Abstract

The thesis entitled "**Total synthesis of biologically active polyacetylenes petrosiol A and E, strongylodiols A, B, C, D, H and I**" has been divided into four chapters. **Chapter-I** deals with the brief introduction to poly acetylenic compounds. **Chapter-II** has been divided in to two sections. **Section A** describes the facile approach for the total synthesis of petrosiol A and **Section B** describes the concise approach for the total synthesis of petrosiol E. **Chapter-III** deals with the stereoselective total synthesis of strongylodiol A, B, C and D. **Chapter-IV** deals with first total synthesis and structural revision of strongylodiol H and I.

Chapter-I: This discribes the brief introduction about various poly acetylenic compounds.

Chapter-II: This is further divided into two sections.

Section A: Facile approach for the total synthesis of petrosiol A:

M. Ojika et.al have isolated five new neurotropic diacetylenic polyols labelled as petrosiols A-E from an extract of the marine Okinawan sponge *Petrosia strongylata*.

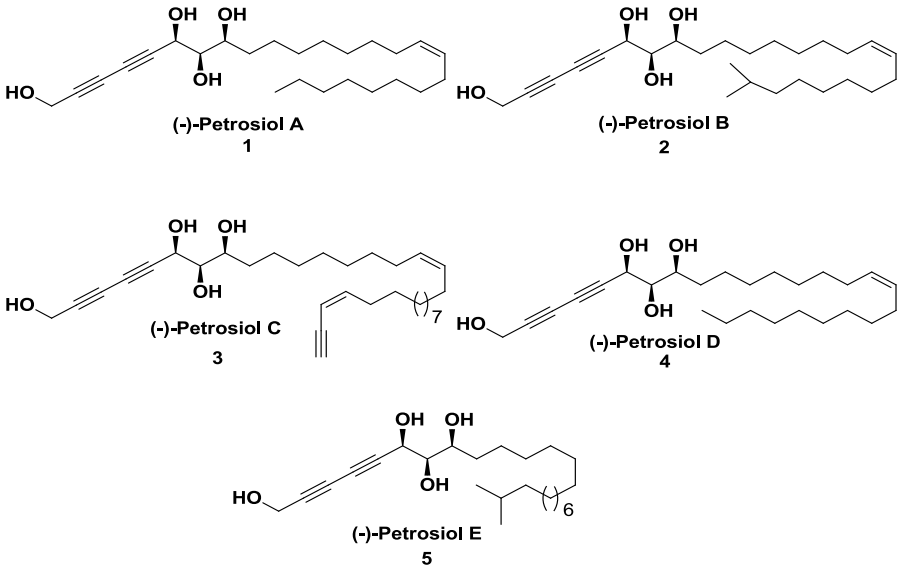


Figure 1: Structures of petrosiols A-E.

The absolute configurations and structures of petrosiols A-E were established based on spectroscopic analysis. Among these petrosiol A **1** and petrosiol D **4** were structurally similar and differed by one methylene group(more in Petrosiol D). In continuation to our interest in synthesizing bioactive molecules (natural products) with an emphasis for

central nervous system related therapeutics, we herein demonstrate the first total synthesis of petrosiol A starting from the inexpensive, commercially available L (+)-diethyltartrate.

Retrosythetically petrosiol A was envisioned to be synthesized by the Cadiot-Chodkiewicz coupling between alkyne **6** and bromoalkyne **7.** Fragment **6** can be obtained from L-(+)diethyltartrate via few functional group modifications. Whereas fragment **7,** can be synthesized from commercially available propargyl alcohol.

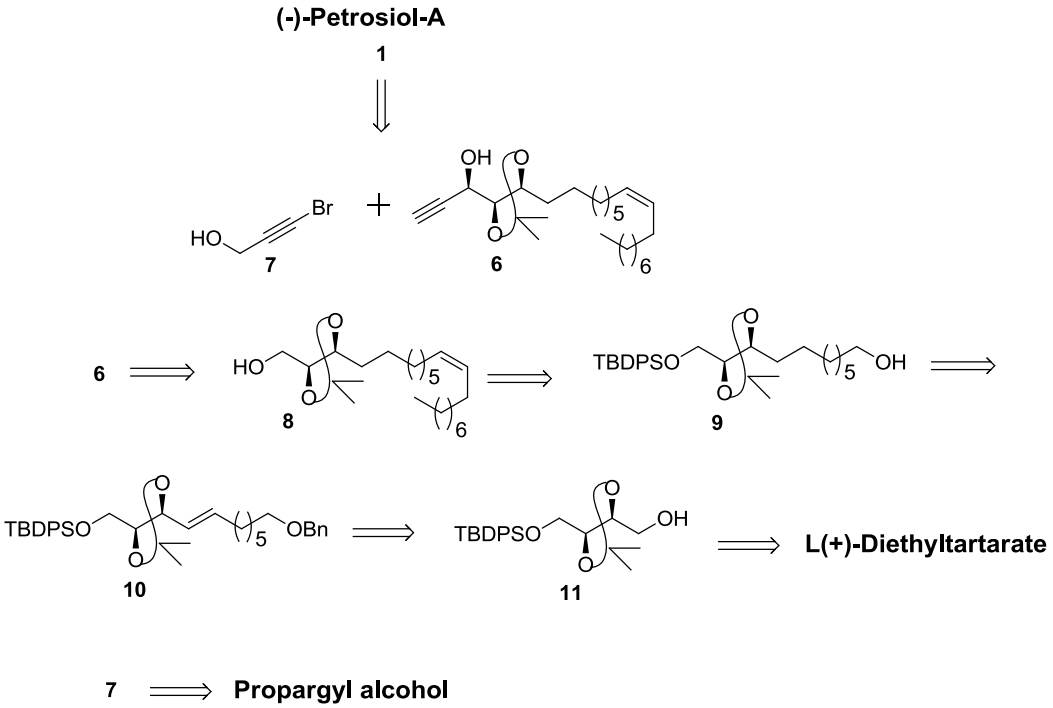
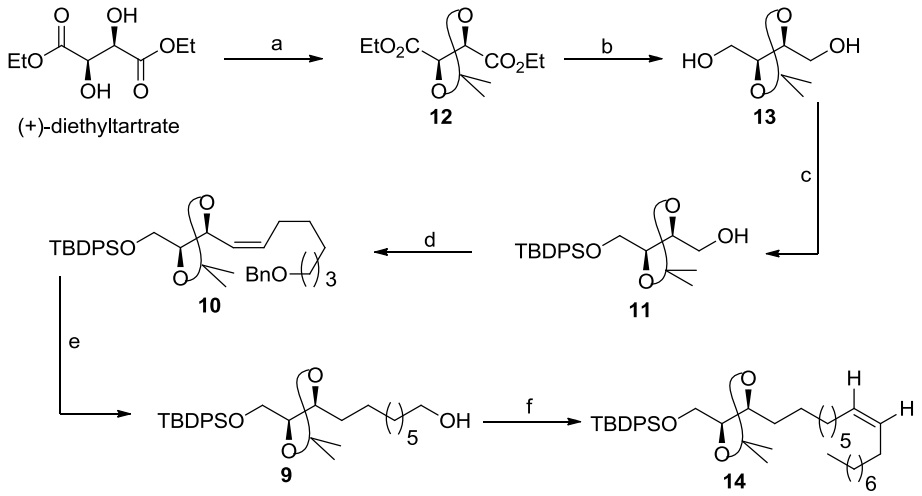


Figure 2: Retrosynthesis of Petrosiol A

Synthesis of alkyne fragment 6:

We initiated the synthesis of fragment **6** from commercially available L-(+)-diethyltartrate. The diol of tartrate was protected as its acetonide using 2,2-DMP, *para*-toluenesulphonic acid to give acetonide diester **12** in 90% yield, which upon treatment with $LiAlH_4$ in THF afforded 1,4 diol **13** in 95% yield. The primary alcohol of **13** was

protected as its mono TBDPS ether using NaH and TBDPSCl to furnish compound **11** in quantitative yield.

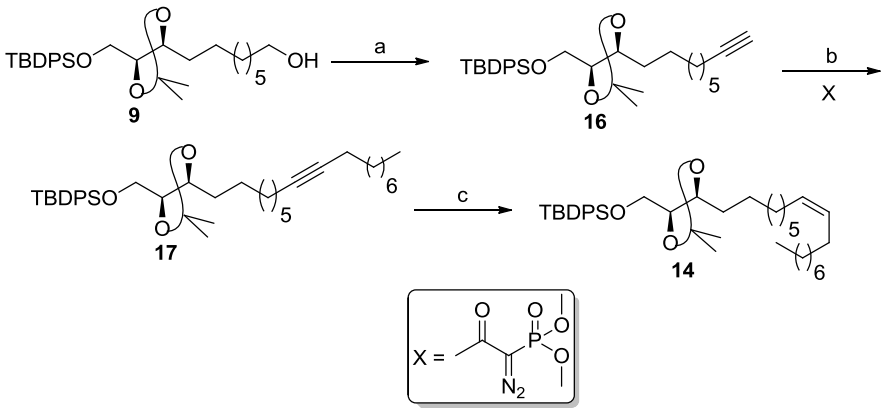


Scheme 1: (a) 2,2-DMP, pTSA, benzene, 81%; (b) $LiAlH_4$, THF,0 ^oC-reflux, 93%; (c) TBDPSCl, NaH, THF, 0 ^oC-rt, 97%; (d) (i) IBX, THF:DMSO, (ii) $BnO\text{-}CH_2\text{-}(CH_2)_4\text{-}CH_2\text{-}P(Ph)_3I$ (**15**), n-BuLi, THF, -78 ^oC-rt, 12 h, 70%; (e) Pd/C, H_2, THF, 24 h, 90%; (f) (i) IBX, THF: DMSO, (ii) $n\text{-}C_9H_{19}P(Ph)_3Br$, n-BuLi, THF, -78 ^oC-rt, 12 h, 84%.

The alcohol **11** when subjected to IBX oxidation followed by Wittig reaction with 7-benzyloxy-n-heptyltriphenylphosphonium iodide **15** with n-BuLi produced the olefin **10** in good yield. One pot debenzylation and saturation of double bond was achieved by using $Pd(OH)_2$ over long time, leading to the formation of product **9** in 90% yield from **10**. The primary alcohol moiety of the compound **9** was subjected to oxidation with 2-iodoxy benzoic acid (IBX) to afford the aldehyde which was subsequently subjected to Wittig reaction with n-nonyltriphenyl phosphonium bromide/n-BuLi at -78 ^oC to afford exclusively *cis* Wittig product **14** in good yield.

