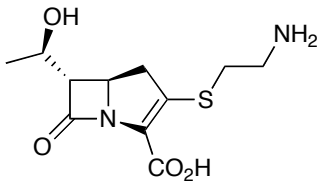
Thienamycin



Isolation:

1. Merck, 1976
2. From *Streptomyces cattleya*
   Merck & Co., Inc., U.S. Patent 3,950,357 (April 12, 1976)

Structure and Absolute Stereochemistry:

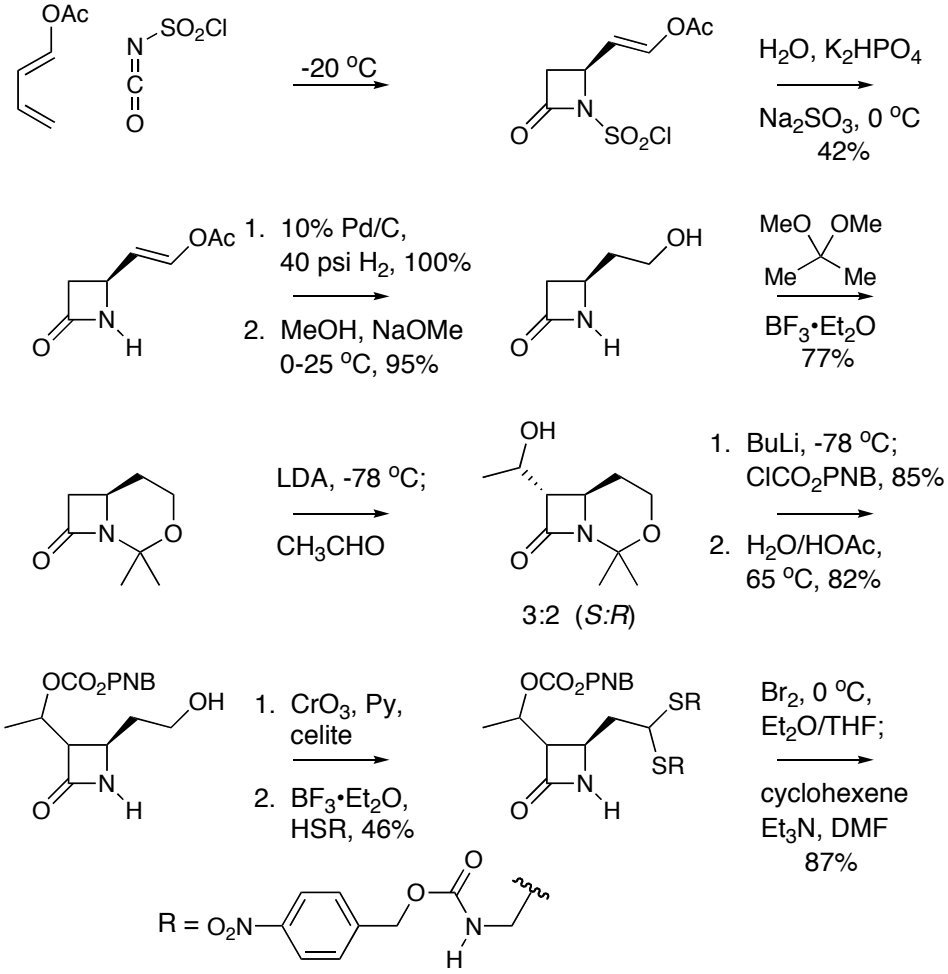
1. Chemical transformation and spectroscopy
2. X-Ray of N-acetylthienamycin methyl ester
   J. Am. Chem. Soc. **1978**, *100*, 6491

Properties:

1. Active against gram-positive and gram-negative bacteria
2. Resistant to bacterial β-lactamase
   J. Antibiotics. **1979**, *32*, 1

First Total Synthesis (Racemic): Merck

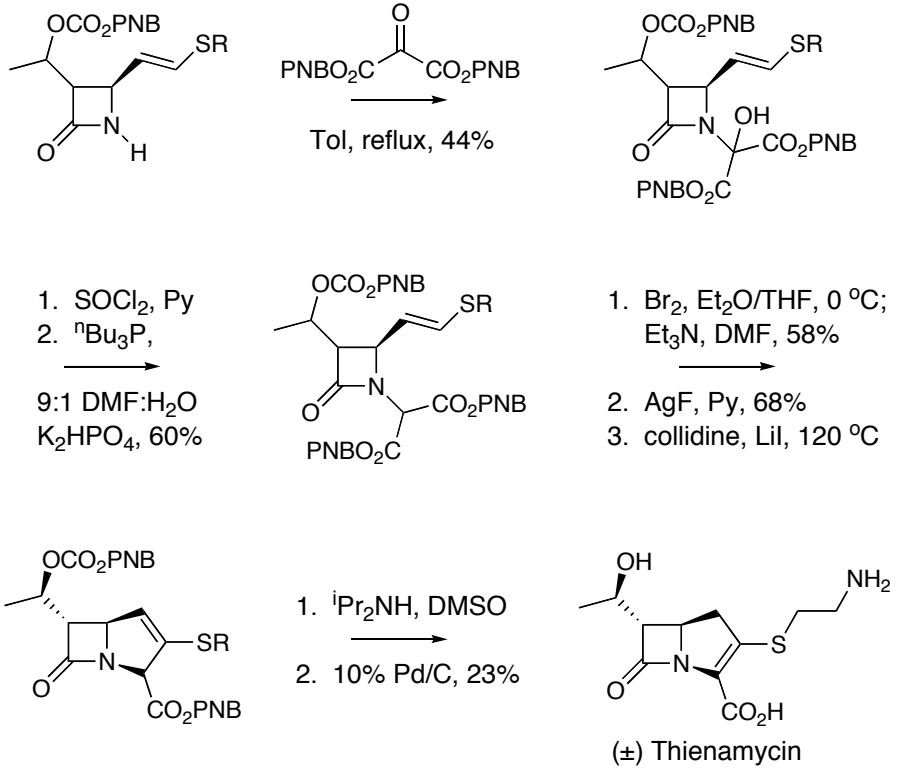
J. Am. Chem. Soc. **1978**, *100*, 313
J. Org. Chem. **1980**, *45*, 1130
J. Org. Chem. **1980**, *45*, 1135
J. Org. Chem. **1980**, *45*, 1142



