Expedited Total Synthesis of Brevianamide A *via* the Strategic Use of Gold(I)-Catalysis

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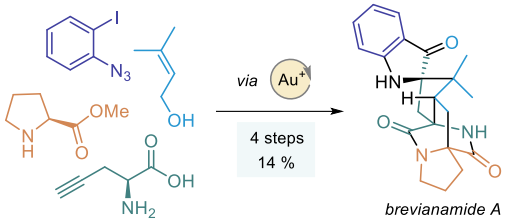
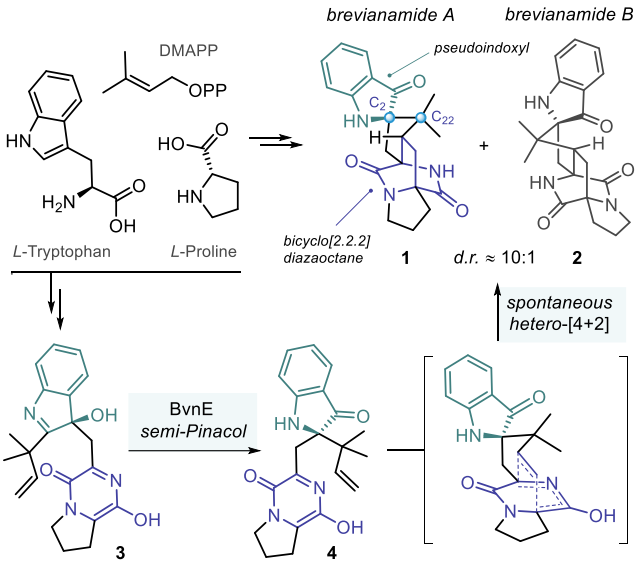


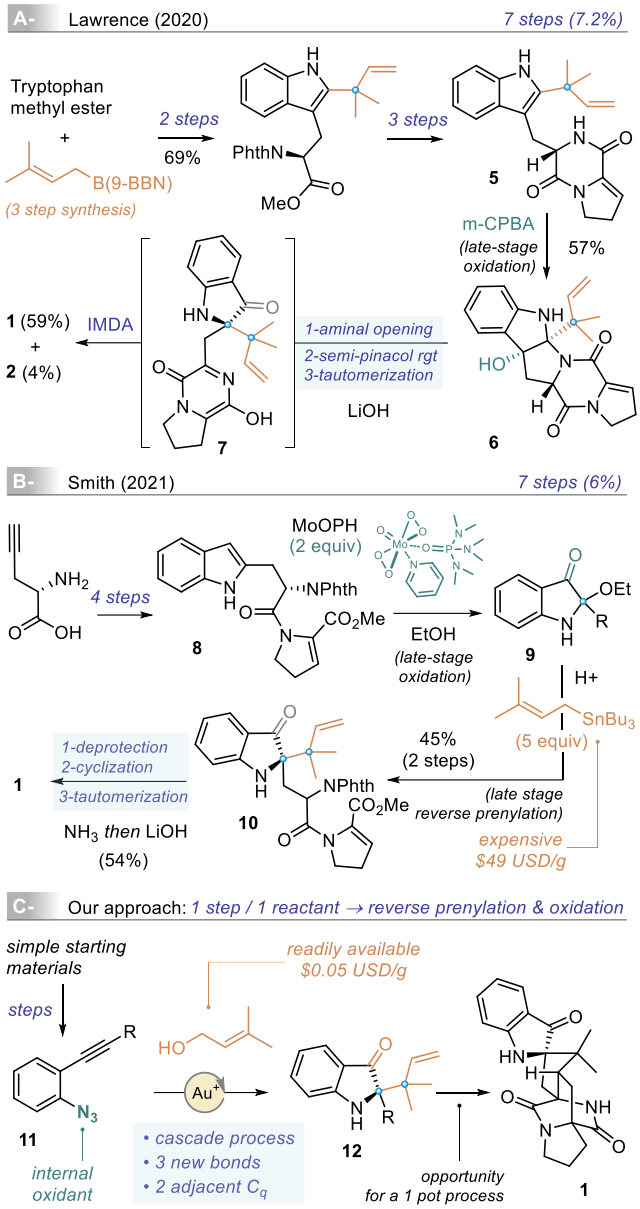
ABSTRACT: Two concise and complementary routes to the polycyclic alkaloid brevianamide A from readily available amino acid building blocks is presented. Key to the synthesis is the strategic use of a gold(I)-catalyzed cascade process that quickly assembles the characteristic pseudoindoxyl motif of the natural product along with the two adjacent quaternary centers in a single step. This sequence, which exemplifies the structural complexity that can be achieved with gold catalysis, allowed for the shortest and highest yielding synthesis of brevianamide A to date (4 steps LLS, 14% overall yield).

