Natural Product Synthesis

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The Total Synthesis of (−)-Nitidasin**

*Daniel T. Hog, Florian M. E. Huber, Peter Mayer, and Dirk Trauner**

Dedicated to Clayton Heathcock

Abstract: *Nitidasin is a pentacyclic sesterterpenoid with a rare 5-8-6-5 carbon skeleton that was isolated from the Peruvian folk medicine "Hercampuri". It belongs to a small class of sesterterpenoids that feature an isopropyl trans-hydrindane moiety fused to a variety of other ring systems. As a first installment of our general approach toward these natural products, we report the total synthesis of the title compound. Our stereoselective, convergent route involves the addition of a complex alkenyl lithium compound to a trans-hydrindanone, followed by chemoselective epoxidation, ring-closing olefin metathesis, and redox adjustment.*

The Peruvian herbal infusion "Hercampuri", derived from *Gentianella nitida* and *Gentianella alborosea*, has been used since ancient times as a remedy against hepatitis, diabetes, and hypertension.[1] Investigations into its chemical constituents have revealed a variety of bitter phenolic compounds that occur together with a limited number of terpenoids (Figure 1). The most complex of these, the sesterterpenoid nitidasin,[2] features a rare 5-8-6-5 carbon framework, which includes ten stereogenic carbons. The relative configuration of this intriguing natural product was established by extensive NMR studies and X-ray diffraction. Nitiol is a simpler congener that has only undergone partial cyclization,[3] whereas alborosin appears to be an oxidative degradation product of nitidasin.[4]

Nitidasin can also be classified as a sesterterpenoid that features an oxygenated *trans*-hydrindane moiety, the five-membered ring of which bears an isopropyl substituent *cis* to an angular methyl group. Compounds of this type include the unusual fungal metabolite astellatol,[5] as well as YW-3699[6] and YW-3548,[7] two inhibitors of mammalian GPI-anchor biosynthesis (Figure 1). Owing to their complex ring systems and oxygenation patterns, these natural products pose considerable challenges for synthesis.[8] Accordingly, only a limited number of synthetic studies have been reported and no total synthesis of a natural product shown in Figure 1 has been disclosed to date.[9]

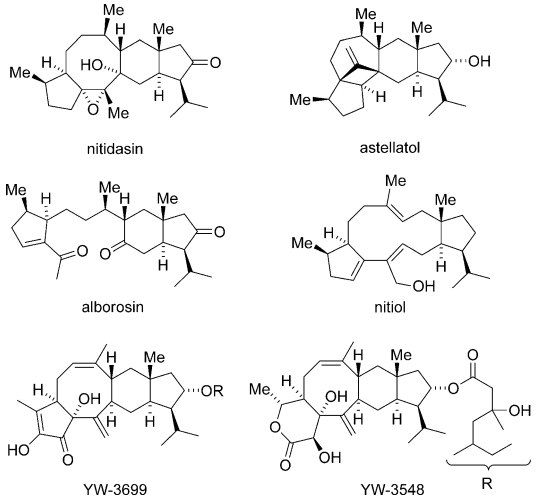
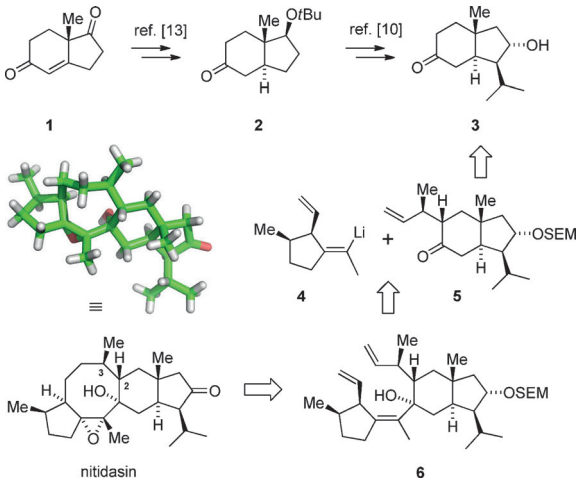


Figure 1. Sesterterpenoids isolated from "Hercampuri" and related compounds.

