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Total synthesis of Asperdinones B, C, D, E and Terezine D

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Abstract

The total synthesis of new members of prenylated indole alkaloids exhibiting α-glucosidase activity is described. Asperdinones B, C, D, and E are characterized by the presence of a 10*R* 3-indolylmethyl benzodiazepine-2,5-dione unit at C-3 of the C4-C7 prenylated indoles. Methods of direct and indirect prenylation of indole and tryptophane were explored. Different approaches were adopted for functionalization of C4-C7 prenyl indoles at C3 using Negishi cross-coupling methods. The asperdinones are among the rare tryptophane-derived indole alkaloids which appear to have undergone epimerization due to genetic alteration of specific gene clusters that code for a C10 *R* configuration

Introduction

Alkaloids constitute an important family of naturally occurring compounds with a rich history in the annals of bioactive compounds [1]. Among these, the family of indole alkaloids is known for its biomedical importance [2]. These alkaloids have been isolated from plant [3] and marine sources [4], and they are particularly relevant primarily because of their potent pharmacological activities as among other, anticancer drugs, but also for their architecturally intricate structures [5]. For these reasons, and considering the structural and stereochemical complexities of some members, indole alkaloids have been prime compounds of interest for total synthesis with spectacular successes [2,6,7]. A subset of simple indole alkaloids contains a prenyl group at various positions in the indole ring [8]. The importance of the indole core structure and the nature and position of prenylation is reflected by the observation that 6-prenyl indole but not 6-isopropyl indole has been reported to exhibit antifungal activity [9]. Tryptophanes containing a prenyl group at the 5, 6, or 7 positions are found as naturally occurring metabolites from diverse plant and bacterial sources [9–11]**.** The biosynthesis of prenyl tryptophanes is well studied and involves a series of prenyl transferases [12,13].

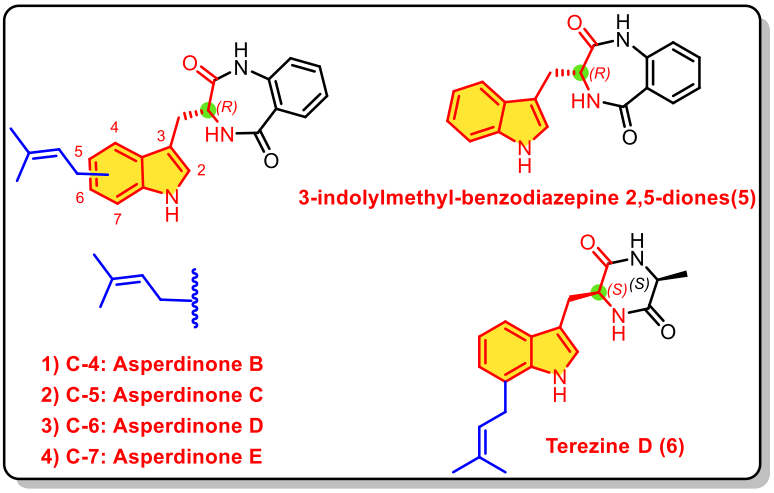


Figure 1: Structures of prenyl indole alkaloids derived from tryptophane.

A series of 4, 5, 6, and 7-prenylated 3-indolylmethyl-benzodiazepine 2,5-diones known as asperdinones B, C, D, and E (**1-4)** exhibiting moderate α-glucosidase inhibitory activity were recently isolated from cultures of *Aspergillus spinosus* WHUF0344 (Figure 1) [14]. The putative biogenetic precursor, (10*R*) 3-indolylmethyl benzodiazepine-2,5-dione **5** was also isolated as a metabolite. Historically, (10*S*) 3-indolyl benzodiazepine-2,5-dione (ent-**5**) was isolated for the first time as a natural metabolite from the fungal culture extract of *Aspergillus flavipes* by Barrow and Sun [15] and synthesized by the condensation of isatoic anhydride and L-tryptophane as previously reported by Bock in 1987 [16]. It is of interest that although the biosynthesis of 3-indolylbenzoquinone 2,5-dione (*ent*.**5**) is initiated with L-tryptophane and anthranilic acid [17], the resulting natural products **1-4** possess a (10*R*)-configuration. This is because of an epimerization mediated by the non-ribosomal peptide synthetase AnaPS within the genetic machinery of these microorganisms during biosynthesis [18,19]. Subsequently, post translational enzymatic processes mediated by prenyl transferases (AnaPT) lead to prenylation at C4-C7 sites in the indole unit.

