A simple stereoselective synthesis of (+)-[6]-gingerdiol

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1. Introduction

(+)-[6]-Gingerdiol (1) is an important constituent of the rhizomes of ginger (Zingiber officinale) [1,2]. The compound possesses a trisubstituted aromatic ring bearing an aliphatic chain. The side chain contains two hydroxyl groups with β-configuration. The compound exhibits various important medicinal properties including anti-oxidant, anti-inflammatory and anti-fungal activities [3-5]. The synthesis of the compound was achieved earlier by a French group applying the demetallation of tricarboxyliron diene complexes [6]. In continuation of our work on the stereoselective construction of bioactive natural products here we report a simple synthesis of (+)-[6]-gingerdiol (1) [7-12] via alternative route.

2. Experimental

All the chemicals were purchased from Sigma Aldrich with purity not less than 99.9%. All reactions were carried out under an inert atmosphere of N2. Analytical Thin Layer Chromatography (TLC) was carried out by using silica gel 60 F254 precoated plates. Visualization was accomplished with UV lamp and I2 stain. All products were characterized by their NMR and Mass spectra.

2.1. Instrumentation

1H NMR and 13C NMR were recorded on Varian Gemini 200 MHz (400 MHz) and 50 MHz (100 MHz) spectrometers in CDCl3 using TMS as the internal standard and chemical shifts were reported in parts per million (ppm, δ) downfield from the tetramethyl silane. FT-IR spectra were recorded with Perkin Elmer RX1 FT-IR spectrophotometer and Mass spectra were recorded with VG Autospec instrument in m/z ratio. Optical rotations were determined with Jasco Dip 360 digital polarimeter at 25 °C. Column chromatography was carried out with silica gel (BDH 100-200 Mesh) and TLC with silica gel 60 F254 precoated plates.

2.2. Synthesis

2.2.1. 4-(Butyl dimethyl siloxy)-3-methoxy benzaldehyde (5)

To a stirred solution of compound 4 (1.0 g, 6.57 mmol) and imidazole (1.78 g, 26.28 mmol) in dry DCM (15 mL) was added tert-butyl chloro (dimethyl) silane (TBS-Cl) (1.98 g, 13.15 mmol) slowly at 0 °C. The mixture was then kept at room temperature for 5 h, then quenched with H2O. The dichloromethane (DCM) layer was separated and the aqueous layer was extracted with DCM (2 x 10 mL). The combined organic layers were washed with H2O, brine, and dried (anhydrous Na2SO4). The solvent was removed in vacuo, and the residue was purified by column chromatography on silica gel (2% EtOAc/hexane) to form 5 as a colorless oil [Scheme 1]. Yield: 88%, 1.54 g. IR (KBr, ν, cm⁻¹): 1720, 1612, 1513, 1443, 1247. 1H NMR (200 MHz, CDCl3, δ, ppm): 9.80 (s, 1H, Ar-C); 7.38 (d, 1H, J = 2.0 Hz, o-Ar-H); 7.30 (dd, 1H, J = 8.0, 2.0 Hz, o-Ar-H); 6.91 (d, 1H, J = 8.0 Hz, m-Ar-H); 3.85 (s, 3H, Ar-O-C); 1.00 (s, 9H, Si-C(CH3)3); 0.20 (s, 6H, Si-(CH3)2). 13C NMR (50 MHz, CDCl3, δ, ppm): 189.8, 151.4, 150.8, 130.4, 125.8, 120.6, 110.0, 55.2, 25.3, 18.1. ESI-MS (m/z): 289 [M+Na]+. [α]D25 = +5.65 (c 1.75, CHCl3). Anal. calc. for C16H19O2Si: C, 63.15; H, 8.27. Found: C, 63.05; H, 8.28%.

2.2.2. (E)-Ethyl 3-(4-(tert-butyldimethylsiloxy)-3-methoxyphenyl) acrylate (6)