Several years ago, we set out to develop a general synthetic approach toward isopropyl *trans*-hydrindane sesterterpenoids.[10,11] We identified hydrindane **3** as a key building block that could be used in the synthesis not only of nitidasin, but also of astellatol, alborosin, and the YW compounds (Scheme 1). Starting from ketone **1**, which is readily available through asymmetric Robinson annulation,[12] we were able to obtain hydrindanone **2** by capitalizing on a *trans*-selective



Scheme 1. Preparation of hydrindanone **3** and a retrosynthetic analysis of nitidasin.

[*] Dr. D. T. Hog,[+] Dipl.-Chem. F. M. E. Huber,[+] Dr. P. Mayer, Prof. Dr. D. Trauner
Department of Chemistry and Center for Integrated Protein Science
Ludwig-Maximilians-Universität München
Butenandtstr. 5–13, 81377 München (Germany)
E-mail: Dirk.Trauner@cup.uni-muenchen.de
Homepage: http://www.cup.uni-muenchen.de/oc/trauner/

[+] These authors contributed equally to this work.

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hydrogenation.[13] Unsaturation of the five-membered ring, conjugate addition, redox adjustment, and hydroboration/oxidation delivered our key building block **3**. Overall, this route was highly stereoselective and was able to deliver gram quantities of key ketone **3**.

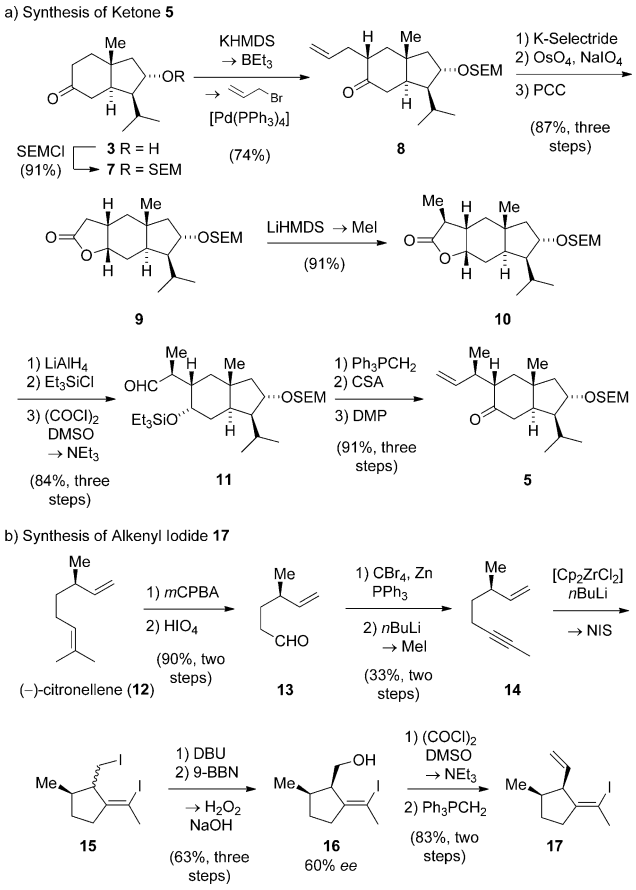
Our retrosynthetic analysis of nitidasin, which evolved from more obvious but unsuccessful disconnections, is also shown in Scheme 1. Eventually, we envisaged tetrasubstituted alkenyl lithium compound **4** and ketone **5** as suitable synthetic precursors that would enable a highly convergent synthesis of the natural product. After stereoselective addition of lithium species **4** to hydrindanone **5**, the resultant tertiary allylic alcohol **6** would undergo ring-closing metathesis (RCM),[14] followed by hydrogenation and epoxidation to eventually afford nitidasin.

