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Stereoselective total synthesis of Botryolide E

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ABSTRACT

Stereoselective total synthesis of botryolide-E has been described. The synthesis started from one-pot selective oxidation of (*R*)-butane-1,3-diol using TEMPO-BAIB followed by Wittig olefination, Appel`s reaction, Sharpless asymmetric dihydroxylation, ring-closing metathesis reactions are the key steps.

Keywords: Botryolide-E, Natural products, one pot selective oxidation and Wittig olefination, Sharpless asymmetric dihydroxylation, Appel's reaction and ring-closing metathesis reaction.

1. INTRODUCTION

The natural product which are having γ-lactone moitif's [1-8] have a wide range of biological activities. Sapinofuranone-B, (4S, 5R)-solerol, Vitamin C, (+)-Muricatacin, Stagonolide G, and iso-cladospolide B are some of the γ-lactone containing natural product which has been shown in figure-II, Botryolide-E is one of them. Botryolide-E (1) is one of the derivatives of γ-lactone containing natural product with three stereogenic centers has been isolated from cultures of the fungicolous *Botryotrichum sp*. (NRRL 38180) by Gloer and co-workers [9] in 2008 and it exhibits an anti-bacterial [10] activity against Bacillus subtilis (MTCC 441), Staphylococcus aureus (MTCC 96), and Escherichia coli (MTCC 443), and an antifungal [10] activity against Aspergillus niger (MTCC 1344) and Saccharomyces cerevisiae (MTCC 171). Botryolide-E (1) also have Cyclo-oxygenase [11], antiproliferative [11], cytotoxic [13] and antitumor [14] properties. The family of Botryolide-A-E has been shown in figure 1 among them only Botryolide C and Botryolide E are the γ-lactones and these are of either bacterial or fungal origin. In continuation of our interest towards the total synthesis of γ-lactone containing natural product [15-18] the fascinating structure and promising biological activities of Botryolide-E attracts our attention towards its total synthesis. The synthesis of Botryolide-E (**1**) starts from commercially available (*R*)-butane-1,3-diol by Wittig olefination, Sharpless asymmetric dihydroxylation, and ring closing metathesis by Grubbs 2nd generation catalyst in 13 linear steps.

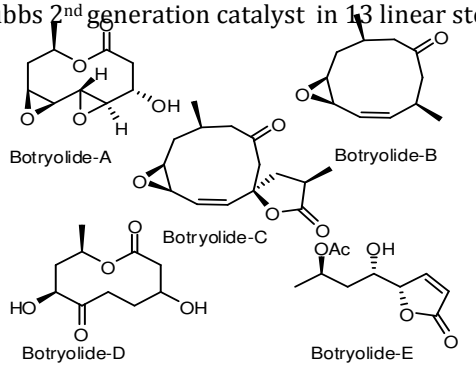


Figure - 1: Structure of Botryolide-A-E.

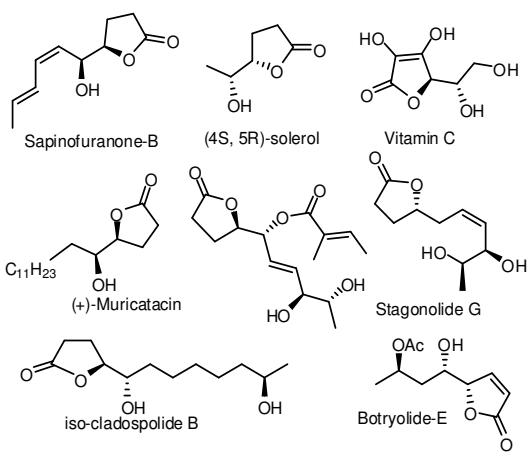
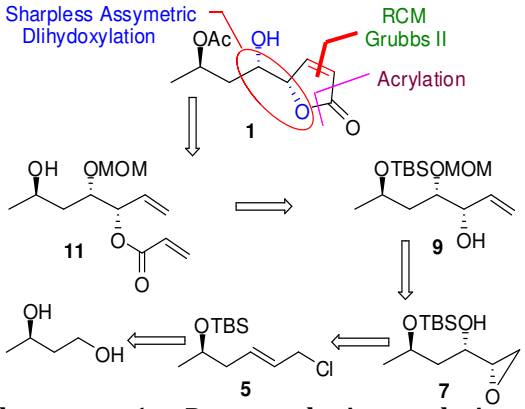


Figure - 2: Structures of γ-lactones containing natural product.

