Natural Product Synthesis

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A Stereoselective Synthesis of the Bromopyrrole Natural Product (−)-Agelastatin A**

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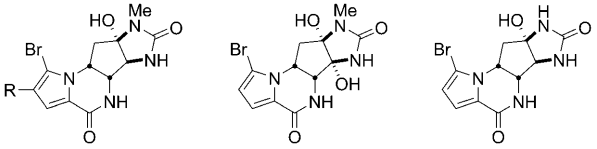
Agelastatin A and its congeners are a structurally intriguing class of bromopyrrole-based natural products, comprised of a densely functionalized cyclopentane core adorned with four contiguous nitrogen groups (Scheme 1).[1] Agelastatin A and



Scheme 1. The agelastatin family of natural products.

B were first isolated in 1993 from a Coral Sea marine sponge, *Agelas dendromorpha*.[2] Subsequently, agelastatin C and D were identified in extracts from the sponge *Cymbastela* sp found in Australian waters.[3] The unique structural features of these compounds, together with their powerful cytotoxic activities against certain human cancer cell lines, have motivated efforts aimed at their de novo synthesis.[4,5] To date, seven completed syntheses of agelastatin A have appeared in the literature, each presenting a decidedly different strategy for assembly of the natural product.[6,7] For our purpose, structures such as that of agelastatin A serve to inspire the development of new catalytic methods for oxidative C–N bond formation. Herein, we detail an 11-step synthesis of this natural product made possible with the advent of a highly selective and efficient intramolecular olefin aziridination method.[8,9] The unique heterocyclic intermediate generated in this sequence is easily manipulated through two selective nucleophilic ring-opening reactions to afford the substituted cyclopentane core of the target. The finished work offers a flexible and highly efficient preparation of (−)-agelastatin A, easily amenable to analogue design.[10]

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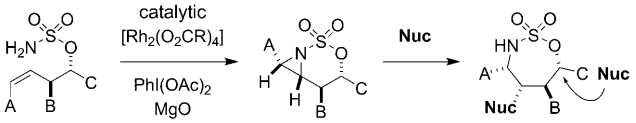
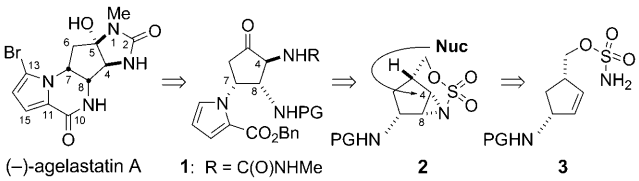
Recent work from our research group and others has demonstrated that homoallyl and bis(homoallyl) sulfamate esters react under oxidative conditions to furnish unique bicyclic aziridine derivatives (Scheme 2).[8,11,12] This process



Scheme 2. Rhodium-catalyzed aziridination: a versatile method for assembling polyfunctionalized amines. Nuc = nucleophile.

generally affords high levels of diastereocontrol with both cyclic and acyclic starting materials. The products can be smoothly converted into polyfunctionalized amine derivatives through sequential, regioselective ring opening. For the purpose of assembling (−)-agelastatin A, an attractive plan emerged that would capitalize on such a sequence of steps and establish the *trans*-substituted vicinal diamine unit embedded at C4 and C8 of the natural product (Scheme 3). Prior to

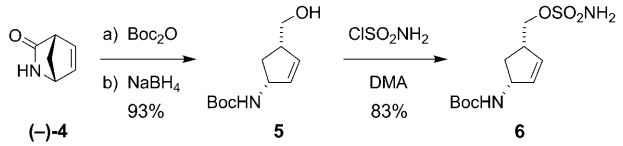


Scheme 3. Retrosynthetic analysis of (−)-agelastatin A. Bn = benzyl, PG = protecting group.

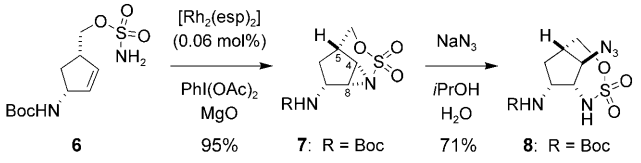
initiating these investigations, we had little appreciation if a substrate such as **3** would undergo chemoselective oxidation to generate the unusual tricyclic structure **2** and whether such a product would be isolable. Selectivity in the subsequent aziridine displacement reaction presented an additional concern. This plan, however, could be quickly assessed due to the ready availability of sulfamate **3**.