To a solution of aldehyde, 5 (1.54 g, 5.78 mmol) in dry DCM (10 mL) ethyl (triphenyl phosphorinylidene) acetate (3.017 g, 8.67 mmol) was added and the mixture was stirred at ambient temperature for 8 h. It was concentrated in vacuum, and the residue was purified by column chromatography (20% EtOAc/hexane) to afford compound 6 (Scheme 1). Yield: 81%, 1.57 g. IR (KBr, ν, cm⁻¹): 1720, 1612, 1513, 1443, 1247.
Reagents and conditions: a) TBSCI, imidazole, CH2Cl2, rt. 5 h, 89%; b) PPh3::CH2OEt, CH2Cl2, rt. 6 h, 81%; c) NiCl2, NaBH4, MeOH, 0 °C. 15 min then 1 h rt. N2 condition, 91%; d) DIBAL-H, CH2Cl2, MeOH, -78 °C to -10 °C. 0.5 h, 77%; e) [CuI]2, DMSO, Et3N, CH2Cl2, -78 °C, 0.5 h, 81%; f) (SS)-4-BuSnCH2=CH2, CH2Cl2, -15 °C to -0 °C, 20 h, 79%; g) BOC-DMAP, MeCN. 5 h, 77%; h) Li, MeCN, -20 °C, 6 h, 67%; i) TBAF, THF, 5 h, 78%; j) K2CO3, MeOH, 20 °C. 30 min, 84%; k) n-C6H5Mglr, Cul, -30°C, 2 h, 71%.

2.2.3. Ethyl 3-(4-(tert-butyl dimethyl silyloxy)-3-methoxy phenyl) propanoate (7)

To a solution of the compound 6 (1.57 g, 4.68 mmol) in dry MeOH (15 mL) at 0 °C was added NiCl2 (0.22 g, 0.936 mmol), after stirring 15 min at 0 °C then added NaBH4 (0.35 g, 9.36 mmol) portion wise under N2 condition. Then allow the residue to room temperature and stir for 1 h, and the residue was quenched with NH4Cl. The MeOH layer was separated and the aqueous layer was washed with DCM (2 x 10 mL) and combined organic layer washed with H2O, brine, and dried over anhydrous Na2SO4. The solvent was removed in vacuum, and the residue was purified by column chromatography on silica gel (2% EtOAc/hexane) to afford the pure compound 7 (Scheme 1). Yield: 91%, 1.43 g. IR (KBr, ν, cm−1): 1735, 1603, 1513, 1465, 1259. 1H NMR (200 MHz, CDCl3, δ, ppm): 6.79 (d, 1H, J = 8.0 Hz, m-Ar-H), 6.72 (d, 1H, J = 2.0 Hz, O-Ar-H), 6.66 (dd, 1H, J = 8.0, 2.0 Hz, o-Ar-H), 4.18 (q, 2H, J = 7.0 Hz, O-Chl=CHl), 3.85 (s, 3H, Ar-O-CH3), 2.92 (t, 2H, J = 7.0 Hz, Ar-C=CH2), 2.69-2.60 (m, 2H, Ar-Ch=CH2), 1.30 (t, 3H, J = 7.0 Hz, O-CH2-CH3), 1.08 (s, 9H, Si-(CH3)3). 13C NMR (50 MHz, CDCl3, δ, ppm): 173.3, 151.2, 143.8, 134.0, 120.8, 120.0, 112.1, 60.0, 55.3, 25.8, 18.2, -4.9. ESI-MS (m/z): 337 [M+H]+. αd = +4.99 (c 0.75, CHCl3). Anal. calcd. for C18H20O5Si: C, 63.90; H, 8.93. Found: C, 63.81; H, 8.89%.

2.2.4. 3-(4-(tert-Butyl dimethyl silyloxy)-3-methoxy phenyl)-propan-1-ol (8)

