Asymmetric Total Synthesis of (–)-Agelastatin A Using Sulfinimine (*N*-Sulfinyl Imine) Derived Methodologies

Davis, F. A.; Deng, J. *Org. Lett.* **2005**, *7*(4), 621.

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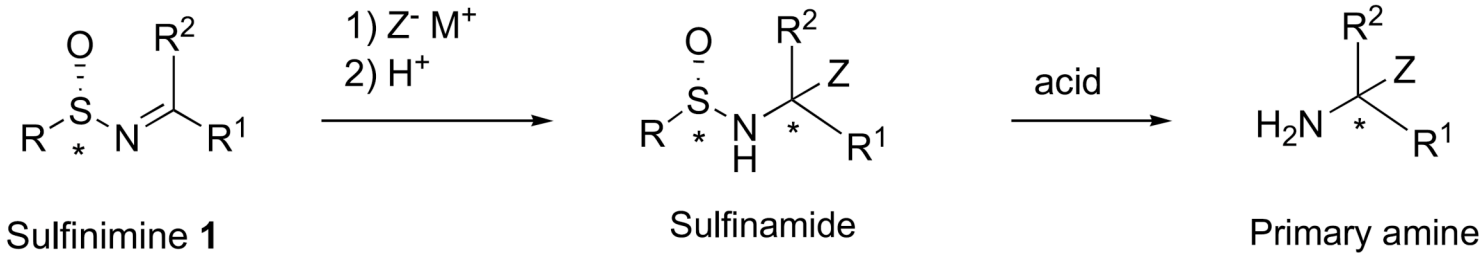
Utility of Chiral Sulfinimines

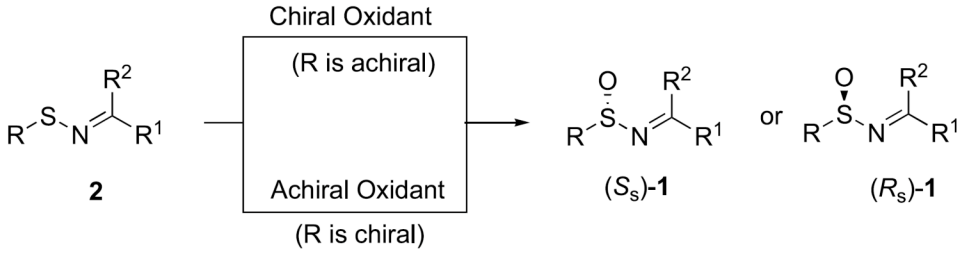


- Provide a general solution to the addition of nucleophiles to chiral imines
  - Sulfinyl group activates the C=N bond to nucleophlic addition
  - Chiral *N*-sulfinyl exerts powerful stereodirecting effects.
  - Nucleophilic addition possible to both enolizable and nonenolizable sulfinimines.
  - Epimerization of newly formed stereocenters inhibited by the ability of the sulfinyl group to stabilize anions at nitrogen.
  - Sulfinyl group can be removed under relatively mild acidic hydrolysis.

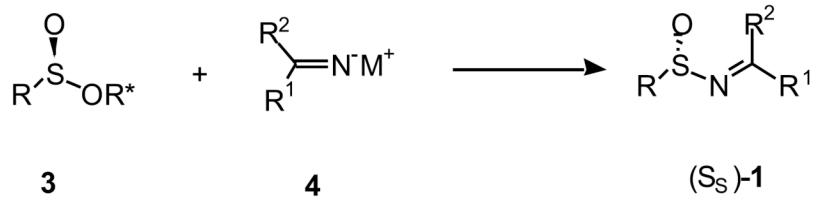
Zhou, P.; Chen, B.-C.; Davis, F. A. *Tetrahedron*, **2004**, *60*, 8003.

