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Synthesis of the indeno[1,2-*b*]indole core of janthitrem B†

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The tetracyclic core structure of the majority of indole diterpenoids features a *trans*-hydrindane moiety that is fused to an indole unit. We report here a novel synthetic route that includes a photo-Nazarov cyclization of a 3-acylindole precursor initially providing the thermodynamically preferred *cis*-hydrindanone. After reduction and conversion to the cyclopentadiene, dihydroxylation and hydrogenation provided the indoline. The key step generated the *trans*-system by stereospecific hydride shift on a dioxaphospholane under Grainger's conditions, for the first time applied to an N-heterocycle. When starting from the corresponding indole, we observed the formation of hitherto unknown methanocyclohepta[*b*]indolones. Deoxygenation of the *trans*-hydrindanone was achieved after conversion to the 1,3-dithiolane, followed by RANEY® Ni reduction.

Introduction

Indole diterpenoids constitute a prominent class of fungal natural products.[1] The core structure of most of the indole diterpenoids is characterized by an indole unit to which is anellated a tri- or tetracyclic terpenoid moiety. Since the indole diterpenoids exhibit versatile biological activities such as tremorgenic,[2] anticancer,[3] anti-insect,[4] and antimicrobial[5] effects, their synthesis is of prime importance for the development of new drugs. Much of the biological data need further analysis, which requires independent routes to the compounds themselves and to derivatives.

Recently, we reported the synthesis of the ABCD tetracyclic part of janthitrem B (**1**), which required the functionalization of the benzene section of the indole core.[6] That particular moiety also occurs in shearinine D, of which the Carreira group recently reported an elegant total synthesis.[7] Common to a larger part of the indole diterpenoid family is the tetracyclic indeno[1,2-*b*]indole partial structure highlighted in Fig. 1, which is found frequently among the nodulisporic acids, paspalines, paxillines, terpendoles, shearinines, janthitrems, and lolitrems. A *trans*-indane moiety is present that seems to be necessary for biological activity. For instance, Giannis and coworkers[8] showed that the *cis*-fused isomer of terpendole E lost the KSP inhibitory activity of the *trans*-fused natural product.

Most of the existing routes to indole diterpenoids assemble the pyrrole section of the indole part after having constructed *trans*-indane unit. In 1986, the Smith group reported the cyclization of an aldehyde function onto the indole 3-position affording a *trans*-fused indeno[1,2-*b*]indole by treatment with $HNMe_2$ in dioxane, presumably *via* the corresponding iminium ion.[9a] In later work, the Smith group turned to Gassman, Madelung, or Barluenga indole syntheses, *e.g.* in the total syntheses of paspaline, nodulisporic acids, and penitrem.[9b–d]

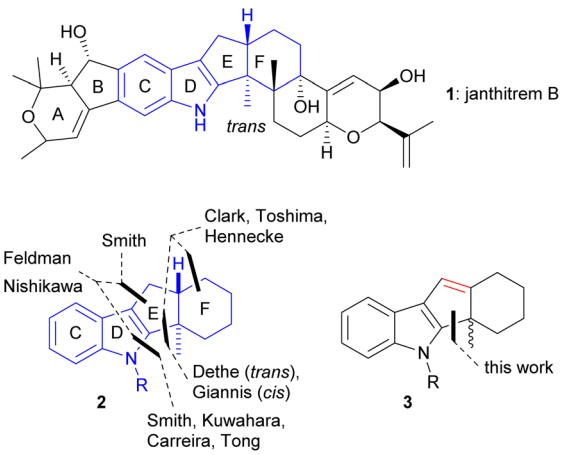

Fig. 1 CDEF core structure present in the majority of indole diterpenoids, earlier approaches to the tetracycle, cyclopentadiene precursor investigated in this work.

