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Highly stereoselective synthesis of antitumor agents: both enantiomers of goniothales diol, altholactone, and isoaltholactone☆

Jhillu Singh Yadav,* Atcha Krishnam Raju, Ponugoti Purushothama Rao and Gurram Rajaiah

Organic Chemistry Division I, Indian Institute of Chemical Technology, Hyderabad 500 007, India

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Abstract—A flexible stereoselective route to synthesize both enantiomers of the highly functionalized substituted tetrahydrofurans and α,β-unsaturated-δ-lactones, goniothales diol, altholactone, and isoaltholactone, from readily available cinnamyl alcohol is described. This approach derived its asymmetry from Sharpless catalytic asymmetric epoxidation and Sharpless asymmetric dihydroxylation reactions. The resulting diols were produced in high enantiomeric excess and were cyclized in a stereoselective manner in the presence of a catalytic amount of camphor sulfonic acid.

1. Introduction

Goniothales diol **1a**, a substituted tetrahydrofuran, can be isolated from the bark of the Malaysian tree *Goniothalamus borneensis* (Annonaceae),[1] and has been shown to have significant cytotoxicity against P388 mouse leukaemia cells, as well as insecticidal activities.[1] Altholactone **2a** and isoaltholactone **3a**, furanopyrones of the styryllactone family, were isolated from an unknown *Polythea* (Annonacae) species,[2] and from various *Goniothalamous*.[3] This family of compounds share a common 5-oxygenated-5,6-dihydro-2*H*-pyran-2-one structural motif. Other members of this family include 5-acetoxygoniothalamin, goniodiol, etc.[4] These natural products possess anti-tumor,[5] anti-fungal,[6] and anti-bacterial properties.[6]

Due to the wide distribution of this class of natural products in nature, many synthetic methodologies have been employed to synthesize them.[7–14] Most syntheses use chiral pool starting materials such as sugars, hydroxy acids, and involve 11–16 steps.

Over the course of our program directed towards the synthesis of antitumor agents,[15] we herein report in detail our synthetic endeavours towards the construction of (+)-goniothales diol **1a**, its enantiomer (−)-goniothales diol **1b**, (+)-altholactone **2a**, its enantiomer (−)-altholactone **2b**, and (+)-isoaltholactone **3a** and its enantiomer (−)-isoaltholactone **3b** employing Sharpless catalytic asymmetric epoxidation and Sharpless asymmetric dihydroxylation reactions starting from the inexpensive and readily available cinnamyl alcohol. Our approach is illustrated retrosynthetically in Scheme 1.

2. Results and discussion

2.1. Synthesis of (+)-altholactone 2a, (−)-altholactone 2b, (+)-isoaltholactone 3a, and (−)-isoaltholactone 3b

The synthesis began with the Sharpless asymmetric epoxidation[16] of cinnamyl alcohol **7** to afford **6a** and **6b** in 82% and 83% yields, respectively. Oxidation of alcohols **6a** and **6b** using the Swern protocol[17] afforded both aldehydes, which without purification were subjected to Wittig olefination[18] with the stable ylide (ethoxycarbonylmethylene)triphenylphosphorane to afford epoxy esters **8a** and **8b**, respectively, in 87% and 88% yields (Schemes 2 and 3).

α,β-Unsaturated epoxy ester **8a** was subjected to a Sharpless asymmetric dihydroxylation reaction using AD-mix-α, to yield **5a** and **5b** in a ratio of 20:1[19] (78% yield) while treatment with AD-mix-β afforded **5a** and

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* Corresponding author. Tel.: +91 40 27193030; fax: +91 40 27160512; e-mail: yadavpub@iict.res.in

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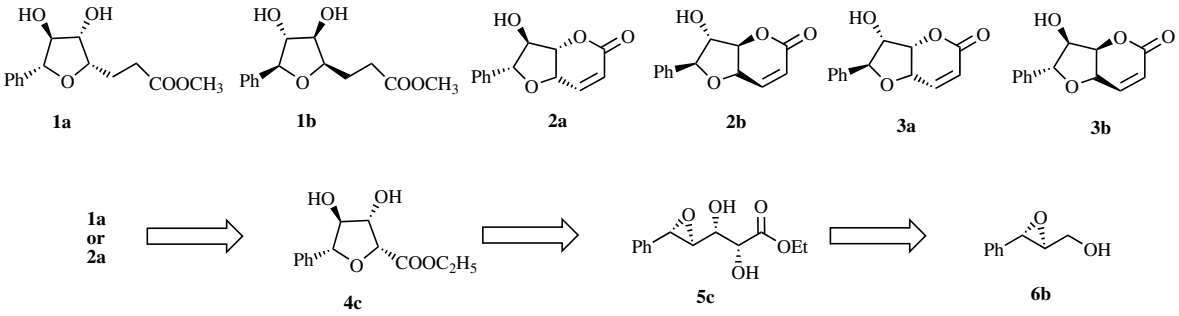
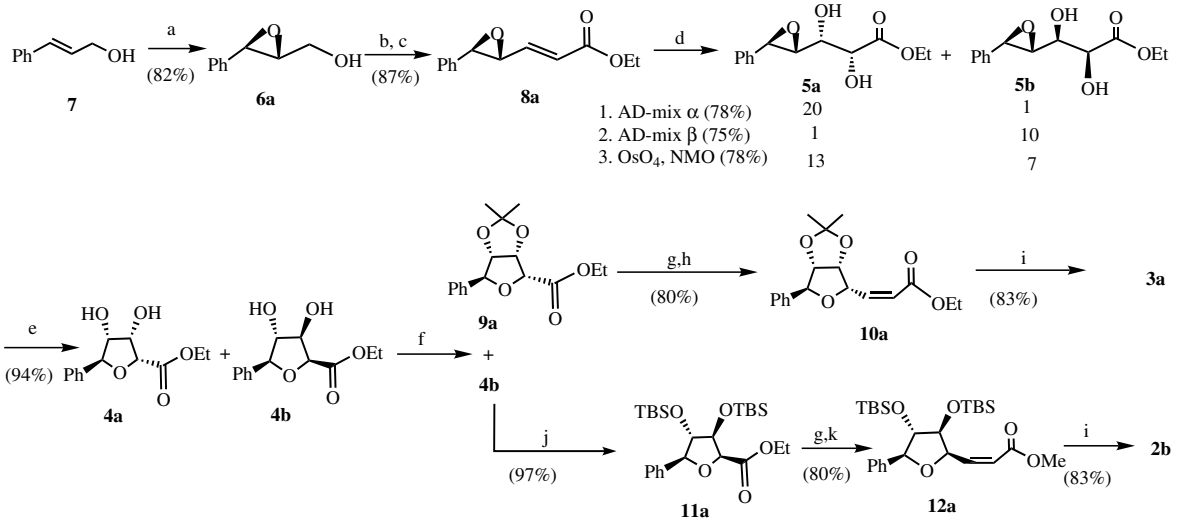


Scheme 1.