In our Retrosynthetic analysis botryolide E (**1**) in **Scheme 1** could be derived from ring-closing metathesis. This led to the key intermediate **11** which could be synthesized by the acrylation of alcoholic compound **9**. The compound **9** in turn to synthesized by the opening epoxide **7** by trimethyl sulfonium iodide (TMSI) and n-butyl lithium. The compound **7** derived from the compound **5** by Sharpless asymmetric hydroxylation and base mediated epoxidation. The compound **5** could be obtained from one-pot selective oxidation of (*R*)-butane-1,3-diol followed by Wittig olefination and reduction.



Scheme - 1: Retrosynthetic analysis to BotryolideE (1).

2. Experimental section

2.1. (*R,E*)-ethyl 5-hydroxyhex-2-enoate (2)

To a solution of (*R*)-butane-1,3-diol 39 (3.0 g, 33.3 mmol) in CH_2Cl_2 (40 ml) were added BAIB (12.3 g, 38.3 mmol) and TEMPO (0.519 g, 3.3 mmol) and leave it to stirr for 3h, at room temperature, then cooled to 0℃ and (carboethoxymethylene)triphenylphosphorane (15 g, 43.3 equiv) was added. The reaction mixture was allowed to warm to room temperature and stirred for 1 h. The solution was poured onto a column of silica gel and eluted with a mixture of ethyl acetate–petroleum ether (1:3) to give pure ethyl 5-hydroxyhex-2-enoate **2** (4.59 g, 87%) as an oil. .

$[\alpha]^{D}_{25}$ −14.9° (c 1.0, $CHCl_3$); IR (neat) = ν_{max} 3019, 1710, 1654, 1370, 1321, 1266, 1214, 1178, 1117, 1042, 982, 930, 749, 667, 625 cm^{-1}. ^1H NMR (300MHz, $CDCl_3$) δ 7.02-6.90 (m, 1H), 5.90 (d, *J* = 15.6 Hz, 1H), 4.22-4.14 (dd, *J* = 7.1, 14.3 Hz, 2H), 4.02-3.92 (m, 1H), 2.40-2.33 (m, 2H), 2.09 (s, 1H), 1.32-1.27 (m, 3H), 1.23 (d, *J* = 6.2 Hz, 3H), ppm. ^{13}C NMR (300 MHz, $CDCl_3$) δ 166.3, 145.0, 123.6, 66.5, 60.2, 41.6, 23.0, 14.0 ppm. ESI-HRMS calcd for $C_8H_{14}O_3$, $[M+Na]^+$: 181.21.

2.2.(*R,E*)-ethyl-5-(tert-butyldimethylsilyloxy) hex-2 enoate (3)

The secondary alcohol **2** (4 g, 25.3 mmol) in dry CH_2Cl_2 (35 ml) was added 5.8 ml of 2,6-Lutidine (50.6 mmol) followed by 9.9 ml, of TBSOTf (37.9 mmol) portion wise, at room temperature. The mixture was stirred for 1 h and quenched with the sat. NH_4Cl soln. and the mixture was extracted with CH_2Cl_2 (40 ml), washed with brine (20 ml), dried (Na_2SO_4), and concentrated in vacuo Purification of the crude by Column chromatography with silica gel afforded **3** (6.34 g, 92%).

