Paths of analysis*
L9

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+1000 000*(CONFLICT+NON_SELECTIVITY+FILTERS+PROTECT)

Chemical scoring formula: SMALLER^ 3,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.

1

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.*
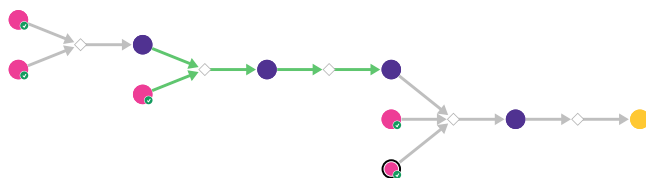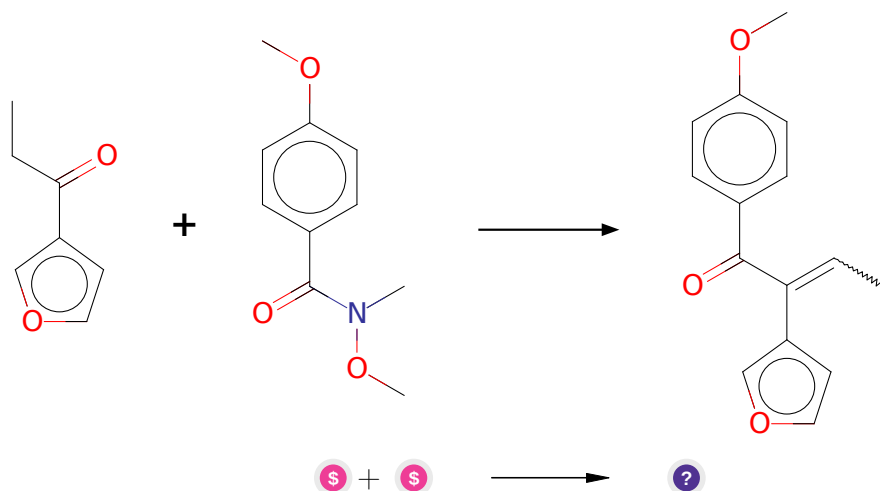
2.1   Path 1

Score: 132.89

Figure 1: Outline of path 1

2.1.1   Shapiro reaction followed by reaction with weinreb's amide

Substrates:

1. N,4-Dimethoxy-N-methylbenzamide - *available at Sigma-Aldrich*

2. 1-(furan-3-yl)propan-1-one - *available at Sigma-Aldrich*

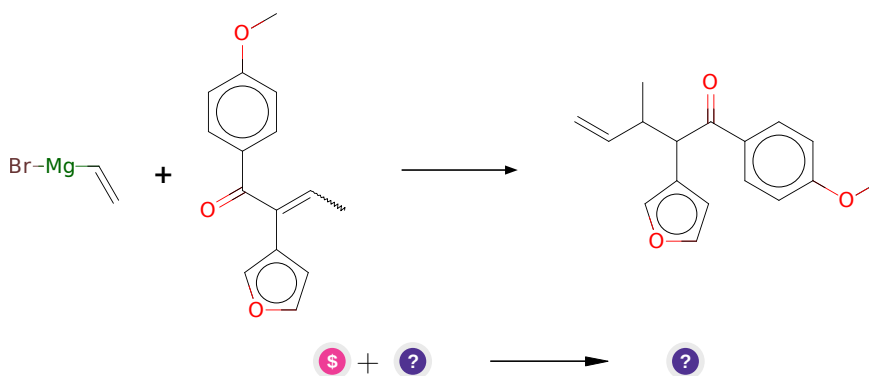**Products:**

1. CC=C(C(=O)c1ccc(OC)cc1)c1ccoc1

Typical conditions: 1.TsNH2NH2.2.Mes2Mg.LiCl.THF.heating then weinreb amide

Protections: none

Reference: *10.1016/S0040-4020(03)00936-0* and *10.1021/ol300652k*

Retrosynthesis ID: 9990447

2.1.2 Conjugate addition of organocuprate

Substrates:

1. Vinylmagnesium bromide solution - *available at Sigma-Aldrich*

2. CC=C(C(=O)c1ccc(OC)cc1)c1ccoc1

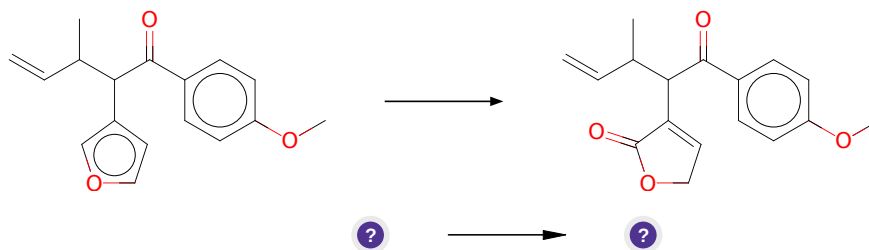**Products:**

1. C=CC(C)C(C(=O)c1ccc(OC)cc1)c1ccoc1

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

Protections: none

Reference: *10.1021/ol036071v* AND *10.1016/j.tet.2011.12.046* AND *10.1002/anie.201007644* AND *10.1002/anie.201007644* AND *10.1055/s-1997-1371*

