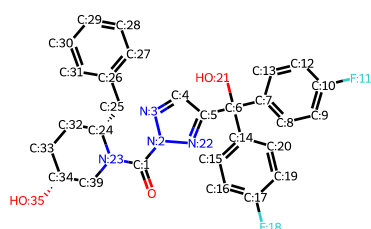


Product SMILES: O=[C:1]([n:2]1[n:3][cH:4][c:5]([C:6]([c:7]2[cH:8][cH:9][c:10]([F:11])[cH:12][cH:13]2)[c:14]2[cH:15][cH:16][c:17]([F:18])[cH:19][cH:20]2)[OH:21])[n:22]1)[N:23]1[C@@H:24]([CH2:25][c:26]2[cH:27][cH:28][cH:29][cH:30][cH:31]2)[CH2:32][CH2:33][C@@H:34]([O:35][CH2:36][C:37]#[CH:38])[CH2:39]1

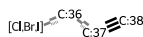
Proposed Transitions

Transition 1

- **Forward Reaction:** Williamson Ether Synthesis
- **Is Chemically Valid:** True
- **Is Template-based:** True
- **Reasoning:** This is the general template for the disconnection of the O:35-C:36 bond. It represents the reaction between the secondary alcohol alkoxide and a primary propargyl halide. The halide SMARTS represents the .
- **Is Smiles Valid:** False
- **Reactant 1:** O=[C:1]([n:2]1[n:3][cH:4][c:5]([C:6]([c:7]2[cH:8][cH:9][c:10]([F:11])[cH:12][cH:13]2)[c:14]2[cH:15][cH:16][c:17]([F:18])[cH:19][cH:20]2)[OH:21])[n:22]1)[N:23]1[C@@H:24]([CH2:25][c:26]2[cH:27][cH:28][cH:29][cH:30][cH:31]2)[CH2:32][CH2:33][C@@H:34]([OH:35])[CH2:39]1
- **Reactant 2:** [Cl,Br,I][CH2:36][C:37]#[CH:38]



R1



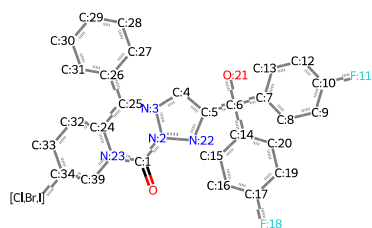
R2

Reactants for Transition 1

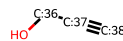
Transition 2

- **Forward Reaction:** Williamson Ether Synthesis
- **Is Chemically Valid:** True
- **Is Template-based:** True
- **Reasoning:** This is the general template for the disconnection of the C:34-O:35 bond. It represents the reaction between propargyl alcohol alkoxide and a secondary halide. The halide SMARTS represents the . Note the required inversion of stereochemistry at C:34 for an SN2 mechanism.
- **Is Smiles Valid:** False

- **Reactant 1:** O=[C:1]([n:2]1[n:3][cH:4][c:5]([C:6]([c:7]2[cH:8][cH:9][c:10]([F:11])[cH:12][cH:13]2)([c:14]2[cH:15][cH:16][c:17]([F:18])[cH:19][cH:20]2)[OH:21])[n:22]1)[N:23]1[C@@H:24]([CH2:25][c:26]2[cH:27][cH:28][cH:29][cH:30][cH:31]2)[CH2:32][CH2:33][C@H:34]([Cl,Br,I])[CH2:39]1
- **Reactant 2:** O[CH2:36][C:37]#[CH:38]



