Published in final edited form as:
Org Lett. 2009 March 19; 11(6): 1341–1344. doi:10.1021/ol900133v.

Total Synthesis of (±)-Agelastatin A, A Potent Inhibitor of Osteopontin–Mediated Neoplastic Transformations

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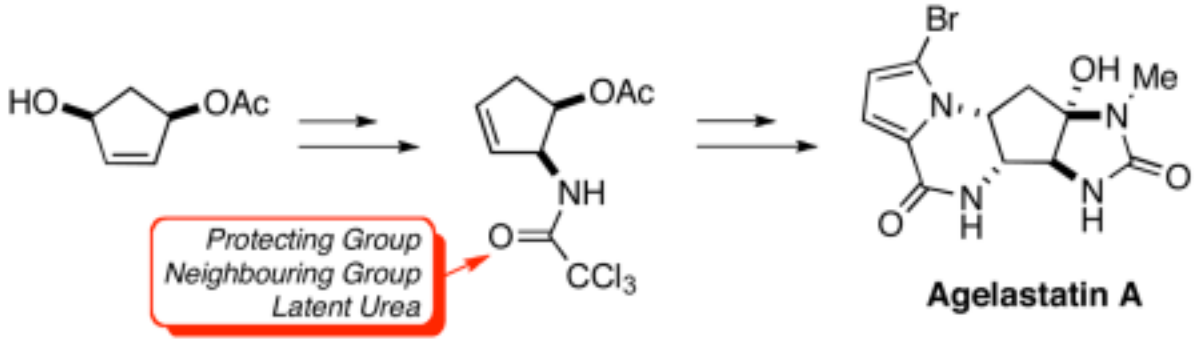
Abstract



A stereoselective synthesis of agelastatin A, a potent cytotoxin and inhibitor of osteopontin (OPN)–mediated neoplastic transformations, has been accomplished in 14 steps (12 operations) with an approximate overall yield of 8%. Notable features of this route include the direct manner in which the pyrroloketopiperazine A-ring of the target is generated and the efficient employment of a trichloroacetamide, introduced through Overman rearrangement, as a protecting group, pendant nucleophile and latent urea.

The agelastatins represent a small yet architecturally interesting subclass of the oroidin family of bromopyrrole marine alkaloids,[1,2] that are also notable for their potent biological activity. Agelastatin A (**1**) and B (**3**) were isolated by Pietra and co-workers in 1993, from the axinellid sponge *Agelas dendromorpha* collected in the Coral Sea off New Caledonia.[3] While there was initial uncertainty as to the stereochemistry of the former compound, this issue was resolved through a combination of NMR studies, molecular modeling and conformational analysis.[4] In addition to confirmation of this assignment through total synthesis (*vide infra*), Pettit has isolated **1** from a Mexican *Agela sp.* and confirmed its structure using X-ray crystallographic analysis.[5] Other members of this family include agelastatin C (**2**) and D (**4**), minor congeners isolated from the Australian sponge *Cymbastela* sp. by Molinski and co-workers.[6] Although biogenetically distinct from the agelastatins, being an apparent dimer of an oroidin-like precursor,[7] the Okinawan marine sponge metabolite nagelamide J (**5**) shares the *trans-cis*-1,2,3-triaminocyclopentanol motif characteristic of this family.[8]

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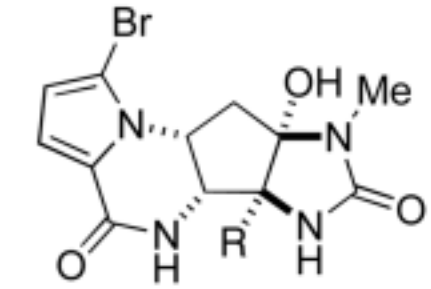
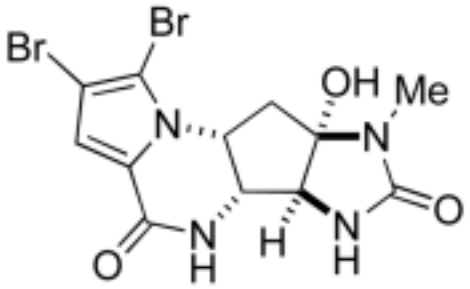
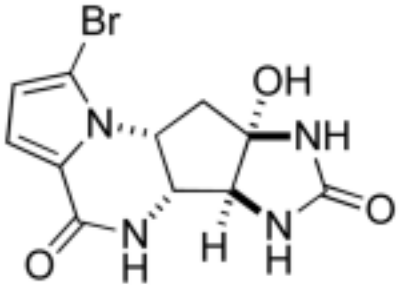


