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Total Synthesis of Bioactive Lactones: Prelactone E, epi-Prelactones V, E, Nonenolides (*Z*-isomers) and Stagonolide E

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ABSTRACT

Thesis is structured in three different parts. The first part is dedicated to the total synthesis of the *Z*-isomers of nonenolide and desmethyl nonenolide using RCM and Yamaguchi cyclization reactions. The second part discusses the stereoselective total synthesis of stagonolide E. This synthetic strategy involves jacobsen's kinetic resolution, sharpless epoxidation, Stille-Gennari and Yamaguchi lactonization reactions. Finally the third part deals with a general synthetic approach for the synthesis of β-hydroxy-δ-lactones: asymmetric total synthesis of prelactone E and epi-prelactones V and E using Evans aldol reaction as the key step.

Keywords: Nonenolide, Desmethyl nonenolide,Prelactone, epi-Prelactone, Stagonolide

Introduction

Poly-substituted chiral δ-lactones have attracted considerable attention in recent years due to their importance as building blocks in natural product synthesis[1-8] and due to the fact that they form part of the structures of polyketide macrolides,[9] which have various biological profiles. Our group has been engaged in the development of practical synthetic approaches towards the bioactive lactones.[10-20] In this review, we report a total synthesis of the Z-isomers of nonenolide, desmethyl nonenolide, Stagonolide E, Prelactone E and epi-Prelactone V and E.

Section-I: Total synthesis of the Z-isomers of Nononenolide and desmethyl nonenolide

Nonenolide, a medium-sized macrolide, was recently isolated as a white solid from C. militaris BCC 2816, and showed antimalarial activity (Figure 1). We herein report the synthesis of Z-isomers of nonenolide **1** and desmethyl nonenolide **2**.[21]

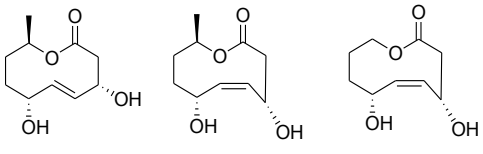
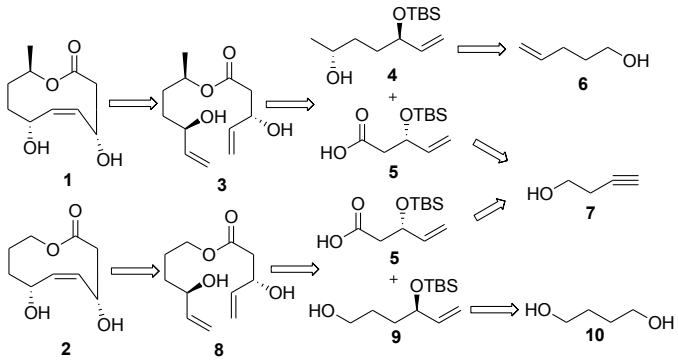


Figure 1

Retrosynthetic analysis:

Our retrosynthetic analysis is depicted in Scheme 1. *Z*-isomers, **1** and **2** could be synthesized by the RCM reaction of **3** and **8**, respectively. These intermediates in turn could be sythesized from the fragments **4**, **5** and **9** via the Yamaguchi esterification. The common fragment **5** for both targets, could be obtained from **7**, fragments **4** and **9** could be derived from the 4-penten-1-ol **6** and commercially available 1,4-butane diol **10**, respectively.



Scheme 1. Reterosynthetic analysis

Synthesis of acid fragment 5:

The synthesis of acid component **5** is based on a sequence of reactions starting from commercially available 3-butyne-1-ol **7** (Scheme 2).

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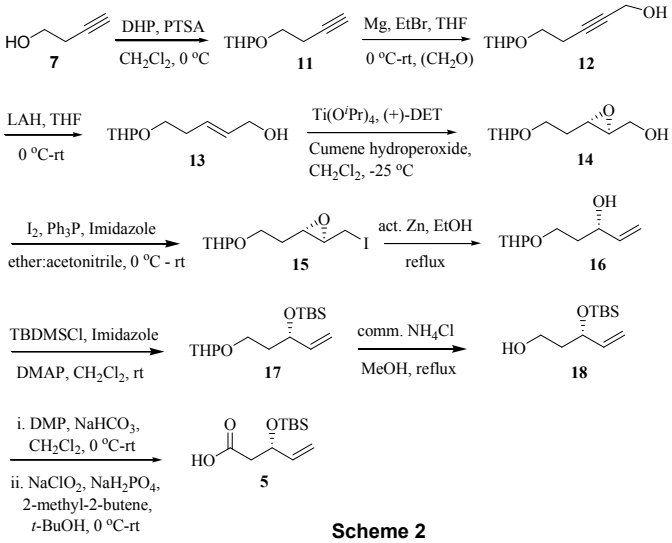
Highlights

1. A new synthetic route for the stereoselective total synthesis of *Z*-isomers of nonenolide and desmethyl nonenolide has been developed.