$[\alpha]^{D}_{25}$ −9.3 ° (c 1.0, $CHCl_3$), IR (neat) ν_{max} 3019, 1214, 928, 930, 749, 667, 625 cm-1. ^1H NMR (300 MHz, $CDCl_3$) δ 7.0-6.89 (m, 1H), 5.86-5.79 (m, 1H), 4.22-4.14 (m, 2H), 3.96-3.86 (m, 1H), 2.34-2.27 (m, 2H), 1.61 (m, 1H), 1.30-1.25 (m, 3H), 1.15 (d, J = 6.0, 3H), 0.88 (s, 9H), 0.05-0.03 (m, 6H) ppm. ^{13}C NMR (300 MHz, $CDCl_3$) δ 166.4, 146.0, 123.1, 67.6, 60.0, 42.3, 25.7, 23.7, 14.2, −4.6, −4.9 ppm. ESI-HRMS calcd for $C_{14}H_{28}O_3Si$, $[M+Na]+$: 295.18

2.3. (*R,E*)-tert-butyl(6-chlorohex-4-en-2-yloxydimethylsilane (4):

To a stirred solution of ester **3** (5 g, 14.7mmol) in CH_2Cl_2, was added DIBAL-H (1M) (5.2 ml, 36.7 mmol) dropwise at 0 ºC over a period of 20 min. The reaction mixtures was stirred at rt. for 1 h, then add saturated solution of potassium sodium tartarate (10 ml) to the reaction mixture, and the aqueous layer was extracted with EtOAc and concentrated under reduced pressure. The crude product was purified by silica gel chromatography using hexane and ethyl acetate (19:1) to afford (R)-alcohol (3.85 g, 91% yield). $[\alpha]^{D}_{25}$ -1.56 (c =0.32, $CHCl_3$). IR (neat) ν_{max} 1524, 1218, 1133, 1093, 1001, 835, 772, 668 cm^{-1}. ^1H NMR (300MHz, $CDCl_3$) δ 5.74-5.66 (m, 2H), 4.10 (d, *J* = 3.9 Hz, 2H), 3.87-3.82 (m, 1H), 2.23-2.13 (m, 2H), 1.13 (d, *J* = Hz, 3H), 1.10-1.07 (d, *J* = 6.0 Hz, 3H), 0.89 (s, 9H), 0.05 (m, 6H) ppm. ^{13}C NMR (300 MHz, $CDCl_3$) δ 132.7, 127.9, 68.1, 45.2, 42.3, 25.8, 23.5, −4.5, −4.7 ppm. ESI-HRMS calcd for $C_{12}H_{26}O_2Si$, $[M+Na]^+$: 253.16.

2.4. (5*S*,7*R*)-7,9,9,10,10-pentamethyl-5-((S)-oxiran-2-yl)-2,4,8-trioxa-9-silaundecane (5)

To a stirred solution of 11 (3.5 g, 8.69 mmol) in anhydrous CCl_4 (26.0 mmol, 4.4 ml) was added triphenylphosphine (3.4 g, 13.0 mmol) under nitrogen atmosphere and then sodium bicarbonate (2.19 g, 26.0 mmol) was added. The mixture was heated under reflux until triphenylphosphine oxide separated from the reaction mixture. After 6 h, the mixture was filtered and the solvent was removed from the

filtrate under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexanes 1:9) to afford compound 16 as a colourless liquid. (2.53 g, 67%).

$[\alpha]^{D}_{25}$ +1.90 (c = 0.157, $CHCl_3$). IR (neat) ν_{max} 3019, 2928, 2855, 2791, 1214, 928, 834, 746, 667, 626 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 5.83-5.73 (m,), 5.70-5.58 (m, 1H), 4.03 (d, J = 6.7 Hz, 1H), 3.87-3.81 (m, 1H), 2.22-2.15 (m, 2H), 1.58 (s, 1H), 1.13-1.11 (d, J = 6.0 Hz, 3H), 0.88 (s, 9H), 0.05-0.03(m, 6H) ppm. ^{13}C NMR (300 MHz, $CDCl_3$) δ 96.1, 75.2, 64.9, 55.0, 55.7, 43.8, 42.6, 25.8, 24.5, 23.3, -3.9, -4.2 ppm. ESI-MS, m/zi, [M+Na]+ : 271.22

