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PAPER

Total synthesis of (+)-anamarine†

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Total synthesis of (+)-anamarine a polyoxygenated δ-pyranone natural product was accomplished *via* cross-metathesis protocol starting from 3-butene-1-ol and glycidol. Other key features of this synthetic strategy include use of Sharpless asymmetric epoxidation, dihydroxylation, and deoxygenation-isomerization through allene rearrangement.

Introduction

(+)-Anamarine (**1**) a member of the polyoxygenated δ-pyranone (5,6-dihydro-2*H*-pyran-2-one) containing natural product family was isolated from the flowers and leaves of an unclassified Peruvian *Hyptis* species.[1] It is structurally similar to other members of the polyhydroxy δ-pyranone family such as synargentolide A (**2**), spicigerolide (**3**), synrotolide (**4**) and hyptolide (**5**). δ-Pyranone is an ubiquitous structural unit found in a number of bioactive natural products of therapeutic significance. Natural products and their analogues possessing this moiety exhibit a number of pharmacological properties such as *anti*-cancer[2] and *anti*-leukemic[3] activity, inhibits HIV protease,[4] induce apoptosis[5,6] and bioactivities in many other biological processes.[7]

As a result of their biological importance, several stereoselective synthetic approaches have been made for anamarine **1**.[8–11] The first synthesis which was accomplished from carbohydrate obviously proved its absolute stereochemical configuration.[8a] Recent approaches to (+)-anamarine **1** exploited asymmetric dihydroxylation,[10] asymmetric epoxidation[11] and aldol reaction.[9] But all of them involved multiple steps and afforded rather low yields.

Results and discussion

As a part of our work, on the synthesis of a novel biologically active compounds,[12] we have ventured into the total synthesis of pharmacological active natural products. In this endeavour the total synthesis of (+)-anamarine **1** is reported (Fig. 1).

Retrosynthetic analysis (Scheme 1) revealed that the target compound **1** is made up of two units, olefine **6** and vinyl lactone **7**. These two substrates olefine **6** and vinyl lactone **7** in turn could be made from the commercially available 3-butene-1-ol and glycidol respectively by sequential reactions. Cross-metathesis reaction of **6** and **7** leads to the target compound.

Synthesis of alkene **6** was accomplished from 3-butenol **10**. Treatment of **10** with benzyl bromide afforded its benzylether **13** in 95% yield. Subsequently **13** was converted into racemic epoxide **14** in 92% yield by epoxidation with *m*-CPBA.

The racemic terminal epoxide **14**, on subjection to solvent free hydrolytic kinetic resolution[13] with (*R*,*R*)-(−)-*N*,*N*^{1}-bis(3,5-di-*tert*-butylsalicyclidene)-1,2-cyclohexanediaminocobalt (III) afforded the required isomer of the chiral epoxide **15** in 42% yield. Reduction of **15** with $LiAlH_4$ gave secondary alcohol **16** which was converted into TBDMS ether **17** in 98% yield by silylation with TBDMSCl (Scheme 2). Selective reductive cleavage of benzyl ether function in **17** by lithium napthalenide led to its primary alcohol **18** in 94% yields.[14] The alcohol **18** on

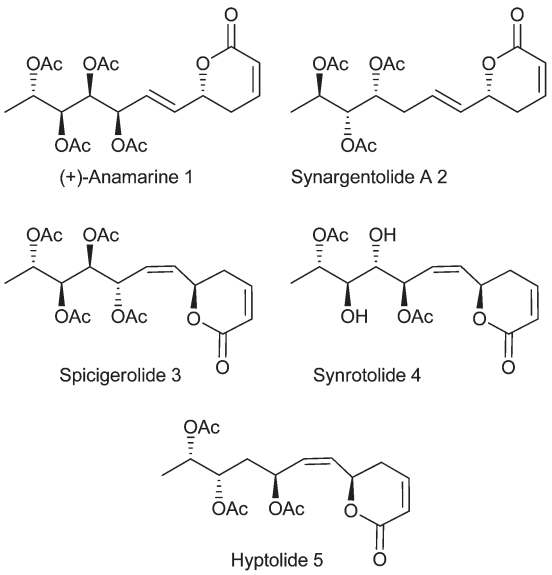

Fig. 1 Polyoxygenated δ-pyranones.

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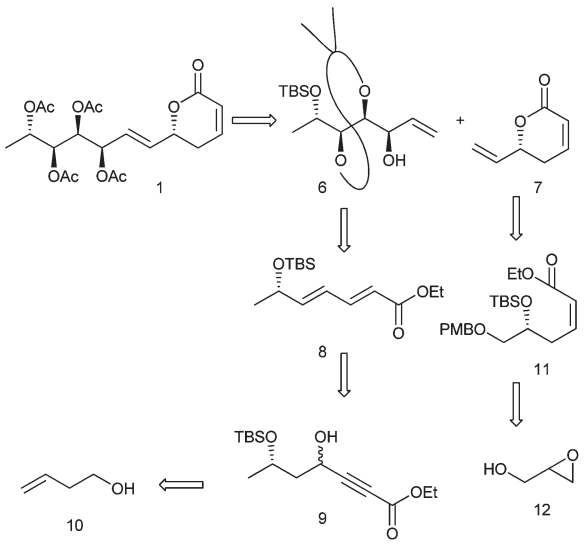
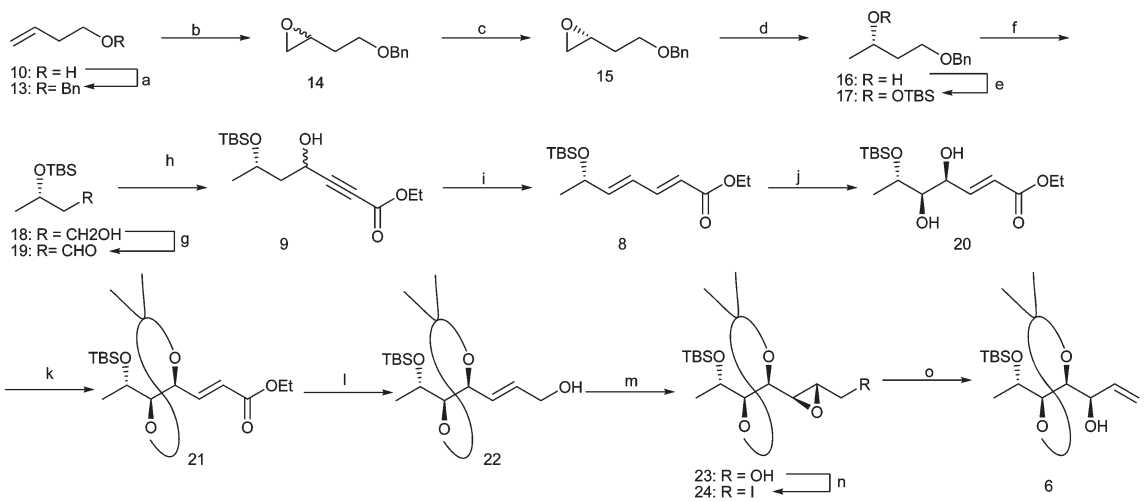
subjection to Swern oxidation followed by addition of lithiated ethylpropiolate gave to the hydroxy alkynoate **9** in 75% yield. The PPh_3-mediated allene type rearrangement of **9** resulted in (*E*,*E*)-diene **8** in 71% yield.[15] On stereo and regioselective asymmetric hydroxylation of **8**[16] *via* Sharpless asymmetric dihydroxylation, using AD-mix-α the diol **20** was obtained in 90% yield with a diastereomeric ratio of 90 : 10. The diol **20** was subsequent converted into its acetonide **21** under standard conditions. Chemoselective reduction of the ester **21** with DIBAL-H at −30 °C afforded the required allylic alcohol **22** in 90% yield. The requisite chiral epoxy alcohol **23** in 88% yield was obtained at this stage *via* a Sharpless asymmetric epoxidation[17] of **22** using (+)-DET. Conversion of epoxy alcohol **23** into the target alkene[18] **6** was effected by initial conversion of **23** to its iodo derivative **24** followed by instantaneous reductive elimination of the epoxy iodide from **24** by rapid addition of *tert*-butyllithium in ether.