Brevianamide A (**1**) is a prototypical dioxopiperazine natural product that was isolated in 1969 by Birch and Wright[1] from the fungus *Penicillium brevicompactum,* and that demonstrates potent antifeedant activity.[2] In addition to its bicyclo[2.2.2]diazaoctane substructure,[3,4] brevianamide A (**1**) possesses a characteristic pseudoindoxyl motif and two adjacent quaternary centers at C_2 and C_{22}. These structural features make this natural product a challenging synthetic target when it comes to generating structural complexity in the most direct and efficient manner (Scheme 1). Interestingly, **1** was also co-isolated in a ~10:1 ratio[5] with its minor diastereomer brevianamide B (**2**) which does not seem to be biologically active. This observation has raised several questions on the potential biogenesis of these two diastereomeric natural products. The most recent biosynthetic hypothesis put forth by the groups of Williams, Sherman and Li has helped shed some light on this decades old question (Scheme 1).[6] It has been proposed that this distribution is influenced by the enzyme BvnE. This co-factor independent isomerase catalyzes a semi-Pinacol rearrangement from an oxidized indolenine precursor **3** to produce the advanced pseudoindoxyl intermediate **4**. Remarkably, the bicyclo[2.2.2]diazaoctane core of the natural product arises from a spontaneous intramolecular *hetero*-[4+2] Diels-Alder (IMDA) reaction leading to the product distribution observed. This sequence has major implications on the development of a successful total synthesis of brevianamide A (**1**), more especially



Scheme 1. Brevianamide A: structural features, and proposed biosynthesis

when one considers that till very recently past syntheses towards brevianamide A have been met with failure primarily due to a common end-game strategy resulting in the synthesis of the minor diastereomer brevianamide B (**2**).[7-12] Brevianamide A finally succumbed to synthesis by Lawrence and coworkers who reported in 2020 a bioinspired chemical route to this natural product (Scheme 2, part A).[13, 14] Their elegant strategy relied on a late-stage domino sequence that involves a semi-pinacol rearrangement that accounts for the stereospecific formation of the azadiene intermediate **7** from a pentacyclic precursor **6**. Brevianamide A and B are produced *in situ* from **7** with a distribution that mirrors closely that observed from natural sources. The key aminal intermediate **6** was formed in a 6-step sequence during which the indole moiety of the starting tryptophane methyl ester is subjected to reverse prenylation before the oxidation of dehydrodeoxybrevianamide E (**5**) into **6** takes place. While this work was in progress, a second seven step total synthesis of brevianamide A (**1**) was achieved by the group of Smith with the same overall efficiency (Scheme 2, part A).[15] Their synthesis relied on a similar end-game domino sequence strategy, but starting from a precursor **10** in which the pseudoindoxyl moiety is already set up.

