Paths of analysis*
L8_DIA

Synthia

October 11, 2022

1   Analysis parameters

Analysis type: Automatic Retrosynthesis

Rules: none selected

Filters: 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

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.*
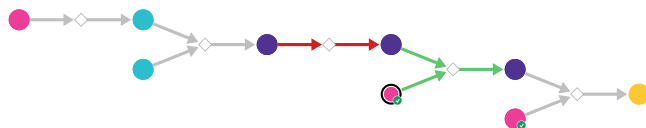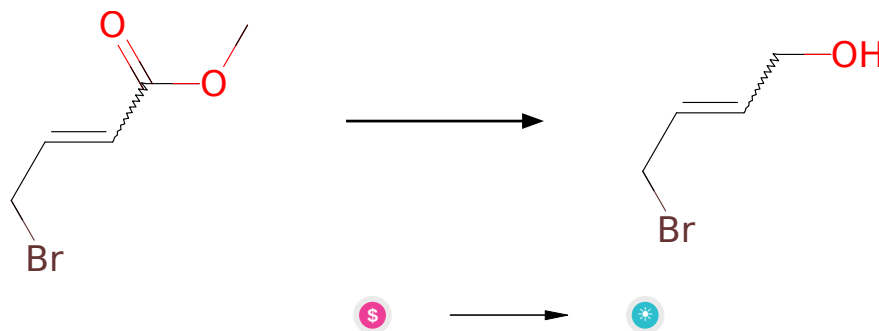
2.1 Path 1

Score: 139.14

Figure 1: Outline of path 1

2.1.1 Reduction of ester to allylic alcohol

Substrates:

1. methyl 4-bromobut-2-enoate - *SYNTHONIXCORPORATION*
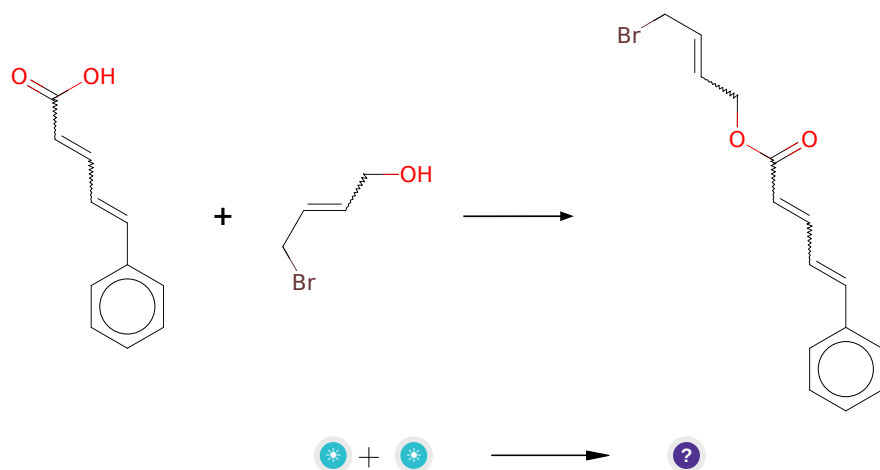
Products:

1. (e)-4-bromo-2-buten-1-ol

Typical conditions: DIBAL-H.DCM

Protections: none

Retrosynthesis ID: 9900043

2.1.2 Acylation of primary alcohols

Substrates:

1. (e)-4-bromo-2-buten-1-ol

2. 5-phenyl-penta-2,4-dienoic acid
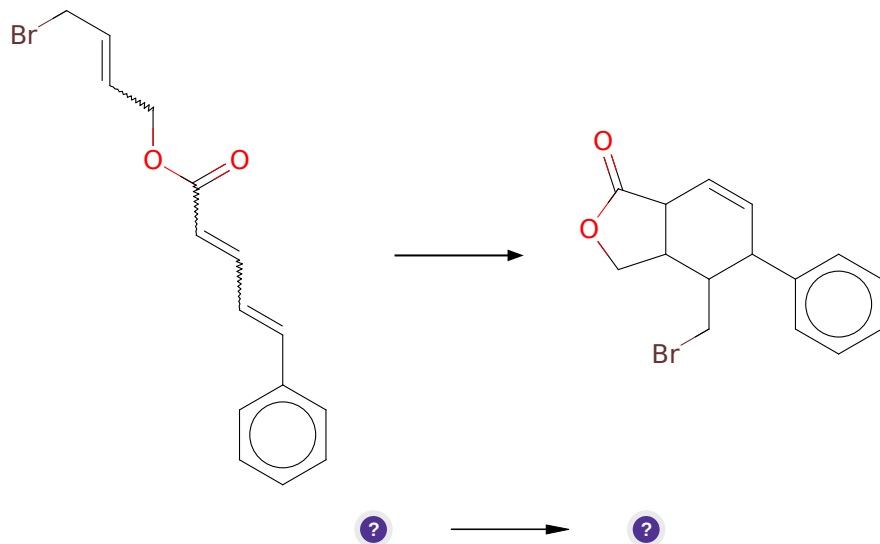
Products:

