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Synthesis of Pandamarilactone-1

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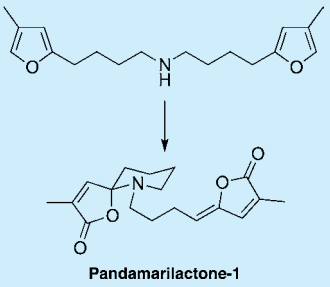
Supporting Information

ABSTRACT: The first total synthesis of pandamarilactone-1, an alkaloid of *Pandanus amaryllifolius*, is reported. The nine-step synthesis features furan oxidation with singlet oxygen and then spiro-*N*,*O*-acetalization and elimination to generate the natural product and further *Pandanus* alkaloids, pandamarilactonines A–D.



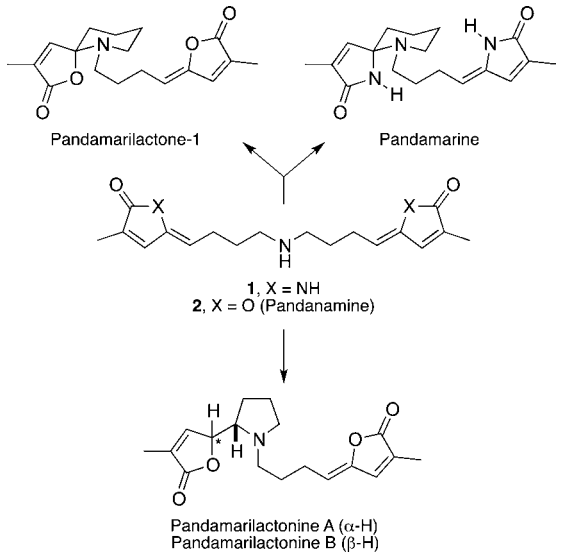
Pandanus amaryllifolius, also known as fragrant screwpine, is one of 52 *Pandanus* species found in the Philippines out of ~700 species known in tropical and subtropical regions.[1] This plant is noted for its scented leaves that find use in Southeast Asia to flavor rice, the main flavorant being 2-acetyl-1-pyrroline. Selected parts of the plant form the basis of traditional medicines with applications in the treatment of a variety of minor ailments (fever, indigestion, headaches) and more serious conditions (leprosy, rheumatism, epilepsy). Associating these reputed effects with individual molecules has been achieved in only a few cases, and there is scope for exploring potential medicinal applications of *Pandanus* constituent molecules, their derivatives, and analogues.

Through our interest in oxidative spirocyclizations of furan substrates we were drawn to the structure reported for pandamarilactone-1 (Scheme 1), which was isolated from *P. amaryllifolius* leaves collected from Manila, Philippines.[2] To the best of our knowledge, the piperidine/butenolide spiro-*N*,*O*-acetal core of this molecule occurs in only one other reported natural product, the alkaloid hederacine B from the perennial plant *Glechoma hederaceae*,[3] but here the piperidine is embedded in a tropane ring system. Intriguingly, a year before the disclosure of pandamarilactone-1, Byrne's group reported pandamarine as the major base from *P. amaryllifolius* leaves.[4]

In the plant samples from which pandamarilactone-1 was obtained there was no evidence of pandamarine; therefore, despite the same apparent plant species having been harvested in both cases, either two different subspecies were involved or differing phytochemical profiles result from local environmental variations (Byrne's *P. amaryllifolius* leaves were collected from Isabela province in the same island, Luzon, as Manila).

Alternatively, because pandamarilactone-1 was isolated apparently in optically active form ($[\alpha]_D$ −33.0 (MeOH)), yet pandamarine was crystallized as the racemate, we speculated that pandamarine could, in principle, be an artifact of the isolation process which uses concentrated ammonia solution to release the alkaloids from acidic solution.[5] Another concern was that while the structure of pandamarine had been secured by X-ray crystallographic analysis, that of pandamarilactone-1 was based primarily on NMR spectroscopic data. With these potentially connected aspects in mind, we set about designing a short synthesis of pandamarilactone-1 to confirm the structure and test experimentally if pandamarine is easily produced upon treatment of pandamarilactone-1 with ammonia.