Alternatively, the compound **14** was synthesized from alcohol **9** in a four step sequence i.e oxidation of primary alcohol **9** with IBX to yield aldehyde and was subjected to Ohira-Bestmann reaction to get the terminal acetylene **16**. The terminal acetylene **16** was further subjected to coupling with n-iodo octane, by using n-BuLi as a base to afford di substituted acetylene **17**.The *syn* hydrogenation of di substituted

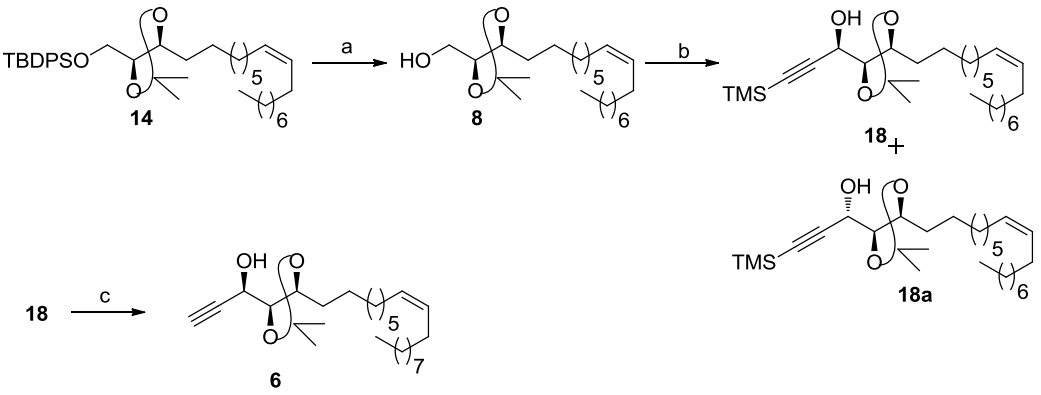
acetylene **17** by using Lindlar's catalyst afforded *cis* olefin **14** in good yield. (Scheme 2).



Scheme 2: *Reagents and conditions*: (a) (i) IBX, THF:DMSO, (ii) MeOH, K_2CO_3, 12 h, 0 ^oC-rt, 80%; (b) $C_8H_{17}I$, n-BuLi, THF, -78 ^oC-rt, 8 h, 74% (c) 5 mol% Pd- $BaSO_4$, H_2, THF, 1 h, 94%.

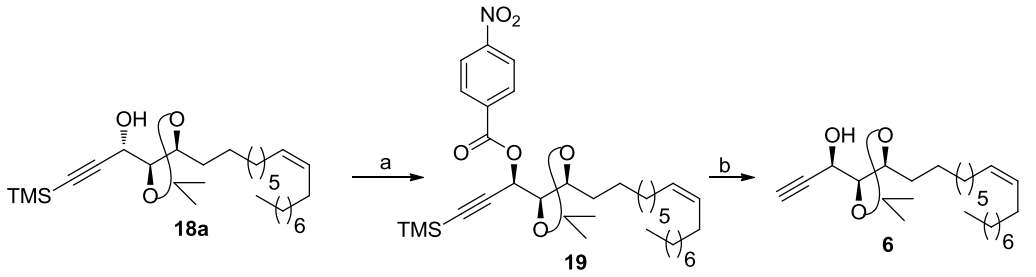
The TBDPS deprotection of compound **14** with 1 Molar solution of n-tetrabutyl ammonium fluoride afforded alcohol **8** in excellent yield. After constructing the right hand portion of the molecule, we proceeded further for the total synthesis of the molecule. Towards this, the alcohol **8** was oxidized under Swern conditions to yield the corresponding aldehyde and was further subjected to an addition reaction with lithium trimethylsilylacetylide to yield a mixture of separable diastereomers **18** and **18a** in (1:1) ratio. The geometry of the resulting chiral center for **18** was confirmed relatively after one step ahead based on its conversion to the similarly known intermediate **6** obtained after TMS deprotection. Also, the diastereomer **18** was converted to the final target molecule (vide infra) thus reconfirming the geometry of the chiral center generated, Towards this TMS deprotection of compound **18** with 1 Molar solution of n-tetrabutylammonium fluoride afforded terminal alkyne **6** in excellent yield(Scheme 3).

Abstract



Scheme 3: *Reagents and conditions*: (a) TBAF, THF, 0 ^{o}C-rt, 4 h, 90% ; (b) (i) DMSO, CH_2Cl_2, $(COCl)_2$, 1 h, -78 ^{o}C, (ii) TMS-acetylene, n-BuLi, THF, -78 ^{o}C-rt, 2 h, 79%; (c) TBAF, THF, 0 ^{o}C-rt, 2 h, 84%.

The undesired stereoisomer **18a** was recycled to the required stereoisomer **6** through the Mitsunobu inversion in order to improve overall yield of the target molecule. Towards this the compound **18a** was derivatized as its *p*-nitro benzoate **19** by using TPP and DIAD in toluene. The crude nitro ester **19** was subjected to one pot hydrolysis and TMS deprotection by using K_2CO_3 and methanol. The analytical data of this compound was found to be identical with compound **6**(Scheme 4).

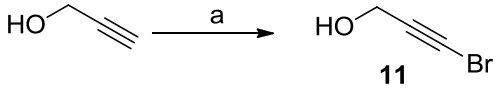


Scheme 4: *Reagents and conditions*: (a) TPP, DIAD, toluene, 8 h; (b) K_2CO_3, MeOH, 1 h, rt, 84%.

Synthesis of bromoalkyne fragment 7:

The synthesis of the bromoalkyne fragment **12** commenced from commercially available propargyl alcohol, acetylenic proton of propargyl alcohol was replaced with

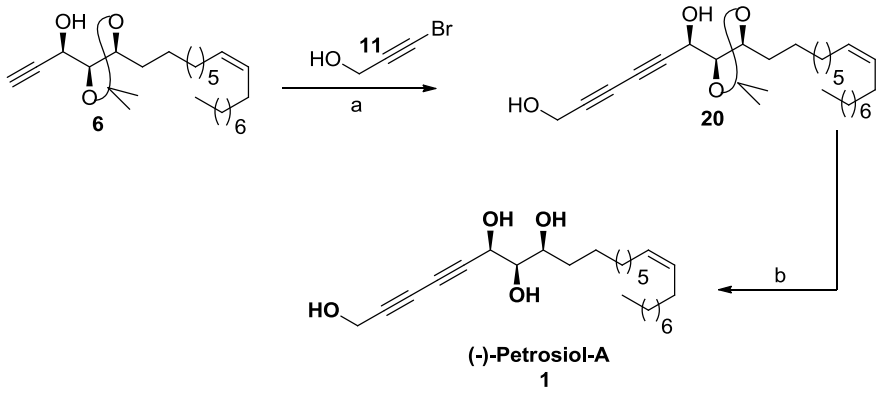
bromine atom by treating propargyl alcohol with NBS, catalyzed by $AgNO_3$ to afford the bromoalkyne **7** in good yield.



Scheme 5: *Reagents and conditions*: *Reagents and conditions*: (a) NBS, $AgNO_3$, acetone, 0 ^oC, 1 h, 82%.

Coupling of the fragments 6 and 7:

The key fragments **6** and **7** were coupled under Cadiot-Chodkiewicz conditions using 30% n-$BuNH_2$/NH_2OH.HCl/CuCl to afford the coupled product **20** in 71% yield, and was then subjected to deprotection of isopropylidine moiety using pTSA in methanol to afford the (-)-petrosiol A **1** (Scheme 6).

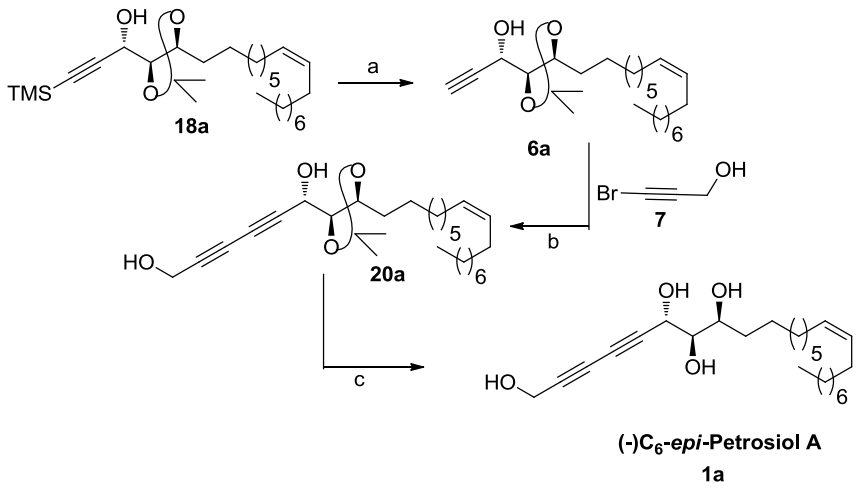


Scheme 6: *Reagents and conditions*: a) (a) CuCl, NH_2OH.HCl, 30% n-$BuNH_2$, Et_2O, 0 ^oC-rt, 30 min, 68%; (b) PTSA, MeOH, 0 ^oC-rt, 20 h, 83%.

Synthesis of C_6-*epi*-petrosiol A:

After successfully accomplishing the total synthesis of natural product from **18**, the other diastereomer **18a** was also utilized further to synthesize C_6-*epi*-petrosiol A following similar set of reactions as used for the synthesis of petrosiol A.

Abstract



Scheme 7: *Reagents and conditions*: (a) TBAF, THF, 0 ^{o}C-rt, 4 h, 84% ; (b) CuCl, $NH_2OH.HCl$, 30% n-$BuNH_2$, Et_2O, 0 ^{o}C-rt, 30 min, 68%; (c) pTSA, MeOH, 0 ^{o}C-rt, 20 h, 83%.

The TMS deprotection of compound **18a** with 1 Molar solution of n-tetrabutylammonium fluoride afforded terminal alkyne **6a** in quantitative yield. Both segments **6a** & **7** were coupled under 30% n-$BuNH_2$/$NH_2OH.HCl$/CuCl conditions to afford the Cadiot-Chodkiewicz coupling product **20a**. Finally substrate **20a** was treated with pTSA over long time to result in the cleavage of acetonide moiety, and afford the (-)-C_6-*epi*-petrosiol A **1a** in quantitative yield.

