ORGANIC LETTERS

2011
Vol. 13, No. 16
4458–4461

Oxidative Coupling as a Biomimetic Approach to the Synthesis of Scytonemin

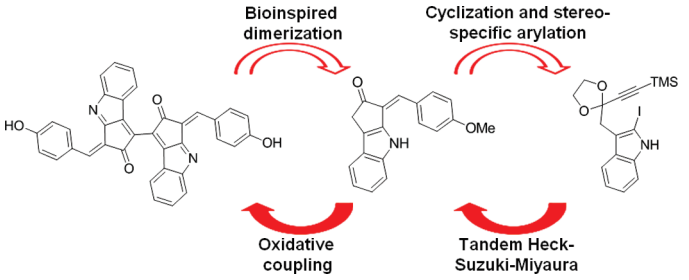
Andreas Ekebergh,[†] Isabella Karlsson,[‡] Rudi Mete,[‡] Ye Pan,[†] Anna Börje,[‡] and Jerker Mårtensson*,[†]

Department of Chemical and Biological Engineering/Organic Chemistry, Chalmers University of Technology, SE-412 96 Gothenburg, Sweden, and Dermatochemistry and Skin Allergy, Department of Chemistry, University of Gothenburg, SE-412 96 Gothenburg, Sweden

jerker@chalmers.se

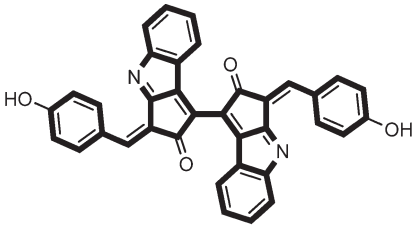
Received July 6, 2011

ABSTRACT



The first total synthesis of the dimeric alkaloid pigment scytonemin is described. The key transformations in its synthesis from 3-indole acetic acid are a Heck carbocyclization and a Suzuki−Miyaura cross-coupling, orchestrated in a stereospecific tandem fashion, followed by a biosynthetically inspired oxidative dimerization. The tandem sequence generates a tetracyclic (*E*)-3-(arylidene)-3,4-dihydrocyclopenta[*b*]indol-2(1*H*)-one that is subsequently dimerized into the unique homodimeric core structure of scytonemin.

The cyanobacterial dimeric alkaloid pigment scytonemin (Figure 1) is characterized by a homodimeric core structure that is unique among natural products and composed of two 1,1′ linked cyclopent[*b*]indole-2(1*H*)-ones. This core in scytonemin is symmetrically appended by 4-hydroxybenzylidene in the 3-position of the fused tricyclic system. The parent skeleton comprising the eight rings has been given the trivial name scytoneman by Proteau et al. who, in 1993, were the first to elucidate the chemical structure of the scytonemin pigment.[1] Scytonemin has been proposed to be formed biosynthetically by a putative tyrosinase NpR1263 promoting an oxidative dimerization of the α,β-unsaturated ketone (**2**) (Scheme 1).[2] The biosynthetic route to the reduced form of this monomeric precursor has been disclosed and shown to commence from L-tryptophan and *p*-hydroxyphenylpyruvic acid.[3] In an alternative suggestion, nostodione A has been put forward as the actual monomeric precursor, and the putative tyrosinase NpR1263 to be essential for the biosynthesis of this monomer.[4]



scytonemin (**1**)

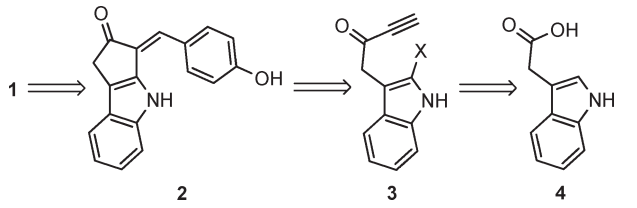
Figure 1. Structure of scytonemin. The scytoneman skeleton is highlighted by bold lines.

[†] Chalmers University of Technology.
[‡] University of Gothenburg.

(1) Proteau, P. J.; Gerwick, W. H.; Garcia-Pichel, F.; Castenholz, R. *Experientia* **1993**, *49*, 825.
(2) Balskus, E. P.; Walsh, C. T. *J. Am. Chem. Soc.* **2008**, *130*, 15260.
(3) Balskus, E. P.; Walsh, C. T. *J. Am. Chem. Soc.* **2009**, *131*, 14648.
(4) Soule, T.; Palmer, K.; Gao, Q.; Potrafka, R. M.; Stout, V.; Garcia-Pichel, F. *BMC Genomics* **2009**, *10*, 336.

