Studies on Total Synthesis of the Cytotoxic Marine Alkaloid Agelastatin A

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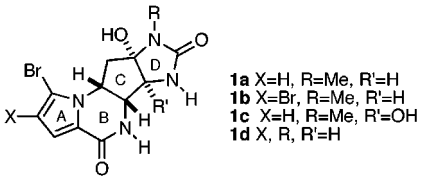
Agelastatin A (**1a**) is a novel heterocyclic natural product recently isolated from the deep water marine sponge *Agelas dendromorpha* collected in the Coral Sea.[1a−c] The metabolite shows significant in vitro cytotoxic activity against leukemia and epithelial tumor lines. Agelastatin B (**1b**) is a minor compound that accompanies agelastatin A in the natural source. More recently, agelastatins C (**1c**) and D (**1d**) have

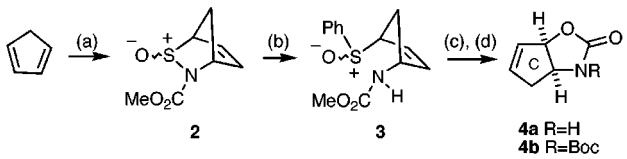


1a X=H, R=Me, R'=H
1b X=Br, R=Me, R'=H
1c X=H, R=Me, R'=OH
1d X, R, R'=H

been isolated from a West Australian sponge *Cymbastela*.[1d] In view of their unique structures and significant biological activity, we are currently attempting to devise a stereoselective strategy for construction of these fascinating natural products, and this paper describes our initial studies toward this goal.[2]

We initally focused on building the tetraamino carbocyclic C-ring of the agelastatins by application of our previously reported *N*-sulfinyl dienophile hetero-Diels−Alder methodology for stereoselective preparation of unsaturated vicinal-amino alcohol derivatives.[3] Therefore, methyl *N*-sulfinylcarbamate[4] was combined with cyclopentadiene to afford adduct **2** (Scheme 1). We were originally uncertain whether this cycloaddition was feasible, since it was reported many years ago that the adduct between cyclopentadiene and *N*-sulfinylbenzenesulfonamide is unstable and undergoes rapid retro Diels−Alder reaction below room temperature.[5] Although cycloadduct **2** is in fact reasonably stable, it is best that the crude material be immediately converted with phenylmagnesium bromide to ring-opened allylic sulfoxide **3**. This compound could then be induced to undergo a [2,3]-sigmatropic rearrangement, followed by reduction and cyclization, to afford cis-fused carbamate **4a**.[3,6,7]

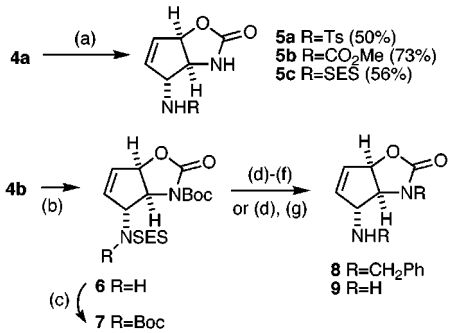
Scheme 1[a]



2 **3** **4a** R=H **4b** R=Boc

[a] Reagents: (a) MeO_2CNSO, PhH, 0 °C; (b) PhMgBr, THF, −60 °C, 86% from cyclopentadiene, (c) HMPT, EtOH, 80 °C (see the Supporting Information); (d) Boc_2O, NEt_3, DMAP, 99%.

Scheme 2[a]



5a R=Ts (50%)
5b R=CO_2Me (73%)
5c R=SES (56%)

6 R=H
7 R=Boc

8 R=CH_2Ph
9 R=H

[a] Reagents: (a) RN=S=NR, PhMe, Δ; $(MeO)_3P$, MeOH; (b) SESN=S=NSES, PhMe, Δ; $NaBH_4$, MeOH; (c) Boc_2O, NEt_3, DMAP, 97%; (d) TFA, CH_2Cl_2; (e) NaH, THF, TBAI, $PhCH_2Br$, −80 °C−rt, 97%; (f) CsF, THF, 95 °C, 98%; (g) TBAF, MeCN, 80 °C, 90%.

We were pleased to find that carbamate olefin **4a** underwent a Sharpless−Kresze ene reaction with bis-tosylsulfur diimide to afford allylic amination product **5a** as a single stereoisomer (Scheme 2).[8] In addition, the bis-methyl carbamate derived sulfur diimide also effects clean allylic amination of **4a**, leading to **5b**. However, it has not been possible to remove either the tosyl or carbamoyl N-protecting groups of **5a** and **5b**, respectively.[2] Thus, we have prepared a new SES-substituted[9] sulfur diimide, which was found to react with **4a** to give a single ene product **5c**, although yields tended to be variable, particularly on a multigram scale. The SES group of **5c** could be removed using TBAF/MeCN to give the corresponding primary amine **9** in 90% yield.

