Communication

Total Synthesis of Paspaline A and Emindole PB Enabled by Computational Augmentation of a Transform-Guided Retrosynthetic Strategy

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Total Synthesis of Paspaline A and Emindole PB Enabled by Computational Augmentation of a Transform-Guided Retrosynthetic Strategy

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Supporting Information Placeholder

ABSTRACT: We report the total syntheses of two indole diterpenoid natural products, paspaline A and emindole PB. Paspaline A is synthesized in a 9-step sequence from commercially available materials. The first total synthesis of emindole PB is accomplished in 13 steps and confirms a previously ambiguous structural assignment. Density functional theory calculations are utilized to interrogate the key carbocationic rearrangement in a predictive capacity to aid in the selection of the most favorable precursor substrate. This work highlights how retrosynthetic design can be augmented with quantum chemical calculations to reveal energetically feasible synthetic disconnections, minimizing time-consuming and expensive empirical evaluation.

Modern computational tools offer powerful new ways to augment retrosynthetic analysis.[1] One of these approaches is the development of algorithms to expedite the identification of strategic bond disconnections.[2–6] An underutilized, yet complementary, strategy is to employ quantum chemical calculations to rigorously predict the feasibility of the most challenging and least precedented aspects of synthetic plans. Herein, we report the application of predictive density functional theory (DFT) calculations to the concise synthesis of two biosynthetically related, but structurally distinct indole diterpenoids, paspaline A (**1**) and emindole PB (**2**) (Figure 1). To the best of our knowledge, this is the first report that demonstrates that iterative DFT calculations can be used to refine and guide the retron selection employed in a transform-based strategy.

These molecules belong to a class of complex indole diterpenoid natural products that have been the subject of synthetic investigations for several decades.[7] The hexacyclic architecture of paspaline A (**1**), a flagship member of the class, includes a pyran ring as well as an indole-fused cyclopentane adjacent to two vicinal quaternary centers.[8] Emindole PB (**2**), a natural product with multiple reported structural assignments,[9,10] has not been the subject of any reported synthetic efforts. Our interest in these compounds was motivated by the biological activity of paspaline A and related natural products, which includes anti-proliferative and anti-metastatic activity in the MDA-MB-231 mammalian breast cancer cell line through modulation of the Wnt/β–catenin signaling pathway.[11] The Wnt signaling pathway is a target of interest in solid tumor cancers with high rates of metastasis, such as breast cancer,

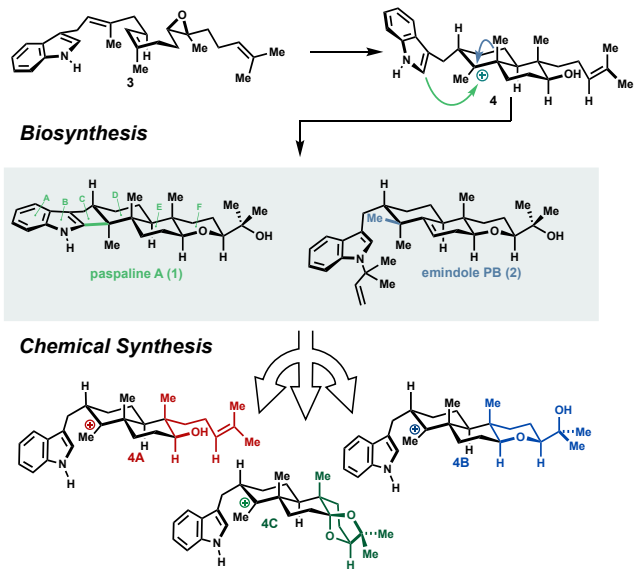


Figure 1. Computationally guided retrosynthesis. Biosynthesis of **1** and **2** via **3** and **4** suggests several potentially viable cyclization precursors for chemical synthesis (**4A**–**4C**).

due to its role in critical cellular processes like proliferation, differentiation and migration.[12]

Previous synthetic strategies towards these indole diterpenoids have relied on a late-stage indole ring synthesis by annulation onto an existing five-membered ring motif.[7a,b,f,g] Inspired by the polyene cascade that assembles the indole diterpenoid skeleton in the putative biosynthesis,[13,14] we planned to directly incorporate an indole motif and leverage its innate nucleophilicity to expedite synthesis of the C-ring (Figure 1). The cascade proceeds through a notable biosynthetic fork in which the operative carbocation **4** is thought to give rise to three distinct subclasses of natural products via Friedel-Crafts cyclization to paspaline A (**1**), methyl migration to emindole PB (**2**), or elimination to give the anthcolorin class of natural products.[15,16]

