Total Synthesis of the Antitumor Marine Sponge Alkaloid Agelastatin A

Didier Stien, Glen T. Anderson, Charles E. Chase, Yung-hyo Koh, and Steven M. Weinreb*

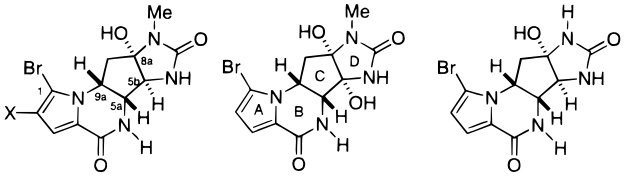
Contribution from the Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802

Received July 14, 1999

Abstract: The first total synthesis of the cytotoxic marine metabolite agelastatin A (**1**) has been achieved in about 14 steps performed in 12 operations in approximately 7% overall yield starting from cyclopentadiene. Hetero Diels−Alder cycloaddition of cyclopentadiene with *N*-sulfinyl methyl carbamate (**7**) afforded cycloadduct **8**, which without purification was converted to allylic sulfoxide **9** and then by a [2,3]-sigmatropic rearrangement into bicyclic oxazolidinone **11**. The C-5a nitrogen was introduced into the oxazolidinone Boc derivative **16** by a Sharpless/Kresze allylic amination with SES sulfodiimide **12c**. Palladium-promoted cyclization of 2-acyl pyrroles **20** and **21** via a π-allylpalladium intermediate **22** led to ABC-tricycles **23** and **24**, respectively. A hydroxyl urea D-ring model system was constructed by hydroborating **24**, leading eventually to keto amide **31** and then to tetracycle **33**. A modified strategy was developed for synthesis of the pivotal tricyclic ketone **58**, involving as key steps a chemoselective hydrolysis of *N*-Boc oxazolidinone **54** and an internal conjugate addition of pyrrolo cyclopentenone **57**. A TMS group was used as a convenient substitute for the C-1 bromine substituent of agelastatin A, and thus silylpyrrole **58** could be converted to bromopyrrole **59**. Finally, the D-ring could be annulated onto an α-amino ketone derived from **59** using methyl isocycanate, providing racemic agelastatin A (**1**).

In 1993 Pietro and co-workers described the isolation of agelastatin A from the deep water marine sponge *Agelas dendromorpha* collected in the Coral Sea near New Caledonia.[1a−c] The structure and relative stereochemistry of this unique tetracyclic metabolite were established as shown in **1** by a series of degradative and spectroscopic experiments. The absolute configuration of agelastatin A at the four stereogenic centers around the carbocyclic C-ring was determined to be 5a*S*,5b*S*, 8a*S*,9a*R* by a combination of molecular modeling of the conformation of the compound and application of a CD exciton-coupling method.[1b] Agelastatin A is accompanied by a small amount of agelastatin B, the corresponding C-1,2 dibromopyrrole **2**. Metabolites **1** and **2** are inseparable, but a derivative of the latter could be obtained in pure form for characterization purposes. More recently, Molinski et al. reported the isolation from the West Australian sponge *Cymbastela* sp. of two new closely related minor metabolites, agelastatin C (**3**) and D (**4**), along with agelastatin A.[2] Agelastatin C is identical to **1**, except that it is hydroxylated at C-5b. Interestingly, this compound does not seem prone to spontaneous loss of *N*-methylurea. Agelastatin D is simply an *N*-demethylated analogue of **1**. Spectroscopic data indicated that **3** and **4** have the same relative and absolute configuration as **1**.

Agelastatin A has been reported to have significant in vitro activity against L1210 and KB tumor cells.[1c] Structure−activity studies indicate that the C-8a hydroxyl group and both NH's



are needed for optimal activity. Alkylation or acylation of these functional groups, as well as removal of the C-1 pyrrole bromine, leads to a significant loss of potency. In addition, agelastatin A is highly toxic in a brine shrimp bioassay and also is insecticidal against beet army worm and corn root worm.[2]

The highly unusual heterocyclic array contained in this small family of marine alkaloids, coupled with the interesting biological activity of agelastatin A, makes them attractive targets for total synthesis.[3,4] We conceived of an approach to the agelastatins via the strategy shown in Scheme 1 starting from cyclopentadiene as the source of the carbocyclic C-ring. The basic plan was to use the two double bonds of cyclopentadiene as handles to introduce the four nitrogens and stereogenic centers of the natural product. The expectation was that the configuration at the equilibratable hydroxy urea center at C-8a would be self-controlled by the fact that the *cis*-fusion of the C and D-rings is calculated to be ∼20 kcal/mol more stable than the *trans* arrangement.[2] Thus, the intent was to convert cyclopen-

(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.