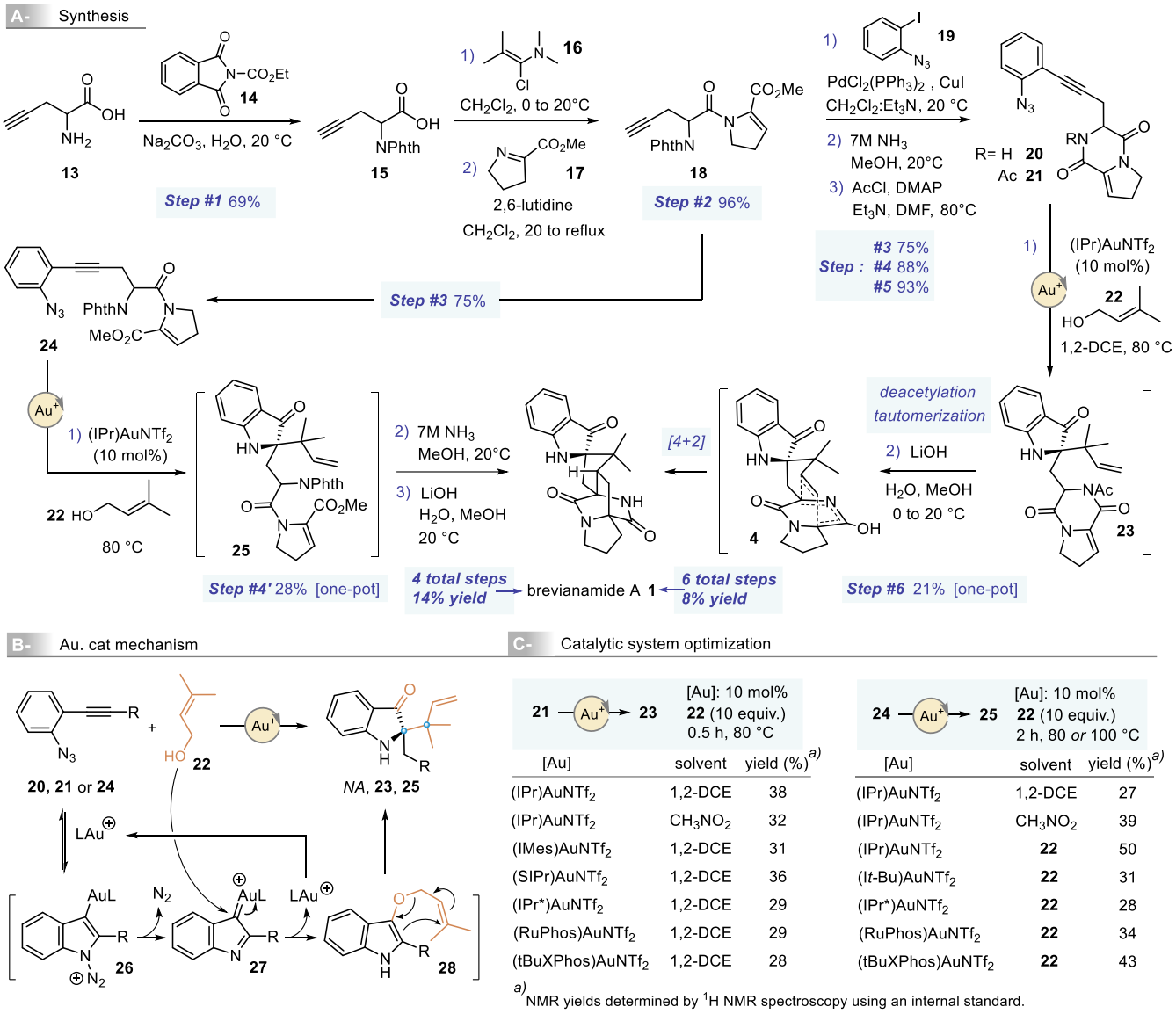


Scheme 2. Previous work towards the synthesis of brevianamide A (**1**), and our approach.

