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RESEARCH ARTICLE

Stereoselective Total Synthesis of (-)-Pyrenophorin

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Abstract: ***Background***: Homo and hetero dimers of macrodilacto cyclic compounds were observed frequently in nature and they were built with different types of functional groups, chemical skeletons and ring sizes. Natural products with macrodiolide frameworks are also known to exhibit a wide range of biological properties including antibiotic, antifungal, antihelmintic, phytotoxic, and antileukemic activities. The main aim of this paper was the stereoselective total synthesis of (-)-Pyrenophorin from commercially available starting material (*S*)-propylene oxide with high yields.

Methods: Stereoselective total synthesis of (-)-Pyrenophorin was done by hydrolytic kinetic resolution, Wittig olefination followed by Mitsunobu reaction.

Results: The disconnection approach analysis (retrosynthetic) of (-)-Pyrenophorin envisions that it would be synthesized through the hydroxyl-acid *via* cyclo dimerisation under the Mitsunobu reaction conditions and followed by deprotection of cyclic ketals. Hydroxy-acid would be achieved from alcohol, while the alcohol would be obtained from (*S*)-propylene oxide.

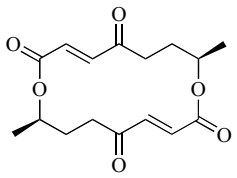
Conclusion: The total synthesis of target molecules achieved from commercially available starting materials, soft reaction conditions, decrease of reaction conditions and high purities with large yields. These type of biologically potent target molecules total synthesis was very important in industrial point of view.

Keywords: (*S*)-propylene oxide, Jacobsen's hydrolytic kinetic resolution, Wittig olefination, Mitsunobu reaction.

INTRODUCTION

Homo and hetero dimers of macrodilacto cyclic compounds were observed frequently in nature and they were built with different types of functional groups, chemical skeletons and ring sizes. Different types of macrodiolides [1-3] and macrocyclic monolactones [4-6] were synthesized by scientists and researchers across the world due to wide range of biological properties including antibiotic, antifungal [7-9], antihelmintic [10-12], phytotoxic [13-15], and antileukemic activities.

The macrolide dilactone pyrenophorin is a good antifungal and herbicidal agent and has been isolated from *Pyrenophora avenae* [16], *Stemphylium radicinum* [17, 19], and *Drechslera avenae* [14]. This C_2-symmetric dilactone is derived by head-to-tail dimerization of two identical C8 units. Due to the promising biological activity and the impressive structural features of (-)-pyrenophorin (**1**), appeared to be an attractive target for total synthesis [18-23]. The structure of (-) - Pyrenophorin is shown in Fig. (**1**).



(-)-Pyrenophorin (**1**)

Fig. (1). Structure of (-) – Pyrenophorin.

Our ongoing research mainly concentrates through the total synthesis of biologically potent and diverse natural products, so we reported the total synthesis of (-)-Pyrenophorin

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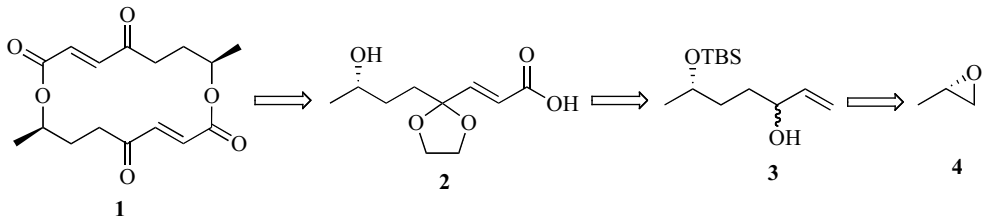


Scheme (1). Retero synthetic analysis of (-) - Pyrenophorin.

(**1**) utilizing the Jacobsen's hydrolytic kinetic resolution and the intermolecular Mitsunobu cyclization.

RESULTS AND DISCUSSION

The retrosynthetic analysis of 1 was shown in Scheme **1** and it would be synthesized through the hydroxylacid 2 via cyclo dimerisation under the Mitsunobu reaction conditions and followed by deprotection of cyclic ketals. Hydroxy-acid **2** would be achieved from alcohol **3**, while the alcohol **3** would be obtained from (*S*)-propylene oxide **4**.