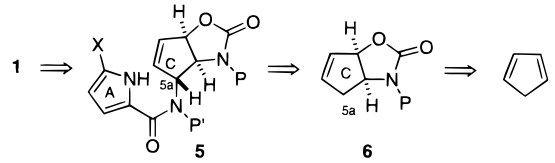
(2) Hong, T. W.; Jimenez, D. R.; Molinski, T. F. *J. Nat. Prod.* **1998**, *61*, 158.

(3) For a preliminary account of some agelastatin model studies, see: Anderson, G. T.; Chase, C. E.; Koh, Y.-H.; Stien, D.; Weinreb, S. M.; Shang, M. *J. Org. Chem.* **1998**, *63*, 7594.

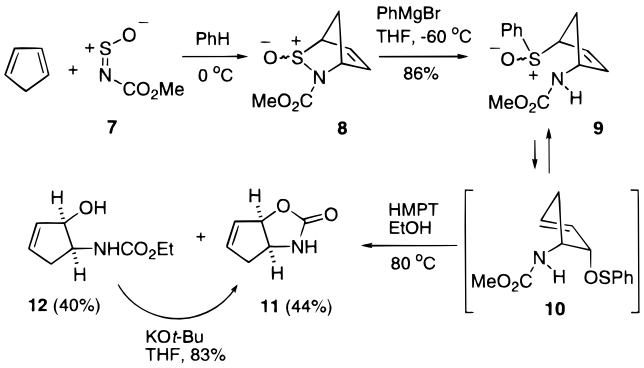
(4) Taken in part from: Anderson, G. T. Ph.D. Thesis, The Pennsylvania State University, 1995.

10.1021/ja992487l CCC: $18.00
Published on Web 09/29/1999

Scheme 1



Scheme 2

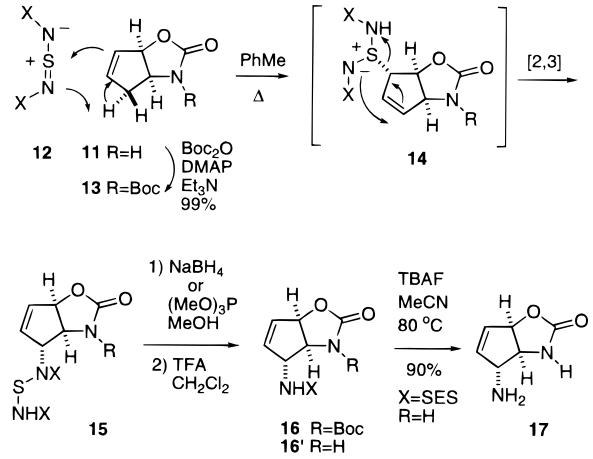


tadiene to cyclic carbamate **6** followed by introduction of the C-5a nitrogen and a 2-acylpyrrole group to give **5**. We had some initial concerns about the possible sensitivity of the bromine in the pyrrole A-ring as well as its compatibility with some of our planned transformations, and thus also considered possible synthetic equivalents of this substituent (vide infra). It might be noted that the C-1 bromine in agelastatin A is reductively removed simply by treatment with sodium hydride.[1b] In this paper we report the successful implementation of this strategy to the first total synthesis of agelastatin A (**1**).

Our approach to bicyclic carbamate **11** was based upon *N*-sulfinyl dienophile Diels−Alder methodology previously developed in these laboratories (Scheme 2).[5] Therefore, condensation of cyclopentadiene and *N*-sulfinyl methyl carbamate (**7**)[6] could be effected at 0 °C in benzene to afford cycloadduct **8** in high yield. This compound was prone to retro Diels−Alder reaction at room temperature upon attempted chromatographic purification[7] and thus was immediately treated with phenylmagnesium bromide to produce allylic sulfoxide **9** (86% yield based upon dienophile **7**). Upon heating with HMPT in ethanol, sulfoxide **9** underwent a [2,3]-sigmatropic rearrangement via the sulfenate ester **10** to afford approximately a 1:1 mixture of the desired olefinic oxazolidinone **11** and the uncyclized hydroxy ethyl carbamate **12**. However, compound **12** could be cyclized to **11** with potassium *tert*-butoxide in high yield.[8]

