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PII: S0040-4039(14)00942-3
DOI: http://dx.doi.org/10.1016/j.tetlet.2014.05.111
Reference: TETL 44702

To appear in: *Tetrahedron Letters*

Received Date: 8 March 2014
Revised Date: 26 May 2014
Accepted Date: 28 May 2014

Please cite this article as: Rajesh, A., Sharma, G.V.M., Damera, K., Towards the Stereoselective Synthesis of C1-C23 Fragment of Spirastrellolide B, *Tetrahedron Letters* (2014), doi: http://dx.doi.org/10.1016/j.tetlet.2014.05.111

Graphical Abstract

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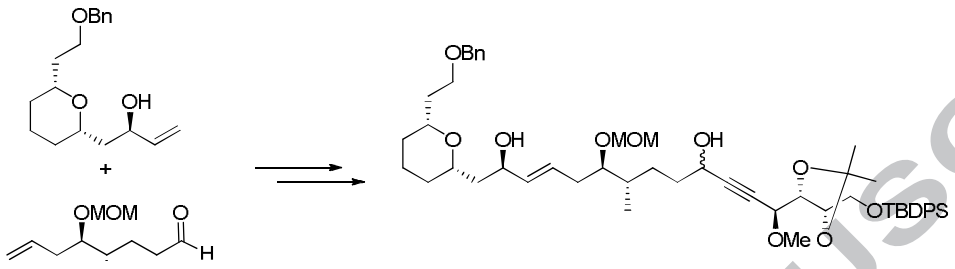

Towards the Stereoselective Synthesis of C1-C23 Fragment of Spirastrellolide B

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Abstract: A convergent synthesis of the protected C(1)-C(23) fragment **4** of the targeted natural product spirastrellolide B is described. The key step of the synthesis is cross metathesis (CM) and TBAF promoted oxa-Michael to construct tetrahydropyran moiety.

Keywords: Sharpless asymmetric epoxidation, oxa-Michael addition, cross metathesis and hydroxylalkynylation.

Spirastrellolide A (**1**) and B (**2**) are two closely related polyketides, isolated by Anderson and co-workers from the marine sponge *Spirastrella coccinea*. The structure of **1** was first disclosed in 2003[1a] while, its structure and biological activity on the inhibition of protein phosphatase 2A (PP2A) was reported in 2004.[1b] A phosphatase like PP2A has progressively been considered as a potential tumor suppressor.[2] X-ray analysis[3] of a derivative of **2** revealed the complete relative and absolute stereochemistry of the core spirastrellolide A.

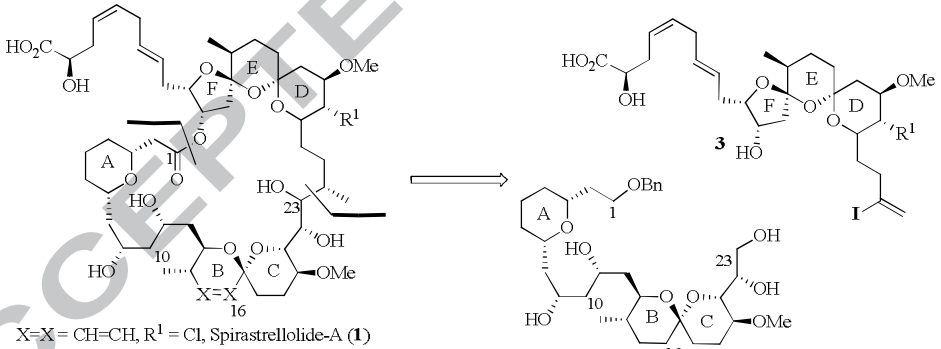

Figure 1

Due to their unique structure and impressive biological activity, spirastrellolide B becomes target for synthesis. The syntheses of fragments of spirastrellolide A (**1**) and B (**2**) molecules have been reported,[4-9] although no total synthesis has yet been described.

