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Total Synthesis of (−)-Agelastatin A: The Application of a Sequential Sigmatropic Rearrangement

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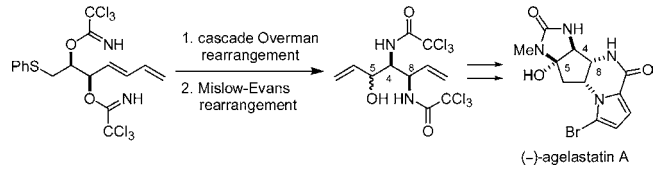
ABSTRACT



An enantioselective total synthesis of (−)-agelastatin A from (−)-2,3-*O*-isopropylidene-D-threitol is described. The sequential Overman/Mislow−Evans rearrangement of the allylic bistrichloroimidate is the key step, which efficiently installed a diaminohydroxy group.

Chirality transfer through the sigmatropic rearrangement of optically active allylic alcohols has been recognized as a useful approach to enantiomerically pure synthetic targets.[1] We have been especially attracted to the utilization of hydroxy groups embedded in naturally occurring organic compounds, such as carbohydrates and tartaric acid, since these compounds are readily available and operationally versatile enantiopure starting materials. In order to render this approach more efficient and practical, our laboratory has been exploring strategies using the cascade sigmatropic rearrangement[2] of allylic vicinal diols for the synthesis of biologically active natural products and their derivatives. To date, we have reported a formal total synthesis of (−)-morphine by a cascade Claisen rearrangement starting from D-glucal[3,4] and a total synthesis of A-315675 by a cascade Overman rearrangement using diisopropyl D-tartrate as a chiral starting material.[5,6]

As part of our ongoing studies aimed at developing chemistry involving sequential sigmatropic rearrangements, our group took an interest in the oroidin alkaloid, (−)-agelastatin A (**1**). Isolated by Pietra in 1994 from the deep water marine sponge *Agelas dendromorpha*,[7] (−)-**1** inhibits a number of human tumor cell lines.[7a,8] The recent excellent report by El-Tanani and Hale has revealed that (−)-**1** acts as an antimetastatic agent through the inhibition

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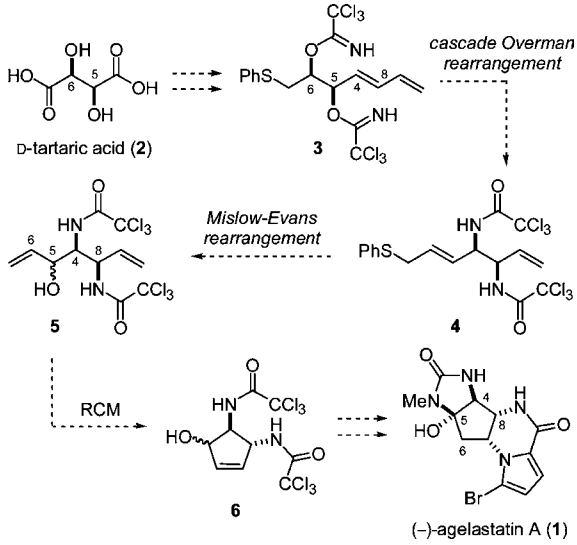
of osteopontin-mediated malignant transformation and the arrest of the cell cycle.[8c] (−)-Agelastatin A (**1**) has also been reported to show insecticidal properties[7c] and to selectively inhibit glycogen synthase kinase-3β (GSK-3β).[9] In addition to the intriguing biological properties of (−)-**1**, its unique architecture including a tetraamino carbocyclic ring and a bromopyrrole unit has inspired a number of synthetic chemists.[10,11] Initially, Weinreb,[10a,b] Feldman,[10c,d] Hale,[10e,f] Davis,[10g,k] Trost,[10h] and Ichikawa[10i] all accomplished the elegant total synthesis of **1** by different strategies. Recently, three more novel total syntheses have been reported.[10j,l,m]