We next moved to introduction of the C-5a nitrogen into oxazolidinone **11**, and investigated applying the Sharpless/Kresze allylic amination procedure to this compound.[9] A particular concern here was the level of regio- and stereoselectivity we might achieve in this process. Initial experiments

Scheme 3[a]



[a] (a) X = Ts; (b) X = CO_2Me; (c) X = SES.

utilized ditosyl sulfodiimide **12a**, which was heated in refluxing toluene with **11**, followed by treatment with trimethyl phosphite in methanol, to produce allylic sulfonamide **16′a** as a single regio- and stereoisomer (50%), presumably via an ene reaction to initally generate **14** and subsequent [2,3]-sigmatropic rearrangement to product **15** (Scheme 3).[4] Our supposition that the bis-sulfodiimide ene reaction would occur as shown from the convex face of **11** was later proven by X-ray crystallography (vide infra). Similarly, heating the bis-carbamate **12b**[10] with olefin **11**, followed by phosphite treatment, afforded a single carbamate **16′b** in 73% yield. Unfortunately, despite some effort we were unable to remove the *N*-protecting group from either sulfonamide **16′a** or methyl carbamate **16′b** to produce the corresponding allylic primary amine **17**.

To solve this deprotection problem, we turned to the SES (β-trimethylsilylethanesulfonyl) derivative.[11] Thus, new sulfodiimide **12c** was easily prepared by standard methodology from β-trimethylsilylethanesulfonamide (SES-NH_2) (see Supporting Information). The reaction of this diimide with alkene carbamate **11**, followed by phosphite treatment, did indeed provide the desired SES-protected allylic amination product **16′c** in 50−60% yields. However, the reaction tended to be unreliable, particularly on large-scale runs. Thus, it was found best that olefin carbamate **11** first be converted to the Boc derivative **13**, which reproducibly underwent the Sharpless/Kresze amination on heating with **12c**, followed by sodium borohydride, to produce the allylic sulfonamide **16c**. This compound proved difficult to purify, but cleavage of the Boc group with TFA afforded compound **16′c** which could be isolated in pure form in high overall yield. Cleavage of the SES group with TBAF subsequently yielded the requisite primary amine **17**. To firmly establish the structure and stereochemistry of these Sharpless/Kresze amination products, sulfonamide **16c** was converted to its bis-*N*-Boc derivative, whose structure was determined by X-ray analysis.[12]

Since amine **17** and some of the later compounds derived from this intermediate tended to be rather polar and water soluble, a second series of compounds was prepared in which the amine and carbamate were *N*-protected with hydrophobic

(5) For reviews and lead references to *N*-sulfinyl dienophile [4 + 2]-cycloadditions, 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.

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

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

(8) For some other syntheses of oxazolidinone **11,** 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.

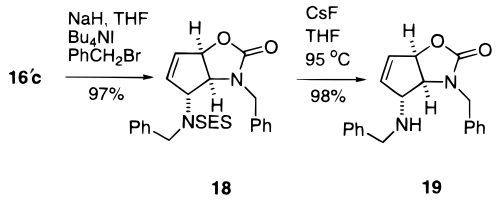
(9) (a) Sharpless, K. B.; Hori, T. *J. Org. Chem.* **1976**, *41*, 176. (b) Bussas, R.; Kresze, G. *Liebigs Ann. Chem.* **1980**, 629.

(10) Kresze, G.; Munsterer, H. *J. Org. Chem.* **1983**, *48*, 3561.

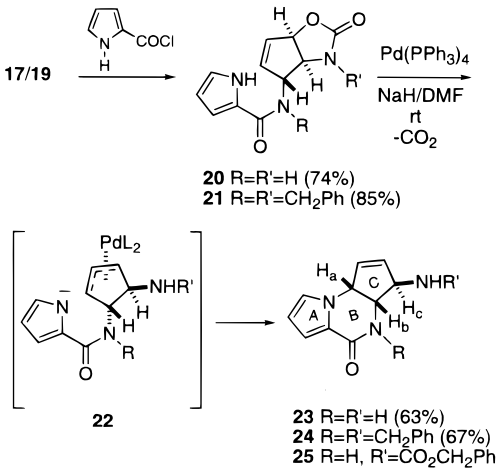
(11) (a) Weinreb, S. M.; Demko, D. M.; Lessen, T. A.; Demers, J. P. *Tetrahedron Lett.* **1986**, *27*, 2099. (b) For an improved preparation of SES−Cl, see: Weinreb, S. M.; Chase, C. E.; Wipf, P.; Venkatraman, S. *Org. Synth.* **1997**, *75*, 161.