The known epoxide **5** [24-28] was treated with allyl magnesium chloride in ethereal solvent followed by the subsequent silylation of the secondary alcohol **5** (TBSCl, imidazole) in CH_2Cl_2 afforded **6** in 70% yield. The compound **6** undergo ozonolysis in CH_2Cl_2 at -78 °C over a period of half an hour yield the corresponding aldehyde, which on immediate treatment with vinylmagnesium bromide in dry THF at -40°C for 4 h led to a diastereomeric mixture of allylic alcohol **3** (*syn anti* 1:1) in 84% yield. Oxidation of alcohol **3** under Swern reaction conditions gave keto compound **7** in 88% yield. Masking of **7** using ethyleneglycol in the presence of PTSA in benzene at reflux for 4 h gave ketal **8** in 71% yield. Ozonolysis of **8** in CH_2Cl_2 gave the particular aldehyde, which further undergo Wittig reaction with (methoxycarbonylmethylene)triphenyl phosphorane in benzene as solvent gave ester **9** in 76% yield and shown in Scheme **2**.

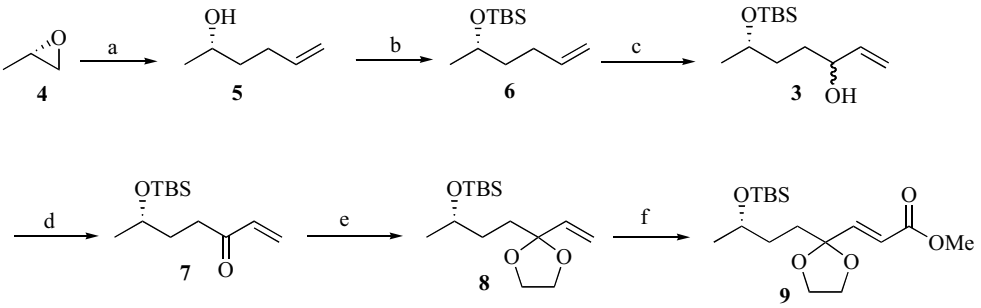
Ester **9** on hydrolysis under basic conditions (LiOH in THF:MeOH:H_2O-3:1:1) gave acid **10** (Scheme **3**) which further desilylation with TBAF in dry tetrahydro furan solvent gave the hydroxy-acid **2** in 86% yield. Hydroxy-acid **2** on cyclodimerisation under the Mitsunobu reaction conditions [30, 31] (Ph_3P and DEAD) for 10 h at -25 °C afforded **11** in 55% yield. Finally, deprotection of ketal with 10% HCl in THF for 5 h afforded the pyrenophorin **1** in 76% yield as a white solid. m.p. 172-174°C {lit. [9] m.p. 175°C}; $[\alpha]_D$ -58.6 (c 0.11, acetone) {lit.[32] $[\alpha]_D$ -54.5 (c 0.48, acetone)}.

