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Total Synthesis of Nostodione A, a Cyanobacterial Metabolite

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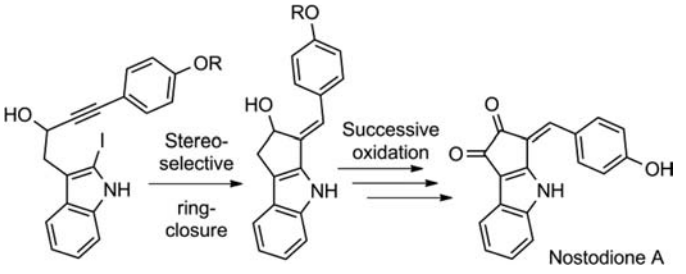
ABSTRACT



The first total synthesis of the mitotic spindle poison nostodione A is described. The inherent oxidative sensitivity of indoles is utilized for a late introduction of a second carbonyl to the cyclopent[*b*]indole-2-one system. The tricyclic system is prepared from indole-3-acetic acid and *O*-silylated 4-ethynylphenol, using a stereoselective intramolecular reductive Heck cyclization as the key transformation.

Nostodione A (**1**) belongs to a small family of alkaloids characterized by a tricyclic cyclopent[*b*]indol-2(1*H*)-one ring system appended by a benzyl or a benzylidene substituent at its 3 position (Figure 1). The molecular structure was first reported in 1993 by Proteau et al. who assigned this structure to a fragment obtained upon ozonolysis of the reduced form of scytonemin (**2**),[1] a natural UV screening alkaloid belonging to the same family as nostodione A. In 1994, nostodione A was for the first time obtained directly from a biological source when Kobayashi et al. isolated it from the cyanobacterium *Nostoc commune*.[2] These authors also showed that the alkaloid in solution exists as a rapidly interconverting equilibrium mixture of its *E* and *Z* isomers (Figure 1). Herein we report the first total synthesis of the alkaloid nostodione A.

Nostodione A has been shown to suppress mitotic spindle formation in sea-urchin eggs[2] and to inhibit chymotrypsin-like proteasome activity *in vitro*.[3] What biological function it may serve in cyanobacteria has yet to be elucidated. However, it has been proposed to serve as a monomeric intermediate in the biosynthesis of scytonemin.[4] In addition to the biological activity shown for nostodione A itself, the fused tricyclic system cyclopent-[*b*]indole on which it is based has been shown to be a privileged scaffold able to provide a new class of selective LXR agonists.[5]

As recounted by Jordan et al.,[6] cyclopent[*b*]indoles have been synthesized by numerous methods. Synthetic routes to cyclopent[*b*]indol-2(1*H*)-ones and cyclopent[*b*]indol-1,2(3*H*,4*H*)-diones on the other hand are rare. The tricyclic ketones have been obtained in low to good yield by the Fischer indole synthesis[7] and by different ring-closing

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(1) Proteau, P. J.; Gerwick, W. H.; Garciapichel, F.; Castenholz, R. *Experientia* **1993**, *49*, 825.
(2) Kobayashi, A.; Kajiyama, S. I.; Inawaka, K.; Kanzaki, H.; Kawazu, K. *Z. Naturforsch., C: J. Biosci.* **1994**, *49*, 464.
(3) Shim, S. H.; Chlipala, G.; Orjala, J. *J. Microbiol. Biotechnol.* **2008**, *18*, 1655.
(4) Soule, T.; Palmer, K.; Gao, Q. J.; Potrafka, R. M.; Stout, V.; Garcia-Pichel, F. *BMC Genomics* **2009**, 10.
(5) Ratni, H.; Blum-Kaelin, D.; Dehmlow, H.; Hartman, P.; Jablonski, P.; Masciadri, R.; Maugeais, C.; Patiny-Adam, A.; Panday, N.; Wright, M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1654.
(6) Jordan, J. A.; Gribble, G. W.; Badenock, J. C. *Tetrahedron Lett.* **2011**, *52*, 6772.
(7) Dashkevich, S. N. *Khim. Geterotsikl. Soedin.* **1978**, 132.
(8) Dominguez, G.; Casarrubios, L.; Rodriguez-Noriega, J.; Perez-Castells, J. *Helv. Chim. Acta* **2002**, *85*, 2856.

