ORGANIC LETTERS

2004
Vol. 6, No. 15
2615−2618

New Total Synthesis of the Marine Antitumor Alkaloid (–)-Agelastatin A

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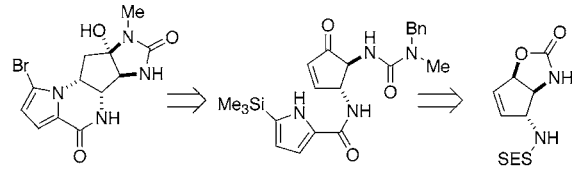
Received May 24, 2004

ABSTRACT



A new total synthesis of (–)-agelastatin A (1) has been achieved from the chiral oxazolidinone (–)-3. Although enone transposition was problematic when the Michael ring closure of 2 was attempted with strong base, the desired cyclization could be effected with Hunig's base after the pyrrole nucleus was brominated. Subsequent reduction and monobromination afforded synthetic (–)-agelastatin A (1).

(−)-Agelastatin A (**1**) is an architecturally unusual antineoplastic alkaloid isolated from the axinellid sponge *Agelas dendromorpha* by Pietra and co-workers.[1] Although (−)-agelastatin A has been shown to potently inhibit the growth of L1210 leukemia in mice, its antitumor profile against solid human tumors or human tumor cell lines has not been thoroughly investigated.[1c] In fact, (−)-agelastatin A has only been screened against a single human KB nasopharyngeal cancer cell line; its IC_{50} was 0.075 μg/mL.[1c]

Given the current scarcity of natural (−)-agelastatin A and our interest in evaluating its growth-inhibitory effects against solid human tumors in mice, we recently embarked on its total synthesis for the purpose of increasing supply.[2] In this Letter, we now report on the successful conclusion of this venture with our recent conversion of (−)-**3** into (−)-**1**.

In mid-2003, we published a fully stereocontrolled enantiospecific total synthesis of the chiral oxazolidinone (−)-**7** (Scheme 1) from D-glucosamine.[2] Racemic **7** had previously been converted into racemic agelastatin A by Weinreb and co-workers in 1999.[3] Although our route constituted an enantiospecific formal total synthesis of (−)-agelastatin A, we sought an alternative endgame to that used by Weinreb et al., as their route had employed the highly dangerous and expensive methyl isocyanate for introducing the cyclic hemiaminal subunit.[3−5]

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(1) (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. (c) D'Ambrosio, M.; Guerriero, A.; Ripamonti, M.; Debitus, C.; Waikedre, J.; Pietra, F. *Helv. Chim. Acta* **1996**, *79*, 727.

(2) Hale, K. J.; Domostoj, M. M.; Tocher, D. A.; Irving, E.; Scheinmann, F. *Org. Lett.* **2003**, *5*, 2927.

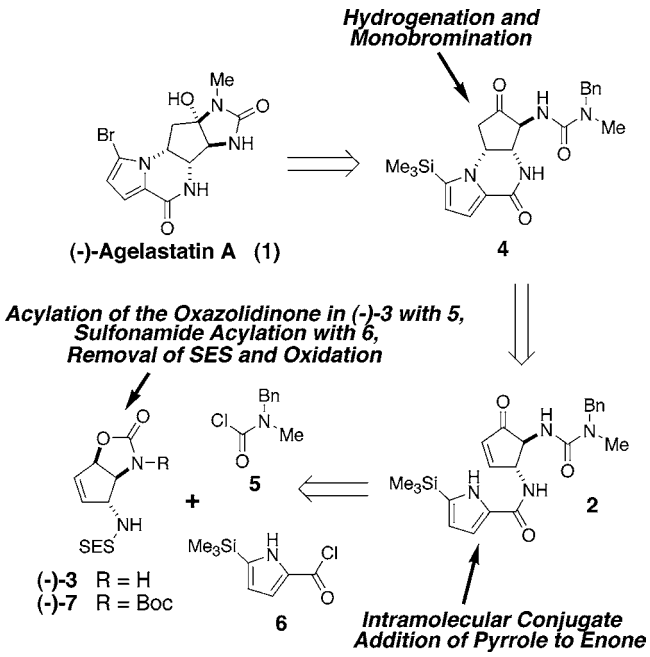
(3) (a) Stein, D.; Anderson, G. T.; Chase, C. E.; Koh, Y−h.; Weinreb, S. M. *J. Am. Chem. Soc.* **1999**, *121*, 9574. (b) Anderson, G. T.; Chase, C. E.; Koh, Y.-h.; Stein, D.; Weinreb, S. M. *J. Org. Chem.* **1998**, *63*, 7594.