2.5. (1*S*,3*R*)-3-(tert-butyldimethylsilyloxy)-1-((*S*)-oxiran-2-yl)butan-1-ol (6)

AD-mix-α (14.11 g) was added to a solution of (*E*)-1-iodo-but-2-ene (9) (2.5 g, 10.08 mmol), methanesulfonamide (0.957 g, 10.08 mmol) and sodium bicarbonate (2.54 g, 30.24 mmol) in t-butanol:water (1:1, 50 ml), and stirred at 0 ºC for 15 h. The reaction was quenched with sodium sulfite (4.5 g), stirred for 15 min at 0 ºC and for 10 min at room temperature, and then extracted with CH_2Cl_2 (3 x 25 ml). The combined extracts were washed with brine, dried and concentrated to furnish a yellowish solid. The crude solid was recrystallized from n-hexane/ethyl acetate (4:1) and purified by "dry-column" flash chromatography (hexane : ethyl acetate, 3:1), yielding (2.474 gm, 87%) a white solid.

$[\alpha]^{D}_{25}$ -11.2 (c = 0.475, $CHCl_3$). IR (neat) ν_{max} 3427, 2956, 2929, 2898, 2857, 1463, 1377, 1255, 1219, 1071, 1017, 972, 939, 836, 772, 676 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 4.15 (m, 1H), 3.73 (d, J = 0.3, 1H), 2.97 (m, 1H), 2.80-2.67 (m, 2H), 1.80-1.55 (m, 3H), 1.24-1.15 (m, 3H), 0.88 (s, 9H), 0.11-0.07 (m, 6H) ppm. ^{13}C NMR (300 MHz, $CDCl_3$) δ 70.5, 68.4, 66.8, 51.5, 42.3, 25.8, 23.5, −4.0, −4.4 ppm. ESI-MS m/z $[M+Na]^+$: 305.11.

2.6. (1*S*,3*R*)-3-(tert-butyldimethylsilyloxy)-1-((*S*)-oxiran-2-yl)butan-1-ol (7)

To a stirred solution of diol **6** (2.3 g, 14.7mmol) in THF, was added NaOH powder (5.2 ml, 36.7 mmol) portion wise at 0 ºC over a period of 20 min. The reaction mixtures was stirred at rt for 1 h, then cold water (20 ml) into the reaction mixture, and the aqueous layer was extracted with EtOAc and concentrated under reduced pressure. The crude product was purified by silica gel chromatography using hexane and ethyl acetate (19:1) to afford epoxide (1.87 g, 87% yield).

$[\alpha]^{D}_{25}$ -17.94 (c = 1.07, $CHCl_3$). IR (neat) ν_{max} 2956, 2928, 2856, 1719, 1667, 1539, 1469, 1376, 1254, 1219, 1077, 1004, 836, 772, 676 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 4.16-3.98 (m, 1H), 3.75-3.59 (m, 1H), 3.73 (d, J = 20.3 1H), 2.97 (m, 1H), 2.80-2.67 (m, 2H), 1.80-1.55 (m, 3H), 1.24-1.15 (m, 3H), 0.88 (s, 9H), 0.11-0.07 (m, 6H) ppm. ^{13}C NMR (300 MHz, $CDCl_3$) δ 70.3, 68.3, 66.0, 55.5, 42.3, 25.8, 23.5, −4.0, −4.4 ppm. ESI-MS, m/z, [M+Na]+ : 269.22

2.7. (5*S*,7*R*)-7,9,9,10,10-pentamethyl-5-((*S*)-oxiran-2-yl)-2,4,8-trioxa-9-silaundecane (8)