2. A general synthetic approach for the synthesis of prelactones and epi-prelactones V and E has been reported using an Evans' aldol reaction as the key step. The methodology presented here is general and should allow access to novel analogues of the prelactones.

3. A simple route to the first total synthesis of stagonolide E is reported utilizing Jacobsen's kinetic resolution, Sharpless epoxidation, Stille–Gennari, and Yamaguchi lactonization.

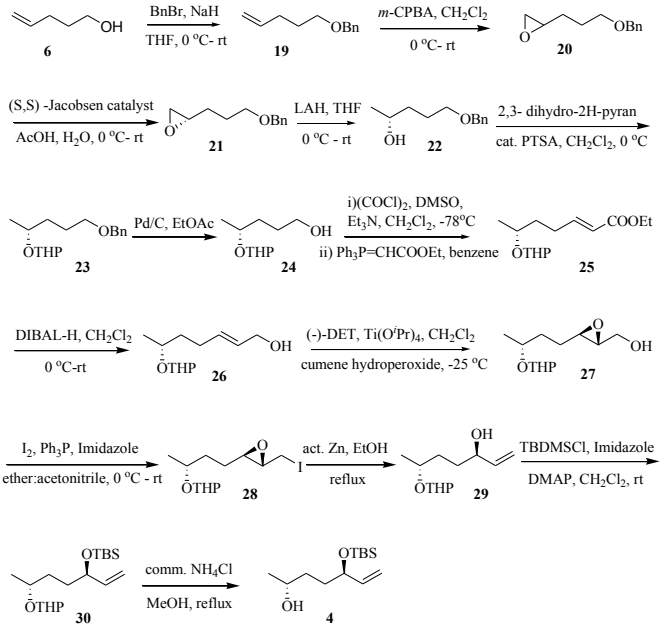


Scheme 2

Treatment of **7** with 3,4-dihydro-2H-pyran and a catalytic amount of PTSA in dry CH_2Cl_2 gave its tetrahydropyranyl derivative **11** in 81% yield. The ether was treated with the Grignard reagent prepared from ethyl bromide & magnesium followed by quenching with para formaldehyde in dry THF to afford compound **12** in 85% yield. Reduction compound **12** with lithium alumunium hydride in dry THF at room temperature produced desired trans olefin **13** in 80% yield. Olefin **13** was subjected to Sharpless asymmetric epoxidation using (+)-DET, $Ti(O^iPr)_4$ and cumene hydroperoxide to furnish the desired epoxide **14** in 75% yield. The epoxy alcohol **14** was converted into the corresponding iodide **15** with iodine, Ph_3P, and imidazole for 1 h in 90% yield, which on reductive elimination with activated Zn dust in refluxing ethanol for 2 h afforded chiral allylic alcohol **16** (80%). The secondary hydroxyl **16** was protected as the silyl ether **17** with TBDMSCl and imidazole in dry CH_2Cl_2. Deprotection of the THP group with solid NH_4Cl in MeOH at reflux temperature for 2 h afforded the alcohol **18** (65%). The primary hydroxyl group in **18** was oxidized with Dess–Martin periodinane (DMP) to afford the corresponding aldehyde, which was oxidized to the acid **5** with $NaClO_2$ in the presence of $NaH_2PO_4.2H_2O$ and 2-methyl-2-butene in 70% yield over two steps.

Synthesis of fragment 4:

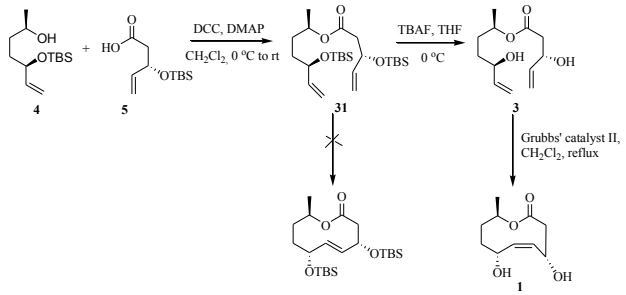
4-penten-1-ol **6** was converted to its benzyl ether **19** in 85% yield by treating with benzyl bromide and sodium hydride in THF at 0 °C. Treatment of **19** with meta-chlolroperbenzoic acid in CH_2Cl_2 afforded the racemic epoxide **20** in 91% yield. The solvent free hydrolytic kinetic resolution on racemic terminal epoxide **20**, with 0.3 mol% (S,S)-salen-Co(III)(OAc) complex [(S,S)-N,N'-bis(3,5-di-tert-butylsalycylidene)-1,2 cyclohexanediamino-Co(III)-acetate] and 0.5 equivalents of water afforded chiral epoxide **21** in 43% yield.