(4) For the first asymmetric synthesis of (−)-agelastatin A, see: (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.

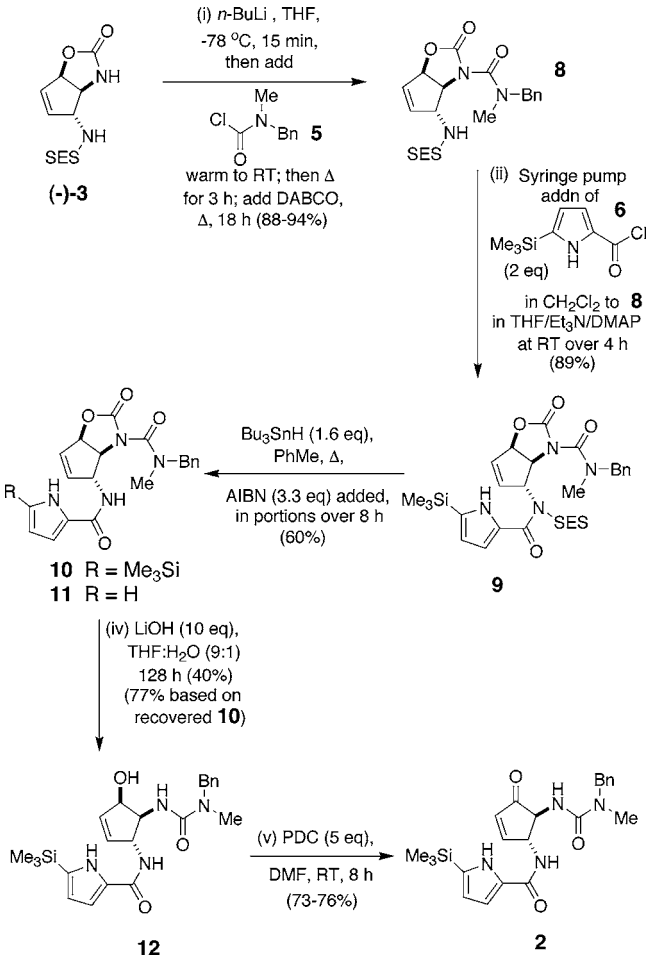
(5) For a synthetic approach to (−)-agelastatin A, see: Baron, E.; O'Brien, P.; Towers, T. D. *Tetrahedron Lett.* **2002**, *43*, 723.

10.1021/ol0490476 CCC: $27.50
Published on Web 06/19/2004

Scheme 1. Our Proposed New Endgame for (−)-Agelastatin A (**1**)



Scheme 2. Route to Cyclopentenone **2**



The new endgame that we envisaged (Scheme 1) would transform (−)-**3** into the chiral cyclopentenone **2** and would exploit a base-catalyzed intramolecular Michael addition to fuse the pyrrole and cyclopentane rings. Ketone **4** would then be hydrogenolyzed and brominated to complete the total synthesis of (−)-**1**.

We commenced our route to (−)-**2** with the selective *N*-carbamoylation of oxazolidinone (−)-**3**[2] with acid chloride **5**[6] (Scheme 2). Using a combination of *n*-BuLi and DABCO as the bases, the *N*-carbamoyl oxazolidinone **8** was readily formed in 88−94% yield. Compound **8** was then subjected to a second *N*-acylation step, on this occasion with 2 equiv of the pyrrole acid chloride **6**, excess Et_3N, and DMAP in CH_2Cl_2 and THF; the desired pyrrolocarboxamide **9** was isolated in 89% yield. The SES group[7] of **9** was then cleaved with Bu_3SnH and AIBN[8] in PhMe at reflux. The free pyrroloamide **10** was typically obtained in 60% yield.

To the best of our knowledge, this is the first time that a SES group has been reductively removed from an amide nitrogen by Bu_3SnH under free radical conditions. Importantly, our new protocol for cleaving amido-SES groups works reasonably well, as demonstrated here. It certainly outperformed all of the fluoride-induced cleavage protocols that we investigated on this and related substrates. A small amount of the *C*-desilylated product **11** (up to 7%) was also sometimes encountered in this Bu_3SnH reduction depending on its overall duration.