In conclusion a facile strategy was demonstrated for the total synthesis of neurotrophically active (-)-petrosiol A and 6-*epi*-petrosiol A by utilizing readily available (+)-diethyl tartrate and propargyl alcohol. The synthesis of petrosiol A was achieved in 11 steps with an overall yield of 9.04% from the known alcohol **11**.

Section B: Concise approach for the total synthesis of petrosiol E:

Retrosynthetically, petrosiol E **5** was envisioned to be made by the addition reaction of terminal acetylene **22** onto the aldehyde (obtained from oxidation of the alcohol **21**) followed by TBS deprotection. Fragment **21** can be obtained from L-(+)diethyltartrate via few functional group modifications. Whereas fragment **22** obtained from commercially available 1, 4 bis trimethylsilyl butadiyne.

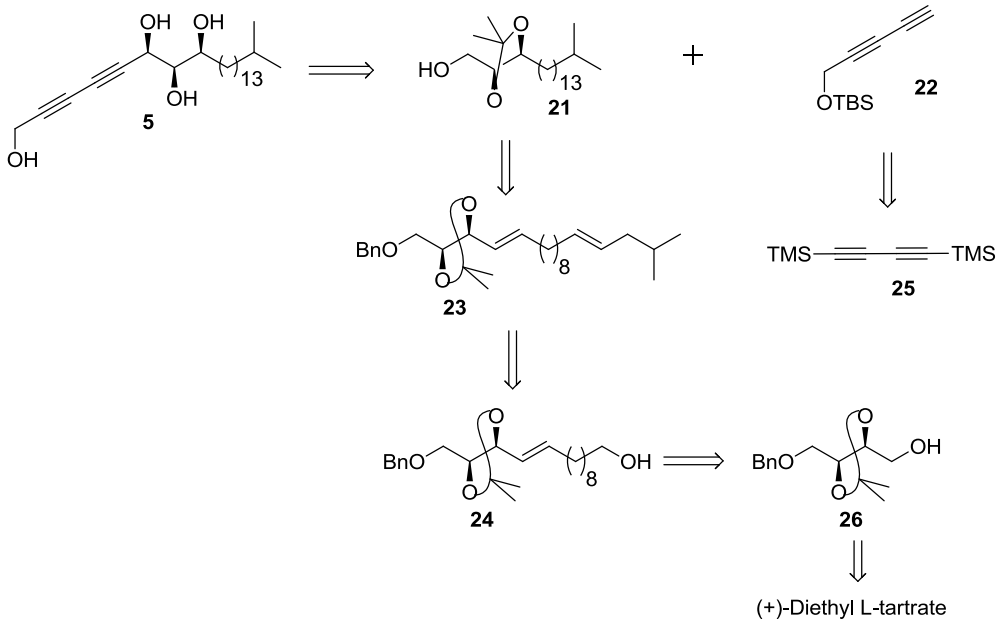
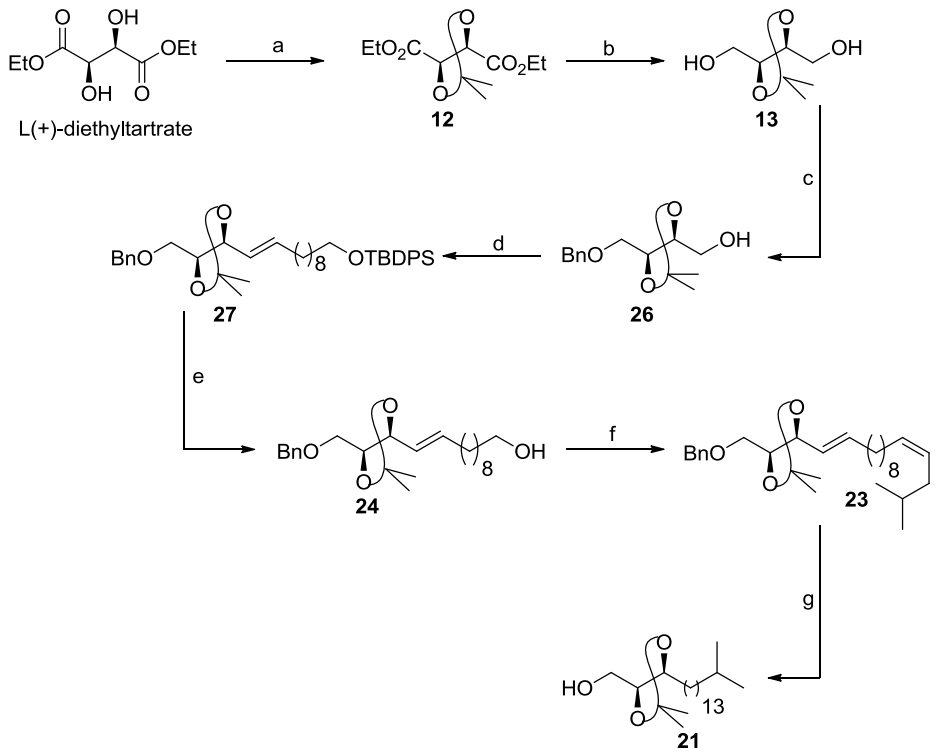


Figure 3: Retrosynthesis of Petrosiol E

Synthesis of alcohol fragment 21:

Our synthesis commenced with the acetonide protection of L(+)-diethyltartrate with 2,2-dimethoxy propane, catalyzed by para toluenesulfonic acid under reflux conditions to afford the acetonide protected diester **12** in quantitative yield. The diester **12** was reduced to diol **13** in excellent yield, upon treating with lithium aluminium hydride under reflux conditions. The diol **13** was mono protected as benzyl ether **26** in a quantitative yield using BnBr/NaH under dilute conditions.



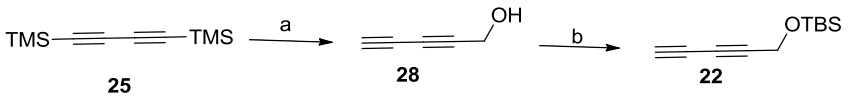
Scheme 8: *Reagents and conditions*: (a) 2,2-DMP, pTSA, benzene; (b) $LiAlH_4$, THF, 0 ^oC-reflux; (c) BnBr, NaH, THF, 0 ^oC-rt; (d) (i) IBX, THF:DMSO, (ii) TBDPSO-CH_2-$(CH_2)_8$-CH_2-$P(Ph)_3I$, n-BuLi, THF, -78 ^oC-rt, 8 h, 86%; (e) TBAF, THF, 3 h, 0 ^oC-rt, 94%; (f) (i) IBX, THF: DMSO, (ii) *iso*-$C_4H_9P(Ph)_3Br$, n-BuLi, THF, -78 ^oC-rt, 12 h, 84%; (g) Pd/C, H_2, THF, 8 h, 94%.

The alcohol **26** was subjected to IBX oxidation followed by Wittig reaction with (10-((tert-butyldiphenylsilyl)oxy)decyl)triphenylphosphonium iodide and *n*-BuLi to produce the olefin **27** in good yield. The desilylation of compound **27** was achieved by treatment with TBAF, leading to the formation of product **24** in excellent yield. The alcohol **24** was subjected to oxidation with 2-iodoxy benzoic acid (IBX) to afford the aldehyde which was subsequently subjected to Wittig reaction with isobutyl triphenylphosphonium bromide/n-BuLi at -78 ^oC to afford the corresponding Wittig product **23** in quantitative yield. Next stage was aimed for debenzylation and saturation of both double bonds of product **23** in one pot procedure. This was achieved by

hydrogenation reaction of Wittig product **23** with $Pd(OH)_2$ over long time, leading to the formation of product **21** in excellent yield.(Scheme 8)

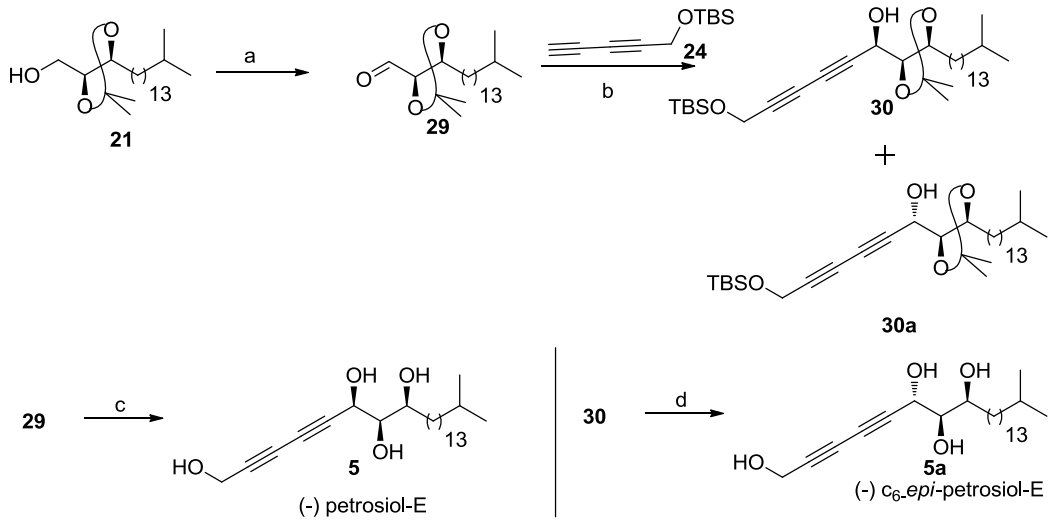
Synthesis of diyne fragment 22:

The diyne **22** was synthesized from commercially available bis(trimethylsilyl)butadiyne **25**. The one pot controlled formylation followed by TMS deprotection was achieved by the MeLi.LiBr in presence of $(HCHO)_n$ with THF as a solvent at -20 ^oC. The free primary hydroxyl group in compound **28** was protected as its TBS ether by using TBSCl and imidazole, in excellent yield. (Scheme 9).



Scheme 9: *Reagents and conditions*: (a) MeLi.LiBr, $(HCHO)_n$, THF, -20 ^oC-rt, 8 h, 84%; (b) TBSCl, Imidazole, 0 ^oC-rt, 1 h, 99%.

