Enantioselective Organocatalytic Formal [3+3] Cycloaddition of α,β -Unsaturated Aldehydes and application to the Asymmetric Synthesis of (-)-Isopulegol Hydrate and (-)-Cubebaol.

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SUPPORTING INFORMATION:

Contents: Experimental procedures and characterization data for compounds **2-24**.

Experimental Section:

General Procedure. All solvents were reagent grade. L-proline (99+%) was purchased from Across, D-proline (>99%) was purchased from Bachem. Other chemicals were purchased from Aldrich Chemical Co. Reactions were normally carried out under argon atmosphere in flame-dried glassware. Merck silica gel 60 (particle size 0.04-0.063 mm) was employed for flash chromatography. HPLC was equipped with the ultraviolet and refractive index detectors. The sample was analyzed and/or separated on a Rainin Dynamax-60A-Si column (41.4 cm x 250 μ m, particle size 8 μ m, pore size 60 Å) by elution with gradient of ethyl acetate and hexane. The flow rate of the indicated elution solvent is maintained at 10 mL/min, and the retention time of a compound is recorded accordingly. Melting points are uncorrected. ^1H NMR and COSY spectra were obtained in CDCl_3 unless otherwise noted at 400 MHz (Bruker DPX-400) or 500 MHz (Varian-Unity INOVA-500). ^{13}C NMR spectra, HMBC, HMQC and DEPT experiments were obtained at 100 MHz or 125 MHz. *E.e.* values were measured by GC-MS (Shimadzu QP 5000, chiral capillary column, gamma-cyclodextrin trifluoroacetyl, Astec Type G-TA, size 30 m x 0.25 mm, flow rate 24 mL/min, temperature range: 60 to 120°C, gradient: 3 °C/min).

Representative Procedures for the [3+3] Cycloaddition of Crotonaldehyde.

To a solution of crotonaldehyde (420 mg, 6.0 mmol) in CH_3CN (15 mL) was added L-(-)-proline (345 mg, 3.0 mmol) at 26°C . The solution was stirred for 3–4 h at room temperature until the reaction was completed, monitored by TLC. To the solution was added H_2O (10 mL), and extracted with Et_2O (15 mL x 2). The organic solution was washed with brine (10 mL), dried over Na_2SO_4 . The solution was analyzed by NMR and GC. GC-MS analysis showed (*SS*)-**2** (retention time: 26.7 min) : (*RR*)-**2** (retention time: 27.5 min) = 45.6% : 54.4%; (*RS*)-**3** (retention time: 29.0 min) : (*SR*)-**3** (retention time: 29.5 min) = 82.6% : 17.4%. The organic solution was concentrated *in vacuo* to give the residue.¹ The crude product was purified by flash column chromatography with 45% Et_2O -pentane (R_f = 0.28 for **2**, R_f = 0.14 for **3** in 50% Et_2O -pentane) to give **2** (117 mg; 28% yield), **3** (66 mg, 16% yield) and trace amount of **4**. Aldehyde **2**, **3** and **4** are volatile; hence the yields were measured relative to the corresponding alcohol (**5**, **7** and 4-methylbenzyl alcohol), isolated from *in situ* NaBH_4 - CeCl_3 reduction of the ether extract. The reaction afforded **5** (183 mg, 43% yield), **7** (98 mg, 23% yield) and 4-methylbenzyl alcohol (37 mg, 10% yield) after chromatography purification.

Selected spectra data for **2**: Mp. $55\text{--}56^\circ\text{C}$; $[\alpha]_{\text{D}}^{20}$ -75.8 (c 3.5, MeOH); IR (neat): 3520, 2954, 2873, 1671, 1198, 1052, 853, 808 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 9.36 (s, 1 H), 6.80 (d, J = 4.0 Hz, 1 H), 4.61 (br.s, 1 H), 3.80 (s, 1 OH), 2.36 (ddd, J = 20.0, 4.5, 4.5 Hz, 1 H), 2.08–2.03 (m, 1 H), 1.92 (dd, J = 20.0, 10.5 Hz, 1 H), 1.68–1.62 (m, 1 H), 1.23 (dd, J = 22.5, 12.0 Hz, 1H), 0.99 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 195.5 (CH), 153.1 (CH), 142.7 (C), 65.7 (CH), 38.4 (CH_2), 35.1 (CH_2), 26.8 (CH), 21.3 (CH_3); MS (m/z , relative intensity): 140 (M^+ , 7), 122 (46), 111 (54), 98 (40), 70 (57), 55 (64), 43 (100); exact mass calculated for $\text{C}_8\text{H}_{12}\text{O}_2$ (M^+): 140.0837; found 140.0842.

Selected spectra data for **3**: colorless oil. $[\alpha]_{\text{D}}^{20}$ -197.2 (c 3.5, MeOH); IR (neat): 3428, 2952, 2924, 2873, 1683, 1642, 1455, 1414, 1180, 1050, 974, 725 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 9.40 (s, 1 H), 6.87 (dd, J = 5.0, 2.5 Hz, 1 H), 4.56 (s, 1 H), 2.90 (br.s, 1 OH), 2.44 (ddd, J = 4.5, 4.5, 19.5 Hz, 1 H), 1.90–2.05 (m, 1 H), 1.75–1.85 (m, 2 H), 1.29 (ddd, J = 13.0, 13.0, 4.5 Hz, 1 H), 0.97 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 194.5 (CH), 153.4 (CH), 142.0 (C), 61.0 (CH), 37.7 (CH_2), 35.0 (CH_2), 23.4 (CH), 21.1 (CH_3); MS (m/z , relative intensity): 140 (M^+ , 6), 122 (40), 111 (60), 98 (46), 70 (49), 55 (53), 43 (100); exact mass calculated for $\text{C}_8\text{H}_{12}\text{O}_2$ (M^+): 140.0837; found 140.0842.