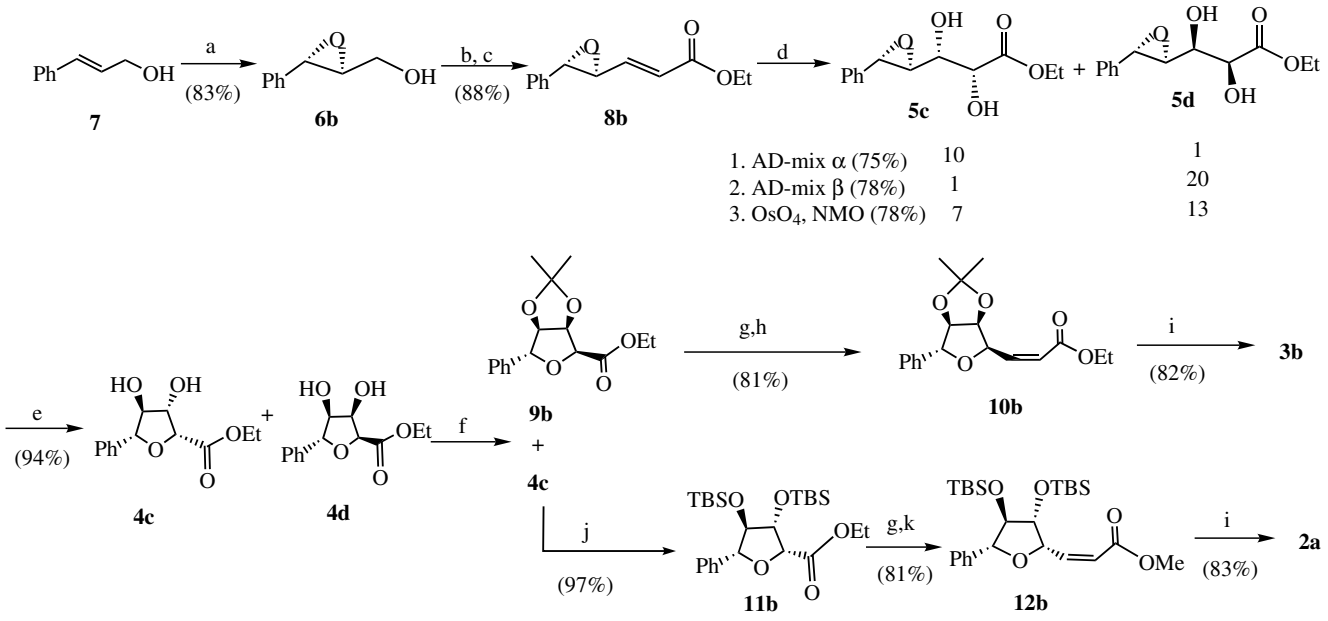
Scheme 2. Reagents and conditions: (a) (−)-DET, $Ti(O^iPr)_4$, TBHP, CH_2Cl_2, −33 °C; (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C; (c) $Ph_3P{=}CH{-}CO_2Et$, benzene, rt; (d) see Scheme 2; (e) CSA, CH_2Cl_2, rt; (f) 2,2-DMP, *p*-TSA, acetone, rt; (g) DIBAL-H, CH_2Cl_2, −78 °C; (h) $Ph_3P{=}CH{-}CO_2Et$, CH_3OH, rt; (i) *p*-TSA, CH_3OH, rt; then benzene, sonication 20–30 min; (j) TBS–Cl, imidazole, DMAP, CH_2Cl_2, 0 °C to rt; (k) $Ph_3P{=}CH{-}CO_2Me$, CH_3OH, rt.

5b in a ratio of 1:10[19] (75% yield), whilst treatment with OsO_4, NMO afforded **5a** and **5b** in a 13:7 ratio (78% yield). The separation of these two isomeric diols **5a** and **5b** was not feasible through simple column chromatography because of their close R_f values. It was therefore decided to purify the mixture in the subsequent steps. The mixture of **5a** and **5b** was subjected to treatment with a catalytic amount of CSA to afford **4a** and **4b** (94% yield) by cyclization. Subsequent treatment of this mixture with 2,2-DMP afforded acetonide **9a** and unreacted **4b**, which were readily separated by column chromatography.

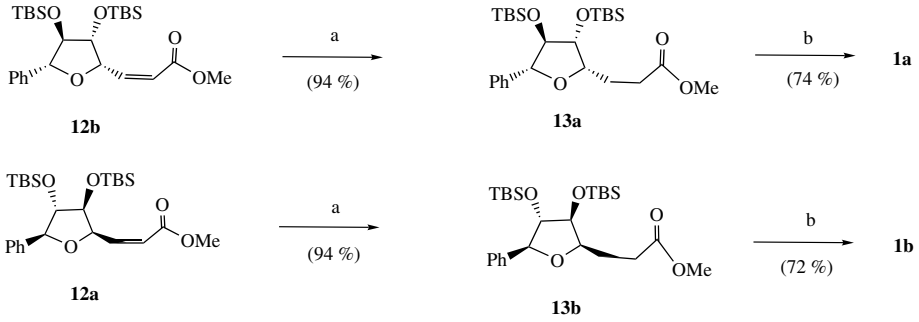
Ester **9a** was reduced to the aldehyde, which was subjected to a Wittig olefination with the stable ylide (ethoxy-carbonylmethylene)triphenylphosphorane in methanol as the solvent to yield *cis*-ester **10a** (80% yield, two steps) predominantly (*cis*:*trans* 95:5).[20] The *trans*-diol **4b** was protected with TBSCl to yield **11a** in 97% yield. As with **9a**, **11a** was also reduced with DIBALH to afford an aldehyde, which was transformed into the *cis*-ester **12a** (82% yield, two steps) using (methoxy-carbonylmethylene)triphenylphosphorane. Compounds **10a** and **12a** on treatment with a catalytic amount of *p*-TSA in methanol afforded a mixture of diol esters and lactones **3a** and **2b**. Removal of methanol by concentration under reduced pressure and sonication after diluting the residue with benzene afforded lactones **3a** and **2b**, respectively (in 83% and 83% yields) (Scheme 2). Epoxy ester **8b** was transformed in a similar fashion to afford **2a** and **3b**, as illustrated in Scheme 3.

2.2. Synthesis of (+)-goniothales diol 1a and (−)-goniothales diol 1b

Hydrogenation of esters **12b** and **12a** was performed employing Pd (black) in 4.4% HCOOH–MeOH,[13] to afford esters **13a** and **13b**, respectively (both in 94% yields). The TBS groups of esters **13a** and **13b** were cleanly deprotected using TBAF in dry THF to give a mixture of lactones and diols **1a** and **1b**, respectively. Removal of THF under reduced pressure and repeated treatment with Amberlyst 15 in methanol provided diols **1a** and **1b** in 74% and 72% yields, respectively (Scheme 4).