Terezine D, (**6**) an indole tryptophane metabolite consisting of a 7-prenylated L-alanyl-L-tryptophane anhydride was isolated from the liquid cultures of *S. teretispora* containing potato broth in the medium. Its structure was based on extensive spectroscopic studies (Figure 1). Terezine D exhibited modest vitro antifungal activity [20]. A related metabolite lacking the C7 prenyl group had been isolated from the cultures of *Aspergillus chevalieri* in 1976 [21]. The structure and absolute stereochemistry were confirmed by synthesis from tryptophane and L-alanine [22]. The isolation of the terezine D and more recently the 10*R*-configured asperdinones as new members of this small subfamily of 7-prenyl tryptophanes with appended diketopiperazine and 2,5-benzodiazepinone units piqued our interest. Herein, we report our efforts toward the total synthesis of C4-C7 prenyl tryptophanes, asperdinones B, D, C, and E (**1-4**) and terezine D (**6**)

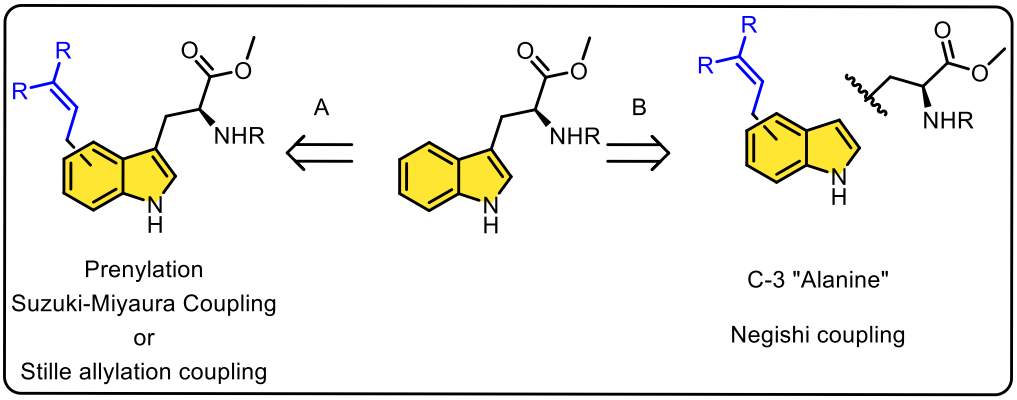


Figure 2: Retrosynthetic considerations for prenyl and allyl tryptophane

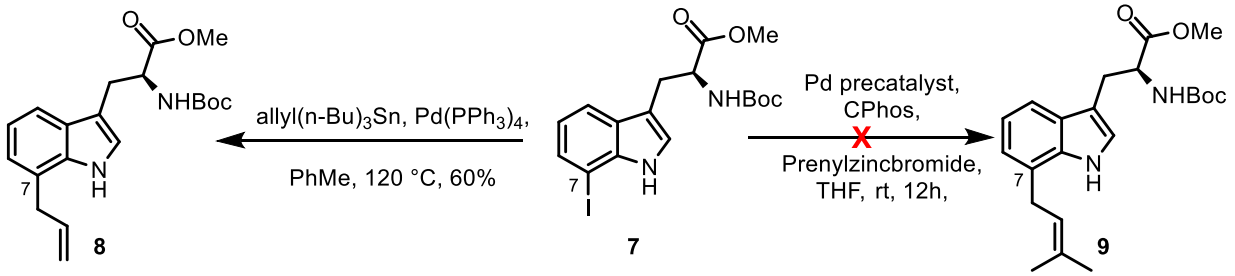
Considering the relatively simple structural complexity of the asperdinones B, C, D and E (**1-4)** and terezine D (**6**), we considered two basic approaches to 4, 5, 6 and 7-prenylated tryptophanes as synthetic precursors which could be converted to the intended natural products by cyclization to diketopiperazines or benzodiazepinones.