Preparation of Chiral Sulfinimines

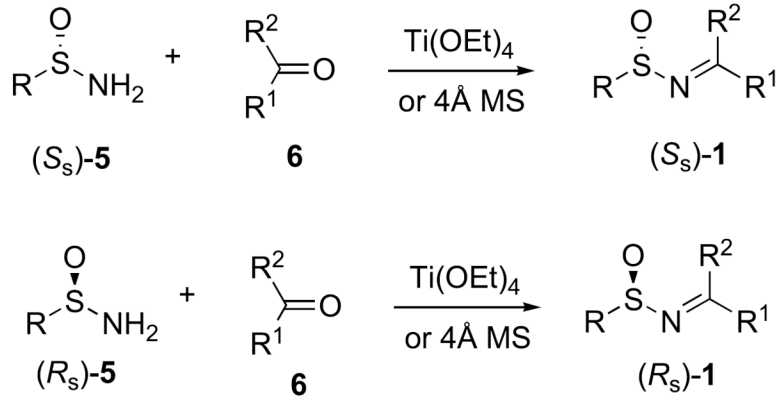
I. Asymmetric oxidation of sulfenimines



II. Asymmetric iminolysis of sulfinates and derivatives



III. Condensation of enantiopure primary sulfinamides with aldehydes and ketones



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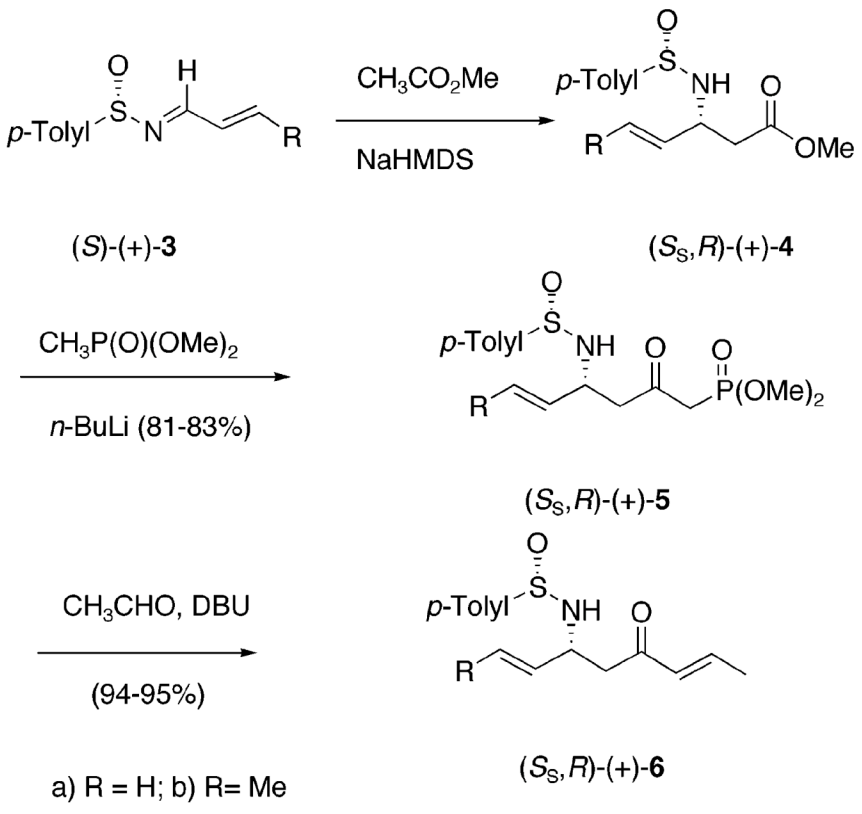
Amino-ketodienes: Precursors in the Synthesis of Chiral 4-Aminocyclopentenones

- Enolate addition to the chiral sulfinimine **3** produced the *N*-sulfinyl-β-amino ester **4**.

- Reaction of **4** with lithium dimethyl methyl phosphonate provided the *N*-sulfinyl-δ-amino-β-ketophosphonate **5**.

- Wittig chain extension provided the desired α, β-unsaturated 2-amino ketone **6** in good yield.



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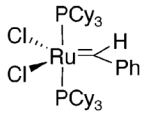
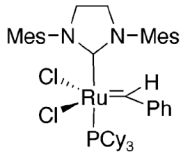
Utilising RCM to Generate Chiral 4-Aminocyclopentenones

Table 1. Ring-Closing Metathesis of Amino Ketodienes with Grubb's Catalysts in DCM at Reflux