Scheme 3. Reagents and conditions: (a) (+)-DET, $Ti(O^iPr)_4$, TBHP, CH_2Cl_2, −33 °C; (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C; (c) $Ph_3P{=}CH{-}CO_2Et$, benzene, rt; (d) see Scheme 3; (e) CSA, CH_2Cl_2, rt; (f) 2,2-DMP, *p*-TSA, acetone, rt; (g) DIBAL-H, CH_2Cl_2, −78 °C; (h) $Ph_3P{=}CH{-}CO_2Et$, CH_3OH, rt; (i) *p*-TSA, CH_3OH, rt; then benzene, sonication 20–30 min; (j) TBS–Cl, imidazole, DMAP, CH_2Cl_2, 0 °C to rt; (k) $Ph_3P{=}CH{-}CO_2Me$, CH_3OH, rt.



Scheme 4. Reagents and conditions: (a) H_2/Pd–carbon (10%), 4.4% HCO_2H–MeOH, rt; (b) TBAF, THF, 0 °C, then Amberlyst 15, MeOH, 3 h.

3. Conclusion

The total syntheses of both enantiomers of goniothales diol, altholactone, and isoaltholactone were achieved in efficient yields from readily available cinnamyl alcohol **7**. The syntheses required only 9 or 10 chemical operations and were highly stereoselective. Sharpless asymmetric dihydroxylation reaction of epoxy esters **8a** and **8b** and CSA catalyzed cyclization of **5a–d** are the key steps of our syntheses. Our route provides a general, efficient, and stereoselective access to related substituted tetrahydrofurans and α,β-unsaturated-δ-lactones.

4. Experimental

4.1. General

Commercial reagents were used without further purification. All solvents were purified by standard techniques. Infrared (IR) spectra were recorded on Perkin–Elmer 683 spectrometer. Optical rotations were obtained on Jasco Dip 360 digital polarimeter. Melting points are uncorrected. NMR spectra were recorded in $CDCl_3$ on a Varian Gemini 200, Bruker 300, or Varian Unity 400 NMR spectrometers. Chemical shifts (δ) are quoted in parts per million and are referenced to the tetramethylsilane (TMS) as the internal standard. Coupling constants (*J*) are quoted in Hertz. Column chromatographic separations were carried out on silica gel (60–120 mesh) and flash chromatographic separations were carried out using 230–400 mesh size silica gel. Mass spectra were obtained on Finnegan MAT 1020B or micro-mass VG 70-70H spectrometer operating at 70 eV using direct inlet system.

4.1.1. 3-Phenyl-(2*R*,3*R*)-oxiran-2-ylmethanol 6a. A mixture of titanium tetraisopropoxide (2.2 g, 7.76 mmol), (−)-diethyl D-tartarate (1.84 g, 8.95 mmol), and 4 g of activated powdered 4 Å molecular sieves was

stirred in 200 mL of anhydrous CH_2Cl_2 at −23 °C for 30 min. To this mixture was added cinnamyl alcohol **7** (8 g, 59.70 mmol) with 15 mL of CH_2Cl_2 at −23 °C. After the resulting mixture was stirred at −23 °C for 30 min, the reaction mixture was treated with *tert*-butylhydroperoxide (49 mL; 3.0 M in toluene) and stirred for 4 h at this temperature. The reaction mixture was allowed to warm to 0 °C and poured into a freshly prepared and cooled (0 °C) solution of ferrous sulfate and tartaric acid (10 g and 3 g, respectively) in deionised water (15 mL). The two-phase mixture was stirred for 25–30 min, aqueous phase separated and extracted with ether. The combined organic phases were treated with a precooled (0 °C) solution of 30% NaOH (w/v) in saturated brine. The two-phase mixture was then stirred for 1 h at room temperature and the aqueous layer separated. It was treated with ether and the combined organic extracts dried over Na_2SO_4 and concentrated under reduced pressure, resulting in a crude product, which was purified by flash column chromatography on silica gel using 17:3 hexane–EtOAc as eluent to give **6a** (7.34 g, 82% yield) as liquid; $[\alpha]_D^{20} = +45.9$ (*c* 1, EtOH); IR (KBr): $\nu = 3580$, 3450, 2980, 1600, 1450, 1380 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 2.20$ (1H, br s), 3.25–3.33 (1H, m), 3.81 (1H, dd, $J = 5.1$ Hz), 3.95 (1H, d, $J = 3.0$ Hz), 4.18 (1H, dd, $J = 3.1$ Hz), 7.20–7.50 (5H, m); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 136.5$, 128.3, 128.1, 125.5, 62.5, 61.4, 55.7; HRMS calcd for $C_9H_{10}O_2$ $[M]^+$ 150.0681, found 150.0687.

4.1.2. 3-Phenyl-(2*S*,3*S*)-oxiran-2-ylmethanol 6b. Compound **6b** was prepared from cinnamyl alcohol **7** by using (+)-diethyl L-tartarate instead of (−)-diethyl D-tartarate in 83% yield employing the similar procedure as explained for the preparation of **6a**. $[\alpha]_D^{20} = -50.1$ (*c* 1, $CHCl_3$); IR (KBr): $\nu = 3580$, 3450, 2980, 1600, 1450, 1380 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 2.20$ (1H, br s), 3.25–3.33 (1H, m), 3.81 (1H, dd, $J = 5.1$ Hz), 3.95 (1H, d, $J = 3.0$ Hz), 4.18 (1H, dd, $J = 3.1$ Hz), 7.20–7.50 (5H, m); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 136.5$, 128.3, 128.1, 125.5, 62.5, 61.4, 55.7; HRMS calcd for $C_9H_{10}O_2$ $[M]^+$ 150.0681, found 150.0687.

4.1.3. Ethyl 3-[3-phenyl-(2*R*,3*R*)-oxiran-2-yl]-(*E*)-2-propenoate 8a. Oxalyl chloride (8.4 g, 66.66 mmol) in CH_2Cl_2 (100 mL) was cooled to −78 °C and DMSO (7.8 g, 99.99 mmol) in CH_2Cl_2 (15 mL) added via cannula. The reaction mixture was stirred at −78 °C for 1 h before a solution of alcohol **6a** (5 g, 33.33 mmol) in CH_2Cl_2 (10 mL) was added dropwise via cannula. The reaction mixture was stirred for 30 min at which point triethylamine (32.3 mL, 233.33 mmol) was added dropwise over 10 min. The reaction mixture was stirred at −78 °C for 15 min and then warmed to 0 °C. This was stirred for 5 min at 0 °C and then quenched by the addition of 0.5 M sodium bisulfate. The organic extracts were washed with water, brine, dried over anhydrous sodium sulfate, and concentrated to give the crude aldehyde, which was taken in dry benzene (100 mL) after which (ethoxycarbonylmethylene)triphenyl-phosphorane (12.6 g, 36.41 mmol) was added. The reaction mixture was stirred for 4 h at rt. After removal of the solvent, the resulting crude product was purified by flash column chromatography on silica gel using 20:1 hexane–EtOAc as eluent to give 6.2 g (87%) of ester **8a** as a colorless liquid: $[\alpha]_D^{20} = +121.9$ (*c* 1.4, $CHCl_3$); IR (KBr): $\nu = 2983$, 1716, 1656, 1263 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 1.30$ (3H, t, $J = 7.1$ Hz), 3.40–3.44 (1H, m), 3.78–3.80 (1H, m), 4.20 (2H, q, $J = 7.1$ Hz), 6.15 (1H, dd, $J = 15.6$, 0.8 Hz), 6.78 (1H, dd, $J = 15.5$, 6.8 Hz), 7.23–7.26 (5H, m); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 165.4$, 143.4, 135.9, 128.5, 125.4, 123.9, 121.1, 60.9, 60.5, 60.4, 14.1; HRMS calcd for $C_{13}H_{15}O_3$ $[M+H]^+$ 219.1021, found 219.1025.

