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Total Synthesis of (+)-Shearilicine

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Abstract

Herein we report the first total synthesis of the indole diterpenoid natural product shearilicine by an 11-step sequence via a generalizable precursor to the highly oxidized subclass of indole diterpenoids. A native chiral auxiliary strategy was employed to access the target molecule in an enantiospecific fashion. The formation of the key carbazole substructure was achieved through a mild intramolecular Heck cyclization, wherein a computational study revealed noncovalent substrate–ligand and ligand–ligand interactions that promoted migratory insertion.

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Notes
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ASSOCIATED CONTENT
Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.2c13584.
Discussions of general experimental details, synthesis methods, computational details, computational methods for attractive dispersion, and determining anion-ligand/substrate interactions, figures of NMR spectra, Gibbs free-energy profiles, and method to evaluate attractive dispersion interactions, and tables of comparison of synthetic and natural ^{1}H and ^{13}C NMR, Cartesian coordinates, and associated distances (PDF)

Carbazole is a heterocycle ubiquitously found in biologically active natural products and medically relevant compounds.[1] Synthetic studies of diverse polycyclic scaffolds comprising carbazole alkaloids have enabled the development of strategies for rapid construction of conjugated aromatic systems embedded in topologically complex structures. For instance, the elegant synthesis of xiamycin (Figure 1A) from Li and co-workers featured an oxidative Heck cyclization to access the target heterocycle.[2] This initial effort was followed by the first total synthesis of aflavazole, which leveraged an alkyne Prins cyclization and 6π-electrocyclization.[3] In 2017, Garg and co-workers utilized a transient indolyne intermediate to install the terminal ring of the carbazole of tubingensin B.[4]

In 2019, the isolation of the carbazole-containing indole diterpenoid shearilicine (**1**) from endophytic *Penicillium* sp. was reported (Figure 1B).[5] Related indole diterpenoids exhibit potent and divergent mechanisms of action leading to the inhibition of BK ion channels,[6] which has motivated many synthetic efforts within the class.[7] Smith et al. pioneered and continues to advance the synthesis of indole diterpenoids, including the first total synthesis of paxilline-type indole diterpenoids,[8,9] the only total synthesis of penitrem D,[10] and more contemporary work on the nodulosporic acids.[11] In these studies, Smith and co-workers employed the enantiopure Wieland–Miescher ketone to construct a 5,6,6-tricyclic intermediate, which enabled indole ring synthesis. Kuwahara and co-workers complemented these efforts in their strategy for paspalinine by realizing the reductive opening of a stereoselectively formed cyclopropane to install vicinal quaternary centers.[12]

In 2019, our group continued efforts in this area, leveraging a bioinspired strategy to the indole diterpenoids.[13] Utilizing quantum chemical analysis enabled us to evaluate the relative energetics of two competing pathways for carbocation reactivity in the key step and design a versatile precursor that facilitated access to two skeletally distinct indole diterpenoids, paspaline A and emindole PB.

Shearilicine (**1**) incorporates a highly oxidized terminal ring, which is a structural feature associated with the most bioactive constituents of the class.[7] Shearilicine (**1**) is the first carbazole-containing metabolite within the family. However, limited quantities have only allowed for evaluation against a few cancer cell lines; nonetheless compelling selective toxicity for L5178Y and A2780 was observed relative to J82 and HEK-293 at low micromolar levels (e.g., L5178Y, IC_{50} = 3.6 μM, SI = 11.3 compared to J82). Additionally, these combined structural features posed a unique synthetic challenge.

Herein we report the development of a strategy that utilizes two key bond formations to merge an indole synthon with a tricyclic terpenoid component via an alkylation and mild Heck cyclization reaction, which defines a broadly applicable approach to carbazole synthesis (Figure 2).

Our retrosynthetic analysis of the oxidized indole diterpenoid framework was informed by two considerations: (1) topological and biosynthetic reasoning suggested synthesis through the ligation of an indole and terpene fragment; and (2) a starting material goal was defined as a chiral pool terpene for enantiospecific synthesis. The key aspects of our strategy hinged upon the Pd-catalyzed Heck cyclization and Achmatowicz rearrangement,

the latter of which has been previously disclosed on related substrates by Saxton[14] and Smith[15] and recently applied by Carreira[16] and Tong.[17] The requisite vinylfuran (**2**) would be elaborated from a butenolide (**3**), an intermediate derived from intramolecular hetero-Pauson-Khand cycloaddition. This disconnection to **4** suggests a vicinal difuctionalization of a cyclohexanone.

