First Total Synthesis of Pandamarine

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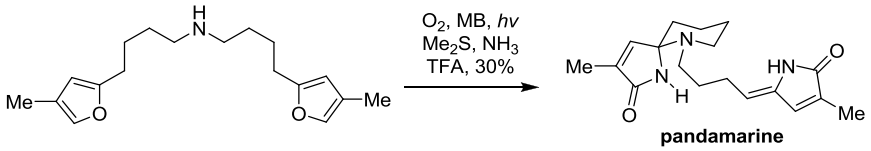
Supporting Information Placeholder



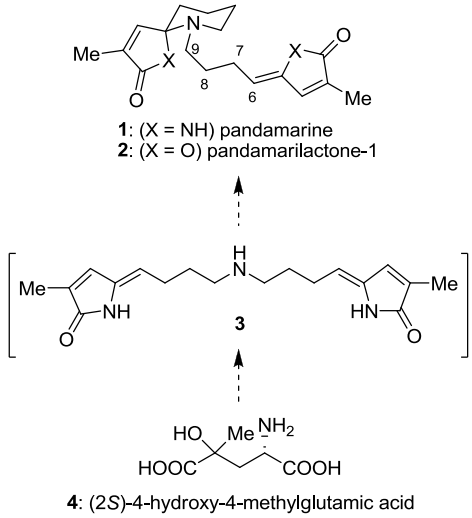
ABSTRACT: The first total synthesis of pandamarine, an alkaloid isolated from *Pandanus amaryllifolius* is reported. The key step of this extremely short (6 steps in total) and protecting group-free synthesis is a highly efficient cascade reaction sequence initiated by the photooxidation of an easily accessible and symmetric difuran precursor.

Pandamarine (**1**, Scheme 1) is an alkaloid that was isolated in 1992 by Byrne's group from the leaves of the tropical plant *Pandanus amaryllifolius*.[1] Pandamarilactone-1 (**2**, Scheme 1), was also isolated from the same plant one year later.[2] Biogenetically, the isolation team have proposed that pandamarine (**1**) might be the spiro-*N*,*N*-ketalization product of a symmetric *bis*-lactam (**3**, Scheme 1).[1,3] This proposal is consistent with the fact that pandamarine (**1**) occurs as a racemate. It was suggested that this possible biogenetic intermediate **3** might in turn be obtained from (2*S*)-4-hydroxy-4-methylglutamic acid (**4**, Scheme 1) since this amino acid was found in a related species, *P. veitchii*.[4] *Pandanus amaryllifolius* is one species out of 600-700 Pandanus trees, or shrub-like plants, that are widely distributed throughout the tropics. Many medicinal applications for extracts from the genus Pandanus have been reported.[5,6] Amongst these reports, it was recently shown that a *Pandanus amaryllifolius* leaf extract has antihyperglycemic effects.[6]

Recently, Robertson's group reported the first total synthesis of pandamarilactone-1 (**2**).[7] Within the same study, it was also proven that pandamarine (**1**) could not be produced by subjecting pandamarilactone-1 (**2**) to acid and then base sequentially (H_2SO_4/NH_3), under conditions that mimicked those used in the isolation in order to separate the alkaloid from non-alkaloidal constituents. Therefore, it was proposed that pandamarine (**1**) is a genuine natural product rather than an artifact of the isolation process.

