An Efficient Enantioselective Synthesis of Natural Gingerols, the Active Principles of Ginger

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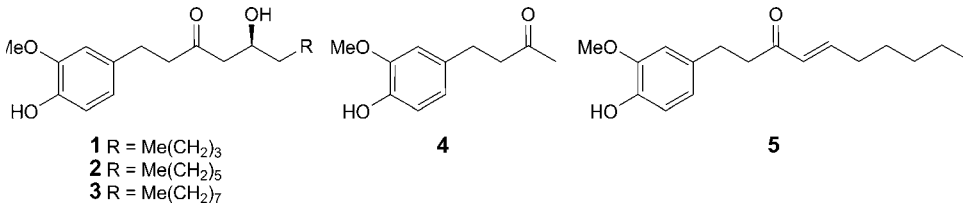
A straightforward synthesis of (*S*)-gingerols **1**–**3** has been described. The requisite stereogenic center in the target molecules was introduced by *Sharpless* asymmetric dihydroxylation using a chiral complex, *AD-mix β*. This route is simple and efficient to prepare the products in very good yields.

Introduction. – The rhizome of ginger (*Zingiber officinale* ROSCOE) is the most abundant and widely used dietary condiment worldwide, and also has the long history as an important traditional medicine in Asian countries [1]. The underground stems or rhizomes of this plant have been used in oriental medicine for the treatment of common cold, disorders of the gastro intestinal tract, neuralgia, rheumatism, colic and motion discomfort [2]. The non-volatile pungent ingredients from ginger include (*S*)-gingerols **1**–**3**, zingerone (**4**), and shogaol (**5**).



1 R = $Me(CH_2)_3$
2 R = $Me(CH_2)_5$
3 R = $Me(CH_2)_7$

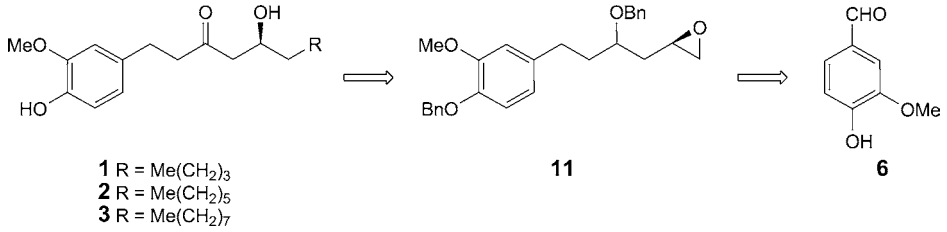
4 **5**

The three natural gingerols, namely (+)-(*S*)-[6]-gingerol (**1**), (+)-(*S*)-[8]-gingerol (**2**), and (+)-(*S*)-[10]-gingerol (**3**), have been isolated from the rhizome of zingiber and have been claimed to be the active principles of ginger [3]. Recently, several population based studies have shown that the gingerols exhibit diverse pharmacological activities such as anti-inflammatory, cardiotonic, antibacterial, antifungal, antioxidant, and antitumor, and antiplatelet aggregation effects [4]. The biological importance of gingerols have attracted researchers to carry out its synthesis *via* different routes [5][6].

Results and Discussion. – As part of our regular research program in the synthesis of biologically active natural products [7], herein, we report an efficient stereoselective synthesis of (*S*)-gingerols **1**–**3** in excellent yields from epoxide **11** which was obtained from vanillin (**6**).

As shown in the retrosynthetic analysis (*Scheme 1*), the synthesis strategy started from commercially available **6**. The phenolic OH was protected as benzyl ether

Scheme 1



1 R = $Me(CH_2)_3$
2 R = $Me(CH_2)_5$
3 R = $Me(CH_2)_7$

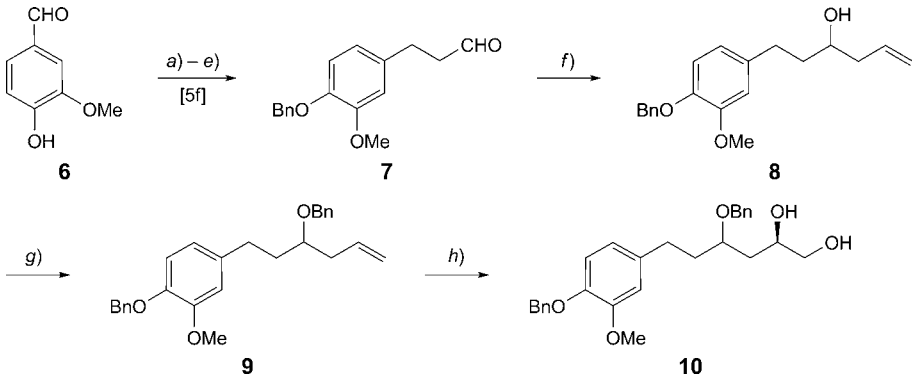
11 **6**

followed by *Wittig* reaction to give the unsaturated ester [8]. The latter was reduced with Mg followed by $LiAlH_4$ to yield the primary alcohol which was oxidized under *Swern* conditions [9] to afford aldehyde **7**. The latter was reacted with allyl bromide in the presence of activated Zn at low temperature to give 1-[4-(benzyloxy)-3-methoxyphenyl]hex-5-en-3-ol (**8**) in 90% yield [10a]. The OH group was protected as benzyl ether by treating with BnBr in the presence of NaH in THF at room temperature to give **9** in 90% yield. The terminal olefin was subjected to asymmetric dihydroxylation using *AD-mix β* in ^{t}BuOH/H_2O (1:1) at 0° to afford a 1:1 mixture of diastereoisomeric 1,2-diols **10** [10b] as shown in *Scheme 2*.

The 1,2-diol **10** was subjected to *Mitsunobu* reaction [11] using Ph_3P and diethyl azodicarboxylate (DEAD) in benzene under reflux for 18 h to afford (2*R*)-2-{2-(benzyloxy)-4-[4-(benzyloxy)-3-methoxyphenyl]butyl}oxirane (**11**) in 93% yield. The latter was reacted with appropriate alkyl magnesium bromides in the presence of CuI at 0° to give the corresponding derivatives **12** with a secondary alcohol group in very good yields.