Envisioning that a native chiral auxiliary would enable a diastereoselective conjugate addition, we elected to utilize (*R*)-carvone (**5**) as the starting material.[18] Following the installation of the butenolide, a C–C bond cleavage was required to remove the isopropylidene unit. Although the invention of this strategy was previously disclosed,[19] it had not been applied to complex molecule synthesis. Notably, this is distinct from other C–C bond cleavage strategies that classically target ring scission[20] and other more recent developments in deconstructive functionalization.[21]

We began our synthesis with the conjugate addition of trimethylsilyl copper acetylide into (*R*)-carvone (**5**, Scheme 1). Subsequent trapping with TMSOTf resulted in the formation of enoxysilane 6 in 57% yield as a single diastereomer (d.r. > 20:1). The high level of diastereoinduction is attributed to the native chiral auxiliary function of the pendant isopropylidene group. The utility of the approach is generally encouraging, as asymmetric additions of alkynes into enones are a notable synthetic challenge.[22] Enoxysilane (**6**) was cleaved with MeLi and treated with the masked acrolein equivalent (**12**)[23] in the presence of $Pd(PPh_3)_4$ to afford the Tsuji–Trost allylation product **7** as an inconsequential mixture of *E*/*Z* isomers (5:1).

The aldehyde functionality was revealed, with concomitant desilylation by treatment with CsF to afford **4**. The clean and reliable reactivity of CsF can be attributed to the mild basicity and high solubility of CsF in MeOH/THF. These conditions were uniquely effective, as more typical basic hydrolytic conditions promoted rapid decomposition of **4**, likely via the engagement of the pendant aldehyde in an intramolecular aldol reaction. Additionally, it is noteworthy that the use of TBAF under analogous conditions was insufficient to effect Bz deprotection.

To avoid decomposition during chromatographic isolation, **4** was directly subjected to the hetero-Pauson–Khand cycloaddition. Treatment with $Mo(CO)_6$ in the presence of a DMSO additive resulted in the formation of the tricycle **8** in 47% overall yield, producing a single diastereomer as observed by ^1H NMR.[24] At this stage, the isopropylidine moiety needed to be excised. While oxidative approaches to access the corresponding enone were considered,[19,25] Kwon's method was well-suited to provide the ketone at the desired oxidation state.[26] With closely monitored and intermittent bubbling of O_3 to avoid decomposition, enantioenriched **3** was obtained in 53% yield.

With tricycle **3** in hand, we proceeded to investigate chemoselective functionalization of the ketone and the butenolide substructures for the installation of the pendant dibrominated indole (**13**). This alkylation reaction required deprotonation of the ketone in the presence of the acidic butenolide. After extensive optimization, the selective alkylation of the ketone was

achieved using $Zn(TMP)_2$ in the presence of TBAI and the electrophile (**13**),[27] producing **9** in 53% yield.

Due to competitive reactivity and acidity of the butenolide exacerbating the general challenge of electrophilic functionalization of neopentyl ketones, direct olefination of **9** proved to be ineffective including the "small" methylenation reagents such as Nysted's reagent. We explored the possibility of converting the butenolide to the base-tolerant vinyl furan substructure (**10**). Given our hypothesis that steric hindrance present at the ketone would preference addition to the butenolide, we subjected **9** to the vinyl Grignard reagent. It was hypothesized that the Grignard addition could be promoted by treatment with a Lewis acid, and additionally, it was expected that this would help facilitate the aromatization process. $Sc(OTf)_3$[28] was found to be the optimal additive for promoting selective reactivity, leading to the isolation of **10** in 32% overall yield.

With the reactivity of the butenolide attenuated through conversion to the furan (Scheme 2), the highly concentrated Wittig condition[29] not only afforded the terminal olefin in 81% yield but also epimerized the homobenzylic position to the desired diastereomer (d.r. > 20:1). Having obtained the key cyclization precursor **2**, we began to investigate the Pd-mediated bond formation.[30] Ligandless conditions with $Pd(OAc)_2$ in the presence of silver salts resulted in general decomposition (Entry 1). Encouragingly, the use of PPh_3 allowed for 8% of the desired product to be obtained (Entry 2). The use of more electron rich but sterically bulky $PBn(Ad)_2$ or bidentate ligands (Entries 3 and 4) were unsuccessful at improving the efficiency. Fortunately, a broad screen of Buchwald ligands identified XPhos as a promising lead, which afforded a yield of 28% (Entry 5). This result suggested testing other monodentate biaryl phosphines that preclude the formation of a bis-ligated complex. We expanded our search beyond the commonly used Buchwald-type ligands and ultimately identified CataCXium type ligand **L1** as the most optimal ligand, affording **15** in 50% yield (Entry 6). The initial product of Heck cyclization (a dihydrocarbazole) was not observed, and instead, only the aromatized product **15** was identified.

