Making Progress Towards The Synthesis of Distaminolyne-B

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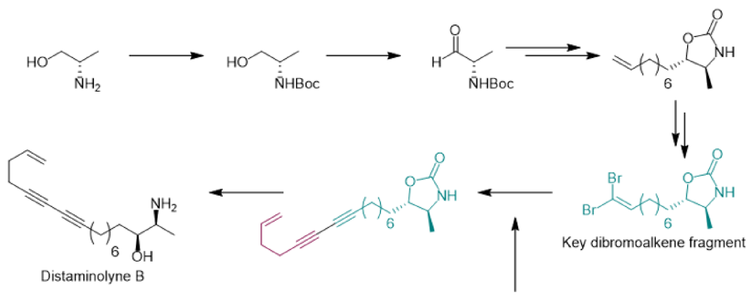
Abstract:

Distaminolyne B, a 2-amino-3-alcohol, extracted from a marine sphingolipid in New Zealand, was reported to be a promising ingredient in pharmaceuticals as it has a wide range of biological activities; such as the inhibition of tumor cells proliferation and antimicrobial benefits. The goal was to synthesize this amino-alcohol in the lab or/and its intermediates. The first reaction involves changing the starting material, alaninol, from primary amine to a secondary amine (N-[(1S)-2-hydroxy-1-methylethyl]-, 1,1-dimethylethyl ester) by adding a nitrogen-protecting group, di-tert-butyl decarbonate. The next step was oxidizing the secondary amino-alcohol to an aldehyde. A solid method was deduced for synthesizing the secondary amine, and a potential method was deduced in synthesizing the aldehyde.

Background:



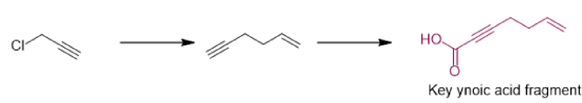


Figure 1 shows A suggested synthetic route for the formation of Distaminolyne-B

A direction to head towards starts with alaninol, the top right corner. Alaninol is purchased from the market (purchased from Sigma Aldrich. The first step involves the nitrogen being protected by a bulky group like di-tertbutyl dicarbonate. Once protection is achieved, alaninol is no longer a primary amine but is now secondary. The next step is oxidizing the Boc2O-protected alaninol into an aldehyde, whilst keeping the nitrogen protected. The next involves making the chain longer perhaps using Grignard catalyst into attaching the bromine groups. Due to the time constrains and the natural process of research, this step had not been explored by myself yet.

References:

Pearce, A. Norrie, et al. "An Acetylenic Lipid from the New Zealand Ascidian Pseudodistoma Cereum: Exemplification of an Improved Workflow for Determination of Absolute Configuration of Long-Chain 2-Amino-3-Alkanols." Journal of Natural Products, *vol. 82, no. 8*, **2019**, pp. 2291–2298., https://doi.org/10.1021/acs.jnatprod.9b00504.

"Tempo, 2,2,6,6-Tetramethylpiperidinyloxy." Organic Chemistry, https://www.organic-chemistry.org/chemicals/oxidations/tempo-2,2,6,6-tetramethylpiperidinyloxy.shtm.

Experimental:

1- To make the protected secondary-amine, alaninol is reacted with di-tertbutyl-dicarbonate (Boc2O) in a 1:1 and one in 1:2 ratio with the reagents shown in Table 1:

Table 1:

Starting Material	Reagents	Solvents	Base	Washing Solvent
Alaninol, 6.7 mmol	Di-tert-butyl dicabonate, 6.7 mmol	THF, 30 mL	DIPEA, 1.6 mL	Dichloromethane
Alaninol, 6.7 mmol	Di-tert-butyl dicabonate, 6.7 mmol	Water 5 mL Dichloromethane, 5 mL		Dichloromethane
Alaninol, 6.7 mmol	Di-tert-butyl dicabonate, 6.7 mmol	Water, 10 mL Dioxane, 10 mL	$NaHCO_{3,\ 5\ g}$	Dichloromethane
Alaninol, 6.7 mmol	Di-tert-butyl dicabonate, 6.7 mmol	Dichloromethane, 10 mL		Ethyl Acetate