(12) We thank Dr. M. Shang (University of Notre Dame) for this analysis. X-ray data for this compound can be found in the Supporting Information for ref 3.

Scheme 4



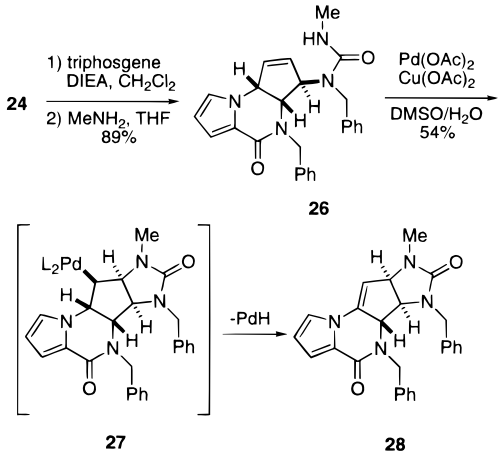
Scheme 5



benzyl groups. Therefore, allylic sulfonamide **16′c** was dialkylated with benzyl bromide to afford **18**, which was then deprotected to provide benzylamine **19** (Scheme 4).

With substrates **17** and **19** in hand, we next turned to construction of an intact ABC-ring tricycle. For the initial feasibility studies, it was decided to simply use pyrrole 2-carbonyl chloride[13] rather than a 5-brominated derivative. Alkylation of amines **17** and **19** with this acid chloride afforded the desired amides **20** and **21**, respectively, in good yields (Scheme 5). We were pleased to find that exposure of amide carbamate **20** to Pd^0 aforded the desired tricyclic amine **23** as a single stereoisomer. This compound proved difficult to isolate and purify and was therefore characterized as the benzyl carbamate derivative **25**. In particular, this tricycle showed a 5% ^{1}H NMR NOE enhancement between protons H_a and H_b, and neither of these protons showed any enhancement with H_c, thereby confirming the stereochemistry of the cyclization product **23**.[4] Similarly, palladium-promoted cyclization of the dibenzyl compound **21** led to the tricyclic alkene **24**. We believe these cyclizations proceed via a π-allylpalladium intermediate **22** which probably forms with inversion from the allylic carbamates **20** and **21**.[14,15] It is known that soft nucleophiles can add either syn or anti to palladium in such η^3-complexes and for stereoelectronic reasons in these cases only syn cyclization of the pyrrole nitrogen onto the π-allylpalladium species is possible, giving the desired *cis*-fused B/C ring products. It should also be added that, although various nitrogen heterocycles including indoles have previously been *N*-alkylated with π-allylpalladium complexes, apparently this is the first time a pyrrole has been used in such a reaction.[16]

Scheme 6



We decided to also explore the possibility of utilizing palladium-based technology for construction of the agelastatin D-ring. Since the dibenzyl compound **24** was better behaved and easier to handle than primary amine **23**, it was used for these studies. Therefore, amine **24** was first converted to *N*-methyl urea **26**, which was then treated with a catalytic amount of $Pd(OAc)_2$ with $Cu(OAc)_2$ as the stoichiometric reoxidant to afford the tetracyclic ene urea **28**, whose structure was confirmed by 2D NMR (HMBC) (Scheme 6).[17,18] It seems reasonable that this transformation occurs via a syn addition of Pd^{2+} and the urea nitrogen to the olefinic double bond of **26** to produce **27**. Subsequent syn β-hydride elimination from **27** would then yield the observed ene urea product **28**. Interestingly, we have been unable to find a close literature analogy for the syn stereochemical outcome of the first step in this process, although related anti additions are known.[19] It is possible that the α-face of olefin **26** is simply too hindered to allow the desired anti addition to occur in this particular case. Since hydration of cyclization product **28** would not afford the correct C/D-ring functionality, this approach was abandoned.[20]

We next turned to an alternative strategy to selectively functionalize the olefinic double bond of tricycle **24**. Thus, amine **24** was converted to the Boc derivative **29**, which could be hydroborated with diborane (Scheme 7). After treatment of the boranes with hydrogen peroxide, the resulting mixture of alcohols was directly oxidized with PDC to provide a mixture of the desired ketone **31** (37% yield from olefin **29**) along with an alcohol tentatively assigned structure **30**. Attempts were made to improve the regioselectivity here, but other hydroborating reagents were either unreactive toward alkene **29** (e.g., 9-BBN) or caused extensive decomposition (e.g., thexyl borane, $BHBr_2$). It was possible, however, to remove the Boc group from **31** with TFA to generate amino ketone **32**, which could be condensed with triphosgene, followed by methylamine to produce the correctly functionalized agelastatin A tetracycle **33**. Although the conversion of tricyclic alkene **24** to ketone **31** proceeded in only mediocre yield, this sequence proved that an

(13) Boatman, R. J.; Whitlock, H. W. *J. Org. Chem.* **1976**, *41*, 3050.