EXPERIMENTAL

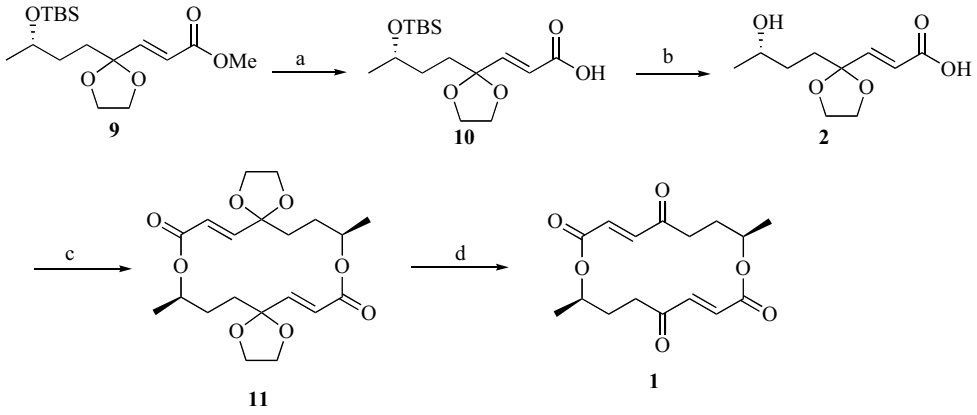
All the chemical reagents and solvents were supplied by Sigma Aldrich and AVRA, India. These solvents are not further purified by using basic purification techniques. The progress of the chemical reactions in this scheme were monitored by TLC plates supplied by Merck company. ^1H and ^{13}C NMR spectra were recorded on Bruker spectrometer with 300 MHz, 150 MHz and 75 MHz resolution. Chemical shifts and coupling constants are reported in δ units and Hertz. Different multiplicities singlet, doublet, double doublet, triplet, quartet and multiplet were indicated by s, d, dd, t, q and m. FT – IR spectra were recorded on Brucker IR spectrophotometer by using KBr Pellet. Mass values are noted as ESI (MS). Digital polarimeter was used to calculate the optical rotation values at 25°C.

(S)-tert.-Butyl (hex-5-en-2-yloxy) dimethylsilane (6) [24, 25]

A suspension of Mg (3.97 g, 165.5 mmol) was dipped in 30 mL of dry ether and treated with allyl chloride (6.8 mL, 82.55 mmol) at 25°C. The reaction mixture allowed for stirring over a period of 30 min. Further this reaction mass was cooled to -78°C. Now a solution of **4** (4 mL, 55.17 mmol) in dry ether (10 mL) was added very slowly dropwise to the above mixture and the mixture was allowed for stirring at the same temperature over a period of 2 h. Further, the reaction mixture was neutralized with aq. NH_4Cl solution (10 mL) followed by extraction with ether (2 × 50 mL). The two organic layers are combined and washed with 30 mL brine



Scheme (2). *Reagents and conditions*: (**a**) i) allyl chloride, Mg, dry ether, -78°C, 2 h; **b**) TBSCl, Imidazole, CH_2Cl_2, rt, 4 h; (**c**) i) O_3, CH_2Cl_2, -78°C, 30 min; ii) vinylMgBr, THF, -40°C, 4 h; (**d**) $(COCl)_2$, DMSO, Et_3N CH_2Cl_2, -78°C, 2 h; (**e**) $HO(CH_2)_2OH$, PTSA, benzene, reflux, 4 h; (**f**) i) O_3, CH_2Cl_2, -78°C, 15 min; ii) Ph_3P=CHCOOMe, Benzene, reflux, 2 h.



Scheme (3). *Reagents and conditions*: (**a**) LiOH, THF:MeOH:H_2O (3:1:1), rt, 4 h; (**b**) TBAF, THF, 0°C to rt, 3 h; (**c**) Ph_3P, DEAD, toluene: THP (10:1) -25°C, 10 h; (**d**) 10% aq. HCl, THF, 0°C to rt, 5 h.

solution. Finally, the organic layers were dried on Na_2SO_4 followed by concentration gave the crude alcohol **5** (5.0 g, 90%) as a colorless liquid. This crude was used as same without further purification for next reaction.

Imidazole (10.2 g, 150 mmol) and the above crude alcohol **5** (5 g, 50 mmol) in dry CH_2Cl_2 (50 mL) was reacted with TBSCl (8.29 g, 55 mmol) at 0 °C under inert conditions. This reaction mass was allowed for stirring at room temperature over a period of 4 h. Now the reaction mixture was neutralised with aq. NH_4Cl solution (10 mL) and mixed with CH_2Cl_2 (2 × 50 mL). The two organic layers were combined and washed with water (30 mL) followed by brine (30 mL) solution. Finally it was dried on Na_2SO_4 followed by concentrated. The crude residue was eludated by column chromatography (60-120 Silica gel, *n*-Hexane) afforded **6** (7.5 g, 70%) as a colorless liquid. $[\alpha]_D$ -57.4 (*c* 0.76, $CHCl_3$).