To a stirred solution of **7** (1.6 g, 6.5 mmol) in dry CH_2Cl_2 (20 ml) at 08 was added diisopropylethylamine (2.6 ml, 15.2 mmol), and stirred for 30 min at 0 °C under nitrogen atmosphere and MOMCl (0.73 ml, 9.75 mmol) was added to the reaction mixture in CH_2Cl_2 (10 mL) at same temperature. After completion of the reaction (monitored by TLC) the resulting mixture was stirred for 2 h at room temperature and then the reaction was quenched by adding H_2O (10 ml), and the mixture was extracted with CH_2Cl_2 (10 ml). The org. extracts were washed with brine (10 ml), dried over Na_2SO_4, and concentrated under reduced pressure to remove the solvent, and the crude was purified by column chromatography to afford **8** (1.736 gm, 92%); $[\alpha]^{D}_{25}$ -5.76 (c = 0.278, $CHCl_3$). IR (neat) ν_{max} 3019, 1215, 928, 742, 667, 626 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ4.89-4.68 (m, 2H), 4.09-3.96(m, 1H), 3.06-2.96(m, 1H), 2.80-2.74(m, 1H), 2.56-2.53(m, 1H), 2.51-2.47(m, 1H), 1.69-1.52(m, 2H), 1.17(*dd, J* =6.0, 2.3, 3H), 0.90-0.85(m, 9H), 0.09-0.05(m, 6H) ppm. ^{13}C NMR (300 MHz, $CDCl_3$) δ 96.1, 75.2, 64.3, 55.8, 55.0, 43.8, 42.6, 25.8, 24.6, 23.3, -4.2, -3.9 ppm. ESI-MS m/z [M+Na]+ : 313.19.

2.8. (3*S*,4*S*,6*R*)-6-(tert-butyldimethylsilyloxy)-4 (methoxymethoxy)hept-1-en-3-ol (9)

To the solid trimethylsulfoxonium iodide (5.27 g, 25.86 mmol) in dry THF, at −25 °C, *n*-butyl-lithium (0.66 ml, 2.5M) was added dropwise. The reaction mixture was stirred for 30 minutes, ylide was generated to that the epoxide compound **8** (1.5 g, 5.17 mmol) in dry THF, was added, then cooled to 0 °C over a period of 30 minutes. The reaction mixture was then stirred for a further 4 h, at the same temperature and quenched with water, and extracted with ethyl acetate. The organic extracts were combined and dried with Na_2SO_4, and the solvent was removed under reduced pressure. The crude material was then purified by silica gel chromatography.

$[\alpha]^{D}_{25}$ -6.38 (c = 0.502, $CHCl_3$). IR (neat) ν_{max} 2954, 2926, 2855, 1731, 1464, 1376, 1253, 1218, 1149, 1100, 1037, 920, 835, 807, 771, 668 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 5.94-5.76(m, 1H), 5.40-5.30 (m, 1H), 5.25-5.18(m, 1H), 4.73-4.71(m, 2 H), 4.69-4.66(m, 1H), 4.0-3.95(m, 1H), 3.83-3.75(m, 1H), 3.42(s, 3H), 1.701.54(m, 2H),

1.17(dd, *J*=6.0, 2.3), 0.90-0.87(m, 9H), 0.07-0.06(m, 6H)ppm. ^{13}C NMR (300 MHz, $CDCl_3$) δ 137.3, 117.1, 97.7, 82.0, 75.5, 65.3, 55.7, 42.0, 29.7, 25.8, 24.5, −4.6, −3.7 ppm. ESI-MS. m/z $[M+Na]^+$: 327.26.

2.9. (3S,4S,6R)-6-(tert-butyldimethylsilyloxy)-4-(methoxymethoxy)hept-1-en-3-yl acrylate (10)

$[\alpha]^{D}_{25}$ -3.39 (c = 0.239, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.48-6.40(m, 1H), 6.23-6.10(m, 1H), 5.95-5.81(m, 2H), 5.50-5.44(m, 1H), 5.37-5.31(m, 1H), 5.29(s, 2H), 4.73-4.71(m, 1H), 4.03-3.90(m, 1H), 3.88-3.80(m, 1H), 3.66(s, 3H), 1.65-1.56(m, 2H), 1.16(d, J= 6.8, 3H), 0.90-0.84(m, 9H), 0.06-0.04(m, 6H)ppm. ^{13}C NMR (300 MHz, $CDCl_3$) δ 168.9, 146.0, 128.9, 128.1, 122.01, 122.0, 130.4, 65.0, 55.9, 40.1, 29.7, 25.9, 24.4, -3.9, -4.7 ppm. IR (neat) ν_{max} 3445, 2955, 2929, 2856, 1731, 1636, 1466, 1405, 1377, 1294, 1259, 1189, 1152, 1101, 1039, 921, 835, 807, 774 cm^{-1}. ESI-MS m/z $[M+Na]^+$: 381.04.