The other required component for accomplishing the final synthesis of (+)-anamarine (**1**) is the vinyl lactone **7**. It was synthesized from the racemic glycidol **12**. Treatment of **12** with *p*-methoxybenzyl bromide gave its PMB derivative **25** in 92% yield which was subjected to solvent free hydrolytic kinetic resolution[19] with (*S*,*S*)-(–)-*N*,*N*^{1}-bis(3,5-di-*tert*-butylsalicyclidene)-1,2-cyclohexanediaminocobalt (III) to afford the chiral epoxide **26** in 42% yield. Simple opening of the epoxide ring in **26** with the anion generated from ethyl propiolate in the presence of $BF_3{\cdot}OEt_2$ delivered quantitatively the known alkyne **27**[20] which was subsequently converted into cis alkene **11** by Lindlar's reduction. The alkene ester **11** was cyclized with *p*-PTS in benzene to obtain the pyran derivative **28**. The PMB masked hydroxyl group of the lactone **28** was released by its deprotection using DDQ and the free alcohol **29** was subjected to Swern oxidation followed by Wittig reaction with triphenyl phosphonium methyl iodide to give the desired lactone intermediate **7**[21] (Scheme 3).

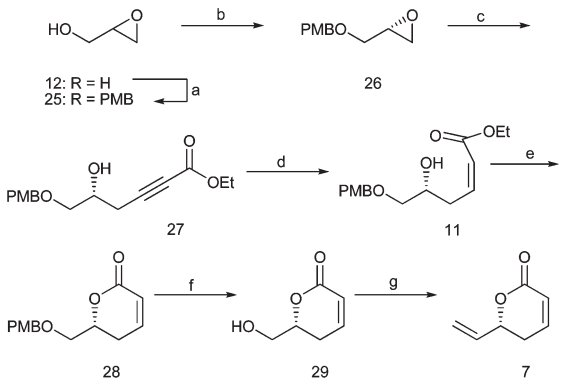
The alkene **6** on cross-metathesis reaction with the vinyl lactone **7** using second-generation Grubb's ruthenium complex as the catalyst (**Catalyst A**) affords the desired lactone **30** in 86% yield.[11,22] In the cross-metathesis of **6** and **7** they were used in 1 : 2 stoichiometric ratio to facilitate easy identification of the product formed in the reaction from the substrates in TLC monitoring and also in the separation of the product. Removal of acetenoide and TBS protecting groups and acetylation of the resulting tetrahydroxy derivative afforded (+)-anamarine **1** in 80% yield (Scheme 4). The spectral and specific rotation data of the synthesized sample **1** are in complete agreement with that reported in the literature.[9–11]



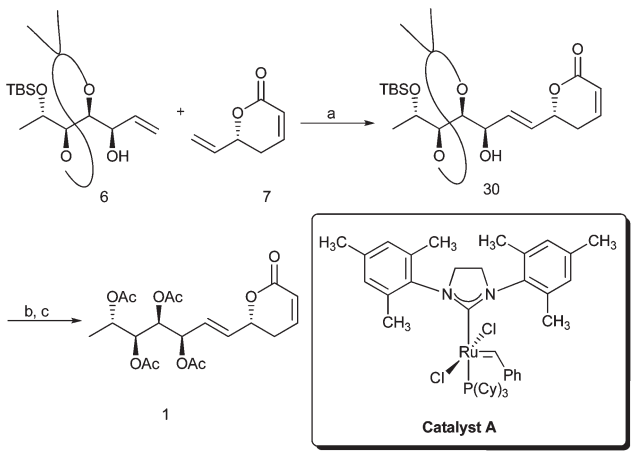
Scheme 1 Reterosynthetic analysis of anamarine 1.



Scheme 2 Reagents and conditions; (a) NaH, BnBr, TBAI, anhydrous THF, 0 °C to rt, 12 h, 95%; (b) *m*-CPBA, CH_2Cl_2, 0 °C, 2 h, 92%; (c) (*R*,*R*)-Jocobsen's catalyst, water, 36 h, 42%; (d) $LiAlH_4$, THF, 0 °C to rt, 3 h, 95%; (e) TBDMSCl, Imidazole, CH_2Cl_2, 0 °C to rt, 3 h, 98%; (f) Li, Napthalene, THF, −20 °C, 2 h, 94%; (g) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 3 h; (h) Ethyl propiolate, LiHMDS, THF, −78 °C, 1 h, 75% (for two steps); (i) PPh_3, benzene, rt, 6 h, 71%; (j) AD-mix-*α*, $CH_3SO_2NH_2$, ^{t}BuOH–H_2O (1 : 1), 0 °C, 3 days, 90% (90 : 10); (k) 2,2-DMP, CSA (cat.), CH_2Cl_2, 0 °C to rt, 1 h, 92%; (l) DIBAL-H, anhydrous CH_2Cl_2, −30 °C, 1 h, 90%; (m) (+)-DET, $Ti(O^iPr)_4$, TBHP, anhydrous CH_2Cl_2, −20 °C, 24 h, 88%; (n) PPh_3, I_2, CH_2Cl_2, 0 °C-reflux, 1 h; (o) ^{t}BuLi, THF, −90 °C, 20 min, 96%.



Scheme 3 Reagents and conditions; (a) NaH, PMB-Br, TBAI, DMF, 20 h, 92%; (b) (*S,S*)-Jacobsen's catalyst, water, 36 h, 42%; (c) Ethyl propiolate, *n*-BuLi, $BF_3.OEt_3$, THF, −78 to 0 °C, 1 h, 99%; (d) Lindlar's catalyst, quinoline (cat), H_2, Ethyl acetate, 2 h; (e) *p*-TSA (cat), Benzene, 85% (for two steps); (f) DDQ, CH_2Cl_2:H_2O (8 : 2), 3 h, 82%; (g) (i) Dess–Martin periodinate, CH_2Cl_2, 0 °C to rt, 1 h; (ii) Triphenyl phosphonium methyl iodide, *n*-BuLi, THF, −78 °C, 1 h, 70%.



Scheme 4 Reagents and conditions; (a) **Catalyst A**, anhydrous CH_2Cl_2, reflux, 5 h, 86%; (b) 1 N HCl, MeOH–AcCN (1 : 1), 0 °C to rt, 8 h (c) Ac_2O, TEA, DMAP, anhydrous CH_2Cl_2, 0 °C to rt, 0.5 h, 80%.