¹ Hydroxyaldehyde **2** and **3** are easy to be sublimated, it is necessary to evaporate with caution.

For hydroxylaldehyde **4**: NMR, GC analysis was identical with the *p*-tolualdehyde purchased from Arcos chemical company.

Crystallographic data for **2**: C₈H₁₂O₂, M = 140.18, monoclinic, space group *P*2₁, T = 298 K, *a* = 7.773(2), *b* = 6.401(2), *c* = 8.075(3) Å, β = 103.792(5)°, *V* = 390.1(2) Å³, *Z* = 2, *D* = 1.193 g/cm³, λ (Mo-*K*α) = 0.71073 Å, 3456 reflections collected, 1746 unique reflections, 96 parameters refined on *F*², *R* = 0.0518, *wR*2[*F*²] = 0.1301 [1583 data with *F*² > 2σ(*F*²)].

X-ray ORTEP of 2

To a solution of *cis*-6-hydroxy-4-methylcyclohex-1-enecarbaldehyde (**2**, 36 mg, 0.26 mmol) in THF (5 mL) was added LiAlH₄ (20 mg, 0.52 mmol) at 0 °C. The solution was stirred for 1h at room temperature until the reaction was completed, monitored by TLC. The reaction was quenched by the addition of EtOAc (1 mL) and ice water (5 mL). The solution was extracted with EtOAc (30 mL), dried over Na₂SO₄, concentrated in *vacuo* to give the crude

product. The residue was purified by flash column chromatography with 60% EtOAc-hexane ($R_f = 0.28$ in 66% EtOAc-hexane) to give diol **5** as a yellow oil (32 mg, 86% yield). $[\alpha]_D^{20} -111$ (c 3.5, CHCl_3); IR (neat): 3348, 2925, 1455, 1012, 907, 783, 758 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 5.69 (d, $J = 4.0$ Hz, 1 H), 4.40-4.46 (m, 1 H), 4.18 (s, 2 H), 2.52 (br.s, 2 OH), 2.00-2.10 (m, 2 H), 1.60-1.75 (m, 1 H), 1.20-1.30 (m, 2 H), 0.96 (d, $J = 6.0$ Hz, 3 H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 138.6 (C), 127.2 (CH), 69.9 (CH), 65.9 (CH_2), 41.5 (CH_2), 33.9 (CH_2), 28.1 (CH), 21.8 (CH_3); MS (m/z , relative intensity): 124 ($\text{M}^+ - \text{H}_2\text{O}$, 21), 111 (70), 82 (100), 69 (60), 67 (55), 55 (66), 41 (45) 39 (38); exact mass calculated for $\text{C}_8\text{H}_{12}\text{O}$ ($\text{M}^+ - \text{H}_2\text{O}$): 124.0888; found 124.0886.

To a solution of *trans*-6-hydroxy-4-methylcyclohex-1-enecarbaldehyde (**3**, 60 mg, 0.42 mmol) in THF (10 mL) was added LiAlH_4 (32 mg, 0.85 mmol) at 0 °C. The solution was stirred for 1h at room temperature until the reaction was completed, monitored by TLC. The reaction was quenched by the addition of EtOAc (3 mL) and ice water (10 mL). The solution was extracted with EtOAc (50 mL), dried over Na_2SO_4 , concentrated in *vacuo* to give the crude product. The residue was purified by flash column chromatography with 60% EtOAc-hexane ($R_f = 0.28$ in 66% EtOAc-hexane) to give diol **7** as a yellow oil (53 mg, 88% yield). $[\alpha]_D^{20} -139.0$ (c 4.8, CHCl_3); IR (neat): 3343, 2923, 1455, 1166, 1049, 1000, 936, 785, 754 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 5.77 (d, $J = 5.0$ Hz, 1 H), 4.21 (s, 1 H), 4.13 (d, $J = 12.0$ Hz, 1 H), 4.09 (d, $J = 12.0$ Hz, 1 H), 3.08 (br.s, 2 OH), 2.12 (ddd, $J = 17.5, 5.0, 5.0$ Hz, 1 H), 1.80-1.90 (m, 1 H), 1.78 (d, $J = 14.0$ Hz, 1 H), 1.55 (dd, $J = 10.5, 16.5$ Hz, 1 H), 1.31 (ddd, $J = 13.0, 12.0, 4.5$ Hz, 1 H), 0.95 (d, $J = 7.0$ Hz, 3 H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 137.2 (C), 128.4 (CH), 66.6 (CH_2), 66.3 (CH), 39.5 (CH_2), 33.8 (CH_2), 23.2 (CH), 21.4 (CH_3); MS (m/z , relative intensity): 142 (M^+ , 8), 141 ($\text{M}^+ - 1$, 5), 77 (27), 44 (5), 31 (5); exact mass calculated for $\text{C}_8\text{H}_{14}\text{O}_2$ (M^+): 142.0994; found 142.0989.