4.1.4. Ethyl 3-[3-phenyl-(2*S*,3*S*)-oxiran-2-yl]-(*E*)-2-propenoate 8b. Compound **8b** was prepared from alcohol **6b** in 88% yield employing the same procedure as explained for the preparation of **8a**. Compound **8b** (colorless liquid): $[\alpha]_D^{20} = -136.5$ (*c* 1.6, $CHCl_3$); IR (KBr): $\nu = 2983$, 1716, 1656, 1263 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 1.30$ (3H, t, $J = 7.1$ Hz), 3.40–3.44 (1H, m), 3.78–3.80 (1H, m), 4.20 (2H, q, $J = 7.1$ Hz), 6.15 (1H, dd, $J = 15.6$, 0.8 Hz), 6.78 (1H, dd, $J = 15.5$, 6.8 Hz), 7.23–7.26 (5H, m); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 165.4$, 143.4, 135.9, 128.5, 125.4, 123.9, 121.1, 60.9, 60.5, 60.4, 14.1; HRMS calcd for $C_{13}H_{15}O_3$ $[M+H]^+$ 219.1021, found 219.1025.

4.1.5. Ethyl (2*R*,3*S*)-dihydroxy-3-[3-phenyl-(2*R*,3*R*)-oxiran-2-yl]-(2*R*)-propanoate 5a. To a solution of ester **8a** (1.03 g, 5 mmol) in a 1:1 mixture (30 mL) of water–*tert*-butyl alcohol were added sequentially 4.95 g (15 mmol) of potassium ferricyanide, 2.07 g (15 mmol) of potassium corbonate, and 0.195 g (1.25 mmol) of $(DHQ)_2$-PHAL, 37 mg (1 mmol) of potassium osmatedihydrate, and 0.48 g (5 mmol) of methane sulfonamide. The resulting mixture was stirred at rt for 12 h, and 50 mg of sodium metabisulfite was then added. After the mixture was stirred for an additional 45 min, it was filtered through Celite, Florisil, and $MgSO_4$. The filter cake was thoroughly rinsed with EtOAc–hexane (20:1). The combined filtrates were concentrated and purified by flash column chromatography on silica gel using 4:6 EtOAc–hexane as eluent to give 0.92 g (78%) of diol **5a** as a semi-solid. Compound **5a** (semi-solid): $[\alpha]_D^{20} = +45.7$ (*c* 1, $CHCl_3$); IR (KBr): $\nu = 3474$, 2983, 1738, 1376, 1217 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 1.32$ (3H, t, $J = 7.2$ Hz), 2.71 (1H, br s), 3.13–3.17 (1H, m), 3.32 (1H, br s), 3.89–3.92 (3H, m), 4.28 (2H, q, $J = 7.2$ Hz), 7.23–7.29 (5H, m); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 172.5$, 136.4, 128.3, 127.7, 125.6, 79.9, 72.5, 71.7, 62.1, 55.0, 13.9; HRMS calcd for $C_{13}H_{16}O_5Na$ $[M+Na]^+$ 275.0895, found 275.0906.

4.1.6. Ethyl (2*S*,3*R*)-dihydroxy-3-[3-phenyl-(2*R*,3*R*)-oxiran-2-yl]-(2*S*)-propanoate 5b. Compound **5b** was prepared from ester **8a** by using $(DHQD)_2$-PHAL instead of $(DHQ)_2$-PHAL in 75% yield employing the similar procedure as explained for the preparation of **5a**. Compound **5b** (semi-solid): $[\alpha]_D^{20} = +43.5$ (*c* 1.8, $CHCl_3$); IR (KBr): $\nu = 3455$, 2980, 1731, 1368, 1221 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 1.32$ (3H, t, $J = 6.5$ Hz), 2.60 (1H, br s), 3.12–3.29 (2H, m), 3.85–3.93 (1H, m),

4.10–4.19 (1H, m), 4.23–4.42 (3H, m), 7.23–7.39 (5H, m); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 172.3$, 136.1, 128.1, 127.1, 125.3, 83.8, 72.1, 71.4, 62.0, 57.1, 13.8; HRMS calcd for $C_{13}H_{16}O_5Na$ $[M+Na]^+$ 275.0895, found 275.0906.

4.1.7. Ethyl (2*R*,3*S*)-dihydroxy-3-[3-phenyl-(2*S*,3*S*)-oxiran-2-yl]-(2*R*)-propanoate 5c. Compound **5c** was prepared from ester **8b** in 75% yield employing a similar procedure as explained for the preparation of **5a**. Compound **5c** (semi-solid): $[\alpha]_D^{20} = -45.7$ (*c* 1, $CHCl_3$); IR (KBr): $\nu = 3455$, 2980, 1731, 1368, 1221 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.32$ (3H, t, $J = 6.5$ Hz), 2.60 (1H, br s), 3.12–3.29 (2H, m), 3.85–3.93 (1H, m), 4.10–4.19 (1H, m), 4.23–4.42 (3H, m), 7.23–7.39 (5H, m); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 172.3$, 136.1, 128.1, 127.1, 125.3, 83.8, 72.1, 71.4, 62.0, 57.1, 13.8; HRMS calcd for $C_{13}H_{16}O_5Na$ $[M+Na]^+$ 275.0895, found 275.0906.

4.1.8. Ethyl (2*S*,3*R*)-dihydroxy-3-[3-phenyl-(2*S*,3*S*)-oxiran-2-yl]-(2*S*)-propanoate 5d. Compound **5d** was prepared from ester **8b** by using $(DHQD)_2$-PHAL instead of $(DHQ)_2$-PHAL in 78% yield employing the similar procedure as explained for the preparation of **5a**. Compound **5d** (semi-solid): $[\alpha]_D^{20} = -55.3$ (*c* 1, $CHCl_3$); IR (KBr): $\nu = 3474$, 2983, 1738, 1376, 1217 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.32$ (3H, t, $J = 7.2$ Hz), 2.71 (1H, br s), 3.13–3.17 (1H, m), 3.32 (1H, br s), 3.89–3.92 (3H, m), 4.28 (2H, q, $J = 7.2$ Hz), 7.23–7.29 (5H, m); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 172.5$, 136.4, 128.3, 127.7, 125.6, 79.9, 72.5, 71.7, 62.1, 55.0, 13.9; HRMS calcd for $C_{13}H_{16}O_5Na$ $[M+Na]^+$ 275.0895, found 275.0906.