Conclusion

In conclusion, we have developed an efficient enantioselective route for the synthesis of (+)-anamarine **1**. The key steps in the route feature a deoxygenative rearrangement of an alkynol, and a highly enantio and diastereo controlled dihydroxylation, asymmetric epoxidation and cross-metathesis.

Experimental section

General methods

Flasks were oven or flame dried and cooled in a desiccator. Dry reactions were carried out under an atmosphere of Ar or N_2. Reagents and chemicals were purchased from Aldrich. All solvents and reagents were purified by standard techniques. THF was freshly distilled over Na-benzophenone ketyl. Crude products were purified by column chromatography on 100–200 silica gel. Light petroleum ether (bp 60–80 °C) was used. Yields refer to chromatographically and spectroscopically (^{1}H, ^{13}C NMR) homogeneous material. Air-sensitive reagents were transferred by syringe or double-ended needle. Evaporation of solvents was performed at reduced pressure on a Buchi rotary evaporator. IR spectra were recorded on Perkin–Elmer 683 spectrometer. Optical rotations were obtained on a Horiba 360 digital polarimeter. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on Brucker, Avance 300, 400, Varian Gemini 500 MHz. Chemical shifts are reported in parts per million with respect to the internal TMS. Mass spectra were recorded on VG micromass-7070H (70 Ev).

1-(3-Butenyloxymethyl)benzene (13)

To a suspension of NaH (6.656 g, 277.354 mmol, 60% w/v dispersion in mineral oil) in anhydrous THF (300 mL) was added drop wise a solution of 3-buten-1-ol **10** (10.000 g, 138.670 mmol) at 0 °C. To this reaction mixture TBAI (0.150 g) and benzyl bromide (18.140 mL, 152.544 mmol) were added and stirring was continued for 2 h at the same temperature and overnight at room temperature. The reaction mixture was quenched by small crushed ice flakes until a clear solution (biphasic) had formed. The reaction mixture was extracted with ether and the extract was washed with water (1 × 100 mL), brine (1 × 100 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvents followed by column chromatography (9.5 : 0.5 hexane : EtOAc) afforded the pure product **13** (27.38 g, 95% yield) as a colourless liquid. IR (KBr): 3033, 2927, 2864, 1454, 1363, 1105, 739 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32–7.20 (m, 5H), 5.86–5.76 (m, 1H), 5.08–5.00 (dd, J = 17.00, 10.01 Hz, 2H), 4.50 (s, 2H), 3.04–2.99 (m, 1H), 2.73 (t, J = 4.86 Hz, 1H), 2.47 (dd, J = 4.86, 2.9 Hz, 1H), 1.91–1.85 (m, 1H), 1.77–1.71 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.37, 135.18, 128.28, 127.57, 127.47, 116.30, 72.82, 69.52, 34.18; GC-MS: 162 [M$^+$]; Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70; found C, 81.40; H, 8.65.

2-(2-(Benzyloxy)ethyl)oxirane (14)

Crude benzyl ether **13** (15.000 g, 92.592 mmol) was dissolved in dry CH_2Cl_2 (300 mL) and the solution was cooled to 0 °C. $NaHCO_3$ was added (23.362 g), followed by m-CPBA (45.333 g, 185.185 mmol, 70% w/w). The solution was stirred for 16 h before being filtered through a pad of celite and concentrated under reduced pressure. The residue was then dissolved in water (100 mL) and extracted with Et_2O (3 × 50 mL). The combined organic extracts were then washed with 3 M NaOH (3 × 50 mL), followed by brine (50 mL), dried over Na_2SO_4 and evaporated. Chromatography on silica gel (4 : 1 hexane : EtOAc), gave **14**, as a colourless oil (15.162 g, 92%). IR (KBr): 3031, 2969, 2916, 2871, 1452, 1368, 1094, 738 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32–7.23 (m, 5H), 4.50 (s, 2H), 3.62–3.56 (m, 2H), 3.14–2.99 (m, 1H), 2.74 (dd, J = 5.84, 4.61 Hz, 1H), 2.47 (dd, J = 5.84, 2.92 Hz, 1H), 1.91–1.85 (m, 1H), 1.77–1.71 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.19, 128.34, 127.57, 126.82, 73.03, 66.97, 50.05, 47.06, 32.88;

GC-MS: 178.10 [M^+]; Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.09; H, 7.88.

(*R*)-2-(2-(Benzyloxy)ethyl)oxirane (15)

A mixture of (*R*,*R*)-(−)-*N*,*N*^{1}-Bis(3,5-di-*tert*-butylsalicyclidene)-1,2-cyclohexanediaminocobalt (II) (0.240 g, 0.391 mmol) toluene and AcOH (0.05 mL, 0.793 mmol) was stirred while open to the air for 1 h at room temperature. The solvent was removed under reduced pressure and the brown residue was dried over high vacuum. The oxirane **14** (14 g, 78. 65 mmol) was added in one portion, the stirred mixture was cooled in an ice water bath. Water (0.780 mL, 43.261 mmol) was slowly added and the temperature of the reaction mixture was maintained in such a way that it never rises more than 20 °C. Addition was complete in 1 h. The ice bath was removed and the reaction mixture was stirred for 36 h at room temperature and purified by column chromatography to afford the (*R*)-epoxide **15** (4 : 1 hexane : EtOAc) as a colourless oil (5.880 g, 42%); $[\alpha]_D^{20}$ = +15.8 (*c* 2.0, $CHCl_3$).

(*S*)-4-(Benzyloxy)butan-2-ol (16)

To a suspension of LAH (2.134 g, 56.179 mmol) in anhydrous THF (50 mL) was added drop wise a solution of (*R*)-epoxide **15** (5.000 g, 28.089 mmol) in THF (30 mL) at 0 °C. The mixture was stirred at room temperature for 1 h and then re-cooled to 0 °C. To the resultant mixture saturated solution of sodium sulfate (6.440 mL) was added and stirred for 3 h and the mixture was filtered through Celite. The filtrate was concentrated *in vacuo* and the residue was chromatographed (eluent: EtOAc : petroleum ether = 4 : 6) to afford secondary alcohol **16** (4.803 g, 95% yield). $[\alpha]_D^{20}$ = −3.1 (*c* 2.1, $CHCl_3$); IR (KBr): 3414, 3032, 2969, 2870, 1452, 1367, 1094, 738 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33–7.20 (m, 5H), 4.49 (s, 2 H), 3.99–3.92 (m, 1H), 3.69–3.63 (m, 1H), 3.62–3.56 (m, 1H), 2.63 (br s, 1H), 1.76–1.64 (m, 2H), 1.16 (d, *J* = 6.39 Hz, 3H); ^{13}C NMR (75.468 MHz, $CDCl_3$): δ 137.80, 128.30, 127.56, 127.51, 73.11, 68.85, 67.19, 37.98, 23.19; GC-MS: 181 [M^+]; Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95; found C, 73.27; H, 8.92.