To a solution of **5** (8 mg, 0.056 mmol), Et_3N (1 mL) and 4-Dimethylaminopyridine (2 mg, 0.016 mmol) in CH_2Cl_2 (5 mL) was added Benzoyl chloride (0.03 mL, 0.224 mmol) at room temperature. The solution was stirred for 2h at room temperature. The reaction was quenched by the addition of H_2O (1 mL); the solution was extracted with EtOAc (50 mL), dried over

Na₂SO₄, concentrated in *vacuo* to give the crude product. The residue was purified by flash column chromatography with 4% EtOAc-hexane (R_f = 0.32 in 4% EtOAc-hexane) to give diol **6** as a yellow oil (18 mg, 90% yield). $[\alpha]_D^{20}$ -25.1 (c 7.0 CHCl₃); IR (neat): 2952, 1719, 1452, 1274, 1069, 785, 710, 785, 753 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 8.00 (d, J = 7.5 Hz, 2 H), 7.95 (d, J = 7.5 Hz, 2 H), 7.48-7.53 (m, 2 H), 7.34-7.40 (m, 4 H), 6.08 (br.s, 1 H), 5.84-5.87 (m, 1 H), 4.87 (d, J = 12.5 Hz, 1 H), 4.83 (d, J = 12.5 Hz, 1 H), 2.31 (dd, J = 12.0, 6.0 Hz, 1 H), 2.18-2.23 (m, 1 H), 1.95-1.90 (m, 1 H), 1.86-1.78 (m, 1 H), 1.40-1.50 (m, 1 H), 1.02 (d, J = 6.5 Hz, 3 H); ¹³C NMR (CDCl₃, 125 MHz): δ 166.3 (C), 166.2 (C), 132.9 (CH), 132.8 (CH), 132.0 (C), 131.3 (CH), 130.3 (C), 130.1 (C), 129.59 (two CH), 129.58 (two CH), 128.31 (two CH), 128.27 (two CH), 70.6 (CH), 65.3 (CH₂), 37.0 (CH₂), 33.5 (CH₂), 27.6 (CH), 21.5 (CH₃); MS (m/z , relative intensity): 351 (M^+ -1, 4), 230 (64), 229 (100), 105 (64), 77 (18), 51(3); exact mass calculated for C₂₂H₂₂O₄ (M^+): 350.1518; found 350.1521.

To a solution of **7** (40 mg, 0.28 mmol), benzoic acid (137 mg, 1.12 mmol) and PPh₃ (294 mg, 1.12 mmol) in THF (10 mL) was added diethyl azodicarboxylate (0.2 mL, 1.12 mmol) at room temperature. The solution was stirred for 6h at room temperature and concentrated in *vacuo* to give the residue. The crude product was purified by flash column chromatography with 4% EtOAc-hexane (R_f = 0.32 in 4% EtOAc-hexane) to give diol **6** as a yellow oil (18 mg, 90% yield). $[\alpha]_D^{20}$ -29.8 (c 4.8 CHCl₃).

To a solution of *cis*-6-hydroxy-4-methylcyclohex-1-enecarbaldehyde (**2**, 70 mg, 0.50 mmol) and 2-methyl-2-butene (2 mL, 18.8 mmol) in *t*-BuOH (10 mL) was added a freshly prepared solution of sodium chlorite (140 mg, 1.55 mmol) in 20 %_{w/w} aqueous NaH₂PO₄ (2.4 g in 12 mL of H₂O) at room temperature and the resulting solution was stirred for 4h. The mixture was diluted with ethyl acetate (30 mL), washed with water (4 mL). The aqueous phase was extracted with ethyl acetate (30 mL) and the combined organic layers were dried over Na₂SO₄, concentrated in *vacuo* to give the crude product. The residue was purified by flash column chromatography with 60% EtOAc-hexane (R_f = 0.26 in 66% EtOAc-hexane) to give diol **8** as a yellow oil (66 mg, 84% yield). $[\alpha]_D^{20}$ -55.6 (c 5, CHCl₃); IR (neat): 3460, 2926, 1687, 1420, 1257, 1104, 787, 757 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 7.13 (d, J = 4.5 Hz, 1 H), 4.59 (br.s, 1 H), 2.26 (dd, J = 14.5, 5.0 Hz, 1 H), 2.05-2.14 (m, 1 H), 1.80-1.90 (m, 1

H), 1.65-1.76 (m, 1 OH), 1.20-1.32 (m, 2 H), 1.00 (d, $J = 7.0$ Hz, 3 H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 171.5 (C), 144.7 (CH), 131.8 (C), 66.2 (CH), 38.7 (CH_2), 34.7 (CH_2), 27.3 (CH), 21.4 (CH_3); MS (m/z , relative intensity): 156 (M^+ , 3), 139 (16), 138 (100), 114 (30), 110 (18), 96(41), 68 (21), 41 (10); exact mass calculated for $\text{C}_8\text{H}_{12}\text{O}_3$ (M^+): 156.0786; found 156.0779.