First, is the evident use of tryptophane as a starting chiral synthon (chiron), and to regioselectivity install a prenyl group at different sites on the indole moiety (Figure 2, Approach A) [23,24]. This would formally mimic the post-translational biosynthetic pathway wherein a prenyl group would be inserted at C4-C7 selectively via the prenyl transferase AnaPT. A second less evident approach would involve starting with a prenyl indole, then introducing an *R*- or *S*- 2-amino propionate (D-alanine) unit at C3 by a Negishi cross-coupling reaction (Figure 2, Approach B). Although each approach has precedents in different contexts, achieving regioselective bond formation and functional group compatibility presented unforeseen challenges.

Methods for the chemical synthesis of prenyl tryptophanes (Method A) are scarce [25,26]. Adopting a bio-inspired approach, Ishikawa treated tryptophane ethyl ester with prenyl alcohol in the presence of 2 equivalents of H_2SO_4 in water to give a mixture of six C-prenylated tryptophanes from which the 7-prenyl isomer could be isolated in 4% after chromatography on a 10g scale [27]. This direct prenylation method was then adapted for the synthesis of terezine D which was isolated as a pale-yellow amorphous powder. Viswanathan [25] and Chen [28] reported C2 prenylation of tryptophane methyl ester mediated by acid salts and Lewis acids respectively.

Results and Discussion

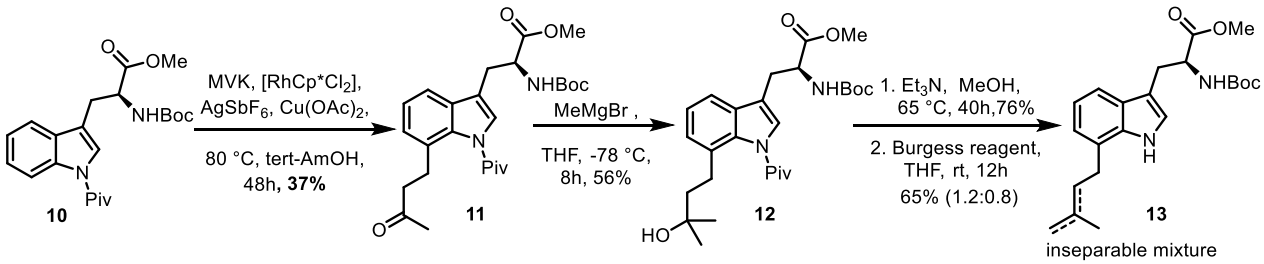
Adopting Approach A, we considered prenylation of the known Movassaghi [29] 7-iodo N-Boc tryptophane ethyl ester **7** with prenylzincbromide catalyzed by XPhos-Pd-G3 as a Pd pre-catalyst exemplified by the C6-prenylation of 6-bromo indole in 94% yield by Buchwald (Scheme 1) [30]. However, under the same reported conditions only unreacted starting material was recovered. In a single example, C7 allylation of **7** was possible via a Stille coupling protocol to give **8** (Scheme 1)[31].



Scheme 1: C7 functionalization of N-Boc L-tryptophane methyl ester

As an alternative approach to C7 functionalization of N-Boc tryptophane methyl ester, we chose a CH activation protocol [32].

Treatment of **10** with methyl vinyl ketone in the presence of $[RhCp^*Cl_2]_2$ catalyst according to Ma [33] led to the 7-(3-keto-1-butyl) alkylated product **11** in 37% yield (Scheme 2). Despite the mediocre yield, product **11** was transformed to the corresponding tertiary alcohol **12**. Removal of the N-Piv group and dehydration with the Burgess reagent [34] led to an inseparable mixture of olefins slightly in favor of the exo- olefin isomer. Dehydration in the presence of the N-pivaloyl group led to the same mixture of isomers. Numerous conditions to change the ratio were not successful [35]. (SI, Table 01).



Scheme 2: C7 Prenylation via C-H activation

In view of the above discussed issues, we considered chemically more challenging protocols starting with allyl or prenyl indoles (Figure 1, Approach B) which would rely on a Negishi cross-coupling reaction [36,37] using Jackson's 3-iodozinc N-Boc serine methyl ester [38] and 3-iodo allyl or prenyl indoles. (Figure 3). Related Negishi cross-coupling reactions have been reported for 7-alkyl N-Boc indole [39] and 7-methyl N-

Boc indole [40] in excellent yields. The Negishi cross-coupling reaction with iodozinc N-Boc serine methyl ester **35** has been used to prepare various aryl substituted tryptophanes in 76-96 % yields [41]. In principle, this protocol should be applicable to all the C4-C7 substituted indoles as well as to the corresponding allyl indoles. In the latter case a Grubbs olefin cross-metathesis reaction with 2 butene would indirectly introduce the prenyl appendage [42–44].

