Facile Total Synthesis of Isopregomisin†

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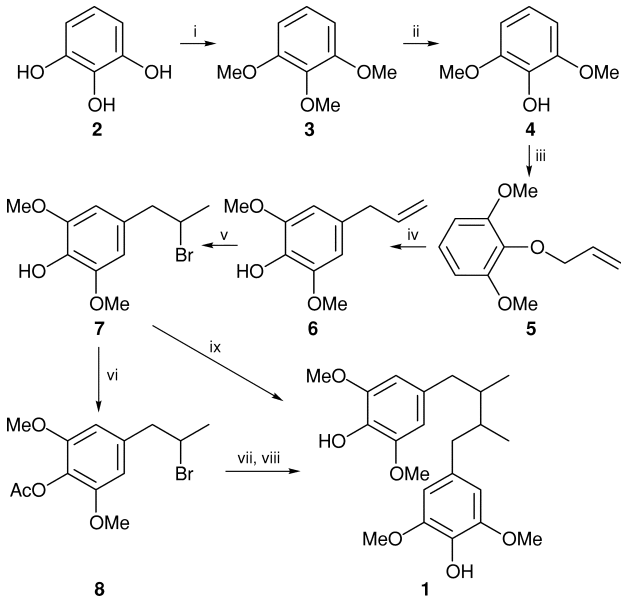
Isopregomisin, a diarylbutane-lignan, has been synthesized by a short and efficient route starting from pyrogallol; the synthesis involves a novel selective demethylation reaction and the coupling reaction of the Grignard reagent produced from an aryl bromopropane with (*E*)-2-*tert*-butyl-3-phenyloxaziridine.

Isopregomisin, a diarylbutane-lignan, isolated from the twigs of *Prolieria chilensis Johnston* (Zygophyllaceae) in 1989,[1] has good antioxidant activity.[2] In this paper, we report a new short synthetic route to isopregomisin.

Our synthetic strategy (outlined in Scheme 1) started from pyrogallol **2**, which was easily converted into trimethyl pyrogallol **3**. Treatment of **3** with $ZnCl_2$/propionic acid gave 2,6-dimethoxyphenol (**4**) in a yield of 71%.[3] Previously, the most effective method to prepare this compound has been the methylation of pyrogallol **2** with CH_3Br, whose products were complicated and the yield of **4** rather low.[4] However, when $ZnCl_2$/propionic acid was used as a demethylation agent, **4** can be easily obtained in a higher yield from trimethyl pyrogallol **3** and was almost the sole product. Compound **5**, readily available in near quantitative yield by the reaction of **4** with allyl bromide, was submitted to a Claisen rearrangement in a sealed tube to give **6** in 88% yield (lit.[5] 48%). Reaction of **6** with HBr (40%, in acetic acid) led to the bromide **7** in a yield of 84%. According to the published report,[6] isopregomisin (**1**) could be directly synthesized by treatment of **7** with Mg/I_2, but the yield was only 8%. Fortunately, compound **8**, readily obtained by protection of **7** with acetyl chloride in 95% yield, was coupled with magnesium and (*E*)-*tert*-butyl-3-phenyloxaziridine[7] followed by hydrolysis with a 10% ammonia solution to give the target molecule **1** in a yield of 51%. The spectra and elemental analysis of **1** are compatible with those reported.



Scheme 1 *Reagents*: i, $(CH_3)_2SO_4$; ii, $ZnCl_2/C_2H_5CO_2H$; iii, CH_2CHCH_2Br/K_2CO_3; iv, 170–180 °C; v, HBr/CH_3CO_2H; vi, CH_3COCl/pyr; vii, Mg/(*E*)-2-*tert*-butyl-3-phenyloxaziridine; viii, 10% NH_3, H_2O; ix, Mg/I_2

Experimental

Melting points were determined with a Kofler micro-melting point apparatus and are uncorrected. Mass spectra were recorded on a ZAB-HS spectrometer, NMR spectra were taken on a FT-80A and a Bruker 400 instrument in $CDCl_3$ with Me_4Si as internal standard, and IR spectra were obtained on a FT-170SX spectrometer. Elemental analysis were performed on a Carlo-Erba-1106 instrument. All compounds were purified by column chromatography on silica gel H, from the Qingdo Marine Chemical Factory, eluting with the solvent mixture of light petroleum (bp 60–90 °C) and ethyl acetate.

Allyl 2,6-*dimethoxyphenyl Ether* **5**.—A mixture of compound **4** (7.7 g, 0.05 mol), allyl bromide (9.0 g, 0.075 mol) and NaH (1.2 g, 0.05 mol) in dry acetone (50 ml) was stirred at room temp. for 24 h. The solvent and excess allyl bromide were removed with a rotary evaporator. The residue was purified by column chromatography to afford **5** as a pale-yellow oil (14.4 g, 99%) (lit.[5] 88%): *m*/*z* (EIMS) 194 (M^+, 56), 167 (5), 153 (100), 125 (95); δ_H 3.73 (s, 6 H, $ArOCH_3$); 4.46 (d, $J = 8.0$ Hz, 2 H, OCH_2), 5.0–5.9 (m, 3 H, $CH{=}CH_2$, 6.0–7.1 (m, 3 H, ArH); ν_{max}/cm^{-1} (film) 2942, 1594, 1479, 1112.