We envisioned applying a variant of this transform to enable divergent access to several structurally distinct members of the class in a single reaction. Within the framework of this transform-based strategy, there is flexibility with respect to structural

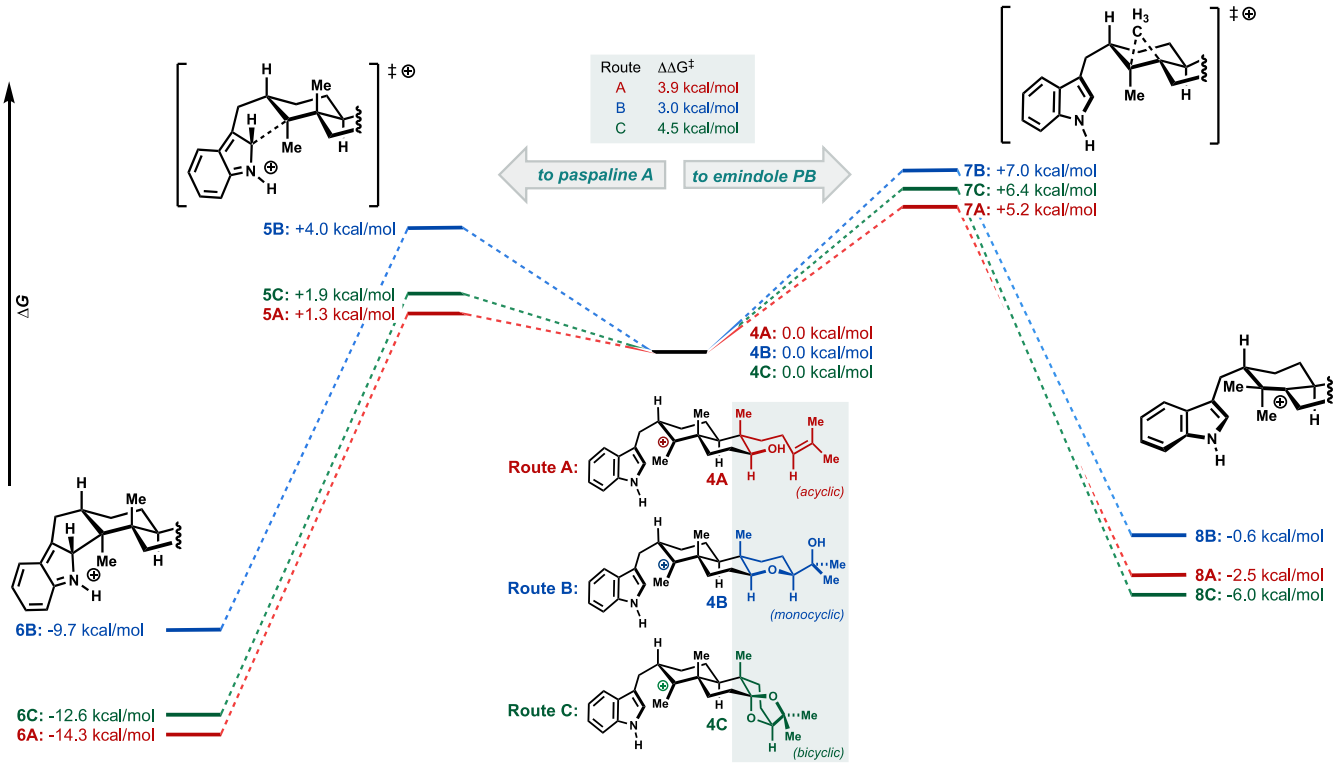


Figure 2. Gas-phase computational evaluation of three variations on F-ring structures were investigated using DFT. These calculations predicted that **4C** possess the largest inherent substrate bias ($\Delta\Delta G^{\ddagger}$) favoring C-ring cyclization over the 1,2-methyl shift. (Calculations at the mPW1PW91/6-31+G(d,p)//B3LYP/6-31G* level of theory, energies of intermediates **5-8** are relative to their respective carbocation **4**)

variation of the F-ring, with each of these variants requiring their own retrosynthetic disconnections. It was our hope that DFT calculations could be used to select the most energetically favorable retron for the key carbocationic rearrangement and thereby guide the remainder of our retrosynthetic search, rather than assist in selection of specific reaction conditions which are more easily screened empirically.

