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Polyene cyclizations to indole diterpenes. The first synthesis of (+)-emindole SA using a biomimetic approach†

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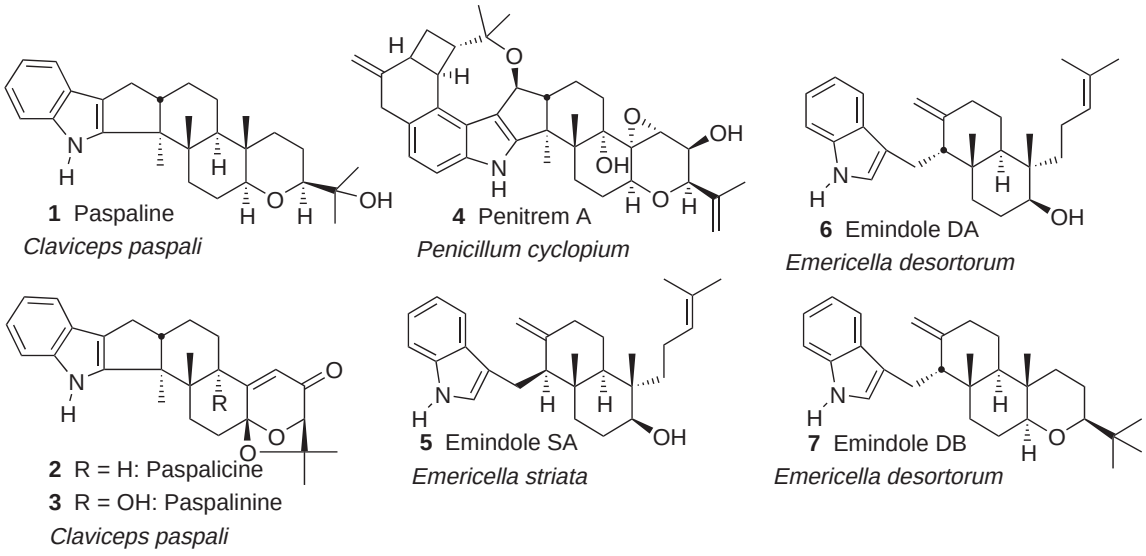
Abstract

A biomimetic synthesis of the indole diterpene emindole SA (**5**) has been achieved via Lewis acid promoted polyene cyclization.

Keywords: indole alkaloids; acid-promoted polyene cyclization; biomimetic synthesis.

Paspaline (**1**) and paspalicine (**2**), the first members of the family of fungal indole diterpenes, were isolated in 1966 by Fehr and Acklin in the Arigoni laboratories from the ergot fungus *Claviceps paspali*.[1] Subsequently, other indole diterpene fungal metabolites having a similar framework were also isolated [cf. paspalinine (**3**)[2] and penitrem A (**4**)[3]] and shown to possess significant tremorgenic activity.



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† This article is dedicated to Professor Harry H. Wasserman, colleague and friend, on the occasion of his 80th birthday.

