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Asymmetric Total Synthesis and Stereochemical Revision of Gymnangiamide

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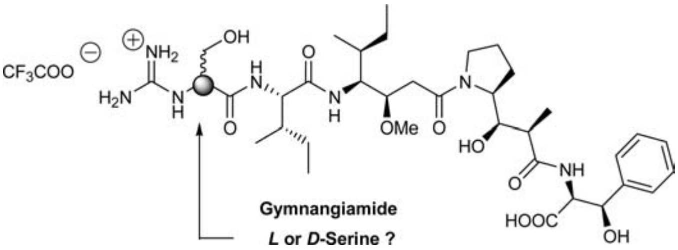
ABSTRACT



The asymmetric total synthesis of the originally proposed structure of gymnangiamide, a cytotoxic pentapeptide isolated from the marine hydroid *Gymnangium regae Jaderholm*, has been achieved. Key to the synthesis was the use of asymmetric hydrogenation of α-substituted *β*-ketoesters through dynamic kinetic resolution for the preparation of nonproteinogenic chiral amino acids. The disparity of the NMR spectra between the synthetic material containing the L-serine residue and the natural product required a revision of the proposed structure.

Gymnangiamide **1** is a cytotoxic pentapeptide isolated by Gustafson and co-workers[1] in 2004 from the marine hydroid *Gymnangium regae Jaderholm*, collected in the Philippines. On the basis of spectroscopic investigations, chemical degradation, and derivatization studies, structure **1** depicted in Figure 1 was assigned as gymnangiamide. In addition to the amino acids (2*S*,3*S*)-isoleucine (Ile) and (2*S*,3*R*)-phenylserine (Pser), this pentapeptide contains three nonstandard amino acid residues, *N*-desmethyl-dolaisoleuine (Ddil), *O*-desmethyl-dolaproine (Ddap), and a rare α-guanidino-L-serine (Gser), which has not previously been reported in a natural product. Furthermore, and to the best of our knowledge, there is no report on the total synthesis of gymnangiamide.

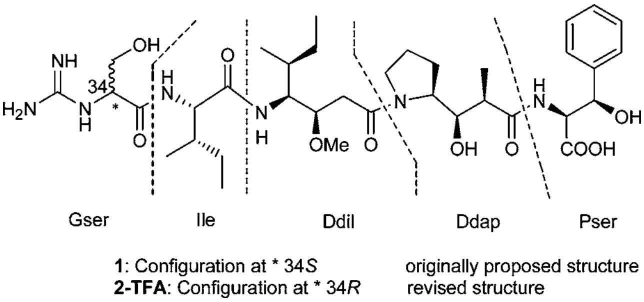


Figure 1. Originally proposed (**1**) and revised structure (**2-TFA**) of gymnangiamide.

In this paper, we describe the asymmetric total synthesis of gymnangiamide and in turn clarify its configuration since we also report that structure **1** (34*S*) does not correspond to

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(1) Milanowski, D. J.; Gustafson, K. R.; Rashid, M. A.; Pannell, L. K.; McMahon, J. B.; Boyd, M. R. *J. Org. Chem.* **2004**, *69*, 3036.

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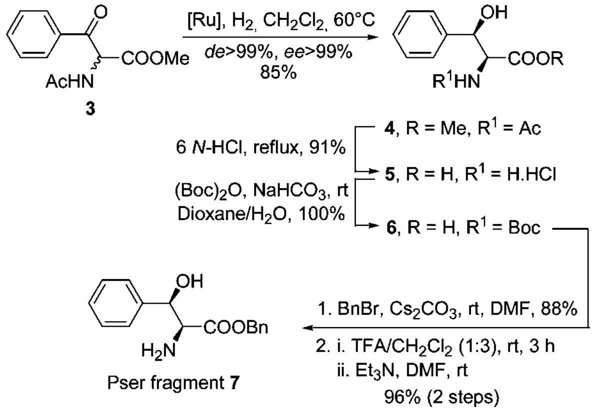
Scheme 1. Synthesis of the Pser Fragment **7**



natural gymnangiamide. We give synthetic evidence that compound **2-TFA** (34*R*), incorporating a D-serine instead of L-serine amino acid residue, corresponds to the natural product. The approach we have chosen for assembling the five units of the peptide involves the construction of the subunits (2*S*,3*R*)-phenylserine (Pser) and *O*-desmethyl-dolaproine (Ddap) in diastereochemically pure form using ruthenium-promoted asymmetric hydrogenation through dynamic kinetic resolution (DKR)[2] and the coupling with other fragments.