Thienamycin

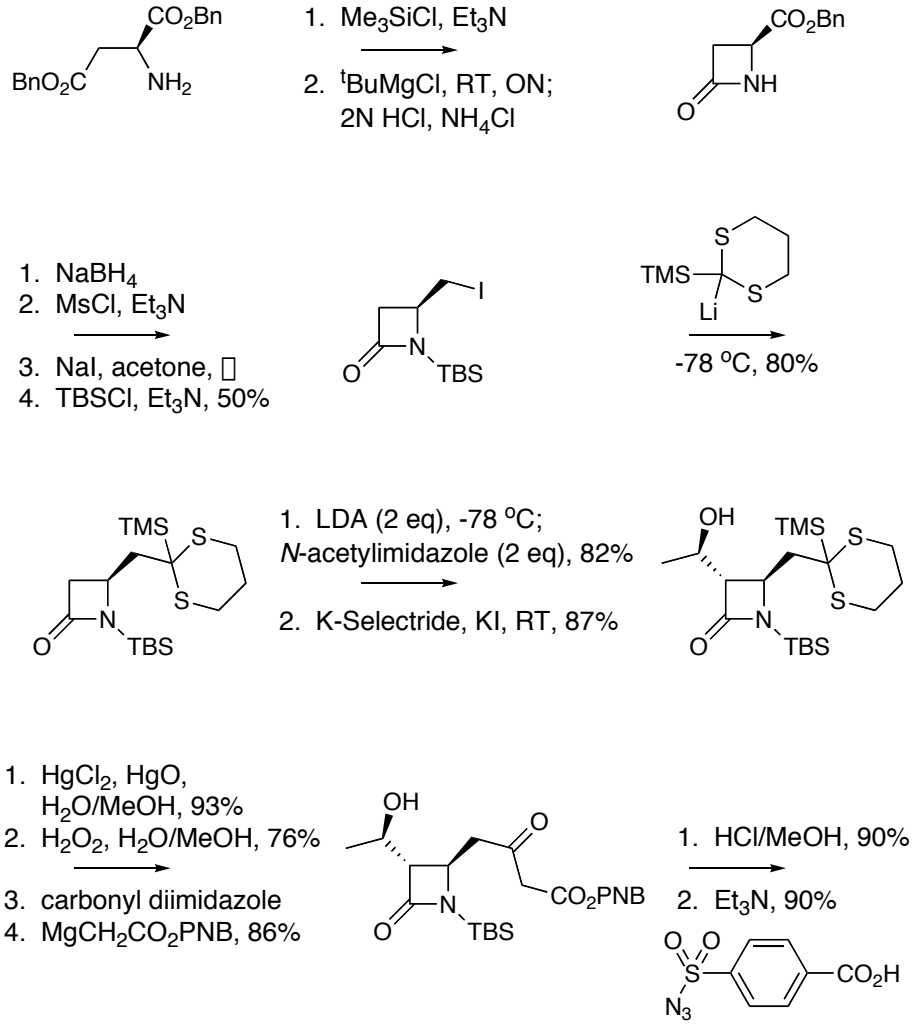
First Total Synthesis (Racemic): Merck

J. Am. Chem. Soc. **1978**, *100*, 313
J. Org. Chem. **1980**, *45*, 1130
J. Org. Chem. **1980**, *45*, 1135
J. Org. Chem. **1980**, *45*, 1142