The OH groups of **12a**–**12c** were protected as respective (*tert*-butyl)(dimethyl)silyl ethers **13a**–**13c** by reacting with TBDMS–Cl in the presence of 1*H*-imidazole at room temperature. The protected compounds **13a**–**13c** were treated with Pd/C in AcOEt

Scheme 2

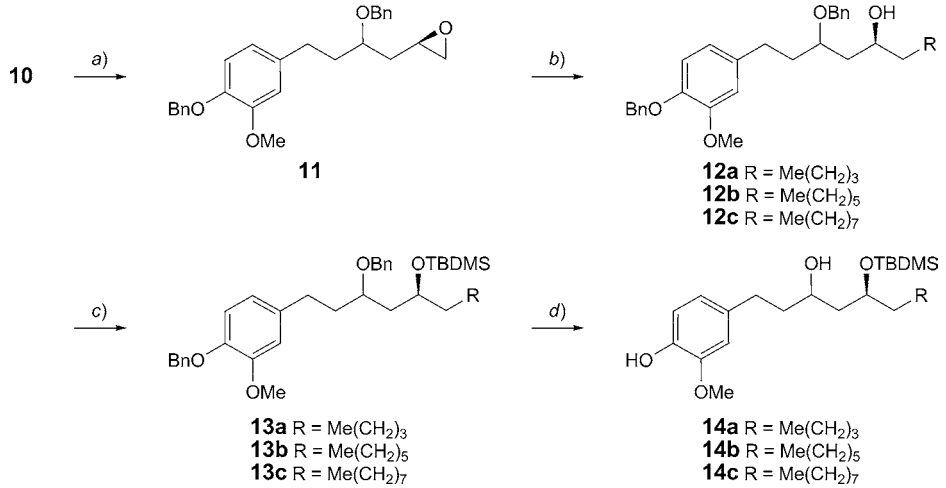


6 **7** **8**

9 **10**

a) BnBr, K_2CO_3, acetone, reflux, 3 h; 90%. *b*) Ph_3P=CHCOOEt, benzene, reflux, 2 h; 92%. *c*) Mg, MeOH, r.t., 4 h; 85%. *d*) $LiAlH_4$, THF, 0° – r.t., 2 h; 74%. *e*) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78°, 1 h; 85%. *f*) Allyl bromide, activated Zn, THF, aq. NH_4Cl soln., 0° – r.t., 3 h; 90%. *g*) BnBr, NaH, THF, 0° – r.t., 6 h; 90%. *h*) *AD-mix β*, ^{t}BuOH/H_2O 1:1, 0°, 24 h; 90%.

Scheme 3



a) Ph_3P, DEAD, benzene, reflux, 18 h; 93%. *b*) $Me(CH_2)_3MgBr$, CuI, THF, 0° – r.t., 2 h; 85%, or $Me(CH_2)_5MgBr$, CuI, THF, 0° – r.t., 2 h; 87%, or $Me(CH_2)_7MgBr$, CuI, THF, 0° – r.t., 2 h; 90%. *c*) TBDMS–Cl, 1*H*-imidazole, CH_2Cl_2, 0° – r.t., 3 h; 92%. *d*) H_2 (40 psi), 10% Pd/C, AcOEt, r.t., 5 h; 90–92%.

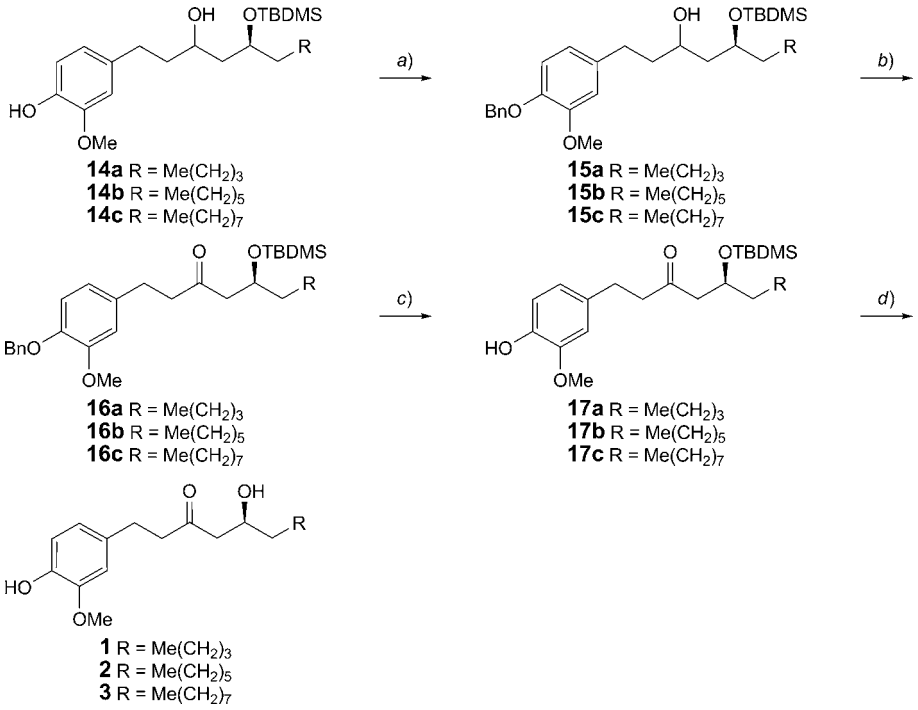
under H_2 atmosphere to give the debenzylated products **14a**–**14c** in very good yields as shown in the *Scheme 3*.

The dihydroxy compounds **14** were subjected to oxidation with various oxidative catalysts to convert the aliphatic OH group to the ketone, but it was not successful. Then, **14a**–**14c** were treated with BnBr in the presence of K_2CO_3 to protect the phenolic OH group [12] leading to the corresponding derivatives **15** in very good yields, which were then treated with *Dess–Martin* periodinane in CH_2Cl_2 at room temperature to afford ketone **16** in excellent yields. Subsequent deprotection of the benzyl ether with Pd/C in AcOEt under H_2 atmosphere afforded **17a**–**17c** in very good yields (*Scheme 4*).