This key structural unit was obtained from a C_2 substituted indole intermediate **8** that was oxidized (**8**→**9**) prior to being submitted to reverse prenylation (**9**→**10**). Despite the conciseness and overall efficiency of both syntheses, it was considered that some improvement could potentially be made regarding the oxidation step and the introduction of the *tert*-prenyl moiety, more especially in terms of step and atom economy, productivity, and cost. These two steps are indeed critical to introduce the functionalities required for the formation of the key 2-*tert*-prenyl pseudoindoxyl moiety involved in the terminal IMDA reaction. The combined oxidation and reverse prenylation steps are moderately efficient in both approaches (Lawrence: 39%, Smith: 45%). In the synthesis by Lawrence, an early-stage redox process with the use of an external oxidant (*t*-BuOCl, 1 equiv.) and a two-fold excess of *B*-prenyl-9-BBN was employed to *tert*-prenylate a phthalimido protected tryptophane methyl ester (69% yield, see Scheme 1, part A). This non commercially available boron-based reagent required a three-step synthesis from 2-methyl-3-butyn-2-ol that was reported by the authors as low yielding (32%). In the work by Smith and co-workers, the oxidation step and the reverse prenylation are performed successively later in the synthesis (see Scheme 1, part B). Two equivalents of a pyridine/HMPA molybdenum oxide complex (MoOPH) are used to access the pseudoindoxyl intermediate **9**, which is then treated with a large excess (5 equiv.) of an expensive prenyl-stannane reagent under acid catalysis.[16] Based on these considerations, a new synthetic approach toward Brevianamide A (1) that would have the potential to shortcut and improve the access to the key 2-*tert*-prenyl pseudoindoxyl moiety was designed (Scheme 1, part C). The well established biosynthetic *hetero*-[4+2] IMDA[17-21] was retained as an end-game strategy as it is arguably an incredibly powerful disconnection to access the bicyclo[2.2.2]diazaoctane core of the natural product. In addition, the gold catalysis developed in our group to produce pseudoindoxyl derivatives **12** by reaction of 2-alkynylaryl azides **11** with allylic alcohols was considered as an ideal tool to access the required IMDA precursor in an expedite manner.[22] In this scenario, and in contrast with the two previous syntheses, the oxidation and *tert*-prenylation steps would be advantageously achieved in a cascade process.[23] The transformation would allow for a significant increase in structural complexity with the creation of the indoxyl moiety, three new bonds and two quaternary adjacent centers in a single operation. In addition, the transformation would be highly atom economic and cost efficient: no additional oxidant would be required, a role played internally by the azide moiety in **11**, and prenyl alcohol, a costless multi ton production commodity chemical, would be used as the *tert*-prenylating agent.[16]

We report herein the successful implementation of this strategy with the development of two complementary and highly concise syntheses of the polycyclic natural product brevianamide A (**1**).

Similarly to what was reported by Lawrence, and by Smith, our synthesis began with the protection of an amino acid as a phthalimide derivative (Scheme 3, part A). The commercially available *DL*-propargylglycine **13** was reacted with *N*-carbethoxyphthalimide **14**, at room temperature under basic conditions to produce **15** in 69% yield.[24,25] The more classical use of phthalic anhydride at higher temperature proved to be less efficient. Carboxylic acid **15** was then converted into its acyl chloride using the Ghosez reagent[26] **16** and subsequently reacted with imine[27] **17** as described by Li and Seipel in their synthesis of virginiamycin M1.[28] The resulting key enamide intermediate **18** was thus produced in 66% yield over two steps. When the coupling of the imine and the acyl chloride was realized with the *N*-Boc protected version of propargyl glycine **13** only trace amounts of the desired enamide product were formed. The Ghosez chloroenamine **16** was also found to be the reagent of choice for the generation of the acyl chloride. The alternative use of $SOCl_2$, $(COCl)_2$ or various peptide coupling reagents were completely unsuccessful regardless of the nature of the *N*-protecting group employed. A Sonogashira coupling with 1-azido-2-iodobenzene **19**,[29] followed by phthalimide deprotection with methanolic ammonia and acetylation of the resulting



Scheme 3. Synthesis of brevianamide A (**1**).

