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Asymmetric Total Synthesis of Distaminolyne A and Revision of Its Absolute Configuration

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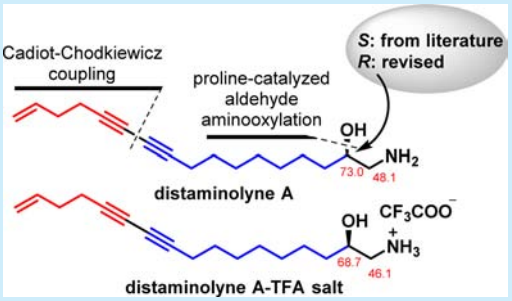
Supporting Information

ABSTRACT: The first total synthesis of a marine derived polyacetylene, distaminolyne A, and its enantiomer were achieved from the commercially available undec-10-en-1-ol. A key proline-catalyzed asymmetric α-aminooxylation of an aldehyde intermediate was used to introduce the chiral center en route to the enantiomerically pure 1,2-amino alcohols. The absolute configuration of both synthesized enantiomers of distaminolyne A was confirmed by using chiral derivatizing agents, leading to revision of the natural product absolute configuration from 2*S* to 2*R*. Antibacterial, pancreatic lipase (PL) inhibitory, and protein-tyrosine phosphatase 1B (PTP1B) inhibitory activities were evaluated.



Polyacetylenic natural products are widely distributed in a variety of organisms, such as plants, mosses and lichens, fungi, bacteria, insects, marine algae, sponges, or tunicates.[1,2] Although these secondary metabolites tend to be unstable, their unique rod-like structure and often conjugated character enable them to display extensive biological activities, including cytotoxicity, antimicrobial activity, HIV (human immunodeficiency virus) reverse transcriptase inhibition, and pancreatic lipase (PL) inhibition.[1,2] Marine organisms constitute a major source of naturally occurring polyacetylenes, which attracted a lot of attention for their chemical and pharmacological value.[1a] Our group has long been engaged in the research of bioactive marine polyacetylenes, and numerous secondary metabolites spanning a wide range of structural classes and various biogenetic origins have been isolated or synthesized.[3] For example, several new brominated polyacetylenes were discovered from the Chinese sponge *Xestospongia testudinaria* with significant PL inhibitory activities.[3d] Further total syntheses and structure modifications of these PL inhibitory compounds,[3a,b,e] such as xestospongenyne[3a] (**1**, with stronger inhibitory activity than the positive control Orlistat) (Figure 1), have also been achieved by our group, which may provide an insight for antiobesity drug discovery.

Recently, Copp and co-workers isolated an antibacterial acetylenic amino alcohol, distaminolyne A (originally proposed as **2a**), from the New Zealand ascidian *Pseudodistoma opacum*.[4] This is the first discovery of a chiral 1,2-amino alcohol structurally related to xestospongenyne (**1**), thus making it a potential PL inhibitor. In addition, the chiral 1,2-amino alcohol group is an important structural functional group in biologically active compounds, as found in β-adrenergic receptor blockers or immune stimulants.[5a,c] All the above evidence led us to embark on the total synthesis and biological activity evaluation of distaminolyne A (Figure 1).

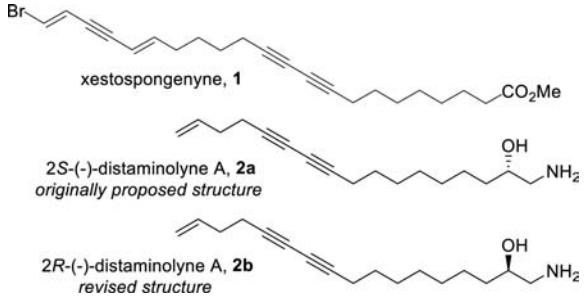


Figure 1. Structures of xestospongenyne (**1**) and distaminolyne A as originally proposed (**2a**) and revised (**2b**).

From a retrosynthetic analysis (Figure 2), the terminal chiral amino alcohol of compound **2a** could be installed by a D-proline catalyzed asymmetric α-aminooxylation of the aldehyde **3** using Cordova's methodology,[5a] followed by a formal transamination. The diynyl group would be introduced by a Cadiot–Chodkiewicz coupling of brominated acetylene **4** and pent-4-yn-1-ol. Finally, the commercially available undec-10-en-1-ol (**3**) will serve as a starting material, being oxidized, protected, and brominated toward functional intermediate **4**.

