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Graphical Abstract

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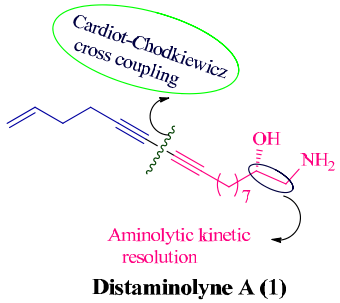

Distaminolyne A (1)

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Total Synthesis of Distaminolyne A

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ABSTRACT

Herein we report the stereoselective total synthesis of first occurance distaminolyne A *via* aminolytic kinetic resolution, Corey-Fuch's reaction for alkyne formation and Cardiot-Chodkiewicz cross coupling followed by Wittig olefination as the key steps.

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Introduction

Most of the polyacetylenic compounds are widely spread in Nature in the form of fatty acids and alcohols, and is sequestered within a wide range of organisms including plants, fungi and algae.[1] Many of these acetylene derivatives exhibited various biological activities such as anti-cancer on binding with DNA (Eg. enediynes), anti-trypanosomal drugs and anti microbial.[2] Distaminolyne A[3] (**1**) (Figure 1) is a first occurrence diacetylene 1-amino 2- alcohol isolated from the New Zealand ascidian *Pseudodistoma opacum* showed a modest anti-microbial activity toward *Escherichia coli, Staphylococcus aureus* and *Mycobacterim tuberculosis*. Determination of the absolute configuration i.e. '*S*' at the lone stereogenic carbon atom was confirmed by negative Cotton effect on CD spectra.[3] Following our interest in the total synthesis of natural products containing long chain acetylenic fatty acid molecules,[4] we embarked on the synthesis of distaminolyne A (**1**) which possesses structurally impressive polar long chain amino alcohol carbon framework.

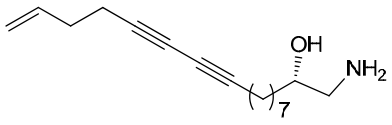
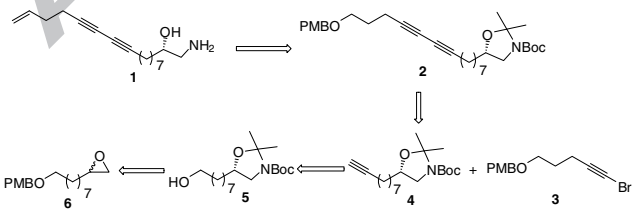


Figure 1: Structure of distaminolyne A (**1**)

Retrosynthetic analysis

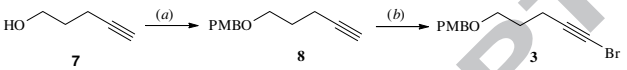
The retrosynthetic analysis of distaminolyne A (**1**) (Scheme 1) was mainly conceived by a Cardiot-Chodkiewicz cross-coupling between terminal alkyne **4** and bromoalkyne **3** to build a crucial acetylenic amino alcohol **2**.[5] Initially the formation of precursor **4** with a required configuration was conceived *via* aminolytic kinetic resolution[6] of racemic epoxide **6**, Next the deprotection of *p*-methoxy benzyl (PMB) alcohol ether in **6** would form a primary alcohol **5** which could be converted into terminal alkyne **4** by Corey-Fuch's reaction[7] in two consecutive steps. Respectively another precursor could be obtained by 4-pentyn-1-ol (**7**), which on PMB ether protection followed by bromination could yield bromo alkyne derivative **3**. Finally the deprotection of PMB ether of diacetylenic amino alcohol **2** and the oxidation of the ensuing alcohol to aldehyde, followed by one carbon Wittig reaction would furnish the natural product **1**.