(14) 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.

(15) 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.

(16) Cf. Billups, W. E.; Erkes, R. S.; Reed, L. E. *Synth. Commun.* **1980**, *10*, 147.

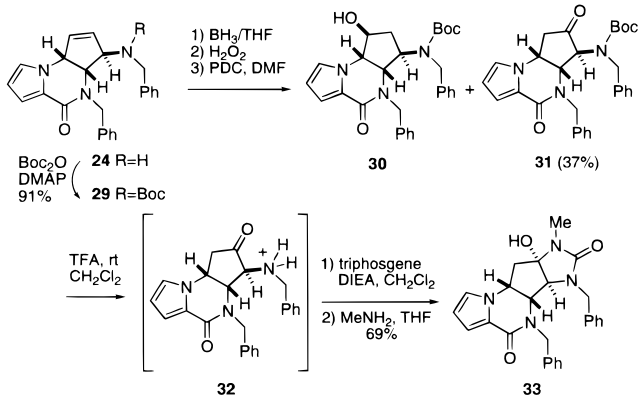
(17) van Benthem, R. A. T. M.; Hiemstra, H.; Longarela, G. M.; Speckamp, W. N. *Tetrahedron Lett.* **1994**, *35*, 9281.

(18) For reviews of heteroatom/olefin cyclizations promoted by electrophiles, see: (a) Harding, K. E.; Tiner, T. H. Electrophilic Heteroatom Cyclizations. In *Comprehensive Organic Synthesis;* Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol 4, p 363. (b) Frederickson, M.; Grigg, R. *Org. Prep. Proced. Int.* **1997**, *29*, 33, 63.

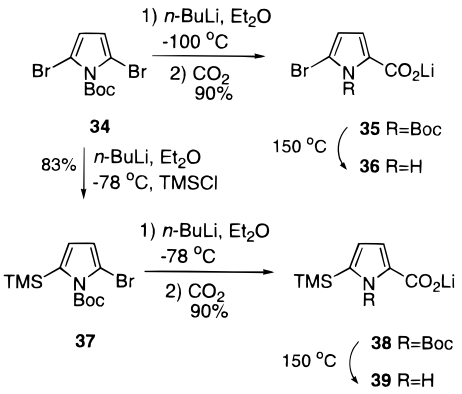
(19) See, for example: Backvall, J.-E.; Andersson, P. G. *J. Am. Chem. Soc.* **1990**, *112*, 3683. Andersson, P. G.; Aranyos, A. *Tetrahedron Lett.* **1994**, *35*, 4441.

(20) Several unsuccessful attempts were also made to effect selenocyclization of alkene urea **26** using PhSeX.[18]

Scheme 7



Scheme 8

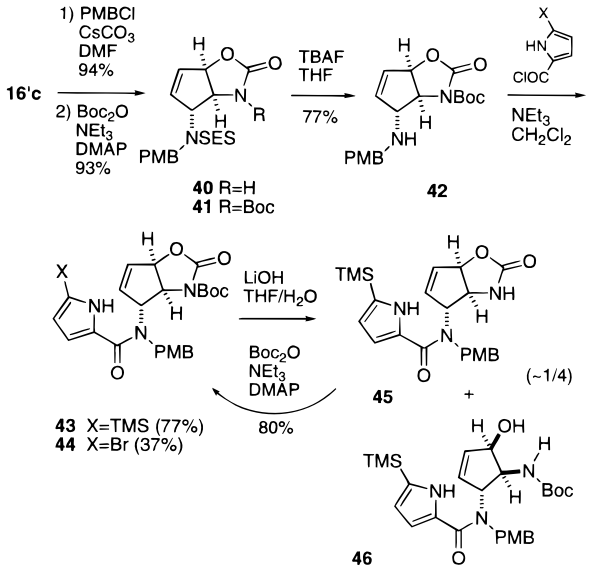


intermediate like **31** is, in fact, useful for annulation of the agelastatin D-ring and thus prompted a change in our synthetic strategy.