Finally, the TBDMS ethers were cleaved by treating with Bu_4NF in THF [13] at room temperature to obtain the target molecules, (5*S*)-5-hydroxy-1-(4-hydroxy-3-methoxyphenyl)decan-3-one (**1**) in 87% yield with $[\alpha]_D^{25} = +24.3$ ($c = 1$, $CHCl_3$) ($[\alpha]_D^{25} = +25.1$ ($c = 1$, $CHCl_3$) [5c]), (5*S*)-5-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-dodecan-3-one (**2**) in 90% yield with $[\alpha]_D^{25} = +25.8$ ($c = 1$, $CHCl_3$) ($[\alpha]_D^{25} = +26.2$ ($c = 1$, $CHCl_3$) [5c]), and (5*S*)-5-hydroxy-1-(4-hydroxy-3-methoxyphenyl)tetradecan-3-one (**3**) in 90% yield with $[\alpha]_D^{25} = 18.9$ ($c = 1$, $CHCl_3$) ($[\alpha]_D^{25} = 19.8$ ($c = 1$, $CHCl_3$) [5c]), respectively. The products were characterized by their ^{1}H- and ^{13}C-NMR, IR, and MS data analyses.

Conclusions. – In summary, we have reported an efficient enantioselective synthesis of (*S*)-gingerols **1**–**3** in excellent yields. The key intermediate was the epoxide **11**, which was achieved from vanillin (**6**). All the reactions were very clean in terms of conversions as well as in isolation of products.

Scheme 4



a) BnBr, K_2CO_3, acetone, reflux, 3 h; 90–92%. *b*) *Dess–Martin* periodinane, $NaHCO_3$, CH_2Cl_2, 1 h; 87–92%. *c*) H_2 (40 psi), 10% Pd/C, AcOEt, r.t., 5 h; 87–92%. *d*) Bu_4NF, dry THF, r.t., 6 h; 87–90%.

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Experimental Part

All the solvents and chemicals or reagents used were purchased from standard commercial suppliers and used as such. M.p.: *Büchi* cap. melting-point (*R-535*) apparatus. Optical rotations: *Rudolph AUTOPOL IV* automatic polarimeter. IR Spectra: *PerkinElmer FT-IR 240C* spectrophotometer; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR spectra: *Brucker-300* spectrometer at 300 (^1H) and 75 (^{13}C) MHz, resp.; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. MS: *Finnigan-MAT 1020* mass spectrometer operating at 70 eV; in *m*/*z* (rel. %).

3-[4-(Benzyloxy)-3-methoxyphenyl]propanal (**7**). To a soln. of $(COCl)_2$ (3 g, 23 mmol) in CH_2Cl_2 (40 ml) at $-78°$ was added DMSO (3.95 g, 50 mmol) over 20 min. The resulting mixture was stirred for an additional 15 min, and 3-(4-(benzyloxy)-3-methoxyphenyl)propan-1-ol (4.3 g, 15 mmol) dissolved in CH_2Cl_2 (10 ml) was added. The mixture was stirred for 30 min, and Et_3N (8 g, 79 mmol) was added dropwise. The mixture was allowed to warm to r.t. and was stirred for 1 h. Then, the reaction was quenched with H_2O and extracted with CH_2Cl_2 (2 × 25 ml). The combined org. layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by column chromatography (CC) on silica gel (SiO_2, 60–120 mesh; AcOEt/hexane 2:8) to afford **7** (3.7 g, 85%) as colorless solid. ^1H-NMR ($CDCl_3$): 2.65–2.75 (*m*, 2 H); 2.80–2.85 (*m*, 2 H); 3.92 (*s*, 3 H); 5.08 (*s*, 2 H); 6.65 (*d*, *J* = 7.0, 1 H); 6.75 (*t*, *J* = 7.0, 2 H); 7.30–7.45 (*m*, 5 H); 9.80 (*s*, 1 H). EI-MS: 270 (10, M^+), 268 (20), 246 (30), 229 (20), 201 (10), 150 (10), 104 (10), 90 (100), 76 (25), 64 (30), 51 (25), 43 (35).

1-[4-(Benzyloxy)-3-methoxyphenyl]hex-5-en-3-ol (**8**). To a cold and well-stirred mixture of **7** (3.7 g, 13 mmol), Zn dust (1.7 g, 27 mmol), and allyl bromide (2.36 ml, 27 mmol) in THF (50 ml) was added a sat. aq. soln. of NH_4Cl (30 ml) dropwise within 10 min. The mixture was stirred for 4 h at ambient temp. until the aldehyde was totally consumed (by TLC). The mixture was filtered, and the precipitate was thoroughly washed with $CHCl_3$. The combined org. layer was washed successively with H_2O and brine. After solvent removal under reduced pressure, the residue was separated by CC (SiO_2, 60–120 mesh; AcOEt/hexane 3:7) to afford **8** (3.8 g, 90%) as colorless oil. IR (KBr): 3432, 2976, 1718, 1650, 1262, 1160, 1050. ^{1}H-NMR ($CDCl_3$): 1.65–1.78 (*m*, 2 H); 2.08–2.34 (*m*, 2 H); 2.53–2.77 (*m*, 1 H); 3.55–3.65 (*m*, 1 H); 3.88 (*s*, 3 H); 5.05–5.14 (*m*, 4 H); 5.70–5.85 (*m*, 1 H); 6.58–6.64 (*m*, 1 H); 6.68–6.76 (*m*, 2 H); 7.28–7.42 (*m*, 5 H). ESI-MS: 335 ($[M+Na]^+$).

