Stereoselective Synthesis of (+)-Paeonilide and Confirmation of its Absolute Configuration

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Abstract: The first diastereoselective synthesis of paeonilide, a novel anti-PAF-active monoterpenoid, starting from *R*-(–)-carvone was reported. The absolute configuration for paeonilide was also established.

Key words: diastereoselective synthesis, (+)-paeonilide, absolute configuration, monoterpenoid, carvone

Paeonia root bark, 'mu-dan-pi' or 'dan-pi' in Chinese, is one of the most important herbal drugs used in traditional Chinese medicine. Representative chemical constituents isolated from different species of Paeonia are a number of structurally related monoterpenes that feature with a highly oxygenated cyclohexane nucleus (Figure 1).[1] In 2000, a novel monoterpenoid, named paeonilide, was isolated from the roots of *Paeonia delavayi*.[2] Its new skeleton was established by a combination of spectroscopic and X-ray crystallographic analysis. The bioassay indicated that paeonilide selectively inhibited the platelet aggregation induced by PAF (the platelet activating factor) with an IC_{50} value of 8 μg/mL, with no inhibitory effect on ADP- or AA-induced platelet aggregation. Due to its important biological activity as well as its potential to be developed to a new lead for medicinal chemistry, synthesis of paeonilide and its analogues were thus initiated. In this communication, we report the first diastereoselective synthesis of paeonilide.

Inspection of paeonilide revealed that it could be synthesized from a highly oxygenated carvone derivative **3**, which could be prepared from commercially available (*R*)-(–)-carvone. The retrosynthetic analysis is shown in Scheme 1.

Although intermediate **3** had been synthesized in the literature by an 8-step procedure in 27% overall yield,[3] utilization of organic selenium as well as expensive catecholborane made the process less attractive to us. An alternative way toward the synthesis of intermediate **3** was

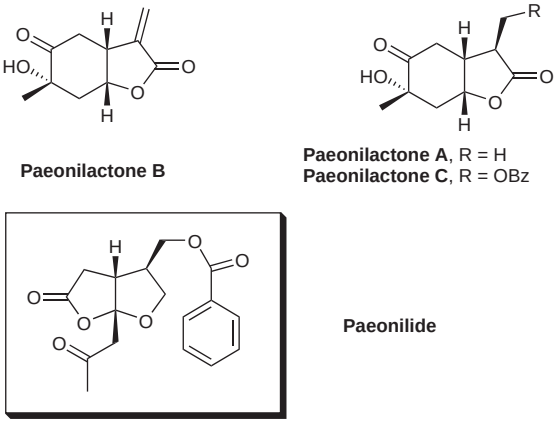
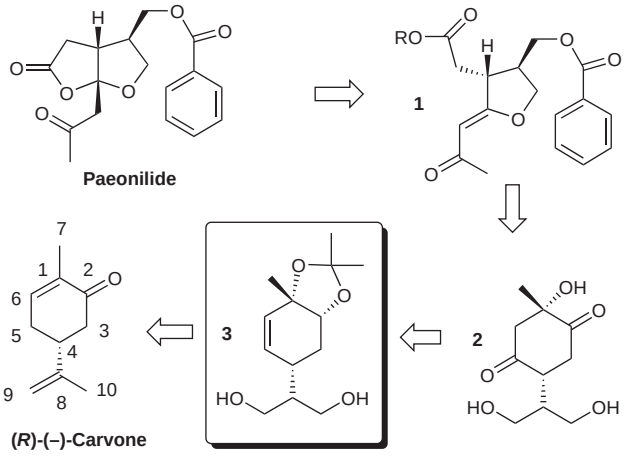


Figure 1 Examples of tetrahydrofuran containing natural products.

thus investigated. Starting from (*R*)-(–)-carvone, a bromination reaction was carried out with NBS following a literature procedure.[4] The allylic bromide **5** was then subjected to an S_N2 substitution with silver acetate in acetic acid to give an allylic acetate **6**. Luche reduction[5] with sodium borohydride and following by MCPBA epoxidation[6] of the resultant hydroxyalkene **7** afforded epoxide **8** in 88% yield over two steps (Scheme 2). The epoxide was initially treated with lithium bromide by following a literature procedure.[7] Unfortunately no desired



Scheme 1 Retrosynthetic analysis of paeonilide from (*R*)-(–)-carvone.