CataCXium ligand **L1** has been utilized extensively for Suzuki,[31] Buchwald–Hartwig,[32] and Sonogashira coupling reactions.[33] We were inspired to test **L1** due to successful applications in Heck reactions between allylic alcohols and aryl halides.[34] To understand the molecular basis for this ligand's efficiency, we computed the full pathway and analyzed the stabilizing forces provided by **L1** relative to PPh_3. We first determined that the migratory insertion step has the highest transition state energy (see the Supporting Information (SI) for details).[35]

Consistent with experimental observation, the transition state for the migratory insertion step was computed to be lower in energy with **L1** relative to PPh_3 by 4.9 kcal/mol (Figure 3). We then evaluated differential weak noncovalent interactions in accordance with the method disclosed by Liu and co-workers,[36] wherein we found favorable interactions between the apical methyl group on the *trans*-decalin and the indole unit of the CataCXium ligand (2.7 Å, 1.6 kcal/mol) and between the CataCXium *tert*-butyl groups and the indole unit of the substrate (3.2 Å, 2.3 kcal/mol). PPh_3 exhibits analogous dispersive interactions with its phenyl substituents: between one phenyl group and the indole (2.5 Å, 1.9 kcal/mol) and between the other two phenyl groups of PPh_3 and the apical methyl group (2.4 Å, 1.0

kcal/mol; 3.0 Å, 0.9 kcal/mol). Combined, the extended structure of CataCXium provides greater stabilization by 1.1 kcal/mol.

In addition to these weak noncovalent interactions, the acetate anion coordinates more closely to the Pd-center for **TS-PPh$_3$** (2.2 vs 2.6 Å),[37] because the steric bulk of the CataCXium ligand forces the acetate anion away from the Pd center in **TS-L1**, leading to contacts with the ligand and substrate. In **TS-L1**, one oxygen atom of the acetate anion displays interactions with two sites: (1) with the substrate's indole N–H (1.7 Å) and (2) with the CataCXium *t*-Bu C–H (2.3 Å). The other oxygen atom of the acetate anion is involved in contacts with three sites on the substrate and the ligand: (1) with the vinylic C–H of the substrate (2.4 Å), (2) with the CataCXium indole C3–H (2.1 Å), and (3) with a proximal substrate methylene (2.2 Å). In **TS-PPh$_3$**, there are only two such interactions: between one oxygen with the substrate's indole N–H (1.7 Å) and the other oxygen of acetate anion and the PPh_3 phenyl group (2.4 Å). The contacts with the proximal methylene and with the vinylic C–H are absent. While solvation likely plays a role and calculations with explicit solvation were not evaluated, this computational study shows striking differences in the transition states that provide a template for understanding mechanistic distinctions across ligands.

With a key step completed, carbazole **15** was subjected to Sharpless dihydroxylation conditions at low temperature. Extended reaction time allowed the intermediate furan diol **16** to further undergo Achmatowicz rearrangement in the same vessel, affording diol **17** in 40% yield with a d.r. of 3:1 favoring the desired diastereomer. The pendant alcohol was then ketalized through treatment with TsOH and $CuSO_4$, leading to the formation of the natural product shearilicine (**1**).

In summary, we have completed the first total synthesis of shearilicine by an 11-step sequence, featuring: (1) a removable native chiral auxiliary to control conjugate addition facial selectivity and (2) a mild Heck reaction to form the carbazole core. The use and removal of native chiral auxiliaries to overcome selectivity challenges in multistep synthesis may be a broadly applicable strategy and compliments other developments in the use of C–C bond cleavage reactions.

