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The first total synthesis of (*R*)-7-butyl-6,8-dihydroxy-3-pentylisochroman-1-one

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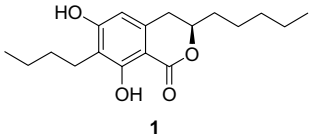
Abstract—The enantioselective synthesis of 7-butyl-6,8-dihydroxy-(3*R*)-pentylisochroman-1-one has been achieved for the first time in which Sharpless asymmetric dihydroxylation is the key step.

1. Introduction

(3*R*)-7-Butyl-6,8-dihydroxy-3-pentylisochroman-1-one **1** (Fig. 1), a member of the dihydroisocoumarin derivatives, was isolated by bioassay-guided fractionation from an endophytic fungus and its absolute configuration was determined to be *R*,[1] which is of great interest because of its diverse antimalarial and antifungal properties.[1] To the best of our knowledge, the total asymmetric synthesis of the title compound has not yet been reported. In order to study the relationship between structure and activity of the compound, we herein report the first enantioselective synthesis from the easily available[2] dimethyl acetal **2**.



1

Figure 1.

2. Results and discussion

As shown in Scheme 1, starting from 3,4,5-trimethoxybenzaldehyde dimethyl acetal **2**, benzaldehyde **3** was easily prepared according to a previous report.[2] Wittig olefination of **3** with the ylide derived from *n*-hexyltriphenylphosphonium bromide led to **4** as an *E*:*Z* (1:1) mixture as revealed by ^{1}H NMR. Irradiation of this *E*:*Z* diene mixture **4** in the presence of iodine generated the eventual predominance of the desired product (*E*)-**4**,[3] with an *E*:*Z* ratio >95:5. Treatment of (*E*)-**4** with AD-mix-β stereoselectively afforded *cis*-diol **5** in 92% yield.[4a] The ee of **5** was determined as >95% by HPLC analysis, while its configuration was anticipated to be (1*R*,2*R*) according to the Sharpless model.[4b] This was confirmed by converting **5** to compound **1** and comparing its specific rotation to that reported for natural (*R*)-**1**. Hydrogenolysis of **5** in ethyl acetate over 10% Pd/C furnished **6** in 70% yield[5] (ee >93%), which was easily converted into the corresponding methyl ether **7** in 99% yield. Its bromination with NBS in DMF,[6a,b] at room temperature afforded monobromo compound **8** in 96% yield. Lithiation of **8** with *n*-BuLi and subsequent reaction with ethyl chloroformate gave ester **9** in 93% yield. Finally, ester **9** on treatment with BBr_3 directly afforded **1** in 40% yield via demethylation and concomitant esterification.[7] The rotation value of **1** $\{[\alpha]_D^{25} = -24$ (*c* 0.1, $CH_3OH)\}$ agreed well with that reported for natural (*R*)-**1** $\{[\alpha]_D^{25} = -20$ (*c* 0.1, $CH_3OH)\}$, establishing the absolute configuration of **5** as assigned above.

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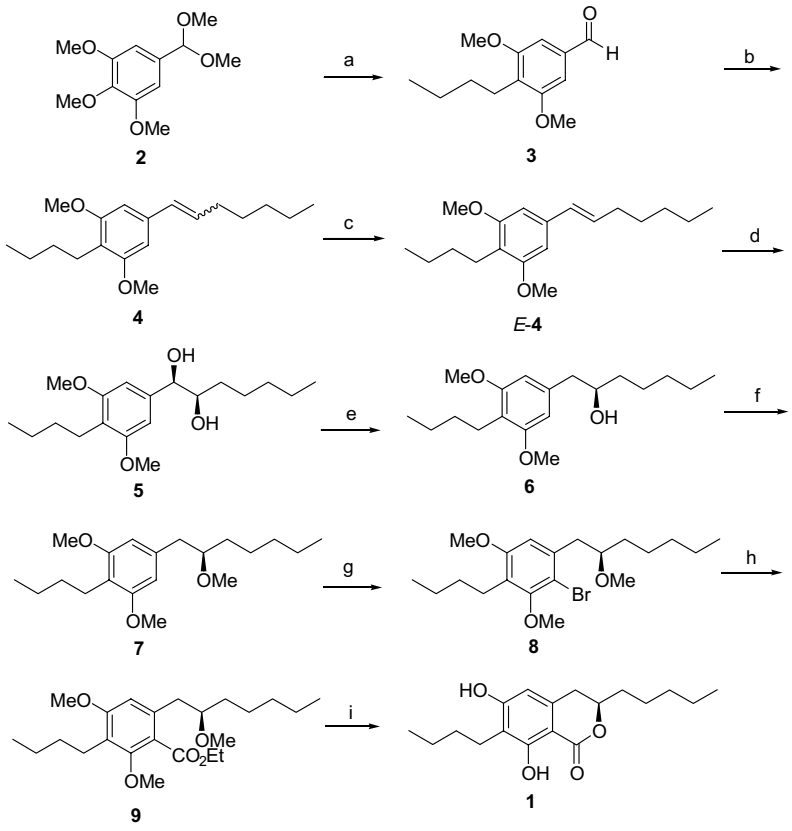