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For the synthesis of the *trans*-indane unit itself, several routes exist. In their total synthesis of shearinine G and paspalicine, the Carreira and Tong groups, respectively, assemble the *trans*-indane moiety by one-electron reduction of hydrogenated cyclopropa[*c*]inden-2-ones, where a cyclopropane ring was installed *trans* to the bridge-head hydrogen. In both routes, the indole section is assembled by subsequent Pd-catalyzed anellation of a protected *o*-stannylaniline to an alkenyltriflate functionality.[7,10] This strategy was developed by Kuwahara in 2012 during their total synthesis of paspalinine.[11] A recent approach to the *trans*-system by Nishikawa and coworkers features a tandem palladium-catalyzed cyclization of an *N*-tosylated *o*-alkynylaniline precursor.[12]

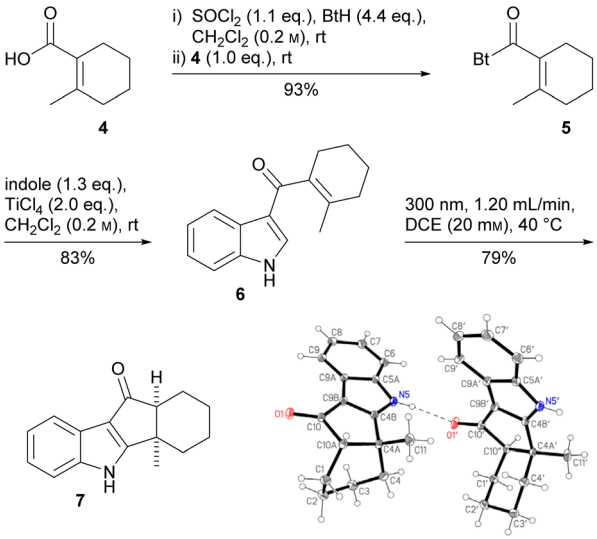
Fewer approaches towards the *trans*-fused indeno[1,2-*b*]indole start from an intact indole. A biomimetic cascade by Toshima and coworkers provided a tetracyclic product in good yield by Lewis-acid-mediated cyclization of 3-(6,7-epoxygeranyl)indole. For sesqui- and diterpenoid analogs, mixtures of products were formed.[13] A similar approach to the *trans*-indeno[1,2-*b*]indole was employed by the Hennecke group, who submitted a 3-geranyl-substituted indole to a bromocyclization with excellent diastereoselectivity and good yield.[14] Feldman and coworkers prepared indeno[1,2-*b*]indole constructs, among them the unprotected indole, by a cyclization cascade of an alkenyl sulfide tethered to a 2-azido-1-allenylbenzene core or by cationic cyclization of a tethered alkenyl sulfide.[15] Dethe and coworkers published the TMSOTf-mediated cyclization of N-free 3-allylated indoles to indeno[1.2-*b*]indoles.[16]

Another option is the use of a photo Nazarov reaction for the assembly of ring E that has been employed to the synthesis of 16-*epi*-terpendole E.[8] The product obtained by Giannis and coworkers suffers from a *cis*-fusion of rings E and F.

In this work, we analyze how this route could be saved by converting the photo Nazarov product to a *trans*-fused indeno[1,2-*b*]indole *via* the cyclopentadiene intermediate **3** (Fig. 1). Our study was encouraged by findings by the Grainger group, who reported the construction of *trans*-hydrindane systems by intramolecular hydride transfer.[17] Indole derivatives were not subjects of these studies.

Results and discussion

First, we had to develop a new, efficient route to the literature-known[18] carboxylic acid **4**, which was obtained in four steps (23% overall yield, 200 mmol scale) from cyclohexanone without requiring column chromatography (see the ESI†). Acid **4** was transformed to acyl benzotriazole **5**, which was used for the selective acylation of indole in the 3-position,[19] affording the desired, new Nazarov precursor **6** (Scheme 1). Dialkenyl ketone **6** underwent smooth photo-Nazarov cyclization (79%), yielding the *cis*-hydrindanone **7** diastereoselectively. In the crystal, two conformers are present in a 1 : 1 ratio. The *cis*-hydrindanone is more stable than the desired *trans*-isomer.[20] The photochemical conditions lead to an isomerization of the cyclohexene double bond to the strained (*E*)-alkene, which



Scheme 1 Synthesis of *cis*-hydrindanone **7** and its crystal structure.