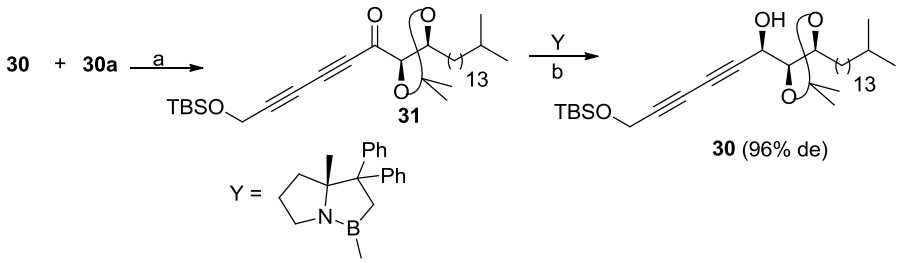
At this stage with both the key precursors i.e. alcohol **21** and diyne **22** are in hand, next we proceeded for the Sweren oxidation of alcohol provide the corresponding aldehyde which was subjected to an addition reaction with diyne **24,** to give the corresponding separable diastereomers in 1:1 ratio. The compounds **30** and **30a** were individually subjected to one pot cleavage of isopropylidine moiety as well of TBS group by treating with pTSA over long time, resulted in the cleavage of isopropylidine moiety as well as deprotection of TBS group to afford the (-)-petrosiol **E 5** and (-)-C_{6}-*epi*-petrosiol **5a** with good productivity.(Scheme 10)



Scheme 10: *Reagents and conditions*: (a) DMSO, CH_2Cl_2, $(COCl)_2$, -78 ^oC, 1 h, Et_3N ; (b) **24** n-BuLi, THF, -78 ^oC -rt, 8 h, 79%; (c) pTSA, MeOH, 0 ^oC-rt, 20 h, 91%.

In order to synthesize the diastereorich chiral compound **30,** the diastereomeric mixture of **30** and **30a** was oxidized by using DMP as an oxidizing agent in CH_2Cl_2 to provide the corresponding propargylic ketone **21** in excellent yield.

The ketone **21** was subjected to stereoselective reduction following Corey's protocol with CBS catalyst to provide the corresponding diastereorich propargylic alcohol **30** in quantitative yield with an excellent diastereoselectivity(96%)(Scheme 11).



Scheme 11: *Reagents and conditions*: (a) DMP, CH_2Cl_2, 0 ^oC, 1 h, 92%; (b) **Y**, BH_3.DMS, THF, -40 ^oC, 24 h, 89%.

In conclusion the stereoselective total synthesis of neurotrophically active (-)-petrosiol E and (-)C_6-*epi*-petrosiol E has been achieved in a linear fashion by utilizing readily available (+)-diethyl tartrate and propargyl alcohol. Overall strategy was very facile and is flexible to access other petrosiols.

Chapter-III: Stereoselective total synthesis of strongylodiols A, B, C and D.

Watanabe et al have isolated seven novel diacetylenic diol natural products strongylodiols A-J from Okinawan marine sponge of the genus *Petrosia* (*Strongylophora*). The structures of these compounds were elucidated on the basis of spectroscopic analysis and chemical reactions.

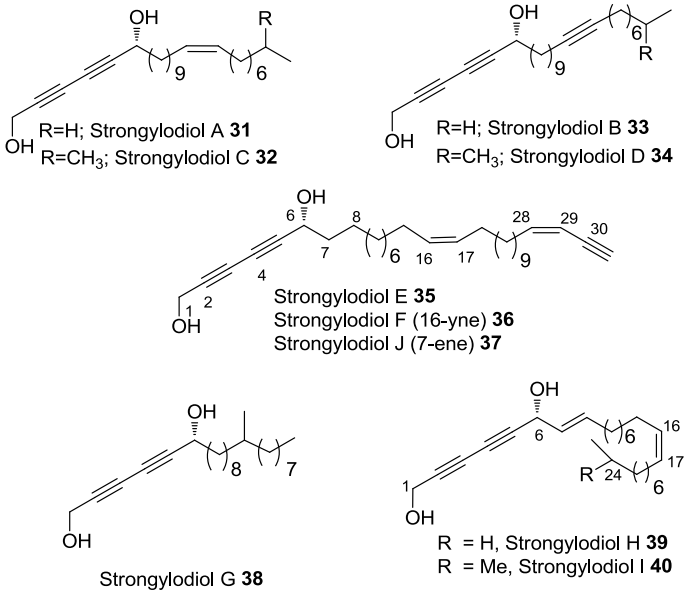


Figure 4: Structures of petrosiols A-E.

Interestingly, each of the strongylodiols were found to be an enantiomeric mixture in a different ratio as analyzed by the corresponding MNA esters of each natural product strongylodiol A (91:9), stronglylodiol B (97:3), strongylodiol C (84:16) and strongylodiol D (95:5) (strongylodiol H (94:6), stronglylodiol I (97:3) with the major compound having *R* configuration in all the four molecules. In continuation to our research interest on the synthesis of acetylenic compounds for accessing them towards

screening the biological activities, we herein reported the total syntheses of strongylodiols A, B, C and D starting from commercially available D (-)-diethyltartrate.

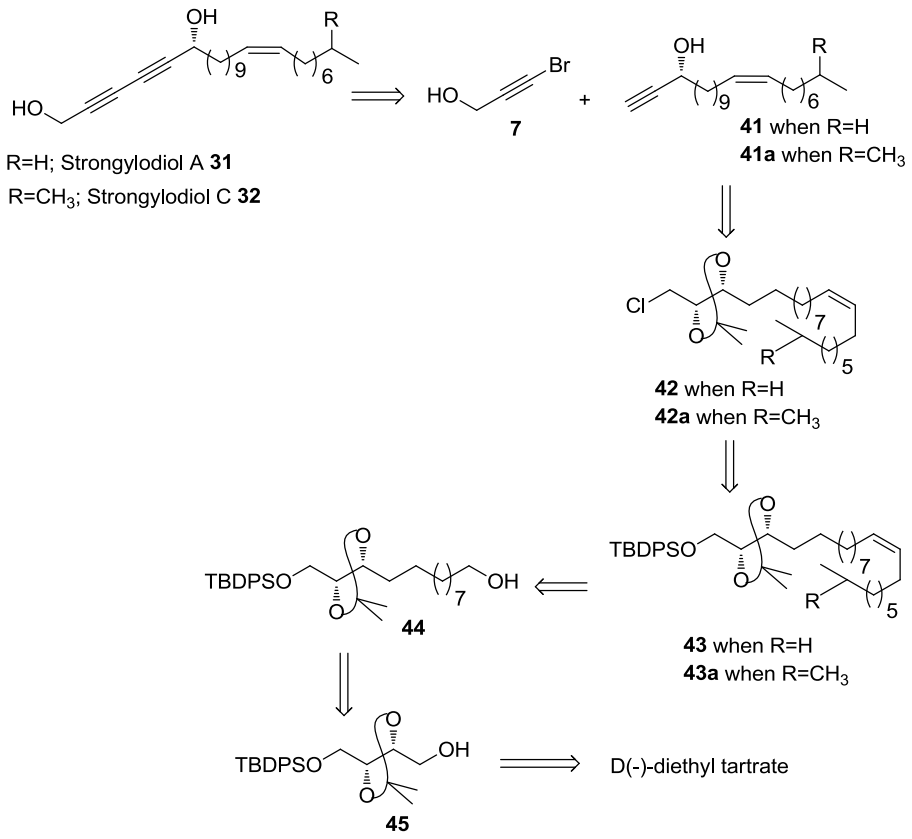
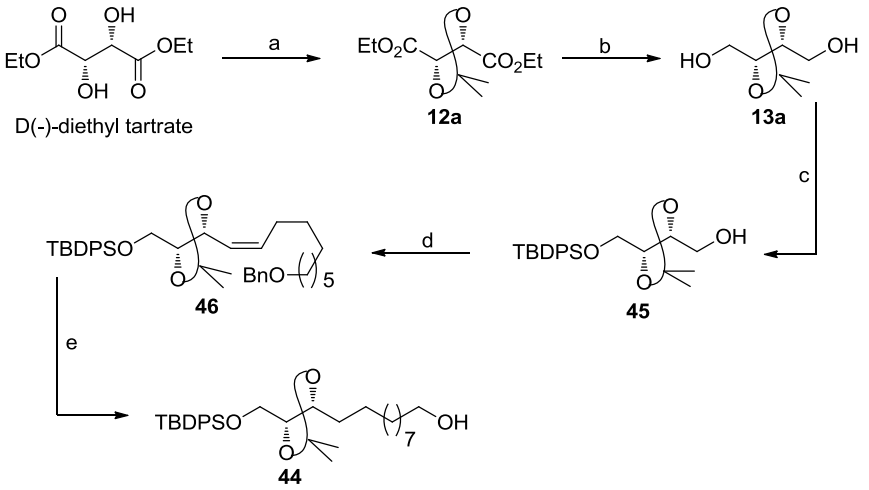


Figure 5: Retrosynthesis of Strongylodiol A and C

Retrosynthetically, strongylodiol A and strongylodiol C were envisaged to be synthesized by Cadiot-Chodkiewicz coupling reaction of 3-bromo-2-propyne-1-ol **7** with chiral propargyl alcohol **41** and **41a** respectively. Fragment **41** and **41a** can be obtained from D-(-)diethyltartrate via few functional group modiffications, whereas fragment **7** can be obtained from commercially available propargyl alcohol.