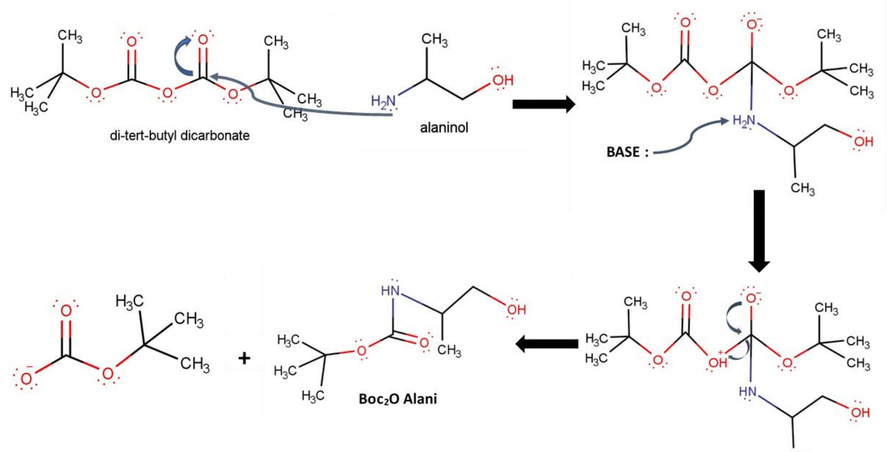


Figure 2 shows the predicted mechanism upon the reaction of alaninol with di-tert-butyl decarbonate and base.

2- After the completion of the reactions (overnight), the product was washed with DCM or ethyl acetate, and dried with MgSO4, vacuum filtered and the remaining solvent was evaporated using the rotary evaporator.

Table 2 shows the procedures done in attempts of making the protected aldehyde version of alanine:

Starting Material	Stoichiomtric	Solvent	Salt	Base	Washing Solvent
Boc2O Alaninol, 1.5 g	TEMPO, 0.0073 g	Dichloromethane, 4 mL	KBr, 2M, 75 mL NaOCl, 6%, 25 mL	$NaHCO_{3,\ 0.5000\ g}$	Dichloromethane
Boc2O Alaninol, 1.5 g	TEMPO, 0.0022 g	Ethyl Acetate, 10 mL Toluene, 10 mL H_2o, 10 mL	NaBr, 0.1600 g NaOCl, 0.35 M, 6.1 mL	$NaHCO_3$, 0.3675 g	Ethyl Acetate
Boc2O Alaninol, 1.5 g	TEMPO, 0.0022 g	Ethyl Acetate, 10 mL Toluene, 10 mL H_2o, 10 mL	NaBr, 0.1600 g NaOCl, 0.35 M, 4.7 mL	$NaHCO_3$, 0.3675 g	Ethyl Acetate
Boc2O Alaninol, 1.5 g	TEMPO, 0.0022 g	Ethyl Acetate, 10 mL Toluene, 10 mL H_2o, 10 mL	KBr, 2M, 14.40 mL NaOCl, 0.35 M, 4.7 mL	$NaHCO_3$, 0.3675 g	Ethyl Acetate
Boc2O Alaninol, 1.5 g	Triethylamine, 2 mL Sulfur trioxide pyridine, 1.28 g	Dichloromethane, 10 mL DMSO, 10 mL			Ethyl Acetate