Scheme 3

The reduction of **21** with LAH in THF at 0 °C for 2 h afforded secondary alcohol **22** in 80% yield. The secondary alcohol **22** was protected as THP ether **23** with 2,3-dihydropyran in the presence of PTSA in CH_2Cl_2 in 81% yield. Further we have intended to deprotect benzyl group with Pd/C in EtOAc to afford **24** (85%). The primary hydroxyl group of compound **24** was oxidized under Swern oxidation conditions using $(COCl)_2$, DMSO and Et_3N at –78 °C followed by Wittig reaction. Thus reaction of aldehyde with the Wittig ylide, (ethoxycarbonylmethylene) triphenyl phosphorane in the benzene afforded α,β-unsaturated ester **25** in 90% overall yield for the two step sequence. Ester **25** was reduced with DIBAL-H in CH_2Cl_2 at 0 °C to allylic alcohol **26** in 85% yield. Sharpless epoxidation of allylic alcohol **26** with (-)-DET, $Ti(O^iPr)_4$, and cumene hydroperoxide in dry CH_2Cl_2 for 5 h afforded **27** (75%). The epoxy alcohol **27** was converted to the corresponding epoxy iodide **28** in 90% yield by treating with triphenylphosphine, iodine and imidazole in a mixture of ether and acetonitrile in 3:1 ratio at room temperature. Compound **28** was converted in to a secondary allylic alcohol **29** in 80% yield by refluxing with activated zinc in ethanol. The secondary hydroxyl **29** was protected as the silyl ether with TBDMSCl and imidazole in dry CH_2Cl_2 to afford the compound **30** in 95% yield. Deprotection of the THP group with solid NH_4Cl in MeOH at reflux temperature for 2 h afforded the alcohol fragment **4** (65%) (Scheme 3).

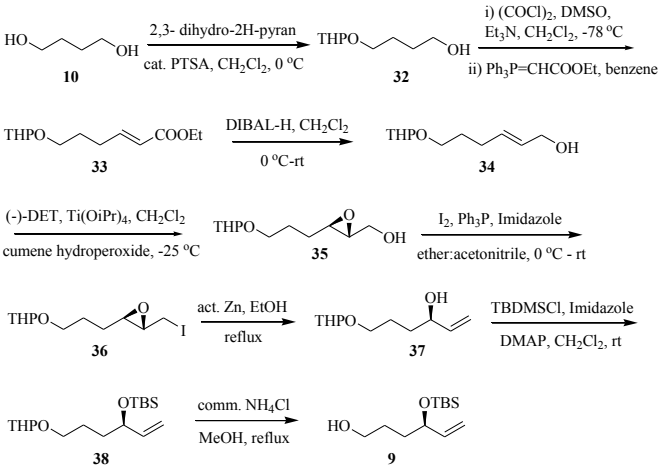
Construction of *Z*-isomer of nonenolide 1:



Scheme 4

Treatment of alcohol **4** with acid **5** using DCC, DMAP in dry CH_2Cl_2 for 3 h at 0 °C provided the corresponding ester **31** in 85% yield. It is important to note that the RCM reaction did not proceed when the two hydroxyl groups were protected as TBS ethers. Therefore, two TBS groups in **31** were subjected to desilylation using TBAF in THF to afford diol **3** in 70% yield. The compound **3** was exposed to RCM reaction in refluxing CH_2Cl_2 for 3 h using 10 mol% Grubbs' second generation catalyst to afford the *Z*-isomer of nonenolide **1** in 70% yield (Scheme 4).

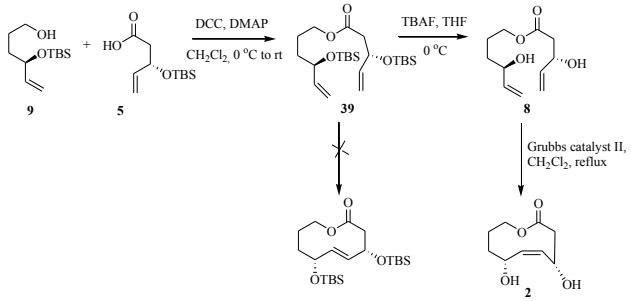
Synthesis of fragment 9:



Scheme 5

The synthesis of **9** began with the commercially available 1,4- butane diol **10** by following reactions (Scheme 5). Thus, mono protection of diol compound **10** with 3,4-dihydro-2H-pyran and a catalytic amount of PTSA in dry CH_2Cl_2 gave its tetrahydropyranyl derivative **32** in 81% yield. Swern oxidation of the primary free hydroxyl of **32** using $(COCl)_2$, DMSO and Et_3N at –78 °C followed by Wittig reaction. Thus reaction of aldehyde with the Wittig ylide, (ethoxycarbonylmethylene) triphenyl phosphorane in the benzene afforded α,β-unsaturated ester **33** in 90% overall yield in two steps. Next reduction of ester functionality of compound **33** with DIBAL-H in CH_2Cl_2 at 0 °C gave allylic alcohol **34** in 85% yield. Sharpless epoxidation of allylic alcohol **34** with (-)-DET, $Ti(O^iPr)_4$, and cumene hydroperoxide in dry CH_2Cl_2 for 5 h afforded **35** (75%). The epoxy alcohol **35** was converted to the corresponding epoxy iodide **36** in 90% yield by treating with triphenylphosphine, iodine and imidazole in a mixture of ether and acetonitrile in 3:1 ratio at room temperature. Compound **36** was converted in to a secondary allylic alcohol **37** in 80% yield by refluxing with activated zinc in ethanol. The secondary hydroxyl **37** was protected as the silyl ether with TBDMSCl and imidazole in dry CH_2Cl_2 to afford the compound **38** in 95% yield. Deprotection of the THP group with solid NH_4Cl in MeOH at reflux temperature for 2 h afforded the alcohol fragment **9** (65%).