To put this plan into practice, we first investigated the seemingly straightforward conversion of ketone **3** into *trans*-hydrindanone **5** (Scheme 2a). In light of literature precedent, we were aware that the installation of the two adjacent stereogenic centers at C2 and C3 (nitidasin numbering) would be a challenge.[15] While initial attempts based on Claisen rearrangements proved nonviable, we eventually developed a reliable and scalable sequence: protection of hydrindane **3** gave the corresponding SEM ether **7**. This was followed by a regio- and diastereoselective Pd-catalyzed allylation performed according to a protocol developed by Negishi.[16,17] By contrast, attempts to obtain hydrindanone **8** with standard alkylation procedures were unsuccessful.[18]

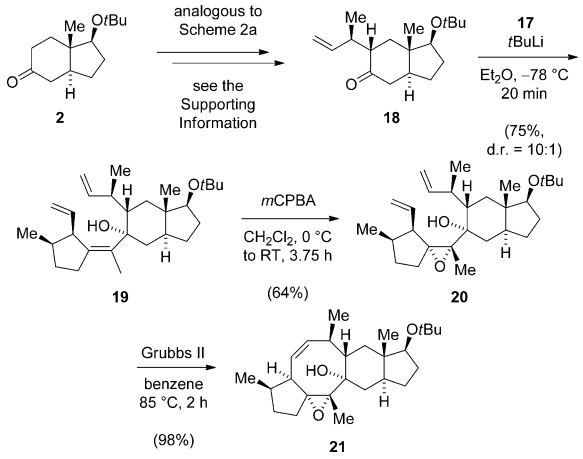
Exposure of ketone **8** to K-Selectride resulted in a diastereoselective reduction of the carbonyl group. After Lemieux–Johnson cleavage of the terminal alkene[19] and chromium-mediated oxidation of the intermediate lactol to lactone **9**, the stage was set for the installation of the C3 methyl group. As anticipated, reaction of the lithium enolate with MeI occurred from the convex face of the tricyclic ring system, thereby giving rise to a single diastereomer **10**. Reduction of lactone **10** with $LiAlH_4$, followed by double silylation and chemoselective oxidation under carefully optimized Swern conditions[20] provided efficient access to aldehyde **11**. Finally, a three-step protocol consisting of Wittig olefination, chemoselective deprotection, and subsequent oxidation gave *trans*-hydrindanone **5**, which bears five out of the ten stereocenters of nitidasin.[21]

The preparation of alkenyl iodide **17**, the precursor of lithium species **4**, is outlined in Scheme 2b. Although metallaene reactions were initially considered, they were eventually ruled out owing to difficulties associated with the required *cis* relationship of the two adjacent substituents on the cyclopentane ring. Our successful sequence commenced with oxidative cleavage of commercially available (−)-citronellene (**12**) to yield known aldehyde **13**.[22] This was followed by Corey–Fuchs homologation with in situ trapping of the intermediary alkynyl lithium species with MeI, which afforded enyne **14**.[23] Next, we employed a Zr-mediated cyclometalation developed by Negishi[24] to install the five-membered ring and the tetrasubstituted alkenyl iodide. The reaction of enyne **14** with Cp_2Zr, generated in situ, and subsequent quenching with excess NIS[25] provided diiodide **15** as a mixture of diastereomers. Subsequent elimination of the primary iodide with DBU and hydroboration with 9-BBN gave alcohol **16** with the correct *cis* relationship of the two adjacent substituents. At this stage, we determined the *ee* of intermediate **16** through Mosher ester analysis.[26] This intermediate was obtained with just 60% *ee* owing to the low optical purity of commercially available (−)-citronellene (**12**). Swern oxidation of primary alcohol **16** and Wittig methenylation then yielded iodo diene **17**. Epimerization at the aldehyde stage was not observed under these conditions, presumably owing to the considerable allylic strain that an intermediary enolate would encounter.