1. O=C(C=CC=Cc1ccccc1)OCC=CCBr

Typical conditions: DCC.DMAP.DCM

Protections: none

Retrosynthesis ID: 9998689

2.1.3 Diels-Alder

Substrates:

1. O=C(C=CC=Cc1ccccc1)OCC=CCBr
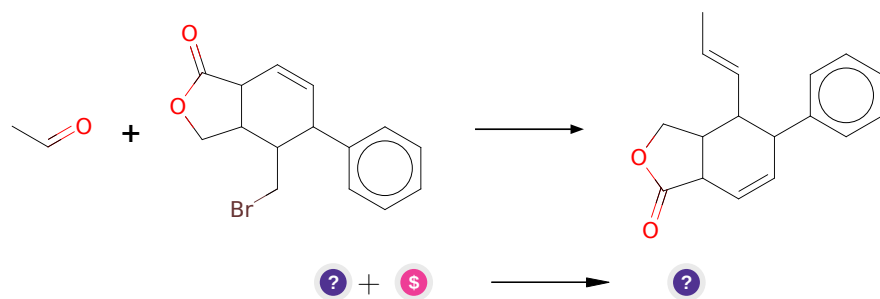
Products:

1. O=C1OCC2C1C=CC(c1ccccc1)C2CBr

Typical conditions: Lewis acid or chiral Lewis acid. Solvent.

Protections: none

Retrosynthesis ID: 18116

2.1.4 Wittig-Schlosser olefination

Substrates:

1. O=C1OCC2C1C=CC(c1ccccc1)C2CBr

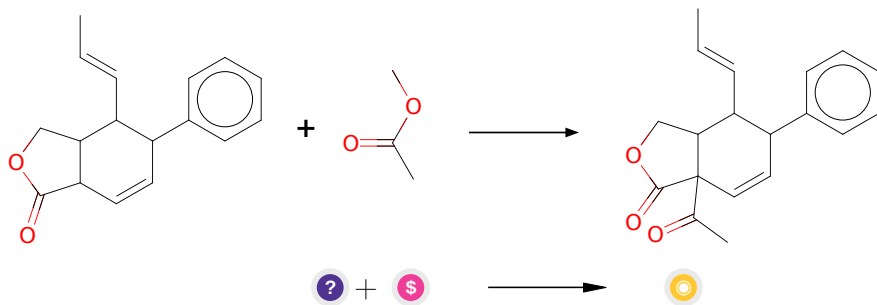2. Ethanal - *available at Sigma-Aldrich*

Products:

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

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

2.1.5 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
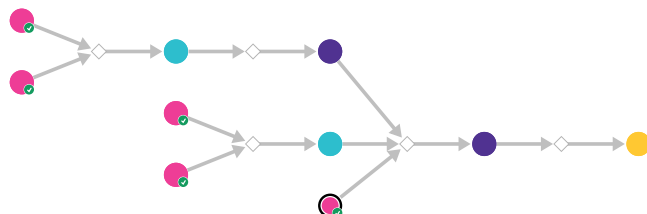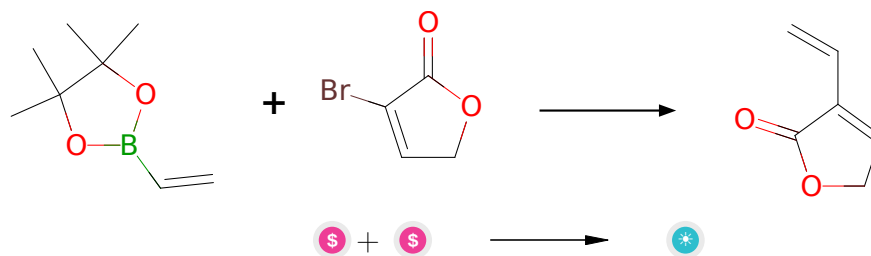
2.2 Path 2

Score: 146.56

Figure 2: Outline of path 2

2.2.1 Suzuki coupling of vinyl bromides with alkenyl boronic acids pinacol esters

Substrates:

1. 3-bromo-2,5-dihydrofuran-2-one -   *available at Sigma-Aldrich*

2. Vinylboronic acid pinacol ester -   *available at Sigma-Aldrich*

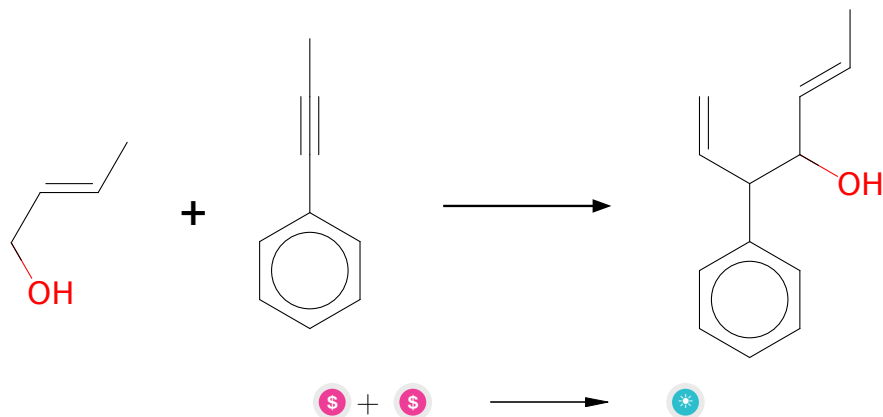**Products:**

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: 25028

2.2.2 Coupling of alkynes and alcohols

Substrates:

1. 2-Buten-1-ol - *available at Sigma-Aldrich*

2. 1-Phenyl-1-propyne - *available at Sigma-Aldrich*
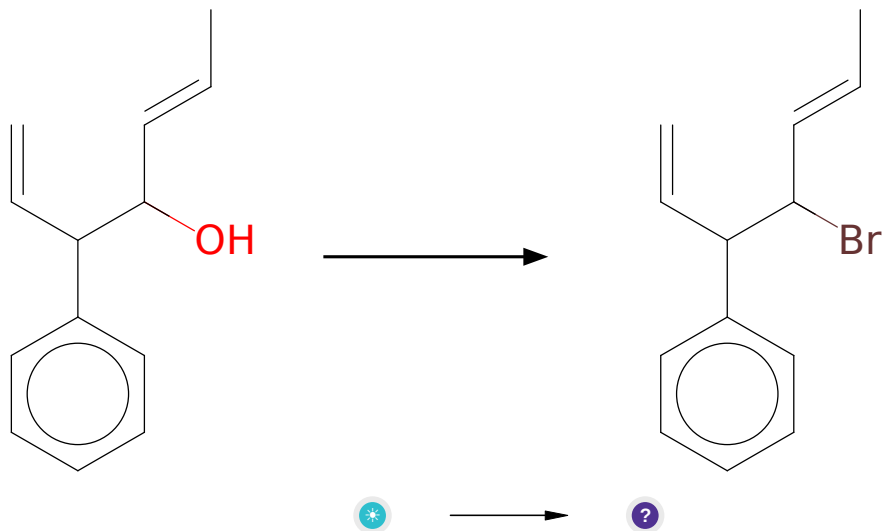
Products:

1. C13H16O

Typical conditions: H2Ru(CO)(PPh3)3.2,4,6-(iPr)3PhSO3H.SL-J009-1.TBAI.IPA.THF.95C

Protections: none

Retrosynthesis ID: 9895

2.2.3 Appel Reaction

Substrates:
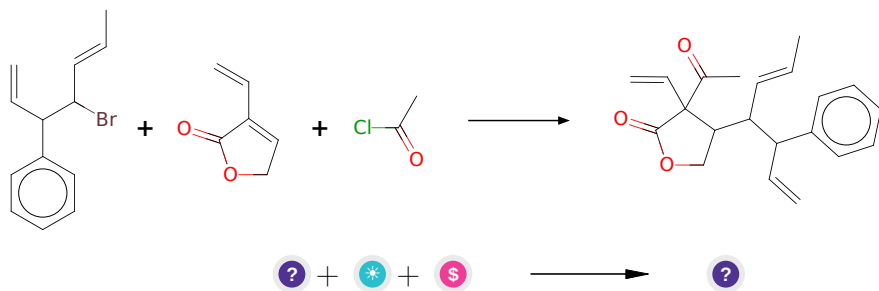
1. C13H16O

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

2.2.4 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

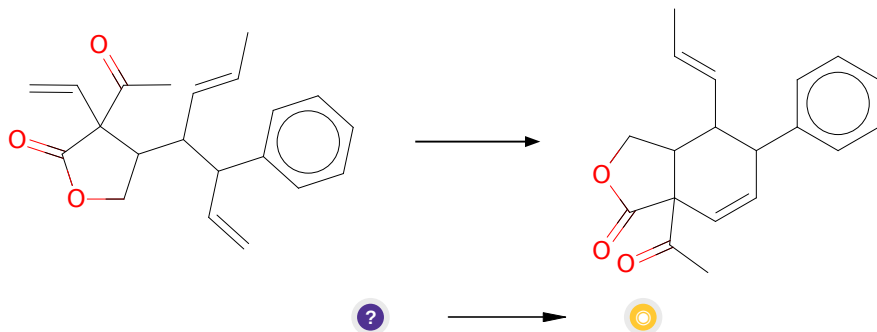3. Acetyl chloride - *available at Sigma-Aldrich*