4.1.9. Ethyl 3,4-dihydroxy-5-phenyl-(2*R*,3*S*,4*S*,5*S*)-tetrahydro-2-furancarboxylate 4a. Diol **5a** (1 g, 3.96 mmol) was taken in CH_2Cl_2 (20 mL) to which was added a catalytic amount of camphor sulfonic acid at 0 °C. The reaction mixture was stirred for 3–4 h and neutralized with saturated aqueous $NaHCO_3$, the solvent was then removed under reduced pressure. The crude residue was purified by column chromatography using EtOAc–hexane (1:1) as eluent to afford **4a** (0.94 g, 94%) as semi-solid. Compound **4a** (semi-solid): $[\alpha]_D^{20} = -14.5$ (*c* 1.8, $CHCl_3$); IR (KBr): $\nu = 3357$, 2928, 1759, 1713, 1452, 1372 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.34$ (3H, t, $J = 6.6$ Hz), 3.23–3.48 (2H, m), 3.92–4.02 (1H, m), 4.28 (2H, q, $J = 6.6$ Hz), 4.43–4.53 (1H, m), 4.80 (1H, d, $J = 5.9$ Hz), 5.02 (1H, d, $J = 5.9$ Hz), 7.25–7.34 (5H, m); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 171.0$, 139.2, 128.9, 128.0, 125.8, 83.9, 80.2, 78.1, 72.1, 61.6, 14.1; HRMS calcd for $C_{13}H_{16}O_5Na$ $[M+Na]^+$ 275.0895, found 275.0906.

4.1.10. Ethyl 3,4-dihydroxy-5-phenyl-(2*S*,3*R*,4*S*,5*S*)-tetrahydro-2-furancarboxylate 4b. Compound **4b** was prepared from diol **5b** in 94% yield employing the same procedure as explained for the preparation of **4a**. Compound **4b** (colorless needles): mp 98 °C; $[\alpha]_D^{20} = -22.5$ (*c* 1.9, $CHCl_3$); IR (KBr): $\nu = 3419$, 2933, 1748, 1452, 1383 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.33$ (3H, t, $J = 6.9$ Hz), 2.72–3.01 (2H, m), 4.03–4.16 (1H, m), 4.20–4.40 (3H, m), 4.61–4.71 (2H, m), 7.22–7.60 (5H, m); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 170.3$, 138.9, 128.4, 128.0, 126.3, 85.3, 82.5, 79.5, 78.2, 61.5, 14.1; HRMS calcd for $C_{13}H_{16}O_5Na$ $[M+Na]^+$ 275.0895, found 275.0906.

4.1.11. Ethyl 3,4-dihydroxy-5-phenyl-(2*R*,3*S*,4*R*,5*R*)-tetrahydro-2-furancarboxylate 4c. Compound **4c** was prepared from diol **5c** in 78% yield employing the same procedure as explained for the preparation of **4a**. Compound **4c** (colorless needles): mp 98–100 °C; $[\alpha]_D^{20} = +24.5$ (*c* 1, $CHCl_3$); IR (KBr): $\nu = 3419$, 2933, 1748, 1452, 1383 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.33$ (3H, t, $J = 6.9$ Hz), 2.72–3.01 (2H, m), 4.03–4.16 (1H, m), 4.20–4.40 (3H, m), 4.61–4.71 (2H, m), 7.22–7.60 (5H, m); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 170.3$, 138.9, 128.4, 128.0, 126.3, 85.3, 82.5, 79.5, 78.2, 61.5, 14.1; HRMS calcd for $C_{13}H_{16}O_5Na$ $[M+Na]^+$ 275. 0895, found 275.0906.

4.1.12. Ethyl 3,4-dihydroxy-5-phenyl-(2*S*,3*R*,4*R*,5*R*)-tetrahydro-2-furancarboxylate 4d. Compound **4d** was prepared from diol **5d** in 78% yield employing the same procedure as explained for the preparation of **4a**. Compound **4d** (semi-solid): $[\alpha]_D^{20} = +15.5$ (*c* 1.4, $CHCl_3$); IR (KBr): $\nu = 3357$, 2928, 1759, 1713, 1452, 1372 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.34$ (3H, t, $J = 6.6$ Hz), 3.23–3.48 (2H, m), 3.92–4.02 (1H, m), 4.28 (2H, q, $J = 6.6$ Hz), 4.43–4.53 (1H, m), 4.80 (1H, d, $J = 5.9$ Hz), 5.02 (1H, d, $J = 5.9$ Hz), 7.25–7.34 (5H, m); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 171.0$, 139.2, 128.9, 128.0, 125.8, 83.9, 80.2, 78.1, 72.1, 61.6, 14.1; HRMS calcd for $C_{13}H_{16}O_5Na$ $[M+Na]^+$ 275.0895, found 275.0906.

4.1.13. Ethyl 2,2-dimethyl-6-phenyl-(3a*S*,4*R*,6*S*,6a*S*)-perhydrofuro[3,4-*d*][1,3]dioxole-4-carboxylate 9a. A mixture of **4a** (2 g, 79.36 mmol), 2,2-dimethoxy propane (0.9 g, 87.30 mmol), and a catalytic amount of *p*-TSA in acetone (30 mL) was stirred for 2 h, neutralized with saturated aqueous $NaHCO_3$ and then concentrated. The residue was purified by silica gel column chromatography (EtOAc–hexane 1:20) to give **9a** (2.2 g, 97%) as a liquid: **9a** (viscous liquid): $[\alpha]_D^{20} = +17.5$ (*c* 1.8, $CHCl_3$); IR (KBr): $\nu = 2986$, 1761, 1453, 1378, 1207, 1107 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.32$ (3H, t, $J = 7.4$ Hz), 1.33 (3H, s), 1.52 (3H, s), 4.25 (2H, q, $J = 7.4$ Hz), 4.55 (1H, dd, $J = 5.2$, 0.7 Hz), 4.80–4.98 (2H, m), 5.33 (1H, s), 7.25–7.32 (5H, m); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 167.8$, 137.6, 128.6, 127.7, 125.5, 113.8, 86.3, 85.1, 81.8, 80.1, 61.0, 26.2, 25.2, 14.2; HRMS calcd for $C_{16}H_{21}O_5$ $[M+H]^+$ 293.1389, found 293.1392.

4.1.14. Ethyl 2,2-dimethyl-6-phenyl-(3a*R*,4*S*,6*R*,6a*R*)-perhydrofuro[3,4-*d*][1,3]dioxole-4-carboxylate 9b. Compound **9b** was prepared from compound **4d** in 94% yield employing the same procedure as explained for the preparation of **4a**. Compound **9b** (viscous liquid): $[\alpha]_D^{20} = -19.5$ (*c* 1.1, $CHCl_3$); IR (KBr): $\nu = 2986$, 1761, 1453, 1378, 1207, 1107 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.32$ (3H, t, $J = 7.4$ Hz), 1.33

(3H, s), 1.52 (3H, s), 4.25 (2H, q, $J = 7.4$ Hz), 4.55 (1H, dd, $J = 5.2$, 0.7 Hz), 4.80–4.98 (2H, m), 5.33 (1H, s), 7.25–7.32 (5H, m); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 167.8$, 137.6, 128.6, 127.7, 125.5, 113.8, 86.3, 85.1, 81.8, 80.1, 61.0, 26.2, 25.2, 14.2; HRMS calcd for $C_{16}H_{21}O_5$ $[M+H]^+$ 293.1389, found 293.1392.