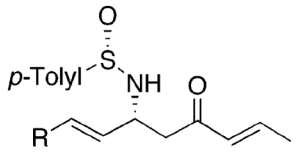
entry	amino ketodiene	catalyst/conditions	products (% isolated yields)
1	(+)-**6a** (R = H)	**I** (2−30 mol %) 40 h	NR
2		**II** (5 mol %) 16 h	(*R*)-(+)-**9** (85)
3	(+)-**6b** (R = Me)	**I** (2−30 mol %) 40 h	NR
4		**II** (5 mol %) 16 h	(*R*)-(+)-**9** (25)
5	(−)-**7a** (R = H)	**I** (2 mol %) 18 h	(*R*)-(+)-**10** (94)
6		**II** (5 mol %) 18 h	(*R*)-(+)-**10** (95)
7	(−)-**7b** (R = Me)	**I** (2−30 mol %) 40 h	NR
8		**II** (5 mol %) 18 h	(*R*)-(+)-**10** (8)
9	(−)-**8a** (R = H)	**I** (2 mol %) 18 h	(*R*)-(+)-**1** (97)
10		**II** (2 mol %) 16 h	(*R*)-(+)-**1** (97)
11	(−)-**8b** (R = Me)	**I** (2 mol %) 16 h	NR
12		**II** (2 mol %) 16 h	(*R*)-(+)-**1** (21)
13	(+)-**13a** (R = H)	**I** (20 mol %) 18 h	(+)-**14** (58)
14		**II** (5 mol %) 18 h	(+)-**14** (93)
15	(+)-**13b** (R = Me)	**I** (10 mol %) 16 h	NR
16		**II** (5 mol %) 16 h	(+)-**14** (84)



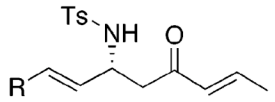
I



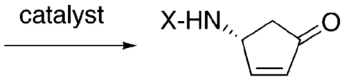
II



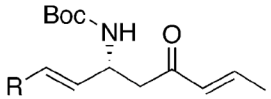
(S_S,*R*)-(+)-**6**



(*R*)-(-)-**7**

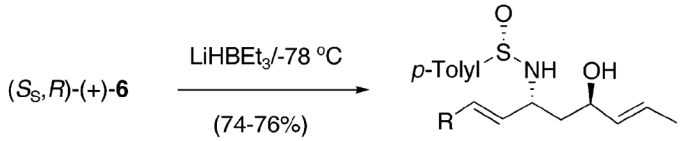


(*R*)-(+)-**1**: X = Boc
(*R*)-(+)-**9**: X = *p*-TolyS(O)
(R)-(+)-**10**: X = Ts



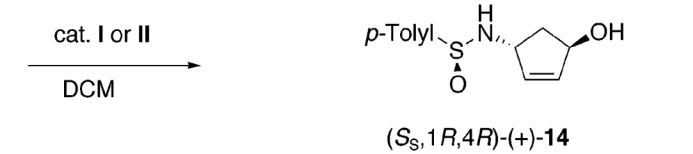
(*R*)-(-)-**8**

a) R = H; b) R= Me

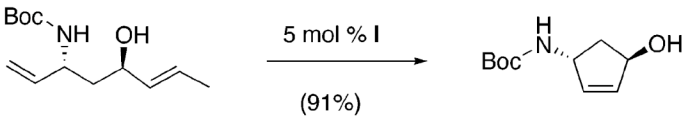


(+)-**13**

a) R = H, b) R = Me



(S_S,1*R*,4*R*)-(+)-**14**



(4*R*,6*R*)-(-)-**15**

(1*R*,4*R*)-(+)-**16**

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Asymmetric Synthesis of *syn*-(2*R*, 3*S*)-Ethyl Diamino-3-phenylpropanoates

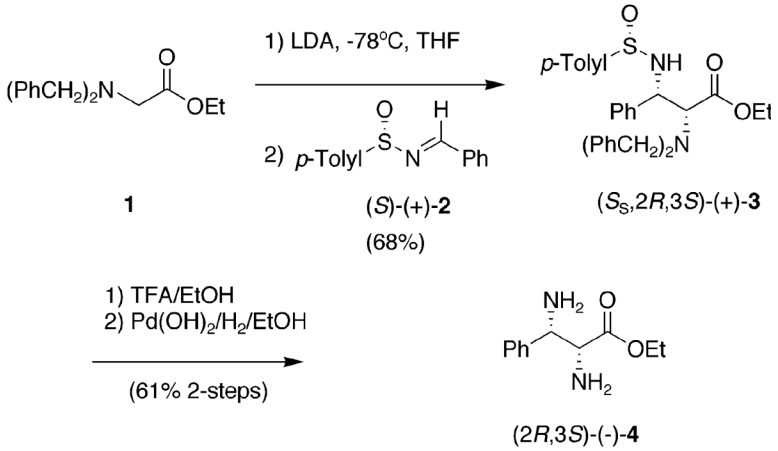

Table 1. Reaction of Glycine Enolates with (*S*)-(+)-*N*-(Benzylidene)-*p*-toluenesulfinamide (**2**) at −78 °C

