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

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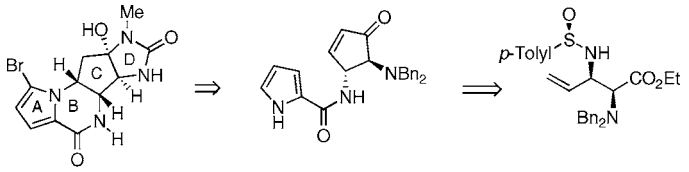
ABSTRACT



The asymmetric synthesis of the cytotoxic marine metabolite (−)-agelastatin A (1) has been achieved from the C-ring intermediate 4,5-diamino cyclopenten-2-enone (−)-2. This key intermediate was efficiently prepared from the sulfinimine-derived α,*β*-diamino ester 4 using ring-closing metathesis.

The aim of new synthetic methodologies is to solve important problems in synthesis. In this regard we have been engaged in developing new sulfinimine-based methodologies for the asymmetric synthesis of biorelevant nitrogen compounds.[1] Recently we introduced a new procedure for the asymmetric synthesis of (+)-4-aminocyclopentenone, an important chiral building block for the synthesis of antitumor carbocyclic nucleosides, from a sulfinimine-derived *N*-sulfinyl amino *β*-ketodiene using ring-closing metathesis (Figure 1).[2] Another procedure concerned a new method for the asymmetric synthesis of *syn*- and *anti*-α,*β*-diamino acids via the addition of *N*-protected glycine enolates to enantiopure sulfinimines (Figure 1).[3] It occurred to us that these two methods could be employed in the synthesis of the key cyclopentane C-ring core of (−)-agelastatin A (**1**) and result in an expeditious total asymmetric synthesis of this novel antitumor agent (Figure 1).

(−)-Agelastatin A (**1**) is an architecturally unique cytotoxic tetracyclic alkaloid. Pietra and co-workers first isolated (−)-**1** from the axinellid marine sponge *Agelas dedromorpha* in 1993,[4] and Molinski et al. have recently reported the isolation of (−)-**1**, along with two minor congeners, from the West Australian sponge *Cymbastela* sp.[5] Importantly, at low concentration this alkaloid exhibits potent cytotoxicity against L1210 in mice and human KB nasopharyngeal tumor cell lines.[6] To date the mechanism of antitumor activity has not been elucidated. (−)-Agelastatin A (**1**) is also reported to selectively inhibit GSK-3*β* (glycogen synthase kinase-3*β*) at low concentrations and could play a role in preventing Alzheimer's disease[7,8] and inhibiting neuronal apoptosis after stroke. This alkaloid might also function as an insulin mimetic.[8] Potent insecticidal activity against beet army worm larvae and corn rootworm has also been reported.[5]

(1) Zhou, P.; Chen, B.-C.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8030.
(2) Davis, F. A.; Wu, Y. *Org. Lett.* **2004**, *6*, 1269.
(3) Davis, F. A.; Deng, J. *Org. Lett.* **2004**, *6*, 2789.
(4) (a) D'Ambrosio, M.; Guerriero, A.; Debitus, C.; Ribes, O.; Pusset, J.; Leroy, S.; Pietra, F. *J. Chem. Soc., Chem. Commun.* **1993**, 1305. (b) D'Ambrosio, M.; Guerriero, A.; Chiasera, G.; Pietra, F. *Helv. Chim. Acta* **1994**, *77*, 1895.
(5) Hong, T. W.; Jimenez, D. R.; Molinski, T. F. *J. Nat. Prod.* **1998**, *61*, 158.
(6) D'Ambrosio, M.; Guerriero, A.; Ripamonti, M.; Debitus, C.; Waikedre, J.; Pietra, F. *Helv. Chim. Acta* **1996**, *79*, 727.
(7) Meijer, L.; Thunnissen, A.-M. W. H.; White A. W.; Garnier, M.; Nikolic, M.; Tsai, L.-H.; Walter, J.; Cleverley, K. E.; Salinas, P. C.; Wu, Y.-Z.; Biernat, J.; Mandelkow, E.-M.; Kim, S.-H.; Pettit, G. R. *Chem. Biol.* **2000**, *7*, 51.
(8) For a discussion of and leading references on selective inhibition of GSK-*β*, see: Hale, K. J.; Domostoj, M. M.; Tocher, D. A.; Irving, E.; Scheinmann, F. *Org. Lett.* **2003**, *5*, 2927.