Scheme 1. Reagents and conditions: (a) 3 equiv Na, THF, rt, 24 h, 1.5 equiv *n*-BuBr, 0 °C, 24 h then aqCH_3COOH, reflux, 5 h, 85%; (b) *n*-$C_6H_{13}PPh_3Br$, *n*-BuLi, THF, 0 °C, 96%; (c) hν, I_2, hexane–ether = 3:2 v/v, 2 h, 99%; (d) AD-mix-β, $MeSO_2NH_2$, *t*-BuOH/H_2O, 0 °C, 24 h, 92%; (e) 10% Pd/C, CH_3CO_2Et, 70%; (f) NaH, CH_3I, THF, 99%; (g) NBS, DMF, 96%; (h) *n*-BuLi, $ClCO_2Et$, 93%; (i) excess BBr_3, −78 °C to rt, 24 h, 40%.

3. Conclusion

In summary, we have successfully achieved a highly enantioselective synthesis of **1** in 18.4% overall yield from the readily available dimethyl acetal **2**. This synthesis required only nine chemical operations. The absolute stereochemistry was introduced by employing a Sharpless AD reaction. Application of this sequence to enantioselective synthesis of other types of more complex natural products incorporating the corresponding crucial dihydroisocoumarin core structures is currently ongoing in our group.

4. Experimental

4.1. General

Melting points were measured on a Kofler apparatus and are uncorrected. The ^1H and ^{13}C NMR data were recorded in $CDCl_3$ solution with a Varian Mercury 300 BB spectrometer. The chemical shifts are reported in ppm relative to TMS. The optical rotations were determined with a JASCO J-20C polarimeter with 0.2 dm tube. The mass spectra were measured with EI (70 eV) technique. HPLC analysis was performed on Varian Dynamax SD-300 using chiralcel column CDMPC (150 × 4.6 mm∅) with hexane/isopropyl alcohol as eluant. Column chromatography was generally performed on silica gel (200–300 meshes) eluting with petroleum ether and ethyl acetate.

4.2. 4-Butyl-3,5-dimethoxybenzaldehyde 3

To a suspension of the freshly cut sodium (0.276 g, 12 mmol) in anhydrous THF (30 mL), a solution of **2** (0.968 g, 4 mmol) in anhydrous THF (5 mL) was added dropwise under a dry argon atmosphere. The mixture was stirred at room temperature for 24 h, cooled to 0 °C after which *n*-BuBr (0.816 g, 6 mmol) in anhydrous THF (5 mL) was slowly added, and the resulting mixture stirred for 24 h. The reaction was quenched by the slow dropwise addition of H_2O (10 mL) (caution!). Subsequently the mixture was hydrolyzed (CH_3COOH–H_2O = 5:1, 10 mL, reflux, 5 h) and extracted with ether. The organic phase was washed with saturated aqueous $NaHCO_3$, dried, and evaporated. The residue was flash chromatographed using petroleum ether and ethyl acetate (50:1, v/v) to give compound **3** as a colorless oil, which on standing gave a colorless solid (0.755 g, 85%). Mp 46–48 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 0.89 (t, J = 6.6 Hz, 3H), 1.31 (m, 2H), 1.33 (m, 2H), 2.64 (t, J = 6.3 Hz, 2H), 3.81 (s, 6H), 6.98 (s, 2H), 9.82 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8, 22.7, 23.0, 30.8, 55.5, 104.5, 127.0, 135.0, 158.3, 191.6. MS (EI): *m/z* 222 (M^+, 21), 179 (100), 151 (26), 119 (27), 91 (44), 77 (31).

