Natural Product Synthesis

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Total Synthesis of the Tremorgenic Indole Diterpene Paspalinine**

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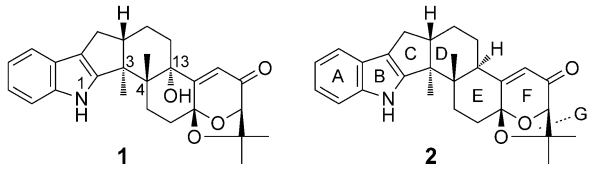
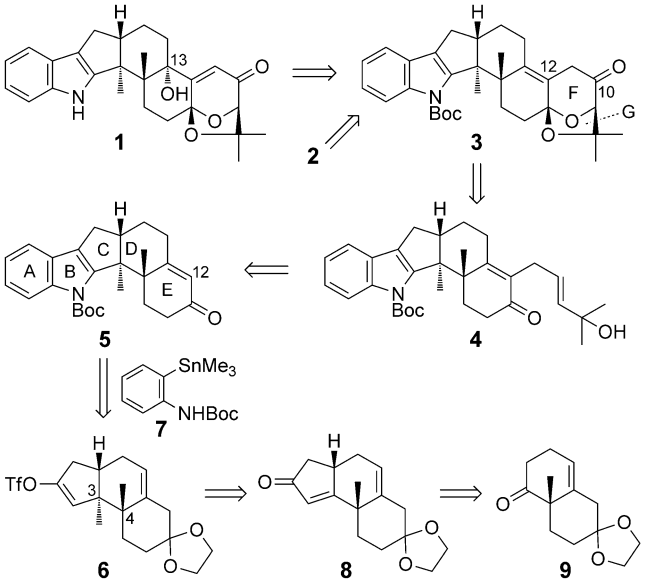
Paspalinine (**1**) and paspalicine (**2**) produced by the ergot fungus *Claviceps paspali* belong to a large family of natural products, known as indole diterpenoids, that is characterized by a unique hybrid molecular architecture comprising an indole nucleus and a cyclic diterpenoid moiety of high structural diversity (Scheme 1).[1–3] As observed in many



Scheme 1. Structures of paspalinine (**1**) and paspalicine (**2**).

other indole diterpenoids, paspalinine (**1**), which bears a hydroxy group at the C13 position, exhibits mammal toxicity and often causes tremorgenic neurological disorders called "paspalum staggers" in domestic animals when they graze the pasture grass *Paspalum dilatatum* infected with *C. paspali*;[3c,4,5] however, its congener **2**, which lacks the hydroxy function, induces no such symptoms.[1] In addition to tremorgenicity, this family of natural products has a variety of intriguing biological properties, such as insecticidal,[6] mito-inhibitory,[7] and anti-MRSA activities.[8] Owing to their impressive polycyclic ring system as well as the pharmacologically and agriculturally important biological profiles, indole diterpenoids have long become the subject of studies from various aspects including biosynthesis,[9] structure–activity relationship,[1,6] biosynthetic genes,[10] and action mechanism.[11] The total synthesis of indole diterpenoids has also been addressed by many research groups, and a series of extensive studies by Smith and co-workers successfully led to the total syntheses of as many as seven indole diterpenes including **1** and **2**,[12] while synthetic efforts by other groups toward naturally occurring indole diterpenoids have, so far, not yet come to completion.[13,14] In their total synthesis of **1** and **2**,[12b–d] the Smith research group achieved highly stereoselective construction of a *trans-anti-trans* CDE ring intermediate containing the C3/C4 contiguous quaternary stereocenters (one of the most challenging tasks for the total synthesis of indole diterpenoids), but required a considerably lengthy multistep sequence from a protected form of the Wieland–Miescher ketone to obtain the tricyclic fused ring system. We describe herein a novel total synthesis of paspalinine (**1**) together with a formal synthesis of paspalicine (**2**) that features not only a concise stereoselective formation of the CDE ring system but also a high-yielding convenient installation of the indole moiety and an efficient introduction of the C13 tertiary hydroxy group through allylic selenoxide rearrangement.

