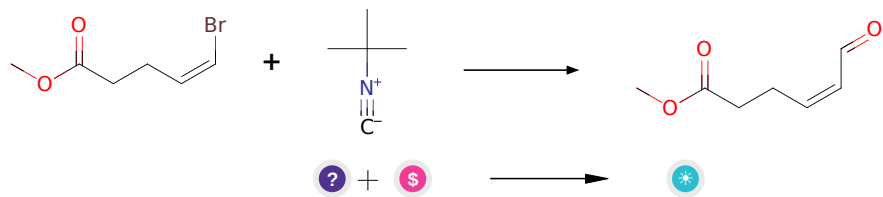
Typical conditions: 1. CBr₄.Ph₃P.TEA.THF.cooling to rt. 2. nBu₃SnH.Pd(PPh₃)₄.toluene.rt

Protections: none

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

Retrosynthesis ID: 10001762

2.3.2 Pd-catalyzed formylation of vinyl halides



Substrates:

1. COC(=O)CC/C=C\Br
2. tert-Butyl isocyanide - *available at Sigma-Aldrich*

Products:

1. methyl 6-oxo-4(z)-hexenoate

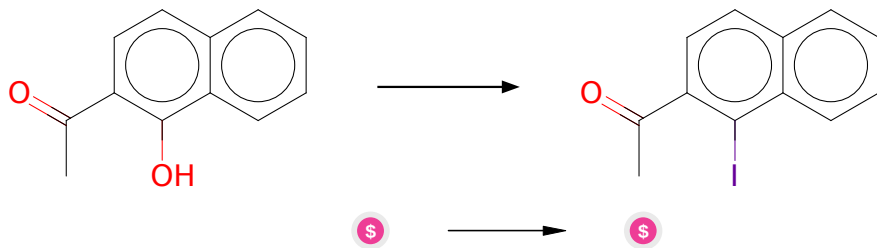
Typical conditions: Pd(OAc)₂.JohnPhos.Na₂CO₃.H₂O.Et₃SiH.DMF.65°C

Protections: none

Reference: DOI: [10.1021/ol5014262](https://doi.org/10.1021/ol5014262)

Retrosynthesis ID: 3104

2.3.3 Synthesis of haloarenes via triflates



Substrates:

1. 2-Acetyl-1-naphthol - *available at Sigma-Aldrich*

Products:

1. 1-(1-iodonaphthalen-2-yl)ethan-1-one - *available at Sigma-Aldrich*

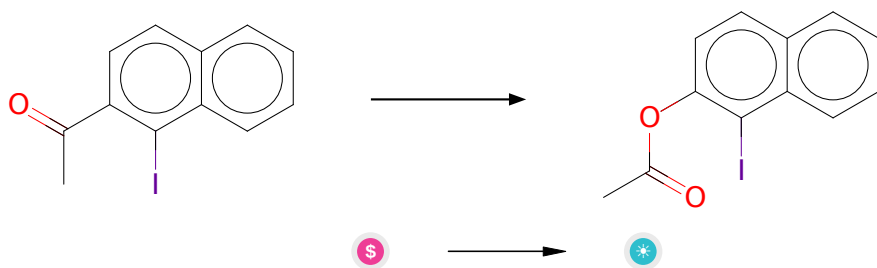
Typical conditions: 1. Tf₂O 2. [Pd].MX

Protections: none

Reference: [10.1016/j.tetasy.2012.04.008](#) and WO2007/136577 (p46) and [10.1021/ol202098h](#) and [10.1021/ol402859k](#) and [10.1021/jacs.5b09308](#)

Retrosynthesis ID: 23940

2.3.4 Bayer-Villiger oxidation



Substrates:

1. 1-(1-iodonaphthalen-2-yl)ethan-1-one - *available at Sigma-Aldrich*

Products:

1. acetic acid-(1-iodo-[2]naphthyl ester)