(*S*)-4-(Benzyloxy)butan-2-yloxy (*tert*-butyl)dimethylsilane (17)

To a solution of secondary alcohol **16** (4.500 g, 25.000 mmol) cooled in ice-bath, imidazole (6.805 g, 100.000 mmol) in anhydrous CH_2Cl_2 (50 mL) was added a solution of TBDMSCl (4.875 g, 32.510 mmol) in anhydrous CH_2Cl_2 (50 mL). The mixture was stirred at room temperature for 2 h, then diluted with water (50 mL) and extracted with ether (3 × 60 mL). The combined organic extracts were washed with brine (50 mL) and dried over anhydrous Na_2SO_4. After filtration and concentration *in vacuo*, and the residue was purified by column chromatography (eluent: EtOAc : petroleum ether = 2 : 8) to give TBS ether **17** (7.203 g) as colourless oil with 98% yield. $[\alpha]_D^{20}$ = +5 (*c* 1.0, $CHCl_3$); IR (KBr): 3033, 2957, 2931, 2858, 1459, 1374, 1254, 1113, 835, 775 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33–7.19 (m, 5H), 4.50–4.39 (m, 2H), 4.05–3.93 (m, 1H,), 3.58–3.42 (m, 2H), 1.72–1.61 (m, 2H), 1.13 (d, *J* = 6.04 Hz, 3H), 0.87 (m, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75.468 MHz, $CDCl_3$): δ 138.60, 128.35, 127.71, 127.51, 73.02, 67.32, 65.62, 39.65, 25.91, 24.17, 18.12, −4.38, −4.83; HRMS for $C_{17}H_{30}O_2Si$+Na calcd 317.1912; found 317.1910.

(*S*)-3-(*tert*-Butyldimethylsilyloxy)butan-1-ol (18)

To a stirred solution of naphthalene powder (6.791 g, 53.060 mmol) in dry THF (100 mL) lithium metal (0.285 g, 40.816 mmol) was added. The mixture was stirred for 3 h at room temperature then cooled to −20 °C and compound **17** (6.000 g, 20.408 mmol) was added and the reaction mixture was stirred for 2 h. After completion of reaction, it was quenched with saturated aqueous NH_4Cl solution and extracted with ethyl acetate (2 × 200 mL). The organic layer was washed with water, followed by brine and dried over Na_2SO_4. Solvent was removed under reduced pressure and purification by silica gel column chromatography (eluent: EtOAc : petroleum ether = 4 : 6) afforded primary alcohol **18** (3.916 g, 94% yield) as a colourless liquid. $[\alpha]_D^{20}$ = +30.4 (*c* 1.0, $CHCl_3$); IR (KBr): 3456, 2923, 2852, 1218, 773 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.14–4.03 (m, 1H), 3.84–3.73 (m, 1H), 3.72–3.62 (m, 1H), 2.38 (br s, 1H), 1.81–1.68 (m, 1H), 1.67–1.54 (m, 1H), 1.19 (d, *J* = 6.04 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75.468 MHz, $CDCl_3$): δ 68.21, 60.33, 40.43, 25.71, 23.35, 17.86, −4.43, −5.03; LC-MSD: 205 [M + H]$^+$; Anal. Calcd for [$C_{10}H_{24}O_2Si$+1]: C, 58.77; H, 11.84; found C, 58.74; H, 11.79.

(*S*)-Ethyl 6-(*tert*-butyldimethylsilyloxy)-4-hydroxyhept-2-ynoate (9)

To a cooled and stirred solution (−78 °C) of oxalyl chloride (2.260 mL, 34.288 mmol) in CH_2Cl_2 (50 mL) was added DMSO (4.890 mL, 68.576 mmol) drop wise under nitrogen atmosphere. After 10 min a solution of alcohol **18** (3.500 g, 17.144 mmol) in CH_2Cl_2 (15 mL) was added in 5 min. The reaction mixture was stirred for another 15 min and Et_3N (14.290 mL, 102.864 mmol) was added at same temperature. After being stirred for 10 min at −78 °C, the cooling bath was removed and water (30 mL) was added at room temperature. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL) and combined organic layers were washed with brine (60 mL), dried over anhydrous Na_2SO_4 and evaporated to furnish the aldehyde **19**, which was used for further reaction without any purification.

To a stirred solution of ethylpropiolate (2.120 mL, 22.280 mmol) in THF (70 mL), was added LiHMDS (45.770 mL, 25.716 mmol, 1 M in toluene) at −78 °C and stirred the solution at same temperature for 45 min. Then the crude aldehyde (19) dissolved in freshly distilled dry THF (50 mL) was added to the reaction mixture slowly over 15 min at same temperature. It was stirred for another 30 min. Reaction mixture was quenched with aqueous saturated NH_4Cl at −78 °C and diluted with water (75 mL). Then it was allowed to warm to room temperature and stirred for 1 h. The two layers were separated and aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic fraction was dried over anhydrous Na_2SO_4 and the solvent was evaporated *in vacuo*. The residue upon column chromatography of the residue over silica gel using

1 : 9 EtOAc : petroleum ether yielded the hydroxy alkynoate **9** (3.871 g, 75%) as a light brownish oil. $[\alpha]_D^{20}$ = +23 (*c* 1.5, $CHCl_3$); IR (KBr): 3420, 2957, 2932, 2858, 2237, 1717, 1368, 1249, 838, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.61 (t, *J* = 6.79 Hz, 1H), 4.22 (q, *J* = 6.79 Hz, 1H), 4.14–4.00 (m, 1H), 2.75 (br s, 1H), 2.02–1.90 (m, 1H), 1.88–1.76 (m, 1H), 1.32 (t, *J* = 6.79 Hz, 3H), 1.22 (d, *J* = 6.04 Hz, 3H), 0.88 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (75.468 MHz, $CDCl_3$): δ 153.37, 87.40, 67.49, 62.05, 61.00, 45.50, 25.74, 24.12, 17.86, 13.95, −4.095, −4.998; HRMS for $C_{15}H_{28}O_4Si$ + Na calcd 323.1654; found 323.1653.

(*S*,2*E*,4*E*)-Ethyl 6-(*tert*-butyldimethylsilyloxy)hepta-2,4-dienoate (8)

To a stirred solution of hydroxy alkynoate **9** (3.200 g, 10.624 mmol) dissolved in dry benzene (75 mL), was added PPh_3 (3.340 g, 12.759 mmol) at room temperature and stirred for 6 h under N_2-atmosphere. Then to the reaction mixture, a little excess MeI (1 mL) was added to remove the unreacted PPh_3 in form of $+PPh_3MeI-$ salt. The salt was removed by simple filtration through a sintered funnel and washed with ether. The combined filtrate was dried over anhydrous Na_2SO_4, solvent was evaporated *in vacuo* and column chromatography over silica gel using (0.5 : 9.5 ethylacetate–petroleum ether) afforded the diene ester **8** (2.143 g, 71%) as a yellowish oil. $[\alpha]_D^{20}$ = +10 (*c* 0.9, $CHCl_3$); IR (KBr): 2957, 2932, 2859, 1723, 1660, 1368, 1258, 835, 778 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.22 (dd, *J* = 15.11, 11.33 Hz, 1H), 6.28 (dd, *J* = 15.11, 11.33 Hz, 1H), 6.07 (dd, *J* = 15.11, 4.53 Hz, 1H), 5.83 (d, *J* = 15.11 Hz, 1H), 4.44–4.33 (m, 1H), 4.17 (q, *J* = 6.79 Hz, 2H), 1.34–1.20 (m, 6H), 0.90 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75.468 MHz, $CDCl_3$): 166.23, 146.12, 131.13, 129.22, 119.08, 69.54, 60.36, 25.76, 21.28, 17.92, 14.13, −4.364, −4.600; LC-MSD: 308.0 $[M + Na]^+$; Anal. Calcd for $C_{15}H_{28}O_3Si$+Na: C, 63.33; H, 9.92; found C, 63.30; H, 9.90.