Scheme 2 outlines our retrosynthetic analysis of **1** and **2**. Paspalinine (**1**) possessing the C13 hydroxy group would be derived by oxidative migration of the C12/C13 double bond of



Scheme 2. Retrosynthetic analysis of **1** and **2**. Boc = *tert*-butoxycarbonyl, Tf = trifluoromethanesulfonyl.

the β,γ-unsaturated ketone **3** followed by removal of the N-Boc protecting group on the indole ring, while paspalicine (**2**), which is devoid of the hydroxy group, should also be obtained from the common precursor **3** by N-Boc deprotection and conjugation of the double bond with the C10 carbonyl. The construction of the FG ring moiety of **3** would be achievable through oxidation of the double bond on the side chain of **4**

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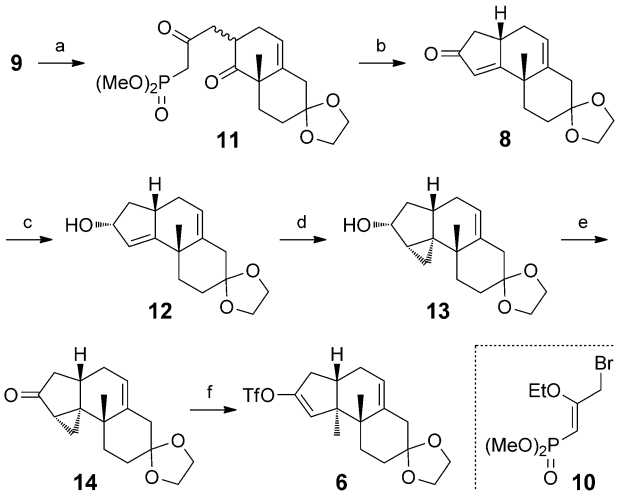
and subsequent intramolecular bicyclic acetal formation. To obtain **4**, we planned to regioselectively introduce an appropriate side chain fragment at the C12 position of pentacyclic ring system **5**. For the construction of the A–E ring core structure **5**, we envisaged a two-step protocol consisting of the Stille coupling of triflate **6** with aniline derivative **7** and oxidative cyclization of the resulting coupling product to form the indole ring. The enol triflate **6**, bearing two contiguous methyl groups at the C3 and C4 quaternary carbon atoms in *trans* fashion, was considered to be obtainable from enone **8**, which would readily be prepared from known bicyclic ketone **9**.

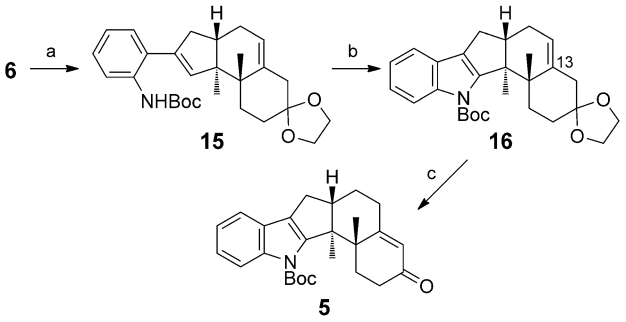
Our two-step preparation of the tricyclic enone **8** from **9** and its highly stereoselective elaboration into the CDE segment **6** in four steps is delineated in Scheme 3. The known starting material **9**, prepared from the (+)-Wieland–



Scheme 3. Preparation of CDE ring portion **6**. Reagents and conditions: a) LDA, **10**, HMPA, THF, −78 °C→room temperature, then aq HCl (1 M), acetone, room temperature, 68 %; b) Cs_2CO_3, THF, 50 °C, 77 %; c) $LiB(sBu)_3H$, THF, −40 °C→room temperature, 99 %; d) CH_2I_2, Et_2Zn, CH_2Cl_2, 0 °C; e) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −75 to 0 °C, 77 % (2 steps); f) $Na(C_{10}H_8)$, THF, −75 °C, then isoprene, Comins' reagent, HMPA, THF, −75 to −10 °C, 42 %. LDA = lithium diisopropylamide, HMPA = hexamethylphosphoramide.