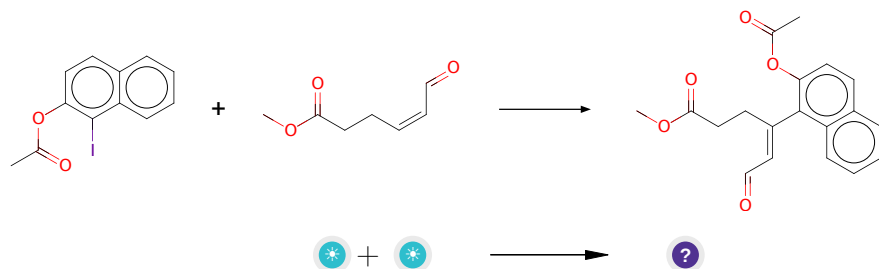
Typical conditions: mCPBA.NaHCO₃.DCM

Protections: none

Reference: [10.1021/ol702571c](#) and [10.1021/ja00272a051](#) and [10.1080/00397910801997835](#)

Retrosynthesis ID: 4811

2.3.5 Heck Reaction



Substrates:

1. acetic acid-(1-iodo-[2]naphthyl ester)
2. methyl 6-oxo-4(z)-hexenoate

Products:

1. COC(=O)CC/C(=C\C=O)c1c(OC(C)=O)ccc2ccccc12

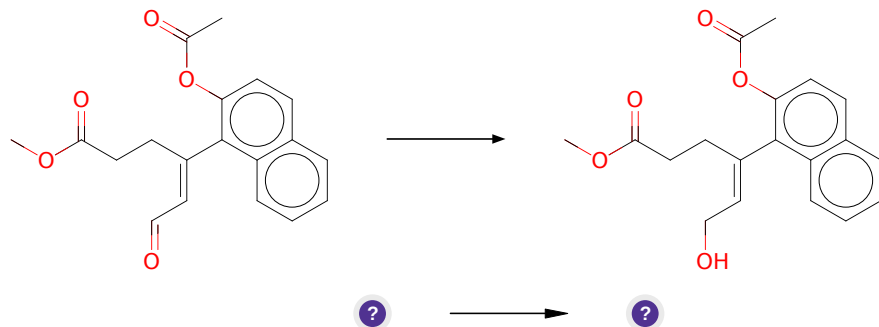
Typical conditions: Pd (cat). Ligand e.g. TXPTS. Base. Temp

Protections: none

Reference: [10.1016/j.tetlet.2013.01.077](#) or [10.1002/9780470716076](#) or [10.1016/j.tetlet.2010.08.057](#) or [10.1021/op050106k](#) or [10.1021/ol0360288](#) or [10.1021/ol702755g](#) or [10.1055/s-0033-1340319](#) or [10.1016/j.tet.2004.10.049](#)

Retrosynthesis ID: 9189

2.3.6 Reduction of aldehydes with NaBH₄



Substrates:

1. COC(=O)CC/C(=C\C=O)c1c(OC(C)=O)ccc2ccccc12

Products:

1. COC(=O)CC/C(=C\CO)c1c(OC(C)=O)ccc2ccccc12

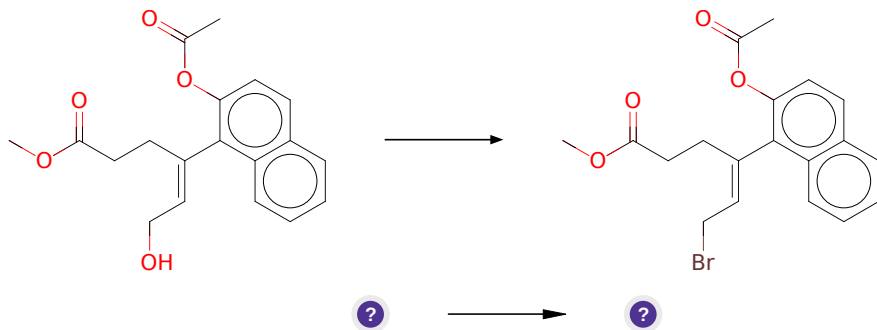
Typical conditions: NaBH₄.MeOH

Protections: none

Reference: [10.1016/j.ejmech.2012.07.010](#) p. 126, 128 and
[10.1016/j.bmc.2006.04.038](#) p. 5565, 5571