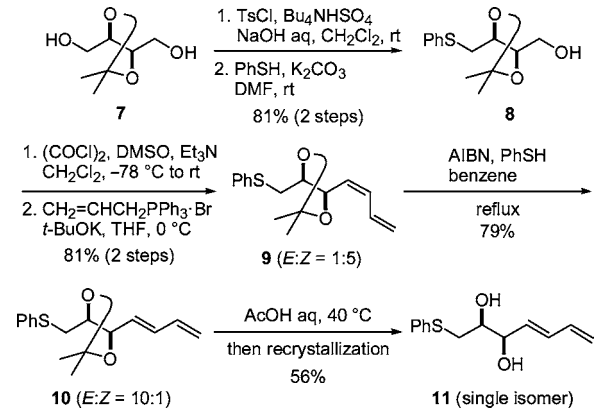
In designing a synthetic route toward (−)-agelastatin A (**1**), we envisioned that cyclopentene **6** possessing a diaminohydroxy group would be a promising intermediate, and cyclopentene **6** was itself expected to be derived from acyclic compound **5** through RCM[12] (Scheme 1). Our major challenge in the synthesis of (−)-**1** would be the efficient installation of the diaminohydroxy group [C8, C4, and C5 (agelastatin numbering)] through the sequential Overman/Mislow−Evans rearrangement of bistrichloroimidate **3**.[13−15] The two nitrogen-substituted stereocenters[16] (C4, C8) could be established by the cascade Overman rearrangement of **3** in a single operation. The subsequent Mislow−Evans rearrangement of allylic sulfide **4** could introduce a hydroxy group at the C5 carbon center. Bistrichloroimidate **3**, with its two chiral stereocenters, was expected to be readily prepared from D-tartaric acid **2**.

Scheme 1. Synthetic Strategy toward (−)-Agelastatin A (**1**)



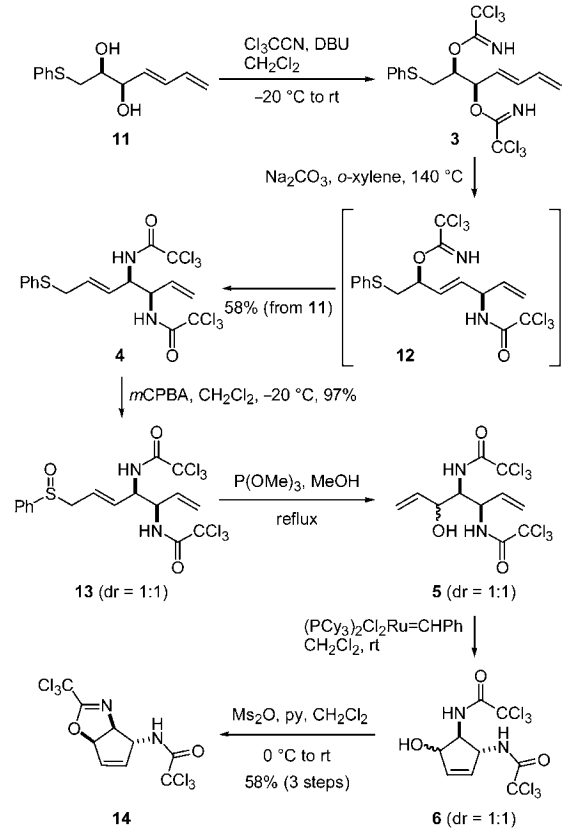
The synthesis of (−)-agelastatin A (**1**) commenced with the monotosylation of commercially available (−)-2,3-*O*-isopropylidene-D-threitol **7**,[17] which is derived from D-tartaric acid, followed by thiophenol installation to produce alcohol **8** (Scheme 2). After Swern oxidation[18] of the primary alcohol, the Wittig reaction with allylphosphorous ylide provided diene **9** in a *Z*-selective manner. To set the appropriate stereochemical configuration in the cascade Overman rearrangement, *Z*-diene **9** was isomerized to *E*-diene **10** with thiophenol and AIBN under radical conditions.[19] Removal of the acetonide followed by recrystallization furnished allylic diol **11** as a single isomer.

Scheme 2. Synthesis of Allylic Vicinal Diol **11**



With allylic diol **11** in the (*E*)-arrangement, the stage was now set for the crucial sequential sigmatropic rearrangement. Treatment of **11** with trichloroacetonitrile and DBU in CH_2Cl_2 gave allylic bistrichloroacetimidate **3** (Scheme 3).