Initially, we synthesized the putative gymnangiamide **1** (Figure 1). The synthesis started with the valuable (2*S*,3*R*)-phenylserine (Pser) fragment **7**, which was prepared through DKR of racemic **3** using 1 mol % of $[(\mathrm{RuCl}((R)\text{-SYNPHOS})_2(\mu\text{-Cl})_3][\mathrm{NH_2Me_2}]$[3] catalyst, at 60 °C in dichloromethane under 120 bar. Under these optimized reaction conditions, the two chiral centers of Pser were established in one step, providing after recrystallization from ethyl acetate the optically pure compound (2*S*,3*R*)-**4** in 85% isolated yield. Treatment of **4** in refluxing 6 N HCl gave the (2*S*,3*R*)-phenylserine HCl salt **5**, which was converted into the *N*-Boc derivative **6** followed by esterification and deprotection of the *N*-Boc protective group providing the (2*S*,3*R*)-phenylserine (Pser) fragment **7** in 68% overall yield (Scheme 1).

The diastereochemically pure unusual *O*-desmethyl-dolaproine (Ddap)[4] residue **8** was prepared on multigram scale from *N*-Boc-(*S*)-proline through DKR using ruthenium-catalyzed asymmetric hydrogenation as a key step (Scheme 2).

The synthesis of the *N*-desmethyl-dolaisoleuine (Ddil) residue **10** was readily obtained from *N*-Boc-L-isoleucine as a single diastereoisomer in 44% overall yield through a four-step sequence involving Masamune reaction,[5] ketone reduction, selective O-methylation,[6] and hydrogenolysis.

Having established a scalable access to the three amino acids derivatives Pser **7**, Ddap **8**, and Ddil **10**, the stage was now set for their assembly and elaboration into gymnangiamide **1** using iterative DEPC-mediated couplings. The (2*S*,3*R*)-phenylserine (Pser) fragment **7** was coupled with the Ddap fragment **8** to provide the dipeptide **9** in 94% yield. Cleavage of the N-terminal Boc protective group of **9** followed by coupling with Ddil fragment **10** gave the desired tripeptide **11** in 89% isolated yield. The peptide chain was further elongated by coupling **11** with the dipeptide *N*-Boc-L-Ser-Ile-OH in the presence of DCC-HOBt as condensating agent to give the linear pentapeptide in 85% yield (Scheme 2). Finally, treatment of the latter under mild acidic conditions followed by guanidinylation[7] of the resulting free amine and subsequent hydrogenolysis of both the Cbz and benzyl ester protective groups afforded fully synthetic free pentapeptide **1** in stereopure form and good yield after recrystallization from MeOH. Surprisingly, the spectroscopic and physical properties of our synthetic sample[8] were distinctively different from those of the natural gymnangiamide **1**.

Careful examination of the original isolation procedure revealed that the reported data were most likely the data of the corresponding trifluoroacetic salt.[9] Thus, pentapeptide **1** was converted into its corresponding **TFA** salt **1-TFA** (Scheme 2). However, the ^{1}H and ^{13}C NMR still unexpectedly showed some different chemical shifts from those reported in the literature for the natural product, although the patterns of the peaks were quite similar.[10] We then directed our efforts toward ascertaining the nature

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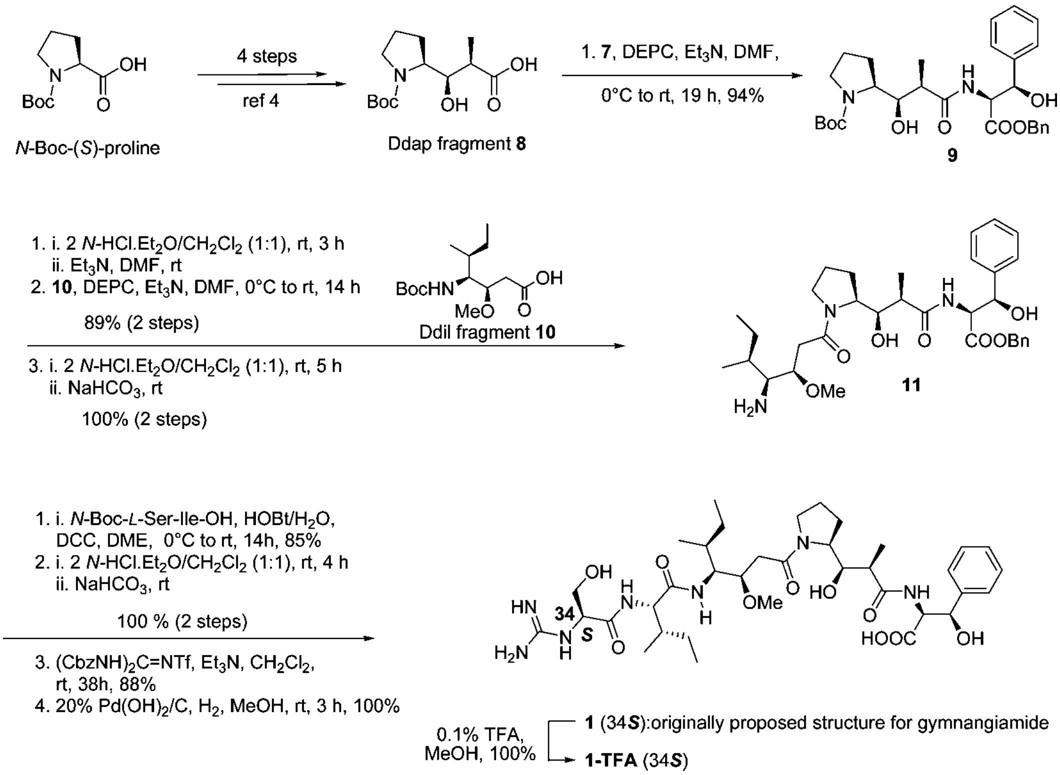
(8) The optical rotation of synthetic **1**, $[\alpha]^{27}_{D}$ -18.5 (*c* 0.22, MeOH), did not match the value $[\alpha]^{27}_{D}$ -32.5 (*c* 0.24, MeOH) of the natural product. See Supporting Informationfor NMR data.