diketopiperazine **20** provided **21** in an excellent 61% yield over three steps. The acetyl protecting group was chosen considering it could be easily cleaved under the conditions used for the endgame IMDA sequence. The viability of the programmed key gold-catalyzed cascade was then studied using the experimental conditions we previously reported for the formation of variously substituted pseudoindoxyl derivatives.[22] The general mechanism of this transformation is presented in Scheme 3, part B. Upon activation of the alkyne moiety in the substrate by a gold(I) complex, a reversible 5-*endo-dig* cyclization can initially produce an intermediate adduct **26**. A subsequent elimination of dinitrogen allows for the generation of a reactive α-imino gold carbene **27** which can be trapped with prenyl alcohol to furnish **28** with concomitant regeneration of the catalyst. A final [3,3]-sigmatropic rearrangement is responsible for the formation of the pseudoindoxyl motif, the introduction of the *tert*-prenyl unit at C_2 with formation of two adjacent quaternary centers. The reaction was initially attempted with substrate **20** lacking the acetyl group on the deketopiprazine unit. Unfortunately, only products derived from a competitive intramolecular addition of the amide onto the alkyne could be observed when **20** was reacted with 10 mol% of (IPr)AuNTf$_2$ and a large excess of prenyl alcohol (10 equiv.) in 1,2-DCE at 80 °C. Under the same experimental conditions, the acetylated derivative **21** could be converted into the desired pseudoindoxyl **23** albeit in a modest 38% yield in addition to unidentified impurities and some decomposition. Attempts to improve the process by modifying the catalytic conditions were unsuccessful (see Scheme 3, part C and SI).[30] Having identified optimal conditions for this Au-catalyzed cascade reaction, we went ahead and attempted to access brevianamide A directly from precursor **21**. To our delight, the *in situ* treatment of the crude Au-catalyzed reaction with a solution of LiOH in a mixture of water and methanol induced the cleavage of the acetate moiety, followed by the previously reported tautomerization into azadiene **4** and [4+2] IMDA. The targeted

brevianamide A (**1**) was thus produced in 21% yield in one-pot from the 2-alkynyl phenylazide **21**. Overall, this route allowed access to brevianamide A (**1**) in only six steps (LLS) from commercially available building blocks in 8% overall yield, thus equaling the routes described by Lawrence and by Smith in terms of efficiency. We also recognized that the Sonogashira coupling product **24** resulting from step #3 could advantageously serve as a precursor for the gold-catalyzed cascade reaction. In case of success, the phthalimido protecting group could be cleaved *in situ*, thus allowing us to shortcut the previously established route. After much optimization (see Scheme 3, part C, and SI), we discovered that treating **24** with 10 mol% of (IPr)AuNTf$_2$ in prenyl alcohol used as the solvent at 80 °C provided pseudoindoxyl **25**, an intermediate in the synthesis of brevianamide A by Smith, in 47% isolated yield (50% NMR yield). We concluded our study by attempting to convert pseudoindoxyl **24** into brevianamide A in one pot manner, similarly to what was achieved with **21**. Gratifyingly, the treatment of **25** with ammonia in MeOH induced the deprotection of the phthalimide group, and the subsequent diketopiperazine formation. Further addition of LiOH ultimately furnished brevianamide A (**1**) which was isolated in 28% yield for the three steps one-pot sequence.

In summary, we have achieved the shortest and highest yielding (four steps LLS, 14% overall yield) synthesis of brevianamide A (**1**) to date. The successful execution of this strategy relies on the use of a gold(I)-cascade process which forged the key pseudoindoxyl motif of the natural product in one step using simple prenyl alcohol to introduce the *tert*-prenyl unit at position C$_2$ and generate the two adjacent quaternary centers. Thanks to the general compatibility of the experimental conditions used for the gold-catalyzed steps with basic media, we were also able to telescope the synthesis such that no isolation or purification of late-stage intermediates was required.

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Author Contributions

The project was conceptualized and supervised by F.G. Experiments and data analysis were performed by A.M. Results were discussed in between all authors and the evolution of the project resulted from a common agreement. The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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REFERENCES

(1) Birch, A. J.; Wright, J. J., The brevianamides: a new class of fungal alkaloid. *J. . Chem. Soc. D:* **1969,** 12, 644b–645.