Synthesis of strongylodiol A:

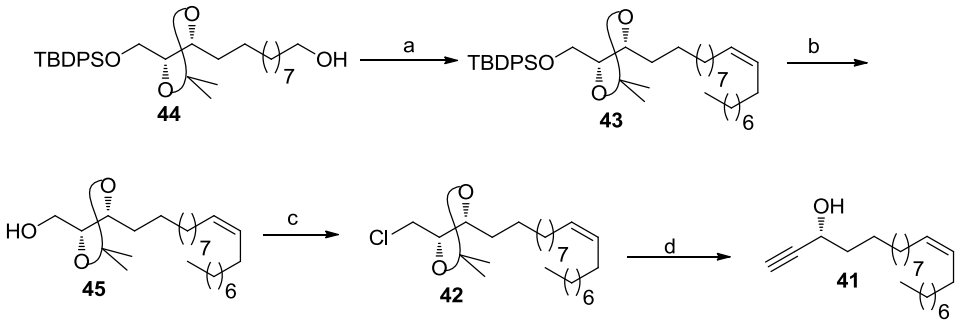
Our synthesis started with the acetonide protection of (-)-diethyltartarate employing 2,2-dimethoxy propane, catalyzed by *para*-toluenesulfonic acid under reflux conditions to afford the acetonide protected diester **11a** in quantitative yield. The diester **12a** was reduced to diol **13a** in excellent yield, through lithium aluminiumhydride reduction under reflux conditions. The diol **45** was mono protected as TBDPS ether **45** in a quantitative yield using TBDPSCl/NaH under dilute conditions. The alcohol **45** was subjected to IBX oxidation followed by Wittig reaction with 7-benzyloxy-n-nonyltriphenylphosphonium iodide **X** with n-BuLi to produce olefin **46** in good yield. Next stage was aimed for debenzylation and saturation of double bond of product **46** in one pot procedure. This was achieved by hydrogenation reaction of Wittig product **46** with $Pd(OH)_2$ over long time, leading to the formation of product **44** in excellent yield(Scheme12).



Scheme 12: *Reagents and conditions*: (a) 2,2-DMP, pTSA, benzene, 92%; (b) $LiAlH_4$, THF, 0 ^oC-reflux, 89%; (c) TBDPSCl, NaH, THF, 0 ^oC-rt; (d) (i) IBX, THF:DMSO, (ii) $BnO\text{-}CH_2\text{-}(CH_2)_7\text{-}CH_2\text{-}P(Ph)_3I$ (**X**), n-BuLi, THF, -78 ^oC-rt, 12 h, 87%, over twosteps; (e) Pd/C, H_2, THF, 24 h, 95%.

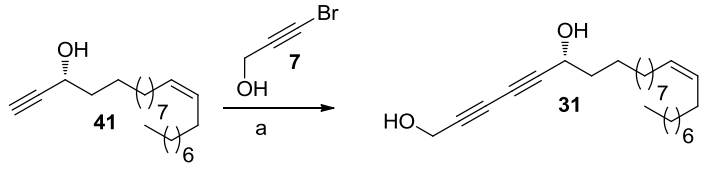
The primary alcohol moiety of the compound **44** was subjected to oxidation with 2-iodoxy benzoic acid (IBX) to afford the aldehyde which was subsequently subjected

to Wittig reaction with n-nonyltriphenyl phosphonium bromide and n-BuLi at -78 ^{o}C to afford exclusively *cis* Wittig product **43** in good yield. The TBDPS deprotection of compound **43** was acheived with 1 Molar solution of n- tetrabutylammonium fluoride to afford alcohol **45** in excellent yield. The primary alcohol **45** was converted to corresponding chloride **42** by using TPP and carbon tetrachloride. The chloro compound **42** was subjected to Yadav's protocol for the generation of chiral propargyl alcohol[11] employing 6 eq. of n-BuLi to provide **41**(Scheme13).



Scheme 13: *Reagents and conditions*: (a) (i) IBX, THF: DMSO, (ii) n-$C_9H_{19}P(Ph)_3Br$, n-BuLi, THF, -78 ^{o}C-rt, 12 h, 87%; (b) TBAF, THF, 0 ^{o}C-rt, 4 h, 95% ; (c) TPP, CCl_4, $NaHCO_3$, 80 ^{o}C, 8 h, 79%; (d) n-BuLi, THF, 0 ^{o}C, 0.5 h, 83%.

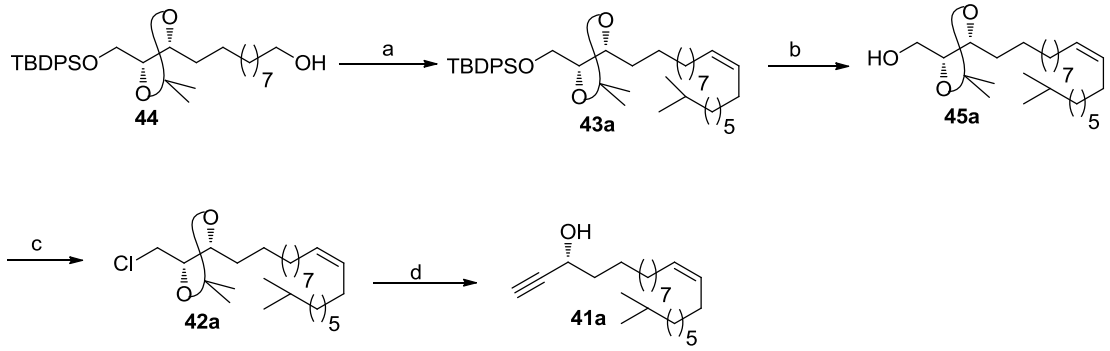
At this stage, with both the coupling precursors i.e. alkyne **41** and bromo alkyne **7** in hand, we proceeded for the Cadiot-Chodkiewicz coupling. Both the substrates **41** & **7** underwent coupling under 30% n-$BuNH_2$/NH_2OH.HCl/CuCl conditions to afford the strongylodiol A **31**.



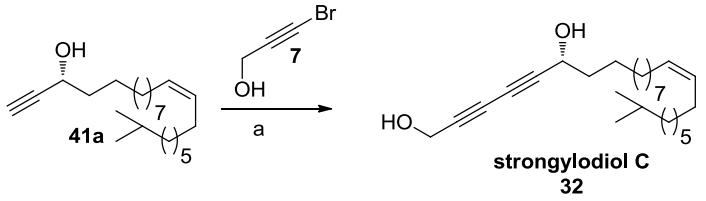
Scheme 14: *Reagents and conditions*: (a) CuCl, NH_2OH.HCl, 30% n-$BuNH_2$, Et_2O, 0 ^{o}C-rt, 30 min, 73%.

Synthesis of strongylodiol C:

In order to synthesize the strongylodiol C, the primary alcohol moiety of the compound **44**(Scheme12) was subjected to oxidation with 2-iodoxy benzoic acid (IBX) to afford the aldehyde which was subsequently subjected to Wittig reaction with (iso-decyl)triphenyl phosphonium iodide and n-BuLi at -78 ^{o}C to afford exclusively *cis* Wittig product **43a** in good yield. The TBDPS deprotection of compound **43a** was achieved with 1 Molar solution of n-tetrabutylammonium fluoride to afford alcohol **45a** in excellent yield. The primary alcohol **45a** was converted to corresponding chloride **42a** by using TPP and carbon tetrachloride. The chloro compound **42a** was subjected to Yadav's protocol for the generation of chiral propargyl alcohol employing 6 eq. of n-BuLi to provide **41a**.



Scheme 15: *Reagents and conditions*: (a) (i) IBX, THF: DMSO, (ii) iso-$C_{10}H_{21}P(Ph)_3I$ **Y**, n-BuLi, THF, -78 ^{o}C-rt, 12 h, 85%.(b) TBAF, THF, 0 ^{o}C-rt, 4 h, 93% ; (c) TPP, CCl_4, $NaHCO_3$, 80 ^{o}C, 8 h, 71% ;(d) n-BuLi, THF, 0 ^{o}C, 0.5 h, 74%.



Scheme 16: *Reagents and conditions*: (a) CuCl, $NH_2OH.HCl$, 30% n-$BuNH_2$, Et_2O, 0 ^{o}C-rt, 30 min, 68%.

Abstract

The chiral propargylic alcohol **41a** was subjected to Cadiot-Chodkiewicz coupling with bromo alkyne **7** (Scheme 5) by using 30% n-$BuNH_2$/NH_2OH.HCl/CuCl to afford the strongylodiol C **32**.

Strongylodiols B and D were envisaged to be synthesized by coupling of 3-bromo-2-propyne-1-ol **7** with alkyne **46** and **46a** respectively. The chiral propargyl alcohols **46** and **46a** can be obtained from D-(-)diethyltartrate via few functional group modiffications. Whereas fragment **7** can be synthesized from commercially available propargyl alcohol.

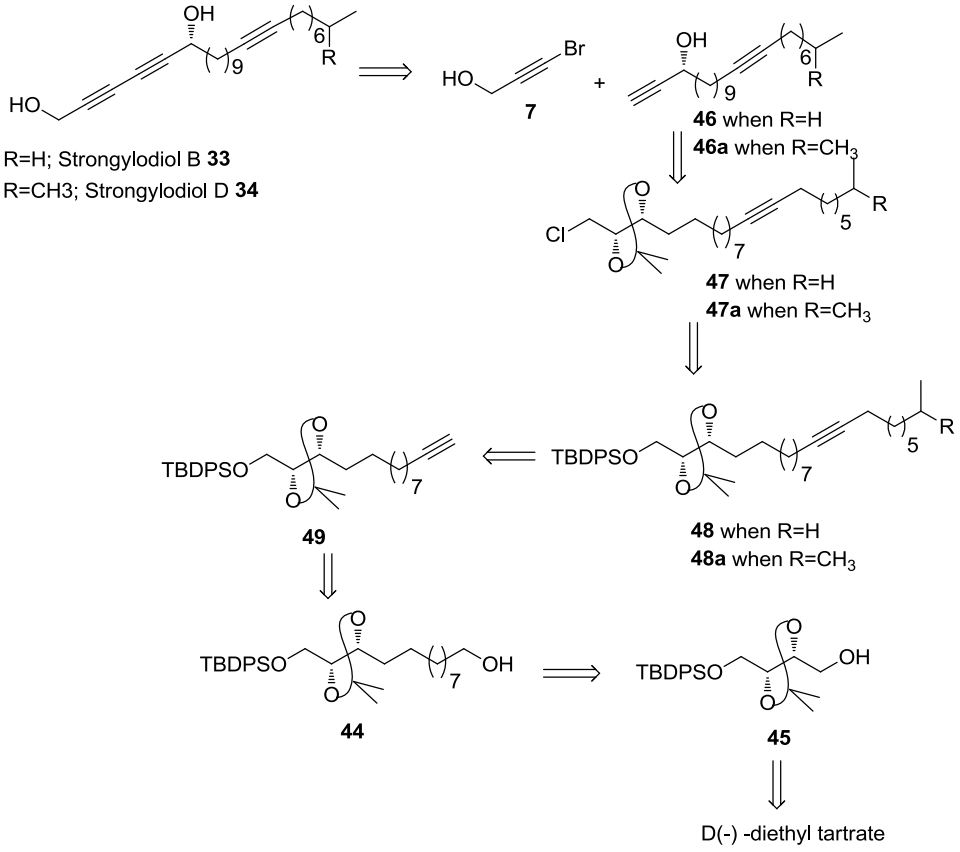
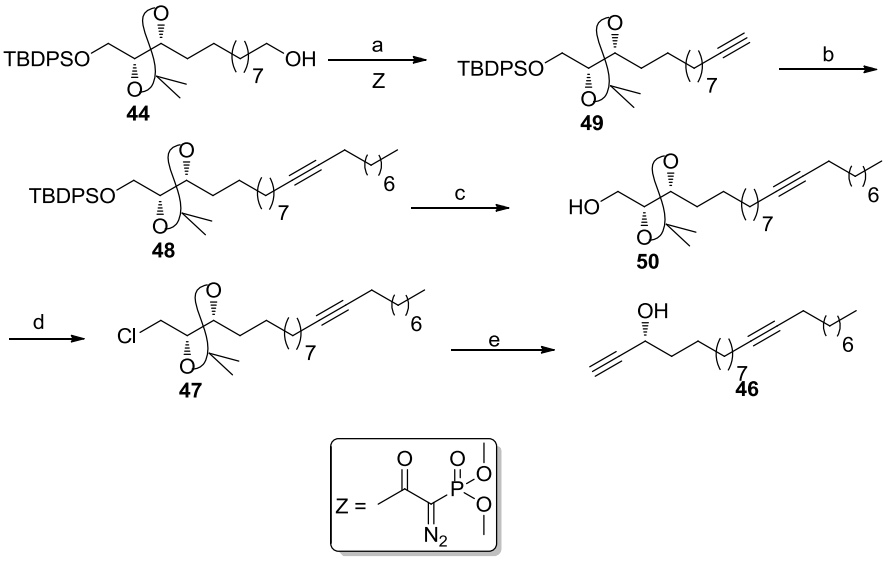