Scheme 1. *Pandanus* Alkaloids from Pandanamine and Its Dilactam Analogue



The proposed biosynthesis of pandamarine involves spirocyclization of symmetrical dilactam **1**, which is envisaged to be obtained from 4-hydroxy-4-methylglutamic acid since this

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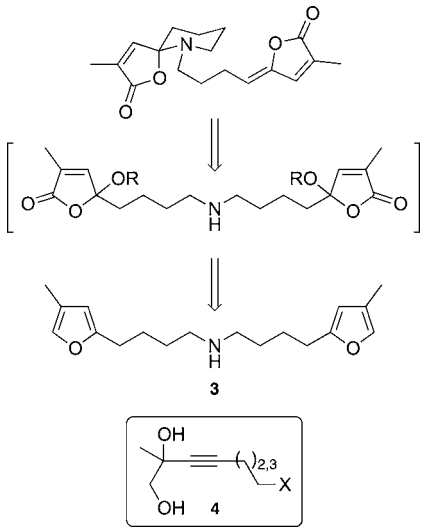
amino acid occurs in the related *P. veitchii*.[4] By extension, the biosynthesis of pandamarilactone-1 and other *Pandanus* lactones, such as pandamarilactonines A and B, is thought to proceed via analogous dilactone **2**,[6] later found in *P. odorus* and named pandanamine.[7] The key step in Takayama's biomimetic synthesis of pandamarilactonines A and B proceeds via pandanamine **2**, but under these reaction conditions, no pandamarilactone-1 was observed.[6]

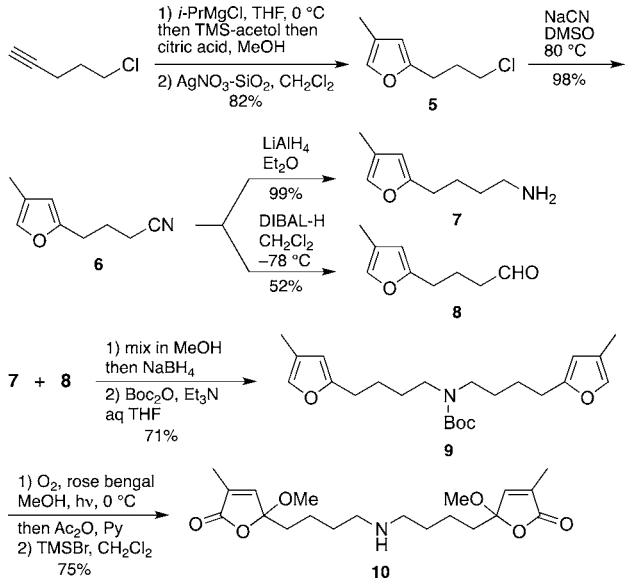
Following strategically similar lines, we projected a synthesis of pandamarilactone-1 from symmetrical di(furylalkyl)amine **3** (Scheme 2), the oxidation of which would allow spirocyclization and elimination to complete the route. In this context, we reported two general methods for butenolide spiro-*N*,*O*-acetal formation from ω-aminoalkylfurans.[8] In the first, oxidation with MCPBA generates the hydroxybutenolide; in the second, $^1O_2$ generates the analogous methoxybutenolide. In both methods, subsequent addition of H_2SO_4 was required in order to complete spiro-*N*,*O*-acetalization and only sulfonyl protecting groups were compatible with this overall process. Extension of this methodology to the oxidation and spirocyclization of amine **3** requires a nitrogen protecting group that is able to survive the oxidation and be cleaved easily without destroying the butenolide functionality. Trials with simple 2-(4-aminobutyl)-furan derivatives[9] showed carbamate protecting groups to meet these criteria, and Boc was selected with the intention of combining the *N*-deprotection and spirocyclization steps into a single process. Access to amine **3** required an efficient synthesis of an appropriately functionalized 2,4-dialkylfuran for which the most direct solution appeared to be Lewis acid mediated cyclodehydration of an alkynyl diol precursor (*cf.* **4**). Although this approach was reported almost 60 years ago (with $HgCl_2$ as the catalyst),[10] versions with improved catalysts continue to be published.[11]

The synthesis of amine **3** initiated with a brief survey of the reactions of appropriately functionalized acetylide organometallics with hydroxyacetone (acetol). In our hands, use of unprotected acetol with an excess of alkynyl Grignard reagents gave only moderate yields of diol. Protection of acetol as its TBS derivative allowed just a slight excess of alkynyl organometallic to be used (Grignard or organolithium), and yields were high; however, a separate deprotection step is required with this robust protecting group. The most effective result was found in TMS-acetol which is trivial to prepare on a large scale,[12] undergoes organometallic addition cleanly, and the TMS group cleaves during workup with citric acid/MeOH. For the cyclodehydration, we selected Knight's $AgNO_3$–SiO_2 variant because the catalyst is inexpensive, the procedure is operationally very straightforward, and the products are generated in a state of excellent purity straight from the reaction mixture following filtration.[13] Through these procedures 2-(3-chloropropyl)-4-methylfuran (**5**, Scheme 3) was obtained from 5-chloro-1-pentyne in excellent yield on a multigram scale.

