

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.

Strategies: none selected

FGI Coeff: 0

Tunnels Coeff: 0

JSON Parameters: {}

2 Paths

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

2.1 Path 1

Score: 112.89

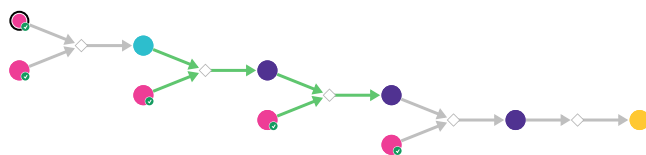
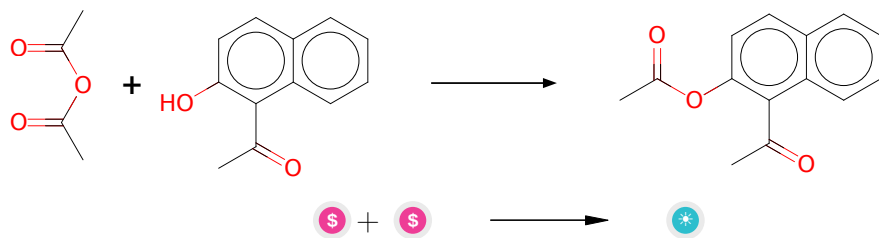


Figure 1: Outline of path 1

2.1.1 Cu(OTf)₂ catalyzed acylation of phenols



Substrates:

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

Products:

1. 1-(2-acetoxy-1-naphthyl)-ethanone

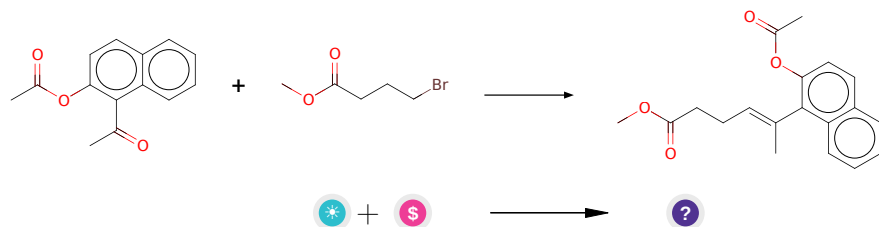
Typical conditions: Cu(II).triflate.DCM.RT

Protections: none

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

Retrosynthesis ID: 11601

2.1.2 HWE/Wittig Olefination



Substrates:

1. 1-(2-acetoxy-[1]naphthyl)-ethanone
2. Methyl 4-bromobutanoate - [available at Sigma-Aldrich](#)

Products:

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

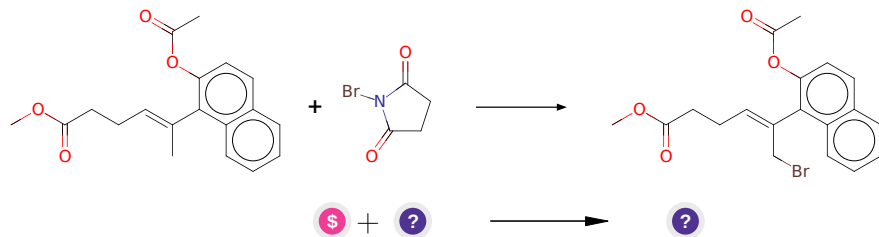
Typical conditions: 1.PPh₃ or trialkylphosphite.2.base.aldehyde

Protections: none

Reference: [10.1002/anie.200705005](https://doi.org/10.1002/anie.200705005) and [10.1021/ol052106a](https://doi.org/10.1021/ol052106a) and [10.1021/jo00075a064](https://doi.org/10.1021/jo00075a064) and [10.1021/ol3027297](https://doi.org/10.1021/ol3027297) and [10.1080/00397910008087436](https://doi.org/10.1080/00397910008087436)

Retrosynthesis ID: 9554

2.1.3 Wohl-Ziegler Bromination



Substrates:

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

Products:

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

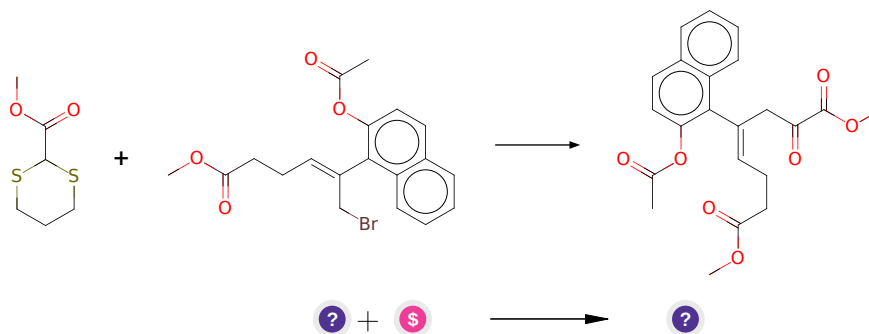
Typical conditions: NBS.AIBN or (BzO)₂ or heat