10.1021/ol201812n
Published on Web 07/25/2011

Scheme 1. Retrosynthetic Analysis of Scytonemin



The biological role of scytonemin has been ascertained to be as a UV-absorbing pigment to protect important cellular components in the cyanobacteria against harmful UV radiation.[5] Its critical biological importance for the cyanobacterial survival is highlighted by the facts that the pigment is found in more than 300 species of cyanobacteria and that the scytonemin biosynthetic gene cluster is highly conserved across several studied cyanobacterial lineages.[6]

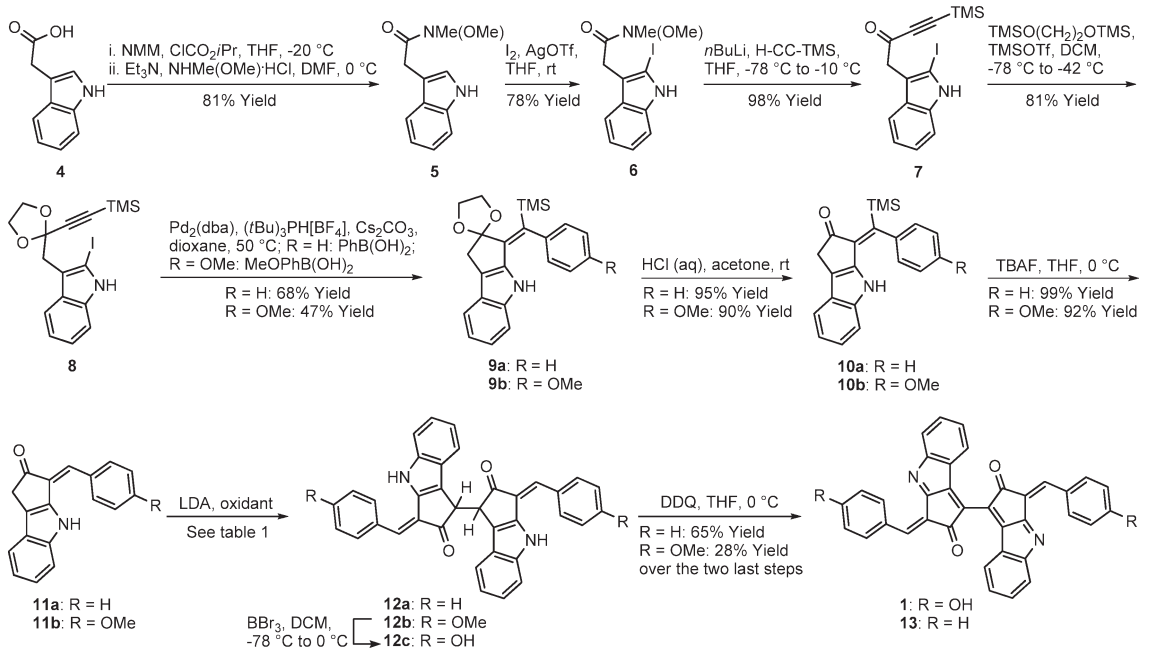
Scytonemin received attention when it was reported to be the first characterized small molecule inhibitor of *polo*-like kinase 1 and to inhibit other cell cycle regulatory kinases as well.[7] In compliance with these observations, it has been shown to possess both anti-inflammatory and antiproliferative properties.[8] Scytonemin has therefore been proposed to serve as a new pharmacophore that could be used in the development of a chemically new class of therapeutically useful drugs.

In a project aimed at exploring the photochemistry and photophysics of scytonemin we need access to derivatives of both the dimeric form as well as its monomeric precursor. Our plan to prepare these compounds takes its starting point in the molecular symmetry and the prospect of stereospecific formation of the exocyclic double bond; see Scheme 1. Initial disconnection of the C1−C1′ bond generates the monomeric precursor (**2**). Inspired by the proposed biosynthetic route to scytonemin, and attracted by the possibility to couple two identical moieties without the need of prior installation of any functional group lost in the subsequent coupling, we set out to complete the synthesis of the scytoneman skeleton by an oxidative coupling of two identical halves. Further disconnection of two *cis*-vinylic bonds at the exocyclic double bond produces an alkynyl haloindole (**3**). This intermediate was expected to participate in a palladium-mediated *syn*-addition of the indolyl group and an aryl group to the triple bond, to create both the fused tricyclic skeleton and the exocyclic double bond with the correct stereochemistry in a single operation.[9] The final disconnection, which corresponds to an acyl substitution, generates the commercially available 3-indole acetic acid (**4**).