At this stage of the synthesis, procedures were developed for preparation of pyrrole-2-carboxylic acid derivatives bearing the bromine, or a synthetic equivalent. Unfortunately 5-bromopyrrole-2-carboxylic acid cannot be made efficiently by bromination of pyrrole-2-carboxylic acid since a complex mixture of regioisomers is produced.[21] Thus, we have utilized methodology reported by Cava, et al. to synthesize some potentially useful pyrrole A-ring substrates for the agelastatins.[22a,23] Readily available dibromopyrrole **34**[22] can be monometalated with *n*-butyllithium and then carboxylated to provide lithium carboxylate **35** in high yield (Scheme 8). It was found most convenient to remove the *N*-Boc group from pyrrole **35** simply by heating the neat salt at 150 °C, affording **36** in quantitative yield.[22b] Similarly, treatment of the mono lithio derivative of **34** with TMSCl cleanly gave silylpyrrole **37**. This compound could be lithiated again, and then carboxylated to provide lithium salt **38**. Thermolysis of **38** led to clean removal of the Boc-protecting group, yielding salt **39**.

Our newly conceived strategy for preparation of a tricyclic ketone substrate like **31** was based upon the possibility of effecting an intramolecular conjugate addition of a pyrrole nitrogen to a cyclopentenone to generate the B-ring (vide infra). To test this approach, we explored the synthesis of an appropriate cyclization substrate by a sequence of reactions which required some critical chemoselective steps. Thus, oxazolidinone

Scheme 9



16′c could be selectively alkylated on the sulfonamide nitrogen with *p*-methoxybenzyl chloride to give **40**, thereby introducing a PMB-protecting group (Scheme 9). This substituent was used for purposes of improving organic solubility of intermediates and also since we believed it would have a beneficial effect in some of the subsequent operations (vide infra). The alkylation product **40** was then converted to Boc derivative **41**, and the SES group could be removed with TBAF to yield the secondary amine **42**. It was then possible to acylate amine **42** in good yield with the 5-TMS-pyrrole-2-carbonyl chloride, prepared from lithio carboxylate **39** and oxalyl chloride, affording silyl pyrroloamide **43**. The corresponding bromo pyrroloamide **44** could be prepared similarly from lithio carboxylate **36**, but only in poor yield.[24] We were pleased to find that with LiOH chemoselective hydrolysis of the oxazolidinone moiety of **43** occurred in preference to that of the Boc group to give a 4/1 mixture of **46**/**45**. In addition, no hydrolytic cleavage of the pyrroloamide functionality was observed in this step. We initially believed that the hydrolysis preference for the cyclic carbamate was due to a blocking of the Boc group by the PMB substituent, but this supposition later proved to be incorrect (vide infra).

Since compounds **45** and **46** were not easily separable, the mixture was exposed to PDC in DMF to yield a chromatographically separable mixture of the desired enone **47** (61% overall yield from oxazolidinone **43**) along with recovered **45** (Scheme 10). The latter compound **45** could then be recycled by conversion to **43** in good yield. Attempts also were made to repeat this same sequence with bromopyrrole substrate **44**, but only extensive decomposition occurred on basic hydrolysis, and this series of compounds was therefore abandoned.

In the key step of our strategy, we found that, on exposure to cesium carbonate in methanol, pyrrolo cyclopentenone **47** cyclizes in quantitative yield to tricyclic ketone **48**. We were originally concerned about the viability of this step since the internal Michael cyclization requires what appears to be the unfavorable amide rotamer shown in the structure **47**. One of the reasons for installing the PMB group on the amide nitrogen was to try to populate this rotamer, and subsequent results indicate that indeed this substituent does appear to have a significant affect (vide infra).

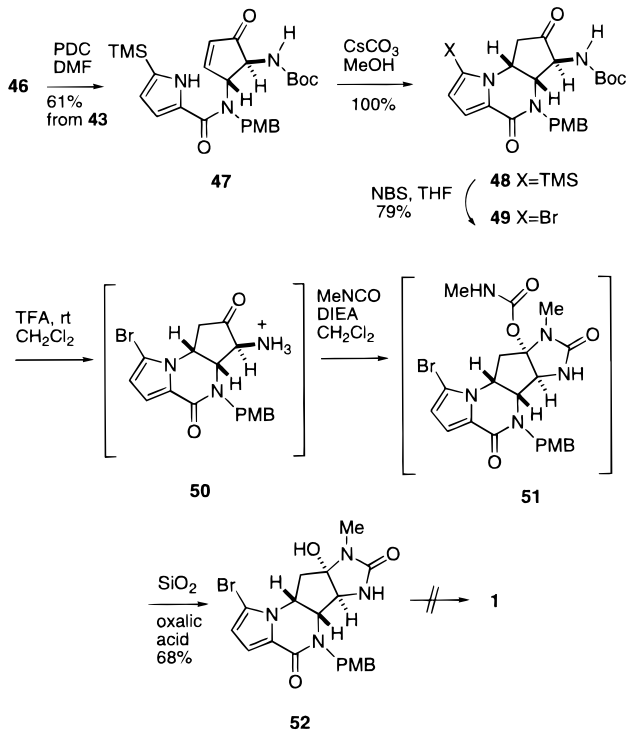
(21) Anderson, H. J.; Lee, S.-F. *Can. J. Chem.* **1965**, *43*, 409.