We identified a set of substructures that would lead to step efficient routes, yet were structurally distinct enough to elicit measurable energetic differences with respect to the behavior of the tertiary carbocation: the acyclic biosynthetic intermediate **4A**, a monocyclic tetrahydropyran **4B**, and a bicyclic ketal **4C** (Figure 2). Despite these obvious structural differences, the distal nature of the modifications made it challenging to predict from first principles which of these substrates would optimally promote access to both the cyclization and 1,2-methyl shift. Therefore, we sought to use DFT calculations to refine our selection of the key carbocationic rearrangement precursor as a function of F-ring structure by comparing the energetic barriers for the two possible diastereomeric cyclizations and the methyl shift.

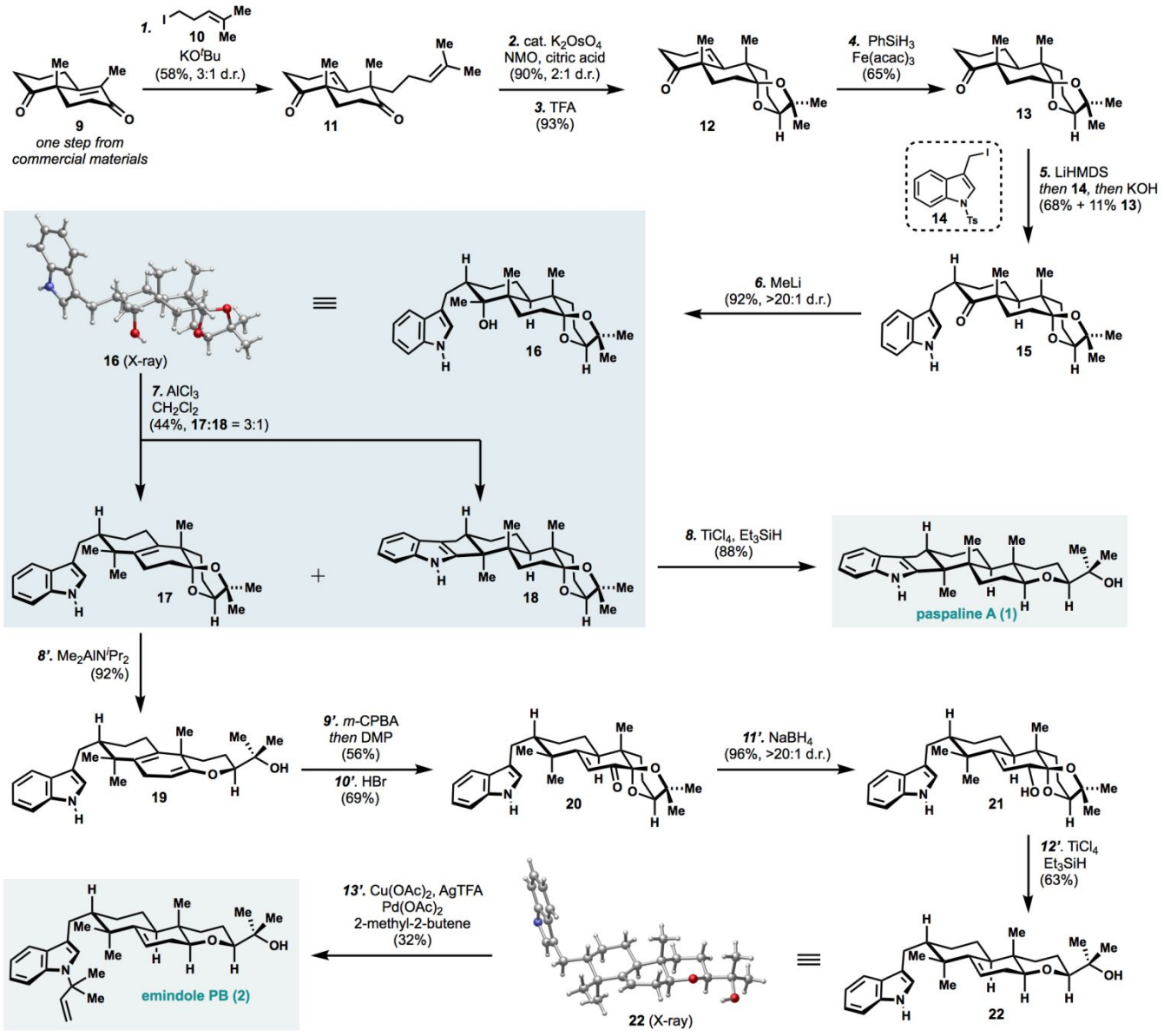
In considering which mechanistic pathway to model, we reasoned that the 1,2-methyl shift could occur via a concerted or stepwise pathway, however the cyclization to form vicinal quaternary centers is presumably limited to the carbocationic pathway.[17] As our goal was to select a route rather than predict exact conditions, our calculations were conducted with a simplified system (i.e. the gas phase carbocation). Although it would be interesting to calculate the propensity of the concerted methyl migration as a function of the substrate, comparison of these results to the energetics of the stepwise cyclization would be challenging. This is due to the two pathways requiring different assumptions and simplifications (e.g. analysis of several leaving groups or counterions, variable dependence on reagents, etc.), which may mask the subtle differences that arise due to substrate structural modification.