entry	glycine	conditions base/equiv/solvent	α,β-diamino ester (isomer ratio)[a] % isolated yield[b]
1	1	LDA/1.6/THF	(+)-**3** (20:3:2:4) 30[c]
2		LDA/5.0/THF	(20:3:2:3) 68
3		LDA/5.0/Et_2O	(20:4:3:0) 50
4		LiHMDS/5.0/THF	(20:2:2:4) 65
5		NaHMDS/5.0/THF	(20:7:6:7) 80[c]
6		KHMDS/5.0/THF	(20:3:10:6) 76[c]

[a] Estimated from the ^1H NMR of the crude reaction mixture by monitoring the C(3) and NH protons. [b] Isolated yield of the pure major diastereoisomer. [c] Conversion yield, isomers not separated.

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Asymmetric Synthesis of *anti*-(2*R*, 3*S*)-Ethyl Diamino-3-phenylpropanoates

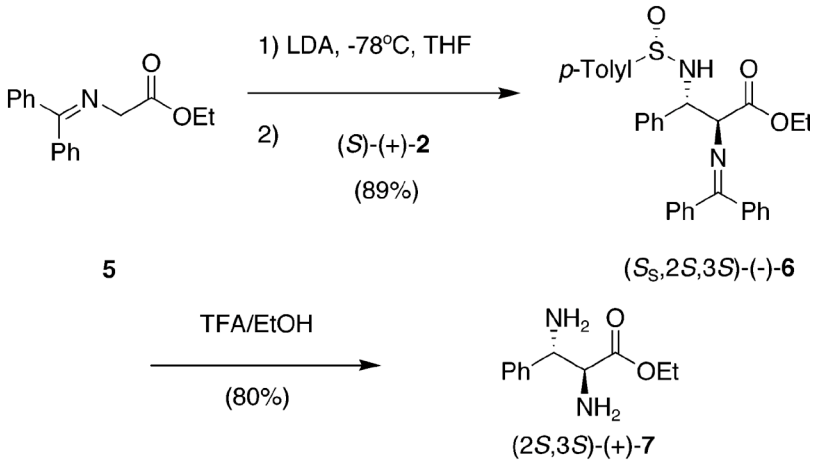

Table 1. Reaction of Glycine Enolates with (*S*)-(+)-*N*-(Benzylidene)-*p*-toluenesulfinamide (**2**) at −78 °C

entry	glycine	conditions base/equiv/solvent	α,β-diamino ester (isomer ratio)[a] % isolated yield[b]
7	5	LDA/1.1/THF	(−)-**6** (10:0:5:3) 36
8		LDA/1.6/THF	(100:0:2:2) 89
9		LDA/2.0/THF	(10:0:4:3) 34

[a] Estimated from the ^{1}H NMR of the crude reaction mixture by monitoring the C(3) and NH protons. [b] Isolated yield of the pure major diastereoisomer. [c] Conversion yield, isomers not separated.