Protections: none

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

Retrosynthesis ID: 245554

2.1.4 Corey-Seebach



Substrates:

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

Products:

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

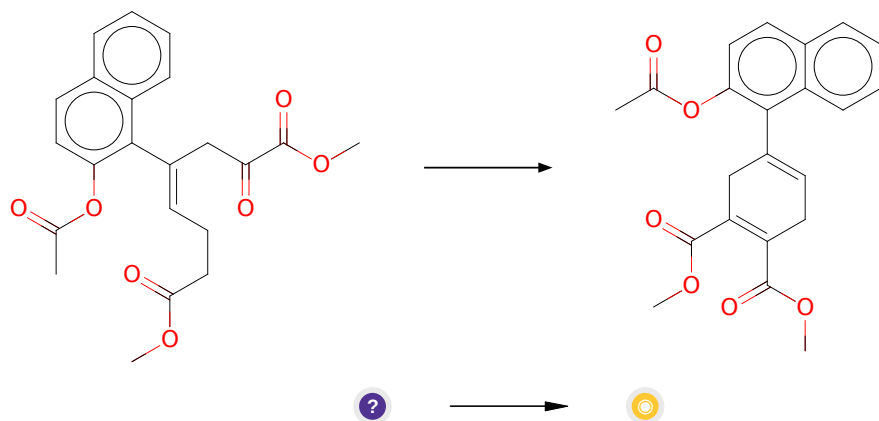
Typical conditions: 1.BuLi.TMEDA.2.TCCA

Protections: none

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

Retrosynthesis ID: 15272

2.1.5 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

2.2 Path 2

Score: 166.11

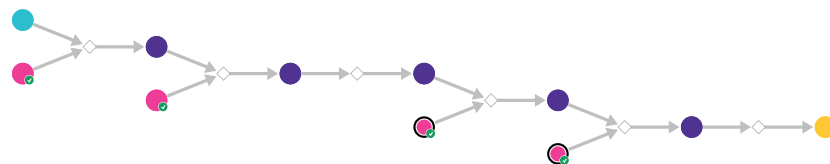
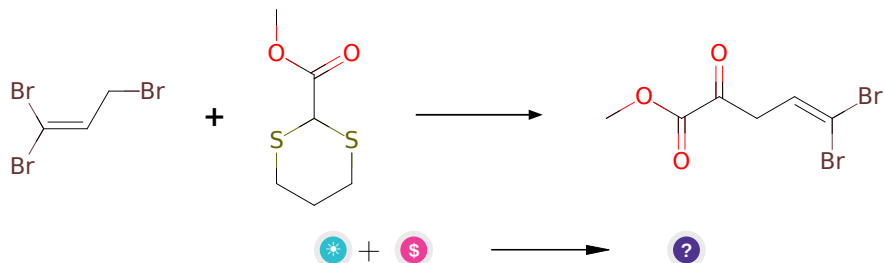


Figure 2: Outline of path 2

2.2.1 Corey-Seebach



Substrates:

- 1,1,3-tribromo-propene
- methyl 1,3-dithiane-2-carboxylate - *available at Sigma-Aldrich*

Products:

- COC(=O)C(=O)CC=C(Br)Br

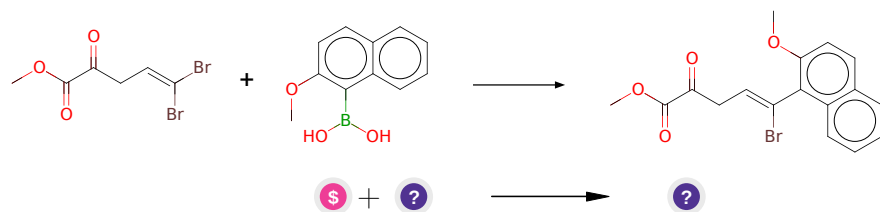
Typical conditions: 1. BuLi. TMEDA. 2. TCCA

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

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



Substrates:

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

Products:

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

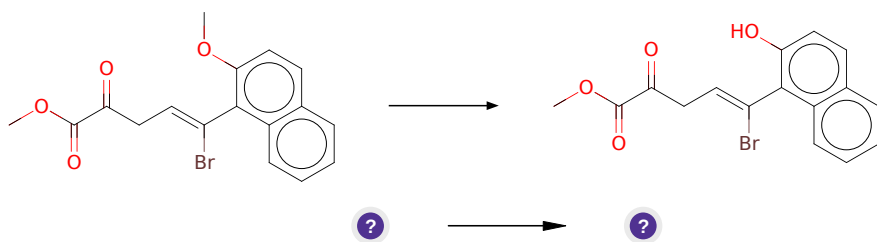
Typical conditions: Pd catalyst.base.solvent