Retrosynthesis ID: 10003577

2.1.3 Oxidation furans to 2-(5H)-furanones

Substrates:

    1. C=CC(C)C(C(=O)c1ccc(OC)cc1)c1ccoc1

Products:

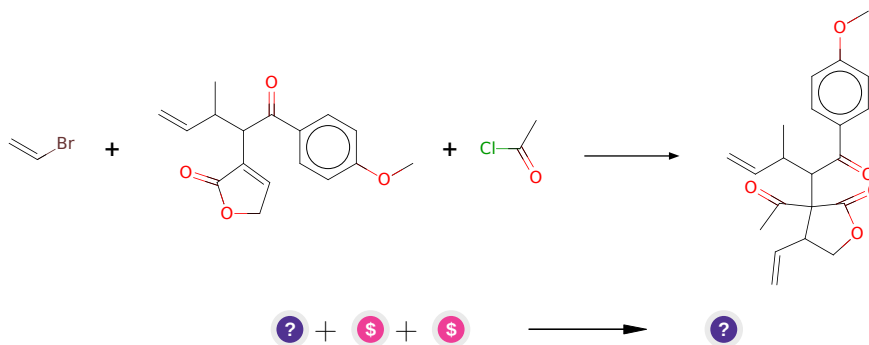   1. C=CC(C)C(C(=O)c1ccc(OC)cc1)C1=CCOC1=O

Typical conditions: 1. NBS.CHCl3.EtOH.rt 2. HCl.acetone.H2O.rt

Protections: none

Reference: DOI: *10.1055/s-2005-869865*

Retrosynthesis ID: 50717

2.1.4 Alkenylation-Acylation of enones and enoate esters

Substrates:

    1. C=CC(C)C(C(=O)c1ccc(OC)cc1)C1=CCOC1=O

    2. Bromoethylene -   *available at Sigma-Aldrich*

    3. Acetyl chloride -   *available at Sigma-Aldrich*

Products:
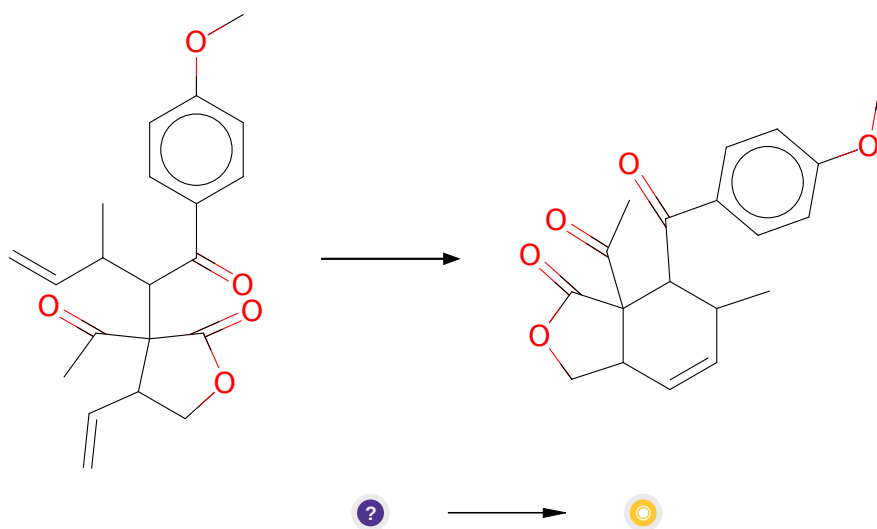
1. C=CC(C)C(C(=O)c1ccc(OC)cc1)C1(C(C)=O)C(=O)OCC1C=C

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

Protections: none

Reference: *10.1246/cl.1989.1063* AND *10.1248/cpb.33.1815* AND *10.1021/ja0320018* AND *10.1016/S0040-4039(01)80891-1* AND *10.1016/S0040-4020(01)82115-3*

Retrosynthesis ID: 13032

2.1.5 Ring-Closing Metathesis

Substrates:

1. C=CC(C)C(C(=O)c1ccc(OC)cc1)C1(C(C)=O)C(=O)OCC1C=C

Products:

1. COc1ccc(C(=O)C2C(C)C=CC3COC(=O)C32C(C)=O)cc1

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
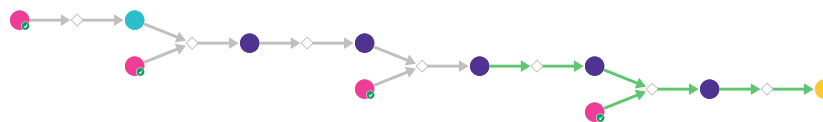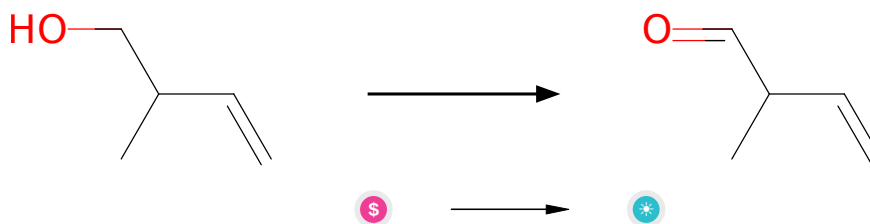
2.2 Path 2