(22) (a) Chen, W.; Stephenson, E. K.; Cava, M. P.; Jackson, Y. A. *Org. Synth.* **1991**, *70*, 151 and references therein. (b) Rawal, V. H.; Jones, R. J.; Cava, M. P. *J. Org. Chem.* **1987**, *52*, 19.

(23) Cf. Denat, F.; Gaspard-Iloughmane, H.; Dubac, J. *J. Organomet. Chem.* **1992**, *423*, 173.

(24) 5-Bromopyrrole-2-carboxylic acid and its acid chloride are known to be unstable, and this is probably the reason for the poor yield of **44**.[21]

Scheme 10

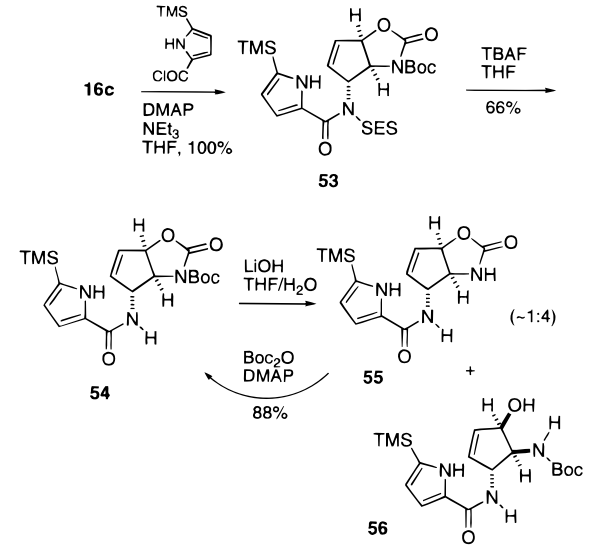


The next important operation in the synthesis was to replace the TMS group of **48** with a bromine. Since *ipso* substitutions of silylpyrroles are not well documented,[23] we were gratified to find that **48** could in fact be cleanly converted to bromopyrrole **49** with NBS. To annulate the D-ring onto tricyclic ketone **49**, the Boc group was removed with TFA as was previously done with **31** (cf Scheme 7) to give keto ammonium salt **50**. In this case, however, concentration of salt **50** led to formation of a dimeric pyrazine, whereas with intermediate **32** having a benzyl group on the amine nitrogen was not prone to such a dimerization. Thus, it was necessary to treat **50** in situ under dilute conditions with methyl isocyanate and Hunig's base, affording a mixture of **51** and **52**. Acid hydrolysis of this mixture then yielded 5-PMB-agelastatin A (**52**). Unfortunately, despite extensive effort we have been unable to remove the PMB group from **52** using a number of different reagent combinations (CAN, DDQ, $AlCl_3$, TFA, HBr, etc). In most cases only decomposition occurred, and no trace of agelastatin A was observed. In addition, the PMB group could not be cleaved from earlier intermediates **48** or **49**.

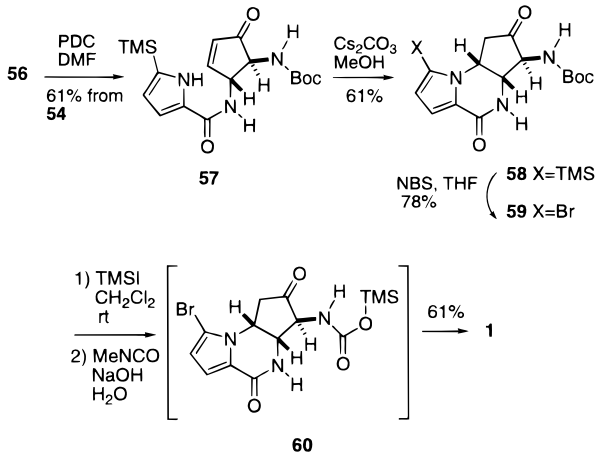
In view of our inability to deprotect **52**, we decided to explore the possibility of modifying the chemistry described above to avoid the use of a protecting group on the *N*-5 amide nitrogen. Toward this end, oxazolidinone **16′c** was converted to *N*-Boc derivative **16c** (cf Scheme 3), and this compound was acylated with the acid chloride derived from silylpyrrole carboxylate **39** to afford *N*-acylsulfonamide **53** (Scheme 11). Fluoride-induced cleavage of the SES group from **53** then led to amide **54**. We were pleased to discover that hydrolysis of **54** with LiOH proceeded in a manner identical to that of the PMB-substituted compound **43** to afford an inseparable 1/4 mixture of **55** and **56**, thus indicating that the bulk of the PMB group is not responsible for the selectivity in this step.[25] Oxidation of this mixture with PDC gave the requisite enone **57** along with