Asymmetric Total Synthesis: Merck

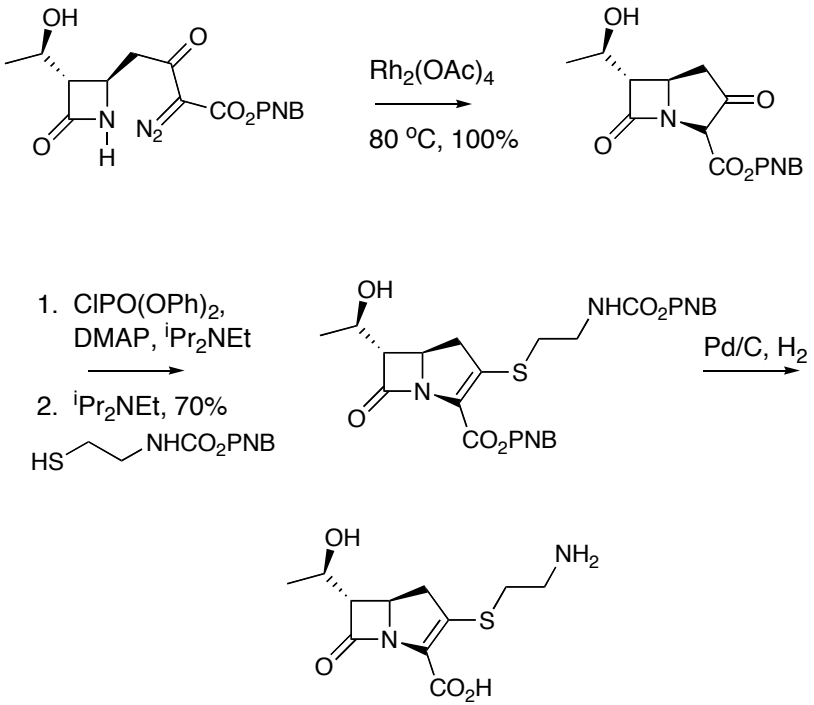
J. Am. Chem. Soc. **1980**, *102*, 6161



Thienamycin

Asymmetric Total Synthesis: Merck

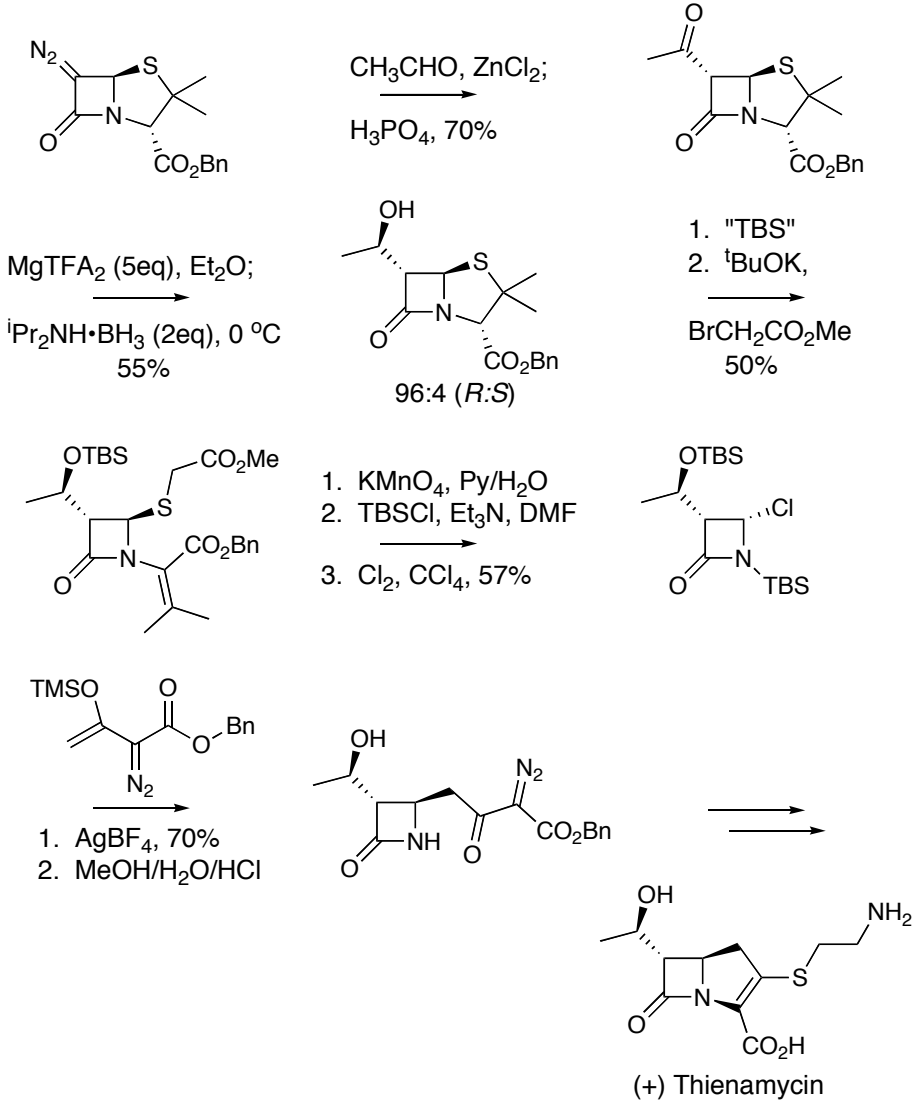
J. Am. Chem. Soc. **1980**, *102*, 6161



(+) Thienamycin

Asymmetric Total Synthesis from Penicillin: Merck

J. Am. Chem. Soc. **1981**, *103*, 6765

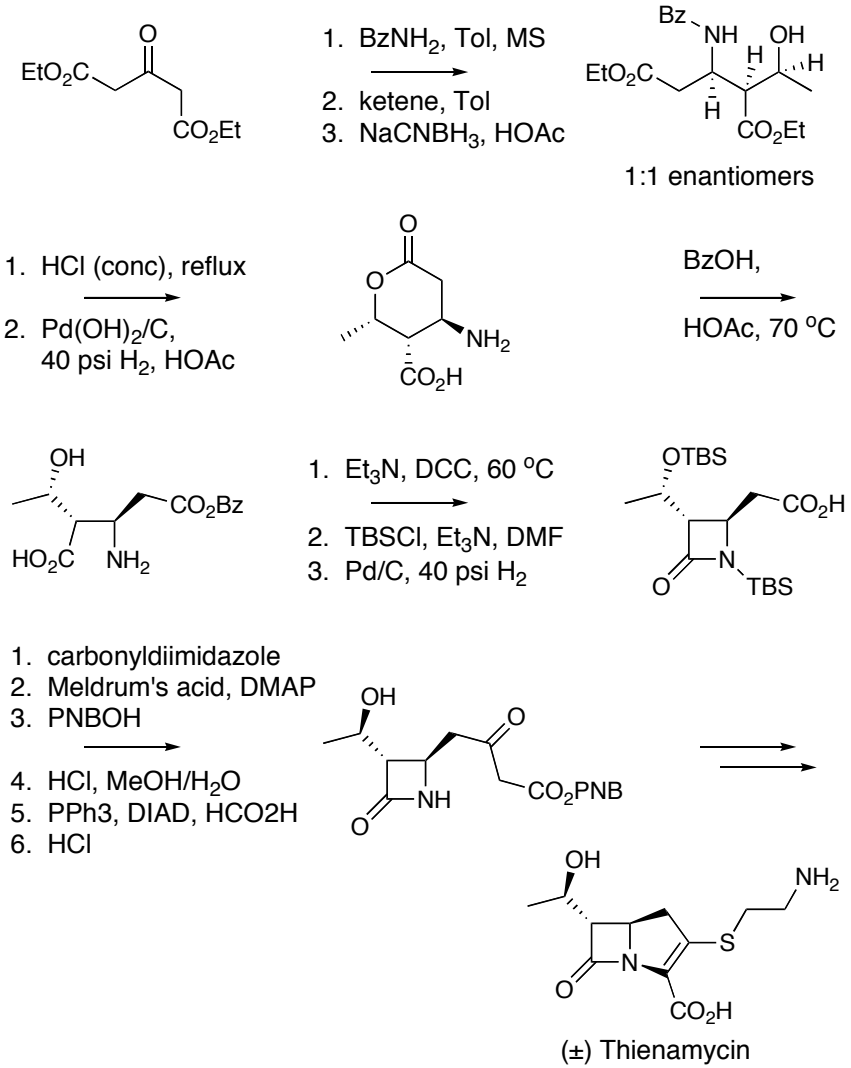


(+) Thienamycin

Thienamycin

Racemic Total Synthesis: Merck Process

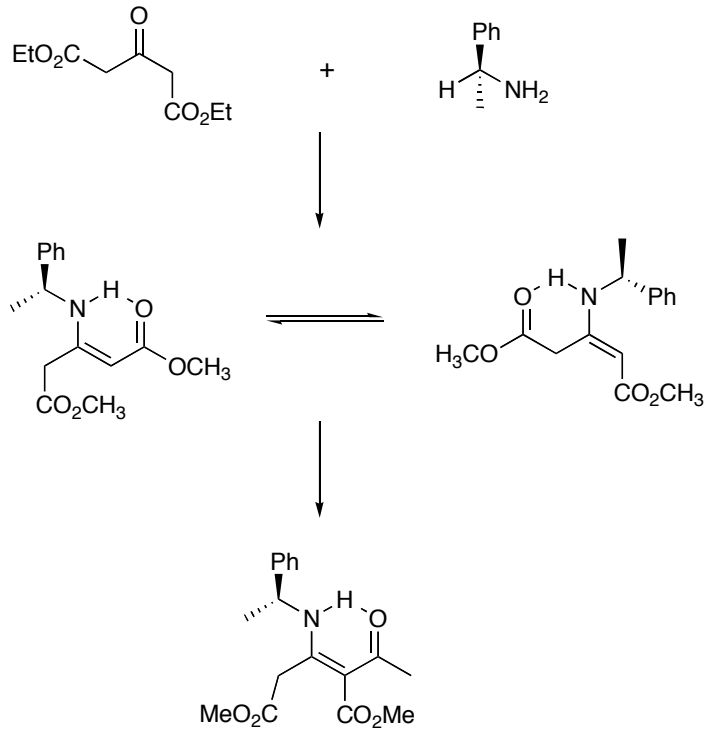
Tetrahedron Lett. **1980**, *21*, 2783



Asymmetric Total Synthesis: Merck Process

J. Org. Chem. **1986**, *51*, 1498

Formation of chiral enamino ketone:



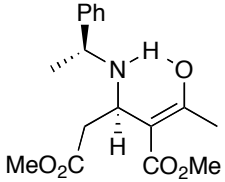
1. Not necessary to isolate after condensation step
2. Use of a catalytic amount of HOAc doubles rate of condensation, supresses byproduct formation, helps establish equilibrium
3. Once equilibrium established, introduce ketene gas and reaction is instantaneous with >95% yield.

Asymmetric Total Synthesis: Merck Process

J. Org. Chem. **1986**, *51*, 1498

Reduction with boron reagents.

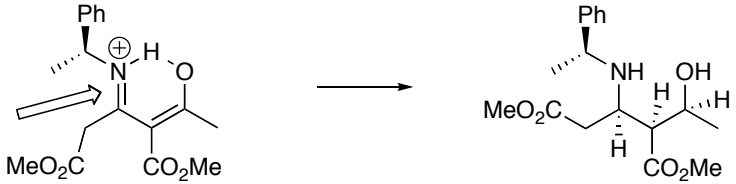
1. Acidic borohydride reductions resulted in no stereocontrol
2. Catechol borane at -78 ^{o}C resulted in desired reduction to give:



3. Sodium cyanoborohydride reduction with acetic or propionic acid resulted in rapid reduction of the enol
4. Reduction product was <50% yield and elimination was a major competing reaction

Catalytic Hydrogenation

1. Conditions: Pt/C, H_3PO_4 (2 eq), HOAc, RT, 90-1000 psi H_2
2. Reduction proceeds from most accessible face (back) to give >60% yield of product
3. High H_2 pressure supresses side product formation and enhances stereoselectivity

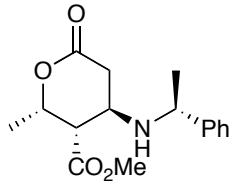


Asymmetric Total Synthesis: Merck Process

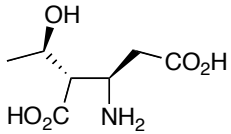
J. Org. Chem. **1986**, *51*, 1498

Completion of Synthesis of Key Intermediate

1. Intermediate above isolated by conversion to the lactone and crystallization (>90% yield) to give pure:



2. Hydrolysis of the ester proceeded in >98% yield with concentrated HCl at 85 ^{o}C with no purification necessary
3. Remove solvent by vacuum distillation.
4. Remove the protecting group with Pd/C and H_2 and crystallize the product in >90% yield.
5. Allows generation of the key intermediate below in 50% overall yield with only two purification steps



Detailed Study of the Mitsunobu Reaction as Applied to the Synthesis of Thienamycin.

J. Am. Chem. Soc. **1988**, *110*, 6487

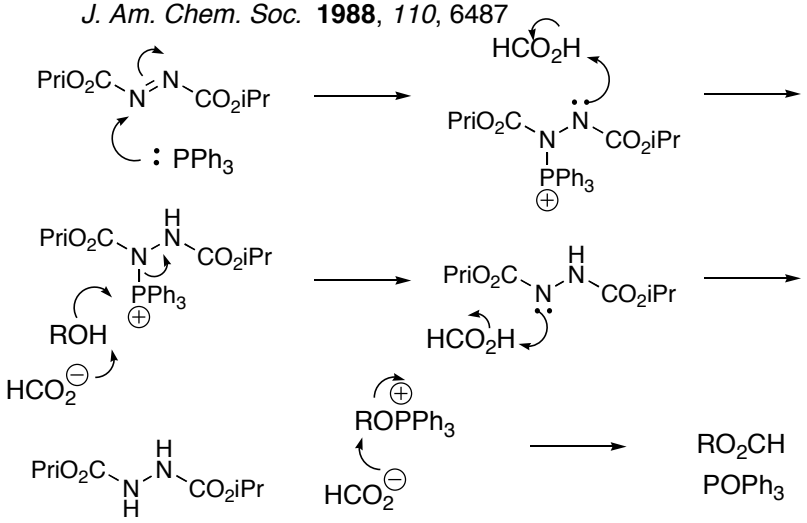
Could invert the stereocenter as above, or invert intramolecularly on the compound above.

Tetrahedron Lett. **1981**, *22*, 913

Thienamycin

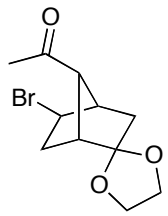
Mitsunobu Mechanism

J. Am. Chem. Soc. **1988**, *110*, 6487

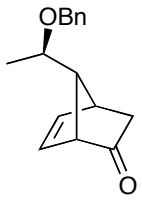


Racemic Formal Synthesis: Grieco

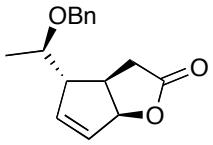
J. Am. Chem. Soc. **1984**, *106*, 6414



1. $LiAlH(OMe)_3$, THF, -100 °C, 91%
2. DBU
3. NaH, HMPA, THF, BnBr, $^nBu_4NI$, 85%



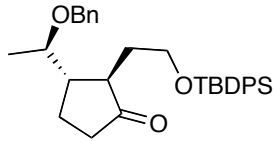
1. 10% NaOH, 30% H_2O_2,
2. $BF_3 \cdot Et_2O$ 78%



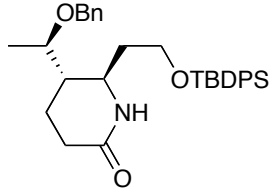
1. LAH
2. $NaBH_4$, $NiCl_2$
3. TBDPSCl, Et_3N, DMAP
4. PCC, NaOAc 74%