To a solution of compound 7 (1.43 g, 4.23 mmol) in dry DCM (10 mL) cooled to -78 °C DIBAL-H (7.58 mL, 10.62 mmol) was added drop wise and the mixture was then stirred at the same temperature for 1 h. The reaction mixture was quenched by slowly addition of dry MeOH (10 mL) and was brought to room temperature. Saturated aqueous potassium tarterate solution (10 mL) was added to the reaction mixture and stirred until two layers separated (2 h). Dichloro methane was evaporated and the residue was extracted with EtOAc (2 x 50 mL). The combined organic extracts were washed with brine, dried over anhydrous Na2SO4 and concentrated in vacuum, purification of the residue by column chromatography (30% EtOAc/hexane) afforded pure compound 8 (Scheme 1). Yield: 77%, 0.964 g. IR (KBr, ν, cm−1): 3363, 1512, 1466, 1285. 1H NMR (200 MHz, CDCl3, δ, ppm): 6.72 (d, 1H, J = 8.0 Hz, m-Ar-H), 6.66 (dd, 1H, J = 2.0 Hz, O-Ar-H), 6.60 (dd, 1H, J = 8.0, 2.0 Hz, o-Ar-H), 3.79 (s, 3H, Ar-O-CH3), 3.69 (brs, 1H, 3’-CH=OH), 3.62
To a solution of TiCl₄ (0.28 ml, 263 mmol) in dry DCM (10 ml) was added MeOH (1.0 ml) and left under nitrogen atmosphere and was allowed to warm to rt, after 1 h silver(I) oxide (0.060 g, 0.263 mmol) was added at room temperature and the mixture was stirred for 5 h under exclusion of direct light. The mixture was diluted with DCM (30 ml) and treated with (S)-BINOL (0.150 g, 0.526 mmol) at rt, for 2 h to furnish the chiral bis-Ti(IV) oxide (S,S)-I. The in situ generated (S,S)-I was cooled to -15 °C and treated sequentially with aldehyde 3 (0.775 g, 2.63 mmol) and allyltributyltin (tributyl(prop-2- en-1-yl)stannane (1.22 ml, 3.419 mmol) at the same temperature. The mixture was allowed to warm to 0 °C and stirred for 20 h, then the mixture was quenched with saturated aqueous NaHCO₃ (50 ml) and extracted with EtOAc (3 x 50 ml). The organic extracts were dried over anhydrous Na₂SO₄. Evaporation of the solvents and purification of the residue by column chromatography on silica gel (20% EtOAc/hexane) gave compound 2 (Scheme 1). Yield: 79%, 0.699 g. IR (KBr, v cm⁻¹): 3445, 2929, 1648, 1513, 1463, 1283. 1H NMR (200 MHz, CDCl₃, δ, ppm): 6.70 (d, 1H, J = 8.0 Hz, m-Ar-H), 6.62 (d, 1H, J = 2.0 Hz, o-Ar-H), 6.59 (dd, 1H, J = 8.0, 2.0 Hz, o-Ar-H), 5.72 (m, 1H, CH₂-C(6H₃)), 5.12-5.01 (m, 2H, CH₂-C(6H₃)), 3.79 (s, 3H, O-C(6H₃)), 3.67 (brs, 1H, 3°-CH(OH)), 3.62 (m, 2H, 3°-Cl(OH)), 2.70-2.51 (m, 2H, Ar-CH₂-C(6H₃)), 2.46-2.31 (m, 2H, 4°-Cl₃C₆H₄), 1.30-1.22 (m, 2H, Ar-CH₂-C(6H₃)), 1.00 (s, 9H, Si-C(6H₃)). 13C NMR (50 MHz, CDCl₃, δ, ppm): 150.5, 143.2, 132.5, 120.6, 115.8, 113.0, 71.0, 55.3, 34.2, 32.0, 25.9, 18.2, -4.8. ESI-MS (m/z): 337 [M⁺]+. [α]D 25 = +50.65 (c 2.55, CHCl₃). Anal. calcld. for C₄₁H₂₉O₅Si: C, 66.05; H, 6.11%. Found: C, 65.9; H, 6.1%.}

2.2.7. (R)-tert-butyl 1-(4-(tert-butyl dimethyl silyl)-3-methoxyphenyl)-hex-5-en-3-yl carbonate (9)

To a stirred solution of compound 2 (0.200 g, 0.595 mmol) in dry MeCN (10 ml) was added B(OEt)₃ (0.75 ml, 3.12 mmol) and DMAP (0.101 g, 0.832 mmol) at 0 °C. After 5 h of stirring the solvent was evaporated under reduced pressure. The residue was taken up in EtOH (15 ml), and imidazole was added in catalytic amount. The resulting mixture was washed with 5% HCl solution, dried (anhydrous Na₂SO₄), filtered, and concentrated in vacuo, purification of the residue by column chromatography on SiO₂ (1% EtOAc/hexane) gave compound 9 (Scheme 1). Yield: 78%, 0.199 g. IR (KBr, v cm⁻¹): 1710, 1631, 1540, 1486, 1263. 1H NMR (200 MHz, CDCl₃, δ, ppm): 6.69 (d, 1H, J = 8.0 Hz, m-Ar-H), 6.61 (d, 1H, J = 2.0 Hz, o-Ar-H), 5.65 (dd, 1H, J = 8.0, 2.0 Hz, o-Ar-H), 5.73 (s, 1H, 5°-Cl₃C₆H₄), 5.11-5.02 (m, 2H, 6°-Cl₃C₆H₄). 13C NMR (50 MHz, CDCl₃, δ, ppm): 150.3, 143.4, 134.6, 124.0, 120.0, 112.1, 67.8, 56.0, 51.0, 46.3, 38.2, 37.0, 32.1. ESI-MS (m/z): 238 [M⁺]+. [α]D 25 = +19.37 (c 0.20, CHCl₃). Anal. calcld. for C₁₉H₁₄O₃Si: C, 65.54; H, 7.56%. Found C, 65.49; H, 7.51%.
2.2.11. (3R,5S)-1-(4-hydroxy-3-Methoxyphenyl) decane-3,5-diol (1)