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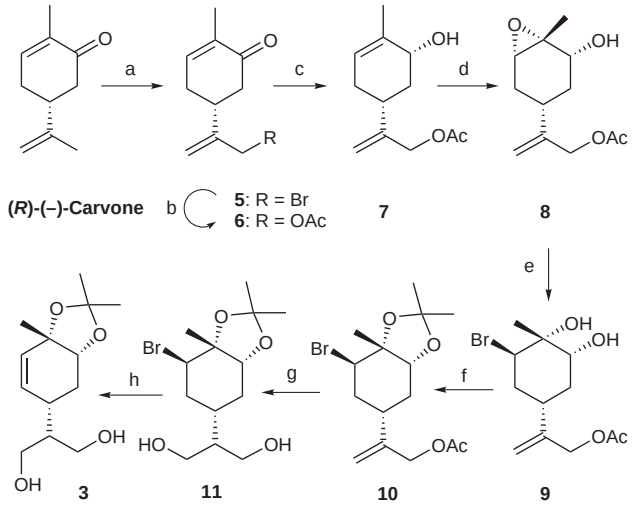
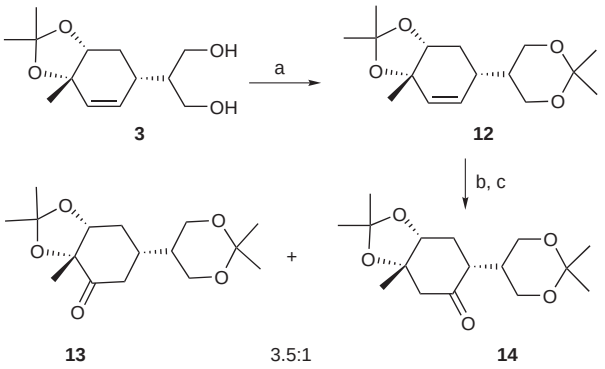
product was observed. The opening of epoxide was finally achieved with lithium bromide generated in situ from reacting *n*-butyllithium with acetyl bromide in anhydrous THF. After protection of the diol system with dimethoxy propane (DMP) in the presence of catalytic ammount of *p*-toluenesulfonic acid, compound **10** was put to a hydroboration with borane-dimethyl sulfide complex. To our delight, the 1,3-diol was produced in high yield with no hydrolysis of the bromo moiety in the ring system. The 1,3-diol compound was then directly treated with potassium *tert*-butoxide in DMF and cyclohexene derivative **3** was obtained in good isolated yield. Our modification led to intermediate **3** from (*R*)-(–)-carvone in a total 22% yield over 8 steps (Scheme 2).



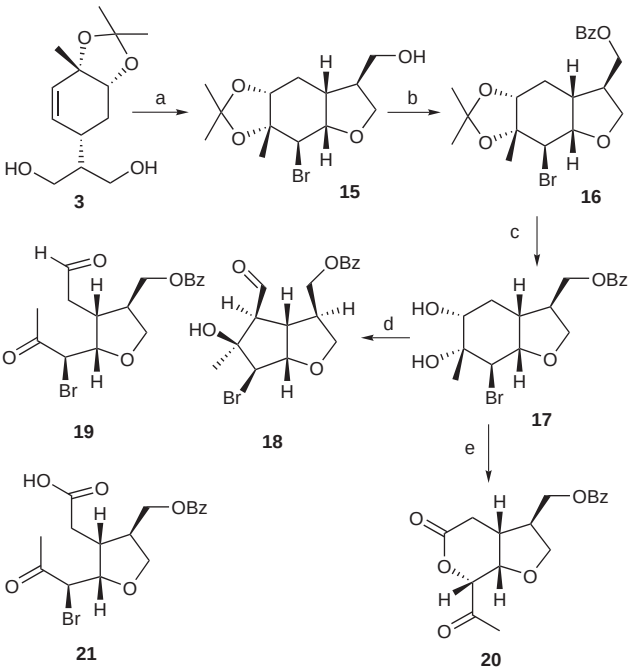
Scheme 2 Synthesis of intermediates for paeonilide.
Reagents and conditions: a) NBS, NaOAc, AcOH, CH_2Cl_2, 35%; b) AgOAc, acetone, reflux, 92%; c) $NaBH_4$, $CeCl_3$, MeOH, 95%; d) MCPBA, CH_2Cl_2, $NaHCO_3$, 93%; e) LiBr, generated in situ, THF, AcOH, 97%; f) DMP, CH_2Cl_2, TsOH, 40 °C, 95%; g) $BH_3{\cdot}SMe_2$, THF, H_2O_2 (30%), 6 N NaOH, 89%; h) *t*-BuOK, DMF, 95%.