2.10. (3S,4S,6R)-6-hydroxy-4-(methoxymethoxy)hept-1-en-3-yl acrylate (11)

To a stirred solution of the TBS-protected alcohol **10** (1.3 g, 3.63 mmol) in THF (15 mL) was added TBAF (1.9 mL of a 1.0 M solution in THF). This mixture was stirred for 48 h. The mixture was diluted with ethyl acetate (30 mL) and quenched with saturated sodium bicarbonate (10 mL). The layers were separated and the aqueous layer was washed with ethyl acetate (2 x 10 mL). The combined organic layers were washed with brine (10 mL) and dried over sodium sulfate. Removal of the solvents in vacuo, and chromatography on silica gel yielded secondary alcohol **11** as a colorless oil (754 mg, 85%).

$[\alpha]^{D}_{25}$ -29.22 (c = 0.243, $CHCl_3$). IR (neat) ν_{max} 3422, 2926, 2855, 1765, 1463, 1377, 1254, 1082, 1023, 835, 774 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.44-6.35(m, 1H), 6.16-6.04(m, 1H), 5.91-5.77(m, 2H), 5.42-5.33(m, 1H), 5.29-5.22(m, 1H), 4.75-4.66(m, 2H), 4.59-4.54(m, 1H), 4.12-3.96(m, 1H), 3.55-3.47(m, 1H), 3.41(s,3H), 1.94-1.79(m, 1H), 1.70-1.62(m, 1H), 1,29(dd, *J*= 6.2, 2.3, 3H) ppm. ^{13}C NMR (300 MHz, $CDCl_3$) δ 165.7, 136.8, 130.5, 128.7, 117.4, 98.3, 81.4, 75.3, 67.8, 56.0, 38.3, 29.6 ppm. ESI-MS m/z, [M+Na]+ : 253.18

2.11. (2R,4S)-4-(methoxymethoxy)-4-((S)-5-oxo-2,5-dihydrofuran-2-yl)butan-2-yl acetate (13)

The compound **12** (0.25 g, 0.52 mmol) in dry CH_2Cl_2 (180 ml) was first flushed by bubbling with an argon gas flow, for 30 minutes after which Grubbs 2nd generation catalyst (0.021 g, 0.026 mmol) was added at once, and the resulting mixture was heated under argon gas flow for 8 h. After cooling, the solvent was evaporated and the residue was purified by Column Chromatography with silica gel (AcOEt/hexane 2/8) and afforded the compound **13** in 70 mg, 77% yield.

$[\alpha]^{D}_{25}$ +19.71 (c = 4.32, $CHCl_3$). IR (neat) ν_{max} , 2924, 2853, 1737, 1460, 1373, 1245, 1160, 1093, 1033, 919, 824, 609, 541 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53(*dd*, *J= 6.0. 1.5, 1H*), 6.22(*dd*, *J*=6.0, 2.2, 1H), 5.06-4.97(m, 1H), 4.00-3.89(m, 1H), 3.36(s, 3H), 1.72-1.60(m, 1H), 1.55-1.44(m, 1H), 1.23(*d*, *J*=6.79, 3H) ppm. ^{13}C NMR (300 MHz, $CDCl_3$) δ 172.5, 170.6, 153.5, 123.0, 97.9, 83.8, 74.4, 66.9, 56.2, 36.6, 29.6, 20.6 ppm. ESI-HRMS: Calcd for $C_{12}H_{18}O_6$ $[M+Na]^+$: 281.0995, found : 281.0993.