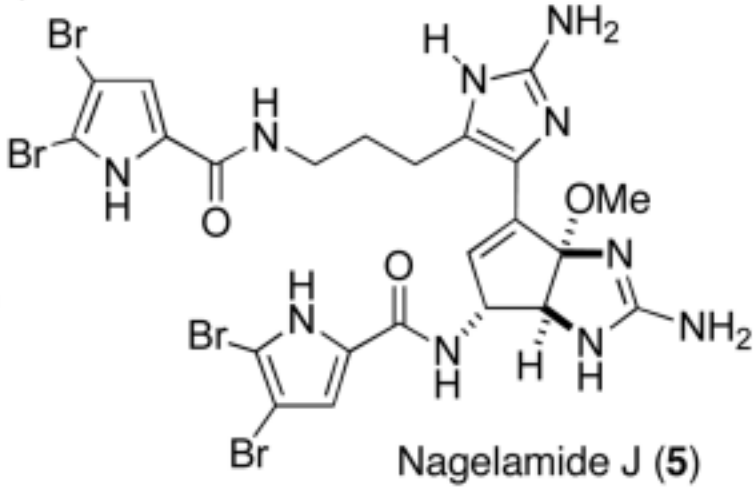
Agelastatin A (**1**; R = H)
Agelastatin C (**2**; R = OH)



Agelastatin B (**3**)



Agelastatin D (**4**)



Nagelamide J (**5**)

Much of the attention garnered by the agelastatins, stems from the diverse range of biological activities displayed by compound **1**, which include selective inhibition of glycogen synthase kinase-3β,[9] a potential target for the treatment of Alzheimer's disease[10] and bipolar disorder;[11] toxicity towards arthropods;[6] and an ability to potently inhibit the growth of a number of human tumor cell lines.[3–5,12] The potential clinical importance of **1** as an antineoplastic agent has recently been underscored by El-Tanani and Hale,[13] who have demonstrated that agelastatin A is also a powerful antimetastatic agent, which operates through two distinct mechanisms: as an inhibitor of osteopontin-mediated malignant transformations[14] and by arrest of the cell cycle.

The biological activity, unique structure and limited availability of the agelastatins has provoked sustained interest in their preparation.[15] Weinreb was first to develop a route to racemic agelastatin A (**1**) and B (**2**), in which hetero-Diels-Alder and Sharpless/Kresze ene reactions were employed to establish the densely functionalized C-ring.[16] Feldman, in an elegant demonstration of the utility of alkynyliodonium salts, subsequently completed the first enantioselective synthesis of both **1** and **2**.[17] Hale has likewise reported enantioselective routes to **1** from the Hough-Richardson aziridine.[18] Employing sulfinimine-based methodology and ring-closing metathesis to establish the C-ring, Davis and Deng have prepared (−)-agelastatin A (**1**),[19] while Trost and Dong have utilized the sequential Pd-mediated allylic *N*-alkylation of pyrroles and *O*-methyl hydroxamates to access its enantiomer.[20] Ichikawa has employed the [3,3]-sigmatropic rearrangements of allyl cyanates to establish the vicinal diamine moiety present in the carbocyclic ring.[21] Most recently, Yoshimitsu has utilized an aziridine ring-opening strategy to establish the *trans*-1,2-diamido functionality of **1**.[22] Herein we report the

development of an efficient synthetic route to (±)-agelastatin (**1**) in which a trichloracetamide group, introduced via Overman rearrangement, plays a central role in that it subsequently mediates cyclofunctionalization, acts as a protecting group and serves as a latent urea for the preparation of the imidazolidinone, D-ring of the natural product.