(2) Paterson, R. R. M.; Simmonds, M. J. S.; Kemmelmeier, C.; Blaney, W. M., Effects of brevianamide A, its photolysis product brevianamide D, and ochratoxin A from two Penicillium strains on the insect pests Spodoptera frugiperda and Heliothis virescens. *Mycol. Res.* **1990**, *94*, 538–542.

(3) Finefield, J. M.; Frisvad, J. C.; Sherman, D. H.; Williams, R. M., Fungal Origins of the Bicyclo[2.2.2]diazaoctane Ring System of Prenylated Indole Alkaloids. *J. Nat. Prod.* **2012,** *75*, 812–833.

(4) Klas, K. R.; Kato, H.; Frisvad, J. C.; Yu, F.; Newmister, S. A.; Fraley, A. E.; Sherman, D. H.; Tsukamoto, S.; Williams, Robert M., Structural and stereochemical diversity in prenylated indole alkaloids containing the bicyclo[2.2.2]diazaoctane ring system from marine and terrestrial fungi. *Nat. Prod. Rep.* **2018,** *35* (6), 532-558.

(5) Bird, B. A.; Remaley, A. T.; Campbell, I. M., Brevianamides A and B Are Formed Only After Conidiation Has Begun in Solid Cultures of Penicillium brevicompactum. *Appl. Environ. Microbiol.* **1981,** *42*, 521–525.

(6) Ye, Y.; Du, L.; Zhang, X.; Newmister, S. A.; McCauley, M.; Alegre-Requena, J. V.; Zhang, W.; Mu, S.; Minami, A.; Fraley, A. E.; Adrover-Castellano, M. L.; Carney, N. A.; Shende, V. V.; Qi, F.; Oikawa, H.; Kato, H.; Tsukamoto, S.; Paton, R. S.; Williams, R. M.; Sherman, D. H.; Li, S., Fungal-derived brevianamide assembly by a stereoselective semipinacolase. *Nat. Catal.* **2020,** *3*, 497–506.

(7) Williams, R. M.; Glinka, T.; Kwast, E., Facial selectivity of the intramolecular SN2' cyclization: stereocontrolled total synthesis of brevianamide B. *J. Am. Chem. Soc.* **1988,** *110*, 5927–5929.

(8) Williams, R. M.; Glinka, T.; Kwast, E.; Coffman, H.; Stille, J. K., Asymmetric, stereocontrolled total synthesis of (-)-brevianamide B. *J. Am. Chem. Soc.* **1990,** *112*, 808–821.

(9) Williams, R. M.; Sanz-Cervera, J. F.; Sancenón, F.; Marco, J. A.; Halligan, K. M., Biomimetic diels–alder cyclizations for the construction of the brevianamide, paraherquamide, sclerotamide, asperparaline and VM55599 ring systems. *Bioorg. Med. Chem.* **1998,** *6*, 1233–1241.

(10) Adams, L. A.; Valente, M. W. N.; Williams, R. M., A concise synthesis of d,l-brevianamide B via a biomimetically-inspired IMDA construction. *Tetrahedron* **2006,** *62*, 5195–5200.

(11) Greshock, T. J.; Williams, R. M., Improved Biomimetic Total Synthesis of d,l-Stephacidin A. *Org. Lett.* **2007**, *9*, 4255–4258.

(12) Frebault, F. C.; Simpkins, N. S., A cationic cyclisation route to prenylated indole alkaloids: synthesis of malbrancheamide B and brevianamide B, and progress towards stephacidin A. *Tetrahedron* **2010,** *66*, 6585–6596.

(13) Godfrey, R. C.; Green, N. J.; Nichol, G. S.; Lawrence, A. L., Total synthesis of brevianamide A. *Nature Chem.* **2020,** *12*, 615–619.

(14) Godfrey, R. C.; Jones, H. E.; Green, N. J.; Lawrence, A. L., Unified total synthesis of the brevianamide alkaloids enabled by chemical investigations into their biosynthesis. *Chem. Sci.* **2022,** *13*, 1313–1322.