4.1.15. Ethyl 3-[2,2-dimethyl-6-phenyl-(3a*R*,4*S*,6*S*,6a*S*)-perhydrofuro[3,4-*d*][1,3]dioxol-4-yl]-(*Z*)-2-propenoate 10a. To a solution of ester **9a** (2 g, 6.84 mmol) in CH_2Cl_2 (50 mL) at −78 °C was added DIBAL-H (1.01 M solution in hexane, 3.5 mL, 6.84 mmol). After being stirred at −78 °C for 2 h, the reaction was quenched with saturated aqueous potassium sodium tartarate. The resultant mixture was diluted with ethyl acetate and stirred vigorously at room temperature until the layers became clear. The organic layer was separated and washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude aldehyde, which was treated with (ethoxycarbonyl-methylene)triphenylphosphorane (2.3 g, 6.81 mmol) in dry methanol (50 mL). The reaction mixture was stirred at rt for 6–8 h. After removal of the solvent, the resulting crude product was purified by flash column chromatography on silica gel using 20:1 hexane–EtOAc as eluent to give 1.72 g (80%) of ester **10a** as a colorless viscous liquid. Compound **10a** (viscous liquid): $[\alpha]_D^{20} = +97.3$ (*c* 1.5, $CHCl_3$); IR (KBr): $\nu = 2985$, 1716, 1651, 1382, 1195 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.29$ (3H, t, $J = 7.4$ Hz), 1.34 (3H, s), 1.55 (3H, s), 4.15 (2H, q, $J = 7.4$ Hz), 4.93–5.03 (2H, m), 5.21 (1H, s), 5.34–5.42 (1H, m), 5.95 (1H, dd, $J = 11.8$, 1.4 Hz), 6.42 (1H, dd, $J = 11.8$, 6.7 Hz), 7.21–7.36 (5H, m); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 165.5$, 145.4, 138.5, 128.5, 127.3, 125.4, 120.8, 112.6, 87.3, 85.0, 82.9, 78.1, 60.2, 26.3, 24.9, 14.1; HRMS calcd for $C_{18}H_{23}O_5$ $[M+H]^+$ 319.1545, found 319.1546.

4.1.16. Ethyl 3-[2,2-dimethyl-6-phenyl-(3a*S*,4*R*,6*R*,6a*R*)-perhydrofuro[3,4-*d*][1,3]dioxol-4-yl]-(*Z*)-2-propenoate 10b. Compound **10b** was prepared from compound **9b** in 81% yield employing the same procedure as explained for the preparation of **10a**. Compound **10b** (viscous liquid): $[\alpha]_D^{20} = -92.1$ (*c* 2, $CHCl_3$); IR (KBr): $\nu = 2985$, 1716, 1651, 1382, 1195 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.29$ (3H, t, $J = 7.4$ Hz), 1.34 (3H, s), 1.55 (3H, s), 4.15 (2H, q, $J = 7.4$ Hz), 4.93–5.03 (2H, m), 5.21 (1H, s), 5.34–5.42 (1H, m), 5.95 (1H, dd, $J = 11.8$, 1.4 Hz), 6.42 (1H, dd, $J = 11.8$, 6.7 Hz), 7.21–7.36 (5H, m); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 165.5$, 145.4, 138.5, 128.5, 127.3, 125.4, 120.8, 112.6, 87.3, 85.0, 82.9, 78.1, 60.2, 26.3, 24.9, 14.1; HRMS calcd for $C_{18}H_{23}O_5$ $[M+H]^+$ 318.1545, found 319.1546.

4.1.17. Methyl 3,4-di-*tert*-butyldimethylsilanyloxy-5-phenyl-(2*S*,3*R*,4*S*,5*S*)-tetrahydro-2-furancarboxylate 11a. To a solution of **4b** (2 g, 7.93 mmol) in anhydrous CH_2Cl_2 (80 mL) were added *tert*-butylchlorodimethylsilane (2.6 g, 17.46 mmol) and imidazole (1.3 g, 19.84 mmol) at 0 °C. After being stirred for 4 h, the reaction mixture was diluted with ethyl acetate, washed with saturated aqueous NH_4Cl, brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, EtOAc–hexane 1:20 as eluent) gave **11a** (3.6 g, 97%) as a colorless clear oil: **11a** (viscous liquid): $[\alpha]_D^{20} = +19.2$ (*c* 1.8, $CHCl_3$); IR (KBr): $\nu = 2934$, 1737, 1467, 1256, 1095 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = -0.10$ (3H, s), 0.01 (3H, s), 0.10 (3H, s), 0.20 (3H, s), 0.72 (9H, s), 0.92 (9H, s), 1.45 (3H, t, $J = 7.2$ Hz), 4.12–4.25 (3H, m), 4.30–4.41 (1H, m), 4.71–4.79 (1H, m), 4.90 (1H, s), 7.15–7.29 (2H, m), 7.45–7.56 (3H, m); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 169.5$, 140.2, 127.9, 127.1, 126.4, 89.3, 83.8, 82.0, 80.1, 60.9, 25.6, 25.3, 17.6, 14.1, −4.4, −4.5, −4.8, −5.3; HRMS calcd for $C_{25}H_{45}O_5Si_2$ $[M+H]^+$ 481.2805, found 481.2811.

4.1.18. Methyl 3,4-di-*tert*-butyldimethylsilanyloxy-5-phenyl-(2*R*,3*S*,4*R*,5*R*)-tetrahydro-2-furancarboxylate 11b. Compound **11b** was prepared from compound **4a** in 97% yield employing the same procedure as explained for the preparation of **11a**. Compound **11b** (viscous liquid): $[\alpha]_D^{20} = -16.2$ (*c* 1, $CHCl_3$); IR (KBr): $\nu = 2934$, 1737, 1467, 1256, 1095 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = -0.10$ (3H, s), 0.01 (3H, s), 0.10 (3H, s), 0.20 (3H, s), 0.72 (9H, s), 0.92 (9H, s), 1.45 (3H, t, $J = 7.2$ Hz), 4.12–4.25 (3H, m), 4.30–4.41 (1H, m), 4.71–4.79 (1H, m), 4.90 (1H, s), 7.15–7.29 (2H, m), 7.45–7.56 (3H, m); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 169.5$, 140.2, 127.9, 127.1, 126.4, 89.3, 83.8, 82.0, 80.1, 60.9, 25.6: *m*/*z*, 25.3, 17.6, 14.1, −4.4, −4.5, −4.8, −5.3; HRMS calcd for $C_{25}H_{45}O_5Si_2$ $[M+H]^+$ 481.2805, found 481.2811.