Racemic Formal Synthesis: Grieco

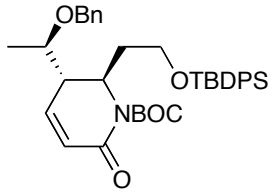
J. Am. Chem. Soc. **1984**, *106*, 6414



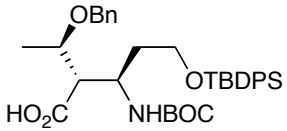
1. $H_2NOH \cdot HCl$, NaOAc
2. TsCl, DMAP, Py 80%



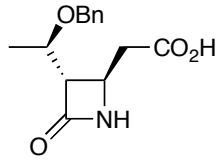
1. BOC_2O, Et_3N, DMAP
2. LDA; PhSSPh
3. mCPBA, -78 °C
4. Tol, 100 °C, 73%



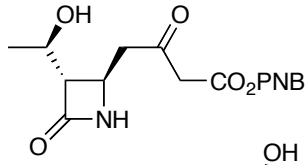
1. $KMnO_4$, $NaIO_4$, $H_2O/^tBuOH$, $NaHCO_3$
2. NaOMe, MeOH 65%

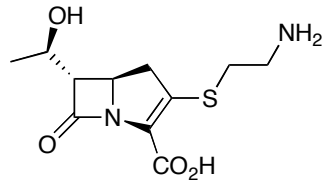


1. TFA
2. Et_3N; DCC, 84%
3. $^nBu_4NF$
4. Jones, 80%



1. Pd, H_2, 100%