A solution of **8** (30 mg, 0.19 mmol) and aqueous HCl (1.2 M, 0.1 mL) in ethanol (20 mL) was heated to reflux for 5 h. The solution was cooled to room temperature, added Et_3N (5 mL) and stirred for 10 min. The solution was diluted with EtOAc (100 mL) and washed with brine. The combined organic layers were dried over Na_2SO_4 , concentrated in *vacuo* to give the crude product. The residue was purified by flash column chromatography with 4% EtOAc-hexane ($R_f = 0.59$ in 16% EtOAc-hexane) to give diol **9** as a yellow oil (26 mg, 74% yield).² $[\alpha]_{\text{D}}^{21} -84.3$ (c 3.5, CHCl_3); IR (neat): 3510, 2925, 1690, 1372, 1257, 1097, 1051, 783 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 7.00 (br.s, 1 H), 4.56-4.60 (m, 1 H), 4.20 (q, $J = 7.0$ Hz, 2 H), 2.21-2.28 (m, 1 H), 2.05-2.12 (m, 1 H), 1.78-1.85 (m, 1 H), 1.62-1.78 (m, 1 H), 1.20-1.32 (m, 1 H), 1.30 (t, $J = 7.0$ Hz, 3 H), 1.00 (d, $J = 6.5$ Hz, 3 H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 167.3 (C), 141.9 (CH), 132.7 (C), 66.3 (CH), 60.6 (CH_2), 38.9 (CH_2), 34.6 (CH_2), 27.3 (CH), 21.5 (CH_3), 14.2 (CH_3); MS (m/z , relative intensity): 184 (M^+ , 4), 142 (40), 139 (43), 138 (100), 115 (35), 114 (62), 111, (51), 96 (67), 86 (31), 68 (49), 55 (38), 43 (28); exact mass calculate for $\text{C}_{10}\text{H}_{16}\text{O}_3$ (M^+): 184.1099; found 184.1094.

To a solution of **9** (30 mg, 0.17 mmol) in THF (5.0 mL) was added a solution of MeLi (1.5 M in hexane, 0.46 mL) at 0 °C and the resulting solution was stirred for 2 h. The reaction was quenched by the addition of aqueous NH_4Cl (4 mL) and stirred for 5 min. The solution was diluted with EtOAc (50 mL), washed with brine, dried over Na_2SO_4 , and concentrated in *vacuo* to give the crude product. The residue was purified by flash column chromatography with 50% EtOAc-hexane ($R_f = 0.35$ in 33% EtOAc-hexane) to give diol **10** as a colorless oil (27 mg, 93% yield). $[\alpha]_{\text{D}}^{20} -37.8$ (c 4.0, CHCl_3); lit. $[\alpha]_{\text{D}}^{20} -27.2$ (CHCl_3)³; IR (neat): 3327,

² For an alternative preparation of the methyl ester (mixture of isomers) by a tandem Morita–Baylis–Hillman (MBH) and ring-closing-metathesis (RCM) sequence, see: Krafft, M. E.; Song, E.-H.; Davoile, R. J. *Tetrahedron Lett.* **2005**, 46, 6359.

³ Schulte-Elte, K. H.; Gadola, M.; Mueller, B. L. *Helv. Chim. Acta.* **1971**, 54, 1870.

2951, 2925, 1455, 1375, 1155, 1042, 943, 907, 853, 744 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 5.64 (d, J = 5.0 Hz, 1 H), 4.61 (s, 1 H), 3.84 (br.s, 2 OH), 2.07-1.95 (m, 2 H), 1.70-1.60 (m, 2 H), 1.38 (s, 3 H), 1.36 (s, 3 H), 1.35-1.20 (m, 1 H), 0.92 (d, J = 6.0 Hz, 3 H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 142.9 (C), 123.2 (CH), 74.0 (C), 69.2 (CH), 41.7 (CH_2), 34.1 (CH_2), 29.7 (CH_3), 29.6 (CH_3), 27.8 (CH), 21.6 (CH_3); MS (m/z , relative intensity): 170 (M^+ , 8), 155 (20), 152 (61), 137 (100), 110 (36), 109 (63), 95 (40), 93 (40), 82 (35), 59 (29), 43, (95); exact mass calculated for $\text{C}_{10}\text{H}_{18}\text{O}_2$ (M^+): 170.1307; found 170.1312.

A suspension of **10** (30 mg, 0.18 mmol) and Pd-C (3 mg, 10%) in EtOAc (8 mL) was stirred at room temperature under hydrogen (1 atm) for 18h. The mixture was filtered through Celite® and the filtrate was concentrated in *vacuo* to give the crude product. The residue was purified by flash column chromatography with 50% EtOAc-hexane (R_f = 0.50 in 50% EtOAc-hexane) to give diol **11** (24 mg, 77%) as the white solids.⁴ Mp 77-78 °C; lit. 77.3-78.3 °C;⁵ $[\alpha]_{\text{D}}^{20}$ -12.4 (c 0.9, CHCl_3); $[\alpha]_{\text{D}}^{20}$ -12.6 (c 0.9, MeOH);⁶ lit. $[\alpha]_{\text{D}}$ -12.5 (c 10, CHCl_3);⁷ lit. $[\alpha]_{\text{D}}$ -10.6 (c 0.5, CHCl_3);⁸ lit. $[\alpha]_{\text{D}}^{20}$ -14.4 (c 0.5, CHCl_3);⁹ lit. $[\alpha]_{\text{D}}^{23}$ -11.4 (c 0.5, MeOH)¹⁰; IR (neat): 3343, 2953, 2922, 2873, 1713, 1454, 1158, 1007, 869, 727 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 3.70 (ddd, J = 10.0, 10.0, 4.0 Hz, 1 H), 3.06 (br.s, 2 OH), 1.92 (d, J = 11.5 Hz, 1 H), 1.60-1.70 (m, 4 H), 1.30-1.45 (m, 2 H), 1.20 (s, 6 H), 0.95-1.05 (m, 1 H), 0.90 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 75.2 (C), 72.9 (CH), 53.4 (CH), 44.6 (CH_2), 34.5 (CH_2), 31.3 (CH), 30.1 (CH_3), 27.1 (CH_2), 23.7 (CH_3), 22.0 (CH_3);¹¹ MS (m/z , relative intensity): 154 ($\text{M}^+ - \text{H}_2\text{O}$, 2), 139 (14), 121 (11), 96 (68), 81 (100), 59 (82), 54 (32), 43 (47); exact mass calculated for $\text{C}_{10}\text{H}_{18}\text{O}$ ($\text{M}^+ - \text{H}_2\text{O}$): 154.1358; found 154.1362.