Optically enriched lactam **4** is prepared on an industrial scale and may be purchased in either enantiomeric form at a relatively low cost (Scheme 4).[13] In two high-yielding transformations this material was converted into alcohol **5**, which is also an item of commerce. Sulfamoylation of **5**, according to a standard protocol that involved the in situ generation of $ClSO_2NH_2$, was then easily accomplished.[14]

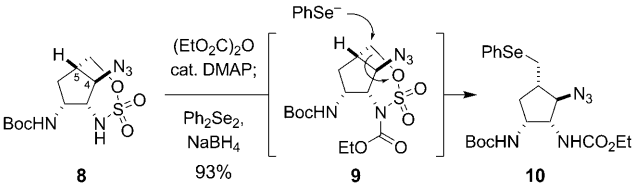
Exposure of sulfamate **6** to a dimeric Rh^{II} catalyst, 1.1 equivalents of $PhI(OAc)_2$, and MgO, afforded aziridine **7**



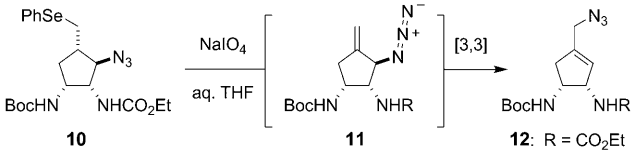
Scheme 4. Homoallylic sulfamate synthesis from the commercially available lactam **4**. Boc = *tert*-butoxycarbonyl, DMA = *N*,*N*-dimethylacetamide.



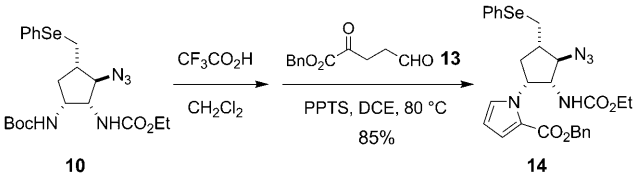
Scheme 5. Catalytic aziridination and regioselective ring opening affords the desired oxathiazepane heterocycle **8**. $[Rh_2(esp)_2]$ = bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)].



Scheme 6. Activation of oxathiazepane **8** and ring opening. DMAP = 4-dimethylaminopyridine.



Scheme 7. Rearrangement of allylic azide **11** necessitates strategic modification.



Scheme 8. Paal–Knorr condensation installs the pyrrole unit. DCE = 1,2-dichloroethane, PPTS = pyridinium 4-toluenesulfonate.

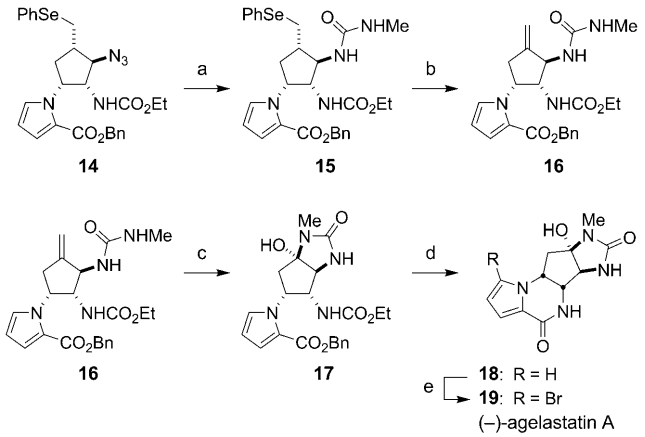
as a single diastereomer in 95% yield (Scheme 5). Less than 1% of the five-membered ring product resulting from allylic C–H insertion was obtained in this transformation. By capitalizing on the use of our recently developed $[Rh_2(esp)_2]$ catalyst, loadings as low as 0.06 mol% (>1500 turnovers) could be employed, thus enabling the reaction to be easily and inexpensively scaled.[15] The novel tricylic structure is quite stable and can be isolated in pure form by column chromatography on silica gel. When treated with NaN_3 in aqueous isopropanol, regioselective attack at C4 (agelastatin numbering) proceeded at ambient temperature to yield predominantly the bridging [1,2,3]-oxathiazepane-2,2-dioxide **8** (C4/C8 regioselectivity 9:1).[16,17] This versatile intermediate incorporates three of the four stereogenic carbamine centers found in the natural product, all differentially masked. Accordingly, this aziridination/ring opening reaction sequence should offer ready access to several forms of agelastatin.