Construction of *Z*- isomer of desmethyl nonenolide 2: Treatment of alcohol **9** with acid **5** using DCC, DMAP in dry CH_2Cl_2 for 3 h at 0 °C provided the corresponding ester **39** in 85% yield.



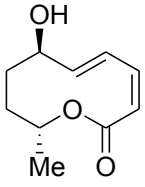
Scheme 6

The RCM reaction in **39** was not successful as was the case with **31** in (Scheme 6). Selective deprotection of two secondary silyl groups was achieved using TBAF in THF to afford diol **8** in 70% yield. Finally, treatment of **8** with Grubbs' catalyst II in CH_2Cl_2 at reflux temperature for 3 h to afford the *Z*-isomer of desmethyl nonenolide **2** in 70% yield.

In conclusion, the total synthesis of the *Z*-isomers of nonenolide and desmethyl nonenolide has been accomplished. The highlights of the synthesis are the utilization of RCM and Yamaguchi cyclization reactions as the key steps.

Section-II: Total synthesis of Stagonolide E

Stagonolides E (Fig. 2) represent a family of novel 10-membered ring lactones produced recently from Stagonospora cirsii, a fungal pathogen of Cirsium arvense causing necrotic lesions on leaves.

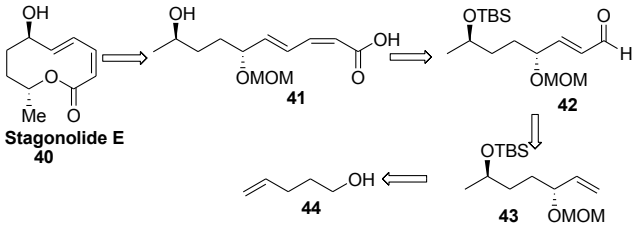


Stagonolide E
40

Figure 2

Among them stagonolide A was found to be phytotoxic and stagonolide B exhibited potent antifungal, antibacterial, and cytotoxic activities. Our continued interest on the synthesis of 10-membered lactones, led us to take up the first synthesis of stagonolide E.[22]

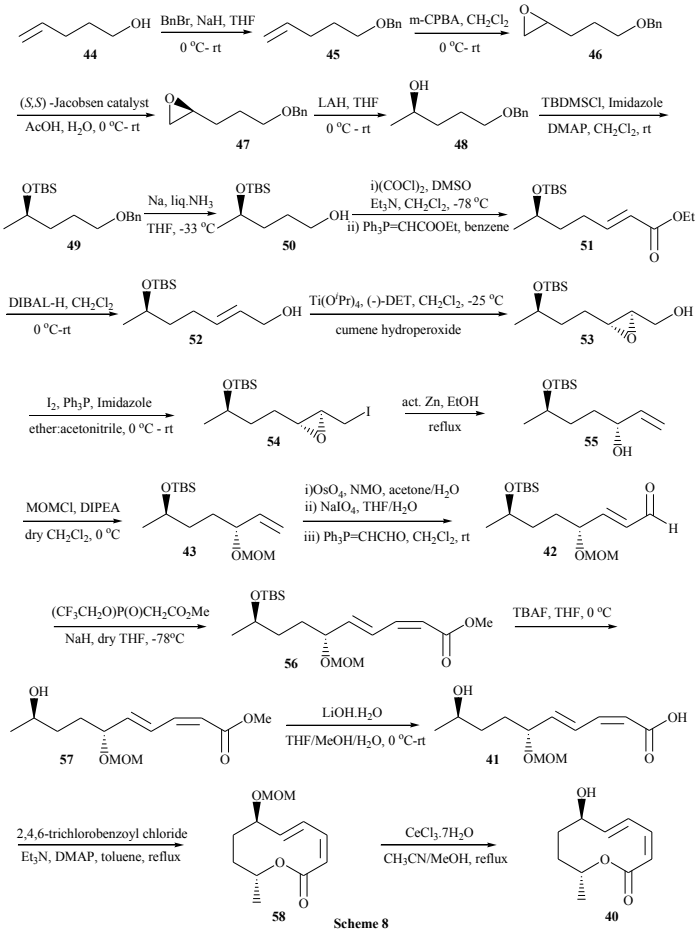
Retrosynthetic analysis: Retrosynthetically (Scheme 7), we envisaged that the target molecule **40** can be obtained from seco acid **41** by Yamaguchi lactonization followed by MOM deprotection. The seco acid **41** in turn can be made from aldehyde **42** using Stille–Gennari reaction. Compound **42** can be obtained from **43** by dihydroxylation and cleavage of the diol, while the allylic alcohol **43** is readily obtained from 4-penten-1-ol **44** by standard transformations.