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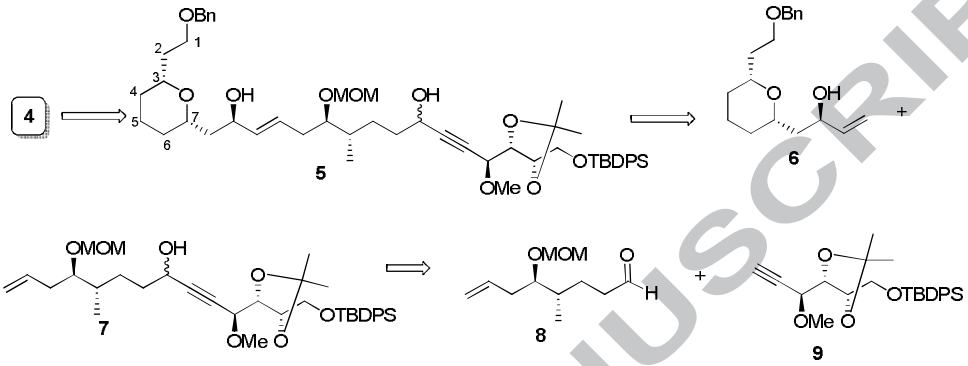
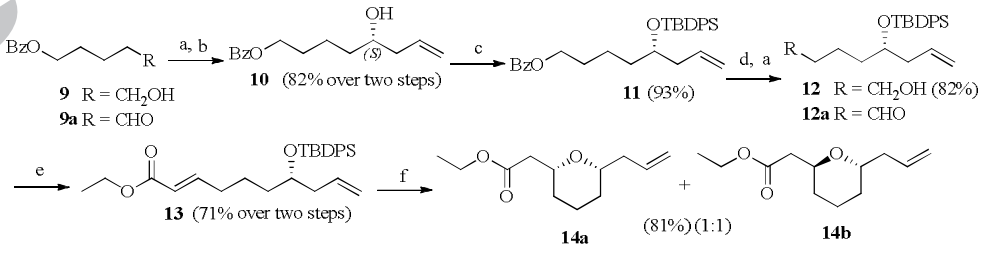
The overall plan consists of the assembly of two large fragments (**3** and **4**) by a combination of Nozaki-Hiyama-Kishi reaction and lactonization. Further synthesis of C1-C23 subunit **4** carbon framework could be realized from **5** by acid catalyzed spiroketalization. Fragment **5** could be synthesized by cross metathesis (CM) of **6** and **7**. Alternatively, propargyl alcohol **7** can be achieved by addition of acetylene **9** to the aldehyde **8** (Scheme 1).



Scheme-1. Retrosynthetic analysis of fragment C(1)-C(23)

For the construct pyran derivative of C(1)-C(10) fragment, starts with oxidation of 1,5-pentane diol derivative **9**[10] under Swern reaction conditions gave the aldehyde **9a**, enantioselective allylation of the resulted aldehyde using allyltri-*n*-butyltin,[11] furnished **10,** the secondary alcohol in compound **10** was silylated using TBDPSCl and imidazole to silyl ether **11**. Compound **11** was treated with K_2CO_3 in MeOH to furnish alcohol **12**, subsequent oxidation of alcohol to aldehyde **12a** using Swern oxidation. Wittig olefination of aldehyde **12a** with (ethoxycarbonylmethylene)triphenyl phosphorane gave corresponding ester **13** in 71% yield, which was treated with TBAF to cleave the silyl ether and cause a spontaneous oxa-Michael addition[12] with formation of 1:1 diastereomeric mixture of **14a** and **14b** (81%), while, **14a** was obtained in 49% yield by chromatographic separation.



Scheme 2: *Reagents and conditions*: (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C; (b) Allyltributyltin, (*R,R*)-Binol, $Ti(O^iPr)_4$, CH_2Cl_2, -78 °C; (c) TBDPSCl, imidazole, CH_2Cl_2, 0 °C-rt; (d) K_2CO_3, MeOH, 0 °C-rt; (e) Ph_3P=CHCOOEt, benzene, reflux; (f) TBAF, THF, 0 °C-rt