4.3. 2-Butyl-5-((*E*)-hept-1-enyl)-1,3-dimethoxybenzene (*E*)-4

To a solution of *n*-hexyltriphenylphosphonium bromide (8.88 g, 20.82 mmol) in THF (40 mL), *n*-BuLi (3.30 M, 6.35 mL) was added dropwise and stirred for 30 min under a stream of argon at 0 °C. Compound **3** (4.20 g, 18.92 mmol) in THF (20 mL) was added dropwise to the above solution at 0 °C and stirred for 2 h at room temperature. After quenching the reaction with brine, it was extracted with ethyl acetate and dried and evaporated. The residue was flash chromatographed using petroleum ether and ethyl acetate (50:1, v/v) to give an *E*:*Z* mixture **4** as a colorless oil (5.26 g, 96%). The oil was dissolved in hexane–ether (500 mL; v/v = 3:2) and a couple of iodine crystals were added to the solution, which was exposed to sunlight for 1 h. After washing with aqueous sodium thiosulfate and water, the solution was dried, and evaporated to dryness to give (*E*)-**4** as a colorless oil (5.25 g, 99%). ^{1}H NMR (300 MHz, $CDCl_3$): ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89–0.93 (m, 6H), 1.34–1.55 (m, 10H), 2.20 (m, 2H), 2.61 (t, J = 7.2 Hz, 2H), 3.82 (s, 6H), 6.20 (m, 1H), 6.34 (d, J = 15.9 Hz, 1H) 6.54 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 22.6, 22.8, 29.1, 31.4, 31.6, 32.9, 55.6, 101.5, 118.6, 130.1, 130.4, 136.4, 158.3. MS (EI): *m*/*z* 290 (M^+, 25), 247 (100), 84 (44). HRMS calcd for $C_{19}H_{31}O_2$ (M+H): 291.2319. Found $(M+H)^+$: 291.2314.

4.4. (1*R*,2*R*)-1-(4-Butyl-3,5-dimethoxyphenyl)heptane-1,2-diol 5

To a stirred solution of *tert*-BuOH (5 mL) and H_2O (5 mL), AD-mix-β (1.40 g) and $MeSO_2NH_2$ (95 mg) were added and the mixture stirred at room temperature until both phases were clear, cooled to 0 °C and (*E*)-**4** (0.290 g, 1.00 mmol) then added immediately into it. The mixture was stirred vigorously at 0 °C and judged by TLC. The reaction was quenched at 0 °C by addition of Na_2SO_3 (1.50 g), warmed to room temperature and stirred for 0.5 h. The reaction mixture was extracted with ethyl acetate. The combined organic layer was washed with a 2 N KOH solution, water, and dried. The solvent was distilled off, and the residue was flash chromatographed using petroleum ether and ethyl acetate (2:1, v/v) to afford the diol **5** as a white solid (0.298 g, 92%). Mp 84–86 °C. $[\alpha]_D^{25} = -3.0$ (*c* 1.0, CH_3OH, ee 95%); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.83–0.93 (m, 6H), 1.25–1.48 (m, 12H), 2.40 (s, 1H), 2.61 (t, J = 7.2 Hz, 2H), 2.68 (s, 1H), 3.68 (m, 1H), 3.81 (s, 6H), 4.37 (d, J = 6.0 Hz, 1H), 6.50 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 22.5, 22.8, 25.3, 31.4, 31.7, 32.6, 55.6, 75.8, 78.3, 102.1, 119.0, 139.8, 158.1. HRMS calcd for $C_{19}H_{34}O_4Na$ (M+Na): 347.2193. Found $(M+Na)^+$: 347.2191.

