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E: ISSN NO.: 2349-980X **Shrinkhla Ek Shodhparak Vaicharik Patrika**

Design and Synthesis of Synthetic Precursor Involved in Total Synthesis of Stagonolide B

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Abstract

In this paper synthesis of (1R,2S)-benzyl 2-((S)-1-(5-(dimethoxyphosphoryl)-4-oxopentanoyloxy)butyl)-4,4-dimethylcyclopen tanecarboxylate, a synthetic precursor of Stagonolide B is described starting from commercially available D- diethyltartarate and succinic anhydride by applying Swern oxidation, Grignard reaction and Steglich esterification as key steps.

Keywords: Macrolide, Stagonolide B, Precursor, Grignard Reagent, Grubbs Catalyst, Yamaguchi Macrolactonization, HWE Reaction etc.

Introduction

Maclolides are naturally occurring macrocyclic lactones. These compounds are produced by number of organisms including actinomycetes, myxobacteria, lichens, fungi, algae, plants, invertebrates, insects etc. Macrolides are composed of macrocyclic rings possessing 8-62 atoms of carbon and oxygen[1]. Macrolides containing a macrocyclic lactone ring of 12 or more atoms possess variety of bioactivities including antibiotics, antifungal, anticancer, and immune-suppressant activities. The macrolides containing 14-, 15-, and 16-membered rings belong to the family of antibiotics[2]. Small ring macrolides, particularly 10 membered lactones, including nonenolides, stagonolides B-I and modiolide A (Figure 1), on the other hand, have attracted both chemists and biologists during recent years, due to their interesting biological properties particularly cytotoxic, phytotoxic, antimalarial antifungal, antibacterial and antimicrofilament activities[3].Stagonolides are nonenolides isolated from the fungus *Stagonospora circii*, pathogen of a weed *Cirsium arvense* possessing phytotoxic activities[4]. A number of Stagonolides named as Stagonolide A-I were isolated and characterised by spectroscopic mehods[4].

Review of Literature

During recent years numbers of asymmetric syntheses of Stagonolide B and other Stagonolides are reported in the literature. Pabbaraja Srihari *et al* synthesized Stagonolide A starting from trans-2-hexenol by applying ring closing metathysis and epoxide ring opening reactions as key steps[5]. Awadut G. Giri and coworkers synthesized Stagonolide B from pentene-1-ol and studied the effect of allylic substituents on ring closing metathysis reactions[6].Tapas Das *et al* synthesized Stagonolide B by successfully applying chemoenzymatic hydroxynitrile lyase (ParsHNL) mediated asymmetric synthesis of cyanohydrin, Sharpless asymmetric dihydroxylation, cross metathesis reaction, stereoselective Keck allylation reaction etc followed by Yamaguchi macrolactonization in penultimate step for construction of 10-membered lactone ring[7]. In short all the reported synthetic strategies for total synthesis of Stagonolide B and other Stagonolides involve either RCM (ring closing metathesis) reaction using Grubbs olefin metathesis catalyst or Yamaguchi macrolactonization reaction for construction of 10-membered macrolactone ring[8-12].

Aim of the Study

In present study, I designed a new synthetic route for total synthesis of Stagonolide B, starting from commercially available D-diethyltartarate and succinic anhydride and by applying Horner-Wadsworth-Emmons Reaction (HWE reaction) for dual purpose of ring formation and creation of Trans double bond present in Stagonolide B. I successfully synthesized (1R,2S)-benzyl 2-((S)-1-(5-(dimethoxy phosphoryl) -4-oxopentanoyloxy) butyl)-4,4-

Dimethylcyclopentanecarboxylate (Compound A, Schemes 1-4) by applying Swern oxidation, Grignard reaction and Steglich esterification as key steps. Compound A may serve as a suitable synthetic precursor for total synthesis of Stagonolide B. Compound A can be converted into Stagonolide B by benzyl deprotection of hydroxy group, oxidising it into aldehyde followed by applying intramolecular HWE reaction for ring closing and creation of trans double bond.

