Tetrahedron 94 (2021) 132340

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

# Synthesis of agelastatin A and derivatives premised on a hidden symmetry element leading to analogs displaying anticancer activity

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ARTICLE INFO

*Article history:*
Received 3 May 2021
Received in revised form
30 June 2021
Accepted 6 July 2021
Available online 10 July 2021

*Keywords:*
Natural product
Alkaloids
Molecular modeling
Docking
Anticancer activity

ABSTRACT

Concise total syntheses of (±)-7-hydroxy debromo agelastatin A (AglA), (±)-AglA, and 11-nitro AglA are presented based on an identified pseudo-symmetry element. This synthetic strategy was developed based on a desire to improve solubility of this potent anticancer agent while also developing a synthetic strategy that would enable late-stage variation of the pyrrole moiety. A stability study of pyrrole-derived carbinolamines revealed critical substituent effects impacting the equilibrium between the cyclic carbinolamine and keto pyrrole forms. 7-Hydroxy AglA existed primarily in the ketopyrrole form however the des-bromo variant existed primarily in the cyclic carbinolamine form. Cytotoxicity assays revealed activity for a 13-nitro AglA derivative (~14–63 μM) for breast cancer cells (MDA-MB-231 and MCF7) and a glioblastoma cell line (U87) while for 7-hydroxy des-bromo AglA, measurable activity was only observed against the glioblastoma cell line.



Agelastatin A (AglA, Fig. 1, **1**) is one of the most prominent members of the pyrrole-2-aminoimidazole (P-2-AI) family of marine alkaloids owing to its unique structure and broad spectrum of biological activities leading to great interest from both synthetic chemists and biologists.[1] Isolated by Pietra in 1993,[2] this tetracyclic marine alkaloid demonstrated therapeutic potential as a drug lead in the treatment of a variety of cancers including leukemia, breast, lung and glioblastoma.[3] In one study, AglA demonstrated inhibition of osteopontin (OPN, encoded by *SPP1*), whose overexpression is believed to be associated with neoplastic transformation, cancer progression, and metastasis in a variety of cancers [3c]. Furthermore, because of its excellent blood-brain barrier penetration, AglA is particularly attractive for the treatment of brain tumors,[4] as OPN is also significantly expressed by primary brain tumors such as glioblastoma multiforme, astrocytoma, and primary central nervous system (CNS) lymphoma. In addition, AglA also inhibits the expression of the glycogen synthase kinase-3β [3a].

Not surprisingly, since its discovery, extensive research has been devoted to the synthesis of AglA and development of a structure-activity-relationship (SAR) profile toward cancer cell lines. A number of total or formal syntheses have been reported featuring a number of elegant synthetic strategies.[5] These studies have led to an extensive understanding of structural requirements for bioactivity and development of several novel derivatives with improved potency.[6] Recently, our collaborative team disclosed the cellular target of AglA, and a working mechanism was elucidated to account for the potent anticancer effects.[7] In HeLa cells, AglA binds to the peptidyl transfer center (PTC) of the ribosome, leading to protein synthesis inhibition and ultimately apoptosis. Moreover, the X-ray structure of the complex of AglA with the S80 subunit of the yeast ribosome opened the possibility of designing novel drug leads based on AglA. In particular, the X-ray structure revealed a number of key hydrogen bonding and π–π stacking interactions and a rare halogen-π interaction. We previously described a biomimetic synthesis of AglA which led to a concise entry to this class of alkaloids and supported a proposed biosynthesis from an acyclic

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https://doi.org/10.1016/j.tet.2021.132340
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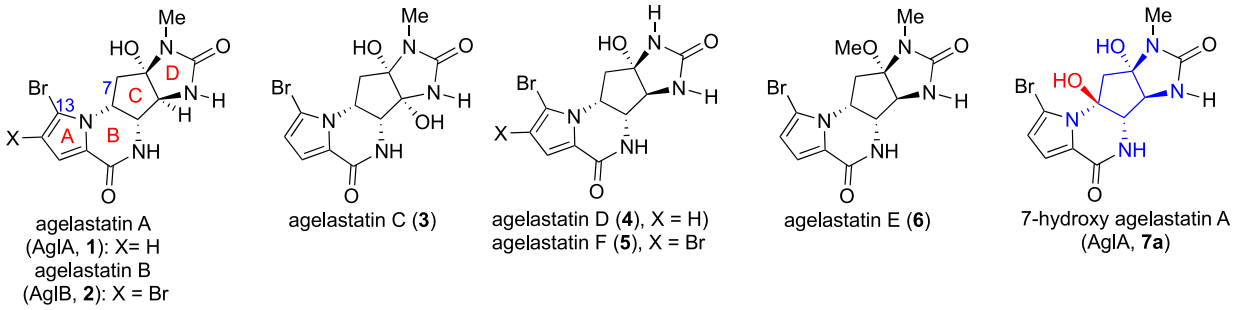