Scheme 7. Retrosynthesis

The synthesis of compound **40** is based on a sequence of reactions starting from commercially available 4-penten-1-ol **44** (Scheme 8). Compound of **44** was converted to its benzyl ether **45** in 85% yield by treating with benzyl bromide and sodium hydride in THF at 0 °C. Treatment of **45** with *meta*-chlolroperbenzoic acid in CH_2Cl_2 afforded the racemic epoxide **46** in 91% yield. The solvent free hydrolytic kinetic resolution on racemic terminal epoxide **46** with 0.3 mol% (*S,S*)-salen-Co(III)(OAc) complex [(*S,S*)-*N,N'*-bis(3,5-di-*tert*-butylsalycylidene)-1,2-cyclohexanediamino-Co(III)-acetate] and 0.5 equivalents of water afforded chiral epoxide **47** in 43% yield.

The reduction of **47** with LAH in THF at 0 °C for 2 h afforded secondary alcohol **48** in 80% yield. The secondary alcohol **48** was protected as TBS ether using *t*-butyldimethylsilyl chloride and imidazole in CH_2Cl_2 at room temperature to afford **49** in 95% yield. In the next step the compound **49** was subjected to debenzylation using Li metal in liq. NH_3 to afford primary alcohol **50** in 75% yield. The primary hydroxyl group of compound **50** was oxidized under Swern oxidation conditions using $(COCl)_2$, DMSO and Et_3N at –78 °C followed by Wittig reaction. Thus reaction of aldehyde with the Wittig ylide, (ethoxycarbonylmethylene) triphenyl phosphorane in the benzene afforded α,β-unsaturated ester **51** in 90% overall yield. Ester **51** was reduced with DIBAL-H in CH_2Cl_2 at 0 °C to allylic alcohol **52** in 85% yield. Sharpless epoxidation of allylic alcohol **52** with (-)-DET, $Ti(O^iPr)_4$, and cumene hydroperoxide in dry CH_2Cl_2 for 5 h afforded **53** (75%). The epoxy alcohol **53** was converted to the corresponding epoxy iodide **54** in 90% yield by treating with triphenylphosphine, iodine and imidazole in a mixture of ether and acetonitrile in 3:1 ratio at room temperature. Compound **54** was converted in to a secondary allylic alcohol **55** in 80% yield by refluxing with activated zinc in ethanol.The resulting alcohol **55** was protected as its MOM ether using MOMCl, *N,N*-diisopropylethyl amine in CH_2Cl_2 to afford **43** in 80% yield. The terminal olefin in **43** was subjected to dihydroxylation with OsO_4 to give vicinal diol, which on oxidative cleavage with $NaIO_4$ provided an aldehyde, which was subjected to two-carbon homologation using triphenylphosphoranylideneacetaldehyde (Ph_3P=CHCHO) afforded **42** in 73% yield. The compound **42** was then subjected to Stille–Gennari reaction using methyl



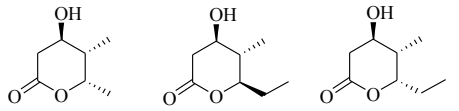
Scheme 8

P,P'-bis(2,2,2-trifluoroethyl) phosphonoacetate in the presence of NaH, in dry THF at -78 °C to afford the *cis* α,β-unsaturated methyl ester **56** as a major isomer in 80% yield along with the traces of *trans* isomer, that could be separated by column chromatography. Cleavage of the TBS ether in **56** using TBAF in THF afforded **57** in 70% yield. Hydrolysis of ester group in **57** using LiOH in THF and H_2O provided seco acid **41** in 90% yield, which without purification followed by Yamaguchi lactonization (2,4,6-trichlorobenzoylchloride, Et_3N in THF followed by treatment with DMAP in refluxing toluene) to provide macrolactone **58** (ee >95%) in 70% yield. Finally, cleavage of the MOM ether in macrolactone **58** under neutral conditions using $CeCl_3.7H_2O$ in CH_3CN/MeOH at reflux completed the synthesis of the target molecule, stagonolide E **40** in 60% yield.

In conclusion, a simple route to the first total synthesis of stagonolide E is reported utilizing Jacobsen's kinetic resolution, Sharpless epoxidation, Stille–Gennari, and Yamaguchi lactonization as key steps.

Section-III: Synthesis of *epi*-prelactone V, prelactone E and *epi*-prelactone E.

