European Journal of Chemistry 4 (3) (2013) 191-194

European Journal of Chemistry

Journal homepage: www.eurjchem.com

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

Rathod Aravind Kumar, Jajula Kashanna, Paramesh Jangili, and Biswanath Das *

Organic Chemistry Division-I, CSIR-Indian Institute of Chemical Technology, Hyderabad-500007, India

**Corresponding author at: Organic Chemistry Division-I, CSIR-Indian Institute of Chemical Technology, Hyderabad-500007, India. Tel.: +91.40.27160512; fax: +91.40.27193241. E-mail address: biswanathdas@yahoo.com (B. Das).*

ARTICLE INFORMATION

Received: 11 March 2013
Received in revised form: 03 April 2013
Accepted: 12 April 2013
Online: 30 September 2013

KEYWORDS

Vanilline
Gingerdiol
Syn-epoxy alcohol
Maruoka allylation
Electrophilic cyclization
Stereoselective synthesis

ABSTRACT

A simple stereoselective synthesis of (+)-[6]-gingerdiol has been accomplished starting from vanillin. The synthetic sequence involves Mouroka allylation, diasterioselective iodine induced electrophilic cyclization and ring-opening of an epoxide as the key steps.

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 N_2. Analytical Thin Layer Chromatography (TLC) was carried out by using silica gel 60 F_{254} precoated plates. Visualization was accomplished with UV lamp and I_2 stain. All products were characterized by their NMR and Mass spectra.

2.1. Instrumentation

^{1}H NMR and ^{13}C NMR were recorded on Varian Gemini 200 MHz (^{1}H) and 50 MHz (^{13}C) spectrometers in $CDCl_3$ 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 F_{254} precoated plates.

2.2. Synthesis

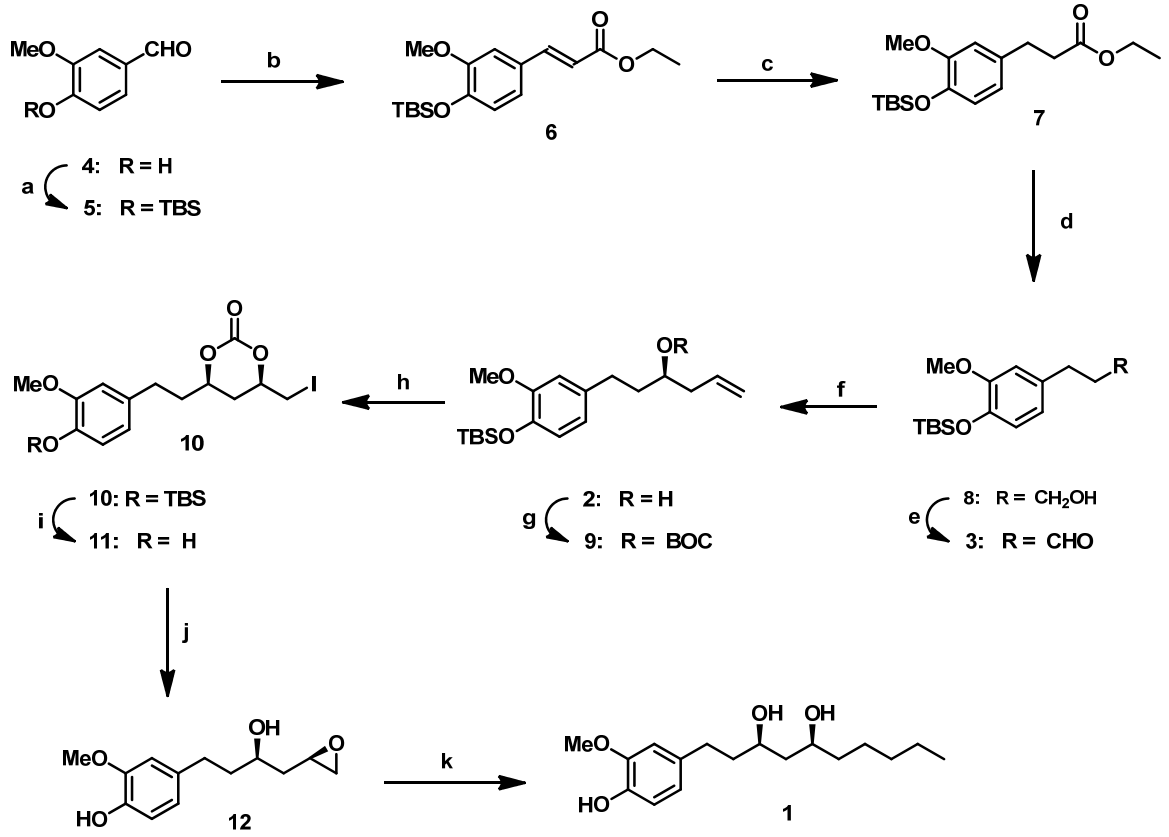
2.2.1. 4-(tert-Butyl dimethyl silyloxy)-3-methoxy benzaldehyde (5)

