Paths of analysis*
L8

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

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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.*
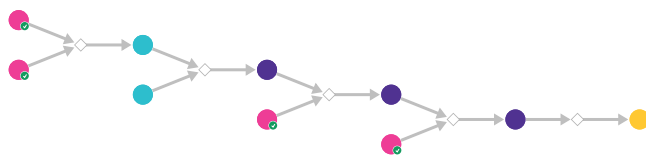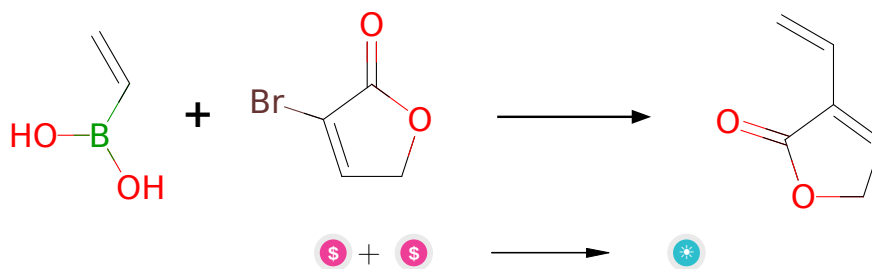
2.1 Path 1

Score: `164.14`

Figure 1: Outline of path 1

2.1.1 Suzuki coupling of vinyl bromides with alkenyl boronic acids

Substrates:

1. Vinylboronic acid - *available at Sigma-Aldrich*

2. 3-bromo-2,5-dihydrofuran-2-one - *available at Sigma-Aldrich*

Products:

1. 3-vinyl-2(5h)-furanone

Typical conditions: Pd catalyst.base.solvent

Protections: none

Reference: *10.1021/cr00039a007* and *10.1007/3418_2012_32* and *10.1021/cr0505268* and *10.1016/j.jfluchem.2016.01.018* and *10.1039/C3CS60197H*

Retrosynthesis ID: 24926

2.1.2 Michael addition
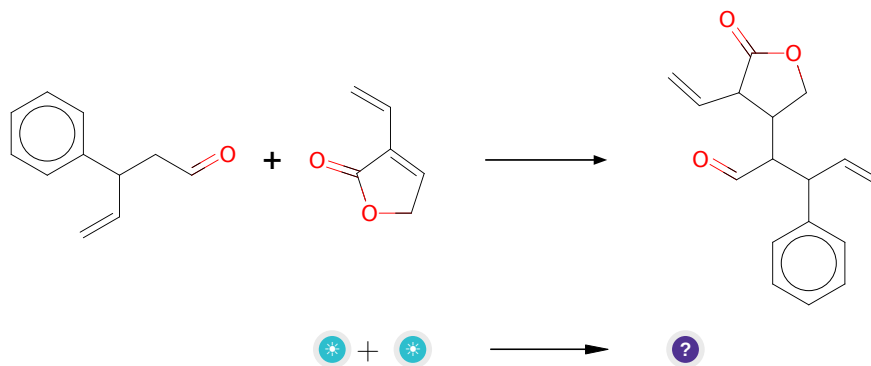
Substrates:

1. 3-vinyl-2(5h)-furanone

2. 3-phenyl-4-pentenal

Products:

1. C=CC1C(=O)OCC1C(C=O)C(C=C)c1ccccc1

Typical conditions: EtONa or other base

Protections: none

Reference: *10.1016/j.tetlet.2011.02.073* AND *10.1016/j.molstruc.2010.12.005* AND *10.1016/S0040-4039(97)00695-3* AND *10.1021/ol016401g* AND *10.1002/ejoc.200500330*

Retrosynthesis ID: 15774

2.1.3 Wittig-Schlosser olefination
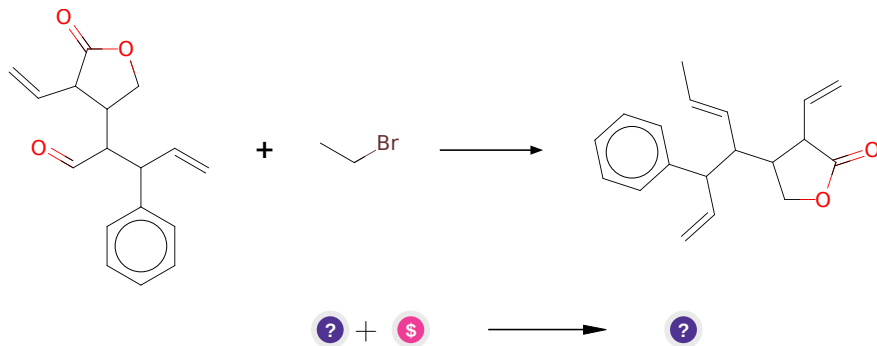
Substrates:

1. C=CC1C(=O)OCC1C(C=O)C(C=C)c1ccccc1

2. Bromoethane - *available at Sigma-Aldrich*

Products:

1. C=CC1C(=O)OCC1C(/C=C/C)C(C=C)c1ccccc1

Typical conditions: 1.PPh3 or trialkylphosphite.2.base.aldehyde.3.base

Protections: none

Reference: *10.1021/ol049701h* and *10.1021/ja00535a063* and Kurti and Czako; Strategic Applications of Named Reactions in Organic Synthesis. 1st edn., 488-489.