2. carbonyldiimidazole; $MgO_2CCH_2CO_2PNB$ 50%



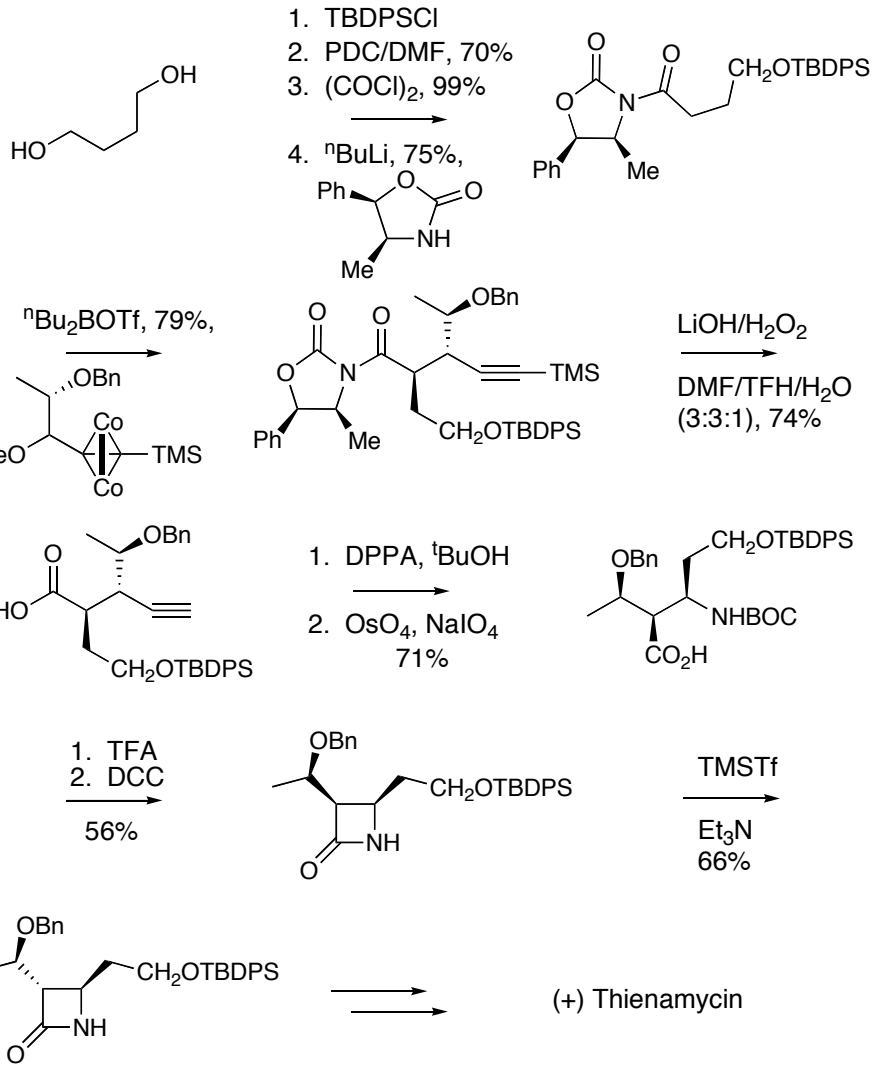


(±) Thienamycin

Asymmetric Formal Synthesis: Jacobi

Making Grieco Asymmetric

J. Org. Chem. **1996**, *61*, 2413

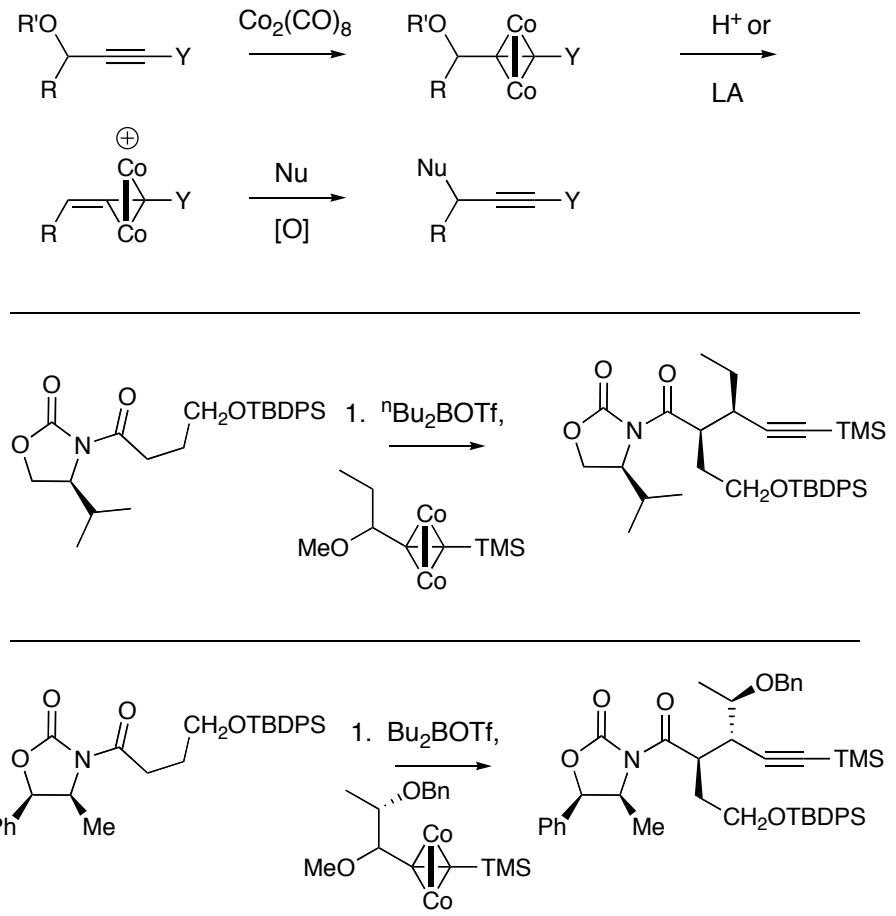


Asymmetric Formal Synthesis: Jacobi

Nicholas Reaction

J. Org. Chem. **1996**, *61*, 2413

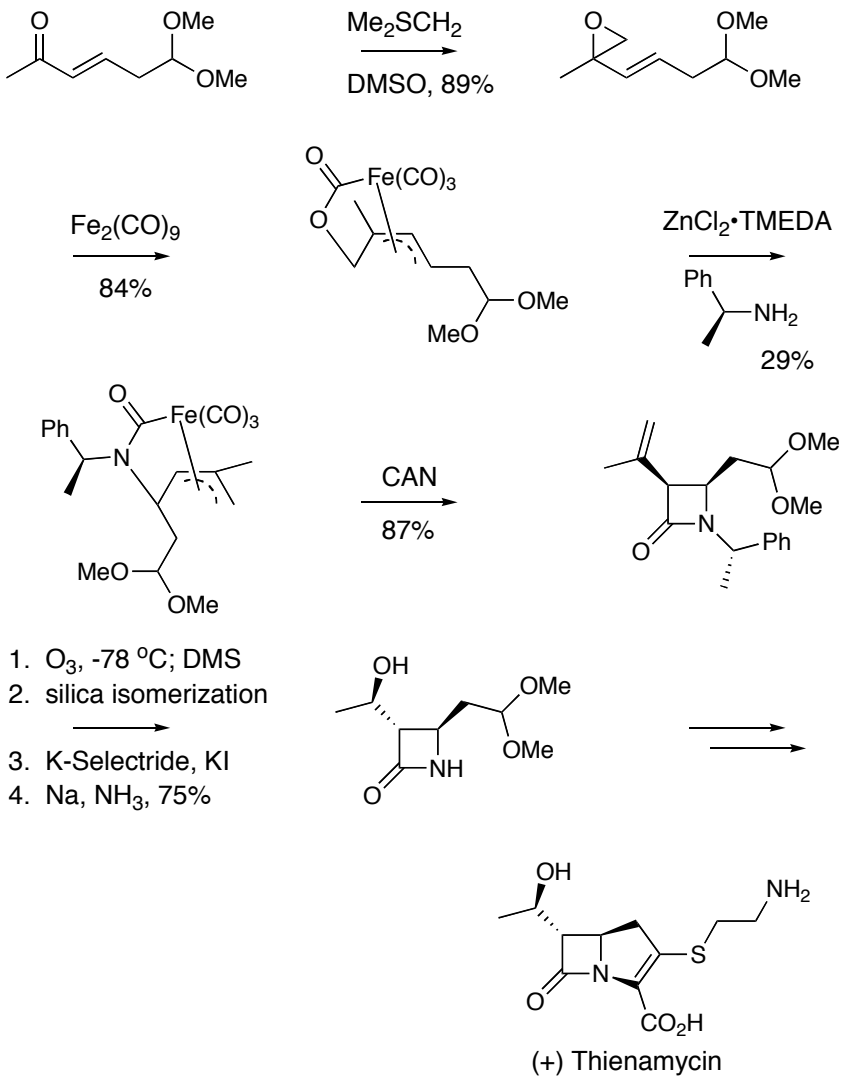
J. Am. Chem. Soc. **1987**, *109*, 5749. Schreiber asymmetric Nicholas



Thienamycin

Asymmetric Formal Synthesis: Ley

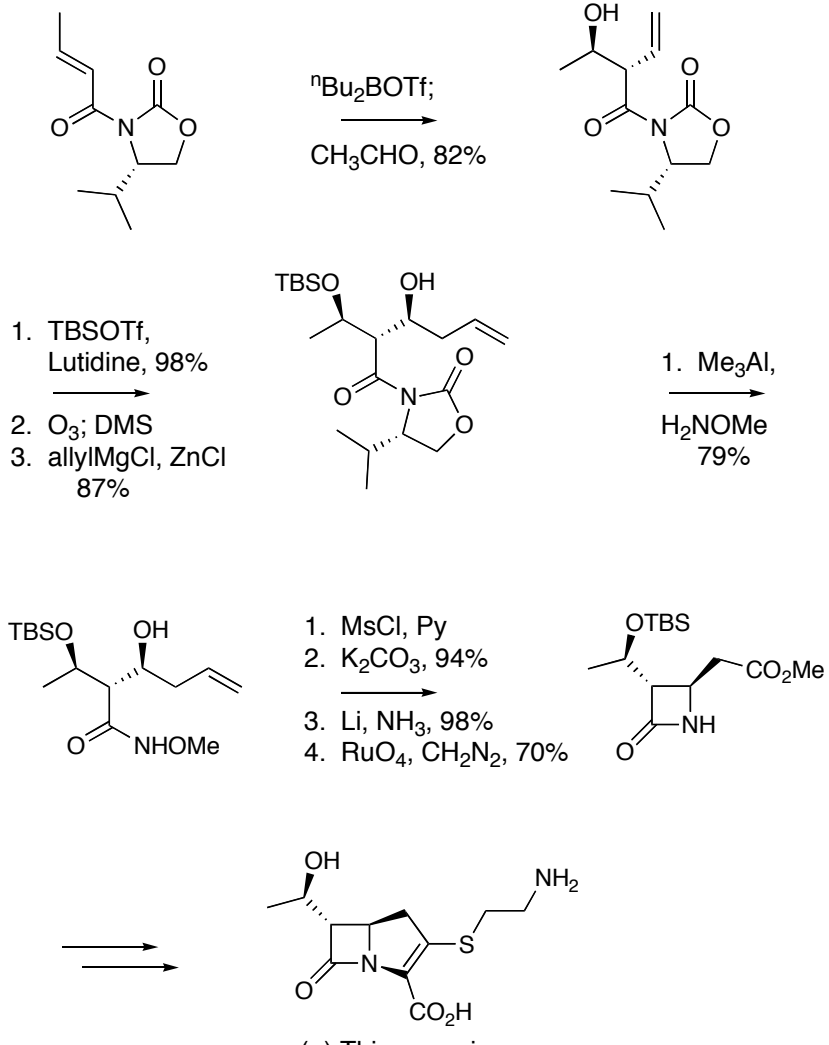
J. Chem. Soc., Chem. Commun. **1984**, 494