2.12. (2*R*,4*S*)-4-hydroxy-4-((*S*)-5-oxo-2,5-dihydrofuran-2-yl)butan-2-yl acetate (1)

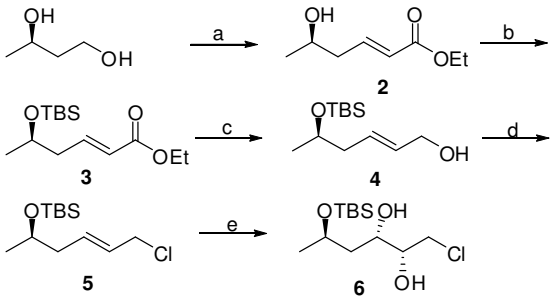
To the stirred solution of RCM compound **13** (50 mg, 0.19 mmol) in CH_2Cl_2 (3 ml), TMSBr (0.10 ml, 0.77 mmol) was added dropwise at −40 °C for 30 minutes and allow it to stirr at 0 °C for additional 3 h. The residue was poured into saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. The extract was dried over Na_2SO_4, concentrated, and subjected to column chromatography to afford **1** (30 mg, 72%)

$[\alpha]^{D}_{25}$ -38.2 (c = 0.05, $CHCl_3$). IR (neat) ν_{max} 3446, 2926, 1738, 1374, 1248 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48(*dd*, *J*=6.0, 1.15, 1H), 6.19(*dd*, *J*=6.0, 2.2, 1H), 5.17-5.0(m, 1H), 3.96-3.83(m, 1H), 2.03(*s*, 3H), 1.94-1,85(m, 1H), 1.81.1.72(m, 1H), 1.27(*d*, *J*= 6.0, 3H) ppm. ^{13}C NMR (300 MHz, $CDCl_3$) δ 172.7, 170.8, 153.7, 122.7, 85.4, 68.8, 68.6, 39.1, 21.3, 20.1, ppm. ESI-HRMS: Calcd for $C_{10}H_{14}O_5$ $[M+Na]^+$: 237.0733, found : 237.0734.

3. RESULTS AND DISCUSSIONS

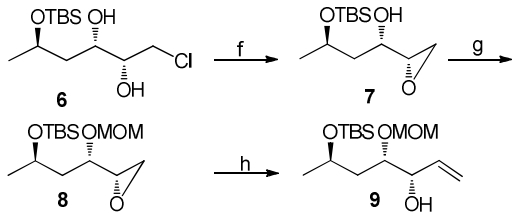
The synthesis of Botryolide E (**1**) was started from the oxidation of commercially available (*R*)-butane-1,3-diol. The diol underwent oxidation by using 2,2,6,6-tetra-methyl-1-piperidenyloxy (TEMPO) and bis(acetoxy)iodo-benzene (BAIB) in CH_2Cl_2 at room temperature followed by Wittig olefination [19] by the addition of stabilized ylide (carboethoxymethylene) triphenylphosphorane at room temperature to give an *α,β*-unsaturated ester **2** in single operation with 87% yield with good trans olefin selectivity. The secondary OH group of compound **2** was protected as its *tert*-butyldimethylsilyl (TBS) ether by using tert-Butyldimethylsilyl triflate (TBSOTf) and 2,6-lutidine [20] as a base in CH_2Cl_2 to furnish compound **3** in 95% yield. The unsaturated ester compound **3** was reduced to alcohol by using DIBAL-H [21] in CH_2Cl_2 at −10 °C to gave the alcohol compound **4** in 93% yield. The primary alcohol of compound **4** was converted to

chloro compound **5** by Appel's reaction [22] which was synthesized by the reaction between triphenylphosphine (TPP), sodiumbicarbonate ($NaHCO_3$) and tetrachloromethane (CCl_4) in 77% yield. Now the chloro olefinic compound **5** underwent asymmetric dihydroxylation by using ADMix-α by the Sharpless asymmetric dihydroxylation protocol [23] to gave compound **6** with 89% yield.