Scheme 1: Retrosynthesis of distaminolyne A

Results and Discussion

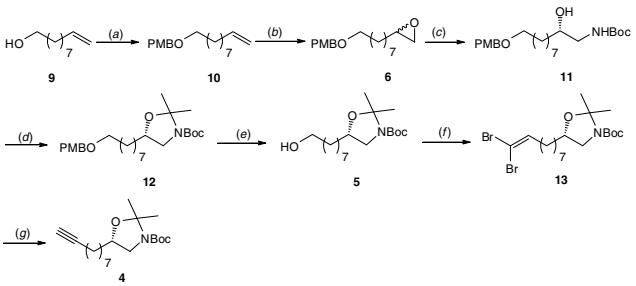
Accordingly, our synthetic strategy to access bromoalkyne derivative **3** (Scheme 2) begun with the inexpensive 4-pentyn-1-ol (**7**) as the starting material. Thus, the primary alcohol[8] of **7** was protected as its PMB ether under PMB-OH/amberlyst-15 conditions to form **8** (90%) and next the terminal triple bond was converted into its bromoalkyne **3** using *N*-bromosuccinimide (NBS) and catalytic amount of silver nitrate in 80% yield.[9]



Reagents and conditions: *a*) PMB-OH, Amberlyst-15, CH_2Cl_2, reflux, 12 h, 90%; *b*) *N*-Bromosuccinimide (NBS), $AgNO_3$, acetone, 0 °C, 2 h, 80%.

Scheme 2: Synthesis of compound **3**

The synthesis of another Cardiot-Chodkiewicz coupling precursor **4** (Scheme 3) began with the readily available 9-dacene-1-ol (**9**) which was protected as PMB ether **10** under known procedure.[8] Later on epoxidation of terminal olefin **10** by treating with *meta*-chloroperoxybenzoic acid (*m*-CPBA) afforded a racemic epoxide **6** in 76% yield.[10] Herein we invoked the asymmetric aminolytic kinetic resolution (AKR) of racemic terminal epoxides using carbamates as nucleophiles to generate optically pure 1,2-amino alcohol moiety under the (Salen)Co^{III} catalytic conditions developed by Bartoli and co-workers.[6] Thus, compound **6** on AKR using complex (*R,R*)-salen-Co^{II}, 4-nitro benzoic acid, *tert*-butylcarbamate, ^{t}BuOMe to afford *N*-Boc protected 1,2-amino alcohol **11** in quantitative yield 32% in highly enantiopurity (>97% *ee, Vide infra Ref.* 12), which was determined by chiral HPLC of enantiomerically pure isomer **11** [by ChiralPak AD-H 250X4.6 mm 5u, 10% *i*-PrOH-hexane (flow rate: 0.75 mL/min), 225 nm, t_R = 13.033 min (1.213%), 14.197 min (98.787%)]. The absolute stereochemistry of the 'OH' bearing stereogenic carbon was assumed to be '*S*' based on literature procedure,[6] which was confirmed at a later stage. Next *O*, *N*-protection of **11** as its acetonide using 2,2-dimethoxy propane in presence of 10-camphorsulfonic acid gave the compound **12** in 73% yield.[11]



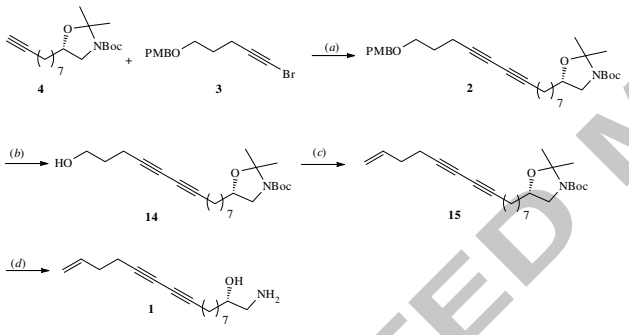
Reagents and conditions: a) *para*-Methoxy benzyl alcohol (PMB-OH), Amberlyst-15, CH_2Cl_2, reflux, 12 h, 87%; *b*) *meta*-Chloroperoxybenzoic acid *(m*-CPBA), $CHCl_3$, 0 °C, 3 h, 76%; *c*) (*R,R*)-salen-Co^{II}, 4-nitro benzoic acid, *tert*-butylcarbamate, ^{t}BuOMe, rt, 24 h, 32%; *d*) 2,2-DMP, acetone, 10-CSA, rt 3 h, 73%; *e*) 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), CH_2Cl_2:H_2O (19:1), 0 °C to rt, 1 h, 89%; *f*) (i) Des-Martin periodinane (DMP), dry CH_2Cl_2, 0 °C, 1 h; (ii) CBr_4, Triphenyl phosphine (TPP), dry CH_2Cl_2, TEA, -10 °C, 3 h, 86% (over two steps); *g*) *n*-BuLi, dry THF, -78 °C, 1 h, 90%.