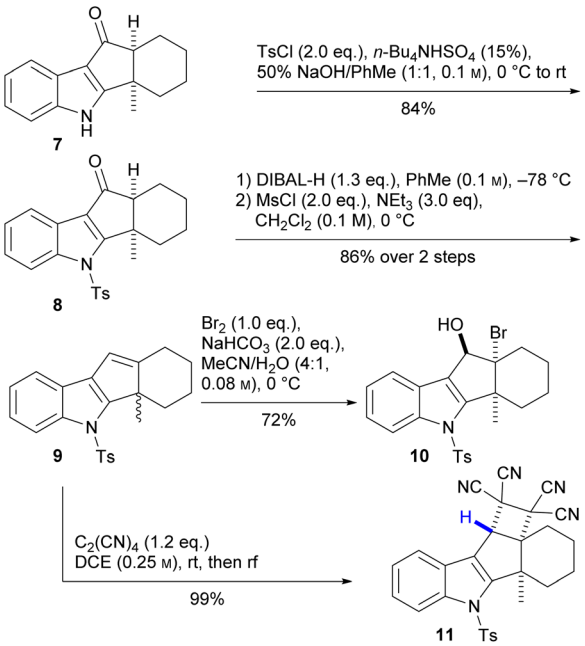
allows the subsequent 4π electrocyclization without the need for further activation of the carbonyl group.[21] Surprisingly, it was not possible to reduce the keto function, a vinylogous amide, of **7** to the secondary alcohol, as had been achieved with $LiBH_4$/*i*-PrOH in course of the total synthesis of *epi*-terpindole E.[8] Since we suspected the indole NH to be responsible, we also synthesized the *N*-methylated analog of **7** (see the ESI†). Unfortunately, we could not functionalize this either.

We synthesized a number of 3-allylated indoles that did not contain the vinylogous amide present in precursor **6**. Unfortunately, all our attempts to induce cyclization to the desired tetracyclic systems were unsuccessful (see the ESI† for details).

We then returned to our successful Nazarov cyclization providing *cis*-hydrindanone **7**. We were able to tosylate indole **7**, rendering the vinylogous amide more electrophilic (Scheme 2). Gratifyingly, reduction of **8** with DIBAL-H afforded a mixture of diastereomeric alcohols in high yield. Elimination ($MsCl/NEt_3$) finally gave cyclopentadiene **9** (86% from **8**).

We considered structure **9** as a versatile synthetic intermediate and probed its reactivity. Exposure of **9** to bromine in water afforded bromohydrin **10**. The bromine is introduced from the same face as the methyl group of **9** (NOESY analysis). Reaction of cyclopentadiene **9** with tetracyanoethylene afforded cyclobutane **11** in a formal [2 + 2] cycloaddition, which probably proceeds *via* radical intermediates and has been described for 3-vinylindoles.[22] The tetracyanoethylene is added on the side of the methyl group (NOESY analysis). Importantly, these reactions identify the sterically less hindered face of the tetracyclic indeno[1,2-*b*]indole **9**, predicting *cis*-diastereoselectivity of other additions to that double bond.

The cycloaddition forming **11** puts the methine hydrogen in a position opposite to the methyl group. Therefore, to achieve the desired *trans*-fusion, we turned to a [1,2]-hydride shift strategy. The methine hydrogen of other cycloaddition products of **9** could potentially be shifted as hydride to a car-

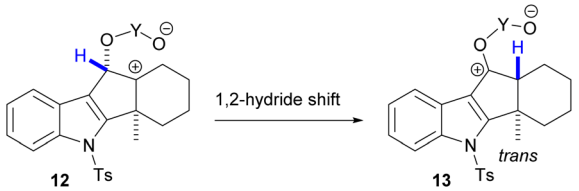


Scheme 2 Synthesis and reactivity probing of the key tetracyclic cyclopentadiene **9**.

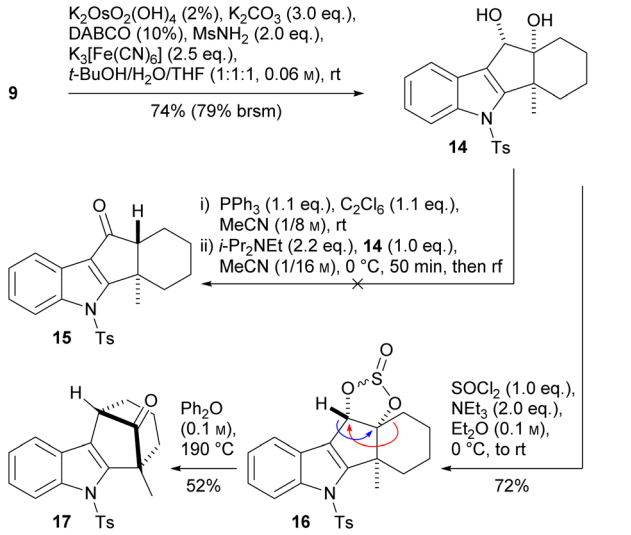
benium ion to be formed at the neighboring bridge-head (**12**, Scheme 3), leading to formation of a *trans*-hydrindane moiety (**13**). Precursors of that carbenium ion would be cyclic sulfites or dioxaphospholanes.