To copper iodide (0.002 g, 0.0116 mmol) in anhydrous THF (5 mL) (0.08 mL, 0.087 mmol), n-butyl magnesium chloride was added drop wise at -30 °C and after 5 min compound 11 (0.014g, 0.058 mmol) was added. The mixture was allowed to warm at 0 °C and maintained at this temperature for 2 h, and the mixture was extracted with DCM (2 x 10 mL) and the extract was dried over anhyd. NaSO4. The crude product was subjected to purification by column chromatography on silica gel (20% EtOAc/hexane) to give pure compound 1 (Scheme 1).

Yield: 71%, 0.012 g, IR (KBr, v, cm⁻¹): 3414, 1564, 1442, 1250. ¹H NMR (200 MHz, CDCl₃, δ, ppm): 6.83 (d, 1H, J = 8.0 Hz, m-Ar-H), 6.70 (d, 1H, J = 2.0 Hz, o-Ar-H), 6.64 (dd, 1H, J = 8.0, 2.0 Hz, o-Ar-H), 5.53 (brs, 1H, p-Ar-Oh), 4.02 (m, 1H, 5'-CH(OH)), 3.88 (s, 3H, Ar-0-Ch3), 3.64 (m, 1H, 5'-CH(OH)), 3.50 (brs, 2H, 3'-CH-OH & 5'-CH-OH), 2.72-2.64 (m, 2H, Ar-CH₂), 1.70-1.28 (m, 2H, Ar-CH₂-CH₂), 1.47-1.22 (m, 10H, 4',6',7' & 8'-CH₃), 0.89 (t, 3H, J = 7.0 Hz, 10'-CH₃). ¹³C NMR (50 MHz, CDCl₃, δ, ppm): 151.3, 142.5, 142.5, 134.2, 120.2, 120.0, 112.1, 67.9, 56.0, 51.0, 46.3, 38.2, 37.0, 32.1, 20.4, 18.3, 14.2. ESI-MS (m/z): 296 [M⁺]. [α]D₂⁵ = +7.32 (c 1.52, CHCl₃). Anal. calcd. for C₁₉H₂₀O₄C: C 68.92; H 9.46. Found: C, 68.1; H, 9.52%.

3. Results and discussion

The present synthesis of [+]-[6]-gingerdil (1) was initiated by protecting the hydroxyl group of vanillin (4) by treatment with TBSCI and imidazole to form the TBSCI-ether (5) (Scheme 1). The compound 5 underwent Wittig olifination with PPh₂CHCOOEt to produce the unsaturated ester 6 which was reduced with NaBH₄ to form the saturated ester, 7. The reduction of this ester 7 with DiBAL-H to the corresponding alcohol, 8, followed by Swern oxidation yielded the desired aldehyde 3. This aldehyde (3) was subjected to Maruoka asymmetric allylation [13] using the titanium complex (S,S)-1 (Figure 1) and allyl (tributyl) tin to produce the homoallylic alcohol, 2 (see 97%). The later was treated with di (tetr-butyl) carbonate in the presence of DMAP to form the homoallylic tert-butyl carbonate, 9. The treatment of compound 9 with L in MeCN at -20 °C furnished the iodocarbonate 10 which was subsequently treated with K₂CO₃ in MeOH to afford the silyloxy alcohol 11. The cleavage of the TBSCI ether group also took place simultaneously [14,15]. Finally, the reaction of compound 11 with Grignard reagent, n-C₄H₉MgBr using CuI produced the target molecule, (+)-[6]-gingerdil (1) [16]. The optical and spectral properties of the compound were found to be identical to those reported for the natural product [1,2].

Figure 1. Structure of complex catalyst (S,S)-1.

4. Conclusion

In conclusion, we have developed an efficient stereoselective synthesis of (+)-[6]-gingerdil involving some simple steps and easily available reagents. To our knowledge, this is the second report of the synthesis of this medicinally important compound. The method may be utilized for the preparation of various analogues of this compound.

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