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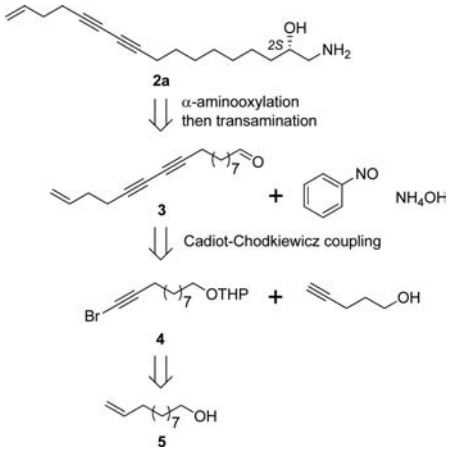
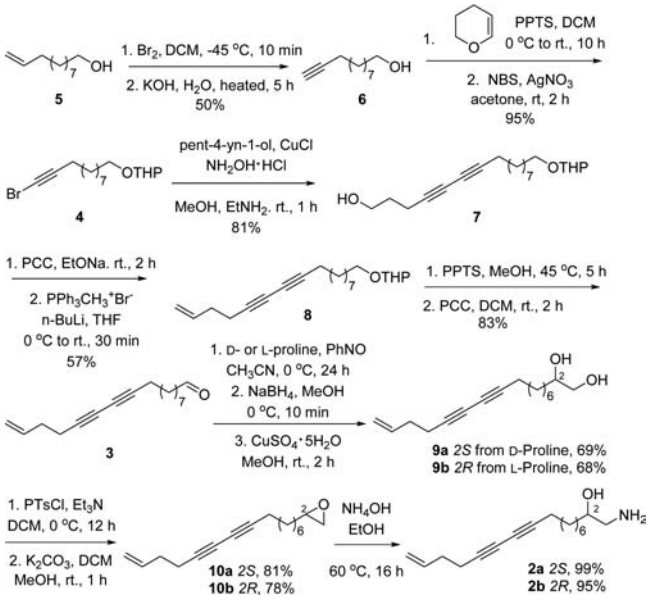


Figure 2. Retrosynthetic analysis of 2*S*-distaminolyne A (**2a**).

As shown in Scheme 1, the forward synthesis commenced with the preparation of **4**. The addition of bromine to undec-10-en-1-ol (**5**) led to the dibromo-alcohol, which was followed by an elimination in the presence of potassium hydroxide to afford the alkynyl alcohol **6**, with 50% overall yield.[6] The alcohol was then protected in the presence of 3,4-dihydro-2*H*-pyran in acidic medium and its terminal acetylene was brominated in the presence of NBS and $AgNO_3$ to yield 95% of key bromoalkyne intermediate **4**.[3b] Cadiot−Chodkiewicz coupling was then carried out between **4** and pent-4-yn-1-ol in the presence of CuCl and $NH_2OH{\cdot}HCl$ in the solvent system $EtNH_2$/MeOH, leading to the desired diynyl alcohol **7** in 81% yield.[3a] The primary alcohol was then oxidized in the presence of PCC and sodium ethanolate (EtONa), followed by a Wittig reaction with the resulting aldehyde toward enyne **8** in 57% overall yield. It is worth to mention that EtONa was important in the oxidation step to prevent the deprotection of the THP group. Enyne **8** was then treated by PPTS in MeOH for THP deprotection, and the deprotected hydroxyl was oxidized by PCC to generate 83% of key enyne aldehyde **3**.

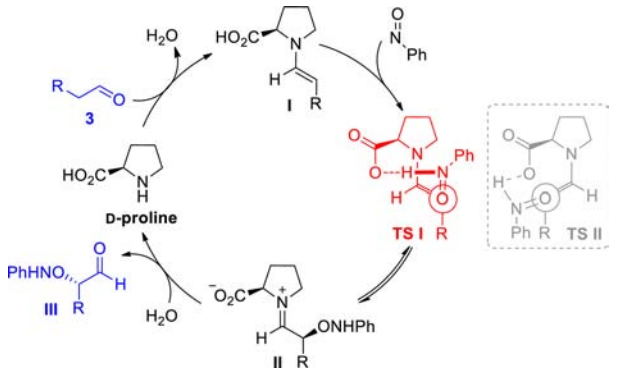
Scheme 1. Synthesis of Both Enantiomers of Distaminolyne A (2a and 2b)



The next and most important step was the introduction of the chiral hydroxylated carbon in C-2 position of the natural product, which was achieved using Cordova's method[5a] by applying a metal-free asymmetric α-aminooxylation of **3** in the presence of nitrosobenzene and D-proline (20 mol %) as a catalyst.[5a] The aldehyde was then reduced by $NaBH_4$, and the aniline functional group was removed in the presence of catalytic $CuSO_4{\cdot}5H_2O$ in MeOH[5a,b] to give diol **9a** in 69% yield over the three steps (Scheme 1).

