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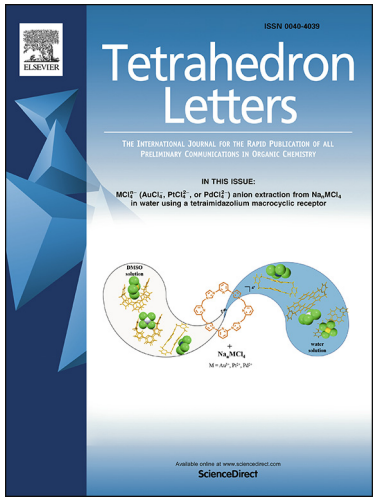

Studies towards the total synthesis of Phostriecin

Gavireddy Chaithanya kumar, Katta Muralikrishna, Vavilapalli Satyanarayana, Chintakrinda Suresh kumar, Jhillu Singh Yadav

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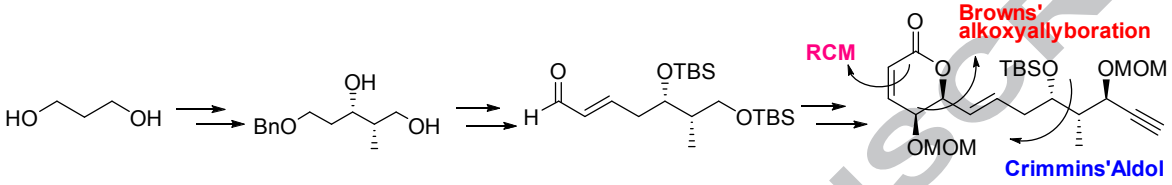

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Studies towards the total synthesis of Phostriecin

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ABSTRACT

A synthetic approach toward the phostriecin, an antitumor natural product is described. The key features of the present synthesis are Wittig reaction, synthesis of homoallylic alcohol using Brown's protocol (alkoxyallylboration) and RCM for the creation of unsaturated lactone moiety of phostriecin.

Phostriecin is a structurally unique phosphate ester produced by *Streptomyces roseiscleroticus* No.L827-7 which was isolated from a soil sample of Gujarat state in India.[1] (Figure **1**) Initially the natural product was represented as Sultriecin and assigned as C-9 sulfate ester at the time of its isolation and its structure was proposed without the precision of its relative and absolute stereochemistry. Studies with original compound confirmed that phostriecin, but not sultriecin is an efficient and selective inhibitor of protein phosphatase 2A (PP2A), which is responsible for its antitumor activity[2].

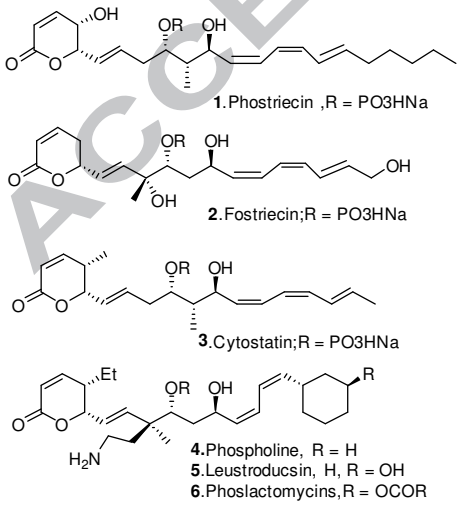
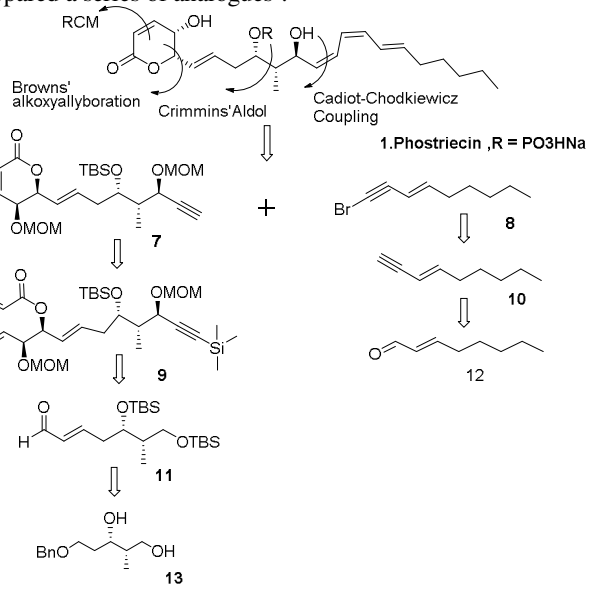


Figure 1: Structures of Phostriecin and related natural products

Phostriecin also showed a broad spectrum of antifungal activity *in vitro* and moderate *in vivo* cytotoxic activity against human cell lines[3a]. Natural products structurally related [3b] to phostriecin were Fostriecin, Cytostatin, Leustroducsin and Phoslactomycin. From structural perspective phostriecin contains an electrophilic unsaturated lactone and the hydrophobic *Z,Z,E*-triene tail and contains a central functionalized 1,3 diol. Recently, Boger *et al* [4] reported the first total synthesis of phostriecin (aka sultriecin) and also established their relative, absolute configuration and prepared a series of analogues[5].