Our next objective was to hydrolyze the oxazolidinone ring of **10** while leaving the urethane unit intact. Although this reaction could be accomplished cleanly with aqueous LiOH in THF at room temperature, it did require long reaction times (128 h) to deliver workable yields of product. In this regard, the desired allylic alcohol **12** could usually be isolated in 37−40% yield along with 48% of **10**, which was then recycled. On the basis of the quantity of **10** that was typically recovered, the yield of **12** was calculated to be 77%.

Of the various oxidants that were evaluated for converting **12** into **2**, pyridinium dichromate in DMF was by far the most effective. Enone **2** was usually fashioned in 73−76% yield by this method (Scheme 2). The TPAP/NMO system could also be used, but the yields were approximately 10% lower (ca. 65%).

We next investigated the base-mediated ring closure of enone **2** to secure ketone **4** (Schemes 1 and 3). Et_3N in MeOH or 10 mol % Bu_3P in THF[9] were completely

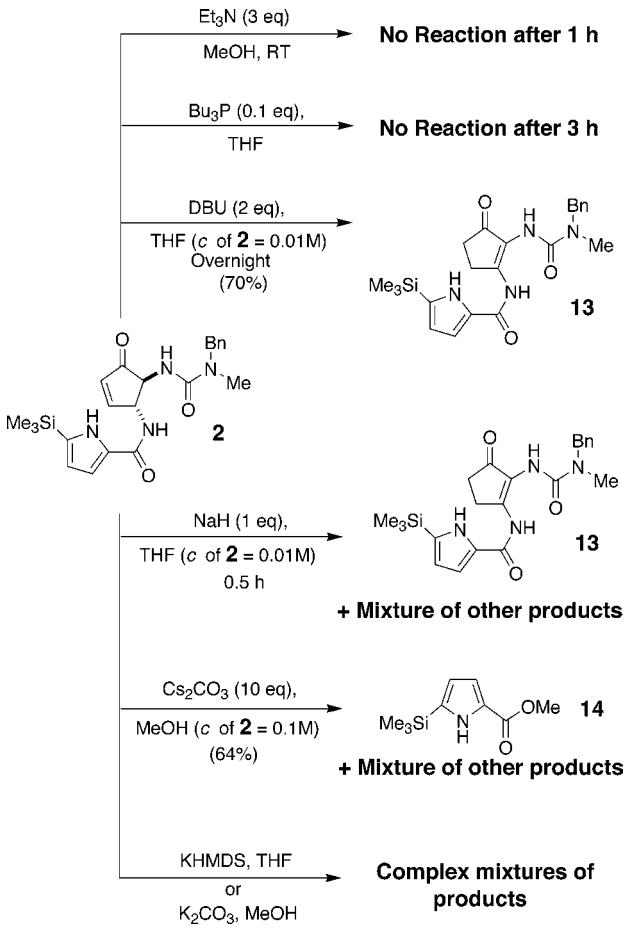
(6) Yoakim, C.; Ogilvie, W. W.; Cameron, D. R.; Chabot, C.; Guse, I.; Hache, B.; Naud, J.; O'Meara, J. A.; Plante, R.; Deziel, R. *J. Med. Chem.* **1998**, *41*, 2882.

(7) (a) Weinreb, S. M.; Demko, D. M.; Lessen, T. A.; Demers, J. P. *Tetrahedron Lett.* **1986**, *27*, 2099. (b) Weinreb, S. M.; Chase, C. E.; Wipf, P. Venkatraman, *Org. Synth.* **1997**, *75*, 161.

(8) (a) For the first report of phenylsulfonyl groups α to a carbonyl being reductively removed by Bu_3SnH and AIBN, see: (a) Smith, A. B., III; Hale, K. J.; McCauley, J. A., Jr. *Tetrahedron Lett.* **1989**, *30*, 5579. (b) For the first application of this method to arylsulfonylated amides, see: Parsons, A. F.; Pettifer, R. M. *Tetrahedron Lett.* **1996**, *37*, 1667.

(9) Stewart, I. C.; Bergman, R. G.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 8696.