The mechanism of the proline-catalyzed asymmetric α-aminooxylation is shown in Scheme 2. First, the aldehyde reacts with D-proline to give an enamine (**I**), which would then react with nitrosobenzene to afford the enantiomerically pure iminium adduct **II** through transition state **TS I**. After hydrolysis, **II** would release the α-aminooxylated aldehyde product **III** and the D-proline catalyst. As for the transition state (TS), the outcome of our asymmetric reaction, together with the previous density functional theory (DFT) calculation by Cordova and co-workers for both **TS I** and **TS II** of a similar intermediate,[5a] confirmed that **TS I** is the favorite transition state of the reaction, with a cyclic Zimmermann−Traxler-type intermediate involving the acidic proton of proline.

Scheme 2. Cordova's Plausible Mechanism of Proline-Catalyzed α-Aminooxylation of Aldehyde 3



Next, the primary alcohol of **9a** was activated by *p*-TsCl in the presence of Et_3N and was then treated by potassium carbonate to obtain 81% yield of chiral epoxide **10a**. Finally, amination proceeded in the presence of NH_4OH in EtOH to open the epoxide ring at the terminal position of **10a**, giving the expected natural product distaminolyne A (**2a**) in 99% yield (Scheme 1).[5a] However, the NMR data of synthesized compound **2a** (2*S*-distaminolyne A) did not match those of the natural product,[4] especially on the chiral center and its neighboring carbons and protons. Particularly, the ^1H and ^{13}C NMR data of the originally proposed structure at $\delta_H = 2.75$ (H_a-1), 3.01 (H_b-1), 3.75 (H-2) and $\delta_C = 46.1$ (C-1), 68.7 (C-2) were shifted on the synthesized one to be $\delta_H = 2.55$ (H_a-1), 2.70 (H_b-1), 3.53 (H-2) and $\delta_C = 48.1$ (C-1), 73.0 (C-2), respectively (Figure 3A). With this puzzle, we reviewed Copp's paper, finding that TFA was used in the solvent system when purifying distaminolyne A by HPLC. Therefore, we generated a TFA salt of **2a** and retested its NMR spectra, which turned to be identical to the originally reported one. Although the $[\alpha]_D$ values of both isolated and synthesized distaminolyne A were near 0 [+0.8 (c 1.0, MeOH) and +1.2 (c 0.1, MeOH) for **2a** and its TFA salt, respectively, while −1 for Copp's natural product], the opposite rotations questioned us on the veracity of their absolute configuration.

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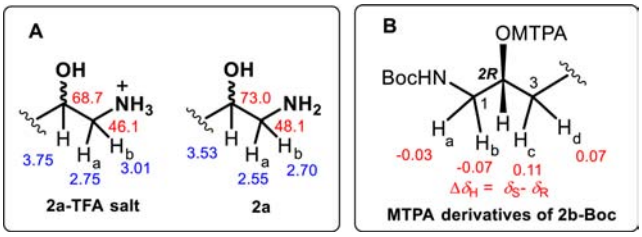

Figure 3. (A) Comparison of the key NMR data of **2a-TFA** salt (data of the original proposed structure) and **2a**. (B) The result of modified Mosher's method for **2b**.

As a consequence, the enantiomeric structure **2b** was synthesized by using the same protocol as for **2a** (Scheme 1), with the only replacement of D-proline by L-proline in the asymmetric reaction. Upon comparison, the NMR data of both **2b** and its TFA salt were identical to those of **2a** and the natural product, respectively. However, the $[\alpha]_D$ values of −2.0 (c 0.1, MeOH) for **2b** and −0.9 (c 0.1, MeOH) for its TFA salt, were nearly as that of the natural product, suggesting the 2*R* configuration for the natural product.

As to further confirm our synthetic results, chiral derivatizing agents (CDA) were introduced for the determination of the absolute configuration at C-2 position of both **2a** and **2b**. According to Riguera and co-workers,[7] double derivatization by the chiral reagent α-methoxyphenylacetic acid (MPA) was applied by the treatment of **2a** with (*R*)-MPA and (*S*)-MPA, respectively, in the presence of EDC·HCl and DMAP in CH_2Cl_2, affording bis(*N*,*O*)-MPA derivatives **2a-1** (*R*) and **2a-2** (*S*). By comparing their NMR data, especially those of CαH and OMe on MPA ester and MPA amide, we found that $\Delta\delta_R$ ($\delta_{C\alpha H\text{-ester}} - \delta_{C\alpha H\text{-amide}}$ or $\delta_{OMe\text{-ester}} - \delta_{OMe\text{-amide}}$ of **2a-1**) ≪ $\Delta\delta_S$ ($\delta_{C\alpha H\text{-ester}} - \delta_{C\alpha H\text{-amide}}$ or $\delta_{OMe\text{-ester}} - \delta_{OMe\text{-amide}}$ of **2a-2**) (Figure 4), confirming the 2*S* configuration of **2a**, as predicted by Cordova's reaction mechanism (Scheme 2).[5a]