The network of interactions about the Pd-center observed in this study highlights the ability of noncovalent bonding between substrates and ligands to influence selectivity in complex systems. In the context of natural product synthesis, the steric, electronic, and broader topological complexity of late-stage intermediates frequently induces deviations from selectivity and reactivity trends observed in simple substrates. Thus, obtaining a precise, molecular-level view of noncovalent bonding networks in key transition states could guide the design of specialized ligands for these complex high-value substrates and may represent a general and translatable mechanistic approach to improve catalysis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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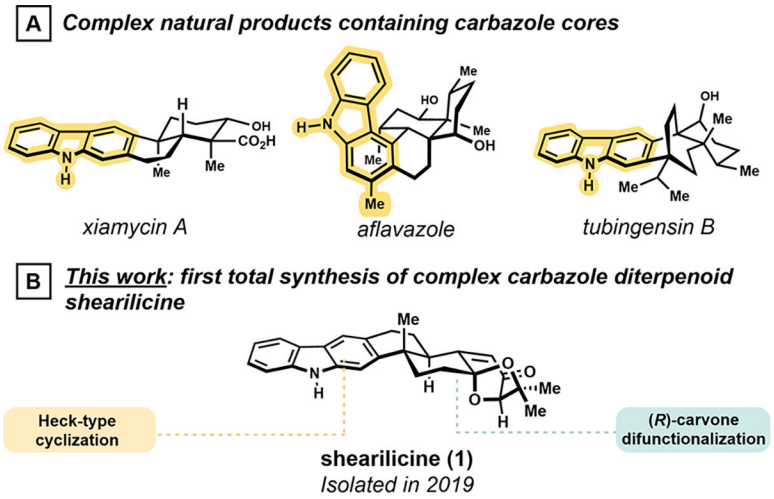


Figure 1.
Complex carbazole-containing natural products.

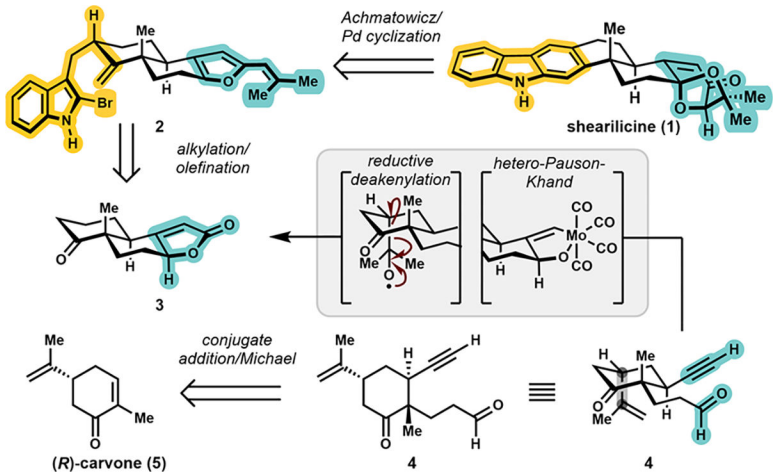


Figure 2.
Retrosynthetic analysis of shearilicine (**1**).