**Fig. 1.** Structure of agelastatins (AglA) A-E and a proposed unnatural derivative, 7-hydroxy AglA (**7a**) revealing hidden pseudo C2-symmetry of a bis-carbinolamine, bis-hydroxy cyclopentane core.

precursor [5r]. Our interest in improving the solubility of AglA and developing a synthetic strategy that was more readily amenable to varying the pyrrole moiety to further probe π−π interactions led to the hidden C2-symmetry based strategy described herein that led to conception of 7-hydroxy AglA (**7a**) as a synthetic target.

Structurally, AglA bears four nitrogen atoms attached to the central C ring in a *syn-anti-syn* relationship. We recognized that addition of a C7-hydroxyl group would impart pseudosymmetry to AglA leading to a second carbinolamine, derived from addition of a pyrrole nitrogen to a pendant ketone leading to a hydroxyl-substituted dihydropyrazinone (Fig. 1, **7a**). We surmised that addition of an additional hydroxyl group would also impart greater water solubility relative to AglA (clogP: 7-OH AglA (**7a**), −2.13; AglA (**1**), −1.23) while also potentially leading to an additional hydrogen bond at the binding site. We docked 7-OH AglA into the X-ray structure of the ribosome-AglA complex [7] using Molecular Operating Environment (MOE) software and found a potential weak (extended, 3.52 Å) hydrogen bond that could be formed between the pyrimidinedione of uracil 2875 (U2875) and the C7−OH in a low energy pose that resembles that of AglA (see Fig. 2).

We also wanted to ensure that introduction of the C7-hydroxyl would not significantly impact the overall topology of AglA and ensure that low energy conformations corresponding to AglA were also attainable by 7-OH AglA. Molecular dynamics and minimization in MOE and also DFT calculations for both AglA and 7-OH AglA showed two similar low energy conformers (**A**/**B** and **A'**/**B'**) differing only by the envelope conformations adopted by the cyclopentane ring (C-ring) of these otherwise quite rigid molecules (Fig. 3). In the case of AglA, the two lowest energy conformers **A**/**B** differed by ~4−5 kcal/mol. A ΔG of ~0.5 kcal/mol (MOE) at 25 °C for the two conformers of 7-OH AglA **A'**/**B'** suggests that they would both be readily accessible at physiological temperatures with one envelope conformation corresponding to the lower energy conformation of AglA.

These preliminary computational studies supported our described synthetic strategy involving a late-stage pyrrole annulation strategy to more readily vary this region of the molecule and expand the known SAR of the agelastatins. This provided further impetus to explore the synthesis of 7-hydroxy AglA based on the described hidden C2-symmetry element found in this targeted derivative and forms the basis of our retrosynthetic strategy (Scheme 1). In addition, this strategy, following reduction of the C7-carbinolamines **7a**/**7b**, could also lead to non-C7-hydroxylated AglA derivatives again with variations in the pyrrole ring. The C7-carbinolamine would be derived from intramolecular cyclization of the pyrrole NH of ketone precursor **9**. Bicyclic urea **9** could in turn be synthesized from three fragments: pyrrole **11**, azide **12** and *N*-methylisocyanate (**10**) through acylation with the isocyanate followed by cyclization onto the ketone. The azide **12** could be introduced by ring cleavage of the aziridine **13**, which in turn would be derived from the known cyclopentenone iodide **14**, readily available from furfural by a reported procedure. [8]

Carbinolamines are theoretically formed reversibly and can exist in equilibrium with their aldehyde and amine components.[9] Pyrrolocarbinolamines, which are formed by nucleophilic addition of a pyrrole to aldehydes or ketones are reasonably stable and can be purified and isolated, serving as aldehyde protecting groups, but can also be reverted to their carbonyl pyrrole precursors upon