Retrosynthesis ID: 9546

2.1.4 Claisen Condensation
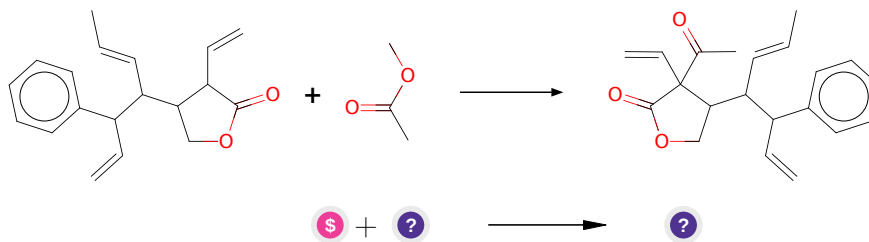
Substrates:

1. Methyl acetate - *available at Sigma-Aldrich*

2. C=CC1C(=O)OCC1C(/C=C/C)C(C=C)c1ccccc1

Products:

1. C=CC(c1ccccc1)C(/C=C/C)C1COC(=O)C1(C=C)C(C)=O

Typical conditions: Base.Solvent

Protections: none

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

Retrosynthesis ID: 5015

2.1.5 Ring-Closing Metathesis
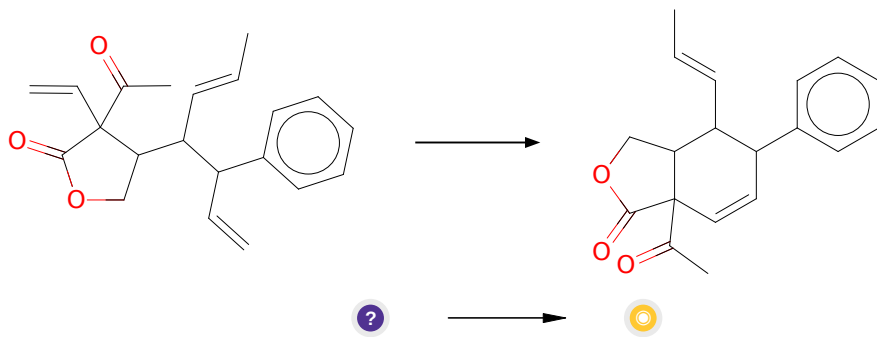
Substrates:

1. C=CC(c1ccccc1)C(/C=C/C)C1COC(=O)C1(C=C)C(C)=O

Products:

1. C/C=C/C1C(c2ccccc2)C=CC2(C(C)=O)C(=O)OCC12

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: 189.20
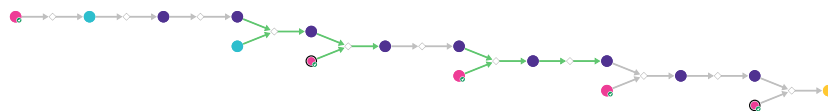
Figure 2: Outline of path 2

2.2.1 Brown Hydroboration of Alkenes
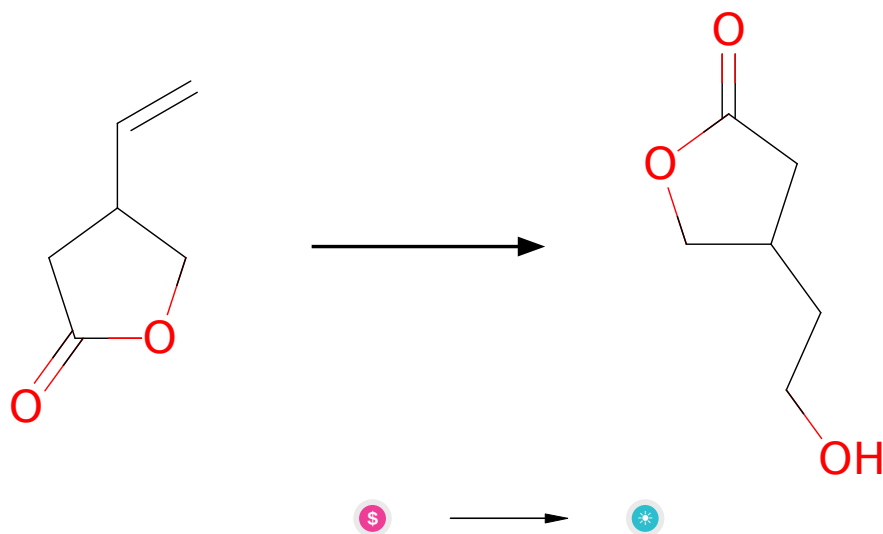
Substrates:

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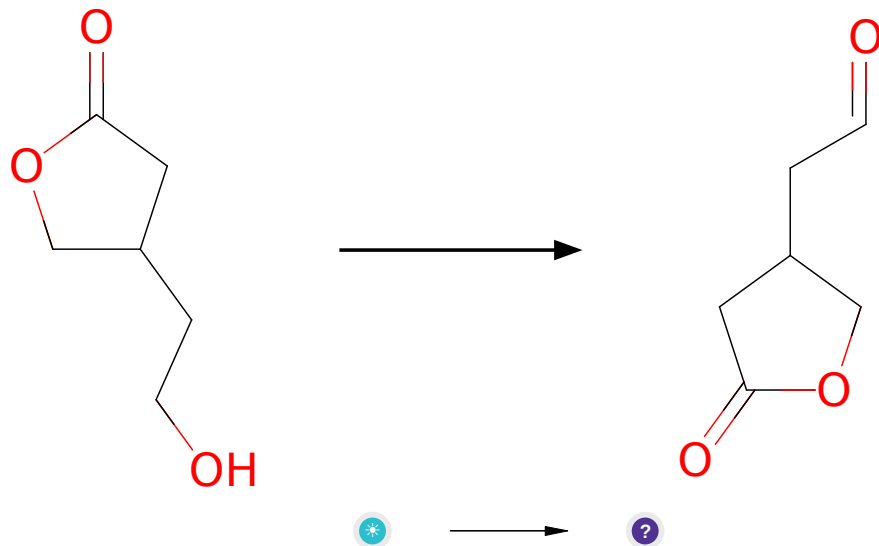
Products:

1. 4-(2-hydroxy-ethyl)-dihydro-furan-2-one

Typical conditions: B2H6.H2O2.THF.NaOH

Protections: none

Reference: *10.1002/9780470638859.conrr118*

Retrosynthesis ID: 4772

2.2.2 Oxidation of primary alcohols with DMP

Substrates:

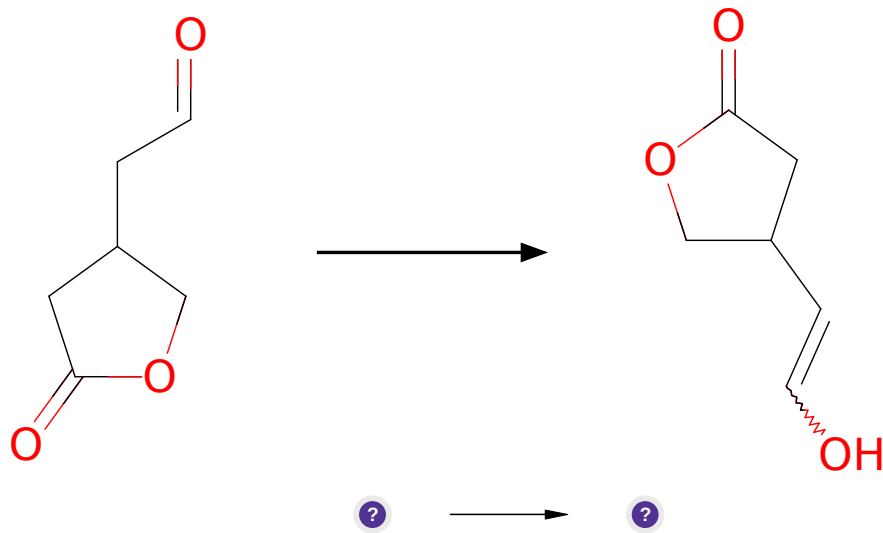1. 4-(2-hydroxy-ethyl)-dihydro-furan-2-one

Products:

1. O=CCC1COC(=O)C1

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

2.2.3 Keto-Enol Tautomerism

Substrates:

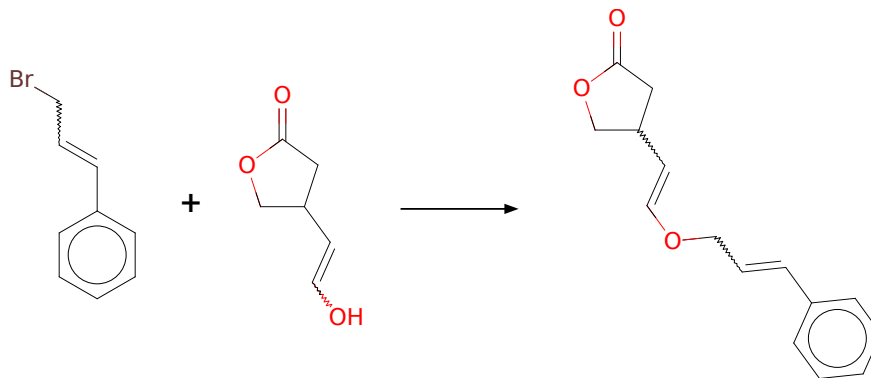 1. O=CCC1COC(=O)C1

Products:
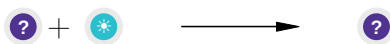
  1. O=C1CC(C=CO)CO1

Typical conditions: solvent

Protections: none

Reference: *10.1021/jo8012385 10.1021/ja01065a003*

Retrosynthesis ID: 8718

2.2.4 Enolate O-Alkylation

Substrates:

1. O=C1CC(C=CO)CO1

2. cinnamyl bromide

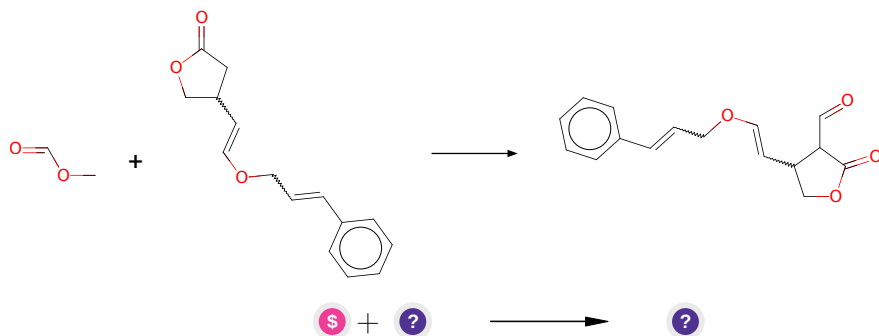**Products:**

1. O=C1CC(C=COCC=Cc2ccccc2)CO1

Typical conditions: Cs2CO3.DMF

Protections: none

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

Retrosynthesis ID: 14841

2.2.5 Condensation of esters with carbonyl compounds

Substrates:

1. Methyl formate - *available at Sigma-Aldrich*

2. O=C1CC(C=COCC=Cc2ccccc2)CO1
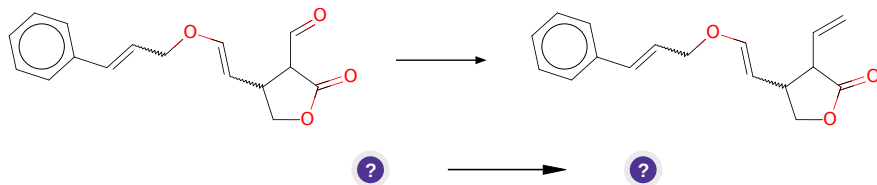
Products:

1. O=CC1C(=O)OCC1C=COCC=Cc1ccccc1

Typical conditions: LDA.THF

Protections: none

Reference: *10.1021/op040006z* AND *10.1016/j.bmcl.2005.10.104*

Retrosynthesis ID: 14987

2.2.6 Tebbe Olefination

Substrates:

1. O=CC1C(=O)OCC1C=COCC=Cc1ccccc1

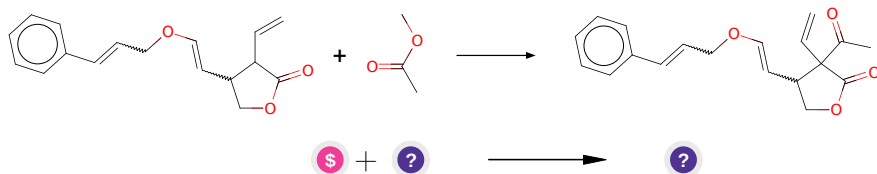**Products:**

1. C=CC1C(=O)OCC1C=COCC=Cc1ccccc1

Typical conditions: Cp2TiCl2.AlMe3.toluene

Protections: none

Reference: *10.1016/j.tet.2007.03.015* and *10.1002/9780470638859.conrr617*

Retrosynthesis ID: 11714

2.2.7 Claisen Condensation

Substrates:

1. Methyl acetate -   *available at Sigma-Aldrich*

2. C=CC1C(=O)OCC1C=COCC=Cc1ccccc1

Products:

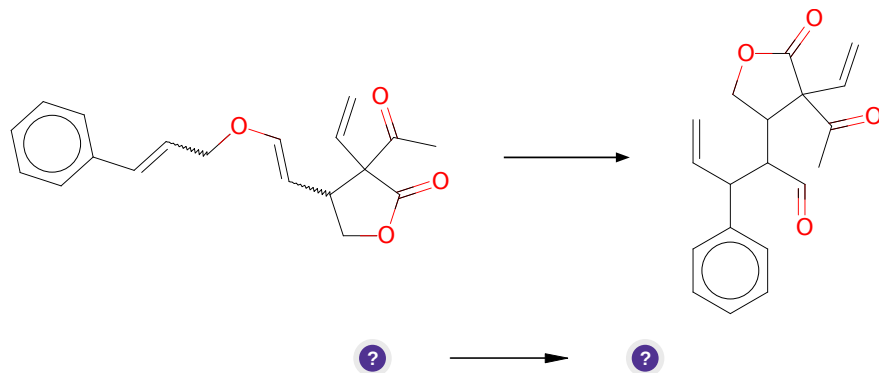1. C=CC1(C(C)=O)C(=O)OCC1C=COCC=Cc1ccccc1

Typical conditions: Base.Solvent

Protections: none

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

Retrosynthesis ID: 5015

2.2.8 Claisen Rearrangement

Substrates:

1. C=CC1(C(C)=O)C(=O)OCC1C=COCC=Cc1ccccc1

Products:

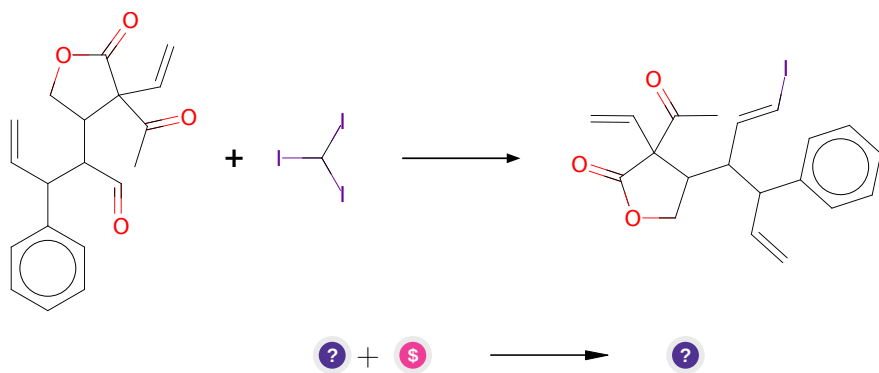1. C=CC(c1ccccc1)C(C=O)C1COC(=O)C1(C=C)C(C)=O

Typical conditions: heat

Protections: none

Retrosynthesis ID: 1226

2.2.9 Takai olefination

Substrates:

1. C=CC(c1ccccc1)C(C=O)C1COC(=O)C1(C=C)C(C)=O

2. Iodoform - *available at Sigma-Aldrich*

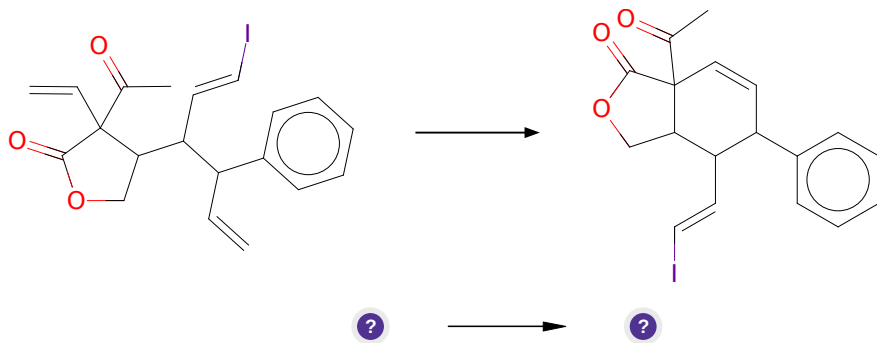**Products:**

1. C=CC(c1ccccc1)C(/C=C/I)C1COC(=O)C1(C=C)C(C)=O

Typical conditions: CrCl2.THF

Protections: none

Reference: *10.1021/ja00283a046* and *10.1021/ja00237a081*

Retrosynthesis ID: 10497

2.2.10 Ring-Closing Metathesis

Substrates:

1. C=CC(c1ccccc1)C(/C=C/I)C1COC(=O)C1(C=C)C(C)=O
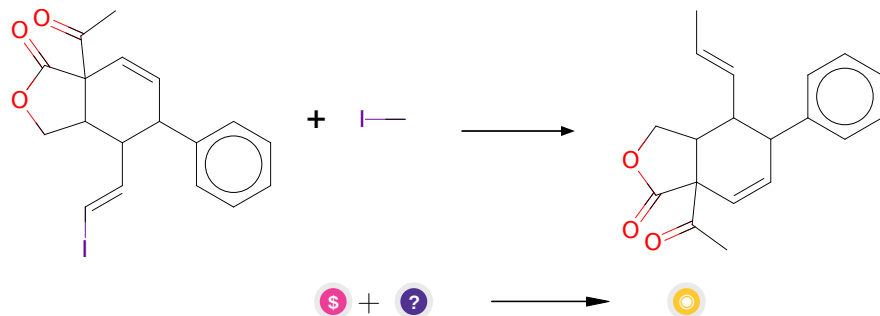
Products:

1. CC(=O)C12C=CC(c3ccccc3)C(/C=C/I)C1COC2=O

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

2.2.11 Palladium catalysed methylation of vinyl iodides

Substrates:

1. Iodomethane - *available at Sigma-Aldrich*

2. CC(=O)C12C=CC(c3ccccc3)C(/C=C/I)C1COC2=O

Products:

1. C/C=C/C1C(c2ccccc2)C=CC2(C(C)=O)C(=O)OCC12

Typical conditions: MeMgBr/Me2Zn/Me4Sn.[Pd].or.CuI

Protections: none

Reference: *10.1021/ja049323b* and *10.1055/s-2002-20971* and *10.1021/ja049323b* and *10.1016/S0040-4039(01)80470-6* and *10.1016/j.tetlet.2006.08.128* and *10.1002/ejoc.201000642*

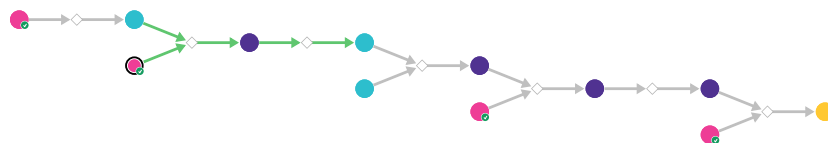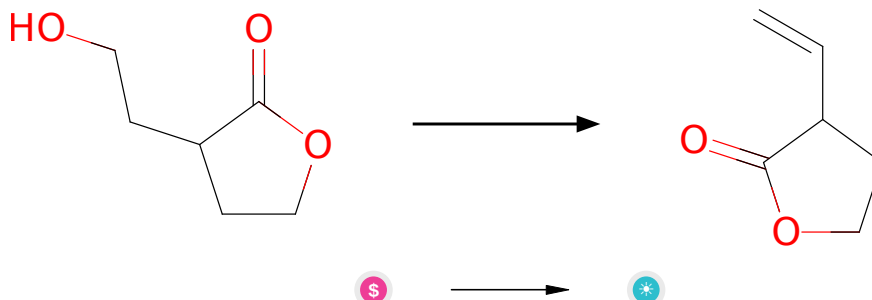**Retrosynthesis ID:** 25156

2.3 Path 3

Score: 191.61

Figure 3: Outline of path 3

2.3.1   Synthesis of alkenes from alcohols

Substrates:

1. 3-(2-hydroxyethyl)oxolan-2-one -   *available at Sigma-Aldrich*

Products:

1. 3-vinyl-dihydro-furan-2-one

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

2.3.2   Enol esters and ethers synthesis

Substrates:

1. 3-vinyl-dihydro-furan-2-one

2. TMSCl -   *available at Sigma-Aldrich*

Products:

1. C=CC1=C(O[Si](C)(C)C)OCC1
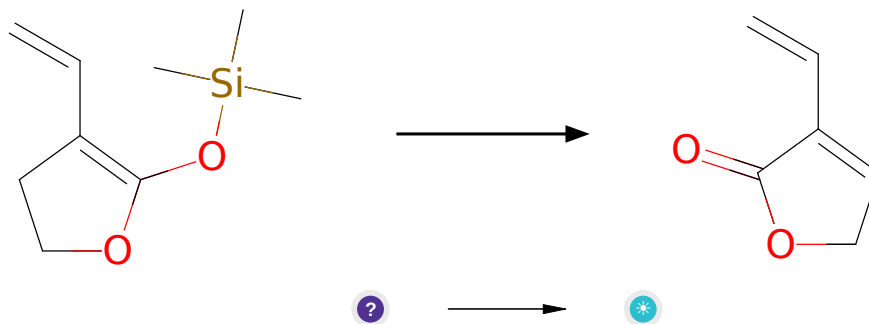
Typical conditions: 1. Et3N.Electrophile

Protections: none

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

Retrosynthesis ID: 7799

2.3.3 Dehydrogenation of silyl enol ethers

Substrates:

1. C=CC1=C(O[Si](C)(C)C)OCC1
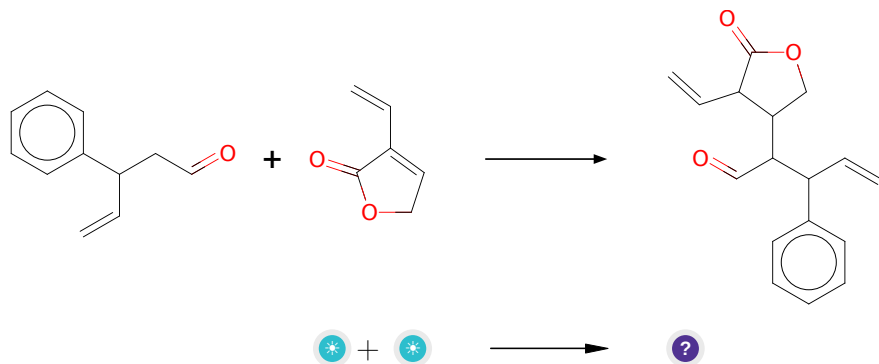
Products:

1. 3-vinyl-2(5h)-furanone

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

2.3.4 Michael addition

Substrates:

1. 3-vinyl-2(5h)-furanone

2. 3-phenyl-4-pentenal

Products:
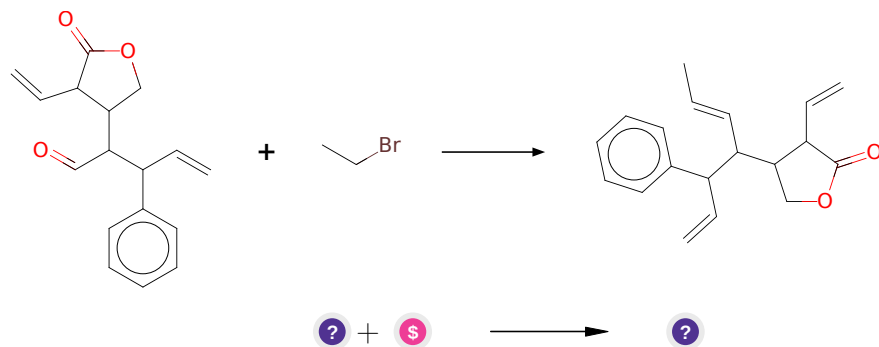
1. C=CC1C(=O)OCC1C(C=O)C(C=C)c1ccccc1

Typical conditions: EtONa or other base

Protections: none

Reference: *10.1016/j.tetlet.2011.02.073* AND *10.1016/j.molstruc.2010.12.005* AND *10.1016/S0040-4039(97)00695-3* AND *10.1021/ol016401g* AND *10.1002/ejoc.200500330*

Retrosynthesis ID: 15774

2.3.5 Wittig-Schlosser olefination

Substrates:

1. C=CC1C(=O)OCC1C(C=O)C(C=C)c1ccccc1

2. Bromoethane - *available at Sigma-Aldrich*
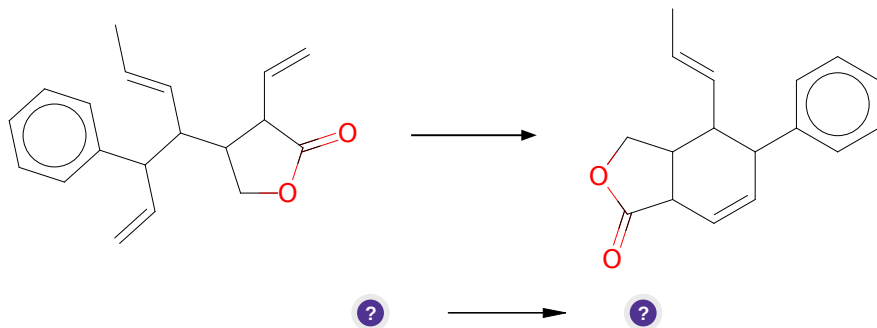
Products:

1. C=CC1C(=O)OCC1C(/C=C/C)C(C=C)c1ccccc1

Typical conditions: 1.PPh3 or trialkylphosphite.2.base.aldehyde.3.base

Protections: none

Reference: *10.1021/ol049701h* and *10.1021/ja00535a063* and Kurti and Czako; Strategic Applications of Named Reactions in Organic Synthesis. 1st edn., 488-489.

