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 aldo 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 and due to the fact that they form part of the structures of polyketide macrolides, which have various biological profiles. Our group has been engaged in the development of practical synthetic approaches towards the bioactive lactones. 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 Nonenolide 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.

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 synthesized 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-butyn-1-ol 7 (Scheme 2).

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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.

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-dihydroxypropan in the presence of PTSA in CH₂Cl₂ 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 Et₃N at ~78 °C followed by Wittig reaction. Thus reaction of aldehyde with the Wittig ylide, (ethoxy)carbonylmethylene) triphenylphosphorane 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 CH₂Cl₂ at 0 °C to allicylic alcohol 26 in 85% yield. Sharpless epoxidation of allicylic alcohol 26 with (-)-DET, Ti(O′Pr)₄ and cumene hydroperoxide in dry CH₂Cl₂ 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 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 CH₂Cl₂ to afford the compound 30 in 95% yield. Deprotection of the THP group with solid NH₂Cl in MeOH at reflux temperature for 2 h afforded the alcohol fragment 4 (65%) (Scheme 3).
Construction of Z-isomer of nonenolid 1:

Treatment of alcohol 4 with acid 5 using DCC, DMAP in dry CH₂Cl₂ 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 CH₂Cl₂ for 3 h using 10 mol% Grubbs’ second generation catalyst to afford the Z-isomer of nonenolid 1 in 70% yield (Scheme 4).

Synthesis of fragment 9:

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 CH₂Cl₂ at reflux temperature for 3 h to afford the Z-isomer of desmethyl nonenolid 2 in 70% yield.

In conclusion, the total synthesis of the Z-isomers of nonenolid and desmethyl nonenolid 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.

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 CH₂Cl₂ gave its tetrahydropyranyl derivative 32 in 81% yield. Swern oxidation of the primary free hydroxyl of 32 using (COCl)₂, DMSO and Et₃N 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 CH₂Cl₂ at 0 °C gave allylic alcohol 34 in 85% yield. Sharpless epoxidation of allylic alcohol 34 with (+)-DET, Ti(O'Pr)₄ and cumene hydroperoxide in dry CH₂Cl₂ 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 CH₂Cl₂ to afford the compound 38 in 95% yield. Deprotection of the THF group with solid NH₄Cl in MeOH at reflux temperature for 2 h afforded the alcohol fragment 9 (65%).

Construction of Z-isomer of desmethyl nonenolid 2:

Treatment of alcohols 9 with acid 5 using DCC, DMAP in dry CH₂Cl₂ for 3 h at 0 °C provided the corresponding ester 39 in 85% yield.

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 CH₂Cl₂ at reflux temperature for 3 h to afford the Z-isomer of desmethyl nonenolid 2 in 70% yield.

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

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.

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.

![Stagonolide E](image)

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-chloroperbenzoic acid in CH₂Cl₂ 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-butylsalicylidene)-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 i-PrOCl, i-PrOH and imidazole in a 1:4:1 ratio 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. NH₃ 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 Et₃N at −78 °C followed by Wittig reaction. Thus reaction of aldehyde with the Wittig ylide, (ethoxyacrylonymethylene) triphenyl phosphorane in the benzene afforded α,β-unsaturated ester 51 in 90% overall yield. Ester 51 was reduced with DIBAL-H in CH₂Cl₂ at 0 °C to allylic alcohol 52 in 85% yield. Sharpless epoxidation of allylic alcohol 52 with (+)-DET, Ti(OPr)₃, and cumene hydroperoxide in dry CH₂Cl₂ for 5 h afforded 53 (75%). The epoxide alcohol 53 was converted to the corresponding epoxide iodide 54 in 90% yield by treating with triphenylphosphine, iodine and imidazole in a mixture of ether and acetone tri-nitrite 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-diisopropylamyl amine in CH₂Cl₂ to afford 43 in 80% yield. The terminal olefin in 43 was subjected to dihydroxylation with OsO₄ to give vicinal diol, which on oxidative cleavage with NaIO₄ provided an aldehyde, which was subjected to two-carbon homologation using triphenylphosphoranylidenediacetaldehyde (Ph₃P=CHCHO) afforded 42 in 73% yield. The compound 42 was then subjected to Stille–Gennari reaction using methyl...
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 CH₂Cl₂ at room temperature to give aldehyde 64 in 92% yield. The asymmetric aldol reaction of the aldehyde 64 with 4-benzylloxazolidinone 65 using dibutylborantriflate and triethylamine in CH₂Cl₂ at −78 °C to 0 °C for 1 h provided syn aldo product 66 as a single diastereoisomer in 89% yield. The compound 66 was protected with TIPS ether using trisopropylsilylethoxydisulphonate and 2.6-lutidine in CH₂Cl₂ at 0 °C for 1 h to give 67 in 92% yield. The amide compound 67 treated with LiBH₄ 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 CH₂Cl₂ at 0 °C to room temperature for 3 h to furnish aldehyde 69 in 74% yield. Grignard reaction of aldehyde 69 with MeMgl in dry Et₂O 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 acetone 72 using 2,2-dimethoxypropane and catalytic amount of PPTS in dry CH₂Cl₂ 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 afforded debenzylated product 73 in 79% yield. The resultant alcohol 73 was oxidized to aldehyde 74 by using IBX, dry DMSO in dry CH₂Cl₂ at 0 °C to room temperature for 3 h in 74% yield. The aldehyde 74 was converted into acid by the oxidation using NaClO₂, NaH₂PO₄·2H₂O in DMSO and H₂O at room temperature, filtered without further characterization, the acid was converted to its methyl ester 75 using freshly prepared diazomethane in Et₂O at 0 °C in 89% yield. Treatment of compound 75 with AcOH/H₂O (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.

Synthesis of Prelactone E:
Grignard reaction of aldehyde 69 with EtMgBr in THF at 0 °C for 2 h afforded 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 triacetoxoroborohydride 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 CH₂Cl₂ for 1 h at room temperature to furnish 80 in 90% yield. In that consequence benzy 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 CH₂Cl₂ 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 NaClO₂, NaH₂PO₄·2H₂O in DMSO and H₂O at room temperature to afford acid. Then the acid was subjected to esterification using freshly prepared diazomethane in Et₂O at 0 °C to afford methyl ester 83 in 88% yield. Finally the cyclization of 83 was achieved with AcOH/H₂O (4:1) to afford prelactone E, 60 in 90% yield.
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 CH₂Cl₂ 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 NaClO₃, NaHPO₄·2H₂O in DMSO and H₂O 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 EtO at 0 °C to afford methyl ester 88 in 85% yield. Reaction of 88 with AcOH/H₂O (4:1) at room temperature afforded final compound epi-prelactone E, 61 in 90% yield.

In conclusion, we have accomplished the stereoselective synthesis of prelactones V, E and epi-prelactone E, 61 using an Evans’ aldol reaction as the key step.

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References and notes


Supplementary Material

Spectroscopic data for key intermediates and lactones along with copies of ¹³C and mass spectra are accessible online from article page.