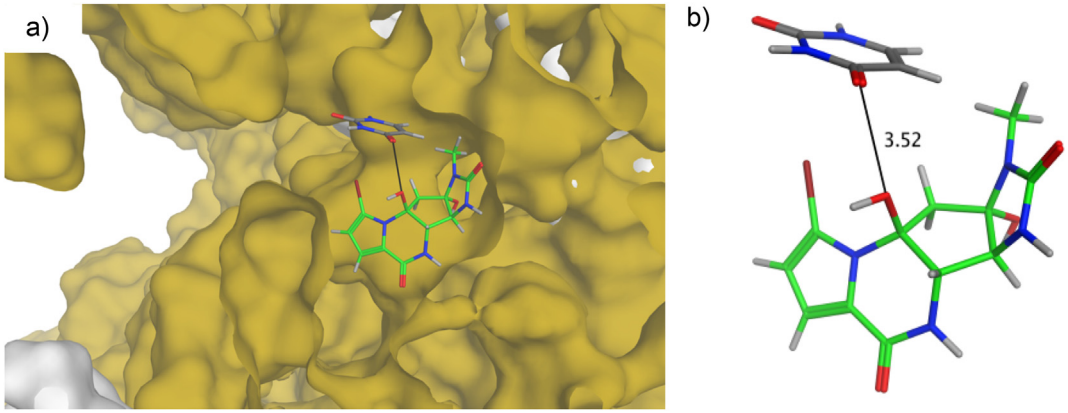



**Fig. 2.** Docking of 7-hydroxy AglA (**7a**) with the X-ray structure of the AglA-yeast 80 S ribosome complex using MOE. (a) Full view of binding site (yellow-rRNA; white, protein) showing a possible but weak (3.52 Å) hydrogen bond between the C7-hydroxyl and U2875. (b) Isolated view of 7-hydroxy AglA (**7a**) and the pyrimidinedione of U2875.

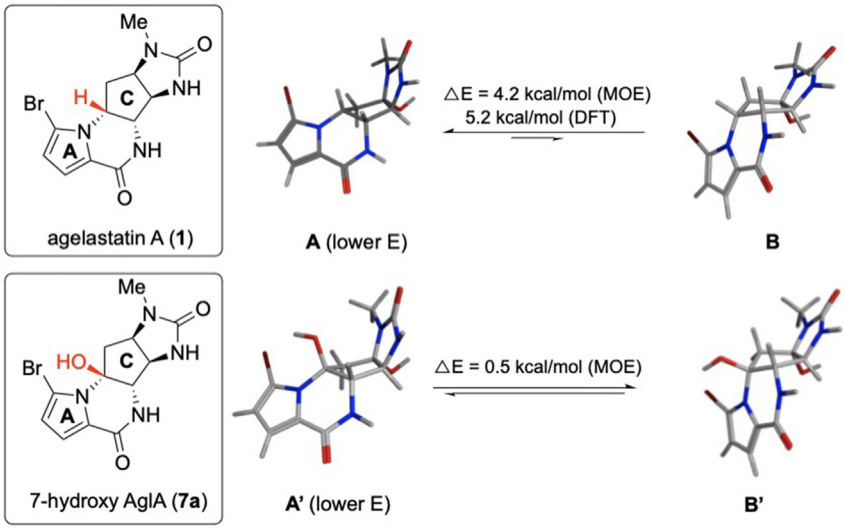
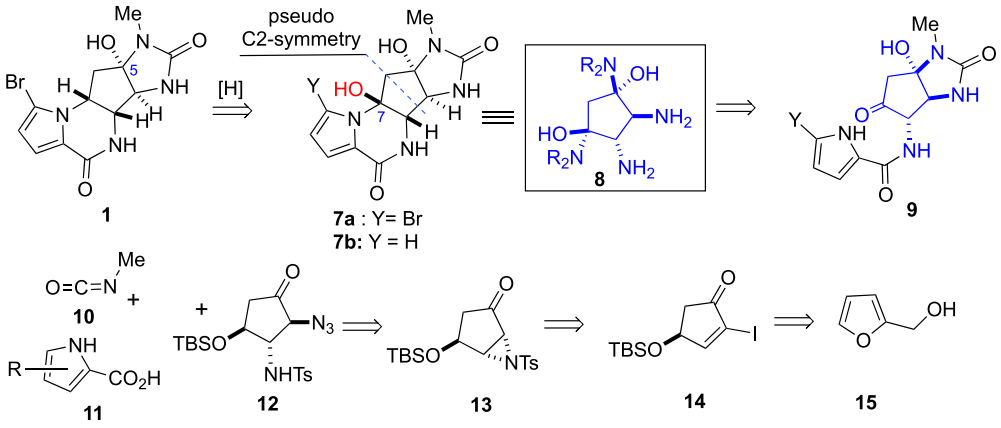