4-*Allyl*-2,6-*dimethoxyphenol* **6**.—An ampoule charged with compound **5** (6.0 g, 0.031 mol) was sealed and placed in an anti-pressure tube followed by further sealing. This doubly-sealed tube was soaked in a oil-bath and heated at 170–180 °C for 7 h. The crude product obtained was then purified by column chromatography to give a pale-yellow oil (5.3 g, 88%) (lit.[5] 54%): *m*/*z* (FABMS) 195 (M + 1), 194 (M^+); δ_H 3.33 (d, $J = 7.0$ Hz, 2 H, CH_2), 3.83 (s, 6 H, $ArOCH_3$), 4.8–5.3 (m, 3 H, $CH{=}CH_2$), 5.5 (bs, ArOH, D_2O exchanged), 6.36 (s, 2 H, ArH); ν_{max}/cm^{-1} (film) 3521, 3451, 2973, 1613, 1513, 1214.

1-(3,5-*Dimethoxy*-4-*hydroxyphenyl*)-2-*bromopropane* **7**.—A mixture of compound **6** (2.5 g, 13 mmol), HBr (40%, in glacial acetic acid, 15 ml) was shaken and placed in a darkroom for a week. Then the bulk of the acetic acid was removed under reduced pressure and the remaining acetic acid was removed by co-distillation with ethanol. The residue was cooled in a ice-bath and slowly mixed with anhydrous K_2CO_3 (1–2 g), and the resultant mixture was purified by column chromatography to obtain **7** as a colourless oil (3 g, 84%): *m*/*z* (EIMS) 276, 274 (M, 21), 195(32), 167(100); δ_H 1.68 (d, $J = 6.3$ Hz, 3 H, CH_3), 2.9–3.2 (m, 2 H, $ArCH_2$), 3.87 (s, 6 H, $ArOCH_3$), 4.3 (m, 1 H, CHBr), 5.30 (s, 1 H, ArOH, D_2O exchanged), 6.42 (s, 2 H, ArH); (Found: C, 48.0; H, 5.34. $C_{11}H_{15}BrO_3$ requires C, 48.0; H, 5.5%).

1-(4-*Acetoxy*-3,5-*dimethoxyphenyl*)-2-*bromopropane* **8**.—To a solution of compound **7** (1.1 g, 4 mmol) in anhydrous THF (20 ml) was added pyridine (20 ml), cooled to −30 °C. Subsequently acetyl chloride (1 ml) was added dropwise and the mixture was stirred at −30 °C for 1 h, and then at room temp. overnight. The resulting mixture was washed with ice–water and aq. HCl (10%) to remove the pyridine. The standard ethereal workup followed by purification by FCG afforded the desired product **8** as a white solid (1.2 g, 95%): mp 78–80 °C; *m*/*z* (EIMS) 318, 316 (M^+), 276, 237 (6) 274 (36), 195 (23), 167 (100); δ_H 1.69(d, $J = 6.8$ Hz, 3 H, CH_3), 2.33 (s, 3 H, CH_3CO), 2.9–3.2 (m, 2 H, $ArCH_2$), 3.80 (s, 6 H, $ArOCH_3$), 4.3 (m, 1 H, CHBr), 6.45 (s, 2 H, ArH); (Found C, 49.2; H, 5.4. $C_{13}H_{17}BrO_4$ requires C, 49.2; H, 5.4%).

Isopregomisin **1**.—To the Grignard reagent made from magnesium turnings (72 mg, 3 mmol) and compound **8** (640 mg, 2 mmol) in dry THF (10 ml) was added dropwise a solution of (*E*)-2-*tert*-butyl-3-

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phenyloxaziridine (180 mg, 1 mmol) in THF (10 ml) at 0 °C and the resultant mixture stirred at room temp. overnight. The precipitate formed was filtered off and the filtrate evaporated to dryness. The residue was dissolved in 10% ammonia solution (50 ml) and stirred at room temp. for 2 h. After the addition of Et_2O (30 ml), the mixture was acidified with 6 M HCl and extracted with Et_2O. The standard ethereal workup followed by column chromatography gave a light-yellow oil (210 mg), which was crystallized from light petroleum to provide **1** as a white crystalline solid (199 mg, yield 51%): mp 109–111.5 °C (lit[1] 110–112 °C); *m*/*z* (EIMS) 390 (M^+, 12), 388 (M − 2, 46), 167 (100); ν_{max}/cm^{-1} (KBr) 3370, 1610, 1510; δ_H 0.83 (d, $J = 6.6$ Hz, 6 H, $2 \times CH_3$), 1.75 (m, 2 H, $2 \times CH$), 2.2–2.7 (m, 4 H, $2 \times CH_2$), 3.80 (s, 12 H, $4 \times OCH_3$), 5.29 (brs, 2 H, $2 \times OH$, D_2O exchangable), 6.32 (s, 4 H, ArH); (Found C, 67.85; H, 7.8. $C_{22}H_{30}O_6$ requires C, 67.7; H, 7.7%). All spectral data were in good agreement with that previously reported.

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