(25) The presence of a substituent at C-5a is important, however, since LiOH hydrolysis of the unsubstituted system **13** affords a 2:1 ratio of Boc cleavage product **11** to the product of cleavage of the cyclic carbamate.

Scheme 11



Scheme 12



recovered oxazolidinone **55** (Scheme 12). It was also possible to selectively replace the Boc group on **55** to give **54**, thus allowing recycling of the undesired minor hydrolysis product.

With the key pyrrolo cyclopentenone **57** in hand, we next investigated the pivotal internal conjugate addition step. Indeed, treatment of **57** with cesium carbonate in methanol led to the desired tricycle **58**. However, the yield of **58** here, although acceptable (61%), was not as high as in the case of **47**. Similar results were obtained by doing the cyclization with potassium carbonate in THF/water. It is therefore reasonable to assume that the *N*-5 substituent does actually play a role in inducing a significant population of the required amide rotamer. The stereochemistry of tricycle **58** was firmly secured by its eventual conversion into agelastatin A. It was then possible to replace the silyl group of **58** with NBS as done previously to afford bromopyrrole **59**.

Annulation of the D-ring onto intermediate **59** required some experimentation. Removal of the Boc group of **59** with TFA at room temperature produced a compound which appeared to rapidly dimerize even in dilute solution. Boc cleavage with triflic acid at low temperature (−78 °C) followed by treatment with methyl isocyanate and Hunig's base afforded only a trace of agelastatin A, along with what was presumably dimeric material. Finally, we discovered that we could cleave the Boc group of **59** with excess trimethylsilyl iodide at room temperature, and subsequent addition of methyl isocyanate followed immediately

by dilute NaOH led to formation of agelastatin A (**1**) (61%). We believe that this annulation process involves initial formation of a silyl carbamate like **60** (perhaps also *N*-silylated)[26] and upon addition of aqueous base this intermediate is converted to the free amine which is rapidly trapped in situ by the methyl isocyanate. Synthetic agelastatin A had TLC behavior and proton NMR spectrum identical to those of an authentic sample.

In conclusion, we have successfully achieved the first total synthesis of the tetracyclic marine sponge metabolite agelastatin A (**1**). The synthesis requires approximately about 14 steps performed in 12 operations (~7% overall yield) starting from cyclopentadiene, which is the precursor of the carbocyclic C-ring. Key steps include an *N*-sulfinyl dienophile hetero Diels–Alder reaction, a Sharpless/Kresze allylic amination using a new SES-substituted sulfodiimide, an internal Michael addition of a pyrrole nitrogen to a cyclopentenone, and a D-ring annulation by addition of methyl isocyanate to an α-amino ketone.

(26) Jung, M. E.; Lyster, M. A. *J. Chem. Soc., Chem. Commun*. **1978**, 315. Lott, R. S.; Chauhan, V. S.; Stammer, C. H. *J. Chem. Soc., Chem. Commun*. **1979**, 495. Cf. also: Sakaitani, M.; Ohfune, Y. *Tetrahedron Lett*. **1985**, *26*, 5543.

Acknowledgment. We are grateful to the National Science Foundation (CHE-97-32038) for generous financial support of this research and to Dr. Alan Benesi for help in obtaining and interpreting 2D NMR data. We thank the National Institutes of Health for a postdoctoral fellowship (1 F32 GM17949) to C.E.C. and the Ministry of Foreign Affairs (France) for a Lavoisier Postdoctoral Fellowship to D.S.. We are also grateful to Professor T. Molinski for a TLC sample and a copy of the proton NMR spectrum of natural agelastatin A.

Supporting Information Available: Experimental details and spectral data for all new compounds, along with copies of proton and carbon NMR spectra (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA992487L