(4*S*,5*R*,6*S*,*E*)-Ethyl-6-(*tert*-butyldimethylsilyloxy)-4,5-dihydroxyhept-2-enoate (20)

To a 1 : 1 mixture of ^{t}BuOH (45 mL) and water (45 mL), was added AD-mix-α (9.840 g, 1.400 g of AD-mix-α per mmol of olefin) and methane sulphonamide (0.668 g, 7.010 mmol). The mixture was stirred for 10–15 min to get clear solution. The reaction bath was cooled to 0 °C and then diene ester **8** (2.000 g, 7.030 mmol) dissolved in minimum volume of ^{t}BuOH (5 mL) was added. The reaction mixture was stirred for 3 days at 0 °C (at night, the reaction mixture was kept in freeze). Then the reaction mixture was quenched with solid sodium sulphite (Na_2SO_3) (15.000 g) at room temperature and stirred for another 30 min. The reaction mixture was diluted with EtOAc and two layers were separated. The aqueous layer was extracted with EtOAc (3 × 75 mL). The combined organic fraction was dried over anhydrous Na_2SO_4 and the solvent was evaporated *in vacuo*. The residue upon column chromatography over silica gel using 2 : 8 EtOAc–petroleum ether as eluent yielded the diol ester **20** (2.001 g, 90%) as a light yellowish oil. $[\alpha]_D^{20}$ = +8.1 (*c* 1.2, $CHCl_3$); IR (KBr): 3480, 2951, 2933, 2859, 1462, 1373, 1254, 1086, 834, 776 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.96 (dd, *J* = 15.86, 4.54 Hz, 1H), 6.12 (d, *J* = 15.86, 1H), 4.50–4.44 (m, 1H), 4.18 (q, *J* = 6.79 Hz, 2H), 3.91–3.89 (m, 1H), 3.62–3.53 (m, 1H), 1.30 (t, *J* = 6.80 Hz, 3H), 1.22 (d, *J* = 6.04 Hz, 3H), 0.91 (s, 9H), 0.089 (s, 3H), 0.085 (s, 3H); ^{13}C NMR (75.468 MHz, $CDCl_3$): δ 166.25, 146.16, 121.25, 84.66, 71.61, 69.61, 60.42, 25.83, 21.35, 17.98, 14.19, −4.311, −4.539; HRMS for $C_{15}H_{30}O_5Si$ + Na calcd 341.1864; found 341.1861.

(E)-Ethyl 3-((4*S*,5*R*)-5-((*S*)-1-(*tert*-butyldimethylsilyloxy)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (21)

To the stirred solution of diol **20** (1.800 g, 5.687 mmol) in dry CH_2Cl_2 (50 mL), was added 2,2-DMP (1.742 mL, 14.219 mmol) and CSA (cat.) at 0 °C under N_2-atmosphere and stirred for 1 h at room temperature. After completion of reaction, the reaction mixture was quenched by addition of aqueous saturated $NaHCO_3$ solution at room temperature. The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined CH_2Cl_2 layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated *in vacuo*. The residue upon silica gel chromatography using 1 : 9 EtOAc–petroleum ether yielded the acetonide **21** (1.873 g, 92%) as a light yellow oily liquid. $[\alpha]_D^{20}$ = −3 (*c* 0.66, $CHCl_3$); IR (KBr): 2985, 2935, 2861, 1726, 1661, 1373, 1256, 1163, 1101, 1070, 835, 778 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.95 (dd, *J* = 15.86, 4.53 Hz, 1H), 6.08 (d, *J* = 15.86, 1H), 4.53–4.85 (m, 1H), 4.17 (q, *J* = 6.79 Hz, 2H), 3.93–3.83 (m, 1H), 3.64–3.52 (m, 1H), 1.40 (s, 3H), 1.37 (s, 3H), 1.30 (t, *J* = 6.79 Hz, 3H), 1.22 (d, *J* = 6.04 Hz, 3H), 0.91 (s, 9H), 0.09 (s, 3H), 0.086 (s, 3H); ^{13}C NMR (75.468 MHz, $CDCl_3$): δ 166.23, 146.12, 121.22, 109.59, 84.60, 77.55, 69.556, 60.36, 27.00, 26.56, 25.76, 21.29, 17.92, 14.13, −4.364, −4.600; HRMS for $C_{18}H_{34}O_5Si$ + Na calcd 381.2073; found 381.2089.

(*E*)-3-((4*S*,5*R*)-5-((*S*)-1-(*tert*-Butyldimethylsilyloxy)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)prop-2-en-1-ol (22)

To a stirred solution of acetonide protected (*E*)-α,β,-unsaturated ester **21** (1.50 g, 4.189 mmol) dissolved in CH_2Cl_2 (30 mL), was added DIBAL-H (1 M solution in hexane, 10.491 mL, 10.475 mmol) at –30 °C under N_2 atmosphere. Then the reaction mixture was stirred for 1 h at the same temperature. The reaction mixture was quenched with saturated aqueous sodium potassium tartrate (40 mL) at 0 °C and stirred for 6 h at room temperature. Then the two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. Crude product was purified through silica gel chromatography (3 : 7 EtOAc–petroleum ether) to afford allyl alcohol **22** (1.192 g, 90%) as an on oily liquid. $[\alpha]_D^{20}$ = +6 (*c* 1.0, $CHCl_3$); IR (KBr): 3423, 2929, 2857, 1462, 1372, 1251, 1083, 831, 774 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.95 (tt, *J* = 16.02, 5.01 Hz, 1H), 5.76 (dd, *J* = 16.02, 7.01 Hz, 1H), 4.38 (t, *J* = 7.01 Hz, 1H), 4.14 (d, *J* = 5.01 Hz, 2H), 3.92–3.87 (m, 1H), 3.54 (dd, *J* = 7.01, 6.01 Hz, 1H), 1.383 (s, 3H), 1.376 (s, 3H), 1.18 (d, *J* = 7.01 Hz, 3H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (75.468 MHz, $CDCl_3$): δ 132.65, 129.80,

108.78, 84.92, 78.08, 68.86, 62.83, 27.05, 25.82, 20.94, 18.04, −4.403, −4.512; HRMS for $C_{16}H_{32}O_4Si$+Na calcd 339.1967; found 339.1960.