R1

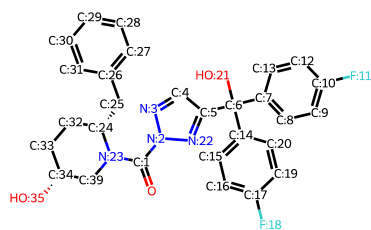


R2

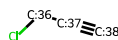
Reactants for Transition 2

Transition 3

- **Forward Reaction:** Williamson Ether Synthesis
- **Is Chemically Valid:** True
- **Is Template-based:** False
- **Reasoning:** This option is valid. It involves the SN2 reaction between a secondary alkoxide and a primary electrophile (propargyl chloride). This is a highly plausible and synthetically favorable pathway. The reaction retains the stereochemistry at C:34 and is expected to be chemoselective, as the secondary alcohol is more reactive than the tertiary alcohol at C:6.
- **Is Smiles Valid:** True
- **Reactant 1:** O=[C:1]([n:2]1[n:3][cH:4][c:5]([C:6]([c:7]2[cH:8][cH:9][c:10]([F:11])[cH:12][cH:13]2)([c:14]2[cH:15][cH:16][c:17]([F:18])[cH:19][cH:20]2)[OH:21])[n:22]1)[N:23]1[C@@H:24]([CH2:25][c:26]2[cH:27][cH:28][cH:29][cH:30][cH:31]2)[CH2:32][CH2:33][C@H:34]([OH:35])[CH2:39]1
- **Reactant 2:** Cl[CH2:36][C:37]#[CH:38]



R1

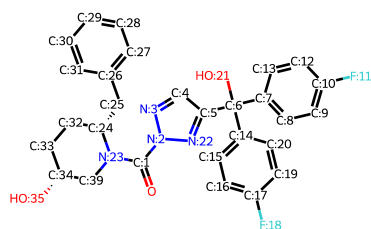


R2

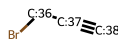
Reactants for Transition 3

Transition 4

- **Forward Reaction:** Williamson Ether Synthesis
- **Is Chemically Valid:** True
- **Is Template-based:** False
- **Reasoning:** This option is valid. Propargyl bromide is an excellent electrophile for this SN2 reaction. The pathway involving the secondary alkoxide and primary halide is kinetically favored, sterically accessible, and avoids elimination side reactions. The stereocenter at C:34 is unaffected.
- **Is Smiles Valid:** True
- **Reactant 1:** O=[C:1]([n:2]1[n:3][cH:4][c:5]([C:6]([c:7]2[cH:8][cH:9][c:10]([F:11])[cH:12][cH:13]2)([c:14]2[cH:15][cH:16][c:17]([F:18])[cH:19][cH:20]2)[OH:21])[n:22]1)[N:23]1[C@@H:24]([CH2:25][c:26]2[cH:27][cH:28][cH:29][cH:30][cH:31]2)[CH2:32][CH2:33][C@@H:34]([OH:35])[CH2:39]1
- **Reactant 2:** Br[CH2:36][C:37]#[CH:38]



R1

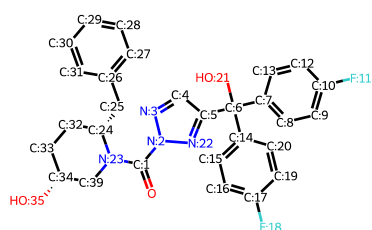


R2

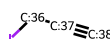
Reactants for Transition 4

Transition 5

- **Forward Reaction:** Williamson Ether Synthesis
- **Is Chemically Valid:** True
- **Is Template-based:** False
- **Reasoning:** This option is valid. Iodide is an excellent leaving group, making propargyl iodide a highly reactive electrophile. The reaction with the secondary alkoxide is expected to proceed efficiently via an SN2 mechanism, retaining stereochemistry at C:34. This is a very strong synthetic option.
- **Is Smiles Valid:** True
- **Reactant 1:** O=[C:1]([n:2]1[n:3][cH:4][c:5]([C:6]([c:7]2[cH:8][cH:9][c:10]([F:11])[cH:12][cH:13]2)[c:14]2[cH:15][cH:16][c:17]([F:18])[cH:19][cH:20]2)[OH:21])[n:22]1)[N:23]1[C@@H:24]([CH2:25][c:26]2[cH:27][cH:28][cH:29][cH:30][cH:31]2)[CH2:32][CH2:33][C@@H:34]([OH:35])[CH2:39]1
- **Reactant 2:** I[CH2:36][C:37]#[CH:38]



