General Synthetic Entry to Dihydrooxepine-spiroisoxazoline Natural Products: Total Synthesis of Psammaplysin A

Jan Paciorek†, Denis Höfler†, Kevin Rafael Sokol†, Klaus Wurst§, Thomas Magauer*†

†Institute of Organic Chemistry and Center for Molecular Biosciences, Leopold-Franzens-University Innsbruck, Innrain 80–82, 6020 Innsbruck, Austria
§Institute of General, Inorganic & Theoretical Chemistry, Leopold-Franzens-University Innsbruck, Innrain 80–82, 6020 Innsbruck, Austria

ABSTRACT: Here, we report a general synthetic entry to dihydrooxepine-spiroisoxazoline (DOSI) natural products that culminated in the first total synthesis of psammaplysin A. For the synthesis of the unique spirocyclic fragment we employed a strategy that features two key transformations: (i) The use of a diastereoselective Henry reaction/cyclization sequence granted access to the C7 hydroxylated isoxazoline scaffold in one step. (ii) A regioselective Baeyer–Villiger ring expansion enabled selective installation of the fully substituted dihydrooxepine and avoided the risk of a previously observed oxepine-arene oxide rearrangement. The overall synthesis proceeds in 13 steps from inexpensive starting material.

Dihydrooxepine-spiroisoxazoline (DOSI) natural products are a structurally unique family of marine alkaloids that comprises the psammaplysin, ceratinamides, ceratinadins, and frondolysins. Amongst them, the psammaplysin stand out as the largest class (>35 members) displaying anticancer, antimalarial, anti-HIV or antibiotic activities. In 1982, psammaplysin A (1) was isolated as the first member from the marine sponge Psammaplysilla purpurea by Kashman (Scheme 1A). The structure of 1 was initially proposed to feature a C6 cyclohexadiene-spiroisoxazoline motif as present in aerothionin (2). While this assignment was already revised by Clardy based on detailed NMR studies and single-crystal X-ray crystallographic analysis in 1985, it took another 30 years to validate the proposed absolute configuration. The structurally unique dihydrooxepine motif is thought to biosynthetically derive from the oxidation of dibromotyrosine (3) followed by ring opening. For the formation of aerothionin (2), a direct intramolecular opening of the putative epoxide intermediate at C6 was postulated and a 6π-electrocyclic ring-opening event that initiates the rearrangement of the arene oxide to the oxepine might be involved for the formation of 1 (compare Scheme 1B). This divergent process was investigated in seminal work by Clardy and enabled formal synthesis of 2, but did not lead to 1. The glutamic acid (4) derived three-carbon amide linker connects the DOSI to a modified dibromotyrosine and distinguishes 1 from its natural congeners, some of which possess an additional C19 stereocenter. The intriguing biological properties and unique functionalization pattern of the molecular framework render 1 a formidable synthetic target. Surprising-
During preliminary studies in our laboratories, we found that aldehyde 6, obtained from the dehydration with Martin’s sulfurane and oxidation of 5 with Dess–Martin periodinane (DMP), undergoes spontaneous arene oxide-oxepine rearrangement to 7 in 30% yield (Scheme 1b). We initially considered oxepin 7 as a valuable precursor for 1, but 7 turned out to be unstable upon storage and underwent slow decomposition to unidentified aromatic by-products. Unexpectedly, attempted conversion of 7 to ester 8b was even more problematic as arene oxide 9 was obtained as the only product. A second key observation was made when we investigated the hydroxylation of isoxazoline 10, the product of a preceding nitrile oxide [3+2]-cycloaddition reaction (see Supporting Information for details). In this case, hydroxylation to 11 was outcompeted by rapid ring opening of the aza enolate to give isoxazole 12 as the sole product in 65% yield. These key insights were crucial for our further synthetic planning and ultimately led us to the development of the revised retrosynthetic outline in Scheme 2.

Scheme 2. Retrosynthetic Strategy for Psammaplysin A

We began with the disconnection of the known linker sidechain moloka‘iamine (13) from 1 and focused our further analysis on the obtained DOSI 14. We anticipated that the lack of a fully intact oxepin should prevent the risk of unwanted arene oxide formation. Sequential removal of the enol ether decoration of 14 revealed structurally simplified 15. The lactone acetal contains the retron for a Baeyer–Villiger oxidation of C6 producing spirocyclic ketone 16. To avoid potential ring opening as observed for 10, we considered simultaneous installation of the requisite C7 hydroxy group and the isoxazoline scaffold in one step employing a powerful diastereoselective Henry reaction/cyclization protocol. This to end, intermediate 16 was traced back to commercially available 2-hydroxymethylencyclohexanone (17).