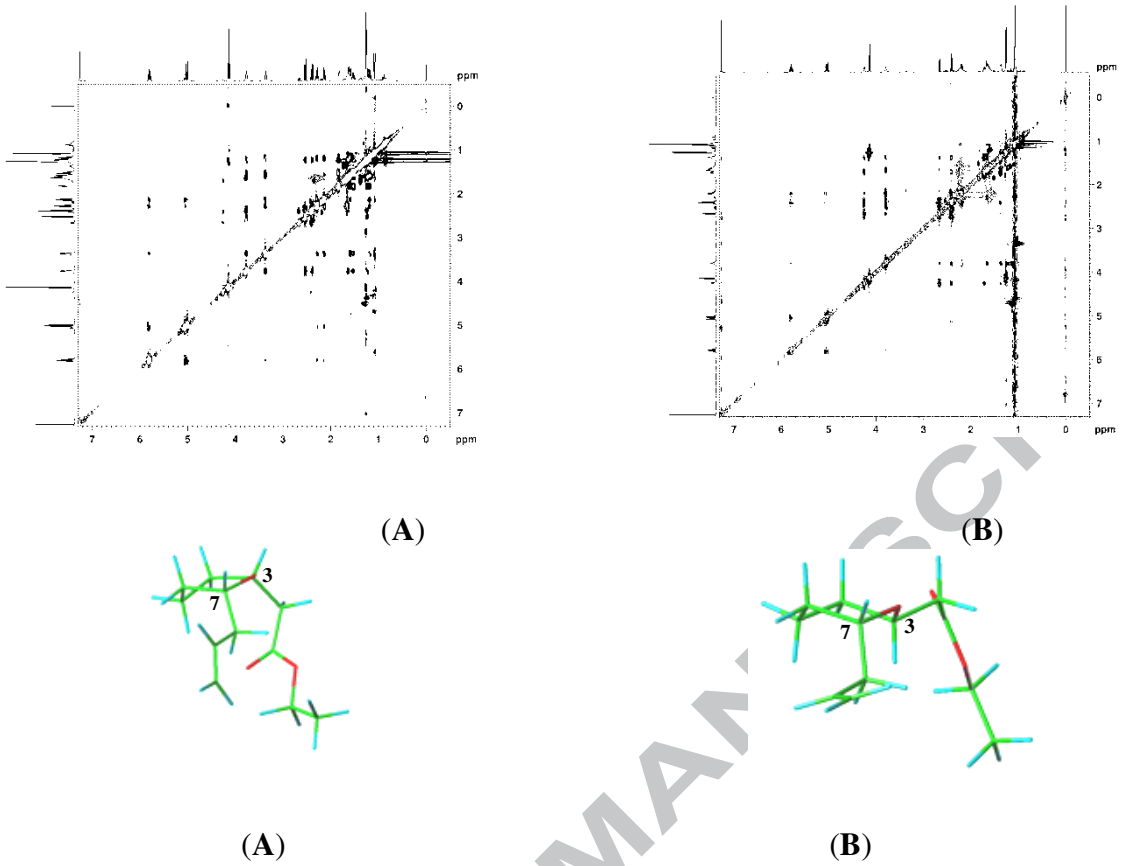
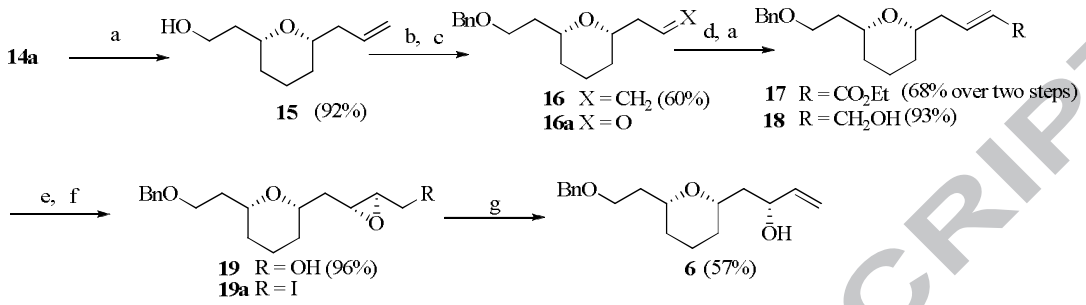


Figure 2: NOESY spectra (600MHz, 298K, $CDCl_3$) and energy minimized structures of (**A**) **14a** and (**B**) **14b**.

The stereochemistry in **14a** and **14b** was established by ^{1}H NMR (500 MHz, $CDCl_3$) data and assignments made with the help of TOCSY and NOESY experiments. The characteristic nOe between C_3H/C_7H in **14a** (Figure 2) suggested that both the protons are on the same face while, the characteristic nOe between C_3H/C_7H in **14b** (Figure 2) suggested that both the protons are on the opposite face.