**Fig. 3.** Conformational searching of AglA and 7-OH AglA by MOE and DFT calculations.

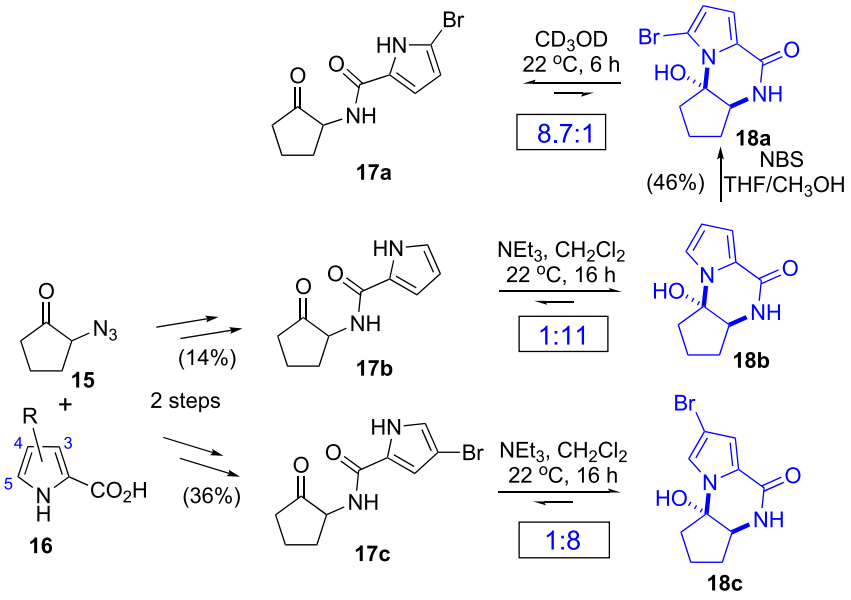



**Scheme 1.** Retrosynthetic analysis based on a hidden C2 symmetry element, upon addition of a C7-hydroxyl, enabling late-stage pyrrole variation.

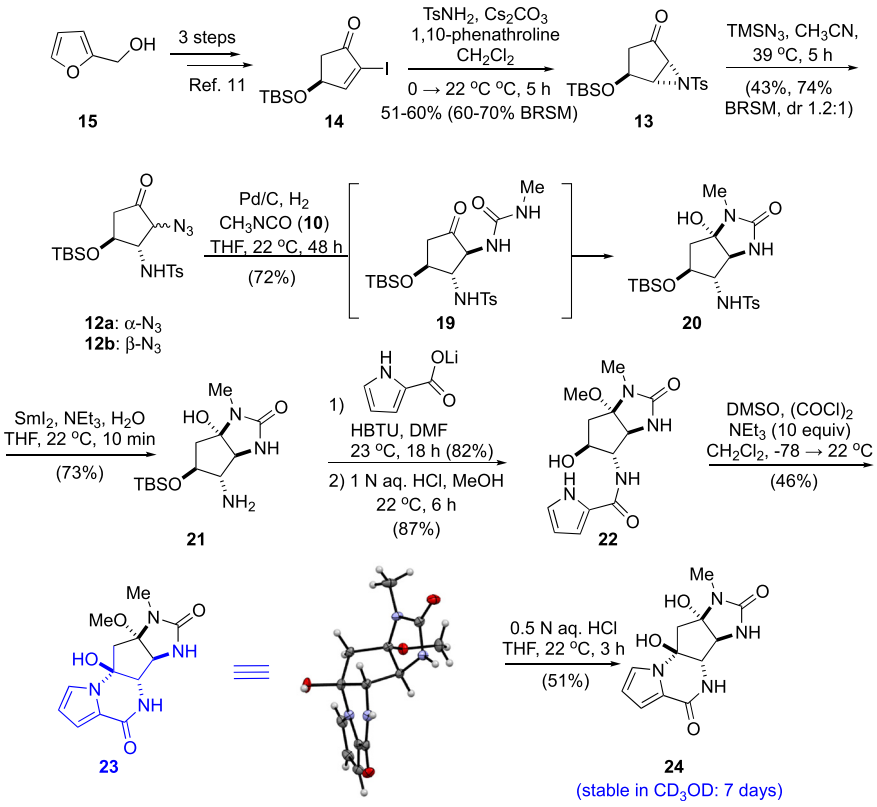
treatment with base.[10] It is well known that the C5-carbinolamine of AglA, leading to a hydroxy imidazolidinone exists primarily in the ring-closed form. However, we were unsure of the same equilibrium for the proposed hydroxy dihydropyrazinone **7** derived from cyclization of the pyrrole nitrogen addition onto the pendant ketone. To address this question, we initially performed model studies to probe the stability of such keto pyrrole-derived carbinolamines leading to dihydropyrazinones.