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, and then quenched with H_2O. The dichloro methane (DCM) layer was separated and the aqueous layer was extracted with DCM (2 x 10 mL). The combined organic layers were washed with H_2O, brine, and dried (anhydrous Na_2SO_4). 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}): 1728, 1636, 1512, 1462, 1282. ^{1}H NMR (200 MHz, $CDCl_3$, δ, ppm): 9.80 (s, 1H, Ar-C*H*O), 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-CH_3), 1.00 (s, 9H, Si-C(CH_3)$_3$), 0.20 (s, 6H, Si-(CH_3)$_2$). ^{13}C NMR (50 MHz, $CDCl_3$, 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]$^+$. $[\alpha]_D^{25}$ = +5.65 (*c* 1.75, $CHCl_3$). Anal. calcd. for $C_{14}H_{22}O_3Si$: C, 63.15; H, 8.27. Found: C, 63.05; H, 8.28%.

2.2.2. (E)-Ethyl 3-(4-(tert-butyldimethylsilyloxy)-3-methoxy-phenyl) acrylate (6)

To a solution of aldehyde, **5**, (1.54 g, 5.78 mmol) in dry DCM (10 mL) ethyl (triphenyl phosphornylidene) 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.

ISSN 2153-2249 (Print) / ISSN 2153-2257 (Online)
DOI:10.5155/eurjchem.4.3.191-194.768



Reagents and conditions: a) TBSCl, imidazole, CH_2Cl_2. 5 h, 88%: b) $PPh_3CHCOOEt$, CH_2Cl_2, rt, 6 h, 81%; c) $NiCl_2$, $NaBH_4$, MeOH, 0 °C, 15 min then 1 h rt, N_2 condition, 91%; d) DIBAL-H, CH_2Cl_2, MeOH, -78 °C to -10 °C, 0.5 h, 77%; e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C , 0.5 h, 81%; f) (*S,S*)-**I**, $Bu_3SnCH_2CH=CH_2$, CH_2Cl_2, -15 °C to -0 °C, 20 h, 79%; g) BOC_2O, DMAP, MeCN, 5 h, 77%; h) I_2, MeCN, -20 °C, 6 h, 67%; i) TBAF, THF, 5 h, 78%; j) K_2CO_3, MeOH, 20 °C, 30 min, 84%; k) *n*-C_4H_9MgBr, CuI, -30 °C, 2 h, 71%.