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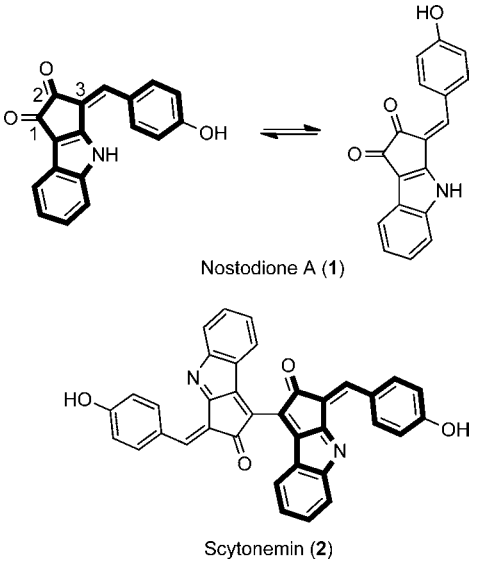


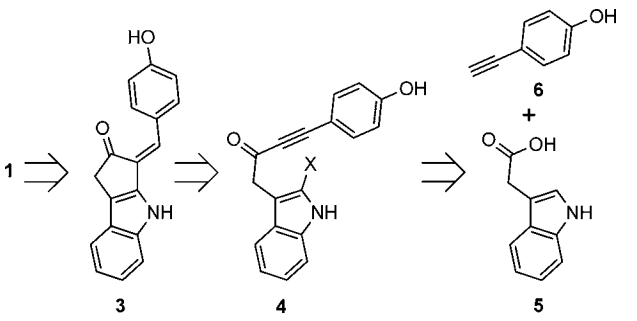
Figure 1. Structures of nostodione A (**1**) and scytonemin (**2**). The tricyclic cyclopent[*b*]indol-2(1*H*)-one ring system with the appended benzylidene substituent is highlighted.

strategies for the formation of the five-membered ring annulated to the indole system.[6,8−11]

Our interest in the cyclopent[*b*]indol-2-one and -1,2-dione skeleton originates from our efforts to prepare a series of scytonemin derivatives for photophysical measurements, to disclose its mode of action as a UV screening compound. Within this campaign we need access to both mono- and dimeric structures of cyclopent[*b*]indol-2-one and, if possible, to derivatives with both *E* and *Z* configuration around the exocyclic carbon−carbon double bond present in both nostodione A and scytonemin. To date, our recent publication on the synthesis of scytonemin, based on an *E* selective tandem Heck−Suzuki−Miyaura reaction, constitutes the only report on the syntheses of cyclopent[*b*]indol-2(1*H*)-ones with an exocyclic carbon−carbon double bond in their 3 position.[12] The route to nostodione A described herein is the offspring of continued search for different methods to add functionalities and substituents at position 1 of the cyclopent[*b*]indol-2(1*H*)-one skeleton and to install the exocyclic double bond at the 3 position stereoselectively.

Accordingly, the assembly of nostodione A was intended to be accomplished by three major operations: (1) late introduction of the 1,2-diketone motif by selective oxidation of a complete nostodione A skeleton **3** (Scheme 1), (2) stereospecific ring closure of a 3-arylethynyl-2-haloindole **4**, and (3) alkynylation of a suitable derivative of the commercially available indol-3-ylacetic acid **5**.