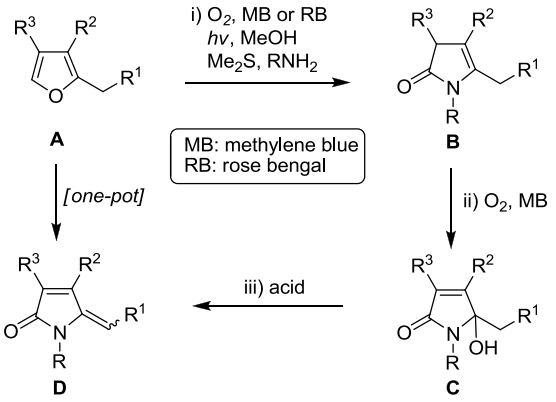
Pandamarine's structure was determined by X-ray diffraction[1] and consists of both a diazaspiro[4.5] and a 5-ylidenepyrrol-2(5*H*)-one unit, connected by a carbon chain (C7-C9, **1**, Scheme 1). The diazaspiro[4.5] motif is found in a small number of other natural products such as: haplophytine,[8] isoschizogamine[9] and the related alkaloids leuconoxine,[10] the leuconodines[11] and melodinine E.[12] In contrast, the 5-ylidenepyrrol-2(5*H*)-one unit is ubiquitous appearing in many natural products and pharmaceuticals.[13,14] Unsurprisingly, reports dealing with the synthesis of diazaspiro[4.5] scaffolds are limited,[15] while many methods have been developed for the synthesis of 5-ylidenepyrrol-2(5*H*)-one motifs.[13]

Scheme 1. Proposed Biosynthetic Origin of Pandamarine[1,3]



We recently developed a methodology for the synthesis of 5-hydroxy-1*H*-pyrrol-2(5*H*)-ones of type **C** and their dehydrated counterparts 5-ylidenepyrrol-2(5*H*)-ones **D** (Scheme 2) starting from furans and using a variety of primary amines, or ammonia, as the nitrogen source.[16] More specifically, a complex cascade reaction sequence begins with the oxidation of substituted furans by singlet oxygen, generated using methylene blue (MB), or rose bengal (RB), and visible light. The initial products of this sequence are 2-pyrrolidinones of type **B** (Scheme 2).[17,18] The reaction sequence can easily be extended to the synthesis of α,β-unsaturated γ-hydroxy lactams of type **C** through the catalytic oxidation of the 2-pyrrolidinones **B** by MB in the presence of molecular dioxygen.[16] We found that this second oxidation step is accelerated by the basic environment of the reaction mixture at this stage. The dehydrated

Scheme 2. Synthesis of 5-Ylidenepyrrol-2(5*H*)-ones D from Furans



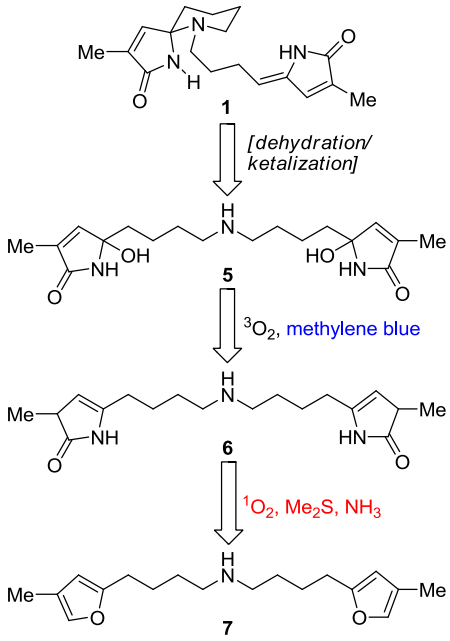
counterparts (**D**, Scheme 2) can be the final product of the sequence if next a Brönsted acid (HCOOH, TFA, or PTSA) is used.[16] Now, we wanted to investigate if this methodology could be applied to a difuran precursor (**7**, Scheme 3) and in the presence of an unprotected secondary amine appended as part of the alkyl side chain.