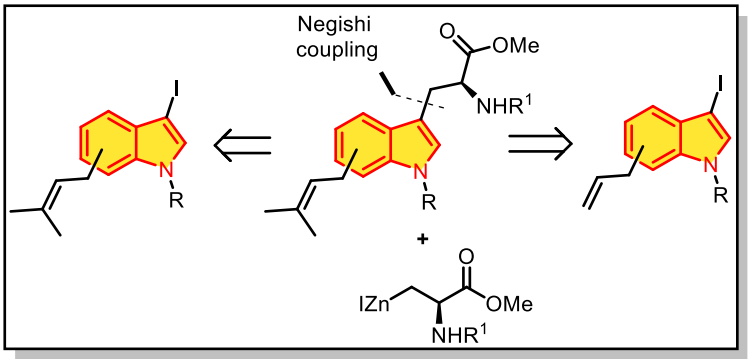
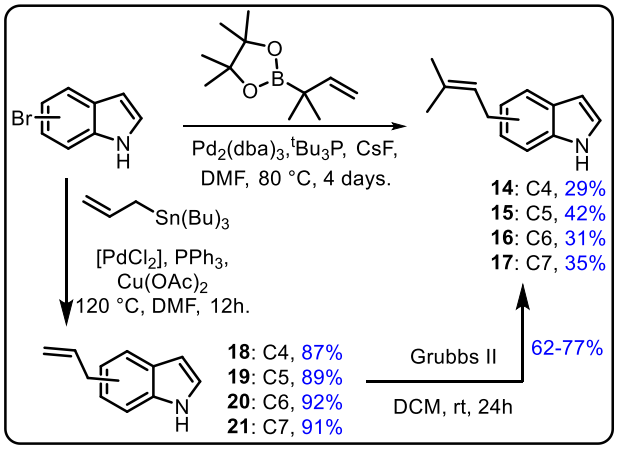


Figure 03: Negishi cross- coupling of allyl and prenyl indoles.

The synthesis of 7-prenyl indole from 2-iodo aniline and di-tert-butyl dicarbonate was reported in 1996 [45,46]. Subsequently Pirrung reported two practical syntheses of 7-prenyl indole [47,48]. Regioselective C-7 prenylation of indole has been achieved by directing group C-H activation as reported by Snieckus [49]. However, the deprotection of the preferred N-bis-t-butylphosphinoyl directing group required conditions that would be incompatible with the presence of an amino acid appendage at C-3. 7-Prenyl indole has been prepared from N-Boc indoline in the presence of sec. BuLi, TMEDA and prenyl bromide at -78 ºC, followed by oxidation with MnO_2 [50].

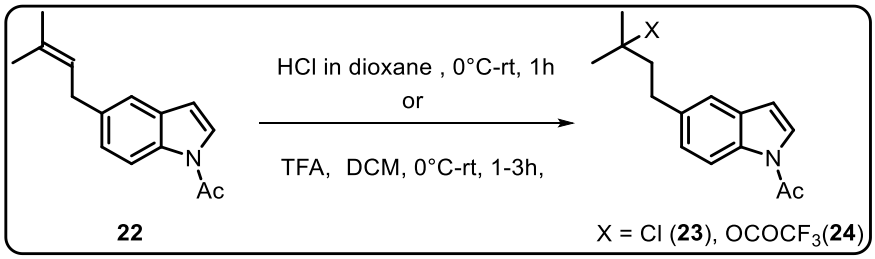
We deemed it necessary to explore alternative synthetic methods to prenyl and allyl indoles as starting points toward the synthesis of asperdinones B, C, D and E (**1-4**) as well as to terezine D (**6**). To access 4-prenyl indole, we adopted a Pd-catalyzed Suzuki coupling of 3,3-dimethyl-1 butene pinacol boronate to bromo indoles [51]. Unfortunately, despite the relatively simple protocol (Pd $(PPh_3)_4$ toluene, NaOH, 90 ºC, 12h) and the reported high yield of 4-prenyl indole, we consistently obtained inseparable mixtures of the desired prenyl indole and the reverse indole products. Mixtures of prenylated compounds have been observed under the same conditions with 4-t-butlyl bromobenzene [52]. We then adopted a prenylation method used by Knölker for carbazole derivatives bromo indoles using $Pd(dba)_2$ [53]. Pleasingly, this led to the corresponding prenyl indoles **14-17** without forming the isomeric reverse prenyl adducts, although starting material was recovered intact resulting in modest yields of coupling products (Scheme 3). It is of interest that 5, 6, and 7 prenyl indoles are found as naturally occurring metabolites from diverse plant sources [9,11,54].