Figure 6: Retrosynthesis of Strongylodiol A and C

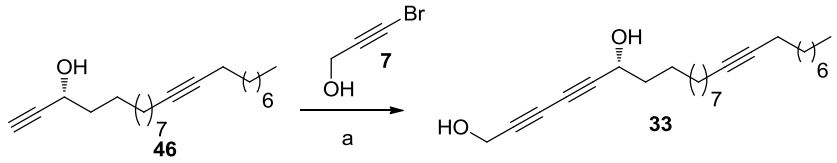
Synthesis of strongylodiol B:

The key fragment **44** which was utilized for the total synthesis of strongylodiol A and C are also used for the total synthesis of strongylodiol B and C, towards this the key fragment **44** (Scheme 12) was subjected to oxidation with IBX to yield aldehyde and was subjected to Ohira-Bestmann reaction to get the terminal acetylene **49**. The terminal acetylene **49** was further subjected to coupling with n-iodo octane, by using n-BuLi as a base to afford disubstituted acetylene **48**. The silyl (TBDPS) deprotection of compound **48** was acheived with 1 Molar solution of n-tetrabutylammonium fluoride to afford alcohol **50** in excellent yield. The primary alcohol **50** was converted to corresponding chloride **47** by using TPP and carbontetrachloride. The chloro compound **47** was subjected to Yadav's protocol for the generation of chiral propargyl alcohol employing 6 eq. of n-BuLi to provide **46**. The compound **46** was utilized for next step without further purification, as on long standing the compound gets decomposed.



Scheme 17: *Reagents and conditions*: (a) (i) IBX, THF:DMSO; (ii) **Z**, MeOH, K_2CO_3, 12 h, 0 ^oC-rt, 87%; (b) $C_8H_{17}I$, n-BuLi, THF, -78 ^oC-rt, 8 h, 79%; (c) TBAF, THF, 0 ^oC-rt, 4 h, 95%; (d) TPP, CCl_4, $NaHCO_3$, 80 ^oC, 8 h, 72%; (e) n-BuLi, THF, 0 ^oC, 0.5 h.

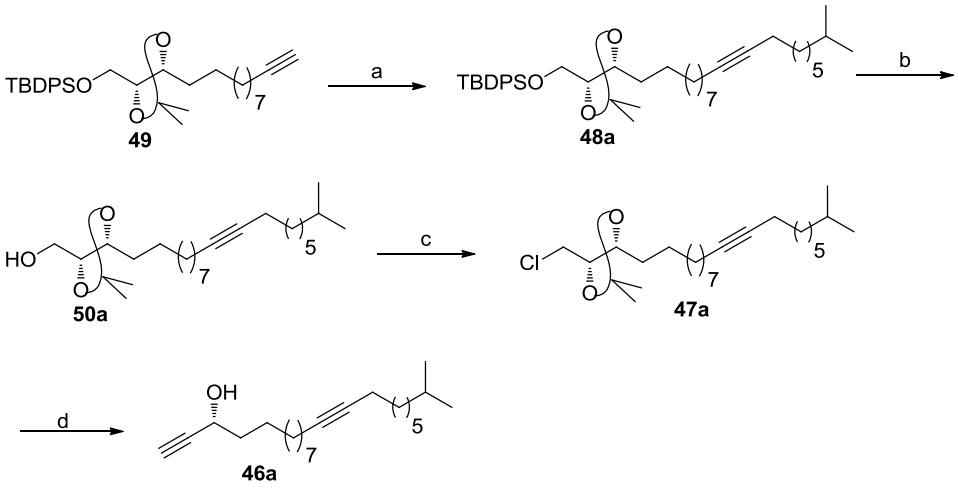
The chiral propargylic alcohol **46** was subjected to Cadiot-Chodkiewicz coupling with bromo alkyne **7** (Scheme 5) by using 30% n-$BuNH_2$/NH_2OH.HCl/CuCl to afford the strongylodiol B **33**.



Scheme 18: *Reagents and conditions*: (a) CuCl, NH_2OH.HCl, 30% n-$BuNH_2$, Et_2O, 0 ^oC-rt, 30 min, 61%.

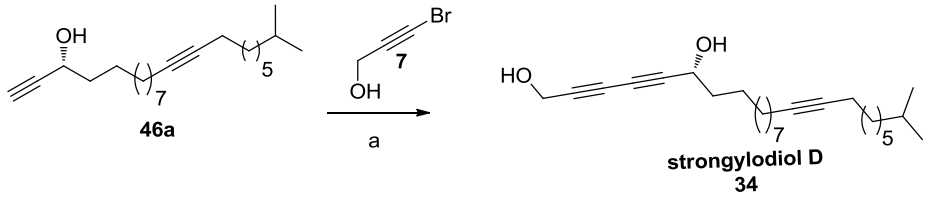
Synthesis of strongylodiol D:

The terminal alkyne **49** (Scheme 17) which was utilized for the synthesis of strongylodiol B, was also used for the total synthesis of strongylodiol D. Towards this the terminal alkyne **49** was subjected to coupling with 7-methyl-1-iodo octane, by using n-BuLi as a base to afford di substituted acetylene **48a**. The TBDPS deprotection of compound **48a** was acheived with 1 Molar solution of n- tetrabutyl ammonium fluoride to afford alcohol **50a** in excellent yield. The primary alcohol **50a** was converted to corresponding chloride **47a** by using TPP and carbon tetrachloride. The chloro compound **47a** was subjected to Yadav's protocol for the generation of chiral propargyl alcohol employing 6 eq. of n-BuLi to provide **46a**.



Scheme 19: *Reagents and conditions*: (a) *iso*-$C_9H_{19}I$, n-BuLi, THF, -78 ^oC-rt, 8 h, 77% (b) TBAF, THF, 0 ^oC-rt, 4 h, 95% ; (c) TPP, CCl_4, $NaHCO_3$, 80 ^oC, 8 h, 72% ;(d) n-BuLi, THF, 0 ^oC, 0.5 h, 75%.

The chiral propargylic alcohol **46a** was subjected to Cadiot-Chodkiewicz coupling with bromo alkyne **7** (Scheme 5) by using 30% n-$BuNH_2$/NH_2OH.HCl/CuCl to afford the strongylodiol D **34**.



Scheme 20: *Reagents and conditions*: (a) CuCl, NH_2OH.HCl, 30% n-$BuNH_2$, Et_2O, 0 ^oC-rt, 30 min, 59%.

In conclusion, we developed a chiron approach for the total synthesis of strongylodiol A, B, C and D by utilizing readily available D-(-)-diethyl tartrate and propargyl alcohol. The synthesis of strongylodiol A and C, B and D were achieved in 9 and 10 longest linear steps with an overall yield of 32.7, 20.9, 23.7, 16.8 % respectively from the known alcohol **45**.

Chapter-IV: First total synthesis and structural revision of strongylodiol H and I:

The target molecules strongylodiol H **39** and strongylodiol I **40** can be synthesized by a Wittig reaction of an aldehyde **51** with the phosphonium Wittig salts **52** and **53** individually, followed by the desilylation (TBDPS removal) of the Wittig products. The common intermediate aldehyde **51** can be synthesized from chiral propargylic alcohol **54** in three steps i.e., TBDPS protection and TBS deprotection followed by oxidation of the primary alcohol. The chiral propargylic alcohol **54** in turn can be obtained from prochiral ketone **55** by a stereoselective reduction reaction. The ketone **55** can be easily accessible from compounds **56** and **57** in two-step sequence i.e., Cadiot–Chodkiewicz coupling reaction followed by an oxidation reaction. The compound **56** is easily accessible from commercially available propargyl alcohol in two-

step sequence that is TBDPS protection followed by bromination on alkyne moiety. The compound **57** can be synthesized by a coupling reaction of TMS-acetylene with aldehyde **58** followed by TMS deprotection. The compound **58** in turn can be obtained from **59** by partial reduction of alkyne functionality to *trans* olefin followed by oxidation of the resulting allyl alcohol. Compound **59** can be easily synthesized using commercially available propargyl alcohol and 1,8-octane diol in three-step sequence via mono TBS protection of 1,8-octane diol, iodination of free primary alcohol and C-alkylation on alkyne(Figure 7).