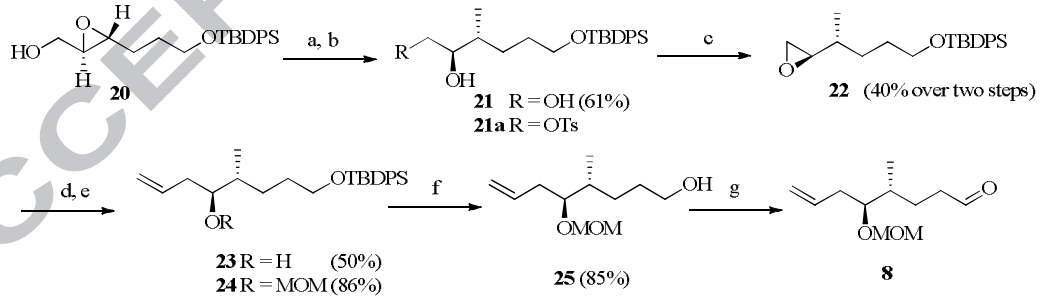
To achieve one of the key intermediate **6** with required stereochemistry, we have used **14a** for further reactions. Reduction of ester in **14a** with DIBAL-H furnished alcohol **15** (92%), the resulted alcohol was protected as benzyl ether using benzyl bromide in the presence of NaH gave **16** in 60% yield. To make the precursor for Sharpless asymmetric epoxidation, olefin **16** was ozonized to yield the corresponding aldehyde **16a**, which on subjecting to Wittig olefination with (ethoxycarbonylmethylene)triphenyl phosphorane in benzene at reflux afford **17** in 68% yield, simultaneous reduction of the ethyl ester of **17** was accomplished with DIBAl-H. Sharpless asymmetric epoxidation of **18** with (-)-DIPT furnished epoxy alcohol **19** in 96% yield.

The epoxide **19** was opened using triphenylphosphine in CCl_4 to give chloro epoxide **19a**, which on treatment with sodium metal in ether gave allylic alcohol **6**.[13]



Scheme 3: *Reagents and conditions*: a) DIBAL-H, CH_2Cl_2, 0 °C-rt; (b) BnBr, NaH, THF, 0 °C-rt; (c) O_3, CH_2Cl_2, dimethylsulphide, -78 °C; (d) Ph_3P=CHCOOEt, benzene, reflux; (e) (-)-DIPT, $Ti(O^iPr)_4$, cumene hydroperoxide, 4 Å molecular sieves, CH_2Cl_2, -20 °C; (f) Ph_3P, I_2, imidazole, CH_2Cl_2, 0 °C-rt; (g) NaI, Zn, MeOH, reflux.

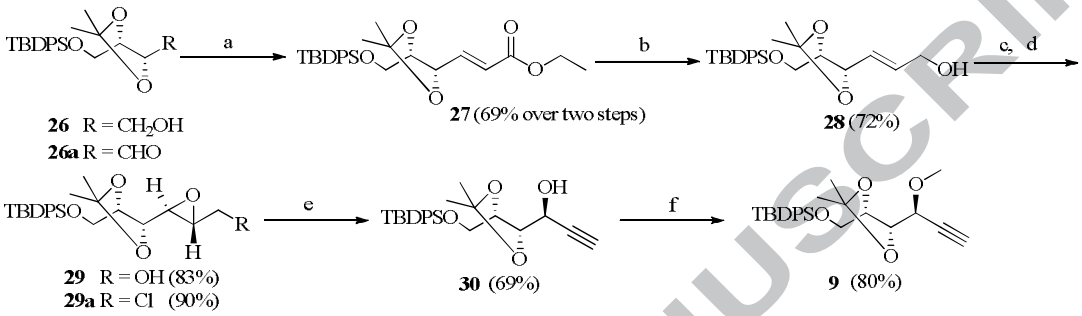
The synthesis of the **7** was initiated from known compound **20**.[14] Accordingly, regioselective opening of epoxide **20** with Me_3Al[15] in hexane at 0 °C furnished 1,2-diol **21** in 61% yield. Diol **21** on selective tosylation[16] with *p*-TsCl in CH_2Cl_2 gave **21a**, which, on further reaction with K_2CO_3 in methanol furnished the epoxide **22** in 40% yield. Copper mediated opening of epoxide[17] with vinylmagnesium bromide in THF at -20 °C yielded corresponding homoallylic alcohol **23** (50%), newly generated secondary alcohol was then capped with a MOM group **24** in 86% yield. A standard desilylation of **24** using TBAF gave corresponding primary alcohol **25**, which was oxidized under Dess-Martin periodinane condition, afforded the aldehyde **8**.