Score: 173.93

Figure 2: Outline of path 2

2.2.1 Oxidation of primary alcohols with DMP

Substrates:

1. 2-Methyl-3-buten-1-ol - *available at Sigma-Aldrich*
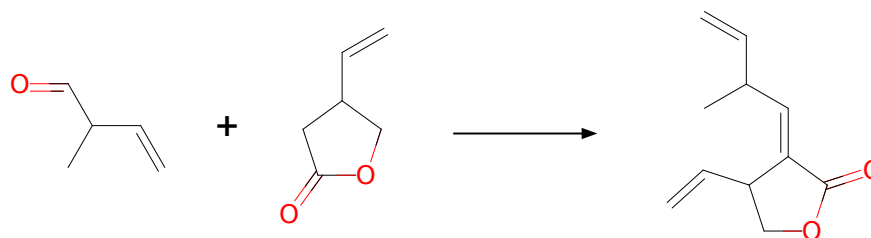
Products:

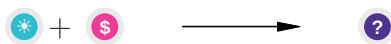1. 2-methyl-but-3-enal

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

2.2.2 Condensation of esters with aldehydes

Substrates:

1. 2-methyl-but-3-enal

2. 4-ethenyloxolan-2-one -   *available at Sigma-Aldrich*
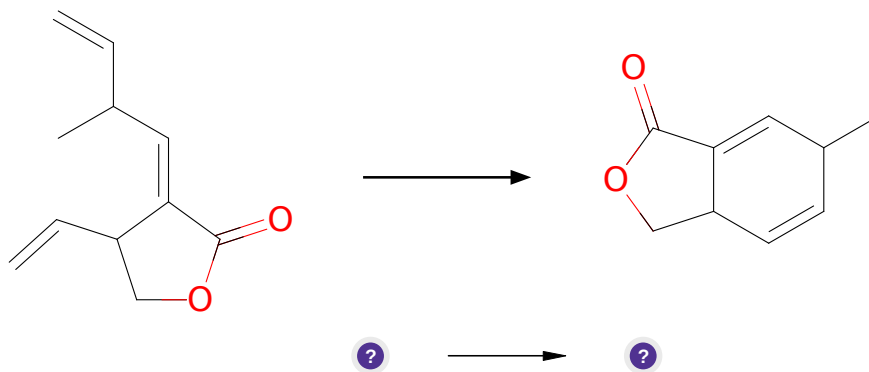
Products:

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

Typical conditions: 1.LDA.2RCHO

Protections: none

Reference: *10.1021/jo970387x* AND *10.1021/jo00076a051* AND *10.1016/S0040-4039(97)10827-9* AND *10.1055/s-2002-25767* AND *10.1039/P19920003277*

Retrosynthesis ID: 14981

2.2.3 Ring-Closing Metathesis

Substrates:

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

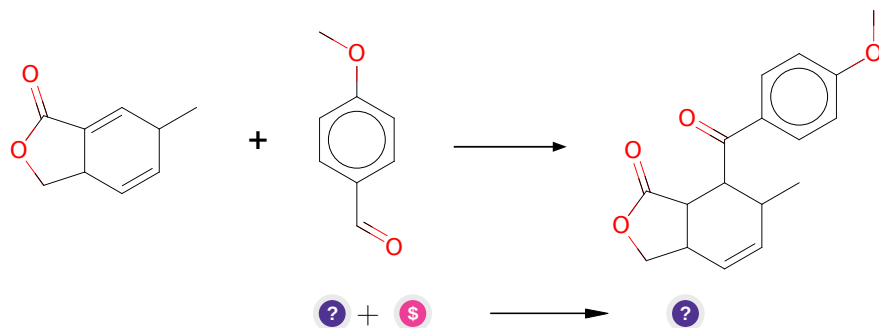**Products:**

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

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

2.2.4 Stetter reaction

Substrates:

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

2. AubA(c)pine -   *available at Sigma-Aldrich*
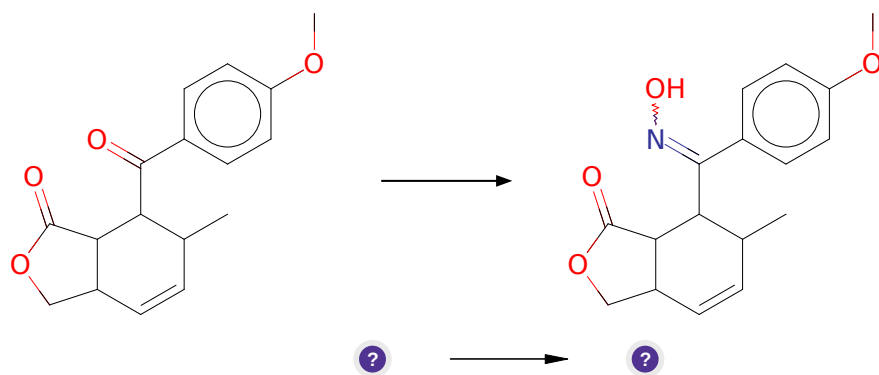
Products:

1. COc1ccc(C(=O)C2C(C)C=CC3COC(=O)C32)cc1

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: 23588

2.2.5 Synthesis of oximes

Substrates:

1. COc1ccc(C(=O)C2C(C)C=CC3COC(=O)C32)cc1

Products:
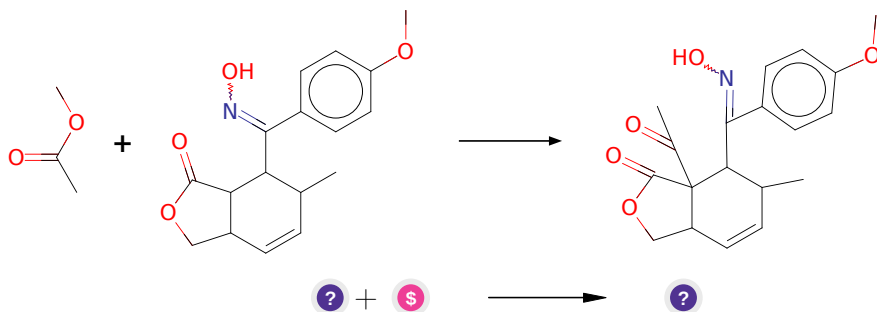
1. COc1ccc(C(=NO)C2C(C)C=CC3COC(=O)C32)cc1

Typical conditions: NH2OHxHCl.NaOAc.EtOH or NH2OHxHCl.pyridine.MeOH.reflux

Protections: none

Reference: *10.1016/j.ejmech.2019.111885* p. 4, 15 and *10.1016/j.ejmech.2020.112933* p. 4, 12, 15

Retrosynthesis ID: 5128

2.2.6 Claisen Condensation

Substrates:

1. COc1ccc(C(=NO)C2C(C)C=CC3COC(=O)C32)cc1

2. Methyl acetate - *available at Sigma-Aldrich*
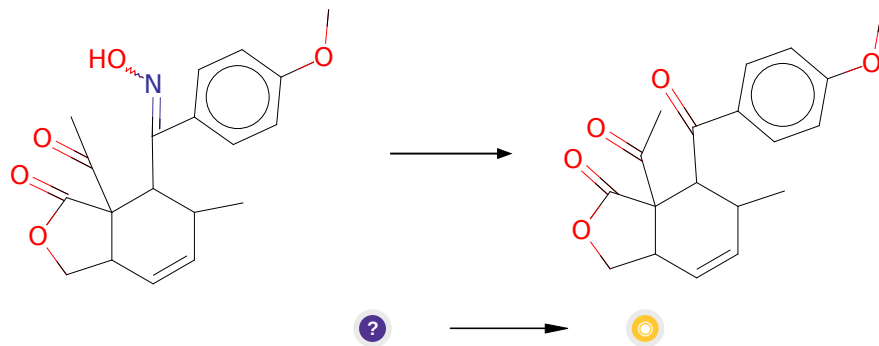
Products:

1. COc1ccc(C(=NO)C2C(C)C=CC3COC(=O)C32C(C)=O)cc1

Typical conditions: Base.Solvent

Protections: none

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

Retrosynthesis ID: 5015

2.2.7 Oxidative cleavage of oximes

Substrates:

1. COc1ccc(C(=NO)C2C(C)C=CC3COC(=O)C32C(C)=O)cc1

Products:

1. COc1ccc(C(=O)C2C(C)C=CC3COC(=O)C32C(C)=O)cc1

Typical conditions: IBX or Oxone or Ozone

Protections: none

Reference: *10.1055/s-1998-1835* and *10.1080/00397919708005905* and *10.1002/chem.201100605* (Scheme 2)

Retrosynthesis ID: 245558

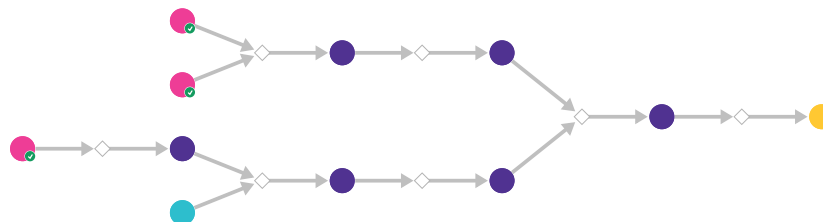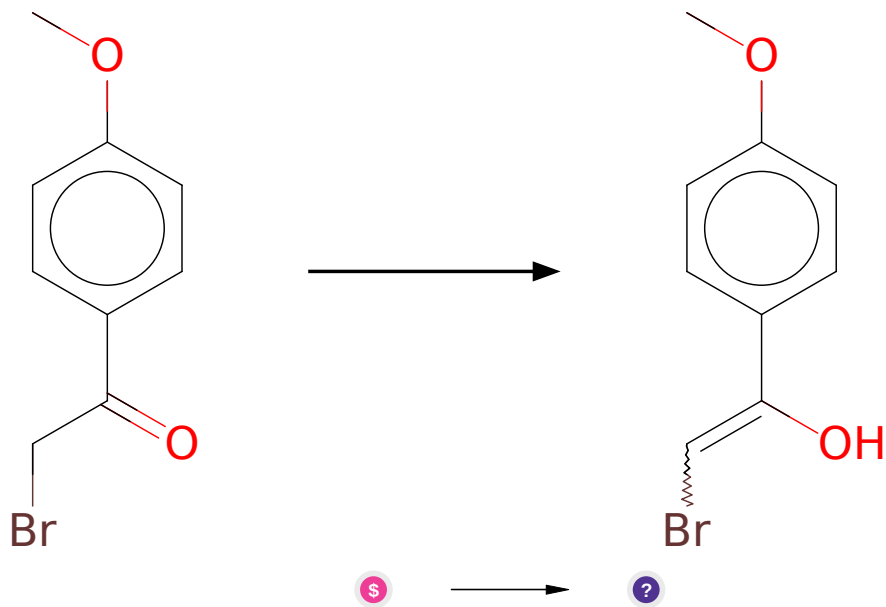## 2.3 Path 3