Scheme 3: Synthesis of prenyl and allyl indoles.

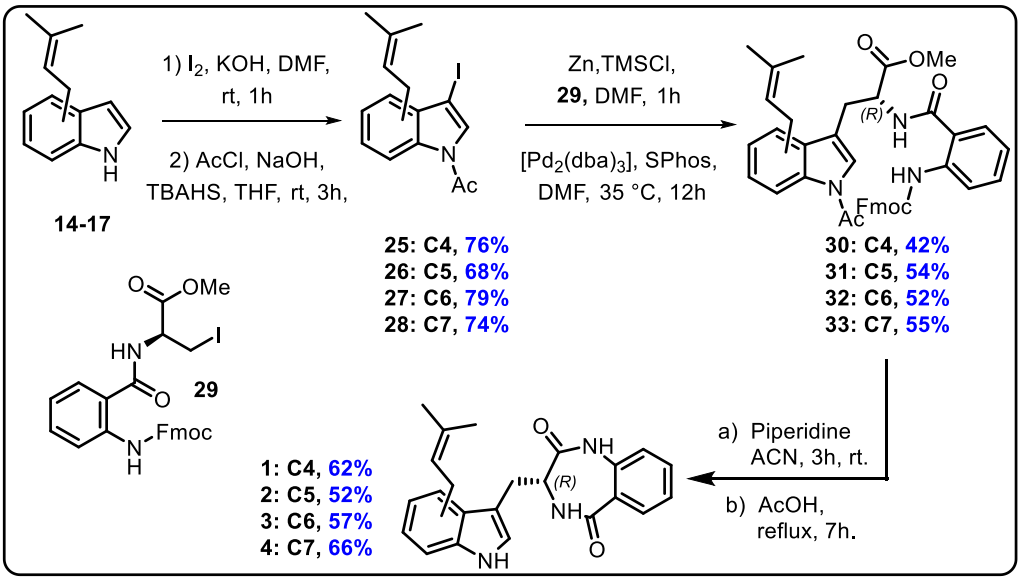
The synthesis of allyl indoles **18-21** was realized in excellent yields via a Stille coupling of the corresponding bromo indoles (Scheme 3) [42,55]. Grubbs cross-coupling [56] afforded the corresponding prenyl indoles **14-17** in excellent yields.

Prior to initiating a synthesis toward our intended target molecules **1-4** (Figure 1), we tested the stability of prenyl indoles under the acidic conditions required for the removal of the N-Boc group from the intended Negishi coupled products. Not surprisingly, treatment of N-acetyl 5-prenyl indole **22** with HCl in dioxane or TFA led to Markovnikov hydrochlorination and trifluoro acetylation of the prenyl group respectively (Scheme 4) [57,58]. This result led to the use of an N-protecting group in the iodozinc amino acid reagent that could be deprotected under non-acidic conditions after the cross-coupling reaction. To this end, we prepared iodo D-alanyl N-Fmoc anthranylamide (**29**) from *R*-serine.



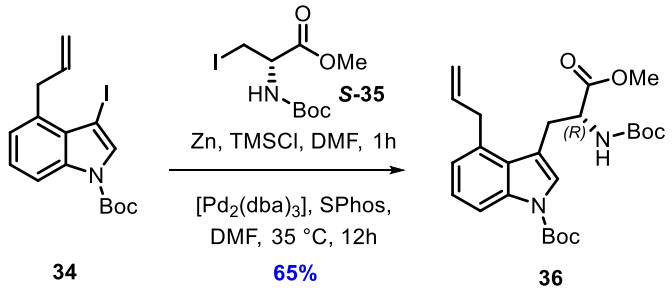
Scheme 4: Markovnikov hydrochlorination and hydrotrifluoroacetylation.