1-(Benzyloxy)-4-[3-(benzyloxy)hex-5-en-1-yl]-2-methoxybenzene (**9**). To a stirred suspension of freshly activated NaH (0.53 g, 22 mmol) in dry THF (15 ml) at 0° was added dropwise a soln. of **8** (3.5 g, 22 mmol) in dry THF (30 ml). After 30 min, BnBr (2.1 g, 12 mmol) was added, and the mixture was warmed to r.t. and stirred for 6 h. The reaction was quenched with an aq. NH_4Cl soln. (20 ml) and extracted with AcOEt (2 × 20 ml). The combined org. layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure to afford a crude product, which was purified by CC (SiO_2, 60–120 mesh; AcOEt/hexane 1.5:8.5) to afford **9** (4 g, 90%) as colorless liquid. IR (neat): 3064, 3031, 2932, 2861, 1589, 1512, 1456, 1417, 1379, 1345, 1262, 1226, 1139, 1071, 1029, 914, 851, 804, 737, 697. ^{1}H-NMR ($CDCl_3$): 1.70–1.85 (*m*, 2 H); 2.30–2.40 (*m*, 2 H); 2.50–2.60 (*m*, 1 H); 2.63–2.74 (*m*, 1 H); 3.38–3.48 (*m*, 1 H); 3.82 (*s*, 3 H); 4.42 (*d*, *J* = 11.0, 1 H); 4.60 (*d*, *J* = 11.0, 1 H); 5.01–5.12 (*m*, 4 H); 5.72–5.90 (*m*, 1 H); 6.58 (*d*, *J* = 7.0, 1 H); 6.65 (*s*, 1 H); 6.71 (*d*, *J* = 7.0, 1 H); 7.20–7.45 (*m*, 10 H). EI-MS: 403 (90, M^+), 312 (10).

*(2*R*)-4-(Benzyloxy)-6-[4-(benzyloxy)-3-methoxyphenyl]hexane-1,2-diol* (**10**). A mixture of *AD-mix β* (12.6 g) in ^{t}BuOH/H_2O 1:1 (90 ml) was stirred for *ca.* 30 min at 0°, and then the olefin compound **9** (3.6 g, 9 mmol) was added. The resulting mixture was stirred for 24 h at 0°. Then, the reaction was quenched by adding Na_2SO_3, and the mixture was filtered, the solid was washed with AcOEt (2 × 50 ml). The filtrate was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure to obtain a crude product, which was purified by CC (SiO_2, 60–120 mesh; AcOEt/hexane 5:5) to afford a 1:1 mixture of diastereoisomers **10** (3.5 g, 90%) as colorless syrup. IR (KBr): 3416, 2925, 2857, 1512, 1456, 1263, 1226, 1030, 739. ^{1}H-NMR ($CDCl_3$): 1.23–1.30 (*m*, 2 H); 1.76–2.01 (*m*, 2 H); 2.50–2.60 (*m*, 2 H); 3.33–3.90 (*m*, 7 H); 4.40–4.65 (*m*, 2 H); 5.05 (*s*, 2 H); 6.50–6.75 (*m*, 3 H); 7.2–7.45 (*m*, 10 H). ESI-MS: 437 ($[M+H]^+$), 459 ($[M+Na]^+$).

*(2*R*)-2-{2-(Benzyloxy)-4-[4-(benzyloxy)-3-methoxyphenyl]butyl}oxirane* (**11**). A mixture of **10** (3.3 g, 7 mmol), Ph_3P (2.97 g, 11 mmol), and diethyl azodicarboxylate (DEAD; 1.97 g, 11 mmol) in benzene (35 ml) was heated under reflux for 18 h, and the complete conversion of the starting material was confirmed by TLC. Then, the solvent was removed under reduced pressure, and the residue was diluted with Et_2O (35 ml) to precipitate Ph_3P=O, which was removed by filtration. The filtrate was concentrated, and the crude product was purified by CC (SiO_2, 60–120 mesh; AcOEt/hexane 1:9) to afford diastereoisomers of epoxide **11** (3 g, 95%) as colorless liquid. IR (KBr): 3032, 2927, 2861, 1593, 1512, 1456, 1416, 1380, 1346, 1262, 1226, 1141, 1075, 1029, 916, 849, 806, 742, 698. ^{1}H-NMR ($CDCl_3$): 1.70–2.01 (*m*, 4 H); 2.40–2.45 (*m*, 1 H); 2.55–2.75 (*m*, 3 H); 2.97–3.02 (*m*, 1 H); 3.52–3.65 (*m*, 1 H); 3.83 (*s*, 3 H); 4.51–4.60 (*m*, 2 H); 5.05 (*s*, 2 H); 6.50–6.75 (*m*, 3 H); 7.20–7.40 (*m*, 10 H). EI-MS: 418 (10, M^+), 401 (20), 383 (15), 375 (25), 357 (10), 343 (30), 321 (100), 311 (15), 308 (10), 277 (12), 249 (10), 225 (10), 192 (15), 181 (12), 165 (20), 153 (10).

*(5*S*)-3-(Benzyloxy)-1-[4-(benzyloxy)-3-methoxyphenyl]decan-5-ol* (**12a**). To a suspension of Mg turnings (0.28 g, 11 mmol) in dry THF (5 ml) was added BuBr (0.98 g, 7 mmol) dropwise under N_2 atmosphere at 0°. The mixture was allowed to stir for 30 min at r.t. Catalytic amount of CuI was then added at 0°, the mixture was stirred at r.t. for another 30 min, then a soln. of epoxide **11** (1 g, 2 mmol) in dry THF (10 ml) was added dropwise at 0°, and the mixture was stirred at r.t. Progress of the reaction was monitored by TLC. After completion of the reaction, an aq. NH_4Cl soln. (10 ml) was added, and the mixture was extracted with Et_2O. The combined org. extracts were washed with brine (10 ml), dried (Na_2SO_4), and the solvent was removed under vacuum to give a crude product, which was purified by CC (SiO_2, 60–120 mesh; AcOEt/hexane 1.5:8.5) to afford the distereoisomeric product **12a** (0.96 g, 85%) as

pale-yellow liquid. IR (KBr): 3442, 3031, 2925, 2856, 1591, 1512, 1457, 1418, 1380, 1263, 1227, 1144, 1068, 1029, 852, 804, 741. ^{1}H-NMR ($CDCl_3$): 0.88 (*t*, *J* = 6.0, 3 H); 1.22 – 1.35 (*m*, 5 H); 1.75 – 1.98 (*m*, 3 H); 2.10 – 2.20 (*m*, 1 H); 2.55 – 2.65 (*m*, 2 H); 3.35 (*t*, *J* = 6.0, 2 H); 3.60 – 3.75 (*m*, 1 H); 3.88 (*s*, 3 H); 3.90 – 3.96 (*m*, 1 H); 4.10 – 4.20 (*m*, 1 H); 4.40 – 4.60 (*m*, 2 H); 5.12 (*s*, 2 H); 6.58 (*d*, *J* = 7.0, 1 H); 6.65 (*s*, 1 H); 6.70 – 6.80 (*m*, 1 H); 7.20 – 7.45 (*m*, 10 H). EI-MS: 477 (100, M^+), 474 (20), 441 (25), 433 (10), 412 (10), 358 (10), 329 (10), 291 (10), 279 (15), 277 (10), 222 (15), 205 (10), 201 (15), 159 (20), 139 (12), 116 (20).