Scheme 2. Synthetic Approach to Pandamarilactone-1



Scheme 3. Synthesis of a Pandanamine Equivalent



The remainder of the synthesis to Boc-protected **3** (i.e., **9**) proved straightforward. The supply of cyanide **6** was split into two portions for parallel reductions to the amine **7** and aldehyde **8**. The DIBAL-H reduction was somewhat capricious and even with relatively dilute reaction mixtures and careful addition of DIBAL-H, oligomerization of imine intermediates resulted in a lowering of yields. Reductive amination and *N*-protection afforded oxidation substrate **9**. Of the two methods for furan oxidation, the $^1O_2$-mediated process has become our method of choice for amine substrates, and the double oxidation, under these conditions, gave bis(methoxybutenolide) derivative Boc-**10** cleanly.[14] Direct oxidation of the free amine **3** under the same conditions gave complex product mixtures and unacceptably low yields of butenolide products. Finally, treatment with TMSBr released the free amine **10** without affecting the acid-sensitive acetal functionality.[15]

We envisaged that mild acid treatment of bis(methoxybutenolide) **10**, a masked form of pandanamine, would initiate ionization (to ion **13** or **14**, Scheme 4), spirocyclization, and elimination steps to produce pandamarilactone-1 directly. It turned out that finding a balance between no reaction and unproductive decomposition was surprisingly difficult and initial studies with both protic and Lewis acids were unsuccesful.[16] Eventually, based on a combination of conditions used in the original isolation paper[2] and procedures that we had developed in spiro-*N*,*O*-acetalization model studies,[17] we found that a vigorously stirred biphasic mixture of H_2SO_4/CH_2Cl_2

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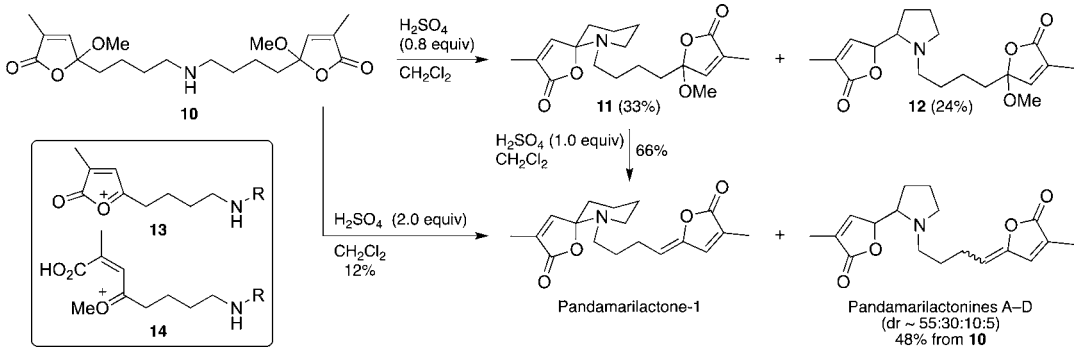
Scheme 4. Completion of the Synthesis of Pandamarilactone-1 and Pandamarilactonines A–D



gave promising results. For example, with 0.8 equiv of H_2SO_4 in CH_2Cl_2 the reaction progressed part way to give the pandamarilactone-1 and pandamarilactonine A/B variants **11** and **12**, respectively. Resubmission of intermediate **11** to the reaction conditions (with 1.0 equiv of H_2SO_4) completed the process successfully, with elimination of methanol and the production of pandamarilactone-1. The whole process could be achieved in a single reaction using 2.0 equiv of H_2SO_4 at the outset, and pandamarilactone-1 was produced in 12% yield, with the majority of the rest of the product being a mixture of pandamarilactonines A–D.[18,19] Despite several attempts to improve the yields and reproducibility of these reactions, 12% was the optimum for the single-flask process.