(+) Thienamycin

Asymmetric Formal Synthesis: Evans

Tetrahedron Lett. **1986**, *27*, 4961



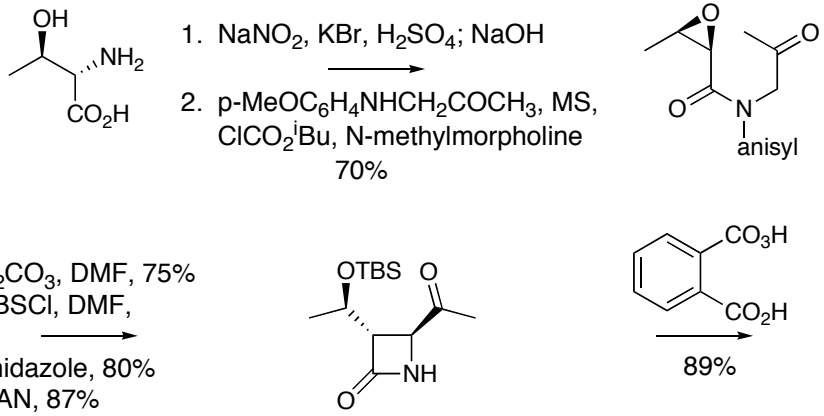
(+) Thienamycin

Thienamycin

Asymmetric Formal Synthesis: Hanessian

J. Am. Chem. Soc. **1985**, *107*, 1438

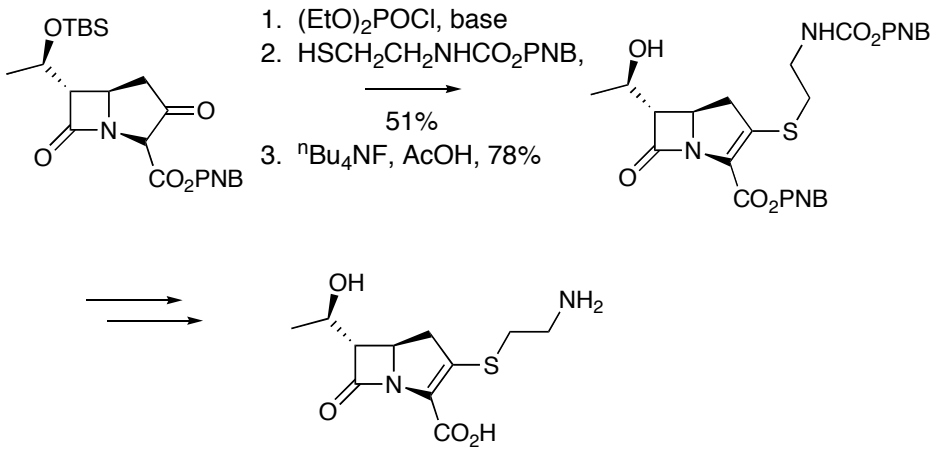
J. Org. Chem. **1990**, *55*, 3098



Asymmetric Formal Synthesis: Hanessian

J. Am. Chem. Soc. **1985**, *107*, 1438

J. Org. Chem. **1990**, *55*, 3098

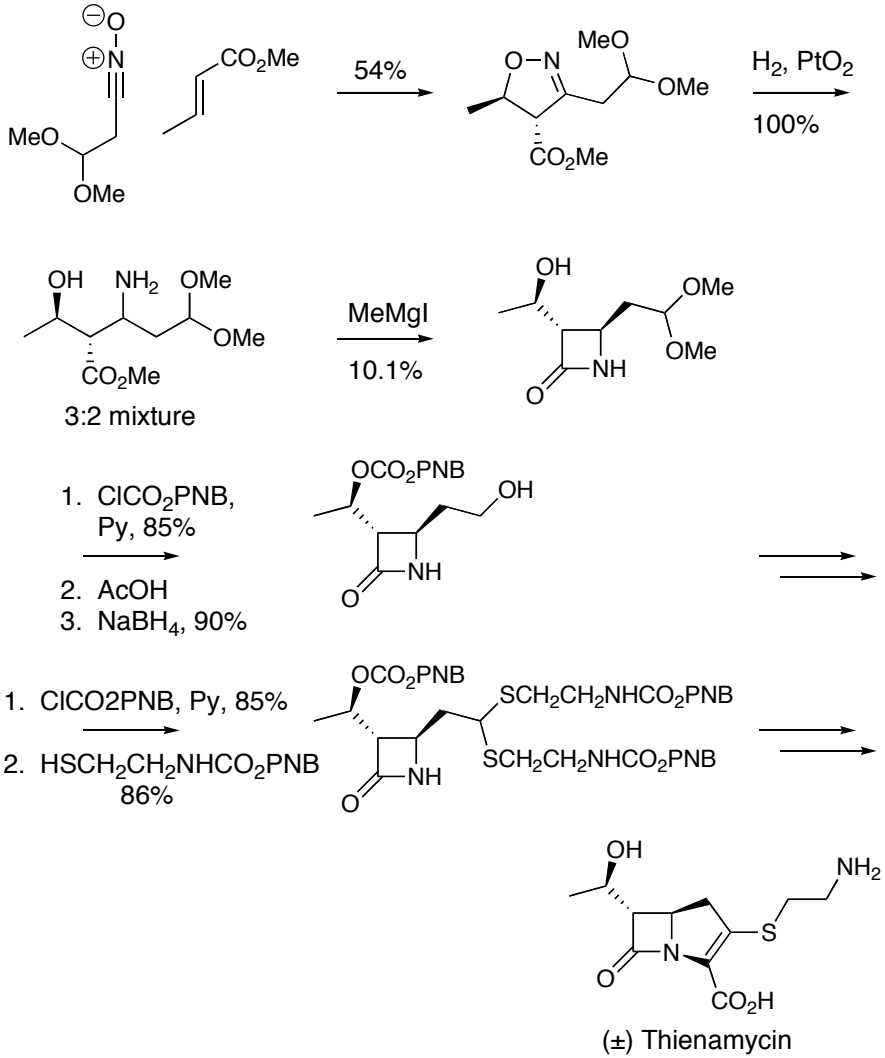


(±) Thienamycin

Thienamycin

Racemic Formal Synthesis: Kametani

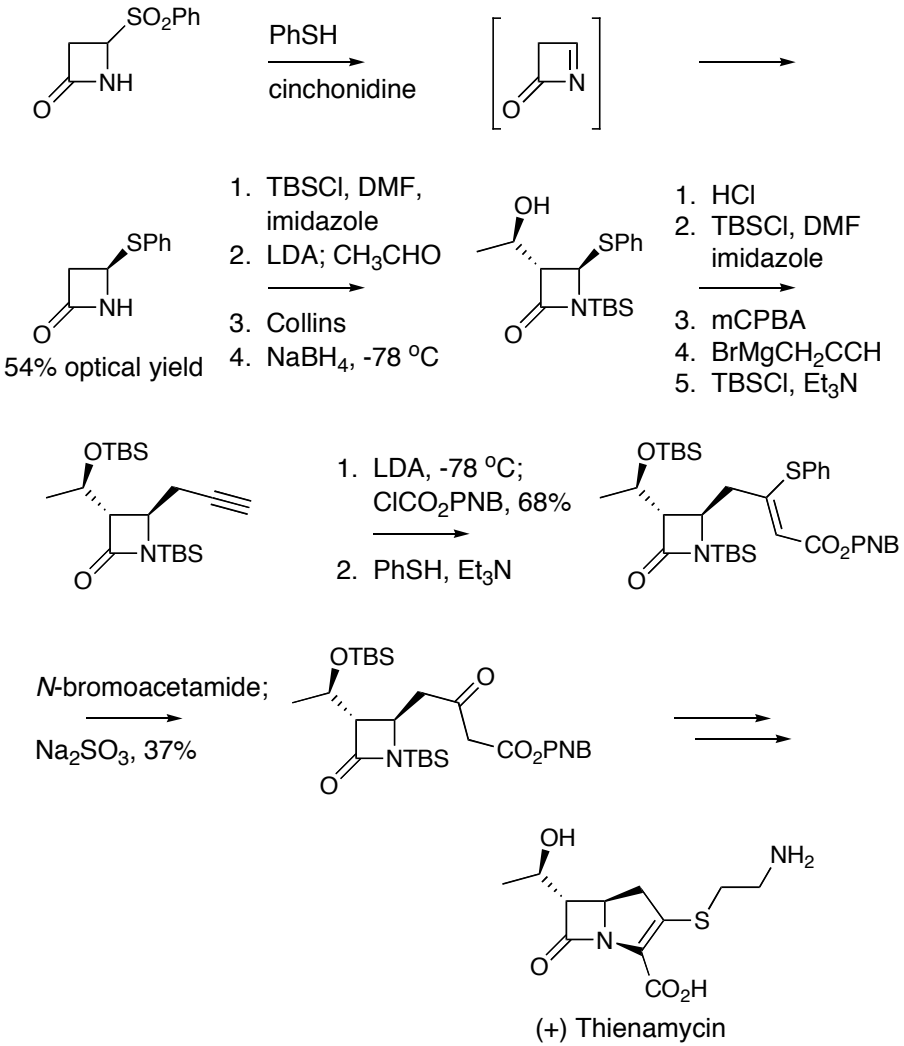
J. Am. Chem. Soc. **1980**, *102*, 2060



Asymmetric Formal Synthesis: Shibasaki

J. Chem. Soc., Chem. Commum. **1982**, 1324

Tetrahedron Lett. **1982**, *23*, 2875



Thienamycin

Summary of Selected Syntheses

1978, Merck Med. Chem. Racemic Total Synthesis
19 steps, ca 0.2% yield

1980, Merck Med. Chem. Asymmetric Total Synthesis
19 steps, ca 9.8% yield

1981, Merck Process. Asymmetric Total Synthesis
13 steps from Penicillin, ca 5.4% yield

1980, Merck Process. Racemic Total Synthesis
21 steps, >10% yield

1986, Merck Process. Asymmetric Total Synthesis
17 steps, >10% yield

1984, Grieco. Racemic Formal Synthesis
29 steps, ca 3.2% yield

1996, Jacobi. Asymmetric Formal Synthesis
21 steps, ca 1.8% yield

1984, Ley. Asymmetric Formal Synthesis