The prelactones are highly functionalized chiral δ-lactones isolated from various polyketide macrolide producing microorganisms (Figure 3). These lactones exhibit properties such as ATPase inhibition and antibacterial, antifungal and immunosuppressive activities. Herein we report a general route for the synthesis of prelactone E and epi-prelactones V and E.[23]

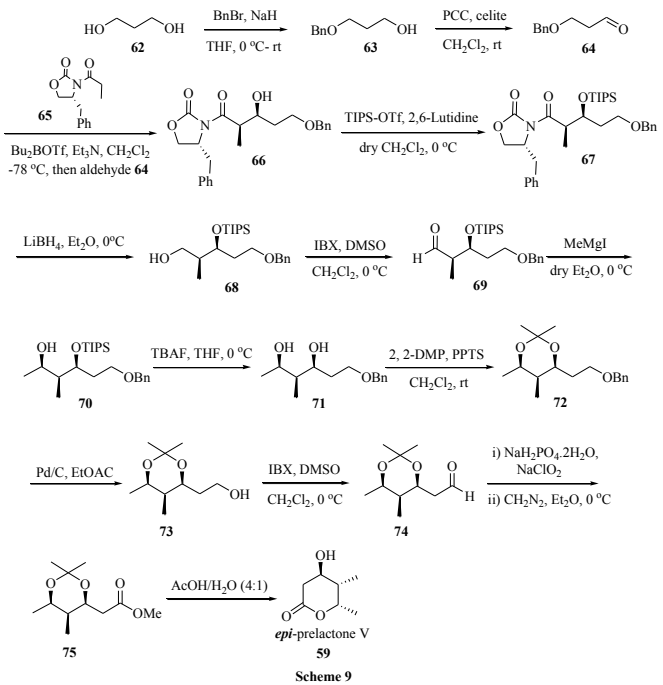


epi-Prelactone V **59** Prelactone E **60** *epi*-Prelactone E **61**

Figure 3

Synthesis of *epi*-Prelactone V:

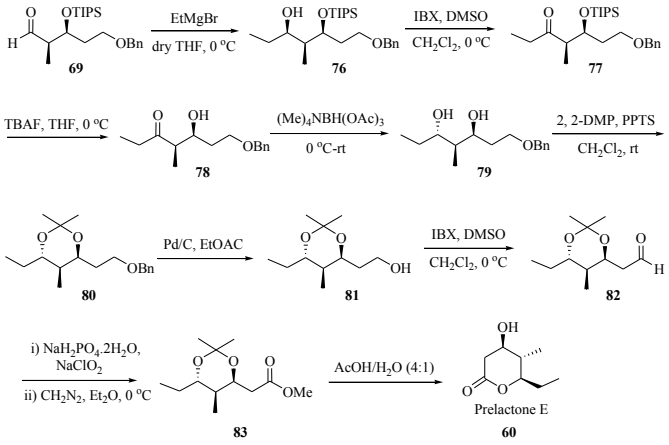
The synthesis of *epi*-prelactone V **59** began with the commercially available 1,3-propanediol **62** by following reactions (Scheme 9). Thus, monobenzylation of propane 1,3-diol compound **62** treating with benzyl bromide and sodium hydride in THF at 0 °C afforded **63** in 85% yield. The monobenzylated compound **63** was subjected to PCC oxidation in CH_2Cl_2 at room temperature to give aldehyde **64** in 92% yield. The asymmetric aldol reaction of the aldehyde **64** with 4-benzyloxazolidinone **65** using dibutylborantriflate and triethylamine in CH_2Cl_2 at –78 °C to 0 °C for 1 h provided *syn* aldol product **66** as a single diastereoisomer in 89% yield. The compound **66** was protected with TIPS ether using triisopropylsilyl triflouoromethanesulphonate and 2,6-lutidine in CH_2Cl_2 at 0 °C for 1 h to give **67** in 92% yield. The amide compound **67** treated with $LiBH_4$ in ether and few drops of water at 0 °C for 1 h to give the corresponding alcohol **68** in 90% yield. The alcohol **68** was subjected to oxidation with IBX, dry DMSO in dry CH_2Cl_2 at 0 °C to room temperature for 3 h to furnish aldehyde **69** in 74% yield. Grignard reaction of aldehyde **69** with MeMgI in dry Et_2O at 0 °C for 2 h afforded the 1,3-*syn* product **70** in 89% yield. The compound **70** was desilylated with TBAF in THF at 0 °C to afford diol **71** in 85% yield. The diol **71** was protected as its acetonide **72** using 2,2-dimethoxy propane and catalytic amount of PPTS in dry CH_2Cl_2 at ambient temperature for 1 h in 96% yield. Hydrogenolysis of the benzyl ether **72** using Pd/C in EtOAc at room temperature for 2 h afford debenzylated product **73** in 79% yield. The resultant alcohol **73** was oxidized to aldehyde **74** by using IBX, dry DMSO in dry CH_2Cl_2 at 0 °C to room temperature for 3 h in 74% yield. The aldehyde **74** was converted into acid by the oxidation using $NaClO_2$, $NaH_2PO_4.2H_2O$ in DMSO and H_2O at room temperature, filtered without further characterization, the acid was converted to its methyl ester **75** using freshly prepared diazomethane in Et_2O at 0 °C in 89% yield. Treatment of compound **75** with AcOH/H_2O (4:1) at room temperature for 2 h resulted in acetonide cleavage and subsequent lactonization afforded the target *epi*-prelactone V, **59** in 90% yield.