*(5*S*)-3-(Benzyloxy)-1-[4-(benzyloxy)-3-methoxyphenyl]dodecan-5-ol* (**12b**). Yield: 87%. IR (KBr): 3454, 3031, 2925, 2855, 1716, 1592, 1512, 1457, 1263, 1030, 850, 737, 697. ^{1}H-NMR ($CDCl_3$): 0.88 (*t*, *J* = 5.85, 3 H); 1.23 – 1.43 (*m*, 16 H); 2.43 – 2.64 (*m*, 2 H); 3.62 – 3.72 (*m*, 1 H); 3.82 – 3.92 (*m*, 4 H); 4.40 – 4.65 (*m*, 2 H); 5.10 (*s*, 2 H); 6.55 – 6.80 (*m*, 3 H); 7.22 – 7.45 (*m*, 10 H). ESI-MS: 505 ($[M+H]^+$), 527 ($[M+Na]^+$).

*(5*S*)-3-(Benzyloxy)-1-[4-(benzyloxy)-3-methoxyphenyl]tetradecan-5-ol* (**12c**). Yield: 90%. IR (KBr): 3459, 3031, 2924, 2854, 1719, 1591, 1511, 1263, 1029, 849, 736, 696. ^{1}H-NMR ($CDCl_3$): 0.88 (*t*, *J* = 6.9, 3 H); 1.22 – 1.50 (*m*, 20 H); 2.50 – 2.65 (*m*, 2 H); 3.63 – 3.74 (*m*, 1 H); 3.75 – 3.90 (*m*, 4 H); 4.42 – 4.68 (*m*, 2 H); 5.10 (*s*, 2 H); 6.55 – 6.80 (*m*, 3 H); 7.22 – 7.50 (*m*, 10 H). ESI-MS: 533 ($[M+H]^+$), 555 ($[M+Na]^+$).

*({(5*S*)-3-(Benzyloxy)-1-[4-(benzyloxy)-3-methoxyphenyl]decan-5-yl}oxy)(*tert*-butyl)dimethylsilane* (**13a**). To a soln. of **12a** (0.9 g, 1 mmol) and 1*H*-imidazole (0.5 g, 7 mmol) in dry CH_2Cl_2 (5 ml) at 0° under N_2 atmosphere, TBDMS–Cl (0.56 g, 3.7 mmol) was added, and the mixture was stirred for 3 h and allowed to warm to r.t. The mixture was diluted with H_2O (3 ml) and extracted with CH_2Cl_2 (2 × 5 ml). The combined org. layers were washed with brine (5 ml), dried (Na_2SO_4), filtered, and concentrated under vacuum to afford a crude product, which was purified by CC (SiO_2, 60 – 120 mesh; AcOEt/hexane 1 : 9) afforded distereoisomeric product **13a** (1.17 g, 92%) as colorless liquid. IR (KBr): 3032, 2929, 2857, 1592, 1512, 1460, 1417, 1378, 1258, 1139, 1076, 1037, 835, 774, 735. ^{1}H-NMR ($CDCl_3$): 0.21 (*s*, 6 H); 0.85 (*s*, 9 H); 0.90 (*t*, *J* = 6.0, 3 H); 1.20 – 1.45 (*m*, 10 H); 1.68 – 1.90 (*m*, 3 H); 2.55 – 2.70 (*m*, 2 H); 3.50 – 3.70 (*m*, 1 H); 3.80 (*s*, 3 H); 4.40 – 4.58 (*m*, 2 H); 5.10 (*s*, 1 H); 6.60 (*d*, *J* = 7.0, 1 H); 6.68 (*s*, 1 H); 6.75 (*d*, *J* = 7.0, 1 H); 7.20 – 7.45 (*m*, 10 H). EI-MS: 590 (100, M^+), 460 (15), 441 (10), 351 (10), 299 (15), 274 (10), 252 (20), 218 (12), 168 (10), 91 (12).

*({(5*S*)-3-(Benzyloxy)-1-[4-(benzyloxy)-3-methoxyphenyl]dodecan-5-yl}oxy)(*tert*-butyl)dimethylsilane* (**13b**). Yield: 92%. IR (KBr): 3450, 2926, 2855, 1212, 1460, 1257, 1075, 835, 773, 697. ^{1}H-NMR ($CDCl_3$): 0.01 – 0.06 (*m*, 6 H); 0.86 – 0.96 (*m*, 12 H); 1.22 – 1.48 (*m*, 14 H); 1.70 – 1.91 (*m*, 2 H); 2.53 – 2.69 (*m*, 2 H); 3.45 – 3.75 (*m*, 1 H); 3.83 – 3.91 (*m*, 4 H); 4.42 – 4.57 (*m*, 2 H); 5.11 (*s*, 2 H); 6.58 – 6.78 (*m*, 3 H); 7.24 – 7.48 (*m*, 10 H). ESI-MS: 619 ($[M+H]^+$), 641 ($[M+Na]^+$).

*({(5*S*)-3-(Benzyloxy)-1-[4-(benzyloxy)-3-methoxyphenyl]tetradecan-5-yl}oxy)(*tert*-butyl)dimethylsilane* (**13c**). Yield: 92%. IR (KBr): 3446, 2924, 2854, 1731, 1460, 1258, 1075, 773, 697. ^{1}H-NMR ($CDCl_3$): 0.01 – 0.06 (*m*, 6 H); 0.87 – 0.94 (*m*, 12 H); 1.22 – 1.48 (*m*, 18 H); 1.73 – 1.95 (*m*, 2 H); 2.52 – 2.72 (*m*, 2 H); 3.44 – 3.77 (*m*, 2 H); 3.85 – 3.89 (*d*, *J* = 4.9, 3 H); 4.44 – 4.56 (*m*, 2 H); 5.10 (*s*, 2 H); 6.59 – 6.79 (*m*, 3 H); 7.20 – 7.48 (*m*, 10 H). ESI-MS: 669 ($[M+Na]^+$).

