Communication

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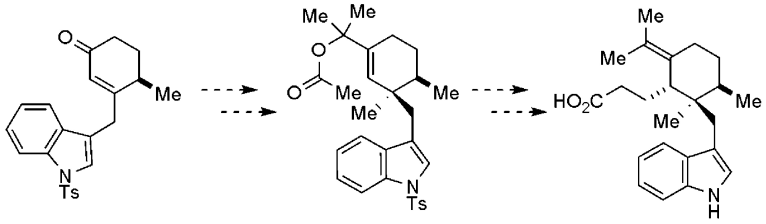

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Total Synthesis of (+)-Suaveolindole: Establishment of Its Absolute Configuration

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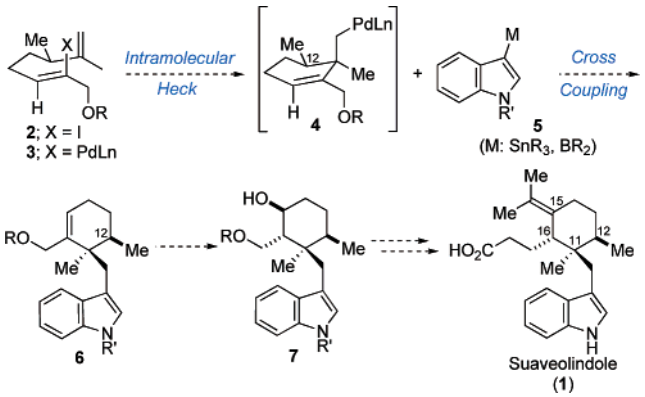
Historically, small molecule natural products (SMNPs) as well as structures derived from or inspired by SMNPs have played a large role in the discovery of novel antibiotics to improve human health.[1] One need go no further than β-lactams (cf. penicillin and cephalosporin), aminoglycosides (the streptomycin family), macrolides (cf. erythromycin and its congeners), anthracyclines (cf. tetracyclines), and vancomycin to establish this point. With the apparent curtailment of pharma's commitment to SMNP discovery platforms, there have come fewer new antibiotic leads for optimization. It was in this setting that our group took an interest in the indolic isoprenoid, suaveolindole (**1**). Isolated in microgram quantities from the fruit of the plant *Greenwayodendron suaveolens*, suaveolindole demonstrates activity against the gram-positive bacteria *Bacillus subtilis* (MIC 4 μg/mL), *Staphylococcus aureus* (MIC 8 μg/mL), and methicillin-resistant *S. aureus* (MIC 8 μg/mL).[2] While the antibiotic data reported for **1** are not yet development worthy, its activity against gram-positive bacteria drew our attention. Clearly, increasing concern as to the problem of antibiotic resistance adds urgency to the need for evaluating new candidate structure types for advancement.

While our long-term motivation in identifying **1** as a total-synthesis candidate was that of molecular editing[1] directed to enhancement of its gram-positive antibacterial activity, the novel structure of the natural product encouraged us to explore some unconventional approaches for its synthesis. We began with the thought, first incubated in our lab in 1983, that a substrate represented as **2**, could undergo palladative insertion (see **3**) en route to cyclization (see **4**).[3] Continuing from this line of conjecture, we wondered whether cross-coupling of the initial transient sp^3 species, **4**, with a suitably protected indole, primed at its β-position with a tin- or boron-based moiety (see **5**), would afford **6**. From there, we hoped to reach **1**, possibly via substructure type **7**.

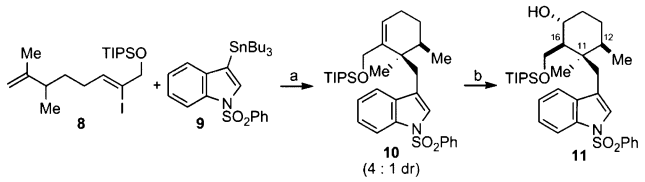
Compound **8** was synthesized as described.[4] Eventually, we arrived at conditions under which it indeed underwent apparent sequential 6-*exo*-Heck cyclization (cf. **4**) followed by sp^3 Stille coupling with stannane **9** to afford a 4:1 mixture of indole **10** and its C_{11} epimer (not shown here).[5] Upon exposure to hydroboration/oxidation conditions,[6] a single stereoisomer was isolated. The relative configuration was determined by NOESY experiments to be that shown in **11**.