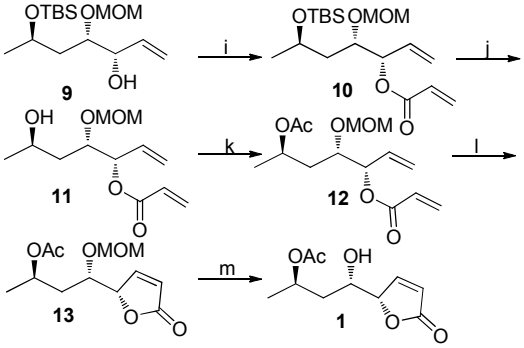
Scheme - 2: Reagents and conditions. ((a) TEMPO, BAIB, CH_2Cl_2, 0 °C, 1 h, 87%; (b) TBSOTf, 2,6-Lutidine, CH_2Cl_2, 0 °C, 1 h, 95%; (c) DIBAL-H, CH_2Cl_2, −10 °C, 2 h, 93%; (d) TPP, $NaHCO_3$, CCl_4, reflux, 6 h, 77%; (e) AD Mix-α, t-BuOH:H_2O (1:1), 0 °C, 24 h, 89%).

The compound **6** was subjected to epoxidation through the base mediated SN^2 attack by hydroxyl group to the chloro carbon afforded epoxide product [24] **7** in 87% yields by using NaOH powder in tetrahydropyrane. The secondary hydroxyl group of epoxide **7** [25] was protected as its methoxy methyl (MOM) ether with Hunig's base and methoxy methyl chloride (MOMCl) in dichloromethane to gave the MOM protected compound **8** with 92% yield. Reductive ring opening of epoxide **8** was carried out by using dimethylsulfonium methylidene which was formed by trimethylsulphoniumiodide (TMSI) and *n*-butyl lithium in tetrahydropyrane at −78 °C afforded vinylic alcohol compound **9** [26] in 88% yield.



Scheme - 3: Reagents and conditions. ((f) NaOH powder, THF, 0 °C, 2 h,87%;(g) DIPEA, MOMCl, CH_2Cl_2, 0 °C, 2 h, 92%; (h) TMSI, *n*-Butyl Lithium, THF, −20 °C, 4 h, 88%).

The hydroxy group of compound **9** was acrylated by using acryl chloride and Hunig's base in dichloromethane afforded an acrylate ester [27] **10** in 93% yield. Now the *tert*-butyldimethylsilyl group of compound **10** was deprotected with tetrabutylammoniumfloride in tetrahydropyrane to afford an alcohol compound **11** in 85% yield. The alcohol in **11** was acetylated with Ac_2O, [19] pyridine and catalytic amount of DMAP in dichloromethane (CH_2Cl_2) to afforded compound **12** with 87% yield. The compound **12** was subjected to ring closing metathesis reaction induced by Grubbs'2nd generation catalyst [20] in dry dichloromethane (CH_2Cl_2) to afford a unsaturated γ-lactone **13** in 77%yield. The secondary methoxy methyl ether (MOM) of compound **13** underwent deprotection with Me_3SiBr [21] in CH_2Cl_2 afforded target natural product Botryolide E (1) in 73%.



Scheme - 4: Reagents and conditions. ((i) acryl chloride, DIPEA,CH_2Cl_2, 0 °C to rt, 3 h, 93%; (j) TBAF, THF, 0 °C to rt, 85%; (k) $(Ac)_2O$, pyridine, DMAP, CH_2Cl_2, 0 °C to rt, 3h, 87%; (l) Grubbs'2nd generation catalyst, CH_2Cl_2, reflux, 8 h, 77%; (m) Me_3SiBr, CH_2Cl_2, 3 h, −40 °C to rt, 73%).

4. CONCLUSION

In Conclusion, we have accomplished the stereoselective total synthesis of Botryolide E (**1**) from commercially available (*R*)-butane-1,3-diol, Wittig olefination, Appel`s reaction, sharpless asymmetric dihydroxylation, ring-closing metathesis reactions by Grubbs'2nd generation catalyst were successfully utilized for the completion of the total synthesis of Botryolide-E in 13 linear steps.

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