4.1.19. Methyl 3-[3,4-di-*tert*-butyldimethylsilanyloxy-5-phenyl-(2*R*,3*S*,4*S*,5*S*)-tetrahydro-2-furanyl]-(*Z*)-2-propenoate 12a. Compound **12a** was prepared from ester **11a** by using (methoxycarbonylmethylene)triphenylphosphorane instead of (ethoxycarbonylmethylene)triphenylphosphorane in 80% yield and employing the similar procedure as explained for the preparation of **10a**. Compound **12a** (viscous liquid): $[\alpha]_D^{20} = -96.3$ (*c* 1.0, $CHCl_3$); IR (KBr): $\nu = 2954$, 1742, 1467, 1363, 1256 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = -0.20$ (3H, s), −0.09 (3H, s), 0.01 (3H, s), 0.10 (3H, s), 0.72 (9H, s), 0.92 (9H, s), 3.71 (3H, s), 4.01–4.09 (1H, m), 4.23–4.30 (1H, m), 4.75 (1H, s), 5.45–5.55 (1H, m), 5.91 (1H, dd, $J = 12$, 1.6 Hz), 6.50 (1H, dd, $J = 12$, 6.4 Hz), 7.15–7.41 (5H, m); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 147.3$, 130.1, 128.0, 127.1, 126.6, 120.5, 109.7, 89.9, 85.8, 81.4, 80.0, 54.3, 51.3, 32.3, 25.7, 7.9, −4.4, −4.5, −4.7, −5.1; HRMS calcd for $C_{26}H_{45}O_5Si_2$ $[M+H]^+$ 493.2805, found 493.2825.

4.1.20. Methyl 3-[3,4-di-*tert*-butyldimethylsilanyloxy-5-phenyl-(2*S*,3*R*,4*R*,5*R*)-tetra-hydro-2-furanyl]-(*Z*)-2-propenoate 12b. Compound **12b** was prepared from ester **11b** by using (methoxycarbonylmethylene)triphenylphosphorane instead of (ethoxycarbonylmethylene)triphenylphosphorane in 81% yield and employing the similar procedure as explained for the preparation of **10a**. Compound **12b** (viscous liquid): $[\alpha]_D^{20} = +103.1$ (*c* 1, $CHCl_3$); IR (KBr): $\nu = 2954$, 1742, 1467, 1363, 1256 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = -0.20$ (3H, s), −0.09 (3H, s), 0.01 (3H, s), 0.10

(3H, s), 0.72 (9H, s), 0.92 (9H, s), 3.71 (3H, s), 4.01–4.09 (1H, m), 4.23–4.30 (1H, m), 4.75 (1H, s), 5.45–5.55 (1H, m), 5.91 (1H, dd, $J = 12$, 1.6 Hz), 6.50 (1H, dd, $J = 12$, 6.4 Hz), 7.15–7.41 (5H, m); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 147.3$, 130.1, 128.0, 127.1, 126.6, 120.5, 109.7, 89.9, 85.8, 81.4, 80.0, 54.3, 51.3, 32.3, 25.7, 7.9, −4.4, −4.5, −4.7, −5.1; HRMS calcd for $C_{26}H_{45}O_5Si_2$ $[M+H]^+$ 493.2805, found 493.2825.

4.1.21. (+)-Isoaltholactone 3a. A solution of compound **10a** (0.1 g, 0.431 mmol) in methanol (15 mL) was treated with a catalytic amount of *p*-TSA at rt to afford a mixture of diol ester and lactone **3a**. Removal of methanol by concentration under reduced pressure and sonication after diluting the residue with benzene (20 mL) afforded the crude lactone **3a**. The crude product was purified by flash column chromatography on silica gel using 1:1 hexane–EtOAc as eluent to give 60 mg (83%) of **3a** as colorless needles: mp 102–103 °C (lit.[3b] mp 103.5–104.5 °C); $[\alpha]_D^{20} = +34.5$ (*c* 0.50, EtOH) {lit.[3b] $[\alpha]_D^{20} = +32$ (*c* 0.013, EtOH)}; IR (KBr): $\nu = 3500$, 3030, 1730, 1645 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 3.31$ (1H, br s), 4.26–4.29 (1H, m) 4.78 (1H, d, $J = 7.5$ Hz), 4.86 (1H, t, $J = 5.5$, 4.4 Hz), 5.05 (1H, t, $J = 5.7$ Hz), 6.20 (1H, dd, $J = 10.0$, 0.7 Hz), 6.85 (1H, dd, $J = 9.9$, 4.5 Hz), 7.25–7.40 (5H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 161.9$, 141.7, 138.6, 128.5, 128.1, 125.6, 122.4, 83.1, 78.6, 78.4, 67.7; HRMS calcd for $C_{13}H_{13}O_4$ $[M+H]^+$ 233.0814, found 233.0815.

4.1.22. (−)-Altholactone 2b. Lactone **2b** was prepared from **12a** in 83% yield employing the same procedure as explained for the preparation of **3a**. Compound **2b** (colorless oily material): $[\alpha]_D^{20} = -163.9$ (*c* 0.25, EtOH) {lit.[9a] $[\alpha]_D = -166$ (*c* 0.50, EtOH)}; IR (KBr): $\nu = 3418$, 2925, 1731 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 3.79$–4.01 (1H, m), 4.44 (1H, dd, $J = 5.6$, 2.3 Hz), 4.63 (1H, t, $J = 5.1$ Hz), 4.73 (1H, d, $J = 5.5$ Hz), 4.92 (1H, dd, $J = 5.1$, 2.2 Hz), 6.21 (1H, d, $J = 9.9$ Hz), 6.95 (1H, dd, $J = 9.9$, 4.8 Hz), 7.26–7.38 (5H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 161.9$, 140.7, 138.3, 128.5, 128.1, 126.2, 123.5, 86.5, 86.1, 83.4, 68.1; HRMS calcd for $C_{13}H_{13}O_4$ $[M+H]^+$ 233.0814, found 233.0808.

4.1.23. (+)-Altholactone 2a. Lactone **2a** was prepared from **12b** in 83% yield employing the same procedure as explained for the preparation of **3a**. Compound **2a** (colorless needles): mp 108–109 °C (lit.[3a] mp 110 °C); $[\alpha]_D^{20} = +183.1$ (*c* 0.20, EtOH) {lit.[2] $[\alpha]_D = +188$, lit.[3a] $[\alpha]_D = +184.7$}; IR (KBr): $\nu = 3418$, 2925, 1731 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 3.79$–4.01 (1H, m), 4.44 (1H, dd, $J = 5.6$, 2.3 Hz), 4.63 (1H, t, $J = 5.1$ Hz), 4.73 (1H, d, $J = 5.5$ Hz), 4.92 (1H, dd, $J = 5.1$, 2.2 Hz), 6.21 (1H, d, $J = 9.9$ Hz), 6.95 (1H, dd, $J = 9.9$, 4.8 Hz), 7.26–7.38 (5H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 161.9$, 140.7, 138.3, 128.5, 128.1, 126.2, 123.5, 86.5, 86.1, 83.4, 68.1; HRMS calcd for $C_{13}H_{13}O_4$ $[M+H]^+$ 233. 0814, found 233.0808.