Scheme 3. Sequential Overman/Mislow−Evans Rearrangement

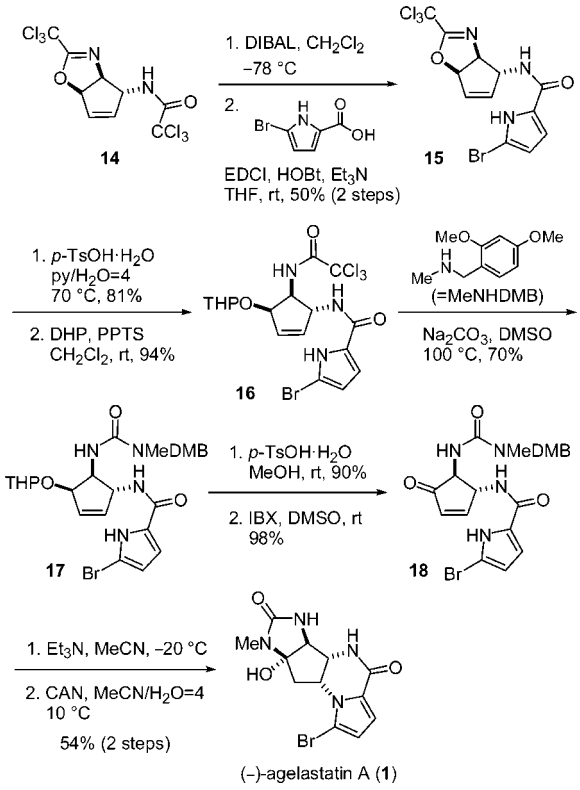


To our delight, the cascade Overman rearrangement of **3** under thermal conditions at 140 °C in *o*-xylene in a sealed

tube in the presence of Na_2CO_3[20] provided desired bistrichloroacetamide **4** in 58% yield from allylic diol **11**. The reaction proceeded in a stereoselective manner probably through the known chair transition state,[5] and **4** was isolated as the sole product. The allylic sulfide in **4** was subsequently oxidized to sulfoxide **13**, which underwent the Mislow-Evans rearrangement with $P(OMe)_3$ in refluxing MeOH to give a 1:1 mixture of two diastereomers **5**.[21] Although the stereoselectivity of the Mislow−Evans rearrangement was poor, both isomers could be used in the synthesis without separation. The ring-closing metathesis of **5** provided a 1:1 mixture of cyclopentene **6**. Then, the treatment of **6** with methanesulfonic anhydride and pyridine generated the oxazoline **14** in 58% yield (three steps from **13**).[22] It is noteworthy that two isomers derived from the Mislow−Evans rearrangement converged to a single oxazoline, and the two trichloroacetamides on the carbocyclic ring were successfully differentiated in this reaction.

With oxazoline **14** now available by the sequential Overman/Mislow−Evans rearrangement, we turned our attention to the installation of the piperazinone ring with the sensitive bromopyrrole (Scheme 4). Removal of the trichloroacetyl group in **14** with DIBAL[23] and condensation of the resulting amine with 2-bromopyrrole carboxylic acid[24] afforded amide **15**. After hydrolysis of the oxazoline of **15** with *p*-TsOH·H_2O in pyridine/H_2O,[10k,25] the resulting secondary alcohol was protected as the THP acetal. In order to construct the piperazinone ring, an intramolecular aza-Michael reaction of the pyrrole was envisaged. Originally developed by Weinreb,[10b] the reaction has been extensively investigated by several groups,[10c,d,f,g,i,k] with Hale[10f] and Ichikawa[10i] revealing that lowering pK_a of the pyrrole nitrogen is often highly beneficial and sometimes necessary in the aza-Michael addition. Ichikawa employed the dibromopyrrole and Hale employed a number of bromopyrroles to effect cyclization, and in both cases, the adducts were transformed into the monobromopyrrole in the final step. We took into account their critical findings and explored a more direct and efficient procedure that used the monobromopyrrole unit and a 2,4-dimethoxybenzyl (DMB) group as a protecting group for the *N*-methylurea. The one-pot formation of the urea from trichloroacetamide **16** with 2,4-dimethoxybenzylmethyl amine and Na_2CO_3 in DMSO at 100 °C efficiently furnished protected *N*-methylurea **17** in 70% yield.[26] Removal of the THP group on the secondary alcohol followed by IBX oxidation[27] gave α,β-unsaturated ketone

Scheme 4. Total Synthesis of (−)-Agelastatin A (**1**)



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18, which was exposed to Et_3N in MeCN to induce the crucial aza-Michael addition. Due to the instability of the aza-Michael product, the next deprotection was immediately performed. The 2,4-dimethoxybenzyl group was successfully cleaved with CAN in $MeCN/H_2O$ at 10 °C without affecting the bromopyrrole group, thus affording (−)-agelastatin A (**1**) in 54% over two steps from **18**. Our synthetic sample was found to be indistinguishable from a natural sample based on ^1H NMR, ^{13}C NMR, HRMS, and IR, as well as its optical rotation.[7a,c]

In summary, we have achieved a total synthesis of (−)-agelastatin A (**1**), using a sequential Overman/Mislow−Evans rearrangement as the key step. The cascade Overman rearrangement has thus been shown to be a powerful tool for the stereoselective one-step construction of diamino moieties in complex natural products. Progress toward the development of a new series of sequential sigmatropic rearrangements and their applications are ongoing.

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Supporting Information Available: Experimental procedures; copies of ^1H NMR and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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