We began our forward synthesis with the bromination of compound 17 (Scheme 3A), which was on large scale obtained from the formylation of cyclohexanone in 89% yield. The use of N-bromosuccinimide (NBS) afforded the crude α-bromo ketoaddehyde in excellent yields, however, we found it to be unstable upon exposure to air. For this reason, we decided to telescope the following step and conduct the overall process as a one-pot reaction. According to the seminal report of Rosini,27 the intermediate bromide was treated with ethyl nitroacetate and triethylamine to give 16a and 16b as a 3:1 mixture of diastereomers at C7 as determined from the crude 1H NMR. After chromatographic separation of the highly polar 16b, we obtained 16a in 5% yield. The relative configuration of the desired diastereomer 16a was validated by single crystal X-ray analysis. Performing the reaction in acetonitrile at −25 °C was crucial as lower diastereoselectivities were observed when performing the reaction at higher temperatures or changing the solvent to methanol for which an equimolar mixture of 16a and 16b was obtained. We then proceeded with the deoxygenation of 16a employing triethyl phosphate in 1,4-dioxane at 100 °C to isolate the spirocyclic isoxazoline 18 in up to 99% yield.

Having installed the 4-hydroxisoxazoline motif and with multigram amounts of ketone 18 in hand, our attention was directed toward investigation of the Baeyer–Villiger oxidation to enable installation of the DOSI motif. We were pleased to see that exposure of 18 to m-chloroperbenzoic acid (m-CPBA) in the presence of disodium hydrogen phosphate afforded the corresponding lactone 19 in nearly quantitative yield. To our surprise, the protection of the hydroxy group with tert-butylmethylsilyl trifluoromethanesulfonate (TBOTf) and triethylamine failed to give the silyl ether. Instead, formation of carbonate 20 was observed. This product might be derived from the reaction of 19 with ethyl cyanoformate, itself formed by decomposition of 19. A similar isoxazoline fragmentation as part of the biosynthesis of ceratinamine was studied by Ganem.34

In parallel, we took advantage of the reaction of 16a with dimethylvinylsilyl chloride in the presence of imidazole.35 Under these conditions, clean silylation of the C7 hydroxy group followed by intramolecular 1,3-dipolar cycloaddition of the vinyl group with the nitronate took place to furnish the tricyclic acetal 21 in 95% yield. This motif serves a dual role as it (i) protects the hydroxy group and (2) should enable one-step masking of the isoxazoline as described by Rosini.36 The following Baeyer–Villiger oxidation provided 22 as the only regiosomer in 88% yield. However, subsequent attempts to form the ketone acetal phosphate 23 employing Nicolau’s conditions (diphenyl chlorophosphate, KHMD, THF, HMPA, −78 °C),37 were low yielding due to decomposition of the product upon attempted isolation.

For this reason, we returned to isoxazoline 18 and protected the hydroxy group (imH, TBSCI) prior to the ring expansion. The subsequent Baeyer–Villiger oxidation proceeded with excellent regioselectivity and furnished the desired lactone 15 in 87% yield over two steps on a 6-gram scale. When performing the following ketene acetal phosphate formation at −78 °C, varying yields between 36-67% of 24 were obtained and large amounts of lactone 15 were recovered. After further optimization, we found that slow addition of a solution of potassium hexamethyldisilazide (KHMDS) in THF at −95 °C was crucial for complete consumption of the starting material and to give 24 in reproducible 86% yield. The palladium-catalyzed reduction of the ketene acetal phosphate to enol ether 25 also required some optimization. The use of Pd(PPh3)4 and Et3Al gave 25 as a complex mixture together with an unstable byproduct resulting from a competing cross-coupling reaction with Et3Al. We then switched to LiBH4 as the reductant,38 however, this led to competing reduction of the ester moiety. The chemoselectivity issue could be avoided by replacing LiBH4 with formic acid/triethylamine buffer. This allowed for clean conversion of 24 to tetrahydroxepine-spiroisoxazoline 25 for the first time. Further screening revealed PhMe3SiH as the ideal reagent to give 25 in 66% yield.
Scheme 3. Synthesis of Psammaplysin A a