Os-catalyzed dihydroxylation afforded the *cis*-diol **14** with both hydroxy groups pointing to the same face as the methyl group (Scheme 4). In their work on the synthesis of dictyoxetane, Grainger and coworkers[17] reported an interesting phosphorane-mediated, pinacol-like rearrangement of a *cis*-diol *via* a formal 1,2-hydride shift, affording a *trans*-hydrindane. As intermediate, a dioxaphospholane was formed, which opened thermally to the carbenium ion. The method was later used by Baran and coworkers in their synthesis of (+)-calcipotriol.[23] However, when we applied these conditions to indole **14**, we obtained an intractable product mixture.

As alternative, the Grainger group published the use of cyclic sulfites, which were employed for the synthesis of bridged bicyclic lactams.[24] We converted diol **14** to the cyclic sulfite **16** by treatment with $SOCl_2/NEt_3$. Surprisingly, heating the product in diphenyl ether (190 °C) did not result in the desired 1,2-hydride shift (blue arrow) but instead in ring expansion with loss of SO_2.



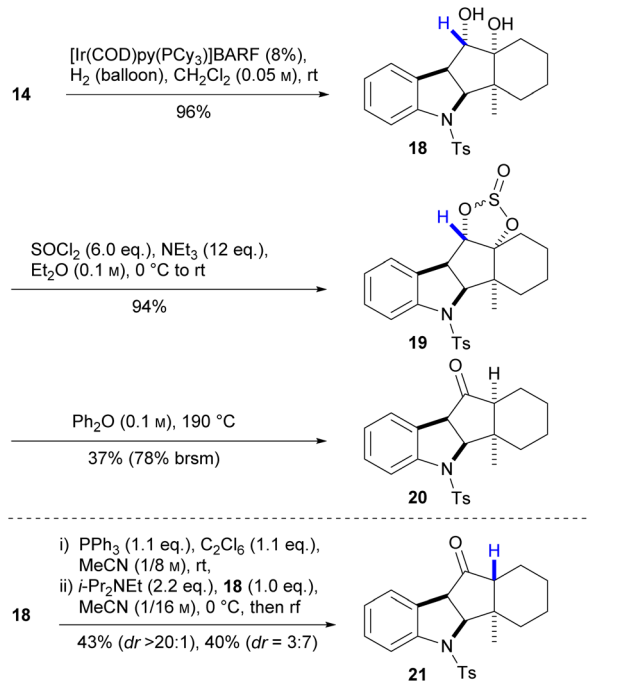
Scheme 3 Envisaged access to the *trans*-hydrindane moiety from a pentacyclic precursor by 1,2-hydride shift.



Scheme 4 Unexpected pinacol rearrangement starting from cyclic sulfite **16**.

It seems that formation of a benzylic carbenium ion outcompetes that of a tertiary carbocation, which undergoes pinacol rearrangement to the [3.2.1] bicyclic partial structure of ketone **17**.

To solve this problem, we switched to indolines. Indole **14** was hydrogenated employing Crabtree's catalyst affording indoline **18** in perfect diastereoselectivity, with both bridge-head hydrogens introduced on the side of the hydroxy groups (Scheme 5). The relative configuration of **18** is based on



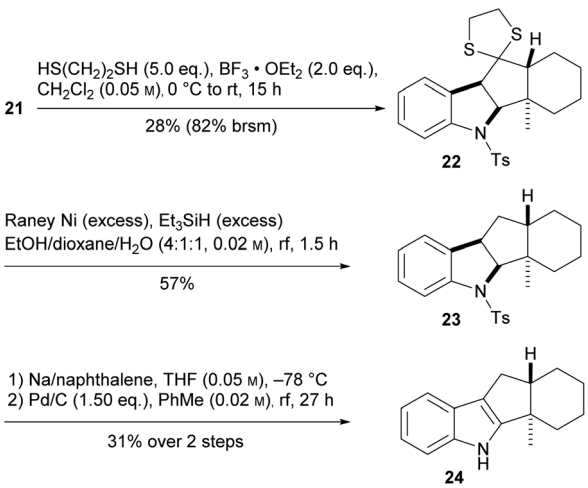
Scheme 5 Synthesis of *cis*- and *trans*-hydrindanones **20** and **21** under Grainger's conditions.