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

2.2.5 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
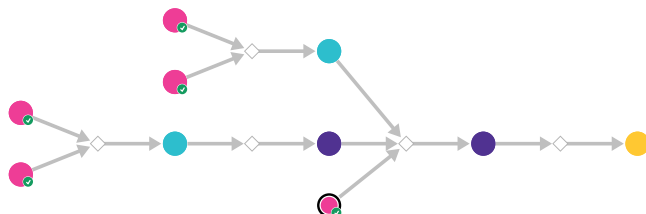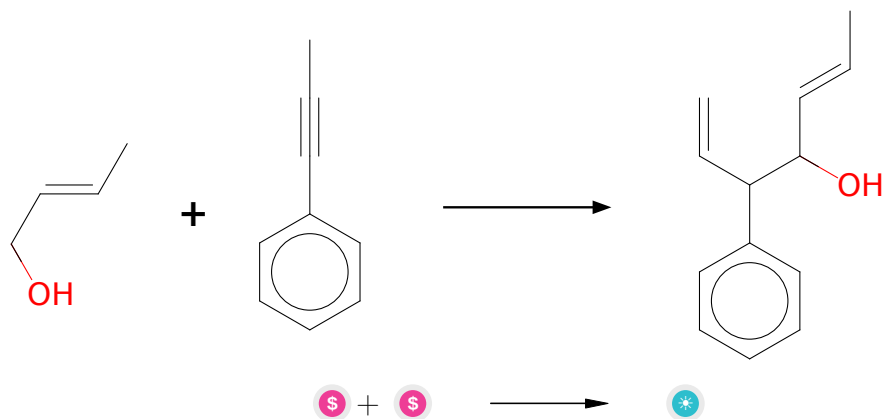
2.3 Path 3

Score: 146.56

Figure 3: Outline of path 3

2.3.1 Coupling of alkynes and alcohols

Substrates:

1. 2-Buten-1-ol -   *available at Sigma-Aldrich*

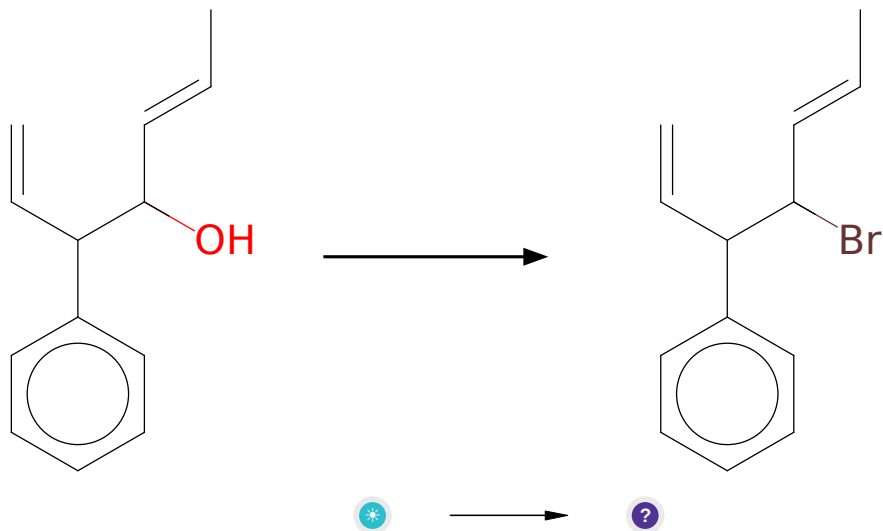2. 1-Phenyl-1-propyne -   *available at Sigma-Aldrich*

Products:

1. C13H16O

Typical conditions: H2Ru(CO)(PPh3)3.2,4,6-(iPr)3PhSO3H.SL-J009-1.TBAI.IPA.THF.95C