We synthesized pyrrole carboxylic amides **17a-c** to study the equilibrium between the corresponding carbinolamines and pyrrolo ketones (Scheme 2). Reduction of 2-azidocyclopentanone and condensation with pyrrole-1*H*-carboxylic acid gave amide **17b**. Upon treatment of ketone **17b** with $Et_3N$, cyclization gave the corresponding carbinolamine **18b** in 73% yield (>19:1 dr, 600 MHz $^1$H NMR). Carbinolamine **18b** was very stable, could be purified by silica gel chromatography, and was stable in $CD_3OD$ for several days. When resubjected to $NEt_3/CH_2Cl_2$ at ambient temperature (22 °C) for 16 h, only a small amount of the ring-opened keto pyrrole **17b** was generated leading to an equilibrium ratio of 11:1 (**18b**/**17b**) favoring the cyclized form as judged by $^1$H NMR. Likewise, the 4-bromopyrrole derived carbinolamine **18c** was stable under neutral conditions (*e.g.* in $CD_3OD$), but led to a mixture of **18c** and **17c** in an 8:1 ratio in $NEt_3/CH_2Cl_2$ at 22 °C again favoring the cyclized form. In contrast, the 5-bromo pyrrole analog **17a**, that most closely mimics the targeted 7-hydroxy AglA, disfavored the closed form **18a**. Not only did the precursor keto pyrrole **17a** not cyclize to **18a** under similar conditions as for **17b** and **17c**, even if the cyclic carbinolamine **18a** was targeted through bromination of carbinolamine **18b**, the brominated adduct **18a** opened rapidly in $CD_3OD$ forming a mixture of **17a**/**18a** in an 8.7:1 ratio, favoring the keto pyrrole **17a**. Overall, these results suggested that substituents present on C5 of the pyrrole ring disfavor the cyclic carbinolamine, thus we initially pursued the non-brominated C7—OH AglA **7b**.

Synthesis of racemic 7-hydroxy-13-des-bromo AglA (**24**) commenced with aziridination of known iodide **14**, available in 3 steps from furfuryl alcohol (Scheme 3) [8]. Aziridination with *p*-toluenesulfonamide under basic conditions installed the aziridine **13** by the method of Maycock.[11] Aziridine cleavage with azide anion was studied next however instability of both the aziridine and the derived azide to both acidic and basic conditions was observed. Following extensive experimentation, trimethylsilyl azide was found to be optimal for aziridine ring opening. This led to the azidocyclopentanone **12** as a mixture of diastereomers (43%, dr 1.2:1), likely due to an unselective α-protonation of the intermediate silyl enol ether. The desired *anti*-diastereomer **12b** was isolated by column chromatography, while the undesired




**Scheme 2.** Stability studies of pyrrole-derived carbinolamines 18a-c.




**Scheme 3.** Synthesis of 13-des-bromo 7-hydroxy AglA **24** (inset: X-ray structure of bis-aminal **23**).

diastereomer **12a** could be re-equilibrated by subjecting to 4 Å molecular sieves in acetonitrile for 6 days leading to an ~1:1 ratio and isolation of additional quantities of the desired *anti*-diastereomer. Hydrogenation of azide **12a** in the presence of *N*-methyl isocyanate (**10**) to furnish the bicyclic intermediate **20** in a single step through known cyclization to the cyclic urea. To introduce the pyrrole moiety, the *N*-tosyl group was cleaved using $SmI_2/H_2O/NEt_3$,[12] providing the primary amine **21**. Subsequent amide coupling with the lithium carboxylate of pyrrole 2-carboxylic acid was initially problematic and could not be pushed to completion due to the insolubility of primary amine **21** which was found to be only partially soluble in typical organic solvents for amide couplings (*e.g.* $CH_2Cl_2$, DMF). Ultimately, it was found that a suspension of the amine **21** in DMF would dissolve completely upon heating to ~100 °C providing a homogenous solution. After cooling to ambient temperature, coupling proceeded smoothly to afford the desired

pyrrole amide **22** in 82% yield.

Deprotection of the TBS ether was achieved with HCl in MeOH which also served to mask the hemiaminal as the methoxy aminal **22**. Swern oxidation led to an intermediate ketone, which in the presence of excess triethylamine, cyclized to deliver the carbinolamine **23** directly in 46% yield. This is consistent with our model studies (cf. Scheme 2, **18b**) which suggested this equilibrium would favor the cyclic form of the C7-carbinolamine and this was further confirmed by X-ray crystallography of carbinolamine **23** (inset, Scheme 3). Interestingly, the conformation in the solid state corresponds to the lower energy conformation found through conformational searching (*vide supra*). Hydrolysis of the methoxyaminal **15** was achieved under mild conditions to deliver the targeted 7-hydroxy-13-des-bromo AglA (**24**), which was found to be quite stable as determined by $^1$H NMR when stored in $CD_3OD$ or DMSO-$d_6$ at ambient temperature (22 °C) for 7 days.