Thus, our synthetic sequence toward scytonemin commenced with a standard transformation of 3-indole acetic acid (**4**) into its corresponding Weinreb amide (**5**) (Scheme 2),[10] which was subsequently iodinated in the 2-position using molecular iodine and silver triflate.[11] Careful addition of silver triflate and use of slightly less than 1 equiv of iodine were crucial to avoid formation of a diiodinated product, which in our hands was impossible to separate from the desired product. Treatment of the iodinated Weinreb amide **6** with preformed trimethylsilylethynyl lithium gave the alkynyl ketone **7**. This ketone was converted into its corresponding acetal (**8**) by the procedure reported by Tsunoda et al.[12] Accordingly, 1,2-bis(trimethylsiloxy)ethane was used as the acetalizing agent and trimethylsilyl trifluoromethanesulfonate as the catalyst. Of several screened conditions these were the only ones that effected satisfactory acetal formation. The formation of the tricyclic cyclopent[*b*]indole-2-one skeleton and the exocyclic double bond with correct stereochemistry was accomplished by a tandem Heck−Suzuki−Miyaura reaction. Effective use of the tandem sequence of Heck carbocyclization of five-membered rings and Suzuki−Miyaura coupling in stereoselective formation of substituted exocyclic double bonds has recently been reported in the literature.[9,13] We chose to follow a protocol described by Littke et al.[14,15] It has been successfully applied to both Suzuki−Miyaura and Heck-type cross couplings separately but, to the best of our knowledge, not in tandem reactions. Consequently, the alkynyl iodoindole **8** was treated with an arylboronic acid in the presence of cesium carbonate and a catalytic amount of palladium and tri-*tert*-butylphosphine. It was discovered that the conditions of this domino reaction needed careful tuning to favor the desired reaction pathway. Using phenylboronic acid in excess (1.5 equiv of $PhB(OH)_2$ and 2.5 equiv of Cs_2CO_3) yielded the cyclized product **9a** exclusively, while the same excess of 4-methoxyboronic acid produced a significant amount of the undesired 2-(4-methoxyphenyl)-indole together with the wanted product **9b**. The electron-rich boronic acid increased the rate of reaction for the intermolecular Suzuki coupling to the degree where it successfully competed with the intramolecular Heck cyclization. Decreasing the excess of boronic acid and base (1.1 equiv of $MeOPhB(OH)_2$ and 1.8 equiv of Cs_2CO_3) suppressed the unwanted cross coupling but had an unfortunate effect on the overall conversion. Further screening and evaluation of reaction conditions to circumvent this problem are

(5) Cockell, C. S.; Knowland, J. *Biol. Rev. Cambridge Philos. Soc.* **1999**, *74*, 311.
(6) Sorrels, C. M.; Proteau, P. J.; Gerwick, W. H. *Appl. Environ. Microbiol.* **2009**, *75*, 4861.
(7) Stevenson, C. S.; Capper, E. A.; Roshak, A. K.; Marquez, B.; Eichman, C.; Jackson, J. R.; Mattern, M.; Gerwick, W. H.; Jacobs, R. S.; Marshall, L. A. *J. Pharmacol. Exp. Ther.* **2002**, *303*, 858.
(8) Stevenson, C. S.; Capper, E. A.; Roshak, A. K.; Marquez, B.; Grace, K.; Gerwick, W. H.; Jacobs, R. S.; Marshall, L. A. *Inflammation Res.* **2002**, *51*, 112.
(9) Arthuis, M.; Pontikis, R.; Florent, J. C. *Tetrahedron Lett.* **2007**, *48*, 6397.
(10) Duval, E.; Cuny, G. D. *Tetrahedron Lett.* **2004**, *45*, 5411.
(11) Baran, P. S.; Shenvi, R. A. *J. Am. Chem. Soc.* **2006**, *128*, 14028.
(12) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357.
(13) Cheung, W. S.; Patch, R. J.; Player, M. R. *J. Org. Chem.* **2005**, *70*, 3741.
(14) Littke, A. F.; Fu, G. C. *J. Org. Chem.* **1999**, *64*, 10.
(15) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020.

Scheme 2. Synthetic Route to Scytoneman-2,2′-dione and Scytonemin



currently being undertaken. Acid catalyzed acetal hydrolysis and fluoride induced desilylation completed the synthesis of the monomers **11a** and **11b**.

