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A concise and stereoselective synthesis of both enantiomers of altholactone and isoaltholactone☆

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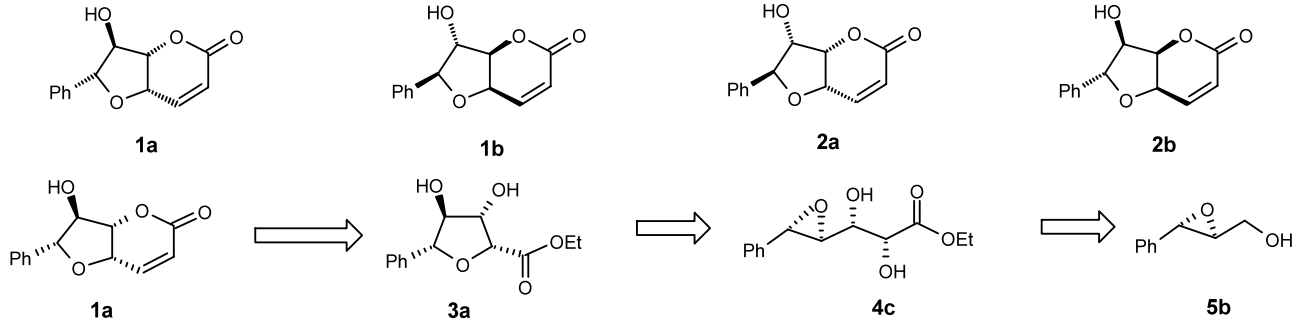
Abstract—A concise and flexible stereoselective route to synthesize both enantiomers of the highly functionalized α,β-unsaturated-δ-lactones, altholactone and isoaltholactone, from readily available cinnamyl alcohol is described. This approach derived its asymmetry from Sharpless catalytic asymmetric 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 sulphonic acid.

Altholactone **1a** and isoaltholactone **2a**, furanopyrones of the styryllactone family, were isolated from an unknown *Polythea* (Annonacae) species,[1] and from various *Goniothalamous*.[2] 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.[3] These natural products possess anti-tumor,[4] anti-fungal[5] and anti-bacterial properties.[5]

Due to the wide distribution of the styryllactone class of natural products in nature, many synthetic methodologies have been employed to synthesize them.[6–10] Most syntheses use chiral pool starting materials such as sugars, hydroxy acids and involve 11 to 16 steps. Due to the unusual structure and biological significance of this class of compounds, we were encouraged to design a concise and flexible stereoselective route towards the construction of (+)-altholactone **1a**, its enantiomer (−)-altholactone **1b**, (+)-isoaltholactone **2a** and its enantiomer (−)-isoaltholactone **2b** from the inexpensive and readily available cinnamyl alcohol.[11] Retrosynthetically our approach is illustrated in Scheme 1.

The synthesis began with the Sharpless asymmetric epoxidation[12] of cinnamyl alcohol **6** to afford **5a** and **5b** in 82% and 83% yields, respectively. Oxidation of alcohols **5a** and **5b** using the Swern protocol[13] afforded both aldehydes, which without purification were subjected to Wittig olefination[14] with the stable ylide (ethoxycarbonyl–methylene)triphenylphosphorane to afford epoxy esters **7a** and **7b**, respectively, in 87% and 88% yields (2 steps) Schemes 2 and 3.



Scheme 1.