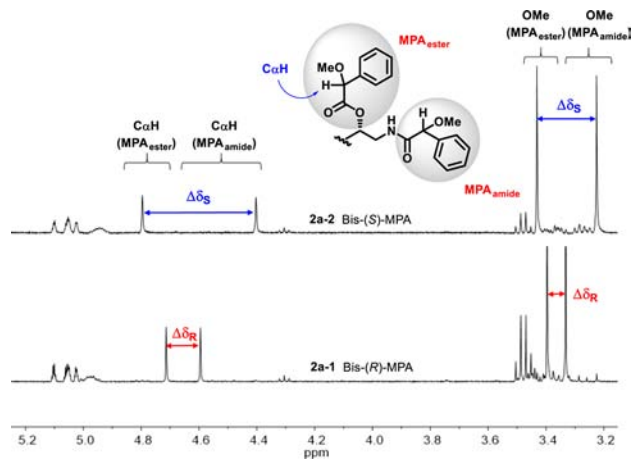

Figure 4. ^{1}H NMR comparison of the CDA derivatives of **2a**.

For **2b**, a modified Mosher's method[8] was applied by the treatment of its NBoc protected derivative (**2b-Boc**) with (*S*)- and (*R*)-α-methoxy-α-trifluoromethylphenyl acetyl chloride (MTPCl) in the presence of pyridine to give the 2-(*R*)-MTPA ester (**2b-1**) and 2-(*S*)-MTPA ester (**2b-2**), respectively. In their ^{1}H NMR spectra, the chemical shifts of H_2-1 in **2b-2** could be observed at higher fields ($\Delta\delta_H = \delta_S - \delta_R$: negative value), while those of H_2-3 resonated at a lower field ($\Delta\delta_H$: positive value) (Figure 3B) when comparing with those of **2b-1**. This confirmed an *R* configuration at C-2 in **2b**.

Finally, the two different CDA-introduced methods unambiguously confirmed the absolute configuration of **2a** and **2b** and furthermore showed them to be optically pure products with trustable $[\alpha]_D$ values. Since **2b** and the natural product shared the same levorotation, the absolute configuration of the natural distaminolyne A should be revised as 2*R*.

The two enantiomers were tested for their antibacterial, PL, and PTP1B inhibitory activities. In the antibacterial assay,[9] **2a** and **2b** exhibited moderate activities against Gram-positive bacteria *Staphylococcus aureus* Newman strain with MIC values of 40 μg/mL, while both compounds were not active on the Gram-negative bacteria *Pseudomonas aeruginosa* PAO1 strain. This observation, together with Copp's antibacterial results,[4] indicated that both (+)- and (−)-distaminolyne A are selectively active on Gram-positive bacteria. In the PL inhibitory assay,[3d,10] both compounds displayed weak activity with inhibitory rate of 36.7% and 24.7% at 50 μM, respectively. Interestingly, in the PTP1B (a recognized target for diabetes and obesity) inhibitory assay,[11] only compound **2b** showed significant activity with IC_{50} value of 8.4 μg/mL (positive control oleanolic acid: IC_{50} = 1.2 μg/mL), suggesting that the 2*R* configuration played an important role in PTP1B inhibitory effect.

In summary, the first asymmetric total syntheses of both enantiomers of distaminolyne A were accomplished in 15 steps with 10.1% (**2a**) and 9.2% (**2b**) overall yields, respectively, relying on a direct proline-catalyzed asymmetric α-amino-oxylation of an aldehyde to introduce the chiral center. The originally proposed absolute configuration of the natural product was revised to be 2*R* by the comparison of its $[\alpha]_D$ values with our synthetic enantiomers, after careful confirmation of their absolute configuration by two CDA-introduced methods. In the bioassay, moderate antibacterial and weak PL inhibitor activities were observed for both enantiomers, while selective PTP1B inhibitory activity were detected for **2b**, suggesting the value of further investigation of the natural product distaminolyne A or derivatives as potential antidiabetes drug leads. Other extensive biological activities related to the structural features of these polyacetylenic amino alcohols and their derivatives shall be investigated in the future.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03892.

General information on the experiment, experimental procedures, characterization data, biological activity assays, and NMR spectra for all the new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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