Scheme 1. Retrosynthetic Analysis of Nostodione A



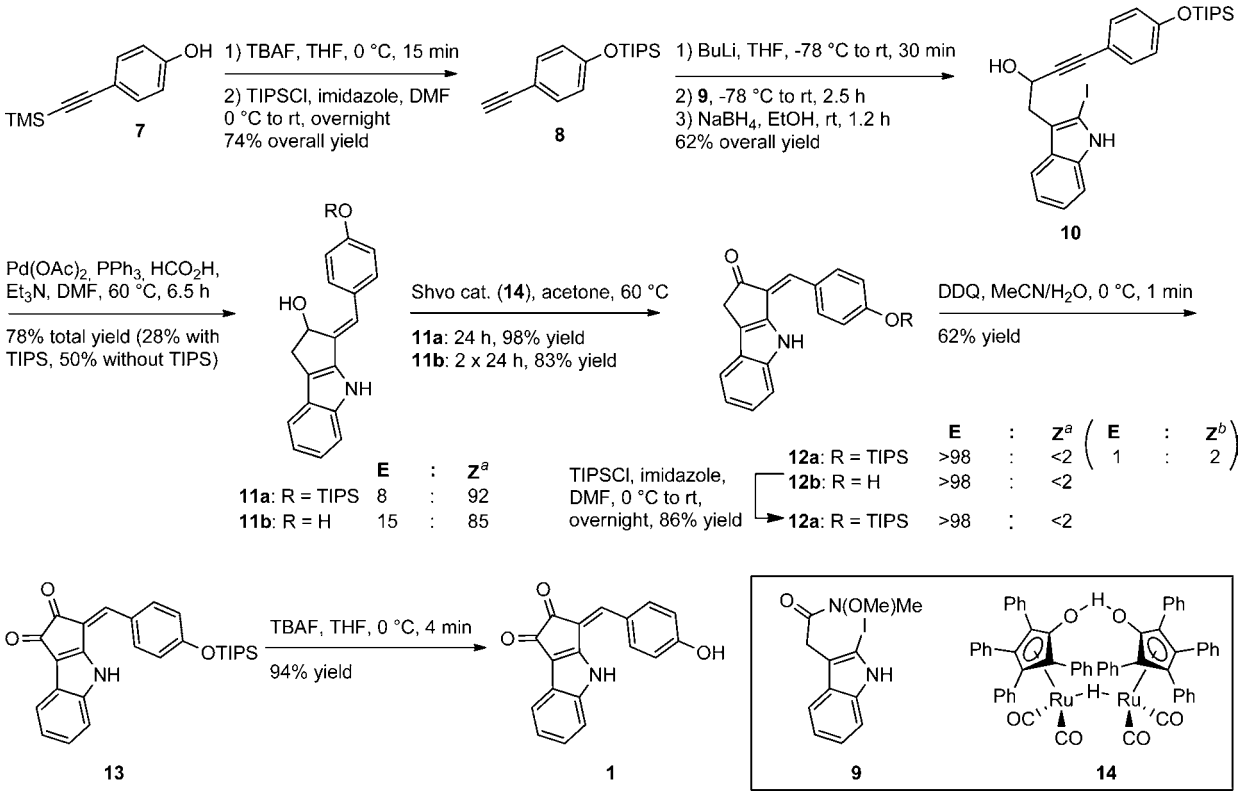
The characteristic 1,2-diketone motif of nostodione A was assumed to be possible to form with high selectivity by DDQ-mediated oxidation at the 1 position of the cyclopent[*b*]indol-2(1*H*)-one skeleton *via* a Yonemitsu oxidation.[13] During this oxidation the electron-rich indole system substituted with an alkyl group in the C3 position has been suggested to undergo efficient DDQ-mediated dehydrogenation forming a vinylogous iminium cation. In an aqueous environment this α,*β*-unsaturated iminium system is readily attacked in the *β*-position by water and the formed alcohol is subsequently oxidized by a second equivalent of DDQ to the corresponding ketone.

In conformity with the majority of the reported routes to the cyclopent[*b*]indol-2(1*H*)-one skeleton, our strategy for the synthesis of nostodione A is based on the formation of the five-membered ring annulated to the indole system. This was expected to be accomplished by ring closure of an arylethynyl haloindole *via* a palladium-mediated *syn*-addition to the triple bond of the indolyl group and a hydrogen in an intramolecular reductive Heck cyclization. The intervening *syn*-carbo-palladation not only strongly favors the formation of a five-membered ring but also, concurrently with the ring-closure, stereospecifically delivers the *Z* configuration of the excocyclic double bond. The reaction has previously been successfully applied to the stereoselective construction of medium sized rings with exocyclic double bonds.[14−16]

Accordingly, our synthetic endeavor toward nostodione A began with the syntheses of the two building blocks **8** and **9** (Scheme 2). The terminal alkyne **8** was prepared in two steps from the 4-ethynylphenol **7**,[17] and the Weinreb amide **9** was prepared from indol-3-acetic acid according to our previously reported procedure.[12] The two building blocks were merged effectively by treating the terminal alkyne **8** with butyl lithium and reacting the formed acetylide with the Weinreb amide **9**. The formed ketone