Scheme 1

^{1}H NMR (200 MHz, $CDCl_3$, δ, ppm): 7.81 (d, 1H, *J* = 16.0 Hz, Ar-C*H*=CH), 7.25-7.17 (m, 2H, *o*-Ar-*H*), 7.02 (d, 1H, *J* = 8.0 Hz, *m*-Ar-*H*), 6.49 (d, 1H, *J* = 16.0 Hz, Ar-CH=C*H*), 4.43 (q, 2H, *J* = 7.0 Hz, O-C*H*$_2$-CH$_3$), 4.02 (s, 3H, Ar-O-C*H*$_3$), 1.53 (t, 3H, *J* = 7.0 Hz, O-CH$_2$-C*H*$_3$), 1.18 (s, 9H, Si-C(C*H*$_3$)$_3$), 0.19 (s, 6H, Si-(C*H*$_3$)$_2$). ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 172.2, 150.8, 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 $[M+H]^+$. $[\alpha]_D^{25}$ = +22.65 (*c* 0.17, $CHCl_3$). Anal. calcd. for $C_{18}H_{28}O_4Si$: C, 64.28; H, 8.39. Found: C, 64.19; H, 8.34%.

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 $NiCl_2$ (0.22 g, 0.936 mmol), after stirring 15 min at 0 °C then added $NaBH_4$ (0.35 g, 9.36 mmol) portion wise under N_2 condition. Then allow the residue to room temperature and stirr for 1 h, and the residue was quenched with NH_4Cl. The MeOH layer was separated and the aqueous layer was washed with DCM (2 x 10 mL) and combined organic layer washed with H_2O, brine, and dried over anhydrous Na_2SO_4. 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. ^{1}H NMR (200 MHz, $CDCl_3$, 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-C*H*$_2$-CH$_3$), 3.85 (s, 3H, Ar-O-C*H*$_3$), 2.92 (t, 2H, *J* = 7.0 Hz, Ar-C*H*$_2$-CH$_2$), 2.69-2.60 (m, 2H, Ar-CH$_2$-C*H*$_2$), 1.30 (t, 3H, *J* = 7.0 Hz, O-CH$_2$-C*H*$_3$), 1.08 (s, 9H, Si-C(C*H*$_3$)$_3$), 0.20 (s, 6H, Si-(C*H*$_3$)$_2$). ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 173.3, 151.2, 143.8, 121.0, 120.2, 112.5, 60.1, 55.2, 35.6, 35.4, 25.4, 19.1, 14.8, -4.9. ESI-MS (*m/z*): 339 $[M+H]^+$. $[\alpha]_D^{25}$ = +4.99 (*c* 0.75, $CHCl_3$). Anal. calcd. for $C_{18}H_{30}O_4Si$: 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 sodium 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 Na_2SO_4 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. ^{1}H NMR (200 MHz, $CDCl_3$, δ, ppm): 6.72 (d, 1H, *J* = 8.0 Hz, *m*-Ar-*H*), 6.66 (d, 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-C*H*$_3$), 3.69 (brs, 1H, 3'-CH$_2$-O*H*), 3.62

(t, 2H, *J* = 7.0 Hz, 3'-C*H*$_2$-OH), 2.61 (t, 2H, *J* = 7.0 Hz, Ar-C*H*$_2$), 1.91-1.79 (m, 2H, Ar-CH$_2$-C*H*$_2$), 1.00 (s, 9H, Si-C(C*H*$_3$)$_3$), 0.14 (s, 6H, Si-(C*H*$_3$)$_2$). ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 150.8, 143.1, 135.2, 120.5, 120.2, 112.7, 62.1, 55.3, 34.3, 32.0, 26.1, 18.4, -4.9. ESI-MS (*m/z*): 297 $[M+H]^+$. $[\alpha]_D^{25}$ = +4.32 (*c* 1.50, $CHCl_3$). Anal. calcd. for $C_{16}H_{28}O_3Si$: C, 64.86; H, 9.45. Found: C, 64.78; H, 9.49%.