With the 9,10-diol **3** in hand, introduction of an oxy function to the C_5-position of the ring system was initiated. After protection of the 1,3-diol system as an acetonide, a Brown hydroboration reaction was conducted. Hydroboration of compound **12** led to an inseparable mixture of regioisomers (Scheme 3). The mixture was further oxidized with CrO_3 in pyridine to afford two ketone isomers. To our disappointment, the major product was the isomer with oxy function being introduced at the C_6-position, and only a small amount of desired C_5-ketone **14** was formed. This approach was therefore abandoned.

Having failed to introduce the key oxy function to the C_5-position, a bromoetherification was then carried out by treatment of diol **3** with NBS in anhydrous THF at room temperature (Scheme 4). The desired furan derivative **15** was obtained in nearly quantitative yield with excellent diastereoselectivity.[8] We observed only one diastereoisomer in this cyclization reaction and this transformation represents a good example of diastereotopic group selective reaction.[9] The relative configuration of the intermediate **15** was established by NOE experiment. The primary alcohol was converted to benzoyl ester **16**, and the ketal protecting group was removed in the presence of 6 N HCl in methanol at room temperature.



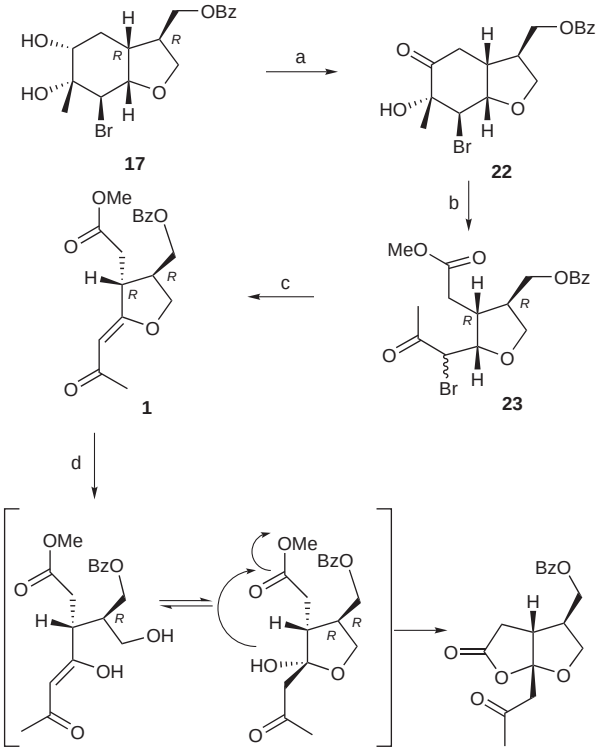
Scheme 3 Introduction of C_5 oxy function by hydroboration.
Reagents and conditions: a) DMP, CH_2Cl_2, TsOH, 40 °C, 95%; b) $BH_3{\cdot}SMe_2$, THF, H_2O_2 (30%), 6 N NaOH; c) CrO_3, pyridine, CH_2Cl_2, 60%.



Scheme 4 Introduction of C_5 oxy function by bromoetherification.
Reagents and conditions: a) NBS, THF, 95%; b) BzCl, pyridine, CH_2Cl_2, 99%; c) 6 N HCl, MeOH, 92%; d) $NaIO_4$, acetone–H_2O, 65%; e) $NaIO_4$, $KMnO_4$, acetone–H_2O, 58%.