((2*S*,3*R*)-3-((4*S*,5*R*)-5-((*S*)-1-(*tert*-Butyldimethylsilyloxy)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)oxiran-2-yl)methanol (23)

In a two neck round-bottomed flask, was weighed 3 g of 4 A° molecular sieves (dry powder) under N_2 atmosphere and dry CH_2Cl_2 (10 mL) was added and the mixture was then cooled to –23 °C. To this cold suspension, was added $Ti(O^iPr)_4$ (0.190 g, 0.630 mmol) followed by D-(+)-diethyl tartrate (0.141 g, 0.790 mmol) and the mixture was stirred vigorously at –23 °C for 45 min. Then allyl alcohol **22** (1.000 g, 3.162 mmol) dissolved in CH_2Cl_2 (15 mL) was added slowly at –23 °C, stirred for 30 min and *tert*-butyl hydroperoxide (2 mL, 5.20 mmol) was added to the reaction mixture being maintained at the same temperature and stirred for 24 h. After completion of the reaction, the reaction mixture was filtered through a celite pad, washed with CH_2Cl_2 (3 × 20 mL). The filtrate was quenched by addition of water (2 mL), 10% NaOH solution (0.66 mL), stirred for 1 h at −5 °C. The filtrate was dried over anhydrous Na_2SO_4 and concentrated to give crude epoxy alcohol, which was purified through silica gel chromatography (2 : 8 EtOAc–petroleum ether) to afford epoxy alcohol **23** (0.920 g, 88%) as a white solid. $[\alpha]_D^{20}$ = +20 (*c* 1.2, $CHCl_3$); IR (KBr): 3413, 3031, 2870, 1452, 1367, 1094, 738 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.47–4.42 (dd, *J* = 7.55, 6.79 Hz, 1H), 4.36–4.47 (dd, *J* = 8.31, 6.04 Hz, 1H), 4.00–3.60 (m, 3H), 3.21–3.01 (m, 2H), 1.41 (br s, 1H), 1.37 (s, 6H), 1.34 (d, *J* = 6.79 Hz, 3H), 0.90 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75.468 MHz, $CDCl_3$): δ 120.74, 88.85, 88.37, 71.96, 69.60, 60.97, 55. 71, 29.68, 27.08, 26.66, 25.80, 20.94, 14.11, −4.418, −4.578; LC-MSD: 333.0 $[M + H]^+$; Anal. Calcd for $C_{16}H_{32}O_5Si$: C, 57.79; H, 9.70; found C, 57.75; H, 9.68.

(*R*)-1-((4*S*,5*R*)-5-((*S*)-1-(*tert*-Butyldimethylsilyloxy)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)prop-2-en-1-ol (6)

To an ice-bath cooled solution of epoxy alcohol **23** (0.700 g, 2.108 mmol), TPP (0.580 g, 2.213 mmol), I_2 (0.273 g, 2.150 mmol), imidazole (0.286 g, 4.220 mmol) in anhydrous CH_2Cl_2 (15 mL) was added. The reaction mixture was stirred at 0 °C later kept under reflux for 1 h, then diluted with water (20 mL) and extracted with ether (3 × 8 mL). The combined organic phases were washed with brine (20 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (eluent : EtOAc : petroleum ether = 4 : 6) to give TBS ether **24** as colourless oil.

To a stirred suspension of iodide derivative **24** in dry THF (5 mL) kept at −78 °C, ^{t}BuLi in hexane (2.2 equ) was added drop wise under N_2 atmosphere. After 15 min the reaction mixture was quenched with saturated NH_4Cl solution (5 mL) and extracted with diethyl ether (2 × 10 mL). The combined organic extracts were washed with brine (2 × 10 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue on purification by column chromatography (ethyl acetate–hexane, 2 : 8) afforded pure **6** (0.601 g, 96%) as a pale yellow liquid. $[\alpha]_D^{20}$ = +7 (*c* 1.0, $CHCl_3$); IR (KBr): 3467, 3032, 2926, 2864, 1454, 1363, 1105, 739 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.94 (dddd, *J* = 17.20, 10.39, 5.66, Hz, 1 H), 5.34 (dd, *J* = 7.37, 1.51 Hz, 1 H), 5.10 (dd, *J* = 10.39, 1.51 Hz, 1 H), 4.05 (dd, *J* = 5.66, 5.47 Hz, 1 H), 3.82–3.58 (m, 3H), 2.7 (br s, 1H), 1.37 (s, 3H), 1.35 (s, 3H), 1.27 (d, *J* = 6.04, 3H), 0.91 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (75.468 MHz, $CDCl_3$): δ 137.40, 114.30, 109.65, 84.42, 76.06, 71.96, 65.27, 26.66, 25.80, 20.84, 18.51, −4.42, −4.576; HRMS for $C_{16}H_{32}O_4Si$ + Na calcd 339.6221; found 339. 6197.

2-((4-Methoxybenzyloxy)methyl)oxirane (25)

A solution of glycidol **12** (5.000 g, 54.036 mmol) in DMF (20 mL) was added to a stirred suspension of sodium hydride (3.242 g, 60% dispersion in oil, 81.054 mmol) in DMF (50 mL) at −20 °C. The resulting mixture was stirred until effervescence ceased and then 4-methoxybenzyl chloride (9.386 mL, 75.651 mmol) and $^nBu_4NI$ (20 mg, cat.) were added. The mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with water and ether. The layers were separated and the aqueous phase extracted three times with Et_2O. The combined organic extracts were washed twice with cold water, once with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography, eluting with hexane–ethyl acetate (5 : 1) to provide PMB-ether **25** (9.644 g, 92%) as a clear, colourless oil. IR (KBr) 2999, 2838, 1514, 1249 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.50 Hz, 2H), 6.84 (d, *J* = 8.50 Hz, 2H), 4.54–4.44 (m, 2H), 3.80 (s, 3H), 3.66 (dd, *J* = 11.33, 3.21 Hz, 1H), 3.39 (dd, *J* = 11.33, 5.67 Hz, 1H), 3.15–3.07 (m, 1H), 2.75 (dd, *J* = 5.10, 4.15 Hz, 1H), 2.56 (dd, *J* = 5.10, 2.64 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.31, 129.92, 129.40, 113.83, 72.90, 70.54, 50.80, 55.22, 44.31; HRMS for $C_{11}H_{14}O_3$ calcd 194.0943, found 194.0944.

(*R*)-2-((4-Methoxybenzyloxy)methyl)oxirane (26)

A mixture of (*S,S*)-(–)-*N,N*^{1}-Bis(3,5-di-*tert*-butylsalicyclidene)-1,2-cyclohexanediaminocobalt (II) (0.140 g, 0.232 mmol) toluene (1mL) and AcOH (0.027 mL, 0.464 mmol) was stirred while open to the air for 1 h at room temperature. The solvent was removed under reduced pressure and the brown residue was dried over high vacuum. The (glycidol PMB-ether (±)**25** (9.000 g, 46.391 mmol) was added in one portion, the stirred mixture was cooled in an ice water bath. Water (0.459 mL, 25.515 mmol) was slowly added and the temperature of the reaction mixture was maintained in such a way that it never rises more than 20 °C. After 1 h addition was complete. The ice bath was removed and the reaction mixture was stirred for 36 h. the crude reaction mixture was purified by silica gel column chromatography to afford the (*R*)-glycidol PMB–ether **26** (4 : 1 hexanes : EtOAc) as a colourless oil (3.781 g, 42%); other characterization data were identical to those reported for the compound. $[\alpha]_{20}^{D}$ = +4.2 (*c* 0.95, $CHCl_3$).