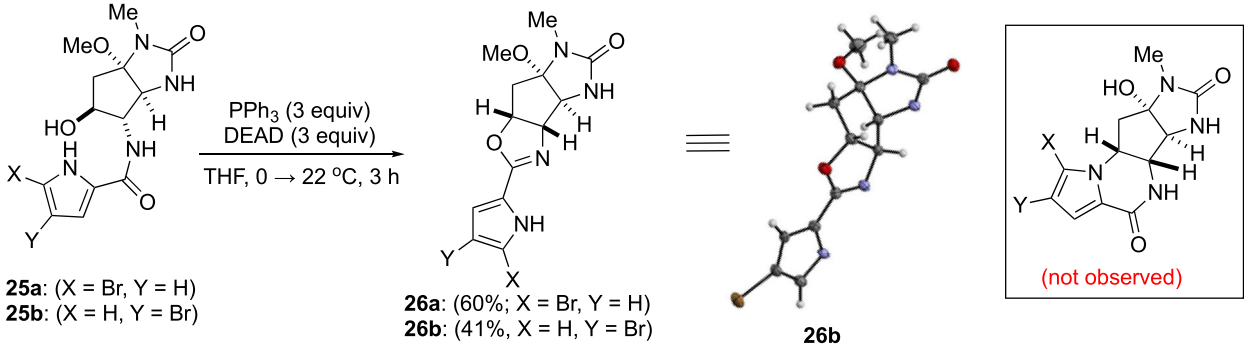
In efforts to convert the mono-carbinolamine **23** to the core structure of AglA, we explored several direct methods however direct reduction was not fruitful under a variety of Lewis acid/hydride addition conditions. Alternatively, we considered direct intramolecular stereoinvertive displacement of alcohols **25a** and **25b**, derived from amine **21** (see SI for synthesis of **25a**,**b**), through Mitsunobu reaction to form the B ring. However, while cyclization indeed occurred, it was the amide oxygen atom that served as nucleophile leading to oxazolines **26a** and **26b** as confirmed by X-ray crystallography in the case of oxazoline **26b** (Scheme 4).

We next considered an alternative strategy to form the B ring that we successfully employed in our previous biomimetic strategy toward AglA [5r], namely a 5-exo, aza-Michael ring closure. Attempted dehydration of alcohol **25a** to directly install the $C_6$–$C_7$ alkene was very low yielding due to multiple side reactions (not shown).[13] We thus returned to an earlier intermediate, silyl ether **20**, and following generation of the methoxy carbinolamine and desilylation, we introduced the required $C_6$–$C_7$ alkene through a Grieco elimination to give cyclopentene **28** in 42% yield for the 2 steps (Scheme 5). Cleavage of the tosyl group with $SmI_2$ and acylation with the pyrrole acid chloride provided amide **30**, which was hydrolyzed to carbinolamine **31** to intercept the same intermediate in our previous biomimetic synthesis of AglA. Carbinolamine was subjected to mild heating with silica gel to initiate the aza-Michael addition and this was again successful to deliver AglA [5r]. However, we sought alternative reaction conditions for this transformation since it was not readily scalable. We anticipated that if the concentration of the ring opened C-ring enone of carbinolamine **31** could be achieved under mild basic conditions, this would facilitate the desired aza-Michael reaction. After some experimentation with a variety of bases, we found that a substoichiometric amount of base, namely 0.25 equiv $K_2CO_3$ in MeOH, furnished AglA (**33**) in 43% yield (2 steps) along with the known 3,4-bis-*epi*-AglA (**34**). The spectra of both products matched that previously reported [5r].