R1

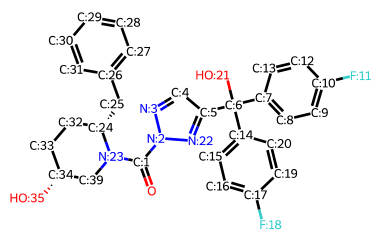


R2

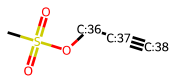
Reactants for Transition 5

Transition 6

- **Forward Reaction:** Williamson Ether Synthesis
- **Is Chemically Valid:** True
- **Is Template-based:** False
- **Reasoning:** This option is valid. Using propargyl mesylate as the electrophile is an excellent alternative to halides. The mesylate is a superb leaving group, promoting a clean SN2 reaction with the secondary alkoxide. This pathway is highly plausible and synthetically useful.
- **Is Smiles Valid:** True
- **Reactant 1:** O=[C:1]([n:2]1[n:3][cH:4][c:5]([C:6]([c:7]2[cH:8][cH:9][c:10]([F:11])[cH:12][cH:13]2)[c:14]2[cH:15][cH:16][c:17]([F:18])[cH:19][cH:20]2)[OH:21])[n:22]1)[N:23]1[C@@H:24]([CH2:25][c:26]2[cH:27][cH:28][cH:29][cH:30][cH:31]2)[CH2:32][CH2:33][C@@H:34]([OH:35])[CH2:39]1
- **Reactant 2:** CS(=O)(=O)O[CH2:36][C:37]#[CH:38]



R1

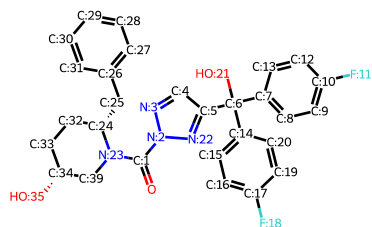


R2

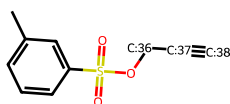
Reactants for Transition 6

Transition 7

- **Forward Reaction:** Williamson Ether Synthesis
- **Is Chemically Valid:** True
- **Is Template-based:** False
- **Reasoning:** This option is valid. Propargyl tosylate is a common, stable, and highly effective electrophile for Williamson ether synthesis. The tosylate leaving group ensures a rapid and clean SN2 reaction. This is a standard and robust method for this transformation.
- **Is Smiles Valid:** True
- **Reactant 1:** O=[C:1]([n:2]1[n:3][cH:4][c:5]([C:6]([c:7]2[cH:8][cH:9][c:10]([F:11])[cH:12][cH:13]2)([c:14]2[cH:15][cH:16][c:17]([F:18])[cH:19][cH:20]2)[OH:21])[n:22]1)[N:23]1[C@@H:24]([CH2:25][c:26]2[cH:27][cH:28][cH:29][cH:30][cH:31]2)[CH2:32][CH2:33][C@@H:34]([OH:35])[CH2:39]1
- **Reactant 2:** c1ccc(C)cc1S(=O)(=O)O[CH2:36][C:37]#[CH:38]



R1

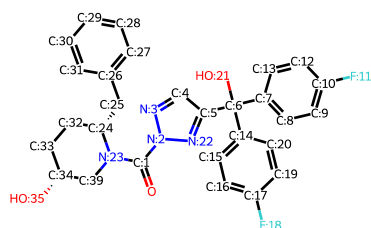


R2

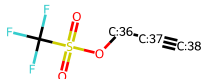
Reactants for Transition 7

Transition 8

- **Forward Reaction:** Williamson Ether Synthesis
- **Is Chemically Valid:** True
- **Is Template-based:** False
- **Reasoning:** This option is valid. Propargyl triflate is an extremely reactive electrophile due to the excellent triflate leaving group. The reaction with the secondary alkoxide would be very fast. This pathway is highly plausible, offering a very efficient route to the product.
- **Is Smiles Valid:** True
- **Reactant 1:** O=[C:1]([n:2]1[n:3][cH:4][c:5]([C:6]([c:7]2[cH:8][cH:9][c:10]([F:11])[cH:12][cH:13]2)[c:14]2[cH:15][cH:16][c:17]([F:18])[cH:19][cH:20]2)[OH:21])[n:22]1)[N:23]1[C@@H:24]([CH2:25][c:26]2[cH:27][cH:28][cH:29][cH:30][cH:31]2)[CH2:32][CH2:33][C@@H:34]([OH:35])[CH2:39]1
- **Reactant 2:** FC(F)(F)S(=O)(=O)O[CH2:36][C:37]#[CH:38]