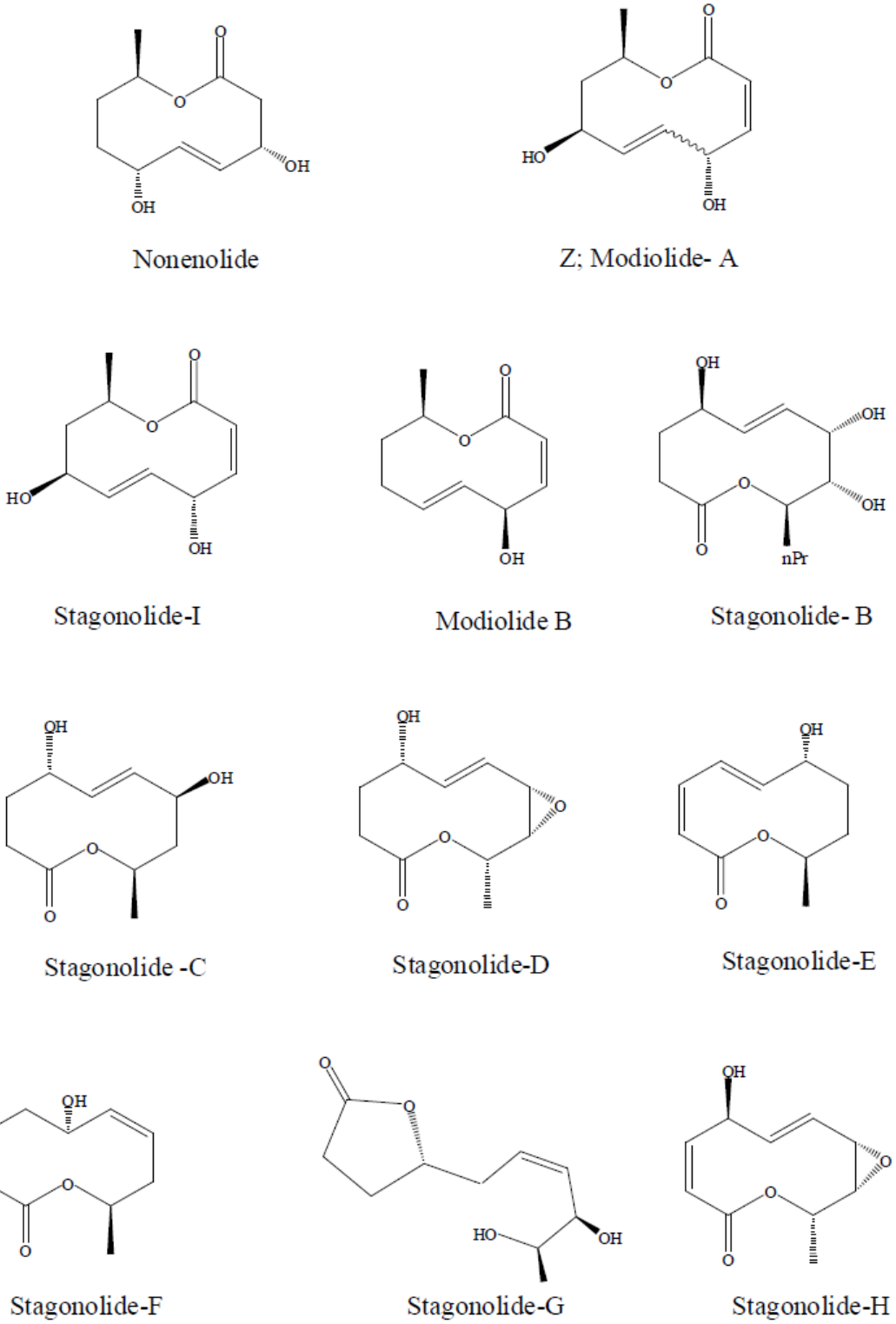

Figure 1. Naturally occurring Nonenolide

Research Design: Retrosynthesis

Retrosynthesis of Stagonolide B (I) revealed that it can be made by using succinic anhydride and D-(-)-diethyltartarate as starting materials (Scheme-1). Macrolactonisation (Ring formation) and trans double bond can be introduced by intramolecular HWE reaction between phosphonate and aldehyde groups present in compound II (which in turn can be synthesised from compound A).Compound A can be synthesised by carboxylic acid B and secondary alcohol C by Steglich esterification. Compounds B and C in turn can be prepared by succinic anhydride and D-diethyltartarate respectively through multi-step synthesis. The configurations of two hyrdoxy groups of Stagonolide B were inherited in D-diethyltartarate. Configuration of propyl chain can be fixed by chemical modifications in D-diethyltartarate.

Experimental:

Materials

All the chemicals were purchased from Merk and SD fine pvt ltd. IR spectra were recorded by using KBr pellets. NMR spectra were recorded on 200MHz instruments by using $CDCl_3$ and MeOD as solvent.

Synthesis of (1R, 2S)-benzyl 2-((S)-1-(5-(dimethoxyphosphoryl)-4-oxopentanoyloxy) butyl)-4, 4-dimethylcyclopentanecarboxylate (Compound A), a precursor of Stagonolide B

Total synthesis of Stagonolide B is depicted in schemes 2-4. Here, in this contest, I have successfully synthesised compound **A** by using straightforward methods of organic synthesis as described below:

Synthesis of (4S,5S)-diethyl 2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate(Fragment C, Scheme 2)