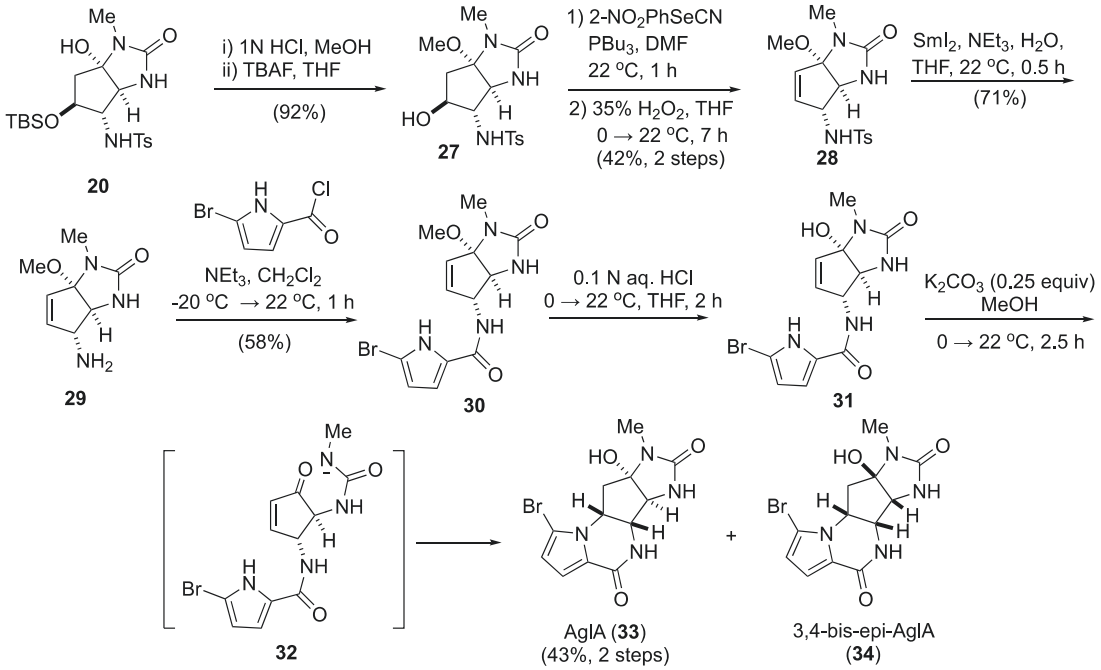
Previous SAR studies of AglA have shown electron withdrawing groups on the pyrrole moiety are beneficial for the potency of derivatives (*e.g.* Cl, $CF_3$) [6c,d]. This observation is consistent with the observed π–π stacking observed with nucleotide bases from ribosomal RNA in the X-ray structure of AglA bound to the A-site of the ribosomal peptidyl transfer center.[14] We therefore targeted the electron withdrawing nitro group to demonstrate the utility of this late stage pyrrole annulation strategy, despite the potential liabilities of the nitro group from a medicinal chemistry perspective.[15] The substrate for the key aza-Michael cyclization was readily prepared from amine **29** in a similar manner as described above for AglA but using the *N*-hydroxysuccinimide (NHS) ester of the nitro substituted pyrrole **35** to avoid the bis-epimerization at C1,C5 (cf. **34**) of bicyclic imidazolidinone **29** found to occur readily under even mild acidic conditions (Scheme 6). In a similar fashion, the aza-Michael cyclization proceeded smoothly to furnish 13-nitro AglA (**37**) in 41% yield over 2 steps. Interestingly, this AglA derivative **27** precipitated as a light-yellow solid from the reaction mixture, and a simple filtration and washing with methanol afforded nitro AglA derivative **37** in pure form.

The cytotoxicity of the synthesized novel AglA derivatives was determined against four cancer cell lines in comparison to both (−)-AglA and (±)-AglA (Table 1). The bis-carbinolamine **24**, lacking the C13-bromo substituent, did not show activity against MCF7, Caco2, and MDA-MB-231 cell lines up to 250 μM. This is not surprising based on the apparent halogen-π interaction observed in the X-ray structure [7], and the previously demonstrated ~500X drop in potency of 13-des-bromo AglA HeLa cells compared to AglA [6c]. Unfortunately, as suggested by our model studies (*vide supra*, Scheme 2, **17a**), 7-OH AglA (**24**), bearing the C5-bromo substituent, was found to exist primarily as the ring opened ketopyrrole tautomer which led to instability and thus could not be assayed. However, a measurable $EC_{50}$ value (171.0 ± 8.0 μM) could be obtained for the bis-carbinolamine **24** against the glioblastoma cell line, U87. The oxazoline **26a** showed no activity against any cell line studied.

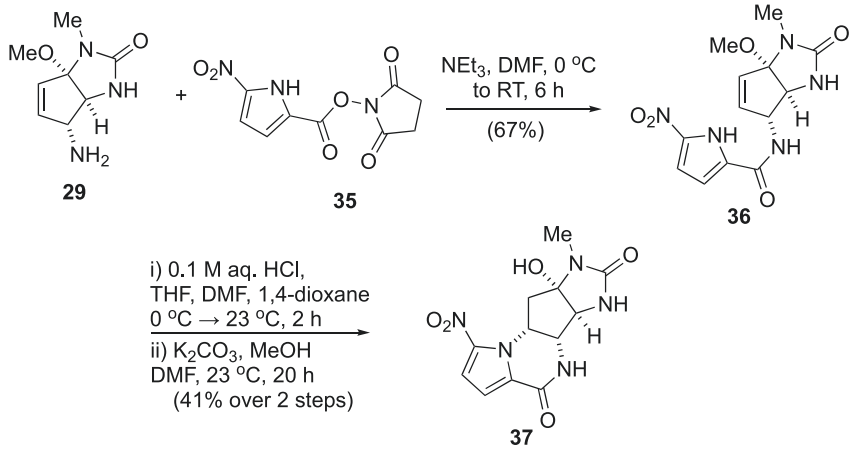
The reduced bioactivity of the des-bromo variant of 7-OH AglA (**24**) encouraged us to perform a conformational analysis of this derivative (Fig. 4). Of particular interest was a comparsion of the C-ring cyclopentane conformational preferences compared to AglA. Indeed, the envelope ring conformer **A**″ was determined to be of lower energy (ΔE = 3.4 kcal/mol) than the lowest energy cyclopentyl conformer **A** of AglA (cf. Fig. 3) and thus the lower