*4-[(5*S*)-5-{[*tert*-Butyl(dimethyl)silyl]oxy}-3-hydroxydecyl]-2-methoxyphenol* (**14a**). To a stirred soln. of **13a** (1.1 g, 1 mmol) in AcOEt (15 ml) was added 10% Pd/C (100 mg), and the stirring was continued under H_2 atmosphere at r.t. for 5 h. The progress of reaction was monitored by TLC, then, the mixture was filtered, and the catalyst was washed with AcOEt (2 × 10 ml). The solvent was concentrated under reduced pressure. The residue was separated by CC (SiO_2, 60 – 120 mesh; AcOEt/hexane 1.5 : 8.5) to afford a mixture of diastereoisomeric product **14a** (0.68 g, 90%) as colorless liquid. IR (KBr): 3449, 2931, 2858, 1610, 1515, 1462, 1373, 1261, 1152, 1038, 834, 768. ^{1}H-NMR ($CDCl_3$): 0.20 (*s*, 6 H); 0.70 (*s*, 9 H); 0.90 (*t*, *J* = 6.0, 3 H); 1.12 – 1.30 (*m*, 8 H); 1.34 – 1.48 (*m*, 2 H); 1.50 – 1.70 (*m*, 2 H); 2.48 – 2.75 (*m*, 2 H); 3.55 – 3.70 (*m*, 1 H); 3.85 (*s*, 3 H); 3.88 – 3.98 (*m*, 1 H); 5.30 (*s*, 1 H); 6.60 – 6.70 (*m*, 2 H); 6.75 (*d*, *J* = 7.0, 1 H). EI-MS: 411 (100, M^+), 391 (10), 319 (12), 286 (10), 279 (12), 261 (40), 163 (15), 137 (15).

*4-[(5*S*)-5-{[*tert*-Butyl(dimethyl)silyl]oxy}-3-hydroxydodecyl]-2-methoxyphenol* (**14b**). Yield: 90%. IR (KBr): 3435, 2927, 2856, 1726, 1515, 1460, 1262, 1078, 1037, 834, 774. ^{1}H-NMR ($CDCl_3$): 0.04 – 0.10 (*m*, 6 H); 0.84 – 0.92 (*m*, 12 H); 1.16 – 1.43 (*m*, 14 H); 1.48 – 1.74 (*m*, 2 H); 2.48 – 2.76 (*m*, 2 H); 3.62 – 3.77 (*m*, 1 H); 3.84 – 4.01 (*m*, 4 H); 5.30 (*s*, 1 H); 6.62 – 6.78 (*m*, 3 H). ESI-MS: 439 ($[M+H]^+$), 461 ($[M+Na]^+$).

*4-[(5S)-5-{[*tert*-Butyl(dimethyl)silyl]oxy}-3-hydroxytetradecyl]-2-methoxyphenol* (**14c**). Yield: 92%. IR (KBr): 3448, 2926, 2855, 1515, 1463, 1261, 1080, 1037, 835, 776. ^{1}H-NMR ($CDCl_3$): 0.05–0.10 (*m*, 6 H); 0.84–0.94 (*m*, 12 H); 1.20–1.36 (*m*, 16 H); 1.35–1.78 (*m*, 4 H); 2.44–2.76 (*m*, 2 H); 3.62–3.74 (*m*, 1 H); 3.82–3.97 (*m*, 4 H); 5.30 (*s*, 1 H); 6.62–6.78 (*m*, 3 H). ESI-MS: 467 ($[M+H]^+$), 489 ($[M+Na]^+$).

*(5S)-1-[4-(Benzyloxy)-3-methoxyphenyl]-5-{[*tert*-butyl(dimethyl)silyl]oxy}decan-3-ol* (**15a**). To a stirred soln. of **14a** (0.6 g, 1 mmol) and K_2CO_3 (0.4 g, 2 mmol) in acetone (20 ml) was added BnBr (0.25 g, 1 mmol) at r.t., and the mixture was stirred under reflux for 3 h. The progress of the reaction was monitored by TLC, then, the solvent was removed under reduced pressure, and the residue was dissolved in H_2O and extracted with AcOEt (2 × 15 ml). The org. layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure to afford a crude product, which was purified by CC (SiO_2, 60–120 mesh; AcOEt/hexane 1:9) to obtain a mixture of diastereoisomers **15a** (0.65 g, 90%) as colorless liquid. IR (KBr): 3451, 2926, 2855, 1672, 1512, 1461, 1378, 1258, 1138, 1074, 1036, 835, 771, 697. ^{1}H-NMR ($CDCl_3$): 0.20 (*s*, 6 H); 0.85 (*s*, 9 H); 0.92 (*t*, *J* = 6.0, 3 H); 1.20–1.40 (*m*, 10 H); 1.45–1.80 (*m*, 2 H); 2.50–2.70 (*m*, 2 H); 3.60–3.75 (*m*, 1 H); 3.85 (*s*, 3 H); 3.88–3.98 (*m*, 1 H); 5.10 (*s*, 2 H); 6.62 (*d*, *J* = 7.0, 1 H); 6.75 (*d*, *J* = 7.0, 2 H); 7.20–7.42 (*m*, 5 H). EI-MS: 501 (100, M^+), 369 (15), 351 (60), 253 (10), 227 (10), 130 (10).

*(5S)-1-[4-(Benzyloxy)-3-methoxyphenyl]-5-{[*tert*-butyl(dimethyl)silyl]oxy}dodecan-3-ol* (**15b**). Yield: 92%. IR (KBr): 3512, 3924, 2854, 1461, 1259, 1078, 1033, 836, 775. ^{1}H-NMR ($CDCl_3$): 0.05–0.14 (*m*, 6 H); 0.84–0.97 (*m*, 12 H); 1.32–1.45 (*m*, 14 H); 1.48–1.76 (*m*, 2 H); 2.51–2.77 (*m*, 2 H); 3.66–3.74 (*m*, 1 H); 3.84–3.95 (*m*, 4 H); 5.07 (*s*, 2 H); 6.59–6.82 (*m*, 3 H); 7.20–7.45 (*m*, 5 H). ESI-MS: 529 ($[M+H]^+$), 551 ($[M+Na]^+$).