4.1.24. (−)-Isoaltholactone 3b. Compound **3b** was prepared from **10b** in 82% yield employing the same procedure as explained for the preparation of **3a**. Compound **3b** (colorless oily material): $[\alpha]_D^{20} = -32.2$ (*c* 0.30, EtOH); IR (KBr): $\nu = 3500$, 3030, 1730, 1645 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 3.31$ (1H, br s), 4.26–4.29 (1H, m) 4.78 (1H, d, $J = 7.5$ Hz), 4.86 (1H, t, $J = 5.5$, 4.4 Hz), 5.05 (1H, t, $J = 5.7$ Hz), 6.20 (1H, dd, $J = 10.0$, 0.7 Hz), 6.85 (1H, dd, $J = 9.9$, 4.5 Hz), 7.25–7.40 (5H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 161.9$, 141.7, 138.6, 128.5, 128.1, 125.6, 122.4, 83.1, 78.6, 78.4, 67.7; HRMS calcd for $C_{13}H_{13}O_4$ $[M+H]^+$ 233.0814, found 233.0815.

4.1.25. Methyl-3-[3,4-di-*tert*-butyldimethylsilanyloxy-5-phenyl-(2*S*,3*R*,4*R*,5*R*)-tetra-hydro-2-furanyl]propanoate 13a. Compound **12b** (0.5 g, 1.01 mmol) was treated with 10% of Pd/C (10 mg) in 4.4% HCOOH–MeOH under a hydrogen atmosphere at room temperature for 3 h, and filtered through Celite. The filter cake was washed twice with ethyl acetate. The solvent was removed in vacuo to provide the crude compound, which was purified by column chromatography on silica gel using 20:1 hexane–EtOAc as eluent to give 0.47 g (94%) of **13a** as colorless liquid: $[\alpha]_D^{20} = +18.2$ (*c* 1, $CHCl_3$); IR (KBr): $\nu = 2954$, 1742, 1465, 1359, 1256 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = -0.18$ (3H, s), 0.01 (3H, s), 0.04 (3H, s), 0.10 (3H, s), 0.78 (9H, s), 0.91 (9H, s), 1.82–1.95 (1H, m) 2.05–2.18 (1H, m), 2.40–2.61 (2H, m), 3.63 (3H, s), 3.81–3.85 (1H, m), 3.93–3.97 (1H, m), 4.03–4.14 (1H, m), 4.62 (1H, s), 7.10–7.39 (5H, m); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 173.9$, 140.9, 127.9, 127.0, 126.6, 88.8, 85.4, 81.0, 79.9, 51.5, 31.0, 25.7, 25.6, 24.6, 17.8, −4.5, −5.0; HRMS calcd for $C_{26}H_{47}O_5Si_2$ $[M+H]^+$ 495.2962, found 495.2975.

4.1.26. Methyl 3-[3,4-di-*tert*-butyldimethylsilanyloxy-5-phenyl-(2*R*,3*S*,4*S*,5*S*)-tetrahydro-2-furanyl]propanoate 13b. Compound **13b** was prepared from **12a** in 94% yield employing the same procedure as explained for the preparation of **13a**. Compound **13b**: $[\alpha]_D^{20} = -18.9$ (*c* 1, $CHCl_3$); IR (KBr): $\nu = 2954$, 1742, 1465, 1359, 1256 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = -0.18$ (3H, s), 0.01 (3H, s), 0.04 (3H, s), 0.10 (3H, s), 0.78 (9H, s), 0.91 (9H, s), 1.82–1.95 (1H, m) 2.05–2.18 (1H, m), 2.40–2.61 (2H, m), 3.63 (3H, s), 3.81–3.85 (1H, m), 3.93–3.97 (1H, m), 4.03–4.14 (1H, m), 4.62 (1H, s), 7.10–7.39 (5H, m); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 173.9$, 140.9, 127.9, 127.0, 126.6, 88.8, 85.4, 81.0, 79.9, 51.5, 31.0, 25.7, 25.6, 24.6, 17.8, −4.5, −5.0; HRMS calcd for $C_{26}H_{47}O_5Si_2$ $[M+H]^+$ 495.2962, found 495.2975.

4.1.27. (+)-Goniothales diol 1a. To a stirred solution of compound **13a** (0.3 g, 0.60 mmol) in dry THF was added TBAF (0.33 g, 12.75 mmol) in THF (5 mL) at room temperature. The reaction mixture was stirred for 2 h at room temperature. The reaction was then quenched with Et_2O and saturated aqueous $NaHCO_3$. The two phases were separated and the aqueous layer extracted with Et_2O. The combined organic fractions were dried over Na_2SO_4, and concentrated to give a residue, which was treated with Amberlyst 15 in methanol to provide the target compound **1a** in 74% (0.11 g) yield: **1a** (yellow oil): $[\alpha]_D^{20} = +6.9$ (*c* 0.7, EtOH) {lit.[1] $[\alpha]_D^{25} = +7.5$ (*c* 0.23, EtOH)}; IR (KBr): $\nu = 3443$,

2951, 2919, 1742, 1451, 1374, 1219, 1165 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 2.01$–2.12 (2H, m), 2.42–2.62 (2H, m), 3.65 (3H, s), 3.97–4.07 (3H, m), 4.59 (1H, d, $J = 4.5$ Hz), 7.25 (1H, d, $J = 7.0$ Hz), 7.33 (2H, t, $J = 7.0$ Hz), 7.41 (2H, d, $J = 7.0$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 174.9$, 139.8, 128.7, 127.9, 126.3, 86.1, 85.3, 80.7, 79.0, 51.9, 30.6, 23.7; HRMS calcd for $C_{14}H_{18}O_5Na$ $[M+Na]^+$ 289.1051, found 289.1059.

4.1.28. (−)-Goniothales diol 1b. Compound **1b** was prepared from diol **13b** in 74% yield employing the same procedure as explained for the preparation of **1a**. Compound **1b** (yellow oil): $[\alpha]_D^{20} = -7.0$ (c 0.54, EtOH) {lit.[13] $[\alpha]_D^{27} = -7.1$ (c 0.15, EtOH)}; IR (KBr): $\nu = 3443$, 2951, 2919, 1742, 1451, 1374, 1219, 1165 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 2.01$–2.12 (2H, m), 2.42–2.62 (2H, m), 3.65 (3H, s), 3.97–4.07 (3H, m), 4.59 (1H, d, $J = 4.5$ Hz), 7.25 (1H, d, $J = 7.0$ Hz), 7.33 (2H, t, $J = 7.0$ Hz), 7.41 (2H, d, $J = 7.0$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 174.9$, 139.8, 128.7, 127.9, 126.3, 86.1, 85.3, 80.7, 79.0, 51.9, 30.6, 23.7; HRMS calcd for $C_{14}H_{18}O_5Na$ $[M+Na]^+$ 289.1051, found 289.1059.

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