From a retrosynthetic perspective, we envisioned that agelastatin A (**1**) could be accessed from cyclopentenone **6**, through 1,4-addition of the pyrrole unit, a biomimetic[23] approach succesfully adopted by a number of other groups (Scheme 1).[16–19,21] Formation of the key *trans*-1,2-diamido functionality present in the C-ring of the target could then be accomplished via displacement of the C-4 hydroxy group of **7** with a suitable nitrogen nucleophile. Through electrophile-promoted cyclofunctionalization[24] and eliminative ring-opening, **7** could be accessed from *N*-allylic trichloroacetamide **8**. Finally, this compound could be readily prepared from known allylic alcohol **9**[25] by [3,3]-sigmatropic rearrangement of the corresponding trichloroacetimidate.[26] Although the use of the Overman rearrangement in this manner offered an attractive method with which to both establish the C-5b stereocenter and provide a handle for subsequent manipulation of the cyclopentane C-ring, the challenge of removing a trichloroacetyl group under forcing conditions[27] was a serious potential drawback. In this regard, Isobe[28] and others[29] have reported that, upon heating in the presence of alkali metal carbonates, trichloroacetamides undergo detrichloromethylation to generate isocyanates, which can be intercepted with alkylamines to form ureas. In the case of substrate **7**, implementation of this one-pot process would not only offer a mild method of deprotection, but simultaneously serve to generate the *N*-methylurea group required for formation of the D-ring of agelastatin A (**1**).

Our route to **1** commenced from *cis*-3-acetoxy-5-hydroxycyclopent-1-ene (**9**), which was readily prepared from cyclopentadiene, via peracetic acid epoxidation and subsequent Pd(0)-catalyzed *syn*-1,4-addition of acetic acid.[25] Treatment of **9** with trichloroacetonitrile in the presence of DBU[30] cleanly provided imidate **10**, which upon heating in xylenes for 18 h, was then tranformed to trichloroacetamide **11** in 78% yield, over two steps (Scheme 2). As anticipated, given the high stereoselectivity associated with this type of [3,3]-sigmatropic rearrangement,[26] product **8** was found to be a single diastereomer by ^{1}H NMR spectroscopy. Further evidence for the relative *cis* stereochemistry of this product was obtained from the NOESY spectrum of **8**, which revealed the correlation shown in Scheme 2.

Despite *N*-allylic trichloacetamides having previously been reported to undergo 5-*exo*-*trig* cyclofunctionalization with both iodinating and brominating reagents,[31] treatment of **8** with a range of conventional activators, including NBS, I_2, and Br_2, failed to mediate cyclization. In these cases, only products arising from alkene addition were isolated, suggesting that the electron-deficient amide group was insufficiently nucleophilic to participate in halonium ion ring-opening. Interestingly, exposure of this substrate to *N*-bromoacetamide (NBA)[32] in refluxing CH_2Cl_2 did provide **10** in good yield.[33] Dehydrobromination of **11**, in the presence of DBU in refluxing toluene, then generated allylic acetate **12**. Hydrolysis of this dihydrooxazole, with *p*-toluenesulfonic acid in aqueuous pyridine,[34] proceeded smoothly to regenerate the trichloroacetamide group and provide all *cis*-substituted cyclopentene **7**.

While attempts to now install the *trans*-1,2-diamido subunit of **1**, through activation of the C-4 hydroxyl. group of **7** and inversion with azide, were twarted by competitive S_N2' displacement at the C-2 position,[35] treatment of **7** wih phthalimide, under Mitsunobu conditions, provided cyclopentene **13** as a single diastereomer in high yield (Scheme 3). In this case, it appears that the greater steric bulk of the imide anion, in comparison to azide, is necessary for discriminaton of the two potential reaction sites within the alkoxyphosphonium ion derived from **7**.

Proceeding to now unmask the urea functionality latent within compound **13**, a solution of this substrate in DMF was heated at 100 °C in the presence of *N*-methylbenzylamine and $NaHCO_3$[36] to provide compound **14** (R = Bn) in good yield. Although it had not been our original intention to incorporate an *N*-benzyl protecting group at this stage, the corresponding *N*-methylurea **14** (R = H) proved to be too polar to be convieniently carried forward in the synthetic sequence.