2.2.5. 3-(4-(tert-butyldimethyl silyloxy)-3-methoxy phenyl)-propanal (3)

To a solution of oxalyl chloride (0.42 mL, 4.875 mmol) in dry DCM (5 mL) at -78 °C, DMSO (0.73 mL, 10.4 mmol) was added drop wise with stirring under N_2 condition, after 15 min compound **8** (0.964 g, 3.25 mmol) was added to the reaction mixture. After stirring for 0.5 h at -78 °C, Et_3N (2.2 mL, 16.25 mmol) was added and the mixture was stirred for another 0.5 h at -78 °C and then for 0.5 h at 0 °C. The reaction mixture was quenched with saturated NH_4Cl solution (10 mL) at 0 °C and extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with H_2O, brine, dried over anhydrous Na_2SO_4 and concentrated in vacuum. The aldehyde, **3**, thus obtained (0.775 g, 2.63 mmol) was directly used after flash column chromatography for the next reaction (Scheme 1).

2.2.6. (R)-1-(4-(tert-butyl dimethyl silyloxy)-3-methoxy phenyl) hex-5-en-3-ol (2)

To a solution of $TiCl_4$ (0.28 mL, 2.63 mmol) in dry DCM (10 mL) was added dried $Ti(OiPr)_4$ (2.48 mL, 7.89 mmol) at 0 °C under nitrogen atmosphere and was allowed to warm to r.t., 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 r.t, 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 $NaHCO_3$ (50 mL), and extracted with Et_2O (3 x 30 mL). The organic extracts were dried over anhydrous Na_2SO_4. Evaporation of the solvents and purification of the residue by column chromatography on silica gel (2% EtOAc/hexane) gave compound **2** (Scheme 1). Yield: 79%, 0.699 g. IR (KBr, ν, cm^{-1}): 3445, 2929, 1648, 1513, 1463, 1283. ^{1}H NMR (200 MHz, $CDCl_3$, 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, CH$_2$-C*H*=CH$_2$), 5.12-5.01 (m, 2H, CH$_2$-CH=C*H*$_2$), 3.79, (s, 3H, Ar-O-C*H*$_3$), 3.67 (brs, 1H, 3'-CH(O*H*)), 3.62 (m, 1H, 3'-C*H*(OH)), 2.70-2.51 (m, 2H, Ar-C*H*$_2$-CH$_2$), 2.46-2.31 (m, 2H, 4'-C*H*$_2$), 1.30-1.22 (m, 2H, Ar-CH$_2$-C*H*$_2$), 1.00 (s, 9H, Si-C(C*H*$_3$)$_3$), 0.12 (s, 6H, Si-(C*H*$_3$)$_2$). ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 150.5, 143.2, 135.2, 120.6, 120.5, 116.8, 113.0, 71.0, 55.3, 34.2, 32.0, 25.9, 18.2, -4.8. ESI-MS (*m/z*): 337 $[M+H]^+$. $[\alpha]_D^{25}$ = +50.65 (*c* 2.55, $CHCl_3$). Anal. calcd. for $C_{19}H_{32}O_3Si$: C, 67.85; H, 9.52. Found: C, 67.78; H, 9.52%.