Fragment C was synthesized from D (-) diethyltartarate (1) as depicted in scheme -2. First it was acetonide protected by adding BF_3-etharate (1.2 equiv) drop wise in its acetone solution at 0^0C and stirred for 1h. The reaction was quenched by $NaHCO_3$ and extracted with ethyl acetate. The organic layer was concentrated and purified by column chromatography on silica gel 60-120 mesh size using 9:1 hexane/ethylacetate to give 2 (yield = 70%).

^{1}H-NMR ($CDCl_3$, 300 MHz, δ ppm): 4.77 (s, 2H), 4.34-4.23 (q, J = 8.0 Hz, 4H), 1.50 (s, 6H), 1.32 (t, 6H, J = 8.0 Hz).

Synthesis of ((4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)dimethanol (3)

In the solution of compound **2** (1 equiv.) in THF, slurry of $LiAlH_4$ (2.5 equiv.) in THF was added at 0^oC. The resultant mixture was stirred for 2 h at room temperature and then quenched by drop wise adding saturated solution of Na_2SO_4. After stirring for 1.5 h the mixture was filtered on Celite bed followed by rinsing with ethylacetate. The filtrate was concentrated in vacuo and the crude material was purified by chromatography on silica gel using 50% ethylacetate in hexane to yield 3.

IR (neat) υ (cm^{-1}): 3400 (br), 2977, 2881, 1648, 1372, 1250, 1228, 1150, 1060, 850^{1}H-NMR ($CDCl_3$, 300 MHz, δ ppm): 3.98-3.95 (m, 2H), 3.79–3.66 (m, 4H), 2.88 (br, 2H), 1.41 (s, 6H); ^{13}C NMR ($CDCl_3$, 60 MHz, δ ppm): 109.5, 79.2, 62.4, 28.3

Synthesis of ((4R, 5R)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl benzoate (4):

To the stirred suspension of NaH (1.5equiv) in DMF, compound **3** was added drop wise at 0^oC in nitrogen atmosphere and stirred for 1h. Benzyl bromide (1.1 equiv) was then added drop wise and the mixture was further stirred for 5 h at 0^oC. The reaction was quenched by adding cold water, extracted with diethyl ether three times, organic layers were concentrated in vacuo and purified by chromatography on silica gel (30% ethylacetate in hexane) to yield mono benzyl protected alcohol (4).