**Scheme 4.** Attempted access to the AglA core structure through an intramolecular Mitsunobu.




**Scheme 5.** Synthesis of AglA via base-promoted aza-Michael ring closure.




**Scheme 6.** Synthesis of 13-nitro AglA (**37**).

**Table 1**
Cytotoxicity ($EC_{50}$, μM) of AglA derivatives against various cancer cell lines.

| Cell Line | Type | $EC_{50}$ (μM)[a] | | | | |
|---|---|---|---|---|---|---|
| | | (−)-AglA | (±)-AglA | (±)-13-nitro AglA (37) | 7-hydroxy-13-des-bromo AglA (24) | oxazoline 26a |
| MDA-MB-231 | breast (TNBC) | 0.77 ± 0.30 | 1.16 ± 0.41 | 62.6 ± 7.6 | >250[b] | >250[b] |
| MCF7 | breast (ER+) | 0.52 ± 0.17 | 1.61 ± 0.44 | 14.5 ± 2.5 | >250[b] | >250[b] |
| Caco2 | colon | 0.14 ± 0.04 | 0.97 ± 0.25 | ND | >250[c] | >250[c] |
| U87 | glioblastoma | 0.82 ± 0.32 | 2.52 ± 0.86 | 35.4 ± 17.2 | 171.0 ± 8.0 | >250[c] |

[a] $EC_{50}$ values are from at least 3 biological replicates.
[b] Highest concentration tested was 142 μM.
[c] Highest concentration tested was 800 μM. (TNBC = triple negative breast cancer; ER+ = estrogen receptor positive).

concentration of the AglA-like envelope conformer may contribute to the reduced cytotoxicity.

In summary, we developed a novel synthetic strategy based on a hidden symmetry element leading to bis-carbinolamine derivatives of AglA (*e.g.* C7-hydroxy dibromo AglA (**24**)) with the important feature of enabling late stage variations of the pyrrole moiety. This design was guided by our recently disclosed X-ray structure of the AglA-ribosome complex and molecular modeling. While the targeted 7-hydroxy AglA was found to primarily reside in the ring-opened keto pyrrole form and was found to be unstable, 7-

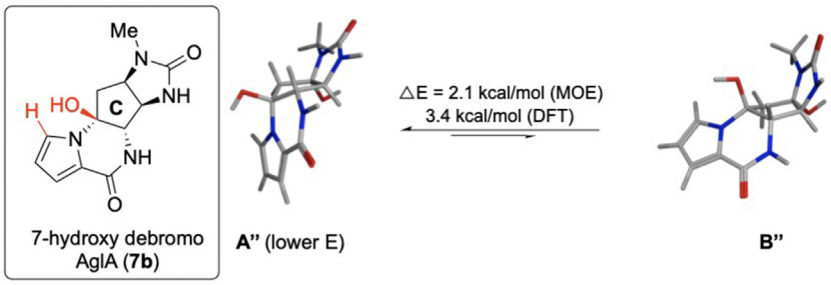



**Fig. 4.** Conformational searching of 7-OH des-bromo AglA (**24**) by MOE and subsequent DFT calculations to determine relative energies.

hydroxy des-bromo AglA could be synthesized and isolated. In addition, a new set of conditions was developed for a final 6-exo-trig, aza-Michael ring closure previously described in our biomimetic strategy to AglA and this was utilized to access 13-nitro AglA (**37**). The biological activities of new AglA derivatives were measured against four cancer cell lines and a novel C5-nitro AglA showed activity against all cell lines studied (1.16–35.4 μM) except the colon cancer line, Caco-2. However, 7-OH des-bromo AglA (**24**), despite missing the critical C5-bromo substituent, did exhibit cytotoxicity toward the glioblastoma cell line tested (U87, $EC_{50} = 171.0 \pm 8.0$ μM).

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgments

We gratefully acknowledge support by the National Institute of General Medical Sciences of the National Institutes of Health (R37 GM052964 and R35 GM134910) and the Robert A. Welch Foundation (AA-1280). We acknowledge support for the Baylor Undergraduate MiniPharma Team by the National Science Foundation (CHE-1800411). We thank Dr. Morgan Jounneau (current address: Sygnature Discovery, UK) for the synthesis of (−)-AglA. We thank Prof. Kevin Klausmeyer and Ms. Amy Jackson (Baylor) for single-crystal X-ray structure determination. We thank Nathanyal J. Truax (Baylor) for performing DFT calculations.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2021.132340.

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