Miescher ketone (> 99 % *ee*) by slightly modifying Smith's procedure,[12b,d] was alkylated with bromide **10**,[15] and the enol ether moiety of the resulting product was chemoselectively hydrolyzed in one pot to give **11** as an epimeric mixture. Exposure of the mixture to intramolecular Horner–Wadsworth–Emmons olefination conditions brought about a stereoconvergent cyclization to afford **8** as a single diastereomer. Reduction of **8** with L-Selectride proceeded highly stereoselectively, thereby giving **12** in an excellent yield of 99 %; the stereochemistry of **12** was established by observing diagnostic NOE correlations (see the Supporting Information). The allylic alcohol **12** was subjected to hydroxy-directed Simmons–Smith cyclopropanation to afford **13** as a single diastereomer,[16] which was then oxidized to cyclopropyl ketone **14** in 77 % yield for the two steps. Reductive cleavage of the cyclopropane ring of **14** with sodium naphthalenide in THF and subsequent in situ trapping of the resulting enolate intermediate with the Comins' reagent furnished the desired triflate **6** with the C3 and C4 quaternary stereocenters correctly installed.[17,18]

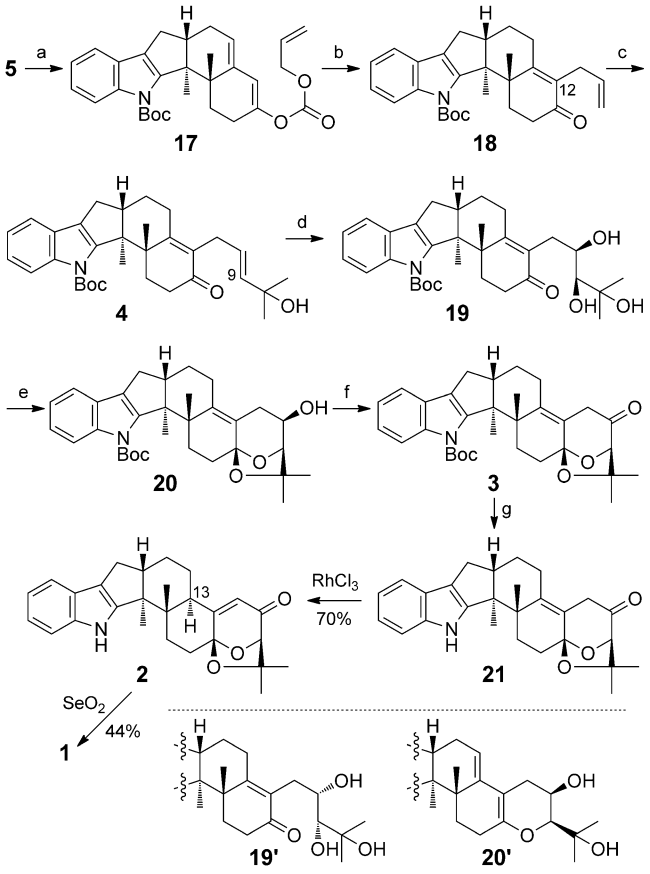
The installation of the indole ring portion was performed by an efficient two-step sequence (Scheme 4). First, the enol triflate **6** was subjected to the Stille coupling reaction with the



Scheme 4. Construction of A–E ring moiety **5**. Reagents and conditions: a) $[Pd(PPh_3)_4]$, CuCl, LiCl, DMSO, **7**, 50 °C, quant; b) $Pd(OCOCF_3)_2$, NaOAc, DMSO, 60 °C, 90 %; c) aq HCl (2 M), THF, 45 °C, 93 %.