(*R*)-Ethyl 5-hydroxy-6-(4-methoxybenzyloxy)hex-2-ynoate (27)

To a −90 °C solution of ethyl propiolate (3.779 mL, 37.209 mmol) in THF (mL) was added dropwise *n*-BuLi (14.910 mL of a 2.5 M solution in hexanes, 37.198 mmol). After 20 min, $BF_3{\cdot}Et_2O$ (4.720 mL, 37.198 mmol) was added, the mixture was brought to −78 °C, and stirred for 10 min. Subsequently, a solution of (*R*)-glycidol PMB-ether **26** (2.410 g, 12.422 mmol) in THF (10 mL) was added dropwise, the resulting solution allowed to reach to 0 °C, and stirred for 30 min. After addition of saturated NH_4Cl solution, the organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed (brine), dried (Na_2SO_4), and concentrated *in vacuo*. The residue thus obtained was purified by silica gel column chromatography (hexanes : EtOAc, 2 : 1 to 1 : 1) to give 3.589 g (99%) of ester **27** as a colourless oil. $[\alpha]_{20}^{D}$ = +15.8 (*c* 1.05, $CHCl_3$); IR (KBr) 3421, 2956, 2931, 2858, 2237, 1717, 1464, 1368, 1250, 1143, 1074, 837, 776 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.31 Hz, 2H), 6.84 (d, *J* = 8.31 Hz, 2H), 4.49 (s, 2H), 4.20 (q, *J* = 6.80 Hz, 2H), 4.02–4.00 (m, 1H), 3.81 (s, 3H), 3.59–3.40 (m, 2H), 2.57 (dd, *J* = 6.043, 2.26 Hz, 1H), 2.37 (br s, 1H), 1.32 (t, *J* = 6.80, Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 153.5, 129.7, 129.4, 113.9, 85.0, 74.8, 73.1, 72.2, 68.3, 61.9, 55.2, 23.7, 14.0; MS (ESI) calcd for $C_{16}H_{20}NaO_5$ $[M + Na]^+$: 315.1.

(*R,Z*)-Ethyl 5-hydroxy-6-(4-methoxybenzyloxy)hex-2-enoate (11)

Quinoline (10 μL) and Pd–$CaCO_3$ poisoned with lead (Lindlar's catalyst, 5 wt%, 1 g) were added to a solution of **27** (2.00 g, 6.849 mmol) in AcOEt (20 mL). The mixture was shaken under hydrogen (1–2 atm) until TLC showed complete conversion. The suspension was filtered through a short pad of Celite. The organic layer was washed with 2 N HCl (2 × 10 mL) and brine, dried over $MgSO_4$, and evaporated under reduced pressure. Purification by chromatography with silica gel (hexane/AcOEt 9 : 1) gave **11** as colourless oil (1.853 g, 92%). $[\alpha]_{20}^{D}$ = +56.0 (*c* 1.0, $CHCl_3$); IR (KBr) 3319, 3032, 2957, 2931, 2858, 1725, 1458, 1374, 1254, 1112, 836, 776 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.20 (d, *J* = 8.31 Hz, 2H), 6.83 (d, *J* = 8.31 Hz, 2H), 6.42–6.31 (m, 1H), 5.85 (d, *J* = 12.09 Hz, 1H), 4.49 (s, 2H), 4.46 (s, 2H), 4.15 (q, *J* = 7.55 Hz, 2H), 3.93–3.83 (m, 1H), 3.80 (s, 3H), 3.51–3.30 (m, 2H), 2.90–2.61 (m, 2H), 1.57 (br s, 1H), 1.29 (t, *J* = 7.55 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.87, 159.72, 144.29, 129.84, 129.64, 122.44, 114.87, 78.52, 73.29, 72.32, 55.87, 31.87, 14.29.

(*R*)-6-((4-Methoxybenzyloxy)methyl)-5,6-dihydropyran-2-one (28)

To a stirred solution of compound **11** (1.850 g, 6.292 mmol) in benzene was added a catalytic amount of *p*-TSA under an N_2 atmosphere. After stirring for 3 h at room temperature, the reaction mixture was quenched with solid $NaHCO_3$ and filtered off, the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography to afford compound **28** as a yellow liquid (1.357 g, 87%). $[\alpha]_{D}^{20}$ = +70.3 (*c* 0.6, $CHCl_3$); IR (KBr) 3454, 2928, 1747, 1257, 1095, 831 cm^{-1}; ^1H NMR (300 MHz, CDCl3): δ 7.26 (d, *J* = 8.5 Hz, 1H), 6.88 (d, *J* = 8.5 Hz, 1H), 6.32–6.09 (m, 1H), 5.59 (d, *J* = 12.16 Hz, 1H), 4.54–4.49 (m, 3H), 3.73 (s, 3H), 3.71 (dd, *J* = 12.27 Hz, 1H), 3.65 (m, H), 2.77–2.60 (m, 1H), 2.39–2.32 (m, 1H), ^{13}C NMR (75.468 MHz, $CDCl_3$): 163.86, 159.73, 144.53, 129.88, 129.86, 122.48, 114.85, 88.52, 74.29, 72.92, 55.84, 28.27; MS-EIMS: *m/z* 249 $[M + H]^+$.

(*R*)-6-(Hydroxymethyl)-5,6-dihydropyran-2-one (29)

DDQ (1.794 g, 7.903 mmol) was added to a stirred mixture of **28** (1.400 g, 5.645 mmol) in CH_2Cl_2 (15 mL) and H_2O (3 mL) at room temperature. After 3 h the reaction was quenched slowly with saturated $NaHCO_3$ (20 mL) followed by of H_2O (40 mL) and then extracted with CH_2Cl_2 (5 × 20 mL). The combined organic layers were washed with saturated $NaHCO_3$, water, brine, dried (Na_2SO_4), and then concentrated to an yellow oil that was purified by column chromatography (2 : 8 ethyl AcOEt–pentane) to provide **29** a colourless oil (0.593 g 82%). $[\alpha]_{D}^{20}$ = 120.4 (*c* 0.4, $CHCl_3$); IR (KBr) 3400, 2929, 1713, 1260, 1039, 816 cm^{-1}; ^1H NMR (300 MHz, CDCl3): δ 6.97–6.91 (m, 1H), 5.98 (dd, *J* = 2.26, 9.82 Hz, 1H), 4.57–4.47 (m, 1H), 3.87 (m, *J* = 12.27 Hz, 1H), 3.71 (dd, *J* = 12.27 Hz, 1H), 3.48 (br s, 1H), 2.66–2.54 (m, 1H), 2.38–2.28 (m, 1H), ^{13}C NMR (75.468 MHz, $CDCl_3$): 164.14, 145.57, 120.71, 78.41, 63.55, 25.17; MS-EIMS: *m/z* 129 $[M + H]^+$.

