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A Novel Approach to Indoloditerpenes by Nazarov Photocyclization: Synthesis and Biological Investigations of Terpendole E Analogues

Fátima Churruca,[†] Manolis Fousteris,[†,‡] Yuichi Ishikawa,[†,⊥] Margarete von Wantoch Rekowski,[†] Candide Hounsou,[§] Thomas Surrey,[§] and Athanassios Giannis*[,†]

Department of Chemistry and Mineralogy, Institute of Organic Chemistry, University of Leipzig, Johannisallee 29, 04103 Leipzig, Germany, and European Molecular Biology Laboratory, Cell Biology and Biophysics Programme, Meyerhofstrasse 1, 69117 Heidelberg, Germany

giannis@uni-leipzig.de

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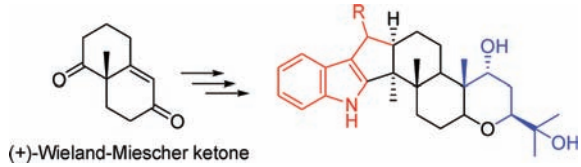
ABSTRACT



The application of the Nazarov photocyclization as a mild and efficient method for access to the basic core of novel indoloditerpenoid derivatives is reported. The detailed synthesis of these new analogues of terpendole E, as well as their evaluation as potential inhibitors of KSP, is described.

The kinesin spindle protein (KSP, also known as Eg5) is a protein exclusively active in mitosis and essential for the assembly and stabilization of the bipolar mitotic spindle.[1] Inhibition of KSP results in cell cycle arrest and apoptosis while other microtubule-dependent processes remain unaffected. Thus, KSP inhibition represents a novel and specific strategy of targeting the mitotic spindle. Since the discovery of monastrol, the first specific KSP inhibitor,[2] many new small molecule modulators of KSP have been developed and some of them are currently undergoing clinical studies.[3] However, there are only two natural products identified as KSP inhibitors, adociasulfate-2[4] and terpendole E[5] (Scheme 1).

Terpendoles are a family of fungal indoloditerpenes[6] isolated from the culture broth of a soil-isolated fungus *Albophoma yamanashiensis* and they showed weak to

[†] University of Leipzig.
[‡] Present address: Department of Pharmacy, Laboratory of Medicinal Chemistry, University of Patras, 26500 Rion-Patras, Greece.
[§] European Molecular Biology Laboratory.
[⊥] Present address: Department of Chemistry, Faculty of Science and Technology, Keio University, Hiyoshi 3-14-1, Kohoku-ku, Yokohama 223-8522, Japan.

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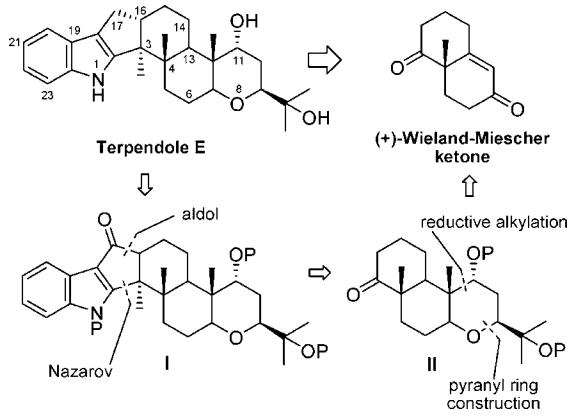
Scheme 1. Retrosynthetic Analysis



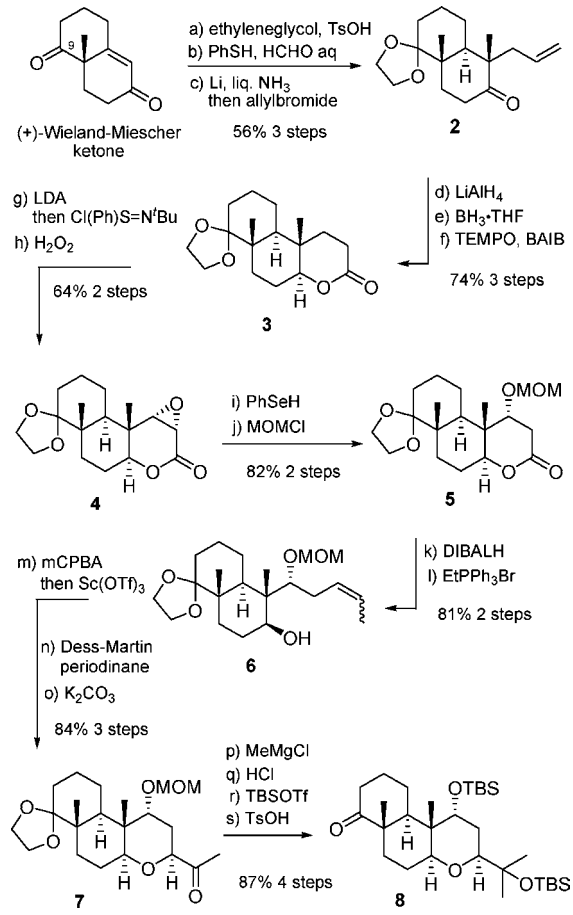
moderate biological activity as acyl-CoA:cholesterol acyltransferase (ACAT) inhibitors[7] and as tremorgens.[8] Nevertheless, terpendole E was rediscovered as a novel KSP inhibitor by Osada and co-workers in 2003.[5] The unique biological profile and challenging structural features of terpendole E elicited our interest toward the synthesis of the parental compound as well as structurally resembling derivatives in order to investigate their potential KSP inhibitory activity.