o-stannylated aniline derivative **7** under Corey's conditions to give **15** quantitatively.[19–21] The *o*-alkenyl aniline derivative **15** was then treated with $Pd(OCOCF_3)_2$ in DMSO at 60 °C for 24 h in the presence of sodium acetate to successfully furnish **16** embedded with an indole ring in 90 % yield.[22] This type of Pd^{II}-mediated indole ring formation from *o*-alkenyl aniline derivatives has sparsely been documented for preparing much simpler indole derivatives with no substituent at the 2- and 3-positions of the indole nucleus,[23] and has never been applied to the total synthesis of complex natural products.[24–26] Finally, selective removal of the acetal protecting group with hydrochloric acid accompanied by concomitant migration of the C13–C14 double bond gave the conjugated enone **5**.

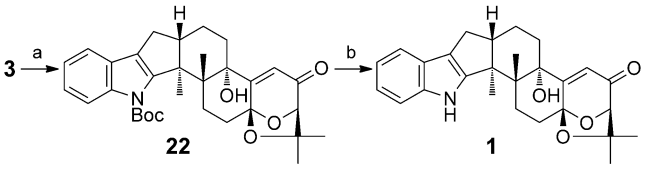
After having achieved the concise nine-step preparation of the pentacyclic core intermediate **5** from the Wieland–Miescher ketone derivative **9**, we set about the construction of the bicyclic FG ring moiety (Scheme 5). At first, an allyl group was regioselectively installed at the C12 position of the enone **5** by Tsuji's palladium-catalyzed allylation protocol to afford **18** via carbonate **17**.[13d,27] Chain elongation of **18** by cross-metathesis with 2-methyl-3-buten-2-ol proceeded uneventfully, thus giving tertiary allylic alcohol **4**. Based on some successful precedents of highly enantioselective dihydroxylation of achiral tertiary allylic alcohols,[28] we anticipated that subjection of **4** to the asymmetric dihydroxylation protocol would give rise to **19** with a high level of diastereoselectivity. Contrary to our expectation, however, the facial selectivity of the dihydroxylation in this particular case proved to be modest, thus providing an inseparable 62:38 mixture of the desired product **19** and its diastereomer **19'** in 64 % yield (86 % based on recovered **4**).[29] Treatment of the mixture with 2,4,6-collidinium *p*-toluenesulfonate in methanol afforded a 4:1 mixture of desired cyclic acetal **20** and the



Scheme 5. Formal synthesis of paspalicine (**2**) and paspalinine (**1**). Reagents and conditions: a) *t*BuOK, Alloc-Cl, THF, room temperature; b) $[Pd(PPh_3)_4]$, Ph_3P, DME, room temperature, then DBU, room temperature, 72% (2 steps); c) $CH_2{=}CHC(OH)Me_2$, Grubbs' 2nd generation catalyst, CH_2Cl_2, reflux, 78%; d) $K_2OsO_2(OH)_4$, $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, $NaHCO_3$, *t*BuOH/H_2O, 15 °C, 64% (62:38 mixture of **19** and **19′**, 86% based on recovered starting material); e) CPTS, MeOH, 5 °C, 49% (4:1 mixture of **20** and **20′**); f) DMP, $NaHCO_3$, CH_2Cl_2, room temperature, 71%; g) SiO_2, ca. 133 Pa, 90–100 °C, 71%. Alloc = allyloxycarbonyl, DME = 1,2-dimethoxyethane, DBU = 1,8-diazabicyclo[5.4.0]undec-7ene, $(DHQD)_2PHAL$ = bis(dihydroquinidino)phthalazine, CPTS = 2,4,6-collidinum *p*-toluenesulfonate, DMP = Dess–Martin periodinane.