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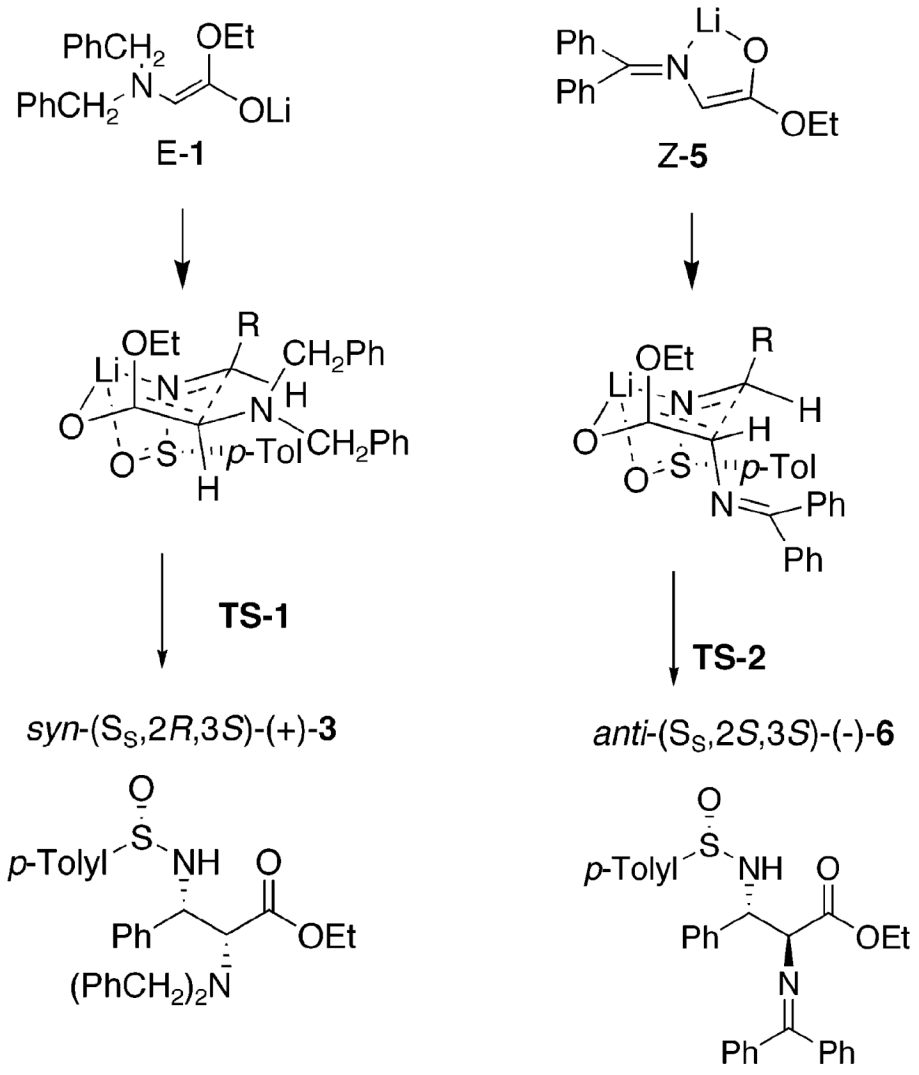
Proposed Mechanism of Stereoinduction



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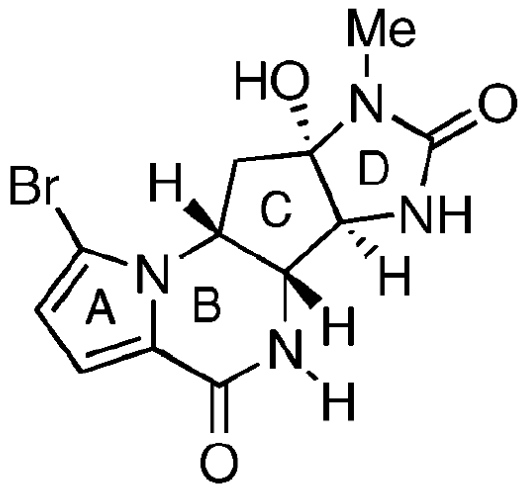
(–)-Agelastatin A

- Isolated in 1993 by Pietra and co-workers from the marine sponge *Agelas dedromorpha*
- Unique tetracyclic alkaloid possessing potent cytotoxic activity
- Syntheses of this natural product have been reported by Weinreb (racemic), Feldman, and Hale