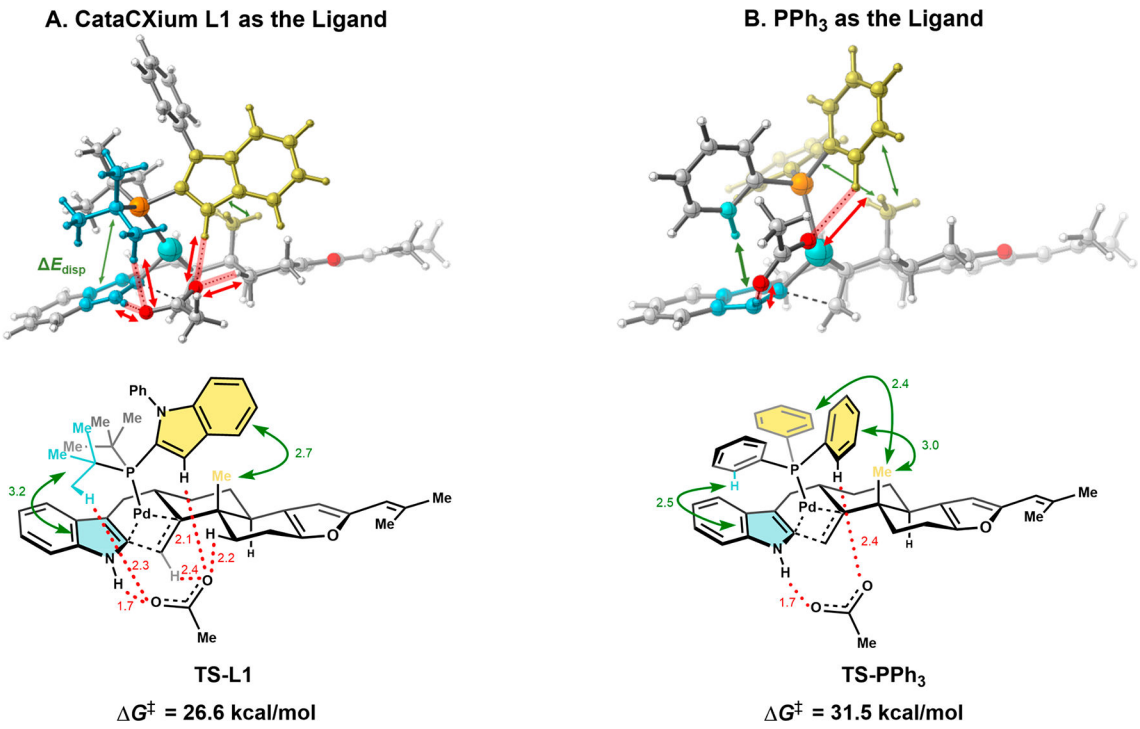
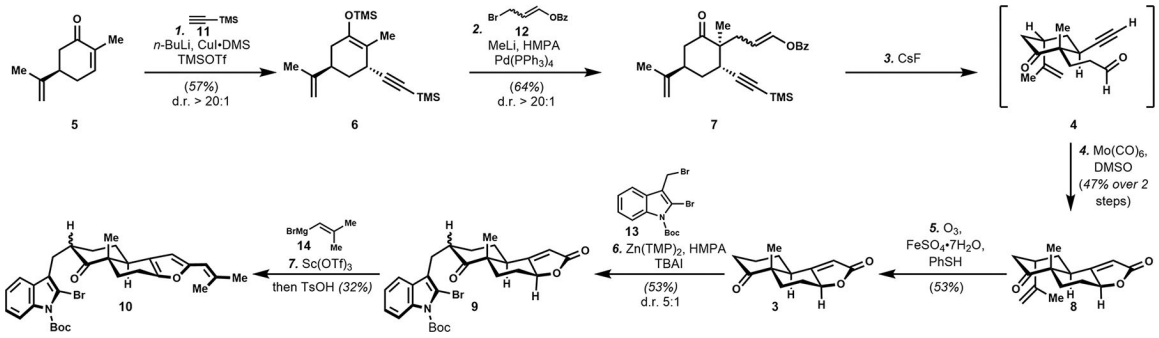
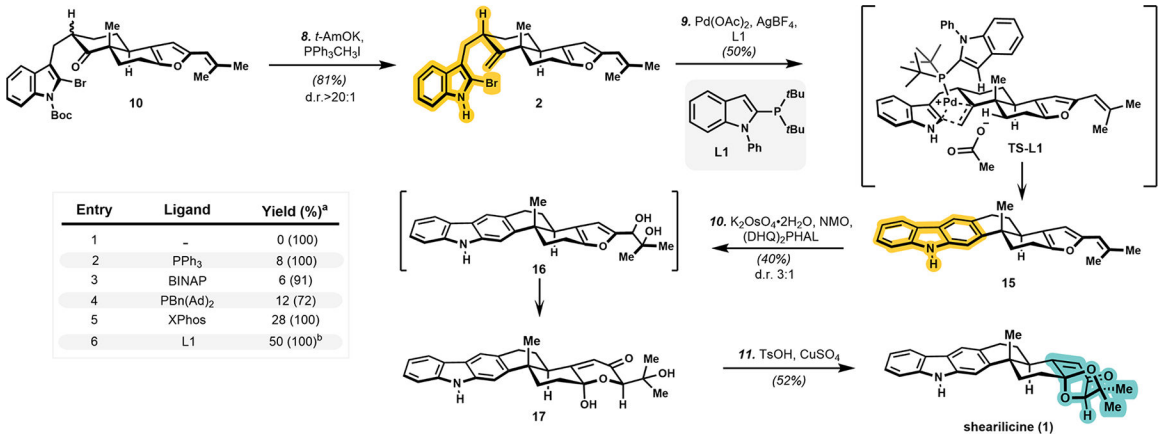


Figure 3.

Significant differences between **TS-L1** and **TS-PPh$_3$** in ligand–substrate interactions of the migratory insertion step of the key Heck reaction. Computed at the rωb97xd/SDD(Pd)/6–311+G**//rB3LYP/LANL2DZ (Pd)/6–31G* level of theory. Distances shown in Å.



Scheme 1. Enantiospecific Synthesis of 10



Entry	Ligand	Yield (%)[a]
1	-	0 (100)
2	PPh_3	8 (100)
3	BINAP	6 (91)
4	$PBn(Ad)_2$	12 (72)
5	XPhos	28 (100)
6	L1	50 (100)[b]

Scheme 2. Synthesis of Shearilicine (1) and Ligand Studies for the Heck Cyclization