Scheme 3: Synthesis of fragment **4**

Next deprotection of *p*-anisyl group (PMB) in **12** under 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) conditions

led to the primary alcohol **5** (89%). Further the alcohol **5** was oxidized to aldehyde using Dess-Martin periodinane (DMP), and the thus obtained aldehyde was converted into vinyl dibromide **13** under Corey-Fuch's reaction conditions using CBr_4/TPP, which on subsequent elimination reaction with *n*-BuLi in THF afforded alkyne **4** (90% over three steps).[7]

Having the requisite fragments **3** and **4** in hand, (Scheme 4) we conducted the copper-catalyzed Cardiot-Chodkiewicz cross-coupling[5] to obtain the long chain diacetylene 1-amino 2-alcohol[5] **2** in 84% yield. This was supported by ^{1}H NMR spectrum which revealed the characteristic two sets of propargylic methylenic protons at δ 2.37, 2.24 ppm as triplets as well as benzylic protons.[12] Simultaneously deprotection of the PMB group in **2** under 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) conditions led to the primary alcohol **14** (87%). Next, oxidation of alcohol **14** to aldehyde under Dess-Martin periodinane (DMP) conditions followed by one-carbon Wittig olefination ($PPh_3Me^+Br^-$) gave the terminal alkene **15** in 61% yield over two steps.[13] Finally, deprotection of acetonide **15** under acidic condition furnished natural product **1**(as HCL salt) in a 60% yield. The spectral data matched with the reported values (See the supporting information).[12]



Reagents and conditions: *a*) CuCl, 30% *n*-$BuNH_2$, $NH_2OH.HCl$, rt, 5 h, 84%; *b*) 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), CH_2Cl_2:H_2O (19:1), 0 °C to rt, 1 h, 87%; *c*) (i) Dess-Martin periodinane (DMP), dry CH_2Cl_2, 0 °C, 1 h; (ii) *n*-BuLi, $PPh_3Me^+Br^-$, dry THF, -78 °C to rt, 1 h, (over two steps) 61%; *d*) 4M HCl, 1,4-dioxane, 0 °C to rt, 5 h, 60%.

Scheme 4: Synthesis of distaminolyne A (**1**)

In summary, we have accomplished the first total synthesis of distaminolyne A (**1**) as its HCl salt mainly *via* aminolytic kinetic resolution to furnish the amino alcohol moiety in high enantiomeric purity and the Cardiot-Chodkiewicz reaction for the construction of a linear diacetylene scaffold followed by Wittig olefination to result in the natural product. The spectral data (^{1}H and ^{13}C NMR) and a sign of the optical rotation of synthetic **1**, $[\alpha]_D^{25}$-5.0 (*c* 0.1, methanol), to those reported natural product $[\alpha]_D^{20}$-1.0 (*c* 0.44, methanol), were nearly identical.[12]

While this work was under revision, there appeared a publication on the synthesis of distaminolyne A[14] wherein Guo *et al* have observed differences in the NMR spectra and hence made a TFA salt which then correlated with the reported data. However the sign of the optical rotation varied which showed $[\alpha]_D^{25}$ +0.8 (and +1.0 for the TFA salt against -1.0 reported by Copp) and in order to rationalize the differences in optical rotation values between the synthetic **1** and natural product, a thorough study using modified Mosher esters was undertaken. Their study resulted in stereochemical revision of distaminolyne A as '*R*' instead of '*S*' (originally proposed by Copp).

However we are intrigued by dissimilar optical rotational values reported by Guo *et al* since our values matched with the reported one. Also, its equally important to note that we adopted an unambiguous and well established synthetic protocols to gather the lone stereogenic center; and the reason for these inconsistencies might be due to the low optical rotational values.

Acknowledgements

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HIGHLIGHTS

Title: Total synthesis of Distaminolyne A

- Stereoselective
- Diacetylenic amino alcohol
- AKR