(9) The natural product was isolated by preparative HPLC using CH_3CN/H_2O with 0.1% TFA as eluent. Generally, peptides tend to retain variable amounts of water and acids (as counterions or residual acid) resulting from the final stage of purification or isolation. Sewald, N., Jakubbe, H.-D., Eds. *Peptides: Chemistry and Biology*; Wiley-VCH: Weinheim, Germany, 2002; Chapter 2, pp 5−59.

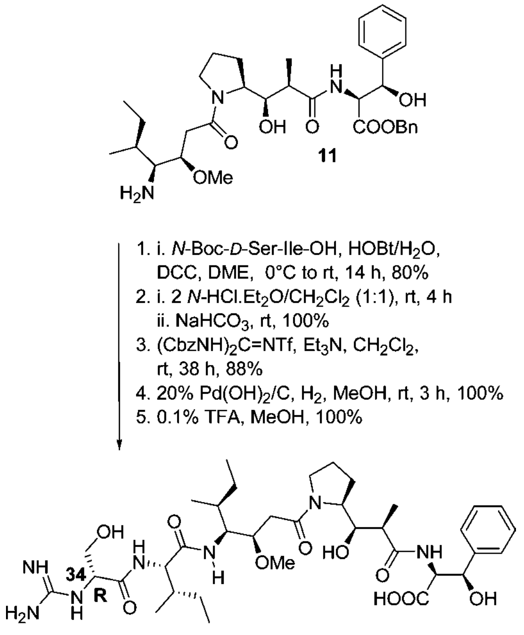
(10) The NH region was especially demonstrative of the solved discrepancies between the two isomers, with a strict superimposition between the published ^{1}H spectrum of the natural product and that of synthetic **2-TFA**. $[\alpha]^{27}_{D}$ -32.5 (*c* 0.16, MeOH), which matched the value $[\alpha]^{27}_{D}$ -32.5 (*c* 0.24, MeOH) of the natural product.

Scheme 2. Completion of the Synthesis of the Originally Proposed Structure **1** for Gymnangiamide



of the discrepancy. After careful reinspection of the original published procedure used by Gustafson et al.[1] for the assignment of the absolute stereochemistry of **1**, we suspected that the stereochemical assignment of the α-guanidino serine residue might be incorrect and we further favored a revision to the TFA salt of **1** from a L-serine to D-serine. Working as described for the synthesis of **1-TFA** but coupling the tripeptide **11** with *N*-Boc-D-Ser-Ile-OH and following the sequence depicted in Scheme 3, we synthesized **2-TFA**, which matches all available spectroscopic data of the natural gymnangiamide. Thus, we conclude that the α-guanidino serine residue in the natural gymnangiamide has the *R* configuration.

Scheme 3. Synthesis of the Revised Structure **2-TFA** for Gymnangiamide



2-TFA (34*R*): revised structure for gymnangiamide

In conclusion, the asymmetric total synthesis of gymnangiamide (**1**) has been accomplished through successful Ru-SYNPHOS asymmetric hydrogenation and has implied the stereochemical reassignment of the natural product from **1** to **2-TFA**. In addition to the structural revision, the described chemistry renders the natural substance readily available and opens the way to design analogues in amounts suitable for a thorough investigation of their biological properties.

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Supporting Information Available: Experimental procedures and full analyses of products **1**, **1-TFA**, and **2-TFA**. This material is available free of charge via the Internet at http://pubs.acs.org.

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