It has proven more effective, however, first to protect the NH of carbamate olefin **4a** with a Boc group, affording **4b**, followed by an ene reaction with the SES sulfur diimide to afford **6**, since yields are now more reproducible on a larger scale. Cleavage of the Boc group with TFA then provided **5c** in 86% overall yield from **4b**. We have assigned the stereochemistry of the amination products **5a**−**c** and **6** as shown since we expected that the ene reactions would occur on the more exposed convex face of alkenes **4a**,**b**. An X-ray analysis of bis-Boc compound **7** derived from ene product **6** subsequently confirmed this supposition.

† Author to be contacted about the X-ray crystal structure determination.

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(2) Taken in part from: Anderson, G. T. Ph.D. Thesis, The Pennsylvania State University, 1995.

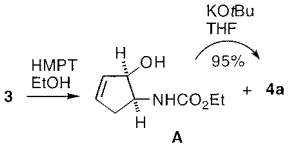
(3) For reviews and lead references, see: (a) Weinreb, S. M. *Acc. Chem. Res.* **1988**, *21*, 313. (b) Boger, D. L.; Weinreb, S. M. *Hetero Diels−Alder Methodology in Organic Synthesis*; Academic Press: San Diego, 1987; Chapter 1. (c) Weinreb, S. M. Heterodienophile Additions to Dienes. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, p 401.

(4) Garigipati, R. S.; Freyer, A. J.; Whittle, R. R.; Weinreb, S. M. *J. Am. Chem. Soc.* **1984**, *106*, 7861.

(5) Macaluso, A.; Hamer, J. *J. Org. Chem.* **1966**, *31*, 3049.

(6) For alternative preparations of oxazolidinone **4a** see: Mulvihill, M. J.; Gage, J. L.; Miller, M. J. *J. Org. Chem.* **1998**, *63*, 3357. Muxworthy, J. P.; Wilkinson, J. A.; Procter, G. *Tetrahedron Lett.* **1995**, *36*, 7539.

(7) Reaction of sulfoxide **3** with HMPT in ethanol led to a mixture of cyclic carbamate **4a** (44%) and uncyclized ethyl carbamate **A** (40%). Compound **A** could be cyclized in high yield to **4a** with potassium *tert*-butoxide (see the Supporting Information).



(8) (a) Sharpless, K. B.; Hori, T. *J. Org. Chem.* **1976**, *41*, 176. (b) Bussas, R.; Kresze, G. *Liebigs Ann. Chem.* **1980**, 629.

(9) (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, S. *Org. Synth.* **1997**, *75*, 161.

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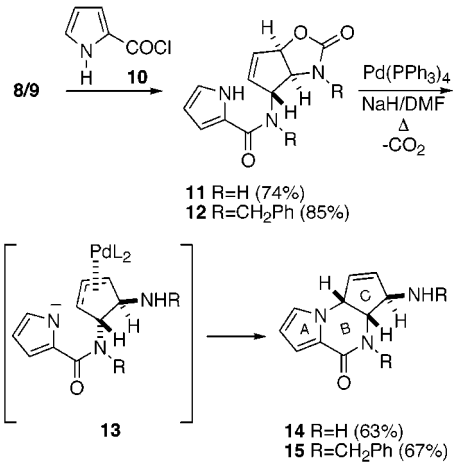
Scheme 3



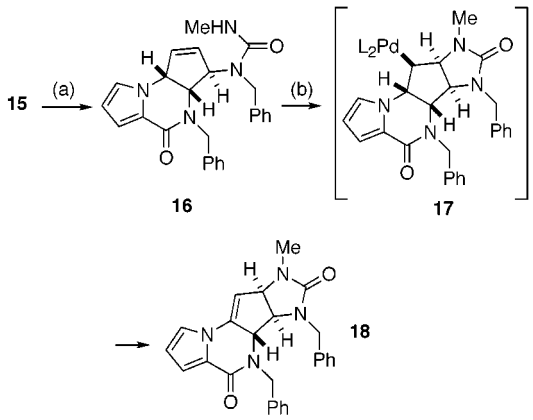
At this point, we have opted to pursue model studies with a pyrrole lacking the C-5 bromine atom.[10] Thus, the pyrroloamide **11** was prepared from pyrrole-2-carbonyl chloride (**10**)[11] as shown in Scheme 3. As we had hoped, Pd(0)-promoted cyclization of this compound led to ABC-tricycle **14**, presumably via π-allylpalladium intermediate **13**.[12] It is known that soft nucleophiles can be induced to add either syn or anti to palladium in such η^3-complexes.[13] For stereoelectronic reasons, syn cyclization of π-allylpalladium species **13** was expected, giving the desired cis-fused B/C ring product **14**. We have established the cis BC ring fusion stereochemistry of this tricycle by ^{1}H NMR NOE experiments on the corresponding benzyl carbamate derivative of the primary amine.[2] It should also be noted that various nitrogen heterocycles including indoles have previously been N-alkylated with π-allylpalladium complexes, but apparently not pyrroles.[14] Since amine **14** proved very polar and rather difficult to isolate, the sequence has also been repeated with the *N*,*N*-dibenzyl analogue **8**, prepared in two steps from ene product **5c** (Scheme 2), giving a good yield of tricycle **15**, which is more easily purified and handled than **14**.