Thus, the stepwise pathways were modeled by DFT to assess which of these three aforementioned substrates would be most optimal for cyclization rather than methyl shift. When the relative energies ($\Delta\Delta G^{\ddagger}$) between the gas phase transition states leading to cyclization and methyl-shift for each carbocationic substrate were compared at the mPW1PW91/6-31+G(d,p)//B3LYP/6-31G* level of theory, it was found that **4C** possessed the largest energetic bias (4.5 kcal/mol) towards cyclization via this stepwise pathway.[18] A limitation of this approach is that the degree of error associated with these calculations is uncertain.

An additional challenge in effecting the desired indole cyclization reaction to form paspaline is that this ring formation would need to result in a *trans*-fused 5-membered ring, despite the fact that cyclization reactions that form fused 5-membered rings generally lead to the formation of *cis*-fused ring systems.[19] Both stereochemical outcomes have been observed in synthetic studies of other indoloterpenoid scaffolds.[20] In one such instance, a study by Ang Li and co-workers, which involves the formation of vicinal quaternary centers results in the formation of the *cis*-fused ring system.[20a] Conversely, a report by Dethe and co-workers discloses the *trans*-stereoselectivity – though notably to form a different ring system in the absence of vicinal quaternary centers.[20b] Fortuitously, DFT analysis of all four diastereomeric cyclization intermediates of precursor **4C** predicted that our desired stereochemical outcome (*trans*-C/D-fusion) was the more energetically favorable pathway by at least 1.3 kcal/mol (see Supporting Information Figure S2).

With a substrate defined for application of our transform goal, a subsequent structure-goal strategy identified a Wieland-Miescher ketone derivative as our starting material. We began our synthesis with the thermodynamic alkylation of known Wieland-Miescher ketone derivative **9**, which was prepared in one step from commercial materials by Robinson annulation with homoprenyl iodide **10**, resulting in formation of diketone **11** with a diastereomeric ratio (d.r.) of 3:1 (Fig. 3).[21] Dihydroxylation of the more exposed alkene gave a separable mixture of diastereomers

Scheme 1. Total Synthesis of Paspaline A (**1**) and Emindole PB (**2**)



Reagents and conditions: (1) KO^{t}Bu (1.2 equiv), THF, 60 ˚C; then **10** (1.3 equiv), THF, 0 ˚C to 23 ˚C, 58% yield, 3:1 d.r. (2) K_2OsO_4 (2.5 mol%), citric acid (10 mol%), NMO (3.0 equiv), ^{t}BuOH:H_2O (1:1 v:v), rt, 90% yield, 2:1 d.r. (3) CF_3CO_2H (1.0 equiv), CH_2Cl_2, 23 ˚C, 93% yield. (4) $Fe(acac)_3$ (1.2 equiv), $PhSiH_3$ (3.0 equiv), EtOH, 65% yield. (5) LiHMDS (1.2 equiv), THF, 0 ˚C, then **14** (1.0 equiv); then KOH (10.0 equiv), EtOH, 80 ˚C, 68% yield and 11% recovered **13**. (6) MeLi (4.0 equiv), THF, 0 ˚C, 92% yield, >20:1 d.r. (7) $AlCl_3$ (1.1 equiv), CH_2Cl_2, –15 ˚C, 44% yield, **17**:**18** = 3:1. (8) $TiCl_4$ (1.3 equiv), Et_3SiH (2.0 equiv), CH_2Cl_2, 0 ˚C, 88% yield. (8') $AlMe_3$ (5.0 equiv), $^iPr_2NH$ (6.0 equiv), DCE, 80 ˚C, 92% yield. (9') *m*-CPBA (1.2 equiv), THF, 0 ˚C; then Dess-Martin periodinane (4.0 equiv), THF, 23 ˚C, 56% yield. (10') HBr (0.5 equiv), THF, 23 ˚C to 40 ˚C, 69% yield. (11') $NaBH_4$ (4.0 equiv), THF:MeOH (1:1 v:v), 0 ˚C, 96% yield, >20:1 d.r. (12') $TiCl_4$ (3.0 equiv), Et_3SiH (3.0 equiv), CH_2Cl_2, 0 ˚C, 63% yield. (13') $Cu(OAc)_2$ (2.0 equiv), AgTFA (2.0 equiv), $Pd(OAc)_2$ (30 mol%), 2-methyl-2-butene (30.0 equiv), MeCN, 32% yield.