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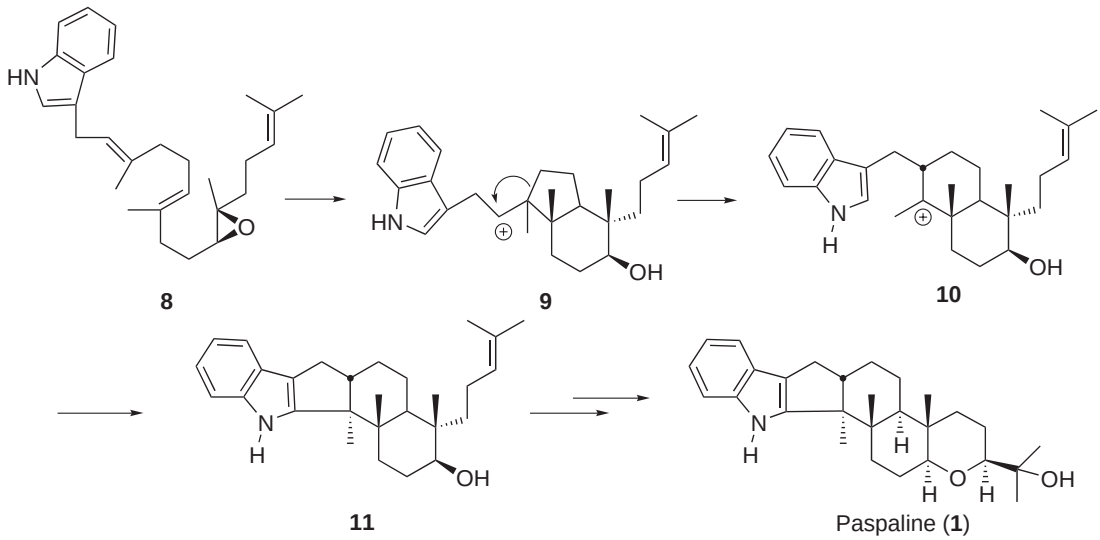
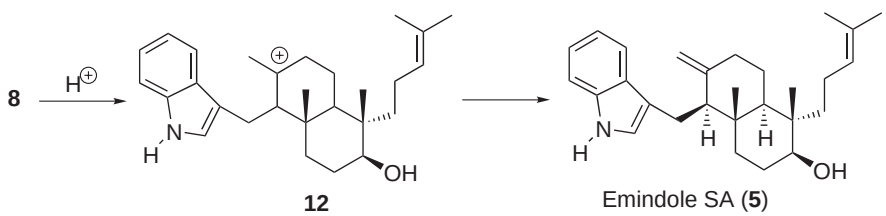
In 1977 Arigoni and coworkers, exploiting ^{13}C labeled intermediates, reported that paspaline (**1**), the common biosynthetic precursor of these metabolites, is formed via condensation of tryptophan and geranylgeranylpyrophosphate.[4] Presumably, subsequent dealkylation of the amino acid side chain and selective epoxidation of the internal olefin provides the polyene cyclization precursor **8**. Transformation of **8** into the paspaline precursor **11** in turn comprises an intriguing process not only involving a polyene cyclization to **9** but also skeletal rearrangement to **10** (Scheme 1).



Scheme 1.

It also appears that fungi are capable of inducing a more conventional polyene cyclization of **8**. After isolating the emindoles SA,[5] DA,[6] and DB[7] in the late 1980s, Kawai and coworkers proposed that these indole diterpenes also arise from **8** but via tertiary carbocation **12** instead of the secondary cation **9** (Scheme 2).[5]

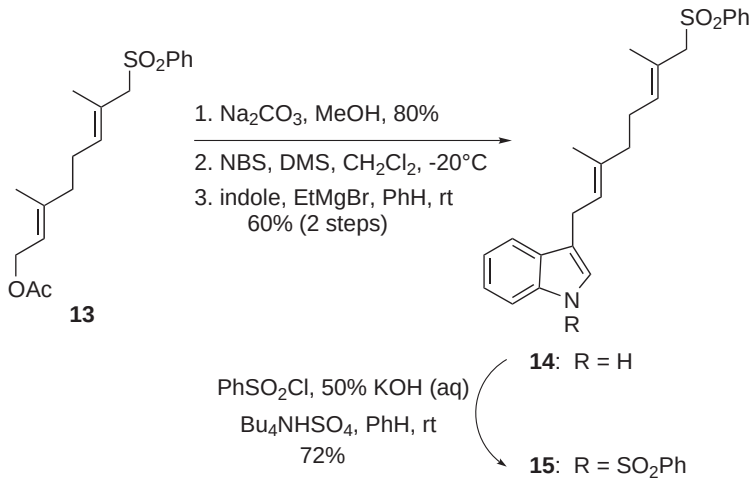


Scheme 2.

Our long standing interest in the chemical synthesis of indole terpenes[8–10] led us to consider a biomimetic approach to these targets. The development of a polyene cyclization approach to both the emindoles and to paspaline would clearly demonstrate the viability of the proposed biosyntheses. In addition, it seemed reasonable that a polyene cyclization of an appropriately functionalized indole diterpene might lead to an efficient entry into this class of natural products.[11] Herein we report our initial experiments in this area, including the first total synthesis of (+)-emindole SA (**5**).