We have also investigated some routes for construction of the D-ring of the agelastatins. Thus, amine **15** was converted to the *N*-methylurea **16** with triphosgene/methylamine (Scheme 4). Exposure of olefin urea **16** to Pd(II) unfortunately afforded the undesired regioisomeric tetracyclic ene urea **18**.[15,16] This cyclization presumably occurs via a syn addition of palladium and the urea nitrogen across the olefinic double bond of **16** to give **17**, which then undergoes a syn β-hydride elimination leading to the observed product **18**.

We have tested the feasibility of an alternative strategy for D-ring annulation. Therefore, tricyclic amino olefin **15** was first protected as its Boc derivative (Scheme 5). This compound could then be hydroborated (88%), and the resulting mixture of alcohols was oxidized with PDC to afford the desired cyclopentanone **20** (37% from the mixture of alcohols), along with a regioisomeric compound tentatively assigned alcohol structure **19**.[16] Interestingly, all attempts to oxidize alcohol **19** to the corresponding ketone led only to decomposition products. Removal of the Boc group from ketone **20** and treatment of the resulting amine with triphosgene/$MeNH_2$ afforded the desired tetracyclic hydroxy urea **21** (69%) closely related in structure to the agelastatins. The structure and stereochemistry of tetracycle **21** was confirmed by ^{1}H NMR NOE experiments.

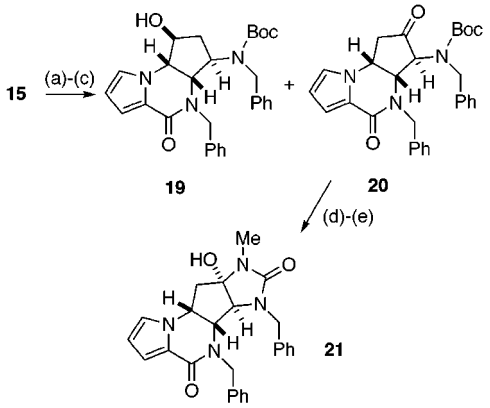
We are currently attempting to apply the methodology descibed in this paper to a total synthesis of agelastatin A. In particular, studies are underway on introduction of the bromine into the pyrrole A ring and to improve the regioselectivity of the hydroboration step or find a better method to convert olefin **15** to ketone **20**.

Scheme 4[a]



[a] Reagents: (a) $CO(OCCl_3)_2$, CH_2Cl_2, DIEA, −80 °C−rt; $MeNH_2$, THF, −80 °C−rt, 89%; (b) $Pd(OAc)_2$, $Cu(OAc)_2$, DMSO/H_2O (6/4), 80 °C, 54%.

Scheme 5[a]



[a] Reagents: (a) Boc_2O, THF, DMAP, rt, 91%; (b) BH_3−THF, THF, rt; H_2O_2, NaOH, 88%; (c) PDC, DMF, rt, 37%; (d) TFA, CH_2Cl_2, rt; (e) $(CCl_3O)CO$, DIEA; $MeNH_2$, THF, 69% from **20**.

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Supporting Information Available: Experimental details for preparation of new compounds, and an ORTEP plot and X-ray data for bis-Boc derivative **7** (14 pages).

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(10) Debromoagelastatin A, prepared by $LiAlH_4$ reduction of **1a**, retains antitumor activity, although at a reduced level.[1c]

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(12) For formation of π-allylpalladium complexes from oxazolidinones, see: Cook, G. R.; Shanker, P. S. *Tetrahedron Lett.* **1998**, *39*, 3405. Cook, G. R.; Shanker, P. S. *Tetrahedron Lett.* **1998**, *39*, 4991.

(13) For reviews of the stereochemistry of allylic palladations, see: (a) Frost, C. G.; Howarth, J.; Williams, J. M. J. *Tetrahedron: Asymmetry* ***1992***, *3*, 1089. (b) Bäckvall, J. E. *New J. Chem.* **1990**, *14*, 447.

(14) See, for example: Billups, W. E.; Erkes, R. S.; Reed, L. E. *Synth. Commun.* **1980**, *10*, 147. N vs C alkylation of indole can be controlled by an appropriate choice of reaction conditions.

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(16) The structures of intermediates **18** and **20** were established by 2D NMR (HMBC).