The last carbon−carbon bond required to complete the scytoneman skeleton is part of a 1,4-carbonyl moiety. There are ample examples in the literature of successful assembly of this structural element by oxidative coupling of carbonyl enolates.[16−18] Often oxidative coupling of enolates entails copper or iron, in the form of different salts, similar to enzymatic coupling conditions.[16] Hypervalent iodine reagents are also employed to accomplish the oxidative coupling of enolates.[17] To find appropriate reaction conditions for the oxidative coupling, the more accessible monomer **11a** together with a small set of diverse coupling reagents were selected for screening. Thus, the monomer **11a** was treated with LDA to give the corresponding lithium enolate, which was subsequently treated with an appropriate oxidant (Table 1). Cuprous triflate showed poor reactivity giving the monomer back, whereas cupric chloride consumed the monomer but without producing the wanted product. The hypervalent iodine demonstrated very potent reactivity with polymerization as a possible side reaction. In accordance with the mechanism for oxidative coupling with hypervalent iodine reagents proposed by Kita et al.,[19] it was found that about 0.5 equiv of the oxidant in combination with 1 equiv of LDA gave a better yield compared to equimolar amounts. Of the screened oxidants, ferric chloride showed the most potential. Slightly more than 2 equiv of LDA combined with 2 equiv of $FeCl_3$ with respect to the monomer gave the highest yield (Table 1, entry 5). Reducing the reagents to 1 equiv each decreased the yield by 16% (Table 1, entry 4). On the other hand a cleaner reaction where the unreacted monomer could be recovered quantitatively was obtained.

Employing the iron based conditions on the scytonemin precursor **11b** afforded its dimeric counterpart **12b** in higher yield than that obtained for the monomer **11a** used in the small prescreening study. This agrees with a recent report showing that enolates conjugated with electron-rich aromatic groups increase the efficiency of iron mediated couplings, while electron-deficient aromatic groups suppress the reactivity.[13]

Table 1. Screening of Reaction Conditions for Oxidative Coupling of the Unsaturated Ketones **12a** and **12b**[a]

entry	R (compd[a])	oxidant (equiv)	LDA (equiv)	yield (%)	time (h)
1	H (**12a**)	CuOTf (2.4)	2	trace[b]	70
2	H (**12a**)	$CuCl_2$ (1.2)	1.1	0	0.7
3	H (**12a**)	$PhI(OAc)_2$ (0.6)	1.1	25	2
4	H (**12a**)	$FeCl_3$ (1.1)	1.1	40	24
5	H (**12a**)	$FeCl_3$ (2.2)	2.1	56	24
6	OMe (**12b**)	$FeCl_3$ (2.2)	2.1	70	24

[a] See Scheme 2, step 8. General conditions: THF, −78 °C to rt. CuOTf was added as a MeCN solution. $CuCl_2$ and $FeCl_3$ were added as DMF solutions. [b] Trace quantity could be observed by LC/MS.

(16) DeMartino, M. P.; Chen, K.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 11546.

(17) Kim, J. W.; Lee, J. J.; Lee, S. H.; Ahn, K. H. *Synth. Commun.* **1998**, *28*, 1287.

(18) Krygowski, E. S.; Murphy-Benenato, K.; Shair, M. D. *Angew. Chem., Int. Ed.* **2008**, *47*, 1680.

(19) Kita, Y.; Yakura, T.; Tohma, H.; Kikuchi, K.; Tamura, Y. *Tetrahedron Lett.* **1989**, *30*, 1119.

Scytoneman-2,2′-dione **13** was obtained directly from the corresponding reduced dimer **12a** by oxidation with DDQ. To obtain scytonemin, the methoxy functionalities of **12b** had to be converted into its corresponding hydroxyl groups before oxidation. Employing standard Lewis acidic demethylating conditions afforded the wanted conversion into tetrahydroscytonemin **12c**, albeit with a moderate decay of the substrate. Utilizing the oxidizing properties of DDQ in the last synthetic procedure provided scytonemin (**1**). Interestingly, reversing the order of the two last synthetic operations, and thus demethylating the methoxy scytonemin analogue, yielded no product at all. It has previously been reported that scytonemin is sensitive toward alkaline and Brønsted acidic conditions,[20] a list which now can be supplemented with Lewis acidic conditions. The sensitivity to basic conditions impeded our initial plan to use a silyl protective group on the phenolic oxygen and then remove both this and the vinylic TMS group at the same time in a final global deprotection. Despite several attempts, we failed to develop reaction conditions strong enough to enforce excision of the vinylic TMS group but mild enough not to cause decomposition of scytonemin or its tetrahydro analogue.

(20) Garcia-Pichel, F.; Castenholz, R. W. *J. Phycol.* **1991**, *27*, 395.

In summary, we have completed the synthesis of the cyanobacterial alkaloid scytonemin. The parent structure, the scytoneman skeleton, was assembled by a ferric chloride induced oxidative coupling of two identical fragments. This tetracyclic fragment was effectively constructed stereospecifically, with respect to the exocyclic double bond, by a tandem Heck–Suzuki–Miyaura cyclization as a key reaction. The synthetic route is flexible and allows for effective synthesis of numerous scytonemin analogues. We anticipate that this could pave the way for the scytoneman skeleton as a lead structure in the development of new anti-inflammatory and anticancer drugs and potentially also new UV stabilizers.

Acknowledgment. We thank the Swedish Research Council and the Centre for Skin Research at University of Gothenburg for financial support.

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