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

2.2.3 Demethylation of Phenols



Substrates:

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

Products:

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

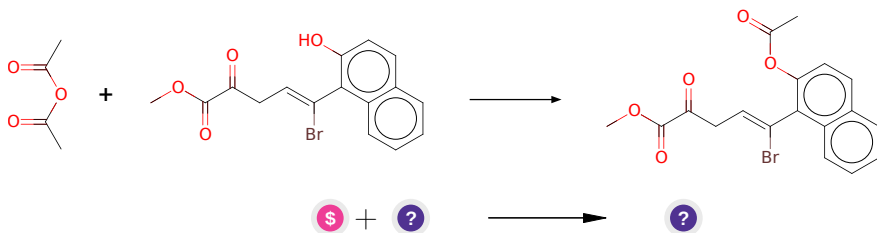
Typical conditions: BBr₃.CH₂Cl₂

Protections: none

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

Retrosynthesis ID: 10011837

2.2.4 Cu(OTf)₂ catalyzed acylation of phenols



Substrates:

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

Products:

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

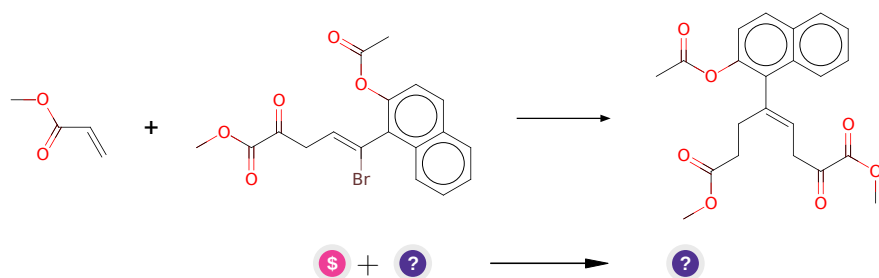
Typical conditions: Cu(II).triflate.DCM.RT

Protections: none

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

Retrosynthesis ID: 11601

2.2.5 Suzuki alkyl-vinyl coupling



Substrates:

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

Products:

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

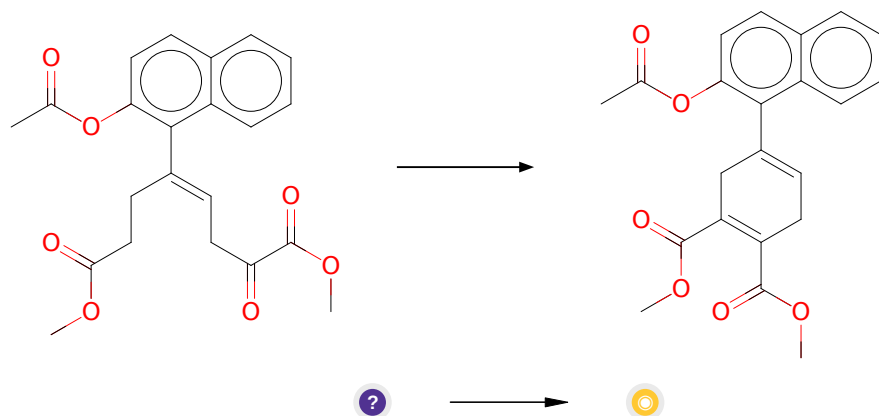
Typical conditions: 1. 9BBN-H. or. PinB-Bpin. Cu. 2. [Pd]. Ligand. Base

Protections: none

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

Retrosynthesis ID: 10034492

2.2.6 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

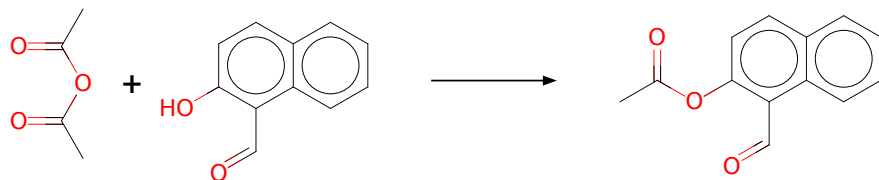
Reference: [10.1016/j.tet.2014.12.099](#) AND [10.1021/ol403461b](#) AND [10.1016/0040-4039\(96\)01843-6](#) AND [10.1016/S0968-0896\(99\)00312-0](#)