⁴ NMR data are consistent with the database (Spectral Database for Organic Compounds, SDBS) and the compound purchased from TCI Chemical company: *trans-p*-methane-3,8-diol (*trans*-isopulegol hydrate), catalog number M1129, CAS# 3564-98-5. However, the compound purchased from TCI is a racemate with zero alpha value.

⁵ Nishimura, H.; Nakamura, T.; Mizutani, J. *Phytochemistry* **1984**, 23, 2777.

⁶ Lit. for its enantiomer, $[\alpha]_{\text{D}}^{25}$ + 50 (c 0.06, MeOH); Rahman, A.; Yaqoob, M.; Farooq, A.; Anjum, S.; Asif, F.; Choudhary, M. I. *J. Nat. Prod.* **1998**, 61, 1340.

⁷ Naves, O. *Helv. Chim. Acta.* **1964**, 47, 51.

⁸ Asakawa, Y.; Matsuda, R.; Tori, M.; Hashimoto, T. *Phytochemistry* **1988**, 27, 3861.

⁹ Yuasa, Y.; Tsuruta, H.; Yuasa, Y. *Org. Proc. Res. Dev.* **2000**, 4, 159.

¹⁰ Nishimura, H.; Kaku, K.; Nakamura, T.; Fukazawa, Y.; Mizutani, J. *Agric. Biol. Chem.* **1982**, 46, 319.

¹¹ Lit. ^{13}C NMR δ 75.1, 72.9, 53.4, 44.6, 34.4, 31.4, 30.1, 27.1, 23.7, 22.0; Rahman, A.; Yaqoob, M.; Farooq, A.; Anjum, S.; Asif, F.; Choudhary, M. I. *J. Nat. Prod.* **1998**, 61, 1340.

To a solution of *cis*-6-hydroxy-4-methylcyclohex-1-enecarbaldehyde (**3**, 264 mg, 1.89 mmol) and 2-methyl-2-butene (3 ml, 28.23 mmol) in *t*-BuOH (20 mL) was added a freshly prepared solution of sodium chlorite (420 mg, 4.62 mmol) in 20 %_{w/w} aqueous NaH₂PO₄ (7.2 g in 36 ml of H₂O) at room temperature and the resulting solution was stirred for 4h. The mixture was diluted with ethyl acetate (60 mL), washed with water (8 mL). The aqueous phase was extracted with ethyl acetate (30 mL) and the combined organic layers were dried over Na₂SO₄, concentrated in *vacuo* to give the crude product. The residue was purified by flash column chromatography with EtOAc (*R_f* = 0.20 in 85% EtOAc-hexane) to give diol **12** as a yellow oil (251 mg, 85% yield). $[\alpha]_{\text{D}}^{21}$ -71.3 (c 4.3, CHCl₃); IR (neat): 3459, 2918, 1696, 1419, 1215, 1025, 909, 755 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 7.12 (br.s, 1 H), 4.51 (br.s, 1 H), 2.28-2.33 (m, 1 H), 1.80-2.00 (m, 2 H), 1.65-1.72 (m, 1 H), 1.20-1.30 (m, 1 H), 0.94 (d, *J* = 6.5 Hz, 3 H); ¹³C NMR (CDCl₃, 125 MHz): δ 171.2 (C), 145.1 (CH), 131.1 (C), 63.0 (CH), 38.0 (CH₂), 34.5 (CH₂), 22.4 (CH), 21.1 (CH₃); MS (*m/z*, relative intensity): 138 (*M*⁺-H₂O, 100), 115 (18), 114 (41), 96 (53), 86 (26), 68 (55), 55 (23), 41 (23), 39 (26); exact mass calculated for C₈H₁₀O₂ (*M*⁺-H₂O): 138.0681; found 138.0674.

A solution of **12** (30 mg, 0.19 mmol) and aqueous HCl (1.2 M, 0.1 mL) in ethanol (20 ml) was heated to reflux for 5 h. The solution was cooled to room temperature, added Et₃N (5 mL) and stirred for 10 min. The solution was diluted with EtOAc (100 mL) and washed with brine. The combined organic layers were dried over Na₂SO₄, concentrated in *vacuo* to give the crude product. The residue was purified by flash column chromatography with 4% EtOAc-hexane (*R_f* = 0.51 in 16% EtOAc-hexane) to give diol **13** as a yellow oil (27 mg, 77% yield). $[\alpha]_{\text{D}}^{21}$ -101.0 (c 3.1, CHCl₃); IR (neat): 3444, 2927, 1708, 1253, 1045, 771 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 7.03 (dd, *J* = 5.0, 2.5 Hz, 1 H), 4.50 (d, *J* = 2.0 Hz, 1 H), 4.17 (q, *J* = 7.0 Hz, 2 H), 2.62 (br.s, 1 OH), 2.30-2.22 (m, 1 H), 1.86-1.90 (m, 2 H), 1.72-1.65 (m, 1 H), 1.18-1.30 (m, 1 H), 1.25 (t, *J* = 7.0 Hz, 3 H), 0.95 (d, *J* = 6.5 Hz, 3 H); ¹³C NMR (CDCl₃, 125 MHz): δ 167.3 (C), 142.7 (CH), 131.8 (C), 63.2 (CH), 60.5 (CH₂), 38.0 (CH₂), 34.4 (CH₂), 22.6 (CH), 21.1 (CH₃), 14.2 (CH₃); MS (*m/z*, relative intensity): 185 (*M*⁺-1, 5), 184 (*M*⁺, 7), 142 (44), 139 (62), 138 (100), 114 (44), 111 (51), 86 (34), 68 (37), 55 (37), 43 (30); exact mass

calculate for $C_{10}H_{16}O_3$ (M^+): 184.1099; found 184.1096.