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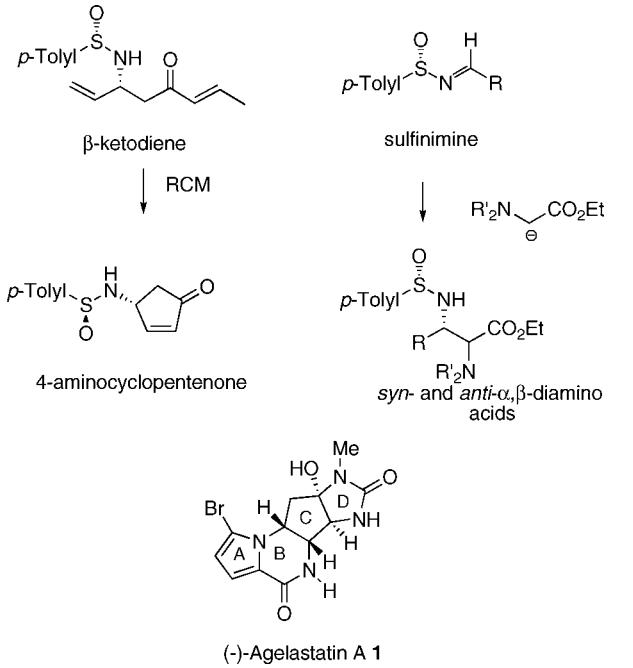
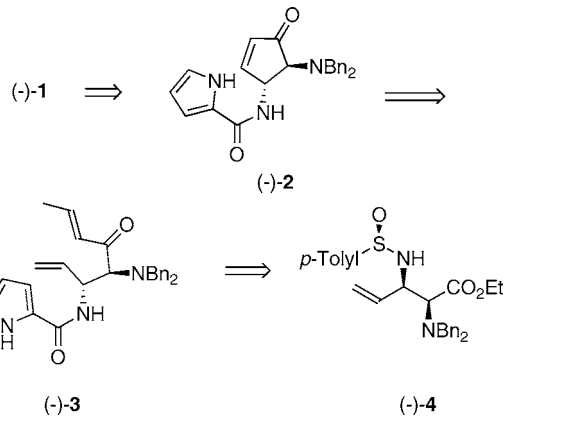


Figure 1. New sulfinimine-derived methodologies.

Isolated from natural sources, the scarcity of this biologically significant alkaloid makes a total enantioselective synthesis of (−)-**1** of prime importance for further biological evaluation and analogue synthesis. Weinreb and co-workers employed a hetero Diels−Alder cycloaddition reaction and a Sharpless/Kresze allylic amination protocol in the first racemic synthesis of **1**.[9] The key step in the Feldman and Saunders enantioselective synthesis of (−)-**1** was a unique vinylcarbene C−H insertion sequence for preparation of the C-ring core.[10] A formal asymmetric synthesis of (−)-**1** was accomplished by Hale et al. in their enantioselective synthesis of Weinreb's C-ring intermediate from a Hough−Richardson aziridine.[8] This group recently described the total synthesis of (−)-agelastatin A (**1**) from a chiral bicyclic cyclopentene oxazolidinone intermediate.[11] In each of these syntheses construction of central C-ring core from a bicyclic cyclopentene oxazolidinone proved to be the critical step.[12] Our total asymmetric synthesis of (−)-**1** differs primarily in the synthesis of the C-ring cyclopentene and is presented below.

In our retrosynthetic route to (−)-**1**, which draws on the Weinreb,[9] Feldman,[10] and Hale[8,11] syntheses, we chose to construct a 4,5-diamino cyclopent-2-enone (−)-**2** as our C-ring intermediate (Scheme 1). The methodology we devised for the synthesis of 4-aminocyclopentenone (Figure 1) would be employed to prepare (−)-**2** from diamino ketodiene (−)-**3** using ring-closing metathesis (RCM).[2] Hale et al. also used RCM in the construction of their C-ring intermediate.[8] Addition of the enolate of (dibenzylamino)-acetate to an acrolein-derived sulfinimine was expected to furnish (−)-**4**.[3] Finally, we envisioned that the conversion of (−)-**2** to (−)-**1** could be accomplished using chemistry similar to that reported by Weinreb and co-workers in their racemic synthesis of **1**.[9]