(S)-6-(tert.-Butyldimethylsilyloxy) hept-1-en-3-ol (3) [29]

The compound **6** (7.4 g, 34.57 mmol) was soluble in 70 mL dichloro methane solution and cooled this solution to -78°C. Ozone was passed to the above solution until pale blue color was appeared. 2 mL of Me_2S was used to remove the excess ozone and the reaction mixture was allowed for stirring over a period of 30 min at 0°C. The reaction mass was concentrated under pressure conditions afforded aldehyde, which was straightly used for next reaction without further purification.

To a stirred solution of above aldehyde in dry THF (60 mL) at -40°C, a solution of vinylmagnesium bromide (2.0 *N* solution in THF) (20.5 mL, 41.5 mmol) was added dropwise. After the completion of addition, the reaction mixture was stirred for 4 h and neutralized with aq. NH_4Cl solution (30 mL) dropwise. The residue was filtered through celite and filtrate was diluted with ethyl acetete (2 × 50 mL). The organic layers were mixed, dried on dry Na_2SO_4 and evaporated under pressure conditions. Finally, chromatographic technique was applied to purify the crude product (60-120 Silica gel, 10% EtOAc in pet. ether) furnished **3** (6.8 g, 84%) as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.84 (m, 1H, olefinic), 5.11 (m, 2H, olefinic), 4.02 (m, 1H, -CH), 3.83 (m, 1H, -CH), 1.60-1.39 (m, 4H, 2 × -CH_2), 1.06 (dd, 3H, *J* = 5.2 Hz, -CH_3), 0.84 (s, 9H, 3 × -CH_3), 0.01 (s, 6H, 2 × -CH_3); ESIMS: 267 $(M+Na)^+$.

(S)-6-(tert-Butyldimethylsilyloxy)hept-1-en-3-one (7)

Dropwise addition of dry DMSO (2.63 mL, 33.78 mmol) was done to a mixture of oxalyl chloride (1.43 mL, 16.89 mmol) was soluble in dry CH_2Cl_2 (10 mL) at -78°C and this reaction mixture was allowed for stirring over a period of 20 min. A solution of **3** (2.5 g, 11.26 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise to the above solution and stirred over a period of 2 h at -78 °C. Same above work up procedure was also followed and available crude was purified through column chromatography (60-120 Silica gel, 5% EtOAc in pet. ether) to give ketone **7** (2.14 g, 84%) as a colourless liquid. $[\alpha]_D$ +20.5 (*c* 0.31, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.37 (dd, 1H, *J* = 15.8, 9.7 Hz, olefinic), 6.03 (d, 1H, *J* = 15.8 Hz, olefinic), 5.78 (d, 1H, *J* = 9.7 Hz, olefinic), 3.86 (m, 1H, -CH), 2.28 (m, 2H, -CH_2), 1.460 (m, 2H, -CH_2), 1.08 (d, 3H, *J* = 5.8 Hz, -CH_3), 0.98 (s, 9H, 3 × -CH_3), 0.03 (s, 6H, 2 × -CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.2, 139.3, 133.6, 66.7, 38.0, 36.1, 25.9, 23.6, 18.4, -4.2, -4.7; IR (KBr): 2955, 2931, 2858, 1722, 1465, 1253, 1045, 835 cm^{-1}; ESIMS: 265 $(M+Na)^+$.

(S)-tert-Butyldimethyl(4-(2-vinyl-1,3-dioxolan-2-yl)butan-2-yloxy) silane (8)