*(5S)-1-[4-(Benzyloxy)-3-methoxyphenyl]-5-{[*tert*-butyl(dimethyl)silyl]oxy}tetradecan-3-ol* (**15c**). Yield: 90%. IR (KBr): 3511, 2928, 2856, 1512, 1460, 1259, 1033, 836, 776. ^{1}H-NMR ($CDCl_3$): 0.04–0.11 (*m*, 6 H); 0.84–0.94 (*m*, 12 H); 1.16–1.33 (*m*, 16 H); 1.34–1.75 (*m*, 4 H); 2.52–2.73 (*m*, 2 H); 3.65–3.74 (*m*, 1 H); 3.83–3.97 (*m*, 4 H); 5.08 (*s*, 2 H); 6.60–6.78 (*m*, 3 H); 7.22–7.41 (*m*, 5 H). ESI-MS: 557 ($[M+H]^+$).

*(5S)-1-[4-(Benzyloxy)-3-methoxyphenyl]-5-{[*tert*-butyl(dimethyl)silyl]oxy}decan-3-one* (**16a**). To a stirred soln. of **15a** (0.6 g, 1 mmol) in dry CH_2Cl_2 (10 ml) were added sequentially $NaHCO_3$ (0.3 g, 3 mmol) and *Dess–Martin* periodinane (0.76 g, 1 mmol), and the mixture was stirred for 1 h at 0°. The completion of reaction was confirmed by TLC, and the mixture was extracted with CH_2Cl_2 (2 × 10 ml). The combined org. layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure to afford a crude product, which was purified by CC (SiO_2, 60–120 mesh; AcOEt/hexane 5:95) to afford the pure product **16a** (0.5 g, 85%) as colorless liquid. IR (KBr): 2926, 1738, 1677, 1609, 1547, 1457, 1371, 1301, 1213, 1155, 1090, 1053, 854, 754. ^{1}H-NMR ($CDCl_3$): 0.20 (*s*, 6 H); 0.75 (*s*, 9 H); 0.90 (*t*, *J* = 6.0, 3 H); 1.20–1.38 (*m*, 8 H); 2.35–2.42 (*m*, 1 H); 2.50–2.60 (*m*, 1 H); 2.65–2.85 (*m*, 4 H); 3.88 (*s*, 3 H); 4.10–4.20 (*m*, 1 H); 5.10 (*s*, 2 H); 5.60 (*d*, *J* = 7.0, 1 H); 6.70 (*s*, 1 H); 6.75 (*d*, *J* = 7.0, 1 H); 7.28–7.45 (*m*, 5 H). EI-MS: 499 (100, M^+), 481 (20), 367 (50), 269 (10), 227 (15), 215 (50).

*(5S)-1-[4-(Benzyloxy)-3-methoxyphenyl]-5-{[*tert*-butyl(dimethyl)silyl]oxy}dodecan-3-one* (**16b**). Yield: 87%. IR (KBr): 2927, 2856, 1714, 1513, 1461, 1258, 1077, 1032, 836, 775. ^{1}H-NMR ($CDCl_3$): 0.01–0.08 (*m*, 6 H); 0.83–0.93 (*m*, 12 H); 1.24–1.34 (*m*, 12 H); 2.34–2.58 (*m*, 2 H); 2.65–2.85 (*m*, 4 H); 3.88 (*s*, 3 H); 4.10–4.17 (br. *s*, 1 H); 5.08 (*s*, 2 H); 5.58–5.75 (*m*, 3 H); 7.26–7.43 (*m*, 5 H). ESI-MS: 527 ($[M+H]^+$), 549 ($[M+Na]^+$).

*(5S)-1-[4-(Benzyloxy)-3-methoxyphenyl]-5-{[*tert*-butyl(dimethyl)silyl]oxy}tetradecan-3-one* (**16c**). Yield: 85%. IR (KBr): 2925, 2855, 1715, 1640, 1460, 1256, 1141, 1135, 855, 771. ^{1}H-NMR ($CDCl_3$): 0.01–0.08 (*m*, 6 H); 0.82–0.94 (*m*, 12 H); 1.22–1.34 (*m*, 16 H); 2.34–2.59 (*m*, 2 H); 2.65–2.85 (*m*, 4 H); 3.87 (*s*, 3 H); 4.05–4.18 (*s*, 1 H); 5.08 (*s*, 2 H); 5.58–5.76 (*m*, 3 H); 7.26–7.43 (*m*, 5 H). ESI-MS: 555 ($[M+H]^+$), 577 ($[M+Na]^+$).

*(5S)-5-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-(4-hydroxy-3-methoxyphenyl)decan-3-one* (**17a**). To a soln. of **16a** (0.4 g, 8 mmol) in AcOEt (10 ml) was added 10% Pd/C (100 mg), and the mixture was stirred under H_2 atmosphere at r.t. for 5 h. The progress of the reaction was monitored by TLC, then, the mixture was filtered, and the catalyst was washed with AcOEt (2 × 10 ml). The combined org. layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was separated by CC (SiO_2,

60–120 mesh; AcOEt/hexane 1:9) to obtain the pure product **17a** (0.3 g, 92%) as colorless liquid. IR (KBr): 3449, 2922, 2853, 1714, 1516, 1462, 1371, 1262, 1149, 1074, 835, 776, 722. ^{1}H-NMR ($CDCl_3$): 0.20 (*s*, 6 H); 0.82 (*s*, 9 H); 0.90 (*t*, *J* = 6.0, 3 H); 1.18–1.35 (*m*, 8 H); 2.30–2.40 (*m*, 1 H); 2.48–2.58 (*m*, 1 H); 2.65–2.85 (*m*, 4 H); 3.88 (*s*, 3 H); 4.06–4.20 (*m*, 1 H); 5.32 (*s*, 1 H); 6.62 (*d*, *J* = 7.0, 2 H); 6.78 (*d*, *J* = 7.0, 1 H). EI-MS: 409 (90, M^+), 381 (20), 367 (10), 309 (10), 277 (60), 215 (100), 179 (50), 141 (40), 137 (50).