Our retrosynthetic analysis for pandamarine (**1**) is presented in Scheme 3. Pandamarine **1** might be derived by a ketalization/dehydration reaction of the symmetrical *bis*-5-hydroxy-1*H*-pyrrol-2(5*H*)-one **5** which it was hoped might be obtained as the MB-catalyzed oxidation product of the intermediate *bis*-2-pyrrolidinone **6**.[16] This pyrrolidinone might in turn be accessed via photooxygenation of the symmetric difuran **7** using ammonia as a nitrogen source.[16,18]

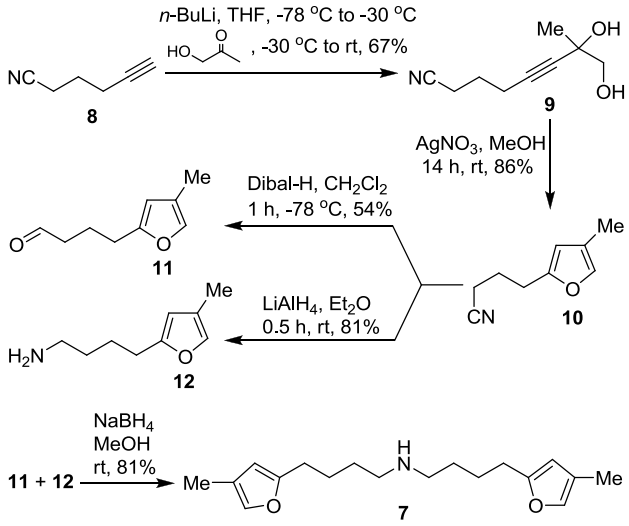
The synthesis of photooxygenation substrate **7** starting from the commercially available 5-hexynenitrile (**8**) is described in Scheme 4. The alkynyl lithium anion of **8** was added to unprotected hydroxyacetone to afford diol **9**. In the next couple of steps, we proceeded as Robertson[7] had in his synthesis of pandamarilactone-1 (**2**) starting initially with the cyclodehydration of alkynyl diol **9** by silver nitrate to furnish furan **10**. However, we performed this reaction in methanol instead of CH_2Cl_2 because of the low solubility of diol **9** in CH_2Cl_2. Nitrile **10** was separated into two portions; the first was reduced to the corresponding aldehyde **11** and the second to amine **12**. Difuran **7** was then obtained via the reductive amination of aldehyde **11** using sodium borohydride and amine **12**.

The photooxygenation reaction of difuran **7**, which, it should be noted, contains an unprotected amine, was performed in methanol (0.3 mmol, final concentration 40 mM) using MB (0.1 mM, 0.25 mol % compared to the furan substrate) as the photosensitizer (Scheme 5). After irradiation of the solution with visible light in the presence of molecular oxygen (bubbling through the solution) the double oxidation of the substrate was complete in just 2.5 minutes (the reaction was monitored by ^{1}H NMR). More MB (6 mol % final ratio, 2.4 mM final concentration) was then added and the photooxidized product reduced with Me_2S (7 equiv, 75 min). Intriguingly, the subsequent addition of aqueous ammonia (4 equiv) afforded within 5 hours intermediate **5**, as evidenced by the crude ^{1}H NMR spectrum. The combination of MB (6 mol %) with ammonia (4 equiv) was proven to be very effective for the formation of the intermediate *bis*-2-pyrrolidinone **6** and its subsequent one-pot oxidation to the desired *bis*-5-hydroxy-