A solution of ketone **7** (2.1g, 9.54 mmol), ethylene glycol (0.88 mL, 14.31 mmol) and *p*-toluenesulphonic acid (10 mol%) in benzene (80 mL) was allowed for reflux over a period of 4h with Dean-Stark apparatus to remove the benzene. Further the residue was soluble in ether (250mL). The etherial mixture was washed with 5% aqeous sodium hydroxide (3 × 20 mL), water (4 × 50mL) followed by brine (30 mL). Finally it was dried on anhydrous Na_2SO_4 and concentrated. Column chromatography technique was performed to purify the crude product by (60-120 Silica gel, 10% EtOAc in pet. ether) to afford **8** (1.78 g, 71%) as a colorless liquid. $[\alpha]_D$ +32.3 (*c* 0.31, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.88 (m, 1H, olefinic), 5.14 (m, 2H, olefinic), 3.89 (m, 4H, O$\underline{CH_2}$-O$\underline{CH_2}$), 3.73 (m, 1H, -CH), 1.60-1.39 (m, 4H, 2 × -CH_2), 1.06 (d, 3H, *J* = 5.2 Hz, -CH_3), 0.84 (s, 9H, 3 × -CH_3), 0.01 (s, 6H, 2 × -CH_3); ^{13}C NMR (75 MHz,

$CDCl_3$): δ 139.1, 118.6, 103.0, 66.6, 64.7, 34.2, 32.3, 25.9, 23.5, 18.3, -4.1, -4.9; IR (KBr): 2963, 2931, 2858, 1465, 1253, 1045, 835 cm^{-1}; ESIMS: 309 $(M+Na)^+$.

(S,E)-Methyl3-(2-(3-(tert-butyldimethylsilyloxy)butyl)-1,3-dioxolan-2-yl)acrylate (9)

The compound **8** (7.4 g, 34.57 mmol) was soluble in 70 mL dichloro methane solution and cooled this solution to -78°C. Ozone was passed to the above solution until pale blue color was appeared. 2 mL of Me_2S was used to remove the excess ozone and reaction mass allowed for stirring over 15 min at 0°C. The reaction mass was under go concentration with reduced pressure afforded aldehyde, which was straightly used for next reaction.

Solution of the above aldehyde in benzene (50 mL) was treated with (methoxy- carbonylmethylene)triphenyl phosphorane (3.54 g, 10.54 mmol) at reflux temperature. After a period of 2 h, solvent was removed from reaction mass and concentrated under reduced pressure and available residue was purified by column chromatography (60-120 Silica gel, 10% EtOAc in pet. ether) to furnish **9** (3.12 g, 84%) as a yellow liquid. $[\alpha]_D$ -48.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.78 (d, 1H, *J* = 15.6 Hz, olefinic), 6.03 (d, 1H, *J* = 15.6 Hz, olefinic), 3.89 (m, 4H, O$\underline{CH_2}$-O$\underline{CH_2}$), 3.73 (s, 3H, OCH_3), 3.61 (m, 1H, -OCH), 1.68 (m, 2H, -CH_2), 1.53 (m, 2H, -CH_2), 1.3 (d, 3H, *J* = 3.0 Hz, -CH_3); 1.01 (s, 9H, 3 × -CH_3), 0.06 (s, 6H, 2 × -CH_3); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 166.5, 147.4, 118.8, 113.5, 66.6, 55.4, 51.6, 35.4, 30.2, 25.6, 24.2, 18.2, -4.8; IR (neat): 2932, 1724, 1612, 1512, 1448, 1386, 1164, 1037 cm^{-1}; ESIMS: 367 $(M+Na)^+$.

(S,E)-3-(2-(3-(tert-Butyldimethylsilyloxy)butyl)-1,3-dioxolan-2-yl) acrylic acid (10)

Compound **9** (2.6 g, 6.16 mmol) was soluble in THF: MeOH: water (3:1:1, 20 mL). To this reaction mixture, LiOH (0.45 g, 18.48 mmol) was added very slowly and allowed for stirring at room temperature over a period of 4h. The reaction mass was acidified with 1N HCl solution and mixed with ethyl acetate (30 mL). Combined organic layers were treated with water (15 mL) followed by brine (15 mL). The organic mass was dried on dry Na_2SO_4 followed by evaporation. Further, reaction mass was concentrated under reduced pressure and available residue was purified by column chromatography (60-120 Silica gel, 30% EtOAc in pet. ether) to give **10** (2.02 g, 80%) as a colourless oil. $[\alpha]_D$ +14.6 (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.81 (d, 1H, *J* = 15.8 Hz, olefinic), 6.01 (d, 1H, *J* = 15.8 Hz, olefinic), 3.97-3.84 (m, 5H, O$\underline{CH_2}$-O$\underline{CH_2}$ & -OCH), 1.82-1.67 (m, 2H, -CH_2), 1.58-1.47 (m, 2H, -CH_2), 1.03 (d, 3H, *J* = 3.0 Hz, -CH_3); 1.01 (s, 9H, 3 x -CH_3), 0.09 (s, 6H, 2 x -CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.8, 151.1, 120.6, 109.6, 68.6, 65.6, 31.2, 29.8, 23.9, 18.2, -4.6; IR (neat): 3540, 3031, 2930, 2857, 1710, 1097 cm^{-1}; ESIMS: 353 $(M+Na)^+$.