The basis for our initial expectations regarding the stereochemistry of the cyclization step (see **3**→**4**) is implied in our rendering of the relevant structures (see Scheme 1). Thus, it was anticipated that the Heck cyclization course would be one in which suprafacial insertion of the palladium carbon σ-bond into the methylene group would have maximum eclipsing overlap.[7] Moreover, the neopentyl metal bond would adopt a "quasi-axial" bias (see **4**), thereby minimizing the allylic A(1,3) strain with respect to the CH_2OR group. It was further hoped that the methyl group at C_{12} would adopt a pre-equatorial disposition. Indeed, these expectations might well have accounted for the actual preference observed in the formation of **10**. However, the selectivity of the process was not high (~4:1), presumably owing to relatively modest "A-value" preferences for a pre-equatorially disposed C_{12} methyl group in this context.

Scheme 1. Original Synthetic Strategy toward Suaveolindole



Scheme 2. Unsuccessful Route toward Suaveolindole[a]



[a] Key: (a) Pd_2dba_3 (2.5 mol %), Ph_3As (5 mol %), Bu_4NCl, DMF, 105 °C, (55%); (b) i) BH_3·THF, ii) $NaBO_3$·$4H_2O$, (56%).

Hydroboration of **10** had led cleanly to **11** as shown (Scheme 2). The double-bond face anti to the indole function was more accessible to attack by the hydroborating agent than was the syn counterpart. Thus, the syn stereochemical relationship between C_{11} and C_{12} is that required to reach **1**. However, the $C_{16}-C_{11}$ stereoconnectivity is inopportune. Moreover, serious difficulties were encountered in preliminary experiments intended to introduce the isopropylidene group at C_{15} from structures derived from **11**. Indeed, we took note of a general paucity of effective methods for installation of tetra-substituted isopropylidene functions exocyclic to a ring in multifunctional settings.[8] In summary then, the key mechanistically driven projections adumbrated in Scheme 1 had been reduced to practice and are likely to be valuable in the future. However, a viable route to suaveolindole itself had eluded us.

The preliminary efforts toward suaveolindole, summarized above, were not without teaching value. They served to focus our thinking around the $C_{11}-C_{15}$ sector and how to achieve the exocyclic isopropylidene pattern while providing the required configurations

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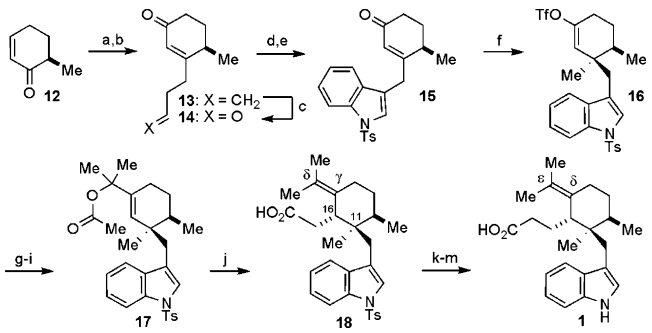
Scheme 3. Synthesis of (+)-Suaveolindole[a]



[a] Key: (a) 4-bromo-1-butene, Mg, THF; (b) PCC, CH_2Cl_2, (47% from **12**); (c) O_3, MeOH, Me_2S, (88%); (d) 2-iodoaniline, $Pd(OAc)_2$ (5 mol %), DABCO, DMF, (68%); (e) TsCl, TBAB, aq NaOH/benzene, (91%); (f) i) CuI, MeLi; ii) $PhNTf_2$, Et_2O/THF; (g) CO, $Pd(PPh_3)_4$, *i*-Pr_2EtN, MeOH/DMF, (45% from **15**); (h) MeLi, Et_2O, (84%); (i) Ac_2O, *i*-Pr_2EtN, DMAP, CH_2Cl_2, (83%); (j) LiHMDS, TMSCl, THF, −78 °C, (56%); (k) i) oxalyl chloride, DMF (cat.), CH_2Cl_2; (ii) CH_2N_2, *i*-Pr_2EtN, THF (62%); (l) CF_3CO_2Ag, Et_3N, THF/H_2O, (74%); (m) naphthalene, Na, DME, (94%).