(-)-Agelastatin A **1**

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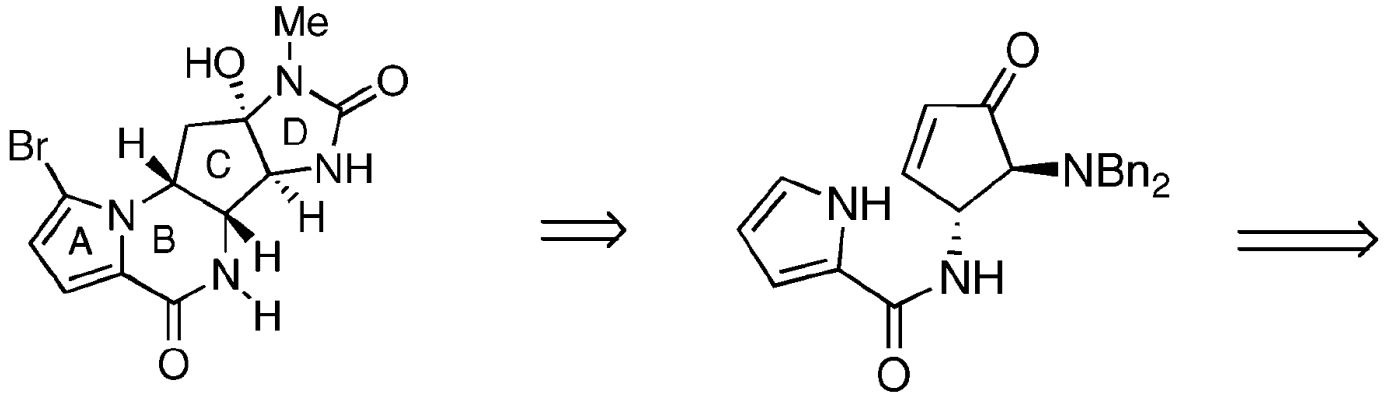
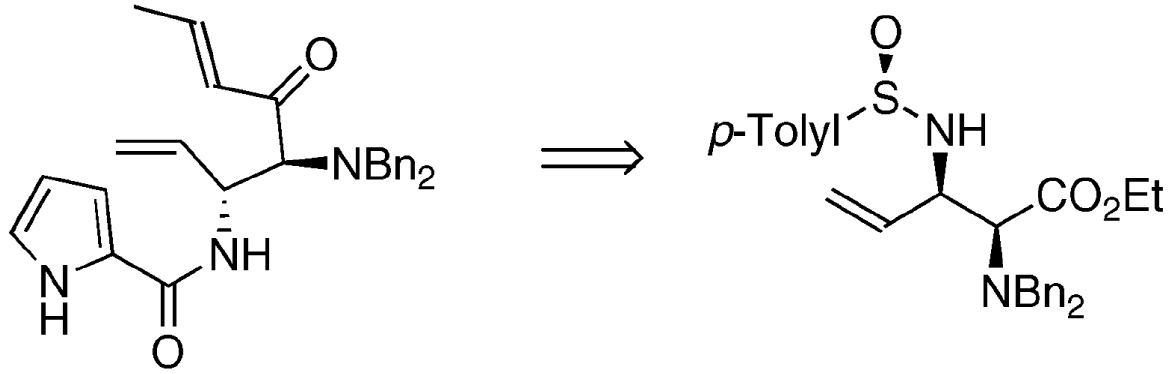
Retrosynthetic Analysis of (–)-Agelastatin A



(-)-Agelastatin A **1**

(-)-**2**



(-)-**3**

(-)-**4**

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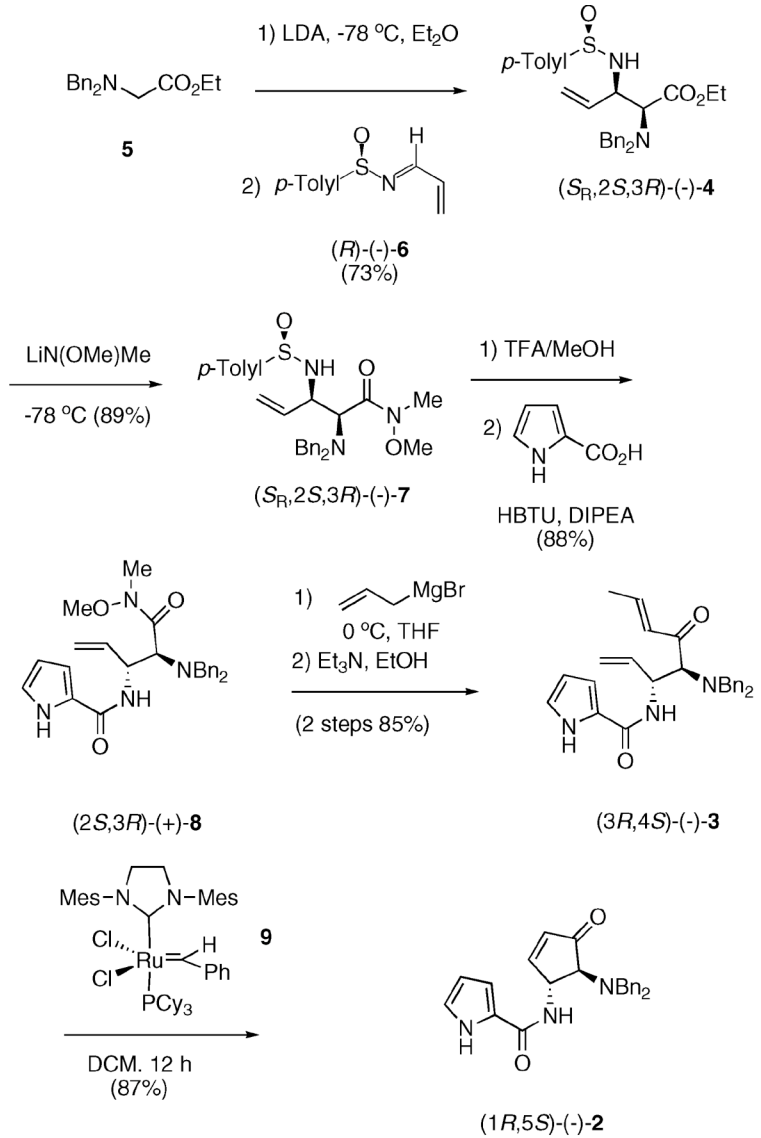
Synthesis of (–)-Agelastatin A -- I.