Hydrazinolysis of the phthalimide group in **14** (R = Bn) now proceeded smoothly to provide the corresponding primary amine, which, because of its instability, was immediately coupled with 2-pyrrole carboxylic acid to provide **15**. Methanolysis of the acetate ester, followed by oxidation of the resulting allylic alcohol with *o*-iodoxybenzoic acid,[37] then generated cyclopentenone 6 in high overall yield. Exposure of this substrate to a variety of Lewis or Brønsted acidic and basic conditions now failed to effect conversion to **16** and resulted in either decomposition of the starting material or formation of tetrasubstituted enone **17**. With regards to the latter outcome, Hale has observed the same type of rearrangement during his second generation route to **1** and ascribed the ease of this process to the formation of an aromatic, cyclopentadienyl anion intermediate.[18b] As part of a study of pyranone ring contraction, Caddick and co-workers have noted that *trans*-4,5-dihydroxycyclopent-2-enones undergo a similar rearrangement, whose rate is highly dependant on both the nature of the reaction solvent and the base employed.[38] Through optimization of these two parameters, we found that tricycle **16** could be successfully generated by heating a solution of **6** in DMSO at 100 °C in the presence of K_2CO_3. Although of moderate yield, this transformation is notable for the direct manner in which it yields the pyrroloketopiperazine A-ring of the target: neither prior bromination of the pyrrole ring (so as to lower its pK_a) or the incorporation of an amide *N*-protecting group being required under these conditions.

Hydrogenolysis of the *N*-benzyl group of **16**, using Pearlman's catalyst, now proceeded smoothly to yield debromoagelastatin (**18**). Annulation of the *N*,*N*′-disubstituted urea generated upon debenzylation with the adjoining ketone occurs spontaneously under the reaction conditions. Treatment of **18** with NBS in a mixture of MeOH and THF, as reported by Feldman,[17] regioselectively provided (±)-agelastatin A (**1**), whose spectral data (^{1}H- and ^{13}C-NMR) were in complete agreement with those previously reported by Hale and co-workers.[18]

In summary, the total synthesis of (±)-agelastatin A (**1**) has been accomplished from a readily available starting material in 14 steps (12 operations) with an overall yield of ~8%. Modification of this synthetic route so as to encompass the antibiotic nagelamide J (**5**) is curently underway and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We thank the National Institutes of Health (GM-67176) and the University of Illinois at Chicago for financial support of this work.