Score: 185.63

Figure 3: Outline of path 3

2.3.1 Keto-enol Tautomerism

Substrates:

1. 4-Methoxyphenacyl bromide - *available at Sigma-Aldrich*
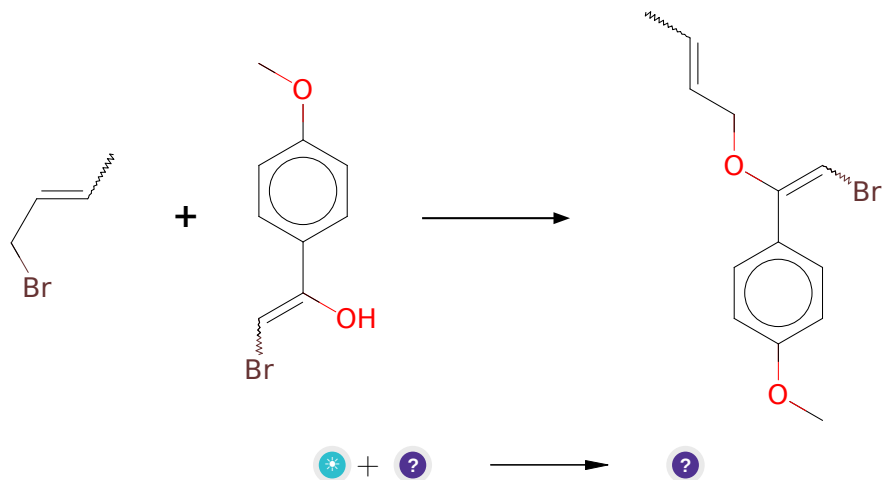
Products:

1. COc1ccc(C(O)=CBr)cc1

Typical conditions: solvent

Protections: none

Reference: *10.1021/ja01065a003* AND *10.1021/jo8012385*

Retrosynthesis ID: 7780

2.3.2 Enolate O-Alkylation

Substrates:

1. crotyl bromide

2. COc1ccc(C(O)=CBr)cc1
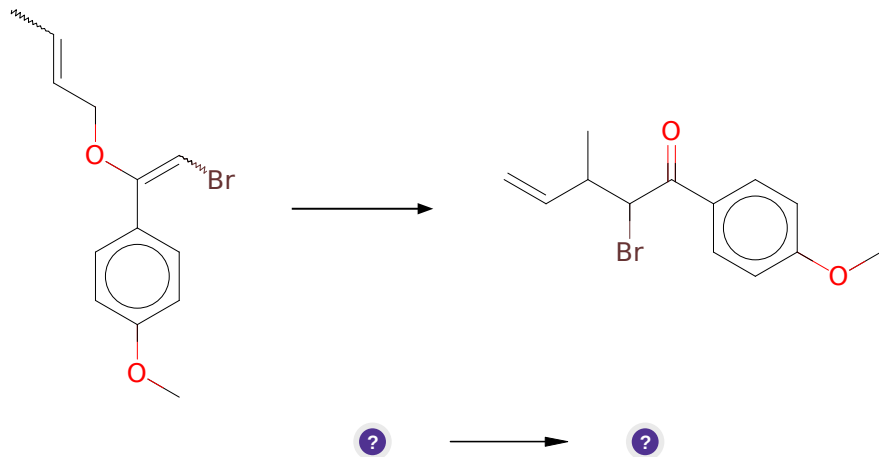
Products:

1. CC=CCOC(=CBr)c1ccc(OC)cc1

Typical conditions: Cs2CO3.DMF

Protections: none

Reference: *10.1016/j.bmcl.2012.05.070* and *10.1039/b612336h*

Retrosynthesis ID: 14841

2.3.3 Claisen Rearrangement

Substrates:

1. CC=CCOC(=CBr)c1ccc(OC)cc1

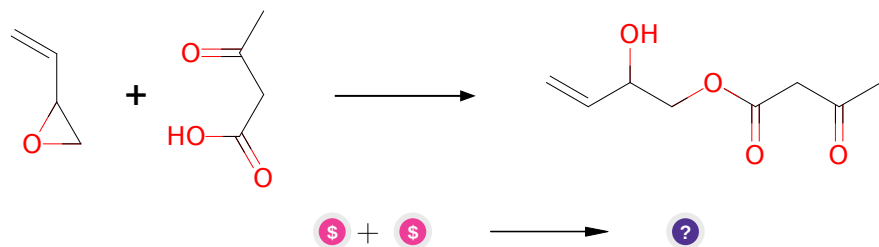**Products:**

1. C=CC(C)C(Br)C(=O)c1ccc(OC)cc1

Typical conditions: heat

Protections: none

Reference: DOI: *10.1021/ja00206a017* and *10.1016/S0022-1139(98)00313-3*

Retrosynthesis ID: 1226

2.3.4 Opening of epoxides with carboxylic acids

Substrates:

1. 2-Vinyloxirane - *available at Sigma-Aldrich*

2. Lithium acetoacetate - *available at Sigma-Aldrich*

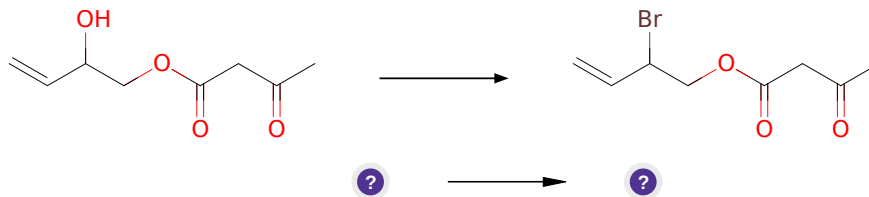**Products:**

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

Typical conditions: RCOOH.catalyst

Protections: none

Reference: *10.1021/ol051051+* AND *10.1016/j.tet.2005.05.050* and US2011/86912 A1 (P.13) and *10.1055/s-2003-42416* and *10.5012/bkcs.2013.34.8.2286*

Retrosynthesis ID: 15151

2.3.5 Appel Reaction

Substrates:

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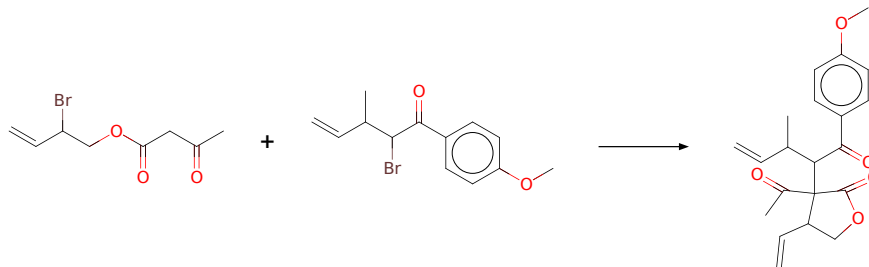
Products:

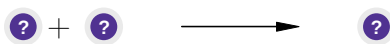   1. C=CC(Br)COC(=O)CC(C)=O

Typical conditions: PPh3.CBr4

Protections: none

Reference: *10.1016/j.jfluchem.2015.03.009* and *10.1016/j.tet.2005.12.006* and *10.1021/jm00161a029* and *10.1055/s-1995-5215*

Retrosynthesis ID: 9990042

2.3.6 Acetoacetic Ester Synthesis

Substrates:

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

2. C=CC(C)C(Br)C(=O)c1ccc(OC)cc1

Products:

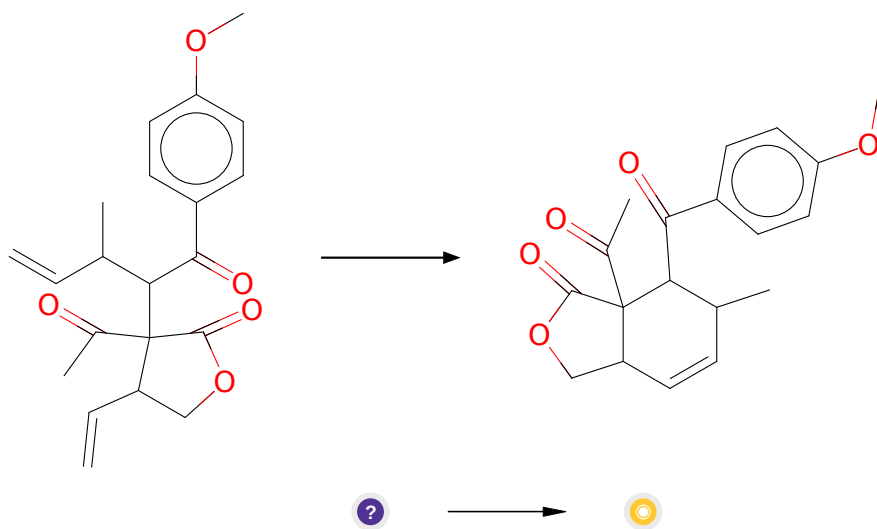1. C=CC(C)C(C(=O)c1ccc(OC)cc1)C1(C(C)=O)C(=O)OCC1C=C

Typical conditions: Exess Typical bases LDA, NaHMDS, LiHMDS.THF

Protections: none

Reference: *10.1002/9780470638859.conrr003*

Retrosynthesis ID: 5037

2.3.7 Ring-Closing Metathesis

Substrates:

1. C=CC(C)C(C(=O)c1ccc(OC)cc1)C1(C(C)=O)C(=O)OCC1C=C

Products:

1. COc1ccc(C(=O)C2C(C)C=CC3COC(=O)C32C(C)=O)cc1

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

Protections: none

Retrosynthesis ID: 31014187

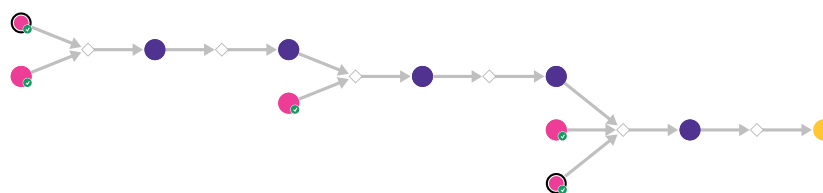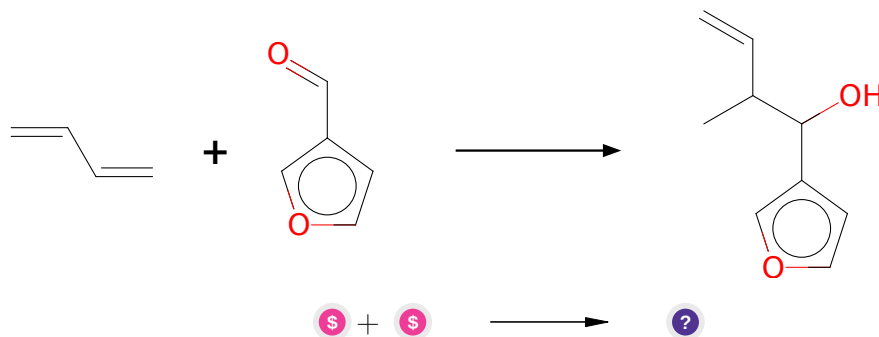## 2.4 Path 4

Score: 193.93

Figure 4: Outline of path 4

2.4.1 Enantioselective crotylation of aldehydes

Substrates:

1. 1,3-Butadiene - *available at Sigma-Aldrich*

2. 3-Furaldehyde - *available at Sigma-Aldrich*
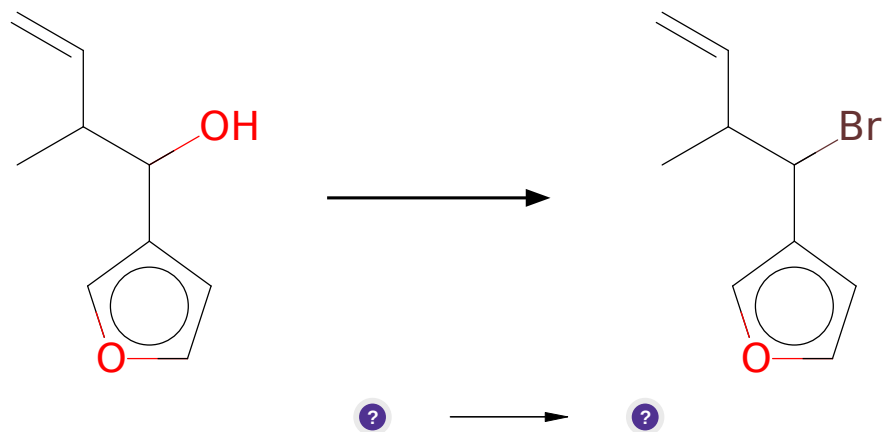
Products:

1. C=CC(C)C(O)c1ccoc1

Typical conditions: RuH2(CO)(PPh3)3.dppf.chiral.acid.THF.95C

Protections: none

Retrosynthesis ID: 10014312

2.4.2 Appel Reaction

Substrates:

1. C=CC(C)C(O)c1ccoc1

Products:

1. C=CC(C)C(Br)c1ccoc1

Typical conditions: PPh3.CBr4

Protections: none

Retrosynthesis ID: 9990042

2.4.3 Grignard reaction with acyl chlorides
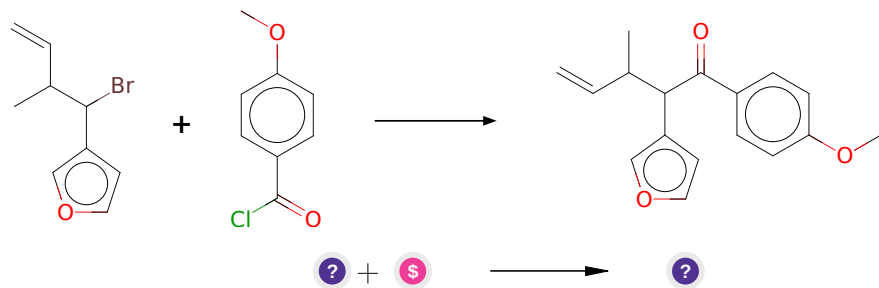
Substrates:

1. C=CC(C)C(Br)c1ccoc1

2. 4-Anisoyl chloride -   *available at Sigma-Aldrich*

Products:
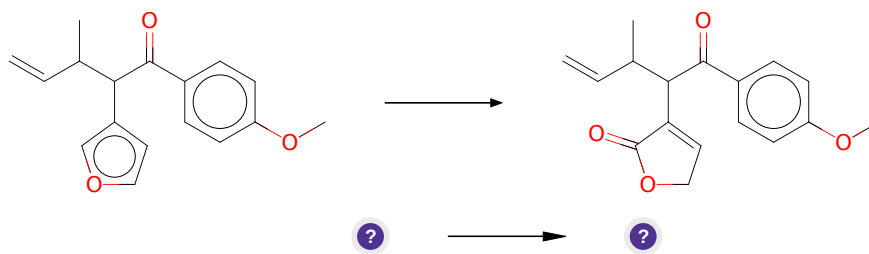
1. C=CC(C)C(C(=O)c1ccc(OC)cc1)c1ccoc1