Scheme 9

Synthesis of Prelactone E:

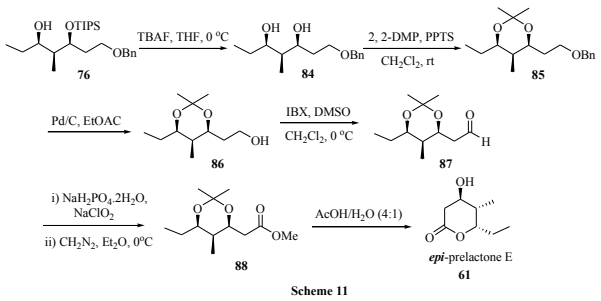
Grignard reaction of aldehyde **69** with EtMgBr in THF at 0 °C for 2 h afford the 1,3-*syn* product **76** in 89% yield. The ethyl alcohol compound **76** was oxidized to the corresponding ketone **77** using IBX in 90% yield. Deprotection of TIPS group of compound **77** was done by treatment with TBAF in THF at 0 °C to afford alcohol **78** in 90% yield. Compound **78** was subjected to stereoselective reduction using tetramethylammonium triacetoxyborohydride in acetic acid at 0 °C for 10 h afford the desired 1,3-*anti* diol **79** (98:2 dr) in 82% yield. Protection of 1, 3 hydroxy groups of compound **79** using 2,2-dimethoxy propane and catalytic amount of PPTS in dry CH_2Cl_2 for 1 h at room temperature to furnish **80** in 90% yield. In that consequence benzyl group of compound **80** was deprotected using Pd/C in EtOAc at room temperature for 2 h afford debenzylated product **81** in 79% yield. Oxidation of compound **81** using IBX (o-Iodoxy benzoic acid), dry DMSO in dry CH_2Cl_2 at 0 °C to room temperature for 3 h to afford aldehyde **82** in 74% yield. The aldehyde **82** was further oxidized into acid using $NaClO_2$, $NaH_2PO_4.2H_2O$ in DMSO and H_2O at room temperature to afford acid. Then the acid was subjected to esterification using freshly prepared diazomethane in Et_2O at 0 °C to afford methyl ester **83** in 88% yield. Finally the cyclization of **83** was achieved with AcOH/H_2O (4:1) to afford prelactone E, **60** in 90% yield.



Scheme 10

Synthesis of *epi*-Prelactone E:

The synthesis of *epi*-prelactone E **61** began with the intermediate ethylene alcohol **76** as illustrated in scheme 11. The compound **76** was subjected to deprotection of TIPS group by using TBAF in THF at 0 °C for 1 h to give alcohol **84** in 85% yield. Diol **84** was protected as its acetonide by standard procedure to give compound **85** in 90% yield.



Scheme 11

Treatment of **85** with Pd/C in EtOAc, atmospheric pressure of hydrogen at room temperature for 2 h resulted in benzyl ether cleavage to furnish alcohol **86** in 79% yield. The compound **86** was oxidized with IBX, dry DMSO in dry CH_2Cl_2 at 0 °C to room temperature for 3 h to afford the aldehyde **87** in 75% yield. The aldehyde **87** was further oxidized into acid using $NaClO_2$, $NaH_2PO_4.2H_2O$ in DMSO and H_2O at room temperature to afford acid. The acid was used directly in the next step without further characterization. Carboxylic acid was subjected to esterification using freshly prepared diazomethane in Et_2O at 0 °C afford methyl ester **88** in 85% yield. Reaction of **88** with AcOH/H_2O (4:1) at room temperature afford final compound *epi*-prelactone E, **61** in 90% yield.

In conclusion, we have accomplished the stereoselective synthesis of prelactones V, E and epi-prelactones V, E using an Evans' aldol reaction as the key step.