R1

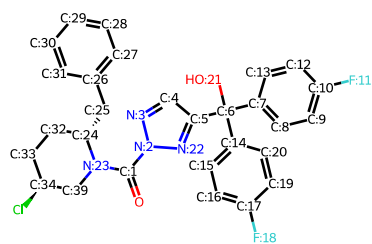


R2

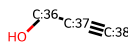
Reactants for Transition 8

Transition 9

- **Forward Reaction:** Williamson Ether Synthesis
- **Is Chemically Valid:** True
- **Is Template-based:** False
- **Reasoning:** This option is chemically possible but less favorable. It requires an SN2 reaction at a sterically hindered secondary carbon. This is kinetically slower and competes with E2 elimination. For the reaction to yield the target product, inversion of configuration at C:34 is required, meaning the starting chloride must have the (S) configuration, represented by [C@H:34].
- **Is Smiles Valid:** True
- **Reactant 1:** O=[C:1]([n:2]1[n:3][cH:4][c:5]([C:6]([c:7]2[cH:8][cH:9][c:10]([F:11])[cH:12][cH:13]2)[c:14]2[cH:15][cH:16][c:17]([F:18])[cH:19][cH:20]2)[OH:21])[n:22]1)[N:23]1[C@@H:24]([CH2:25][c:26]2[cH:27][cH:28][cH:29][cH:30][cH:31]2)[CH2:32][CH2:33][C@H:34](Cl)[CH2:39]1
- **Reactant 2:** O[CH2:36][C:37]#[CH:38]



R1

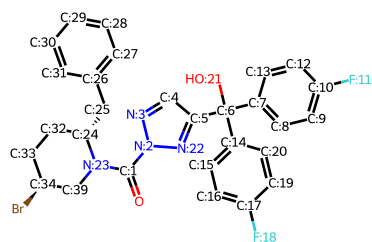


R2

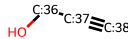
Reactants for Transition 9

Transition 10

- **Forward Reaction:** Williamson Ether Synthesis
- **Is Chemically Valid:** True
- **Is Template-based:** False
- **Reasoning:** This option is valid, though synthetically challenging. The SN2 reaction at the secondary bromide is subject to steric hindrance and E2 elimination. Success would depend heavily on reaction conditions. Stereochemical inversion at C:34 is necessary, requiring the (S)-bromide starting material.
- **Is Smiles Valid:** True
- **Reactant 1:** O=[C:1]([n:2]1[n:3][cH:4][c:5]([C:6]([c:7]2[cH:8][cH:9][c:10]([F:11])[cH:12][cH:13]2)([c:14]2[cH:15][cH:16][c:17]([F:18])[cH:19][cH:20]2)[OH:21])[n:22]1)[N:23]1[C@@H:24]([CH2:25][c:26]2[cH:27][cH:28][cH:29][cH:30][cH:31]2)[CH2:32][CH2:33][C@H:34](Br)[CH2:39]1
- **Reactant 2:** O[CH2:36][C:37]#[CH:38]



R1

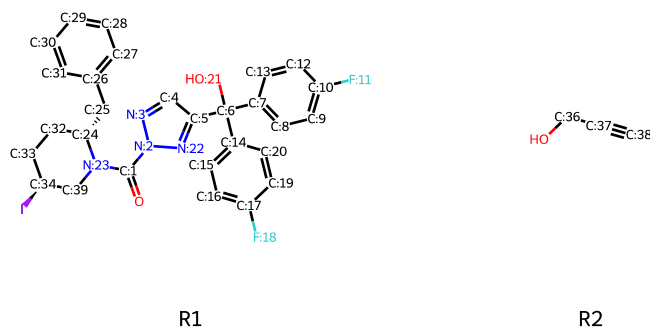


R2

Reactants for Transition 10

Transition 11

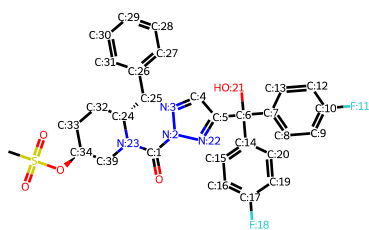
- **Forward Reaction:** Williamson Ether Synthesis
- **Is Chemically Valid:** True
- **Is Template-based:** False
- **Reasoning:** This option is plausible. While SN2 at a secondary center is difficult, iodide is an excellent leaving group which can facilitate the reaction. However, it still competes with E2 elimination. Inversion of configuration at C:34 is required.
- **Is Smiles Valid:** True
- **Reactant 1:** O=[C:1]([n:2]1[n:3][cH:4][c:5]([C:6]([c:7]2[cH:8][cH:9][c:10]([F:11])[cH:12][cH:13]2)[c:14]2[cH:15][cH:16][c:17]([F:18])[cH:19][cH:20]2)[OH:21])[n:22]1)[N:23]1[C@@H:24]([CH2:25][c:26]2[cH:27][cH:28][cH:29][cH:30][cH:31]2)[CH2:32][CH2:33][C@H:34](I)[CH2:39]1
- **Reactant 2:** O[CH2:36][C:37]#[CH:38]