With diol **17** in hand, we came to the final stage of our total synthesis. Cleavage of diol **17** with sodium periodate in acetone and water (3:1) at room temperature led to a cyclopentane derivative **18** rather than expected aldehyde **19**. On the other hand, treatment of diol **17** with sodium periodate in the presence of a secondary oxidative agent such as potassium permanganate in acetone resulted in a lactone **20** which was formed by a concomitant intramolecular lactonization. Although the highly substituted

cyclopentane derivative **18** could be used as a valuable intermediate for the synthesis of iridoid type natural product,[10] it was not a desired compound in this synthesis. The *cis*-diol was thus oxidized with IBX in ethyl acetate[11] at refluxing temperature to provide a ketone **22** (Scheme 5). Utilization of periodic acid in ethyl acetate, oxidative cleavage of α-hydroxyl ketone **22** was achieved and afforded a free acid **21**, which was treated with diazomethane to form the corresponding methyl ester **23**. It was noteworthy that methyl ester **23** existed as a mixture of diastereoisomers probably due to an enol epimerization process. Dehydrobromination of α-bromo ketone with DBU in refluxing benzene finally provided the key intermediate **1** (R = Me), an unstable α,β-unsaturated ketone, in moderate yield. Although furanyl ketone **1** could be purified by chromatography, it was better used in the next step without further purification. After removal of benzene, the residue was treated with 6 N HCl (excess) in ethyl acetate at room temperature and paeonilide was obtained by a cyclization reaction.



Scheme 5 Synthesis of paeonilide, the final stage.
Reagents and conditions: a) IBX, EtOAc, 90%; b) H_5IO_6, EtOAc; then diazomethane in Et_2O, 90%; c) DBU, benzene, reflux; d) 6 N HCl, EtOAc, r.t., 40%.

Although the absolute configuration of paeonilide could be derived biosynthetically from *p*-menthane, no solid evidence was obtained due to the scarcity of available sample. Our synthetic sample has identical IR, ^{1}H NMR and ^{13}C NMR spectra, most of all, the optical rotation compared well to those of an authentic sample.[12] Therefore this synthesis also established the absolute configuration unambiguously for paeonilide.

In summary, the first diasteroselective synthesis of paeonilide, a PAF inhibitory agent, was completed in 16 steps with 6.2% overall yield. Some important intermediates for the synthesis of iridoid natural products were also obtained in this research.[13] The proposed absolute configuration of paeonilide was also confirmed by this synthesis. Synthetic study towards iridoid natural product by utilization of this methodology is currently underway in our laboratory.

Acknowledgment

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(8) In the synthetic work published in ref. 3, discriminating between the two primary hydroxyl groups was achieved by an enzymatic acetylation towards substrate **3** and diastereoisomeric monoacetate of diol **3** was obtained with a ratio of 13: 1. In our case, bromoetherification of diol **3** led to only desired diastereisomer **15**.
(9) (a) Hoffmann, R. W. *Synthesis* **2004**, 2075. (b) Studer, A.; Schleth, F. *Synlett* **2005**, 3033.
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(12) Natural paeonilide was provided by professor J. K. Liu. The optical rotation of synthetic paeonilide compared well to the value of authentic sample.
(13) Compound **3**: colorless solid; mp 84–85 °C; $[\alpha]_D^{20}$ –101.6 (*c* 0.993, $CHCl_3$). IR (film): 3424 (s), 2928 (m), 1632 (m), 1372 (m), 1297 (m), 1281 (m), 1237 (w), 1136 (s), 1099 (w), 1071 (w), 1034 (w) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.67 (1 H, dd, *J* = 3.9, 10.4 Hz), 5.58 (1 H, d, *J* = 10.4 Hz), 4.03 (1 H, br s), 3.92–3.74 (4 H, m), 3.12 (1 H, br s), 2.70 (1 H, br s), 2.49–2.20 (2 H, m), 1.96 (1 H, m), 1.91 (1 H, ddd, *J* = 2.8, 8.3, 15.6 Hz), 1.38 (3 H, s), 1.35 (3 H, s), 1.30 (3 H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 131.7 (d), 128.9 (d), 108.5 (s),

78.3 (d), 77.6 (s), 64.4 (t), 63.9 (t), 46.6 (d), 30.1 (d), 28.3 (q), 27.9 (q), 25.1 (q), 24.9 (t). MS (EI): *m*/*z* (%) = 242 (3) [M$^+$], 227 (3), 211 (5), 191 (13), 167 (52), 149 (36), 105 (91), 57 (100). HRMS: *m*/*z* calcd for $C_{13}H_{22}O_4Na$ [M + 23]$^+$: 265.1415; found: 265.1416.