Retrosynthesis ID: 9546

2.3.6 Ring-Closing Metathesis

Substrates:

1. C=CC1C(=O)OCC1C(/C=C/C)C(C=C)c1ccccc1
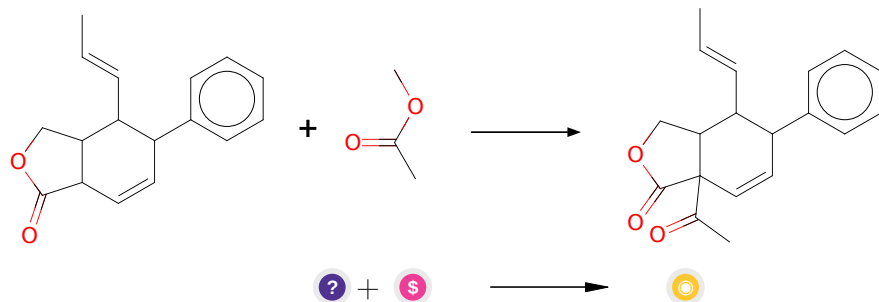
Products:

1. C/C=C/C1C(c2ccccc2)C=CC2C(=O)OCC21

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

2.3.7 Claisen Condensation

Substrates:

1. C/C=C/C1C(c2ccccc2)C=CC2C(=O)OCC21

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

Products:

1. C/C=C/C1C(c2ccccc2)C=CC2(C(C)=O)C(=O)OCC12

Typical conditions: Base.Solvent

Protections: none

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

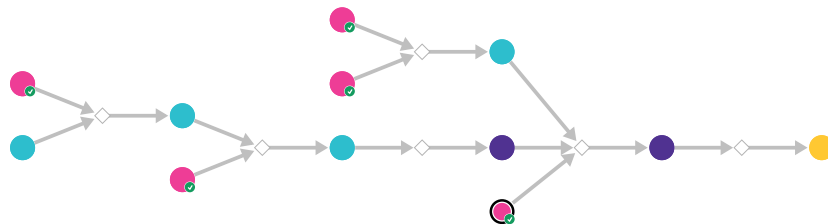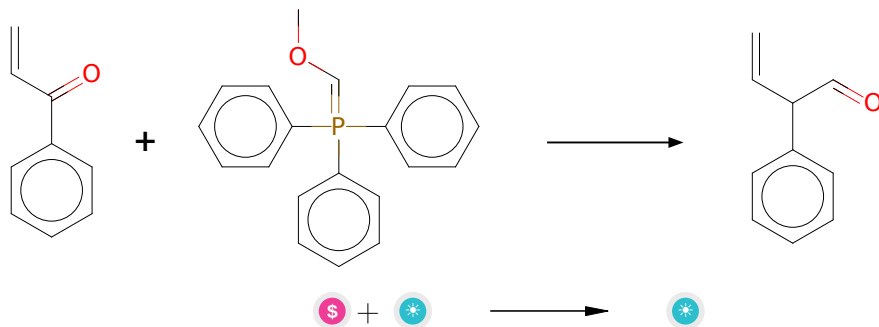**Retrosynthesis ID:** 5015

2.4   Path 4

Score: 195.39

Figure 4: Outline of path 4

2.4.1 Olefination of ketones followed by hydrolysis

Substrates:

1. 1-Phenylprop-2-en-1-one - *available at Sigma-Aldrich*

2. triphenylphosphonium methoxymethylide
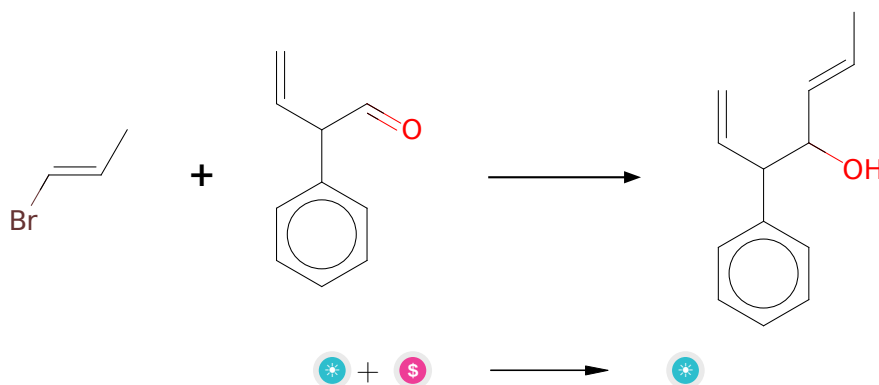
Products:

1. 2-phenyl-but-3-enal

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

2.4.2 Grignard addition to ketone

Substrates:

1. 2-phenyl-but-3-enal

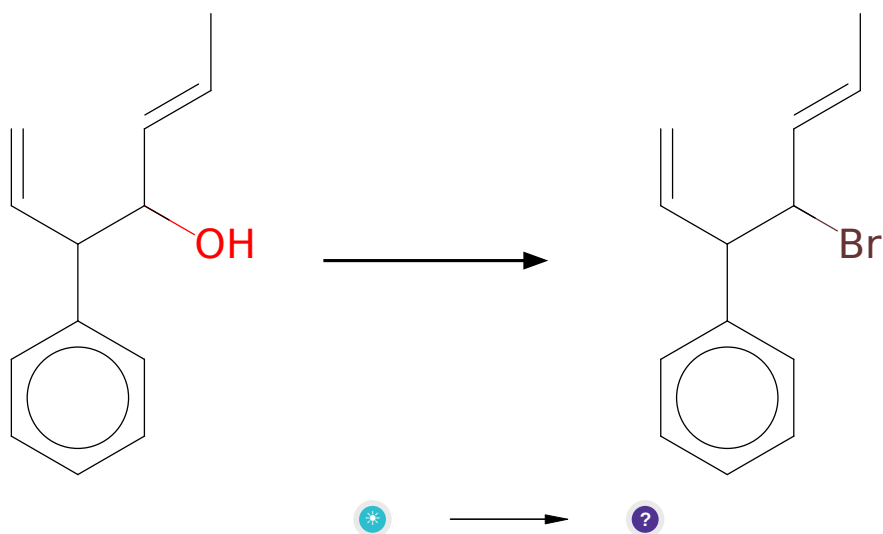2. 1-Propenyl bromide - *available at Sigma-Aldrich*

Products:

1. C13H16O

Typical conditions: Mg.THF.or.iPrMgClxLiCl

Protections: none

Reference: *10.3762/bjoc.9.175* and *10.1016/j.tetlet.2012.08.088* and *10.1002/anie.200504247* (supporting info)

Retrosynthesis ID: 18169

2.4.3 Appel Reaction

Substrates:
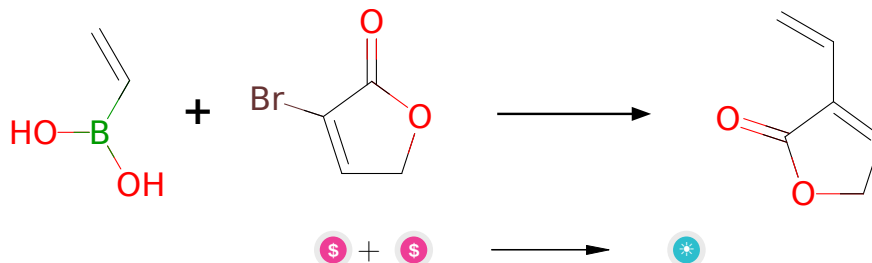
1. C13H16O

Products:

1. C=CC(c1ccccc1)C(Br)/C=C/C

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

2.4.4 Suzuki coupling of vinyl bromides with alkenyl boronic acids

Substrates:

1. Vinylboronic acid -   *available at Sigma-Aldrich*

2. 3-bromo-2,5-dihydrofuran-2-one -   *available at Sigma-Aldrich*
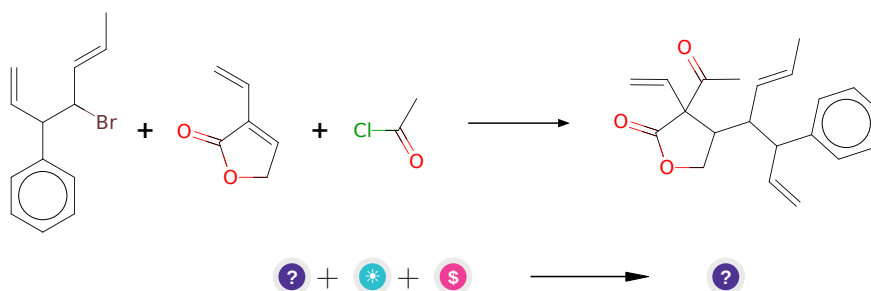
Products:

1. 3-vinyl-2(5h)-furanone

Typical conditions: Pd catalyst.base.solvent

Protections: none

Reference: *10.1021/cr00039a007*   and   *10.1007/3418_2012_32*   and *10.1021/cr0505268* and *10.1016/j.jfluchem.2016.01.018* and *10.1039/C3CS60197H*

Retrosynthesis ID: 24926

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

Substrates:

1. C=CC(c1ccccc1)C(Br)/C=C/C

2. 3-vinyl-2(5h)-furanone

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

Products:

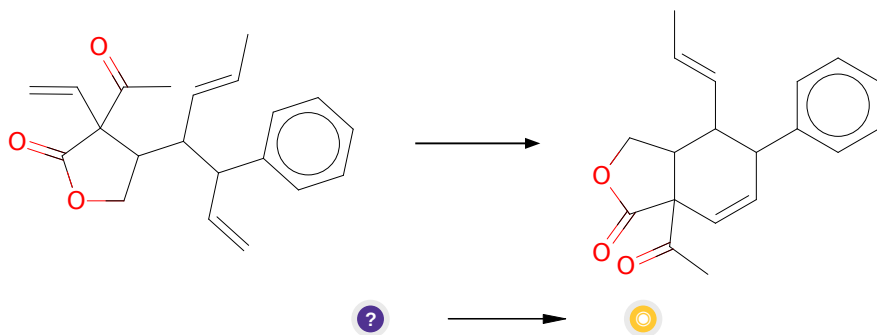1. C=CC(c1ccccc1)C(/C=C/C)C1COC(=O)C1(C=C)C(C)=O

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: 20523

2.4.6 Ring-Closing Metathesis

Substrates:

1. C=CC(c1ccccc1)C(/C=C/C)C1COC(=O)C1(C=C)C(C)=O

Products:

1. C/C=C/C1C(c2ccccc2)C=CC2(C(C)=O)C(=O)OCC12

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