(*R*)-6-Vinyl-5,6-dihydropyran-2-one (7)

To a stirred solution of compound **29** (0.400 g, 3.120 mmol) in CH_2Cl_2 (10 mL), Dess–Martin periodinate (1.456 g, 3.420 mmol) was added at 0 °C for 1 h. After completion of the reaction, the reaction mixture was quenched with saturated sodium thiosulfate solution (10 mL) and saturated aqueous sodium bicarbonate solution (10 mL). The reaction mixture was extracted with dichloromethane (5–7 mL), dried over anhydrous Na_2SO_4 and concentrated at 30 °C *in vacuo* to afford the aldehyde. This was used directly in the next step without further purification.

To a stirred suspension of triphenyl phosphonium methyl iodide (1.356 g, 3.359 mmol) in dry THF (5 mL) at −78 °C, *n*-BuLi in hexane (1.6 M, 1.96 mL, 3.14 mmol) was added dropwise under N_2 atmosphere and was allowed to reach room temperature. After 45 min the reaction mixture was again cooled to −78 °C and the aldehyde obtained above, dissolved in dry THF (5 mL) was added drop wise and stirred for another 45 min. The reaction mixture was quenched with saturated NH_4Cl solution (7 mL) at 0 °C and extracted with diethyl ether (2 × 15 mL). The combined organic extracts were washed with brine (2 × 15 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue on purification by column chromatography (ethyl acetate–hexane, 2 : 8) afforded pure (*R*)-5,6-dihydro-6-vinyl-pyran-2-one **7** (0.210 g, 70%) as a pale yellow liquid. $[\alpha]_{D}^{20}$ = +90.4 (*c* 0.7, $CHCl_3$); IR (KBr): 1723, 1660, 1467, 1368, 1259, 1157 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 6.84 (1H, m), 6.05–5.86 (2H, m), 5.40 (1H, dd, *J* = 12.0, 2.0 Hz), 5.29 (1H, dd, *J* = 7.0, 2.0 Hz), 4.90 (1H, m), 2.51–2.38 (2H, m); ^{13}C NMR (50 MHz): δ 163.88, 144.53, 134.72, 121.48, 117.83,

77.79, 29.26; ESIMS: *m/z* 125 $[M + H]^+$; Anal. Calcd for $C_7H_8O_2$: C, 67.74; H, 6.45. Found: C, 67.65; H, 6.52.

(*R*)-6-((*R*,*E*)-3-((4*S*,5*R*)-5-((*S*)-1-(*tert*-Butyldimethylsilyloxy) ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxyprop-1-enyl)-5,6-dihydro-2*H*-pyran-2-one (30)

A flame-dried round-bottomed flask was charged with alkene **6** (0.072 g, 0.230 mmol) and vinyl lactone **7** (0.057 g, 0.460 mmol) in CH_2Cl_2 (30 mL) and was added Grubb's catalyst (2nd generation, 0.19 g, 0.230 mmol) as a solid. The reaction mixture was refluxed for 5 h to complete the reaction (by TLC) and brought it to room temperature. The mixture was concentrated *in vacuo* and the residue, was purified by silica gel chromatography using petroleum ether–EtOAc (9 : 1) to give **30** (0.081 g, 86% yield). $[\alpha]_D^{20}$ = + 10.1 (*c* 0.4, $CHCl_3$); IR (KBr) 2925, 1739, 1374, 1023, 974 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.87 (dt, *J* = 8.6, 3.8 Hz, 1H), 6.04 (d, *J* = 9.8 Hz, 1H), 5.87 (d, *J* = 15.5 Hz, 1H), 5.83 (d, *J* = 15.3 Hz, 1H), 4.95 (brs, 1H), 4.20 (brd, *J* = 2.3 Hz, 1H), 3.98 (dd, *J* = 6.3, 3.0 Hz, 1H), 3.86 (t, *J* = 6.8 Hz, 1H), 3.79 (dq, *J* = 12.2, 6.0 Hz, 1H), 2.54–2.34 (m, 2H), 1.41 (s, 3H), 1.36 (s, 3H), 1.21 (d, *J* = 5.9 Hz, 3H), 0.87 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.76, 144.55, 131.42, 130.76, 121.63, 109.55, 81.61, 80.70, 77.06, 75.16, 70.53, 29.64, 27.66, 27.11, 25.86, 21.33, 17.98, −4.25, −4.39; HRMS for $C_{21}H_{36}O_6Si$+Na: calcd 435.2179; found: 435.2174.

Synthesis of (+)-anamarine (1)

To a stirred solution of **30** (0.016 g, 0.040 mmol) in a mixture of MeOH–water (9 : 1, 2 mL) was added *p*-PTS (0.005 g, 0.020 mmol) at room temperature, and the reaction mixture was refluxed for 12 h. After completion of the reaction (TLC), $NaHCO_3$ (0.150 g) was added and the mixture was stirred for 5 min. It was filtered through a short pad of Celite and was washed with $CHCl_3$ (15 mL). The residue obtained after evaporation of the solvent was purified by a short-path silica gel column chromatography using EtOAc–MeOH (4 : 1) as eluent to furnish the tetrol, which was used as such in the next step without characterization.

To a precooled (0 °C) solution of the tetrol obtained above in CH_2Cl_2 (1 mL) were added DMAP (0.001 g, 0.007 mmol) and Et_3N (0.055 mL, 0.400 mmol) followed by Ac_2O (0.032 mL, 0.033 mmol) under argon atmosphere. The reaction mixture was stirred at room temperature for 1 h. After completion of the reaction (TLC), it was poured into cold water and extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (5 mL) and dried over Na_2SO_4. Evaporation of solvent followed by column chromatography of the resultant residue using petroleum ether–EtOAc (1 : 1) as eluent furnished (+)-anamarine **1** (0.010 g) in 80% yield as a white solid: mp = 107–109 °C; $[\alpha]_D^{20}$ = + 17.1 (*c* 0.3, $CHCl_3$); lit.[1] for natural anamarine, mp 110–112 °C; $[\alpha]_D$ = +14.5 (*c* 0.06; $CHCl_3$); lit.[1] for natural anamarine, $[\alpha]_D$ = + 28.2 (*c* 0.52; $CHCl_3$), value later revised to + 18.8; lit.[8] for synthetic (+)-anamarine, $[\alpha]_D$ = +15.9 (*c* 0.8; $CHCl_3$); IR (KBr) 2925, 1739, 1374, 1023, 974 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.88 (ddd, *J* = 3.5, 5.2, 9.9 Hz, 1H), 6.05 (ddd, *J* = 1.7, 1.7, 9.9 Hz, 1H), 5.88–5.74 (m, 2H), 5.36 (dd, *J* = 5.2, 7.2 Hz, 1H), 5.30 (dd, *J* = 3.5, 7.2 Hz, 1H), 5.17 (dd, *J* = 3.5, 7.0 Hz,1H), 4.96 (m, 1H) 4.90 (dq, *J* = 6.4, 6.4 Hz, 1H), 2.45 (m, 2H), 2.11 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 1.17 (d, *J* = 6.4 Hz, 3H, CH_3). ^{13}C NMR (75.468 MHz, $CDCl_3$): δ 170.03, 169.87, 169.72, 169.50, 163.57, 144.51, 133.07, 125.53, 121.64, 75.95, 71.91, 71.51, 70.40, 67.50, 29.46, 21.05, 20.90, 20.84, 20.50, 15.89; HRMS for $C_{20}H_{26}O_{10}$+Na: calcd 449.1423; found: 449.1434.

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