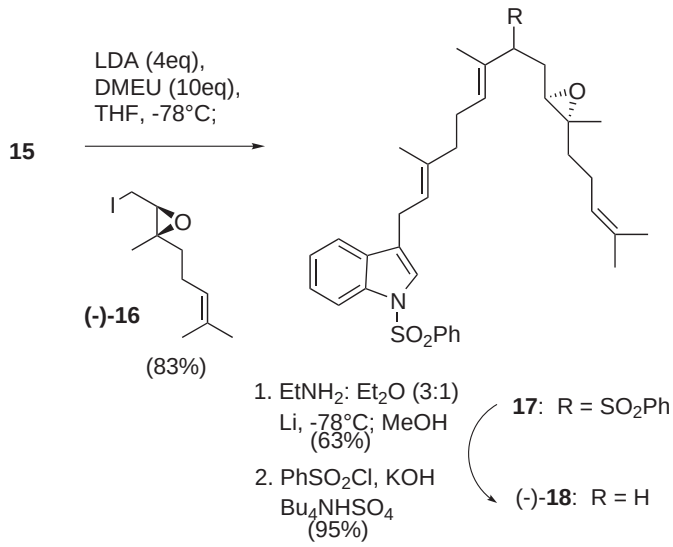
Synthesis of the requisite polyene cyclization precursor (–)-**18** from geraniol is illustrated in Schemes 3 and 4. Noteworthy in the generation of (–)-**18** is the efficient utilization of two molecules of geraniol, the introduction of an epoxide at an internal olefin, and the selective removal of the allylic sulphone in the presence of the epoxide.

Sulphone **13**[12] (Scheme 3) is available in four steps from geranyl acetate. Hydrolysis of the acetate, conversion of the resulting allylic alcohol to the corresponding allylic bromide,[13] and displacement of the bromide with indole magnesium bromide[14] afforded **14**. Protection of the indole nitrogen as the corresponding sulphonamide[15] then provided indole **15** in 34% overall yield for the four steps.



Scheme 3.

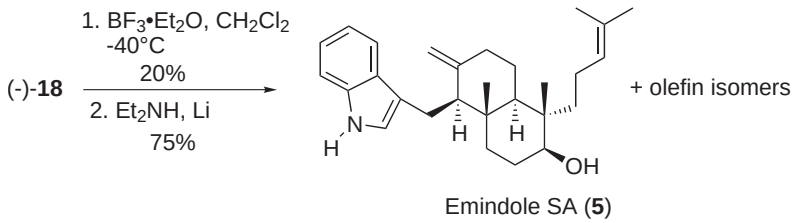
The anionic coupling of **15** with iodo epoxide (–)-**16** (available in three steps from geraniol)[16] afforded a 1:1 mixture of sulphone diastereomers **17** in 83% yield (Scheme 4). The use of DMEU



Scheme 4.

in this coupling proved essential, as the absence led to a dramatic reduction in yield (15% yield). Reductive removal[17] of both the indole and allylic phenyl sulphone groups in the presence of the epoxide provided the polyene cyclization precursor (−)-**18** in 60% yield, after reprotection of the indole. When the reduction was carried out in the absence of ether (i.e. neat $EtNH_2$) or at temperatures higher than −78°C, competitive reduction of the epoxide occurred.

With ready access to polyene (−)-**18**, we investigated a wide variety of acidic conditions to effect cyclization. Our best results were achieved with stoichiometric quantities of $BF_3{\cdot}Et_2O$ at −40°C in CH_2Cl_2. These conditions led to a modest 20% yield of inseparable bicyclic material.[18] Upon removal of the phenyl sulphonyl protecting group, the mixture could be separated to provide emindole SA (**5**) in 8% yield for the two steps.[19] Importantly, an additional 50% of the bicyclic material consisted of two isomeric compounds (ca. 1:1), which have tentatively been assigned as the endocyclic alkene isomers (Scheme 5).



Scheme 5.

In summary, this study indicates that polyene cyclizations can be used to access indole diterpenes, although at present the yield is modest. Further studies on this biomimetic process including investigations of cyclizations leading to paspaline and emindole DA, and efforts to improve the yield of polycyclic material are ongoing in our laboratory.

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18. Other regimes of Lewis acids, temperatures, and solvents led to lower yields and often included significant quantities of monocyclic materials.
19. Synthetic (+)-emindole SA (**5**) was identical [TLC, ^{1}H and ^{13}C NMR, UV, IR, and mass spectral analyses, and optical rotation $[\alpha]_D^{20}$ +30.2 (*c* 0.14, CH_3OH); lit.[2] $[\alpha]_D^{20}$ +32.0 (*c* 1.0, CH_3OH)] with an authentic sample generously provided by Professor Kawai (Hoshi University).