2.2.7. (R)-tert-butyl 1-(4-(tert-butyl dimethyl silyloxy)-3-methoxy phenyl) 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) were added $(BOc)_2O$ (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 Na_2SO_4), filtered, and concentrated in vacuo, purification of the residue by column chromatography on SiO_2 (1% EtOAc/hexane) gave compound **9** (Scheme 1). Yield: 78%, 0.199 g. IR (KBr, ν, cm^{-1}): 1710, 1631, 1520, 1486, 1263. ^{1}H NMR (200 MHz, $CDCl_3$, δ, ppm): 6.69 (d, 1H, *J* = 8.0, *m*-Ar-*H*), 6.61 (d, 1H, *J* = 2.0 Hz, *o*-Ar-*H*), 6.55 (dd, 1H, *J* = 8.0, 2.0 Hz, *o*-Ar-*H*), 5.73 (m, 1H, 5'-C*H*), 5.11-5.02 (m, 2H, 6'-C*H*$_2$), 4.68 (m, 1H, 3'-C*H*(OH)), 3.78 (s, 3H, Ar-O-C*H*$_3$), 2.69-2.52 (m, 2H, Ar-C*H*$_2$-CH$_2$), 2.41-2.32 (m, 2H, 4'-C*H*$_2$), 1.90 (s, 9H, CO-O-C(C*H*$_3$)$_3$), 1.38-1.21 (m, 2H, Ar-CH$_2$-C*H*$_2$), 1.00 (s, 9H, Si-C(C*H*$_3$)$_3$), 0.11 (s, 6H, Si-(C*H*$_3$)$_2$). ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 157.2, 151.3, 143.8, 134.6, 120.8, 120.6, 112.5, 85.3, 80.2, 55.1, 35.3, 35.2, 30.8, 25.4, 18.0, -4.9. ESI-MS (*m/z*): 459 $[M+Na]^+$. Anal. calcd. for $C_{24}H_{40}O_5Si$: C, 66.05; H, 9.17. Found: C, 66.09; H, 9.18%.

2.2.8. *(4R,6R)-4-(4-(tert-butyl dimethyl silyloxy)-3-methoxy phenethyl)-6-(iodomethyl)-1,3-dioxan-2-one (10)*

A mixture of compound **9** (0.060 g, 0.137 mmol) and I_2 (0.034 g, 1.374 mmol) in 10 mL of dry MeCN was stirred mechanically under N_2 atmosphere at -20 °C for 6 h. The mixture was partitioned between 300 mL of 20% aqueous $Na_2S_2O_3$/5% aqueous $NaHCO_3$ and 100 mL of Et_2O. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous sodium sulfate, and evaporated. The crude product was purified by column chromatography on silica gel (10% EtOAc/hexane) to give pure compound **10** (Scheme 1). Yield: 84%, 0.046 g. IR (KBr, ν, cm^{-1}): 1697, 1454, 1372, 1156. ^{1}H NMR (200 MHz, $CDCl_3$, δ, ppm): 6.83 (d, 1H, *J* = 8.0 Hz, *m*-Ar-*H*), 6.69-6.61 (m, 2H, *o*-Ar-*H*), 4.21 (m, 1H, 5'-C*H*), 4.10 (m, 1H, 3'-C*H*), 3.88 (s, 3H, Ar-O-C*H*$_3$), 3.21-3.10 (m, 2H, 6'-C*H*$_2$-I), 2.71-2.53 (m, 2H, Ar-C*H*$_2$), 2.29 (m, 1H, 4'-C*H*$_a$), 2.03 (m, 1H, 4'-C*H*$_b$), 1.82-1.64 (m, 2H, Ar-CH$_2$-C*H*$_2$) 1.21 (s, 9H, Si-C(C*H*$_3$)$_3$), 0.01 (s, 6H, Si-(C*H*$_3$)$_2$). ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 150.1, 148.2, 142.7, 134.3, 120.0, 119.9, 111.8, 77.4, 75.5, 55.4, 33.8, 31.0, 25.1, 17.9, 5.2, -5.1. ESI-MS (*m/z*): 507 $[M+H]^+$. $[\alpha]_D^{25}$ = -7.27 (*c* 1.15, $CHCl_3$). Anal. calcd. for $C_{20}H_{31}IO_5Si$: C, 47.43; H, 6.12. Found: C, 47.50; H, 6.11%.

2.2.9. (4R,6R)–4-(4-hydroxy-3-methoxyphenethyl)-6-(iodo-methyl)-1,3-dioxan-2-one (11)

To a ice cooled solution of compound **10** (0.046 g, 0.092 mmol), in THF (10 mL) was added TBAF (1M THF 0.70 mL, 0.70 mmol). After 15 min of stirring the mixture was brought to room temperature and stirred for another 5 h. After completion of the reaction the mixture was concentrated and purified by column chromatography and the compound **11** was directly utilized immediately to next reaction.