Retrosynthesis ID: 14990

2.3 Path 3

Score: 167.97

2.3.1 Cu(OTf)2 catalyzed acylation of phenols



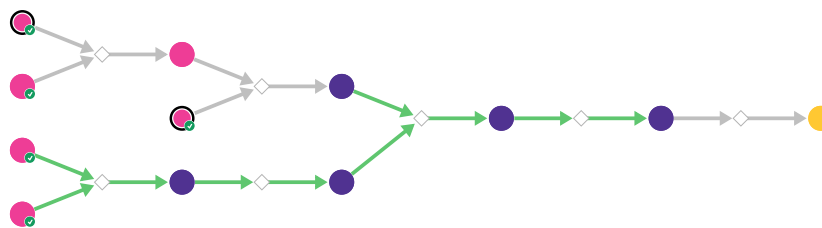
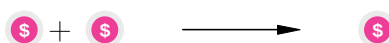


Figure 3: Outline of path 3



Substrates:

1. Acetic anhydride - *available at Sigma-Aldrich*
2. 2-Hydroxy-1-naphthaldehyde - *available at Sigma-Aldrich*

Products:

1. 1-formyl-2-naphthyl acetate - *ChemBridgeCorporation*

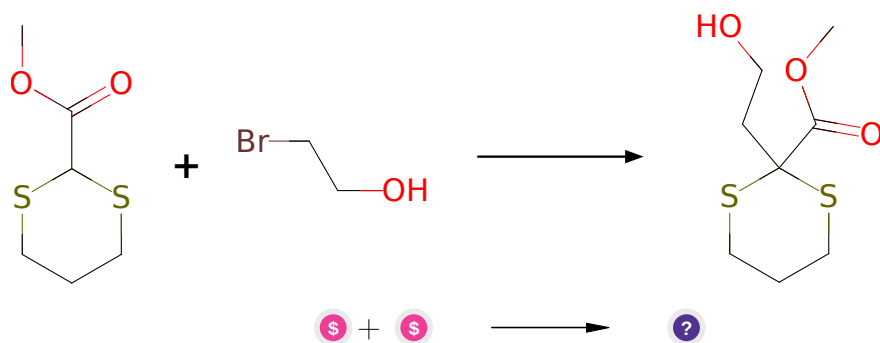
Typical conditions: Cu(II).triflate.DCM.RT

Protections: none

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

Retrosynthesis ID: 11601

2.3.2 Alkylation of thioacetals



Substrates:

1. 2-Bromoethanol - *available at Sigma-Aldrich*
2. methyl 1,3-dithiane-2-carboxylate - *available at Sigma-Aldrich*

Products:

1. COC(=O)C1(CCO)SCCCS1

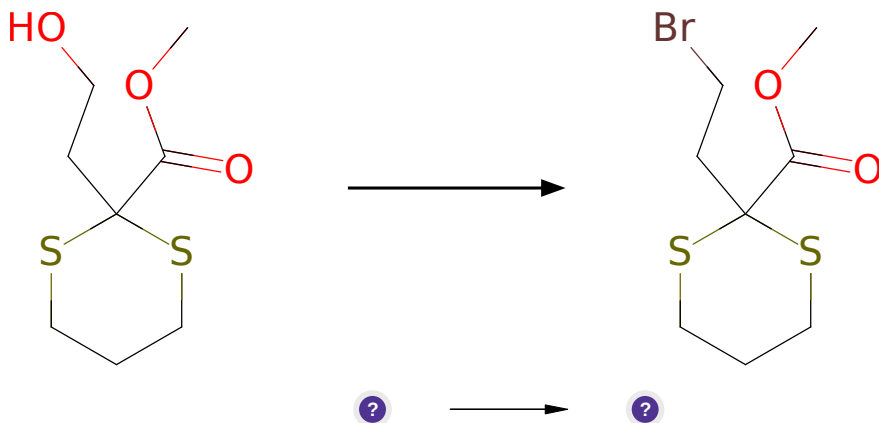
Typical conditions: BuLi.TMEDA

Protections: none

Reference: [10.1039/P19860000183](#) AND [10.1016/S0040-4020\(01\)85646-5](#) AND [10.1039/c5ob00638d](#) AND [10.1016/S0040-4020\(99\)00302-6](#)

Retrosynthesis ID: 15270

2.3.3 Appel Reaction



Substrates:

1. COC(=O)C1(CCO)SCCCS1

Products:

1. COC(=O)C1(CCB)SCCCS1

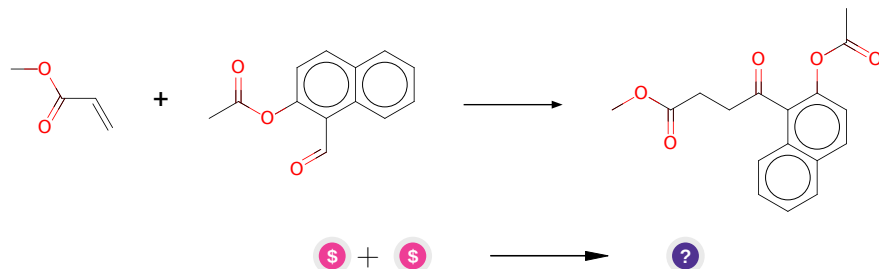
Typical conditions: PPh₃.CBr₄

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

2.3.4 Stetter reaction



Substrates:

1. 1-formyl-2-naphthyl acetate - [ChemBridgeCorporation](#)
2. Methyl acrylate - [available at Sigma-Aldrich](#)

Products:

1. COC(=O)CCC(=O)c1c(OC(C)=O)ccc2ccccc12

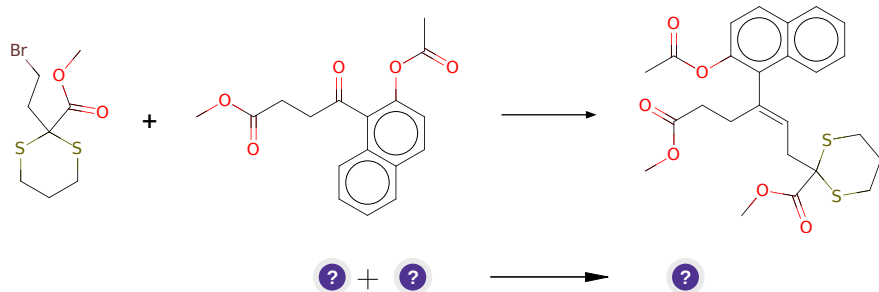
Typical conditions: NaCN.DMF or thiazolium-NHC.catalyst

Protections: none

Reference: [10.1002/0471264180.or040.04](#) and [10.1021/ja058337u](#) and [10.1021/ja805680z](#) and [10.1002/anie.200301702](#)

Retrosynthesis ID: 23591

2.3.5 HWE/Wittig Olefination



Substrates:

1. COC(=O)CCC(=O)c1c(OC(C)=O)ccc2ccccc12
2. COC(=O)C1(CCBr)SCCCS1

Products:

1. COC(=O)CC/C(=C\CC1(C(=O)OC)SCCCS1)c1c(OC(C)=O)ccc2ccccc12

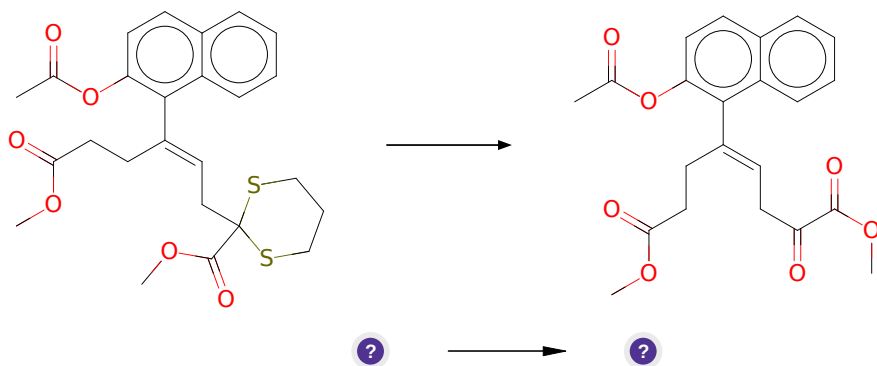
Typical conditions: 1.PPh₃ or trialkylphosphite.2.base.aldehyde

Protections: none

Reference: [10.1002/anie.200705005](#) and [10.1021/ol052106a](#) and [10.1021/jo00075a064](#) and [10.1021/ol3027297](#) and [10.1080/00397910008087436](#)

Retrosynthesis ID: 9554

2.3.6 Synthesis of ketones from dithianes



Substrates:

1. COC(=O)CC/C(=C\CC1(C(=O)OC)SCCCS1)c1c(OC(C)=O)ccc2ccccc12

Products:

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

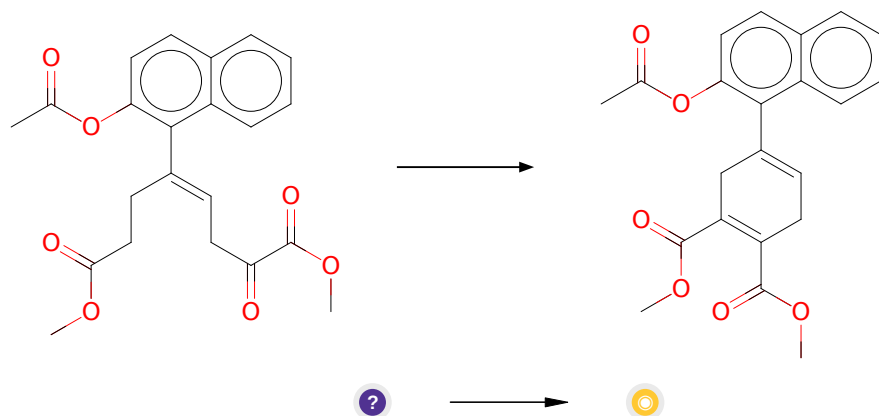
Typical conditions: MeI.CaCO₃

Protections: none

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

Retrosynthesis ID: 31724

2.3.7 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

2.4 Path 4

Score: 195.43

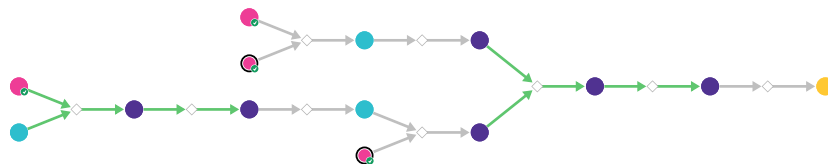
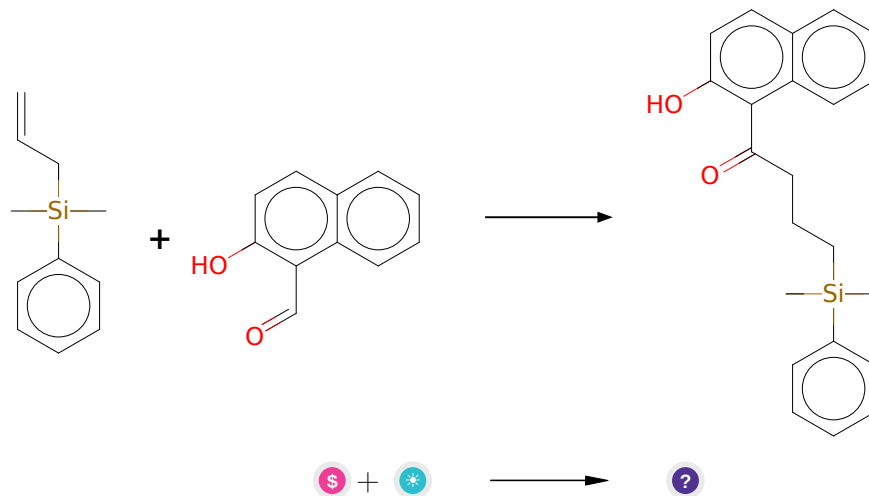


Figure 4: Outline of path 4

2.4.1 Hydroacylation of alkenes



Substrates:

1. 2-Hydroxy-1-naphthaldehyde - *available at Sigma-Aldrich*
2. allyl-dimethyl-phenyl-silane

Products:

1. C[Si](C)(CCCC(=O)c1c(O)ccc2ccccc12)c1ccccc1

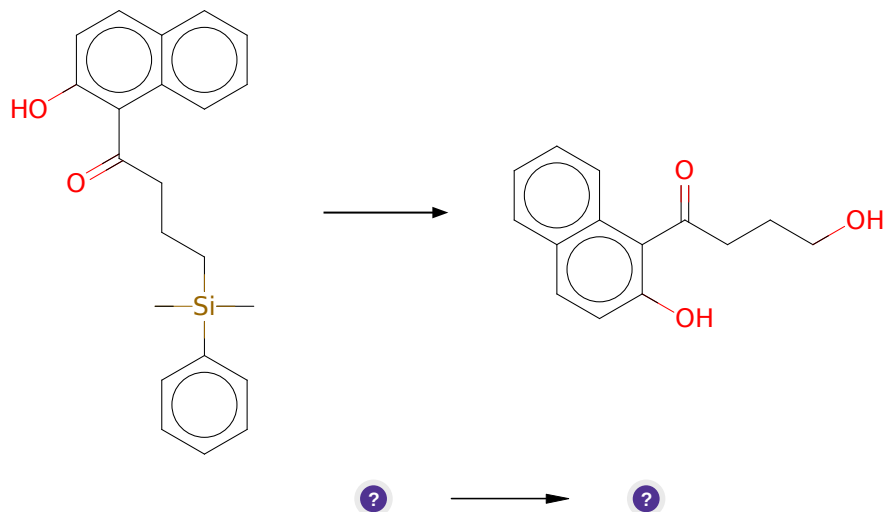
Typical conditions: [Rh].complex.ligand.K₃PO₄.DCE.heat

Protections: none

Reference: *10.1021/ja305593y*

Retrosynthesis ID: 10020500

2.4.2 Oxidation of silanes to alcohols



Substrates:

1. C[Si](C)(CCC(=O)c1c(O)ccc2ccccc12)c1ccccc1

Products:

1. O=C(CCCO)c1c(O)ccc2ccccc12

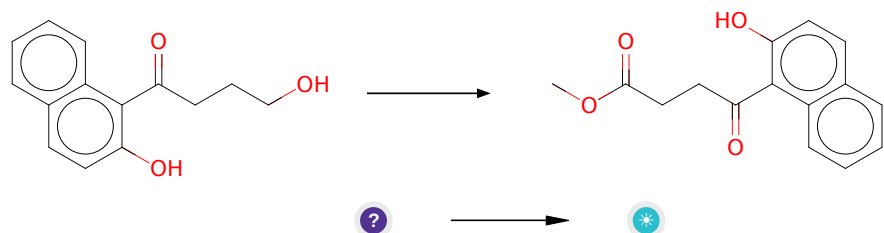
Typical conditions: KBr.AcONa.AcOH.AcOOH

Protections: none

Reference: [10.1016/j.tetlet.2010.10.089](#) and [10.1016/j.tetasy.2011.10.013](#) and [10.1021/ol0270881](#) and [10.1021/ol4033623](#) and [10.1002/anie.200460936](#) and [10.1021/ol201795w](#) and [10.1002/anie.200700841](#)

Retrosynthesis ID: 10012630

2.4.3 Tandem oxidation-esterification



Substrates:

1. O=C(CCCO)c1c(O)ccc2ccccc12

Products:

1. C15H14O4

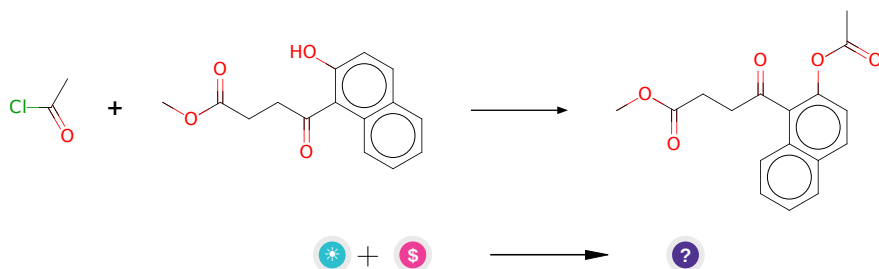
Typical conditions: Oxidant (eg. I2.K2CO3 or Ca(OCl)2).MeOH

Protections: none

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

Retrosynthesis ID: 25234

2.4.4 Reaction of acyl chlorides with alcohols and phenols



Substrates:

1. C15H14O4

2. Acetyl chloride - [available at Sigma-Aldrich](#)

Products:

1. COC(=O)CCC(=O)c1c(OC(C)=O)ccc2ccccc12

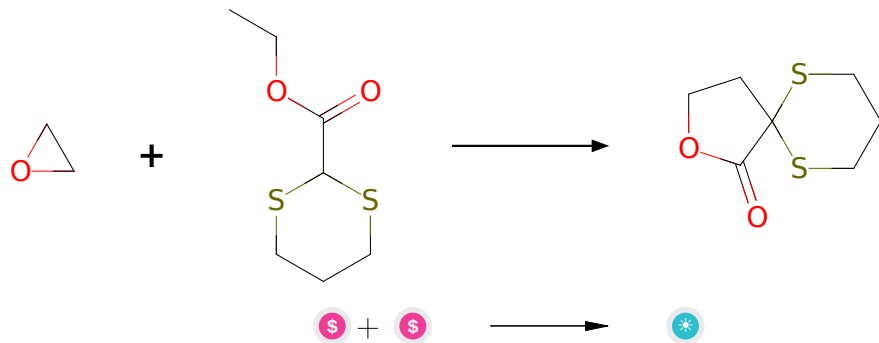
Typical conditions: base.DCM

Protections: none

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

Retrosynthesis ID: 28549

2.4.5 Synthesis of lactones from epoxides



Substrates:

1. Ethyl 1,3-dithiane-2-carboxylate - *available at Sigma-Aldrich*
2. Oxirane - *available at Sigma-Aldrich*

Products:

1. 2-oxa-6,10-dithia-spiro[4.5]decan-1-one

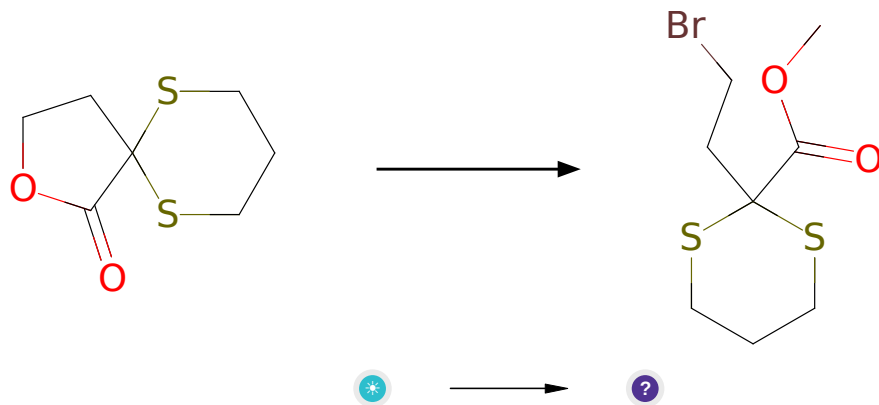
Typical conditions: EtONa.EtOH.rt

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: 21267

2.4.6 Opening of lactones via bromination



Substrates:

1. 2-oxa-6,10-dithia-spiro[4.5]decan-1-one

Products:

1. COC(=O)C1(CBr)SCCCS1

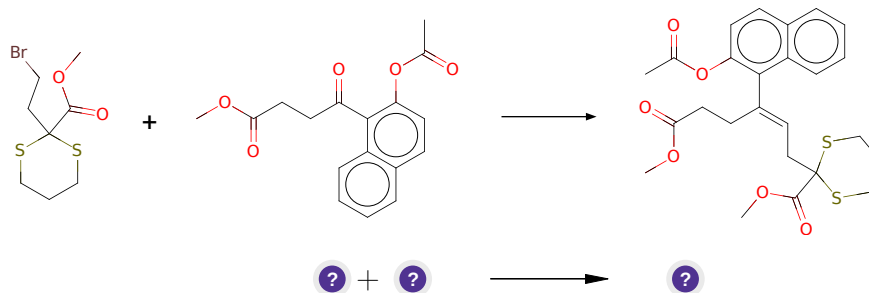
Typical conditions: TMSBr.EtOH.DCM

Protections: none

Reference: [10.1021/jo0709605](#)

Retrosynthesis ID: 24147

2.4.7 HWE/Wittig Olefination



Substrates:

1. COC(=O)CCC(=O)c1c(OC(C)=O)ccc2ccccc12
2. COC(=O)C1(CBr)SCCCS1

Products:

1. COC(=O)CC/C(=C\CC1(C(=O)OC)SCCCS1)c1c(OC(C)=O)ccc2ccccc12

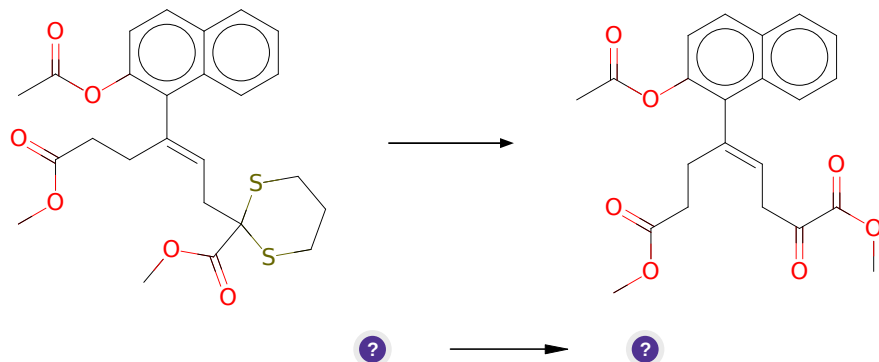
Typical conditions: 1.PPh₃ or trialkylphosphite.2.base.aldehyde

Protections: none

Reference: [10.1002/anie.200705005](#) and [10.1021/ol052106a](#) and [10.1021/jo00075a064](#) and [10.1021/ol3027297](#) and [10.1080/00397910008087436](#)

Retrosynthesis ID: 9554

2.4.8 Synthesis of ketones from dithianes



Substrates:

1. COC(=O)CC/C(=C\CC1(C(=O)OC)SCCCS1)c1c(OC(C)=O)ccc2ccccc12

Products:

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

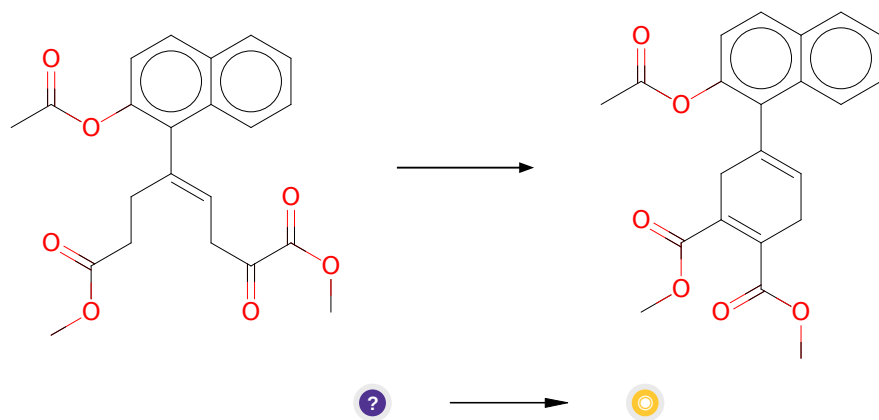
Typical conditions: MeI.CaCO₃

Protections: none

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

Retrosynthesis ID: 31724

2.4.9 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