A) Synthesis of the Spiroisoxazoline Motif

B) Completion of the Synthesis

With a scalable route to 25 in hand, we continued with the investigation of its sequential functionalization (Scheme 3B). For this purpose, we exposed 25 to a panel of oxidation conditions, most of which employed tert-butyl hydroperoxide (TBHP) in combination with a transition metal catalyst (CuBr; Cu; RuCl₃; Mn(OAc)₃; Mn(dpm); Pd(OH)₄/C; see Supporting Information for details). The screening revealed that the desired product 26 was formed under most conditions accompanied only by its regioisomeric α,β-unsaturated lactone 27. The use of Pd(OH)₄/C as the catalyst afforded 26 and 27 as a 2:1 mixture of regioisomers, however, the reaction suffered from low conversion. The best performing conditions with respect to conversion involved Mn(dpm)₃ and syringe pump addition of TBHP overnight to give 26 in 32% isolated yield. Subsequent α-bromination with CuBr, and 2,6-di-tert-butylpyridine (DTBP) in a mixture of chloroform and ethyl acetate at 100 °C proceeded cleanly to deliver the C₄-brominated product in 78% yield. The second bromination was accomplished upon exposure to tetra-n-butylammonium tribromide (TBATB) and DTBP at 60 °C in chloroform to afford 28 in 72% yield. We found that the overall yield of 28 could be improved by telescoping the three oxidations and leaving out the chromatographic purification. In this way, we obtained 28 in 27% yield over three steps from 25. Finally, sequential treatment of 28 with KHMDs and methyl trifluoromethanesulphonate (MeOTf) gave the fully substituted DOSI 14 in 53% yield.

For the late-stage attachment of the protected moloka‘i amine unit 29, which was prepared from tyramine in four steps (see Supporting Information), we first attempted conversion of ethyl ester 14 into the corresponding carboxylic acid. Saponification under aqueous conditions (LiOH, THF, H₂O, 23 °C) followed by isolation of the acid turned out to be impossible in our hands as decomposition, presumably via decarboxylation, was observed even at low temperatures. For this reason, we decided to treat 14 with potassium trimethylsilanolate (TMSOK) at −15 °C under non-aqueous conditions followed by direct addition of ammonium salt 29. N-methylimidazole (NMI) and chloro-N,N,N′,N′-tetramethylformamidinium hexafluorophosphate (TCFHF). This one-pot procedure bypassed the problematic isolation of the acid and allowed us to obtain the desired amide 30 in 79% yield from 14. The following deprotections of the C7 oxygen and C20 nitrogen proceeded smoothly to furnish...

a See the Supporting Information for detailed procedures and characterization data.
psammaplysins A (1) in 60% yield. The analytical data (H-NMR, 13C-NMR, HRMS) for 1 and its bisacetylated derivative fully matched those reported for the natural compound. Overall, psammaplysins A (1) was synthesized in 13 steps from commercially available starting material.

In summary, we have accomplished the first synthesis of psammaplysins A (1) nearly 40 years after its first isolation. The key to success of the developed strategy was the use of a Henry addition/O-alkylation sequence instead of a nitrite oxide [3+2]-cycloaddition. This granted access to the fully substituted C7 hydroxylated heterocyclic scaffold in one step. For the construction of the 7-membered ring-system a high-yielding Baeyer-Villiger oxidation turned out to be the method of choice. This avoided the risk of a previously encountered oxepin-arene oxide rearrangement and paved the way for the selective installation of the fully intact DOSI motif. The late-state attachment of the sidechain ensures high flexibility and modularity of the synthesis. This should allow for the preparation of several structurally related members as well analogs with deep-seated structural modifications thereof and facilitate future bioactivity studies.

ASSOCIATED CONTENT

Supporting Information
Full experimental details are provided in the supporting information. CCDC 2207064–2207066 contain the supplementary crystallographic data for 7, 9, 16a of this paper and can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

AUTHOR INFORMATION

Corresponding Author
Thomas Magauer, thomas.magauer@uibk.ac.at

Funding Sources

T.M. acknowledges the European Research Council under the European Union’s Horizon 2020 research and innovation program HALODRUGSYN (grant agreement No 774049), the Austrian Science Fund FWF (P3023-NBL and P33894-N) and the Center for Molecular Biosciences (CMBI).

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