(9) Franceschetti, L.; Garzon-Aburbeh, A.; Mahmoud, M. R.; Natalini, B.; Pellicciari, R. *Tetrahedron Lett.* **1993**, *34*, 3185.
(10) Salim, M.; Capretta, A. *Tetrahedron* **2000**, *56*, 8063.
(11) Tang, Q.; Chen, X.; Tiwari, B.; Chi, Y. R. *Org. Lett.* **2012**, *14*, 1922.
(12) Ekebergh, A.; Karlsson, I.; Mete, R.; Pan, Y.; Börje, A.; Mårtensson, J. *Org. Lett.* **2011**, *13*, 4458.
(13) Oikawa, Y.; Yonemitsu, O. *J. Org. Chem.* **1977**, *42*, 1213.
(14) Wang, X.; Liu, L. Y.; Chang, W. X.; Li, J. *Eur. J. Org. Chem.* **2010**, 5391.
(15) Donets, P. A.; Van der Eycken, E. V. *Org. Lett.* **2007**, *9*, 3017.
(16) Tietze, L. F.; Schimpf, R. *Chem. Ber.* **1994**, *127*, 2235.
(17) Hirose, T.; Matsuda, K. *Chem. Commun.* **2009**, 5832.

Scheme 2. Synthetic Route to Nostodione A



[a] Measured by NMR integration. [b] Measured by NMR integration on crude product directly after workup.

turned out to be unstable, *vide infra*, and was therefore immediately masked as a racemic alcohol **10** by a sodium borohydride reduction.

Subjecting alcohol **10** to standard reductive Heck conditions gave the wanted cyclization with high stereoselectivity in a total yield of 78%. One-dimensional NOESY experiments were performed to establish the stereochemistry around the exocyclic double bond. A distinct signal due to the nuclear Overhauser effect between the vinylic and the N−H proton was observed for the *Z* isomers. Unfortunately, the majority of the product was isolated without the phenolic silyl group, a protective group which proved necessary for the upcoming Yonemitsu oxidation. Thus, the deprotected ring-closed product **11b** had to be reprotected at a later stage. The excision is believed to stem from residual water, mainly from the formic acid, together with the high polarity of the solvent. Similar reaction conditions have been successfully applied to purposely cleave off phenolic silyl groups.[18] Changing the solvent from DMF to the less polar THF gave less silyl excision but did on the other hand give substantially lower yield.

Next, the allylic alcohol **11a** was converted into ketone **12a** in very high yield by utilizing the ruthenium based Shvo catalyst (**14**)[19] in an Oppenauer type oxidation, as described by Bäckvall and co-workers.[20] The crude product was obtained as an isomeric mixture in which the excess of *Z*-configuration was much lower than in the precursor **11a**. It was found that ketone **12a** spontaneously isomerized to essentially pure *E*-isomer when kept in solution. The change in stereochemistry was determined by 1D-NOESY experiments. Saturating the *ortho*-protons of the *para*-substituted aryl ring gave an enhanced N−H proton signal for the *E* isomer. This oxidation protocol could also be applied to the free phenol **11b**, albeit here the reaction progressed sluggishly and was characterized by premature precipitation of the catalyst. This can be explained by the competitive interaction of the phenol with the catalyst.[20] The free phenol of ketone **12b** could at this stage be reprotected in high yield with triisopropylsilyl chloride. Thus, the total yield of ketone **12a** from **10** is 63%.

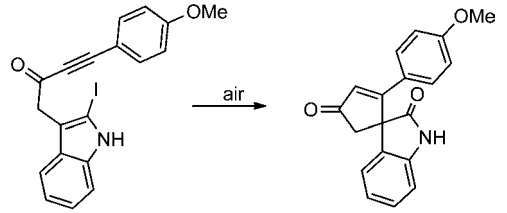
Finally, ketone **12a** was successfully transformed to dione **13** using the oxidation protocol developed by Yonemitsu et al. Subsequent flouride ion based silyl excision produced the target molecule nostodione A (**1**) in excellent yield.

As briefly pointed out above, the initial fusion of the terminal alkyne **8** and Weinreb amide **9** yielded an unstable

(18) Jiang, Z. Y.; Wang, Y. G. *Tetrahedron Lett.* **2003**, *44*, 3859.
(19) Shvo, Y.; Blum, Y. *Isr. J. Chem.* **1984**, *24*, 144.
(20) Almeida, M. L. S.; Beller, M.; Wang, G.-Z.; Bäckvall, J.-E. *Chem.—Eur. J.* **1996**, *2*, 1533.

ketone. To understand and possibly circumvent the degradation, the more accessible and stable 4-ethynylanisole was