^{1}H-NMR ($CDCl_3$, 300 MHz, δ ppm): 7.35 (m, 5H), 4.60 (s, 2H), 4.08 (m, 1H), 3.96 (m, 1H), 3.73(m, 1H), 3.68-3.55 (m, 3H), 2.25–2.10 (br s, 1H, OH), 1.44 (s, 6H).

Synthesis of ((4R,5S)-5-formyl-2,2-dimethyl-1,3-dioxolan-4-yl)methyl benzoate (5):

In a stirred solution of oxalyl chloride (2 equiv) in CH_2Cl_2 solution of DMSO (4 equiv) in CH_2Cl_2 at -78 ^{o}C was added under nitrogen atmosphere over a period of 30 minutes. To the resultant mixture a solution of **4** (1 equiv) in CH_2Cl_2 was added. After 3 h of stirring, the reaction was quenched with triethylamine, allowed to come to room temperature, washed with brine several times and concentrated under reduced pressure to give compound **5** as pale yellow oil.

IR (neat) υ (cm^{-1}): 2998, 2710, 1720, 1620, 1122, 878.

^{1}H-NMR ($CDCl_3$, 300 MHz, δ ppm): 9.66 (s, 1H), 7.30 (m, 5H), 4.58 (s, 2H), 4.18 (m, 2H), 3.60 (t, J = 4.0 Hz, 2H), 1.44 (s, 6H)

^{13}C NMR ($CDCl_3$, 60 MHz, δ ppm): 200.5, 137.7, 128.6, 128.3, 127.8, 127.5, 127.4, 111.8, 82.2, 76.7, 74.1, 70.1, 27.5.

Synthesis of ((4R,5R)-5-((R)-1-hydroxybutyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl benzoate (C)

In dry THF, small pieces of Magnesium (5 equiv) and a pinch of iodine under nitrogen atmosphere was added. After 30 minutes stirring, propyl bromide (2 equiv) was drop wise added. When the colour of the mixture disappeared and Mg turning dissolved, it was assumed that Grignard reagent was formed. To this Grignard reagent, the solution of compound **5** (1 equiv.) in THF was added drop wise. After 3 h stirring the reaction mixture was quenched with saturated solution of NH_4Cl and stirred for 1 h. The mixture was then extracted with diehylether three times. The mixed organic layers were concentrated in vacuo, and the crude material was purified by chromatography over silica gel (5% ethylacetate in hexane) to yield compound **C**.

^{1}H-NMR ($CDCl_3$, 300 MHz, δ ppm): 7.35 (m, 5H), 4.61 (s, 2H), 4.16 (m, 2H), 3.74-3.62 (m, 3H), 2.69 (s, 1H), 1.78-1.28 (m, 10 H), 0.94 (t, J = 6.0 Hz, 3H).

Synthesis of 5-(dimethoxyphosphoryl)-4-Oxopentanoic Acid (B, Scheme-3)

n-BuLi (2.5 equiv) under nitrogen atmosphere was drop wise added to a pre-cooled (-78 ^{0}C) solution of dimethyl methylphophonate (1 equiv) in THF. The mixture was allowed to stir for 1 h.

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Succinic anhydride (2 equiv.) was then rapidly transferred to the mixture. The yellow coloured suspension was formed which was further stirred for 1 h at the same temperature. The progress of the reaction was monitored on TLC. When the reaction was completed, it was quenched by adding saturated aqueous solution of oxalic acid and stirred for 30 minutes. The mixture was then extracted with CH_2Cl_2 three times. The combined organic extracts were dried over anhydrous Na_2SO_4, concentrated in vacuo, purified by chromatography over silica gel (5% MeOH in CH_2Cl_2) to yield compound **B** (yield = 50%).