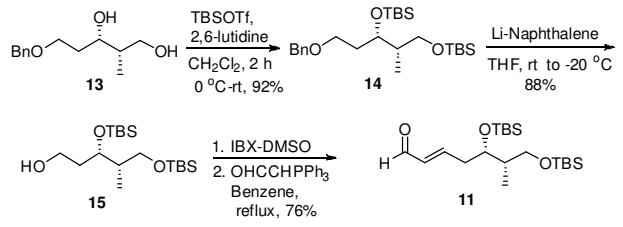


Scheme 1 Retrosynthec analysis of Phostriecin

In continuation of our interest in the synthesis of antitumor natural products, herein we report the synthesis of **C1- C13** and **C14 - C22** fragment of phostriecin. (For the synthesis of the side chain **C14 - C22** fragment see reference [16]). Our retro-synthetic strategy of **1** is illustrated in Scheme **1**, in which the key building block **7** would be transformed into **1** by reduction of alkyne triple bond and introduction of the phosphate group. Compound **7** was in turn obtained from compound **9** using ring-closing metathesis. Compound **9** can be prepared from compound **11** by opting Brown's alkoxyallylboration strategy. Compound **13** could be accessed from 1,3-propanediol using Criminns aldol reaction.

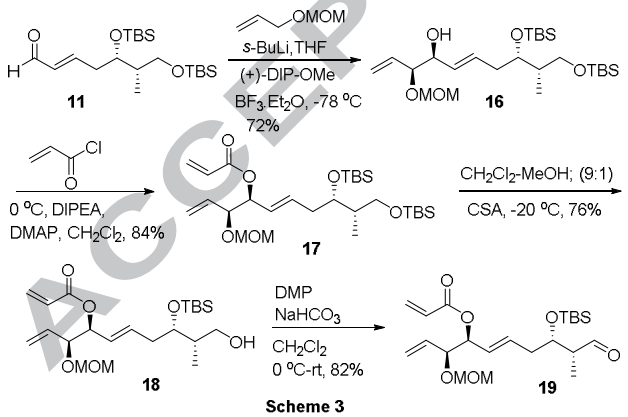
Results and Discussion

Our synthesis began with the diol compound **13** by the application of the Crimmin's method to the known aldehyde which in turn was prepared from 1,3-propane diol according to a literature procedure.[6] The diol was protected as its bis-silyl ether using TBSOTf and 2,6-lutidine in CH_2Cl_2 at 0 °C to get the bis silyl ether compound **14** in quantitative yield. (Scheme 2)



Scheme 2

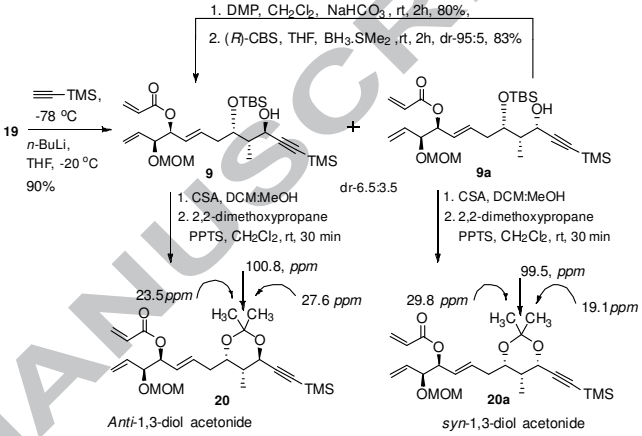
At this stage deprotection of benzyl ether was achieved using Li and naphthalene in THF at -20 °C to get the primary alcohol **15** in 88% yiled. Oxidation of the resulting primary alcohol using IBX: DMSO afforded aldehyde which was subjected to two carbon Wittig reaction by treatment with (triphenylphosphoranylidene)acetaldehyde in benzene under reflux conditions to afford α,β-unsaturated aldehyde **11** in 76 % yield (Scheme 2).[7]