Scheme 3. Oxidative Rearrangement of Model Compound **15**



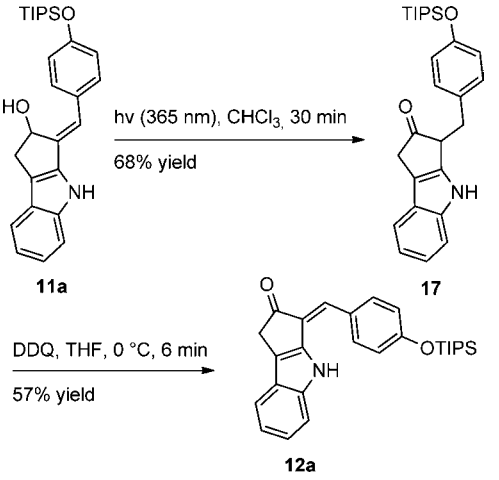
15 **16**

used in a model reaction. When the formed ketone **15** (Scheme 3) was left as a solid in air, complete conversion to the spiro oxo-indoline **16** was observed within a week. This oxidative rearrangement can be ascribed to the well established auto-oxidative sensitivity of indoles, where chemical modification occurs at the 2 and 3 position.[21] The corresponding alcohol did however not show any sign of degradation, an alteration in reactivity we cannot explain.

Having been forced to mask the ketone formed in the alkynylation as an alcohol, we devoted some effort trying to efficiently reoxidize it after its cyclization. Allylic alcohols have been oxidized by DDQ[22] under conditions similar to those employed in the Yonemitsu oxidation. It was therefore envisioned that these oxidations could be executed in a tandem fashion to give dione **13** in a one-pot procedure. However, all our attempts resulted in either rapid degradation or no reaction at all. In the same spirit, attempts were made to sequentially perform the reductive Heck cyclization and a palladium catalyzed oxidation of the formed allylic alcohols **11a** and **b** in the same reaction vessel. To this end a stoichiometric amount of bromomesitylene as a hydride acceptor[23] was added when almost full conversion was reached in the Heck cyclization, but oxidation of the allylic alcohol was never observed. The oxidation of allylic alcohol **11a** was therefore performed as a separate synthetic operation.

It was found that the α,β-unsaturated ketone **12a** could be regenerated by a rearrangement of the allylic alcohol **11a** followed by DDQ-mediated dehydrogenation (Scheme 4). Alcohol **11a** rearranged when irradiated with UV-light in chloroform. In acetone, *p*-toluenesulphonic acid induced the same rearrangement, although less

Scheme 4. Alternative Oxidation of Allylic Alcohol **11a**



effectively. The light driven reaction can be explained either as a photochemical [1,3] hydride shift, as described by Peijnenburg and Buck,[24] or as being catalyzed by hydrochloric acid released from the photochemical oxidation of chloroform.[25] Interestingly, the rearrangement product **17** is a phenol protected counterpart of the last established intermediate in the biosynthesis of scytonemin.[26]

In summary, we report on the first total synthesis of the alkaloid nostodione A. Its fused tricyclic indole core was constructed in good yield by an intramolecular reductive Heck cyclization of an alkynol appended indole. The ring closure occurred with excellent ring-size selectivity and with concurrent highly stereoselective formation of an exocyclic double bond. Two consecutive oxidations transformed the ring closed product to the protected nostodione A. First, the allylic alcohol was converted to an α, β-unsaturated ketone in excellent yield employing the Shvo catalyst. Next, the second carbonyl was introduced in good yield using DDQ in the presence of water *via* a Yonemitsu oxidation. Facile cleavage of the phenolic silyl group then completed the total synthesis.

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Supporting Information Available. Experimental procedures, characterization data, and NMR spectra are supplied for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(21) Witkop, B.; Patrick, J. B.; Rosenblum, M. *J. Am. Chem. Soc.* **1951**, 73.
(22) Walker, D.; Hiebert, J. D. *Chem. Rev.* **1967**, *67*, 153.
(23) Tamaru, Y.; Inoue, K.; Yamada, Y.; Yoshida, Z. *Tetrahedron Lett.* **1981**, *22*, 1801.
(24) Peijnenburg, W. J. G. M.; Buck, H. M. *Tetrahedron* **1988**, *44*, 4927.
(25) Baskerville, C.; Hamor, W. A. *J. Ind. Eng. Chem.* **1912**, *4*, 571.
(26) Balskus, E. P.; Walsh, C. T. *J. Am. Chem. Soc.* **2009**, *131*, 14648.

The authors declare no competing financial interest.