Compound **15**: colorless oil; $[\alpha]_D^{20}$ –4.9 (*c* 0.745, $CHCl_3$). IR (KBr): 3443 (br s), 2985 (s), 2937 (s), 2876 (s), 1458 (s), 1380 (s), 1256 (s), 1215 (s), 1103 (s), 1071 (s), 1029 (s), 990 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.20–4.06 (4 H, m), 3.70–3.57 (3 H, m), 2.28–2.12 (4 H, m), 1.77–1.65 (1 H, m), 1.48 (3 H, s), 1.43 (3 H, s), 1.41 (3 H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 109.5 (s), 83.3 (d), 81.1 (s), 79.4 (d), 69.6 (t), 63.4 (t), 61.3 (d), 48.7 (d), 38.4 (d), 30.9 (t), 28.3 (q), 26.4 (q), 23.3 (q). MS (EI): *m*/*z* (%) = 322 (3) [M$^+$], 320 (2) [M$^+$], 307 (8), 305(7), 197 (7), 183 (10), 169 (12), 155 (16), 127 (27), 111 (27), 97 (38), 85 (64), 71 (100). HRMS: *m*/*z* calcd for $C_{13}H_{22}O_4Na$ [M + 23]$^+$: 343.0520; found: 343.0529.

Compound **16**: colorless oil; $[\alpha]_D^{20}$ –5.7 (*c* 0.764, $CHCl_3$). IR (KBr): 2981 (s), 2953 (s), 2876 (s), 1724 (s), 1688 (s), 1602 (m), 1582 (m), 1453 (s), 1424 (s), 1380 (s), 1325 (s), 1285 (s), 1211 (s), 1180 (s), 1113 (s), 1056 (s), 934 (s), 708 (s) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.98 (2 H, d, *J* = 7.5 Hz), 7.55 (1 H, t, *J* = 7.5 Hz), 7.43 (2 H, t, *J* = 7.5 Hz), 4.33–4.05 (6 H, m), 3.63 (1 H, dd, *J* = 6.9, 9.3 Hz), 2.44 (1 H, m), 2.26–2.17 (2 H, m), 1.72 (1 H, m), 1.45 (3 H, s), 1.40 (3 H, s), 1.37 (3 H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.7 (s), 133.7 (d), 130.1 (s), 129.9 (d), 128.9 (d), 109.9 (s), 83.6 (d), 81.4 (s), 79.7 (d), 69.9 (t), 65.4 (t), 61.2 (d), 46.2 (d), 39.5 (d), 31.3 (t), 28.7 (q), 26.8 (q), 23.7 (q). MS (EI): *m*/*z* (%) = 426 (14) [M$^+$], 424 (15) [M$^+$], 411 (30), 409 (32), 351 (5), 349 (5), 329 (3), 287 (4), 229 (13), 227 (15), 183 (6), 165 (19), 147 (22), 105(100). HRMS: *m*/*z* calcd for $C_{20}H_{25}O_5NaBr$ [M + 23]$^+$: 447.0783; found: 447.0774.

Compound **17**: colorless oil; $[\alpha]_D^{20}$ +23.4 (*c* 1.161, $CHCl_3$). IR (KBr): 3453 (br s), 2977 (s), 2940 (s), 2889 (s), 1719 (s), 1601 (w), 1451 (s), 1394 (s), 1376 (s), 1274 (s), 1117 (s), 1069 (s), 1026 (s), 756 (s), 713 (s) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.01 (2 H, d, *J* = 7.5 Hz), 7.57 (1 H, t, *J* = 7.5 Hz), 7.44 (2 H, t, *J* = 7.5 Hz), 4.43 (1 H, d, *J* = 7.5 Hz), 4.39 (1 H, dd, *J* = 5.7, 11.2 Hz), 4.29 (1 H, dd, *J* = 4.4, 6.7 Hz), 4.23 (1 H, d, *J* = 9.2 Hz), 4.21 (1 H, d, *J* = 9.3 Hz), 3.94 (1 H, t, *J* = 4.5 Hz), 3.73 (1 H, dd, *J* = 7.2, 9.0 Hz), 3.37 (1 H, br s), 2.98 (1 H, m), 2.37 (1 H, m), 2.01–1.90 (2 H, m), 1.33 (3 H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.5 (s), 133.2 (d), 129.8 (s), 129.6 (d), 128.4 (d), 82.5 (d), 74.2 (d), 72.3 (s), 69.6 (t), 65.2 (t), 42.5 (d), 39.6 (d), 28.2 (t), 22.8 (q), 14.2 (q). MS (EI): *m*/*z* (%) = 323 (1), 305(3), 287 (30), 264 (10), 262 (11), 217 (7), 183 (13), 165 (86), 147 (36), 138 (26), 123 (26), 105 (100). HRMS: *m*/*z* calcd for $C_{17}H_{21}O_5NaBr$ [M + 23]$^+$: 407.0470; found: 407.0463.