2.2.10. 4-((R)-3-hydroxy-4-((R)-oxiran-2-yl)butyl)-2-methoxy-phenol (12)

Compound **11** (0.028 g, 0.072 mmol) and K_2CO_3 (0.031 g, 0.228 mmol) in 10 mL of dry MeOH was stirred at 20 °C for 30 min. Et_2O was added and the mixture was washed with 20% aqueous $Na_2S_2O_3$/5% aqueous $NaHCO_3$. The organic portion was separated, dried over anhydrous, and evaporated. The crude product was purified by column chromatography on silica gel (30% EtOAc/hexane) to give compound **12** (Scheme 1). Yield: 84%, 0.014 g. IR (KBr, ν, cm^{-1}): 3311, 1416, 1369, 1254. ^{1}H NMR (200 MHz, $CDCl_3$, δ, ppm): 6.82 (d, 1H, *J* = 8.0 Hz, *m*-Ar-*H*), 6.68-6.60 (m, 2H, *o*-Ar-*H*), 5.53 (brs, 1H, *p*-Ar-O*H*), 3.83 (s, 3H, Ar-O-C*H*$_3$), 3.70 (m, 1H, 3'-C*H*), 3.56 (brs, 1H, 3'-CH-O*H*), 3.14 (m, 1H, 6'-C*H*$_a$), 3.08 (m, 1H, 5'-C*H*), 2.65, (m, 1H, 6'-C*H*$_b$), 2.61,-2.52 (m, 2H, Ar-C*H*$_2$), 1.83-1.61 (m, 4H, 2'-C*H*$_2$ & 4'-C*H*$_2$). ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 150.3, 143.4, 134.6, 120.2, 120.0, 112.1, 67.8, 56.0, 51.0, 46.3, 38.2, 37.0, 32.1. ESI-MS (*m/z*): 238 $[M]^+$. $[\alpha]_D^{25}$ = +19.37 (*c* 0.20, $CHCl_3$). Anal. calcd. for $C_{13}H_{18}O_4$: 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 **12** (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. Na_2SO_4. 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, ν, cm^{-1}): 3414, 1564, 1442, 1250. ^{1}H NMR (200 MHz, $CDCl_3$, 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-O*H*), 4.02 (m, 1H, 3'-C*H*(OH)), 3.88 (s, 3H, Ar-O-CH_3), 3.86 (m, 1H, 5'-C*H*(OH)), 3.58 (brs, 2H, 3'-CH-O*H* & 5'-CH-O*H*), 2.72-2.64 (m, 2H, Ar-CH_2), 1.78-1.62 (m, 2H, Ar-CH$_2$-CH_2), 1.47-1.22 (m, 10H, 4',6',7' & 8'-CH_2), 0.89 (t, 3H, *J* = 7.0 Hz, 10'-CH_3). ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 151.3, 142.5, 134.2, 120.2, 120.0, 112.1, 67.8, 56.0, 51.0, 46.3, 38.2, 37.0, 32.1, 20.4, 18.3, 14.2. ESI-MS (*m/z*): 296 $[M]^+$. $[\alpha]_D^{25}$ = +7.32 (*c* 1.52, $CHCl_3$). Anal. calcd. for $C_{17}H_{28}O_4$: C, 68.92; H, 9.46. Found: C, 68.81; H, 9.52%.