Scheme 4: *Reagents and conditions*: (a) Me_3Al, *n*-Hexane, 0 °C-rt; (b) *p*-TsCl, Et_3N, 0 °C-rt; (c) K_2CO_3, MeOH, 0 °C-rt; (d) Vinylmagnesium bromide, CuI, THF, -20 °C; (e) MOMCl, DIPEA, 0 °C-rt; (f) TBAF, THF, 0 °C-rt; (g) Dess-Martin periodinane, CH_2Cl_2, 0 °C-rt.

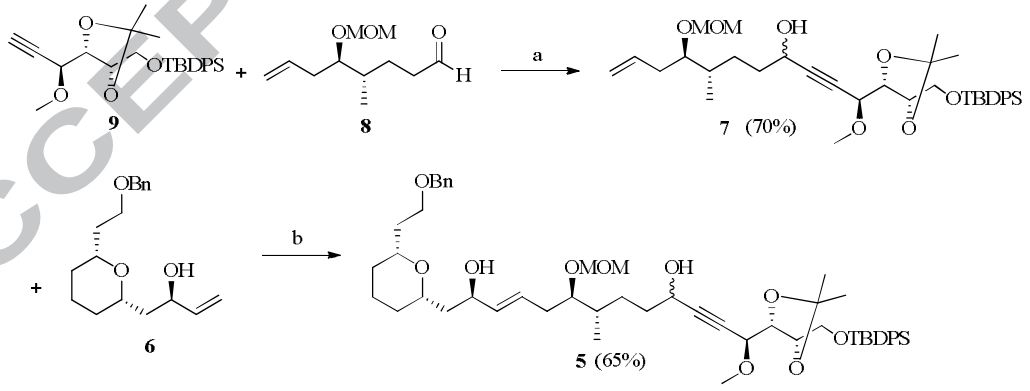
The required coupling partner **9** was initiated from known compound **26**.[18] Accordingly, alcohol **26** on oxidation under Swern conditions gave the aldehyde **26a**, which on Wittig olefination with (ethoxycarbonylmethylene)triphenyl phosphorane in benzene furnished **27** in

69% yield (Scheme 5). Reduction of ethyl ester **27** with DIBAL-H furnished allyl alcohol **28**, which was subjected for Sharpless asymmetric epoxidation with (-)DIPT yielded **29** (83%). The propargyl alcohol **30** derived from **29a** was converted according to the protocol published by Yadav[19], the resulted secondary alcohol was treated with MeI in the presence of NaH furnished **9** in 80% yield.



Scheme 5: *Reagents and conditions*: (a) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C; (ii) Ph_3P=CHCOOEt, benzene, reflux, 2 h; (b) DIBAL-H, CH_2Cl_2, 0 °C-rt; (c) (-)-DIPT, $Ti(O^iPr)_4$, cumene hydroperoxide, 4 Å molecular sieves, CH_2Cl_2, -20 °C; (d) Ph_3P, $NaHCO_3$, CCl_4, 0 °C; (e) DIPA, *n*-BuLi, THF, -40 °C; (f) CH_3I, NaH, THF, 0 °C-rt.

Finally, one of the key fragment **7** was synthesized by base promoted addition of alkyne **9** to aldehyde **8**, afforded diastereomeric mixture of propargylic alcohols **7** in 70% yield (Scheme 6). In a further study the target compound **5** is achieved by cross-methathesis (CM) of olefins **6** and **7** using Grubbs 2nd generation catalyst (10 mol%) in CH_2Cl_2 at room temperature to afford **5** in 65% yield.[20] Spectroscopic analysis of **5** revealed that the newly formed C20-C21 double bond is *trans* (J = 17.0 Hz).



Scheme 6: *reagents and conditions*: (a) *n*-BuLi, THF, -78 °C; (b) Grubbs 2nd generation Catalyst, CH_2Cl_2, rt.

In conclusion, we have established a stereoselective strategy for the synthesis of C1-C23 carbon frame work of spirastrellolide-B. Advanced stage intermediate tetrahydropyra **14a** was achieved by TBAF promoted oxa-Micheal addition, the stereochemistry of the resulted product was established by ^{1}H NMR data and assignments made with the help of TOCSY and NOESY experiments. Finally, construction of olefin C20-C21 by cross metathesis (CM) to complete the synthesis of C1-C23 fragment of Spirastrellolide B.

Acknowledgements

All the authors are thankful for financial support from MLP-0008 of CSIR, New Delhi. A.R. is thankful to CSIR, New Delhi for the research fellowship.

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