Treatment of prenyl indoles **14-17** with iodine and KOH following acetylation afforded the corresponding iodo indoles **25-28** in 68-79 % yields. Negishi cross-coupling according to Jackson [38] with iodo D-alanyl N-Fmoc anthranylamide (**29**) gave the adducts **30-33** in 42 - 55% yields. Removal of the Fmoc and N-acetyl groups with piperidine gave the corresponding anthranylamides, which upon heating with acetic acid [59] afforded asperdinones **1-4** in average total yields of 5 - 9%. In all cases spectroscopic and analytical data were correctly matched with the reported data for the natural products.



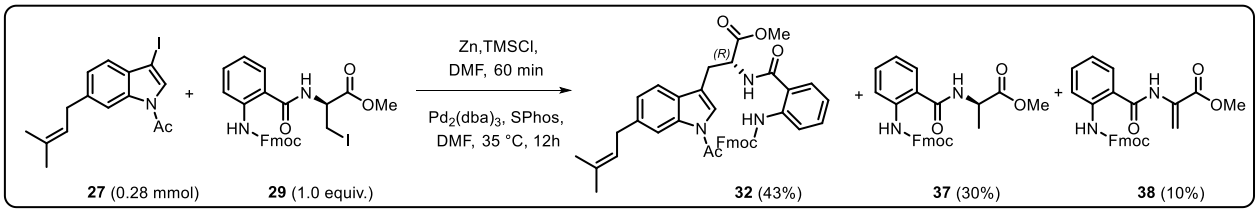
Scheme 5: Synthesis of asperdinones B-E **(1-4)**.

The moderate yield in the Negishi cross-coupling reactions was attributed in part to the nature of the iodo zinc D-alanyl N-Fmoc anthranylamide reagent **29**, since coupling with the Jackson N-Boc iodozinc L-alanine methyl ester reagent (***S*-35**) under the same conditions albeit with an a 4-allylindole improved the yield to 65%. Steric bulk due to the presence of the allyl or propenyl group at different positions does not appear to affect the yields (Scheme 6).



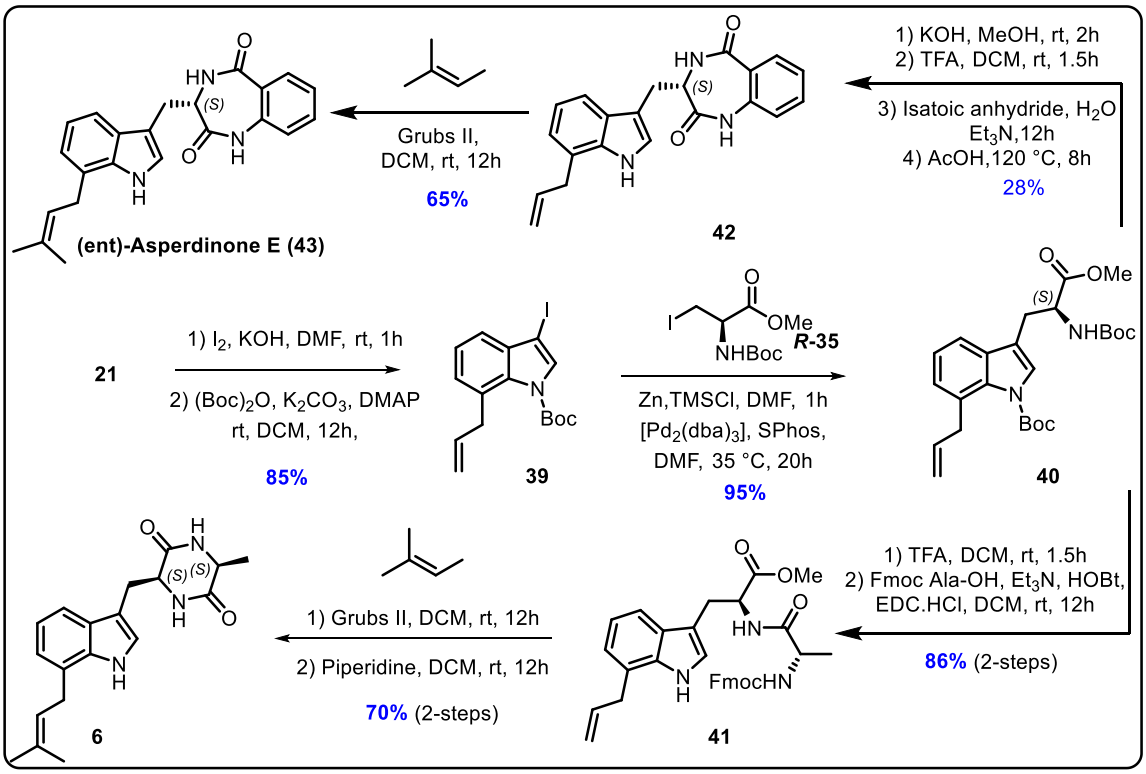
Scheme 6: Control experiment with N-Boc iodozinc reagent *S*-**35**