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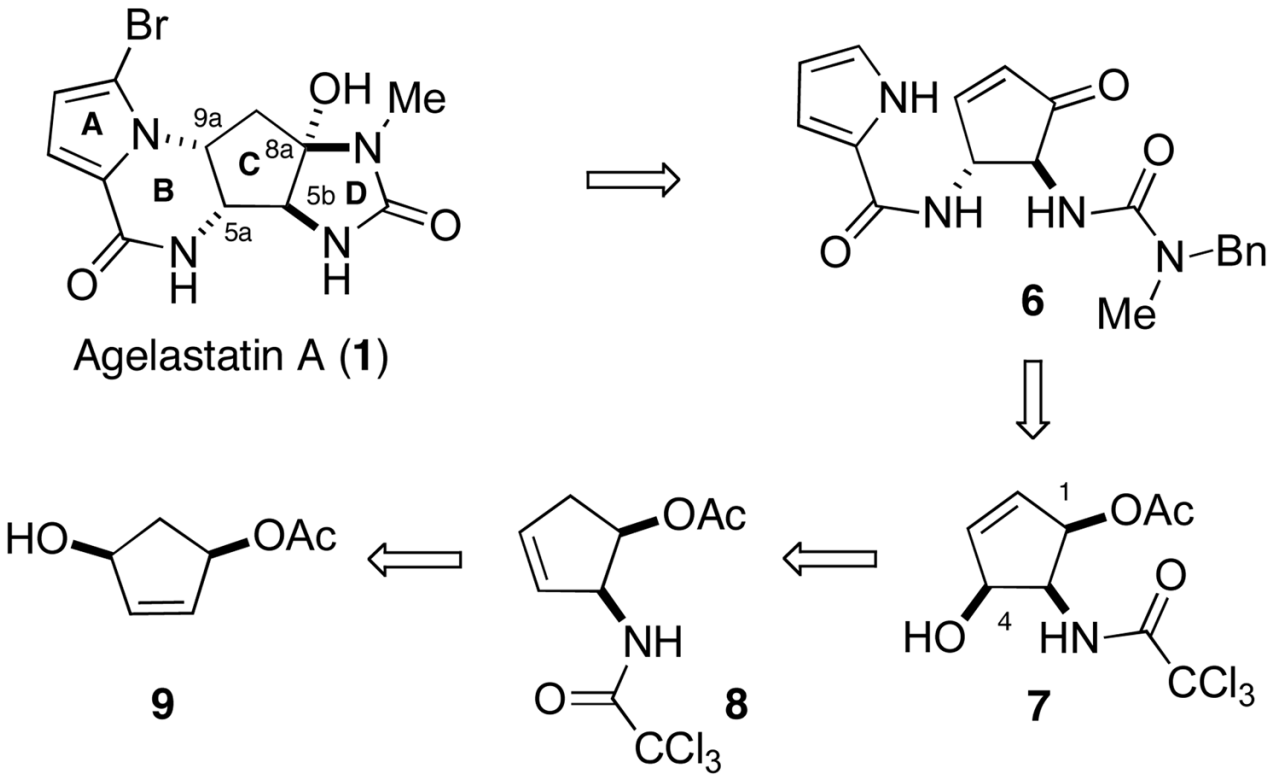
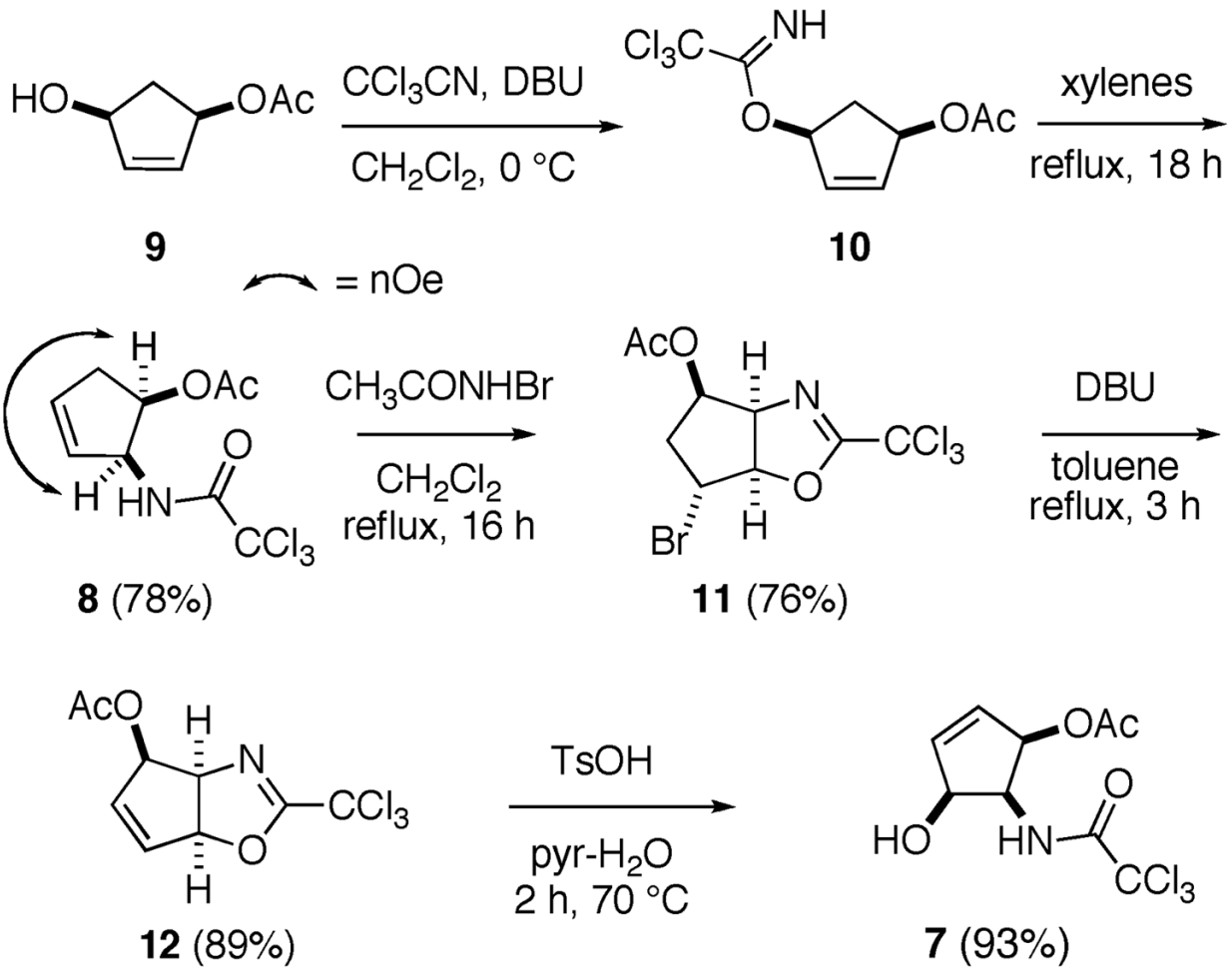
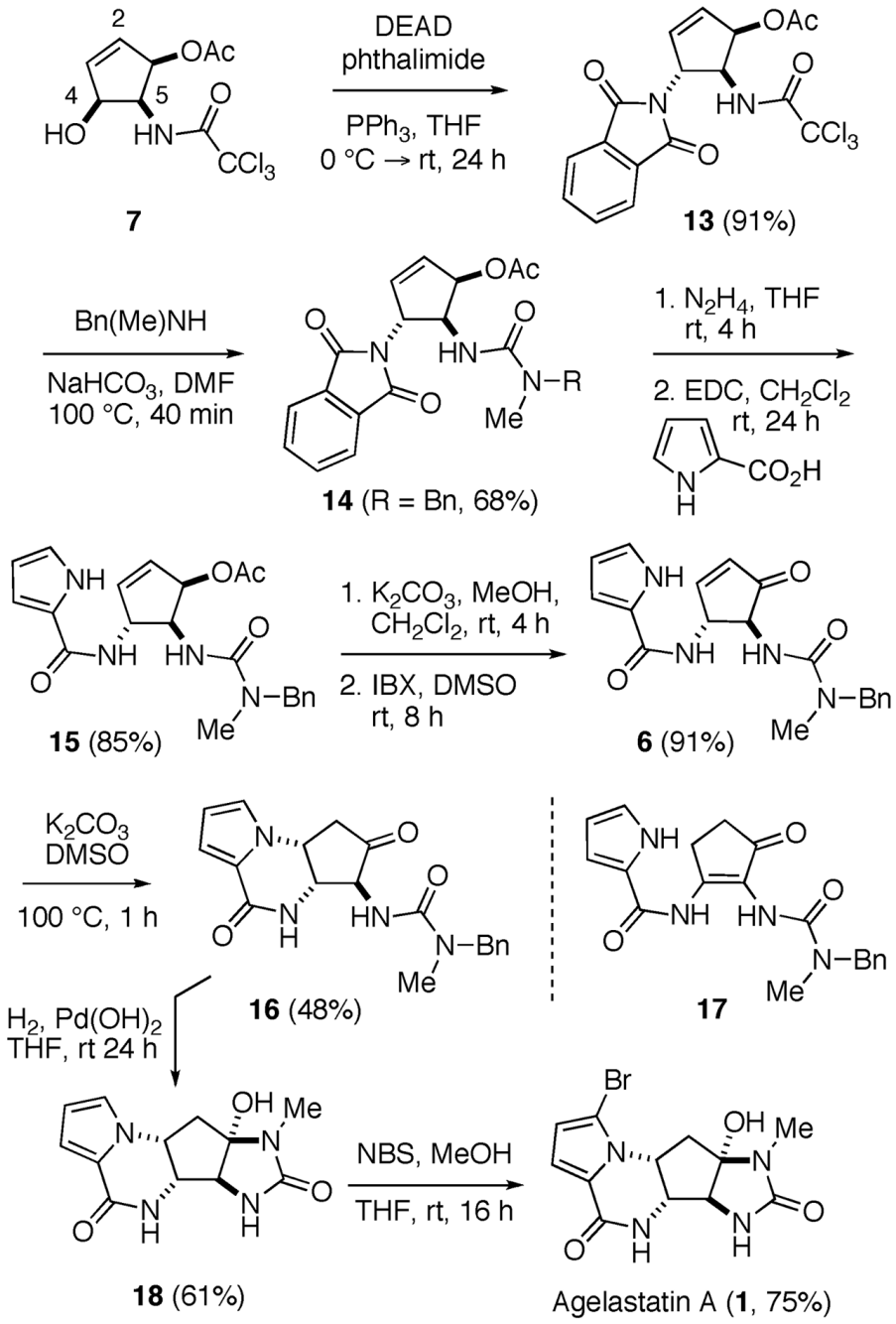


Scheme 1.
Retrosynthetic Analysis of Agelastatin A.



Scheme 2.
Synthesis of Trisubstituted Cyclopentene 7.



Scheme 3.
Total Synthesis of Agelastatin A.