(S,E)-3-(2-(3-Hydroxybutyl) -1,3-dioxolan-2-yl) acrylic acid (2)

TBAF (6.5 mL, 6.5 mmol) was added dropwise to a cooled (0 ^oC) solution of **10** (2.20 g, 5.40 mmol) in dry THF (15 mL) under inert atmosphere and allowed for stirring over a period of 3 h. Now the compound extracted in ethyl acetate solvent (2 × 50 mL). Combined organic layers were treated with water (2 × 10 mL) followed by brine (10 mL). The organic mass was dried on dry Na_2SO_4 followed by evaporation. Finally available crude was purified by coloumn chromatography (60-120 Silica gel, 55% EtOAc in pet. ether) to give **2** (1.38 g, 87%) as a liquid. $[\alpha]_D$ -32.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.81 (d, 1H, *J* = 15.6 Hz, olefinic), 6.11 (d, 1H, *J* = 15.6 Hz, olefinic), 3.93 (m, 1H, -OCH), 3.87-3.79 (m, 4H, O$\underline{CH_2}$-O$\underline{CH_2}$), 1.79-1.66 (m, 2H, -CH_2), 1.55-1.44 (m, 2H, -CH_2), 1.11 (d, 3H, *J* = 5.1 Hz, -CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.6, 150.2, 120.9, 109.3, 68.2, 66.4, 31.2, 28.8, 23.2; IR (neat): 3451, 2929, 2857, 2102, 1722, 1612, 1514, 1360, 1041, 777 cm^{-1}; ESIMS: 239 $(M+Na)^+$.

(10R,22R)-10,22-dimethyl-1,4,9,14,17,21-hexaoxadispiro [4.7.4.7] tetracosa-6,18-diene-8,20-dione (11) [33]

DEAD (0.86 mL, 16.87 mmol) was added to a solution of **10** (0.235 g, 0.93 mmol) and Ph_3P (1.26g, 4.67 mmol) in toluene: THF (10:1, 250 mL) at -20 °C and this reaction mass was stirred under inert atmosphere over 10 h. Further, reaction mass was concentrated under reduced pressure and available residue was purified by column chromatography (60-120 Silica gel, 10% EtOAc in pet. ether) to afford **11** (0.12 g, 56%) as a colorless oil.

Pyrenophorin (1) [33]

To a stirred solution of **11** (45 mg, 0.22 mmol) in THF (2 mL) cooled to 0 °C, treated with 10% aq. HCl (1 mL) and reaction mass allowed for stirring at room temperature for 5 h. The reaction mass was neutralized with sat. $NaHCO_3$ solution (10 mL) and diluted with EtOAc (2 × 20 mL). The combined organic layers were performed with water washing (2 × 25 mL) followed by brine (25 mL). Now this reaction mass was completely dried on anhydrous Na_2SO_4 and evaporated. Finally column chromatography technique employed to purify the crude mass (60-120 Silica gel, 10% EtOAc in pet. ether) to give 40 (26 mg, 78%) as a colourless liquid.

CONCLUSION

Briefly, the total synthesis of (-) - pyrenophorin **1** was accomplished from commercially available starting material (*S)*-propylene oxide. Jacobsen's hydrolytic kinetic resolution and intermolecular Mitsunobu cyclization were key intermediates to construct the above macrolactone, "(-) - pyrenophorin".

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

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Declared none.

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