Compound **18**: colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.82 (1 H, d, *J* = 1.5 Hz), 8.03 (2 H, d, *J* = 7.8 Hz), 7.58 (1 H, t, *J* = 7.9 Hz), 7.45 (2 H, t, *J* = 7.9 Hz), 4.82 (1 H, dd, *J* = 6.3, 8.6 Hz), 4.31–4.20 (2 H, m), 4.00–3.86 (3 H, m), 3.25 (1 H, ddd, *J* = 3.0, 8.9, 9.0 Hz), 2.52–2.33 (3 H, m), 1.48 (3 H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.4 (s), 166.8 (s), 133.6 (d), 130.2 (s), 130.0 (d), 128.9 (d), 90.4 (d), 82.1 (s), 70.5 (t), 65.3 (t), 65.0 (d), 62.1 (d), 45.1 (d), 44.2 (d), 24.6 (q).

Compound **22**: colorless oil; $[\alpha]_D^{20}$ +50.7 (*c* 0.725, $CHCl_3$). IR (KBr): 3442 (br s), 2949 (w), 2892 (w), 1721 (s), 1601 (w), 1451 (w), 1275 (s), 1112 (s), 1071 (w), 1045 (w), 713 (s) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.98 (2 H, d, *J* = 8.4 Hz), 7.56 (1 H, t, *J* = 7.5 Hz), 7.44 (2 H, dd, *J* = 7.5, 8.4 Hz), 4.51 (1 H, dd, *J* = 7.1, 8.3 Hz), 4.33 (2 H, d, *J* = 6.0 Hz), 4.22 (1 H, t, *J* = 9.0 Hz), 4.08 (1 H, d, *J* = 9.0 Hz), 3.79 (1 H, dd, *J* = 8.0, 9.1 Hz), 2.93 (1 H, dd, *J* = 8.0, 16.5 Hz), 2.80–2.67 (2 H, m), 2.49–2.37 (1 H, m), 1.43 (3 H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.0 (s), 166.4 (s), 133.5 (d), 129.8 (s), 129.7 (d), 128.7 (d), 82.2 (d), 76.6 (s), 69.5 (t), 64.4 (t), 59.9 (d), 43.5 (t), 41.3 (d), 36.6 (q), 22.5 (q). MS (EI): *m*/*z* (%) = 303 (15), 285 (4), 274 (5), 257 (3), 189 (8), 181 (48), 163 (13), 153 (14), 138 (20), 121 (11), 105 (100), 95 (13), 77 (24). HRMS: *m*/*z* calcd for $C_{17}H_{19}O_5NaBr$ [M + 23]$^+$: 405.0313; found: 405.0322.