Importantly, it was observed that reduction and ß-elimination of the iodozinc D-alanine Fmoc anthranilamide methyl ester (**29)** took place during the cross-coupling reaction thereby affecting the yield (Scheme 7)[60]. For example, using 1 equivalent of reagent **29**, the cross-coupling of 3-iodo 6-prenyl indole **27** led to the adduct **32** in 43% yield accompanied by the reduced product **37** in 30% and the dehydro product **38** in 10% yield. Control experiments revealed that reagent **29** was unaffected in the presence of the Pd catalyst. It follows that elimination and reduction must occur after Pd insertion and formation of a pallado-zinc intermediate which undergoes ß-elimination and proton transfer. Seminal studies by Jackson [61] have reported related results with the iodozinc N-Boc alanine methyl ester who observed intramolecular proton transfer with partial incorporation of deuterium upon quenching with deuterium oxide. In a different context, the role of the Pd catalyst and the associated ligand was studied in the cross-coupling of iodozinc N-Boc L-alanine methyl ester reagent **35** with 3-iodomethyl furan resulting in a large variation in ratios of coupled products to dehydro N-Boc and reduced N-Boc alanines [60].



Scheme 7: Control experiment of the Negishi cross-coupling reaction with iodozinc reagent **29**

The modest yields starting with the prenylation of the respective bromo indoles, urged us to explore the use of allyl indoles as precursors for the synthesis of terezine D and *ent*-asperdinone E, now using an N-Boc protecting group (Scheme 8). Treatment of 3-iodo indole **39** with iodozinc N-Boc L- alanine Me ester (***R*-35**) under Jackson coupling conditions afforded **40** in excellent yield. Cleavage of the N-Boc group and amide formation with F-moc L-alanine methyl ester gave **41** which was subjected to a cross-metathesis reaction with the Grubbs II catalyst, then deprotection to give terezine D in 44% overall yield. Application of the same protocol using isatoic anhydride led to *ent*-asperdinone E **43** in 13% overall yield. It is interesting that the Negishi cross-coupling reactions took place in excellent yield with the iodozinc reagent **35** in contrast to the iodozinc alanyl anthranilamide reagent **29.**



Scheme 8: Synthesis of terezine D and (*ent*)-asperdinone E.

Conclusion

In summary, we have reported the total synthesis of a new class of prenyl 3-indolyl 2,5-benzodiazepinone dione and diketopiperazine alkaloids by stereocontrolled methods involving Negishi cross-coupling reactions and related methods for C-H functionalization. Insights into the reactivity and stability of an iodozinc alanyl anthranylamide reagent were explored and validated. In view of the prevalent occurrence of prenyl indoles, it is interesting to speculate whether there is an alternative biochemical pathway that

involves prenyl indoles as biogenetic precursors to prenylated tryptophanes. The reverse appears to occur in the biosynthesis of 6-prenyl indole 3-carbaldehyde (6-DMAI-3-carbaldehyde) via a gene cluster that contains a tryptophanase [62]. It is tempting to speculate if prenylated indole 3-carbaldehyde could not be enzymatically transformed to the corresponding prenylated tryptophanes via a biogenetic Strecker-like process.

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