at carbons 11, 12, and 16. Of course, for drug development purposes, we also sought access to enantiopure material, hopefully without recourse to resolution. The heart of our new plan, at the level of relative stereochemistry, was the thought that perhaps the issue of $C_{11}-C_{16}$ stereoconnectivity could be linked to that of fashioning the exocyclic double bond. This line of inquiry led us to project a fairly bold extension of the Ireland ester enolate rearrangement.[9] We asked whether the incipient nucleophilic carbon of a silyl ketene acetal, derived from the acetate of a tertiary allylic alcohol (e.g., **17**), can deliver its two-carbon carboxymethyl "payload" in acceptable yield to an unsaturated neopentylic carbon (e.g., **18**). By appropriate pattern recognition,[10] we anticipated that the usual γ,δ-olefinic acyl relationship associated with the family of Claisen rearrangements could be converted to the required δ,ϵ-connectivity through a one-carbon homologation (see **18**→**1**). Realization of these notions in the context of a remarkably concise inaugural total synthesis of suaveolindole is set forth in Scheme 3.

We began by modification of a known procedure to generate **13** (Scheme 3).[11] Formation of indole was accomplished by ozonolysis of the terminal olefin of **13** and subsequent annulation of aldehyde **14** with 2-iodoaniline.[12] Following protection of the indole, intermediate **15** was in hand. At this stage, the all-carbon quaternary stereocenter was efficiently installed through conjugate addition of $LiMe_2Cu$ to the enone **15**.[13] Subsequent trapping of the resulting enolate as an enol triflate provided compound **16** in 9:1 dr.

We now turned to the preparation of the Claisen precursor, **17**. The carbon framework for the isopropylidene group was installed in two steps through carbomethoxylation of enol triflate[14] **16** and treatment with excess MeLi. The resulting tertiary allylic alcohol was then acetylated in preparation for the key Ireland−Claisen reaction. In the event, upon treatment of allylic acetate **17** with LiHMDS/TMSCl at −78 °C, the desired rearrangement proceeded smoothly, providing **18** as a single stereoisomer in 56% yield. The stereoselectivity of the reaction likely originates from approach of the intermediate silyl ketene acetal from the α-face of the molecule, thereby minimizing abutments with the indole moiety. The relative stereochemical assignment of **18** was made on the basis of NOESY experiments on the methyl ester derivative.[4] We note that this unprecedented use of the Ireland−Claisen reaction allowed for concurrent formation of the C_{16} stereocenter and the isopropylidene moiety in a single step. Carboxylic acid **18** was then homologated in a two-step Arndt−Eistert sequence, which proceeded in 46% overall yield.[15] Finally, removal of the indole protecting group provided synthetic (+)-suaveolindole (**1**), whose spectroscopic properties (^1H NMR, ^{13}C NMR, optical rotation[16]) are fully consistent with those found for the natural product. In addition, the fully synthetic material exhibits the same type of antibacterial activity as the naturally occurring suaveolindole.[4] Since the synthesis started from a known chiral intermediate (i.e., (*R*)-**12**), we are able to thus assign the absolute configuration of the natural product as shown.[17]

In summary, this communication describes the first total synthesis of (+)-suaveolindole. The concise and efficient nature of the route allows for the synthesis of enantiopure material in significant quantities to support further biological assays and the generation of analogues. Results of these efforts will be described in due course as well as other applications of the logic of this synthesis.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) The absolute configuration of (+)-**1** is (*R*,*R*,*S*) for C_{11}, C_{12}, and C_{16} respectively.

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