(2:1 d.r.), the major of which could be ketalized with TFA to provide **12**. Thermodynamic reduction using hydrogen atom transfer conditions with $Fe(acac)_3$ and $PhSiH_3$ afforded tricycle **13** in 65% yield, as a single detectable diastereomer as confirmed by X-ray crystallography.[22,23] The indole moiety was introduced through alkylation of **13** with tosyl-protected indole iodide **14**, which was deprotected in situ by the addition of ethanolic KOH. The key precursor to the biomimetic transformation was obtained through MeLi addition to **15**, yielding the axial tertiary alcohol **16**, as confirmed by X-ray crystallography. The C-ring cyclization to form the cyclopentane ring was found to proceed under a limited set of reaction conditions with the optimal result obtained upon treatment with $AlCl_3$ in CH_2Cl_2. A mixture of the congeners **17** and **18** was isolated in 44% yield in a ratio of 3:1, favoring the methyl migration product **17**.

Given that related 1,2-methyl migrations have been suggested to proceed via either stepwise or concerted pathways,[17] we anticipate the diastereomeric alcohol, which cannot undergo the concerted methyl migration, might provide a higher yield of the cyclization product **18**. Synthesis of the diastereomeric equatorial alcohol was attempted, but was unsuccessful by either modifying the conditions used for nucleophilic addition to the ketone **15** or by alternative strategies, such as alkene hydration or reductive epoxide opening. Additionally, synthesis and acid-mediated activation of the

exocyclic alkene did not result in formation of compounds **17** or **18**.

To complete the synthesis of paspaline A, cyclization product **18** was subjected to ionic reduction conditions with $TiCl_4$ and Et_3SiH to give the natural product (**1**) in 9 steps from commercially available starting materials, which is approximately one third the number of steps as either the landmark 25-step Smith or 27-step Johnson syntheses.

In the formation of compound **17**, the elimination following the methyl migration proceeded directly to the undesired tetrasubstituted alkene. In order to transpose the olefin to the desired position, enol ether **19** was accessed in 92% yield by treatment of **17** with (i-Pr_2N)$AlMe_2$.[24] A Rubottom oxidation of the enol ether, followed by treatment with Dess-Martin periodinane, provided a β,γ-unsaturated ketone. Isomerization of the alkene was then elicited through treatment with HBr to give **20** in 69% yield. Removal of the carbonyl functionality could be effected through reduction of the enone to the allylic alcohol **21**, followed by simultaneous ionic reduction of both the allylic alcohol and ketal to give **22**. Subsequent *N*-reverse prenylation through a one-step protocol described by Baran and co-workers provided emindole PB (**2**) in greater yield (32%) than the conventional two-step propargylation and reduction approach (11%).[25] The material obtained by this route produced spectroscopic data which agreed with that of Kawai and co-workers, and the structure was confirmed through comparative DFT NMR calculations (See Supporting Information) and X-ray crystallography of the penultimate intermediate **22**.

DFT augmented retrosynthesis can assist in selecting substrates to be prioritized for experimentation and significantly streamline synthetic workflows. In this manuscript, we demonstrate how transform-based strategies can be refined through *a priori* DFT calculations, and apply this approach to the synthesis of paspaline A in approximately one third the steps of previous routes as well as the first synthesis of emindole PB. The limitations and capabilities of this computational approach are still unexplored, but further studies in predictive computational evaluation and experimentation will define the boundaries of this framework.

ASSOCIATED CONTENT

Supporting Information.
The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures, X-ray diffraction, spectroscopic data for all new compounds including ^{1}H- and ^{13}C-NMR spectra (PDF), Crystallographic data (CIF).

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Notes
The authors declare no competing financial interest.

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