To a solution of **13** (10 mg, 0.054 mmol) in THF (3.0 mL) was added a solution of MeLi (1.5 M in hexane, 0.15 mL) at 0 °C and the resulting solution was stirred for 2h. The reaction was quenched by the addition of aqueous NH_4Cl (4 mL) and stirred for 5 min. The solution was diluted with EtOAc (50 mL), washed with brine, dried over Na_2SO_4 , and concentrated in *vacuo* to give the crude product. The residue was purified by flash column chromatography with 50% EtOAc-hexane (R_f = 0.22 in 16% EtOAc-hexane) to give diol **14** as a white solid (8 mg, 88% yield).¹² Mp: 60-61 °C. lit. 61-62.¹³ $[\alpha]_D^{21}$ -149.7 (C 1.5, $CHCl_3$); lit. for its enantiomer: $[\alpha]_D^{20}$ +152.0 (C 10, $CHCl_3$);¹⁴ IR (neat): 3361, 2924, 1456, 1151, 1013, 932, 782, 762 cm^{-1} ; ^1H NMR ($CDCl_3$, 500 MHz): δ 5.77 (br.s, 1 H), 4.49 (br.s, 1 H), 2.42 (br.s, 2 OH), 2.20-2.10 (m, 1 H), 1.90-1.80 (m, 2 H), 1.60-1.50 (m, 1 H), 1.41 (s, 3 H), 1.34 (s, 3 H), 1.30-1.20 (m, 1 H), 0.95 (d, J = 6.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 142.9 (C), 124.4 (CH), 73.8 (C), 64.5 (CH), 39.6 (CH_2), 34.1 (CH_2), 30.2 (CH_3), 29.9 (CH_3), 22.6 (CH), 21.5 (CH_3); MS (m/z , relative intensity): 152 ($M^+ - H_2O$, 100), 137 (40), 111 (20), 109 (25), 95 (25), 81 (21), 59 (27), 43 (100), 31 (21); exact mass calculated for $C_{10}H_{16}O$ ($M^+ - H_2O$): 152.1201; found 152.1207.

A suspension of **14** (40 mg, 0.24 mmol) and Pd-C (4 mg, 10%) in EtOAc (5 mL) was stirred at room temperature under hydrogen (1 atm) for 18h. The mixture was filtered through Celite® and the filtrate was concentrated in *vacuo* to give the crude product. The residue was purified by flash column chromatography with 50% EtOAc-hexane (**15**: R_f = 0.50 in 50% EtOAc-hexane) to give diol **15** (27 mg, 66%) as white solid. Mp. 85-86 °C; lit. 86-87 °C;¹⁵ $[\alpha]_D^{21}$ -12.1 (C 0.2, $CHCl_3$); IR (neat): 3334, 2924, 1713, 1459, 1379, 1156, 1057, 871, 785 cm^{-1} ; ^1H NMR ($CDCl_3$, 500 MHz): δ 3.94 (ddd, J = 10.5, 10.5, 4.5 Hz, 1 H), 2.36

¹² (a) For another preparation of **14**, see: Jia, Yan Xing; Li, Xin; Wu, Bin; Zhao, Xue Zhi; Tu, Yong Qiang. *Tetrahedron* **2002**, 58, 1697.

¹³ Skorianetz, W.; Giger, H.; Ohloff, G. *Helv. Chim. Acta.* **1971**, 54, 1797.

¹⁴ Ibid.

¹⁵ Asakawa, Y.; Matsuda, R.; Tori, M.; Hashimoto, T. *Phytochemistry* **1988**, 27, 3861.

(br.s, 2 OH), 2.02-2.08 (m, 1 H), 1.76-1.80 (m, 1 H), 1.21 (s, 3 H), 1.23 (s, 3 H), 0.96 (d, J = 7.5 Hz, 3 H), 0.95-1.52 (m, 6 H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 75.2 (C), 68.8 (CH), 54.5 (CH), 41.5 (CH_2), 31.2 (CH_2), 29.9 (CH_3), 28.1 (CH), 23.8 (CH_3), 22.1 (CH_2), 18.2 (CH_3);¹⁶ MS (m/z , relative intensity): 154 ($\text{M}^+ - \text{H}_2\text{O}$, 9), 139 (6), 96 (24), 95 (42), 81 (100), 59 (57), 43 (40), 41 (16); exact mass calculate for $\text{C}_{10}\text{H}_{18}\text{O}$ ($\text{M}^+ - \text{H}_2\text{O}$): 154.1358; found 154.1349.