Scheme 3. Attempts at CyclizIng the Enone **2** with Various Bases

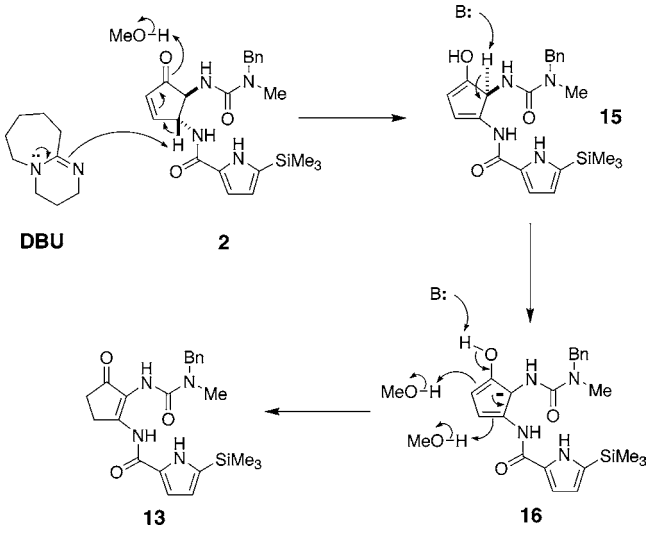


ineffective at mediating this cyclization; enone **2** was always recovered untouched in either case. Surprisingly, when enone **2** was reacted with DBU (2 equiv) in THF at room temperature, an unusual rearrangement took place and the cyclopentenone **13** was isolated in 70% yield (Scheme 3)![10] Presumably enone **13** arose from the γ-deprotonation of **2** to give the cyclopentadienol **15** (Scheme 4), which then underwent facile deprotonation to create the aromatic 6π-anion **16**, which finally reprotonated in the manner shown.

Sodium hydride was also investigated for effecting the desired ring closure of **2**, but yet again this base failed to deliver the cyclized ketone **4** (Scheme 3). Instead, a complex mixture of products arose in which the rearranged cyclopentenone **13** predominated. Potassium hexamethyl-disilazide in THF likewise gave rise to complicated reaction mixtures, as did K_2CO_3 in MeOH. Curiously, Cs_2CO_3 in MeOH[3] produced **14** as the only readily isolable reaction product in 64% yield, along with other decomposition products (Scheme 3).

(10) The cyclopentenone isomerization seen here is analogous to the well-known base-mediated prostaglandin A_1 to B_1 rearrangement reported by Corey in the late 1960s. See: Corey, E. J.; Andersen, N. H.; Carlson, R. M.; Paust, J.; Vedejs, E.; Vlattas, I.; Winter, R. E. K. *J. Am. Chem. Soc.* **1968**, *90*, 3245. See also: Newton, R. F.; Roberts, S. M. In *Prostaglandins and Thromboxanes*; Roberts, S. M., Newton, R. F., Eds.; Butterworths: London, Boston, 1982; Chapter 6, p 84.

Scheme 4. Base-Mediated Isomerization of **2**



In light of all of these failures, several Brønsted and Lewis acids were surveyed for their ability to instigate the desired cyclization. PPTS (5 equiv) in THF and MeOH was initially screened in this capacity. Unfortunately, this led to the pyrrole TMS of **2** being replaced by hydrogen. The latter product was also formed when TMSOTf (1.1 equiv) was used to activate enone **2** in THF; it was coproduced with **13**.