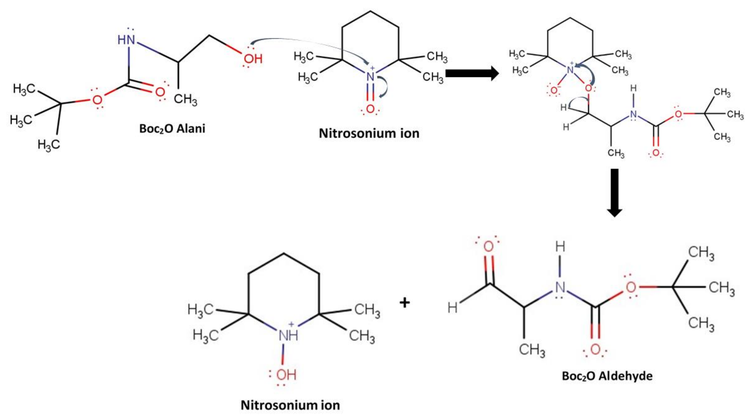


Figure 3 shows the reaction scheme of the oxidation of Boc2O alaninol to Boc2O aldehyde. The Nitrosonium ion is made upon the coupling of the redox reactions between NaOCl (bleach), the salt and TEMPO.

Results:

A Comparison between the NMR spectra of the starting material and the boc2O alaninol is made to ensure the completion of the reaction and further indication on whether the new product is the desired product.

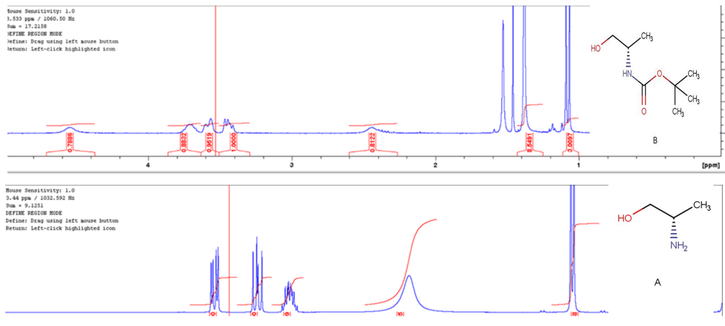


Figure 3 shows the NMR spectra of alaninol, whose structure is labeled as A, and the successful attempt of synthesizing Boc2O alaninol (procedure 4 from table 1), labeled B

The biggest indication is the downfield shift as the electron density has decreased due to the addition of a bulky group (Boc2O). Another indication is the significant drop in the area of the singlet peak at 2.2 ppm, corresponding to the two protons on the nitrogen and the one hydroxyl present in the starting material. It hints at the loss of one of the two hydrogens. The other hydrogen from the hydroxyl perhaps now appears around 4.2 ppm in the product's spectrum. The appearance of a new singlet peak around 1.2 ppm in the product's spectrum corresponds to the nine hydrogens on the tert-butyl peak, also a solid indicator of a successful production of Boc2O alaninol.

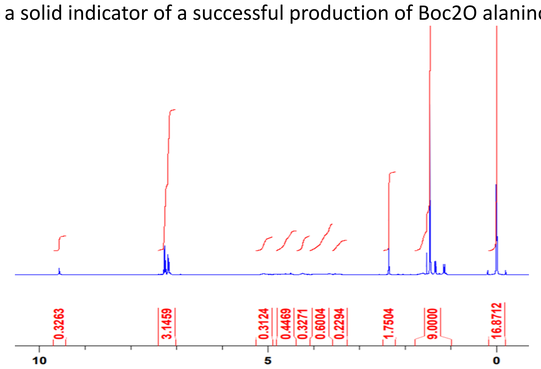


Figure 4 shows the NMR spectrum of procedure four from table 2, with the peak at 9.5 ppm being the most significant

Discussion:

Unlike the theoretical prediction, making Boc2O alaninol did not require a base. The other attempts have failed perhaps because of the mismatch of the polarities between the product and the solvent. Recrystallization was done for procedure 2 in table 1 as the solid initially made was impure. Procedure 4, which is reacting boc2O and alaninol in DCM lead to the right product almost consistently.

Making the aldehyde from Boc2O alaninol was much trickier. In one of the trails with SO3 pyridine, there was no yield at all, perhaps the ethyl acetate and the aldehyde became a homogenous mixture and evaporated. The product made was not an aldehyde as it could not be identified and was liquid majority of the times. The closest attempt to making the aldehyde is with procedure four. It is possible that we always ended up with only the starting material.

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