To a solution of **5** (35 mg, 0.25 mmol), Et_3N (1 mL) and 4-Dimethylaminopyridine (2 mg, 0.016 mmol) in CH_2Cl_2 (5 mL) was added acetic anhydride (0.28 mL, 0.30 mmol) at room temperature. The solution was stirred for 2h at room temperature. The reaction was quenched by the addition of H_2O (1 mL); the solution was extracted with EtOAc (50 mL), dried over Na_2SO_4 , concentrated in *vacuo* to give the crude product. The residue was purified by flash column chromatography with 10% EtOAc -hexane (R_f = 0.23 in 16% EtOAc -hexane) to give acetate **16** as a colorless oil (35 mg, 75% yield).¹⁷ $[\alpha]_{\text{D}}^{20}$ -10.2 (c 1.0 CHCl_3); IR (neat): 3471, 2925, 1737, 1371, 1240, 1024, 781, 758 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 5.79 (d, J = 4.0 Hz, 1 H), 4.93 (d, J = 12.5 Hz, 1 H), 4.34 (d, J = 12.5 Hz, 1 H), 4.23 (br.s, 1 H), 2.40 (br.s, 1 OH), 2.06 (s, 3 H), 2.10-2.00 (m, 2 H), 1.80-1.60 (m, 2 H), 1.25-1.17 (m, 1 H), 0.95 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 171.7 (C), 135.7 (C), 130.2 (CH), 67.2 (CH), 65.7 (CH_2), 40.6 (CH_2), 34.0 (CH_2), 28.0 (CH), 21.7 (CH_3), 21.0 (CH_3); MS (m/z , relative intensity): 184 (M^+ , 3), 167 (30), 166 (31), 124 (86), 81 (41), 67(11), 55 (10), 43 (100); exact mass calculated for $\text{C}_{10}\text{H}_{16}\text{O}_3$ (M^+): 184.1099; found 184.1108.

¹⁶ Lit. ^{13}C NMR (CDCl_3) δ 75.0, 68.8, 54.6, 41.6, 31.4, 29.4, 28.2, 23.8, 22.2, 18.3. Asakawa, Y.; Matsuda, R.; Tori, M.; Hashimoto, T. *Phytochemistry* **1988**, 27, 3861.

¹⁷ For another synthesis of ($\pm$)-**16**, see: Ishizaki, M; Niimi, Y.; Hoshino, O.; Hara, H.; Takahashi, T. *Tetrahedron* **2005**, 61, 4053.

Selected spectroscopic data for **23**: $[\alpha]_D^{20} +207.7$ (c 2.5 CHCl₃); IR (neat): 2825, 1739, 1678, 1577, 1372, 1233, 1178, 1038, 790, 755 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): 9.55 (s, 1 H), 6.95 (d, $J = 5.0$ Hz, 1 H), 6.46 (dd, $J = 5.0, 9.5$ Hz, 1 H), 6.35 (dd, $J = 6.0, 9.5$ Hz, 1 H), 5.39 (d, $J = 6.0$ Hz, 1 H), 3.98 (dd, $J = 11.0, 5.0$ Hz, 1 H), 3.83 (dd, $J = 11.0, 9.0$ Hz, 1 H), 3.34 (dd, $J = 9.0, 5.0$ Hz, 1 H), 2.01 (s, 3 H), 1.99 (s, 3 H); ¹³C NMR (CDCl₃, 125 MHz): δ 191.8 (CH), 170.8 (C), 169.9 (C), 141.0 (CH), 136.6 (C), 130.1 (CH), 126.7 (CH), 65.2 (CH), 61.5 (CH₂), 35.2 (CH), 20.9 (CH₃), 20.8 (CH₃); MS (m/z , relative intensity): 238 (M^+ , 0.8), 178 (4), 165 (11), 136 (10), 107 (42); exact mass calculate for C₁₂H₁₄O₅ (M^+): 238.0841; found 238.0843.

Spectroscopic data for **24**: IR (neat): 2927, 1728, 1654, 1233, 745 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 9.36 (s, 1 H), 6.57 (d, $J = 6.0$ Hz, 1 H), 5.91-5.93 (m, 1 H), 2.08 (s, 2 H), 1.87 (s, 3 H), 1.16 (s, 6 H); ¹³C NMR (CDCl₃, 125 MHz): δ 193.2 (CH), 147.1 (C), 145.0 (CH), 142.4 (C), 118.6 (CH), 46.6 (CH₂), 32.7 (C), 26.04 (CH₃), 25.98 (CH₃), 24.0 (CH₃); MS (m/z , relative intensity): 150 (M^+ , 44), 135 (8), 121 (50), 107 (100), 91 (87), 77 (33); exact mass calculate for C₁₀H₁₄O (M^+): 150.1045; found 150.1047.

Selected spectroscopic data for **25**: $[\alpha]_D^{21} -67.8$ (c 4.6, CHCl₃); IR (neat): 3028, 2926, 2814, 1673, 1565, 1170, 753, 697 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 9.53 (s, 1 H), 7.17-7.25 (m, 4 H), 7.14-7.16 (m, 1 H), 6.96 (d, $J = 5.5$ Hz, 1 H), 6.26-6.29 (m, 1 H), 6.21-6.24 (m, 1 H), 4.04 (d, $J = 10.5$ Hz, 1 H), 2.86 (dd, $J = 19.0, 10.5$ Hz, 1 H), 2.64 (dd, $J = 19.0, 6.0$ Hz, 1 H); ¹³C NMR (CDCl₃, 125 MHz): δ 192.6 (CH), 142.7 (CH), 142.4 (C), 139.3 (C), 135.6 (CH), 128.4 (two CH), 127.1 (two CH), 126.8 (CH), 123.8 (CH), 33.2 (CH), 31.6 (CH₂); MS (m/z , relative intensity): 184 (M^+ , 80), 166 (19), 155 (100), 115 (38), 91 (30), 71 (72); exact mass calculated for C₁₃H₁₂O (M^+): 184.0888; found 184.0887.