Typical conditions: 1.i-PrMgCl.LiCl 2.ZnCl2 3. CuCl

Protections: none

Reference: *10.1016/0040-4039(94)85361-4*   and   *10.1016/0040-4039(96)00258-4*
and *10.1021/jo3005556* AND *10.1016/0040-4039(96)00689-2*

Retrosynthesis ID: 5032

2.4.4   Oxidation furans to 2-(5H)-furanones

Substrates:

1. C=CC(C)C(C(=O)c1ccc(OC)cc1)c1ccoc1

Products:
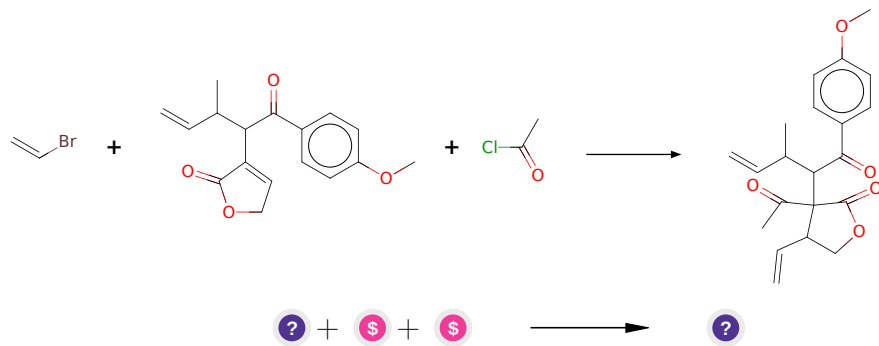
1. C=CC(C)C(C(=O)c1ccc(OC)cc1)C1=CCOC1=O

Typical conditions: 1. NBS.CHCl3.EtOH.rt 2. HCl.acetone.H2O.rt

Protections: none

Reference: DOI: *10.1055/s-2005-869865*

Retrosynthesis ID: 50717

2.4.5 Alkenylation-Acylation of enones and enoate esters

Substrates:

1. C=CC(C)C(C(=O)c1ccc(OC)cc1)C1=CCOC1=O

2. Bromoethylene - *available at Sigma-Aldrich*

3. Acetyl chloride - *available at Sigma-Aldrich*

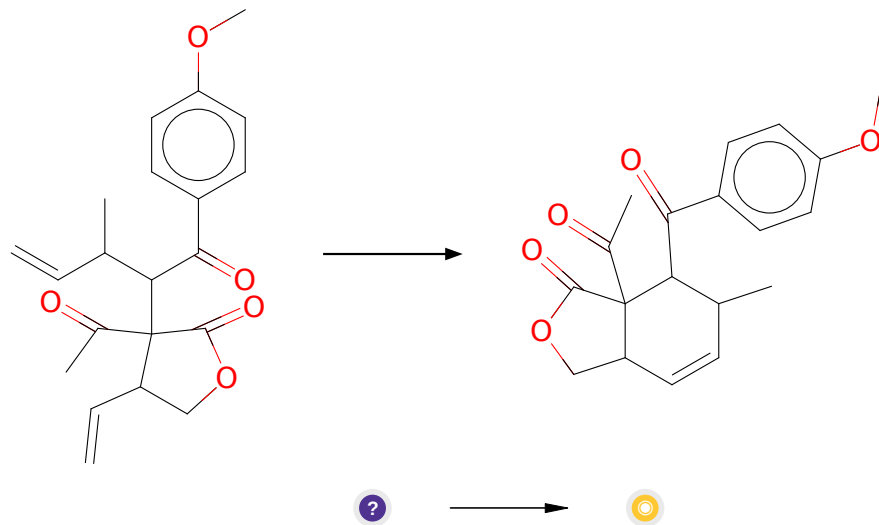**Products:**

1. C=CC(C)C(C(=O)c1ccc(OC)cc1)C1(C(C)=O)C(=O)OCC1C=C

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

Protections: none

Reference: *10.1246/cl.1989.1063*   AND   *10.1248/cpb.33.1815*   AND *10.1021/ja0320018*   AND   *10.1016/S0040-4039(01)80891-1*   AND   *10.1016/S0040-4020(01)82115-3*

Retrosynthesis ID: 13032

2.4.6 Ring-Closing Metathesis

Substrates:

    1. C=CC(C)C(C(=O)c1ccc(OC)cc1)C1(C(C)=O)C(=O)OCC1C=C

Products:

    1. COc1ccc(C(=O)C2C(C)C=CC3COC(=O)C32C(C)=O)cc1

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