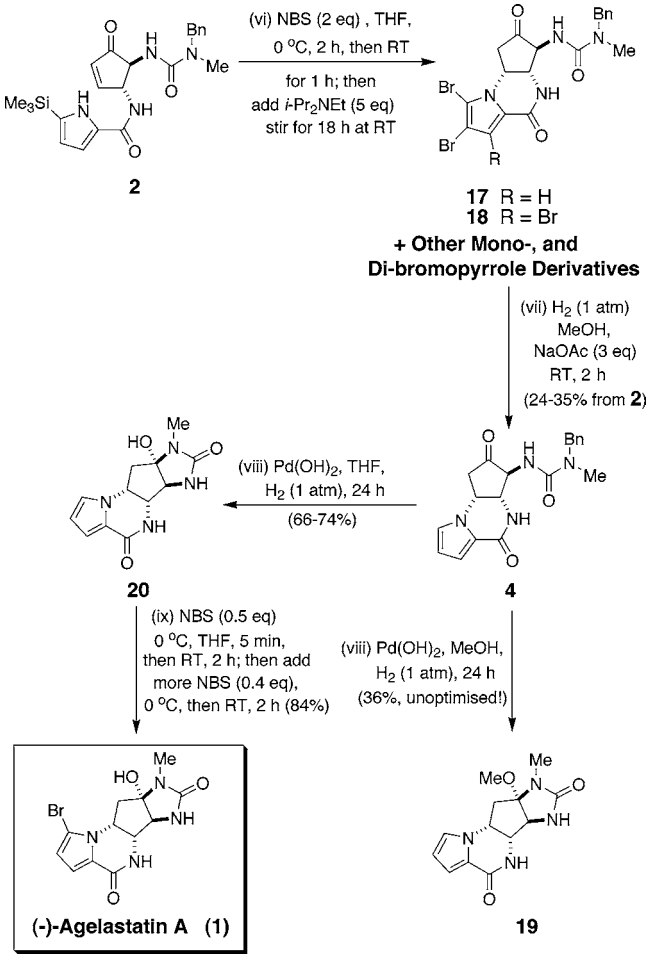
Given all of these disappointments, a step backward was taken, and the Swern oxidation and in situ cyclization of **12** was attempted under conditions analogous to those reported by Feldman and Saunders on a related system.[4] With our substrate, this led to a 16% isolated yield of **13**, a 20% yield of the enone **2**, and a 62% recovery of **12**.

Because Et_3N in MeOH had already been shown to leave enone **2** unrearranged, we postulated that we might be able to bring about cyclization under similar conditions, if we could somehow lower the pK_a of the pyrrole nitrogen in **2**.

With this in mind, **2** was reacted with 2 equiv of *N*-bromosuccinimide (NBS) in THF for 3 h, in the expectation that a single 2,3-dibromopyrrole **17** would form, whose pK_a would be considerably lower (Scheme 5). To our surprise, a multicomponent mixture of mono-, di-, and tribromo pyrroles arose, and none of the starting enone **2** remained.[11] Therefore, rather than attempting to purify the individual products, Hunig's base (5 equiv) was added directly to the reaction mixture, and the reactants were allowed to stir at room temperature overnight to bring about the requisite Michael ring closure. The crude mixture was then extractively worked up and directly dehalogenated by catalytic hydrogenation over 10% Pd on C (wet, 0.1 equiv) in MeOH for 2 h, in the presence of NaOAc (3 equiv). After this operation, TLC analysis became much clearer (see Supporting Information), with the desired ketone **4** now appearing as a chromato-

(11) The only component of this mixture that we could ever obtain in reasonably pure condition was the tribromopyrrole **18**; it is the major product of this reaction, as far as we can tell. Use of 3 equiv of NBS for the bromination does not increase the amount of **18** that is formed but, instead, causes overbromination and significant product decomposition.

Scheme 5. Completion of the Total Synthesis of (−)-1



graphically resolvable slower-moving spot that could typically be isolated in 24−35% overall yield for the three steps from **2**.

Although TLC revealed that several faster-moving products were also usually formed in this combined reaction sequence, none of them could ever be easily purified or unambiguously characterized.

Initially, we attempted the N-debenzylation of **4** through catalytic hydrogenation in MeOH over Pearlman's catalyst (20% $Pd(OH)_2$ on C). Unfortunately, this led to the methyl acetal **19** being produced as a single product in 36% yield (not optimized). Importantly, this undesired course for the reaction could be completely avoided, simply by conducting the hydrogenation in THF for 24 h.[4] Under these conditions, **20** was obtained in 66−74% yield.

The final step of the synthesis was the site-selective monobromination of **20** with NBS (0.9 equiv) in THF and MeOH as described by Feldman and Saunders.[4] This provided synthetic (−)-agelastatin A in 84% yield. Significantly, our new route to (−)-agelastatin A has so far delivered 223 mg of the natural product in a highly reproducible fashion.

This material is now being evaluated against xenografted solid human tumors in mice and for investigations into the mechanism of antitumor action. The results of these studies will be published in due course.

Acknowledgment. We thank Ultrafine (Manchester), Merck, Sharp & Dohme (Harlow), Pfizer (Sandwich), and Novartis Pharma AG (Basel) for their much appreciated financial support.

Supporting Information Available: Full experimental procedures and detailed spectral data of all key compounds, copies of 500 MHz ^1H and 125 MHz ^{13}C spectra, and HRMS data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0490476