18 steps, ca 0.2% yield

1986, Evans. Asymmetric Formal Synthesis
20 steps, ??% yield

1990, Hanessian. Asymmetric Formal Synthesis
20 steps, ca 0.84% yield

1980, Kametani. Racemic Formal Synthesis
14 steps, 0.1% yield

1982, Shibasaki. Asymmetric Formal Synthesis
20 steps, ca 4.3% yield

Selected Other Synthese Not Presented

1982, Hanessian. Asymmetric Formal Synthesis
Can. J. Chem. **1982**, *60*, 2292

1982, Shiozaki. Racemic Formal Synthesis
Tetrahedron. **1982**, *38*, 3457

1985, Georg. Asymmetric Formal Synthesis
J. Chem. Soc., Chem. Commun. **1985**, 1433

1986, Fleming. Asymmetric Formal Synthesis
J. Chem. Soc., Chem. Commun. 1986, 1198

1986, Buynak. Racemic Formal Synthesis
J. Chem. Soc., Chem. Commun. **1986**, 941

1986, Shibasaki. Formal Synthesis
Chem. Pharm. Bull. **1986**, *34*, 1434

1987, Meyers. Asymmetric Formal Synthesis
Tetrahedron Lett. **1987**, *28*, 5103

1987, Cainelli. Asymmetric Formal Synthesis
J. Chem. Soc., Perkin Trans. I. **1987**, 2637

1990, Palomo. Asymmetric Formal Synthesis
J. Chem. Soc., Chem. Commun. **1990**, 1390

1994, Tanimori. Racemic Formal Synthesis
Heterocycles. **1994**, *38*, 1533

1995, Davies. Asymmetric Formal Synthesis
Tetrahedron: Asymmetry. **1995**, *6*, 2507

2000, Tatsuta. Asymmetric Formal Synthesis
J. Antibiotics. **2000**, *53*, 1231