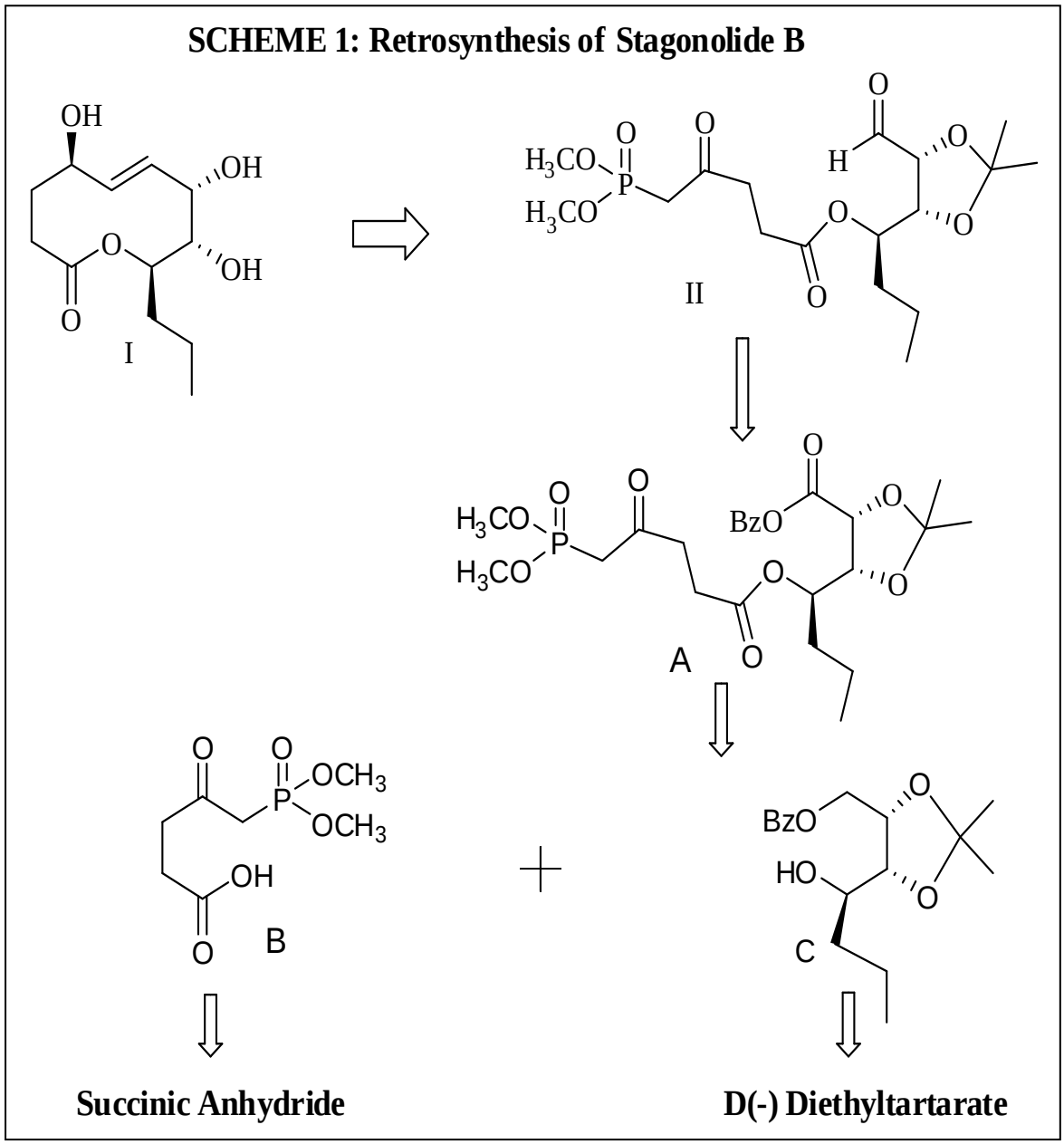
^{1}H-NMR ($CDCl_3$, 300 MHz, δ ppm): 3.80-3.66 (m, 6H), 3.13 (d, J (H,P) = 21.0 Hz, 2H), 2.96-2.91 (t, J = 6.0 Hz, 2H), 2.61-2.57 (t, J = 6.0 Hz, 2H);

Synthesis of Compound A (Scheme-4)