NOESY analyses, which revealed a U-shaped conformation of the tetracyclic core. Diol **18** was converted to the cyclic sulfite **19**. Upon heating of **19** in diphenyl ether (190 °C), conversion was significantly slower than in the case of sulfite **16**. Even after 12 h we recovered 43% of the starting material. We obtained hydrindanone **20** in 37% yield, but, depressingly, with *cis*-fused rings E and F. Apparently, complete epimerization occurred at the α-carbon under the harsh reaction conditions.

Thus, we returned to the use of dioxaphospholane intermediates, which can be removed under milder conditions, even in refluxing MeCN. Treatment of diol **18** first with PPh_3/C_2Cl_6 in MeCN in the presence of Hünig's base and then refluxing (Grainger's conditions) afforded a mixture of *cis*- and *trans*-hydrindanones **20** and **21**. We were able to separate them to some extent by column chromatography and obtained pure *trans*-hydrindanone **21** (43%). Epimerization during silica chromatography could mostly be suppressed by the addition of 1% NEt_3 to the mobile phase.

We studied the deoxygenation of both diastereomeric tetracycles **20** and **21** employing a Barton–McCombie sequence starting from the corresponding secondary alcohols obtained smoothly by reduction with DIBAL-H. In the *cis* case we achieved deoxygenation, but not in the *trans* case (see the ESI† for details). We were neither able to transform the sterically hindered ketone **21** into an alkenyl triflate (LDA/$PhNTf_2$) or a tosyl hydrazone ($TsNHNH_2$).

Deoxygenation of *trans*-compound **21** required the synthesis of a dithioketal. Upon exposure to ethylene dithiol and $BF_3{\cdot}OEt_2$, ketone **21** was converted to dithiolane **22** (Scheme 6). For the sake of diastereospecifity, the reaction was stopped after 15 h, which allowed the isolation of diastereomerically pure dithiolane **22** in 28% yield. We re-isolated 54% of unreacted starting material (*dr* = 20 : 1), which could be used in further batches (82% brsm). Finally, desulfurization with RANEY® nickel afforded the desired *trans*-hydrindane **23**.



Scheme 6 Conversion of *trans*-hydrindanone **21** to the target compound *trans*-hydrindane **24**.

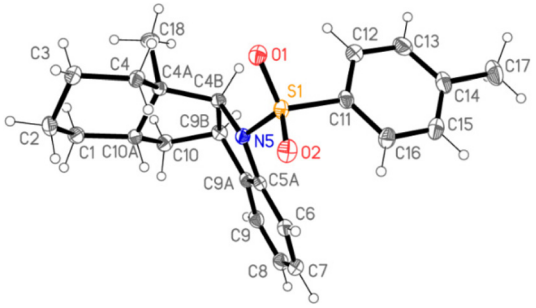


Fig. 2 Crystal structure of *trans*-hydrindane **23**.

The relative configuration of *trans*-hydrindanone **23** was determined by NOESY analysis and proved by single crystal X-ray diffraction analysis (Fig. 2). Tosylindoline **23** was converted to the corresponding indole **24** by detosylation (Na/naphthalene) and dehydrogenation (Pd/C) in 31% yield.

Conclusions

In summary, we have shown that the photo-Nazarov route is a viable approach to *trans*-fused indeno[1,2-*b*]indoles. We were able to overcome the *cis*-selectivity of the initial cyclization of alkenyl indolyl ketone **6** to the cyclopentenone **7** by conversion to the cyclopentadiene, dihydroxylation, reduction to the indoline, and Grainger's hydride shift, for the first time applied to an N-heterocyclic system. When starting from the corresponding indole, we observed the formation of hitherto unknown methanocyclohepta[*b*]indolones. The deoxygenation of *trans*-indanone **21** was possible after conversion to the 1,3-dithiolane, followed by RANEY® Ni reduction. Finally, *trans*-hydrindanone **23** was deprotected by sodium naphthalide and dehydrogenated by palladium on charcoal, giving the *trans*-fused indeno[1,2-*b*]indole **24** (2.5% yield, 12 steps starting from indole).

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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