3. Results and discussion

The present synthesis of (+)-[6]-gingerdiol (**1**) was initiated by protecting the hydroxyl group of vanillin (**4**) by treatment with TBSCl and imidazole to form the TBS-ether (**5**) (Scheme 1). The compound **5** underwent Wittig olifination with $PPh_2CHCOOEt$ to produce the unsaturated ester **6** which was reduced with $NaBH_4/NiCl_2$ 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*)-I (Figure 1) and allyl (tributyl) tin to produce the homoallylic alcohol, **2** (ee 97%). The later was treated with di (*tert*- butyl) carbonate in the presence of DMAP to form the homoallylic *tert*- butyl carbonate, **9**. The treatment of compound **9** with I_2 in MeCN at -20 ^{0}C furnished the iodocarbonate **10** which was subsequently treated with K_2CO_3 in MeOH to afford the *syn*-epoxy alcohol **11** The cleavage of the TBS ether group also took place simultaneously [14,15]. Finally, the reaction of compound **11** with Grignard reagent, *n*-C_4H_9MgBr using CuI produced the target molecule, (+)-[6]-gingerdiol (**1**) [16]. The optical and spectral properties of the compound were found to be identical to those reported for the natural product [1,2].

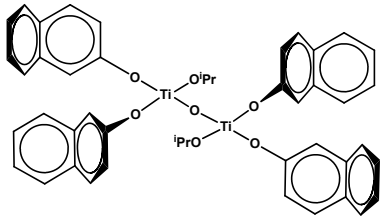


Figure 1. Structure of complex catalyst (*S, S)*-I.

4. Conclusion

In conclusion, we have developed an efficient stereoselective synthesis of (+)-[6]-gingerdiol 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.

Acknowledgements

The authors thank Council of Scientific and Industrial Research and University Grants Commission, New Delhi for financial assistance.

References

[1]. Murata, T.; Shinohara, M.; Miyamoto, M. *Chem. Pharm. Bull.* **1972**, *20,* 2291-2292.
[2]. Kikuzaki, H.; Tsai, S.-M.; Nakatani, N. *Phytochemistry.* **1992**, *31,* 1783-1786.
[3]. Sekiva, Y.; Kubota, K.; Kobayashi, A. *J. Agric. Food Chem.* **2000**, *48,* 373-377.
[4]. Schuhbaum, H.; Burgermeister, J.; Paper, D. H.; Franz, G. Pharmaceu. *Pharmocol. Lett.* **2000**, *10,* 82-85.
[5]. Ficker, C.; Smith, M. L.; Apkagana, K.; Glessor, M.; Zhang, H.; Durst, H.; Assabgui, R.; Arnason, J. T. *Phytother Res.* **2003**, *17,* 897-902.
[6]. Franck-Neumann, M.; Geoffroy, P.; Bissinger, P.; Adelaide, S. *Tetrahedron Lett.* **2001**, *42,* 6401-6404.
[7]. Das, B.; Krishnaiah, M.; Nagendra, S.; Reddy, Ch, R. *Lett. Org. Chem.* **2011**, *8*, 244-248.
[8]. Das, B.; Balasubramanyam, P.; Veeranjaneyulu, B.; Reddy, G. C. *Helv. Chem. Acta.* **2011**, *94*, 881-884.
[9]. Das, B.; Kumar, D. N. *Synlett.* **2011**, 1285-1287.
[10]. Satyalakshmi, G.; Suneel, K.; Shinde, B. D.; Das, B. *Tetrahedron: Asymm.* **2011**, *22*, 1000-1005.
[11]. Das, B.; Laxminarayana, K.; Krishnaiah, M.; Kumar, D. N. *Helv. Chem. Acta.* **2009**, *92*, 1840-1844.
[12]. Nagendra, S.; Krishnaiah, M.; Reddy, K. R.; Das, B. *Eur. J. Chem.* **2012**, *3,* 337-339.
[13]. Hanawa, H.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125,* 1708-1709.
[14]. Bartlett, P. A.; Predows, J. D.; Brown, E. G.; Morimoto, A.; Jernstedt, K, K. *J. Org. Chem.* **1982**, *47*, 4013-4018.
[15]. Bougini, A.; Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *J. Org. Chem.* **1982**, *47,* 4626-4633.
[16]. Kumar, P.; Gupta, P.; Naidu, S. V. *Chem. Eur. J.* **2006**, *12,* 1397-1402.