Pandamarilactone-1 was reported to be an amorphous solid;[2] however, efforts to obtain a crystalline sample of our synthetic product or various salts for X-ray crystallographic analysis were fruitless and structural confirmation had to be based on NMR evidence. First, the ^{13}C NMR data were essentially identical to those reported (see Supporting Information). In ^{1}H NMR spectra run in $CDCl_3$ the low-field resonances corresponded well to those reported but most of the methylene resonances in the 1.5–3.0 region were broadened, resulting in poor quality HMBC and HSQC data. However, in methanol-d_4, the spectra sharpened sufficiently to enable convincing HMBC data to be obtained in support of the spiro-*N*,*O*-acetal core, all other aspects of the structure being unambiguous. Figure 1 shows characteristic correlations.

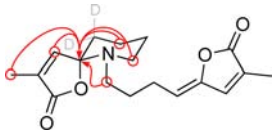
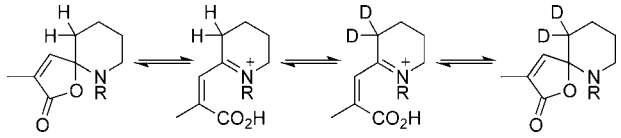


Figure 1. Diagnostic HMBC correlations (H→C) supporting a spiro-*N*,*O*-acetal. Note the deuteration; see text.

In the ^{13}C NMR spectrum of pandamarilactone-1 in methanol-d_4 the resonance at 36.2 ppm is a 1:2:3:2:1 'quintet' (J = 20 Hz) and the spiro-carbon at 107.7 ppm appears broadened and of low intensity. We attribute this to dideuteration of one of the methylenes, and reference back to the ^{1}H spectrum showed the integration of the methylenes to be reduced by an amount corresponding to two protons. Full proton integration was restored when the sample was allowed to stand in undeuterated methanol. An acid-catalyzed H/D exchange process, as sketched in Scheme 5, is consistent with these observations. This rapid (minutes) H/D exchange suggests that pandamarilactone-1 should racemize quickly in

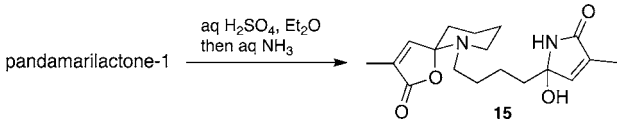
Scheme 5. H/D Exchange in a Sample of Pandamarilactone-1 Dissolved in Methanol-d_4, Reversed in Methanol-d_0



methanol; therefore, the significant specific rotation reported[2] is surprising. Nevertheless, this chemical reactivity, combined with the HMBC data, provide strong corroboration of the assigned structure of pandamarilactone-1.

With a sample of pandamarilactone-1 in hand we tested our speculation that pandamarine might be an artifact formed during the basification step of its isolation. Two preliminary experiments were performed: (i) a 4.4 mg sample in 0.5 mL of THF containing aq NH_3 (5.0 equiv) remained unaffected after 14 h at rt; (ii) a 2.1 mg sample in THF/aq NH_3 (1:1, 0.4 mL) gave a complex mixture of lactam products after a similar reaction time. Next, in an attempt to more closely replicate the conditions described in the original isolation,[4] an ether solution of pandamarilactone-1 was stirred with dilute H_2SO_4. The aqueous layer was rendered basic with aq NH_3, and the products were extracted into chloroform. This gave a mixture of pandamarilactone-1 and the hydroxy-lactam **15** (Scheme 6) in roughly equal proportion. Because pandamarine was not observed in any of these experiments, we conclude that it is most likely a genuine natural product.

Scheme 6. Attempted Conversion of Pandamarilactone-1 to Pandamarine



In conclusion, we have completed the first total synthesis of pandamarilactone-1 in corroboration of the proposed structure and have investigated a potential chemical correlation of this alkaloid with pandamarine.

■ ASSOCIATED CONTENT

Supporting Information

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

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Notes

The authors declare no competing financial interest.

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(15) The choice of TMSBr in this deprotection was guided by an application of this reagent to eliminate methanol from cyclic acetal systems, resulting in enol ethers, our original intention being to form *N*-Boc pandanamine; see: Sheldrake, H. M.; Jamieson, C.; Pascu, S. I.; Burton, J. W. *Org. Biomol. Chem.* **2009**, *7*, 238.
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(19) Ratios varied; typically 55:30:10:5 for pandamarilactonines A−D, respectively.