Keywords: altholactone; isoaltholactone; cinnamyl alcohol; sharpless asymmetric epoxidation; sharpless asymmetric dihydroxylation.
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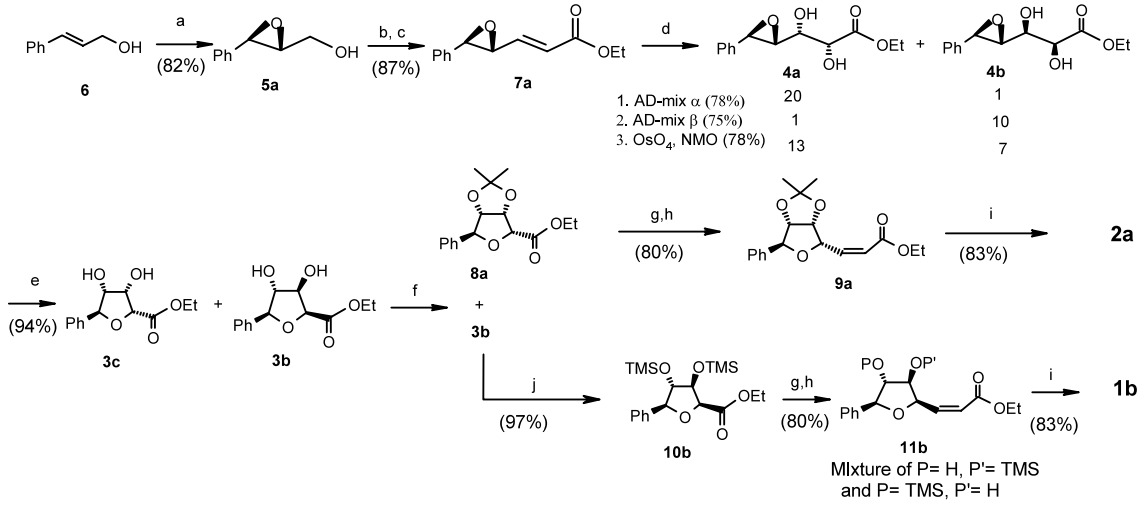
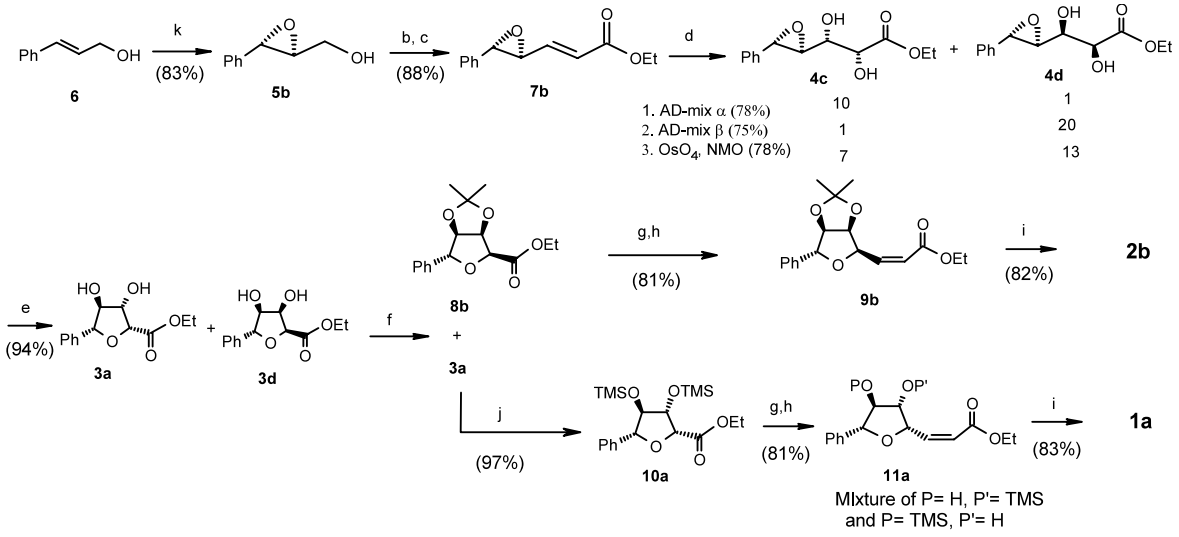
α,β-Unsaturated epoxy ester **7a** was subjected to a Sharpless asymmetric dihydroxylation reaction using AD-mix α, to yield **4a** and **4b** in a ratio of 20:1[15] (78% yield) and treatment with AD-mix β afforded **4a** and **4b** in a ratio of 1:10[15] (75% yield), whilst treatment with OsO_4, NMO afforded **4a** and **4b** in a 13:7 ratio (78% yield). The separation of these two isomeric diols **4a** and **4b** was not feasible through simple column chromatography because of their close R_f values. It was therefore decided to purify the mixture in the forthcoming steps. The mixture of **4a** and **4b** was subjected to treatment with a catalytic amount of CSA to afford **3b** and **3c** (94% yield) by cyclization. Subsequent treatment of this mixture with 2,2-DMP afforded acetonide **8a** and unreacted **3b** which were readily separated by column chromatography.

The ester **8a** was reduced to the aldehyde, which was subjected to Wittig olefination with the stable ylide (ethoxycarbonylmethylene)triphenylphosphorane in methanol as the solvent to yield the *cis*-ester **9a** (80% yield, 2 steps) predominantly (*cis*:*trans* 95:5).[16] The *trans*-diol **3b** was protected with TMSCl to yield **10b** in 97% yield. As with **8a**, **10b** was also reduced with DIBAL-H to afford an aldehyde, which was transformed into the *cis*-ester **11b** (82% yield, 2 steps). Compounds **9a** and **11b** on treatment with a catalytic amount of *p*TSA in methanol afforded a mixture of diol esters and lactones **2a** and **1b**. Removal of methanol by concentration under reduced pressure and sonication after diluting the residue with benzene afforded lactones **2a** and **1b**, respectively (both in 83% yields). Epoxy ester **7b** was transformed in a similar fashion to afford **1a** and **2b** as illustrated in Scheme 3.