Scheme 3. Retrosynthetic Analysis



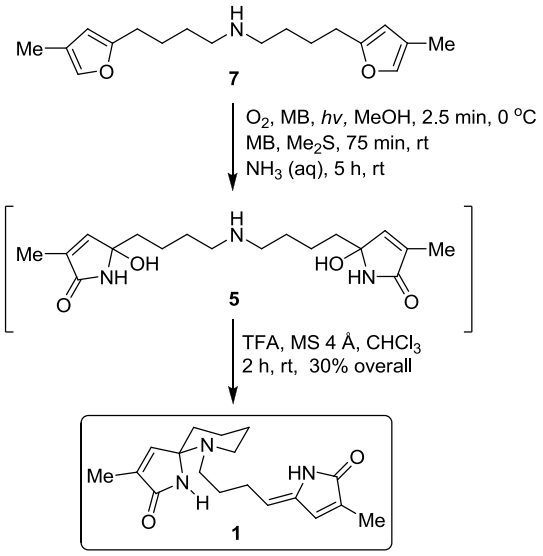
Scheme 4. Synthesis of Difuran 7



1*H*-pyrrol-2(5*H*)-one **5** (Scheme 5). The final step of the reaction sequence was to effect the ketalization/dehydration of **5**. This transformation turned out to be quite tricky as the direct addition of TFA in $CHCl_3$ did not yield pandamarine (**1**). However, the complete removal of the volatile contaminants from the reaction mixture before the addition of TFA was the key to success. More precisely, after the bulk of the solvent had been removed using a rotary evaporator, the residue was subjected to high vacuum at 50 °C for 5 hours prior to the addition of the acid. To our delight, in this case, the addition of TFA (2 equiv) to a solution of **5** in $CHCl_3$ containing molecular sieves (4 Å) afforded pandamarine (30% overall isolated yield starting from **7**, Scheme 5) in 2 hours. The ^{1}H and ^{13}C NMR data are in full agreement with those reported in the isolation paper.[1]

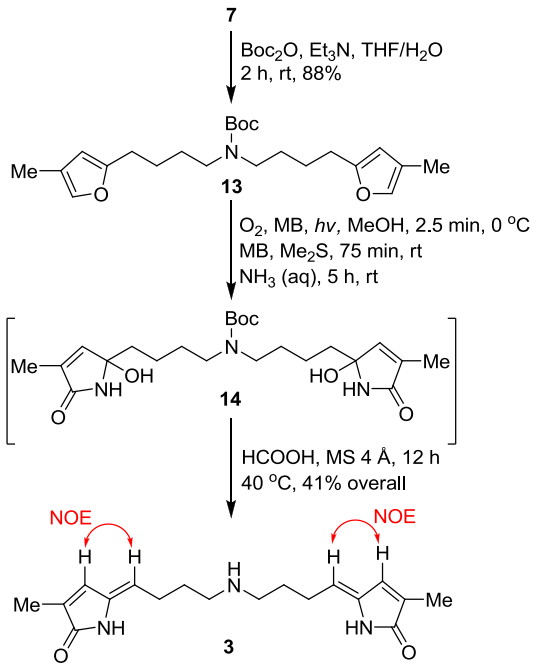
In order to find out if lactam **3** was indeed the precursor of the natural product (**1**), under the conditions we had employed,

Scheme 5. Synthesis of Pandamarine from Difuran 7



compound **3** was prepared independently starting from the Boc-protected di(furylalkyl)amine **13** (Scheme 6). Subsequent application of the early stages of the protocol we had developed, led to the transformation of **13** into the Boc-protected *bis*-5-hydroxy-1*H*-pyrrol-2(5*H*)-one **14** which was then dehydrated and deprotected to furnish the desired *bis*-lactam **3** when the reaction mixture was treated with HCO_2H at 40 °C (41% overall isolated yield starting from **13**). The *Z,Z* geometry of **3** was proven by NOE studies. Treatment of **3** under the conditions applied for the transformation of **5** to **1** (Scheme 5), or under even harsher conditions (6 equiv TFA, 18 h) did not give the natural product (recovery of starting material). This experiment would suggest that under our conditions, the spiro-*N*,*N*-ketalization of **5** precedes the dehydration. In other words, **3** is not an intermediate in the transformation of **5** to **1**.

Scheme 6. Synthesis of *bis*-Lactam 3



In conclusion, we have presented the first total synthesis of pandamarine (**1**), as well as, its proposed biogenetic intermediate (**3**). The developed synthetic strategy is very practical and extremely fast (just 6 steps from **8** to **1**). No protecting groups are used in the pandamarine (**1**) synthesis, oxygen is the terminal oxidant and the step-economy is very good. The key step of this approach is a cascade reaction sequence initiated by singlet oxygen which leads to the transformation of a very simple linear difuran precursor **7** into the natural product.

Supporting Information

Experimental procedures, full spectroscopic data and copies of ^{1}H and ^{13}C-NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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