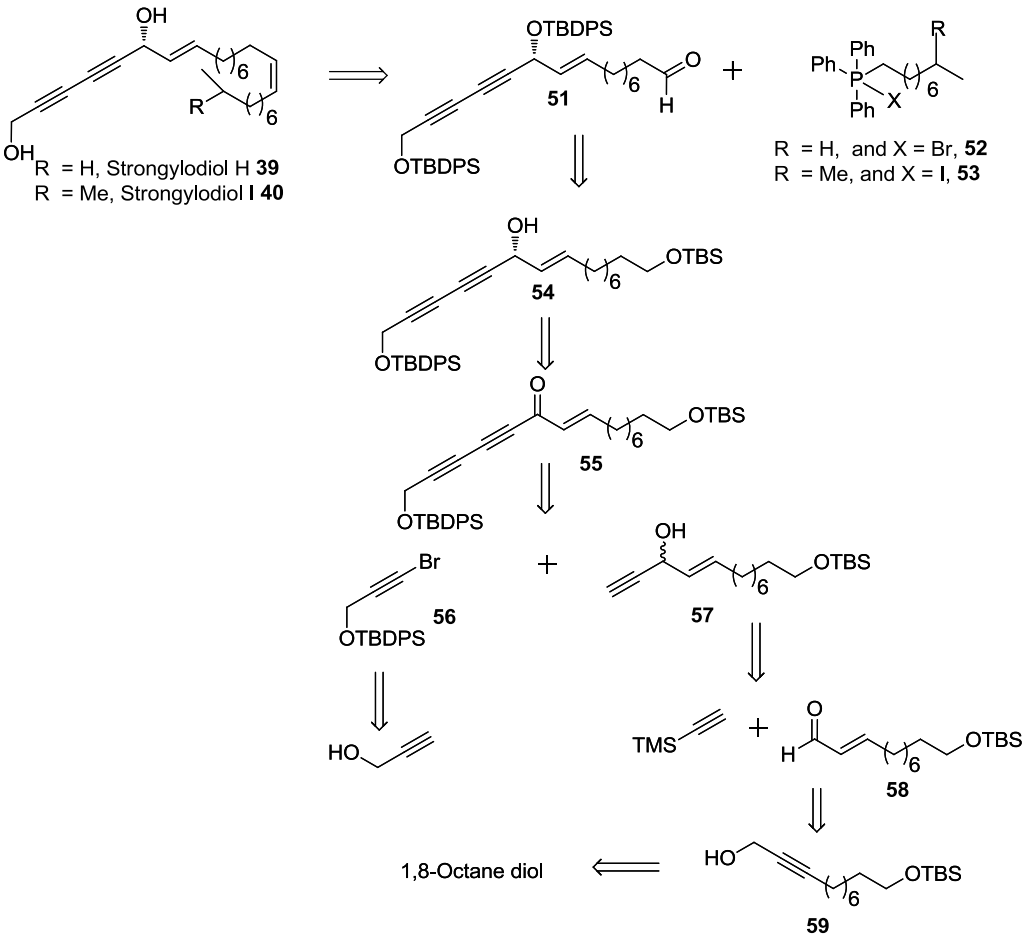
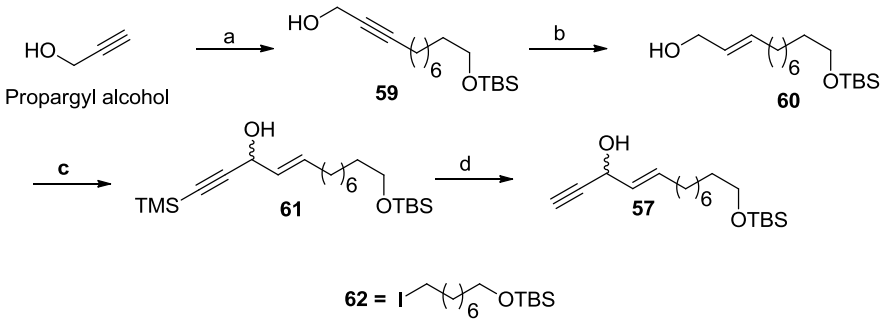


Figure 7: Retosynthesis of Strongylodiol H and I.

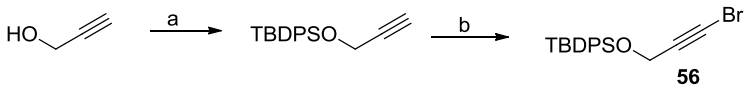
Synthesis of Strongylodiol H and I

Our synthesis began with the C-alkylation reaction of propargyl alcohol with *tert*-butyl ((8-iodooctyl) oxy) dimethylsilane **62** in the presence of *n*–BuLi to provide alkynol **59** in good yield. The trans reduction of the alkyne **59** was achieved by using sodium bis(2-methoxyethoxy)aluminumhydride (Red-Al) as a hydride transfer reagent in an excellent yield under dilute conditions to furnish the corresponding (*E)*-allylic alcohol **60**. The alcohol **60** was oxidized under Swern conditions to yield the corresponding aldehyde and was further subjected to an addition reaction with lithium trimethylsilylacetylide to yield a mixture of enantiomers **61** and **61a** in (1:1) ratio. TMS deprotection of compound **61** with K_2CO_3 in MeOH afforded terminal alkyne **57** in excellent yield.



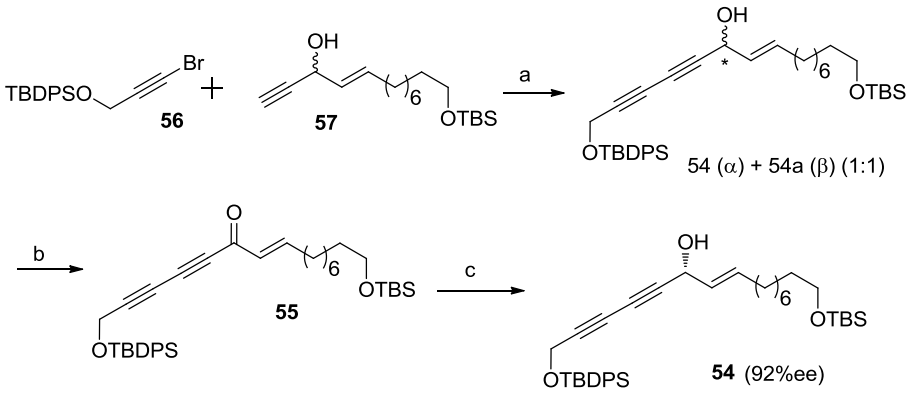
Scheme 4.1.2: *Reagents and conditions*: (a) n- BuLi, THF, -78 ^oC, **62**, 12 h, 72%, (b) Red Al, Anh. Et2O, -20 ^oC, 8 h, 95% (c) DMSO, CH_2Cl_2, $(COCl)_2$, -78 ^oC, ≡—TMS, n BuLi, THF, -78 ^oC, 1 h, 89%. (d) K_2CO_3, MeOH, rt, 2 h, 83%.

Next our target was to synthesize the bromo alkyne **56** from readily available propargyl alcohol. TBDPS protection of propargyl alcohol with TBDPSCl/NaH produced the TBDPS protected propargyl alcohol. Acetylenic proton of this compound was replaced with bromine atom by treating the substrate with NBS, catalysed by $AgNO_3$ to afford the Cadiot-Chodkiewicz coupling precursor **56** in good yield.



Scheme 22: *Reagents and conditions*: (a) TBDPSCl, Imidazole, 0 ^{o}C - rt, 1 h, 92%, (b) NBS, $AgNO_3$, Acetone, 0 ^{o}C - rt, 1 h, 82%.

At this stage with both the coupling precursors i.e. alkyne **57** and bromo alkyne **56** in hand, next we proceeded further for the Cadiot-Chodkiewicz coupling. Both the substrates **57** & **56** were coupled under 30% n-$BuNH_2$/NH_2OH.HCl/CuCl conditions to afford the Cadiot-Chodkiewicz coupling product **54** and **54a**. The enantiomeric mixture of **54** and **54a** was oxidized by using DMP as an oxidizing agent in CH_2Cl_2 to provide the corresponding ynone **55** in excellent yield. The ketone **55** was subjected to stereoselective reduction following Corey's protocol with CBS catalyst to provide the corresponding enantiorich propargylic alcohol **54** in quantitative yield with an excellent enantio selectivity(92%)(Scheme 23).



Scheme 23: *Reagents and conditions*: (a) CuCl, NH_2OH.HCl, 30% n- $BuNH_2$, Et_2O, 1 h, 68%, (b) DMP, CH_2Cl_2, 0 ^{o}C - rt, 1 h, 87%, (c) (*S*)-CBS Catalyst, BH_3.DMS, THF, -50 ^{o}C, 16 h, 85%.

The absolute stereochemistry of the newly generated secondary hydroxyl bearing carbon center (C6) was determined by modified Mosher's ester analysis as *R* stereochemistry at C_6.

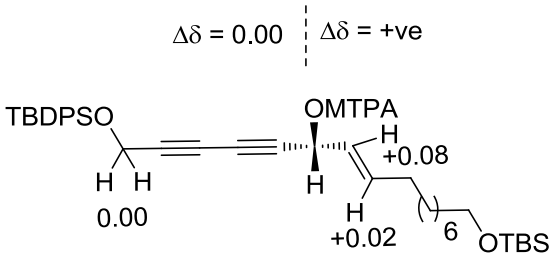
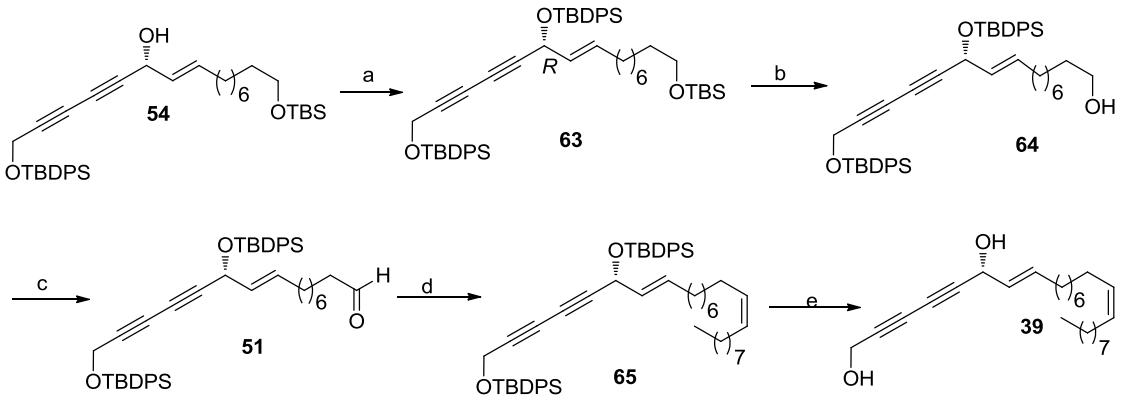


Figure 8. $\Delta\delta = \delta_S - \delta_R$ for *R*- and *S*- MTPA Ester of alcohol **54.**

Having determined the stereochemistry at the newly generated carbon center in intermediate **54**, we proceeded further to extend the chain at the right hand side. Towards this, the free secondary hydroxyl group was masked as its corresponding TBDPS-ether **63**. The primary TBS group was selectively deprotected in presence of other silyl groups (TBDPS) was achieved with PPTS in MeOH to provide the primary alcohol **64** in 87% yield. The alcohol **64** was subjected to IBX oxidation followed by Wittig reaction with (n-Noyl)triphenylphosphonium iodide **52** with n-BuLi to produce the *Z*- olefin **65** in excellent yield. The TBDPS deprotection of compound **65** with 1 Molar solution of n- tetrabutylammonium fluoride afforded *R*- Strongylodiol H **39** in good yield.