corresponding enol ether form **20'** (49% yield). Interestingly, this bicyclic ring formation took place preferentially for **19**, and a substantial amount of its diastereomer **19′** was recovered unchanged. Oxidation of the mixture of **20** and **20′** with the Dess–Martin periodinane afforded ketone **3** in 71% yield after chromatographic purification. In view of the potential acid lability of the allylic acetal unit in the FG ring of **3**, removal of the N-Boc protecting group was conducted by heating **3** adsorbed on SiO_2 in vacuo,[30] thereby furnishing **21** in 71% yield, the ^1H and ^{13}C NMR spectral data of which were identical with those reported by Smith and co-workers.[12d] Since the β,γ-unsaturated ketone **21** has previously been transformed into paspalicine (**2**) and paspalinine (**1**; Scheme 5),[12d] the present synthesis of **21** constitutes a formal total synthesis of **1** and **2**.

Although we have succeeded in the formal total synthesis of paspalinine (**1**) as described above, we decided to explore a more efficient route for the conversion of the intermediate **3** into **1**, since the oxidative migration of the double bond of **21** to give **1** by Smith and co-workers required two steps, resulting in a modest yield of 31% (see Scheme 5). To our delight, treatment of **3** with KHMDS in THF and subsequent enolate trapping with PhSeCl gave an α-selenenylated ketone intermediate, which, upon in situ exposure to hydrogen peroxide, underwent oxidation to the corresponding selenoxide followed by concomitant [2,3]-sigmatropic rearrangement to furnish **22** in an acceptable yield of 57% (Scheme 6).[31] Finally, removal of the Boc protecting group in 67% yield completed our efficient total synthesis of paspalinine (**1**), the spectral data of which showed good agreement with those reported by Smith and co-workers.[12d]



Scheme 6. Completion of the total synthesis of paspalinine (**1**). Reagents and coditions: a) KHMDS, PhSeCl, THF, −70 to −15 °C, then aq H_2O_2, $NaHCO_3$, room temperature, 57%; b) SiO_2, ca. 133 Pa, 90–110 °C, 67%. KHMDS = potassium hexamethyldisilazide.

In conclusion, the concise total synthesis of paspalinine (**1**), which required only two protecting groups, was accomplished from the known Wieland–Miescher ketone derivative **9** by the seventeen-step sequence (0.67% overall yield)[32] that features the efficient introduction of the C3 quaternary methyl group *trans* to the C4 methyl group through the hydroxy-directed cyclopropanation of the allylic alcohol **12**, the palladium-mediated two-step indole ring formation leading to the A–E ring moiety **5** in high yield, and the one-pot installation of the C13 tertiary hydroxy group through allylic selenoxide [2,3]-sigmatropic rearrangement. The ready access to **5** (14% overall yield from **9** in nine steps), which is a common structural motif in all paspalane-type indole diterpenoids, would facilitate synthetic endeavors toward other natural products of the paspalane family with complex molecular architectures as well as important biological activities.

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[17] Compound **8** had previously been prepared by an alternative three-step sequence from **9** by Saxton et al. and successfully transformed into the keto form of **6** via **14** by a four-step protocol analogous to that in Scheme 3, although their attempt to trap an enolate anion generated by dissolving-metal reduction (Li, liq. NH_3) of **14** with the intention of obtaining the corresponding α-substituted ketone derivatives such as α-halo ketones was not realized. For details, see Ref. [13a].
[18] We also attempted direct conversion of **8** into **6** by conjugate addition of a methyl anion species to **8** followed by trapping of the resulting enolate as the triflate **6**. As anticipated from undesirable results reported by Saxton et al.,[13a] however, this endeavor was unsuccessful owing to the almost complete inertness of the enone **8** to such conjugate addition conditions as Me_2CuLi/Et_2O-THF and $Me_2Zn/[Ni(acac)_2]/Et_2O$.[12b]
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