Compound **23**: colorless oil, mixture of α-bromoketones. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.05–8.01 (4 H, m), 7.58 (2 H, t, *J* = 7.5 Hz), 7.48–7.43 (4 H, m), 4.53–4.27 (8 H, m), 4.18 (1 H, dd, *J* = 7.8, 9.0 Hz), 3.97 (1 H, d, *J* = 10.2 Hz), 3.76–3.70 (2 H, m), 3.68 (3 H, s), 3.65 (3 H, s), 2.85–2.62 (4 H, m), 2.50–2.39 (2 H, m), 2.42 (3 H, s), 2.36 (3 H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.9/200.2 (s), 172.4 (s), 166.7 (s), 133.6 (d), 130.0 (s), 130.0 (d), 128.9 (d), 80.4/80.0 (d), 70.9/70.4 (t), 65.7/65.6 (t), 54.5/49.3 (d), 52.4 (q), 44.6/43.7 (d), 41.3/40.9 (d), 33.8/33.4 (t), 27.7/26.1 (q). MS (EI): *m*/*z* (%) = 333 (25), 277 (20), 259 (6), 211 (30), 179 (15), 155 (35), 151 (29), 105(100). HRMS: *m*/*z* calcd for $C_{18}H_{21}O_6NaBr$ [M + 23]$^+$: 435.0419; found: 435.0421.

Compound **1** (R = Me): colorless oil, $[\alpha]_D^{20}$ +58.8 (*c* 1.822, acetone). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8. 01 (2 H, d, *J* = 7.2 Hz), 7.56 (1 H, t, *J* = 7.5 Hz), 7.43 (2 H, dd, *J* = 7.2, 7.5 Hz), 5.82 (1 H, s), 4.39 (1 H, dd, *J* = 6.0, 9.6 Hz), 4.32–4.21 (3 H, m), 3.93 (1 H, dd, *J* = 3.0, 11.7 Hz), 3.67 (3 H, s), 2.93 (1 H, dd, *J* = 3.0, 16.5 Hz), 2.78 (1 H, q, *J* = 6.0 Hz), 2.48 (1 H, dd, *J* = 10.8, 16.5 Hz), 2.12 (3 H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.3 (s), 177.5 (s), 172.2 (s), 166.7 (s), 133.6 (d), 130.1 (s), 130.0 (d), 128.8 (d), 99.7 (d), 72.4 (t), 65.8 (t), 52.3 (q), 42.6 (d), 42.1 (d), 35.6 (t), 31.7 (q). MS (EI): *m*/*z* (%) = 333 (1) [M$^+$ + 1], 290 (2), 259 (5), 247 (5), 210 (22), 193 (12), 137 (15), 105(100). HRMS: *m*/*z* calcd for $C_{18}H_{20}O_6Na$ [M + 23]$^+$: 355.1157; found: 355.1152.

Paeonilide: colorless needles; $[\alpha]_D^{20}$ +50.6 (*c* 0.775, acetone). Authentic sample: $[\alpha]_D^{20}$ +53.5 (*c* 0.340, acetone). IR (KBr): 3438 (s), 1763 (s), 1709 (s), 1281 (s), 1119 (s), 1041 (m), 949 (m), 922 (m), 717 (s) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.01 (2 H, d, *J* = 7.5 Hz), 7.59 (1 H, t, *J* = 7.5 Hz), 7.44 (2 H, t, *J* = 7.5 Hz), 4.29 (1 H, dd, *J* = 7.2, 11.1 Hz), 4.17 (1 H, dd, *J* = 8.1, 11.1 Hz), 4.02 (2 H, m), 3.41 (1 H, d, *J* = 17.8 Hz), 3.34 (1 H, dd, *J* = 10.5, 18.5 Hz),* 2.96 (1 H, d, *J* = 18.4 Hz), 2.94 (1 H, m), 2.54 (1 H, dd, *J* = 2.8, 18.4 Hz),* 2.54 (1 H, m), 2.19 (3 H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 204.5 (s), 174.6 (s), 166.5 (s), 133.6 (d), 129.8 (s), 129.7 (d), 128.7 (d), 115.1 (s), 68.1 (t), 65.1 (t), 49.7 (t), 46.9 (d), 44.5 (d), 36.8 (t), 31.1 (q). MS (EI): *m*/*z* (%) = 196 (15), 178 (9), 152 (52), 139 (12), 105(100), 94 (53). HRMS: *m*/*z* calcd for $C_{17}H_{18}O_6Na$ [M + 23]$^+$: 341.1001; found: 341.1001. *A few typing errors were found for the assignment of protons at C_{13} position in the original paper published in *Biosci. Biotechnol. Biochem.* (see ref. 2). It should be corrected as 3.34 (1 H, dd, *J* = 10.5, 18.5 Hz) and 2.55 (1 H, dd, *J* = 2.8, 18.5 Hz).