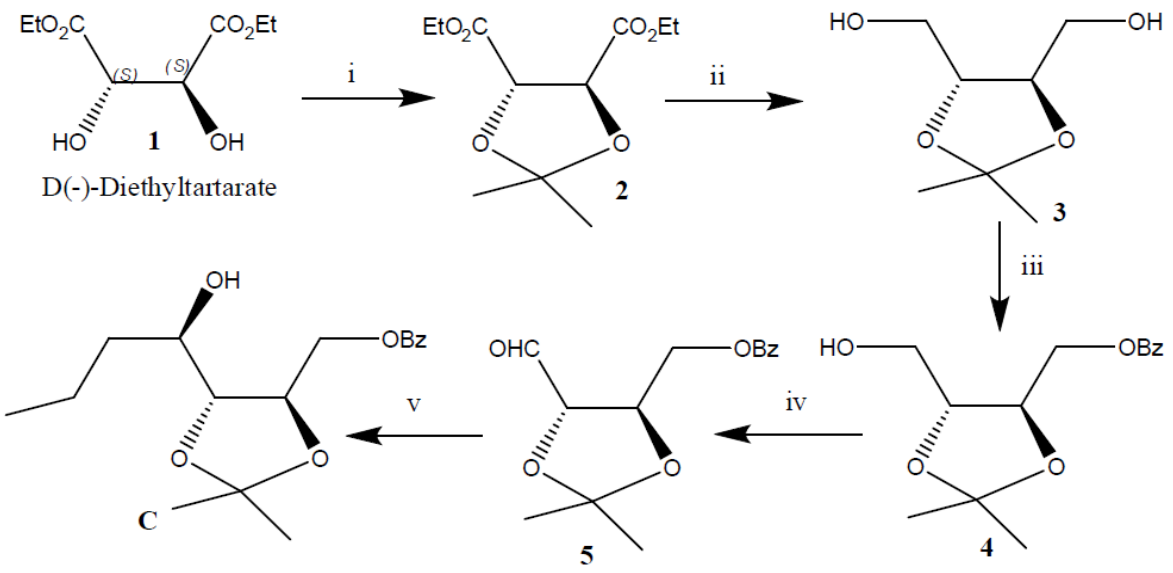
A solution of compound **C** in CH_2Cl_2 was cooled to 0^0C. DCC (1.5 equiv) was then added in several portions to get a white precipitate formed quickly. After 15 minutes stirring, alcohol **B** (1 equiv) was added as a solution in CH_2Cl_2 along with a little amount of DMAP. The stirring was continued for 12 h at room temperature. The solution was filtered and the solvent was distilled off. The residue was purified by column chromatography over silica gel (2% ethyl acetate in hexane) to yield compound A.

^{1}H-NMR ($CDCl_3$, 300 MHz, δ ppm): 7.35 (m, 5H), 4.60 (s, 2H), 4.16 (m, 2H), 3.84-3.50 (m, 9H), 3.15 (d, J (H,P) = 21.0 Hz, 2H), 2.98-2.92 (m, 2H), 2.60-2.55 (m, 2H), 1.80-1.25 (m, 10 H), 0.92 (t, J = 6.0 Hz, 3H).