To forward the synthetic plan, a series of maneuvers was needed that would ultimately enable a single carbon excision and introduction of a keto group at C5 (see Scheme 3). Six- and seven-membered ring cyclic sulfamate substrates possess intrinsic reactivity as electrophilies, which can be modulated as a result of functionalization at the nitrogen center.[14b,18] Taking advantage of this property, oxathiazepane **8** was first treated with diethyl pyrocarbonate to furnish the N-acylated species **9**; subsequent introduction of NaSePh (prepared in a separate reaction vessel) displaced the oxathiazepane C–O bond to afford in a single operation selenide **10** (Scheme 6). Access to this product in just four steps from **5** underscores the effectiveness of our aziridination process for the rapid assembly of stereochemically complex, orthogonally protected polyamine intermediates.

Oxidation of selenide **10** and elimination of the transient selenoxide was intended to furnish the C5 *exo* methylene product **11** (Scheme 7). Such a reaction did occur, however, the resulting allylic azide species underwent a facile [3,3]-sigmatropic rearrangement and afforded cyclopentene **12**.[19] As it was not possible to prevent this isomerization process, a decision was made to postpone the introduction of the *exo* methylene unit until the latter steps of the synthesis. Accordingly, we opted to fashion first the requisite pyrrole unit from **10** (Scheme 8). Removal of the Boc group with CF_3CO_2H preceded an efficient Paal–Knorr condensation, which employed tricarbonyl **13** and mild acid catalysis to forge the heterocycle.[20,21] The desired pyrrole **14** was generated in 85% yield over this two-step sequence.

To complete the synthesis of (–)-agelstatin A, azide **14** was reduced chemoselectively under Staudinger conditions (Me_3P, THF/H_2O; Scheme 9). Once reduction was complete, MeNCO was added to the reaction vessel to produce urea **15**. This compound was easily purified by normal-phase silica gel column chromatography in spite of the presence of the polar *N*-methyl urea moiety. Exposure of **15** to *m*CPBA induced selenoxide formation and elimination to afford alkene **16**. While attempts to cleave the *exo* methylene unit at C5 under ozonolytic conditions gave only intractable mixtures of products, successful installation of the carbonyl group at C5 was realized when a combination of OsO_4 (2.5 mol%) and $NaIO_4$ was used. Once the C5-ketone was exposed, addition of the urea was highly favored and the product was isolated exclusively as hemiaminal **17**.

The stability of the hemiaminal unit in **17** obviates protection as the *N*,*O*-acetal. As such, assembly of the final target was accomplished by first exposing **17** to KO*t*Bu in *tert*-amyl alcohol (Scheme 9).[22] This protocol generated the desired six-membered lactam with concomitant cleavage of the ethyl carbamate group. Having intercepted the penulti-



Scheme 9. a) Me_3P, THF/H_2O (10:1); then MeNCO, 81%; b) *m*CPBA, DCE, 0°C; then Et_3N, 80°C, 89%; c) OsO_4 (2.5 mol%), $NaIO_4$, THF/H_2O (1:1), 45°C, 81%; d) KO*t*Bu, *t*AmOH, 45°C, 77%; e) NBS, THF/MeOH (2:1), 0→25°C, 75%. *m*CPBA = *meta*-chloroperbenzoic acid, NBS = *N*-bromosuccinimide, *t*AmOH = *tert*-amyl alcohol, THF = tetrahydrofuran.

mate intermediate formed in prior syntheses of agelastatin A, a literature procedure that used *N*-bromosuccinimde smoothly and selectively brominated the pyrrole unit and gave the natural product as a white, crystalline solid.[6e] Spectroscopic and optical rotation data for the synthetic material were identical in all respects to those reported for the natural product.[2,6e] Overall, by starting from commercially available **5**, the 11-step sequence has been executed in a single pass to deliver more than 200 mg of the natural product (15% overall yield).

An efficient, easily scaled, and flexible route to (−)-agelstatin A has been made possible following the development and application of a selective rhodium-catalyzed aziridination method. With the aid of $[Rh_2(esp)_2]$, this reaction proceeded in high yield at negligible catalyst loadings. The resulting tricycle **7** represents a unique heterocyclic structure that could be efficiently transformed into a differentially protected cyclopentyltriamine **10**. New protocols for manipulating the intermediate oxathiazepane and for crafting the pyrrole lactam also distill from this work. Overall, the preparation of (−)-agelastatin A is illustrative of the manner in which modern oxidative methods for C–N bond formation can alter the retrosynthetic logic of complex chemical synthesis.[23]

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