Scheme 1



Our synthesis began with the preparation of the requisite unsaturated α,*β*-diamino ester (−)-**4**, by addition of the acrolein-derived sulfinimine (*R*)-(−)-**6** to 5.0 equiv of the preformed lithium enolate of ethyl (dibenzylamino)acetate (**5**). Three of the four possible diastereoisomers were detected in a ratio of 18:1:5 with the major syn diastereoisomer (−)-**4** being isolated in 73% yield (Scheme 2). Treatment of ester (−)-**4** with 5.0 equiv of lithium *N*,*O*-dimethylhydroxylamine gave the corresponding Weinreb amide (−)-**7** in 89% isolated yield. Deprotection of the *N*-sulfinyl amino group (TFA/MeOH) gave the amine, which was not isolated but immediately reacted with pyrrole-2-carboxylic acid, the coupling reagent HBTU, and DIPEA (Hunig's base) to afford amide (+)-**8** in 88% isolated yield for the two steps. Next the amide was treated with 2 equiv of allylmagnesium bromide at 0 °C to give, presumably, an intermediate *γ*,*β*-unsaturated ester (not shown), which was isomerized with Et_3N/EtOH to afford the diamino ketodiene (−)-**3** in 85% yield for the two-step sequence (Scheme 2).[13] Refluxing (−)-**3** in DCM with 20 mol % of Grubb's second generation catalyst **9** for 12 h resulted in 4,5-diamino cyclopenten-2-enone (−)-**2** in 87% yield, our key C-ring intermediate.

With our C-ring intermediate in hand we planned to construct the B-ring of (−)-**1** by an intramolecular Michael cyclization in a fashion similar to that described in earlier syntheses of agelastatin A (**1**).[9,11] Indeed, with an intermediate similar to **2**, Weinreb and co-workers reported that the cyclization occurred in 61−64% yield in the presence of Cs_2CO_3/MeOH.[9] On the other hand, the Hale group, with a

(9) (a) Stein, D.; Anderson, G. T.; Chase, C. E.; Koh, Y.-H.; Weinreb, S. M. *J. Am. Chem. Soc.* **1999**, *121*, 9574. (b) Anderson, G. T.; Chase, C. E.; Koh, Y.-h.; Stein, D.; Weinreb, S. M. *J. Org. Chem.* **1998**, *63*, 7594.

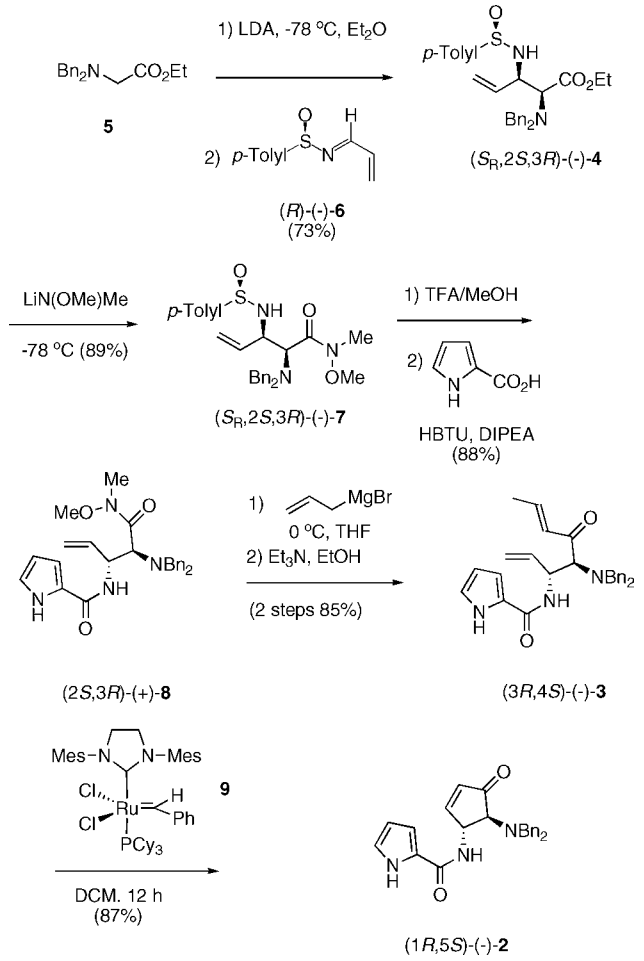
(10) (a) Feldman, K. S.; Saunders, J. C. *J. Am. Chem. Soc.* **2002**, *124*, 9060. (b) Feldman, K. S.; Saunders, J. C.; Laci Wrobleski, M. *J. Org. Chem.* **2002**, *67*, 7096.