SCHEME 1: Retrosynthesis of Stagonolide B



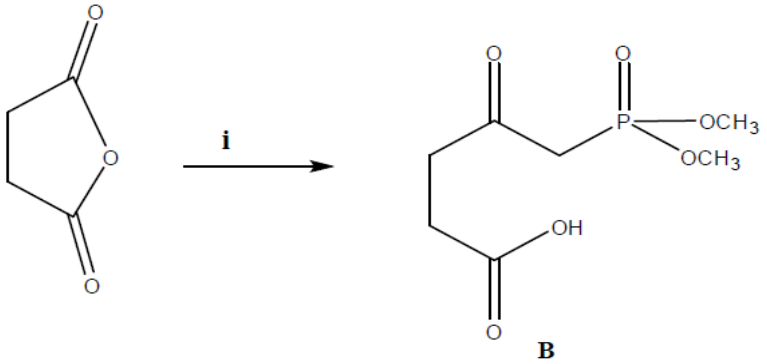
SCHEME-2



Reagents and conditions (i) Boron trifluoride ethyl etharate, acetone, 0^{o}-rt, 1h (ii) Lithium aluminium hydride , THF, 3h (iii) Sodium hydride, DMF, 5h (iv) Oxalyl chloride, DMSO, TEA, DCM, -78^{0}C, 3h. (v) a.$CH_3CH_2CH_2MgBr$, b. NH_4Cl/ H_2O

Scheme-2 illustrates synthesis of fragment C concerned with total synthesis of Stagonolide B.

SCHEME-3



Reagents and conditions (i) a.Dimethylmethyl Phosphonate, BuLi, -78^{0}C, b. oxalic acid

Scheme-3 illustrates the synthesis of fragment B concerned with total synthesis of Stagonolide B.

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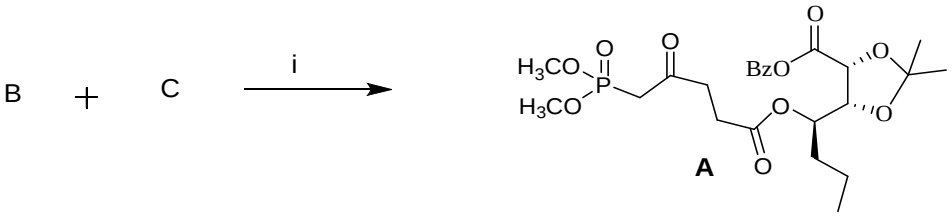
SCHEME 4



Reagents and conditions: (i) DCC, DCM, 12h

Scheme -4 illustrates synthesis of compound A, precursor of Stagonolide B

Results and Discussion

The retro synthetic analysis of stagonolide A is outlined in Scheme 1. The intermediates C and B were prepared from commercially abundant D-(-) Diethyltartarate and succinic anhydride respectively. Compound A was prepared by Steglich esterification of acid B and alcohol C.

As outlined in Scheme 2, intermediate **C** was prepared from D-(-) Diethyltartarate (1), following different procedures reported earlier. First D-(-) diethyltartarate was acetonide protected by reacting it with BF_3-etharate in acetone at 0 ^{0}C in 70 % yield to give 2. Diester 2 was then reduced to diol 3 by lithium aluminium hydride ($LiAlH_4$) in THF in 50 % yield. Diol 3 was mono benzyl protected by reacting it with controlled amount of benzyl bromide and NaH in DMF at 0 ^{0}C to give mono benzyl protected alcohol 4 in 30 % yield. Primary alcohol 4 was oxidised to aldehyde 5 by Swern oxidation which was used directly and immediately for further reaction without purification. Solution of aldehyde 5 in THF was transferred to freshly prepared THF solution of $CH_3CH_2CH_2MgBr$. Compound C, after necessary purification, was obtained from nucleophilic addition of Grignard reagent ($CH_3CH_2CH_2MgBr$) to the aldehyde 5.

Fragment B was synthesised by adding THF solution of succinic anhydide to a cooled (-78 ^{0}C) solution of n-BuLi and dimethyl methylphophonate in 50% yield (Scheme-3).

Acid B and alcohol C were then converted to ester A, a precursor of Stagonolide B by Steglich esterification using by DCC and DMAP in dry CH_2Cl_2 (Scheme 4).

Compound A may serve as an important precursor for total synthesis of Stagonolide B if it will be undertaken by organic chemists for future course of their researches.

Conclusion

In conclusion, I successfully synthesised (1R,2S)-benzyl 2-((S)-1-(5-(dimethoxyphosphoryl)-4-oxopent anoyloxy)butyl)-4,4-dimethylcyclopentane carboxylate (Compound A) by following simple and economic route**,** which may serve as important precursor for the total synthesis of Stagonolide B from easily available starting materials.

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