(15) Xu, F.; Smith, M. W., A general approach to 2,2-disubstituted indoxyls: total synthesis of brevianamide A and trigonoliimine C. *Chem. Sci.* **2021,** *12*, 13756–13763.

(16) Price search performed online on August 28, 2022. Less expensive price/gram for prenyl(tri-*n*-butyl)stannane was offered by the Alfa Aesar company (49USD/gram). The Sigma Aldrich company listed prenyl alcohol at a 0.05 USD/gram.

(17) Porter, A. E. A.; Sammes, P. G., A Diels–Alder reaction of possible biosynthetic importance. *J. Chem. Soc. D* **1970,** *17*, 1103a-1103a.

(18) Sanz-Cervera, J. F.; Glinka, T.; Williams, R. M., Biosynthesis of the brevianamides: quest for a biosynthetic Diels-Alder cyclization. *J. Am. Chem. Soc.* **1993,** *115*, 347–348.

(19) Sanz-Cervera, J. F.; Glinka, T.; Williams, R. M., Biosynthesis of brevianamides A and B: in search of the biosynthetic diels-alder construction. *Tetrahedron* **1993,** *49*, 8471–8482.

(20) Stocking, E. M.; Williams, R. M., Chemistry and Biology of Biosynthetic Diels–Alder Reactions. *Angew. Chem. Int. Ed.* **2003,** *42*, 3078–3115.

(21) Williams, R. M.; Kwast, E.; Coffman, H.; Glinka, T., Remarkable, enantio-divergent biogenesis of brevianamide A and B. *J. Am. Chem. Soc.* **1989**, *111*, 3064–3065.

(22) (a) Wetzel, A.; Gagosz, F., Gold-Catalyzed Transformation of 2-Alkynyl Arylazides: Efficient Access to the Valuable Pseudoindoxyl and Indolyl Frameworks. *Angew. Chem. Int. Ed.* **2011,** *50* (32), 7354–7358. See also: (b) Lu, B.; Luo, Y.; Liu, L.; Ye, L.; Wang, Y.; Zhang, L. Umpolung Reactivity of Indole through Gold Catalysis. *Angew. Chem. Int. Ed.* **2011,** *50*, 8358–8362. (c) Li, N.; Wang, T.-Y.; Gong, L.-Z.; Zhang, L. Gold-Catalyzed Multiple Cascade Reaction of 2-Alkynylphenylazides with Propargyl Alcohols. *Chem. Eur. J.* **2015**, *21*, 3585–3588.

(23) Interestingly, the synthesis by Smith utilizes a gold-catalyzed reaction to produce the indole ring shown in intermediate **8**

(24) Nefkens, G. H. L.; Tesser, G. I.; Nivard, R. J. F. A Simple Preparation of Phthaloyl Amino Acids via a Mild Phthaloylation. *Recl. Trav. Chim. Pays-Bas* **1960**, *79*, 688–696.

(25) An improved 82% yield of the phthalimido protected amino acid **15** was obtained when the reaction was performed from the non commercially available TFA-salt of the free amino acid **14**. The overall yield of each route would be boosted by approximately 2% when taking this improvement into consideration.

(26) Haveaux, B.; Dekoker, A.; Rens, M.; Sidani, A. R.; Toye, J.; Ghosez, L. α-chloro Enamines, Reactive Itermediates For Synthesis: 1-Chloro-*N*,*N*,2-Trimethylpropenylamine. *Org. Synth.*, **1979**, *59*, 26.

(27) Huy, P.; Neudörlf, J.-M.; Schmalz, H.-G. A Practical Synthesis of Trans-3-Substituted Proline Derivatives through 1,4-Addition. *Org. Lett.* **2011**, *13*, 216–2019.

(28) Qi Li, Ian B. Seiple, Modular, Scalable Synthesis of Group A Streptogramin Antibiotics, *J. Am. Chem. Soc.* **2017**, *139*, 13304–13307.

(29) 1-azido-2-iodobenzene **19** was produced in one step from the parent aniline. See SI.

(30) Using prenyl alcohol as the solvent did not help in this case. Cleavage of the acetyl group was observed.