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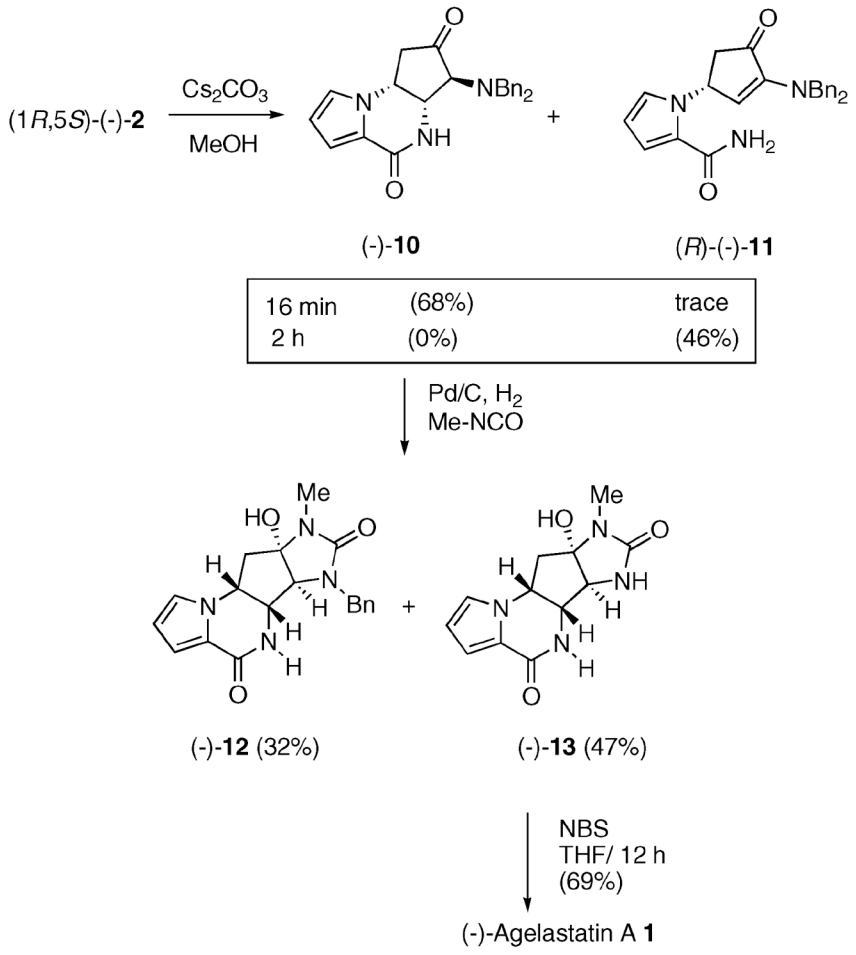
Synthesis of (–)-Agelastatin A -- II.



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Conclusions

- Total Asymmetric synthesis of the marine alkaloid (–)-agelastatin A has been described in 11 steps and 9% overall yield.
- Highlights of the synthesis included the sulfinimine-mediated, enantioselective synthesis of a *syn*-α, β-diamino ester, ring closing metathesis of a diaminoketodiene to provide a C-ring core intermediate, and D-ring formation by the addition of methyl isocyanate under reductive conditions.

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