(11) Domostoj, M. M.; Irving, E.; Scheinmann, F.; Hale, K. J. *Org. Lett.* **2004**, *6*, 2615.

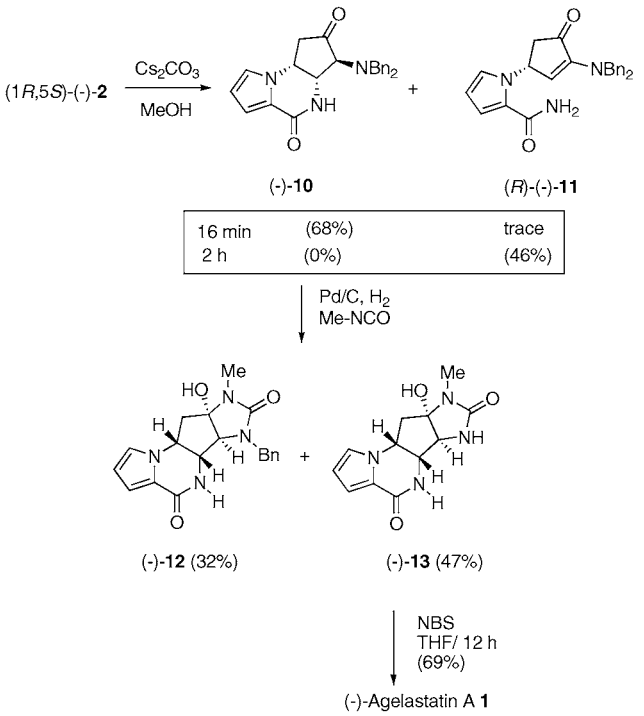
(12) For an asymmetric synthesis of a C-ring intermediate, see: Baron, E.; O'Brien, P.; Towers, T. D. *Tetrahedron Lett.* **2002**, *43*, 723.

(13) TLC indicated the presences of a new spot that was converted to (−)-**3** on exposure to Et_3N.

Scheme 2



Scheme 3



species similar to **3**, was unable to affect the cyclization using the Weinreb conditions.[11] Nevertheless we found that treatment of (−)-**2** with 10 equiv of Cs_2CO_3/MeOH for 16 min resulted in a 68% yield of the desired tricyclic ring system (−)-**10** along with trace amounts of cyclopentenone (−)-**11**. Longer reaction times, 2 h, produced the enone as the major product.

Next it was necessary to remove the *N*-benzyl protecting groups, treat the free amine with methyl isocyanate to give the D-ring, and finally brominate to complete the synthesis of (−)-agelastatin A (**1**). Unfortunately, hydrogenation under a variety of conditions ($Pd(OH)_2$, Pd/C, various solvents) failed to produce characterizable products. Hydrogenation followed by treatment of the crude reaction mixture with methyl isocyanate gave similar results. Fortunately, we discovered that if (−)-**10** and methylisocyanate were hydrogenated together in one pot, *N*-benzyl debromoagelastatin A (**12**) and debromoagelastatin (**13**) were isolated in 32% and 47% yields, respectively (Scheme 3). To date attempts to debenzylate **12** have been unsuccessful, which suggests that **12** is not an intermediate in the formation of **13**. Twelve-hour bromination of (−)-**13** with NBS in THF, according to the Feldman protocol, afforded (−)-agelastatin A (**1**) in 69% isolated yield.[10]

In summary, the total asymmetric synthesis of the novel cytotoxic tetracyclic marine alkaloid (−)-agelastatin A (**1**) has been accomplished using new sulfinimine-based methodologies in approximately 11 steps under eight operations (9% overall yield) from sulfinimine (−)-**6** and commercially available materials. Highlights of our synthesis include the sulfinimine-mediated enantioselective synthesis of *syn*-α,*β*-diamino ester (−)-**4**, ring-closing metathesis of diamino ketodiene (−)-**3** to give the C-ring core intermediate (−)-**2**, and the D-ring formation by the addition of methyl isocyanate to (−)-**2** under reductive conditions.

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Supporting Information Available: Detailed experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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