4.5. (*R*)-1-(4-Butyl-3,5-dimethoxyphenyl)heptan-2-ol 6

The diol **5** (300 mg, 0.926 mmol) was hydrogenated using 10% Pd/C (30 mg) in dry ethyl acetate (30 mL) and two drops of 98% H_2SO_4 for 6 h at room temperature and atmospheric pressure. After neutralization with solid Na_2CO_3, the catalyst was filtered off. The solvent was distilled off and flash chromatographed using petroleum ether and ethyl acetate (10:1, v/v) to afford compound **6** as a white solid (200 mg, 70%). Mp 56–57 °C. $[\alpha]_D^{25} = -12$ (*c* 1.0, CH_3OH, ee 93%); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89–0.94 (m, 6H), 1.28–1.49 (m, 10H), 1.53 (m, 2H), 1.62 (s, 1H), 2.55 (dd, J = 13.5 Hz, 4.2 Hz, 1H), 2.57 (t, J = 6.9 Hz, 2H) 2.80 (dd, J = 13.5 Hz, 3.9 Hz, 1H), 3.79 (s, 6H), 3.80 (m, 1H), 6.39 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 22.5, 22.6, 22.9, 25.5, 31.6, 31.9, 36.9, 44.6, 55.7, 72.6, 104.8, 117.7, 137.0, 158.3. HRMS calcd for $C_{19}H_{33}O_3$ (M+H): 309.2424. Found $(M+H)^+$: 309.2423.

4.6. (*R*)-2-Butyl-1,3-dimethoxy-5-(2-methoxyheptyl)-benzene 7

To a solution of **6** (183 mg, 0.594 mmol) in THF (20 mL) were added NaH (60%, 28.5 mg, 0.713 mmol) and MeI (101 mg, 0.713 mmol) and the mixture stirred under a stream of argon at room temperature for 12 h. On completion of the reaction, water was added to the solution. It was extracted with ether and the organic extracts were washed with water, dried with anhydrous Na_2SO_4, and the solvent evaporated. The residue was flash chromatographed using petroleum ether and ethyl acetate (25:1, v/v) to give compound **7** as a colorless oil (189 mg, 99%). $[\alpha]_D^{25} = +14$ (*c* 1.0, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90 (t, J = 7.2 Hz, 3H), 0.93 (t, J = 7.5 Hz, 3H), 1.30–1.68 (m, 12H), 2.61 (t, J = 7.2 Hz, 2H), 2.65 (dd, J = 13.5 Hz, 6.0 Hz, 1H), 2.81 (dd, J = 13.5 Hz, 6.6 Hz, 1H), 3.34 (s, 3H), 3.38 (m, 1H), 3.81 (s, 6H), 6.40 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 22.5, 22.6, 22.8, 24.9, 31.7, 32.0, 33.6, 40.9, 55.7, 57.0, 82.4, 104.9, 117.3, 137.8, 158.0. HRMS calcd for $C_{20}H_{35}O_3$ (M+H): 323.2581. Found $(M+H)^+$: 323.2576.

4.7. (*R*)-2-Bromo-4-butyl-3,5-dimethoxy-1-(2-methoxy-heptyl)benzene 8

To a solution of **7** (683 mg, 2.12 mmol) in dry DMF (12 mL) was added NBS (378 mg, 2.12 mmol) and the mixture stirred at room temperature for 24 h. The reaction mixture was poured into ice water (50 mL) and extracted with ethyl acetate. The combined organic layer was washed with brine and dried with anhydrous Na_2SO_4. After column chromatography purification using petroleum ether and ethyl acetate (25:1, v/v), the compound **8** was obtained as a colorless oil (814 mg, 96%). $[\alpha]_D^{25} = -4.0$ (*c* 1.0, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, J = 7.2 Hz, 3H), 0.92 (t, J = 7.2 Hz, 3H), 1.27–1.54 (m, 12H), 2.63 (t, J = 7.2 Hz, 2H), 2.82 (dd, J = 13.5 Hz, 6.0 Hz, 1H), 2.93 (dd, J = 13.5 Hz, 7.2 Hz, 1H), 3.32 (s, 3H), 3.46 (m, 1H), 3.79 (s, 3H), 3.80 (s, 3H), 6.59 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 14.0, 22.6, 23.0, 24.4, 24.9, 32.0, 34.0, 41.4, 55.6, 57.3, 61.0, 80.5, 109.9, 110.9, 124.5, 137.3, 155.4, 157.2. HRMS calcd for $C_{20}H_{37}BrNO_3$ ($M+NH_4$): 418.1951. Found $(M+NH_4)^+$: 418.1949.