Protections: none

Reference: DOI: *10.1021/jacs.5b00747*

Retrosynthesis ID: 9895

2.3.2 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

2.3.3 Suzuki coupling of vinyl bromides with alkenyl boronic acids
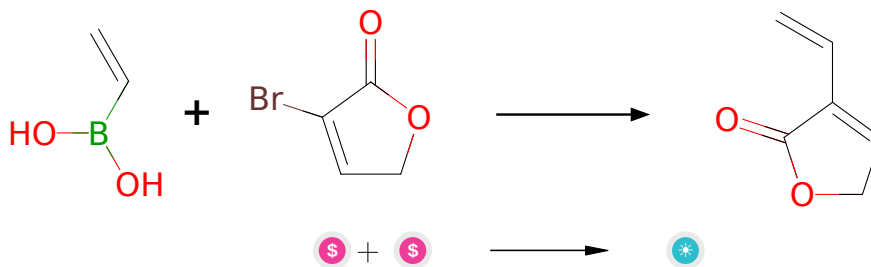
Substrates:

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

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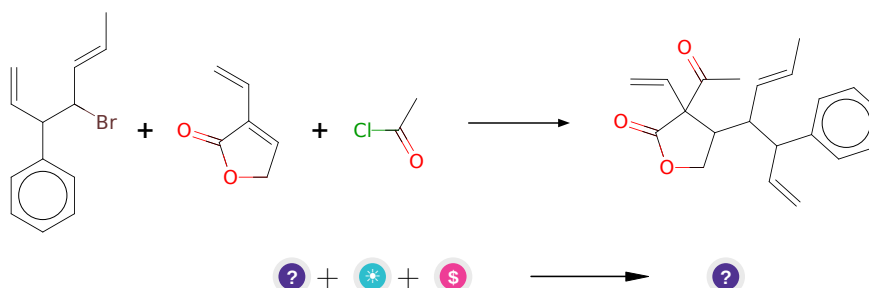
Products:

   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

2.3.4   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:

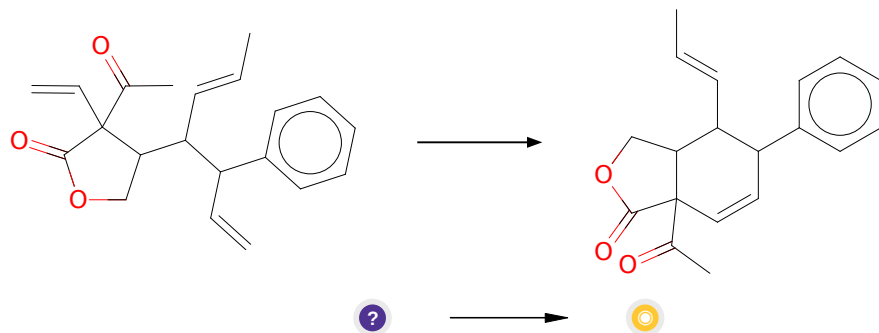   1. C=CC(c1ccccc1)C(/C=C/C)C1COC(=O)C1(C=C)C(C)=O

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

2.3.5   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

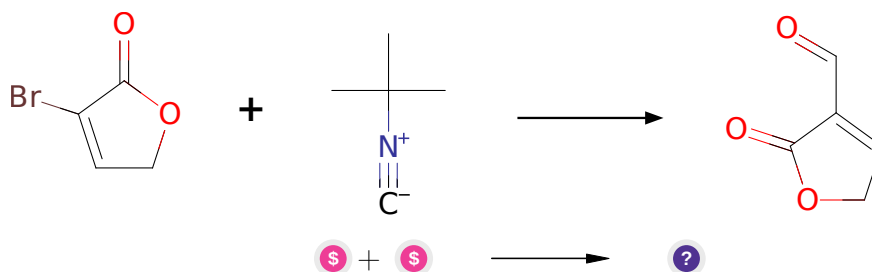**Typical conditions:** catalyst e.g. Hoveyda-Grubbs . solvent e.g. CH2Cl2

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

2.4   Path 4

Score: 154.38

2.4.1   Pd-catalyzed formylation of vinyl halides
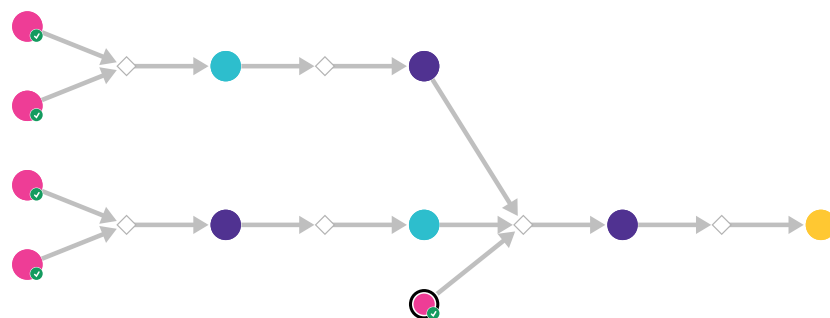

Substrates:

Figure 4: Outline of path 4

1. tert-Butyl isocyanide - *available at Sigma-Aldrich*

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

Products:

1. O=CC1=CCOC1=O
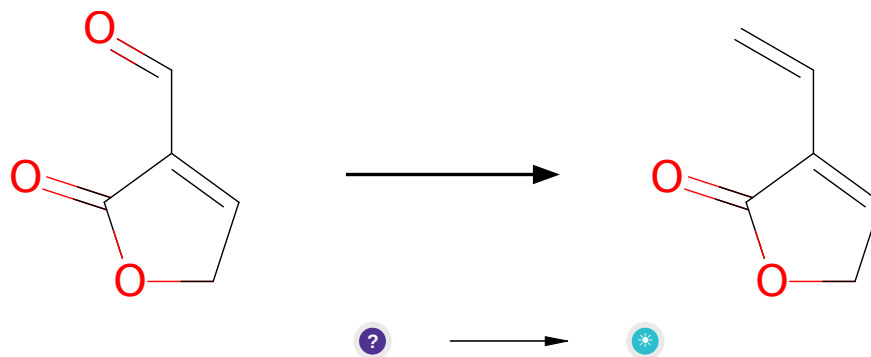
Typical conditions: Pd(OAc)2.JohnPhos.Na2CO3.H2O.Et3SiH.DMF.65C

Protections: none

Reference: DOI: *10.1021/ol5014262*

Retrosynthesis ID: 3104

2.4.2 Tebbe Olefination

Substrates:

1. O=CC1=CCOC1=O

Products:

1. 3-vinyl-2(5h)-furanone
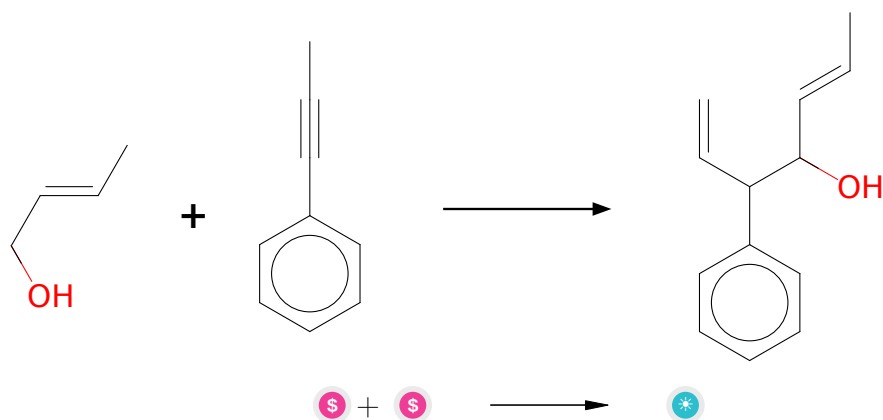
Typical conditions: Cp2TiCl2.AlMe3.toluene

Protections: none

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

Retrosynthesis ID: 11714

2.4.3 Coupling of alkynes and alcohols

Substrates:

1. 2-Buten-1-ol - *available at Sigma-Aldrich*

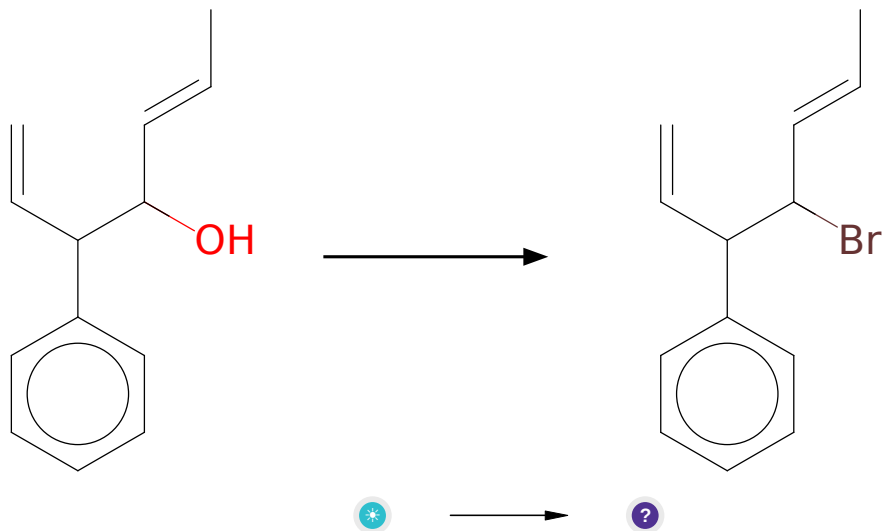2. 1-Phenyl-1-propyne - *available at Sigma-Aldrich*

Products:

1. C13H16O

Typical conditions: H2Ru(CO)(PPh3)3.2,4,6-(iPr)3PhSO3H.SL-J009-1.TBAI.IPA.THF.95C