Several reports have been published on the total synthesis of indole-diterpene natural products, in which different entries to their basic core have been described.[9] We envisaged an alternative synthetic strategy (Scheme 1) for the generation of the indoloditerpene skeleton that involves a Nazarov cyclization as a key step,[10] a well-established reaction that nevertheless has never been applied to the construction of this natural product scaffold. The advantage of this approach is that cyclopentanone **I** represents an important intermediate for the synthesis of new indoloditerpenoid analogues via functionalization of the C-17 carbonyl group. Cyclopentanone **I** was envisioned as a straightforward fragment assembly derived from the coupling of an easily accessible indole derivative with the ketone **II** in an aldol reaction/elimination sequence. The pyranyl ring construction leading to ketone **I** could be achieved from a suitably functionalized *trans*-decalone, readily available from the (+)-Wieland−Miescher ketone.

Our synthesis began with *trans*-decalone **2**,[9b] a compound that has already been prepared from the (+)-Wieland−Miescher ketone,[11] a very well-known chiral building block in natural products synthesis such as steroids and diterpenes among others.[9,12]

According to the literature,[9b] selective protection of the C-9 carbonyl group in the (+)-Wieland−Miescher ketone was followed by a phenylthiomethylation-reductive alkylation sequence to afford *trans*-decalone **2** (Scheme 2).

Scheme 2. Synthesis of Diterpene **8**



Stereoselective reduction of the carbonyl group with $LiAlH_4$ and hydroboration−oxidation of the terminal alkene with borane−THF complex and H_2O_2 gave a diol, which was treated with TEMPO/BAIB in an intramolecular oxidative cyclization leading to lactone **3** in good yield. The introduction of the 4β-hydroxy group was accomplished chemo- and stereoselectively as follows: After several attempts to oxidize the lactone ring into the corresponding α,β-unsaturated derivative with standard methods such as using $Pd(OAc)_2$,[13] Saegusa oxidation,[14] or IBX,[15] the dehydrogenation of

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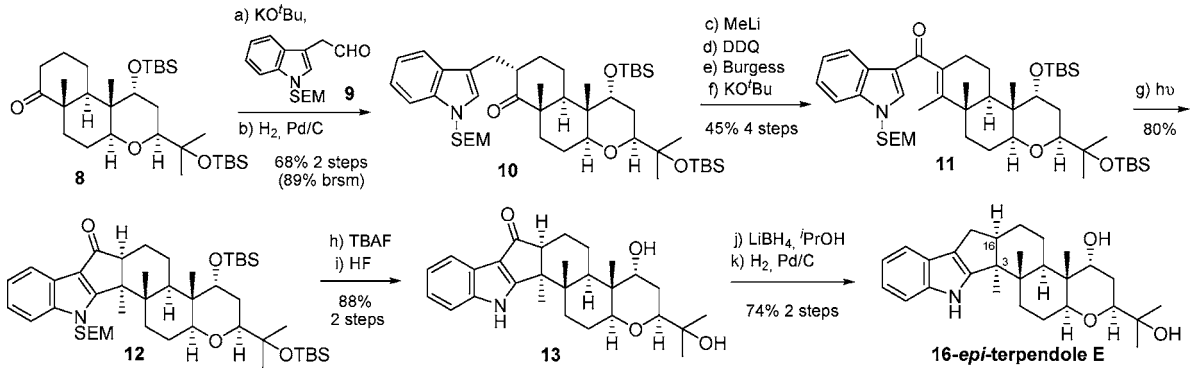
Scheme 3. Synthesis of 16-*epi*-Terpendole E



lactone **3** was successfully achieved by treating the corresponding lithium enolate with *N*-*tert*-butylbenzenesulfinimoyl chloride.[16] Then, epoxidation of the double bond from the less hindered face under mild reaction conditions with H_2O_2 afforded α,β-epoxy lactone **4**. The organoselenium-mediated reduction[17] and consequent ring-opening of the oxirane with in situ generated benzeneselenol (PhSeH) proceeded selectively via α-substitution process to afford the β-hydroxylactone as a single diastereomer, which was then protected with an in situ generated MOMCl.[18] Lactone **5** was selectively reduced with DIBALH to the corresponding lactol, and subsequent Wittig olefination afforded alkene **6** as a mixture of isomers in good yield. Epoxidation of the double bond with *m*CPBA was followed by a Lewis acid-catalyzed intramolecular cyclization to lead to a mixture of pyranyl alcohols which were oxidized with Dess−Martin periodinane. The mixture of pyranyl ketones thus obtained was isomerized with K_2CO_3 in THF−MeOH into the desired compound **7**. This pyranyl ketone **7** was then reacted with MeMgCl before full removal of the protecting groups in HCl−MeOH. Finally, TBS protection of the two alcohols yielded ketone **8**, the suitably substituted diterpene subunit of terpendole E.