4.8. Ethyl (*R*)-3-butyl-2,4-dimethoxy-6-(2-methoxyheptyl)benzoate 9

To a solution of **8** (750 mg, 1.875 mmol) in dry THF (10 mL), *n*-BuLi (2.60 M, 0.865 mL) was added dropwise under a stream of argon at −78 °C. The resulting reaction mixture was allowed to warm to 0 °C gradually. The reaction mixture was cooled to −78 °C after 2 h, after which ethyl chloroformate (0.215 mL, 2.25 mmol) in THF (10 mL) was added to the above solution. The resulting reaction mixture was allowed to warm to room temperature gradually. The mixture was stirred until TLC revealed the absence of **8**. Brine was then added to the reaction mixture, which was extracted with ethyl acetate and the organic extract dried, and evaporated. The residue was flash chromatographed using petroleum ether and ethyl acetate (30:1, v/v) to give the compound **9** as a colorless oil (687 mg, 93%). $[\alpha]_D^{25} = +12$ (*c* 1.02, CH_3OH); ^1H NMR (300 MHz, $CDCl_3$): δ 0.86 (t, $J = 6.9$ Hz, 3H), 0.91 (t, $J = 7.2$ Hz, 3H), 1.16–1.53 (m, 12H), 1.37 (t, $J = 6.9$ Hz, 3H), 2.57 (t, $J = 7.8$ Hz, 2H), 2.64 (dd, $J = 13.8$ Hz, 5.7 Hz, 1H), 2.82 (dd, $J = 13.8$ Hz, 7.2 Hz, 1H), 3.24 (s, 3H), 3.31 (m, 1H), 3.76 (s, 3H), 3.80 (s, 3H), 4.35 (q, $J = 7.2$ Hz, 2H), 6.53 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 14.0, 14.2, 22.6, 23.1, 23.5, 24.9, 31.8, 31.9, 34.0, 38.4, 55.5, 57.2, 60.9, 62.6, 81.9, 108.6, 121.4, 122.8, 136.1, 156.3, 159.0, 168.6. HRMS calcd for $C_{23}H_{39}O_5$ (M+H): 395.2792. Found $(M+H)^+$: 395.2788.

4.9. (*R*)-7-Butyl-6,8-dihydroxy-3-pentylisochroman-1-one 1

To a solution of BBr_3 (0.87 mL, 9.39 mmol) in freshly distilled CH_2Cl_2 (5 mL) at −78 °C was added a solution of **9** (122 mg, 0.313 mmol) dropwise in CH_2Cl_2 (3 mL). The resulting reaction mixture was allowed to warm to room temperature and stirred for 24 h. The reaction carefully quenched with cold water (2 mL) and stirred vigorously for 2 h, extracted with ethyl acetate and dried over Na_2SO_4. The solvent was evaporated and the residue flash chromatographed using petroleum ether and ethyl acetate (20:1, v/v) to give compound **1** as a colorless solid (38 mg, 40%). Mp 148–149 °C. $[\alpha]_D^{25} = -24$ (*c* 0.1, CH_3OH, ee 93%), lit.[1] $[\alpha]_D^{25} = -20$; ^1H NMR (300 MHz, $CDCl_3$): δ 0.89 (t, $J = 6.9$ Hz, 3H), 0.93 (t, $J = 7.2$ Hz, 3H), 1.33 (m, 2H), 1.40 (m, 2H), 1.53 (m, 2H), 1.62 (m, 2H), 1.70 (m, 2H), 1.86 (m, 2H), 2.63 (t, $J = 7.5$ Hz, 2H), 2.80 (m, 2H), 4.50 (m, 1H), 6.19 (s, 1H) 11.44 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 22.2, 22.5, 22.8, 24.5, 30.9, 31.5, 32.9, 34.7, 79.3, 101.6, 105.9, 114.6, 138.3, 159.9, 162.2, 170.5. HRMS calcd for $C_{18}H_{25}O_4$ (M−H): 305.1758. Found $(M-H)^-$: 305.1752.

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