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) $Ph_3P{=}CH\text{-}CO_2Et$, benzene, rt; (d) see Schemes 2 and 3; (e) CSA, CH_2Cl_2, rt; (f) 2,2-DMP, *p*TSA, acetone, rt; (g) DIBAL-H, CH_2Cl_2, −78°C; (h) $Ph_3P{=}CH\text{-}CO_2Et$, CH_3OH, rt; (i) *p*TSA, CH_3OH, rt; then benzene, sonication 20–30 min; (j) TMS-Cl, imidazole, CH_2Cl_2, 0°C to rt; (k) (+)-DET, $Ti(O^iPr)_4$, TBHP, CH_2Cl_2, −33°C.



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) $Ph_3P{=}CH\text{-}CO_2Et$, benzene, rt; (d) see Schemes 2 and 3; (e) CSA, CH_2Cl_2, rt; (f) 2,2-DMP, *p*TSA, acetone, rt; (g) DIBAL-H, CH_2Cl_2, −78°C; (h) $Ph_3P{=}CH\text{-}CO_2Et$, CH_3OH, rt; (i) *p*TSA, CH_3OH, rt; then benzene, sonication 20–30 min; (j) TMS-Cl, imidazole, CH_2Cl_2, 0°C to rt; (k) (+)-DET, $Ti(O^iPr)_4$, TBHP, CH_2Cl_2, −33°C.

Thus, total syntheses of both enantiomers of altholactone and isoaltholactone were achieved in efficient yields from readily available cinnamyl alcohol **6**. The syntheses required only nine or ten chemical operations and were highly stereoselective. Sharpless asymmetric dihydroxylation reactions of epoxy esters **7a** and **7b** and the CSA catalyzed cyclization of **4a–d** are the key steps of our syntheses. Our route provides a general, efficient and stereoselective access to related α,β-unsaturated-δ-lactones.

Acknowledgements

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Spectral data for selected compounds: Compound **7b** (colorless liquid): $[\alpha]_D = +121.9$ (*c* 1.4 $CHCl_3$); IR (KBr): $\nu = 2983$, 1716, 1656, 1263 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.3$ (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), 6.78 (1H, dd, $J = 15.5$, 6.8), 7.23–7.26 (5H, m); EI-MS: $m/z = 218$ (M^+).
Compound **4a** (semi solid): $[\alpha]_D = +45.7$ (*c* 1.0 $CHCl_3$); IR (KBr): $\nu = 3474$, 2983, 1738, 1376, 1217 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.32$ (3H, t, $J = 5.9$ Hz), 2.71 (1H, bs), 3.13–3.17 (1H, m), 3.32 (1H, bs), 3.89–3.92 (3H, m), 4.23–4.34 (2H, q, $J = 7.4$ Hz), 7.23–7.29 (5H, m); EI-MS: $m/z = 252$ (M^+).
Compound **3c** (semi solid): $[\alpha]_D = -14.5$ (*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), 4.23–4.33 (2H, q, $J = 6.6$ Hz), 4.43–4.53 (1H, m), 4.80 (1H, d, $J = 5.9$ Hz), 5.02 (1H, d, $J = 5.9$), 7.25-7.34 (5H, m); EI-MS: $m/z = 252$ (M^+).
Compound **8a** (viscous liquid): $[\alpha]_D = +17.5$ (*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, d, $J = 5.2$, 0.7 Hz), 4.80–4.98 (2H, m), 5.33 (1H, s), 7.25–7.32 (5H, m); EI-MS: $m/z = 292$ (M^+).
Compound **9a** (viscous liquid): $[\alpha]_D = +97.3$ (*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), 6.42 (1H, dd, $J = 11.8$, 6.7 Hz), 7.21–7.36 (5H, m); EI-MS: $m/z = 318$ (M^+).
Compound **2a** (colorless needles): Mp 102–103°C; $[\alpha]_D^{20} = +34.5$ (*c* 0.50 EtOH); IR (KBr): $\nu = 3500$, 3030, 1730, 1645 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 3.31$ (1H, bs), 4.28 (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 ($CDCl_3$, 50 MHz): $\delta = 161.9$, 141.7, 138.6, 128.5 (2), 128.1, 125.6 (2), 122.4, 83.1, 78.6, 78.4, 67.7; EI-MS: $m/z = 232$ (M^+), 126, 122, 107, 97, 91, 77.