With ketone **8** in hand, the access to enone intermediate **11** was conveniently accomplished as follows: The convergent connection between both parts was successfully achieved by the aldol condensation of compound **8** with a readily available SEM-protected indole-3-carbaldehyde **9**.[19] Chemoselective reduction of the carbon−carbon double bond in the so-obtained conjugated enone with H_2 and Pd/C gave the desired ketone **10** as a single diastereomer in good yield (89% brsm over 2 steps). Its subsequent transformation into enone **11** was completed by the addition of MeLi to the carbonyl group, thus generating a tertiary alcohol, which was treated with DDQ to promote the corresponding allylic oxidation prior to being dehydrated under mild reaction conditions with Burgess reagent. Finally, isomerization of the terminal alkene under basic conditions afforded the desired enone **11** in good yield (Scheme 3).

The possibility of affecting Nazarov cyclization was then examined. Nazarov reaction is a 4π-electrocyclization whose synthetic utility has been traditionally compromised by the requirement of strong Lewis or protic acids,[20] quite often in excess, and the lack of torquoselectivity. Nevertheless, recent advances in the field have overcome most of this handicap by the employment of milder Lewis acids[21] and directing functional groups in the substrates.[22] Moreover, the cyclization can also be promoted by light, under mild photochemical conditions, leading in a disrotatory fashion to complementary products.[23] In our case, when we irradiated enone **11** at 350 nm we were delighted to obtain compound **12** as a unique diastereomer[24] in good yield. To study the scope and limits of the Nazarov reaction in indoloditerpenoids, we decided to also test the acid-mediated cyclization conditions, where, in view of the previous results, we were expecting to obtain complementary diastereomeric compounds. To our surprise, a screen of various Lewis and protic acids in different solvents and at several temperatures produced either no reaction or eventual decomposition of our starting material,

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(24) The relative configuration was elucidated by NOE spectroscopic analysis. When H16 was irradiated, a NOE enhancement was observed for C3-Me and not for C4-Me.

accompanied by the loss of the protecting groups. The failure of the reactions could be attributed to the steric hindrance derived from the substitution of the enone.[25]

Having successfully constructed the indoloditerpenoid derivate **12**, we next proceeded to the removal of the silicon protecting groups affording compound **13** in good yield. It should be noticed that compared to indole diterpene alkaloids, the configuration of the C-16 stereocenter in **13** is inverted.[24] Initial efforts to isomerize the corresponding enolizable proton were attempted under basic conditions, and to our surprise, derivate **13** was recovered as a unique diastereomer. In view of these results, which suggest that the most stable isomer is the complementary one compared to natural indoloditerpenes, we were very interested in the biological evaluation of this new derivative, unnaturally occurring and of difficult access by standard synthetic routes.[6,7] Moreover, the corresponding C-16-epimer of terpendole E was effectively obtained by the full reduction of the carbonyl group with lithium borohydride followed by H_2 and Pd/C.

Hence, the evaluation of the KSP inhibitory activity of the new derivatives **13** and 16-*epi*-epiterpendole E was consequently performed by using an in vivo steady-state ATPase assay.[26] Neither of these compounds proved to be active, showing that the absolute configuration of the terpendole E skeleton is essential for the inhibitory activity against KSP.

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In summary, we have successfully developed a new synthetic approach to accomplish the construction of the indole diterpene skeleton based on a Nazarov-photocyclization reaction. The mildness of the reaction conditions and the selective activation of the enone system allowed the facile transformation of the key intermediate **11**. The obtained indoloditerpene derivative **12**, which possesses a characteristic carbonyl group and is difficult to achieve with already described methods,[6,7] is suitable for further transformation and synthesis of new indoloditerpenoid derivatives. Biological evaluation of both compound **13** and 16-*epi*-terpendole E revealed that the correct configuration of the C-16 is crucial for the maintenance of the KSP inhibitory activity.

Further studies focused on epimerization of this C-16 center in **12** as well as the preparation of additional analogues by the functionalization of the C-17 carbonyl group are currently in progress, and will be reported in due course.

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Supporting Information Available: Experimental procedures, compound characterization, ^{1}H NMR and ^{13}C NMR data for all new compounds, and NOE difference spectra for compound **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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