Acknowledgments

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References and notes

1. S. Hanessian. Total Synthesis of Natural Products: The Chiron Approach; Pergamon Press: Oxford, **1983**.
2. J. W. Scott. In Asymmetric Synthesis; J. D. Morrison, J. W. Scott, Eds.; Academic Press: New York, **1984**, *4*, 1–226.
3. K. Mori. Synthesis of optically active pheromones. *Tetrahedron* **1989**, *45*, 3233–3298.
4. H. Kotsuki, A. Miyazaki, M. Ochi. A new enantioselective synthesis of (4S,5S)-5-(N-Boc)-amino-6-cyclohexyl-4-hydroxy-hexanoic acid lactone, a hydoxyethylene dipeptide isostere precursor. *Tetrahedron Lett*. **1991**, *32*, 4503–4504.
5. S. S. C. Koch, A. R. Chamberli. Enantioselective preparation of β-alkyl-γ-butyrolactones from functionalized ketene Dithioacetals. *Journal of Organic Chemistry* **1993**, *58*, 2725–2737.
6. D. Buisson, R. Azerad. A chemoenzymatic preparation of both enantiomers of ω-hydroxymethyl-substituted lactones. *Tetrahedron: Asymmetry* **1996**, *7*, 9–12.
7. W. H. Pearson, E. J. Hemre. A Practical Synthesis of (-)-Swainsonine. *Journal of Organic Chemistry* **1996**, *61*, 7217–7221.
8. E. Warmerdam, I. Tranoy, B. Renoux, J. P. Gesson. Study of butyrolactones related to sub-type 3 annonaceous acetogenins. Structure revision of itrabin, jetein, laherradurin and otivarin. *Tetrahedron Lett*. **1998**, *39*, 8077–8080.
9. D._Hagen. In The Polyketide Metabolites; O_Hagen, D.,Ed.; Ellis Harwood: New York, **1991**; pp 116–137.
10. G. Sabitha, K. Sudhakar, N. M. Reddy, M. Rajkumar, J. S. Yadav. Chelation-controlled reduction: an enantioselective synthesis of (−)-tarchonanthuslactone. *Tetrahedron Lett*. **2005**, *46*, 6567–6570.
11. G. Sabitha, F. Narjis, R. Swapna, J. S. Yadav. Asymmetric Total Syntheses of (*R*)-(-)-Argentilactone and (*S*)-5-Hexadecanolide. *Synthesis* **2006**, *17*, 2879–2884.
12. G. Sabitha, E. V. Reddy, K. Yadagiri, J. S. Yadav. Total synthesis of insect pheromones (R)-4-dodecanolide and (S)-5- hexadecanolide. *Synthesis* **2006**, *19*, 3270–3274.
13. G. Sabitha, K. Sudhakar, J. S. Yadav. Application of the Cosford cross-coupling protocol for the stereoselective synthesis of (*R*)- (+)-goniothalamin, (*R*)-(+)-kavain and (*S*)-(+)-7,8-dihydrokavain. *Tetrahedron Lett*. **2006**, *47*, 8599–8602.
14. G. Sabitha, V. Bhaskar, J. S. Yadav. The first asymmetric total synthesis of (*R*)-tuberolactone, (*S*)-jasmine lactone and (*R*)-δ- Decalactone. *Tetrahedron Lett*. **2006**, *47*, 8179–8181.
15. G. Sabitha, R. Swapna, E. V. Reddy, J. S. Yadav. Synthesis of (-)-(5*R*,6*S*)-6-Acetoxyhexadecanolide, a Mosquito Oviposition Attractant Pheromone of *Culex pipiens fatigans Synthesis* **2006**, *24*, 4242–4246.
16. G. Sabitha, M. Bhikshapathi, J. S. Yadav. Radical Cyclization Route to the Stereoselective Synthesis of (+)-*trans*-Cognac Lactone and (+)-*trans*-Aerangis Lactone. *Synth. Commun*. **2007**, *37*, 559–567.
17. G. Sabitha, K. Yadagiri, J. S. Yadav. Synthesis of the *Janus integer* pheromone (4*R*,9*Z*)-9-octadecen-4-olide. *Tetrahedron Lett*. **2007**, *48*, 1651–1652.
19. G. Sabitha, K. Yadagiri, J. S. Yadav. A short and efficient synthesis of renealtins A and B. *Tetrahedron Lett*. **2007**, *48*, 8065–8068.
20. G. Sabitha, V. Bhaskar, S. Siva sankara Reddy, J. S. Yadav. Stereoselective total synthesis of (+)-(6*R*,2′*S*)-cryptocaryalactone and (−)-(6*S*,2′*S*)-*epi* cryptocaryalactone. *Tetrahedron* **2008**, *64*, 10207–10213.
21. G. Sabitha, P. Padmaja, K. Sudhakar, J. S. Yadav. Total synthesis of *z*-isomers of nonenolide and desmethyl nonenolide. *Tetrahedron Asymmetry* **2009**, *20*, 1330–1336.
22. G. Sabitha, P. Padmaja, P. Narayana Reddy, Surender Singh Jadav, J. S. Yadav. Stereoselective total synthesis of stagonolide E. *Tetrahedron Letters* **2010**, *51*, 6166–6168.
23. G. Sabitha, P. Padmaja, K. Bhaskar Reddy, J. S. Yadav. A general synthetic approach for the synthesis of *β*-hydroxy-*δ*-lactones: asymmetric total synthesis of prelactones and epi-prelactones V and E. *Tetrahedron Letters* **2008**, *49,* 919–922.

Thesis Details

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Supplementary Material

Spectroscopic data for key intermediates and lactones along with copies of ^1H, ^{13}C and mass spectra are accessible online from article page.