Protections: none

Reference: DOI: *10.1021/jacs.5b00747*

Retrosynthesis ID: 9895

2.4.4   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

2.4.5   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

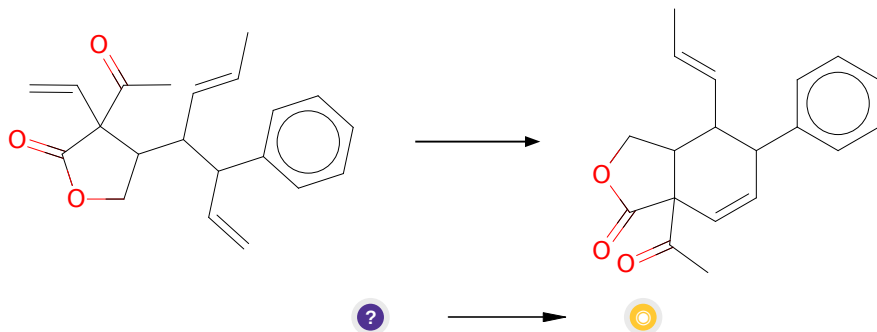3. Acetyl chloride -   *available at Sigma-Aldrich*

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
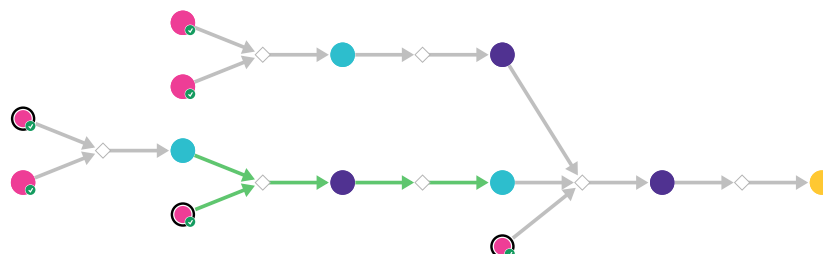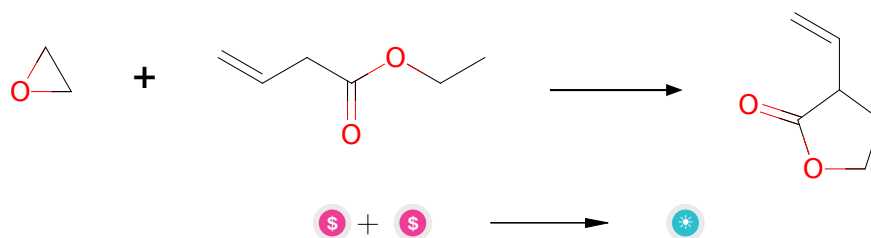
2.5 Path 5

Score: 164.14

Figure 5: Outline of path 5

2.5.1 Synthesis of lactones from epoxides

Substrates:

1. Oxirane - *available at Sigma-Aldrich*

2. Ethyl but-3-enoate - *available at Sigma-Aldrich*

Products:

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

Typical conditions: EtONa.EtOH.rt

Protections: none

Reference: *10.1021/ja9049959* and *10.1016/j.tetlet.2014.12.024* and *10.1021/jo00077a012* and *10.1016/0040-4039(96)00494-7* and *10.1002/chem.201403294*

Retrosynthesis ID: 21258

2.5.2 Enol esters and ethers synthesis

Substrates:

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

2. TMSCl - *available at Sigma-Aldrich*

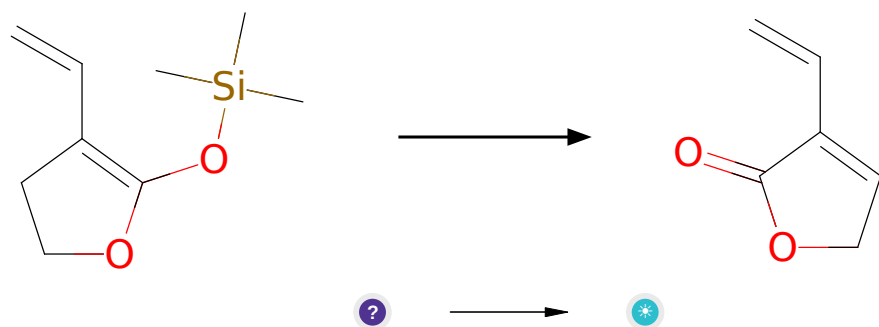**Products:**

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

2.5.3 Dehydrogenation of silyl enol ethers

Substrates:

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

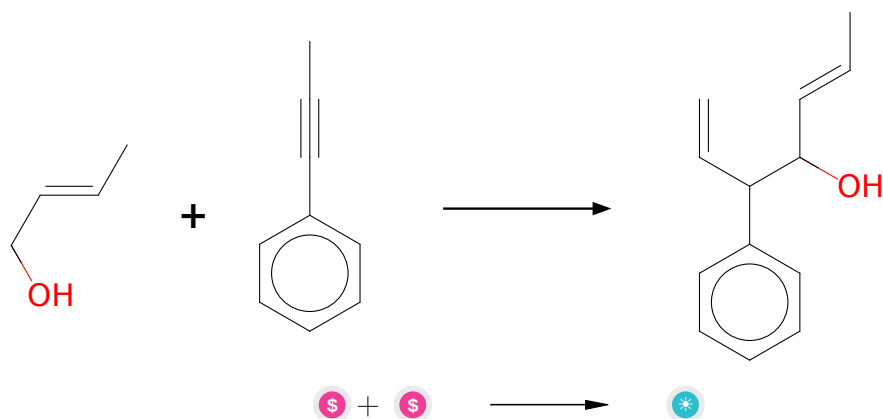**Products:**

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

2.5.4 Coupling of alkynes and alcohols

Substrates:

1. 2-Buten-1-ol - *available at Sigma-Aldrich*

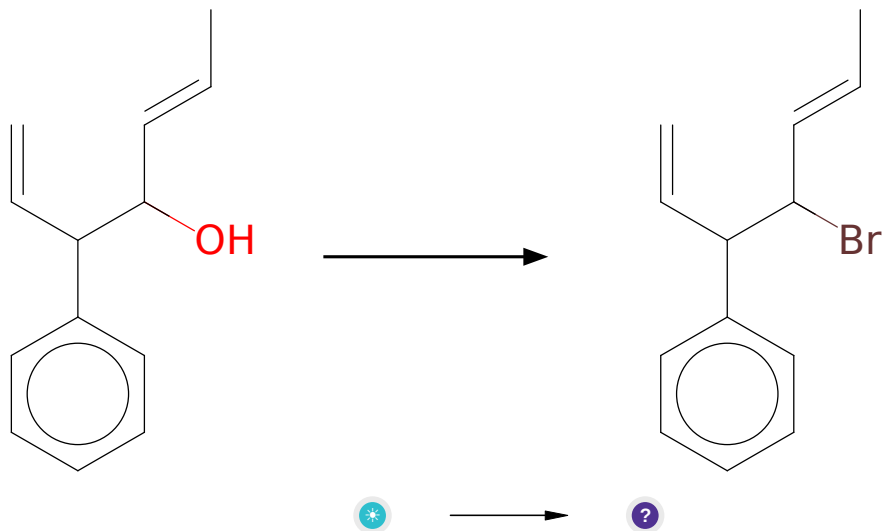2. 1-Phenyl-1-propyne - *available at Sigma-Aldrich*

Products:

1. C13H16O

Typical conditions: H2Ru(CO)(PPh3)3.2,4,6-(iPr)3PhSO3H.SL-J009-1.TBAI.IPA.THF.95C

Protections: none

Reference: DOI: *10.1021/jacs.5b00747*

Retrosynthesis ID: 9895

2.5.5   Appel Reaction

Substrates:

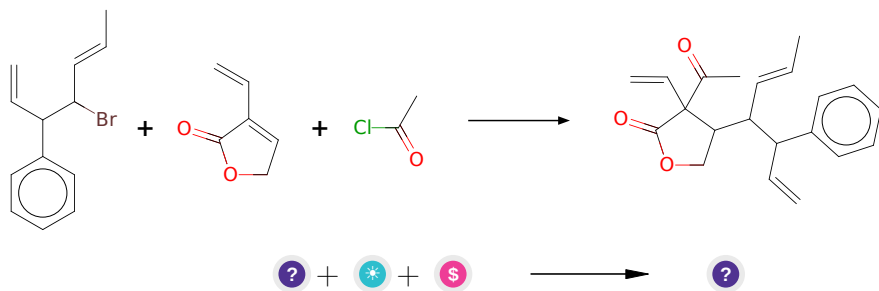1. C13H16O

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

2.5.6   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:

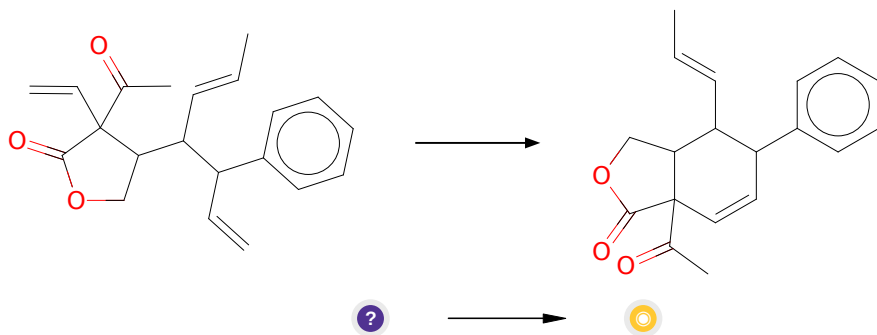1. C=CC(c1ccccc1)C(/C=C/C)C1COC(=O)C1(C=C)C(C)=O

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

2.5.7   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