Scheme 3

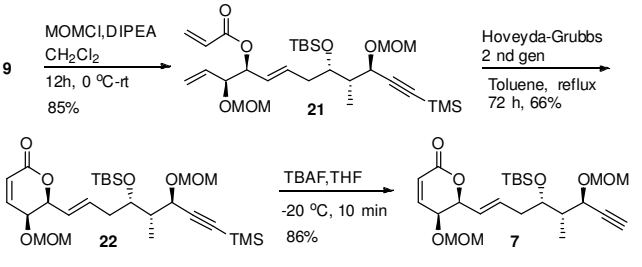
Having prepared the key intermediate aldehyde compound **11** in hand we then investigated the synthesis of homoallylic alcohol using Brown's protocol[8] (alkoxyallylboration). Accordingly treatments of aldehyde using (+)-Ipc2BOMe as the chiral-source produced chiral homoallylic alcohol 16 in 72% yield. Acrylolation of compound **16** using acryloyl chloride in the presence of DIPEA and a catalytic amount of DMAP in CH_2Cl_2 at 0 °C for 2 h afforded the corresponding ester **17** in good yield.[9] Selective deprotection of primary TBS ether group using a catalytic amount of CSA in CH_2Cl_2-MeOH (9:1) mixture at -20 °C to gave the primary alcohol **18** in 76% yiled. (Scheme 3)

Oxidation of the resulting primary alcohol using DMP[10] in CH_2Cl_2 afforded aldehyde **19**, which was purified and subjected to next reaction directly. Addition of TMS protected acetylene on aldehyde **19** in THF at -20 °C provided 65:35 diastereomeric mixture of the secondary alcohols **9** and **9a** respectively in 90% yield and the resulting diastereomeric mixture was separated by column chromatography.[11] (Scheme 4)



Scheme 4

Rychnovsky's protocol was used for confirmation of the stereochemistry at newly generated chiral center by ^{13}C NMR analysis.[12] To achieve this separately little amount of both the compounds **9** and **9a** were subjected to TBS ether deprotection using a catalytic amount of CSA in CH_2Cl_2 : MeOH (9:1) mixture at -20 °C provided the secondary alcohols in good yields. 1,3-diol protection as the acetonide in CH_2Cl_2 at 0 °C using 2,2-dimethoxypropane and a catalytic amount of CSA to get the corresponding isopropylidene derivatives **20** and **20a** in good yield. The geometry at the newly created hydroxy center was established as *anti* for compound **20** and *syn* for **20a** based on the ^{13}C NMR value for the 1,3-diol acetonide carbons. In order to convert the minor quantities of the undesired diastereomer to a required diastereomer, we further proceeded with a two-step sequence. Accordingly compound **9a** was oxidized under DMP conditions to provide the ketone, which was again reduced with (*R*)-CBS catalyst to get the desired alcohol **9** in good yield.[13] (Scheme 4)



Scheme 5

At this stage protection of the required secondary alcohol **9** as its MOM ether was carried out using MOMCl, in the presence of DIPEA in CH_2Cl_2 at 0 ^oC to RT for 12 h, furnished the MOM ether **21** in good yield. Having prepared the key intermediate in hand we next turned our attention to RCM reaction, accordingly the resulting MOM ether **21** was then subjected to undergo ring-closing metathesis using Hoveyda-Grubbs second generation catalyst in refluxing toluene lead to the formation of the desired lactone **22** in 66% yield.[14] Finally deprotection of TMS group in lactone **22** using TBAF in THF at **-**20 ^oC for 10 min furnished the required alkyne **7** in 86% yield.[15] (Scheme 5)

Conclusions

In conclusion we have achieved the pivotal **C1 - C13** and **C14 - C22** fragments of the antitumor natural product phostriecin. The synthesis of an advanced intermediate **7** from compound **13** in **11** steps with **10**% overall yield. The key steps involved are Wittig reaction, Browns' alkoxyallylboration, CBS reduction and Rring-closing metathesis. Further research was under progress for the completion of total synthesis of phostriecin and will be reported in due course.

Acknowledgements

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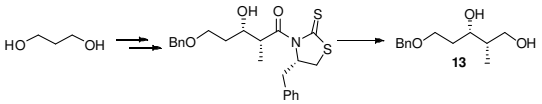

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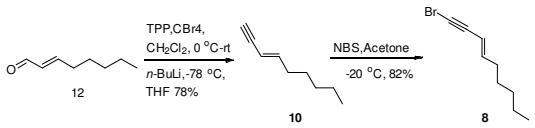

Supplementary Material: Experimental procedures, spectral data, copies of ^1H NMR and ^{13}C NMR spectra available.

Highlights of The Phostriecin Synthesis

- **C1 - C13 fragment of the antitumor natural product phostriecin was synthesized.**
- **Synthesis of chiral homoallylic alcohol by using Brown's protocol.**
- **Creation of lactone moiety by using Hoveyda-Grubbs second generation catalyst.**
- **Key steps are Wittig reaction, Brown's protocol, CBS reduction and RCM.**
- **The advanced intermediate 7 was achieved in 11 steps with 10% overall yield.**