Spectroscopic data for **26**: $[\alpha]_D^{20}$ -68.7 (c 5.0 CHCl₃); IR (neat): 2924, 1670, 1577, 1195, 792, 755, 699 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 9.49 (s, 1 H), 7.17-7.24 (m, 4 H), 7.14-7.16 (m, 1 H), 6.90 (d, J = 5.5 Hz, 1 H), 6.02-6.05 (m, 1 H), 4.06 (d, J = 9.5 Hz, 1 H), 2.80-2.87 (m, 1 H), 2.44 (dd, J = 18.5, 0.5 Hz, 1 H), 1.86 (s, 3 H); ¹³C NMR (CDCl₃, 125 MHz): δ 191.9 (CH), 147.1 (C), 144.0 (CH), 143.0 (C), 137.1 (C), 128.2 (two CH), 126.8 (two CH), 126.5 (CH), 119.3 (CH), 36.8 (CH₂), 34.0 (CH), 24.0 (CH₃); MS (m/z, relative intensity): 198 (M⁺, 72), 183 (47), 169 (100), 154 (62), 91 (83), 77 (59); exact mass calculate for C₁₄H₁₄O (M⁺): 198.1045; found 198.1042.

Spectroscopic data for **27**: $[\alpha]_D^{20}$ -15.3 (c 4.6 CHCl₃); IR (neat): 2924, 1671, 1577, 1456, 1200, 799, 750 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 9.44 (s, 1 H), 6.73 (d, J = 5.5 Hz, 1 H), 5.85-5.87 (m, 1 H), 2.63 (dd, J = 9.5, 6.0 Hz, 1 H), 2.35 (dd, J = 9.5, 18.0 Hz, 1 H), 2.25 (d, J = 18.0 Hz, 1 H), 1.86 (s, 3 H), 1.72-1.77 (m, 1 H), 0.82 (d, J = 7.0 Hz, 3 H), 0.76 (d, J = 7.0 Hz, 3 H); ¹³C NMR (CDCl₃, 125 MHz): δ 193.0 (CH), 148.3 (C), 144.9 (CH), 138.2 (C), 119.2 (CH), 34.7 (CH), 30.9 (CH₂), 30.2 (CH), 23.9 (CH₃), 20.3 (CH₃), 18.7 (CH₃); MS (m/z, relative intensity): 164 (M⁺, 10), 121 (31), 120 (19), 119 (36), 107 (14), 93 (100), 77 (53); exact mass calculate for C₁₁H₁₆O (M⁺): 164.1201; found 164.1199.

Selected spectroscopic data for **28**: $[\alpha]_D^{20}$ -4.5 (c 4.2 CHCl₃); IR (neat): 3019, 2925, 2858, 1688, 1459, 1216, 759 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 9.43 (s, 1 H), 6.68 (d, J = 5.5 Hz, 1 H), 5.91 (dd, J = 2.5, 1.5 Hz, 1 H), 2.67-2.73 (m, 1 H), 2.37-2.43 (m, 1 H), 2.18 (d, J = 18.0 Hz, 1 H), 1.89 (s, 3 H), 1.20-1.40 (m, 2 H), 0.82 (t, J = 7.5 Hz, 3 H); ¹³C NMR (CDCl₃, 125 MHz): δ 192.7 (CH), 147.5 (C), 143.9 (CH), 139.4 (C), 119.0 (CH), 33.2 (CH₂), 30.2 (CH), 24.7 (CH₂), 24.3 (CH₃), 11.0 (CH₃); MS (m/z, relative intensity): 150 (M⁺, 22), 121 (23), 93 (100), 77 (58); exact mass calculate for C₁₀H₁₄O (M⁺): 150.1045; found 150.1042.

Spectroscopic data for **29**: IR (neat): 2926, 1684, 797, 743 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 9.44 (s, 1 H), 6.72 (d, $J = 5.5$ Hz, 1 H), 5.94 (d, $J = 5.0$ Hz, 1 H), 2.43 (t, $J = 10.0$ Hz, 2 H), 2.22 (t, $J = 10.0$ Hz, 2 H), 1.90 (s, 3 H), ^{13}C NMR (CDCl_3 , 125 MHz): δ 192.5 (CH), 148.9 (C), 144.3 (CH), 135.0 (C), 119.6 (CH), 28.5 (CH_2), 24.0 (CH_3), 18.5 (CH_2); MS (m/z , relative intensity): 122 (M^+ , 71), 107 (61), 91 (77), 77 (100), 65 (30), 51 (40); exact mass calculate for $\text{C}_8\text{H}_{10}\text{O}$ (M^+): 122.0732; found 122.0731.

Spectroscopic data for **30**: $[\alpha]_{\text{D}}^{20}$ -5.7 (c 4.5 CHCl_3); IR (neat): 2925, 1685, 1255, 805, 738 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 9.39 (s, 1 H), 6.63 (d, $J = 5.5$ Hz, 1 H), 5.90-5.92 (m, 1 H), 2.82-2.86 (m, 1 H), 2.46 (dd, $J = 18.0, 9.0$ Hz, 1 H), 1.97 (d, $J = 18.0$ Hz, 1 H), 1.87 (s, 3 H), 0.88 (d, $J = 7.0$ Hz, 3 H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 192.4 (CH), 147.0 (C), 143.0 (CH), 140.1 (C), 118.6 (CH), 36.4 (CH_2), 24.4 (CH_3), 23.7 (CH), 18.0 (CH_3); MS (m/z , relative intensity): 136 (M^+ , 43), 121 (22), 107 (68), 93 (58), 91 (100), 77 (61); exact mass calculate for $\text{C}_9\text{H}_{12}\text{O}$ (M^+): 136.0888; found 136.0885.