Scheme 24: *Reagents and conditions*: (a)TBDPSCl, Imidazole, CH_2Cl_2, 0 ^oC - rt, 1 h, 95%,(b) PPTS, MeOH, 0 ^oC - rt, 2 h, 95%, (c)IBX, THF + DMSO,0 ^oC - rt, 1 h, 97%, (d) **52**, n- BuLi, THF, -78 ^oC - rt, 2 h, 83%, (e) TBAF, THF, 0 ^oC - rt, 1 h, 85%.

The ^{1}H NMR and ^{13}C NMR spectra of the synthesized product were in full agreement with those of the reported natural product. However, the specific rotation of our synthetic product was observed to be $[\alpha]^{25}_{D}$ = +42.2 (*c* 0.81, $CHCl_3$), whereas the specific rotation for the natural product from isolation studies was reported to be $[\alpha]^{25}_{D}$ = -43.8 (*c* 0.35, $CHCl_3$). Having identical spectral data, with opposite sign of rotation, it is clear evident that the proposed structure is the enantiomer of the natural product. Based on the outcome of our synthesis, we unambiguously revise the structure of the natural product as **39a** which is an enantiomer of proposed structure **39** (Figure 9).

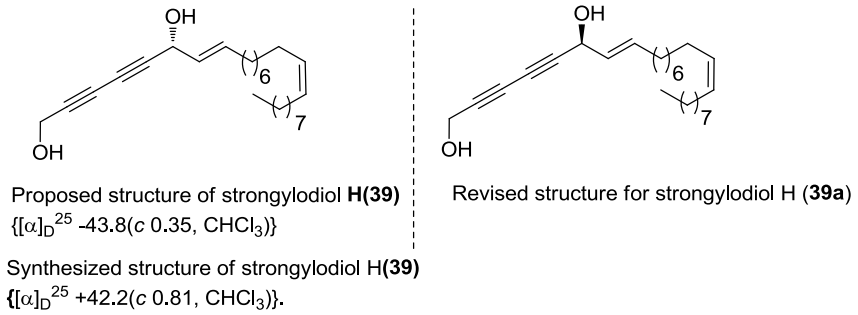
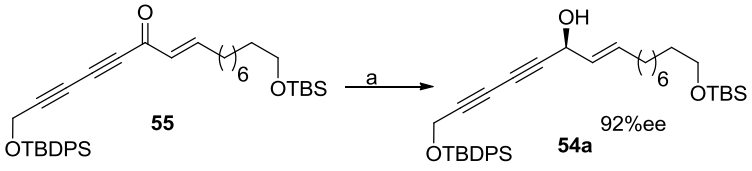


Figure 9. Proposed and revised structure of strongylodiol H.

Further, to reconfirm the structural revision, we investigated to synthesize the other enantiomer of strongylodiol H.

The stereoselective reduction of prochiral ketone **55** (Scheme 23) with *R*-CBS catalyst furnished the chiral propargylic alcohol **54a** with 92% ee (Scheme 25).

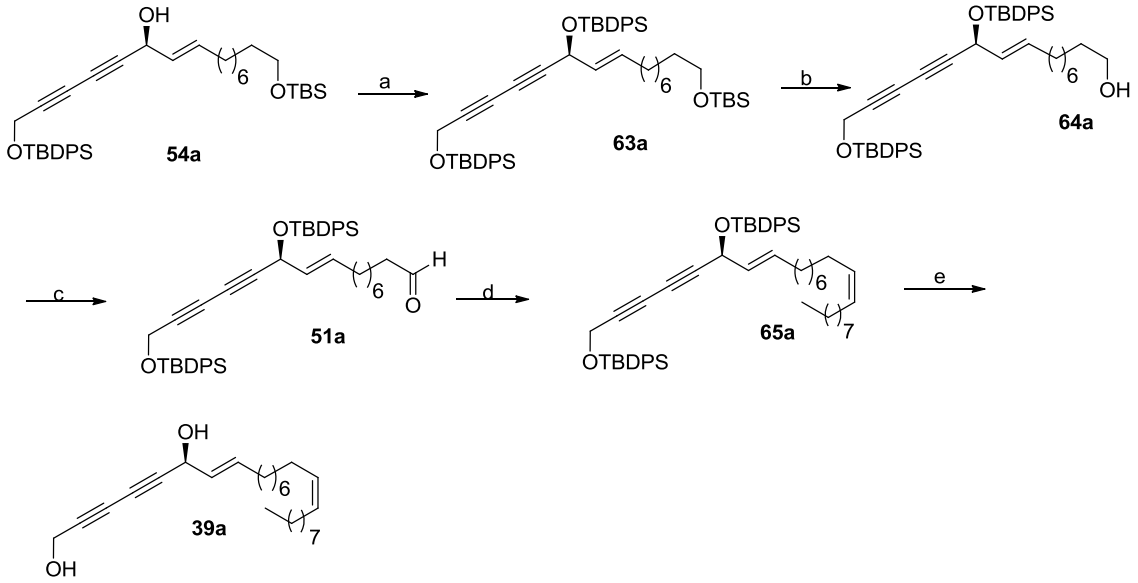


Scheme 25: *Reagents and conditions*: (a) (*R*)-CBS Catalyst, BH_3.DMS, -50 ^{o}C, 16 h, 86%

The absolute stereochemistry at C6 in compound **54a** was determined once again by using modified Mosher's ester analysis.

Abstract

After securing the stereochemistry of the generated center of the secondary hydroxy group in **54a,** the hydroxy group was masked with TBDPSCl as the corresponding TBDPS-ether **63a** and exposed to PPTS in MeOH to provide the primary alcohol **64a** in 87% yield. The alcohol **64a** was further oxidized with IBX to provide aldehyde **51a** and subjected to Wittig reaction with triphenylphosphonium salt of n-nonyl bromide **52** in presence of n- BuLi to produce the corresponding *Z*-olefin **65a** in 85% yield. The compound **65a** upon exposure to n-tetrabutylammonium fluoride furnished the target product (*S*)–strongylodiol H **39a** in 82% yield (Scheme 26).



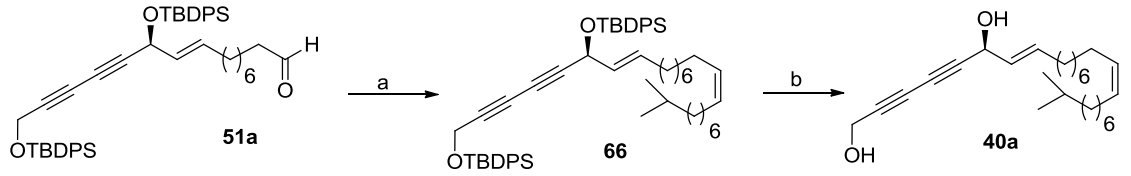
Scheme 26: *Reagents and conditions*: (a)TBDPSCl, Imidazole, CH_2Cl_2, 0 ^oC - rt, 1 h, 96%,(b) PPTS, MeOH, 0 ^oC - rt, 2 h, 87%, (c)IBX, THF + DMSO,0 ^oC - rt, 1 h, 98%, (d) **52**, n- BuLi, THF, -78 ^oC - rt, 2 h, 85%, (e) TBAF, THF, 0 ^oC - rt, 1 h, 82%.

The optical rotation of **39a** {$[\alpha]^{25}_D$ = -40.3 (*c* 0.72, $CHCl_3$)} was similar to that of the reported isolated natural product {$[\alpha]^{25}_D$ = -43.8 (*c* 0.35, $CHCl_3$)}. Thus, the total synthesis of the natural product (-)-strongylodiol H has been accomplished. This synthesis has further reconfirmed the absolute stereochemistry of the chiral center and

was in line with our structural revision of the natural product compared to the proposed stereochemistry.

After successful accomplishment of the total synthesis of natural product strongylodiol **H**, we proceeded further for the total synthesis of strongylodiol **I**, which bears an additional methyl moiety on C24 carbon.

The aldehyde **51a** was further subjected to Wittig reaction with isodecyltriphenylphosphonium iodide **53** with n-BuLi to produce the *Z*- olefin **66** in good yield. The TBDPS deprotection of compound **66** with 1 Molar solution of *n*-tetrabutylammonium fluoride afforded *S*- strongylodiol I **40a**. The ^{1}H NMR and ^{13}C NMR spectra of the synthesized product were in full agreement with those of the reported natural product.



Scheme : *Reagents and conditions*: (a) **53**, n- BuLi, THF, -78 ^{o}C - rt, 2 h, 83%, (b) TBAF, THF, 0 ^{o}C - rt, 1 h, 85%.

In conclusion, we demonstrated a facile strategy for the first enantioselective total synthesis of two diacetylenic diol natural products strongylodiols H and I. The synthesis of an antipode of strogyodiol H was also accomplished. Our synthesis assisted us to revise the structure of the proposed structure of the natural product strongylodiol H and accordingly strongylodiol I. The natural products strongylodiol H and I were obtained in 16.2%, 15.4% yields respectively from the commercially available propargyl alcohol involving 13 longest linear steps respectively.