With enantiomerically pure building block **5** and scalemic **17** in hand, we were in a position to investigate the joining of the two fragments and the formation of the central eight-membered ring. To conserve our valuable *trans*-hydrindanone **5**, however, this was first done using model compound **18**, which was accessible from hydrindane **2** by using the strategy outlined above (Scheme 3 and the Supporting Information). Treating iodide **17** with *t*BuLi at −78 °C followed by the gradual addition of ketone **18** afforded tertiary allylic alcohol **19** in good yield. This reaction is remarkable for several



Scheme 2. Synthesis of hydrindanone **5** and alkenyl iodide **17**. SEM = 2-(tri-methylsilyl)ethoxymethyl, KHMDS = potassium bis(trimethylsilyl)amide, K-Selectride = potassium tri-*sec*-butylborohydride, PCC = pyridinium chlorochromate, LiHMDS = lithium bis(trimethylsilyl)amide, CSA = camphor-10-sulfonic acid, DMP = Dess–Martin periodinane, *m*CPBA = *meta*-chloroperbenzoic acid, NIS = *N*-iodosuccinimide, DBU = 1,8-diazabicyclo[5.4.0]-undec-7-ene, 9-BBN = 9-borabicyclo[3.3.1]nonane.



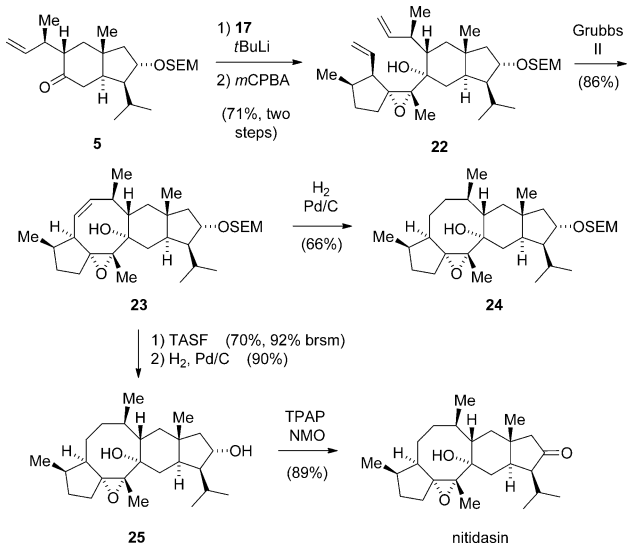
Scheme 3. Model studies: synthesis of the tetracarbocyclic nitidasin core **21**.

reasons: First, tetrasubstituted alkenyl lithium species are rarely used in synthesis. To our knowledge, additions of these organometallic species to ketones, particularly sterically hindered ones, such as **18**, are unprecedented.[27] Second, the addition was highly stereoselective with respect to the *trans*-hydrindanone. Finally, the diastereomeric mixture of 10:1 obtained under these reaction conditions reflects a kinetic resolution of the scalemic lithium species **4** (e.r. = 4:1).

Having successfully linked the two fragments, we next turned to the closure of the central eight-membered ring through RCM. Initial attempts to effect this reaction with substrate **19** were frustrated by the unexpected participation of the tetrasubstituted alkene resulting in the formation of a cyclopentene. We therefore decided to change the order of events and explore the introduction of the epoxide first. Gratifyingly, treatment of triene **19** with *m*CPBA led to a clean, chemoselective, and stereoselective reaction at the tetrasubstituted double bond to provide epoxide **20** as a single diastereomer. Virtually no epoxidation of the terminal double bonds was observed under the applied reaction conditions, even when a large excess of reagent was used.

Single-crystal X-ray analyses of both triene **19** and epoxide **20** not only confirmed the correct configuration of all stereogenic centers, but also provided insight into the preferred conformations of the molecules (Figure 2).[28] Both structures show a close proximity of their terminal double bonds, thus requiring only a 120° rotation around the C2–C3 bond for an RCM to occur. Accordingly, exposure of diene **20** to the Grubbs second-generation catalyst in refluxing benzene gave the tetracyclic model compound **21** within two hours and in almost quantitative yield.