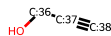
Reactants for Transition 11

Transition 12

- **Forward Reaction:** Williamson Ether Synthesis
- **Is Chemically Valid:** True
- **Is Template-based:** False
- **Reasoning:** This option is plausible. The use of a mesylate, an excellent leaving group, increases the likelihood of a successful SN2 reaction at the secondary center compared to halides. Nevertheless, steric hindrance and potential elimination remain concerns. Stereochemical inversion at C:34 is required.
- **Is Smiles Valid:** True
- **Reactant 1:** O=[C:1]([n:2]1[n:3][cH:4][c:5]([C:6]([c:7]2[cH:8][cH:9][c:10]([F:11])[cH:12][cH:13]2)[c:14]2[cH:15][cH:16][c:17]([F:18])[cH:19][cH:20]2)[OH:21])[n:22]1)[N:23]1[C@@H:24]([CH2:25][c:26]2[cH:27][cH:28][cH:29][cH:30][cH:31]2)[CH2:32][CH2:33][C@H:34](OS(=O)(=O)C)[CH2:39]1
- **Reactant 2:** O[CH2:36][C:37]#[CH:38]



R1

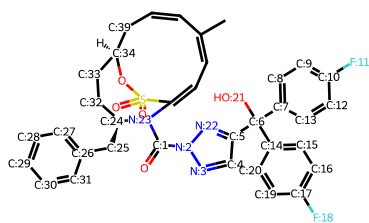


R2

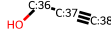
Reactants for Transition 12

Transition 13

- **Forward Reaction:** Williamson Ether Synthesis
- **Is Chemically Valid:** True
- **Is Template-based:** False
- **Reasoning:** This option is plausible. A tosylate is a very good leaving group, making SN2 at the secondary center more feasible. This is one of the better options for this less-favored pathway, though it is still inferior to the primary electrophile pathway. Requires inversion of stereochemistry at C:34.
- **Is Smiles Valid:** True
- **Reactant 1:** O=[C:1]([n:2]1[n:3][cH:4][c:5]([C:6]([c:7]2[cH:8][cH:9][c:10]([F:11])[cH:12][cH:13]2)([c:14]2[cH:15][cH:16][c:17]([F:18])[cH:19][cH:20]2)[OH:21])[n:22]1)[N:23]1[C@@H:24]([CH2:25][c:26]2[cH:27][cH:28][cH:29][cH:30][cH:31]2)[CH2:32][CH2:33][C@H:34](OS(=O)(=O)c1ccc(C)cc1)[CH2:39]1
- **Reactant 2:** O[CH2:36][C:37]#[CH:38]



R1

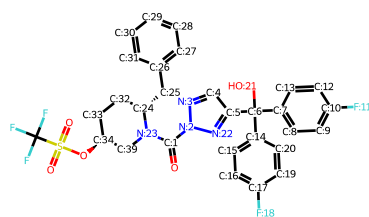


R2

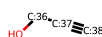
Reactants for Transition 13

Transition 14

- **Forward Reaction:** Williamson Ether Synthesis
- **Is Chemically Valid:** True
- **Is Template-based:** False
- **Reasoning:** This option is plausible. The triflate is an exceptionally good leaving group, which can often overcome the steric hindrance of a secondary center to allow for SN2. This represents the most likely successful permutation for this pathway, but still requires careful control of conditions to minimize elimination. Inversion of configuration at C:34 is mandatory.
- **Is Smiles Valid:** True
- **Reactant 1:** O=[C:1]([n:2]1[n:3][cH:4][c:5]([C:6]([c:7]2[cH:8][cH:9][c:10]([F:11])[cH:12][cH:13]2)[c:14]2[cH:15][cH:16][c:17]([F:18])[cH:19][cH:20]2)[OH:21])[n:22]1)[N:23]1[C@@H:24]([CH2:25][c:26]2[cH:27][cH:28][cH:29][cH:30][cH:31]2)[CH2:32][CH2:33][C@H:34](OS(=O)(=O)C(F)(F)F)[CH2:39]1
- **Reactant 2:** O[CH2:36][C:37]#[CH:38]



R1



R2

Reactants for Transition 14