*(5*S*)-5-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-(4-hydroxy-3-methoxyphenyl)dodecan-3-one* (**17b**). Yield: 90%. IR (KBr): 3448, 2924, 2854, 1705, 1660, 1515, 1460, 1271, 1034, 764. ^{1}H-NMR ($CDCl_3$): 0.02–0.08 (*m*, 6 H); 0.82–0.93 (*m*, 12 H); 1.22–1.34 (*m*, 12 H); 2.34–2.56 (*m*, 2 H); 2.66–2.88 (*m*, 4 H); 3.88 (*s*, 3 H); 4.10–4.15 (*m*, 1 H); 5.32 (*s*, 1 H); 6.60–6.78 (*m*, 3 H). ESI-MS: 437 ($[M+H]^+$), 459 ($[M+Na]^+$).

*(5*S*)-5-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-(4-hydroxy-3-methoxyphenyl)tetradecan-3-one* (**17c**). Yield: 87%. IR (KBr): 3428, 2924, 2854, 1715, 1461, 1372, 1257, 1082, 835, 772. ^{1}H-NMR ($CDCl_3$): 0.01–0.08 (*m*, 6 H); 0.82–0.95 (*m*, 12 H); 1.20–1.35 (*m*, 16 H); 2.32–2.55 (*m*, 2 H); 2.65–2.88 (*m*, 4 H); 3.89 (*s*, 3 H); 4.10–4.17 (*m*, 1 H); 5.32 (*s*, 1 H); 6.62–6.78 (*m*, 3 H). ESI-MS: 465 ($[M+H]^+$), 487 ($[M+Na]^+$).

(+)-(S)-[6]-Gingerol (=*(5*S*)-5-Hydroxy-1-(4-hydroxy-3-methoxyphenyl)decan-3-one*; **1**). To a stirred soln. of **27** (0.25 g, 0.6 mmol) in dry THF (5 ml) under N_2 atmosphere at 0° was added Bu_4NF (1M, THF, 0.60 ml) dropwise, and the mixture was allowed to be stirred at r.t. The progress of the reaction was monitored by TLC, after completion of the reaction, the solvent was removed under reduced pressure, and the residue was dissolved in H_2O and extracted with AcOEt (2 × 5 ml). The combined org. layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure to afford a crude product, which was purified by CC (SiO_2, 60–120 mesh; AcOEt/hexane 2:8) to obtain the pure product **1** (0.15 g, 87%) as colorless oil. $[\alpha]_D^{25} = +24.3$ (*c* = 1, $CHCl_3$) ($[\alpha]_D^{25} = +25.1$ (*c* = 1, $CHCl_3$) [5c]). IR (KBr): 3362, 2925, 2855, 1712, 1659, 1516, 1462, 1273, 1124, 653. ^{1}H-NMR ($CDCl_3$): 0.89 (*t*, *J* = 6.5, 3 H); 1.12–1.38 (*m*, 8 H); 2.42–2.48 (*m*, 2 H); 2.69 (*t*, *J* = 6.5, 2 H); 2.80 (*t*, *J* = 6.5, 2 H); 3.88 (*s*, 3 H); 3.90–4.02 (*m*, 1 H); 5.32 (*s*, 1 H); 6.62 (*d*, *J* = 7.0, 2 H); 6.78 (*d*, *J* = 7.0, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 14.0; 22.6; 25.1; 29.3; 29.7; 31.7; 33.7; 36.3; 45.4; 49.3; 55.8; 110.9; 114.0; 114.3; 120.7; 132.5; 143.9; 211.5. ESI-MS: 295 ($[M+H]^+$), 317($[M+Na]^+$).

(+)-(S)-[8]-Gingerol (=*(5*S*)-5-Hydroxy-1-(4-hydroxy-3-methoxyphenyl)dodecan-3-one*; **2**). Yield: 90%. $[\alpha]_D^{25} = +25.8$ (*c* = 1, $CHCl_3$) ($[\alpha]_D^{25} = +26.2$ (*c* = 1, $CHCl_3$) [5c]). IR (KBr): 3450, 2923, 2854, 1715, 1462, 1264, 1075, 835, 776. ^{1}H-NMR ($CDCl_3$): 0.89 (*t*, *J* = 6.7, 3 H); 1.22–1.36 (*m*, 12 H); 2.34–2.55 (*m*, 2 H); 2.69 (*t*, *J* = 6.7, 2 H); 2.81 (*t*, *J* = 6.7, 2 H); 3.88 (*s*, 3 H); 3.92–4.02 (*m*, 1 H); 5.32 (*s*, 1 H); 6.58–6.79 (*m*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 14.2; 22.5; 25.3; 29.1; 29.4; 29.8; 31.7; 36.4; 45.3; 49.2; 55.8; 67.6; 110.9; 114.3; 120.6; 132.5; 143.9; 146.4; 211.4. ESI-MS: 323 ($[M+H]^+$), 345 ($[M+Na]^+$).

(+)-(S)-[10]-Gingerol (=*(5*S*)-5-Hydroxy-1-(4-hydroxy-3-methoxyphenyl)tetradecan-3-one*; **3**). Yield: 90%. $[\alpha]_D^{25} = +18.9$ (*c* = 1, $CHCl_3$) ($[\alpha]_D^{25} = +19.8$ (*c* = 1, $CHCl_3$) [5c]). IR (KBr): 3449, 2924, 2854, 1635, 1463, 1217, 1019, 766. ^{1}H-NMR ($CDCl_3$): 0.88 (*t*, *J* = 5.0, 3 H); 1.24–1.40 (*m*, 16 H); 2.43–2.49 (*m*, 2 H); 2.68 (*t*, *J* = 6.8, 2 H); 2.80 (*t*, *J* = 7.5, 2 H); 3.87 (*s*, 3 H); 3.92–4.01 (*m*, 1 H); 5.34 (*s*, 1 H); 6.59–6.78 (*m*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 14.1; 22.6; 24.6; 25.4; 28.7; 29.2; 29.3; 29.5; 29.6; 29.7; 29.8; 31.4; 31.8; 31.9; 33.7; 36.4; 45.4; 49.3; 55.8; 67.6; 110.9; 114.3; 120.7; 125.0; 132.6; 143.9; 211.4. ESI-MS: 351 ($[M+H]^+$), 373 ($[M+Na]^+$).

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