Encouraged by our model studies, we next exposed our key *trans*-hydrindanone **5** to alkenyl lithium species **4** (Scheme 4). In agreement with our previous results, the addition to the carbonyl was found to be highly diastereoselective concerning the formation of the newly formed stereogenic center. The diastereomers originating from scalemic intermediate **4** were readily separable by column chromatography and yielded 7% of the undesired adduct. The major isomer **6**, however, was unstable upon concentration and was thus immediately subjected to epoxidation conditions. This two-step protocol furnished metathesis substrate **22** as single diastereomer and in an excellent yield of 71%, thus suggesting that in analogy to the model system, a kinetic resolution took place. The subsequent RCM proceeded smoothly to yield cyclooctene **23**, which features a total of eleven stereogenic centers. Its structure was unambiguously confirmed by X-ray diffraction (Figure 3).



Scheme 4. Completion of the total synthesis of nitidasin. TASF = tris-(dimethylamino)sulfonium difluorotrimethylsilicate, brsm = based on recovered starting material, TPAP = tetrapropylammonium perruthenate, NMO = 4-methyl-morpholine *N*-oxide.

In order to complete the total synthesis, we initially aimed at hydrogenation of the double bond of alkene **23** to obtain cyclooctane **24**. The use of stoichiometric amounts of Pd/C resulted in a fast conversion to intermediate **24**, the structure of which was again established by single-crystal X-ray analysis

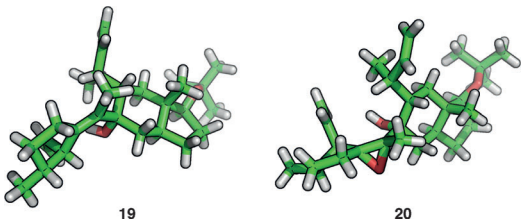


Figure 2. Crystal structures of model compounds **19** and **20**.

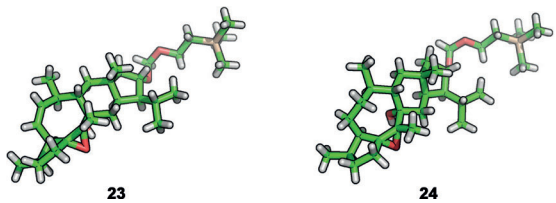


Figure 3. Crystal structures of intermediates **23** and **24**.

(Figure 3). Since this substrate proved to be sensitive, we decided to cleave the SEM ether in tetracarbocycle **23** first. After some experimentation, we found that treatment with excess TASF in HMPA in the presence of molecular sieves at elevated temperatures cleanly unmasked the corresponding secondary alcohol.[29] Subsequent hydrogenation of the double bond under the previously established reaction conditions gave "nitidasol" **25**. This compound may well be a biosynthetic precursor of nitidasin and could potentially be found as a natural product. Finally, the oxidation of alcohol **25** by using TPAP/NMO[30] furnished synthetic nitidasin.

The NMR spectral data for our synthetic nitidasin were identical in all respects to those reported by Kawahara and co-workers.[2] Carefully purified acid-free $CDCl_3$ was required to obtain clean spectroscopic data for comparison. Otherwise, a rapid conversion to an *exo*-methylene cyclooctane that resembles the YW compounds was observed (see the Supporting Information). The identity of our synthetic sample of nitidasin was also confirmed by X-ray crystallography (see the Supporting Information). The optical rotation of our synthetic material was determined to be levorotary as reported for the natural product (synthetic: $[\alpha]_D = -102°$, $c = 0.10$, $CHCl_3$; natural: $[\alpha]_D = -41.4°$, $c = 0.28$, $CHCl_3$). The absolute configuration of nitidasin has thus been established.

In conclusion, we have developed a total synthesis of nitidasin, which was a primary goal of our program on isopropyl *trans*-hydrindane sesterterpenoids. Our convergent synthesis is marked by several highly stereoselective transformations, which allowed for the installation of the ten stereogenic centers of the target molecule. These include a facile, diastereoselective addition of a complex tetrasubstituted alkenyl lithium compound to a *trans*-hydrindanone. Another key step of our synthesis is an efficient RCM to form a highly substituted eight-membered ring, a reaction that benefits from conformational pre-organization of the substrate. In addition, our synthetic route established the absolute configuration of the natural product. The total synthesis of astellatol from key ketone **5** and synthetic approaches toward the YW molecules are currently under active investigation.

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