Retrosynthesis ID: 50431

2.3.7 Appel Reaction



Substrates:

1. COC(=O)CC/C(=C\CO)c1c(OC(C)=O)ccc2ccccc12

Products:

1. COC(=O)CC/C(=C\CBr)c1c(OC(C)=O)ccc2ccccc12

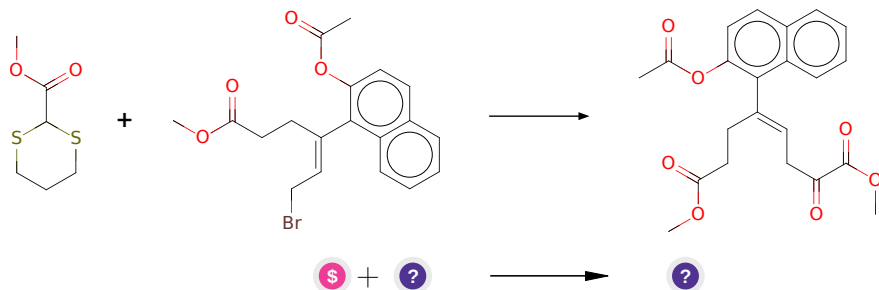
Typical conditions: PPh₃.CBr₄

Protections: none

Reference: [10.1021/ja800574m](#) and [10.1016/j.tet.2012.05.010](#) and
[10.1016/j.tet.2004.09.021](#) (experimental)

Retrosynthesis ID: 9990037

2.3.8 Corey-Seebach



Substrates:

1. methyl 1,3-dithiane-2-carboxylate - *available at Sigma-Aldrich*
2. COC(=O)CC/C(=C\CBr)c1c(OC(C)=O)ccc2ccccc12

Products:

1. COC(=O)CC/C(=C\CC(=O)C(=O)OC)c1c(OC(C)=O)ccc2ccccc12

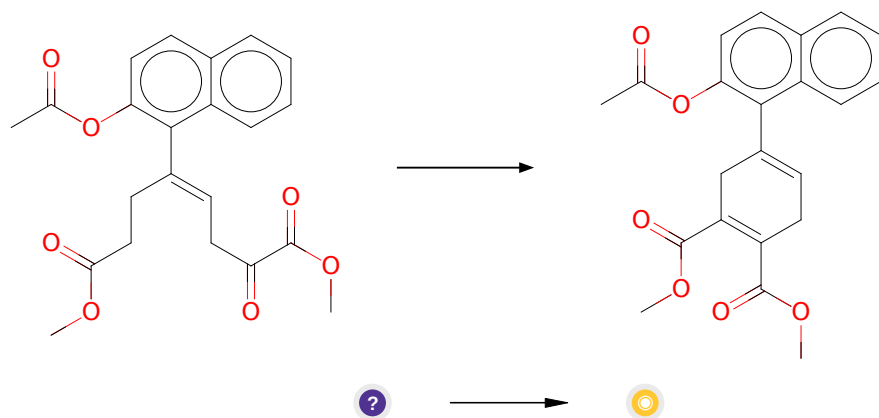
Typical conditions: 1. BuLi. TMEDA. 2. TCCA

Protections: none

Reference: [10.1039/P19860000183](#) AND [10.1016/S0040-4020\(01\)85646-5](#) AND [10.1039/c5ob00638d](#) deprotection: [10.1016/j.tetlet.2006.06.131](#)

Retrosynthesis ID: 15272

2.3.9 Addition of enolate anion to 1,2-dicarbonyl compounds followed by dehydration



Substrates:

1. COC(=O)CC/C(=C\CC(=O)C(=O)OC)c1c(OC(C)=O)ccc2ccccc12

Products:

1. COC(=O)C1=C(C(=O)OC)CC(c2c(OC(C)=O)ccc3ccccc23)=CC1

Typical conditions: TiCl₄.NEt₃.

Protections: none

Reference: [10.1016/j.tet.2014.12.099](#) AND [10.1021/ol403461b](#) AND
[10.1016/0040-4039\(96\)01843-6](#) AND [10.1016/S0968-0896\(99\)00312-0](#)

Retrosynthesis ID: 14990